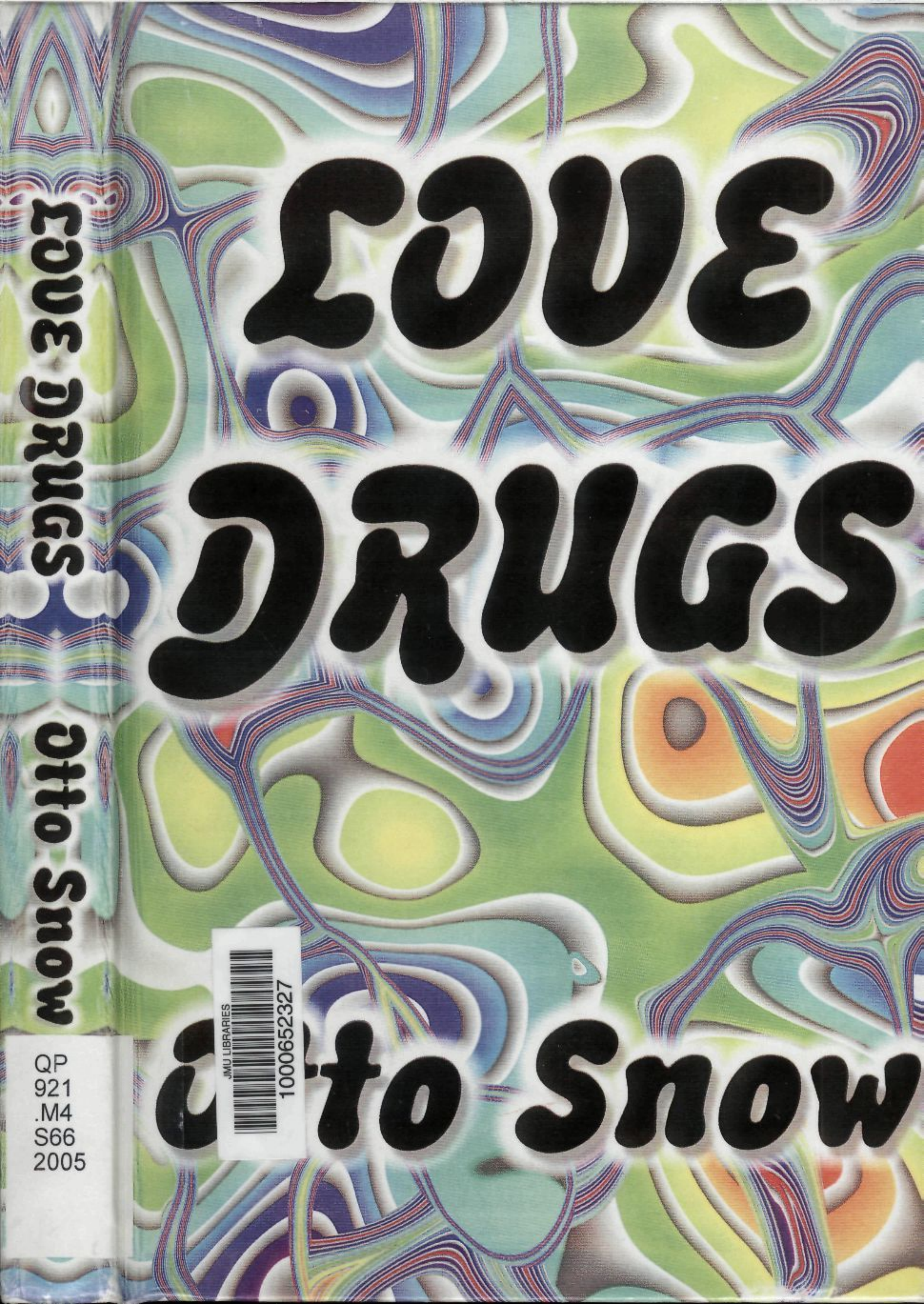
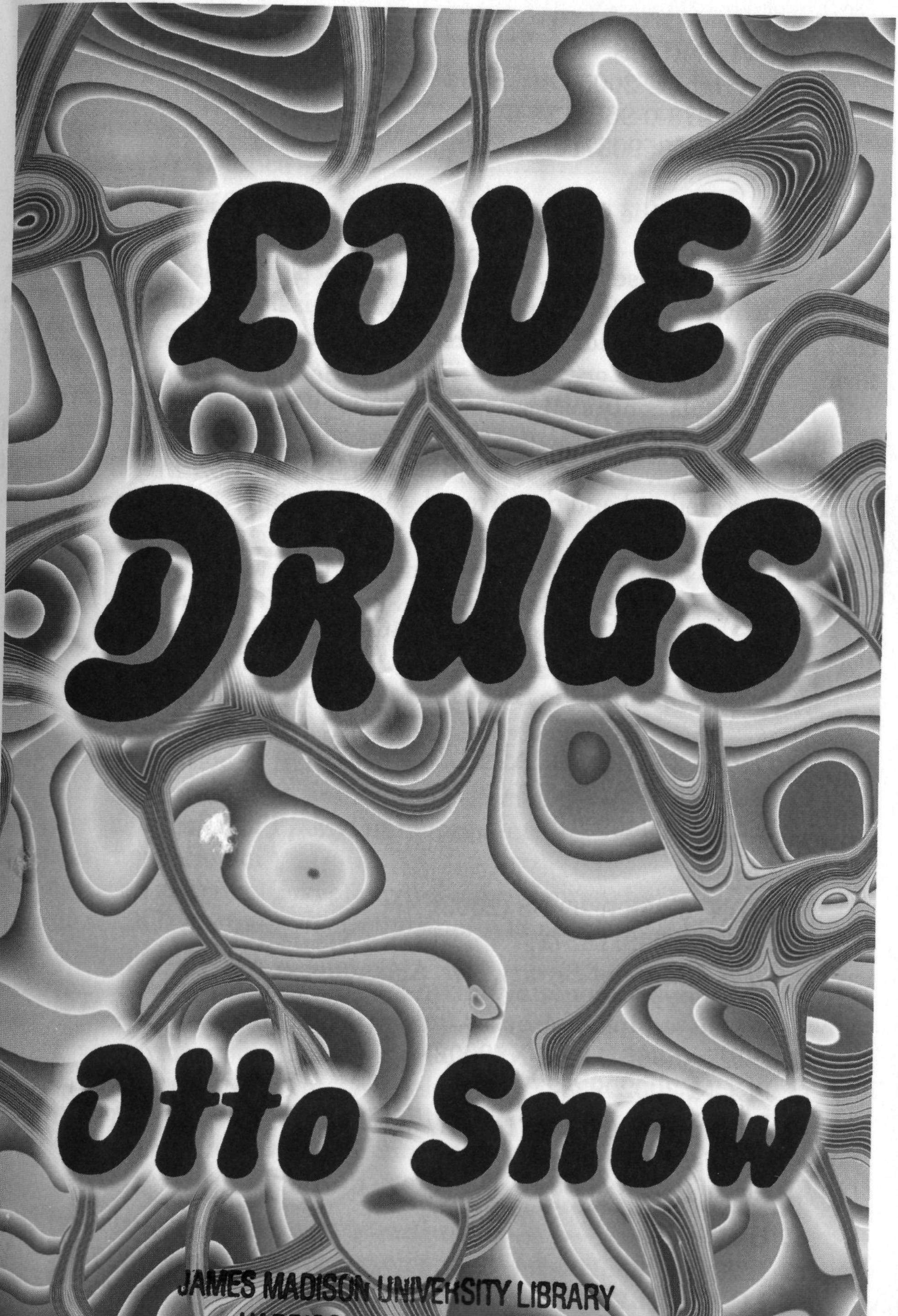


LOVE DRUGS

Otto Snow

Love Drugs Otto Snow



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Operation of Volatile-Oil Stills

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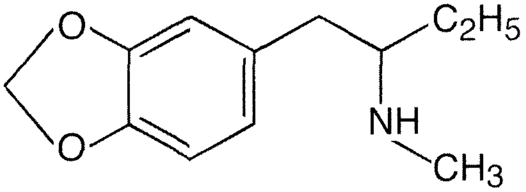
This book is a tool for the legal, medical, scientific and political professions and should not be misconstrued as a 'cookbook'. Publisher and author take no responsibility for inaccuracies, omissions, or typographical errors. References and sources are included for those seeking unedited detailed descriptions on the construction of any specific molecule. All chemicals and reactions are potentially toxic, explosive & lethal.

This book is for information purposes only. No person is allowed to produce controlled substances without proper permits and authorization. To take/give substances for human consumption whether legal or illegal without a very thorough knowledge of the substance and the health (mental as well as physical) condition/s of the individual is destined to produce catastrophic results and legal ramifications.

Series and individual reactions are overviewed and extensively referenced. Many different routes are described on altering the molecular structures of known and unknown neurochemicals. The terms and explanations are simplified and interwoven with historical data.

This guide is an asset and a necessity for:
lawmakers, attorneys, teachers, counselors,
law enforcement and students alike.



N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine

Introduction

MDA (3,4-methylenedioxyamphetamine) was available in the 1960's. The molecule produces empathy in human subjects. In the 1970's, MDMA (3,4-methylenedioxy-N-methylamphetamine) appeared, followed by MDEA (3,4-methylenedioxy-N-ethylamphetamine) in the 1980's. All of these molecules were placed in schedule 1 because they were being abused.

Entactogens are a unique class of substances. They have been successfully used by rape victims, couples counseling and victims of terrorism. Unfortunately, these medications are only available thru illegal channels. No companies are willing to develope medications which are listed in schedule 1.

The companies that supply intermediates to organized crime continue to do so with impunity. I spoke with a major supplier to global organized crime a few years ago. They supply illegal drug manufacturing syndicates with multi tons of intermediates. The sales person laughed when I mentioned the word ethics.

Salesman: "If we don't sell them the chemicals someone else will. Its better that the US makes the money."

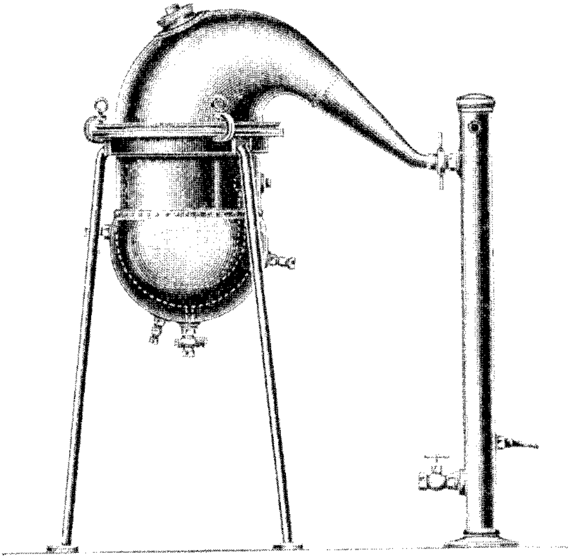
Otto: "Uncle Sam is going to get wise to it and will block your sales to these countries."

Salesman: "No chance, they interfere with sales and we will ship chemicals to another country and have tankers take the chems across the borders. When they block one chemical we will replace it with substitutes that will work just as well."

Last time I checked, this supplier was offering $35 to $50 a barrel for people to illegally dispose of toxic waste in 1000 barrel loads.

Patients continue to be drugged with chronic addictive medications as pharmaceutical firms profit from our suffering. Cocaine and ecstacy are at an all time low price. People interesting in developing medications and researching the entactogen series (legally) have been terrorized by law enforcement for money, with federal prosecutors in complicity.

Scientific inquisitiveness has always been regarded as corner stone of our great democracy. The entactogens offer hope for many patients. It is important that research continues in the development of safe and effective entactogens...



Distilling apparatus used for the Rectification of Essent. Oils.

Mescaline Analogs: Chapter 1

Substitutions at the 4-Position

by Ulrich Braun, Gisela Braun, Peyton Jacob III, David E. Nichols, and Alexander T. Shulgin

Mescaline, 3,4,5-trimethoxyphenethylamine, is one of the longest known and best studied of the psychotomimetic drugs. It has served as the structural paradigm for the synthesis and study of a large number of analogs. Many of the molecular changes have resulted in increased potency, and have established structural parameters felt to be necessary for maximum neurotoxic activity. One of these is the extension of the carbon chain from two carbons to three, by the addition of an *alpha*-methyl group adjacent to the basic nitrogen. This simple homologation appears to protect the nitrogen atom from metabolic removal, and to effectively increase the potency of the drug. In the examples in the earlier literature where direct comparisons between the two-carbon and the three-carbon counterparts were made, there was certainly an increase in potency. However, the metabolic argument is clouded by the fact that in those examples where the chain was extended to four carbons (providing as complete a structural hindrance to metabolic attack as a three-carbon chain) there was also a consistent decrease in biological activity.

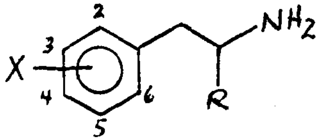
A second parameter is the positioning of the groups of the aromatic ring. The relocation of substituents from the 3,4,5-orientation of mescaline to the 2,4,5-pattern has, again in the earliest reports (Shulgin 1964), resulted in a substantial increase in psychotomimetic potency. As a result of these generalizations, both the two-carbon phenethylamines and the 3,4,5- "mescaline like" substitution pattern have been largely ignored in the synthesis and evaluation of psychotomimetic drugs and have played only a small role in structure activity relationship studies. In recent years, several discoveries have renewed interest in compounds more closely allied to mescaline in structure. First, a number of potent ring-substituted phenethylamines have been reported, chemicals that are the two-carbon analogs of known psychotomimetic phenylisopropylamines. Second, there has been an increasing awareness of the importance of the 4-position in the substitution pattern of the 2,4,5-orientation. Third, there have been recent correlations between psychotomimetic potency and physical properties such as lipophilicity, which have suggested that modest chain-lengthening within a set system of aromatic substituents might affect biological potency (Barfknecht *et al.* 1975). The purpose of this paper is to review these parameters, to present experimental data concerning several new compounds, and to discuss the possible reasons for their activity.

Initially, mescaline was the only two-carbon psychotomimetic known. Although many variations on its structure had been made leading to a variety of compounds with greatly increased potency, it was only recently that the logical step was taken of investigating the two-carbon counterparts of the more potent phenylisopropylamines. The phenethylamines which have been studied, and their reported potencies in human subjects, are presented in table 1 in direct comparison to the corresponding substituted amphetamine homologs. It is immediately apparent that, in all cases, the three-carbon homolog is more potent than the corresponding phenethylamine, sometimes by as much as an order of magnitude. In some entries, the absence of defined action in man makes the comparison between the two groups uncertain.

Structural changes at the 4-position of the psychotomimetic phenylisopropylamines can modify both the quantitative and the qualitative effects that are produced. The potency increases as the nature of the group in the 4-position varies from H < OR < SR < R < X wherein R is an alkyl group and X is a halogen. Within each of these families, small groups of close homologs have been studied and the comparative quantitative relationships of these are shown in table II. In general, those series that represent progressive homologous sets of compounds have their maximum potency with the methyl or the ethyl substituent. However, of particular interest to this study is the unusual enhancement of activity seen in the ethoxy compound 3,5-dimethoxy-4-ethoxyphenylisopropylamine. The relatively minor change of potency seen upon replacing a methoxy group with an ethoxy group, or a methyl group with an ethyl group, at the 4-position (as seen in the comparison of TMA-2 to MEM, of *para*-DOT to aleph-2, and of DOM to DOET) is exaggerated when this alkoxy group is flanked with methoxy substituents (see table II). The unusual five fold increase in activity of 3,5-dimethoxy-4-ethoxyphenylisopropylamine over the 4-methoxy counterpart TMA may emphasize the importance of steric considerations in the action of these drugs. In the case of the 3,4,5-substitution pattern, an ethoxy group in the 4-position is of necessity directed away from the plane of the aromatic ring.

TABLE I

HUMAN ACTIVITY OF 2-CARBON AND ANALOGOUS 3-CARBON-CHAIN PSYCHOTOMIMETICS (a)



X =	2-Carbon R=H		3-Carbon R=CH$_3$		Rel. potency CH$_3$ v. H
4-OCH$_3$	MPEA	>400mg (b)	PMA	60mg (c)	>5x
3,4-OCH$_3$	DMPEA	1500mg (d)	3,4-DMA	~400mg (e)	4x
3,OCH$_2$O-4		>200mg (f)	MDA	100mg (e)	>2x
3,4,5-OCH$_3$	mescaline	350mg (g)	TMA	200mg (h,i)	2x
2,3,4-OCH$_3$	2,3,4-TMPEA	~400mg (j)	TMA-3	>100mg (e)	?
2,4,5-OCH$_3$	TMPEA	>300mg (k,l)	TMA-2	20mg (m)	>15x
2,5-OCH$_3$-4-Br		10mg (n)	DOB	1mg (o)	10x
2,5-OCH$_3$-4-I		>8mg (e)	DOI	1mg (e)	>8x
2,5-OCH$_3$-4-CH$_3$		20mg (n)	DOM(STP)	5mg (e)	4x
2,5-OCH$_3$-4-Et		20mg (p)	DOET	4mg (e)	5x
2-OCH$_3$-3-OCH$_2$O-4		>60mg (c)	MMDA-3a	30mg (e)	>2x
3-OCH$_3$-4-OCH$_2$O-5		>250mg (q)	MMDA	150mg (r)	>2x
3,5-OCH$_3$-4-OEt	escaline	60mg (e,s)		40mg (p)	1½x
3,5-OCH$_3$-4-OPr	proscaline	60mg (e,s)		?	?
3,5-OCH$_3$-4-SCH$_3$	thiomescaline	30mg (s)		?	?

References for Table 1

a. Compounds listed with > are inactive in man at the stated value, which are total doses.

b. **Brown, W.T., McGeer, P.L., and Moser, I.** (*Can Psychiat. J.*, 31: 91, 1968.

c. **Shulgin, A.T., Sargent, T., and Naranjo**, C. *Nature*, 221: 537, 1969

d. **Vojtechovsky, M., and Krus, D.** Acta Nerv Sup, 381, 1967.

e. **Shulgin, A.T.** In: Iversen, Iversen, and Snyder, eds. *Handbook of Psychopharmacology* Vol. II. New York: Plenum Press, 1978.

f. **Alles, G.A.** In: Abramson, ed. *Neuropharmacology* (Trans 4th Conf) J Macy Jr. Foundation, 1959.

g. **Shulgin, A.T.** *Lloydia*, 36:40, 1973.

h. **Peretz, D.I., Smythies, J.R., and Gibson, W.C.**; *J Ment Sci*, 101 317, 1955.

i. **Shulgin, A.T., Bunnel, S., and Sargent, T.;** *Nature* 189: 1011, 1961

j. **Slotta, K.H. and Muller, J.**, *Z. Physiol. Chem.*; 238: 14, 1936.

k. **Jansen, M. P.J.M.**; *Rec Trav Chim*, 50: 291, 1931.

l. **Dittrich, A.** *Psychopharmacologia*, 21: 229, 1971.

m. **Shulgin, A.T.**, *J. Psyched Drugs* 8:169, 1976.

n. **Shulgin, A.T., and Carter, M.F.** *Psychopharm Commun.*, 1: 93, 1975

o. **Shulgin, A.T., Sargent, T., and Naranjo, C.**; *Pharmacology*, 5: 103 1971.

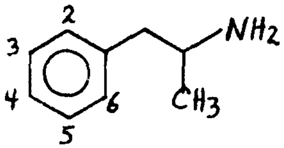
p. **Shulgin, A.T.** Unpublished data.

q. **Shulgin, A.T.** In: Gordon, ed. *Psychopharmacological Agents* Vol. 4 New York: Academic Press, 1976.

r. **Shulgin, A.T., Sargent, T. , and Naranjo, C.** *Pharmacology*, 10: 12 1973.

TABLE II

RELATIVE POSTENCIES IN MAN OF DIMETHOXYPHENYLISOPROPYLAMINE PSYCHOTOMIMETICS WITH VARIOUS SUBSTITUENTS ON THE 4-POSITION



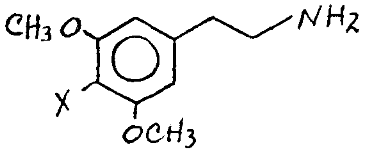
Substitution Pattern on the Phenylisopropyl Amine	R =	Name	Potency (total dose mg/man
2,5-OCH_3-4-OR	CH_3	TMA-2	20 mg (a)
	C_2H_5	MEM	30 mg (b)
	C_3H_7 (n)	MPM	50 mg (c)
2,5-OCH_3-4-SR	CH_3	para-DOT	10 mg (d)
	C_2H_5	aleph-2	5 mg (b)
	C_3H_7 (i)	aleph-4	8 mg (c)
2,5-OCH_3-4-R	CH_3	DOM(STP)	5 mg (b)
	C_2H_5	DOET	4 mg (b)
	C_3H_7 (n)	DOPR	5 mg (e)
	C_4H_9 (n)	DOBU	10 mg (e)
	C_4H_9 (t)	DOTB	>25 mg (d,f)
	C_5H_{11} (n)	DOAM	40 mg (e)
2,5-OCH_3-4-X	Br	DOB	1 mg (g)
	I	DOI	1 mg (b)
3,5-OCH_3-4-R	OCH_3	TMA	200 mg (h,i)
	$OCH_2C_6H_5$		150 mg (b)
	OC_2H_5		40 mg (c)
	Br		6 mg (j)

References for Table II

a. **Shulgin, A.T.** *J Psyched Drugs*, 8, 69, 1975
b. **Shulgin, A.T.** In: Irverson, Iversen, and Snyder eds. *Handbook of Psychopharmacology* Vol. II., New York: Plenum Press, 1973.
c. **Shulgin, A.T.** Unpublished data.
d. **Shulgin, A.T., and Nichols, D.E.** In: Stillman, R., and Willette, R. eds. *Psychopharmacology of Hallucinogens*. New York: Pergamon Press, 1978.
e. **Shulgin, A.T., and Dyer, D.C.**; *J Med Chem*, 18: 1201 1975.
f. A > symbol indicates the absence of any activity at the stated dosage.
g. **Shulgin, A.T., Sargent, T., and Naranjo, C.** *Pharmacology*, 5: 103, 1971
h. **Peretz, D.I., Smythies, J.R., and Gibson, W.C.** *J Ment Sci*, 101: 317, 1955.
i. **Shulgin, A.T., Bunnell, S., and Sargent, T.**; *Nature*, 189: 1011, 1961.
j. **Nichols, D.E., Shulgin, A.T., and Dyer, D.C.** *Life Sci*, 21: 569, 1977.

These possible steric effects have been evaluated by an approach involving partition coefficients. In this way, an estimate of comparative lipophilicity can be made since this property is felt to influence the ease of membrane transport and thus eventual availability to the site of action. A number of psychotomimetic phenylisopropylamines have been studied in an octanol-water partition system, and the correlation of the resulting values, with central activity has provided a relationship that suggests an optimum lipophilicity for maximum biological activity (Barfknecht *et al.* 1975). These partition values have been correlated to serotonin receptor stimulation capability (Nichols and Dyer 1977) and have recently been extended to a number of phenethylamine compounds (Nichols et al. 1977).

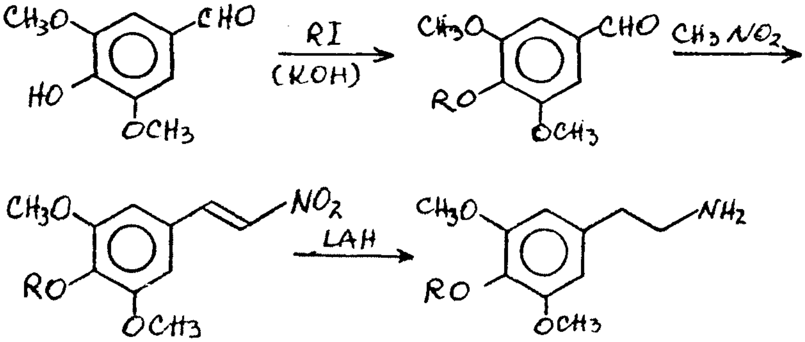
We have undertaken a project directed towards an investigation of a number of compounds that represent a return to the 3,4,5-orientation and the two-carbon chain features of mescaline, but that are modified in some way by the substituent that is found at the 4-position. These are compounds of the general structure:



wherein X = R, OR, SR and halogen. In this report we will discuss the chemistry and the psychopharmacology of the first three compounds studied in this direction.

Two of the compounds described here are 4-alkoxy homologs of mescaline. These have been prepared by the appropriate alkylation of syringaldehyde with either ethyl or propyl iodide followed by the formation of a nitrostyrene with nitromethane. These intermediates were then reduced with LAH to form the product amines 4-ethoxy-3,5-dimethoxyphenethylamine (1) and 4-propoxy-3,5-diimethoxyphenethylamine (2), respectively. These products have been called escaline and proscaline in keeping with the well-established trivial name mescaline for the 4-methoxy counterpart. These reactions are shown in scheme I.

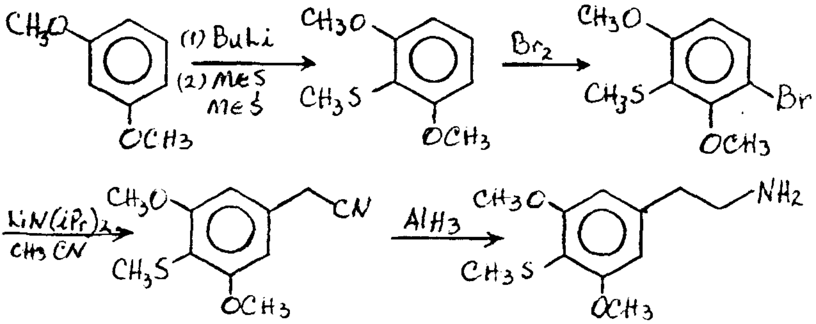
SCHEME I



The third compound studied is the 4-thio analog of mescaline, 4-methylthio-3,5-dimethoxyphenethylamine. This was prepared (see scheme II) by the reaction, of lithiated m-dimethoxybenzene with dimethyldisulfide to form 2,6-dimethoxythioanisole. This underwent bromination uniquely adjacent to the methoxy group, and the resulting bromodimethoxythioanisole underwent a smooth benzyne reaction with acetonitrile to form the benzyl cyanide shown, which was reduced to the desired end product (3) with aluminum hydride in THF.

These three mescaline analogs (table I) have been assayed in normal subjects by procedures previously outlined (Shulgin *et al.* 1969). Both of the alkoxy homologs are effective as psychotomimetics at dosages of 60 mg. orally, with clear threshold effects being noted in some subjects at levels as low as 10 mg. These bases differ from mescaline in that the onset of action occurs sooner (within the first hour) and there is no nausea noted, but otherwise the time course and much of the qualitative content of the intoxication are similar to those of mescaline. The sulfur compound thio-mescaline (3) is also of unexpectedly high potency and is an effective psychotomimetic in man at oral doses of 30 mg. The initial indicators of intoxication are apparent during the second half of the first hour following administration, and a plateau of intoxication is maintained for approximately three hours. The qualitative content of the experience resembles LSD more closely than it does mescaline in that there are few reports of color enhancement but rather considerable involvement with intellectualization. The overall content of the intoxication is closely related to the "aleph" effects which are characteristic of the several 4-thioalkyl-2,5-dimethoxyphenylisopropylamine compounds listed in table II.

SCHEME II



There are several appealing explanations for the unexpectedly high potency of these three compounds. The most direct explanation is the one suggested above, that the presence of two methoxy groups adjacent to the 4-position (the 3,4,5-orientation) forces the group in that position completely out of the plane of the aromatic ring. With the 4-methoxy group as found in mescaline, there is only a minor protuberance from the plane of the ring and there is a relatively low order of potency. However, with the ethoxy and the propoxy groups the alkyl "tail" of the alkoxy group is conspicuously inserted into the surrounding area. This steric necessity may inordinately affect both the pharmacokinetics and the pharmacodynamics of the molecule. The aliphatic nature of this "tail" could modify the local lipophilicity of the molecule, which will influence its bioavailability. These effects might be related to partition properties, as mentioned earlier. There could also be a major dissymetry introduced into the molecule by this out-of-plane forcing which would potentially change the closeness of fit of the drug at some receptor site. Further, the change of the orbital hybridization of the heteroatom at the 4-position, especially in the case of the 4-methylthio example, could allow a change of availability of the molecule to metabolism and thus to eventual distribution in the body. An immediate challenge to these possibilities may be found in the 4-thioethyl compound, which has not yet been evaluated pharmacologically. If the enhancement seen from the methoxy to the higher alkoxy (6-fold increase over mescaline) and the enhancement seen from the methoxy to the methylthio (12-fold increase over mescaline) may be expected to be general in applicability, the ethylthio compound may be expected to be an exceptionally potent psychotomimetic.

Yet another group at the 4-position deserves more attention than it has received. The 4-alkyl analog of mescaline, 4-methyl-3,5-dimethoxyphenethylamine has been prepared and studied in cats (Benington, Morln, and Clark 1968). Although the geometric change induced by the replacement of the methoxy group with the methyl group is minor, there was nonetheless a dramatic change in animal response observed. A rage reaction was elicited, a property not observed with mescaline itself. With longer-chain homologs, the “tail” of the molecule would again be forced out of the plane of the aromatic ring, but there would be less metabolic susceptibility.

Studies of alkyl and thioalkyl analogs of mescaline are currently underway.

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Benington, F.; Morin, R.D.,; Clark, L.C.; Mescaline Analogs X. 3,4-Dimethyl-3,4-dichloro-, and 3,5-Dimethoxy-4-methylphenethylamines. *J Org. Chem.*, 25: 2066-2067, 1960.

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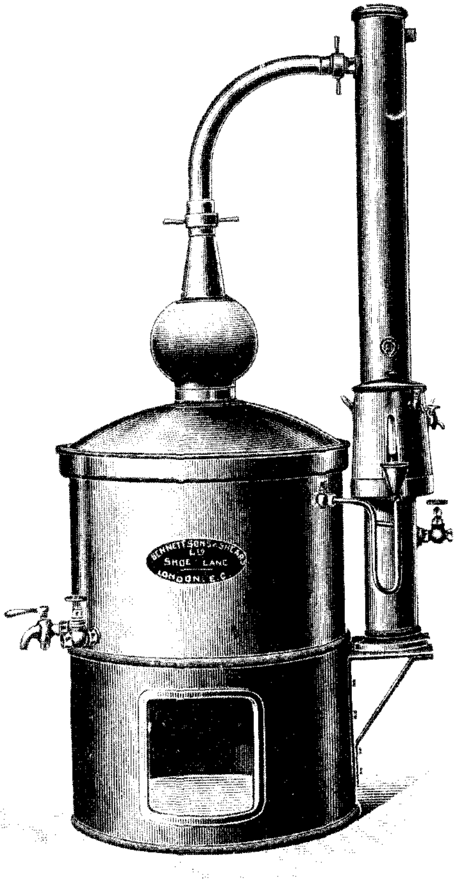
Source: Braun 1978



Still used for the Extraction of Essential Oils. It is fitted with a separator and connection for returning the aqueous distillate to the still.

Raney Nickel Reductions: Chapter 2

2,5-Dimethoxyphenylethylamine

by Milton Green

Highlands, Massachusetts August 7, 1961

The present invention is directed to a simple and efficient process for preparing amines by reductive amination of ketones. It is known is to prepare amines by hydrogenation of ketones in the presence of excess ammonia gas. However, so far as is known, it has never been suggested that amines can be prepared efficiently by catalytic hydrogenation of a ketone in the presence of an ammonium salt of an organic acid. It has been discovered by the applicant that if the catalytic hydrogenation of the ketone takes place in the presence of an ammonium salt of an organic acid, a surprisingly high yield of amine is obtained in a simple and efficient process.

As examples of ketones within the above formula, mention may be made of ethyl benzyl ketone, methyl *para*-isopropylbenzyl ketone, methyl *meta*-tolyl ketone, methyl butyl ketone, methyl phenylisopropyl ketone, methyl benzyl ketone and methyl *para*-dimethoxybenzyl ketone.

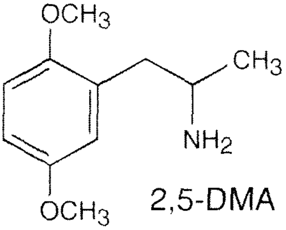
The ammonium salt employed may be the salt of any of the organic acids well known in the art and the particular organic acid employed is not critical. Examples of ammonium salts which may be employed are the ammonium salts of acetic, propionic, butyric, valeric, lactic, tartaric and formic acids.

As was indicated previously, the process of this invention contemplates a catalytic hydrogenation of a ketone in the presence of the ammonium salt of an organic acid. The catalyst employed is preferably a Raney nickel catalyst. However, it is within the scope of the invention to employ other suitable catalysts of equivalent function. As examples of other catalysts which may be employed, mention may be made of palladium on barium sulfate and "Girdler G 49A" nickel catalyst (a stabilized catalyst with a molecular film of oxygen).

The ketone, the hydrogenation catalysts and the ammonium salt are present in an aqueous solution which may also contain a suitable organic solvent or solvents inert to the reactants and the products formed by the reaction As examples of useful organic solvents, mention may be made of alcohols such as methanol, ethanol and propanol; ethers such as ethyl ether, propyl ether and ethyl hexyl ether esters such as methyl acetate, ethyl formate and amyl acetate, and various acids and hydrocarbon solvents well known in the art.

The temperatures and pressures at which the novel synthesis of this invention may be carried out are not critical and may vary over a wide range. In general, temperatures and pressures heretofore used in hydrogenation processes may be employed in the process of this invention. For example, temperatures on the order of 40 to 100° C. and pressures on the order of 500 to 2,000 pounds per square inch have been found to give good results. The reaction time will vary, as will be appreciated by those skilled in the art, and is at least in part dependent upon the starting materials utilized and is at least in part dependent upon the temperature and pressure at which the reaction is carried out. Generally, the reaction may be considered as complete when no further measurable amount of hydrogen is taken up and/or no noticeable amount of ketone remains in the reaction mixture.

Preparation of *p*-Dimethoxyamphetamine



2,5-DMA

An autoclave was charged with the following materials:

p-Dimethoxyphenyl acetone	kg 3
Ammonium acetate	kg 1.2
Acetic acid	mL. 180.0
Methanol	L. 9.5
Water	mL 300.0
Raney nickel catalyst	g 500.0

The autoclave was closed, heated to 90° C., and hydrogen was then introduced at a pressure of 1,200 pounds per square inch. There was no rise in temperature. No measurable hydrogen was taken up after two hours, although the reaction was permitted to continue overnight. At the end of this time, no noticeable amount of ketone remained. Analysis showed a 95% yield of ß-(2',5'-dimethoxyphenyl)-*alpha*-methyl ethylamine, 3% distillation residues and 2% acid insolubles.

Source: Green 1965

Preparation of *p*-Methoxy-N-methylamphetamine

by Knoll A.G.
Ludwigshafen a. Rein, Germany May 26, 1936

164 gms. of *p*-methoxybenzylmethylketone, 100 ccs. of 40% aqueous methylamine solution, 200 gms. of 25% nickel catalyst and 700 ccs. of methanol are stirred for 2 hours at about 80° with hydrogen under 15 to 20 atmospheres excess pressure. The solution is filtered and evaporated to dryness. The residue is taken up in dilute hydrochloric acid and non-basic constituents are removed by shaking out with ether. On adding alkalies the ß-(*p*-methoxyphenyl)-isopropylmethylamine separates out. Source: Knoll 1938

Imines and Amphetamines from P-2-P using Raney Nickel

by American Home Products
New York, New York December 9, 1949

Preparation of the N-Methylimine of Phenylacetone

To 31 g. 51.0 mole) of liquid methylamine in a flask fitted with a dry ice reflux condenser was added over a period of one hour with rapid stirring 134 g. (1.0 mole) of phenylacetone. Stirring was continued for one hour at room temperature, when 25 g. of potassium hydroxide pellets were added. After standing over-night at 5°C., the water removed by the alkali indicated the reaction had gone to about 70% completion. The organic layer was separated and 7 g. of potassium hydroxide added and again allowed to stand over-night at 5°. The reaction by water removal, had gone to 90% theory. Separation of the organic layer and distillation at 1.0 mm. in nitrogen atmosphere over 4 g. of potassium hydroxide yielded a colourless liquid producing the following properties: b.p. 63-66° C. N/D 20 1.5270; 20/d/20 0.9631

Preparation of 1-Phenyl-2-methyl-aminopropane Desoxyephedrine

20.6 Grams of the ketimine as produced was dissolved in 45 cc. of ethyl acetate as a solvent. To this was added 10 grams of 5% palladium on charcoal and the mixture reduced by the addition of hydrogen until 1.39 moles of hydrogen was absorbed. The catalyst was removed and the product distilled. Distillation gave the desired desoxyephedrine boiling at 58-61.5° C at 1.1 mm. pressure.

Source: American Home Products 1954

Preparation of 1-Phenyl-2-propanone

by Alfred G. Susie Boston, Massachusetts
and Henry B. Hass La Fayette, Indiana
November 15, 1939

In the second stage of our reduction process the oxime obtained in the first stage is further; reduced to the amine. Any suitable means for reducing the oxime without undue hydrolysis may be employed for this purpose. Among these methods may be mentioned reduction with sodium amalgam and acetic acid, reduction with metallic sodium in alcohol solution, and hydrogenation with a platinum, palladium or nickel catalyst. We prefer to employ hydrogenation with a nickel catalyst, and this process is illustrated in the example below:

Example

Approximately 9 parts by weight of the oxime of phenylpropanone was dissolved in approximately 60 parts by weight of 95% ethanol, containing 5 parts by weight of a nickel catalyst, prepared by dissolving aluminum from a nickel-aluminum alloy by means of caustic alkali. The resulting mixture was sealed in a bomb under a hydrogen pressure of 1880 lbs. per sq. in. and reduction was effected for a period of 3-1/3 hrs. at a temperature of 25° C., at the conclusion of which period the pressure was found to have dropped to approximately 1680 lbs. per sq. in. The pressure was then released and the catalyst removed by filtration. The filtrate was acidified with concentrated hydrochloric acid and the product was recovered by crystallization as the hydrochloride of 1-phenyl-2-amino-propane (melting point 144-146° C). A conversion of 78%, based on the original oxime was obtained.

It is to be understood, of course, that the above examples are merely illustrative should do not limit the scope of our invention. Although our invention is particularly adapted to the production of 1-phenyl-2-aminopropane ("Benzedrine"), any of the arylnitroalkenes of the type may be reduced in accordance with our process. In this formula AR may represent any aryl group, but preferably phenyl or substituted phenyl, and R may represent any alkyl group. It will be apparent to those skilled in the art that the procedures employed in the above examples could be modified in numerous respects, and the use of any such modifications or any equivalents which would naturally occur to those skilled in the art is to be considered within the scope of our invention. Source: Susie 1941

Reduction of P-2-P

by Hoffmann-La Roche & Co.
Basle Switzerland March 19, 1941

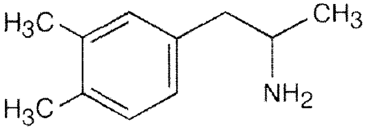
50 parts by weight of a 26% solution of methylamine in absolute methyl-alcohol are treated with 20 parts by weight of (*p*-methyl-phenyl)-acetone while cooling with a freezing mixture. 2 parts by weight of a nickel catalyst, prepared in accordance with Raney, which has been rendered anhydrous as far as possible by washing with methyl-alcohol, are added immediately and the mixture is hydrogenated at gauge pressure of a few atmospheres and a temperature of 90-100° C. The calculated quantify of hydrogen is taken in a short time.

After cooling, the product is sucked off from the catalyst, the solvent evaporated and the residue fractionated in vacuo. *alpha*-(4-methyl-phenyl)-ß-methyl-amino-propan is obtained in good yield as a colourless oil of boiling point 104-106° C. Its smell is that of a base.

Source: Hoffmann-La Roche

Preparation of 3,4-Dimethyl-phenylisopropylamine

by Hoffmann La Roche
Basle, Switzerland November 13, 1942



200 Parts by weight of a 30 per cent. solution of ammonia in methyl alcohol are added to 162 parts by weight of (3,4-dimethyl-phenyl)-acetone while cooling. 6 Parts by weight of a nickel catalyst are immediately added and the product is hydrogenated in a hydrogen atmosphere under a gauge pressure of about 15 atmospheres at a temperature of between 70 and 90° C. The calculated quantity of hydrogen is taken up in a short time. After cooling, the product is separated from the catalyst by suctional filtration, the solvent distilled off and the residue fractionated in vacuo. The colourless *alpha*-(3,4-dimethyl-phenyl)-ß-amino-propane boils at 116-118° C. under a pressure of 12 mm Hg. It is of basic character and can be converted into neutral salts by means of acids. The hydrobromide melts h at 132—133° C.

If a methyl alcoholic methylamine solution is used instead of the ammonia solution, then under otherwise identical conditions *alpha*-(3,4-dimethyl-phenyl)-methylamino-propane is obtained as a colourless liquid having a basic odour and boiling at 121—123° C. under 12 mm Hg. The hydrobromide melts at 142—143° C.

Source: Hoffmann-La Roche

Preparation of Benzedrine

by John B. Tindall
Terre Haute, Indiana May 11, 1949

A mixture consisting of 250 g. (1.53 mols) of 1-phenyl-2-nitro-1-propene, 85 cc. (1.48 equivalents of acetic acid, 600 cc. of methanol and

20 g. of Raney nickel catalyst was placed in a rocking bomb hydrogenation unit and reduced at 1000 pounds pressure at a temperature which varied from 40 to 100° C. The reaction required three hours for completion. At the end of this period, the product was filtered and treated with a solution of 45 cc. of sulfuric acid and 1000 cc. of water. The resultant mixture was then distilled through a fractionating column, in order to remove acetic acid and excess methanol in the form of methyl acetate. Distillation was continued until the oily-appearing liquid ceased to come over. The oil layer thus obtained consisted of phenylacetone and amounted to 9.8 g. corresponding to a yield of 4.7 % based on the 1-phenyl-2-nitro-1-propene used. The residue from the distillation was decanted off and made alkaline with sodium hydroxide. An oil layer formed on the addition of the base and was separated. The remaining water layer was then extracted with benzene and the combined oil layer and benzene extracts were fractionated. After the water and benzene had been removed, 124.1 g. of 2-amino-1-phenyl-propane, boiling at 105° C. (35 mm.) was obtained. This yield corresponded to 60% of the theoretical. Source: Tindall 1953

Preparation of Phenylaminopropanol

by John B. Tindall
Terra Haute, Indiana July 12, 1941

Into a hydrogenation apparatus of the Adkins type was introduced 194 parts of 2-nitro-2,4-dimethyl-3-pentanol, 72 parts of acetic acid, 600 parts of methyl alcohol, and 20 parts of Raney nickel catalyst. Hydrogen was then introduced into the apparatus, and the hydrogen pressure maintained at 1000 pounds per square inch. The apparatus was constantly agitated during hydrogenation, which took place at approximately 60-70° C., and after the reaction was found to be substantially complete, the mixture was withdrawn from the apparatus, and filtered to remove the catalyst. The filtrate was then distilled at atmospheric pressure to remove the methyl alcohol, after which 200 parts of water was added to the residue. This mixture was next extracted with 50 part portions of ether until the extract was clear, denoting the absence of non basic impurities in the raffinate. A 50 per cent sodium hydroxide solution was then added In an amount slightly in excess of the acetic acid employed. Upon addition of the alkali, the crude 2-amino-2,4-dimethyl-3-pentanol was liberated and rose to the top of the mixture in the form of an oil. This oil layer was then separated, and the water layer extracted with several portions of ether, after which these extracts were combined with the original oil layer, and distilled at 60 mm. up to a liquid temperature of 100° C. The still residue was then fractionated at 2 mm. until substantially all the volatile matter therein had been removed. The distillate thus obtained was again fractionated through a packed column at 15 mm. pressure. This distillate was then dissolved in aqueous hydrochloric acid, and repeatedly extracted with ether, after which a solution of sodium hydroxide was added thereto, liberating the free amino alcohol from its salt. The oil layer thus obtained, and which consisted principally of 2-amino-2,4-dimethyl-3-pentanol, was dried over solid sodium hydroxide, and distilled. The fraction boiling at 79° C. (15 mm.) consisting of substantially pure 2-amino-2,4-dimethyl-3-pentanol, was then collected.

Preparation of Phenylaminopropanol

A mixture consisting of 254 parts of 2-nitro-1-phenyl-1-propanol, 600 parts of methanol, 90 parts of acetic acid, and 7 parts of Raney nickel catalyst, was reduced with molecular hydrogen under conditions similar to those set forth in Example 1. At the conclusion of the reduction, the charge was removed from the hydrogenation apparatus, and filtered. The filtrate was then distilled at atmospheric pressure up to a temperature of 80° C. to remove the methanol present. The still residue was next extracted with a 100-part portion of a 50-50 mixture of benzene butanol, in order to remove non-basic impurities from the crude reduction product. After considerable agitation, the resulting mixture was allowed, to settle, and the upper benzene-butanol layer discarded. To the aqueous solution of the phenyl amino propanol acetate (salt) was added 60 parts of sodium hydroxide in the form of a 50 percent solution. This treatment resulted in the formation of two separate layers. The upper layer, containing principally free phenyl amino propanol, was separated and distilled under reduced pressure (60-70 mm.) up to a temperature of 100° C. At this point the pressure was further reduced (1-2 mm), and substantially pure phenyl amino propanol was collected at 125° C.

Source: Tindall 1944

Preparation of 1-(2,4,5-Trimethoxyphenyl)-2-oximinopropane

Merck & Co.
Ralway, New Jersey June 26, 1962

2,4,5-Trimethoxyphenylacetone (25.0 g.— 0.111 mole). hydroxylamine hydrochloride (9.3g.—0.134 mole) and potassium acetate (15.6g.—158 mole) were added to 400 mL. of 70% ethyl alcohol contained in a liter flask fitted with a reflux condenser. The mixture was heated on a steam bath to gentle reflux for 3-1/2 hours. The cooled reaction mixture was evaporated to dryness under reduced pressure and the residue extracted four times with 150 mL. portions of benzene. The combined benzene extracts were washed twice with 75 mL. portions of water and then dried over a anhydrous $MgSO_4$. Evaporation of the benzene under reduced pressure left a tan oil (26.8 g.), which was redissolved in benzene and diluted by dropwise addition of petroleum ether until white crystals appeared. After completion of the crystallization, filtration yielded 20.1 g.; m.p. 80—85°C. Recrystallization from benzene-petroleum ether yielded 18.1 g. white crystals—m.p. 91.5—93°C.

Anal. Calcd. for $C_{12}H_{17}O_4N$: C, 60.23, H, 7.16; N, 5.85. Found: C, 60.22; H, 7.21; N, 5.84

2,4,5-Trimethoxy-α-methylphenethylamine

1 - (2,4,5-Trimethoxyphenyl)-2-oximino propane (18.1g., 0.075 mole) was dissolved in 200 mL. of methyl alcohol and subjected to hydrogenation in the presence of one teaspoon of Raney nickel at 100° C. and 1700 p.s.i. Observed pressure drop at 20°C was 100 p.s.i.

The reaction mixture was filtered to remove the catalyst and the solvent evaporated under reduced pressure to leave a dark yellow residue. The residual oil was dissolved in excess ether and sufficient 4 N alcoholic hydrochloric acid added to precipitate the hydrochloride of the product. The amine hydrochloride was filtered and washed with ether. It weighed 17.5 and melted at 178—181° C. Recrystallization from isopropyl alcohol yielded 14.9 g. of white crystals—m.p. 186.5—187.2° C.

Anal. Calcd. for $C_{12}H_{20}O_3NCl$: C, 55.06; H, 7.70, N, 5.35. Found after drying in vacuo/P_2O_3 at 100°C. for 5 hours: C, 55.26; H, 7.71; N, 5.41. Source Merck 1966

Preparation of 1-(3,4-Dihydroxyphenyl)-2-hydroxyaminopropane

by Lepett S.P.A.
Milan, Italy February 19, 1965

A mixture of 36.2 g. of 3,4-dihydroxybenzyl methyl ketone oxime, 3.7 g. of platinum oxide, 19.5 mL. of concentrated hydrochloric acid and 750 mL. of butanol is hydrogenated at room temperature until no more hydrogen is absorbed. The mixture is made neutral by the addition of sodium bicarbonate, and about 150 g. of sodium sulphate are added and the mixture is filtered. To the filtrate, a solution of 11.5 g. of succinic acid in 100 mL. of butanol are added, the solution is concentrated to a volume of about 100 mL. and cooled. The succinate of 1-(3,4-dihydroxyphenyl)-2-hydroxaminopropane precipitates and is collected and dried. Yield 27 g., m.p. 157—159°C.

From the succinate the free hydroxamino compound can be obtained by treatment with aqueous sodium bicarbonate, extraction with diethyl ether and evaporation to dryness of the solvent. The product has m.p. 120—123°C.

Into a mixture of 180 g. of 1-(3,4-dihydroxyphenyl)-2-nitroproplene, 1000 mL. of methanol, 750 mL. of water and 300 mL. of about 12% aqueous hydrochloric acid, in the presence of 18 g. of 19% palladium on charcoal, hydrogen is bubbled until absorption, practically ceases. The mixture is filtered and the filtrate is concentrated to a volume of about 1000 mL. and extracted with ethyl acetate. On evaporation of the solvent, 131 g. (78%) of 3,4-dihydroxybenzyl methyl ketone oxime are obtained, with m.p. 145—148°C. Source: Lepett 1967

Preparation of Oximes

30 Grams of 4-benzyloxy-3,5-dimethoxy-nitrostyrene are dissolved in 90 cc. of glacial acetic acid and 180 cc. of alcohol and then mixed, while cooling, with 30 grams of zinc dust. After filtering the excess of zinc dust, the residue is mixed with water and extracted several times with ether. After the ether has been distilled, the residue, consisting of the oxime of the 4-benzyloxy-3,5-dimethoxy-1-phenyl-acetaldehyde.

Instead of zinc dust also other heavy metals, such as iron powder or alumina in the form of amalgam can be used. Source: Friedrich 1911

4-benzyloxy-3,5-dimethoxy-phenylethylamine hydrochloride; white crystals with a melting point of 163° C. which are easily soluble in water. Source: Gesellschaft 1931 See: Friedrich Bayer & Company 1911

Preparation of Raney Nickel Catalyst

by Murray Raney
Chattanooga, Tennessee May 14, 1926

The proper proportions of nickel, aluminum and silicon are either melted separately, or together, and if the former, poured together in a suitable vessel. If this procedure is to be used, great care should be exercised, as the alloy is formed in an exothermic reaction.

The melt may be made in a graphite crucible in any desired type of furnace or fire, care being used to prevent contamination of the melt by impurities from the fire.

After the melt has fused and been thoroughly commingled, it is allowed to cool and is then pulverized in any desired apparatus.

In its ground form it is then subjected to the action of a solvent such as caustic soda, or the like, which will dissolve all of the alloyed material with the exception of the nickel. After this treatment the subnatent fluid is decanted and the residue, consisting of finely divided nickel thoroughly washed.

The nickel thus produced is ready for use as a catalyzer.

I have found a satisfactory proportion of the aluminum nickel alloy to be 50% aluminum and 50% nickel, and in the three-metal alloy, 50% nickel, 40% silicon, and 10% aluminum, although obviously I do not wish to be limited to the exact proportions...

I have gotten efficient results in the nickel and aluminum compound between the ranges of from 10% to 85% nickel, and from 90% to 15% aluminum respectively

The aluminum nickel alloy possesses the characteristics which are not possessed by an alloy containing these same substances and silicon. That is, the nickel aluminum ally) may be either very finely pulverized, say to 200 mesh, or it may be broken in pieces the size- of peas or smaller. In either condition the alloy may be treated with caustic soda or the aluminum removed with the use of some other solvent. In ease the larger pieces are used, the nickel is left in a more or less spongy and porous state, somewhat similar to a cinder, and for certain classes of work is is necessary and desirable to have the catalyzer in this condition. I find this characteristic peculiar to the aluminum nickel alloy. Source: Raney 1927

Preparation of Raney Nickel Catalyst

by Murray Raney
Lookout Mountain, Tennessee September 26, 1958

Six grams of 42% nickel, 58 % aluminum catalyst powder, all of which would pass a 150 mesh screen, was mechanically mixed in a porcelain mortar with ten grams of the elemental nickel powder for fifteen minutes. The calculated nickel content of the nickel aluminum powder was 2.52 grams, so that the added nickel was practically four times the nickel contained in the nickel aluminum alloy. The added nickel was not combined chemically with the aluminum, but was thoroughly mixed mechanically with the nickel aluminum powder. The six grams of 42% nickel, 58% aluminum powder had a calculated content of 3.48 grams of aluminum. Seven grams of 76% flake sodium hydroxide were used to make a 25% sodium hydroxide water solution. Potassium hydroxide or other caustic alkali solution may be used in place of sodium hydroxide and nickel carbonyl powder may be used in place of elemental nickel powder. Also, a nickel silicon alloy or an alloy of nickel with another alkali soluble metal may be used in place of the nickel aluminum alloy.

Source: Raney 1961

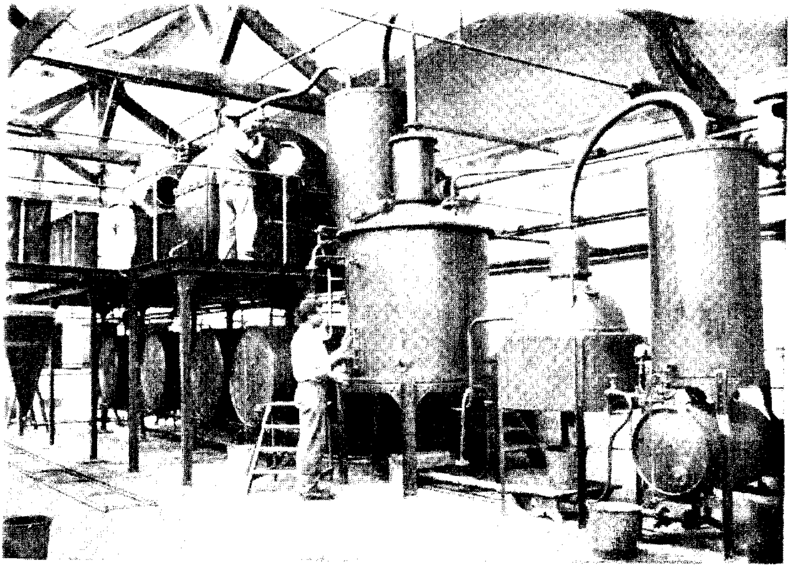
Preparation of Raney Nickel Catalyst

by Max Goldberger
Wapping, Connecticut June 3, 1970

Nickel-aluminum alloys containing from 45 to 55 percent nickel and 55 to 45 % aluminum melt at temperatures between about 1,100° C. and 1,300° C.

The Raney alloy... are leached in aqueous alkaline solutions to remove aluminum. The preferred solutions are dilute aqueous solutions of sodium or potassium hydroxide. Aluminum reacts with the aqueous caustic solution, resulting in the formation of hydrogen. If hot or concentrated solutions are used, reaction proceeds very rapidly with the immediate evolution of large quantities of hydrogen. This destroys the desired mechanical structure of the product. To prevent this occurrence, the leaching is instituted in relatively cool and dilute aqueous caustic solutions, *i.e.*, initial room temperature leaching with solutions containing up to about 5 percent sodium hydroxide or potassium hydroxide. When hydrogen evolution ceases, the temperature is increased stepwise to a maximum of about 80° C. It is known that it is not possible to leach all the aluminum from Raney alloys. Thus, the Raney metals resultant from the leaching of Raney alloys often contain up m about 5 percent of residual aluminum.

The Raney... after leaching are highly pyrophoric. Within a relatively short time, e.g., 5 to 30 seconds, of contact with air, the surface rapidly oxidizes with evolution of a great deal of heat. The degree of pyrophoric activity varies with the particular Raney metal, the percentage porosity, etc. The Raney metal... may be stored in an inert atmosphere or in liquids which permit little or no oxygen to reach the metal. It has been discovered that a nonpyrophoric Raney metal... may be prepared by immersion in oxygen-containing water for several days, e.g., 2 to 3 days. Sufficient oxygen is supplied to the water by continuous aeration, such as commonly employed in fish tanks. The preparation of the nonpyrophoric material is preferably carried out by adding a small amount of hydrogen peroxide, e.g., 0.03 percent by weight, to the water. It is preferred that the hydrogen peroxide should be added some time after the Raney metal is immersed in the liquid e.g., one-half day later. The resultant nonpyrophoric Raney metal may be stored and handled in air. Although the surface is slightly oxidized, it is suitable for use in most applications. Source: Goldberger 1972



(*Pilar Frères.*

Extraction with Volatile Solvents.

Apparatus for Catalytic Reduction

by Roger Adams and V. Voorhees.
Checked by Henry Gilman and S. A. Harris.

1. Procedure

I. The Apparatus (Fig. 1). A Prest-o-lite tank A from which the filling has been removed (Note 1), or any other similar tank of about 8-10 L. capacity, may be conveniently used as a container for hydrogen. The top of the tank contains two openings B and C. In B is welded a tube holding a gauge and valve, and through this tube the hydrogen from a large cylinder D is introduced into the tank. In C is welded another tube controlled by a needle valve. E is used for the vacuum, a manometer G being introduced into this system, and F for a tube leading to the reaction bottle H. These outlets are so arranged that it is possible to shut off the tank from either outlet and also to make a direct connection between the vacuum and the bottle H, leaving tank A out of the circuit. The connection between the tank A and the bottle H is a heavy taped rubber tube (Note 2) which is in turn connected to a glass tube inserted through the stopper of the bottle. The rubber tube and stopper should be high-grade and must be carefully boiled with alkali before being used (Note 3). The arrangement for shaking the bottle is shown in the diagram (Note 4). The driving pulley is connected to the reaction bottle by a wooden or preferably a metal rod. The rod in turn is attached by a yoke to a metal ring which circles the bottom of the bottle. The ring opens on the back side of the bottle and is held together by a wing-nut and bolt. In order to hold the stopper in the bottle when the latter is filled with hydrogen under pressure, a metal strip I is clamped tightly over the stopper. This strip is screwed to the long wooden bottle holder which extends between the bearings, and a short wooden piece which fits around the neck of the bottle is attached to the longer one by means of screws held by wing-nuts. This arrangement permits removal of the bottle from the apparatus without detaching the metal strip.

The chief precautions in setting up this reduction outfit are first to have every piece free from catalytic poisons and second, to be certain that there are no leaks (Note 5). The latter are sometimes an annoying factor and the complete apparatus should be carefully tested before attempting any reductions for standardizing the hydrogen tank. The apparatus is put together in final form with the empty reduction bottle attached to the hydrogen tank exactly as it is arranged in a reduction.

The tank is then filled with hydrogen until the gauge reads 2.5-3 atm. (40-45 lbs.) and the temperature of the tank recorded. The reading of the gauge is observed as soon as equilibrium is reached and the bottle is then shaken for six to eight hours. Observations are made of the drop in pressure, taking into account any change of temperature which may occur during this time.

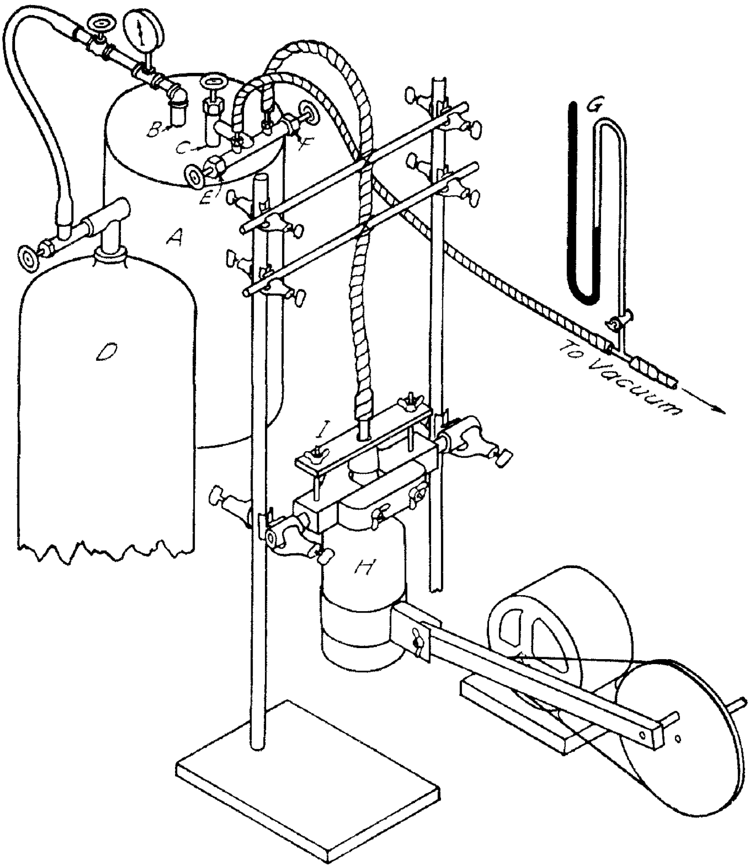


FIG. 1.

In general if the drop in pressure is less than 0.03 atm. (0.5 lb.) in the time indicated the apparatus may be considered sufficiently free from leaks for ordinary work.

For some reactions it is advantageous to heat the mixture, and the following arrangement is very satisfactory for this purpose. The bottle H is wrapped with moistened asbestos paper to a thickness of about 3 mm. and the paper is then allowed to dry. When the asbestos is thoroughly dry the bottle is wound with a coil of No. 24 Nichrome wire, beginning the coil at the bottom of the bottle and making the turns about 9 mm. apart. The wire is then covered with a 3 mm. layer of asbestos, which is moistened and allowed to dry, after which the wire is wound around the bottle in another coil from top to bottom. The second coil is covered with asbestos as before, and the ends of the wire are connected to the terminal wires from a source of current. These wires are led along the bottle to the neck and held by means of tape in order to avoid excessive shaking. A variable resistance in the circuit is used to regulate the temperature.

II. Use of the Apparatus.—The tank A is filled with hydrogen to a pressure of 3-3.5 atm. from the cylinder D (Note 6). The solution, in a suitable solvent, of the substance to be reduced is poured into the bottle H and the platinum oxide is added (Note 7). The bottle is attached to the apparatus and evacuated by opening valves E and F and closing C. In the case of low-boiling solvents, the evacuation is continued only until the solvent begins to boil; in other cases it is continued until the pressure as recorded by the manometer remains fairly constant. The valve E is then closed and hydrogen is admitted to the bottle H from the tank A by opening valve C (Notes 8 and 9). When the pressure in the bottle has become adjusted the pressure of the hydrogen and the temperature of the tank A are recorded. Shaking is started. Within a few minutes the brown platinum oxide turns black (see Note 5, p. 95) and the absorption of hydrogen begins. The shaking is continued until the theoretical amount of hydrogen has been absorbed. The hydrogen remaining in the bottle is removed, air is admitted and the mixture allowed to stand or, if necessary, shaken for a few minutes in order to aid the settling of the catalyst. In certain cases where the catalyst settles spontaneously at the end of the reduction it is not necessary to shake the mixture with air. The solution may be decanted from the main portion of the catalyst and a second reduction carried out. In cases where the catalyst cannot be used directly for another reduction (see Note 8, p. 97) the solution is filtered, preferably through an asbestos filter (Note 10) and fresh solvent is used for washing. The reduction product is isolated from the filtrate, usually by distilling off the solvent. The reduction of ethyl *p*-nitrobenzoate to ethyl *p*-aminobenzoate (p. 66) and benzalacetophenone to benzylacetophenone (p. 36) are described in detail in this volume.

III. Standardization of the Apparatus.—After making certain that there are no leaks in the apparatus (Note 5) the hydrogen tank may be standardized by reducing 11.6 g. (0.1 mole) of pure maleic acid (Note II) dissolved in 150 cc. of 95 per cent alcohol using 0.1 g. of catalyst (p. 92). The reduction is carried out according to the procedure described in part II. Shaking of the mixture is continued until no more hydrogen is absorbed; the theoretical amount is absorbed by 0.1 mole of maleic acid within twenty or thirty minutes. The temperature of the tank is recorded. The decrease in pressure corresponds to 0.1 mole of hydrogen at the observed temperature. If the succinic acid is desired it may be recovered merely by filtering the platinum, evaporating the alcohol and crystallizing from about 10—15 cc. of boiling water. The yield of product is 10—11.5 g. (84-98 per cent of the theoretical amount) depending on the care used in crystallization.

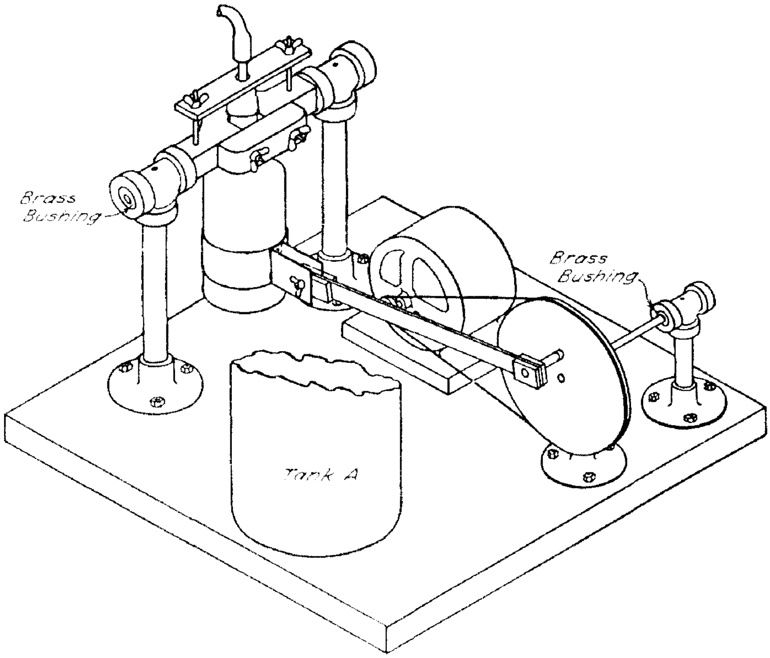


FIG. 2.

2. Notes

1. The bottom of the tank is cut off, the filling removed, and the bottom welded on again.

2. A copper tube may be used for this connection but is less satisfactory since the shaking tends to wear it out at the joints.

3. It is advisable to boil the tube and stopper with several portions of 20 per cent sodium hydroxide until the solution is no longer colored yellow, after which the boiling is carried out several times with distilled water.

4. The motor, pulley and the supports for the reaction vessel must be attached firmly to a heavy wooden stand which will allow as little motion as possible in the apparatus during shaking, thus reducing to a minimum the possibility of the gradual formation of leaks.

The arrangement for shaking should be so made that the reaction bottle is agitated at a rate above which no difference in the speed of reduction is observed. In this laboratory the motor used is a 1/30 h.p., 1760 r.p.m., the pulley on the motor 2.5 cm. in radius, and the wooden driving pulley 7.5 cm. in radius. The distance from the center of the pulley to the hole for attaching the rod to the reaction bottle is 3.2 cm., the distance from the center of the pulley on the motor to the center of the driving pulley to the bottle attachment is 30 cm. Considerable latitude is possible in these measurements. Although the apparatus in Fig. I is readily set up in any laboratory, a more compact and more stable form is shown in Fig. 2. The uprights which support the bottle consist of 1.3 cm. (one-half inch) piping surmounted by T-couplings. The uprights, driving pulley, and motor are firmly screwed down to a heavy wooden stand. An apparatus similar to this can be purchased complete from the Standard Calorimeter Co., East Moline, Ill.

5. It is quite necessary that the welding of the tank is perfect and free from pin holes. Leaks frequently appear where the tubes are welded in the top of the tank. These may be eliminated by brazing the joints. A less satisfactory way is to use a cement of litharge and glycerol. This cement may also be used with success on leaky valves. Occasionally leaks occur in the rubber tubing or its connections with the bottle or tank, but these are unusual.

6. Electrolytic hydrogen was used in all experiments. This hydrogen is essentially free from all impurities except oxygen. Since oxygen in general has no harmful effect upon the reduction, no purification is necessary. If, however, oxygen-free hydrogen is needed, it must be passed over heated platinized asbestos.

7. This procedure may be varied in certain cases where it seems advantageous to reduce the platinum oxide to platinum black in the presence of the solvent alone (see Note 12, p. 98)

8. During the reductions it is usually advisable not to allow the pressure in the tank A to drop below about 2 atm. if the reduction is to be carried out in minimum time. When the gauge registers 2 atm. the tank is closed off from the reducing bottle and the pressure is increased to about 3-3.5 atm. by the admission of more hydrogen from D.

9. Ordinarily traces of air in the hydrogen have no deleterious effect upon the reductions. If in any experiment, absolute freedom from air is desired the bottle may be evacuated and refilled with hydrogen two or more times. In this way the air is all washed out of the bottle.

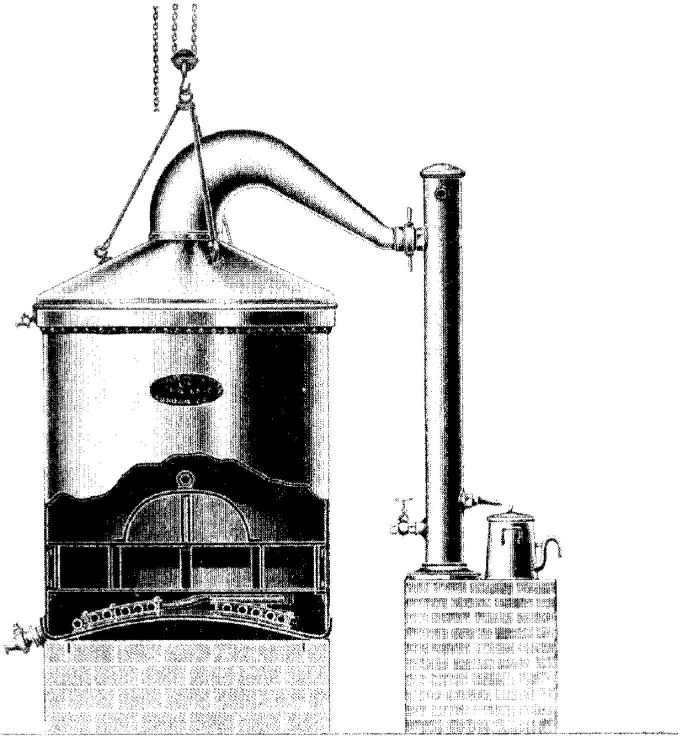
10. When paper filters are used the rapid suction of air through the paper in the presence of the catalyst often causes spontaneous combustion of the filter. Paper filters may be used, however, if care is taken to keep the filter covered with solvent while suction is being applied; just before the last portion of solvent has run through, the suction is stopped.

11. Instead of pure maleic acid, 10.6 g. (0.1 mole) of pure benzaldehyde may be used for the standardization. In this case 1 cc. of 0.1 molar ferrous sulfate is added to the mixture of benzaldehyde, alcohol and catalyst before the reduction is started (see Note 13, p. 98). The reduction is complete in fifteen to thirty minutes.

3. Forms of Apparatus

Other forms of catalytic reduction apparatus which may be used in the laboratory have been described in the following articles.

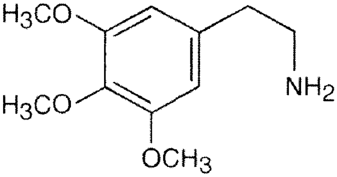
Paal and Amberger, *Ber.* 38, 1390 (1905); **Paal and Gerum**, *Ber.* 41, 813 (1908); **Waser**, Ueber Derivate des Cyclooctans (Promotionsarbeit) *Zurich*, 1911, p. 54; **Willstatter and Hatt**, *Ber.* 45, 1472 (1912); **Skita and Meyer**, *Ber.* 45, 3594 (1912); **Stark**, *Ber.* 46, 2335 (1913); **Boeseken, Van der Weide and Mom**, *Rec. trav. chim.* 35, 267 (1916); **Rosenmund and Zetzsche**, *Ber.* 51, 580 (1918); **Adams and Voorhees**, *J. Am. Chem. Soc.* 44, 1403 (1922); **Klimont**, *Chem. Ztg.* 46, 275 (1922); **Escourrou,** *Parfums France* 26, 88 (1925). Source: Adams 1928



Type of apparatus used for the distillation of plants such as Peppermint and Lavender. It has a capacity of 1,000 gallons and will take a charge of one ton. The exhausted herb is discharged by lifting the false bottom.

Reductions Using Palladium: Chapter 3
Trialkoxyphenylethylamines

by Gesellschaft Für Chemische Industrie
Basle, Switzerland January 8, 1930



Mescaline

To a suspension of 40 grams of triethoxynitrostyrene in 700 cc. of alcohol, there is added a solution of 1 gram of palladious chloride in 40 cc. of water and 25 cc. of concentrated hydrochloric acid, and the solution is then reduced with hydrogen at 15° C. in a shaking flask.

When absorption of hydrogen is finished, the separated palladium is filtered and the alcohol distilled until nearly to dryness. The residue is made alkaline and extracted with ether. The ether is distilled and the residue extracted in dilute hydrochloric acid. The portion insoluble in acid is separated by means of ether and the base is precipitated by means of caustic soda lye, extracted and fractionated. At 140° C. at 1 mm. pressure colourless triethoxyphenylethylamine distills. The hydrochloride forms white crystals soluble in water and of melting point 178—179°

10 grams of 4-*n*-butoxy-3,5-dimethoxynitrostyrene are dissolved in 200 cc. of glacial acetic acid containing, 1.5 grams of hydrochloric acid. After addition of 0.2 gram of palladious chloride as a catalyst, the whole is reduced with hydrogen at ordinary temperature. The glacial acetic acid is distilled in a vacuum and the crystalline residue, which is the hydrochloride of the 4-*n*-butoxy-3,5-dimethoxy-phenylethylamine is recrystallised from ethyl acetate. It forms white crystals of melting point 153—154° C. which are easily soluble in water.

In place of palladious chloride also colloidal palladium, chloroplatinic acid, colloidal platinum, platinum black, etc. may be used.

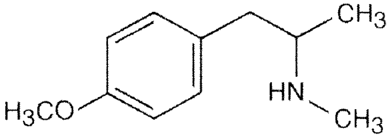
3,4,5-triethoxy-phenylethylamine hydrochloride; white crystals soluble in water and a melting point 178—179° C.

4-*n*-Butoxy-3,5-dimethoxyphenylethylamine hydrochloride; white crystals of melting point 153—154°, which are easily soluble in water.

Source: Gesellschaft 1931

p-Methoxy-N-methylamphetamine Preparation

by Knoll A.G.
Ludwigshafen a. Rein, Germany May 26, 1936



N-Methyl-PMA

1 mol. (164 gms.) of *p*-methoxy-benzylmethyl ketone, 500 ccs. of ether, 150 ccs. of 1% colloidal platinum solution, 15 ccs. of 10% platinum chloride solution and 121 ccs. of 40% aqueous methylamine solution are shaken for 4 hours with hydrogen under 3 atmospheres excess pressure in a shaking machine. After completion of the hydrogen absorption the resulting base is taken up in ether and the ethereal solution is extracted with dilute acid. On adding alkali to the acid solution the resulting base ß-(*p*-methoxyphenyl)-isopropyl-methylamine separates out as an oil. The oil is separated from the mother liquor. Source: Knoll 1938

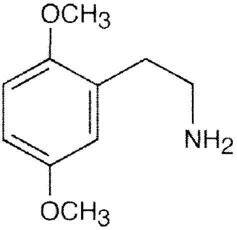
p-Dimethoxyphenylethylamine Preparation

by Milton Green
Cambridge, Mass June 8, 1955

The reduction is preferably performed in a mixture of acetic and sulfuric acids as the reaction medium. Suitable reaction conditions are room temperature and a pressure of 2 to 3 atmospheres. The reaction is preferably run for a short period after hydrogen uptake ceases.

Conventional palladinized barium sulfate catalysts may be used in this process. A preferred catalyst comprises about 7-8 %, by weight, of palladium. It may be prepared by precipitating barium sulfate in the presence of freshly precipitated palladium.

2,5-Dimethoxyphenethylamine



2,5-dimethoxy-nitrostyrene (5 g.) is dissolved in a mixture of glacial acetic acid (125 mL.) and concentrated sulfuric acid (19 g.). Five grams of palladinized barium sulfate are added and hydrogen is passed through the mixture at room temperature. The mixture is shaken continually during the reaction. Ninety percent of the theoretical amount of hydrogen (4 moles) is absorbed in 10 minutes, after which no further hydrogen uptake is noted. Shaking of the mixture is continued for a half hour, after which the mixture is cooled and sufficient 5 N sodium hydroxide is added to neutralize the sulfuric acid. Methanol (250 mL.) is then added to complete precipitation of sodium sulfate. The salt is washed and filtered with methanol and the combined filtrates and mother liquor are evaporated in vacuo. The residue is made strongly alkaline and extracted with 100 mL. of ether. The extract is dried over potassium hydroxide after which the solvent is removed and the residue distilled giving 3 g. (68% yield) of 2,5-dimethoxyphenethylamine boiling at 148° C./8 mm. The product is a pale yellow oil, which forms a white hydrochloride melting at 139° C. Source: Green 1962

Hydrogenations Using Platinum

by Imperial Chemical Industries Limited
London, UK October 31, 1961

22.8 Parts of ethyl 1-(3-methoxyphenyl)-ß-nitropropyl ether are dissolved in 135 parts of acetic acid, and 25 parts of 4N sulphuric acid, 1 part of 5% palladised charcoal and 0.3 part of platinum oxide are added to the resulting solution. The mixture is stirred in an atmosphere of hydrogen at a pressure of 100 atmospheres and at 18—23°C. until absorption is complete. The mixture is filtered and the filtrate is evaporated to small volume in vacuo. The residue is stirred with

200 parts of water and 50 parts of ether. The aqueous layer is separated and evaporated to small volume in vacuo. 100 Parts of 4N sodium hydroxide are added to the residue and the mixture is extracted with 400 parts of ether. The ethereal extract is washed with saturated sodium chloride solution, dried and evaporated to dryness in vacuo. A solution of 12.9 parts of the residual oil thus obtained in 20 parts of acetone is added to a solution of 7.8 parts of oxalic acid dihydrate in 60 parts of acetone. When the separation of solid is substantially complete, the mixture is filtered and the residual solid is crystallised from a mixture of ethanol and ethyl acetate. There is thus obtained 2-ethoxy-2-(3-methoxyphenyl)-1-methylethylamine hydrogen oxalate, m.p. 142—143°C.

A mixture of 2 parts of 2-methoxy-2-(3-methoxyphenyl)ethylamine hydrochloride, 20 parts of saturated aqueous sodium chloride solution and 5 parts of 4N sodium hydroxide solution is extracted with 50 parts ether. The ether extract is washed with saturated aqueous sodium chloride solution, dried and evaporated. The residual oil consists of 2-methoxy-2-(3-methoxyphenyl)ethylamine.

Source: Imperial Chemical Industries Limited 1966

2-(N-Methylamino)-2-methyl-1-phenyl-propane Preparation

by William F. Bruce, Joseph Lester Szzabo
and Samuel Tubis
Delaware, Pennsylvania December 23, 1948

250 mg. of 1-chloro-2-(N-methylamino)-2-methyl-1-phenyl propane hydrochloride was dissolved in 2 cc. of warm methanol and hydrogenated in the presence of 250 mg. of palladium barium carbonate catalyst with provision for the absorption of the carbon-dioxide formed. When the theoretical amount of hydrogen had been taken up the mixture was filtered to remove the catalyst, concentrated to small volume and extracted with ether. After separating the ether the residue was further concentrated yielding a white crystalline solid. This solid on solution in water, strongly alkalizing, extraction with ether and removal of the ether yielded 2-(N-methylamino)-2-methyl-1-phenyl propane identified as the picrate by melting point 155-156° and mixed melting point 154.0 - 154.5°, with an authentic sample melting at 150-153°.

Source: Bruce 1952

Ephedrine from Methyl Phenyl Di-ketone

by Richard H.F. Manske
Indianapolis, Indiana July 31, 1928

The methyl phenyl di-ketone, sometimes called 1-phenyl, 1,2-propanedione, which would be the di-ketone used for condensation with methylamine and the subsequent hydrogenation in the presence of a catalyst to produce ephedrine, is known, as are certain other di-ketones.

7.4 parts of methyl phenyl di-ketone, whether obtained as above outlined or in some other manner, is now treated with 50 parts of ethyl alcohol, and an alcoholic solution of methylamine containing about 3 parts of methylamine is added. A slight temperature rise is noted, due to the formation of the imido-carbonyl compound... A small amount of platinum catalyst (0.2) parts is a convenient quantity), suitably prepared to make it effective as a catalyst as outlined in the literature, is added; and the flask is filled with hydrogen. The mixture is suitably agitated, until hydrogenation is complete. In this action, the hydrogen reacts with the imido-carbonyl compound that had been produced, with the platinum acting as a catalyst, and produces hydrogenation of such imido-carbonyl compound.

When the hydrogenation is completed, which is indicated by the fact that no more hydrogen is taken up, air is admitted; whereupon the catalyst readily coagulates, and may be removed by filtration. The filtrate is evaporated, preferably under reduced pressure, to a small volume; is made faintly acid with hydrogen chloride; and is evaporated again; whereupon on cooling, ephedrine hydrochloride usually separates out as a white crystalline salt, which is separated from the liquid This crystalline salt consists mainly of racemic ephedrine hydrochloride, with a relatively smaller amount of racemic pseudoephedrine hydrochloride. These may be separated by known methods, as by fractional crystallization from chloroform. A substantially pure racemic ephedrine hydrochloride may thus be obtained, whose melting point is about 186° C. The racemic ephedrine hydrochloride has the formula:

Source: Manske 1931

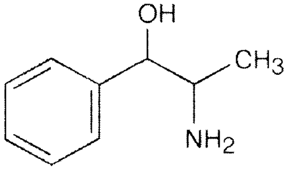
Reductions Using Aluminum Amalgam

164 gms of *p*-methoxybenzyl-methyl-ketone, 2500 ccs. of ether, 500 ccs. of methanol, 100 ccs. of 40 % aqueous methylamine solution and 100 gms. of activated aluminium turnings are stirred for 6 to 7 hours with occasional slight warming. On completion of the conversion the mixture is filtered and the resulting base ß-(*p*-methoxyphenyl)-isopropylmethylamine separated from the solution by adding dilute acid thereto. On adding alkalies the free base is obtained in the form of an oil. Source: Knoll 1938

Replacement of P-2-P with phenylacetaldehyde produces phenylethylamine.

2-Amino-2-methyl-1-phenyl-1-propanol Preparation

by William F. Bruce, Joseph Lester Szzabo
and Samuel Tubis
Delaware, Pennsylvania December 23, 1948

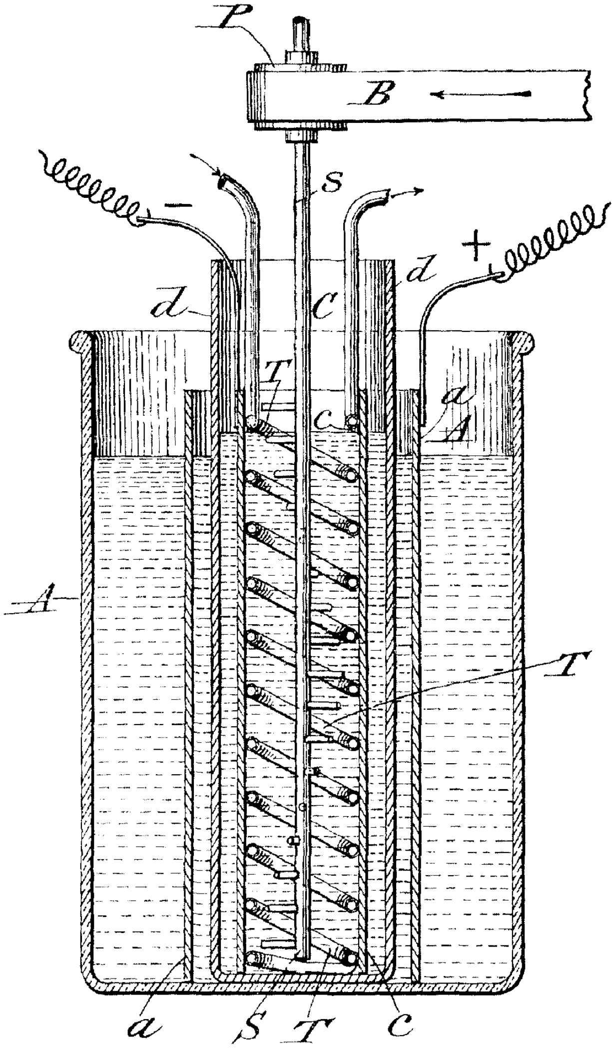


Phenylpropanolamine

Six gms. of nitro compound are dissolved in 50 mL. of 95% ethanol, and 20 gms. of zinc pellets (20 mesh) are added, together with a few drops of ferric chloride. Then while stirring and with the temperature maintained at 40° C., 35 mL. of 12 N. sulfuric acid are added, drop wise, during the course of 1 hour. Stirring is continued at 40° C. for six hours, then for an additional 18 hours at 20-25° C. The solution is then decanted from the zinc, made very alkaline, and extracted with ether. Concentration of the latter yielded crystals of 2-amino-2-methyl-1-phenyl-1-propanol having a melting point prior to purification of 80-89° C. Recrystallization from hot benzene raised the melting point to 99-99.5° C.

Source: Bruce 1952

Electrolytic Preparation: Chapter 4



Witnesses.

Bertha M. Mueck.

Anton Gletzner

Inventor:

Max Buchner,

By Georgii & Massie,

his Attorneys.

Electrolytic Preparation of 2,5-Dimethoxyphenylethylamine

9 g 2,5-dimethoxynitrostyrene were suspended in a mixture of 200 ccm alcohol, 100 ccm glacial acetic acid and 30 ccm conc. hydrochloric acid and 4 hours with 30-35° at a prepared lead cathode were reduced (current density 0.07 Amp./ cm2 cathode). The received colorless solution was processed in usual way and 4 g 2,5-dimethoxy-phenylethylamine received, with 148° and 8 mm distilled over. The hydrochloride formed colorless needles melting point. 139° according to literature.

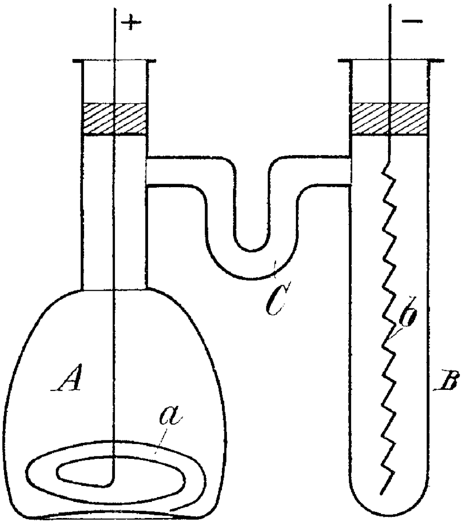
Source: Sugasawa 1941 Translated by Otto

Preparation of Vanillin from Isoeugenol

by Martus Otto and Albert Verley
Courbevoie, France July 8, 1895

The object of of invention is to obtain vanillin in a cheap and expeditious manner by synthesis. To effect this object we oxidize a solution of isoeugenate of soda (or other convenient base) and treat the resulting product with an acid and separate the vanillin so produced. This oxidation may be effected by electrolyzing an alkaline solution of isoeugenate of soda, either cold or warm preferably at the temperature of an ordinary water-bath. This electrolysis may be conveniently effected by placing the solution of isoeugenate of soda in a vessel standing in a water-bath and connected with a vessel containing, a solution of soda by a U -shaped tube which passes through the sides of the respective vessels at a convenient height above the bottoms of the vessels. Electrodes, preferably of platinum, are placed in the vessels and connected to the respective poles of a source of electricity, the electrode in the vessel containing the solution of isoeugenate of soda being at the bottom and connected by an insulated wire, so that the current may pass through the whole mass of the fluid and oxidize the isoeugenate of soda. By this arrangement the oxidation is collected without any substantial mixing of the two liquids. The reaction which takes place is the oxidation of the isoeugenate of soda as before explained, and thereby its change into vanillate of soda. The subsequent treatment with an acid (which may for instance be oxalic acid or sulphuric acid diluted with its own volume of water) forms a sodium salt in accordance with the acid used and sets free the vanillin.

MANUFACTURE OF VANILLIN



Witnesses.
Pierre Lewis
W. R. Edelen

Inventors,
Marius Otto & Albert Verley
by Pollok & Mauro
their attorneys,

To ascertain if the oxidation of the isoeugenate of soda is complete the quantity of by drop, in which is set free at the negative pole may be measured and from it be deduced the quantity of oxygen set free at the positive pole; or the test may be simply made by reference to the quantity of oxygen at the positive pole; but the invention is not limited, of course, in any way to any particular test.

The accompanying drawing illustrates diagrammatically an apparatus which may conveniently be used in carrying out our process.

The solution of isoeugenate of soda is placed in the vessel A. In the vessel B we place solution of soda serving merely as a conductor between the positive electrode and the negative electrode b. These vessels are connected by a U-shaped tube C at a convenient distance above the bottoms of the vessels, so that while the liquid forms a continuous path closing the internal circuit of the electrolytic bath there will be no mixing of the products formed around the respective electrodes. This arrangement is adopted for economy and to increase the yield from the operation. The products of oxidation formed around the positive electrode are those utilized in our process of making vanillin, and it is preferred that they should not be contaminated by the products formed at the negative pole. The electric circuit is completed by connecting the terminals of electrodes a and b respectively with the positive and negative poles of an electric generator preferably one furnishing a continuous current of low tension.

When the oxidation is judged to be complete the solution is treated with an acid which sets free the vanillin. It can be purified with bisulphide of soda and by repeated crystallization, as may be found requisite.

Source: Otto 1896

The Electrolytic Preparation of Salicylic Aldehyde from Salicylic Acid (1)

by Kendall S. Tesh with Alexander Lowe (2)

Salicylic aldehyde is prepared electrolytically by the reduction of salicylic acid (sodium salt) to the aldehyde. The ordinary type of diaphragm cell is used with a mercury cathode, using boric acid and sodium sulfate as catholyte. A current density of 6 amp. per sq. dm. is used, and the temperature is kept between 15° and 18° by means of a freezing mixture. The aldehyde is fixed as soon as formed by means of sodium bisulfite, and is recovered by means of acid hydrolysis and steam distillation. Up to the present stage of the process the best yield obtainable is 55 per cent.

The purpose of this research was to study the experimental details for the preparation of salicylic aldehyde by the reduction of salicylic acid (sodium salt) electrolytically.

In 1906 Dr. Hugo Weil patented a process (3) for the reduction of salicylic acid to salicylic aldehyde electrolytically. However, a number of important experimental details were omitted and no yields were stated. Two years later an article by Carl Mettler (4) appeared on the electrolytic reduction of salicylic acid (sodium salt) to salicylic aldehyde which was identical with the patent of Weil.

Several important details are lacking in the publication. The article claims from 30 to 50 per cent yield of salicylic aldehyde, but the best yield the writers could obtain by following the details given was 20 per cent. It was for the purpose of increasing the yield and working out the details of the process that this research was undertaken.

When salicylic acid is reduced with the reducing agents commonly employed in the laboratory, the chief product is salicyl alcohol (5). This salicyl alcohol on treatment with acids is converted into a resinous product forming "saliretin." The reduction, however, should take place in two stages, going first to the aldehyde and then to the alcohol, as follows:

Since the second step in the reduction seems to take place more readily than the first, it is evident that something should be put into the solution, which will remove the aldehyde produced as fast as it is formed, either by extraction or combination, thus protecting it from further reduction to the alcohol.

A number of different methods were tried to accomplish this result. First, removal by steam distillation as fast as formed; second, extraction with benzene; and third, combination with *p*-toluidine, *p*-naphthylamine and sodium bisulfite. Up to the present point in the research, combination with sodium bisulfite seems to give the best results.

Experimental Part

The usual diaphragm type of electrolytic cell is used in all of the experiments except those at a boiling temperature. (Experiment No. 10, Table 1.) The cell is immersed in a cooling mixture or cold water to maintain the desired temperature. A mechanical stirrer is used in all experiments. Unless otherwise stated, the mercury layer is not stirred with the mechanical stirrer. In all cases a platinum spiral anode is used.

A typical experiment is as follows:

The bottom of a 600 cc. low form beaker is covered to a depth of 1 cm. with mercury, which serves as the the cathode. This gives an area of 50 sq. cm. Two cylindrical porous cups (8 x 2 cm.) are suspended from the sides of the beaker so that the bottoms of the cups are about 2 cm.

from the surface of the mercury. These hold the anodes which consist of two coils of platinum wire. The anolyte is 10 per cent sodium sulfate solution. The cathode mercury layer is connected to the source of current by means of a platinum wire encased in glass tubing.

Into the cell is then placed a solution of 15 g. sodium sulfate. 15. g. boric acid and 14 g. of salicylic acid (0.1 mole), just neutralized with the calculated amount of sodium hydroxide. The solution is then diluted to, 175 cc. All the boric acid not dissolve in this quantity of solution, but is kept in suspension by means of rapid mechanical stirring. The cell is placed in a cooling mixture, and when the temperature reaches 15° to 18° the current is turned on. A temperature of 15° to 18° is maintained throughout the experiment. A current of 3 amp. (6 amp. per sq. dm.) is then passed through the solution for a period of 1 hr. 55 min., which is slightly more than the calculated amount (5.4 amp.-hr.) necessary to reduce the salicylic acid to salicylic aldehyde. During the electrolysis 20 g. sodium bisulfite are added at the rate of about 1.5 g. every 10 min. It has been found best not to begin the addition of the sodium bisulfite until the electrolysis has been started about 5 min, since the bisulfite reduced to sulfur when added to soon, or too rapidly thereafter.

At the conclusion of the electrolysis the porous cups are removed, washed with distilled water, and the white precipitate, which usually collects on the outside, scraped off and returned to the solution. This white precipitate consists chiefly of boric and salicylic acids. The stirring is continued for 30 min. the current is shut off in order to make use of the sodium amalgam, which is built up during the electrolysis. The solution is then decanted from the mercury, which is washed several times with 50 cc. portions of distilled water. Then 20 cc. concentrated $H2SO4$, in 100 cc. of water are added to the solution and steam distilled.

The salicylic aldehyde distills over as a very pale yellow oil, heavier than water, and collects at the bottom of the received. The steam distillate is then extracted with ether, the extract treated with $NaHCO3$ to neutralize any acid which distills over, then dried over $Na2SO4$ and distilled. The residual liquor after steam distillation always contains some resin (0.2-2.0 g.) It is filtered hot and allowed to cool, in order to recover any unused salicylic acid. In this experiment no salicylic acid is recovered.

Yield of salicylic aldehyde 6.7 g., 55 per cent. Current efficiency the same. The yield was calculated on the total amount of salicylic acid started with.

It is found that the use of sodium bisulfite materially increases the yield of salicylic aldehyde. Further, that the lower temperatures (15° to 18°) favor the yield of salicylic aldehyde. At higher temperatures less salicylic aldehyde is produced and more of the resinous product. Up to a current density of 8 amp./sq. dm. the yield of salicylic aldehyde is increased. Intermittent electrolysis or stirring after electrolysis is necessary for good current efficiency since a sodium amalgam is built up during the electrolysis. Increasing the time of electrolysis seems to increase the quantity of resin formed. Increasing the concentration of salicylic acid (sodium salt) has little or no effect.

Further work is in progress to increase the yield of salicylic aldehyde.

References:

1. Manuscript received February 12, 1924.
2. Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa.
3. *D. R. P., 196,239* (1906).
4. *Ber.*, 41, 4,148 (1908).
5. *Ber.*, 39: 2,933 (1906).

Source: Tess 1924

Preparation of Gallic Acid from Tea Leaves and other Tannin Containing Materials

by Paul A. Krueger, Lawrence A. Patterson,
Robert J. Turner, Ferguson, Robert D. Rands, Jr.,
Greendale, Montanna April 19, 1952

It has been customary to prepare gallic acid by hydrolysis of tannin. The tannin is generally produced from certain tannin-containing materials such as Chinese nut galls, by extraction with water or some other solvent followed by evaporation to obtain the tannin in solid form or in the form of a concentrated solution. However, the process is slow, large amounts of solvent must be evaporated and the soluble gums and resins also present in the tannin-containing material interfere with extraction of the concentrated liquors and purification of the gallic acid. Moreover, the gallic acid so obtained still contains impurities which must be removed by further processing before the produce is suitable for many purposes.

According to one embodiment of this invention, tannin- containing materials are hydrolyzed with a hydrolyzing agent such as an acid or alkali and the gallic acid thus formed is extracted from the hydrolysis liquors with a water-immiscible solvent for gallic acid. After separation from the aqueous phase the solvent extract is steam distilled to remove the solvent. The resulting aqueous solution can then be treated with iron-free activated carbon and filtered if desired, after which crystals of gallic acid are obtained on cooling the concentrated aqueous liquor by this process almost all of the non-gallic acid material and the residual coloring matter remain in the hydrolysis liquor and the resulting gallic acid is of light color and good quality.

Although tannin-containing vegetable substances are preferably hydrolyzed in accordance with the present invention without prior isolation of the tannin, tannin or tannin-containing liquors obtained by any suitable procedure may also be utilized as a starting material for the acid or alkali hydrolysis disclosed herein. Acid hydrolysis, such as by heating the tannin-containing material with sulfuric acid for thirty to forty hours, normally yields only seventy-five to eighty per cent as much gallic acid as is obtained by a one-hour hydrolysis with sodium hydroxide. Alkaline hydrolysis is also advantageous for the reason that less color is formed in the reaction mixture, and therefore a lighter colored product is obtained.

The gallic acid can be isolated by crystallizing it directly from the hydrolysis mixture but a purer and more desirable produce is obtained by extracting it from the liquor with a water-immiscible solvent.

Illustrative of suitable water-immiscible solvents for gallic acid are methyl isobutyl ketone, methyl isobutyl carbinol, mixtures of isomeric amyl alcohols, isoamyl alcohol, and cyclohexanone.

As a further embodiment of this invention, the amount of water required for the hydrolysis of the tannin-containing materials can be reduced by replacing part of it with a portion of the water-immiscible solvent, in which case less solvent is required in the subsequent extraction step.

Examples of tannin-containing materials are tea leaves, tara pods, Chinese nut galls, divi divi pods, sumac leaves and Aleppo galls.

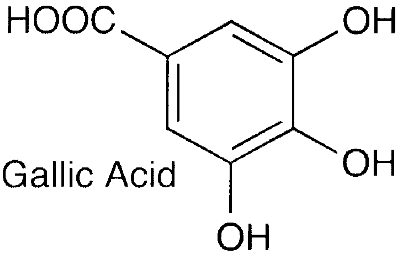
It has also been found that the presence of certain reducing agents during the hydrolysis of the tannin-containing material considerably decreases the amount of color formed during that operation thereby simplifying the purification of the product. A reducing agent such as sodium hydrosulfite, for example, has been found to be particularly effective during alkaline hydrolysis while other reducing agents such as sulfur dioxide and sodium bisulfite have been found to be particularly useful during acid hydrolysis.

Although it is convenient to separate the solvent from the gallic acid by steam distillation, other methods are applicable. For example, the solvent can be evaporated, or distilled off or the gallic acid can be extracted from the solvent with water or an aqueous alkali solution.

Example 1

To ground tara (150 g.) and water (60 mL.) was added 50 per cent sodium hydroxide solution (120 g.) and methyl isobutyl ketone (60 mL.). The mixture was stirred at reflux temperature for one and one-half hours and then cooled. Sufficient 60° Bé. sulfuric acid was, added to neutralize the alkali and liberate the gallic acid from its salts.

The gallic acid was extracted from the hydrolysis liquor with three successive 1500 mL. portions of methyl isobutyl ketone. After separating the ketone extract from the reaction mixture by decantation, it was steam distilled and the hot residual extract was then treated with iron-free activated carbon and allowed to cool. The crude gallic acid which crystallized from the solution was filtered off and dried. Yield 54 g.



To ground Chinese nut galls (120 g.) and methyl isobutyl ketone (60 mL.) mixture was stirred at the reflux temperature for one and one-half hours and then cooled. Sufficient 60° Bé sulfuric acid was added to neutralize the alkali and liberate the gallic acid and its salts. Gallic acid was extracted with three successive 1500 mL. portions of methyl isobutyl ketone which were separated from the reaction mixture by decantation. The ketone extract was steam distilled and the hot residual extract was then treated with iron-free activated carbon and allowed to cool. Crude gallic acid which crystallized from the aqueous solution was filtered off and dried. Yield 59 g.

Example IX

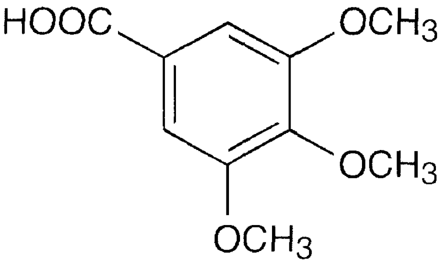
To ground sumac leaves (150 g.) and water (60 mL.) was added 50 per cent sodium hydroxide solution (120 g) and methyl isobutyl ketone (60 mL.). The mixture was stirred at reflux temperature for one and one-half hours and cooled. Crude 60° Bé sulfuric acid was added to neutralize the alkali and liberate the gallic acid from its salts.

The gallic acid was extracted with three successive 1500 mL. portions of methyl isobutyl ketone which were separated from the reaction mixture by decantation. The ketone extract was steam distilled and the hot residual extract was then treated with iron-free activated carbon and allowed to cool. Crude gallic acid crystallized from the aqueous liquor and was filtered off and dried. Yield 33 g.

Source: Krueger 1955 References: Collins 1995, Connolly 1993

Preparation of Trimethoxybenzoate Salts and Trimethoxybenzoic acid

by Muthunadar P. Periasamy
Creve Coeur, MO September 29, 1982



3,4,5-Trimethoxybenzoic Acid

The tannin or tannic acid employed can be any hydrolyzable tannin such as that obtained by extraction thereof from such tannin-containing materials as tara pods, Chinese nut galls, Aleppo galls, sumac leaves, etc. Taratannin (i.e., tannin obtained by extraction from tara pods) is preferred.

Example 1

Preparation of 3,4,5-Trimethoxybenzoic Acid from Aqueous Taratannin

To 250 mL. of aqueous taratannin (gallic acid content approximately 102 grams, 0.6 mole) are added 192 grams of 50% NaOH and 240 grams of dimethyl sulfate in portions at 20°-40°C. over a 3-6 hour period. The reaction mixture is refluxed for 1-3 hours with 48 grams of 50% NaOH. Upon cooling to 30°-60° C., 48 grams of 50% NaOH and 120 grams of dimethyl sulfate are added in portions over a 2-4 hour period. After treating with an additional 48 grams of 50% NaOH, the reaction mixture is refluxed for 1-3 hours. At the end of hydrolysis, the reaction mixture is cooled and acidified with concentrated hydrochloric acid to precipitate 3,4,5-trimethoxybenzoic acid (TMB acid). The precipitated product is isolated and dried to give 107-112 grams of TMB in 84-87% yield.

Example 2

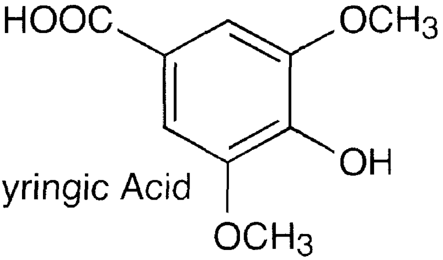
Preparation of 3,4,5-Trimethoxybenzoic Acid from Aqueous Taratannin

To a 50 gallon reactor containing 108 lbs. of aqueous taratannin (gallic acid content approximately 34.6 lbs), charge 72 lb of 50% NaOH and 90 lbs of dimethyl sulfate in portions over a 2-6 hour period while maintaining a temperature of 20°-40° C. Then, the reaction mixture is refluxed for 2-4 hours with 21 lbs of 50% NaOH. Upon cooling to 30°-60° C., the reaction mixture is treated with 45 lbs of dimethyl sulfate and 18 lbs of 50% NaOH over a 2-4 hour period. Then, after the addition of an additional 27 lbs of caustic, the reaction solution is refluxed for 2-4 hours. Upon completion of hydrolysis, the reaction mixture is cooled, acidified to 3-5 pH with concentrated hydrochloric acid to yield 36-37 lbs. of dried 3,4,5-trimethoxybenzoic acid in 84-86% yield.

Source: Periasamy 1985

Syringic Acid from Trimethylgallic Acid

by Marston Taylor Bogert
and Bernard B. Coyne 1929



Syringic Acid

Most of this acid required for the experiment work was obtained from the trimethylgallic acid by the method of Bogert and Ehrlich.

Alimchandani and Meldrum, as well as others, have suggested the use of concentrated sulfuric, in place of the fuming acid, for accomplishing this demethylation but, in our experience, unless the reaction was conducted as follows, the product contained some unchanged trimethylgallic acid.

To 300 g. of concentrated sulfuric acid, 60 g. of trimethylgallic was added all at once and the solution kept for six hours at 40° with occasional agitation. It was allowed to cool, left overnight at room temperature and then stirred into 300 cc. of water without external cooling. The syringic acid which separated was collected, washed with cold water and crystallized from boiling water in the presence of a decolorizing carbon. From the original mother liquor more syringic acid separated on standing and on concentration. Additional amounts may be recovered from the wash waters and second mother liquor; total yield of crude acid, 45 g., or 80%; after one crystallization, 35 g., or 63%. The carefully purified acid was odorless. The melting point varies somewhat depending upon the rapidity of heating and is generally preceded by a sintering or softening. The product obtained as described sintered at 204° and melted at 206.5° (corr.). Koerner and Gadamer reported the m.p. as 202°, Graebe and Martz and Bogert and Ehrlich as 204°, Alimchandani and Meldrum as 206-207° and Anderson and Nabenhauer as 209-210°. Source: Bogert 1929

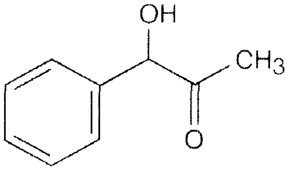
References: Alimchandani 1920, 1926; Balakrishnan 1970; Bogert 1915, 1919; Dev 1963; Gadamer 1897; Koerner 1888; Max 1950, Udupa 1961

Ephedrine Precursor: Chapter 5

3-Hydroxy-4-methoxyphenyl Acetylcarbinol from Isovanillin

by Wilfred William Groves
London, UK October 15, 1930

500 grams of grape sugar are dissolved in 30 litres of water at about 18° C., the solution is mixed with 2 kilos of yeast and fermented for about 15 minutes. A solution of 200 grams of isovanillin in 12 litres of hot water is then added drop by drop in the course of 2 hours. After the liquid has been allowed to ferment for 2 days, the yeast is removed by filtering and the filtrate is salted out with sodium chloride and extracted with ethyl acetate. After the distillation of the extract, 190 grams of a residue are obtained having a specific rotation of [a]20D= -35°. This residue is then diluted with ether and shaken with a sodium bisulphite solution of 40 per cent. strength. The etheral layer is then separated and the remaining bisulphite solution is diluted with water and then mixed with an excess of sodium bicarbonate. The liquid is then extracted with ethyl acetate (or ether) and the ethyl acetate solution is dried by means of anhydrous sodium sulphate. The solvent is distilled and the residue (or, ether is evaporated to leave crystalline mass or oily residue, recrystallize with very dilute alcohol solution to leave a fairly pure final product) is subjected to distillation under reduced pressure, in order to purity it complete. The *laevo*-3-hydroxy-4-methoxyphenylacetylcarbinol is obtained which distills at 135°-136° C. under 3.5 mm. pressure. It has a specific rotation of [a]20D=-120°. Source: Groves 1932



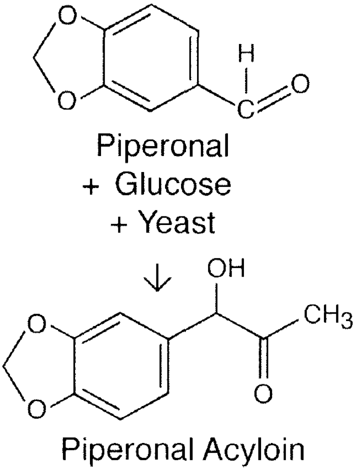
1-Phenylpropan-1-ol-2-one

Preparation of Dihydroxyphenylacetylcarbinol and Dihydroxyphenylpropane-diol

by Wilfred William Groves
London, UK October 15, 1930

1.5 kilos of beer yeast are introduced, while stirring, into 15 litres of a solution of glucose of 10 per cent strength. When the mass is in full fermentation, a solution of 150 grams of protocatechuic aldehyde in 600 cc. of alcohol is slowly introduced in small portions. When the fermentation is finished, the whole is filtered, the clear solution is saturated with sodium chloride and extracted with ethyl acetate. After expelling the extracting agent by distillation, there is obtained a mixture of dihydroxyphenypropane-diol and dihydroxy-phenyl-acetylcarbinol with has a specific rotation of [a]D20°=-17° and can be worked up directly.

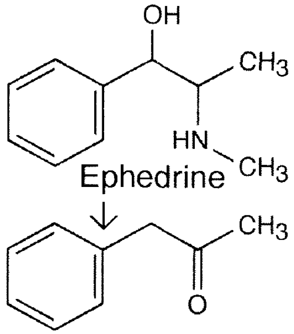
Source: Groves 1933



Phenyl-2-propanone Syntheses: Chapter 6

Preparation of Phenyl-2-Propanone from Ephedrine or *pseudo*-Ephedrine

by Friedrich Brauch and Hans-Joachim Blanke
Minden, Germany January, 7, 1982
Translated by Otto



Phenyl-2-propanone

Example 1

1025 g 75% sulphuric acid are mixed with 2 g AlCl3. Therein 426 g (= 2.58 Mol) ephedrine or pseudoephedrine at 50 to 100°C are added. Subsequently, the mixture on 145 to 150° heated, with 125°C is introduced water vapour in moderate stream for better mixing. At 145°C one increases steam distllation and distills for period of 2-1/2 to 3 hours, the azeotrop phenylacetone/water distills over.

From the distillate one isolates by toluene extraction a raw phenylacetone, which is free from propiophenone. After distillation over a short Vigreux column one receives 270 g (78%) phenylacetone, purity: 99.8%. similar to the one received from norephedrine and/or norpseudoephedrine, phenylacetone in a absolute yield of approx. 80%.

Example 2

1000 g 79% sulphuric acid and 100 g (-)-pseudoephedrine, whereby the H2SO4-concentration is adjusted to 65 to 66%. This solution is given to 2 L three-neck, mixed with 4 g AlCl3 and heated up on 125 to 130°C.

By injecting water vapour one increases the temperature to 145 - 150°C and leaves from now to continuously with a speed of approximately 1 to 5 g/min, 70 to 90° C a warm a solution of (-)-pseudoephedrine into 79% sulphuric acid (weight ratio 1: 1) over a steam-heated dropping funnel flow. The phenylacetone turns into thereby as Azeotrop and similar to example 1.

After in each case 4 hours the reaction is interrupted for 5 minutes and removed at expiration of the 5 minutes so much sulfursour that the output volume is restored. Afterwards the reaction is continued. The taken sulphuric acid can after. Remove from the methyl ammonium hydrogen sulfate developed during the conversion to be reused. The yield at phenylacetone amounts to 76%.

Example 3

In a reaction vessel are submitted to 1350 g 79% sulphuric acid and under agitation with 590 g 95% (+)-ephedrine added. Subsequently, a solution of 10 mL 18 grams TiCl3 are added and the mixture with 125°C beginning and to 145-155° C is treated rising with water vapour. In the period of 2 1/2 h 6 L water vapour distillate became formed, from which by toluene extraction, 358 g phenylacetone were isolated. From it 335 g = 73.6 were received by fractionated distillation over a Vigreux column % phenylacetone, to purity: 99.5%.

Example 5

To 400 kg 60% sulfuric acid in a distillation apparatus are coursepumped 500 kg of 80% sulphuric acid. Into this mixture, with agitation, 400 kg (-)-pseudoephedrine (60%) and 1.5 L aluminium chloride solution (30%) are added. One heats the reaction mixture to 125-130°C up and introduces water vapor to increase temp. to 145-150°C, a mixture of water vapour and phenylacetone distills.

After approx.. 2000 L water has distilled over, the distillation is terminated. From the distillate the heavy phase, consisting of phenylacetone, is separated and the aqueous phase is extracted with approx.. 400 L toluene. The phenylacetone and the toluol extracts are combined and concentrated by distillation. One yeilds 155 kg (80%) pure phenylacetone, after fractional distillation.

Source: Brauch 1983

Phenyl-2-propanones from Propenylbenzenes

Jürgen Smidt, Rolf Sieber, Walter Hafner
and Reinhard Jira
Munch, Germany September 6, 1957

Preparation of Palladium Chloride Catalyst

106.7 g. of metallic palladium were dissolved in aqua regia and this solution evaporated to dryness on a sand bath. The residue was taken up in 200 cc. of 20% HCl and evaporated to dryness again. This latter procedure was repeated three times. A sufficient quantity of 1 N HCl was added to the resulting nitrate free residue so that upon warming complete solution was affected. After the solution cooled, a sufficient quantity of water was added to provide 5.335 liters of solution and a small quantity of HCl was added so that the solution contained 21 mg. HCl per cc. of solution. The resulting solution contained 20 mg. of palladium per cc. and was used in the following example:

4-Methoxy-phenyl-2-propanone Preparation

0.1 mol anethol (4-methoxy-1-propenyl-benzol) was shaken together with 533 cc. of this palladium chloride solution (=0.1 mol palladium) for 4.5 hours at 70° C. *p*-methoxyphenyl acetone was obtained as the reaction product in 91% of the theoretical yield with a 55% conversion. Source: Smidt 1964.

Olefin	Reaction Temp. °C.	Reaction time/min.	Product	Conv.	Yield
Iso-safrole	70	120	3,4-DMP-2-P	69%	89%

Phenyl-2-propanones from Allybenzenes

by Consortium Für Elektrochemische
München, Germany July 23, 1937

2.35 kg. of allylbenzene and 10 litres of an aqueous solution containing 3.56 grams of $PdCl_2$, 136 grams of $CuCl_2.2H_2O$, 40 grams $Cu(CH_3CO_2)_2.H_2O$ and 3.6 grams of HCl per litre were heated in a stirring vessel to 50° C. in an atmosphere of oxygen. Benzyl-methyl-ketone was formed at a rate of 21 grams per hour. Consortium 1961

Olefin	Reaction Temp. °C.	Reaction time/min.	Product	Yield
Allylbenzene	40	40	P-2-P	89%

Source: Consortium 1962
Reaction Products: P-2-P and propenylbenzene, Dal Cason 1984

Phenylacetones from Allybenzenes

by Manora Nakai and Takuji Enomiya

July 29, 1983

Phenylacetone and its derivatives ("phenylacetones" herein below) are useful as intermediates for various agricultural chemicals and pharmaceutical preparations. For example, 4-hydroxy-3-methoxyphenylacetone (HMPA), 3,4-dimethoxyphenylacetone (DMPA), and 3,4-methylenedioxyphenylacetone are utilized as intermediates for producing L-*alpha*-methyldopa, which is used as antihypertensive. Thus, the phenylacetones are practically useful compounds. However, industrially satisfactory processes for producing phenylacetones have not yet been developed.

For instance, British Patent Specification No. 1119612 discloses a process for producing DMPA by reacting 1-(3,4-dimethoxyphenyl)-propylene with peroxides such as peracetic acid, followed by treating the resultant diol type products with acidic substances such as zinc chloride. However, this process is not entirely satisfactory in industrial use because the yield of the treatment step with an acidic substance is low and that the special caution should be taken in the handling of the peroxides because of their explosive properties.

Furthermore, the *Journal of the American Chemical Society* (*J.A.C.S.*) 77, 700 (1955) discloses a process for producing DMPA by reacting 3,4-dimethoxyphenyl acetonitrile with sodium ethoxide in a solvent such as ethyl acetate to form the acetylated product, followed by hydrolysis. However, this process includes problems that water should be completely removed from the reaction system, which sodium ethoxide is used, in order to prevent hydrolysis of the sodium ethoxide, that the yield of the desired product in the hydrolysis step is low, and that the large number of steps in the entire process is required taking into account the steps necessary to prepare the starting 3,4-dimethoxyphenyl acetonitrile from a readily available chemical raw material.

According to the second aspect of the present invention, the

3-phenylpropylene and the alkyl nitrites are reacted in the presence of the alcohols and the palladium catalysts and, further, optionally the amines or copper compounds to form 1-phenyl-2,2-dialkoxypropane or its derivatives as an intermediate, followed by hydrolysis of the reaction product.

The basic reactions of the second aspect of the present invention proceed as follows:

The above-mentioned reaction (B) desirably proceeds in the presence of the above-mentioned alcohols and the above-mentioned palladium catalysts and, optionally, the above-mentioned amines or copper compounds. This reaction can be carried out at a temperature of 0° C. to 150° C., desirably 10° C. to 90° C. optionally in the presence of the above-mentioned inert solvents. The use of a too high reaction temperature tends to cause undesirable side reactions such as an isomerization reaction, whereas the use of a too low temperature is not practical due to the low reaction rate. The pressure within the reaction system during reaction can be an atmospheric pressure to about 200 kg/cm.2 G. The reaction time is desirably 10 minutes to 5 hours, although this depends upon the reaction conditions.

The present reaction (B) can be carried out as follows: For example, the starting 3-phenylpropylenes, the alcohols, the palladium catalysts and the optional amines or copper compounds are charged into a reaction vessel. The alkyl nitrites are added to the mixture, causing it to react under the predetermined reaction conditions. It should be noted, however, that the addition order of the above-mentioned reactants and catalysts is not specifically limited.

After completion of the reaction, the resultant NO gas, the unreacted starting materials, alcohol, the desired intermediate (i.e., 1-phenyl-2,2-dialkoxypropanes), the optional amines and copper compounds are distilled under a reduced pressure and recovered.

The recovered unreacted starting materials and alcohols as well as the optional amines and copper compounds can be again used. Further, NO gas can be used in the production of the alkyl nitrites.

The 1-phenyl-2,2-dialkoxypropanes thus obtained are hydrolyzed in the presence of water as shown in the above-mentioned reaction (C) either after separating it, or without separating it from the reaction mixture. The amount of water used in the hydrolysis is stoichiometrically 1 mole based on 1 mol of the starting 1-phenyl-2,2-dialkoxypropanes, but is desirably 3 to 500 moles based on 1 mol of the starting 1-phenyl-2,2-dialkoxypropanes. In the case where the amount of the water present in the reaction system is small, the use of solvents other than water is desirable. Even in the case where a large amount of water is used, the use of solvents other than water is also desirable in view of the fact that the starting 1-phenyl-2,2-dialkoxypropanes are not readily soluble in water.

The solvents suitable for use in the hydrolysis of 1-phenyl-2,2-dialkoxypropanes are those which dissolved well both the 1-phenyl-2,2-dialkoxypropanes and the water and also which are substantially inert against the hydrolysis. Typical examples of these solvents are lower alcohols such as methanol, ethanol, propanol, and butanol; ethers such as dioxane and tetrahydrofuran; and carboxylic acids such as acetic acid and propionic acid. Of these examples, the use of methanol, ethanol, propanol, butanol, dioxane, and tetrahydrofuran are particularly desirable. Furthermore, slightly water-soluble alcohols such as pentanol, hexanol, and heptanol can be used as a solvent in combination with dioxane and tetrahydrofuran.

These solvents can be desirably used in an amount of about 0.5 to about 10 liters per 1 mole of 1-phenyl-2,2-dialkoxypropanes.

The hydrolysis can be desirably carried out under a neutral or acidic condition rather than under basic conditions, since the reaction rate of the hydrolysis is low under under basic conditions. Optionally, the pH of the reaction mixture can be adjusted to 4 to 7 by adding a mineral acid such as hydrochloric acid or sulfuric acid. The hydrolysis is generally completed at a temperature of about 0° C. to about 80° C. for about 5 minutes to about 90 minutes. The resultant phenylacetones can be isolated from the reaction mixture by any conventional separation technique such as distillation or extraction.

Example 1

A 0.10 mole amount of the starting 3-phenylpropylene 0.25 mole of methyl nitrite, 0.5 liter of methyl alcohol, 36 g of water, and 0.008 mole (1.42 g) of a palladium chloride catalyst were charged into a reaction vessel. Then, the reaction was carried out at a temperature of 25° C. for 2 hours.

After completion of the reaction, the reaction mixture was gas chromatographically analyzed to quantitatively determine the amounts of the unreacted starting material and the resultant desired product. As a result, the conversion of the starting material was 100% and the yield of the desired product (phenylacetone) was 90%.

Precursor: 3-phenylpropylene
Catalyst: .008 mole (1.42 g) of a palladium chloride

Exple.	Temp.	Nitrite	Alcohol	Product	Conv.	Yield
1	25°	methyl	methyl	P-2-P	100%	90%
2	55°	*n*-butyl	*n*-butyl	P-2-P	100%	87%

Precursor: 3-(4-methoxyphenyl)-propylene

5	25°	methyl	methyl	4-MP-2P	100%	95%

Product: 4-methoxyphenylacetone

Precursor: 3-(4-methoxyphenyl)-propylene

6	55°	*n*-butyl	*n*-butyl	4-MP-2P	100%	90%

Product: 4-methoxyphenylacetone

Precursor: 3-(3,4-dimethoxyphenyl)-propylene

10	25°	methyl	methyl	3,4-DMP-2P	100%	93%

Product: 3,4-dimethoxyphenylacetone

Precursor: 3-(3,4-dimethoxyphenyl)-propylene

12	55°	*n*-butyl	*n*-butyl	3,4-DMP-2P	100%	89%

Product: 3,4-dimethoxyphenylacetone

Catalyst: (.008) mole of a palladium bromide
Precursor: 3-(4-methoxyphenyl)-propylene

23	25°	methyl	methyl	4-MP-2P	100%	96%

Product: 4-methoxyphenylacetone

Precursor: 3-(3,4-methylenedioxyphenyl)-propylene

24	25°	methyl	methyl	3,4-MDP-2-P	100%	95%

Product: 3,4-methylenedioxyphenylacetone

Examples 30 to 32

A 0.10 mole amount of the starting 3-(3,4-dimethoxyphenyl) propylene, 0.25 mole of methyl nitrite, 0.5 liter of methyl alcohol, 36 g of water, and 0.008 mole of a catalyst were charged into a reaction vessel. The reaction was carried out at a temperature of 25° C. for 2 hours.

After completion of the reaction, the unreacted starting material and the desired product (3,4-dimethoxyphenylacetone) were quantitatively analyzed in the same manner as in Example 1. The results are shown below.

Example No.	Catalyst	Conversion of Starting Material	Yield of Desired Products
30	Palladium bromide	100%	96%
31	Palladium acetate	66%	28%
32	Palladium nitrate	71%	34%

Example 70: A 0.10 mole amount of the starting 3-phenylpropylene, 0.25 mole of methyl nitrite, 0.5 liter of methyl alcohol, 36 g of water, 0.0005 mole of a palladium chloride catalyst, and 0.0025 mole of cuprous chloride were charged were charged into a reaction vessel. Then, the reaction was carried out at a temperature of 20° C. for 1.5 hours.

After completion of the reaction, the reaction mixture was gas chromatographically analyzed to quantitatively determine the amounts of the unreacted starting material and the resultant desired product. As a result, the conversion of the starting material was 94%, the yield of the desired product was 83%, and the Pd turn-over number was 166.

Examples 71 to 76: The reaction of Example 70 was repeated, except that 0.10 mole of each of various 3-phenylpropylenes listed in Table 10 was used as a starting material and 0.0025 mole of CuCl2 or CuCl was used as a copper compound. The results are shown below.

Starting 3-phenylpropylenes			Desired phenylacetones			
Example No.	Name	Conversion (%)	Copper compound	Name	Yield (%)	Pd turn-over
71	3-(4-hydroxy-3-methoxyphenyl) propylene	92	CuCl2	4-hydroxy-3-methoxyphenylacetone	82	164
72		93	CuCl		82	164
73	3-(3,4-dimethoxy-(phenyl) propylene	96	CuCl2	3,4-dimethoxyphenylacetone	86	172
74		95	CuCl		85	170
75	3-(3,4-methylenedioxyphenyl) propylene	93	CuCl2	3,4-methylenedioxyphenylacetone	84	168
76		93	CuCl		85	170

Example 86: A 0.10 mole amount of the starting 3-(4-hydroxyphenyl) propylene, 0.25 mole of methyl nitrite, 0.5 liter of methyl alcohol, and 0.006 mole of a palladium chloride catalyst were charged into a reaction vessel. Then, the reaction was carried out at a temperature of 20° C. for 1.5 hours.

After the completion of the reaction, the reaction mixture was gas chromatographically analyzed to quantitatively determine the unreacted starting material and the resultant intermediate product (1-(4-hydroxyphenyl)-2,2-dimethoxypropane). As a result, the conversion of the starting material was 100% and the yield of the intermediate product was 85%.

The reaction mixture (containing the intermediate product) obtained above was hydrolyzed at a temperature of 20° C. for 60 minutes by adding 36 g of water.

After completion of the hydrolysis, the desired 4-hydroxyphenylacetone was quantitatively determined by a gas chromatographical analysis. The yield of the desired product was 84%.

Example 90: The reaction of Example 86 was repeated, except that *n*-butyl nitrite and *n*-butyl alcohol were used in lieu of methyl nitrite and methyl alcohol and the reaction temperature was changed to 60° C. and that the hydrolysis conditions were changed to 55° C. and 80 minutes.

As a result, the conversion of the starting material was 100%, the yield of the intermediate 1-(4-hydroxyphenyl)-2,2-di(*n*-butoxy) propane was 82%, and the yield of the desired 4-hydroxyphenylacetone was 80%.

Example 91: The reaction of Example 90 was repeated, except that 3-(4-methoxyphenyl) propylene was used in lieu of 3-(4-hydroxyphenyl) propylene.

As a result, the conversion of the starting material was 100%, the yield of the intermediate 1-(4-methoxyphenyl)-2,2-di(*n*-butoxy) propane was 89%, and the yield of the desired 4-methoxyphenylacetone was 87%.

Example 94: The reaction of Example 86 was repeated, except that 3-(4-methoxyphenyl) propylene was used in lieu of 3-(4-hydroxyphenyl) propylene and the hydrolysis time was changed to 30 minutes.

As a result, the conversion of the starting material was 100%, the yield of the intermediate 1-(4-methoxyphenyl)-2,2-dimethoxypropane was 94%, and the yield of the desired 4-methoxyphenylacetone was 93%.

Example 95: The reaction of Example 94 was repeated, except that 3-(3,4-methylenedioxyphenyl) propylene was used in lieu of 3-(4-methoxyphenyl) propylene.

As a result, the conversion of the starting material was 100%, the yield of the intermediate 1-(3,4-methylenedioxyphenyl)-2,2-dimethoxypropane was 92%, and the yield of the desired 3,4-methylenedioxyphenylacetone was 91%.

Example 107: The reaction of Example 86 was repeated, except that 3-(4-methoxy-3-methylphenyl) propylene, *n*-pentyl nitrite, and *n*-pentyl alcohol were used in lieu of 3-(4-hydroxyphenyl) propylene, methyl nitrite, and methyl alcohol and that the reaction temperature was 60° C. and the hydrolysis was carried out at 50° C. for 60 minutes.

As a result, the conversion of the starting material was 100%, the yield of the intermediate 1-(4-methoxy-3-methylphenyl)-2,2-di(*n*-pentyloxy) propane was 86%, and the yield of the desired 4-methoxy-3-methylphenylacetone was 84%.

Examples 119 to 122: A 0.10 mole amount of the starting 3-(3,4-dimethoxyphenyl)-propylene, 0.25 mole of *n*-butyl nitrite, 0.5 liter of *n*-butyl alcohol, and 0.006 mole of a catalyst were charged into a reaction vessel. The reaction was carried out at a temperature of 60° C. for 1.5 hours. Then, the reaction mixture was hydrolyzed by adding 36 g of water at 55° C. for 80 minutes.

The catalysts used and results are shown in Table 14.

TABLE 14

Example No.	Catalyst	Conversion of starting material	Yield of inter-mediate*1	Yield of desired product*2
119	palladium bromide	100%	90%	88%
120	palladium acetate	60%	23%	22%
121	palladium nitrate	77%	36%	35%
122	palladium sulfate	56%	23%	22%

*1 1-(3,4-dimethoxyphenyl)-2,2-di(*n*-butoxy) propane

*2 3,4-dimethoxyphenylacetone

Example 164: A 0.10 mole amount of the starting 3-phenylpropylene, 0.25 mole of methyl nitrite, 0.5 liter of methyl alcohol, 0.0005 mole of palladium chloride, and 0.0025 mole of cuprous chloride, were charged into a reaction vessel. Then, the reaction was carried out at a temperature of 20° C. for 1.5 hours.

After the completion of the reaction, the reaction mixture was gas chromatographically analyzed to quantitatively determine the unreacted starting material and the resultant intermediate 1-phenyl-2,2-dimethoxypropane. As a result, the conversion of the starting material was 96%, the yield of the intermediate product was 86%, and the Pd turn-over number was 172.

The reaction mixture (containing the intermediate product) obtained above was hydrolyzed at a temperature of 50° C. for 60 minutes by adding 36 g of water thereto.

After the completion of the hydrolysis, the desired phenylacetone was quantitatively determined by a gas chromatographical analysis. The yield of the desired product was 85%.

Examples 165 to 170: The reaction of Example 164 was repeated, except that 0.10 mole of each of 3-phenylpropylenes listed in Table 24 was used as a starting material and that 0.0025 mole of CuCl2 or CuCl was used as a copper compound. The results are shown below.

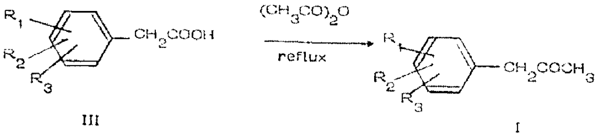
Starting material				Desired product	
Example No.	Name	Conversion (%)	Copper compound	Name	Yield (%)
165	3-(4-hydroxy-3-methoxyphenyl)	93	CuCl2	4-hydroxy-3-methoxyphenyl-	82
166	propylene propane	94	CuCl	acetone	84
167	3-(3,4-dimethoxyphenyl) propylene	98	CuCl2	3,4-dimethoxyphenylacetone	88
168		97	CuCl		88
169	3-(3,4-methylenedioxyphenyl)	96	CuCl2	3,4-methylenedioxyphenyl-	90
170	propylene	96	CuCl	acetone	87

Source: Nakai 1987

3,4-Methylenedioxy-phenyl-2-propanone from 3,4-Methylenedioxy-phenylacetic Acid

by Umakant Davdas Shenoy
London, UK September 28, 1974

The invention provides a process for the preparation of a compound of the general formula I which comprises refluxing the appropriate phenylacetic acid with acetic anhydride preferably for from 1 to 24 hours. The phenylacetic acid starting material has the general formula III and the reaction can be summarized us follows:



wherein R1, R2 and R3 are as above defined.

The invention also provides a process for the preparation of a bisulphite adduct of the general formula II, which comprises treating the appropriate compound of the general formula I, prepared as above, with an alkali metal bisulphite such as sodium bisulphite.

Examples of particularly suitable starting materials are those with the following identities of R1, R2 and R3:

R1=H; R2 and R3 (together)=—O—CH2—O
R1=H; R2 and R3=alkoxy (for example—OCH3)
R1=H; R2 and R3=—OCOCH3
R1 and R2=H: R3=—CF3,—NO2,—OH, alkyl or alkoxy
R1 and R2=H; R3=—CF3,—NO2,—NH2,—OH, alkyl or alkoxy
R1, R2 and R3=—OH.

The reaction may be carried out in the presence of a suitable catalyst such as, anhydrous sodium or potassium acetate, sulphuric acid perchloric acid or pyridine. If a catalyst is used, it may be present in any amount sufficient to have the required catalytic effect, generally from trace amounts in the case of some catalysts to two molar equivalents-per molar equivalent of the phenylacetic acid.

The molar ratio of starting materials is preferably from 1 to 5 molar equivalents of acetic anhydride per 1 molar equivalent of the phenylacetic acid. The acetic anhydride may if desired be used in reaction product may be isolated by extraction with any suitable solvent such as methylene dichloride, chloroform, toluene or diethyl ether, and may be purified by fractional vacuum distillation or by treatment with an excess of sodium or potassium bisulphite solution to separate the crystalline bisulphite adduct.

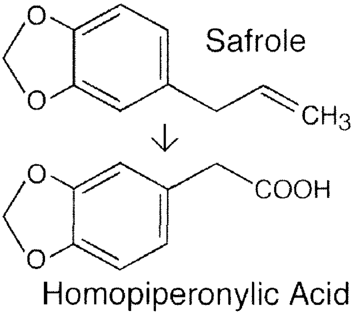
Example 1

A mixture of homoveratric acid (49 g), anhydrous sodium acetate (20.5 g) and acetic anhydride (83 mL) was refluxed for 4 hours, cooled, added to 500 mL. of ice-cold water and stirred for 15 minutes. The resulting reddish bottom layer was separated and retained. The remaining aqueous layer was extracted with two 100 mL. quantities of toluene, and the toluene extracts were combined with the reddish liquid and washed successively with five 100 mL. quantities of 1N sodium hydroxide solution, followed by two 100 mL. quantities of water. The washed product was then filtered through a plug of glass wool and fractionally distilled to remove the toluene and water impurities. The product, 3,4-dimethoxyphenylacetone, was collected at 115°C to 125°C at about 0.4 mm Hg. This product was a pale yellowish oil and was obtained in a yield of 16 g (33% of theoretical yield).

Example 2

A mixture of homoveratric acid (32 g), anhydrous sodium acetate (30.6 g) and acetic anhydride (52 mL) was refluxed for 4 hours, cooled and poured into 300 mL of ice-cold water. The resulting reddish bottom layer was separated and retained. The aqueous layer was extracted with two 50 mL. quantities of toluene and the combination of the reddish liquid and the toluene extracts was washed successively with four 100 mL. quantities of 1N sodium hydroxide solution followed by two 50 mL. quantities of water. It was filtered through a plug of glass wool and distilled to remove the toluene and water. There was thus obtained about 25 g of crude phenylacetone. This was dissolved in 50 mL. IMS and added, with stirring, to 90 mL. of freshly prepared 40 % w/v sodium bisulphite solution. The mixture was stirred for 30 minutes and allowed to stand for 2 hours in a cold water bath. It was again stirred for 30 minutes, washed with 100 mL. of toluene and stirred for a further 15 minutes. It was then filtered and washed with 50 mL. of toluene and air dried. There was thus obtained 30 g of the bisulphite adduct of 3,4-dimethoxyphenylacetone which corresponds to about 17.5 g of 3,4-dimethoxyphenyl acetone which is about 55.4% of the theoretical yield. Source: Shenoy 1974

Homopiperonylic Acid
3,4-Methylenedioxyphenylacetic Acid
Preparation from Safrol



A mixture of 5 parts of safrol and 12.5 parts of potassium permanganate dissolved in water and 5 parts of acetic acid are heated to 70° to 80°, and the liquid rendered alkaline.

The liquid is filtered, and on extraction with ether yields some piperonal (heliotropin), melting at 37°. The residual liquid is boiled with magnesium carbonate, resinous matter extracted with ether, the liquid filtered and the acid set free by means of dilute sulphuric acid. Homopiperonylic acid, melting at 127° to 128°.

If chromic acid be used as the oxidizing agent, piperonal and piperonylic acid, melting at 228°, are formed.

Source: Parry 1922

Preparation of Phenylacetic Acid from *alpha*-Tolunitrile (Benzyl Cyanide)

by Wilhelm Wenner
Montclair, New Jersey January 15, 1947

100 grams of *alpha*-tolunitrile and 300 cc. of concentrated hydrochloric acid are stirred at room a temperature, surrounded by a water bath of 15-20° C. After two and one-half hours stirring, a homogeneous solution is formed. After stirring for two hours more. 100 cc. of water are added. A precipitate appears. Stirring is continued and the

temperature is raised to 40° C. The precipitate redissolves within a few minutes. After about one hour, the mixture becomes turbid and slowly a precipitate forms which augments unto after three more hours a thick paste is obtained. The mixture is filtered yielding colorless phenylacetic acid, M. P. 70-72° C. Extraction of the mother liquor yields additional 5 grams phenylacetic acid.

Example 2

200 grams of *alpha*-tolunitrile and 800 cc. of concentrated hydrochloric acid are stirred for one hour at 50° C. then at 70° C. for five hours. After initial dissolution an oil separates. After six hours the mixture is cooled and diluted with 1500 cc. of water. The mixture is extracted repeatedly with ether. The combined ether extracts are distilled to dryness, phenylacetic acid being obtained.

4-Methoxy-phenylacetic Acid

50 grams of 4-methoxy-*alpha*-tolunitrile and 250 ccs. of concentrated hydrochloric acid are stirred at room temperature for 15 hours. 250 cc. of water are added slowly. The mixture is then heated with stirring to 70° C. for fifteen hours. After cooling, the solution is extracted with ether. The ether layer is evaporated. The residue is distilled in the vacuum. 4-methoxy-phenyl-acetic acid, B. P. 184-186° C. is obtained.

Preparation of Homoveratric acid (3,4-Dimethoxy-phenylacetic acid)

100 grams of 3,4-dimethoxy-*alpha*-tolunitrile are stirred with 200 cc. of concentrated hydrochloric, the temperature being kept below 40° C. by external cooling. When all the nitrile is dissolved (after about three hours), the temperature is raised to 50° C. for two more hours. The mixture is then diluted with 700 cc. of water and refluxed with stirring. After a short time the liquid becomes turbid, and soon an oil starts to separate. After boiling for seven hours, the mixture is cooled. When the temperature reaches 40-45° C. the oil solidifies. It is essential to stir vigorously at this point in order to avoid the formation of a solid cake. The mixture is cooled for several hours to 0° C. The sandy homoveratric acid is filtered and washed with about 40 cc. of ice cold water. The crude acid is purified by dissolving in sodium carbonate, filtering and acidifying with hydrochloric acid. The pure acid melts at 96-97° C.

Preparation of *o*-Homoveratric acid (2,3-Dimethoxyphenylacetic acid)

20 grams of 2,3-dimethoxy-*alpha*-tolunitrile and 100 cc. of concentrated hydrochloric acid are stirred at room temperature for three hours. 300 cc. of water are added and the mixture heated to 80° C. for ten hours with stirring. An oil separates and is extracted with ether. The ether layer is extracted with sodium carbonate solution The sodium carbonate extract is acidified and the mixture is extracted with ether. The ether is distilled leaving crude *o*-homoveratric acid as an oil which crystallizes on standing. The acid is purified by distillation in vacuo. It boils at 235-240° C./20 mm. Source: Wenner 1949

Preparation of Acetic Anhydride

by James Brown
London, UK October 24, 1931

Example 1

26,600 parts of glacial acetic acid are vaporised and the vapour passed through a bath of molten lead at a temperature of 525° Centigrade upon which is heated a layer of titanium dioxide. The vapour after passing through the molten lead and titanium dioxide, are condensed and 25,300 parts of condensate are obtained having a content of 10 per cent, by weight of acetic anhydride.

Example 2

16,200 parts of glacial acetic acid are vaporised and the vapour passed through a molten lead bath at 500° Centigrade upon which is floated a layer of alumina. 13,900 parts of condensed vapours are obtained having a content of 6 per cent. acetic anhydride and 10 per cent. acetone. Source: Brown 1932

Preparation of Acetic Anhydride

by Jan Al
Amsterdam, Netherlands August 9, 1929

The reaction may be carried out with or without the aid of pressure or of vacuum and in the presence or absence of suitable catalysts. For instance it is possible to carry out the reaction by conducting the mixture of acid and ketone through a tube made of any suitable material in the presence of filling and/or contact masses. The filling masses may serve for obtaining the desired state of flow, whereas the contact masses may have a catalytic influence on the reaction.

The contact masses may serve at the same time to act as a filling material or the latter may constitute the carrier of the catalyst.

A mixture of 1 part by volume of acetic acid and 4 parts by volume of acetone were at a temperature of 700° C. and at a velocity of 5 to 7 cc. per minute passed through a tube made of porcelain and filled with pieces of crushed porcelain. Using 360 ccs. (304 Gr.) of the aforesaid mixture, the reaction products consisted of a liquid weighing 271 grams and 41.1 litres (at 25° C.) of gas weighing 34.7 grams.

The liquid after fractionation up to a temperature of 105° C. yielded 171 grams of a liquid consisting of 157.2 grams of acetone and 13.8 grams of acetic acid. The residue after the fractionation weighing 96 Gr. was a mixture of acetic anhydride (62.6%), acetic acid (34.5%) and acetone (2.8%). 48 per cent by weight of anhydride of the theoretically possible quantity was thus obtained. Source: Source 1934

Phenylacetaldehyde from Phenylglycidic acid or ester

by Wilfred William Groves
London, UK May 5, 1932

When the glycidic acid ester is to be further worked up to the phenylacetaldehyde it need not previously be distilled, but the crude ester is saponified with sodium hydroxide while steam is passed through it, and an organic acid, for instance oxalic acid, and sulphuric acid are added. Carbon dioxide is eliminated from the glycidic acid thus liberated and the phenyl-acetaldehyde distills with water.

Source: Groves 1932

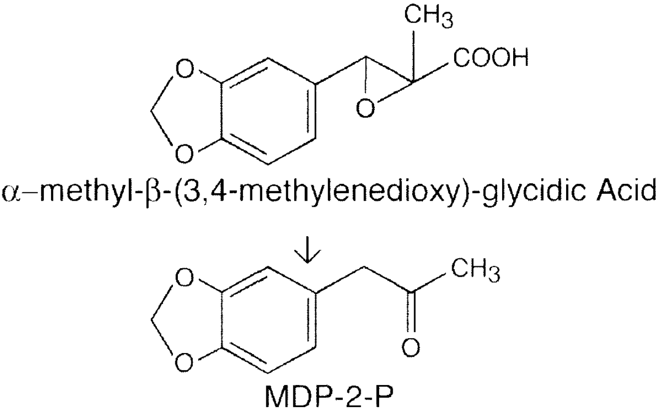
30 g. of sodium 3-(4-isobutylphenyl)-2,3-epoxybutyrate was dissolved in water (200 mL.) and the solution was steam distilled. The distillate was extracted with ether, the extract was dried with anhydrous sodium sulphate and the was evaporated to give 2-(4-isobutylphenyl)-propionaldehyde (Yield: 80% based on the above sodium salt.) Source: Boots 1969

Preparation of Phenyl-2-propanone from *alpha*-Methyl-ß-(phenyl)-glycidic Acid

by Robert Robinson and Arthur Lowe
Oxford and Manchester, UK October 4, 1939

One part *alpha*-methyl-ß-(phenyl)-glycidic acid is mixed with 2 parts of copper chromite and heated at a temperature of 130-140° C. under reduced pressure for 2 hours. The oily product is distilled. The distillate collected is phenyl acetone.

Source: Robinson 1940



α–methyl-β-(3,4-methylenedioxy)-glycidic Acid

MDP-2-P

3,4-Methylendioxyphenyl-2-propanone from ß-3,4-methylenedioxy-phenyl-*alpha*-methylglycide ester, NaOH and dilute HCl see Elks 1943

3,4-Dimethoxyphenyl-2-propanone from 3,4-Dimethoxy-1,2-dihydroxypropane

by W.J. Bush & Co.
London, UK April 20, 1966

One portion (61 parts) of the glycol product was distilled slowly under vacuum (5 mms Hg) in the presence of 0.5% by weight of anhydrous zinc chloride. The product (37 parts) had a boiling point of 155 to 160° C. 15 mm Hg and was crude 3,4-dimethoxyphenylacetone.

A second portion (50 parts) was refluxed with dilute sulphuric acid (250 parts of 4% acid) for two hours. The reaction. mixture was extracted with ether and the extracted ketone recovered by removal of the solvent from the extract. The oily ketone product had a boiling point of 142 to 150°C/3 mms Hg. Source: Bush 1968

Grignard Reaction

by Hugh Edwin Ramsden
New York, New York November 28, 1955

A standard experimental procedure was followed in the examples. When the experimental conditions deviated from standard procedure, it is noted in the description of the experiment.

Magnesium turnings (24.3 grams (1 g. atom)) and a small iodine crystal were charged into a 1,000 mL. (in some cases a 500 mL.) 3 neck flask which was then purged with nitrogen. In another flask, a mixture was prepared by dissolving 1 mole of the organic chloride utilized in 216.0 grams (3 moles) of solvent tetrahydrofuran. Of this mixture 10 mL. was then added to the charge in the 3 neck flask and the reaction was initiated by addition of 2 mL. of ethyl bromide. After initiation of the reaction, the remainder of the organic chloride/tetrahydrofuran mix was slowly added to the 3 neck flask, with constant stirring. The formation of the organic magnesium chloride complexes is usually exothermic. When necessary, external heat is applied to the flask to keep the reaction going and/or to carry it to completion. At the completion of the reaction, the product was titrated in the standard Gilman test to determine the yield of organic magnesium chloride complex.

Benzyl Magnesium Chloride Complex

Benzyl chloride (126.6 grams (1 mole)) was dissolved in the tetrahydrofuran. The reaction started at 73° C and was maintained between 77° C and 80° C. The reaction was completed in 1 hour and 16 minutes. The yield of benzyl magnesium chloride complex as titrated was 49%; magnesium consumed, 69.2%

Benzyl Methyl Ketone (P-2-P)

To benzylmagnesium chloride (one mole) in tetrahydrofuran is added one mole of acetonitrile. The mix is heated at reflux and stirred for one hour and then hydrolyzed hot in 350 mL. of dilute hydrochloric acid (150 mL. water + 200 mL. concentrated hydrochloric acid) to yield, after separation of layers and distillation, benzyl methyl ketone.

Phenylacetic Acid, Dibenzyl Ketone, Tribenzylcarbinol

Dry carbon dioxide gas is bubbled slowly under the surface of a cooled tetrahydrofuran solution of one mole of benzylmagnesium chloride complex until a negative Gilman Schultze color test results. The mixture is then heated to reflux, the addition of carbon dioxide is discontinued, and a further one mole of benzylmagnesium chloride complex is added rapidly (over a period of 20-40 minutes). After completion of addition, the mix is refluxed for 2-4 hours, cooled, and 100-200 mL. of toluene added. The organic solution and suspension is extracted by one 100-mL. portion of water and one 100-mL. portion of 10% sodium carbonate. On acidification of the aqueous extracts, phenylacetic acid is obtained. The organic layer is subjected to distillation to remove solvents and then to vacuum distillation. Dibenzyl ketone and a small amount of tribenzyl carbinol are obtained.

Source: Ramsden 1959

Preparation of 1-Phenyl-2-propanone

by Alfred G. Susie Boston, Massachusetts
and Henry B. Hass La Fayette, Indiana
November 15, 1939

The arylnitroalkenes may be produced by the condensation of aromatic aldehydes and nitroparaffins (Knoevenagel and Walter, Ber. vol. 37, p. 4502 (1904); Worrall, *Jour. Am. Chem. Soc* vol. 56, p. 1556 (1934); Alles, *Jour. Am. Chem Soc.* vol. 54, p. 271 (1932)). Compounds of this type are desirably reduced to form amino compounds and more or less successful reductions have been obtained in the case of compounds such as *omega*-nitrostyrene, obtained by the condensation of nitromethane with an aromatic aldehyde. However, in the case of nitroalkenes of the type; it has been found to be extremely difficult to effect satisfactory reduction. For example, "Benzedrine" (1-phenyl-2-aminopropane) may theoretically be obtained by the reduction of 1-phenyl-2-nitropropene, but in practice it has been found to be almost impossible to effect the desired reaction. Relatively low yields of "Benzedrine" have been secured by electrolytic reduction of the nitropropene but catalytic hydrogenation appears to yield only high molecular weight polymerization products.

We have now discovered that arylnitroalkenes of the type may be successfully reduced to arylalkanones or arylalkanone oximes by a single stage reduction by means of iron, and can be reduced to amino compounds of the "Benzedrine" type in a two-stage reduction in which the initially obtained oxime is further reduced. One advantage of our process is the fact that the initial reduction may be controlled to yield either predominantly the ketone compound or predominantly the oxime, depending upon the reduction conditions. Other advantages, of our process will be evident from the following description.

The initial reduction of our process is effected in aqueous solution in the presence of sufficient finely divided iron to effect the reduction of all of the nitroalkene. An acid need not be employed in conjunction with the iron, but if employed, the concentration of the acid will affect the nature of the reduction process. With no acid or only low concentrations of acid, the re-action product is predominantly the oxime, whereas in the presence of relatively high concentrations of acid the reaction product is predominantly the ketone.

An amount of iron equal to at least 1.5 mol per mol of nitroalkene is required, and the amount required by one of the equations is 3 mols per mol of nitroalkene. At least the lower limit of 1.5 mol of iron should be employed to effect satisfactory reduction, and we prefer, in general, to use more than 3 mols of iron per mol of nitroalkene. An excess of iron is not harmful and it serves to insure as complete reduction as possible.

It may also be seen from the above equations that at least 1 mol of water is required per mol of nitroalkene in order to secure reduction to the oxime. We prefer, however, to utilize a considerable excess of water in order to obtain a mixture which can be satisfactorily handled, and agitated during the reaction. Other solvents can be employed in conjunction with water if desired, but these should preferably be miscible with water in order to maintain a single liquid phase and thus facilitate the reduction. The use of an organic solvent in conjunction with water may be an advantage in controlling the type of reduction product secured. Thus, if it is desired to obtain the oxime rather than the ketone, the use of an aliphatic alcohol in conjunction with water will tend to increase the ratio of oxime to ketone in the products.

Although the reduction to the oxime may be effected in the absence of any acid, we prefer to employ an acid in conjunction with the iron for reduction either to the oxime or to the ketone. Any acid may be utilized for this purpose. and the term acid in this connection is to be construed as a material yielding hydrogen ions. In general, however, we prefer to employ a mineral acid such as hydrochloric acid or a relatively strong organic acid such as acetic acid. The concentration of acid employed will depend upon the nature of the product desired. If it is desired to produce predominantly the oxime, an acid concentration not substantially higher than 0.06 mol of hydrochloric acid per mol of nitro-olefin should be employed, or the equivalent amount of another acid, as for example, 0.03 mol of sulfuric acid. Increasing concentration of acid will produce an increase in the ratio of ketone to oxime in the reduction product. Approximately 2 mols of hydrochloric acid per mol of nitro-olefin will produce almost entirely the ketone with only a trace of the oxime or none at all. Intermediate concentrations of acid can of course be employed if it is desired to produce intermediate ratios of the two products. When employing no acid in conjunction with the iron it is desirable to employ a small amount of an iron salt as a catalyst, for example, ferric chloride. When acid is used in conjunction with the iron, on the other hand, no such catalyst is required since the initial reaction of acid with the iron in the process will produce some of the necessary catalytic material. The use of a catalyst in connection with acid will, however, eliminate the short induction period required for the formation of a salt by the action of acid on the iron, and for this reason it may be advantageous to employ a catalyst in addition to acid, especially for large scale operations. The amount of catalyst to be employed is not critical, amounts ranging from 0.01 mol to 0.10 mol per mol of nitroalkene being generally satisfactory.

The reduction of nitroalkenes to ketones and oximes may be further illustrated by the following specific example:

Example 1

1-phenyl-2-nitropropene was dissolved in water, organic solvent or aqueous organic solvent. Forty mesh iron filings were added and in some cases acid and/or ferric chloride was incorporated into the mixture. The molar quantities of solvent, iron, acid, and catalyst, per mol of 1-phenyl-2-nitropropene, for the various reductions are shown in the table below. In each case the mixture was agitated for a period of approximately 5-1/2 hours in a vessel equipped with a reflux condenser. At the conclusion of this period, the mixture was made alkaline with sodium hydroxide solution and steam distilled. The products were recovered from the steam distillate, dried, and carefully fractionated in a rectifying column to determine the yield of phenylpropanone and of the oxime of phenylpropanone.

Nitroolefin:	Medium	Acid	Amine Yield	Ketone Yield
1-Phenyl-2-nitro-1-butene:	benzene, water	acetic	11.2%	55.0%
1-(*p*-Methoxy-phenyl)-2-nitro-propene:	water	acetic	15.0%	56.6%
1-Phenyl-2-nitro-1-propene (PNP):	water	tartaric	12.7%	59.6%

Run	PNP	Sovent	Acid	Amine Yield	Ketone Yield	Yield
5	100 g.	benzene, 600 cc.	acetic anhydride, 125 g	30.9%	53.3%	84.2%
10	200 g.	water, 600 cc.	formic, 75 g	17.5%	72.0%	79.5%

Source: Susie 1941

Phenyl-2-propanones from ß-Methyl-ß-Nitrostyrenes

by, Thornton W. Sargent, III, Alexander T. Shulgin
and Chester A. Mathis
California, USA May 9, 1985

2,4-Dimethoxybenzylmethyl ketone

A solution of 22 g of the above nitrostyrene in 200 mL. warm glacial acetic acid was added to a suspension of 50 g of electrolytic iron dust in 200 mL. glacial acetic acid. The mixture was heated on a steam bath until reaction commenced as evidenced by copious bubbling and frothing. The resulting paste was maintained on the steam bath for 2 hours after addition of an additional 100 mL. of glacial acetic acid. The dark grey reaction mixture was quenched by the addition of 3 L water and the unreacted Fe removed by suction filtration. The filtered solids were washed with 100 mL. CH2Cl2, the filtrate extracted with 3 x 150 mL. CH2Cl2, the pooled organic extracts washed with 100 mL. 5% NaOH and the solvent stripped in vacuo to yield 21.3 g of a pale straw-colored oil. The oil was distilled (125°-145° C./0.4 mm) yielding 12.7 g of the title ketone as a clear, colorless oil.

In the same manner, the 3,5-dimethoxybenzylmethyl ketone (colorless oil) may be prepared.

2,6-Dimethoxybenzylmethyl ketone

A solution of 11.5 g of 2,6-dimethoxy-ß-methyl-ß-nitrostyrene in 80 mL. warm acetic acid was added to a suspension of 35 g electrolytic iron dust in 150 mL. acetic acid. The mixture was heated on the steam bath until a vigorous reaction set in. The resulting paste was thinned with another 40 mL. acetic acid, and heating was maintained for an hour. The reaction was quenched in 1.5 L water with stirring, decanted from unreacted Fe, and extracted with three times 100 mL. CH2Cl2. The pooled extracts were washed with 50 mL. 5% NaOH, and the solvent was removed in vacuo to yield 10.5 g of a pale amber oil. This was distilled (95°-105° C./0.4 mm) yielding 8.7 g of the title ketone as a colorless oil. Source: Sargent 1987

Preparation of Phenyl-2-Propanones from Phenyl-nitropropenes

by John B. Tindall
Terre Haute, Indiana June 20, 1945

A mixture of 200 parts of 1-phenyl-2-nitro-1-propene, 600 parts of water and 2 parts of 5% palladium on charcoal was placed in a pressure vessel. The vessel was closed and hydrogen was passed in at a temperature between 28 and 36° C. at about 500 lbs./sq. inch pressure until hydrogen absorption substantially ceased. The hydrogenation was discontinued, the catalyst filtered out and to the filtered product (water and oil) was added to a solution of 59 parts of sodium hydroxide in 500 parts of water. The mixture was agitated and heated to 65° C. at which point most of the oil went into solution. There was some undissolved oil. The mixture was added with agitation to a solution of 185 parts of concentrated sulfuric acid in 1180 parts of water at 0-5° C. The reaction mixture was then distilled until oil stopped coming over. There were 2 parts of tarry material left in the residue. The oil layer of the distillate was fractionated to obtain 140.4 parts of phenylacetone boiling at 106-110° (19 mm.) corresponding to a yield of 85.3%.

Phenyl-butanone from 1-Phenyl-2-nitro-1-butene

A mixture of 181.2 parts of 1-phenyl-2-nitro-1-butene, 600 parts of water and 2 parts of 5% palladium on charcoal were placed in a pressure vessel. The vessel was closed and hydrogen was passed in at a temperature between 28 and 36° C. at about 500 lbs./sq. inch pressure until hydrogen absorption substantially ceased. The hydrogenation was discontinued, the catalyst filtered out and to the remainder was added a solution of 48 parts of sodium hydroxide in 300 parts of water. The mixture was heated to 80° C. with agitation, cooled and run into a solution of 150 parts of concentrated sulfuric acid in 960 parts of water at 5° C. The mixture was distilled through a column and 94.5 parts of phenyl-butanone (benzyl ethyl ketone) was recovered, corresponding to a yield of 62%. The ketone product had a refractive index nD20 of 1.513, a specific gravity at 20°/20° C. of 0.991, a purity of 98.3%, and a boiling point at 18 mm. of 114-117° C. Source: Tindall 1947

Sassafras
Sassafras
variifolium

Sassafras: Chapter 7

(*Sassafras officinale*; *Sassafras sassafras*)

by F. Schuyler Mathews

Sassafras may be identified at once by its strongly aromatic taste; not only the root, bark, and twigs, but also the leaves, have a pungent flavor, reminding one of a certain kind of old-fashioned sugar candy. A decoction of the root and bark also contributes largely to the making of root beer. The tree, according to Gray, attains an altitude of 125 feet, and Prof. Apgar records its height as 100 feet.

(*Vide Trees of the Northern United States*, Austin C. Apgar; but in Silva of North America Prof. Sargent places the maximum height at 90 feet.)

This is a surprise to many of us, who possibly have never seen a specimen which exceeded 40 feet. I have frequently found sassafras in the vicinity of Lake Mahopac, Putnam County, N. Y., 10 or 15 feet high, and occasionally in New Jersey, perhaps 25 feet high; in the South, however, it commonly grows to a height of from 50 to 60 feet. Sassafras is found throughout the North and West, from eastern Massachusetts to Iowa, Kansas, and Indian Territory; southward it extends as far as central Florida, and from there to Texas.

Although all parts of the tree are aromatic, (The leaves furnish the flavoring used in gumbo soup.) it will be found that the bark of the roots is bitingly strong, and from this the oil of sassafras is distilled; it is mostly made in Pennsylvania and Virginia. The bark of a young tree is a warm, buffish gray streaked with green; the twigs are shiny yellowish green. The fruit, which is ripe in September, is small, oval, one-seeded, bluish, and has a reddish, rather fleshy, club-shaped stem. The flowers are inconspicuous, greenish yellow, and appear in early spring with the developing leaves. I have never found the sassafras in the White Mountains (N.H.) nor in any part of the country immediately south of them. There are two beautiful little trees, perhaps 12 feet high, in the Arnold Arboretum, of quite symmetrical proportions. On the 21st of October, 1895, I noticed that these trees had scarcely shed a dozen leaves apiece; but three days later (a heavy frost had intervened) not one leaf was left on either tree. The foliage of the sassafras, more than that of any other tree except the horse-chestnut, is conventional to a fault. One is impressed with the similarity between the leafage in an old print of Bewick's that of the sassafras; both are regular and decorative.

In Milton, Mass., there is a tree measuring over 40 feet in height, and in Manchester, Mass., near the center of the town, is another quite as high. Source: Mathews 1905

Sassafras Tree (*Sassafras varifolium*)

by F. Schuyler Mathews

The Sassafras is common in rich woodlands from southern Me. (Wells and North Berwick) southern N.H. and Bellows Falls, Vt., west to southern Ont. central Mich. eastern Ia. eastern Kan. and Okla., and south from southern N.E. to Fla. and the Brazos River, Tex. It is absent in the northerly and scarcely common in the more southerly portions of N.E. In N. Y. it is common and is named "Wah-eh-nak-kas," Smelling Stick, by the Onondaga Indians. It reaches its finest development in southwestern Ark. and Okla. In N.C. it rarely exceeds a height of 50 feet and is most common on the coastal plain and the Piedmont plateau; in Va. it ascends to 3000 feet in the mountains. The wood is light, soft, weak, brittle and coarse-grained, and is slightly aromatic. It is dull orange brown and is largely used in boat-building, cooperage, and fencing, the weight is 31 lbs. to the cubic foot. A strongly aromatic oil is distilled from the bark, twigs, and roots. Source: Mathews 1915

Sassafras

by Julia E. Rogers

The glory of the autumn foliage of the sassafras is like the glory of a sunset—all mingled with purple and red and gold. The three forms of leaves that fascinated us in summer time are here yet, but the shining treetop is the unit now, and we do not look for individual leaves.

The wood of sassafras is light and tough, and makes good fishing rods. Durable in the soil and in water, it is used for posts and rails, and for boats and barrels. The bark, especially of the roots, is strong in a volatile oil used to flavour medicines. The bark itself is sold in drug stores, and people buy it in spring and make sassafras tea "to clear the blood." The leaves and twigs yield a mucilaginous substance which is used in the South to give flavour and consistency to gumbo soups. The useful properties of its various members are as nothing when compared with the beauty and desirability of the living tree, which is beautiful throughout the year—as a towering tree or a roadside sapling.

Source: Rogers 1923

The Sassafras

by Julia Ellen Rogers

The sole remnant of an ancient genus is the aromatic sassafras familiar as a roadside tree that flames in autumn with the star gum and the swamp maples. In the deep woods it reaches a height of more than a hundred feet and is an important lumber tree. In the arctic regions and in the rocky strata of our western mountains, fossil leaves of sassafras are preserved, and the same traces are found in Europe, giving to the geologist proofs that the genus once had a much wider range than now. But no living representative of the genus was known outside of eastern North America, until the report of a recently discovered sassafras in China.

The Indians in Florida named the sassafras to the inquiring colonists who came with Columbus. They explained its curative properties, and its reputation traveled up the Atlantic seaboard. The first cargo of home products shipped by the colonists back to England from Massachusetts contained a large consignment of sassafras roots. Today we look for an exhibit of sassafras bark in drug-store windows in spring. People buy it and make sassafras tea which they drink "to clear the blood." "In the Southwestern states the dried leaves are much used as an ingredient in soups, for which they are well adapted by the abundance of mucilage they contain. For this purpose the mature green leaves are dried, powdered (the stringy portions being separated), sifted and preserved for use. This preparation mixed with soups gives them a ropy consistence and a peculiar flavor, much relished by those accustomed to it. To such soups are given the names gombo file and gombo zab." (Selon.)

Emerson says that in New England a decoction of sassafras bark gave to the housewife's homespun woolen cloth a permanent orange dye.

Sassafras wood is dull orange-yellow, soft, weak, light, brittle, and coarse-grained, but it is amazingly durable in contact with the soil, as the pioneers learned when they used it to make posts and fence rails. It is largely also in cooperage, and in the building of light boats. Oil of sassafras distilled from the bark of the roots is used for perfuming soaps and flavoring medicines.

With all its practical uses listed above, we must all have learned to know the tree if it grows in our neighborhood, and if we observe it closely, month by month throughout the year, we shall all agree that its beauty justifies its selection for planting in our home grounds, and surpasses all its medicinal and other commercial offerings to the world.

In winter the sassafras tree is most picturesque by reason of the short, stout, twisted branches that spread almost at right angles from the central shaft, and form a narrow, usually flat, often unsymmetrical head. The bark is rough, reddish brown, deeply and irregularly divided into broad scaly plates or ridges. The branches end in slim, pale yellow-green twigs that are set with pointed, bright green buds, giving the tree an appearance of being thoroughly alive while others, bare of leaves, look dead in winter.

What country boy or girl has not lingered on the way home from school to nibble the dainty green buds of the sassafras, or to dig at the roots with his jack-knife for a sliver of aromatic bark?

Source: Rogers 1926 Ref.: Grahm 1973

Safrole and Sassfras Oil are Used in the Illicit Manufacture of MDMA

The Drug Enforcement Administration (DEA) and state/local law enforcement authorities throughout the United States have noted an alarming trend involving illicit MDMA production. MDMA (Ecstasy) is a major drug problem in the United States. All businesses engaged in the sale of safrole and essential oils rich in safrole, such as, sassafras oil, "brown" camphor oil or camphor oil 1.070, also referred to as Chinese sassafras oil, should be aware of the use of these products by clandestine MDMA laboratory operators.

Criminal elements routinely use these List I chemicals in the illicit production of MDMA. DEA is aware that these criminals are searching, often over the Internet, for sources of supply for these List I chemicals.

This notice is being provided to:

Make you aware that safrole and essential oils rich in safrole, such as sassafras oil, and brown camphor oil or camphor oil 1.070, are List I chemicals;

Remind all distributors of these products that they must be registered with DEA, obtain identifying information from their customers, keep records, report suspicious orders to DEA, and "know their customer," to avoid unwittingly becoming a supplier to a clandestine MDMA laboratory;

Advise all distributors of these List I chemicals that it is unlawful for any person to possess or distribute a listed chemical knowing, or having reasonable cause to believe, that the listed chemical will be used to manufacture a controlled substance in violation of the Controlled Substances Act...21 U.S.C. 841(c)(2). Persons who violate 21 U.S.C. 841(c)(2) and/or the recordkeeping and reporting requirements are subject to criminal and/or civil penalties. Source: DEA 05/01/03

"Oil of sassafras [*Sassafras albidum*]. About 25,000 pounds produced annually in homemade stills "from Maine to Florida and in the hills of Kentucky and the rolling country of Ohio". The oil goes into root-beer, sarsaparilla, candies, chewing gums, mouthwashes, toothpastes, soaps and perfumes." Source: Fulling 1948

"In 1990, total world production of sassafras oil was perhaps 2,000 tons..." Source: Maia, J., G.; Green, C., L.; Milchard, M., J.; New Sources of Natual Safrole; Perfumer & Flavorist (1993) 18: 19-22

Safrol also occurs in (*Piper hispidinervum)* Rocha 1999

Safrol Containing Botanicals

by Horace Finnemore

Oil of *Asarum Arifolium*

The roots of this American plant, *Asarum arifolium*, Michx., yield from 7 to 7.5 per cent of oil. Miller (*Arch. der Pharm.* 1902, 240, 371) examined 750 grams of oil, having the following characters specific gravity 1.058 to 1.061, αD —2° 55' to 3° 7', n20D 1.5310 to 1.5318. By shaking out with alkali, eugenol (benzoyl eugenol, melting-point 69-70°) in the proportion of 0 5 per cent was extracted, with a second phenol that gave a green colour with ferric chloride (4). *l*-Pinene (nitrolpiperidide, melting-point 119°) was identified.

The dephenolised oil was fractionated under 22-23 mm. and six fractions obtained: 55-105°, 105-125°, 125-130°, 130-135°, 135-140°, 140-170°.

Safrole (oxidation to the corresponding acids) appeared to be the chief constituent; methyl eugenol was also present, and a small quantity of methyl iso-eugenol. Fraction 130-145° was optically active, and showed evidence of the presence of a sesquiterpene, whilst the highest fraction solidified on cooling, and proved to be asarone, melting point 62-63°.

Oil of *Asarum Blumei*, Duch.

The entire plant of the Chinese drug "*Toko*" gave 14 per cent of oil, with a sassafras-like odour, specific gravity 1.0788, [a]D +5° 3', saponification value 0. A terpene-like body, eugenol, and safrole were detected.

Oil of Japanese Anise

The oil distilled from the leaves and poisonous fruit of *Illimum religiosum*, Sieb., the Japanese star anise, was found by Eykman (*Rec. Trav. Chim.* 4, 32-54 via *J. Chem. Soc.* 1886, A. i, 95) to contain a terpene termed "*shikimene*," eugenol and "*shikimol*," now known as safrole.

Tardy (*Bull. Soc. Chim.* 1902, (3) 27, 987) has examined an oil extracted from the fruit with petroleum ether and distilled in vacuo; this contained a small amount of eugenol, cineole and safrole, with some sesquiterpenes and probably borneol. A small quantity of anisic acid was obtained by oxidation of the fractions boiling from 220-230°, so that the presence of anethole or its isomer, methyl chavicol, was indicated.

An oil from the fruit has been examined by Schimmel & Co. (*Report*, April 1909, 57); at—18° separation of safrole took place; on fractionation at 3 5 mm. pressure the oil distilled as follows: below 40°, 21.6 per cent; 40-65°, 8.0 per cent; 65-79°, 17.2 per cent; 79-83°, 32.0 per cent; 83-90°, 4.6 per cent; residue, 16.6 per cent. The first fraction of the oil contained cineole, as shown by the formation of the resorcinol compound; the second appeared to contain linalol, but this was not identified. Fractions 4 and 5 contained safrole, which was thought to be the chief constituent of the oil.

Oil of Australian Sassafras

Atherosperma moschatum, Labill., the Australian sassafras, is a native of Victoria, growing luxuriantly in mountain gullies around Warburton and Healesville. (Scott, *J.Chem.Soc.* 1912, 101, 1612) The leaves yield from 17 to 2.65 per cent of oil, the first portions of which were lighter, the later heavier than water. Three litres of oil were examined, specific gravity 1.027, [α]D +7 5°, nD 1.5211. Sixteen fractions of oil were obtained by distillation under reduced pressure, their densities ranging from 0.881 to 1.034. Pinene was obtained from the fraction boiling from 157-158° and identified by the melting-points of its hydrochloride and nitrosochloride. Camphor was detected in subsequent fractions, but the largest portion of the oil was found to consist of eugenol methyl ether, identified by means of its bromo-derivative, melting about 75°. Safrole was identified in the highest boiling fractions of the oil.

The approximate composition of the oil is: eugenol methyl ether, 50-60 per cent; pinene, 15-20 per cent; camphor, 15-20 per cent, safrole, 5-10 per cent.

Oil of *Daphnandra Aromatica*

The bark gave (Jones and Smith, *Proc. Roy. Soc. Queensland*, 1923, 35, 61-2, via *P.E.O.R.*, 1925, 16,179) 0.3 per cent of a dark amber-coloured oil with the odour of sassafras, specific gravity at 15°/15, 1.077, optical rotation—1 9°, refractive index 1.525. When 150 c.c. were fractionated at 130 mm. pressure, the following fractions were obtained: 70-80°, 4 c.c.; 80-128°, 4 c.c.; 129-130°, 140 c.c. The oil consisted chiefly of safrole (95 per cent).

The air-dried leaves gave about 0.5 per cent of a light yellow oil, specific gravity at 15°/15, 0.9181, optical rotation +337°, refractive index 1.489, ester value 20, acetyl value 3.5. This oil contained 5 to 10 per cent of *d*-pinene, 20 to 25 per cent of *d*-α-phellandrene, 10 to 15 per cent of cineole, sesquiterpenes 30 to 40 per cent, sesquiterpene alcohols 5 to 10 per with traces of aldehydes, phenols and esters.

Oil of Camphor

Camphor oil is distilled from all parts of the camphor tree, *Cinnamomum camphora*, Nees and Eberm., known as the "King of the Forest," a handsome evergreen tree with laurel-like leaves which occurs naturally from Cochin China to Shanghai and from the Island of Hainan to Southern Japan; i.e. between 10° and 34° North Latitude in tropical, to subtropical regions having a moist climate. It has been cultivated in India, Burma, Ceylon, the Malay Archipelago, Java, Australia, East and South Africa, Italy, Algiers, Florida, California, Brazil, the West Indies and Mauritius. The camphor tree grows to a height of 60 to 100 feet with wide spreading branches and a trunk 20 to 40 inches in diameter, attaining sometimes as much as 25 feet or more in circumference. A tree of average thickness will supply a native still for two years.

Brown camphor oil, representing the higher-boiling fractions of the crude camphor oil, has specific gravity 1.018 to 1.026, and contains from 25 to 35 per cent of safrole, of which it forms the chief commercial source, and which may be obtained from it by fractionation and freezing the appropriate fractions. Its value as a source of safrole varies directly with its specific gravity. It is also used as a cheap soap perfume.

"Sassafrassy" camphor oil is sometimes found in commerce; it is a fractionated oil the value of which depends on the amount of safrole it contains, and this is indicated by its specific gravity.

Another fractionated camphor oil having specific gravity about 1.070 is sold as "artificial sassafras oil." It contains about 80 per cent of safrole and is used as a substitute for sassafras oil.

Other fractions of intermediate specific gravity are supplied by the safrole manufacturers.

Chinese camphor oil occasionally comes into the market; it resembles an intermediate fraction of the Japanese oil but contains little, if any, safrole.

Cinnamomum cecicodaphne

Cinnamomum cecicodaptne, Meissn., is a tree growing in Assam and Darjeeling which yields the wood known as Nepal camphor wood or Nepal sassafras. This was formerly known as *C. glanduliferum*, which name, however, is now restricted to the camphor wood or sassafras tree of Northern India. The wood is used in Assam for boat-building and box-making; it is durable, easily worked, and not attacked by insects. Its odour is safrole-like. Pickles (2) examined the oil obtained from 105 lb. of Assam wood, and obtained a yield of 2.95 per cent on the original material, or 4.16 per cent on the wood after grinding. The oil was pale yellow with an odour of safrole and anise, and had the following characters: specific gravity at 15°, 1.103, α20D—0° 4′, saponification value 2.8, ditto after acetylation 7.0, methoxyl content 16 per cent; soluble in one-half its volume of 90 per cent alcohol and in 5 or more of 80 per cent.

This oil is of interest, as it contains neither terpenes nor aldehydes, and only a very small quantity of acids, alcohols and esters; it consists almost entirely of ethers, of which safrole, myristicin and elemicin were identified. The oil distilled almost entirely between 245-280°, and on redistillation of the lower fractions some considerable portion boiled between 233-240°. After the removal of the safrole by fractionation and freezing...

Cinnamomum mercadoi

Cinnamomum mercadoi, Vid., is a large tree called Calingag, very widely distributed throughout the Philippine Islands, (*Phil. J. of Sci.* 1909, 4A,114) in places as many as 150 to the hectare. Twenty-five kilos of bark distilled with steam gave 260 grams of oil (1.04 per cent), specific gravity at 30°/4, 1.0462, n30D° 1.5270, a30D° +4°. The oil contains no aldehydes, it distills between 119 and 130°/10 mm., and consists largely of safrole (piperonylic acid).

Cinnamomum oliveri

Cinnamomum oliveri, Bail, or the Brisbane sassafras, is a handsome tree, with grey, rough bark, growing in the scrubs on the North Coast Railway, Queensland.

Bark Oil.—Hargreaves (*J.Chem.Soc.* 1916, 109,751) found that when distilled in steam 71 kilos of bark gave 1,700 grams of oil, or 2.4 per cent, with specific gravity 1.030, n23D 1.5165. When fractionally distilled at 30 mm. pressure 1,300 grams gave the following four main fractions: below 90°, 98 grams; 90-120°, 291 grams; 120-135°, 326 grams; 135-155°, 533 grams.

The composition of the oil was as follows: pinene, 12 per cent (nitrosochloride, melting at 108°); camphor, 18 to 20 per cent (oxime melted at 119°); safrole, 25 per cent, melting at 8°, specific gravity at 18°, 109, n20D 1.535 (a-nitrosite, melting at 129-130°); eugenyl methyl ether, 40 to 45 per cent, boiling at 244°, n27D 1.5305, proved by its oxidation to veratric acid and by the formation of the tribromo derivative, melting at 77-78°.

Cinnamomum parthenoxylon

From 15.8 kilos of the wood of *Cinnamomum parthenoxylon*, Meissn., the Martaban camphor wood, known in Java as Selasian wood, 124 c.c. of oil were obtained. (*Schimmel's Report*, April 1911, 43). It consists chiefly of safrole, and has the following characters: specific gravity 1080, aD +1° 22', n22D 1.532; soluble in 2.6 volumes of 90 per cent alcohol.

Oil from the wood of *Cinnamomum parthenoxylon*, Meissn., from the Federated Malay States, where it grows as a tall tree, has recently been examined at the Imperial Institute. (*Bull. Imp. Inst.* 1925, 23, 421) Its constants were as follows: specific gravity 1.103, αD 0, nD 1.538, ester value 0.8, ditto after acetylation 3.5, congealing point +10°. The oil consisted almost entirely of safrole.

Cinnamomum pedunculatum

Cinnamomum pedunculatum, Nees., is widely distributed in the southern islands of Japan, where it is known as "Yabunikkei."

The fresh leaves yield 0.7 to 1 per cent of oil with the odour of camphor. Shinosaki (Chem. Abs. 1916,10, 370, via P.E.O.R. 1916, 7, 64) found that it contained 9 per cent of hydrocarbons and cineole; 3 per cent of eugenol; 60 per cent of safrole, and 28 per cent of other oxygenated bodies; isoeugenol is said to be present in some samples. This oil had the following constants: specific gravity 1.060, α20D +175°, acid value 0, ester value 5.6, ditto after acetylation 25.25.

Oil of Sassafras

Oil of sassafras is obtained from the root of *Sassafras officinale*, Nees et Eberm., a tree which grows in Virginia to a height of 20 to 30 feet, in Carolina to 100 feet. Although this tree is widely distributed in the eastern part of the United States, its distillation is mostly confined to Carrol Country, Tennessee. The supply is said to be exhausted throughout large areas, but sufficient remains to meet future demands,provided the price available will cover the cost of collection and distillation.

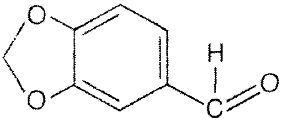
The roots when freshly dug yield about 1 per cent of oil. The root bark is richest, (*Oil, Paint and Drug Report*, 1913, 83, No. 24, 34) containing 6 to 9 per cent. Power and Kleber (*Pharm. Rev.* 1896,14,101) obtained 7.4 per cent from the air-dried root bark. Enormous roots, weighing up to 10 cwt., are cut into chips and distilled in steam in stills of a capacity of 10 tons. Much oil is distilled in a crude way, and the heavier fractions of the oil are sometimes not completely extracted.

The annual consumption of this oil amounts to 90,000 lb., three-fourths of which is used in the United States.

The chief constituent of sassafras oil is safrole, which, when pure, melts at 11°, specific gravity at 15°, 1.1056, to the presence of which the oil owes its high specific gravity and characteristic smell. The latter is agreeably modified, however, by other constituents which give the oil an odour differing appreciably from that possessed by safrole.

Safrole was first observed in the oil by Grimaux and Ruotte, (*Compt. rend.* 1869, 68, 928) but our present knowledge of the other constituents is due to the work of Power and Kleber, (*Pharm. Rev.* 1896,14,101) who examined the oil from the dried bark. From 3,000 grams of oil, with specific gravity 1.075, αD +3° 16°/100 mm., they obtained by freezing 78 per cent of safrole; the residual oil from this was then treated with a 2 per cent caustic soda solution, when 15 grams of a phenol were obtained, and identified as eugenol. The residue was separated by fractionation into several portions. That boiling from 155-165° was identified as a-pinene, by conversion into the nitrosochloride, thence into the benzyl nitrolamine; fractions boiling from 160-170° contained phellandrene, which was identified by its nitrite. That boiling from 170-175° was tested for cineole and for dipentene, but these bodies were not present. Camphor was obtained from the higher fraction, and was identified by reduction to borneol and by conversion into the oxime. A small proportion of cadinene was suspected in the higher fractions. These authors give the approximate composition of the oil as follows: safrole, 80 per cent; pinene and phellandrene, 10 per cent; *d*-camphor, 6.8 per cent; eugenol, 0.5 per cent; cadinene and other constituents, 3 per cent.

Safrole is largely used for the manufacture of heliotropin; it is the methylene ether of allyl benzene, and is readily isomerised to iso-safrole, which, when oxidised by means of potassium bichromate, gives the corresponding aldehyde, piperonal. The latter has the odour of the heliotrope, and is called heliotropin.



Piperonal

Oil of sassafras is employed as a soap perfume and for tooth pastes. It is also used as a parasiticide, but in this connection it is not without danger, for it has been recorded that a dog treated with the oil for lice died after a week's treatment. When taken internally and absorbed, it exerts a poisonous effect on the liver, kidneys and heart.

Genuine oil of sassafras has the following characters: specific gravity 1.070 to 1.080, αD + 2 to + 5°, nD 1.5280 to 1.5290, acid value 0 to 1, ester value 1 to 2; solubility in 90 per cent alcohol 1 in 2.

Sassafras oil is liable to adulteration with camphor oil of approximately the same gravity and safrole content. In order to detect this adulterant (*J. Amer. Pharm, Assoc*, 1920, 9,1065) advantage is taken of the fact that, so far as is known, the only phenol present in sassafras oil is eugenol, whilst in camphor oil the chief phenol appears to be carvacrol, associated with only a small amount of eugenol, and some ethyl guaiacol. Grant has suggested using the difference in the shade obtained with the phenols and diazotised *para*-nitraniline. A purple-red tint is given by sassafras phenols, whilst camphor oil phenols give an orange-red colour. Pure nitraniline is necessary, and the details require further study, but with attention to these, the process should be capable of application, although it is one that could readily be circumvented.

Artificial sassafras. - For industrial purposes safrole is obtained in large quantities from the cheaper camphor oil, and a fractionated camphor oil, having a specific gravity approximating to that of sassafras oil, is sold as artificial sassafras oil, and is used as a cheap substitute. Commercial samples of artificial sassafras oil have usually a specific gravity not lower than 1.070 and contain about 80 per cent of safrole, but samples are on the market having a specific gravity of 1.020, containing not more than 20-25 per cent of safrole.

It is of interest to note how these differ from the constituents contained in the root bark; neither the leaf oil of sassafras nor that of the closely allied camphor tree contains safrole, although the leaves of the allied New South Wales sassafras contain from 30 to 60 per cent. (See below.)

Oil of *Doryphora* Sassafras (The New South Wales Sassafras)

The leaves of *Doryphora* Sassafras, Endlicher, the sassafras tree of New South Wales, which grows to a height of 50 to 80 feet, yield from 0.1 to 0.85 per cent of oil when distilled respectively in May and November, and the oil was found to vary composition according to the district. Leaves (1,225 lb.) from the Monga district gave an oil with the following constants: specific gravity 1.01 to 1.02, nD 1.506 to 1.509, aD +16.2 to +22.2°, ester value 4.6, acetyl value 32.9; solubility in 70 per cent alcohol, 1 in 8 volumes.

When fractionated the following were obtained: 175-210°, 12 per cent; 210-223°, 22 per cent; 223-235°, 50 per cent; 235-250°, 12 per cent; 250-265°, 3 per cent.

d-α-Pinene was present, as when mixed with *l*-pinene an excellent yield of the nitrosochloride (melting-point 109°) was obtained. The fractions boiling between 200 and 219°/762 mm. contained camphor (oxime, melting-point 118-119°). Safrole was obtained from the remaining fractions of the oil on cooling. About 10 per cent of sesquiterpenes and about 1 per cent of eugenol were present, and a trace of piperonal.

A sample from the Currowan district had specific gravity 0.9808, and contained only 30 per cent of safrole; 30 per cent of camphor was present and a small proportion of eugenyl methyl ether, which has not yet been separated from the admixed sesquiterpenes and alcoholic substances.

The approximate composition of these oils is as follows:

	Monga oils Per cent.	Currowan oil Per cent.
Safrole	60-65	30
Camphor	10-15	30
d-a-Pinene	10	10
Eugenol	1	3.5
Sesquiterpenes	10	
Sesquiterpenes and Eugenyl methyl ether		26

Penfold suggests that this oil New South Wales sassafras oil should be distinguished from the Australian variety, as the latter is obtained from *Atherosperma moschatum*, and contains only a small percentage of safrole. (*J and Proc. Roy. Soc. N.S.W.* 1921, 55, 270)

Oil of Massoi Bark

Oil of Massoi, from Papua, from *Cinnamomum massoia*, Schewe, was recently examined at the Imperial Institute. (*Bull. Imp. Inst* 1925, 28, 423) The tree occurs widely distributed in New Guinea all round the island from the Gulf of Papua to the Sepik river. At its largest it is a fine forest tree 60 feet high and 8 to 9 feet in circumference. Two samples of the bark gave oils having the odour of cloves and nutmeg with the following constants:

	No. 1.	No. 2.
Yield, per cont.	6	6.3
Specific gravity at 15°/15	1.060	1.064
Optical rotation	- 0.90°	- 0.34°
Refractive index	1534	1536
Phenols, per cent	60	79

Oil No. 2 freed from phenols had specific gravity 1.035, and then distilled from 175-240°, mostly between 225 and 230°, and consisted chiefly of safrole. This oil contained in addition to the eugenol, which forms all or nearly all of the phenols, safrole 14 per cent; other constituents, principally terpenes, 7 per cent.

Source: Finnemore 1926

Apiol Containing Botanicals: Chapter 8

by Horace Finnemore

Oil of Parsley

All parts of the parsley plant, *Carum petroseltnum*, Benth. et Hook., yield a volatile oil, but that from the leaf and root are not commercial articles. Parsley oil of commerce is invariably obtained from the fruit, which yields from 2 to 6 per cent.

Parsley is cultivated in all temperate climates, but the fruit comes into the market chiefly from Germany and France.

Oil of parsley, obtained by distillation of the fruit, is a yellowish or yellowish-green, thick liquid, specific gravity 1.017 to 1.100, optical rotation 5 to 10°, refractive index 1.488 to 1.507.

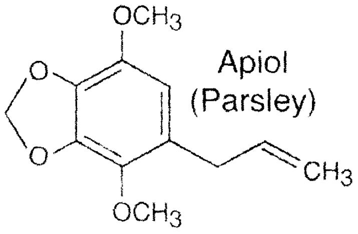
Chemistry

Parsley fruit contains a fairly large quantity of apiole with the corresponding glucoside, apiin. Apiole or parsley camphor is a methoxymyristicin, and is the 2: 5-dimethoxy-3: 4-methylene ether of 1-allyl benzene; it is a crystalline substance at ordinary temperatures, melting-point 30°, boiling point 294°/760 mm. and 179°/33 mm., specific gravity at 15°, 1.178. It is volatile in steam, and occurs in both the French and German oils, sometimes in the latter in such large quantities as to crystallise out at the ordinary temperature.

The difference between the French and German oils appears to be that whilst both contain a small amount of *l*-pinene, the French contains much myristicin, a small amount of apiole, and some 2-, 3-, 4-, 5-methoxy 1-allyl benzene. The German, so far as is known, contains none of the last-named, and only a little myristicin, but a large proportion of apiole. It is to be regretted that no examination has yet been made of the constituents of English fruit.

Parsley oil is used in medicine. Crystalline apiole, yellow and white apioles, and oil of parsley when given intravenously exert an equal degree of toxicity, the essential oil being the most regular in its action. (*Bull, Sci. Pharm*. 1910 17, 7, via *Y.B. of Pharm*. 1910, 207)

Besides the volatile oil, the other products of the fruit are as follows:



Apiole, or liquid apiole: this is a thick, green liquid prepared by extracting the fruit with ether and recovering the solvent. The residue is a liquid or semi-solid green mass, which contains an indefinite amount of fatty oil. After further purification its specific gravity varies from 1.095 to 1.107, and on cooling it may form a crystalline mass. A refined green apiole of commerce is prepared from this by removing the apiin and the fatty oil. Yellow apiole can be prepared from this by removing the fatty and waxy ingredients. Apiolin, or distilled apiole, is the name given to the product obtained by separating the last traces of fats and wax. Source: Finnemore 1926

Production of Parsley

by J. H. Beattie
Bureau of Plant Industry November 1937

Parsley, celery, celeriac, carrots, and parsnips are members of the same group of plants. Parsley has been known and used from time immemorial. Introduced into the United States during the early days of colonization, it has been grown to some extent as a home, market-garden, and truck-crop plant, but its culture has not attained great commercial importance. Market gardeners and truck-crop producers often plant a small area to meet the moderate demand that exists.

Two forms are available, the well-known foliage type, which is used for garnishing and for flavoring soups and stews, and the turnip-rooted sort, which is cooked and used like other root crops. Considerable quantities of rooted parsley are sold in eastern markets where there is a large foreign-born population.

Climatic Limitations

Parsley is a hardy crop that withstands considerable degrees of both heat and cold. In the South it is grown throughout the year except in midsummer, and in the North it is grown from early spring until late autumn, and in milder sections through the winter in cold frames. It is a biennial, and plants carried over winter go to seed early in the spring.

Soil Requirements

Parsley will thrive on almost any fertile, mellow soil. Because of the small size of the seeds and their slowness in germinating, it is especially desirable that the soil be free from any tendency to bake. Rich sandy loams and mucks and peats are desirable soils.

The use of manure and commercial fertilizer on land for parsley will nearly always cause increased yields. If the manure is well decomposed it may be applied broadcast during the final preparation of the soil. The fertilizer may also be broadcast before the seed is sown. A complete mixture, such as a 5-10-5 (1) combination, used at rates of 1,000 to 1,500 pounds per acre, supplemented by two or three 200-pound-per-acre side dressings of nitrate of soda or sulphate of ammonia, will usually give good results.

Percentages of nitrogen, phosphoric acid, and potash respectively.

Varieties

Two forms of foliage parsley are used—the moss or curled-leaved (fig. 1) and the plain-leaved. In quality they are alike, but the curled-leaved is more attractive, and it is grown to the practical exclusion of the other. Moss Curled, Double Curled, and Plain Leaved are well known varieties, The turnip-rooted form, of which Hamburg is the leading variety, is usually listed merely as turnip- or thick-rooted parsley.

Time of Planting

In the North, parsley may be seeded as soon as the ground can be worked in the spring. Earliness and surer results may be obtained by starting the plants indoors and transplanting them to the open ground. Plants should be started about midsummer for the fall crop and for the crop grown during the winter in cold frames.

In the South, parsley is grown mostly as a winter and spring crop. Seeding for the winter crop is usually done in the autumn, when soil conditions are favorable, as it is difficult to obtain good germination during the heat and drought of midsummer. For the spring crop, seedling may be done as early as the ground can be worked.

Methods of Culture

Parsley may be grown by hand culture in rows about 18 inches about, but for horse cultivation the rows should be spaced from 24 to 30 inches apart. On account of the smallness and delicacy of the plants while young, they are better adapted to hand culture.

The seed may be drilled with a hand seed drill, and it should be covered to a depth of not more than one-fourth of an inch. On land of heavy texture that is liable to bake, it is a good plan to cover the seeds with leaf mold, sand, or some other material that will not bake. By keeping the soil moistened, quicker germination may be obtained. The plants should be thinned to stand 6 or 8 inches apart in the rows. Methods used in handling the turnip-rooted type of parsley are practically the same as for the foliage form. The plants should be thinned to 3 to 4 inches apart in the row.

In the section around Norfolk and Portsmouth, Va., and in other sections having a mid winter climate large quantities of parsley are grown in sash-covered cold frames during the late fall, the winter, and early spring. These frames are later used for growing beets and cucumbers. In New Jersey and in southern New England, winter and early spring parsley is grown to some extent in cold frames, in pipe-heated beds, and in sash greenhouses. High class or expensive greenhouses are not required for growing parsley, and a temperature of 45° to 60° F. is all that is required.

Harvesting and Marketing

In harvesting parsley the outer and larger leaves are removed successively, and the plant continues to produce for several weeks. The leaves are tied in bunches and packed in suitable containers, such as hampers, baskets, and barrels. If parsley is packed for shipment or hauling any considerable distance, finely crushed or 'snow' ice is usually placed in the interior of the package. Certain markets require that the parsley be tied in bunches, while others prefer it packed loose, so that it can be made into the size of bunch required on that particular market.

United States standards have been established for parsley, and copies may be obtained by writing the U.S. Bureau of Agricultural Economics, at Washington, D.C.

Source: Beattie 1937

Oil of Dill

Dill oil is distilled from the fruit of *Anethum graveolens*, L., *Peucedanum graveolens*, Benth. et Hook. f., indigenous to Central and Southern Europe, extending from Spain to the Caucasus and Persia, and south to Egypt, Abyssinia, tropical and sub-tropical India; it is cultivated to a small extent in England, at Long Melford and Holbeach.

In Europe it is sown in autumn, in a warm position in light, well-drained soil, usually broadcast or in drills 6 to 12 inches apart. The young plants are thinned in the spring to about 10 inches apart. According to Holmes, in England it is sown in March.

Indian dill is grown as a cold weather crop, but this form has a longer fruit more narrowly winged, and is considered to be a distinct species, Peucedanum Sowa, Kurz, or Anethum Sowa, Roxb.

Japanese fruit from the same botanical source is also employed. As will be seen later, the oils from these fruits differ from that distilled from the European, and cannot be regarded as substitutes.

The yield of oils from fruit grown in different countries is as follows: English 4.0, German 3.8, Russian 4.0, Roumanian 3.5, Galician 3.5, East Indian 2.0 per cent.

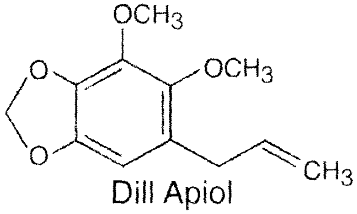
Chemistry

The chief constituent of dill oil is carvone (Gladstone, *J. Chem. Soc.* 1872, 25, 1), which is also the chief constituent of oil of caraway. There is, indeed, very little difference in the composition of these two oils; both owe their odour in the main to the presence of this ketone, but, in the case of caraway oil, traces of sweet-smelling substances are present which give to the oil a secondary strawberry-like odour.

The other constituent of dill oil is *d*-limonene, identical with that from lemon oil. Phellandrene is present in Spanish dill oil, but the samples examined were obtained from the whole herb. Small quantities are present in the German oil, but the nitrite reaction only gave positive results when applied to the lower fractions. It has been suggested that it is also present in English oil, and that its presence, in this case again, is due to the use of the whole herb. Phellandrene, however, is not an invariable constituent of English oil, although possibly present in the oil from imperfectly ripened fruit.

Nietzki, (*Arch. der Pharm*. 4, 1874 370) by fractionation, showed that this oil contains 10 per cent of a low-boiling hydrocarbon, $C10H16$ boiling at 155-160°, not yet identified.

Ciamician and Silber, (*Ber.* 1896, 29, 1799-1811) in 1896, isolated 30 per cent of an apiole from the heavy oil of East Indian fruit, and pointed out that this apiole differed from that of parsley. This substance has since been assigned the following formula:



Dill Apiol

A small quantity of a paraffin, melting-point 64°, was found in a German oil. (*Schimmel's Report*, April 1897, 15)

Oil distilled from the English or European fruits should have the following constants: specific gravity 0.900 to 0.920, optical rotation +70 to +80°, refractive index 1.483 to 1.490.

Oil of Samphire

Samphire oil is distilled from *Crithmum maritimum*, L., a plant growing in France, Italy and Sardinia.

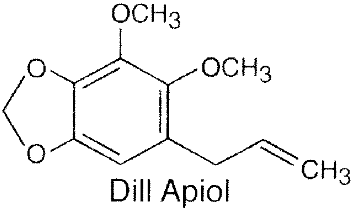
Francesconi and Sernagiotto (*Gazz.* 1912, 42, i, 185-93) have shown that the oil occurs in the assimilating tissues of the plant and is absent from the storage tissues.

On account of the dill-apiole it contains, of which it forms an abundant source, the oil has strong physiological action, although it is not so active as oil of parsley, which contains apiole. The yield of oil from this plant has been studied by Borde, (*Bull. Sci. Pharmacol.* 1909, 16, 132, via *Chem. Centrulbl.* 1909, 80, i, 1566) who collected the plants at different times with the following results:

	Early August		Late August.		September.	
	Leaves and Stems.	Fruit.	Leaves and Stems.	Fruit.	Leaves and Stems.	Fruit.
Yield	03	07	015	08	0154	07
Specific gravity at 4°	1.037	0.969	1.052	0.973	1049	0.966
αD	8° 15	5° 27'	7° 12'	6° 4'	6° 42'	6° 12'

The oil from the leaves has an aromatic, somewhat pungent odour and a deep yellow colour. It is interesting to note that it is heavier than that from the fruit, whereas, in the related oil of parsley the fruit oi contains the larger proportion of the heavy ingredients. The fruits especially when air-dried, gave a pleasant-smelling oil.

For its (dill-apiole) isolation the portion boiling above 200° was separated into two fractions: (*Chem. Centralbl.* 1909, 80, ii, 1335) a dextro-rotatory fraction, boiling at 90-95°/13 mm, which constitutes 5 per cent of the original oil, and (*Compt. rend.* 1909,149, 215-17) an optically inactive fraction boiling at 157-158°/13 mm., specific gravity 1.175, representing 40 per cent of the original oil, and identified as 5: 6-dimethoxy-3: 4-methylene-dioxy-l-allyl benzene, or dill-apiole.

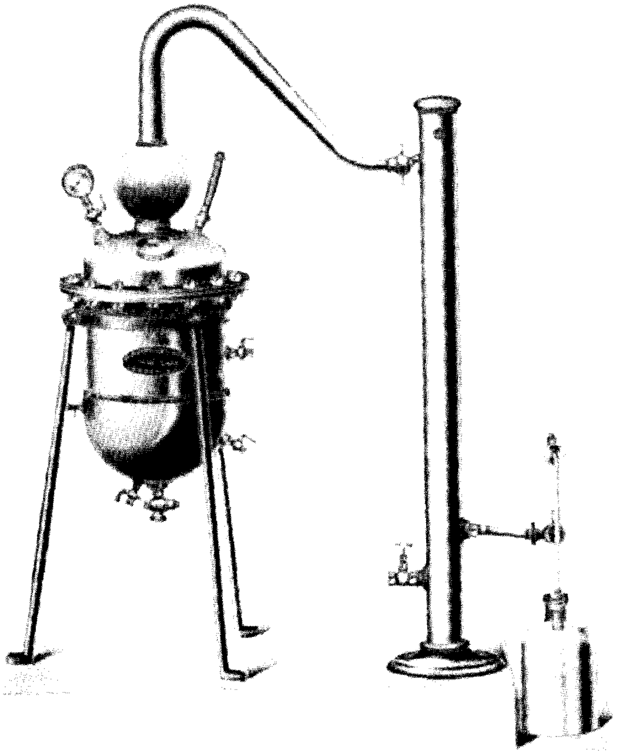


Dill Apiol

This worker also found (*Compt. rend.* 150, 1061-3) by the fractionation of 1 kilo of the oil, *l*-limonene, cymene, thymol methyl ether and *d*-pinene could be separated.

Delepine (*Bull. Soc. Chem.* 1918, 23 (iv), 24-35) states that the plant growing in different parts of France consistently contains the following characteristic substances: dill-apiole, thymol methyl ether and crithmene. In some cases *d*-pinene and a paraffin are also present.

The Sardinian oil has been examined by Francesconi and Sernagiotto. (Atti. *R. Acad. Lincei, Roma*, 1913 (5), 22, i, 231-7 and 313-17, 382-6) It differs from the French oil; the only constituents common to both being dill-apiole, *p*-cymene and crithmene, a new terpene. Crithmene has the formula shown above and appears to be delta,1,7-4,8-menthadiene. It boils at 178-180°, specific gravity at 12°, 0.8679, nD 14806. Source: Finnemore 1926



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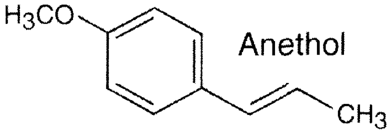
Anethol: Chapter 9

Anethol from Pine Oil

by Lee T. Smith
Kenvil, New Jersey August 11, 1927



Anethol, which has a boiling point of about 235° C. has heretofore been recognized as a constituent of oil of anise and has been derived from anise seed, being used principally as a flavoring. However, anethol has not heretofore been recognized as a constituent of pine oil.

I have discovered that anethol is present in pine oil.

Pine oil is fractionated and cuts having a boiling range below about 220° C. and between about 220° C.-250° C. and above about 250° C., respectively, are obtained. The cut boiling between 220° C. - 250° C., contains the major proportion of the anethol present in the original pine oil.

The cut after treatment is refractionated up to about 250° C. and the distillate refrigerated. The refrigeration of the distillate will result in effecting crystallization of the anethol which may be readily separated from the mother liquor by filtration or centrifugation.

In the carrying out of the process embodying my invention, the cut having about the boiling range indicated may be refractionated up to 250° C., the distillate obtained being cooled to effect crystallization of anethol, which may then be recovered by filtration or centrifugation. Where the cut of higher boiling range is substantially rich in anethol the distillate obtained on refractionation of this cut may be cooled to effect the crystallization of anethol and then filtered, or centrifuged, or the separation of anethol. The filtrate thus obtained and the residue from the fractionation of the cut of higher boiling range may be mixed with the filtrate obtained from the refractionation of the cut of lower boiling point and the mixture refractionated up to 240° C.. The distillate obtained is then cooled to effect separation of the anethol which is separated by filtration, or centrifugation. Source: Smith 1930

Process for the Production of Anethole

by Kurt Bauer and Reiner Mölleken
Germany April 14, 1975

Example 1

(a) Condensation

A mixture of 432 g (4 mols) of anisole and 4 g of concentrated H3PO4 was heated to 150° C. in a reaction vessel equipped with a stirrer, metering unit and descending condenser. After the afore mentioned temperature had been reached, 58 g (1 mol) of propionaldehyde were added through the metering unit over a period of 1.5 hours and, at the same time, the water of reaction formed distilled off. On completion of the addition, the upper phase of the reaction mixture was decanted from the phosphoric acid precipitated and the excess anisole removed from the reaction mixture by distillation, leaving 251.8 g of condensation product consisting of *p,p'*-, *o,p'*- and *o,o'*-1,1-dimethoxy diphenyl propane. The yield amounted to 98.4%, based on the propionaldehyde used.

(b) Splitting

For splitting, 100 g of 1,1-dimethoxy diphenyl propane from the condensation stage (a) were heated to 200° C. in a distillation apparatus fitted with a Claisen attachment, followed by the addition of 0.5 g of concentrated phosphoric acid. The products formed during the splitting reaction distilled off over a period of 15 minutes at about 5 to 30 Torr. According to analysis by gas chromatography, the distillate (95.5 g) contained 32.7 g of unsplit 1,1-dimethoxy diphenyl propane, 24.1 g of *trans-p*-anethole, 9.1 g of *trans-o-* and *cis-p*-anethole and 1.2 g of *p*-propyl anisole, corresponding to a yield of 91.4% of anetholes, based on reacted condensate.

Pure *trans-p*-anethole was obtained from the product of splitting by fractional distillation: b.p. 110° C./10 Torr.

Example 2

A mixture of 324 g (3 mols) of anisole and 4 g of concentrated $H3PO4$ was heated to 150° C. in a 500 mL. capacity reaction vessel equipped with a thermometer, stirrer and dropping funnel. After the above-mentioned temperature had been reached, 64 g (0.432 mol) of *o*-anethole (2-methoxy-propen-1-yl benzene) were introduced into the thoroughly stirred anisole/phosphoric acid mixture over a period of 1 hour, followed by stirring for 1 hour at the same temperature. The excess anisole was then distilled off at 50° C./5 Torr, leaving 110 g of a condensation product consisting predominantly of the *o,p'*-isomers of 1,1-dimethoxy diphenyl propane. The yield was substantially quantitative.

For splitting, the condensate was heated to 200.° C. in the presence of the phosphoric acid left in the condensate. The products of splitting formed, anisole and the *o-p*-anetholes, distil off over a period of 10 minutes at 10 Torr.

Distillation of 55 g of 1,1-dimethoxy diphenyl propane gave 17.8 g of a distillate which contained 14% of *trans-p*-anethole according to analysis by gas chromatography. 24.2 g of condensate were recovered.

The Example illustrates that *o*-anethole can be converted by the process according to the invention into *trans-p*-anethole.
Source: Bauer 1977 Wagner (1952) for a review of anethole production.

Anethol Refinement

by Carlisle H. Bibb
Pensacola, Florida December 4, 1935

372 gallons of crude synthetic anethol prepared by, the, alkali isomerization of methyl chavicol are washed with 100 gallons of dilute, sodium hydroxide solution of about 7% concentration. This is followed by three more washes of 50 gallons each of similar sodium hydroxide solution. The resulting product is then washed five times with 100 gallons of water each time. Thus the impurities which react with or dissolve in sodium hydroxide solution are removed, even though partial extraction is only possible with one wash. Any sodium hydroxide remaining is washed out by water, otherwise upon heating to temperatures sufficient to distill the anethol the sodium hydroxide would generate more phenolic compounds according to the following equation.

$$\mathrm{NaOH+C9OH9OCH3} \rightarrow \mathrm{C9OH9ONa + CH3OH}$$

A high quality of synthetic anethol is thus produced which has a pure taste and odor and does not polymerize when exposed to air. The number of washes of both sodium hydroxide and water can be reduced somewhat if their volumes are materially increased.

If desired the step of distilling the crude anethol may optionally precede or follow the washes with alkali and water if a water white product is desired.

In place of the sodium hydroxide as an alkaline wash I may use any other aqueous solution of a caustic alkali such as for example aqueous solutions of potassium hydroxide, or lithium hydroxide.

Source: Bibb 1936

Anethol Containing Botanicals

by Horace Finnemore

Oil of Kobushi

The fresh leaves and branches of the Kobush tree, *Magnolia kobus*, D.C., which grows in Central Japan, when distilled from July to September, yield about 0.5 per cent of a bright yellow oil which has been examined by Charabot and Laloue (*Compt. rend*, 1908, 183-5); it had specific gravity at 15°, 0.9432, optical rotation -1° 20', was soluble in 1 volume of 90 per cent alcohol, becoming opalescent on dilution. It distilled between 190 and 235°. Anethole was the chief constituent, with probably a small quantity of methyl chavicol and about 15 per cent of citral. Another sample of the oil, specific gravity 0.945, contained cineole and 16 per cent of anethole.

Asahina and Nakamura (*J. Pharm. Soc. Japan*, No. 322, Dec. 1908, via *Schimmel's Report*, April 1909, 59) have obtained somewhat different oil from one-year-old twigs from the Japanese Province of Shizuoka. Its characters were: specific gravity 0.892, optical rotation +6° 8', acid value 4.3, saponification value 19.1, ditto after acetylation 56.5; soluble in 14 volumes of 85 per cent alcohol, opalescent on further dilution. Methyl chavicol was the chief constituent, with 6 per cent of citral; eugenol and cineole. A trace of pinene also seemed to be present with caprinic and oleic acids. It is of interest to note that this oil contained no anethole; it differed from the preceding oils in containing eugenol and in being dextro-rotatory.

Oil of Star Anise

Oil of star anise is obtained from the fruit of *Illicium verum*, Hook. f., a small tree 8 to 15 metres high, 25 to 30 centimetres round the trunk, with evergreen leaves. It is not known wild, but is cultivated in the south of China, chiefly in Kwang-Si, and on the island of Hainan, and within a radius of 20 to 30 kilometres round Langson in Tonquin. Very special climatic conditions are required for its successful cultivation. The rainfall here is 15 metres from April to July, the temperature is often 40°. In August and September the rains become more frequent and the plant revives, while in October the rain ceases, but the sun is overcast all day. In December and January the weather becomes distinctly cold, 5° C. being recorded at night. The atmosphere is charged with moisture. Virgin forest land affords the most suitable soil, and gently sloping declivities. The seeds quickly lose their germinating power, and must be sown immediately, or preserved in layers of dry earth. The seedlings are planted out after a year 5 to 6 metres apart. Shade is useful and almost necessary to the young plantations, which require care to the eighth or tenth year. They are very responsive to manure, and begin to yield from the tenth to the fifteenth year, a full crop being reached at thirty-five years and maintained until 100 years old, 30 to 35 kilos being an average yield, and 5 tons of green fruit per hectare may be gathered. The unripe fruits are collected in August and September and again in February and March, and are distilled at once in small distilleries in Chinese stills. The yield of oil is from 1.7 to 3.5 per cent, but this percentage falls if the fruits are allowed to dry. In Chevalier's opinion, a yield of 5 per cent might be obtained if up-to-date stills were used. (Chevalier, *J. Agric. Trop.* 1914, 14, 40-4)

The chief constituent of star anise oil is anethole, of which it contains over 90 per cent, and upon the presence of a due proportion of which the quality of the oil is judged. This may be estimated either by taking the melting-point, or by determining the solidifying-point, or by observing both these constants, but, as a rule, it is preferable to determine the solidifying- or congealing-point, as it is called. This, generally, should not be lower than +15°. In taking a sample of the oil, it is hardly necessary to emphasise the fact that the whole of the contents of the container must be melted and thoroughly mixed before the sample is drawn. For the purposes of determination, the well-known Beckmann's freezing-point apparatus may be employed. This consists essentially of a wide boiling tube enclosed in a tube of larger diameter, both being placed in a vessel filled with cold water, or with ice and water. The inner tube is provided with a cork carrying a thermometer graduated to 0.5°. The sample of oil is introduced into the inner tube to a height of about 5 cm. and the thermometer inserted. The water in the outer vessel is stirred occasionally until the thermometer has fallen to about 6-8°, that is, about 10° below the expected solidifying-point. At this stage, a small crystal of anethole is introduced and the contents of the tube are stirred by the thermometer. Crystallisation takes place, and by the liberation of the latent heat of fusion the temperature rises, the highest point which it attains being taken as the congealing-point.

The extent of super-cooling has a slight effect upon the final temperature noted, and it should therefore be as small as possible. A low congealing-point may either be due to a low anethole content or to the fact that as the oil ages certain of its constituents polymerise and cause a depression.

Attempts have been made to correlate the percentage composition with the solidifying-point. Jones (*J.Soc.Chem.Ind.* 1922, 41 446 R) has shown that taking the melting-point of anethole as 213°, it should be possible to arrive at the percentage of adulterant by observing the depression of the freezing-point, basing his calculations upon the fact that in an oil containing 93 per cent of anethole, the percentage of impurities is directly proportional to the difference between the observed freezing-point and that of pure anethole.

Oil of Anise

Anise oil is obtained from the fruit of *Pimpinella anisum*, L., which is cultivated chiefly in Russia, but also in Spain, Holland, Bulgaria, France, Turkey, Cyprus and many other places.

Russian aniseed was originally introduced from Spain to the district of Valuiki, whence its cultivation has extended to Voronetz, Ostrogojsk and Biriutch. Attempts to extend its cultivation indiscriminately have been unsuccessful; when grown too far north, it requires too long a period to come to maturity, whilst in the south great heat and drought prevent its development. The average temperature should be 15° in April, 18° in May, 20° in June and July, and 18° in August. (*Schimmel's Report*, Oct. 1913, 22) Good soil with freedom from weeds is essential, as the plants germinate and grow slowly, so they may easily be choked with weeds. Fields on which rye has previously been grown are for this reason often chosen. Cultivation is done in the autumn and the seed is sown in the spring, either broadcast or in rows, 40 lb. or 25 to 30 lb. of seed being required respectively, according to the method adopted. The seeds sprout in about three weeks, and flowering begins about two months later and lasts two or three weeks. While flowering, the plant is exceedingly sensitive to excess of sun, especially after rain, or to cold or hot winds. The fruit ripens in about a month after flowering is over; it then turns a greyish-green colour at the apex. The plant is harvested by pulling it up by the roots in order to eliminate the weeds and to keep the short (1-foot) plants all lying the same way. They are tied up in bundles placed head downwards on the ground to prevent still developing fruits from being dried up too rapidly. The bundles are collected, ripened in cocks 5 to 6 feet high for about a week, then threshed.

The fruit is greyish-green, but is seldom quite uniform in colour, as the central flower-head has developed first. Immature fruits, chaff, seeds of weeds, particles of clay and earth, and coriander which is difficult to eliminate from the fields, are frequently found in anise fruit of commerce, and represent 7 to 8 per cent of foreign substances, and even a higher proportion.

Anise loses weight in storage, and from 0.1 to 0.2 per cent of its oil per annum. The average yield of oil is from 2 to 3.5 per cent. As in the case of other umbeiliferous fruits, it is preferable to crush them before distillation.

Recent figures for the exportation of anise fruit are difficult to obtain. In 1909 and 1910 the Russian harvest amounted to 200,000 poods, or over 6,000,000 lb. From Cyprus. 150 tons were exported in 1917. (*Bull. Imp. Inst.* 1917,15, 300)

Bouchardat and Tardy (*Compt. rend.* 1896,122, 198, 624) examined 22 kilos of commercial Russian oil of feeble dextro-rotatory power. It was cooled to +5° and the oil separated from the impure anethole, which showed a rotation of +0° 36', probably due to the presence of 1 per cent of anisic camphor, $C_{20}H_{16}O_2$, of Landolph, renamed fenchone by Wallach, which is difficult to separate from anethole. The presence of fenchone makes it somewhat doubtful if the oil were authentic.

The liquid extracted from the anethole at +5° amounted to 2 kilos, and had a rotation of 1° 30'. It was cooled to -15°, when a further quantity of anethole and fenchone separated.

Oil of Fennel

Oil of fennel is distilled from the fruit of *Foeniculum vulgare*, Mill., *Foeniculum capillaceum*, Gilib., cultivated in Galicia, Germany, Russia, Roumania, Macedonia, Egypt, Asia Minor, Persia, India and Japan.

Cultivation

Fennel flourishes in open sites in alluvial soil devoid of excess of moisture. Deep digging, followed by harrowing and rolling are necessary and plenty of stable dung. It is sown in France at the end of January to the middle of February, in furrows 28 to 30 inches apart, from 9 to 13 lb. of seed per acre being required. When the young plants have grown to a height of 3 to 4 inches, they are thinned out so as to leave them 4 to 6 inches apart. (Compare cassia, and cinnamon, cloves and pimento) In France the plant is also propagated by lateral shoots, but the plantations are renewed by seed and transplanting. Ripening begins in the centre of the umbel and lasts for about a month. The plants are harvested in August, the yield being about 1,500 kilos per hectre. In the Department of Gard, in France, some 300 hectres are cultivated, producing annually about 300,000 kilos, and in Ardèche 250 hectares. Large quantities of fennel are employed in the liqueur industry, as much as 2,000,000 kilos having been imported annually into France, via Marseilles, three-fourths from Macedonia and the remainder from India.

Fennel oil has specific gravity 0.960 to 0.995, optical rotation +6 to +20°, congealing-point +5 to +10°. It is soluble in 5 to 8 parts of 80 per cent alcohol.

The oil varies to a considerable extent according to its origin. The chief constituent of the sweet fennel oil is anethole, to which the taste is due, but, as is frequently the case, even when, as in this oil, the percentage of the chief constituent is as high as 80 to 90 per cent, the taste is modified by the presence of small quantities of other substances, (Compare cassia, and cinnamon, cloves and pimento) fenchone, for example, giving it a camphoraceous odour.

Fennel oil, like anise oil, in the presence of light and air undergoes marked oxidation and polymerisation, with an increase in the specific gravity and in the solubility, and a fall in the solidifying-point. This change is due to the instability of the anethole, a sample of which, kept for two years, increased in specific gravity at 25°, from 0.9846 to 1.1245; the product was viscous, of a yellow colour and had a disagreeable bitter taste.

Some polymerisation also takes place on merely heating anethole or oils containing it on the water-bath for 4 hours. (*Schimmel's Report*, Nov. 1908, 71)

Japanese fennel fruits somewhat resemble those of anise in appearance, but are more oblong and do not taper to the apex. Umney (*Pharm. J.* 1896, 57, 91) obtained 2.7 per cent of pale yellow oil with the odour of sweet fennel. The solidifying-point was 7° C., melting-point 10°. When fractionated, the following fractions were obtained: below 220°, 26 per cent; 220-225°, 32 per cent; 225-230°, 34 per cent; residue, 8 per cent. According to Umney, this oil probably contains 75 per cent of anethole; 10 per cent of fenchone (by reduction and acetylisation), with some pinene and dipentene; it is not stated how the last two were identified.

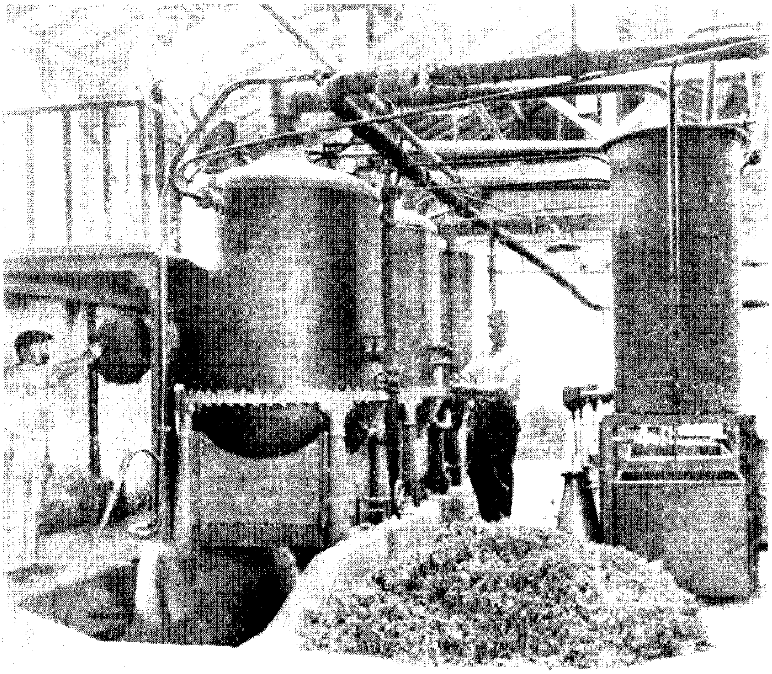
Indian fennel oil is derived from *Foeniculum panmorium*, D.C., a variety of the European. Three samples recently obtained (Rao, Sudborough and Watson, *J. Ind. Inst. Sci.* 1925 8 A, 184) in an average yield of 0.7 per cent.

When fractionally distilled at 7 mm., 38 grams of sample No. 3 gave the following results: 54-75°, 9.7 per cent; 75-90°, 9.7 per cent; 90-100°, 7.0 per cent; 100-101°, 66.6 per cent; residue and loss, 7.0 per cent. About 70 per cent of anethole and 6 per cent of fenchone (oxime, melting-point 164°) were present, with an ester of borneol; methyl chavicol was considered to be absent. Fenchone was separated from Fraction 1 by mixing it with three times its volume of strong nitric acid and after 20 minutes' contact separating, washing and rectifying the unattacked fenchone.

Oil of Sweet Cicely

The roots of *Osmorhiza iongistylis*, D.C., the American sweet cicely, yielded 0.63 per cent of oil, specific gravity 1.011, congealing-point 10-12°, boiling between 225 and 230° and consisting chiefly of anethole, (Eberhardt, *Pharm. Rundschau*, 1887, 5, 149) although the high specific gravity points to the presence of other phenolic ethers.

Source: Finnemore 1926



3,4-Dimethoxy-allybenzene: Chapter 10

3,4-Dimethoxy-allybenzene from Botanicals

by Horace Finnemore

Melaleuca bracteata, F. v. M.

This gives an abnormal oil, cineole being absent, its principal constituent being methyl eugenol, 70 per cent; eugenol, cinnamic aldehyde and acid, and probably cinnamic alcohol; 2 to 3 per cent of *l*-phellandrene is also present, and can readily be separated by distillation from the other ingredients.

One hundred and eighty-one pounds of leaves and terminal branchlets collected in March gave 26 ounces of oil, or 0.898 per cent. In May 360 lb. gave 0.643 per cent; in July 389 lb. gave 0.964 per cent.

The oil is pleasant and aromatic in odour, resembling methyl eugenol. Its characters are: specific gravity at 18°, 1.032 to 1.036, αD - 1.4 to 3.1°, refractive index 1.532 to 1.535, saponification value 5.3 to 20.8. Source: Finnimore 1926

3,4-Dimethoxyphenylpropene from Eugenol

by Thomas Smyth Carswell
St. Louis, Missouri December 22, 1927

1 kg. of an isomeric mixture of methoxyeugenol and methoxyisochavicol obtained as previously described, or in any other way, is dissolved in 6.5 liters of 94% ethyl alcohol, and to this solution is added 0.29 kg. of calcium hydroxide.

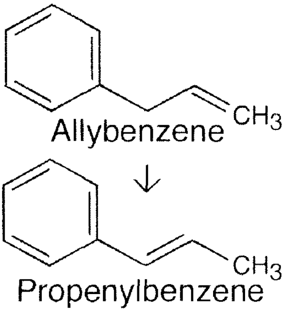
The mixture is stirred for 3 hours and filtered, centrifuged or otherwise treated to remove the insoluble salt.

The filter cake is washed with 1.5 liters of alcohol and then sludged up with 5 liters of water. To this mixture is added 0.4 kg of soda ash and the mass is boiled for 1 hour. After cooling, the mixture is filtered or otherwise treated to remove the insoluble calcium carbonate. The filtrate of this second filtering operation is acidified whereby a yield of 0.6 kg. of methoxychavicol will be obtained. The alcoholic filtrate of the first filtering operation is combined with the alcohol wash liquor and diluted with two liters of water and fractionally distilled to recover the alcohol. The distilled residue is then acidified, whereupon a yield of 0.3 kg. of methoxyisoeugenol is obtained. The separated isomers are then converted into isoeugenol, as specified in the first example described above. Source: Carswell 1930

Isomerisation of Allybenzenes

3,4-Dimethoxypropenylbenzene from 3,4-Dimethoxyallybenzene

by W.J. Bush & Co.
London, UK April 20, 1966



Isoeugenol methyl ether was prepared from eugenol methyl ether by mixing eugenol methyl ether (150 parts) with potassium hydroxide (1.5 parts) and absolute ethyl alcohol (3.2 parts) at 160 to 165°C with stirring. The temperature of the mixture rose rapidly to 190 to 195° C and after 30 minutes the heat was turned off, by which time the temperature had fallen to 170°C. When the mixture reached room temperature, water was added. The oily layer was separated off, dried and vacuum distilled. The distillate (130 parts) was substantially all *cis* and *trans* isoeugenol methyl ether. Source: Bush 1968

For comprehensive review of 3,4-dimethoxyphenylpropene in botanicals see EMEA 2004

Eugenol: Chapter 11
Eugenol (4-hydroxy-3-methoxy-allybenzene) Containing Botanicals

by Horace Finnemore

Cinnamomum culilawan, Bl.

The oil from Culilawan bark, obtained in a yield of 4 per cent, had specific gravity 1.051, and, according to Gildemeister and Stephan, (*Arch. der Pharm.* 1897, 235, 583-92) contained eugenol, 61 to 62 per cent, with a small amount of methyl eugenol, and an unknown substance With the odour of terpineol, boiling between 100-125°/10 mm.

It gives a clear solution with 3 parts of 70 per cent alcohol.

Cinnamomum pedatinervium, Meissn.

The oil from the bark of this tree, indigenous to the Fiji Islands, has a pleasant, aromatic, spicy odour Goulding (*J. Chem. Soc.* 1903, T 1093-1101) has examined the oil obtained by distilling 50 lb. of the bark with steam. The yield was 71 oz. or 0.92 per cent.

It had the following constants: specific gravity 0964, [a]D - 4.96°, nD 1.4963.

When fractionated it gave the following four main fractions: 180-205°, 22 per cent; 205-220°, 30 per cent; 220-230°, 27 per cent; 230-255°, 18 per cent.

The amount of total alcohols, calculated as $C_{10}H_{17}OH$, corresponded to 31.8 per cent, 1.1 per cent being present in the form of esters. The oil contains: an unidentified terpene, 15-20 per cent; alcohols, wholly or in part, linalol, 30 per cent; esters, 1.5 per cent; safrole, 40-50 per cent; eugenol, 1 per cent; eugenyl methyl ether (?), 3 per cent.

Cinnamomum tamala, Nees et Eberm.

The leaves of this species are used in India as a spice The native method of distilling, which is confined to the Western Ghats, has been described by Gopaliah. (*Ind. For.*, 1908, 34, (2), 88-9) Three earthen pots are used as boiler, covering pot (or still-head) and receiver.

The still-head is connected by a bamboo tube, about a foot long, to the condenser, which consists of another bamboo tube, about 3 feet in length, leading to the receiver. The boiler holds half a head load of the fairly matured green leaves, and each charge takes 8 to 12 hours. The oil has a lemon-yellow colour and an odour of cloves and pepper. It contains 78 per cent of eugenol, and has the following constants (*Schimmel's Report*, April 1910,123): specific gravity 1.025, αD +16° 37', n20D 1.526; soluble in 12 volume of 70 per cent alcohol. *d*-α-phellandrene was present. The oil resembles ordinary cinnamon leaf-oil.

Oil of Pimento

Pimento oil is obtained from the fruit of *Pimenta officinalis*, Lindl., indigenous to the West Indies, especially cultivated in Jamaica, Central America, Mexico, Costa Rica and Venezuela, known as allspice and Jamaica pepper. The full-grown but unripe fruit is used, as it loses its aroma on ripening.

The oil is obtained in a yield of 3 to 5 per cent; it has a yellowish to yellowish-brown colour, and an odour somewhat resembling that of cloves, owing to the presence of eugenol and caryophyllene, which they both contain.

Its constants are as follows: specific gravity 1.030 to 1.050, optical rotation 1 to 4°, refractive index 1.5250 to 1.5350, phenols 65 to 80 per cent.

Chemistry

The chief constituent of pimento oil is eugenol, of which it contains from 65 to 80 per cent. The other constituents have been investigated by Schimmel & Co., (*Report*, April 1904, 75) who worked upon 1 kilogram of the first runnings, which had the following constants specific gravity at 15°, 0.9715 αD 11° 30'.

Oil of Pimento Leaf

The oil from pimento leaves, which should be distinguished: from that obtained from *P. acris*, has recently aroused some interest. Following a favourable report on a sample sent to the Imperial Institute in 1909, (*Bull. Imp. Inst.* 1913,11, 438) experimental production was instituted and large-scale distillation begun in 1920, when 2,095 lb. of fresh leaves gave 1.7 per cent of oil. The usual yield ranges from 0.8 to 1.25 per cent. The eugenol content may be as low as 32 per cent, but usually varies from 61 to 93 per cent, and even 97 per cent has been obtained. It is possible to produce 100,000 lb. annually in Jamaica, and, where wood is available as fuel, distillation can be carried on economically.

Oil of Cloves

The clove tree, *Eugenia caryophyllata*, Thunb. (*Caryophyllus aromaticus*, L.), is a native of the Molucca Islands, and is cultivated in Zanzibar, (An account of the clove industry in Zanzibar, by the Director of Agriculture, Mr. R. N. Lyne, will be found in the *Report of International Congress of Tropical Agriculture*, 1910) Pemba, Amboyna, Penang, Madagascar and, to a lesser degree, in the Seyehelles, Reunion, Mauritius and Ceylon. It has also been introduced into Gaboon in the French Congo.

Cloves consist of the unopened flower-buds picked when the fleshy receptacle, which is at first green, has acquired a crimson colour. At this period of its growth the clove is richest in oil

Ninety per cent of the world's supply of cloves is obtained from the two islands Zanzibar and Pemba, where it was introduced from Reunion, via the Moluccas, about 1818, and where it forms the chief industry. As one approaches the islands when the cloves are in bloom, one is struck by their pervading sweet odour, which is infinitely more pleasant than that of the dried flowers or the oil. The industry has undergone many vicissitudes: in 1872 a hurricane practically destroyed most of the plantations in Zanzibar, but Pemba escaped, and the industry has since become very prosperous.

It has been suggested that a clove oil factory might be established in Zanzibar, where the necessary timber for fuel is abundant, but there are many practical difficulties (*For. Office Ann. Series*, No. 2653, via *J. Soc. Chem. Ind.* 1901, 20, 776) and all attempts made hitherto have been unsuccessful.

The area of clove cultivation in Zanzibar and Pemba for the year 1919 was estimated at 52,000 acres, with nearly 5,000,000 trees. The large plantations are held by Arabs, a few by Indians. The yield from each tree varies, especially good crops recurring every three to five years. The average yield per annum from a plantation of 3,000 sixty-year-old trees, owned and managed by Europeans, is 8 lb. per tree, which could be increased by judicious pruning.

An idea of the extent of the clove crop may be gained from the figures for the 1924 harvest, which amounted to between 7,000 and 8,000 tons. For the six months from January to June 1914, 2,764 tons were exported: of this, India took 58 per cent, the United Kingdom 16 per cent, and the United States 10 per cent.

Madagascar cloves, produced on the island of Ste. Marie, amounted to 20 metric tons in 1920-21. (*J. Soc. Chem, Ind,*. 1921, 40, R 235)

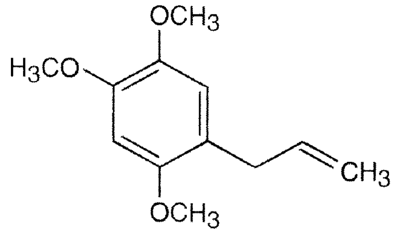
The clove tree requires clay soil, red or brown being preferable to the lighter coloured. Some authorities prefer a deep, well drained soil with shelter from the wind and ample air space. The seeds are softened for about three days before sowing and after germination are planted out in shaded beds. These are kept well watered, the shoots being protected from the sun. After about 9 months, and when about 6 inches high, the cover is gradually removed and the plants allowed to remain in the beds for another 2 months, when they are transferred to their permanent plantations. Planting must be done carefully, the young plants being watered in the dry weather, but they are not protected at this stage against the sun. The average age of a clove tree is 90 years.

The harvest is conducted by men, women and children, who climb the trees and pluck the cloves, placing them in cloths tied round their necks.

Cloves contain from 16 to 19 per cent of volatile oil. They are distilled either in water or with steam. The former method yields an oil of lower specific gravity containing a smaller proportion of eugenol, whilst the oil obtained by the latter method is of slightly higher eugenol content and higher specific gravity. These two varieties of clove oil are known on the market as “opt” and “strong.” Their respective phenol content varies from 84 to 88 and from 88 to 92 per cent. The former variety is used in pharmacy and perfumery, the latter for iso-eugenol and vanillin manufacture.

The constants of clove oil are as follows: specific gravity 1.047 to 1.065, refractive index 1.528 to 1.540, optical rotation 0 to—15°, eugenol by absorption with alkali 82 to 92 per cent. Source: Finnemore 1926

Asarone: Chapter 12



2,4,5-Trimethoxyallybenzene

Asarone Containing Botanicals

by Horace Finnemore

The Oil of *Asarum Europaeum*, L.

The root of European snakeroot gives about 1 per cent of a thick oil heavier than water, with a strong, sweet, aromatic odour and a burning taste. The specific gravity varies from 1.018 to 1.070. On standing, the oil deposits crystals which have been known for over a century as asarone, in which the presence of three methoxyl groups was recognised by Rizza and Butlerow (*Ber.* 1884,17,1159) as long ago as 1884. Asarone gave trimethoxybenzene (i) which Will (*Ber.* 1888, 21, 614) found was identical with the 1: 2: 4 derivative synthetically produced.

Eykman (*Ber.* 1889, 22, 3172) concluded from an optical examination of a mixture of asarone and safrole that the former is a propenyl and not an allyl derivative, and the constitution of asarone was finally determined by Gattermann and Eggers (*Ber.* 1899, 32, 289) by synthesizing asarylic aldehyde (ii) from 1: 2: 4-trimethoxybenzene and then heating this aldehyde with propionic anhydride and sodium propionate, when asarone (iii) was obtained in a yield of 60 per cent. Asarone melts at 62-63° and boils at 296°, specific gravity at 18°, 1.165.

Oil of *Asarum Canadense*

Asarum canadense, L., Canadian snakeroot. The dried rhizome gives 3 to 4 per cent of oil which is used in the United States as a perfume. (An oil obtained from the dried rhizome and herb with an abnormally high specific gravity at 20°, 1.0446, began to congeal at 20°. This oil resembles that of *A. europaeum* (q.v.), and it would be interesting to ascertain if asarone were present. Eugenol is said to be present in the ordinary oil. (Gildemeister and Hoffmann, vol. 2, 355, p. 356, footnote.))

The composition of this oil is, approximately, as follows:

eugenyl methyl ether, 36 per cent;
esters calculated as $C_{10}H_{17}C_2H_3O_2$, 27.5 per cent;
alcohols, $C_{10}H_{18}O$ (free), 13.3 per cent;
d- and *l*-a-pinene, 2.0 per cent;
high-boiling sesquiterpene alcohols, 20 per cent.

Source: Finnemore 1926

Preparation of 2,4,5-Timethoxybenzaldehyde from 2,4,5-Trimethoxycinnamaldehyde

by Arun Kumar Sinha, Bhupendra Prasad Joshi and Ruchi Dogra
Himachal Pradesh, India March 14, 2001

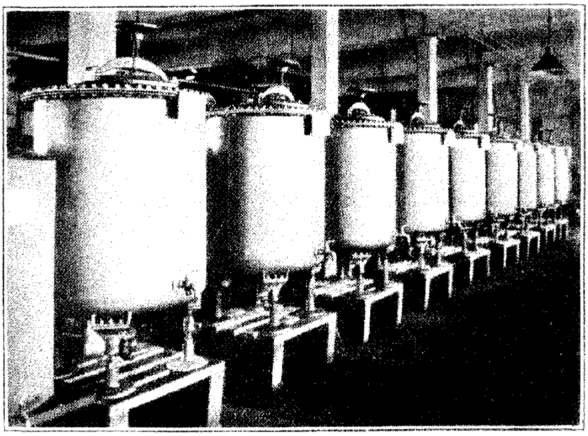
Similarly, a number of substituted cinnamaldehydes such as *ortho*-methoxy cinnamaldehyde (synonym: *ortho*-cumeric aldehyde methyl ether), *para*-methoxy cinnamaldehyde (synonym: *para*-cumeric aldehyde methyl ether), 3,4-dimethoxy cinnamic aldehyde (synonyms: homoconiferaldehyde or methyl ferulaldehyde), *para*-coniferaldehyde (synonyms: ferulaldehyde or maple aldehyde or 4-hydroxy-3-methoxy cinnamic aldehyde), 3,4-methylenedioxycinnamic aldehyde (synonyms: piperonyl acrolein or heliotropylidene acetaldehyde or piperonylidene acetaldehyde), sinapaldehyde (synonym: 2,4-dimethoxy-4-hydroxy cinnamic aldehyde) are also widely used in flavour compositions, however, the odour of these substituted cinnamaldehydes bears a little organoleptic resemblance to that of cinnamaldehyde. In addition, some substituted cinnamaldehydes are known for their biological activities.

Phenylpropenes, widely used in fragrance, flavour, cosmetic, liquor, whisky, and pharmaceutical industries, exist in three isomeric form (i.e. *alpha*, ß and *gamma*), however, *cis*-isomeric form of phenylpropene (such as ß-asarone) has been recently proved to be carcinogenic and toxic (Taylor, J. M., Jones, W. I., Hogan, E. C., Gross, M. A., David, D. A. and Cook, E. L., *Toxicol. Appl. Pharmacol.*, 10: 405 (1967); Keller, K.; Odenthal, K. P. and Leng, P. E., *Planta Medica*, 1: 6-9 (1985) and Kim, S. C., Liem, A., Stewart, B. C. and Miller, J. A., *Carcinogensis*, 20(7), 1303-1307 (1999)) and therefore, banned for any kind of use in flavour, perfumery and pharmaceutical industries. *Cis*-anethol is found to be 15 times more toxic than *trans*-anethol. Similarly, *gamma*-isomeric form of phenylpropene (such as safrole) is also found carcinogenic (Daimon, H., Sawada, S., Asakura, S. and Sagami, F., *Carcinogenesis*, 19(1): 141-146, (1998) and Liu, T. Y., Chen, C. C., Chen, C. L. and Chi, C. W., *Food & Chemical Toxicology*, 37(7): 697-702, (1999). In view of above problem, most affected plant is *Acorus calamus* (family:Araceae) in which percentage of toxic ß-asarone depends upon the varieties of *A. calamus* (Riaz, M., Shadab, Q., Chaudhary, F. M., Hamdard *Medicus* 38(2): 50-62 (1995) and McGuffin, M., Hobbs, C., Upton, R. and Goldberg, A., In: *American Herbal Products Association's Botanical Safety Handbook*, CRC Press, Inc.; Boca Raton, Fla.; USA, 231, (1997)). The content of ß-asarone in the triploid variety is 8-19%, while ß-asarone reaches upto 96% in the tetraploid and hexaploid varieties (extensively found in Asian countries). In contrast, ß-asarone is not found in the diploid variety. As a result, the calamus oil obtained from North American diploid strain (zero, ß-asarone) and East European triploid strain (up to 12% ß-asarone) are allowed for clinical effectiveness and safety while the calamus oil produced in Asian belt (such as India, Pakistan, Bangladesh, Nepal, Japan and China) has diminished the market potential of calamus oil due to high percentage of ß-asarone ranging from 70 to 96% (Mazza, G., *J. of Chromatography* 328:179-206 (1985); Nigam, M. C., Ateeque, A., Misra, L. N. and Ahmad, A., *Indian Perfumer* 34: 282-285 (1990) and Bonaccorsi, I., Cortronco, A., Chowdhury, J. U. and Yusuf, M., *Essenze Derv. Agrum*, 67(4): 392-402 (1997)). Therefore, the applicants' objective is to utilize toxic ß-asarone (*cis*-2,4,5-trimethoxyphenyl-1-propene) as a simple starting material for value added products via its reduced product (2,4,5-trimethoxyphenylpropane) which has recently been found useful as a new aroma molecule with atleast six to four times less toxic than ß-asarone or calamus oil (Sinha, A. K., U.S. Ser. No. 09/652,376 filed Aug. 31, (2000)). Further, 2,4,5-trimethoxyphenylpropane appeared to us as a simple intermediate for the preparation of *trans*-2,4,5-trimethoxyphenyl-1-propene (*alpha*-asarone).

Permanganate Oxidation of 2,4,5-Trimethoxycinnamaldehyde into 2,4,5-Trimethoxybenzaldehyde

A solution of the 2,4,5-Trimethoxycinnamaldehyde (0.5 g) was treated with KMnO4 (0.5 g) in dry acetone (20 ml). The reaction mixture was left at room temperature for 24 hr, manganese dioxide was filtered off and the solvent was removed. The residue was dissolved in ethyl acetate and washed carefully with 10% NaHCO3, brine, and dried over anhydrous Na2SO4. Evaporation of the solvent afforded a crude solid, which was further recrystallised from water to afford 0.2 g 2,4,5-trimethoxybenzaldehyde as a colorless solid, mp 114° C.

Source: Sinha 2003



(United Drug Co., Boston, U.S.A.)

Perfumes stored in "Pfaudler" glass lined steel tanks.

Plant Oils by Steam: Chapter 13

Separation of Plant Oils by Steam Distillation

by Frank Rabak
Bureau of Plant Industry December 9, 1910

A simple still, which consists essentially of three parts, the still body, the condenser, and the receiver, with a suitable means of applying direct heat to the still body, containing material suspended in water, was used early in the eighteenth century. Even at the present time many smaller distillations are still carried on with this form of apparatus. The chief disadvantage of this type of still lies in the fact that the heat, being applied directly, has a tendency to char or burn the materials adjacent to the bottom, and thus appreciably effect the quality of the aromatic product distilled over.

This method has been largely superseded in modern times by distillation with steam, the principles of which depend upon the property of the steam as it passes through the charged apparatus to carry with it the volatile portion of the plant in the form of vapors, which are condensed, together with the excess of watery vapor, and deposited in the receiving vessel. The three steps in the process are (1) the distilling, (2) the condensing of the vapors, and (3) the collecting of the oil. Even though the boiling points of the volatile oils separated by distillation from plants may be considerably higher than the temperature of steam, the odors are readily liberated by the passing steam and carried over.

Apparatus

The apparatus required for the three processes which collectively constitute steam distillation is of comparatively simple construction, consisting of (1) a still, (2) a still head (cover for body), (3) a condenser, and (4) a receiver.

The body of the still, or the receptacle in which is placed the material from which the oil is to be extracted, gives best results when cylindrical in form and may be constructed of various materials, preferably copper. However, some stills are made with wooden bodies.

Galvanized iron heavily tinned on the interior is a suitable material, principally because of its cheapness and durability. The still may be constructed of any size desirable, provided the other parts, the condenser and the receiver, are in proportion, depending upon the amount of material to be used and the extent of production desired.

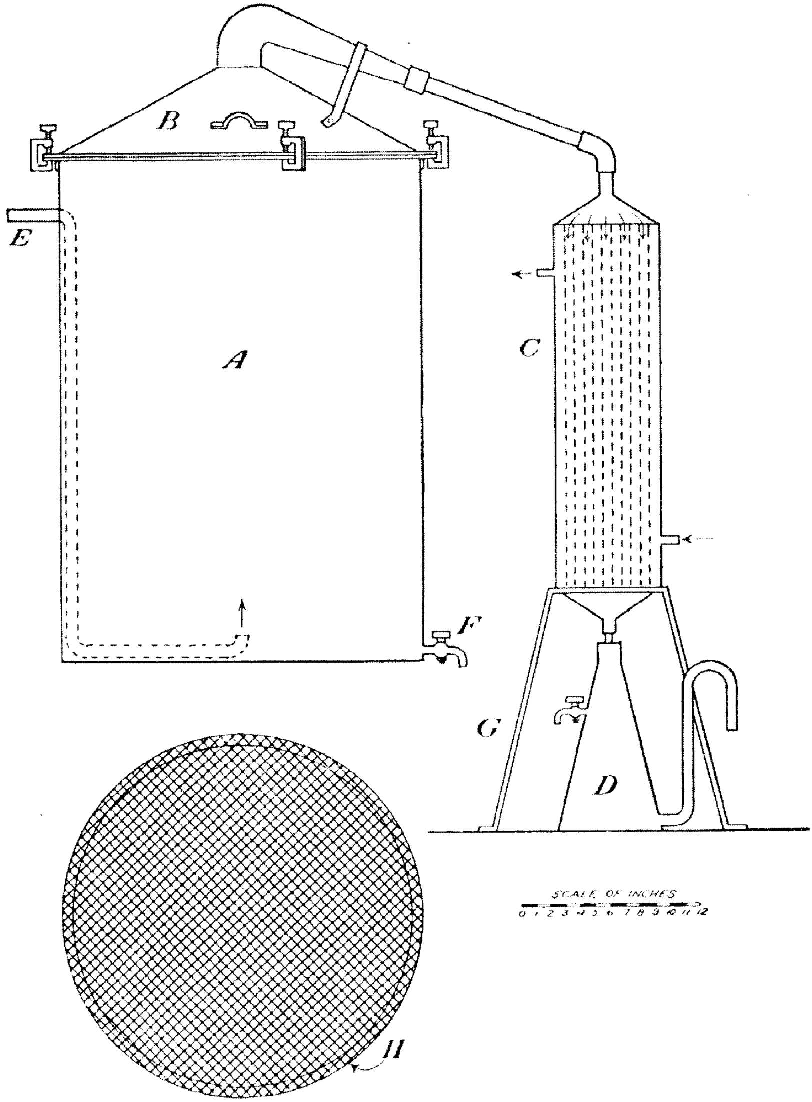


Fig. 4.—Distilling and condensing apparatus. *A*, Still; *B*, still head or cover; *C*, condenser; *D*, receiver; *E*, steam pipe; *F*, spigot; *G*, tripod; *H*, screen.

In figure 4, A represents the still, B the still head, or cover, C: the condenser, and D the receiver. Through the side of the still at the point E passes a galvanized steam pipe from three-fourths to 1 inch in diameter, extending downward and finally terminating in the middle of the still, as shown by the dotted line. A spigot, F, is attached to the bottom of the still for draining the collected water from the apparatus. About 3 inches from the bottom of the still is placed a coarse screen, H, fastened to a wooden frame, which acts as a support for the herb or plant part to be distilled. Encircling the top of the still is an iron collar, which may be conveniently constructed of angle iron, to which the copper or the metal is securely attached.

The still head, or cover, B, is of the same material as the still and is slightly conical in shape, with an exit tube terminating in a union, at which point connection may be made with the condenser. Around the periphery of the cover is securely fastened a flat collar of iron of the same diameter as the angle ion used on the top of the still, so that with the cover in place the two will exactly coincide.

The condenser, C, as shown in figure 4, consists of a group of tubes (inside diameter one-half to 1 inch, depending upon the size of the condenser) surrounded by an outside jacket fitted with an inlet tube at the bottom and an outlet tube at the top, to enable cold water to pass continually through the condenser in an upward direction. The condenser is attached to the still by means of the union joint, as illustrated.

The tripod, G, acts as a support for the condenser while the apparatus is in operation and also while the still is being charged or discharged. Under the bottom opening of the condenser is placed a receiver, D, of copper with a goose-neck siphon tube extending from the bottom to within 2 inches of the top. On the side opposite the siphon tube is fastened a small brass spigot to admit the removal of the oil from time to time.

For the generation of steam, if a source is not otherwise available, a small boiler, such as is illustrated in figure 5, may be conveniently used. A small boiler, A, of light boiler iron fitted with about a dozen flues is capped by the cover, B. Other usual accessories are attached, viz, water gauge, G; pop valve, D; water gauge, E; and steam outlet, F. The boiler may be preferably set upon a gasoline stove or an open fire stove or on a tripod with an open fire beneath. The pop valve may be set at about 8 to 10 pounds, no greater pressure being necessary. To replenish the water in the boiler a funnel tube attached to the pop valve may be used. Connection to the still is made most conveniently by the attachment of a short piece of rubber steam hose to F, as this admits a ready detachment from the still when distillation is completed. A pressure of 5 to 10 pounds of steam is sufficient for ordinary distillation. The size of the boiler may be slightly increased if distillation is to be conducted on a larger scale.

The boiler just described possesses efficiency enough to distill charges of 75 to 150 pounds of herb.

For distillation on a commercial scale a large, stationary, upright boiler may be installed for the generation of steam, or, if convenient, steam may be taken from any high-pressure boiler which may be in use for other purposes. The volume necessary being very slight, indeed, is scarcely perceptible upon the steam gauge.

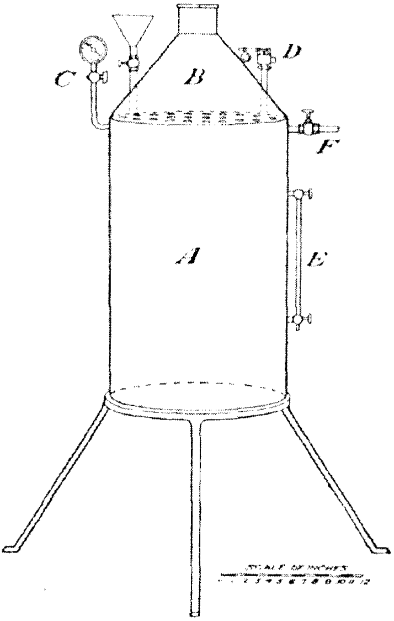


FIG. 5.—Steam generator. A, Boiler; B, cover; C, steam gauge; D, pop valve; E, water gauge; F, steam outlet

Method of Operation

To charge the still, place the false bottom in the still and pack the herb firmly until completely filled. Place a gasket of asbestos rope, heavy cotton wicking, or other suitable material (previously moistened) around the top of the still. Place the cover upon the moistened gasket and clamp securely with heavy steel clamps. Connect the exit pipe from the top of the still to the condenser by means of the union, as indicated in the diagram. Now conduct steam into the still through the inlet pipe, E, slowly at first, and regulate afterwards so that the distillate passing from the end of the condenser is cold or but very slightly warm. The receiving vessel, D, should be previously filled three-fourths full of water and placed under the exit from the condenser. Likewise, the cold water is started flowing through the condenser, as indicated by the arrow. Frequently the oil may be led from the receiver by opening the cock on the side. However, owing to the siphon tube attached to the receiver, overflowing is impossible, since this tube carries off the water which separates in the bottom of the receiver. To ascertain when distillation is completed a few drops of the distillate as it comes from the condenser are collected in a glass test tube. The appearance of oily globules on the surface readily indicates whether appreciable quantities of oil are still passing over. Usually a distillation is completed in from one and one-half to two and one-half hours.

The advantage of steam distillation over other methods of volatile oil extraction lies principally in its wide applicability and speed of operation. Most plants or plant parts, with the exception of the flowers in some few cases, may be extracted most readily and most expeditiously and with a minimum amount of labor by the steam distillation method. The simplicity of the operation is obvious. The removal of the oil is much more complete than by any other process. Furthermore, there is produced as a by-product during the distillation an aqueous distillate which is completely saturated with the oil. The aqueous distillate may in many instances be utilized and sold as an "aromatic water" of commerce, especially in such cases as lavender, orange flowers, rose, etc. The aromatic waters possess excellent odors, largely because of the extreme dilution of the odorous compounds held in solution, and are useful in the perfumery and toilet-preparation industries. When the aqueous distillate from the plant has no marketable value, it may be profitably collected and returned to the boiler. In case of a further distillation of the same plant it will materially add to the yield of oil, since the distillate is a saturated solution of the oil. Many oils are extremely soluble in water. Distillates from oils of this class usually augment considerably the yield of oil when returned to the boiler and transformed into steam and oil vapors.

The spent herb, which on a large scale amounts to no inconsiderable quantity, may be used as fuel and the ash used as fertilizer, or it may be scattered upon a field and plowed under as a mulch. In some cases the spent herb serves as a useful stock food, an example of which is the peppermint grown in Michigan.

The advantages far outnumber the disadvantages of the distillation method, the only disadvantage being the possibility of slight decomposition of the ester bodies in some of the more delicate perfumed plants. However, this is only slight and almost negligible in most herbs

Handling of Volatile Oils, Purification

The volatile oil as it comes from the still is in a crude state, being contaminated by volatile substances which are formed during the distilling process by the action of the steam upon the less stable plant constituents, decomposing them into volatile organic substances, which, although trifling in quantity, nevertheless tend to affect the color, odor, and taste of the oil.

The chemical changes taking place in the still are numerous, the more important being oxidation and reduction of some of the constituents of the oil, as well as of the other plant constituents, saponification of the more unstable esters, and resinification brought about by a polymerization of certain plant constituents, all of which aid in forming volatile substances which mingle with the oil.

Although a process of purification is not always applied to these crude oils, it is important and sometimes highly profitable to subject the crude product to a process of rectification. By rectification is meant a redistillation of the oil with steam, this procedure affecting a moderate separation of the undesirable substances which may have been formed. The substances which detract from the odor of the oil are usually left behind in the apparatus as a heavy, malodorous liquid slightly resinous in character. Rectification usually results in a fine, finished product, free from foreign odors, and leaves an oil much more presentable in color as well as in odor and taste.

This process may be conducted in a miniature still built on the same general plan as the large commercial still. The loss in the amount of oil is more than compensated for by the better quality and the increased salability of the rectified oil.

Separation, Filtration, and Drying

To separate the oil from the aqueous distillate in the receiving vessel, the portion which has not been separated by means of the stop cock on the side of the receiver is poured into a separating funnel of glass and the heavier liquid drawn off. The oils resulting from different distillations of the same plant are then united and subjected to filtration, which process tends to separate any solid particles or emulsion of oil and water. Filtration is conveniently effected by pouring the oil into a glass funnel which has been fitted with a filtering medium, such as filter paper (an unsized, porous paper) or cotton. When cotton is used as a filtering medium a small tuft may be fitted loosely into the neck of the funnel and oil poured upon it. Usually filtration takes place more rapidly through cotton than through paper and with much less loss. Rapidity of filtration is essential to minimize the possibilities of changes taking place in the oil by oxidation, since the oil is more or less exposed to the action of the air and light while undergoing this clarifying process. Hence cotton is to be recommended.

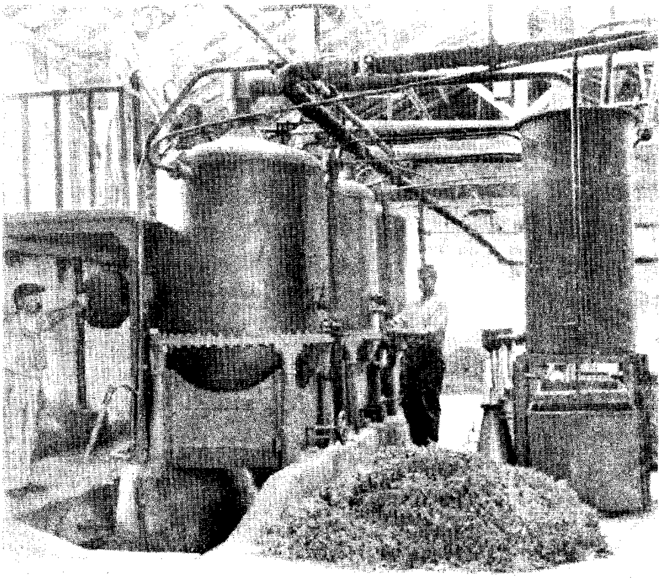
Just as the water that comprises the aqueous distillate is a saturated solution of the oil, so the oil which floats above the distillate is saturated with water. Usually it is of prime necessity that the moisture be removed from all oils, first, because of the subsequent changes that are likely to occur if moisture is present, and, second, because of the turbidity which water imparts to the oil. Hence, after filtration through cotton the oil should be dried by shaking in a bottle with a dehydrating substance, such as anhydrous calcium chloride or anhydrous sodium sulphate, preferably the latter, owing to its lack of action upon the constituents of the oils. The crude sodium sulphate (Glauber's salts) may be dehydrated by heating it in a vessel over direct heat, with constant stirring until a dry, grayish powder results. But a small quantity is necessary to abstract the moisture from an oil. After the oil has been dried it is again filtered through a light plug of cotton. A clear and transparent oil finally results, bearing in every way the appearance of a marketable oil.

Preservation

Many constituents of volatile oils are of such a nature that unless the strictest precautions are observed in storing the oils chemical decomposition takes place, causing them to change in both odor and color, thereby reducing the quality and value. The esters of an oil (combinations of organic acids with alcohols) are very prone to decomposition, as are also many aldehydes and hydrocarbons, which either through saponification, hydration, oxidation, reduction, or polymerization become totally different substances. These chemical processes are usually stimulated by the action of light and air upon the oils. Therefore, in order to guard against these changes and to minimize them as much as possible, the strictest attention should be paid to the proper bottling and storage of the oils.

It is of the utmost importance that all oils should be placed in bottles which are well filled. The absence of air is of the greatest importance in insuring the preservation of an oil. The oxygen of the air, assisted by light, becomes extremely energetic in bringing about some of the changes previously mentioned. It is therefore of import that the oils be kept not only in well-filled, tightly stoppered bottles, but in a dark place. It is sometimes convenient and advisable to use amber-colored bottles in order to prevent the entrance of the actinic rays of light which are so active in causing polymerization. A cool place is also to be preferred for the storage of volatile oils.

All undue exposure of oils to the action of light and air should be avoided as much as possible. It is necessary that an oil from the time it leaves the receiving vessel after distillation or rectification until it is filtered, dried, and bottled should be handled with care and dispatch to insure a product of the best quality and appearance.



Sassafras Oil

A specific example of an important uncultivated plant which yields a volatile oil of considerable value is the sassafras tree. Sassafras oil was one of the first volatile oils distilled in America. The range of the tree is from Florida, where it was originally discovered, to Virginia and Pennsylvania, and even as far north as New York and the New England States. It is quite abundant in the South-Central States, especially Kentucky, Tennessee, and Arkansas. The production of this oil attained commercial significance early in the last century, and it is distilled extensively at present in Kentucky, Tennessee. Pennsylvania, Maryland, and Virginia; also to a less extent in Ohio, Indiana, and New York.

Although the distillation of this very fragrant oil, which is obtained principally from the bark of the root of the sassafras tree (*Sassafras officinalis*), has assumed a strong commercial aspect, the tree has not been grown, strictly speaking, for oil purposes. No doubt the great abundance and the ready accessibility of the trees growing wild are the causes of the noncultivation of this tree for commercial purposes. The leaves and branches of the tree are faintly aromatic, but are not used as a source of the oil. The root bark and wood, which contain from 1 to 8 per cent of volatile oil, form the crude source of supply. The oil is distilled by the ordinary method of steam distillation, the wood and bark of the root being previously coarsely comminuted to admit of better extraction. Source: Rabak 1910

Extraction by Steam Distillation

by A. F. Sievers March 1952

The simplest and most economical method of removing volatile oils from plant material is by distillation with a current of steam. This method cannot he used for flavors having oils that are unfavorably affected by the action of steam. Most volatile oils. however, can all be distilled by steam without serious decomposition. The chief advantages of the method are its simplicity, the comparatively brief time required for its operation, and the fact that large quantities of material can be handled at a small cost. It is the only method economically possible for the extraction of the great number of volatile oils of only nominal value, for which the more tedious processes would be impracticable.

The steam distillation is based on the fact that volatile oils are vaporized when the material containing them is subjected to a current of steam and that, when the mixture of oil and water vapors is condensed, the oil separates as a liquid in a layer that may be readily removed from the water. To accomplish this result it is necessary to supply (1) a tub or retort in which the plant material may be subjected to the action of steam obtained from any conventional source, (2) a suitable condenser for condensing the mixture of vapors, and (3) a receiver in which the condensed water and oil may be collected.

Design and Construction of Volatile-Oil Stills

The details of design and construction of volatile-oil stills vary somewhat, according to the use to which the still is to be put. The capacity of the still, the availability of material for construction, and the acquaintance of the builder with the latest approved details also determine the several modifications of the apparatus in commercial use.

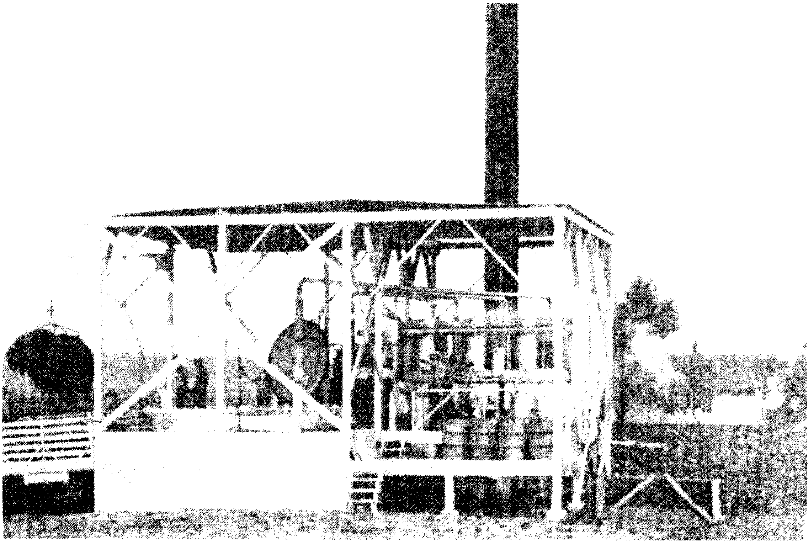
The volatile-oil stills used by mint growers in the United States for the production of peppermint and spearmint oils are of the type required for any large-scale production of volatile oils from plants when the aerial portions or roots are used. Various modifications are possible with respect to capacity, source of steam, method of operation, and other features to fit the particular needs and circumstances. To determine the market possibilities of a volatile oil not already in commercial use a small still that will hold a few hundred pounds of material can be used to advantage. Such a still may have the same general design as a commercial still, but it will cost less.

A distilling unit of the design and capacity widely used by mint growers consists of a high-pressure boiler for generating steam, a tub, a condenser and a receiver. The general arrangement of these parts may vary according to conditions, but the whole equipment should be so assembled that the outfit can be installed at the lowest cost and operated with the greatest saving of labor. Even the smallest distilling units generally include two tubs operated with one condenser, so that one tub will be charged while the other is in operation or is being discharged. For large operations four or more tubs are usually operated in pairs, with a condenser for each pair. Sometimes a single large condenser adequate for as many as four tubs.

All stills, regardless of their purpose must be registered with the U. S. Bureau of Internal Revenue. Applications for the required blank forms should be made to the United states Collector of Internal Revenue of the district in which the still is to be operated.

In most states the laws require periodic inspection of steam boilers of the size and type used for distilling mint.

Several terms. as "tub," "vat," and "retort," are commonly used to designate that part of the distilling equipment in which the herb is packed.

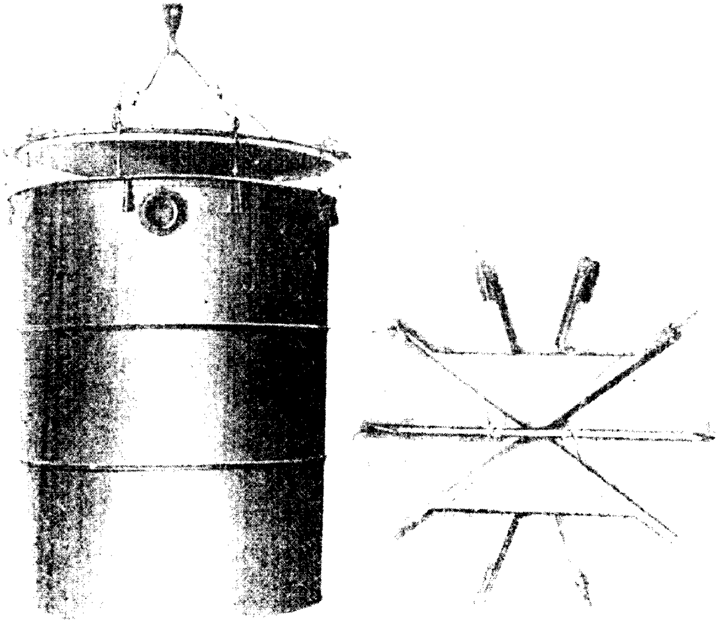


Tubs

Because it takes less time to discharge and reload a tub than to complete the distillation, a more efficient arrangement in a multitub unit is to equip each tub with its own condenser. This makes it possible to keep the tubs in mole nearly continuous operation and to eliminate some heavy iron pipes and valves that at times cause discoloration of the oil. Such a still is shown in figure 1.

The tubs are set down part way in a platform, which serves as a working floor, the tubs projecting usually about 2 feet above this floor. A lifting windlass on a crane or track is mounted in such a position that it can be used for loading and discharging each tub.

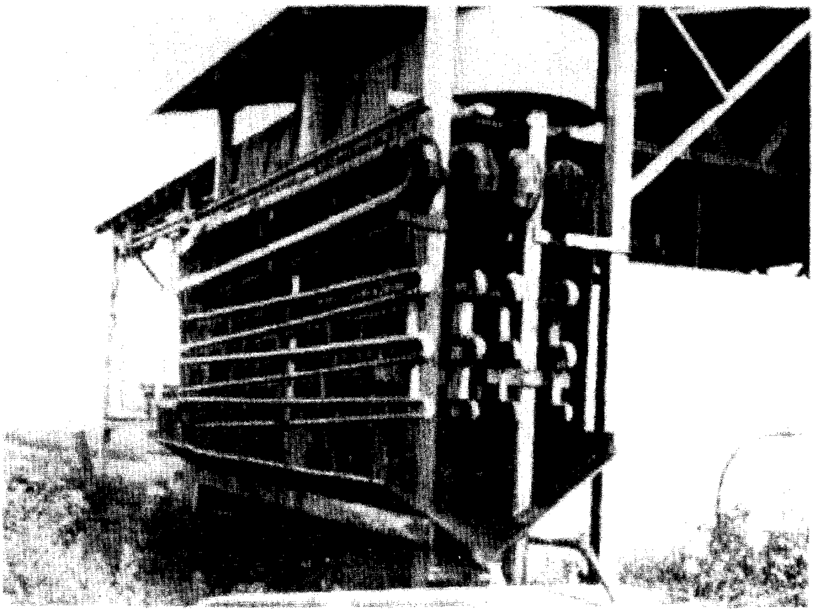
The tubs in use vary somewhat in size. They are 6 to 9 feet deep and 6 to 7 feet in diameter. Some are made slightly larger at the top than at the bottom to facilitate removal of the spent herb. Most of them are made of 16-gage galvanized steel (fig. 2). The steam tight gasket consists of a fiat strip of composition material riveted to the rim of the tub or to the under edge of the cover, which is fastened down with adjustable eccentric clamps.



The steam is admitted from a 1-1/2-inch pipe just above the bottom of the tub. An even distribution of steam through the charge is effected by means of a T with open ends. The outlet for the steam and oil vapors is through a pipe from the side just below the cover. This pipe has a diameter several times larger than that of the inlet pipe, to prevent pressure from building up in the tub. It usually extends upward and then passes overhead to the condenser (fig. 1).

Condenser

The worm-type drip condenser has been in use for many years in one form or another. One type consists of six or eight horizontal sheet-metal pipes joined at the ends by elbows to form a continuous series (fig. 3). The first two lengths of pipe from the top are 7 or 8 inches in diameter; the rest are reduced successively in size, the last one, from which the condensed oil and water flow, being 2 or 2-1/2 inches in diameter.



Condensation is obtained by water flowing over the pipe from a perforated trough mounted directly above the condenser. This water drains into a lead-off trough at the bottom. On some condensers a lead-off trough is mounted below the third pipe, with a second perforated trough immediately below to furnish a fresh supply of cold water to the remaining pipes. The water flows to the troughs by gravity from a reservoir overhead. A steady and ample supply of water is drawn by pumps either from wells or from small streams in the vicinity of the still. The hot water that drips from the condenser is frequently used in the boiler, thus saving fuel. At some convenient point in the upper part of the condenser is an air vent that can be opened when the steam is shut off. The air entering through it will prevent the condenser from collapsing, which otherwise is likely to occur because air cannot enter fast enough through the small end of the condenser.

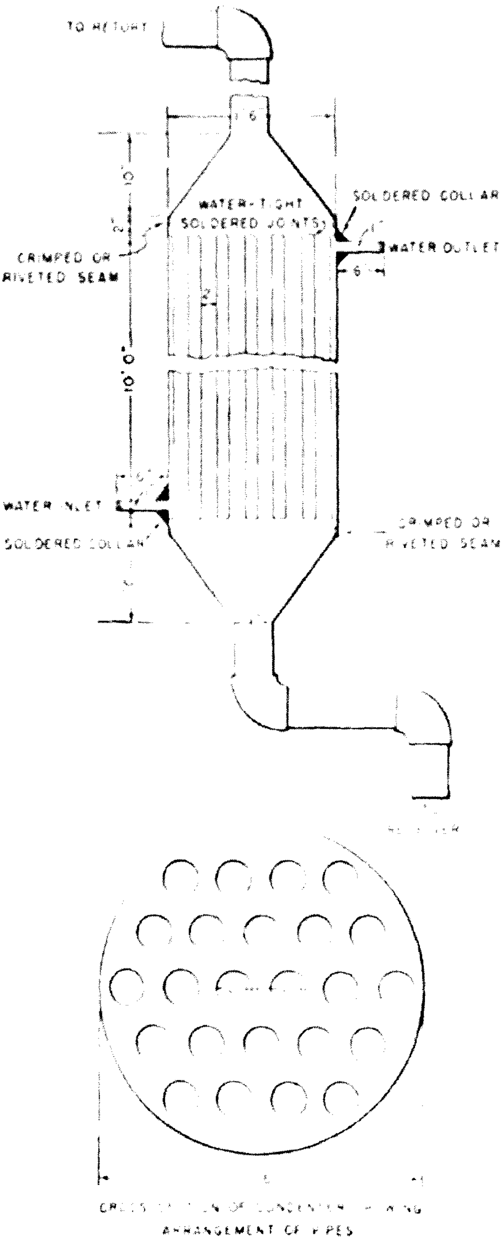
The type of condenser described came into extensive use mainly because It could be constructed at a small cost, but it is soon destroyed by rust. Built of copper pipe lined with tin, it will last many years.

On mint farms the drip-type worm condenser has recently been replaced largely by a tank type, which consists of a worm arrangement similar to that used with the drip type, but having the worm enclosed in a large tank. Water enters the tank continuously, so that the pipes are bathed constantly in cool water. For larger operations tubular condensers are sometimes used. Such a condenser consists of an upright galvanized-steel shell in which are mounted numerous upright galvanized-iron pipes of small diameter, somewhat like the fues in a boiler (fig. 4). As the vapors pass down through the pipes they are condensed by the cold water that circulates around the pipes; the condensed water and oil then flow from a narrow outlet into the receiver. Though rather expensive, such a condenser lasts a long time, requires little space, and is very efficient.

Oil Receiver

The receivers in which the oil is collected are of simple design and construction. They are cylindrical made of galvanised iron, and vary in capacity from a few to 50 gallons, depending on the capacity of the still. Most oils are lighter than water. When they are distilled the water is drawn off the bottom by means of a pipe that extends up along the side of the receiver to within a few inches of the top, where it is fitted with an elbow and a short extension pipe. As distillation proceeds the surface of the oil in the receiver is kept at the desired level by raising or lowering the end of the extension pipe from which the water drains. At a point near the top of the receiver is an outlet through which the oil can be drawn off (fig. 5).

A few oils, such as sassafras and wintergreen, are heavier than water and will separate in a layer on the bottom of the receiver. When distilling such oils, the gooseneck drainpipe is closed and a funnel of suitable size is set in the receiver with its stem extending into the water to about two-thirds of the distance to the bottom. As the mixture of water and oil runs into the funnel, the oil globules continue down through the stem and settle on the bottom of the receiver. From here the oil may be drawn off through a stopcock. The clear water is drained off through the outlet at the top used for drawing off oils lighter than water. This outlet should be of sufficient size to permit the water to drain oil as fast as it flows from the condenser into the receiver.



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Several devices are used to prevent churning of the contents of the receiver by the flow from the condenser, which might cause some of the oil to be drawn off with the water. In the case of oils lighter than water one method is to direct the flow into a funnel-topped pipe that extends about half the distance to the bottom of the receiver, where it is fitted with a short elbow that directs the oil toward the surface. Another method is to admit the flow from the condenser into the receiver through a pipe at a point about two-thirds the way down, a baffle plate immediately below the inlet directing the separated drops of oil toward the surface.

Other Types of Equipment

Some of the volatile oils produced in the United States on a small scale, especially those obtained from wild plants, are distilled with relatively crude equipment, often hand-made in part on the farm. The tubs are sometimes made of wooden staves, and the vapors are condensed by being passed through a long length of iron pipe laid along the ground or a series of such pipes in a wooden trough supplied with water from a small dammed-up stream. Heavy metal tubs are frequently used, in which case water is introduced with the plant material and steam is generated by means of a fire underneath. This eliminates the need for a boiler, thus reducing the cost of the equipment, although the time required to exhaust the charge is much greater.

Where the plants distilled grow wild it is usually necessary to move the stills from place to place as the plant supply is exhausted. Such itinerant stills are usually of the simplest types. They are probably less efficient than the commercial stills used for widely cultivated volatile-oil crops, but appear to serve best the purpose for which they are designed.

Operation of Volatile-Oil Stills

Preparation of Materials for Distillation

Material to be distilled, no matter of what nature, should be in a condition that insures the removal of the oil in the shortest time, due consideration being given to the cost of bringing it into that condition. Bulky material that cannot be readily packed and hence occupies much space should first be ground or chopped, in which condition it can be loaded into the tub more advantageously and the removal of the oil from it hastened. Green and succulent material may frequently be prepared by passing it through a feed cutter; heavy woody material must be chopped either by hand or with hogging machines. In the distillation of pine stumps and sassafras roots, as carried on in the Southeastern States, use is made of these machines. Certain seeds, such as anise, caraway, and coriander, are usually crushed, thus greatly facilitating the removal of the oil. Herbaceous material frequently is dried, either partially or completely, before distillation to obviate the handling of the unnecessary weight due to the large water content of the material. Such partial or complete drying also reduces the time required to exhaust the charge, as well as the volume of steam needed. An example of the practice is the partial drying of mint herb where large acreages are harvested. The wilted herb is referred to as mint hay; in that condition it is convenient to handle but is not dry enough for the leaves to break off and get lost in handling. Herbaceous material that is completely dried usually can be distilled without loss of oil, provided none of the principal oil-bearing portions are lost while being handled in that condition. Some volatile oils, however, suffer serious deterioration if the herbs containing them are allowed to dry before the oil is distilled.

Some plants from which volatile oils may be distilled do not contain the oil as such, but contain certain basal substances, which, under proper conditions, react with one another to form the oil. The oil may then be removed by the usual process. Examples of such oils are wintergreen, sweet birch, bitter almond, and mustard. The chemical reaction that results in the formation of these oils is readily induced by simply macerating the material or soaking the ground or chopped material with water for a suitable period, after which distillation may proceed. The material is usually macerated in the tub of the still, so that no transfer of the mixture is necessary.

The bulk of the oil usually distills over in the early period of the operation. Small quantities continue to collect for some time, depending on the manipulation of the steam current and the nature of the plant material. In most cases the distillation is complete in less than 2 hours; and in large-scale operations in less than an hour. To determine whether all the oil has been distilled over, when the operator is not experienced in the distilling of any particular material, a small quantity of the distillate from the condenser may be collected in a glass cylinder or a large glass test tube. If any small globules of oil separate, the distillation has not been completed. Whether or not it is advisable to continue the process depends on several considerations. If the oil is high-priced, it is well to continue the distillation further; but if it is of only moderate value and an abundance of plant material is available, it is more economical to shorten the process and thus increase the quantity of material that may be handled in a given time.

Disposal of Spent Material

After the charge has been exhausted, the top of the still may be taken off immediately and the spent material removed in any convenient manner. The practice of loading and discharging the still by means of either a derrick or a block and tackle greatly reduces the labor and saves much time. The spent material is often returned to the field as fertilizer; sometimes it may be used for fuel. In the commercial distillation of peppermint the spent herb is dried and used for stock fodder. Economics of this nature reduce production costs.

Care and Handling of Oil

The oil as removed from the receiver contains water, and a layer of emulsion consisting of oil and water is usually present also. It is advisable to let the oil stand in this condition in a suitable container long enough to permit the emulsion to break. Sometimes this takes place rapidly; again, it proceeds very slowly. Much depends on the character of the oil and the amount of churning that took place in the receiver during distillation. If a separatory funnel is available, the last portions of water and the emulsion may be drawn off from the oil and allowed to stand until the emulsion has broken, when the separated portions of the oil can be removed. If on standing the emulsion does not separate readily, transferring it to a funnel containing a folded filter paper may bring it about. On passing through the paper the emulsion is broken up and the oil and water collect in separate layers. The apparatus required for collecting, separating, and filtering the oils when small quantities are being prepared is shown in figure 6.

The presence of moisture in the oils makes them cloudy and detracts from their appearance. Moisture, if not removed, will hasten chemical changes in the oils, especially in the presence of air. This may appreciably affect their value. It is desirable therefore that the oils be dried as soon as possible by filtering through filter paper in an ordinary funnel. Filter paper for this purpose may usually be purchased in drug stores. Large quantities are usually filtered through chamois.

Filtering gives the oil a clear, bright appearance, which is a distinct asset when it is placed on the market. It does not, however, remove all traces of moisture. If the oil is to be kept any length of time and is of such a character that its value is affected by slight changes in composition, it must first be treated with a substance that will absorb this moisture. Dry sodium sulfate has a strong affinity for water, and the addition of small quantities, with occasional shaking, is sufficient to remove all final traces of moisture. The oil may then be filtered and placed in bottles or cans with only slight danger of any change in the composition for some time. It is advisable to fill the containers completely in order to exclude the air. The best bottles for the purpose are made of amber-colored glass; those of plain glass should be kept in a dark cabinet to prevent deterioration of the oil through the action of light.

In steam distillation traces of other volatile substances are sometimes distilled over with the oil, imparting an undesirable odor, which must be removed before the oil can be used. This removal is best accomplished by submitting the oil to a second distillation in an apparatus of the same type but smaller. By this procedure a small portion of heavy, highly colored oil is usually left behind in the still, while the portion distilled over is greatly improved in odor and color. An oil thus treated usually commands a higher price than the crude oil. Oils may also be improved in quality by redistilling them by direct heat under greatly reduced atmospheric pressure in specially designed apparatus. By this method certain undesirable fractions are eliminated. Oils that have been subjected to a process of redistillation are known as rectified oils.

Small distillers do not generally rectify their oil. Large producers who wish to meet a special demand for a superior product or who are themselves users of the oils, however, frequently rectify theirs oils that must conform to legal standards or that are used for the manufacture of products standardized by long practice to a definite flavor or odor must be handled with special care by the producer if a steady market is to be found.

Commercial Production of Volatile Oils in the United States

Of the large number of volatile oils consumed in the industries only a few are produced commercially in the United States. For various reasons the domestic production on the whole has not increased in variety, nor does it appear probable that there will be any appreciable increase in the near future. New sources of valuable oils may be developed to augment the total production, but this no doubt will be offset by the declining production of others, especially those obtained from natural sources that gradually become exhausted. The relatively high cost of labor in the United States has restricted this industry to oils that can he produced by a minimum expenditure of labor. In fact, the relatively high cost of labor acts as a serious bar to the production of a great number of valuable oils from plants that could be grown under our conditions of soil and climate.

The principal commercial oils produced in this country may conveniently be placed in three groups: (1) Those obtained from wild plants; (2) those obtained from plants grown commercially for the purpose; and (3) those obtained as byproducts in other industries.

Oil of Sassafras

The common sassafras (*Sassafras albidum* (Nutt.) Nees), is widespread and abundant on wastelands in the eastern third of the country, is the source of sassafras oil. The oil is widely used as a flavor in carbonated beverages and dentifrices and for its medicinal properties in some pharmaceutical preparations. It is produced mainly in Kentucky, Tennessee, North Carolina, Virginia, and southern Indiana and Ohio. All parts of the sassafras tree contain the oil in varying quantities, but only the roots and stumps are used. Some of the oil is distilled in small, rather primitive stills that are probably moved from one place to another as new supplies of the needed material must be found. There are several larger operators with more modern stills.

The raw materials for them is obtained either from farmers, who procure it from their land and deliver it to the still, or through the distiller's collection crews, who are provided with the necessary equipment. The trees are felled and the stumps pulled out of the ground. The stumps are cleaned of adhering dirt and hauled to the distillery where they are run through a hogging machine and reduced to small chips. The chips are stored above the still, into which they are loaded as needed. The bark of the root contains from 5 to 9 percent oil, whereas the wood contains less than 1 percent. When the sap is flowing in the spring or when the ground is frozen, much of the bark will strip from the roots and remain in the ground when the stumps are pulled. It is the practice, therefore, to engage in this operation in late summer or fall. Distillation is conducted in the usual way. Steam is admitted from a boiler and blown through the chips in the still. The operation is completed in about 4 hours. The yield of oil varies from 1.5 to 2 percent, depending on the proportion, of wood and bark in the charge.

Oil of Dill

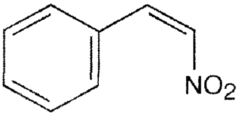
Dill oil, obtained from the herb *Anethum graveolens* L., has come into use as a substitute for the herb in the flavoring of pickles and other food products. It was first produced in the North Central States about 1930 in response to the demands of pickle and kraut manufacturers. Ohio, Indiana, and Michigan were the principal centers of production, which later shifted to Oregon and Idaho. For some time the center of production was in the vicinity of Berne, Ind., where up to 500 acres of dill was grown annually and six or seven stills were in operation. At that time the growers received $4 to $5 a pound under contract. A decline in price resulted in a gradual reduction in acreage until only about 5 percent of the former acreage was being grown there several years ago. Information on the acreage in the Northwest is not generally available, but at present the principal production of the crop is apparently in the Willamette Valley in Oregon.

In Indiana dill is sown, early in spring, directly in the field with a beet or bean drill, in rows about 22 inches apart. The crop is ready to harvest in 90 to 105 days. It is harvested with a grain binder, usually about the middle of July, when the earliest seed has ripened. The herb is allowed to cure in the field for a day or two and then distilled with the equipment used in distilling mint. It takes from 2-1/2 to 3 hours to exhaust the charge. The yield ranges from 15 to 50 pounds an acre. At times a second crop is obtained the same year, but the yield is small and usually unprofitable. There are several varieties of dill, some of which are not suitable for the purpose because they yield less oil or oil of poor quality.

The herb used for flavoring consists of the leaf, stem, and seed, the seed in various stages of maturity. To be a satisfactory substitute for the herb dill oil must have the same flavor. As the leaf oil and seed oil are quite different, it is essential that the oil be distilled from the herb harvested at the stage at which it is used for pickling.

Source: Sievers 1952 Reference: Sievers 1948.

Nitro-styrenes: Chapter 14



ß-Nitrostyrene

It is known that the natural base mescaline (trimethoxyphenylethylamine) which occurs in various kinds of anhalonium can be made synthetically by reducing 3,4,5-trimethoxynitrostyrene. It has now been found that in the same way there can be obtained the hitherto unknown O-homologues of this compound, which also have valuable therapeutic properties and, moreover may be used as parent materials for the manufacture of medicinal products.

Thus 3,4,5-triethoxy-phenylethylamine is obtained by reducing 3,4,5-triethoxynitrostyrene, for instance by treatment with a catalyst and hydrogen or by electrolysis. The compound thus obtained has properties similar to those of mescaline. It is, however, active even in essentially smaller doses.

In like manner the higher homologues or mixed alkoxy-derivatives of phenylethylamine may be made by reducing the corresponding 3,4,5-alkoxy-nitro-styrenes, that is to say such as contain higher or mixed alkoxy-groups.

A solution of 71.4 grams of 3,4,5-triethoxybenzaldehyde (3,4,5-triethoxy-benzaldehyde; white crystals which melt at 69-70°) and 23 grams of nitromethane in 150 cc. of alcohol is mixed in small portions while cooling with a solution of 30 grams of potassium hydroxide in 30 cc, of water and 60 cc. of methanol and the whole is then allowed to stand for a quarter of an hour at the ordinary temperature; it is then poured into 800 cc. of hydrochloric acid of 10 per cent. strength, cooled with ice, whereupon the nitrostyrene separates in the form of a yellow precipitate. When recrystallised from alcohol it forms yellow crystals which melt at 108—109° C.

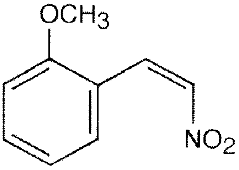
4-*n*-Butoxy-3,5-dimethoxy-benzaldehyde;
white crystals of melting point 54—55°

4-*n*-Butoxy-3,5-dimethoxynitrostyrene;
yellow crystals of melting point 94-96°

4-Benzyloxy-3,5-dimethoxy-benzaldehyde;
melting point 60—66°.

4-Benzyloxy-3,5-dimethoxy-nitrostyrene;
melts at 134—135° Source: Gesellschaft 1931

Preparation of 3-Ethoxy-ß-nitrostyrene



by Imperial Chemical Industries Limited
October 31, 1961 London, UK

A solution of 8.5 parts of potassium hydroxide in 27 parts of methanol is added during 30 minutes to a stirred solution of 50 parts of 3-ethoxybenzaldehyde in a mixture of 24 parts of nitromethane and 55 parts of ethanol at 5°C. The mixture is stirred for 15 minutes and a solution of 6.8 parts of sodium hydroxide in 33.5 parts of water is then added during 15 minutes at less than 10°C. The mixture is stirred for a further 30 minutes and is then poured into 350 parts of ice-cold water. The aqueous solution thus obtained is poured with stirring into a solution of 196 parts of concentrated hydrochloric acid in 235 parts of water. The mixture is filtered and the solid residue is crystallised from ethanol. There is thus obtained 3-ethoxy-ß-nitrostyrene, m.p. 104—105°C. Source: Imperial Chemical Industries Limited 1966

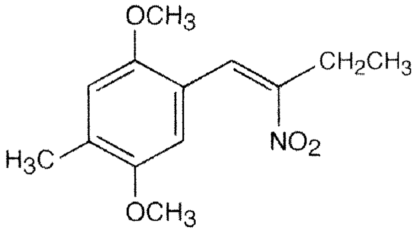
Preparation of 2,4-Dimethoxy-ß-methyl-ß-nitrostyrene

by Thornton W. Sargent, III, Alexander, T. Shulgin and Chester, A. Mathis
California, USA May 9, 1985

A solution consisting of 25 g of 2,4-dimethoxybenzaldehyde (Aldrich) in 200 mL. of nitroethane was treated with 0.5 g anhydrous ammonium acetate and held on a steam bath for 12 hours. The solvent was removed in vacuo from the mixture yielding 22.3 g of yellow crystals, m.p. 80°-81° C., upon cooling in 50 ml of methanol.

Source: Sargent 1987

Preparation of 2-Nitro-1-(2,5-Dimethoxy-4-Methylphenyl)-Butene-1



by Alexander Theodor Shulgin
Lafayette, California November 6, 1972

A mixture of 31.6 g. of 2,5-dimethoxy-4-methylbenzaldehyde, 20.2 mL. of 1-nitropropane, 6 mL. cyclohexylamine, and 50 mL. benzene is kept at reflux in a Dean Stark apparatus for 24 hours. Cooling results in the spontaneous crystallization of an orange product which on filtration and drying weighs 14.9 g. Recrystallization from methanol yields the product 2-nitro-(2,5-dimethoxy-4-methylphenyl)-butene-1 as an orange crystalline material, mp. 115°C. Source Shulgin 1976

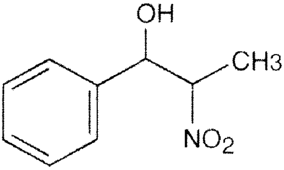
Preparation of 1-(3,4-Dihydroxyphenyl)-2-nitro-propylene

by Lepett S.P.A.
Milan, Italy February 19, 1965

To a solution of 144 g of protocatechualdehyde in 3000 mL. of nitroethane, heated to about 90°C, 14 g. of ammonium acetate are gradually added, the the mixture is heated at 100°C for 3 hours The excess nitroethane is then distilled off. The residue is 1-(3,4-dihydroxyphenyl)-2-nitroproplene, m.p. 148—149°C. Yield 192 g (94%).

Source: Lepett 1967

Preparation of 2-Methyl-2-nitro-phenyl-1-propanol



by William F. Bruce, Joseph Lester Szzabo
and Samuel Tubis
Delaware, Pennsylvania December 23, 1948

1.04 mols of NaOH are added to 80 mL. of water, and 1.00 mol of 2-nitropropane is then added with stirring until all dissolved. A rapid stream of CO2 is bubbled through the solution until pH=8.5 or less is obtained. With the temperature maintained at 40-50° C., 0.96 mole of benzaldehyde is added, dropwise, with rapid stirring. Heating is continued 4 hours, and stirring and CO2 stream are continued 24 hours. The resulting thick mixture is then diluted with three times its volume of water to dissolve the NaHCO3 formed, and extracted three times with 20% portions of ethyl ether. The ether is shaken repeatedly with cold 25% NaHSO3 to free it of unreacted benzaldehyde. The extracted ether solution is then concentrated on a steam bath, and finally freed of unreacted nitropropane by distilling the latter off under vacuum, using a water bath at 30° C., a Dry-Ice cooled receiver, and a pressure of 3-5 mm. of mercury.

The contents of the still-pot are then transferred to a beaker (heating gently to melt, if necessary), cooled in an ice-salt mixture to crystallize, filtered, and drained. Melting point of crude crystals: 57-60 C., after recrystallization from ethanol-water or petroleum ether-ethyl ether: 67° C. Source: Bruce 1952

Benzaldehydes: Chapter 15

Preparation of Vanillin from Peat

by Hermann Pauly and Kurt Feuerstein
Würzburg, Germany September 27, 1928

100 kg. of dry peat powder are mixed with a solution of 30 kg. of chromic acid in 700 kg. glacial acetic acid and oxidised by heating for 10 to 15 hours at a temperature of 40° C. After addition of 30 kg. of concentrated sulphuric acid the mixture is then boiled for 10 hours under reflux. From the solution separated from the crude fibre the sulphuric acid is removed by addition of the corresponding quantity of baryta acid 600 litres of the glacial acetic acid are removed by vacuum distillation. After diluting the residue with 200-litres of common salt solution the vanillin is extracted with ether and purified in the usual way. The yield amounts to about 0.9 kg. of crystallised vanillin.

A further 0.2 kg. of vanillin may be extracted from the acetic acid which has been removed by distillation. The yields obtained when using other substances in place of dry peat powder are as follows:

Water rye straw meal ------- 1.0 kg.
Beech wood meal ------------- 2.3 kg.
Maple wood meal ------------- 2.45 kg.
Elm wood meal ---------------- 3.2 kg.
Brown coal meal -------------- 1.8 kg.

Example 2

Ozone having a concentration of 5—8% is led into a well stirred mixture of 20 kg. of pinewood sawdust in 100 kg. of glacial acetic acid at room temperature until the wood is completely bleached. Seventy litres of the glacial acetic acid are then removed by vacuum distillation and the mixture remaining is diluted with water to its original volume. After addition of 0.3 kg. of sulphuric acid, the whole is hydrolysed by boiling under reflux and the solution and residue are further treated as in the preceding example. The yield of crystallised vanillin is about 2 kg.

Source: Pauly 1931

Benzaldehyde from Toluene and Sulfuric Acid

by Pierre Prosper Monet
Lyons, France April 29, 1898

Example 1

Three hundred kilograms of toluol, and seven hundred kilograms of sulfuric acid of sixty-five per cent. are mixed together in an apparatus fitted with a stirring device, and ninety kilograms of manganese binoxid are slowly added in the form of a fine powder during vigorous stirring The temperature is maintained at about 40° centigrade. After all the binoxid of manganese has been added the stirring device is kept in operation for some time in order to complete the reaction. The mixture of benzaldehyde and toluol is then distilled with steam, and the separation is effected in the well-known manner.

Preparation of Toluyaldehyde, (O.M.P.)

The xylenes are treated as stated in Example 1 at a temperature of about 25°. The oxidation takes place more readily than in the case of toluol.

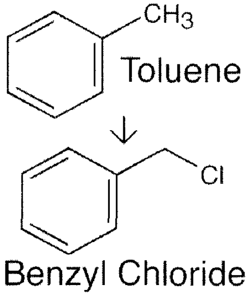
The process of manufacture discovered by me can also be applied to produce substituted aldehydes. For example, *ortho*-chlorbenzaldehyde can be easily produced by treating *ortho*-chlortoluene according to the method described in Example 1.

Nitro derivatives of the hydrocarbons, such as nitrotoluene and nitroxylene, also yield the corresponding aldehydes. The behavior of the hydroxyl derivatives toward oxidizing agents under the above conditions varies. Thus the methyl ether of *para*-cresol gives an aldehyde without difficulty, while the *ortho*-cresol compounds give no aldehyde under the same conditions.

The sulfonio derivatives of aromatic hydrocarbons, their chlorids amids, and esters, as well as the acetylated and methylated amido derivatives, give no aldehydes under the same conditions.
Source: Monnet 1898

Preparation of Benzyl Chloride from Toluene

by Herbert Levinstein and Walter Bader
Manchester, UK July 27, 1918



A sodium hypochlorite solution, containing one molecular proportion of active chlorine is well stirred with 3 molecular proportions of toluene and the mixture cooled to -5° C. or below. One half a molecular proportion of dilute sulphuric acid is then gradually added during six hours. instead of sulphuric acid, hydrochloric acid, boric acid, carbonic acid, acetic acid, etc., or an acid salt, such as sodium hydrogen sulphate, may be used. After standing the two layers are separated and the product of reaction distilled. Unchanged toluene passes over first, followed by pure benzylchloride. The residue contains a small quantity of benzal chloride, and 2% to 3% of highly chlorinated products. The yield of benzylchloride is about 60% to 70% of the theoretical yield calculated on the active chlorine present.

If larger amounts of hypochlorite are used the product contains correspondingly higher percentages of benzalchloride. For the purposes of preparing benzalchloride however, it is better to start with pure benzylchloride instead of toluene.

Example

One molecular proportion of benzylchloride is emulsified with a hypochlorite solution containing one-half of a molecular proportion of active chlorine and cooled to -5° C., or below. The equivalent quantity of dilute acid is then added within six to eight hours. After disappearance of the hypochlorous acid the product is separated from the aqueous solution. The benzalchloride is separated from unaltered benzylchloride and obtained pure by fractional distillation. Source: Levinstein 1919

Benzaldehyde from Benzal Chloride Using Hydrochloric Acid

by Friedrich Brühne and Karl-August Lipper
Krefeld, Germany November 6, 1978

Example 1

322 g (2 mols) of benzal chloride and 750 g of 25 percent strength hydrochloric acid are heated to the reflux temperature in a 1 liter three-necked flask with a stirrer, reflux condenser, gas inlet tube and thermometer, whilst stirring vigorously, and the mixture is kept under light reflux for 2 hours. A sump temperature of 106° C. is established. A weak stream of nitrogen is passed through the flask during the reaction. The off-gas escaping from the reflux condenser is absorbed in a washing tower, packed with Raschig rings, with 600 g of water, which are circulated by means of a pump. After cooling the mixture, 204.0 g of a light yellow coloured oil which, according to the titrimetric determination, contains 98.1% of benzaldehyde (=200.1 g of pure benzaldehyde) are obtained as the organic phase. This corresponds to a yield of 94.3% of theory. The benzaldehyde contains 0.06% of residue which cannot be distilled. Analysis of the benzaldehyde phase by gas chromatography gives a benzal chloride content of 0.1%. 680 g of 21.9 percent strength hydrochloric acid containing benzaldehyde as an impurity are obtained as the aqueous phase. The amount of hydrogen chloride obtained by saponifying the benzal chloride is 99.5% of theory.

In the next batch, the yield of benzaldehyde is increased to 97.6% of theory if the aqueous phase of the last batch is re-used, after filling up to 750 g with hydrochloric acid.

Example 2

1,610 g (10.0 mols) of benzal chloride and 2,100 g of 30.2 percent strength hydrochloric acid are heated to 125° C. in an enamelled stirred autoclave in the course of 35 minutes and the mixture is kept at this temperature for 45 minutes, whilst stirring vigorously, during which a pressure of 30 atmospheres gauge is established. After cooling, the autoclave is let down and the two phases are separated. After washing twice with a total of 188 g of water, the organic phase gives 912 g of pure benzaldehyde (85.8% of theory) with a benzal chloride content of 0.1% and a content of residue which cannot be distilled of 0.06%.

Source: Brühne 1980

Benzaldehyde from Benzal Chloride using Zinc Chloride

by General Aniline
New York, New York February 17, 1960

To 700 parts by weight of distilled benzal chloride there was added 2 parts by weight of anhydrous zinc chloride and the two were mixed thoroughly with stirring while heating to 105—110°C. As soon as the reaction mixture was at 105—110°C. the addition of water was begun at a slow rate, while maintaining the reaction temperature at 110—120°C. The addition of water was continued until a total of 85 parts by weight of water had been added (approximately 5% excess) at which time the evolution of hydrogen chloride ceased. Reaction temperature was maintained for another hour to be sure that all the HCl had been removed, and the benzaldehyde was then removed by vacuum distillation. The yield of benzaldehyde recovered at non-distillation was 95% of theory and the purity of the product better than 96.5%

Source General Aniline 1962

Manufacture of Benzaldehyde from Benzyl Chloride using Hexamine

by Fabriques
Issy, France March 7, 1912

A solution of 14 kilos of hexamethylenetetramine in 40 litres of alcohol of 60 per cent. strength is mixed with 12.5 kilos of benzyl chloride and the mixture is heated on then water bath in a reflux apparatus for 5-6 hours; 20 litres of water are then added, the greater part of the alcohol distilled away and the residue carried over with steam. The liquid carried over is extracted by means of a volatile solvent and the aldehyde is purified by means of its bisulphite compound. The yield of purified benzaldehyde amounts to 7.5 to 9 kilos.

The reaction may also be carried out without addition of alcohol, that is to say in an aqueous solution. Thus, 12.65 kilos of benzyl chloride are heated for two hours with a solution of 14 kilos of hexamethylenetetramine in 60 litres of water, and the aldehyde is then distilled with steam; after purification with sodium bisulphite a good yield of benzaldehyde is obtained. Source: Fabriques 1914

Benzyl Alcohol from Benzyl Chloride

by Louis T. Rosenberg
Ridgefied Park, New Jersey July 27, 1938

100 parts of benzyl chloride and 430 parts of a 10% solution of sodium carbonate are admixed and refluxed for about 3 hours. 12.5 parts of a 45% sodium hydroxide solution are then added, whereupon the mixture is refluxed for an hour. The solution is then cooled and the oily layer (benzyl alcohol) is separated from the aqueous layer, the latter being extracted one or more times with a solvent such as benzol. The benzyl alcohol and benzol extractions are distilled to recover the benzol. In carrying out the above process, 88.5 parts of benzyl alcohol were recovered which amounts to a 98% yield. Source: Rosenberg 1940

Purification of Benzyl Alcohol

by Ralph E. Montonna
Syracuse, New York May 18, 1921

100 parts of crude benzyl alcohol, obtained by the hydrolysis of benzyl chloride with an alkali, are dissolved in 200 parts of benzol, dried with 5 to 10 parts sodium carbonate, filtered and stirred with 100 parts powdered anhydrous calcium chloride. The thick, pasty emulsion which forms with liberation of heat, is allowed to stand for several hours and is then filtered add the filter cake is then washed with approximately 200 parts of benzol.

The filter cake is then stirred with 125 parts of water, the resulting oily layer is separated from the calcium chloride solution, dried with sodium carbonate and then distilled. The resulting alcohol is free from chlorine. Source: Montonna 1922

Benzyl Bromide from Benzyl Alcohol

by Marcia Elizabeth Christy
Perkasie, Pennsylvania January 3, 1975

A suspension of 28.5 g. (0.098 mole) of 2-(4-bromophenethyl)-benzyl alcohol in 150 mL. of 48% hydrobromic acid is stirred at reflux for 3 hours. The cooled two-phase mixture is extracted with benzene. Evaporation of the washed and dried benzene extract under reduced pressure leaves the product as the residual solid, m.p. 63°-75° C. Recrystallization from hexane affords purified material, m.p. 76°-77.5° C. A sample for analysis melts at 76.5°-78° C. after further recrystallization from hexane. Source: Christy 1976

Methylation of Hydroxybenzaldehydes

by Christian Maliverney
Lyons, France October 23, 1995

Ethyl Vanillin Methylation

After a nitrogen atmosphere has been established, 332.4 g of ethyl vanillin are loaded into a 2000 mL. 3-necked round-bottomed flask heated by an electric heating mantle, stirred mechanically, and equipped with two dropping funnels, a condenser, devices for measuring the temperature and the pH, and a nitrogen inlet.

0.5 liter of water is added and the mixture is heated to 90° C.

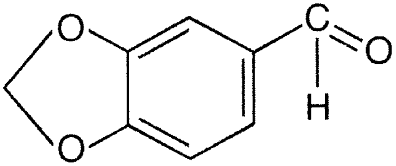
360 g of aqueous 30.5% sodium hydroxide solution (pH=9) are added, followed by 350 g of dimethyl sulphate, over 2 hours.

The reaction medium is left stirring for 1 hour at 90° C. and is then cooled to 70° C. and allowed to separate by settling.

The upper organic layer is washed and is then distilled at 120° C. under a reduced pressure of 10 mm of mercury (1330 Pa), to give 3-ethoxy-4-methoxybenzaldehyde.

The results obtained, after assaying by high performance liquid chromatography, are as follows:

Yield before distillation: 98.4%
Purity before distillation: 97% (3% water)
Purity after distillation: 99.9%
Source: Maliverney 1997



Piperonal

Prepartion of Piperonal: Chapter 16 Process for Preparing Piperonal

by Katsumasa Harada, Masashi Shiral,
Koji Shiba and Toshio Furuya
Ube, Japan February 2, 2001

Piperonal is a base material for preparing a heliotrope type perfume and has widely been used as a perfume for general cosmetics, and in addition, it is a useful compound as a starting material for synthesis of medical and agricultural chemicals and a brightener for metal plating.

As a method for producing piperonal, it has been generally known a method of oxidizing 3,4-methylenedioxy-mandelic acid with nitric acid (for example, P. S. Raman *Current Science*, 27, 22 (1958), *Perfumer & Flavourist*, 14, 13 (1989), *EP* 429316, etc.). Also, it has been known that 3,4-methylenedioxymandelic acid can be produced by reacting 1,2-methylenedioxybenzene and glyoxylic acid in the presence of sulfuric acid, etc. (for example, Japanese Provisional Patent Publication No. 95573/1979, *Perfumer & Flavourist*, 14, 13 (1989), etc.).

In the method of producing piperonal through 3,4-methylenedioxymandelic acid as mentioned above, the 3,4-methylenedioxymandelic acid formed by the initial reaction (hereinafter referred to as addition reaction) of 1,2-methylenedioxybenzene and glyoxylic acid is insoluble in the reaction system and precipitates as crystals. Thus, after separating the crystals of the 3,4-methylenedioxy-mandelic acid by an operation such as filtration, a subsequent reaction (hereinafter referred to as oxidation reaction) of 3,4-methylenedioxymandelic acid and nitric acid has been carried out. However, operations such as filtration, etc. are complicated, and this method is disadvantageous as an industrial preparation process.

On the other hand, it has been known a process for producing piperonal by carrying out an addition reaction and an oxidation reaction continuously without separating and purifying 3,4-methylenedioxymandelic acid in the course of the operations (Japanese Provisional Patent Publication No. 330755/1995). In this process, a relatively high quality piperonal can be produced with high yield. However, at the time of oxidation reaction, 1,2-methylenedioxy-4-nitrobenzene is contaminated in crude piperonal in an amount of 0.5 to 1.0% by weight or so. This

1,2-methylenedioxy-4-nitrobenzene is a compound which can be confirmed to be colored with naked eyes even when it is contaminated in piperonal in an amount of several tens ppm or more, and when it is once formed, it is difficult to remove from piperonal by a general purification method such as distillation, recrystallization, activated charcoal treatment, etc. Thus, there is a problem of lowering quality of the product by causing coloring of piperonal.

An object of the present invention is to provide a process which is capable of producing a high quality piperonal with high yield by completely inhibiting formation of 1,2-methylenedioxy-4-nitrobenzene, without taking out 3,4-methylenedioxymandelic acid which is an intermediate in the course of the reaction as a crystal, and carrying out from the above-mentioned addition reaction step to the oxidation reaction step continuously using 1,2-methylenedioxybenzene as a starting material.

Example 1

In a flat bottom separable flask having an inner volume of 7 liters, 500.0 g (4.09 mol) of 1,2-methylenedioxybenzene and 250 mL. of 4-methyl-2-pentanone were charged under nitrogen atmosphere, and the mixture was cooled to -5° C. while stirring. Then, a mixture comprising 833.4 g (4.44 mol) of a 40% by weight aqueous glyoxylic acid solution and 857.8 g (8.40 mol) of 96% by weight sulfuric acid was gradually added dropwise, and then, the mixture was stirred at -5.° C. for 21 hours.

Then, 3000 mL. of 4-methyl-2-pentanone was added, and 1030.0 g (16.9 mol) of 28% by weight aqueous ammonia was gradually added to the mixture while maintaining the liquid temperature to -10 to 5° C. to effect neutralization. After the neutralization, the mixture was heated to 80° C., and 3,4-methylenedioxymandelic acid was extracted in a 4-methyl-2-pentanone layer (an organic solvent layer). At this time, the reaction mixture was separated into two layers of an organic solvent layer and an aqueous layer.

Then, the aqueous layer was removed, and the organic solvent layer was concentrated (2200 mL. of 4-methyl-2-pentanone was removed). After concentration, the reaction mixture in a slurry state was transferred to a round bottom separable flask with an inner volume of 20 liters, and cooled to 10° C. while stirring under nitrogen atmosphere. Thereafter, 1746.7 g (2.78 mol) of 10% by weight nitric acid was gradually added dropwise, and the temperature of the mixture was raised to 50° C. and the mixture was stirred at the temperature for one hour.

After completion of the reaction, the mixture was cooled to 25° C., 140 mL. (1.00 mol) of a 25% by weight aqueous sodium hydroxide solution was added to the mixture to make up the whole reaction mixture weak basic (pH=7.9). Subsequently, 4-methyl-2-pentanone layer (an organic solvent layer) and an aqueous layer were separated, and the organic solvent layer was analyzed by gas chromatography, then no 1,2-methylenedioxy-4-nitrobenzene which is a by-product was detected. Also, when it was analyzed by high performance liquid chromatography, a conversion of 1,2-methylenedioxybenzene was 97%, and a yield of piperonal was 78% (in terms of mole).

Example 2

In a flat bottom separable flask having an inner volume of 500 mL., 50.0 g (409.4 mmol) of 1,2-methylenedioxybenzene and 50 mL. of acetic acid were charged under nitrogen atmosphere, and then, the mixture was cooled to 0° C. while stirring. Then, a mixture of 83.4 g (450.6 mmol) of a 40% by weight glyoxylic acid aqueous solution and 85.8 g (839.8 mmol) of 96% by weight sulfuric acid was gradually added dropwise, and then, the mixture was stirred at 5° C. for 21 hours.

Then, 200 mL. of ethyl acetate was added to the mixture, and then, 102.0 g (1677 mmol) of 28% by weight aqueous ammonia was gradually added to the mixture while maintaining the liquid temperature to -10 to 5° C. to effect neutralization. After the neutralization, the mixture was heated to 60° C., and the 3,4-methylenedioxymandelic acid was extracted in an ethyl acetate layer (an organic solvent layer). At this time, the reaction mixture was separated into two layers of an organic solvent layer and an aqueous layer.

Then, the aqueous layer was removed, and the organic solvent layer was concentrated (ethyl acetate was completely removed by distillation), 173 mL. of water and 160 mL. of toluene were newly added to the concentrate, and the mixture was cooled to 0° C. while stirring under nitrogen atmosphere. Then, 33.9 g (328.2 mmol) of 61% by weight nitric acid was gradually added dropwise, and the temperature of the mixture was raised to 40° C., and the mixture was stirred at the temperature for one hour.

After completion of the reaction, the mixture was cooled to 0° C., 80 mL. (0.57 mol) of a 25% by weight aqueous sodium hydroxide solution was added to the mixture to make up the whole reaction mixture weak basic (pH=7.9). Subsequently, the toluene layer and the aqueous layer were separated, and the toluene layer was analyzed by gas chromatography, no 1,2-methylenedioxy-4-nitrobenzene which is a by-product was detected. Also, when it was analyzed by high performance liquid chromatography, a conversion of 1,2-methylenedioxybenzene was 97%, and a yield of the piperonal was 80% (in terms of mole).

Source: Harada 2004

Preparation Process for Piperonal

by Christian Sidot and Yani Christidis

France November 2, 1990

The following are mixed together under agitation at ambient temperature:

294.23 g (1.5 mole) of 3,4-methylenedioxy mandelic acid;
562 g of water;
258.75 g of 37% hydrochloric acid being 2.625 moles;
2.1 g of 69% nitric acid being 23 mmoles.

The suspension obtained is heated under agitation at 43°+- 2° C., then 103.5 mg (1.5 mmole) of sodium nitrite dissolved in 4 g of water is introduced rapidly at this temperature, then 107.5 g of 69% nitric acid, being 1.177 mole, is introduced slowly, over about three hours, in such a way so that the temperature of the reaction medium is maintained at between 40° and 50° C. without using external heating or cooling. At the end of the introduction, the reaction medium is left for one our under agitation at 43°+- 2° C., then it is cooled down to ambient temperature and finally extraction takes place three times with 600 g of trichloro-1,1,1-ethane. The re-united organic phases are then washed successively, once with water, three times with a saturated aqueous solution of sodium hydrogen carbonate and finally once with water before being concentrated under reduced pressure.

Thus 220 g (1.46 mole) of crude piperonal is isolated which is purified by distillation under reduced pressure.

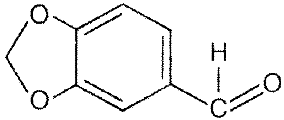
Thus 178 g (1.186 mole) of pure piperonal is isolated distilling at 106° C. under a vacuum of 2.4 mbars and having a melting point of 37°+1°C. The yield is established at 79% of the theoretically calculated value relative to the 3,4-methylenedioxy mandelic acid used.

Source: Sidot 1992

Preparation of Heliotropyl Chloride

by John Warcup Cornforth and John Enest Hawes
Hague, Netherlands May 23, 1975

Heliotropin (also known as piperonal, or 3,4-methylenedioxybenzaldehyde and having the structural formula is an important aroma and flavour chemical and is also an intermediate in syntheses of other aroma chemicals and some pharmaccutical chemicals.



Piperonal

In general heliotropin is manufactured from safrole, which is a component of many essential oils, of which the most important are those of camphor, sassafras, and *Ocotea pretiosa* (Brazil). Safrole is isomerized to isosafrole which is then oxidized to heliotropin, usually with chromic acid or ozone.

It has also been suggested to manufacture heliotropin starting from catechol (*J. Gen. Chem., USSR*, 1938, 8, 1975). This method involves a 3-step process which comprises 1) the preparation of methylenedioxybenzene from catechol, 2) the conversion of methylenedioxybenzene with paraformaldehyde and hydrogen chloride to heliotropyl chloride and 3) the reaction of the latter with hexamethylenetetramine in ethanol to obtain heliotropin with an overall yield of 11—28 % based on catechol. An improvement in the yield of step 1), and thus overall yield, can be obtained by employing a process for preparation of methylenedioxybenzene from catechol as described in U.K. patent specification 1,097,270 which involves the reaction of catechol with a methylene dihalide under alkaline conditions in the presences of a highly polar, aprotic solvent.

Example 1

(a) Paraformaldehyde (3.0 g, 0.1 mole) was suspended in cold (0°C) aqueous hydrogen chloride (20 mL.) that had been saturated at 0°C. Methylenedioxybenzene, hereinafter referred to as MDOB, (12.2 g, 0.1 mole) was added and the reaction mixture was stirred at 0° C for 4 hours. The oil was separated, the aqueous layer extracted three times with methylene chloride (10 ml portions), the total organic layers dried with MgSO4 and the solvent removed in vacuo.

Example 2

Chloromethylation of methylenedioxybenzene

(a) Paraformaldehyde (4.5 g, 0.15 mole) was suspended at 0°C in saturated aqueous hydrogen chloride (20 mL.). MDOB (12.2 g, 0.1 mole) was added and the reaction mixture stirred between 17° and 20°C with a slow stream of hydrogen chloride passing through the mixture. Stirring was continued for 1.5 hours when almost all the MDOB had disappeared. The mixture, composed mainly of heliotropyl chloride together with some bischloromethyl-methylenedioxybenzene and MDOB was separated, the aqueous layer extracted twice with 10 mL. portions of methylene chloride and the total organic layer evaporated at 30°—35°C in vacuo. Source: Cornforth 1979

Preparation of Methylenedioxybenzene

by John W. Cornforth
New York, New York October 13, 1965

Most suitable as highly polar, aprotic solvents are dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide and sulfolane, and of these dimethyl sulfoxide or an analogue thereof is preferred.

Preferably, the highly polar liquid used is a solvent for the reactants and reaction product and sufficient liquid is used to maintain the reaction mixture as a readily fluid solution. In cases where one or both of the reactants and/or the product is not readily and completely soluble in the liquid, sufficient liquid should be used to maintain the reaction mixture in a readily fluid condition. As has already been pointed out, within limits, greater dilution results in higher yields of product. but requires longer reaction times. Based upon all of these considerations, it is desirable to employ at least two parts by weight of the highly polar liquid per part by weight of the aromatic reactant. Preferably the weight ratio, liquid/aromatic reactant, is at least 4/1, with optimum results ordinaryly being obtained when the ratio is from about 5:1 to about 15:1. A liquid/aromatic reactant ratio in excess of about 20/1 is generally unnecessary and undesirable as unduly extending the time required to effect the desired conversion.

Generally speaking, about stoichiometric quantities of the reactants are employed—that is, about one mole of methylene dihalide and two moles of base per mole of aromatic reactant charged. In some cases, it may be desirable to employ a slight to moderate excess—for example 5-50% excess of the base and/or the methylene halide to insure completion of the reaction.

The reaction is conveniently conducted at temperatures of about 80-160° C., temperatures of 100-140° C. generally being most suitable.

Although the enhanced speed of reaction in the highly polar, aprotic solvent makes it possible to effect the reaction in the minimum time, if the optimum yield of product is also desired it is preferable for the concentration of ions in the solvent not to exceed 1 molar. Preferably the concentration of these ions is maintained as low as possible by slowly adding the catechol... to the reaction mixture. During the course of this slow addition the ions react as they are formed, and are therefore always present in a very high dilution. When the alkaline conditions needed for the reaction are provided by the addition of an alkali metal hydroxide to the reaction mixture, it is usually most convenient and satisfactory to add the catechol... and the alkali metal hydroxide separately, simultaneously and slowly to a solution of methylene chloride in the highly polar, aprotic solvent.

The following examples illustrate application of the process of the invention in particular instances. In these examples, parts by weight (w.) bear the same relation to parts by volume (v.) as does the kilogram to the litre.

Preparation of Methylenedioxybenzene

(a) Catechol (11 w.) and methylene chloride (10 w.) were dissolved in dimethyl sulfoxide (40 v.). Powdered sodium hydroxide (8.3 w.) was added and the mixture was heated in a nitrogen atmosphere and under a reflux condenser in a bath at 120° C. The reaction was vigorous. After 10 minutes steam was passed in and steam distillation carried out. The distillate was saturated with salt and extracted with light petroleum (B.P. 40-60° C.). The petroleum layer was washed with aqueous sodium hydroxide and then distilled. Methylenedioxybenzene 5.6 w., 46% yield, was collected at 173-175° C./760 torr as a colorless oil, index of refraction (nD21): 1.5377

Analysis (percent by weight).—Found: C, 68.5; H, 4.7. $C_7H_6O_2$ requires: C, 68.8; H, 4.9.

(b) The reaction was carried out as above using 100 v. of dimethyl sulfoxide. The heating time was 30 minutes. Methylenedioxybenzene was obtained, 8.35 w., 68% yield.

(c) The reaction was carried out as in (a) above using 150 v. of dimethyl sulfoxide. The heating time was 70 minutes. Yield 8.9 w., 73 %.

(f) Dimethyl sulfoxide (500 v.) and methylene chloride (100 v.) were heated at 125-130° C. under nitrogen, in an apparatus designed to allow the addition of solid materials separately and simultaneously.

Catechol pellets (110 w. in 5.5 w. portions) and sodium hydroxide pellets (83 w. in 4.15 w. portions) were added at 5 minute intervals, the total addition time being 105 minutes. The reaction mixture was stirred well throughout and the internal temperature was maintained at 125-130° C.

Twenty minutes after the addition of catechol and sodium hydroxide was complete, further portions of methylene chloride (20 w.) and sodium hydroxide (3 w.) were added at 125-130° C. The reaction was stirred at this temperature for a further 70 minutes and then the solids addition head was replaced by a Vigreux column and a constant take-off distillation head. Water (50 v.) was added and the methylenedioxybenzene/water azeotrope was distilled off at 98-100° C., more water being added slowly to the reaction mixture as distillation proceeded.

Methylenedioxybenzene no longer separated from the distillate after approximately 600 v. of distillate had been collected. Distillation of the residue then recovered dimethyl sulfoxide (490 v.).

The methylenedioxybenzene layer was separated and the aqueous layer extracted with ether (3 x 50 v. portions). The combined methylenedioxybenzene and ether extract was dried and distilled. The yield of methylenedioxybenzene was 91%, B.P. 173-175° C./760 torr.

Preparation of Piperonal
3,4-Methylenedioxybenzaldehyde

The reaction was carried out as in Example 1(f) using protocatechuic aldehyde (13.8 w.) and the product was isolated from the reaction mixture by steam distillation. Piperonal was isolated in 61% yield and was identified by comparison with an authentic sample.

Source: Cornforth 1969

Preparation of Protocatechualdehyde

by Sumio Umemura, Nagaaki Takamitsu, Takuji Enomiya, Hiroshi Shiraishi, and Takato Nakamura
Ube, Japan January 16, 1978

Example 1

To 45 mL. of a 2 N aqueous solution of sodium hydroxide were added 5.50 g of catechol, 14.25 g of a 20 wt % aqueous solution of glyoxylic acid and 2.50 g of aluminium oxide [manufactured by Kishida Chem. Co., Ltd., trade name: Kassei Alumina], and the mixture was subjected to reaction with stirring at 25° C. for 24 hours.

The aluminium oxide was separated from the reaction mixture by filtration and thus a reaction liquid was obtained. The aluminium oxide separated by filtration was washed with 20 mL. of a 1 N aqueous solution of sodium hydroxide and the washing was added to the reaction liquid. The reaction liquid was adjusted to pH 6 by the addition of a 12 N hydrochloric acid and then the unaltered catechol was extracted three times with 50 mL. portions of diethyl ether. From the extract was recovered 1.61 g of catechol.

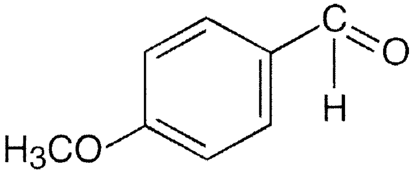
After nitrogen gas was blown into the aqueous layer obtained after extraction to remove the dissolved oxygen, 33 g of sodium carbonate was added thereto to adjust the pH value to 10.5. Further, 20 g of a powdery copper (II) oxide was added thereto, and the mixture was placed into an autoclave and subjected to reaction at 98° C. for 50 minutes with stirring while the pressure was allowed to rise. The pH value of the reaction liquid after reaction was 10.0.

After cooling the reaction mixture, the copper oxide was separated by filtration. To the thus obtained reaction liquid was added a 12 N hydrochloric acid to adjust the pH value to 2. Organic substances in the solution were extracted six times with 150 mL. portions of diethyl ether.

Protocatechualdehyde in the extract was determined by gas chromatography.

The conversion of catechol was 70.7%, the yield of protocatechualdehyde was 4.51 g and the selectivity (based on the catechol consumed in the first step) was 92.4%.

Source: Umemura 1979



Anisaldehyde

p-Methoxybenzaldehyde: Chapter 17 by Oxidation of *p*-Methoxy-toluene

by Arthur Lewinsohn
Berlin, Germany November, 1923

In a lead-lined or enameled stirring vessel of 1,200 litres content, 95 kilos of concentrated sulphuric acid are stirred with 200 litres of of water and cooled. When it is quite cold, 75 kilos of *p*-cresol methyl ether are added at once, and mixture is warmed to 35-37°. At this temperature 75 kilos of finely powdered manganese dioxide (85-90% $MnO2$) are added in lots of 2-3 kilos every five to ten minutes. It is essential to maintain this temperature within narrow limits if a good yield is to be obtained. The operation is begun in the morning, and after all manganese dioxide has been added the stem is turned off and stirring continued until evening (i.e. 5-6 hours longer). Next day the water is run off and the crude aubepine stored for purification.

Purification of Crude Aubepine

A mixture of 200 kilos of water, 230 kilos of crude aubepine, and a solution of 120 kilos of solid sodium bisulphite in 185 kilos of water is heated in an enameled vessel (the oxidation vessel maybe used) to 50° for six hours. The stirred and steam are then stopped and the product is allowed to settle overnight. The aqueous liquor is separated from a certain amount of undissolved oil (Oil R) and stirred in another vessel (fitted with reflux condenser) 50 kilos of benzene for 3-4 hours without heating. The aqueous layer, freed in this way from non-aldehyde constituents, contains the bisulphite compound of anisaldehyde, and is transferred to the fresh vessel again, where it is decomposed by the addition of 60 kilos of soda ash and distilled in steam.

The unattacked "Oil R" is treated in a similar manner with fresh bisulphite. The "Oil R 1" still undissolved by this second treatment is steam-distilled with the addition of 6 kilos of soda ash. *p*-Cresol methyl ether is recovered from the main distillate; the last portions contain also some aubepine, which is added to the next batch for purification.

The benzene extract leaves on distillation an oil from which in the same way *p*-cresol methyl ether and a little aubepine are recovered.

The aubepine is finally distilled in very high vacuum, and is then obtained as a water-white, clear oil with a very pleasant odour.

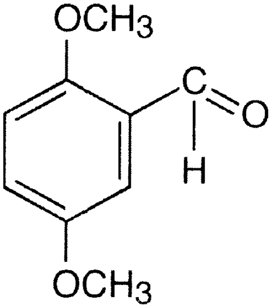
Source: Lewinsohn 1923

p-Cresol Methyl Ether (*p*-Methoxy-toluene) Preparation

by Arthur Lewinsohn
Berlin, Germany November, 1923

To a solution of *p*-cresol in an iron, 300-litre stirring vessel, fitted with reflux condenser, 40 kilos of dimethyl sulphate are added with stirring, the temperature being kept below 30°. The mixture is warmed at 70° for one hour, and then distilled in steam. The cresol methyl ether passes over readily with the steam and forms a heavy oily layer. The crude oil is separated and forms a heavy oily layer. The crude oil is separated and used for oxidation.

Source: Lewinsohn 1923



2,5-Dimethoxybenzaldehyde

2,5-Dimethoxybenzaldehyde: Chapter 18

p-Dimethoxybenzaldehyde Preparation

by Shinichi Imai and Kazuya Sano
Kanagawa, Japan March 13, 1975

Dimethyl sulfate, diethyl sulfate and potassium carbonate used in this invention may be used as the commercially available materials. It is preferred for high yields that the amounts of potassium carbonate and dimethyl sulfate or diethyl sulfate be present in greater than equimolecular amounts to the 2-hydroxy-5-methoxybenzaldehyde. However the reaction will also proceed with amounts less than equimolar amounts. Since amounts in great excess do not give rise to any advantages and add to the cost of the process, generally it is sufficient to use less than 1.5 times the molecular amount. With respect to the reaction temperatures which can be employed, too low a temperature results in a slow reaction rate and, on the other hand, too high a temperature results in too rapid of a reaction rate. For instance when the reaction is carried out at 120° C without a solvent using potassium carbonate and dimethyl sulfate, the reaction mixture resinifies before the completion of the reaction and colors. Therefore, generally, the reaction both in the presence or absence of a solvent is preferably carried out at a temperature between room temperature and 100° C. Generally, when a solvent is used, the reaction is carried out near the boiling point of the solvent.

While reaction solvents are not necessary for the process of this invention, suitable solvents may be employed if desired. If solvents are used it is necessary to select solvents which per se are not alkylated, i.e.,those which are inert to the alkylation effects of the dialkyl sulfate. Suitable such non-alkylatable solvents are diethyl ether, dioxane, acetone methyl ethyl ketone, ethyl acetate, butyl acetate, tetrahydrofuran, and the like. When the desired compound is recovered by pouring the reaction mixture into water after the completion of the reaction, solvents such as dioxane, acetone and methyl ethyl ketone miscible with water are preferably used. For instance, acetone is preferred. Agitation causes the reaction to proceed rapidly. The reaction time can be varied over a wide range depending upon conditions such as reaction temperature and agitation. For example, the reaction time can vary from several tens of minutes to several days. When the reaction is completed, which can be determined by gas chromatographic analysis, for example, the reaction mixture is poured into water and the desired compound is obtained by recovering the precipitated crystals. The compound obtained by such treatments is pure enough that further recrystallization is unnecessary. According to this invention a high yield of near 100 percent is attained with the selection of suitable conditions.

Example 1

50 g of 2-hydroxy-5-methoxybenzaldehyde, 68 g of potassium carbonate and 50 g of dimethyl sulfate were refluxed in 250 mL. of acetone for about 3 hours under stirring. After the reaction, the reaction mixture was filtered and the acetone was distilled off from the filtrate and then the residue was poured into 300 mL. of water. The precipitated crystals were collected by filtration and dried whereby 45 g of 2,5-dimethoxybenzaldehyde having a melting point of 48° C were obtained (yield 82.5%).

Example 2

On standing, the mixture of 2-hydroxy-5-methoxybenzaldehyde, potassium carbonate and dimethyl sulfate as in Example 1 at room temperatures the reaction was completed in 7 days. This was confirmed by gas chromatography. By treating the reaction mixture as described in Example 1, 44.5 g of 2,5-dimethoxybenzaldehyde having a melting point of 47° C were obtained (yield 81.5%).

Example 3

15.2 g of 2-hydroxy-5-methoxybenzaldehyde, 16.6 g of potassium carbonate and 13.9 g of dimethyl sulfate were heated at 100° C with stirring. After 30 minutes the reaction was completed and the reaction mixture was poured into 100 mL. of water. The precipitated crystals were collected by filtration and dried whereby 11.5 g of 2,5-dimethoxybenzaldehyde having a melting point of 47.5° C were obtained (yield 69.5%).

Example 4

By repeating the procedures described in Example 1 except that 61 g of diethyl sulfate were used instead of 50 g of dimethyl sulfate, 53 g of 2-ethoxy-5-methoxybenzaldehyde having a melting point of 47° - 48° C were obtained (yield 97.5%). Anal. Found: C, 66.58; H, 6.74. Calcd. C 66.67; H, 6.67. Source: Imai 1975

2,5-Dimethoxybenzaldehyde from Methylation of 2-Hydroxy-5-methoxybenzaldehyde

by Thomas Elbert Shanks
and Robert Joseph Maleski
Tennesee April 18, 2002

The crude oil of 2-hydroxy-5-methoxybenzaldehyde (6.1 g, 81% assay, 0.33 moles), 25 mL of acetone, 6.8 g of potassium carbonate, and 5 g of dimethylsulfate was refluxed for 3 hours and drowned into 200 mL of water. The dark oil solidified overnight, and the product was collected by filtration and dried to yield 5.6 g of black solid. The weight percent assay was 83%, resulting in an assay yield of 77%. The liquid chromatograph area percentage was only 62%. Source: Shanks 2003

Preparation of 2-Hydroxy-5-methoxybenzaldehyde

by Fuji Photo
Kanagawa, Japan June 19, 1973

Example 1

200 G of hydroquinone monomethyl ether were dissolved in a solution of 190 g of sodium hydroxide in 550 mL of water and the resulting solution was heated to 50° C on a water bath. To the solution maintained at 50° to 60° C, there were added dropwise 420 g of chloroform and a solution of 560 g of sodium hydroxide in 500 mL. of water from two separate dropping funnels and, thereafter, the reaction mixture was heated for 1 hour at a temperature of 50°—60° C and atmospheric pressure. After cooling, the precipitated sodium salt of 2-hydroxy-5-methoxybenzaldehyde was recovered by filtration and washed with 100 mL. of ethanol. The sodium salt thus obtained was dissolved in 800 mL. of water, slightly acidified with dilute sulphuric acid (1200 cc of 3N dilute sulphuric acid were added at room temperature and atmospheric pressure) and then extracted with 200 mL. of toluene. The extract was dried with calcium chloride, distilled to

eliminate toluene and then distilled under reduced pressure to obtain 132 g of 2-hydroxy-5-methoxybenzaldehyde having a boiling point of 110° C/5 mm Hg.

Elementary analysis (%): Theoretical: C 63.15; H 5.18; Found: C 63.18; H 5.26

Example 2

790 G of sodium hydroxide were dissolved in 1,150 mL. of water, and 200 g of hydroquinone monomethyl ether were then dissolved in 1/3 of the resulting solution. The solution was heated to 50° C, and 420 g of chloroform and the balance of the aqueous sodium hydroxide solution were added dropwise thereto (both materials being added from separate dropping funnels) while maintaining the temperature of the solution at 50° to 60° C on a water bath. The solution was thereafter processed in the same manner as in Example 1 to obtain 127 g of the end product. The dropwise addition of the chloroform and sodium hydroxide solution was carried out over a 2 hour period. Source: Fuji Photo 1974

Preparation of 2,5-Dimethoxytoluene

by Alexander Theodor Shulgin
Lafayette, California November 6, 1972

To a solution of 50 g. potassium hydroxide in methanol is added to 50 g. of toluhydroquinone. The resulting solution is heated on a steam bath, and an excess of methyl iodide (75 mL) is added through an effective reflux condenser. The addition is continued over several hours, and the resulting combination heated at reflux for several additional hours. At this time, the reaction mixture is brought to room temperature, acidified with hydrochloric acid, and exhaustively extracted with methylene chloride.

The organic phase of the above extraction is washed with 5% sodium hydroxide solution (to remove all phenolic byproducts), then with water. The solvent remaining is concentrated by evaporation, yielding a residual neutral oil (36.9 g.). This upon distillation yielded 2,5-dimethoxytoluene as a pale amber liquid (b.p.105—111°C @ 20 mm/Hg). The base washes yield, after acidification and extraction, 14.1 g. of a mixture of the two possible monomethylated derivatives which can be recycled in a subsequent repetition of the methylation step.

Source Shulgin 1976

Preparation of Methylhydroquinone (liquid phase)

by Michel Gubelmann and Christian Allandreieu
France October 16, 1989

5.7 g (46 mmoles) of *para*-methoxyphenol and 1 g of ultrastabilized commercial zeolite of the faujasite type (US-Y marketed by Toyo-Soda) were introduced into a 50 cm3 glass tube. The tube was sealed and inserted into a metallic sheath. The assembly was placed in a balancing furnace known as a "Carius" furnace and heated to 200° C. for 2.5 hours.

The solid catalyst was recovered by filtration on fritted glass and washed with ethyl acetate. The solution was analyzed by gas phase chromatography, and the nature of the final products was confirmed by a complete spectroscopic analysis (infrared, nuclear magnetic resonance, mass spectrometry).

The results obtained evidenced that:

(i) the degree of conversion of the *para*-methoxyphenol was 54%;

(ii) the yield of methylhydroquinone and "precursors" from the reaction was 11%.

Source: Gubelmann 1991

Preparation of Substituted Toluenes

by Harvey Gurien and Albert Israel Rachlin
Verona, New Jersey June 22, 1970

Preparation of 3,4-Dihydroxytoluene

Into a 12-liter three-neck flask, equipped with stirrer, thermometer, take-off condenser and under nitrogen was placed 540.5 g. of mixed *meta* and *para* cresols 91 percent pure, equivalent to 492 g. (4.55 moles) of 100 percent material. to this was added 580 g. (5.60 moles, 537 mL.) of 98 percent acetic anhydride, and the resulting mixture was stirred and refluxed (oil bath) for 4 hours. The bath temperature was then slowly raised to 200°, and the excess acetic anhydride and formed acetic acid were distilled. The internal temperature was then adjusted and maintained at 110°-130° and 900 g. of anhydrous aluminum chloride was added with mixing in portions with cooling. Upon completion of the addition of the aluminum chloride, the internal temperature was raised to 165°. (The reaction mixture may become difficult to stir between 110° and 165°, but is fluid at 165°, and stirring is resumed.) The mixture was stirred at 165° for 1 hour, cooled to 140° (internal temperature), and 2.38 L. of 4 N hydrochloric acid was added slowly while cooling to 90°-95°. The mixture was then stirred for 1 hour at 80°-90°, and then for 3 hours at room temperature. The organic layer was separated, and the aqueous phase was extracted with six 250 mL. portions of toluene. The organic layers were combined, concentrated at reduced pressure to remove the solvent, the residual oil was dissolved in 3.75 L. of ethanol and transferred to a 22-liter, 3-neck flask equipped with stirrer, condenser and thermometer. To the stirred solution was added. in portions, an alkaline hydrogen peroxide solution previously prepared from 625 mL. of 30 percent hydrogen peroxide (6.12 moles) in 1.75 L. of water and mixed with a solution of carbonate 580 g. of sodium carbonate (5.47 moles) in 3.75 L. of water at 15° and the whole cooled and stored at 0° 5° while awaiting addition During the addition of the alkaline hydrogen peroxide, the temperature slowly rose, and was kept at 30°-33° by means of external cooling. Upon completion of the addition (45-60 min.), the mixture was stirred for 2 hours at 33°-36°. Sodium bisulfate (50.2 g.) was added portion-wise to destroy the excess hydrogen peroxide as determined by a starch iodide test. The reaction mixture was cooled while being acidified to pH 2 with 320 mL. of concentrated sulfuric acid and then diluted with 6 L. of water to dissolve the salts formed. The mixture was then extracted with four 500 mL. portions of hexane and then with 12-600 mL. portions of ether The combined ether extracts were dried over sodium sulfate and concentrated. The residual oil was distilled at reduced pressure. After collection of a forerun (b.p. 38°-115°/20-19 mm.), the main fraction distilled at 149°-157°/17-20 mm., yielding crude 3,4-dihydroxytoluene, m.p. 56.4°-59.9°. Recrystallization was effected from 2.42 L. of 1:1 benzene-hexane. The solution was brought to the boil, cooled slightly, 20.4 g. Norit A was added and the mixture was again brought to the boil and filtered hot. When the cooling filtrate became turbid, it was seeded and allowed to cool with stirring until well crystallized. It was then refrigerated overnight. Upon filtration and washing with 282 mL. cold 1:1 benzene-hexane and drying in vacuum at 30°, there was obtained product of m.p. 64°-66°. Removal of the solvent from from the mother liquor gave additional crude product which was dissolved in 550 mL. of 1:1 benzene-hexane at room temperature, seeded and refrigerated overnight. Upon filtration, washing with 100 mL. 1:1 benzene-hexane (cold) and drying in vacuum at 30°, there was obtained an additional crop of product of m.p. 64°-66°. Yield: 90.8 percent.

Example 2

Preparation of 3,4-Dimethoxytoluene

A. From distilled, recrystallized 3,4-dihydroxytoluene

Into a 2-liter, five-neck flask equipped with stirrer, thermometer, pH electrode connected to a pH meter, condenser, two dropping funnels at either side of the flask and under nitrogen were placed 100 g. (0.805 mole) of 3,4-dihydroxytoluene (distilled and recrystallized) and 1 L. of water. One dropping funnel was charged with 290 mL. (2.90 mole) of 10 N sodium hydroxide and the other with 304.5 g. (2.42 mole, 229.5 mL.) of dimethyl sulfate. The internal temperature was adjusted to 30°-35°, and during the course of addition of the reagents, the temperature was maintained in that range by occasional cooling with an external ice bath. The pH was next adjusted to 11.5 by the addition of a portion of the alkali, followed by the addition of the dimethyl sulfate over a period of 1 hour. Concurrently, the alkali was added at such a rate as to maintain the pH at 11-11.5. An additional hour was required to complete the addition of the alkali, while maintaining the indicated pH, after which the pH electrode was removed, the reaction mixture was heated to 95° for 10 minutes, and then cooled to room temperature with an external ice bath. The organic phase was separated and the aqueous phase extracted with six 200 mL. portions of dichloromethane. The combined organic phase was washed with 200 mL. of 1 N sodium hydroxide, 200 mL. of water, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuum to give a light yellow oil. Upon distillation there was obtained 3,4-dimethoxytoluene, b.p. 106.5°-110°/ 12.5 mm, m.p. 21.2°; nD23.5= 1.5268. Yield: 96.5 percent of theory form 3,4-dihydroxytoluene.

B. From distilled, unrecrystallized 3,4-dihydroxytoluene

Into a 500-mL., five-neck flask equipped with stirrer, thermometer, pH electrode and meter, two dropping funnels and under nitrogen was placed 24.2 g. (0.195 mole) of 3,4-dihydroxytoluene (distilled, unrecrystallized of 98.0 percent purity), 244 mL. of water, and the temperature was brought to 30°-35°. Into the dropping funnels (arranged to avoid prior mixing as in A above) were placed 70 mL. of 10 N sodium hydroxide and 56.5 mL. (0.584 mole) of dimethyl sulfate. A quantity of the alkali was added to pH 11-11.5. The dimethyl sulfate and sodium hydroxide were then added dropwise and concurrently at rates such that the temperature and pH were maintained at 30°-35° and 11-11.5, respectively. The addition was complete in 20 minutes. After stirring at 30°-35° for an additional 45 minutes, the pH electrode was removed and the reaction mixture was heated to 95°, while the residual sodium hydroxide was added (10-15 minutes) and held at this temperature for 10 minutes. The flask was next cooled externally to room temperature. The organic phase was separated and the aqueous phase was extracted with four 50 mL. portions of methylene chloride. The combined organic extracts were washed with 50 mL. of 1 N sodium hydroxide and 50 mL. of water. After drying over anhydrous magnesium sulfate, the organic phase was concentrated and distilled to give product of b.p. 112/114°/ 18mm. nD22=—1.5307. Yield: 87.5%

Example 3

Preparation of 3,4-Diethoxytoluene

Into a 250-mL., five-neck flask equipped with stirrer, thermometer, two dropping funnels and pH meter, under nitrogen were placed 12.4 g. (0.10 mole) of 3,4-dihydroxytoluene (distilled, recrystallized) and 125 mL. of water. The dropping funnels were charged with 61.6 g. (0.40 mole) of freshly distilled diethyl sulfate and 48.0 mL. of 10 N (0.48 mole) sodium hydroxide, respectively. While maintaining the temperature at 30°-35°, the sodium hydroxide and diethyl sulfate were concurrently added dropwise at a rate such that the pH was maintained at 11.0-11.5 The addition of the diethyl sulfate required 30 minutes. The pH meter was removed and the mixture was heated to 95° as the remainder of the alkali was added. It was held at 95° for 10 minutes and then cooled to room temperature. The organic layer was separated and the aqueous phase was extracted with six 25 mL. portions of methylene chloride. The combined organic phases were washed with 25 mL. of 1 N sodium hydroxide and then with 25 mL. of water. After drying over anhydrous magnesium sulfate and removal of the solvent, the crude product weighed 17.6 g. Upon distillation, 16.6 g. of 3,4-diethoxytoluene was obtained, b.p. 109°-114°/8.9 mm. Source: Gurien 1973

Methyl-2,5-Dimethoxybenzyl Alcohol

by Milton Green, Adam A. Sayigh and Henri Ulrich
Connecticut April 29, 1966

To 138 g. of 2-methyl-4-methoxyphenol in 800 mL. of water 81 g. of 37% formalin was added. To this suspension with cooling under a blanket of nitrogen, 28 g. of CaO was added gradually. The operation was performed in a jar and after the lid was closed tightly all the material went into solution upon shaking. After standing overnight in an ice box, wart-like crystals had separated on the walls of the reaction vessel. Upon shaking, the whole contents of the jar became solid due to formation of the calcium salt of the reaction product. The reaction mixture was diluted with water, acidified with acetic acid and the precipitated oily phenol extracted with ether. The ether extract was washed with NaHCO3 to remove excess acetic acid, washed with water, and dried over Na2SO4. Evaporation afforded 137.5 g. of crude 2-methyl-4-methoxy-6-hydroxymethylphenol. Distillation of the crude product under vacuum resulted in extensive decomposition. The distillate, B.P. 136-140° C. at 1 mm., solidified M.P. 56-57° C.: on crystallization from isohexanes, it melted at 58-59° C. and was found to be 2-methyl-4-methoxy-6-hydroxymethylphenol.

Example 2

137.5 g. of the crude 2-methyl-4-methoxy-6-hydroxymethylphenol prepared in Example 1 was dissolved in 200 mL. of acetone. After addition of 115 g. of anhydrous K2CO3 and 125 g. of methyl iodide, the solution came to reflux due to an exothermic reaction. After the initial reaction ceased, the mixture was refluxed with stirring for 18 hours. It was poured into a large volume of water and the precipitated oil extracted with ether. The ether extract was washed with 2 N NaOH to remove unreacted phenols and after repeated washing with water, dried over Na2SO4. Rectification in vacuo afforded:

(1) 5.8 g., B.P./0.6 mm., 65-85° C.; nD24 1.5215.
(2) 14.2 g., B.P./0.6 mm., 85-109° C.; nD24 1.5232.
(3) 78.5 g., B.P./0.6 mm., 109-114° C.; nD24 1.5327.
(4) 19.7 g., B.P./0.6 mm, 114-116° C.; nD24 1.5344.

The first two fractions are mainly toluhydroquinone dimethylether. Fractions 3 and 4 consist mainly of 3-methyl-2,5-dimethoxybenzylalcohol. The yield was 98.2 g. From the NaOH extract, 7.1 g. of phenolic material was recovered. A sample of fraction 3 was submitted for analysis. Analysis.—Calc. for C10H14O3: C, 65.91; H, 7.74. Found: C, 64.24; H, 7.94. Source: Green 1966

Preparation of 2,6-Dimethoxy-4-(hydroxymethyl)phenol

by Masahiro Iwahara
Tokuyama, Japan July 21, 1987

310 g of 2,6-dimethoxyphenol, 300 g of 38 wt% formalin, and 810 g of 10% (wt%) aqueous sodium hydroxide were reacted for 60 hours at 25° C. under a pressure of 0 kg/cm2 -G, the reaction mixture was and then neutralized with sulfuric acid, to obtain 80 g of 2,6-dimethoxy-4-(hydroxymethyl)phenol. (Yield: 22 mol%) 25 g of the obtained 2,6-dimethoxy-4-(hydroxymethyl)phenol was reacted in 320 mL. of methanol in the presence of 0.375 wt% of platinum-alumina catalyst and hydrogen for 4 hours at 200° C. at 199 kg/cm2 -G, and 15 g of 2,6-dimethoxy-4-methylphenol was obtained. (Yield: 66 mol%) The yield on the basis of the amount of the raw material was 15 mol%.

Source: Iwahara 1988

3,4,5-Trimethoxybenzaldehyde: Chapter 19

3,4,5-Trimethoxybenzaldehyde from Syringaldehyde

by David Michael Findlay and
Terrasse Vaudreuil, Canada June 4, 1976

Example 1

A mixture of 100g of syringaldehyde (0.55 mol), 85.0g of sodium carbonate (0.80 mol) and 106.0g of dimethyl sulfate (0.84 mol) was placed in a round-bottomed flask equipped with a reflux condenser, a stirrer and a dropping funnel. The syringaldehyde was of about 99% purity and was obtained, by distillation, from a crude mixture of vanillin and syringaldehyde produced by alkaline oxidation of waste Kraft liquor. The dimethyl sulfate was of commercial quality (B.P. 75°-77°/15 mm) and the sodium carbonate was of reagent grade in some experiments and of commercial grade in others. The flask was kept in a silicone oil bath on a hot plate. The mixture as prepared at room temperature was a thick paste which could be kneaded but could not be mixed by the stirrer driven by an electric motor. When the temperature of the mixture reached 75° C the mixture became fluid and was easily stirred by the blades of the stirrer. The temperature was further raised to about 85° C and maintained at this temperature with stirring for a total of about 2 hours. After the initial 35 minutes of this period the reaction mixture began to thicken due to the consumption of dimethyl sulfate and, in order to maintain it fluid, water in 5 gram portions was added from time to time through the funnel while the stirring continued. In total about 60g of water were added to the mixture during the reaction period.

At the end of two hours, the heating was discontinued and about 500 mL. of hot water was added to the mixture. The mixture was acidified with concentrated hydrochloric acid and was then extracted three times with about 250 mL. of benzene and the combined extract was washed with water. The benzene was removed by distillation and the solid product was dried in a vacuum oven and weighed. The yield was 106.9 g of 3,4,5-trimethoxybenzaldehyde, representing a yield of 99.3% of the theoretical. Analysis by gas-liquid chromatography (g.l.c.) showed a purity of 99.85% with syringaldehyde as the only detectable impurity.

Example 4

25.0 g syringaldehyde (0.137 mol), 26.6g of dimethyl sulfate (0.211 mol), and 27.7 g. of potassium carbonate (0.201 mol) were heated with stirring as in Example 1. When the temperature reached 45° C the mixture became fluid and carbon dioxide was given off. The temperature was slowly increased to 75° C and held at this value for 1 hour. Addition of water, acidification, and benzene extraction gave a quantitative yield of 3,4,5-trimethoxybenzaldehyde which contained no detectable syringaldehyde or other impurities as determined by g.l.c. analysis.

Example 7

20 g of *p*-hydroxybenzaldehyde (0.164 mol) was reacted with 29.0 g of dimethyl sulfate (0.230 mol) and 22.0 g of sodium carbonate (0.20 mol) for 2 hr. at 75°-80° C. A total of 12 mL. of water was added in small portions over the last hour. Work-up by addition of water, acidification and benzene extraction yielded 22.27 g of *p*-methoxybenzaldehyde (99.9%) containing not more than 0.1% *p*-hydroxybenzaldehyde.

Source: Findlay 1977

Syringaldehyde was first isolated in 1888 by Korner [*Gazz. chim. ital.* 18, 210 (1888)] by the decomposition with the aid of sulfuric acid or emulsion of glucosyringaldehyde which in turn was prepared by the cautious oxidation with dilute chromic acid of syringin, a glucoside isolated from the bark of *Syringa vulgaris* L. (Lilac) and *Ligustrum vulgare* L. (Privet), *Oleaceae*. Source: Pearl 1950

Preparation of 3,4,5-Trimethoxybenzaldehyde from Vanillin via 5-Bromovanillin

by Pius Anton Wehrli
North Caldwell, NJ March 27, 1972

3,4,5-Trimethoxybenzaldehyde is a valuable chemical intermediate for the preparation of medicinal agents such as the sulfonamide potentiator trimethoprim. The present synthesis proceeds via three chemical steps in high yield utilizing relatively inexpensive reagents and solvents and requiring a minimum of manipulative steps. The present process thus represents a major advance over prior art procedures for each of the individual steps involved, and the combination of steps is greatly superior to any prior art method for preparing 3,4,5-trimethoxybenzaldehyde. The present-process is extremely practical for large-scale synthesis.

The overall conversion from vanillin to 3,4,5-trimethoxybenzaldehyde is depicted in the following reaction scheme:

The three steps involved are:

1. bromination of vanillin to afford 5-bromovanillin;
2. hydrolysis of 5-bromovanillin to afford 5-hydroxyvanillin; and
3. methylation of 5-hydroxyvanillin to afford 3,4,5-trimethoxybenzaldehyde.

The bromination of vanillin to afford 5-bromovanillin is performed by contacting vanillin with bromine in an acidic solvent medium. The bromination is generally carried out using at least one mole of bromine for each mole of vanillin. It is preferred to utilize a slight excess, most preferably about 10% excess, bromine in the bromination step.

Suitable acidic solvent media include, for example, concentrated aqueous mineral acids, e.g., concentrated aqueous hydrobromic acid, preferably 48% aqueous hydrobromic acid; glacial acetic acid, and forth.

A critical feature of the present bromination reaction is the addition of a solution of vanillin in the acidic solvent medium to the bromine, while keeping the temperature between 0° and 5°. In this-manner, an exceedingly high yield (=99%) of high purity (>98%) 5-bromovanillin is obtained. This extremely high conversion is particularly advantageous since it is rather difficult to separate large amounts of unreacted vanillin from 5-bromovanillin. Thus, because of the higher purity of product produced in the bromination reaction, less manipulation in terms of recrystallization, etc., is needed in fact, crude reaction product (purity about 98%) can be utilized directly for the next step without any further need for purification. This is a decided advantage over prior art brominations of vanillin (e.g., *J. Am. Chem. Soc.*, volume 51, p. 2193), which afforded substantially lower yields and/or impure product.

The hydrolysis of 5-bromovanillin to 5-hydroxyvanillin is accomplished by contacting the 5-bromovanillin with an alkali metal hydroxide in the presence of copper metal in an aqueous medium.

Any alkali metal hydroxide is suitable for the present reaction. However, sodium hydroxide is preferred. Generally, at least one mole of alkali metal hydroxide is employed for each mole of 5-bromovanillin. Preferably an excess of alkali metal hydroxide, most preferably a 5 to 10 molar excess is employed.

A critical nature of the present hydrolysis reaction is the use of a small amount, from about 1 to about 10 mole %, most preferably about 3 mole %, of copper powder, as compared with the 5-bromovanillin present. In this manner, a relatively minor amount of reduction of

5-bromovanillin to vanillin occurs, and high yields of 5-hydroxyvanillin are obtained.

Surprisingly, it has been found that the use of a small amount of copper powder allows the hydrolysis reaction to proceed at a controllable rate at relatively low temperatures, 50° to 120°, as compared with prior art hydrolysis procedures (e.g., *J. Chem. Soc.*, London, 1930, p. 811) utilizing large amounts of copper metal, and pressure reactions at about 200°. The present reaction is preferably conducted at the reflux temperature of the reaction medium which is about 100° to 120°, and at atmospheric pressure. It should be emphasized that pressure is not a critical parameter; and that while the reaction is preferably conducted at atmospheric pressure, it can be performed as well at sub- or super- atmospheric pressures.

The reaction product, 5-hydroxyvanillin, is suitably isolated from the reaction mixture by a procedure of hot liquid-liquid extraction. In this procedure, the hot reaction mixture, after acidification with a strong acid, preferably a mineral acid such as concentrated hydrochloric acid, is continuously extracted with water immiscible organic solvent at an elevated temperature, preferably between about 60° and about 100°. Suitable solvents for the hot liquid-liquid extraction include hydrocarbons, e g., benzene or toluene; esters, e.g., ethyl acetate, and so forth. An especially preferred solvent for the hot liquid-liquid-extraction is toluene.

The reaction product extracted into the organic solvent in the above step is then purified by recrystallization. An especially preferred solvent for recrystallization is toluene. In a preferred procedure, toluene is used as the extracting solvent in the hot liquid-liquid extraction and also serves by cooling of the hot extract, as a recrystallization solvent.

The methylation of 5-hydroxyvanillin to 3,4,5-trimethoxybenzaldehyde is carried out by contacting the 5-hydroxyvanillin with dimethyl sulfate in the presence of an alkali metal carbonate in an organic medium.

The critical features of the present methylation process are the use of only a slight excess of dimethyl sulfate over the theoretical amount necessary for methylation of two phenol groups, preferably about 15 to 25% excess; the use of powdered alkali metal carbonate as the base; and the use of an organic solvent medium. In this manner, high yields of 3,4,5-trimethoxybenzaldehyde are obtained. This is to be compared with prior art processes (e.g., *J. Chem. Soc.*, London, 1930, p. 811) utilizing large excesses of dimethyl sulfate, alkali metal hydroxides as bases, and aqueous media, affording relatively poor yields of product.

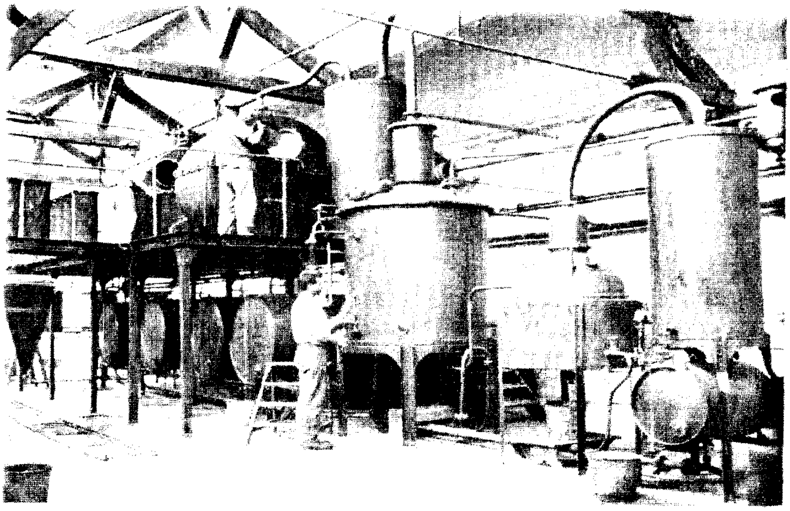
As alkali metal carbonate for the present process there may be utilized, for example, sodium carbonate, potassium carbonate, lithium carbonate, and so forth; sodium carbonate is preferred. It is preferred to utilize from about 20 to about 40% excess carbonate over the two moles necessary, based upon the amount of 5-hydroxyvanillin present.

Suitable organic media for the present reaction include ketones, e.g., acetone and methyl ethyl ketone; ethers' e.g., tetrahydrofuran and dioxane; hydrocarbons, e.g., hexane, heptane, benzene and toluene; and so forth. An especially preferred medium is acetone.

Small amounts of stronger bases, for example alkali metal hydroxides, e.g., sodium hydroxide or potassium hydroxide, may also be added to the reaction mixture, although this is not necessary for the success of the methylation reaction.

The temperatures of the methylation reaction is suitably between about 40° and 120°, preferably the reflux temperature of the reaction medium. The reaction product, 3,4,5-trimethoxybenzaldehyde, is isolated by removal of the reaction solvent, preferably by evaporation, and extraction of the residue with water to remove inorganic material. In this manner, high purity 3,4,5-trimethoxybenzaldehyde is obtained. Higher purity product (99+% pure) may be obtained by standard purification techniques. e.g., distillation of the crude reaction product.

The process of the present invention will be more readily understood by reference to the following specific examples. All temperatures specified are in degrees Centigrade.



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Preparation of 5-Bromovanillin

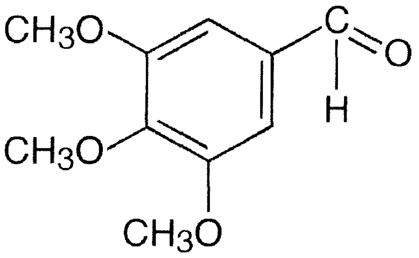
A 2-L. 3-necked flask, equipped with a mechanical stirrer, thermometer and 500 mL. dropping funnel was charged with 115.7 g (0.722 mol, 37.4 mL.) of bromine. In the meantime, a solution of 100 g (0.658 mol) of vanillin (Aldrich Chemical Co., m.p. 82°-84°) in 705 g (470 mL.) of 48% HBr was prepared in the dropping funnel. While the reaction flask was immersed in an ice bath, the solution of vanillin was dropped into the bromine with stirring over a period of 1 hr., keeping the temperature at about 5°. The bromovanillin precipitated as light yellow crystals. The slurry was stirred for an additional hour in the ice bath, diluted with 940 mL. of water and kept for 1 hour at 0°-5° with stirring. The crystals were collected on a sintered glass funnel and washed thoroughly with a total of 1000 mL. of water. The material was dried at room temperature to constant weight. Yield: 150.9 g (99.4%), m.p. 163°-164°, VPC purity 98%.

Preparation of 5-Hydroxyvanillin

Sodium hydroxide, 61.2 g (1.53 mol), was dissolved in 750 mL. of water in a 2-L. round-bottomed flask. To the still-warm solution was added 50.0 g (0.217 mol) of 5-bromovanillin, prepared as in Example 1, and 0.5 g of copper powder (No. 1618, General Chemical Division, Allied Chemical Corporation). A white solid precipitated. The reaction mixture was refluxed vigorously under N2 and with magnetic stirring. The color changed gradually from yellow to green to dark green and, after ca. 6 hours, all of the solid material was dissolved. After 27 hours of refluxing, the reaction was acidified with 113 mL. of conc. HCl (pH~2) and continuously extracted with toluene at 85° for 47 hours while being stirred magnetically. The toluene receiver contained 450 mL. of toluene. The total volume of toluene in the system was ca. 1300 mL. The flask containing the hot toluene extract was disconnected while still hot, and the brown solution was transferred to a 1-L. beaker for crystallization in an ice bath. After cooling for 2 hours, the product was filtered, washed with ca. 100 mL. of ice-cold toluene and dried at 70° to constant weight. Yield: 30.4 g (83.3%) of light brown plates, m.p. 132.5°-134.0°.

3,4,5-Trimethoxybenzaldehyde Preparation

Into a 1-L. round-bottomed flask equipped with a magnetic stirrer and reflux condenser were placed: 50 g (0.298 mol) of 5-hydroxyvanillin prepared as described in Example 2, 500 mL. of acetone, 91.0 g (0.716 mol) of dimethyl sulfate, 100 g (0.806 mol) of finely ground Na2CO3.H2O and 10 mL. of 10% KOH in methanol. The heterogeneous mixture was stirred under vigorous reflux for 24 hours, after which the reflux condenser was replaced with a descending condenser. The solvent was distilled at a bath temperature of ca. 100° until the distillation ceased. To the solid residue was added 400 mL. of water and the heterogeneous mixture was stirred vigorously for 2 hours at room temperature followed by 1 hour at 0°-5°. The light brown crystals were filtered by suction, washed with 3 x 150 mL. of ice water and air dried to constant weight. Yield: 55.1 g (94%), m.p. 72.5°-74°. After distillation at 0.5mm/ 130°, there was obtained a 90% yield of 3,4,5-trimethoxybenzaldehyde, m.p. 73.5°-75.0°, VPC purity 99.3%. Source: Wehrli 1974



3,4,5-Trimethoxybenzaldehyde

3,4,5-Trimethoxybenzaldehyde from Vanillin via 5-Iodovanillin

by Geoffrey K. Cooper Shelton, Washington
Lewis G. Harruff Grapeview, Washington
August 2, 1982

Lignin derived aromatic compounds are frequently inexpensive precursors of a number of valuable organic substances. For example, vanillin is an important precursor chemical of 3,4,5-trimethoxybenzaldehyde, a chemical of well known importance to the pharmaceutical industry. However, known processes for the conversion of vanillin to trimethoxybenzaldehyde have certain drawbacks. *U.S. Pat. No. 3,855,306* describes one such process in which vanillin is brominated to produce 5-bromovanillin using bromine and a concentrated hydrobromic acid solvent. The resulting 5-bromovanillin is then isolated from the reaction mixture and hydrolyzed to the corresponding hydroxyvanillin with sodium hydroxide and a copper catalyst. The resulting reaction mixture includes sodium bromide which is normally not recycled but rather is discarded or used elsewhere. Moreover, bromine and hydrobromic acid are both highly corrosive and hazardous to handle.

Other halogenated vanillin derivatives include 5-chlorovanillin and 5-iodovanillin. It is known however that chlorovanillin is unreactive toward hydroxide ion/copper and yields no hydroxyvanillin using conditions even more drastic than those effective for converting 5-bromovanillin to 5-hydroxyvanillin. Aryl iodides, on the other hand, are known to be more reactive than the corresponding bromocompounds in this kind of reaction. Iodine, however, would be prohibitively expensive if discarded as the bromine is in the above described bromination reaction. Reference to the iodination of vanillin to 5-iodovanillin may be found in H. Erdman, *Svensk. Kem. Tids.*, 47, 223 (1935) *Chem. Abstr.* 30:449. Conversion of 5-iodovanillin to 5-hydroxyvanillin is disclosed in S. Banerjee, M. Manolopoulo and J. M. Pepper, *Canadian Journal of Chemistry*, 40, 2175 (1962). However, the processes there disclosed isolate the intermediate iodovanillin before hydrolysis and do not recover the by-product iodide ion from the various reactions.

A process has now been discovered from the conversion of aromatic compounds to hydroxy aromatic compounds which does not isolate an intermediate haloaromatic compound and which permits economical recovery and reuse of halide by-products produced during the reaction. The process involves the hydroxylation of an aromatic compound by reacting the aromatic compound in the presence of an aqueous solvent with a triiodide salt to form a reaction mixture containing the corresponding iodoaromatic compound, reacting the mixture, without separation of the iodoaromatic compound with a hydroxylating agent to form the corresponding hydroxy aromatic compound and additional iodide salt, separating the hydroxy aromatic compound from the iodide salt and recapturing the iodide salt. The corresponding alkoxy aromatic compound may be produced by alkylation of the hydroxy aromatic compound by known alkylation procedures.

The process of the invention renders cost-effective an otherwise cost-ineffective process using the iodination route. In the case of such processes as the conversion of vanillin to trimethoxybenzaldehyde, the process becomes basically a one-step or "one-pot" process by eliminating the purification of the intermediate 5-iodovanillin. Iodination of vanillin and conversion of the resulting iodovanillin to hydroxyvanillin may be carried out in the same reaction vessel. Moreover, efficient recycle of the by-product iodide salt to the triiodide reagent used in the reaction obviates the need to dispose of the valuable iodine/iodide material. Prior art processes necessarily separated and recovered the bromide or iodide by-product from the halogenation reaction and again from the hydroxylation reaction. In the present process, the iodide salt is recovered only after hydroxylation, at which time it may be oxidized to iodine and the iodine partially reduced to form the starting triiodide reactant. (The triiodide reagent is a solution of iodine in an excess of the iodide salt, e.g., NaI+I2 or NaI3). If chlorine is used as the oxidizing agent, the only net by-product of the reaction is sodium chloride, an obviously inexpensive waste by-product.

The starting materials useful in the practice of the invention are aromatic compounds subject to electrophilic substitution reactions. Such compounds may include benzene but the process is particularly suitable for aromatic compounds containing electron donating nuclear substituents, i.e. mono- or polycyclic aromatic compounds containing one or more hydrocarbon substituents such as an alkyl, cycloalkyl, aryl or aralkyl group and/or one or more hydroxy groups or aldehyde, acid, ester or ether radicals, i.e., alkoxy, carboxy, carboxyl or aldehyde carbonyl groups. The process is not useful with substituents such as poly-nitro, or ketone groups with an *alpha* hydrogen, which either react with the reagent or strongly de-activate the ring. Ketone groups are deactivating, as are aldehyde groups, but ketones containing an *alpha* hydrogen would react with the iodinating agent whereas the aldehydes would not. For example, diaryl ketones would not interfere. Only in the case of severely de-activating groups, such as poly-nitro groups, is the de-activation a problem in carrying out the iodination. Weakly de-activating groups such as aldehyde groups do not interfere with iodination. Useful aromatic compounds are simple monohydric phenols such as phenol, *o*-, *m*- and *p*-cresol and guaiacol; polyhydric phenols such as catechol and resorcinol; phenolic aldehydes such as protocatechualdehyde, vanillin, syringaldehyde, *p*-hydroxybenzaldehyde and 5-formylvanillin; phenolic acids such as vanillic acid, syringic acid, protocatechuic acid and *p*-hydroxybenzoic acid. The preferred aromatic reactants are those having at least one phenolic hydroxyl functionality.

The first step of the reaction involves iodination of the aromatic compound with the triiodide salt in the presence of water as a solvent. The water should contain from 0.7 to 1.25 molar equivalents of a hydroxide, preferably an alkali metal hydroxide, and from 1-2 molar equivalents of an alkali metal triiodide (e.g. iodine plus sodium iodide). The aqueous solvent should also contain from 0.1 to 20 mole % of an acid catalyst, which may be a mineral acid such as sulfuric, hydrochloric or phosphoric acid. Reaction is carried out at temperatures ranging from 20°-120° C. If the starting compound contains a nuclear substituent, iodination will occur in the *ortho* or *para* position on the nuclear ring.

The subsequent step of the reaction, hydroxylation, is carried out directly with the reaction mixture from iodination without any intermediate isolation or other processing of the reactants or by-products. A base, such as an alkali metal hydroxide or a quaternary amine such as tetraalkylammonium hydroxide, is added directly to the reaction mixture to make a final concentration of 0.5 to 6 molar, with 0.1 to 20 mole % copper metal, or cuprous salts such as oxide, chloride or iodide, at temperatures of from 50°-120° C. The preferred conditions are addition of sodium hydroxide to the iodination reaction mixture to give a concentration of 2-5 molar, then addition of 1-5 mole % copper dust, cuprous oxide or cuprous chloride, then allowing reaction at reflux (100°-120° C.) for about 18 hours.

The sodium or other iodide ion by-product may be recovered by neutralizing the caustic in the reaction mixture with an acid such as sulfuric or hydrochloric, extracting the organic product from the water solvent and then treating the water solution with an oxidizing agent. The oxidizing agent may be chlorine, sodium hypochlorite, hydrogen peroxide, persulfate, perborate or electrochemical oxidation may be used. The iodine which precipitates is then recovered from the water solvent by filtration, solvent extraction or distillation/sublimation. The temperature of the water phase may be from 0° to 100° C. The preferred method for iodine recovery is treatment of the water solution with sulfuric acid to neutralize the base, extraction of the hydroxy aromatic compound with organic solvents such as methylene chloride or toluene, oxidation with chlorine or electrochemically and filtration or solvent extraction to recover the iodine. The crude hydroxy aromatic compound may then be used directly in any subsequent alkylation procedure.

A specific description of a preferred practice of the invention with vanillin as the aromatic compound is as follows. Vanillin is dissolved in water with one molar equivalent of sodium hydroxide while the solution is warmed to 50°-100° C. One molar equivalent of iodine and two molar equivalents of sodium iodide are added to water to prepare one molar equivalent of NaI3.NaI. This sodium triiodide solution is added to the sodium vanillate solution along with a catalytic amount of sulfuric acid--preferably from 5 to 10 mole %. The mixture is stirred about one hour at a temperature of 50°-100° C., then sodium hydroxide is added to make the solution alkaline (from 1 to 5N). The copper catalyst is then added and the mixture heated at reflux until the iodovanillin is consumed, about 12 hours. The excess hydroxide is then neutralized and the 5-hydroxyvanillin extracted with a water-immiscible organic solvent. The aqueous phase bearing the sodium iodide is then subjected to oxidizing conditions and the resultant iodine precipitates from solution. The solid element is filtered out, and a sodium triiodide solution prepared by reducing a portion of the iodine to sodium iodide and dissolving the iodine in the iodide to make the sodium triiodide solution.

Alkylation of the hydroxy aromatic compound to the corresponding alkoxy aromatic compound may be performed in accordance with known alkylation procedures in which the hydroxy aromatic compound is reacted with an alkyl sulfate, alkyl halide or alkyl sulfonate in a suitable solvent, usually water, containing a base such as sodium hydroxide. Such reactions are shown at various places in the literature, as for ex. in *Organic Synthesis, Col. Vol. II*, page 619, 1943, in which veratraldehyde is prepared from vanillin. The iodide salt may, if desired, be recaptured subsequent to the alkylation reaction.

The following examples illustrate the practice of the invention. Unless otherwise indicated, all parts and percentages are by weight.

Example 1

Vanillin (28.4 g, 200 mmole (millimole)) was dissolved in 1N NaOH (200 ml) and warmed to 90° C. to avoid precipitation of sodium vanillate. A 2 molar aqueous solution of NaI3.NaI (105 mL., 210 mmole I2) plus 3.55 molar aqueous H2SO4 (5 mL.) was added over 3 hours with stirring. The iodine color was discharged, and a pale tan stirrable precipitate formed. The solution was then cooled to room temperature, acidified to pH 2-3 with 20% aqueous H2SO4, and extracted with 10% methanol/90% chloroform. The organic phase was dried (MgSO4) and the solvent stripped to yield 53 g (99%) of 5-iodovanillin, more than 95% pure as analyzed by nuclear magnetic resonance spectroscopy (NMR).

Example 2

Vanillin (3.04 g., 20 mmole) was dissolved in 1N sodium hydroxide solution (20 mL.), and warmed to 80° C. Then a solution of NaI3.NaI (2N) in water (10.1 mL.) plus 20% aqueous H2SO4 (0.5 mL.) was added dropwise over 30 minutes, and the mixture stirred an additional 30 minutes. Sodium hydroxide (7.6 mL. of 50% solution), and copper dust (128 mg=10 mole %) were then added and the mixture heated at reflux overnight. The solution was cooled, filtered to recover catalyst, neutralized with 20% aqueous H2SO4, and extracted thoroughly with chloroform. The organic base was dried (Na2SO4) and stripped to yield 3.1 g (99%) of organic material consisting of 75% 5-hydroxyvanillin and 25% vanillin.

The aqueous phase was concentrated under vacuum, and treated with the theoretical quantity of chlorine as a water solution. The purple iodine crystals were removed by filtration. As 87% recover of iodine was achieved.

Example 3

Vanillin (2.84 g, 20 mmole) was dissolved in 1N NaOH (20 mL.) at 80° C., then a mixture of 2N (NaI3.NaI)/H2O (10.1 mL.=20.2 mmole I2) plus 20% aqueous H2SO4 (0.5 ml=8 mole %) was added dropwise over 30 minutes. A tan precipitate formed. The reaction mixture was stirred an additional 3.5 hours. A 10% solution of Na2S2O3 (1.5 mL.) was added to reduce excess iodine, then 50% aqueous NaOH (7.6 mL.) was added (to make 4N in NaOH), plus copper dust (128 mg, 2 mmole 10 mole %) added. The mixture was refluxed overnight, cooled to room temperature, filtered to remove catalyst, the pH was adjusted to 2 with 20% aqueous H2SO4, and the solution extracted 5X with 20% methanol

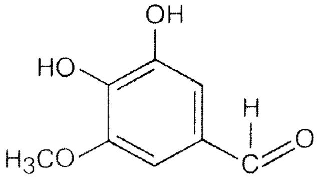
80% chloroform. A yield of 3.1 g (99%) of product was obtained, which NMR showed to consist of about 75% 5-hydroxyvanillin and 25% vanillin.

Example 3 was repeated using concentrations of NaOH base ranging from 1N to 6N, using KOH and LiOH in place of NaOH as the base for the iodination procedure. All gave substantially equivalent results.

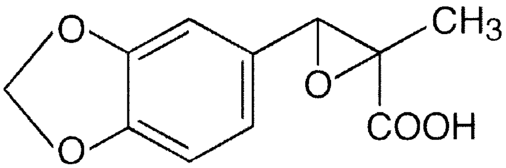
Example 3 was also repeated using from 5 to 10 mole % of cuprous oxide, cuprous chloride, cuprous iodide and copper dust, as the catalyst for conversion of the iodovanillin to hydroxyvanillin. Recovery of 5-hydroxyvanillin was 80-85% (remainder vanillin) with copper dust, from 70-80% with the copper oxide or salts.

Example 4

Vanillin (20 mmole) was iodinated and converted to 5-hydroxyvanillin as set forth in Examples 1-3. The aqueous phase from the extraction of 5-hydroxyvanillin (theoretically containing 80.8 mmole NaI) was then concentrated in vacuum to remove dissolved volatile organics, then chlorine water [42 mmole Cl2 =500 mL. of 0.086M (0.61%) chlorine water] was added slowly. The iodine precipitate was filtered off and washed with water. To determine the quantity recovered, the iodine was washed off the filter with 2N sodium iodide solution (300 mL.), and then titrated (at pH 5) with 0.2N sodium thiosulfate solution until the iodine color disappeared. A quantity of 350 mL. of the 0.2N thiosulfate was consumed showing that 70 mmole I2 was recovered, an efficiency of 87%. Source: Cooper 1984



5-Hydroxy-vanillin



α-Methyl-ß-(3,4,-methylenedioxyphenyl)-glycidic Acid

Phenyl-glycidic Acid: Chapter 20

Preparation of Phenyl-glycidic Acids

by Antoine Adolphe Kaufmann
October 8, 1929 Geneva, Switzerland

To a solution of hypobromite prepared with 100 liters of water, 12 kg. of caustic soda and 16 kg. of bromine, are gradually added with strong stirring 6.6 kg. of cinnamic aldehyde. The reaction takes place at once with an energetic generation of heat and after a short time crystals of phenyl-glycidate of soda begin to settle. The temperature should preferably not exceed 50° C. By cooling it is possible to isolate at least 7.5 kg of the sodium salt free from halogenated organic by products. The solution may also be used direct for the manufacture of phenyl-acetic aldehyde by known methods.

Example 2

330 parts of cinnamic aldehyde are dissolved in the same quantity of alcohol and then mixed with 500 parts of 30% hydrogen peroxide. There will be a slight generation of heat, which becomes however considerable when alkaloid is added, so that it becomes necessary to cool in order to avoid exceeding a temperature of 50° C. The solution rapidly becomes, discolored, and phenyl glycidate of soda is precipitated in the form of glittering crystals when can be dried by centrifuging and washed in alcohol and which are then perfectly pure.

Source: Kaufmann 1930 Reference: Robinson 1940

Submitting a glycidic ester, to an alkaline hydrolysis at a temperature comprised between about 10° C. and about 40° C. for a period of time comprised between 6 and about 24 hours, to obtain an alkaline salt of the epoxyacid. Decarboxylating the compound in acidic ambient, at a temperature comprised between aobut 10° C. and about 40° C., for a period of time comprised between about 1 and about 8 hours, to obtain the ketone. Source: Cannata 1991

Preparation of Cinnamaldehyde

by Henry H. Richmond
Ontario, Canada April 5, 1947

To a 2000 cc. three-necked flask equipped with a thermometer, a reflux condenser, a stirrer, and a calibrated addition burette, jacketed so that it can be cooled by tap water and whose tip is inserted below the surface of the reaction mixture, there is introduced 150 g. of technical benzaldehyde and a solution of 3.0 g. of sodium hydroxide in from 500 to 1300, preferably about 1000 cc. of water. The temperature of the mixture is raised, with stirring, to 70° C. The temperature 70° C. is about the optimum temperature. for high yields concurrent with the other conditions described in this example but the reaction can be carried out in the range 60-80° C. Maintaining this temperature, 48 grams of acetaldehyde is introduced through the addition burette; uniformly over a period of 1-1/2 hours. This constitutes the period for one-half of the reaction. The alkalinity of the reaction mixture is periodically checked and; adjusted so that it is pink to phenolphthalein indicator by the addition of small quantities of sodium hydroxide solution. This acidification is due to the. oxidation of benzaldehyde to benzoic acid. The optimum alkalinity is that indicated by the pink color of the phenolphthalein indicator. The stirring is: continued for another hour and a half at the same temperature.

The reaction mixture is then acidified to pH 4 with 10% aqueous sulfuric acid solution, and allowed to cool to room temperature; the excess sulfuric acid and any benzoic. acid present is neutralized with an excess. of sodium bicarbonate bringing the pH to 8. The slightly alkaline mixture is extracted with a water insoluble, organic solvent: (200 cc. of benzene) and the whole is subsequently poured into a separatory funnel. The organic layer is separated; most of the solvent and all the water is removed by. atmospheric flash distillation, and the residue consisting of benzaldehyde, cinnamaldehyde, and high boiling byproducts, fractionated in vacuo.

The products are: 63.9 g. benzaldehyde boiling at 63° C. and.1 mm. nD=1.546; 86.9 g. cinnamaldehyde boiling at 12.8°- C. and 15 mm nD=1.622, and a higher boiling residue of 25 g. This represents a yield of 81% and a conversion of 46%. By analysis the cinnamaldehyde is found to be 99% pure.

Source: Richmond

Hoffman Reaction: Chapter 21

Preparation of *p*-Methoxyphenylethylamine

27 grams of *p*-methoxyphenylpropionamide is heated with a solution of 7.9 cc. of bromine and 36.5 grams of sodium hydroxide in 150 cc. of water for half an hour; the temperature is best kept below 60°. On extraction of the base with ether, drying and fractionally distilling 8 grams of *p*-methoxyphenylethylamine boiling at 138—140°/20 mm. is obtained. Source: Wellcome 1909

Preparation of ß-3-Methoxy-4: 5-methylenedioxyphenylethylamine

by Arthur Henry Salway

Ninety grams of finely powdered *p*-3-methoxy-4: 5-methylenedioxyphenylpropionamide were added to 1400 c.c. of an alkaline solution of sodium hypochlorite containing 77 grams of active chlorine (compare Graebe, *Ber.*, 1902, 36, 2753), and the mixture was shaken continuously until the amide had completely dissolved, for which about two hours were necessary. The clear solution was then heated for a short time (fifteen minutes) on the boiling-water bath, when a dark-coloured oil separated, which was extracted with ether. The ethereal solution was washed with water, and subsequently shaken with dilute hydrochloric acid until the base was completely extracted. A small portion of this acid solution, when concentrated to a small volume, yielded crystalline hydrochloride, which was purified by recrystallisation from a mixture of absolute alcohol and ethyl acetate. It separated from this solvent in colourless needles, melting at 165°:

The above described acid amide was finely powdered, and shaken continuously with a slight excess of sodium hypochlorite (compare, *Trans.*, 1910, 97, 1210) until the whole had passed into solution. The liquid was then heated to 100° for a short time, and, after cooling, thoroughly extracted with ether. The ethereal solution, which contained the ß-3:5-dimethoxyphenylethylamine formed in the reaction, was agitated with small portions of dilute hydrochloric acid until no further quantity of base was extracted. The, acid extracts were then united, and shaken with an excess of phenylacetyl chloride in the presence of alkali. The crude phenylacetyl derivative thus obtained did not solidify; it was therefore extracted with ether, the ethereal solution washed successively with dilute hydrochloric acid and water, then dried, and the solvent removed. The residue soon solidified, and was purified by crystallisation from dilute alcohol. Source: Salway 1911

Methylamide of Phenyl-propionic Acids

by Fimanz
Liechenstein December 19, 1964

The ester of 3-phenyl-3-(4-pyridyl)-3-hydroxypropionic acid or 3-phenyl-3-(2-pyridyl)-3-hydroxypropionic acid respectively solidifies rapidly; it is collected and crystallised from methanol or hexane.

By treating the ester with an equal weight of 40% by weight aqueous methylamine and by leaving it to rest for 10 days, one obtains the corresponding methyl amide.

Source: Finanz 1968

ß-(2,5-Dimethoxyphenyl)-butyramide

by Richard Baltzly and Johannes S. Buck
Tuckahoe, NY

“The forgoing acid (ß-(2,5-dimethoxyphenyl)-butyric acid) was heated in a stream of ammonia, at 220-230°, for two hours. Recrystallization from benzene the amide forms columnar prism melting at 121°.”

Source: Baltzly 1940 See also: Livshits 1948

References: Dal Cason 1990; Govindachari 1953; Ide 1940; Woodruff 1942

Hoffman Reaction

by Peter Muller and Albrecht Marhold
Germany July 3, 2000

Example 3

21.1 g of sodium hydroxide were initially charged in 70 mL. of water, and 15 g of bromine were added dropwise at room temperature. After the addition had ended, 20 g of the 3-[4-(trifluoromethoxy)-phenyl]-propionamide obtained... were added. The mixture was then heated under reflux for 3 hours. After cooling, the reaction mixture was diluted with 200 mL. of water and extracted three times with in each case 75 mL. of methyl-*t*-butyl ether. The combined organic phases were dried over magnesium sulphate, filtered and concentrated. The residue was distilled under reduced pressure over a short Vigreux column. This gave 10.3 g of 2-[4-(trifluoromethoxy)-phenyl]-ethylamine, which distilled over at from 83 to 86° C. and 11 mbar. According to GC, stated in area percent, the product was 99% pure. This corresponds to a yield of 58% of theory.

Example 4

20 g of the 3-[4-(trifluoromethoxy)-phenyl]-propionamide ... were initially charged in 30 mL.of water. At 60° C., a mixture of 21.1 g of sodium hydroxide, 50 ml of water and 15 g of bromine was added dropwise to this suspension. The mixture was then heated under reflux for 3 hours. The reaction mixture was diluted with 200 mL. of water and then worked up and purified as described in Example 3. This gave 8.8 g of 3-[4-(trifluoromethoxy)-phenyl]-acrylamide which distilled over at from 84 to 87° C. and 11 mbar. According to GC, stated in area percent, the product was 99% pure. This corresponds to a yield of 49% of theory.

Example 5

21.1 g of sodium hydroxide and 20 g of 3-[4-(trifluoromethoxy)-phenyl]-propionamide, prepared according to Example 2, were initially charged in 70 mL. of water, and 15 g of bromine were added dropwise at room temperature. The mixture was then heated under reflux for 3 hours. The reaction mixture was subsequently admixed with 200 mL. of water and worked up and purified as described in Example 3. This gave 12.9 g of 2-[4-(trifluoromethoxy)-phenyl]-ethylamine which distilled over at from 84 to 86° C. and 10 mbar. According to GC, stated in area percent, the resulting product was 99% pure. This corresponds to a yield of 72% of theory. Source: Muller 2001

Preparation of di-(*beta*-phenyl-*alpha*,*alpha*-dimethyl) urea

by Liese L. Abell, William F. Bruce
and Joseph Seifter September 23, 1947

3.5 grams of *alpha, alpha*-dimethyl-*beta*-phenylpropionamide in 420 cc. of water was added to a solution of 87.5 grams of potassium hydroxide and 35 grams of bromine in 350 cc. of water. After 2 hours at 60° C, the product was obtained on crystallization from ethanol, melting at 184° C.

Preparation of *omega*-Phenyl-*tert*-butylamine

24 grams of the urea derivative obtained as indicated above, were well mixed with 96 grams of calcium hydroxide in a flask immersed in an air bath and provided with a dropping funnel the stem of which reached the bottom of the flask. The mixture was heated to 240-260° C (inside temperature) for 7 hours during which time 86 cc. of water was slowly added. The vapors were collectad in a receiver cooled with ice. After extraction with ether and distillation, the product was obtained as a colorless liquid boiling from 80-84° C. at 9 mm.

Source: Abell 1952

Preparation of Ally-phenylethylamines

by Richardson-Merrell
New York, New York April 19, 1963

Amphetamine is well known for its high activity as a central nervous stimulant, and it is used in certain preparations for the control of obesity by depressing the appetite, and for elevating the mood in depressive states by providing a temporary feeling of well being in the patient. It was very surprising, therefore, to find that these allyl substituted derivatives exhibit such excellent properties as analgesia, tranquilizing, antidepressant, and appetite controlling, at doses devoid of central nervous stimulation. This useful separation of desirable from undesirable pharmacological actions would certainly not be expected on the basis of the known actions of amphetamine.

The *alpha*-allyl substituted derivatives may be prepared by the Hoffman degradation reaction of the amide containing one carbon atom more than the resulting *alpha*-allylamine derivative.

Alternatively, a modification of the Hoffman degradation reaction may be used in which the reaction is carried out in methanol to give the intermediate methylcarbamate derivative; which upon alkaline hydrolysis yields the desired *alpha*-allyl substituted amine.

The *alpha*-allyl substituted derivatives are conveniently prepared by reducing the corresponding amides with lithium aluminium hydride.

The Hoffman degradation reaction generally is carried out by dissolving the amide in a very slight excess of cold (—5° to 5°C) aqueous hypholite solution, followed by rapid warming (30° to 70°C.) for fifteen minutes to two hours.

Alternatively, in certain cases because of poor yields, it may be advantageous to use a modification of the Hoffman degradation which consists of carrying out the reaction in alcoholic solution with subsequent hydrolysis of the carbamate so obtained. Generally the hypohalite solution is added rapidly with thorough mixing to a methanolic solution of the amide. Warming the solution completes the reaction in ten to twenty minutes from which the carbamate is readily obtained. Subsequent hydrolysis of the carbamate by refluxing with 40 per cent sodium hydroxide solution for one to three hours yields the desired *alpha*-allyl substituted amine.

alpha-Allylphenethylamine Preparation

A 12-liter flask is fitted with a stirrer and placed in an ice-salt bath. Ten liters of ice water are added to the flask followed by 1440 grams (36 moles) of sodium hydroxide pellets. The stirrer is started and when the temperature of the solution reaches —5° to 0°C., 908 grams (5.7 moles) of bromine is added. The resulting sodium hypobromite solution is stirred for one half hour, whereupon 1134 grams (6 moles) of powdered allylbenzylacetamide is added over a fifteen minute period. When the addition is complete, the suspension is stirred for three hours at 0°C., the cooling bath removed and the reaction mixture is stirred overnight at room temperature. The milky white suspension is then heated to 30° to 35°C. on a steam bath and maintained at this temperature with stirring for two hours. The mixture is then cooled, extracted several times with ether and the combined ether extracts dried over anhydrous potassium carbonate. The ether is evaporated, and the residue distilled. The fraction boiling 60—62°C./0.3 millimeter is collected to give 622 grams of the desired *alpha*-allylphenethyamine, nD°25 =1.5224.

Allylbenzylamine Preparation

A solution of sodium hypobromite was prepared from 36 grams (0.9 mole) of sodium hydroxide and 24 grams (0.15 mole) of bromine in 3,000 milliliters of water and cooled to 0°. To this cooled solution was then added 24 grams (0.15 mole) of *alpha*-allyl-*alpha*-phenylacetamide and stirred for three hours. The reaction mixture was then allowed to warm to room temperature after which it was heated at 70°C. for one hour. After cooling, the reaction mixture was extracted with ether and the ether extracts dried over anhydrous potassium carbonate and filtered. The solvent was removed under vacuum and the residual oil distilled to yield the desired allylbenzylamine boiling at 62°C. at 1 millimeter, nD25=1.5294.

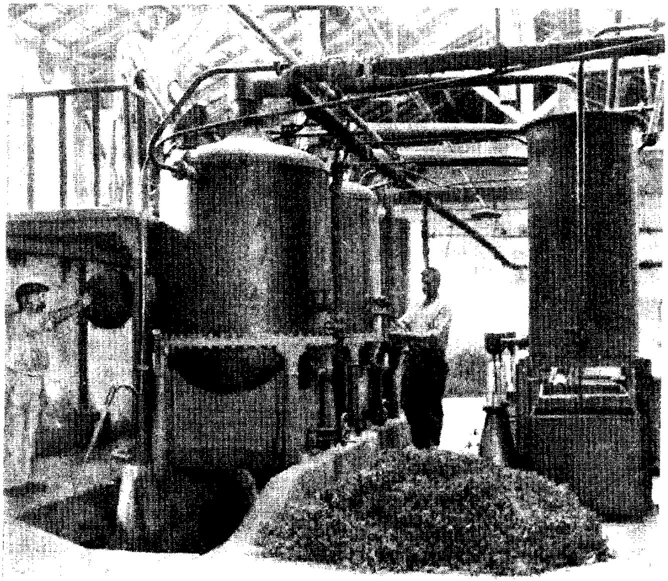
The hydrochloride addition salt of the above reaction product was prepared in customary fashion, that is, by reaction with hydrochloric acid followed by crystallization from ethanol-ether. A second crystallization from acetone-hexane gave the desired allylbenzylamine hydrochloride as a white crystalline solid melting at 233° to 234°C.

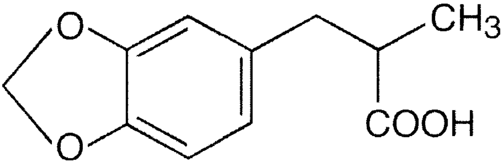
Houben-Weyl, *Methoden Der Organschen Chem.* Vol. XI/1, page 859 (1957) describes the preparation of this compound.

Preparation of *alpha*-Allyl-*gamma*-phenylpropylamine

Methyl-4-(6-phenyl-1-hexenyl) carbamate (5 grams) in 400 milliliters of 40 per cent sodium hydroxide solution was refluxed for two hours. The reaction mixture was then steam distilled and the distillate extracted several times with ether, The ether extracts were dried over anhydrous sodium sulfate, filtered, and the solvent removed by evaporation. The resulting product, *alpha*-allyl-gamma-phenylpropylamine, was converted to the hydrochloride addition salt by the addition of ethereal hydrogen chloride.

The desired *alpha*-allyl-gamma-phenylpropylamine hydrochloride was obtained as a white crystalline solid, from ethanol-ether, melting at 141° to 145°C. Source: Richardson-Merrell





α-Methyl-3,4-methylenedioxy-hydrocinnamic Acid

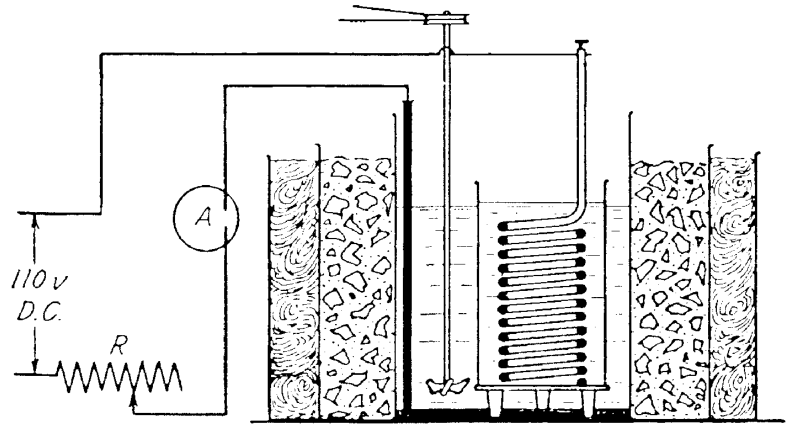
Hydrocinnamic Acid: Chapter 22

by A W. Ingersoll

$C_6H_5CH=CHCO_2Na$ + 2H (electrolytic) →
$C_6H_5CH_2CH_2CO_2Na$ →
$2C_6H_5CH_2CH_2CO_2Na + H_2SO_4$ →
$C_6H_5CH_2CH_2CO_2H + Na_2SO_4$

1. Procedure: Apparatus

The reduction is carried out in a 7 x 10 inch battery jar (Note 1) which is surrounded by a vessel of cold water. The bottom of the battery jar is just covered with mercury which serves as the cathode of the cell. The anode is a coil of heavy sheet lead separated from the catholyte by suspending it in a porous cup. The latter is supported in the battery jar so that it just clears the surface of the mercury (Note 2). The cathode is connected with the circuit by means of a copper wire well insulated with rubber except for one-eighth inch at the end which is immersed in the mercury. Efficient mechanical stirring is provided for the catholyte. The current used for these experiments was drawn from a storage battery delivering 30 volts, through a rheostat and ammeter each capable of carrying 15 amperes. Current may be taken from any source which will supply 80 to 85 ampere-hours at the rate of 5 to 10 amperes. Several reduction cells of the size described may be run at one time by connecting them in series. The diagram given in *Org. Syn.* 5, 94 shows the arrangement of the apparatus.



B. Reduction of Cinnamic Acid

After the apparatus is assembled, 2 L. of 7-8 per cent sodium sulfate solution (Note 3) is placed in the battery jar and the porous cup is filled to the same level with more of this solution. The stirrer is started and 200 g. (1.35 moles) of a good grade of cinnamic acid (Note 4) is suspended in the catholyte. A solution of 35 g. (0.88 mole) of sodium hydroxide in 150 cc. of water is then added at such a rate as to avoid forming lumps of sodium cinnamate (Note 5). The current is turned on and the rheostat adjusted until a steady current of 5 to 10 amperes is flowing (Note 6). From this point only occasional attention is required. The suspended sodium cinnamate and cinnamic acid gradually dissolve as the reduction proceeds. Portions adhering to the walls of the cell should be worked down with a stirring rod and finally with a little water from a wash-bottle. The liquor inside the porous cup should be kept alkaline by adding very concentrated sodium hydroxide solution at about half-hour intervals (Note 5). About 110 g. (2.7 moles) will be required. The reduction will require 76 to 80 ampere-hours (Note 7); considerable hydrogen is evolved near the end. The temperature need not be controlled (Note 8).

When reduction is complete (Note 7) the cathode liquor is decanted or siphoned from the mercury, filtered from traces of solid matter and acidified with an excess of sulfuric acid (sp. gr. 1.1). The hydrocinnamic acid separates as an oil and solidifies on thorough cooling. The yield of crude product, which contains water and other impurities is 180-200 g. It is purified by distillation under reduced pressure. The product boiling at 194-197°/75 mm. (145-147°/18 mm.) is colorless and melts at 47.5-48°. The yield of distilled acid is 160-180 g. (80-90 per cent of the theoretical amount) depending upon the quality of the cinnamic acid used (Note 4).

2. Notes

1. This is a commercial size. Any sturdy glass vessel of similar dimensions may be used.

2. The lead anode should have about the same surface area as the cathode. The porous cup used was 8 x 21 cm., but similar sizes will do. A three-legged desiccator plate makes a convenient support for the cup.

3 Any dilute solution of sodium sulfate may be used. If several runs are to be made, the solution recovered from the filtration of the

hydrocinnamic acid should be neutralized with sodium hydroxide, diluted if necessary, and used again. Traces of hydrocinnamic acid contained in this solution are thus saved. C.P. chemicals are not necessary.

4. The quality of the cinnamic acid used is important. The yield from a commercial C. P. acid melting at 132.5-133° was 86-90 per cent. From a lot melting at 131.5-133° obtained by recrystallizing a crude acid with the use of boneblack the yield was 81-83 per cent. With a technical grade of material the yield fell, in some runs, below 60 per cent, the reduction mixture foamed considerably and much high-boiling residue was left on distillation.

5. The addition of too much sodium hydroxide at this point produces a thick sludge which does not stir well. It should be noted that during the reduction two molecular equivalents of sodium hydroxide are produced at the cathode and an equivalent amount of sulfuric acid at the anode.

6. The current may vary somewhat, especially if the anode liquor becomes too dilute or highly acid. The sodium hydroxide solution added to the anolyte should be concentrated so that the diffusion which always occurs will not dilute the catholyte excessively. High amperage shortens the time required but promotes heating. Seven amperes is a convenient rate.

7. The theoretical quantity of current is 72 ampere-hours. It is necessary to pass an excess of 4 to 8 ampere-hours to insure complete reduction. The end of the reduction is reached when a sample of the catholyte on acidification with excess sulfuric acid precipitates an oil and no solid.

8. The reaction is favored by moderately high temperatures. Excessive heating may be avoided by reducing the amperage or by placing cold water in the cooling bath.

9. It may be noted that this process is essentially a sodium amalgam reduction. By the same procedure ß-furylacrylic acid was reduced to ß-furylpropionic in yields of 60-70 per cent. With suitable modifications it may be applied to the reduction of other substances reducible with sodium amalgam.

Methods of Preparation

Hydrocinnamic acid has been prepared by the reduction of cinnamic acid with sodium amalgam, (1) with hydriodic acid at 100°, (2) and with phosphorus and hydriodic acid; (3) by the action of potassium cyanide on ß-phenylethyl chloride followed by hydrolysis; (4) by the acid hydrolysis of benzyl-acetoacetic ester; (5) and by several other methods of no preparative value. It has also been prepared electrolytically by the reduction of cinnamic acid in alkaline solution on cathodes of lead (8) and mercury (9).

1. **Erlenmeyer and Alexejeff**, *Ann* 121, 375 (1862).
2 **Glaser**, *Zeit. f. Chem.*, 1865, 111
3. **Gabriel and Zimmerman**, *Ber.* 13, 1680 (1880).
4. **Fittig and Kiesow**, *Ann.* 156, 249 (1870).
5. **Merz and Weith**, *Ber.* 10, 758 (1877).
6. **Conrad**, *Ann.* 204, 176 (1880).
7. **Conrad and Hodgkinson**, *Ann.* 193, 302 (1878).
8. **Norris and Cummings**, *J. Ind. Eng. Chem.* 17, 305 (1925).
9. **Marie**, *Compt. rend*, 136, 1331 (1903).

Source: Ingersoll 1928

Preparation of Hydrocinnamic Acid

Marie prepared this acid by the electrolytic reduction of cinnamic acid. He used a mercury cathode, which presented some difficulties.

The first experiments showed that an appreciable amount of sodium cinnamate was transferred to the anodic compartment when the salt was electrolyzed. To avoid this the reduction was carried out in the presence of an excess of sodium hydroxide. The best conditions found were as follows: Cathode sheet lead (area 260 sq. cm.); anode, sheet lead. The cathodic solution was prepared by adding 30 grams of cinnamic acid to a warm solution of 8.1 grams of sodium hydroxide dissolved in 400 cc. water. The solution was transferred to a porous cup, heated to about 50° C., and stirred rapidly. A solution of 25 grams of sodium hydroxide in 100 cc. of warm water was then slowly added. The addition of the excess of alkali caused the precipitation of a part of the sodium cinnamate. The solution was stirred during the electrolysis until the suspended matter dissolved. The temperature was kept at about 60° C. A current density of 5.7 amperes per sq. dm. was maintained until 90.7 per cent of the theoretical current had passed; it was then reduced to 2.4 amperes per sq. dm. until 9.8 per cent excess had passed. The current efficiency therefore was 83 per cent.

The cathodic solution was cooled in ice water, and a large excess of concentrated hydrochloric acid was added. An oil separated, which was filtered off after it had solidified. The hydrocinnamic acid melted at 46.7° to 48° C. The yield was 91 per cent of the theoretical. Source: Norris 1925 References: Marie 1903, Ingersoll 1925, 1928

Preparation of Cinnamic Acids

by Bernard Beitzke, Volkmar Handschuh,
and Heinz U. Blank
Germany June 11, 1985

Example 1

106.1 g of benzaldehyde, 61 g of sodium acetate and 18 g of potassium carbonate were initially introduced into a 2 litre flask with stirrer, reflux condenser, thermometer and dropping funnel, and were heated to 160° C. Then 136 g of acetic anhydride were added dropwise at a constant rate within 80 minutes. The mixture was then heated under reflux for 6 hours and 40 minutes. A sample of 27.1 g of the reaction mixture thus obtained exhibited, as a 10% by weight solution in glacial acetic acid, a Hazen number of 350 (APHA). The volatile constituents were then removed by distillation (111 g). 700 mL. of water and 250 mL. of toluene were added to the residue. The aqueous phase was adjusted to pH 8, and then the phases were separated. Extraction was repeated twice more with 200 mL> of toluene each time, and then the cinnamic acid was isolated from the aqueous phase by acidification. 96.6 g of cinnamic acid with a Hazen number of 200 (APHA), measured as a 10% by weight solution in glacial acetic acid, were obtained. The purity of the cinnamic acid was more than 99%.

Example 4

318.4 g of benzaldehyde, 182 g of sodium acetate and 47 g of potassium carbonate were initially introduced into a 2 litre four-necked flask with stirrer, thermometer, dropping funnel (500 mL.) with facility for passing N2 over, and distillation device, and were heated to 165° C. At a constant bottom temperature of 165° C., 385 mL. (408 g) of acetic anhydride were added dropwise at a constant rate within 260 min. After the addition of about 150 mL. of acetic anhydride, reflux at the top of the column started, and a distillate was removed under normal pressure and at an overhead temperature of 117° C. (maximum 118.5° C.). After the end of the addition of the acetic anhydride, removal of distillate was continued for as long as this was possible at a bottom temperature of 165° (about 15 min.). A sample from the reaction mixture had a Hazen number of 350 (APHA) determined in the manner indicated above. After working up in analogy to Example 1, 318.1 g of cinnamic acid, purity 99.6 %, were obtained. This corresponded to a yield of 71.3 % of the theoretical yield based on the charge of benzaldehyde. The product had a Hazen number of 200 measured as a 10% strength solution in acetic acid. Source: Beitzke 1986 References: Bogert 1932; Woodruff 1938

Preparation of Cinnamic Acid from Benzylidene Acetone

by Arthur Lewinsohn
Berlin, Germany April 1924

A solution of 33 kilos of soda ash in 50 kilos of water is made in a wooden vat, which is provided with an overhead mill, and into which live steam can be injected; 14.6 kilos of benzylidene acetone is added thereto, and the mixture warmed to 45° by means of the live steam. As soon as the benzylidene acetone is melted the mixture is transferred, by means of a pump, to a large lead-lined jacketed mixing vessel. In the now empty wooden vat a mixture is made of 44 kilos of bleaching powder and 50 kilos of water, and this is then transferred to a mixing vessel which has been previously set in operation. The temperature is gradually raised to 60°, and chloroform which is liberated distills through a condenser connected to the still. After about 20 minutes, when no more chloroform comes off, the heating and mixing are stopped and the contents of the vessel blown out into a 15 to 20 hectolitre barrel or iron reservoir, which may advantageously be placed outside the operating room, as the luke-warm mixture still give off chloroform, inhalation of which is known to be dangerous.

As soon as the calcium carbonate, which as been formed in the reaction, has settled to a thick mud, the supernantant liquid is transferred to an enameled vessel, passing it though a filter bag. The clear solution is now very carefully acidified with 10% sulphuric acid solution (violent effervescence ensues on account of the presence of small excess of sodium carbonate). By this means the cinnamic acid is precipitated as a snow-white mass, it is centrifuged off, and washed with cold water until the washings give no precipitate of barium sulphate with barium chloride solution. Source: Lewinsohn 1924

Preparation of Cinnamic Acids from Styryl Ketones

by Hans-Juergen Quadbeck-Seeger
Neustadt, Germany March 6, 1975

It is known from Houben-Weyl, *Methoden der organischen Chemie*, volume 8, pages 415-416, that carboxylic acids can be manufactured by oxidation of methyl ketones with hypohalites in an aqueous medium. The publication recommends dispersing the ketone by means of oxidation-resistant emulsifiers or carrying out the reaction in the presence of dioxane; all the examples were carried out in this way. In most cases the reaction only takes place satisfactorily with hypobromite solutions, which are more expensive and less stable than hypochlorite solutions. For this reason alone, industrial utilization of the reaction is confined to special reactions with aromatic ketones.

It is an object of the present invention to provide a new process for the manufacture of carboxylic acids by a simpler and more economical method and in some cases in better yield and higher purity.

We have found that carboxylic acids are obtained advantageously from methyl ketones by reaction with hypochlorites in an aqueous medium...

Compared to conventional processes, the process of the invention suprisingly gives carboxylic acids more simply and more economically and in some cases in better yield and better purity, and permits the manufacture, even on an industrial scale, of a large number of carboxylic acids by using a hypochlorite. Since the alkaline hypochlorite solution is more stable than the hypobromite solution and its strength barely decreases even after several days, the process of the invention is more reliable, more trouble-free and particularly suitable for industrial operation. Compared to conventional processes which use hypochlorite solutions, the process of the invention gives better overall results with regard to yield or purity of the end product, and a lower consumption of alkali metal hydroxide solution. The uneconomical addition of dioxane is no longer necessary, nor does the ketone have to be converted to a dispersion before preparing the starting mixture. The chloroform obtained as a by-product is a valuable solvent and intermediate and can easily be isolated and used for other syntheses; this of particular value in industrial operation, in furthering the economy and simplicity of the process....

The other starting materials are aqueous hypochlorites, as a rule in the form of aqueous alkaline solutions. The methyl ketone is advantageously used in the form of aqueous suspensions of from 1 to 50% strength by weight. The aqueous hypochlorite solutions in general contain from 5 to 15, preferably from 12 to 14, % by weight of hypochlorite and may in addition contain from 0.2 to 2.5 moles, preferably from 1 to 2.1 moles, of alkali metal hydroxide per mole of hypochlorite. The initial mixture of the two starting materials in general contains a total of from 3 to 5, preferably from 3.1 to 4, moles of hypochlorite per mole of methyl ketone. Sodium hypochlorite and potassium hypochlorite are preferred.

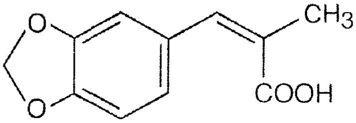
The catalysts used are bromine, iodine, haloamides I and/or polymerization inhibitors, in general in amounts of from 0.0001 to 0.1, preferably from 0.001 to 0.05, mole of catalyst per mole of methyl ketone. Instead of the above catalysts, it is also possible to use compounds which form such catalysts under the reaction conditions, e.g. to use bromides and iodides in place of bromine or iodine. Water-soluble halides are preferred and are advantageously used in the form of their alkaline earth metal salts or, especially,, their alkali metal salts, e.g. calcium bromide, calcium iodide, magnesium bromide, magnesium iodide, lithium bromide, lithium iodide and especially sodium bromide or iodide or potassium bromide or iodide...

The polymerization inhibitors used are compounds which inhibit or greatly retard the polymerization of monomers and thus act as stabilizers for the monomers. These inhibitors may be gaseous, solid or liquid; preferred compounds are those which inhibit the polymerization of vinyl compounds and especially those which inhibit their free radical polymerization. Inhibitors which may be used with advantage are sodium nitrite or inorganic compounds or divalent sulfur, preferably hydrogen sulfide, alkali metal sulfides, e.g. sodium sulfide or potassium sulfide, alkali metal bisulfides, e.g. lithium bisulfide, sodium bisulfide and potassium bisulfide, ammonium sulfide and ammonium polysulfide. Compounds wherein only a part of the sulfur in the molecule is divalent, such as alkali metal thiosulfates, e.g. sodium thiosulfate, may also be used. Phenol and thiophenol are also suitable catalysts....

As a rule, the reaction is carried out at from -10° C to +62° C, preferably at from 10° to 50° C, under atmospheric or superatmospheric pressure, continuously or batchwise. The reaction may, e.g., be carried out as follows. The methyl ketone is introduced into a mixture of hypohalite, catalyst and water and the batch is kept at the reaction temperature for from 1 to 1,000 minutes. The end product is now isolated by conventional methods, e.g. by adding aqueous sodium bisulfite solution acidifying the reaction mixture with a suitable acid such as sulfuric acid, separating off the organic phase formed and distilling the latter. It is also possible first to remove the chloroform layer which separates out, to acidify the aqueous phase, remove the organic phase which hereupon separates out and finally combine the organic phases.

The compounds which can be manufactured by the process of the invention are valuable starting materials for the manufacture of dyes, plant protection agents, tanning agents, pickling agents, bates, vulcanizing agents and scents. Their esters, especially with aliphatic alcohols, are scents, solvents, especially for ethereal oils and aromatic esters, and plasticizers.

Cinnamic Acid from Benzalacetone



Piperonyl-α-methyl-cinnamic Acid

50 parts of benzalacetone are added slowly and in portions, in the course of 20 minutes at from 30° to 35° C, to a mixture of 900 parts by volume of sodium hypochlorite solution (containing 149 parts of sodium hypochlorite), 150 parts by volume of water and 1 part of potassium bromide. After a further reaction time of 1.5 hours at 40° C, the chloroform which has formed is separated off, the aqueous phase is acidified and the organic phase which forms is combined with the chloroform phase. The aqueous solution is extracted by shaking with a further 100 parts by volume of chloroform and the chloroform is distilled from the combined organic phases. 49.5 parts (98.5% of theory) of cinnamic acid melting at 122° C are obtained.

Source: Hans-Juergen 1976

Cinnamic Acids from Coumarins

Cinnamic acids can be created from the methylation of coumarins. Methoxy substituted coumarins produce lower yields than do non-substituted and hydroxy substituted coumarins.

0.5 Moles of substituted coumarin is mixed with 65 mL of dimethyl sulfate and 70 mL. of 33% potassium hydroxide. The reaction is allowed to complete, cooled and mixed with more dimethyl sulfate and potassium hydroxide. The reaction mixture is refluxed with 150 mL of 33% potassium hydroxide for one hour. The reaction mixture is then methylated further with more dimethyl sulfate. Potassium hydroxide is added again and refluxed to hydrolyze the methyl ester that is formed. The solution is then mixed with 3 liters of water and filtered through charcoal. The mixture is chilled, mixed with hydrochloric acid to precipitate the cinnamic acid which is collected by vacuum filtration.

Starting Molecule: 6-Hydroxy-4-methylcoumarin
Product: 2,5-Dimethoxy-ß-methylcinnamic acid
Reference: Woodruff 1942

Starting Molecule: 7-Hydroxy-4-methylcoumarin
Product: 2,4-Dimethoxy-ß-methylcinnamic acid
Reference: Pechman 1884; Woodruff 1942

Naturally Occurring Coumarins

Coumarin occurs in lavender, woodruff (*Asperula*), tonka beans, and sweet clover (*Melilotus*). Coumarin can be extracted from sweet clover with hot water. Reference: (Sethna 1945)

Umbelliferone (7-Hydroxycoumarin) can be obtained from the distillation of the resin from *umbelliferae* species of plants.

Scopoletin (7-Hydroxy-6-methoxycoumarin) occurs in *Solanaceae*, *Convolvulacea* and various other species of plants. It can also be made synthetically.

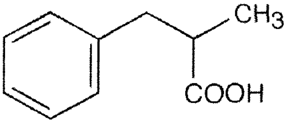
Esculetin (6,7-Dihydroxycoumarin) can be obtained by the hydrolysis of esculin. Esculin occurs in the leaves and bark of the horse chestnut tree (*Hippocastanacea*).

Fraxetin (7,8-Dihydroxy-6-methoxycoumarin) is obtained by heating fraxin with sulfuric acid. Fraxin occurs in the bark of the Common Ash tree (Fraxinus excelsior).

Limettin (5,7-Dimethoxycoumarin) is obtained from West Indian lime oil and various citrus oils.

α, ß-dimethyl-hydrocinnamic acid

by Felix Haffner and Fritz Sommer
Berlin, Germany February 11, 1939



α-Methyl-hydrocinnamic Acid

348 grams of methyl ethyl glycolic acid, and 450 grams of acetic anhydride are heated together for 4 hours on an oil bath at 150° C. The acetic acid is subsequently distilled off. 250 grams of dimethyl acrylic acid are isolated from the distillation residue (84% of the theoretical yield) of dimethylacrylic acid.

30 grams of dimethylacrylic acid (dissolved in 220 grams of thiophene-free, dry benzene) and 100 grams of finely powdered anhydrous aluminum chloride are allowed to stand for 1 week at 40-45° C. Ice and concentrated hydrochloric acid are added to the reaction mixture. The benzene and aqueous layers are thereafter separated and, after evaporation the benzene, 30 grams (56% of theoretical yield) of an acid boiling at 129-132° C. can be isolated from the residue by vacuum distillation at 5 mm. pressure. After one recrystalization from petroleum ether and benzene the melting point is 132° C.

Analysis gave a carbon content of 74.3% and a hydrogen content of 7.95%. For *alpha*-ß-dimethylcinnamic acid the carbon content is calculated to be 74.2 % and the hydrogen content 7.88%.

α, ß-dimethyl-hydrocinnamic acid from α,ß-dimethylcinnamic acid

The *alpha*,ß-dimethyl-cinnamic acid is hydrogenated by dissolving the acid in an equivalent amount of alkali and then hydrogenating it with colloidal palladium according to Paal and Skite. *alpha*,ß-dimethyl hydrocinnamic acid, which can be recrystallized.

Source: Haffner 1944

Benzalacetone: Chapter 23

$$C_6H_5.CHO + CH_3.CO.CH_3 \rightarrow C_6H_5.CH{=}CH.CO.CH_3 + H_2O$$

by N. L. Drake and P. Allen, Jr.

1. Procedure

In a 2-L. bottle equipped with a mechanical stirrer are mixed 635 g. (800 cc.) of U. S. P. acetone (Note 2), 420 g. (400 cc.) of freshly distilled benzaldehyde boiling at 178°-180° (shaken with dilute sodium carbonate just before distillation), and 400 cc. of water. To this mixture, 100 cc. of 10 per cent aqueous sodium hydroxide is slowly added from a dropping funnel (Note 3), while the solution is stirred and cooled by a water bath. The rate of addition of the alkali is so regulated that the temperature remains between 25 and 31°. This requires thirty to sixty minutes. The mixture is now stirred for two and a quarter hours at room temperature (Note 4). At the end of this time dilute hydrochloric acid is added until the mixture is acid to litmus. The two layers which form are separated in a separatory funnel. The lower aqueous layer is extracted with 100 cc. of benzene, and the benzene solution added to the yellow oil which formed the upper layer in the first separation. This benzene solution is shaken with 100 cc. of water and separated. The benzene is then removed by distilling from a steam bath, and the residue distilled under reduced pressure (Note 5), any water which condenses with the forerun being separated (Note 6). A special distilling flask with a fractionating side-arm (Vol. 1, p. 40) is best employed. The material which distills at 148-160°/25 mm., 133-143°/16 mm., or 120-130°/7 mm. weighs 430-470 g. (Note 1); it solidifies to a crystalline mass on standing, and is pure enough for all practical purposes. On redistillation there is obtained 375-450 g. (65-78 per cent of the theoretical amount) of material boiling at 137-142°/16 mm. or 123-128°/8 mm., which solidifies on standing to crystals which melt at 40-42°.

2. Notes

1. Benzalacetone acts as an irritant, and care should be taken that it be not allowed to come in contact with the skin.

2. A large excess of acetone is taken, so as to diminish the formation of dibenzalacetone.

3. If the sodium hydroxide is added too rapidly and without cooling, the mixture darkens and the yield is lowered. The rate of addition is best determined by watching the temperature of the reaction mixture.

4. Instead of stirring the mixture after the addition of the sodium hydroxide, the bottle may be securely stoppered and shaken on a shaking machine for the same length of time.

5. The lower the pressure used in the distillation the less decomposition occurs, and the less residue is left in the distilling flask. This residue contains some dibenzalacetone.

6. The first few cubic centimeters of the distillate have a greenish color, but the rest is light yellow. For this reason it is desirable to collect the first of the distillate separately, if a very light-colored product is desired.

7. On exposure to air benzalacetone gradually turns brown, especially if it is slightly impure. Pure material can be kept for months in an ordinary stoppered bottle without changing color.

3. Other Methods of Preparation

Benzalacetone has been obtained in small yield by dry distillation of a mixture of calcium acetate and calcium cinnamate (1); by heating the sodium derivative of cinnamaldehyde with methyl iodide (2); by heating cinnamaldehyde and methyl alcohol with zinc chloride (2) by heating acetone and benzaldehyde with acetic anhydride or zinc chloride (3). It is also formed when styrene and acetyl chloride are condensed by means of stannic chloride and the product is treated with diethylaniline (4); and when the vapors of cinnamic acid and acetic acid are passed together over ferric oxide at 470-490° (5). The only practical method, however, consists in condensing benzaldehyde and acetone by means of dilute aqueous alkali (6).

1. *Ber.* 6, 254 (1873).
2. *Ber.* 6, 257 (1873).
3. *Ber.* 14, 2461 (1881).
4. *Compt. rend.* 168, 1052 (1919).
5. *Bull. soc. chim.* (4) 16, 326 (1914).
6. *Ann.* 223, 139 (1884); 294, 275 (note) (1897).

Source: Drake 1923

Benzylidene-acetone Preparation

by Arthur Lewinsohn
Berlin, Germany April 1924

In a jacketed mixing vessel of iron-provided with means for heating and cooling by passing steam or water through the jacket-are mixed with 22.5 kilos of acetone and 15 kilos of benzaldehyde. The mixture is cooled to about 10° and 8.7 kilos of 10% caustic soda solution are slowly added during vigorous stirring. The solution becomes lemon yellow in colour. As a result of the reaction, 2.54 kilos of water are produced, and in order to maintain the strength of the solution ten hourly additions of 250 grams of 20% caustic soda solution are made, the mixture is set aside for two days. At the end of this period 20 kilos of cold water are added, thus causing the benzaldehyde to precipitate as a brown oil. After washing with dilute acetic acid and sodium carbonate solution the oil is distilled under diminished pressure, a bright yellow oil coming over at 151-3° under 25 mm. This oil posses a fresh and characteristic odour, and after a short period, especially if seeded with a crystal, the oil solidifies to a bright yellow crystalline solid melting at 41-42° C.

On account of its exceptionally penetrating nature, benzylidene acetone should be used in perfumery with great caution, and only as a 10% solution in alcohol. Its stability to alkali makes it of special value for soap-perfume oils. In its concentrated state benzylidene acetone violently attacks the skin.

Source: Lewinsohn 1924

Benzylidene-methylethylketone Preparation

by Hugh Ryan and Annie Devine
Dublin, Ireland March 28, 1916

A mixture of 130 grams of methylethylketone, and 140 grams of benzaldehyde, with a solution of 50 grams of sodium hydroxide in 1500 ccs. of water, was shaken on a machine for eight days. The oil which separated was extracted with ether, and after evaporation of the latter the residue was distilled in a current of steam. When the benzaldehyde ceased coming over, the residue in the flask was subjected to further distillation in a current of steam, previously heated in a coil to 180° C, while the flask from which the distillation was being conducted was heated to 180° C. in an oil-bath.

The oil which now distilled solidified after short standing, and the solid. when recrystallized from petroleum ether, melted at 38°-39° C.

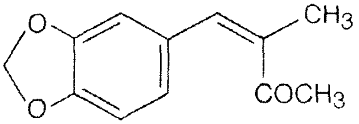
The oil which now distilled solidified after short standing, and the solid when recrystallized from petroleum ether, melted at 38°- 39° C.

Towards the end of the operation the distillate contained a small quantity of another compound which melted at 81°- 83° C.

alpha-Benzylidene-methylethylketone crystallizes from petroleum ether in large plates which are coloured reddish-brown on contact with concentrated sulphuric acid, in which they dissolve forming a reddish-brown solution. Source: Ryan 1916

Preparation of Piperonylidene-methylethyl-ketone

by Hugh Ryan and Patrick J. Cahill
Dublin, Ireland September 15, 1924



A mixture of 15 grams of methylethyl-ketone and 50 grams of piperonal with 750 cc. of dilute aqueous solution of sodium hydroxide was shaken mechanically for seven days. The yellow oily solid, which separated, was filtered, washed with water, and recrystallized several times from petroleum ether. It consisted of nearly colourless plates, which melted at 101-102° C.

Piperonylidene-methylethyl-ketone is insoluble in water, but dissolves easily in alcohol, ether, or chloroform. It is coloured red on contact with concentrated sulphuric acid, in which it dissolves, forming a red solution. Source: Ryan 1924

Intermediate Chemicals: Chapter 24

Methylamine Hydrochloride Preparation

by Emil Alphonse Werner

The proportions of ammonium chloride and formaldehyde (40 per cent. formalin) recommended by Brochet and Camier, namely, one part by weight of the former, and two parts by weight of the latter, were found after several trials to give the best results. Since about 35 per cent. of ammonium chloride has always been recovered unchanged, the molecular ratios $NH_4Cl:2CH_2O$ required by theory are very closely represented by the above proportions.

Two hundred and fifty grams of ammonium chloride and 500 grams of formaldehyde solution were gradually heated in a distillation flask, which carried a thermometer with the bulb well below the surface of the liquid. The temperature was slowly raised to 104°, and was not allowed to rise above this point, at which it was maintained until no more volatile liquid distilled; this required about four and a-half hours. The distillate weighed 110 grams. the product was allowed to cool, and after filtration form 62 grams of ammonium chloride which had separated, was concentrated by evaporation at 100° to about one-half of the original volume. After removal of 19 grams of ammonium chloride (ammonium chloride is very sparingly soluble in a concentrated solution of methylamine hydrochloride, and consequently its separation from the latter salt is very sharp), the liquid was again concentrated by evaporation until a crystalline scum had formed on the surface of the hot solution.

After cooling, 96 grams of methylamine hydrochloride were separated; after further concentration a second crop (18 grams) was obtained. The filtrate was now concentrated as far as possible at 100° and was left for twenty-four hours in a vacuum over sodium hydroxide, after which the semi-soft residue was digested with chloroform, when 20 grams of methylamine hydrochloride which had been washed with chloroform to remove the dimethylamine hydrochloride, were obtained. The total yield was 128 grams. Source: Werner 1917

09.22 Germany 040922-02 A5 Autobahn, near Frankfurt-am-Main. About 20 tonnes of methylamine spilled after a Netherlands-registered tanker was struck by another truck. Incidents, Week 39 2004

Manufacture of Methylamine

by Walter Bander and
Donald Archer Nightingale July 2, 1920

900 lb. of bleaching powder of 30% available chlorine content are suspended in water, in a suitable container fitted with stirring gear and cooling jacket. Milk of lime made with 900 lb. of quick lime is added, and the mixture cooled to + 5° C. An aqueous solution of 200 lb. acetamide is added whilst maintaining the temperature low, and then 2000 lb. sodium carbonate (soda ash) is gradually added and dissolved in the mixture whilst maintaining the cooling, and the resulting mixture is afterwards heated and eventually boiled. The escaping methylamine gas may be condensed or absorbed or otherwise obtained in any suitable form; for example it may be absorbed in hydrochloric acid, and about 200 lb. monomethylamine hydrochloride of high purity obtained.

It is to be understood that our invention is not limited by the particular conditions set out in the examples, which may be varied considerably within the spirit of the invention.

Instead of acetamide, amides of higher alkyls, for example propionamide, may be treated according to the invention to obtain corresponding mono alkylamines, for example ethylamine.

Source: Bader 1921

Preparation of Acetamide

by Wendell, P. Munro, Elmore H. Northey
and Hans Z. Lecher
Plainfield, NJ April 13, 1936

Most of the known processes for producing acetamide present serious operating difficulties if a pure product is desired, and especially where the product must be anhydrous. Thus the usual method of distilling ammonium acetate requires a slow and long distillation. It has also been proposed to bring about reaction between ethyl acetate and ammonia but this process also produces an acetamide which is not pure and which notably contains water due to the great hygroscopicity of the acetamide.

According to the present invention, acetamide is produced by reacting aqueous ammonia on ethyl or particularly methyl acetate which reacts much more rapidly and completely, and the purification is effected after distilling of the water and alcohol formed by washing the acetamide with anhydrous methyl acetate or in the case where ethyl acetate is used as a raw material, with anhydrous ethyl acetate. Methyl acetate and similarly ethyl acetate, have not a high solvent action on acetamide at ordinary temperatures, but tend to dissolve water and thus dry out the acetamide. The acetamide obtained may be further washed with an inert organic liquid like benzene which has but little solvent action on acetamide and which protects the surface of the purified product from absorption of water. As the reaction of the ester with ammonia takes place in aqueous medium, the wet ester resulting from washing the acetamide may be used instead of pure anhydrous ester and the washing step results therefore in no material loss of raw material and acetamide. When a small amount of an inert organic liquid like benzene is used for final washing and coating, the benzene may remain with the ester to be used for the next batch, it will be later distilled off together with water, unreacted ammonia and ester, and the alcohol formed.

In order to obtain a pure product in a good yield, the reaction should be carried out below 80 C., because at higher temperature the formation of ammonium acetate becomes a disturbing factor. The reaction proceeds with sufficient speed and completeness at ordinary temperatures and neither heating nor cooling are therefore necessary which reduces the cost of apparatus.

Example

94 parts of methyl acetate are agitated with 180 parts of 28% aqueous ammonia solution until the methyl acetate is all dissolved. The solution is then allowed to stand for a total time of 20 hours at room temperature. Reacting then being complete, the methyl alcohol, water and excess ammonia, and traces of unreacted methyl acetate are distilled off through a fractionating column. The residue is ground with 47 parts of methyl acetate, the methyl acetate liquor filtered off, the crystals washed once with 47 parts methyl acetate, and twice with 13 parts of benzene, and finally dried in vacuo at 60-70° C. The combined wash liquors are used without further treatment to make another batch of acetamide. The yield of acetamide is good, and the product is obtained as colorless, practically odorless crystals of high quality.

Ethyl acetate may be used in a similar manner but the reaction is not as rapid or as complete as with methyl acetate and the methyl acetate therefore constitutes a preferred embodiment of the invention, particularly as the solvent power of methyl acetate for water is greater than that of ethyl acetate and it is therefore a more efficient washing medium than ethyl acetate so that improved results are also obtained in the second step of the process. It will be apparent that the present invention eliminates costly equipment for a troublesome fractional distillation or for distillation of the acetamide itself and the reaction is not carried out at high temperatures or under high pressures which further eliminates the necessity for expensive apparatus. The expense and loss incident to recrystallization which may be necessary in processes used hitherto, is also avoided without any loss in purity of the acetamide.

Source: Munro 1938

Hydroxylammonium Sulphate Preparation

by Commercial Solvents
New York, New York January 2, 1958

In Example 1 the results of producing hydroxylammonium acid sulphate by the conventional process and by the process according to the invention were compared. In the preparation by the conventional process, a mixture of 4.8 moles of 1-nitropropane and sufficient water to make a total of 4 moles with that present in the sulphuric acid was prepared and heated to reflux. There was then added 4.0 moles of sulphuric acid, either electrolytic grade, 93% or C.P. grade, 96%. The addition was made very slowly over a 3 to 4-hour period and the refluxing of the completed mixture was continued for a total reaction time of 8 hours. The reaction mixture was then cooled to below about 115° C. and the two layers separated. The lower layer or hydroxylammonium acid sulphate layer was analysed for HAS (hydroxylammonium acid sulphate) content and its colour determined on the Gardner 1933 Standard Colour Scale. The upper layer or propionic acid layer was analysed for total acidity which was corrected for sulphuric acid and hydroxylammonium acid sulphate content and the per cent. yield of propionic acid calculated therefrom. The results of these experiments are set out in Table 1A below.

Manufacture of Hydroxylammonium Sulphate

In this example are set forth the details of producing a full scale commercial batch of hydroxylammonium acid sulphate by the use of process according to the invention. There was charged to the reaction vessel 5300 pounds (50.3 moles) of 93% electrolytic grade sulphuric acid and 535 pounds (29.8 moles) of water which, with the water in the sulphuric acid, made a total of 906 pounds (50.4 mole). The mixture was heated to a temperature of from 135 to 140° C. and 5380 pounds (60.3 moles) of 1-nitropropane were added maintaining the temperature at from 135 to 140° C. This addition required a 7-1/2 hour period to complete. At the end of the addition period, the temperature was maintained at from 135 to 140° C. for an additional 1-1/2 hour holding period and then cooled to approximately 70° C. for separation of the layers. There were produced 6178 pounds of hydroxylammonium acid sulphate of a purity of 88.0% HAS. This was equivalent to 5420 pounds of hydroxylammonium acid sulphate on a 100% dry basis which represented a yield of 82.2% on the basis of the sulphuric acid charged.

Example 4

Hydroxylammonium acid sulphate derived from the conventional process by the addition of the sulphuric acid to refluxing 1-nitropropane-water mixtures and by the process according to the invention of the addition of 1-nitropropane to a heated mixture of sulphuric acid and water were converted to the hydroxylammonium chloride salt. The conversion was accomplished by adding 200 grams of hydroxylammonium acid sulphate at a temperature of 75 to 80° C. to a solution of 47 mL. of methanol in 231 grams of aqueous 36% hydrochloric acid solution. The mixture was stirred for from 10 to 20 minutes and allowed to stand at room temperature overnight. The mixture was then filtered and the filter cake washed with two 34-mL. portions of methanol. The product was dried and weighed to determine the percentage yield of hydroxylammonium chloride. The colour of the product was determined by dissolving 5 grams in 10 mL. of water and measuring the per cent. transmittance on a Lumitron 4000 colourimeter with a blue filter using water as a standard. The results of these experiments are set out in Table III below.

Source: Commercial Solvents 1960

Preparation of Dialkyl Sulphates

by Henry Dreyfus
London, UK September, 29, 1920

As is known, the pyrosulphates of alkalies, such as sodium pyrosulphate, can be manufactured according to various methods. The cheapest way of making sodium pyrosulphate, for example, which is a very cheap raw material, is to heat sodium bisulphate in vacuo. The pyrosulphates can also be made by combining sulphur trioxide with a sulphate, such as sodium sulphate. Similarly the chlorosulphonates of alkalies can be made by combining sulphur trioxide with a chloride, such as sodium chloride.

Example 1

228 parts of sodium pyrosulphate and 92 parts of alcohol are mixed at ordinary temperature for 1—2 hours, then heated under a reflux condenser at 80°—100° C. for a further 4—5 hours, the diethyl sulphate so formed being distilled off in vacuo. A high yield of diethyl sulphate can be thus obtained.

Example 2

Alcohol vapour may be passed over sodium pyrosulphate heated to about 150° C. If reduced pressure is maintained in the apparatus the diethyl sulphate will distill off as fast as formed, together with any excess of alcohol. The diethyl sulphate can be isolated in any known or suitable way.

It is to be understood that I do not confine myself to any particular methods or details of working, and that the manner of carrying the invention into effect can be varied within wide limits.

Instead of alcohol, ether may be used.

The sodium pyrosulphate may be used in the proportion of about two molecules to two molecules of alcohol or of about one molecule of the pyrosulphate to one molecule of ether. I do not confine myself to employing the materials in these proportions but may use the alcohol or ether in excess, or otherwise vary the proportions.

Source: Dreyfus 1922

Preparation of Dimethyl Sulphate

by J. Guyot and L. J. Simon, presentee by Mr. C.H. Moureu.

We have established before (1) why the direct action of the sulphuric acid on methanol cannot succeed as an advantageous preparation of the dimethyl sulphate and how one is led to use sulphur trioxide or, at least, with the industrial mixtures of acid and anhydride known under the name of oleums.

The methanol introduction into the sulphuric acid (66° Be) cooled at -18° provides a complex methylsulfuric which one can transform into a binary mixture of acids sulphuric and methylsulfuric.

1° One can employ sulphur trioxide; one condenses, in the complex mixture, the calculated quantity of anhydride coming itself from the distillation of oleum 60%

2° One can employ the oleum directly at 60% while making exterieurement fall the methylsulfuric liquor in this oleum cooled by a mixture from ice and salt.

If account is held that the acid has 66° Be compose SO4H2+ 0,23H20.

By then distilling under reduced pressure the mixtures thus prepares by elevant the temperature during a sufficient time, one thus obtains very satisfactory yields of dimethyl sulphate.

3° One can directly distill by introducing the oleum 60% into cooled methanol.

This formula shows that it is necessary to employ more than 400 parts of oleum at 60% per 100 parts of alcohol. The mixture once realise, one distils like previously: the dimethyl sulfate is formed with the waste of methyl sulphate acid (*loc. cit.*).

These experiments have been repeated and the conditions have have variatios to it; instead of cooling rapidly, there is only to leave the temperature too high; instead of pouring the oleum in alcohol, one made the reverse: in all the cases, the output always has been superior to 90% of theoretical and is raised sometimes up to 95%; in other words, to obtain dimethy sulphate, it must be enough to employ 550 kg to 600 kg of pure methanol.

In the techniques decscribed previously, the dimethyl sulphate is extracted from a sulphuric mixture which, at the end of the operations, correspond respectively has 3mol, 46, 4mol, 76 and 2 mol, 06 of sulphuric acid for a dimethyl sulphate molecule; one cannot espect total extraction from this product and the sulphuric acid, by a phenomenon of equilibre, obstinately retains an acid quantity of methyl sulphate. The small deficit, five to ten centiemes, announces in our experiments, is thus explained; but this deficit accroit if distillation is not sufficiently prolonged and if the temperature of heating eleve not enough. This deficit accroit still when sulphuric mass of acid exagere. However, if one employs a oleum rnoins in less rich, it is necessary to employ increasing quantities of them and, of this chief, the output must still subside.

In summary: the action of the oleum at 60% on pure methanol in proportion calculated leads to the formation of dimethyl sulphate with a superior output at 90%.

(1) *Comples rendus*, t. 169, 1919, p.435.

Source: Guyot 1919

Preparation of Nitroethane

by Leonard A. Stengel and Richard L. Abbott

Terre Haute, Indiana January 23, 1964

n-Propyl nitrite at ambient temperature was allowed to enter a stream of 50% nitric acid vapor preheated to 260° C. at a rate such that the molar ratio of nitrite to nitric acid was maintained at 0.87. The gaseous mixture was fed to a reactor which consisted of a coiled aluminum tube immersed in a molten mixture of potassium and sodium nitrates heated to 400° C. The pressure in the reactor was essentially atmospheric and the contact time was two seconds. The reaction products were condensed and the nitroparaffin layer was separated from the aqueous layer. The nitroparaffin product was 83% nitroethane and 17% nitromethane.

Source: Stengel 1965

Preparation of Nitroalkanes

by Sheldon B. Markofsky
Onlney, Maryland August 2, 1982

Nitromethane is a highly desired product which has many uses. It is a known preservative for chlorinated hydrocarbons, a fuel additive and an intermediate compound in the formation of various other chemicals, such as chlorpicrin. Nitromethane is the most commercially desired compound of the nitroparaffins.

Alkyl Nitrite	Nitrating Agent	Nitroparaffin Produced
Ethyl Nitrite	HNO3	Nitromethane
N-Butyl Nitrite	HNO3	Nitromethane, Nitroethane, Nitropropane
t-Butyl Nitrite	HNO3	Nitromethane
iso-Amyl Nitrite	HNO3	1-Nitro-2-methylpropane, 2-Nitropropane, Nitromethane

A stainless steel reaction vessel of 10 cc volume was charged with 0.56 part sodium nitrite, 0.8 part of distilled water and 0.34 part sodium bicarbonate. The vessel was cooled with liquid nitrogen under a blanket of argon to assure lack of air moisture condensation in the vessel. To the chilled vessel was added 3.9 parts of liquid methyl chloride (measured and weighed at—77° C. with density taken at 1.1). 3.5 parts of the added methyl chloride was excess over that required for stoichiometry. The vessel was sealed and heated at 75° C. for 4 hours with agitation. The resultant material was analyzed by conventional gas chromatographic analysis and showed that nitromethane was obtained in 57 percent yield. The selectivity to nitromethane was 74 percent based on the sodium nitrite.

Example VIII: *n*-Propyl Nitrite; Nitrite Feed 44.8 grams; HNO3 36.5 grams; Mol. ratio nitrite to HNO3 (.87); Preheat 258° C.; Reaction Temp. 400° C.; Oil recovery 113.3 grams; Nitrite recovery 2.81 grams; Nitromethane yield 1.52 grams; Nitroethane yield 7.03 grams; Percent conversion on HNO3 22.1; Percent yield on nitrite 26.9

Source: Markofsky 1984

Preparation of Tetranitromethane

by Kennedy Joseph Previte Orton
Bangor, North Wales August 3, 1918

Tetranitromethane may be made by passing acetylene into nitric acid, which may contain water, or nitrogen peroxide or nitrogen pentoxide. The gas is very readily absorbed, with development of heat, by acid of 100 per cent strength, but the readiness of the absorption diminishes as the acid is reduced in strength, or when the temperature is lowered. When the solution of acetylene is poured upon ice some tetranitromethane is obtained, or when the solution is distilled the nitro-compound is found in the receiver; in either case, however, the yield is very poor. It is improved by mixing the solution with an acid, acid anhydride or dehydrating agent, particularly sulphuric acid, fuming sulphuric acid (either of which can be safely added) or phosphorus pentoxide before pouring upon ice, and very much improved by distilling the solution with such an acid.

It would appear that the chief product of the action of acetylene on nitric acid is an intermediate compound which becomes tetranitromethane when the solution is heated with sulphuric acid.

The object to be attained in the commercial manufacture is the maximum yield of tetranitromethane calculated on the weight of nitric acid and the volume of acetylene used should be absorbed.

Experiments have shown that for the first named object the most favourable concentration of the nitric acid is between 90 and 97.5 per cent. strength and that approximately 3 litres of acetylene per 100 grams of nitric acid diluted to this strength is the best proportion to use. For the second object is is useful to work at a raised temperature, the absorption occurring at about 40° C. at which temperature about 90 per cent. of the acetylene may be absorbed and the yield also improved.

It has been found that the addition of mercury or a mercury salt to the nitric acid, for instance mercuric nitrate added to the extent of 0.2 to 0.6 per cent. of the weight of nitric acid, increases the proportion of acetylene absorbed, without, however, improving the percentage yield at ordinary temperatures, though at 30°-40° C. the percentage yield is much increased as well as the proportion of acetylene absorbed.

When the acetylene has been absorbed by the nitric acid, and operation performed in any apparatus adapted to bring gas and liquid into contact with each other and to withstand nitric acid, the liquid is mixed with sulphuric acid or fuming sulphuric acid under conditions excluding rise of temperature; the proportion added may vary considerably but should not be too small, as the addition of a small proportion is liable to provoke explosion, a danger which is not experienced if the proportion be about twice the weight of the nitric acid used. The mixture is gradually heated in a retort until the tetranitromethane distills. It is generally advantageous, however, when as much as 3 litres of acetylene per 100 grams of nitric acid have been used, to heat the mixture slowly in a reflux apparatus until gas ceases to be evolved, before distilling: addition of a further quantity of absolute nitric acid before heating is also an advantage in this case.

As to whether sulphuric acid or fuming sulphuric acid is used depends on the use that is to be made of the residual acids in the retort. If the fuming acid is used this residue can serve as a nitrating agent without further treatment.

The use of an immiscible solvent, such as carbon tetrachloride, in which tetranitromethane is soluble, is not excluded as a means of isolating the desired product; but addition of such solvents to mixed acids is not recommended. The tetranitromethane may also be directly separated as a supernatant oil, or as crystals at lower temperature, from the mixed acids.

1.66 litres of dry acetylene are passed slowly into 105.5 grams of nitric acid of 96 per cent strength. The speed at which the acetylene may be introduced depends upon the efficiency of the apparatus for bringing the gas into contact with the acid. The temperature is kept at 14-16° C. To the liquid thus obtained, transferred to a retort, 277 grams of fuming sulphuric acid of 25 per cent. strength are slowly added, care being taken to avoid rise of temperature. The mixture is lowly heated to 100°-110° C. when distillation begins, the tetranitromethane distilling, with some nitric acid, until the temperature attains 130° C. Water is added to the contents of the receiver and the crystals therein drained and washed with water.

By this procedure about 1.3 litres of acetylene are absorbed and about 4 grams of tetranitromethane obtained. The nitro-compund is of a very high degree of purity. Source: Orton 1919

Tetranitromethane (TNM) is common byproduct resulting from the nitration of many organic substances. TNM is a toxic material. TNM is also an oxidizer that can form a powerful explosive when mixed with combustible organic materials such as benzene, nitrobenzene, toluene, etc. For example, the presence of TNM has been held responsible for explosions in trinitrotoluene (TNT) manufacturing facilities. Guggenheim 1996

Improved Preparation of Tetranitromethane

by Philip Arthur Newton
London, UK October 22, 1909

100 parts of acetic acid anhydride are slowly introduced into 100 parts of nitric acid (99.5 per cent of HNO3) which has to be constantly stirred and the temperature of which is kept below 35° C. The product of the reaction is poured on to the ice; the tetranitromethane separated partly as oil and the remainder is obtained distillation with steam.

Source: Newton, 1909

Preparation of Methylbenzylcarbinol from 1-Phenyl-propene-2

by Wolfgang Bernhagen and Helmut Springer
translated by Otto

Example 1

In a round-bottom flask one gives to 469 g of 98% formic acid and 130 g *n*-butanol under agitating successively 20 g concentrated sulphuric acid and 264 g 2-methyl-1-phenyl-propene-2, the temperature of the mixture does not exceed 30°C. After completion of the addition, one agitates for another 2 hours at 30°C. Subsequently, the raw product is mixed with 1600 g 30% caustic soda and warmed up briefly to 80°C. After analysis by gas chromatography the organic phase contains:

35.6 % *n*-Butanol
5.4 % 2-Methyl-1-phenyl-propene-2
6.0 % Methyl-1-phenyl-propene-1
50.7 % Dimethylbenzylcarbinol
0.4 % Dimethylcarbonylformate
1.9 % other components

By fractionated distillation from the beginning 212 g dimethylbenzylcarbinol (102°C/15 mbar) are obtained. This corresponds to a yield of 71%, related to assigned olefin.

Example 2

One works as described in the example 1, however at 10°C and using 74 g *n*-butanol. After distillation one receives 228 g dimethylbenzylcarbinol. This corresponds to a yield of 76%, related to assigned olefin.

Example 3

One works as in example 1 described, replaced however *n*-butanol by 64 g methanol and decreases the response time of 120 to 90 minutes.

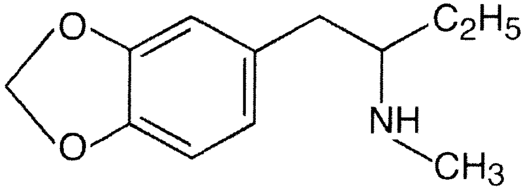
218 g (73% Absolute) dimethylbenzylcarbinol result thereby.

Example: 5

In a round-bottom flask one gives 234 g 98% formic acid and 57 g *n*-butanol under agitating to 10 g concentrated, sulfuric acid and 132 g 2-methyl-1-phenyl-propene-2, whereby the temperature of the mixture is held by cooling at 10°C. After 2 hours of reaction at 20°C the adds to the reaction mixture 600 g of a 30% caustic soda solution. The interior temperature is limited by cooling on maximally 25°C. The organic phase contains after analysis by gas chromatography

2.3 % *n*-Butanol
23.8 % *n*-Butyl formate
5.0 % 2-Methyl-1-phenyl-propene-2
6.6 % 2-Methyl-1-phenyl-propene-1
24.5 % Dimethylbenzylcarbinol
35.9 % Dimethylbenzylcarbinylformate
1.9 % other components

By fractionated distillation receipt one 54 g dimethyl-benzylcarbinol (36 % yield) and 80 g dimethylbenzylcarbinyl-formate (45% yield related to olefin). Source: Bernhagen 1982



N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine

More Molecules: Chapter 25

d-Methamphetamine Separation from *d,l*-Methamphetamine

Theodor Hermann Temmler
Berlin, Germany June 1, 1938

80 Parts of racemic N-methyl-ß-phenylisopropylamine are introduced into a solution of 100 parts of *d*-tartaric acid in 1000 parts of methyl alcohol. After protracted standing, about 100 parts of the precipitated salt are aspirated off, and extracted with hot ethyl alcohol. Since the *d*-tartrate of dextrorotatory N-methyl-ß-phenylisopropylamine is readily soluble in both methyl and ethyl alcohol, whereas the *d*-tartrate of *levo*-rotatory N-methyl-ß-phenylisopropylamine is sparingly soluble, both in methyl alcohol and hot ethyl alcohol, an extremely simple separation of the *d*-tartrates of the optical antipodes of the base.

Source: Temmler 1939

2-Phenyl-3-aminobutane

by Felix Haffner and Fritz Sommer
Berlin, Germany February 11, 1939

Ephedrine differs from adrenaline in that it exhibits stronger central effects which are manifested in an activation of respiration and increase or blood pressure. Ephedrine is an amino-alcohol and thus, like adrenaline, contains a hydroxyl group in the aliphatic sidechain. More recently, the physiological effects of an aliphatic amine substituted by a phenyl radical and free from hydroxyl groups, namely 1-phenyl-2-aminopropane, have been exhaustively investigated. 1-Phenyl-2-aminopropane is distinguished from ephedrine by its still more prominently exhibited central effects; this is especially manifested in the influence of 1-phenyl-2-aminopropane on the psychical functions. For this reason 1-phenyl-2-aminopropane is suitable for combating fatigue conditions, for the relief of depressions and for combating conditions of intoxication.

The stimulants according to the invention, which contain as active principle aliphatic hydrocarbons having 4 carbon atoms and substituted at two adjoining non-terminal carbon atoms by one phenyl and one amino or alkyl amino group, are similar in action but preferable in several respects to 1-phenyl-2-aminopropane. The alkyl groups at the nitrogen atom may be methyl, ethyl, and propyl radicals. One as well as both the hydrogen atoms can be substituted by the above mentioned alkyl groups.

Of special importance among the new stimulants are those which contain 2-phenyl-3-butane as active principle. 2-Phenyl-3-methylaminobutane also has proved very effective.

In comparison with 1-phenyl-2-aminopropane, 2-phenyl-3-aminobutane is distinguished by its very much milder action. Whilst the quantities required to produce the first observable effects are about equally large for the two compounds, and amount in experiments on animals to about. 0.01 mg. per gram weight of the animal, the toxic dose with the previously known 1-phenyl-2-aminopropane Is about ten times the amount the minimum dose, whilst with 2-phenyl-3-aminobutane nothing less than twenty times the amount of the minimum dose has a toxic action. This increase of the quotient toxic dose effective dose is a great advantage of the new stimulants. The action of the new stimulants which contain 2-phenyl-3-aminobutane takes place as rapidly as that of the previously known stimulants containing 1-phenyl-2-aminopropane. An especial advantage of the new stimulants containing 2-pheny-3-aminobutane is however the fact that their action ceases more rapidly than that of stimulants which contain 1-phenyl-2-aminopropane. This more rapid cessation is of especial importance in relation to the fact that it is frequently necessary to combat symptoms of fatigue for a short time only, where as after the expiration of the period during which wakefulness is desired a normal sleep is desired. The shorter period of action of the new stimulants containing 2-phenyl-3-aminobutane as active principle is not detrimental, inasmuch as when a longer period of wakefulness is desired this can at any time be attained by means of a renewed dose.

Owing to their milder action, as described; the new stimulants are principally of importance for combating symptoms of fatigue in normal persons. The practical importance of a stimulant suitable for combating symptoms of fatigue in normal persons is very great. For example, numerous motor accidents when driving at night are due to the driver falling asleep. This danger can effectively be combated by means of the new stimulants. The new stimulants are further of value to persons who suffer from great tiredness at certain times of the day

Such conditions of lassitude are frequently combined with coincident psychical depressions. The new stimulants prove advantageous in all these cases. Since for the most part it will be a matter of a frequently recurring use of the stimulants, it is a great advantage that they show no undesirable secondary affects. For example, the stimulants containing 2-phenyl-3-aminobutane or 2-phenyl-3-methylaminobutane as active principle do not even produce the unpleasant feeling of dryness in the mouth which frequently arises as a consequence of the action of 1-phenyl-2-aminopropane. Further, no habituation to the new stimulants is developed, so that continually increasing doses are not rendered necessary; in addition, no craving for the new stimulants is to be observed.

As has already been described, the stimulants according to the invention which are of the greatest importance are those containing 2-phenyl-3-aminobutane or 2-phenyl-3-methylaminobutane as active principle. It is an especial advantage of the stimulants containing 2-phenyl-3-aminobutane, again in comparison with 1-phenyl-2-aminopropane, that their action with regard to the combating of symptoms of fatigue in normal persons is not weaker but only milder, i.e., of shorter duration and not accompanied by secondary effects.

Source: Haffner 1944

1-(*p*-Chloro-1-phenyl)-2-aminobutane Preparation

by Boehringer Ingelheim

Germany June 23, 1966

The new compounds according to the invention are valuable appetite-reducers which have shown themselves to be superior to similarly constituted known compounds.

The new compounds show a particularly desirable ratio of appetite-reducing to central nervous system-stimulating activity, particularly through lower toxicity than similarly constituted active appetite-reducing substances. The new compounds may be administered orally and have a long duration of action; they may be used in humans at a dose level of about 0.1 to 3.0 mg/kg, preferably from 0.3 to 1.5 mg/kg daily. Particularly useful compounds, from the point of view of their physiological activity include 1-(*p*-chlorophenyl)-2-aminobutane, 1-(*p*-chlorophenyl)-2-methylaminobutane, 1-(*p*-chlorophenyl)-2-aminobutane, 1-(*p*-chlorophenyl)-2-ethylaminobutane, 1-(*p*-fluorophenyl)-2-aminobutane, 1-(*p*-chlorophenyl)-2- methylaminobutane, 1-(*p*-dichorophenyl)-2-aminobutane, 1-(*p*-chlorophenyl}-2-N-carbethoxyaminobutane, 1-(*p*-chlorophenyl) 2-N-carbethoxyaminobutane and 1-(*p*-chlorophenyl)-2-N-theophyllin-(7)-ethylaminobutane. Of these compounds, the first two are particularly important.

(a) 1-(*p*-Chlorophenyl)-2-formylaminobutane.

281 g (2 mol) *p*-chlorobenzaldehyde are boiled m 700 mL. toluene with 178 g (2 mol) 1-nitropropane in the presence of 20 mL. piperidine and 28 g benzoic acid, using a water separator, until the theoretic amount of water has been separated. The oily 1-(*p*-chlorophenyl)-2-nitrobutene-(1) which is formed is crystallized with methanol/petroleum ether after distilling of the toluene. Yield 70% of theoretical. 134 g (0.633 mol) of this 1-(*p*-chlorophenyl)-2-nitro-butene-(1) are converted into the 1-(*p*-chlorophenyl)-butanone-(2) with 246 g iron powder in the presence of 2.5 g FeCl3 480 mL. of water while stirring and boiling under reflux and with the drop-wise addition of 246 mL. concentrated hydrochloric acid. Yield 88 g (76% of the theoretical, boiling point 137° C.).

86 g (0.47 mol) 1-(*p*-chlorophenyl)-butanone-(2) are slowly distilled with 90 g formamide and 25 mL. formic acid using a column, the reaction being completed in approximately 2-1/2 hours. The flask contents are poured into water, made alkaline, the product taken up in ether and the residue induced to crystallize after drying in distillation with petroleum ether. Yield 86 g 1-(*p*-chlorophenyl)-2-formylaminobutane, melting point 86-88°C (from acetonitrile).

(b) 81 g (0.38 mol) 1-(*p*-chlorophenyl)-2-formylaminobutane are boiled for 4 hours with 800 mL. 20% hydrochloric acid. The aqueous solution is extracted with ether after cooling, the aqueous phase concentrated and reacted with some alkali. The free base is dissolved in ether and the ether distilled off after drying. Yield of 1-(*p*-chloro-phenyl)-2-aminobutane 66 g; boiling point 130°C

The hydrochloride can be obtained from the base by the addition of hydrochloric acid. Melting point 188—190°C (from acetonitrile).

Separation into the, optical antipodes

(a) Preparation of the bitartrate of *d*-base

50 g (0.272 mol) racemic base and 41.8 g (0.272 mol) tartaric acid are dissolved hot in 272 mL. methanol/water (2:1). On cooling, the bitartrate crystallizes out. The crystals are vacuum extracted, washed with a little methanol/water (2:1) and dried. Yield 47.5 g, melting point 140-141°C. By triple recrystallization with methanol/ water (2 :1) the melting point of the bitartrate is raised to 147—148°C

(b) Preparation of the *d*-1-(*p*-chloro-phenyl)-2-aminobutane hydrochloride

From 19 g of the bitartrate (melting point 147—148°C) a base is liberated with dilute sodium hydroxide solution, taken up in ether, the ether dried with Na2SO4, and distilled off. Yield 10 g base. The base is converted into the hydrochloride in acetonitrile using etherified hydrochloric acid. Yield 10 g, melting point 170-171°C The resolution of the *d*-1-(4-chlorophenyl)-2-aminobutane hydrochloride [α]D20=+30° (in 2% aqueous solution).

(c) Preparation of the bitartrate of the *l*-base

22.5 g (0.1227 mol) base (obtained from the filtrate of the first tartaric acid decomposition) and 18.4 g (0.1227 mol) tartaric acid are dissolved hot in 120 mL. methanol/water. Upon cooling, the bitartrate of the base crystallizes out (as hydrate). The crystals are vacuum extracted and washed with methanol/water (2:1) melting point 100/134°C.

(d) Preparation of the *l*-1-(4-chlorophenyl)-2-aminobutane hydrochloride

The base is liberated from 10 g of the bitartrate with concentrated caustic soda solution, yield 5 g, and the hydrochloride prepared from this in acetonitrile with etherified hydrochloric acid. Yield 4.5 g, melting point 170-171°C. The resolution is [a]D26=—30° (2% solution in water).

1-(*p*-Chlorophenyl)-2-methylaminobutane

144 g. (0.79 mol) 1-(*p*-chlorophenyl)-butanone-(2) (Example 1) are slowly heated with 186.5 g (3.16 mol) N-methylformamide and 39.5 mL. formic acid. Any water formed is distilled off through a column. In this way, 165 g 1-(*p*-chlorophenyl)-2-(N-methyl-N-formylamino)-butane are obtained which are saponified to give the amine after 4 hours boiling with 20% hydrochloric acid (1.6 L.). 113 g 1-(*p*-chlorophenyl)-2-methylaminobutane are obtained (boiling point 133—136°C). The base gives a hydrochloride with the melting point 154-155°C.

Source: Boehringer Ingelheim 1970

1-(*para*-Halo-phenyl)-2-methyl-2-aminopropane and methylaminopropanes

by Kefalas December 21, 1959

It has been shown in the past that certain sympathomimetic agents exert anorexigenic effects. However, it has also been found that while agents of this nature are in fact highly useful for their appetite suppressant effect, they simultaneously exert a strong stimulatory effect, with resulting symptoms of anxiety, restlessness and insomnia. As examples of sympathomimetic agents already known to play such a dual role may be mentioned amphetamine (1-phenyl-2-aminopropane), methamphetamine (*d*-phenyl-2-methyl-aminopropane), and 1-phenyl-2-methyl-2-aminopropane. It would obviously be highly desirable to have available a composition; which would be anorexigenically active and effective without attendant undesirable central stimulatory effect. For a considerable number of years, investigators have made a determined effort to find such a satisfactory drug in the amphetamine area. Failing here, they have turned to other structural areas. Some of the results of these investigations have been encouraging, and several promising drugs of non-amphetamine type have appeared on the market and are now in use or in advanced stages of clinical trial. Among these may be mentioned phenmetrazine (3-methyl-2-phenylmorpholine), a mixture of phenyl-ethylacetic acid, (phenylmethyl)morpholino-N-ethanolester hydrochloride and phenyl-methyl-morpholino-(dimethylchloro)-xanthinate, 5-methyl-5-(1,2-dibromo-2-phenylethyl)-hydantoin, and others. How ever, all other drugs for one reason or another leave much to be desired. The need for other and improved compositions for the effective reduction of appetite without undesirable central stimulatory effect is apparent.

It is therefore an object of the present invention to provide novel compositions which are useful for the reduction of appetite without the production of undesirable concurrent central stimulatory effect.

More particularly an object of this invention is to provide novel pharmaceutical compositions comprising 1-(*para*-chlorophenyl)-2-methyl-2-aminopropane and 1-(*para*-bromophenyl)-2-methyl-2-aminopropane and nontoxic pharmacologically acceptable acid-addition salts thereof which are particularly well adapted for oral administration to combat excessive appetite and assist in the reduction or control of obesity, either alone or as an adjunct to a controlled diet, without producing an undesirable central stimulatory effect.

Tablet Formulation

A suitable formulation for a tablet containing 25 milligrams of 1-(*para*-chlorophenyl)-2-methyl-2-aminopropane in the form of its hydrochloride is as follows:

1-(*p*-chlorophenyl)-2-methyl-2-aminopropane	25 mg.
Potato starch	50 mg
Lactose	20 mg.
Gelatine	3 mg.
Talcum	15 mg.

Tablets having the above composition were prepared and found effective upon administration to humans in reduction of appetite and control of obesity in accordance with the present invention.

Clinical Evaluation

In clinical tests on human beings, the composition of the invention have shown pronounced anti-appetite effects. Fifty-one obese out-patients were carried through a double-blind weight reduction program employing tablets having the composition of Example 1 and placebo tablets without any essential dietary restrictions. On administration of the composition of the invention they obtained a weight loss significantly in excess of that experienced by the patients on placebo. Objective side effects were negligible and subjective side effects were relatively moderate. Source: Kefalas 1962

Tableting of Phenylethylamines

by Richardson-Merrell
New York, New York April 19, 1963

250 mg tablets

Two hundred and fifty grams of *alpha*-allylphenethylamine hydrochloride is mixed intimately with 12.5 grams of tartaric acid and 50 grams of mannitol. The mixed powders are granulated with 10 per cent starch paste. The granulation is dried and ground to a size suitable for tabletting. Sixteen grams of corn starch, 1.6 grams of talc, and 1.6 grams of magnesium stearate are added and mixed with the granulation by tumbling. The granulation is then compressed into 1000 tablets. Bisected or quadrisected upper punches may be used.

Source: Richardson-Merrell

2-Amino-1-(phenyl)-butane Tablets

by Alexander Theodor Shulgin
Lafayette, California November 6, 1972

	Per tablet, mg
2-amino-1-(2,5-dimethoxy-4-methylphenyl)-butane HCl	10
Cornstarch	100
Methylcellulose 400	175
Magnesium stearate	3
	Total 288

	Per tablet, mg.
2-amino-1-(2,5-dimethoxy-4-methylphenyl)-butane HCl	10
Monocalcium phosphate	70
Dicalcium phosphate	70
Lactose	70
Magnesium stearate	3
	Total 223

A mixture of monocalcium phosphate, dicalcium phosphate and lactose is prepared to which is added magnesium stearate and 2-amino-1-(2,5-dimethoxy-4-methylphenyl)-butane hydrochloride and then tabletted by conventional means. Each tablet contains 10 mg. of active ingredient. Source: Shulgin 1976

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