

THE MANNICH REACTION ON
2,7-DIHYDROXYNAPHTHALENE

PART I

The Attempted Preparation of 1,8-Dimethylnaphthalene
by the Mannich Reaction

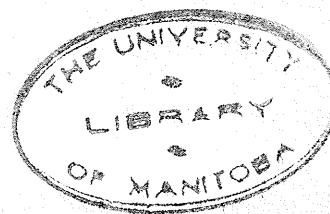
PART II

The Preparation and Characterization of Tetrahydrofurfural
and Tetrahydrofuroic Acid

PART III

The Preparation of Some Unsaturated Malonic Esters and
Barbiturates

by
Douglas G. Hay



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1952

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PART 1

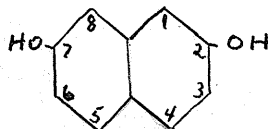
THE ATTEMPTED PREPARATION OF 1,8-DIMETHYLNAPHTHALENE
BY THE MANNICH REACTION

GENERAL INTRODUCTION

The Mannich reaction, known since 1903, was recognized as a type reaction by Mannich in 1917. It consists in the condensation of a compound containing a reactive hydrogen atom with ammonia or a primary or secondary amine and formaldehyde.

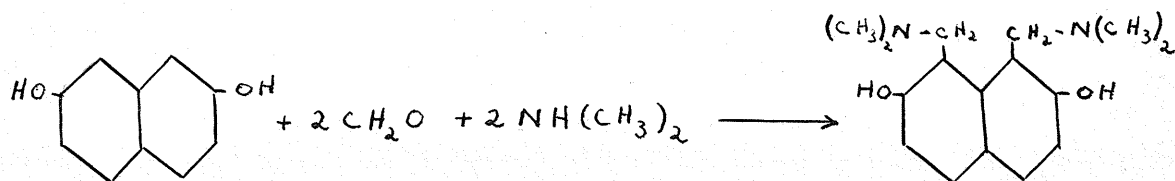
Phenols, and particularly β -naphthol, are known to have reactive hydrogen atoms on the carbon atoms ortho and para to the carbon with the phenolic group. Many Mannich condensations have been carried out with this type of compound, (3), (4), (7), (8).

The compound to be studied for this research is 2,7-dihydroxynaphthalene:

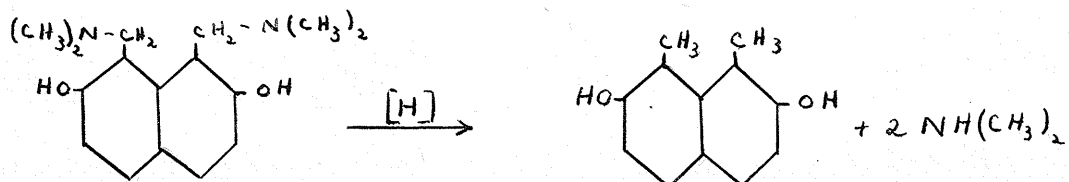


Since the phenolic group of β -naphthol activates the α -hydrogen, it was assumed the two phenolic groups of 2,7-dihydroxynaphthalene would activate the 1 and 8, or peri, hydrogens, thus leading to a disubstituted Mannich base.

The simplest of these would result from the condensation with formaldehyde and dimethylamine.



This Mannich base, would be of no particular interest in itself, but it was desired to reduce this base and similar ones, to obtain 2,7-dihydroxy-1,8-dimethylnaphthalene.

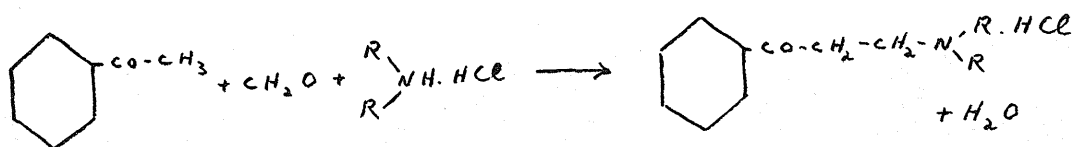


The physical constants of 1,8-dimethylnaphthalene and its derivatives have been variously reported in the literature (1), (11), (14). 2,7-dihydroxy-1,8-dimethylnaphthalene, on treatment with zinc oxide to eliminate the phenolic group, gives rise to 1,8-dimethylnaphthalene. It was therefore the aim of this research to produce this hydrocarbon and fully characterize it in order to clear up the existing confusion.

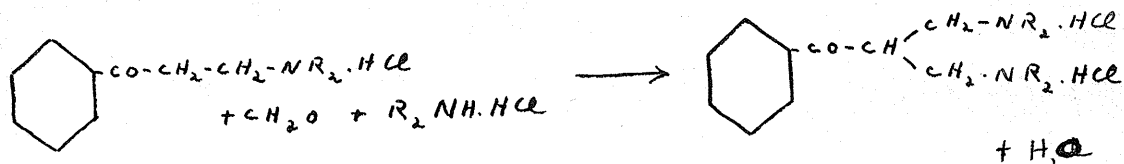
LITERATURE SURVEY OF THE MANNICH REACTION

INTRODUCTION

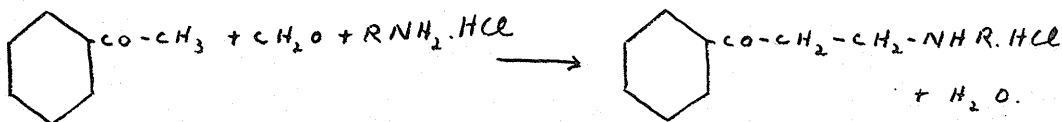
The Mannich reaction consists in the condensation of ammonia or a primary or secondary amine, usually as the hydrochloride, with formaldehyde and a compound containing at least one hydrogen atom of pronounced activity. The essential feature of this reaction is the replacement of the active hydrogen by an aminomethyl or substituted aminomethyl group.



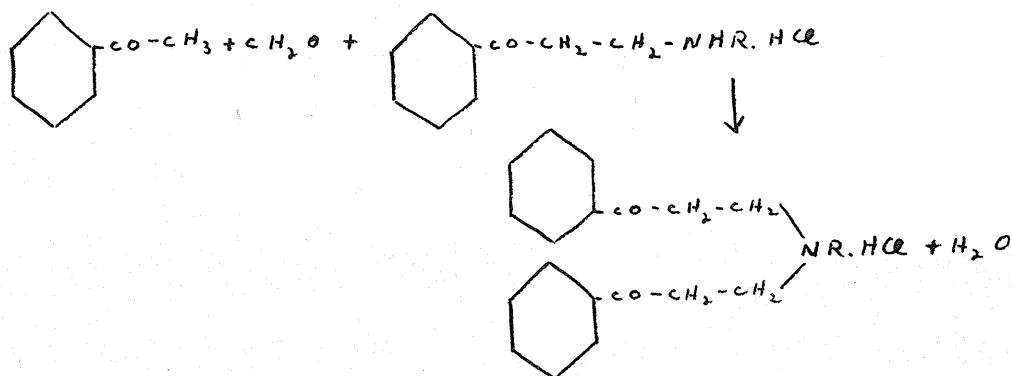
In some cases it is possible to carry the reaction a step further yielding a compound with two basic groups.



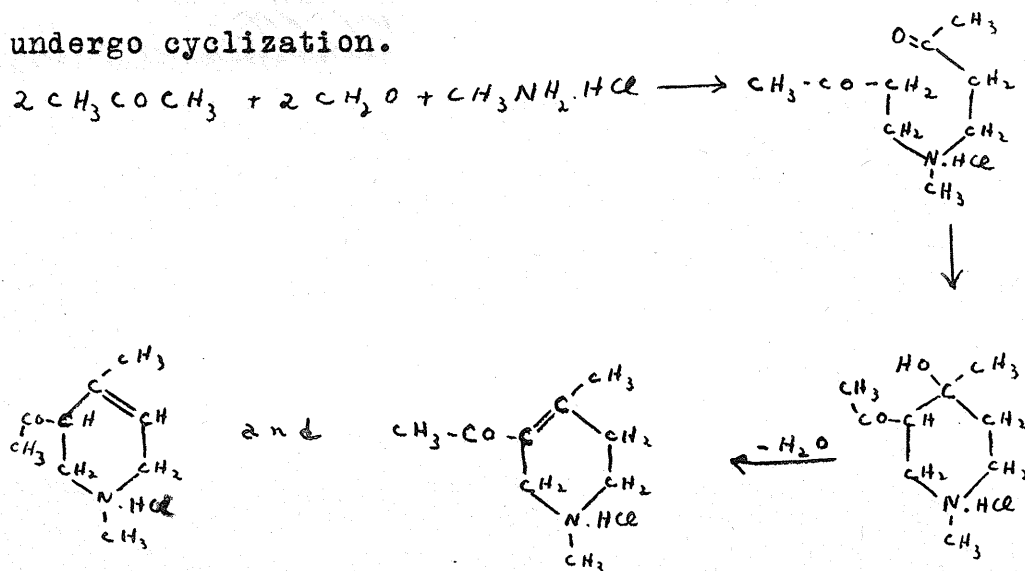
Using a primary amine the product is a secondary amine.



This may react further to give a tertiary amine.



Frequently these products are unstable and undergo cyclization.

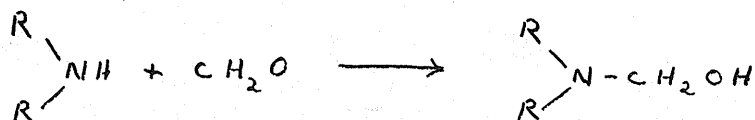


HISTORY

Tollens was the first to observe a condensation of this type. He isolated a tertiary amine from ammonium chloride, formaldehyde, and acetophenone in 1903. Petrenko-Kritschenko studied condensations of this type from 1904 to 1909 but didn't realize the reaction was a general one. Mannich began a detailed study in 1917.

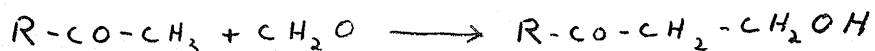
MECHANISM

The mechanism of this reaction is not known. It has been suggested that the primary step consists in the addition of the amine to formaldehyde (2).



However it has been shown that dimethylaminomethanol gives a poorer yield than formaldehyde and the amine. Therefore this hypothesis is improbable.

Another possible initial step is the formation of the methylol from a ketone.



However it has been shown that the methylol does not always condense with the amine.

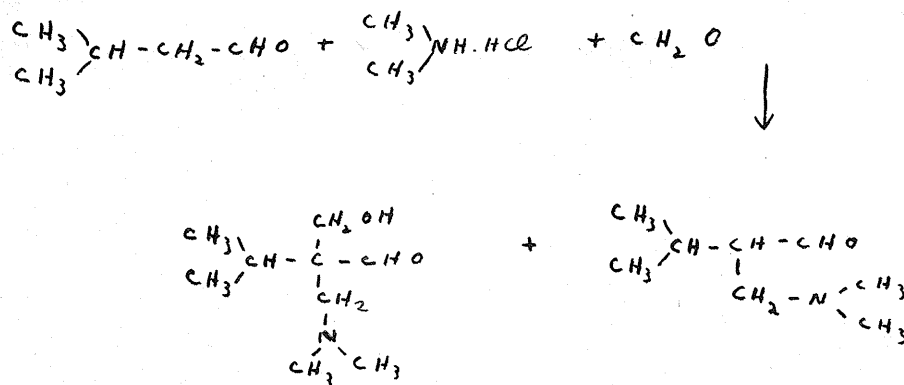
THE USE OF SECONDARY AMINES

1) WITH KETONES

Saturated ketones, cycloalkanones, α - β unsaturated ketones, aliphatic-aromatic ketones, and certain heterocyclic ketones containing a carbonyl group in the ring all undergo the Mannich with secondary amines.

2) WITH ALDEHYDES

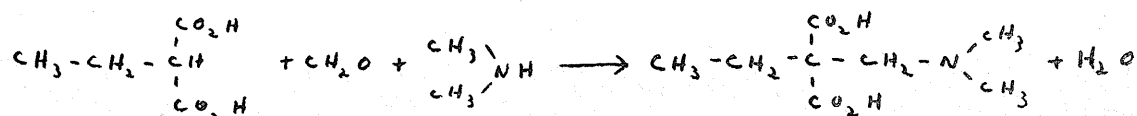
The α -hydrogen atom of the aldehyde is substituted by a dialkylaminomethyl group. Secondary reaction sometimes occurs which involves the simultaneous introduction of a methylol group on the α -carbon.



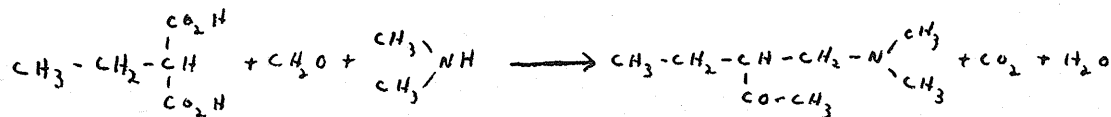
Aldehydes have been much less extensively studied than ketones.

3) WITH ACIDS AND ESTERS

Acids with reactive hydrogen in the alpha position may be used for Mannich condensations instead of aldehydes or ketones. The free secondary amine is used instead of its salt.

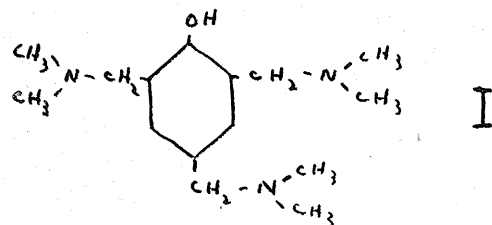


A side reaction which often occurs involves the decarboxylation of the acid.

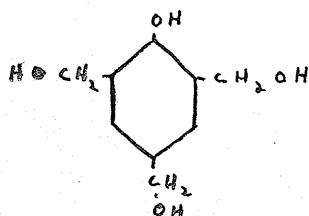


4) WITH PHENOLS

The ortho and para hydrogens of phenols are sufficiently active to enter into the Mannich condensation. From p-cresol, mono- and di-substitution products are obtained. From phenol and m-cresol, tri-substitution products are obtained. For instance, an excess of at least three moles of formaldehyde reacts with phenol in the presence of at least three moles of strongly basic non-aromatic secondary amine to form a phenolic tri-amine.



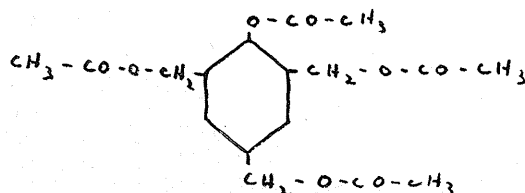
There has been some interest in the compound



which was supposed to have been produced from phenol

in alkaline solution with excess formaldehyde. However attempts to isolate this product and the analagous one from m-cresol, have led to resinification.

Brunsen and MacMullen (3) were able to obtain the tetra-acetate of this product in the following manner: 1-hydroxy-2,4,6-tri(dimethylaminomethyl)-benzene (1) when heated with excess acetic anhydride the tertiary amino groups split off in the form of ^{N,N-disubstituted} ~~acetic tertiary~~ ^{acet} amides and the tetraacetate is produced.



This colorless viscous substance may be distilled under reduced pressure without decomposition or resinification. However, it does resinify in the presence of alkali.

A Mannich reaction has been carried out with p-hydroxy benzaldehyde, the CH₂NH₂ group going ortho to the hydroxy group (5).

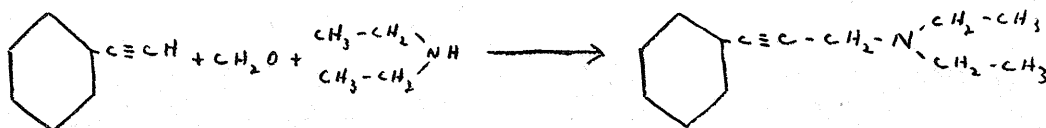
Naphthols undergo the same type of reaction. It is found that β -naphthol gives better yields than α -naphthol. The reactions are usually carried out in an anhydrous solvent such as benzene, water of reaction being

removed by refluxing the solvent through a water trap.

One use to which these phenolic condensation products may be put is for protecting films (9). A self-sustaining film is formed of a rubber hydrochloride with ten percent of its weight of a phenol, formaldehyde, methylamine resin. It is prepared by condensing one mole of phenol, two moles of formaldehyde, and one of methylamine. These films have good resistance to heat and light.

5) WITH ACETYLENES

Phenylacetylene and certain substituted phenylacetylenes (10) react readily with formaldehyde and secondary amines.



The conditions are that the acetylenic compounds must be under pressure and in the presence of copper acetylide catalyst. Yields of seventy percent are common. Hydroxy groups have an inhibiting effect if in the alpha position, but in the beta position good yields are obtained.

6) WITH α -PICOLINES AND QUINALDINES

The α -methyl group in the pyridine or quinoline nucleus has a hydrogen of about the same reactivity as those in the methyl group of a methyl ketone. Therefore

the Mannich ^{reaction} takes place with these substances.

THE USES OF PRIMARY AMINES

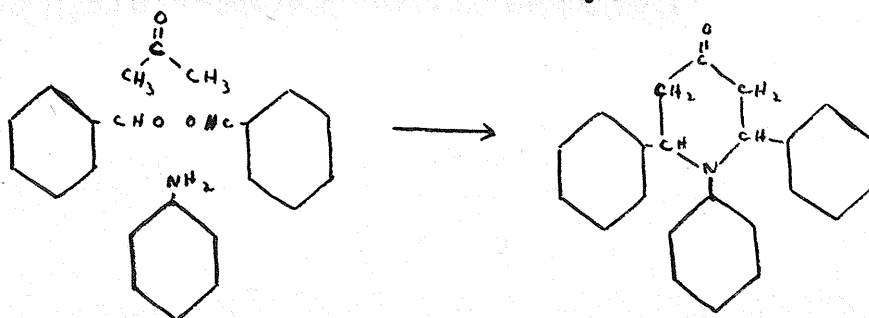
Primary amines may be used with ketones, aldehydes, acids and esters, α -picolines, and quinaldines. The work on these with primary amines has been rather scanty and few examples are quoted in the literature.

No Mannich reactions involving primary amines with phenols and acetylenes have been reported. However β -naphthylamine (6) or α -naphthylamine (13) and formaldehyde have been condensed to give various products.

Ammonia has also been used as the base in condensations with ketones and acids.

RELATED REACTIONS

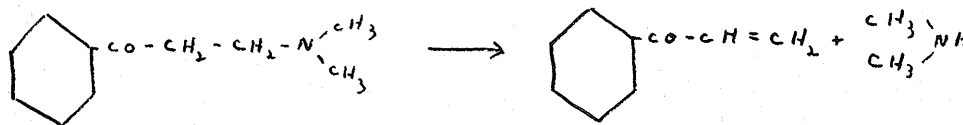
Formaldehyde is not the only aldehyde which may be used in this type of condensation. Others are acetaldehyde, phenylacetaldehyde, benzaldehyde, and anisaldehyde. Ammonia and primary amines seem to be the only substances which will react with these aldehydes.



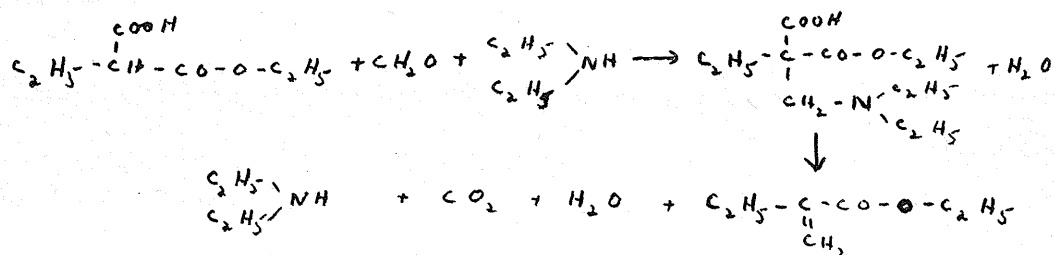
APPLICATION IN SYNTHESIS

1) PREPARATION OF ETHYLENIC COMPOUNDS

Many of the condensation products, especially those derived from secondary amines, decompose into the amine and an unsaturated compound. Some may be distilled under reduced pressure but most decompose when heated or subjected to steam distillation.



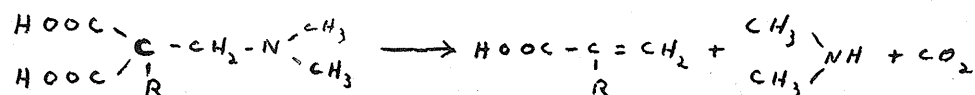
The products decompose spontaneously in a few cases.



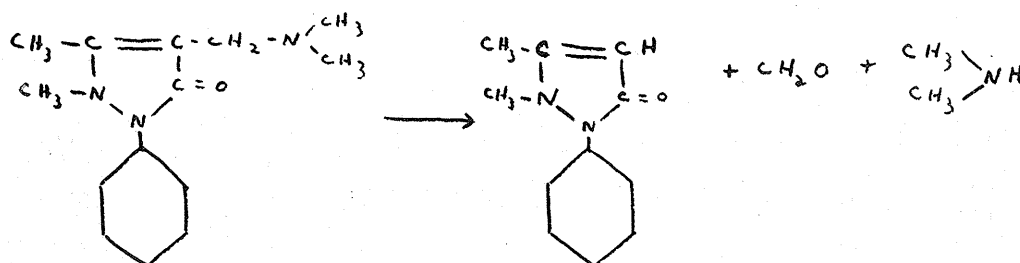
Others will undergo decomposition in the presence of sodium ethylate or dilute alkali.

In some cases when two carboxyl groups are present one is eliminated in the decomposition. This is a method

for synthesizing α -aryl or α -alkyl acrylic acids

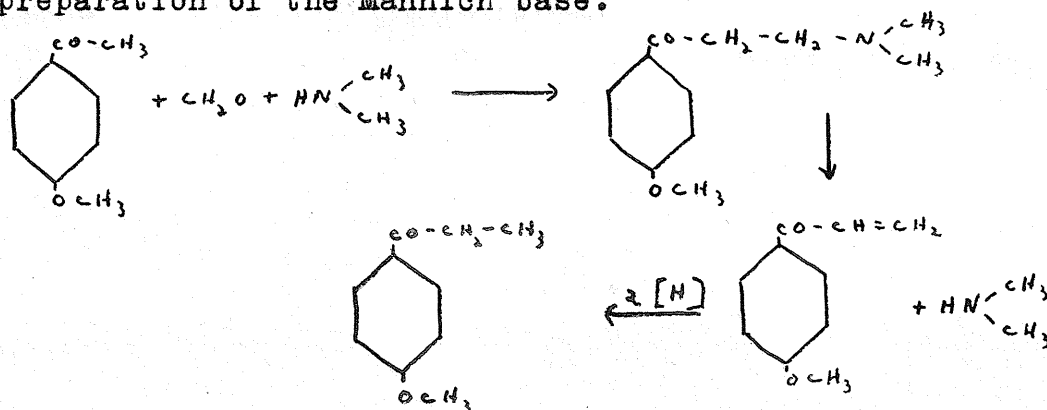


When the active hydrogen in the original compound is a tertiary one, an ethylenic compound cannot be formed by decomposition. It may then decompose to the original reagents.



2) CONVERSION OF A KETONE TO ITS NEXT HIGHER HOMOLOG

The unsaturated ketone arising from the decomposition of a Mannich base may be reduced to form a ketone with one more methylene group than that used in the preparation of the Mannich base.



3) SYNTHESIS DEPENDENT ON THE ACTIVITY OF THE DIMETHYLAMINO GROUP IN DIMETHYLAMINOMETHYLPHENOLS

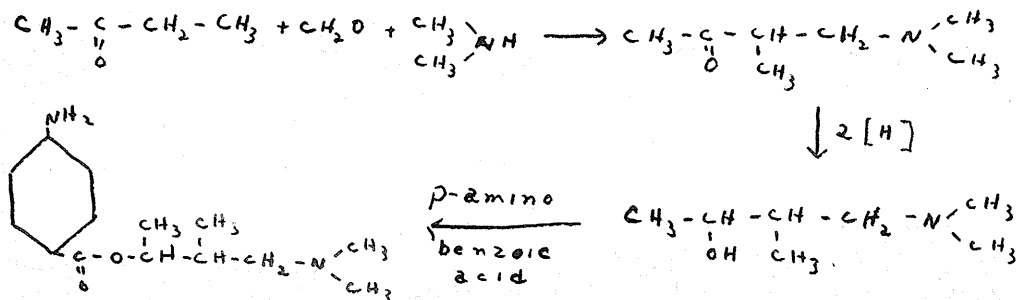
Methyl groups may be introduced into the phenolic ring using the product obtained from the Mannich reaction with phenols. There are two steps (a) the introduction of the dimethylaminomethyl group by the combined action of formalin and dimethylamine upon the appropriate phenol, (b) hydrogenolysis by heating under pressure in dioxane using copper chromite as catalyst (4), or sodium methylate solution at 220 degrees (15). This is the type of reaction which will be carried out in this research.

4) REDUCTION TO AMINOALCOHOLS

β -substituted aminoketones or aldehydes can be reduced to the corresponding γ -substituted aminoalcohols.

The γ -aminoalcohols, in the form of their benzoates and p-amino benzoates, are used as local anesthetics.

The commercial anesthetic Tutocaine is made as follows:



It has been found essential in most cases that the salts of the aminoketones be of a high degree of purity before reduction is attempted (8).

DISCUSSION OF RESULTS

Condensations

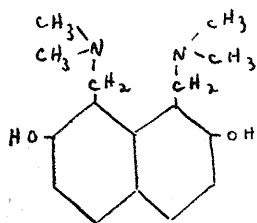
In these Mannich condensations it was assumed that 2,7-dihydroxynaphthalene would react similarly to β -naphthol. Since 2,7-dihydroxynaphthalene is a rather expensive chemical, trial runs were made with β -naphthol first.

The 2,7-dihydroxynaphthalene used was obtained from Eastman. However, it was so costly that attempts were made to synthesize it from the corresponding sulphonic acid. Standard procedure for fusion was used.

The general procedure for the condensation was that of Caldwell and Thompson (4). Aqueous formaldehyde (35%) was used. In the case of dimethylamine, an aqueous solution of this was used also and no solvent was necessary. The only other solvent used was ethanol (95%). The reaction goes under both hot and cold conditions.

It was very difficult to purify these Mannich bases. After repeated recrystallization to constant melting point they still had a yellow color and gave inconsistent combustion results for carbon and hydrogen.

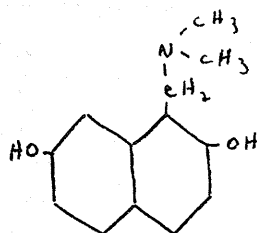
The nitrogen results for the condensation product of 2,7-dihydroxynaphthalene and dimethylamine pose an interesting supposition. They seem to indicate disubstitution in cold solution and monosubstitution in hot solution. For the compound resulting from cold solution the nitrogen combustion agrees fairly well with that calculated from the compound.



Experimental: 10.82% N

Theoretical for $C_{16}H_{22}O_2N_2$: 10.22% N

The combustion results of the compound from hot solution agrees with that calculated for a monosubstituted molecule.



Experimental: 5.98% N

Theoretical for $C_{13}H_{15}O_2N$: 6.44% N

This phase of the reaction is entirely probable but the failure to obtain consistent carbon-hydrogen combustion results for the same compound throws some doubt on the accuracy of the nitrogen results.

Reduction

All attempts at reduction met with failure. Catalytic reduction (hydrogen and platinum) in alcohol failed completely. This bears out the observations of Woodward and Doering (15) who noted that substances which contain a strongly basic nitrogen atom and a phenolic function in the same molecule are remarkably resistant to catalytic reduction.

Sodium amalgam had no effect. Using the standard method of 2% sodium amalgam with dilute hydrochloric acid, the starting material was always quantitatively recovered unchanged.

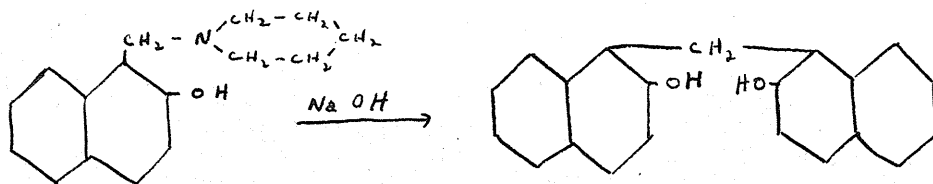
Woodward and Doering (15) used a methanolic solution of sodium methylate heated at 220 degrees for 16 hours to accomplish their reduction. However, an autoclave was not available for this work. A solid brass tube closed at one end, with a long screw top at the other, was made. Attempts to make this apparatus leakproof for an extended period of time proved futile. The methyl alcohol all boiled away in less than one hour at 220 degrees. It was kept at 220 degrees for

the remaining 15 hours without solvent but no reduction took place.

A standard Parr bomb for sulphur determinations was tried. It too, began to leak when the temperature reached about 200 degrees and could not be made to hold the solvent for extended periods. A sealed Pyrex tube reaction was the only other method available to this laboratory. It was accordingly tried but always resulted in an explosion within the first four hours.

The failure of the reduction seemed to be due to the phenolic group, since the reduction of Mannich bases not containing this group are reported to go smoothly. It was thought that by methylation of the phenolic group of the Mannich bases the acidity of the molecule would be effectively reduced.

This was accordingly tried using methyl sulphate. The product in every case was a gum. All attempts at crystallization and identification failed. Decombe (8) found that α -(piperidinomethyl)- β -naphthol when boiled with 10% sodium hydroxide gave methylene bis- β -naphthol.



Since the use of methyl sulphate requires sodium hydroxide it was thought that a compound of this type might be forming the gum. The use of diazomethane for methylation requires no basic reagents. Diazomethane was accordingly prepared and reacted with α -(dimethylaminomethyl)- β -naphthol. However, the product in this case also was a deep red gum. Therefore the resinification is not due to bis-compound formation.

Another line of attack was methylation of the phenolic group before introducing it into a Mannich reaction. Accordingly the methyl ethers of β -naphthol and 2,7-dihydroxynaphthalene were prepared, giving the well known nerolin (Melting point 72 degrees) and 2,7-dimethoxynaphthalene (Melting point 134 degrees) respectively.

It was found that the methyl group completely inactivated the compound as far as Mannich condensations were concerned. Even long boiling in alcohol failed to condense the reactants.

As noted previously (P.8) Brunsen and MacMullen (3) succeeded in isolating the tetraacetate of 1-hydroxy-2,4,6-tri-(dimethylaminomethyl)-benzene. A reduction

was carried out with this compound using copper chromite at 177 atmospheres hydrogen pressure to give 2,4,6-trimethylphenol. It was not possible to obtain ~~the~~ drastic reduction conditions used by Brunsen and MacMullen (in this laboratory), but their work was repeated to obtain the tetraacetate and all the above noted reduction procedures were tried on it. It was thought that the procedure could be extended to the other Mannich bases. However all the reduction procedures available in this laboratory failed to work.

Since all reduction possibilities at the disposal of this laboratory were exhausted with no results, it was felt that further work on this subject should be discontinued.

EXPERIMENTAL

A) PRODUCTION OF 2,7-DIHYDROXYNAPHTHALENE

The 2,7-dihydroxynaphthalene used was produced by potassium hydroxide fusion of naphthalene-2,7-disulphonic acid (sodium salt). Pure potassium hydroxide (120 g) with 5 ml. of water was heated in a nickel crucible to 250 degrees at which temperature the mixture was completely liquified. The sodium sulphonate (25 g), previously dried and powdered, were added slowly with stirring. The mass was stirred continuously with a metal-encased thermometer, and brought to 310 degrees for ten minutes. The mixture was dropped, while still liquid, onto cracked ice. The solution was neutralized with concentrated sulphuric acid and cooled to room temperature. The solid was filtered off and both solution and solid extracted exhaustively with ether. The ether extracts were combined and the ether evaporated, leaving a brown solid. This solid was recrystallized twice from boiling water, using animal charcoal. The 2,7-dihydroxynaphthalene is a pure white solid which melts at 195 degrees.

(B) CONDENSATIONS

The Mannich condensations were carried out in three ways, all more or less similar:

- 1) No solvent, keeping the solution cold,
- 2) No solvent, keeping the solution of 80-90 degrees,
- 3) Alcohol solvent, keeping the solution cold.

The condensations of 2,7-dihydroxynaphthalene and dimethylamine will serve to illustrate these procedures.

1) No solvent-cold

This procedure followed that of Caldwell and Thompson (4). 2,7-Dihydroxynaphthalene (4g,.025 mole) were mixed with 10 g.of 25% dimethylamine solution (.055 mole) in a small three-necked flask equipped with mechanical stirrer, thermometer, and dropping funnel, and surrounded by an ice bath. 7 g.of 35% formalin (.075 mole) were added slowly through the dropping funnel, with vigorous stirring, at such a rate that the temperature did not rise above 20 degrees C. A precipitate formed and the whole mass became solid. This was filtered and washed thoroughly with cold water to remove the excess formaldehyde and dimethylamine. After repeated recrystallization

from ethanol-water, the powder was still pale yellow, with a decomposition point of 149 degrees. Carbon-hydrogen combustion results are inconsistent but nitrogen combustion showed 10.82% (calc.10.22%)

2) No solvent-hot

The same quantities were used. The 2,7-dihydroxynaphthalene, dimethylamine mixture was heated on a water bath until all the 2,7-dihydroxynaphthalene dissolved. The formaldehyde was then added slowly at 80-90 degrees. A precipitate formed while still hot. The mixture was cooled and precipitate filtered and washed with water till all traces of formaldehyde and dimethylamine were removed. Repeated recrystallization from ethanol gave a dark yellow-brown solid with a decomposition point of 195 degrees. Consistent carbon-hydrogen combustion results could not be obtained. Nitrogen combustion gave 5.98% (calc.10.22%).

3) Alcohol Solvent-cold

2,7-Dihydroxynaphthalene (4g) and 10 g. of 25% dimethylamine solution were dissolved in 25 ml. of alcohol. Formalin (7g) was added slowly with stirring keeping temperature below 20 degrees. A precipitate

formed which was filtered and washed thoroughly with water. The pale yellow powder (decomposing at 149 degrees) proved to be the same as that obtained from condensation in the cold with no solvent.

A summary of the condensation products obtained by the above standard methods:

(a) with β -naphthol and

(i) dimethylamine

Condensations in hot or cold solution yielded the same product. Recrystallization from methanol gave colorless leaves (M.P. 73-74 degrees). Experimental; C, 77.82, H, 7.20, N, 7.10: Theoretical for $C_{13}H_{15}ON$; c, 77.61, H, 7.46, N, 6.96.

(ii) Piperidine

In cold solution a white powder was obtained. After recrystallization from methanol it had a melting point of 95 degrees. Decombe (8) reports a melting point of 94-95 degrees for this compound.

(iii) Morpholine

Condensation in cold solution produced a hard pink mass. Recrystallization from ethanol-water

yielded white shiny leaves of Melting Point 115-16 degrees. Experimental; C, 74.23%, H, 6.50%, N, 6.13%: Theoretical for $C_{15}H_{17}O_2N$; C, 74.07%, H, 6.99%, N, 5.76%.

(b) With 2,7-dihydroxynaphthalene and

(i) dimethylamine

In cold solution with no solvent, and also with alcohol solvent, a pale yellow powder was obtained. Repeated recrystallization would not remove the color. The powder had a decomposition point of 149 degrees and nitrogen combustion yielded 10.82% nitrogen.

If the condensation was carried out at 80-90 degrees a deep yellow brown solid was obtained, decomposing at 195 degrees. Consistent carbon - hydrogen results could not be obtained but nitrogen combustion gave 5.98%.

(ii) Piperidine

Condensation in the cold with and without solvent yielded the same product, a tan colored powder decomposing at 155 degrees. No consistent

combustion results could be obtained.

In a hot solution a dark brown solid was obtained. Repeated recrystallization from methanol would not remove the color or change the decomposition point, which was 215 degrees.

(iii) Morpholine

Again both condensations in the cold yielded the same product, a green solid which decomposed about 155 degrees. Two crystallizations from ethanol yielded pure white needles, melting sharply at 164 degrees. These crystals took on a green tinge after standing a few days. Experimental; C, 67.43%, H, 6.92%: Theoretical for $C_{10}H_{10}O_2N_2$; C, 67.04%, H, 7.26%.

The hot reaction, in this case, yielded the same product as the cold, if the solution was allowed to remain hot no longer than half an hour. Prolonged heating yielded a green-yellow powder decomposing at 211 degrees.

C) REDUCTIONS ATTEMPTED.

α -(~~D~~imethylaminomethyl)- β -naphthol was the compound used in the attempted reductions since it

was the cheapest to produce and the reduction product, α -methyl- β -naphthol, is well known.

1) Catalytic

A solution of 2 g. of the Mannich base (.01 mole) in 50 ml. of 95% ethanol was made and 0.1 g. of Adams platinum catalyst added. A standard Parr low pressure hydrogenation apparatus was used. The reduction was carried out at 45 pound pressure. No drop in pressure was noted. After the platinum was filtered off and the alcohol evaporated the base was recovered intact.

2) Sodium Amalgam

The Mannich base (2g., .01 mole) was added to 75 g. of 2% sodium amalgam in a flask. The flask was stopped ^{per} and vigorously shaken. No reaction occurred. After heating, it was subjected to further shaking but no reduction took place. The base was recovered unchanged.

3) Sodium Methylate (15)

Sodium (2g.) was placed in a small glass pressure bottle and 25 ml. of absolute methyl alcohol added. When

reaction had ceased, 2 g. (.01 mole) of the Mannich base were added and the reaction bottle tightly sealed. It was kept in boiling water for 24 hours. The sodium methylate was decomposed with water and the base recovered unchanged.

The same reagents were placed in a brass bomb and tightly sealed with a screw cap. The bomb was placed in an oil bath and heated to 220 degrees. All attempts to make the bomb leakproof met with failure. After an hour, all the excess methyl alcohol had boiled away. The bomb was kept at 220 degrees for 16 hours. On cooling, a green-brown solid was obtained, which dissolved in water to a slightly basic solution. Addition of acid precipitated a brown curdy substance. Recrystallization from benzene yields a brown powder melting at 199 degrees, which proved to be methylene bis- β -naphthol.

4) Sodium Methylate on the Esterified Mannich Base

α -(Dimethylaminomethyl)- β -naphthol (4g., .02 mole) were placed in a flask and dissolved in 10% sodium hydroxide solution. Dimethyl sulphate (3.5 g.) was added slowly with stirring keeping the temperature below 20 degrees. More sodium hydroxide was added

when necessary to keep the solution basic. When all the dimethyl sulphate was added, 4.6 g. of a greenish yellow gum were obtained. No attempts at crystallization of this gum were made, but ^{it} was used directly in the reduction.

The total yield of crude methyl ether was dissolved in 25 ml. of absolute methanol in a pressure flask and 2 g. of sodium added. After the reaction had ceased, the flask was tightly stoppered and put in boiling water for 24 hours. The brown semi-solid was dissolved in 50 ml. of hot water to ^{give} a basic solution. Acidification threw out a brown precipitate decomposing at 174 degrees. Recrystallization from boiling benzene proved it to be methylene-bis- β -naphthol (M.P. 199 degrees).

5) Tetraacetate of 2,4,6-tri-(dimethylamonomethyl)-phenol

The procedure followed was that of Brunson and MacMullen (3).

A mixture of 94 g. of phenol (1 mole) and 720 g. of 25% aqueous dimethylamine (4 moles) were cooled to 20 degrees and stirred while 315 g. of 35% formaldehyde

(3.5 moles) was added dropwise keeping the temperature below 30 degrees. The mixture was stirred for one hour after the addition at 25-30 degrees and finally heated with good stirring under reflux on a steam bath at 90-95 degrees for two hours. To the hot solution 200 g. of sodium chloride ^{was} ~~were~~ added and the mixture stirred for 20 minutes at 90-95 degrees. An oil layer separated and was distilled at 170-185 degrees at 20 mm. Yield 60 g. This was heated with 125 g. of acetic anhydride under reflux at 90-95 for three hours and distilled under reduced pressure. The tetraacetate distilled at 217-220 degrees at 11 mm. It is a clear water-bright oil.

The following reduction methods were tried on this compound:

(a) A solution of 3 g. (1/100 mole) of the tetraacetate in 50 ml. of ether was made and 0.15 g. of palladium-charcoal catalyst added. The mixture was shaken in a Parr hydrogenator at 3 atmosphere for two hours. No fall in pressure was noted and the tetraacetate was recovered unchanged.

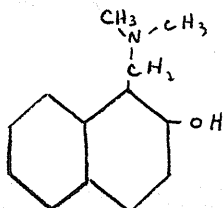
(b) Three g. of the compound were dissolved in 50 ml. of ethanol and 2 g. of copper chromite added. No reduction took place in two hours in the Parr hydrogenator.

(c) The tetraacetate (3 g.) was dissolved in 25 ml. of absolute methanol in a pressure bottle and 2 g. of sodium added. After reaction ceased, the bottle was tightly stoppered and heated in boiling water for 24 hours. The tetraacetate was recovered unchanged.

S U M M A R Y

The following new compounds have been synthesized:-

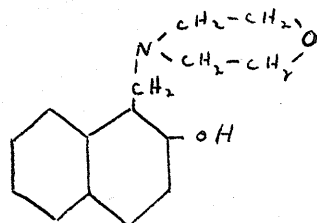
- 1) α -(dimethylaminomethyl)- β -naphthol



Colorless leaves

M.P. 73-75 degrees

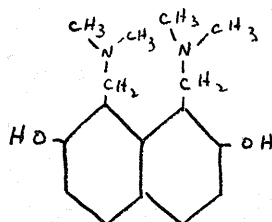
- 2) α -(morpholinomethyl)- β -Naphthol



White shiny leaves

M.P. 115-16 degrees

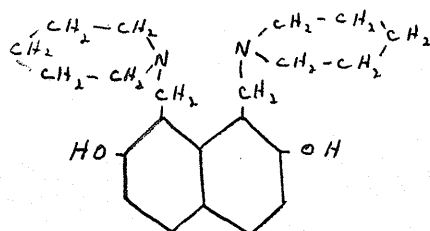
- 3) 1,8-bis-(dimethylaminomethyl)-2,7-dihydroxynaphthalene



Yellow powder

M.P. 149 degrees (dec.)

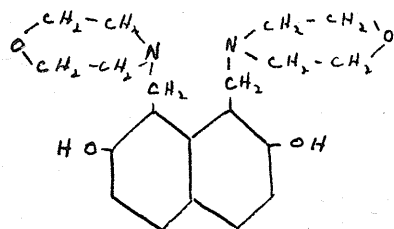
- 4) 1,8-bis-(piperidinomethyl)-2,7-dihydroxynaphthalene



Tan powder

M.P. 155 degrees (dec.)

5) 1,8-dimorpholinomethyl)-2,7-dihydroxynaphthalene



White needles

M.P. 164 degrees.

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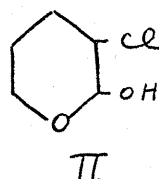
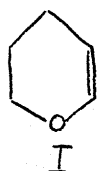
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PART 11

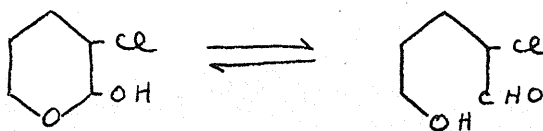
THE PREPARATION AND CHARACTERIZATION OF TETRAHYDROFURFURAL
AND TETRAHYDROFUROIC ACID

INTRODUCTION

Work is being carried out in this institution by A. Giesinger pertaining to the chemistry of dihydropyran (I). The chlorohydrin of this has been obtained (II) and its empirical structure proved by analysis.

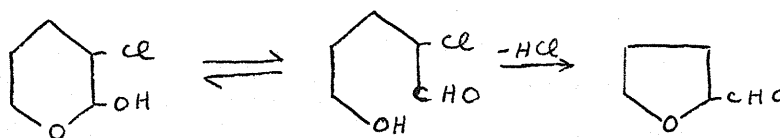


In aqueous systems the chlorohydrin exists in equilibrium with an aldehyde form.



Attempts to produce the 2,4-dinitrophenylhydrazone of this compound yield a product containing no chlorine. This same phenomenon has been observed with the bromohydrin. The 2,4-dinitrophenylhydrazone and the osazone have melting points corresponding to those of tetrahydrofurfural. A hypothesis as to the formation of this aldehyde has

been put forward involving ring cleavage and reformation to a five-membered ring by loss of HCL.



The characterization of tetrahydrofurfural and the corresponding tetrahydrofuroic acid has been rather lightly treated in the literature. The purpose of this research was to prepare these compounds by independent means and to make enough derivatives to fully characterize them.

LITERATURE SURVEY

DIHYDROPYRAN

As this work is not primarily concerned with dihydropyran, no literature survey will be given here. A complete survey has been made by Giesinger (7) in his M.Sc. thesis.

TETRAHYDROFURFURAL

1) PREPARATION

Only three methods of preparation of tetrahydrofurfural have been described in the literature, two using furfural as a starting material and one using tetrahydrofurfuryl alcohol.

The earliest preparation was from the acetal of furfural, first produced by Claisen (2) by reacting orthoformic ester with furfural, and later by Adkins and his co-workers (1) using absolute ethanol and dry hydrogen chloride with furfural. Scheibler, Sotscheck and Friese (17) succeeded in reducing the acetal with hydrogen using colloidal platinum, or

Palladinated charcoal. Later Adkins et al (3) accomplished the same result using Raney nickel at 200 atmospheres hydrogen pressure. The yields by this method are not good and the product is contaminated by impurities, mainly tetrahydrofurfuryl alcohol, which are difficult to remove.

A second and much better procedure is that of reduction of the diacetate of furfural. This was done by Scheibler, Sotscheck and Friese (17). The diacetate is easier and less expensive to produce than the acetal and its reduction gives rise to no undesirable side products. The diacetate is produced by merely refluxing distilled furfural with acetic anhydride and glacial acetic acid and then fractionating the resulting mixture. The solid diacetate is reduced in ether solution using hydrogen and palladinated charcoal. The resulting tetrahydrofurfural diacetate is easily saponified with dilute acid.

The third method was reported by Hinz, Meyer and Schucking (9). It consists in the oxidation of

tetrahydrofurfuryl alcohol. Sodium dichromate in acid solution was the oxidizing agent. A nine percent yield of tetrahydrofurfural is reported along with unchanged alcohol, tetrahydrofuroic acid, and the ester resulting from the latter two.

2) DERIVATIVES

The 2,4-dinitrophenylhydrazone has been variously reported. Hinz, Meyer and Schucking (9) obtained two forms, a yellow one from ice cold solution (M.P. 135-6 degrees) and a red one at room temperature (M.P. 204 degrees). The yellow form is unstable and changes to red on standing. Wilson (21) obtained the 2,4-dinitrophenylhydrazone from aqueous solution and reports the melting point at 130-31 degrees. Hurd and Edwards (10) also made this derivative but no details as to how it was prepared are reported. Their melting point was 133-34 degrees. The last two references make no mention of a higher melting form.

The benzylphenylhydrazone was first obtained by Scheibler, Sotscheck and Friese (17). They produced small weakly yellow crystals of melting point 67 degrees.

Hurd and Edwards (10) made this derivative and give the melting point as 73-74 degrees.

Hurd and Edwards (10) made the osazone from the 2,4-dinitrophenylhydrazones and give the melting point as 242 degrees. These workers also made the p-nitrophenylhydrazone melting at 146-147 degrees.

McElvain (15) in a table in his text book, lists a semicarbazone of tetrahydrofurfural. There is no mention of the source of this information.

These are the only five derivatives of tetrahydrofurfural mentioned in the literature and there seem to be some discrepancies concerning the melting points of some.

TETRAHYDROFUROIC ACID

1) PREPARATION

Wienhaus and Sorge (20) report one method of preparation by the reduction of furoic acid, using a colloidal suspension of palladinous chloride with hydrogen. It was later accomplished by Kaufmann and

Adams (12) using hydrogen and platinum with a small amount of ferrous chloride as catalyst. Paul and Hilly (16) used Raney nickel at high hydrogen pressure to produce the tetrahydrofuroic acid.

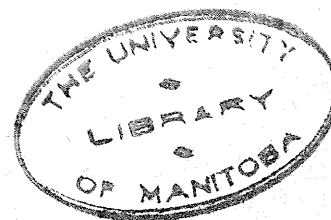
The only other preparative method is that of Hinz, Meyer and Schucking (9) by oxidation of tetrahydrofurfuryl alcohol previously discussed.

2) DERIVATIVES

The tetrahydrofuroamide was prepared by Weinhaus and Sorge (20), who obtained white leaves of melting point 80 degrees. The amide was also reported by Paul and Hilly (16) who give the melting point as 78-9 degrees.

Kleene (13) attempted to make the phenacyl-ester without success. He made the p-phenylphenacyl ester, a white powder of melting point 100 degrees.

These are the only two derivatives of tetrahydrofuroic acid reported in the literature to date.



DISCUSSION OF RESULTS

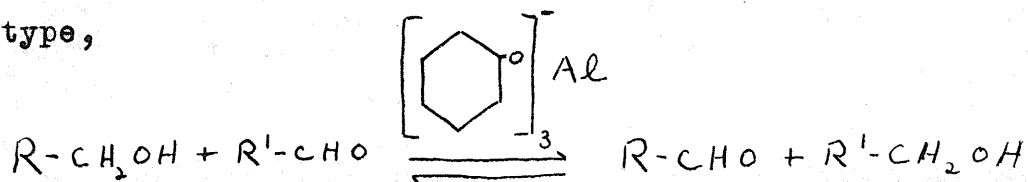
A) PRODUCTION OF TETRAHYDROFURFURAL

Since there were large quantities of tetrahydrofurfuryl alcohol on hand in this laboratory, the oxidation of the alcohol was the first method tried for the preparation of tetrahydrofurfural.

Hinz, Meyer and Schucking (9) used sodium dichromate in acid solution as their oxidizing agent. They obtained a 9% yield of tetrahydrofurfural and 20% yield of tetrahydrofuroic acid. The work was repeated but the best yield obtained was 6% of the aldehyde and no acid at all.

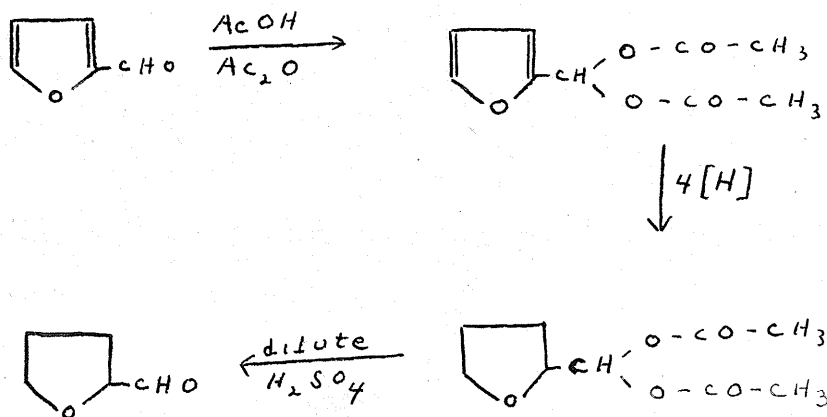
Since the yields were so low, other methods of oxidation were tried. Farkas and Schächter (6) oxidized benzyl alcohol using a mixture of potassium bromate, hydrochromic acid, and water. This method was tried on tetrahydrofurfuryl alcohol but the best yield obtained was 4% of the aldehyde. A modification of this method by the same workers using bromine instead of hydrochromic acid gave a 5% yield.

Oppenauer oxidations were tried of the general type,



Aluminum phenolate-quinone mixtures had no effect on tetrahydrofurfuryl alcohol. Lauchenauer and Sching (14) give a complete method for oxidation using aluminum isopropoxide and anisaldehyde as a hydrogen acceptor. This method produced no tetrahydrofurfural either.

The method of Scheibler, Sotscheck and Frieese (17) proved to be the best both for purity and percent yield. It involves the production of the diacetate of furfural, catalytic hydrogenation of the double bonds, and ~~saponification~~ ^{hydrolysis} of the tetrahydrofurfural diacetate.



An overall yield of 13 percent was obtained and the product contained no furfural as shown by the sensitive

aniline acetate test.

A few of the refinements suggested by Scheibler, Sotscheck and Frieese were found to be quite unnecessary. They state that, since the hydrogenation cannot be interrupted, only 5 g. of diacetate may be reduced at one time. Also these authors claim no hydrogen absorption takes place unless the ether used as solvent be previously washed with sodium hydroxide solution, alkaline permanganate solution, water and dried with calcium chloride and sodium wire. It was found possible to reduce 25 g. in ordinary untreated ether easily in two hours or less if the diacetate was used immediately after recrystallization.

B) DERIVATIVES OF TETRAHYDROFURFURAL

No solid phenylhydrazone was obtained. This agrees with Scheibler, Sotscheck and Frieese (17) who obtained a yellow-red oily product which crystallized only with difficulty and resinified easily. These workers also failed to get a solid derivative with hydroxylamine as was the case in this work.

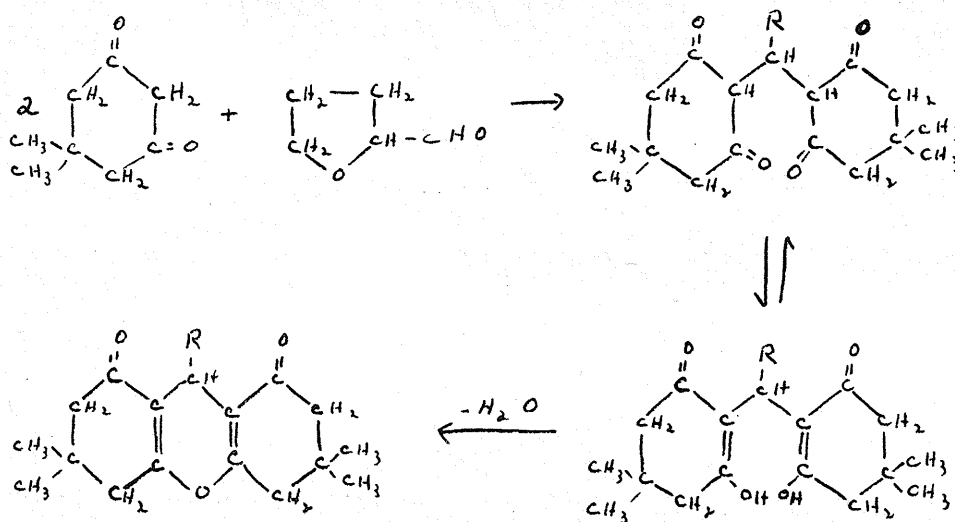
A semicarbazone of tetrahydrofurfural (M.P. 166 degrees) has been reported by McElvain in his text book

(15) but no reference is given. Repeated attempts to obtain this derivative met with failure.

The p-nitrophenylhydrazone was easily obtained whose melting point (146 degrees) agrees with that reported by Hurd and Edwards (10). These workers report a yellow derivative. The one obtained here was red, but on grinding to a fine powder becomes bright yellow. The hydrazone can be further treated to form the osazone by boiling with excess hydrazine in acid solution.

The benzylphenylhydrazone obtained agrees in form and melting point with that of Hurd and Edwards.

Methone (5.5-dimethyldihydroresorcinol) forms a derivative very easily and simply and may easily be cyclized to a second derivative by the general method of Horning and Horning (11)



Benzohydrazide and o-chlorobenzohydrazide, although useful reagents for many carbonyl compounds, failed to yield derivatives with tetrahydrofurfural.

Although semicarbazide gave no derivative, it was thought that substituted semicarbazides might do so, in an analogous manner to phenylhydrazine and substituted phenylhydrazines. Accordingly the phenylsemicarbazide and m-tolylsemicarbazide were prepared and condensed with tetrahydrofurfural to yield the phenylsemicarbazone and m-tolylsemicarbazone respectively.

The hydantoin, recently developed by Henze and Speer (8), failed to give any results under any conditions.

The 2,4-dinitrophenylhydrazone, whose melting point is variously given as 130-31 degrees, 133-34 degrees, 135-36 degrees, 204 degrees, was most easily prepared according to the directions of Shriner and Fuson (8) by the sulphuric acid method. However even after six recrystallizations the maximum melting point obtained was 129 degrees. Various modifications

of this procedure and that of Hinz, Meyer and Schucking (9), using aqueous hydrochloric acid solution, were tried, all with the same result.

The 2,4-dinitrophenylosazone was easily prepared from the corresponding hydrazone in acidic methanol solution. Four recrystallizations are necessary to raise the melting point some forty degrees to a constant value of 241-42 degrees.

C) PRODUCTION OF TETRAHYDROFUROIC ACID

Kaufman and Adams (12) were the first to carry out the reduction of furoic acid in alcohol solution. They report a 40 percent yield from 25 g. of furoic acid, with unidentified low and high boiling fractions. The work was repeated in these quantities with the same results. However, it was found that if only 0.1 mole of furoic acid (11.2 g) ~~was~~ ^{was} used there was obtained an 80 percent yield with no other fractions.

D) DERIVATIVES OF TETRAHYDROFUROIC ACID

Of the three solid ester derivatives prepared,

the p-phenylphenacyl ester is the only one previously reported. Kleene (13) reports it as a white crystalline powder melting at 100 degrees. Repeated preparations with slightly varied procedures always produced a white powder, melting at 84 degrees. The combustion analysis of this compound checks very well with the theoretical, as does Kleene's. There are two possible explanations for this phenomenon. Either there are two allotropic forms of this compound or Kleene has failed to produce an ester but only hydrolyzed the phenacyl bromide to p-phenylphenacyl alcohol.

The second possibility may be ruled out on the grounds of the combustion analysis. The following is a comparison of combustion results:

Calc. for ester	C	73.54	H	5.80
Calc. for alcohol	C	79.24	H	5.66
Kleene's results	C	73.50	H	5.59

Although the hydrogen value would fit the alcohol value better than that of the ester, the carbon comparison removes all doubt, leaving two allotropic forms as the only other possibility.

The phenylhydrazide, prepared by refluxing phenylhydrazine with the aldehyde, is a useful derivative due to its ease of preparation and purification. It has a melting point of 135 degrees.

The water-ether partition coefficient, although a useful means of identification, may only be applied to the acid if it is entirely pure.

EXPERIMENTAL

A) PRODUCTION OF TETRAHYDROFURFURAL

1) Sodium Dichromate Oxidation of Tetrahydrofurfuryl Alcohol (9)

Tetrahydrofurfuryl alcohol (102 g., 1 mole) was mixed with 60 ml. of 1:1 sulphuric acid under cooling and to this solution a mixture of 93 g. of sodium dichromate in 62 ml. of concentrated sulphuric acid and 400 ml. of water was added dropwise with stirring, keeping the temperature below 30 degrees. The reaction was finished only after two days. Sodium sulphate (200 g.) was added to the reaction mixture and the solution extracted several times with ether. The combined extracts were washed with 10 per cent sodium chloride solution, dried over sodium sulphate and fractionated. There were obtained 5.8 g. of tetrahydrofurfural (6% of theory) B.P. 48-52 degrees/30mm., 13.2 g. of unchanged alcohol, and a gum on the bottom of the distillation flask.

2) Potassium Bromate-Bromine Oxidation of Tetrahydrofurfuryl Alcohol. (6)

The alcohol (51 g., .5 mole) 30 g. of water, 36.3 g. of potassium bromate and 2.5 g. of bromine were put in a

200 ml. flask equipped with reflux, thermometer and stirrer. For the first 20 minutes the mixture was kept at 40 degrees; then the temperature raised to 50 degrees and kept constant till the color of the bromine ^abegin~~s~~ to disappear (3 hours). The temperature was slowly raised to 70 degrees and finally to 100 degrees and there the reaction ^{was}brought to completion. The solution was extracted several times with ether; the combined extracts dried and fractionated. There were obtained 2.4 g. of tetrahydrofurfural (5% of theory), 7.4 g. of unchanged tetrahydrofurfuryl alcohol and 10 g. of dark brown viscous gum.

3) Reduction of the Diacetate of Furfural (17)

Redistilled furfural (75 g.) was heated with 135 g. of acetic anhydride and 30 g. of glacial acetic acid for four hours at 160-170 degrees under reflux. The mixture was distilled under reduced pressure, and after a forerun to get unchanged starting materials, 32 g. of diacetate went over at 128-130 degrees at 17 mm. The forerun was refluxed for six hours after the addition of another 135 g.

of acetic anhydride and 10 g. of glacial acetic acid and then allowed to stand at room temperature for three days. This was then distilled under reduced pressure and a further 21 g. of diacetate obtained (total yield 35 %). The greenish solid may be recrystallized from 1:10 ether-petroleum ether giving a pure white solid melting at 52 degrees.

The diacetate (25 g.) was dissolved in 150 ml. of ether, 0.90 g. of palladium charcoal added and put in Parr hydrogenator. The reduction was finished in about two hours. After evaporation of the ether the tetrahydrofurfural diacetate may be isolated by vacuum distillation (B.P. 133 degrees/30mm).

The ether solution was placed in a 2-neck 300 ml. flask and ether distilled off. The residual tetrahydrofurfural diacetate was boiled with an equal volume of 1 normal sulphuric acid in a nitrogen stream for 15 minutes after solution, then cooled in a nitrogen stream. The solution was neutralized with sodium carbonate and extracted with ether. The ether was evaporated and the tetrahydrofurfural distilled under reduced pressure (B.P. 48-52 degrees/30mm). The yield was 6.7 g. (40%). Overall yield was 13%.

B) DERIVATIVES OF TETRAHYDROFURFURAL

1) Phenylhydrazone

Ten drops of tetrahydrofurfural were dissolved in 2 ml. of ethanol and water added to the cloud point. Five drops of phenylhydrazine were added along with a drop of glacial acetic acid and the mixture warmed for a few minutes. On cooling, an oily scum settled to the bottom, which could not be made to crystallize.

2) Semicarbazone

Ten drops of tetrahydrofurfural were dissolved in 5 ml. of ethanol and water added to the cloud point. 0.5 g. of semicarbazide hydrochloride and 0.7 g. of sodium acetate were added and the mixture vigorously shaken. It was heated to 100 degrees for a few minutes, allowed to cool, and then chilled, scratching the sides of the vessel with a glass rod. There was no appearance of crystals after one week in the icebox.

3) Oxime

A mixture of 1 g. of tetrahydrofurfural, 1 g. of hydroxylamine hydrochloride, 5 ml. of pyridine, and 5 ml. of absolute ethanol was refluxed for two hours on a steam bath. The solvents were removed by evaporation in a current of air. The only residue obtained was the original reagent. A more strongly basic solution using sodium hydroxide was tried but no derivative was obtained.

4) ~~p-N~~ Nitrophenylhydrazone

A mixture of 0.5 g. of p-nitrophenylhydrazine, 10 drops of tetrahydrofurfural, and 10 ml. of ethanol was heated to boiling and 1 drop of glacial acetic acid added. The solution was kept hot for a few minutes, then water added to the cloud point and cooled. 0.25 g. of dark red needles were obtained which, after recrystallization from ethanol, melted at 146 degrees. Finer subdivision of the derivative changes the color to a bright yellow.

5) p-Nitrophenylosazone

The p-nitrophenylosazone was prepared by condensing 0.6 g. of the p-nitrophenylhydrazone of tetrahydrofurfural with 1.2 g. of p-nitrophenylhydrazine. A methanol solution of these was refluxed for 4 hours with 4 drops of concentrated hydrochloric acid. A dark red-black powder separates on cooling. Recrystallization from methanol yields a dark red powder melting at 246 degrees with slight decomposition. Experimental; C, 55.81%, H, 4.37%: Theoretical; for $C_{17}H_8O_4N_6$; C, 55.14%, H, 4.86%.

6) Benzylphenylhydrazone

To 100 ml. of a saturated aqueous solution of benzylphenylhydrazine hydrochloride was added 0.5 g. of tetrahydrofurfural and the solution cooled in an icebox. A red mass ~~was~~ precipitated which, after 2 recrystallizations from methanol, ^abecomes nearly colorless plates of melting point 74 degrees.

7) Methone (11)

To a solution of 0.1 g. of tetrahydrofurfural in 4 ml. of 50% ethanol is added 0.4 g. of methone.

One drop of piperidine is added and the mixture gently refluxed for 5 minutes. Water is added to the cloud point and the mixture chilled. The derivative after filtration is washed with 2 ml. of cold 50% alcohol. The yellow crystals melt at 151 degrees, but after recrystallization from methanol-water the very pale yellow sheets have a melting point of 158 degrees. Experimental; C, 69.71%, H, 8.14%: Theoretical for $C_{21}H_{30}O_5$; C, 69.89%, H, 8.29%.

The methone condensation product may be converted to a substitute octahydrozanthene (i.e. cyclized) by boiling a solution of 0.1 g. of the methone derivative in 3 ml. of 80% ethanol adding 1 drop of concentrated hydrochloric acid. After five minutes, water is added to the cloud point and the mixture cooled. Yellow leaves (M.P. 194 degrees) are obtained which, after recrystallization from methanol, are pure white and have a melting point of 195 degrees. Experimental; C, 73.02%, H, 7.95%: Theoretical for $C_{21}H_{28}O_4$; C, 73.25%, H, 8.14%.

8) Benzohydrazone

To prepare the benzohydrazide, 3.5 g. of ethyl benzoate, 1.5 g. of 85% hydrazine hydrate, and 50 ml.

of alcohol were refluxed for 12 hours. The resulting oil, on chilling, precipitated white leaves. The crystals, on recrystallization from ethanol, melt at 112 degrees.

The benzohydrazide could not be made to condense with tetrahydrofurfural under any conditions.

9) o-Chlorobenzhydrazone

The o-chlorobenzohydrazide was prepared as by Sun and Sah (15). Chlorobenzoic acid, (15 g.) ^{was} ~~were~~ dissolved in 50 ml. of ethanol and 10 ml. of concentrated sulphuric acid added. The mixture was refluxed for two hours, cooled and extracted with ether. The ether was washed with water and sodium bicarbonate solution and distilled. The ester boils ^{at} 130-140 degrees at 28mm. Yield 10 g. The ester (10 g.) was refluxed with 10 ml. of 85% hydrazine hydrate for 24 hours. On cooling the whole mass turned ^{to} a pink solid. On recrystallization from ethanol, 8 g. of pure white needles melting at 117 degrees were obtained.

All attempts to form the o-chlorobenzohydrazone of tetrahydrofurfural were unsuccessful.

10) Phenylsemicarbazone

The preparation of phenylsemicarbazide involved a number of steps.

Urea (10 g.) was dissolved in 60 ml. of water and 20 ml. of concentrated nitric acid added. Urea nitrate precipitated immediately and 13 g. was filtered off and dried. Dry powdered urea nitrate (10 g.) was added gradually to 20 ml. of cold, concentrated sulphuric acid keeping the temperature below 3 degrees. The yield of nitrourea was 7.5 g.

Nitrourea, (5.3 g.) was dissolved in 100 ml. of water and 4.7 g. of aniline added (4). The mixture was warmed to initiate the reaction. When the evolution of gas ceased, the solution was cooled and precipitated a brownish powder. On recrystallization from hot water, white needles of phenylurea (M.P.147 degrees) were obtained.

Phenylurea (5.69 g.) and 8.g. of 40% hydrazine hydrate were refluxed in absolute alcohol for 24 hours. Evaporation of the ethanol leaves a white solid with a crude melting point of 108-112 degrees. This crude solid was dissolved in ethanol and equal volumes of concentrated hydrochloric acid added. The hydrochloride

was filtered off and dissolved in water and the free base precipitated with 10% sodium hydroxide solution. It is a pure white powder (M.P. 120-21 degrees).

One g. (.01 mole) of tetrahydrofurfural was dissolved with 1.5 g. of phenylsemicarbazide in 10 ml. of 95% ethanol and 5 ml. of glacial acetic acid. The solution was chilled overnight but no precipitate was formed. The mixture was then refluxed for 17 hours. A white precipitate was obtained on cooling, which had a melting point of 230 degrees. Experimental; C, 61.24%; H, 5.98%; Theoretical for $C_{12}H_{15}O_2N_3$; C, 61.80%, H, 6.43%.

11) m-Tolylsemicarbazone

The m-tolylsemicarbazide was prepared in an exactly analogous manner to that of phenylsemicarbazide. The crude m-tolylurea was recrystallized from water and had a melting point of 142 degrees. Condensation with hydrazine hydrate yields a greyish-purple product which, on purification melts at 110 degrees.

m-Tolylsemicarbazide (1.5 g.) was dissolved in a mixture of 10 ml. of ethanol and 5 ml. of glacial acetic acid and 0.8 g. of tetrahydrofurfural added.

No precipitation occurred. The mixture was then boiled for 17 hours. A brown solid separated on cooling. When recrystallized from alcohol it was pure white with a melting point of 231-232 degrees. Experimental; C, 63.90%, H, 6.64%: Theoretical for $C_3H_7O_2N_3$: C, 63.16%, H, 6.89%.

12) Hydantoin (8)

One g. (.01 mole) of tetrahydrofurfural was dissolved in 25 ml. of 50% ethanol and 4.5 g. (.04 Mole) of ammonium carbonate and 1.3 g. (.02 mole) of potassium cyanide added. The mixture was warmed at 60 degrees for two hours. The solution was then concentrated to two-thirds of its volume and chilled. No hydantoin separated. The solution was acidified with hydrochloric acid in the hood, and further chilled. Still no precipitation occurred. The mixture was evaporated to dryness and extracted with boiling benzene several times. The benzene on evaporation left only a little inorganic residue.

13) 2,4-Dinitrophenylhydrazone

To 0.4 g. of 2,4-dinitrophenylhydrazine was added 2 ml. of concentrated sulphuric acid. Water (3 ml.)

was added dropwise with stirring until solution was complete. Ethanol (10 ml.) was added to this warm solution. This solution was added to a solution of 0.5 g. of tetrahydrofurfural in 20 ml. of alcohol and allowed to stand over night. The red precipitate melts about 100 degrees. Three recrystallizations from ethanol brings the melting point up to 129 degrees and changes the color from red to orange-yellow. A fourth recrystallization from ethanol makes no change in the melting point or color, and two further recrystallizations from toluene have no effect.

A second method for the preparation of this derivative is that of Hinz, Meyer and Schucking (9). One normal hydrochloric acid (100 ml.) was saturated with 2,4-dinitrophenylhydrazine (about .5 g.) at room temperature and 1 g. of tetrahydrofurfural added. A yellow cloudiness forms immediately but on standing a red solid separated which melts about 120 degrees. Repeated recrystallizations from toluene will not raise the melting point above 129 degrees but does change the color of the compound to yellow.

14) 2,4-Dinitrophenylosazone

The 2,4-dinitrophenylhydrazone (.5 g.) was dissolved in 100 ml. of methanol and .8 g. of 2,4-dinitrophenylhydrazine and a few drops of hydrochloric acid added. The solution was boiled under reflux for 6 hours and cooled. A red precipitate formed, melting about 205 degrees. Four recrystallizations from nitromethane bring the melting point up to 241-42 degrees and change the color to a bright orange.

C) PRODUCTION OF TETRAHYDROFUROIC ACID

The acid was produced by the reduction of furoic acid, which in turn was obtained by oxidation of furfural.

1) Furoic Acid (5)

Potassium permanganate (10.5 g.) dissolved in 400 ml. of water was added slowly at 20 degrees to a mixture of 9.6 g. of furfural, 26 g. of potassium hydroxide and 400 ml. of water. The manganese dioxide was filtered off and the solution acidified with sulphuric acid and evaporated to about 40 ml. Bone charcoal

was added and the mixture boiled for 20 minutes. On filtering and cooling 5.8 g. of furoic acid (M.P. 128-130 degrees) were obtained, a 52% yield.

2) Reduction of furoic acid.

Furoic acid (11.2 g., .1 mole) was dissolved in 100 ml. of 95% ethanol and .9 g. of palladium charcoal catalyst added. The mixture was reduced in a Parr low pressure hydrogenator in two hours. The catalyst was filtered off and the solution evaporated under reduced pressure. A clear colorless oil (9.5 g.) went over at 133-138 degrees at 14 mm. pressure, representing an 80% yield.

The reduction was also attempted on a double scale, using 22.4 g. of furoic acid. On distillation there was obtained, after the alcohol boiled off, a forerun up to 130 degrees at 12 mm. of 11.8 g. of clear water bright liquid. The tetrahydrofuroic acid came off at 130-136 degrees (9.8 g.) leaving a dark brown residue amounting to 2.3 g. This is a 42% yield of the acid.

D) DERIVATIVES OF TETRAHYDROFURIC ACID

1) p-Bromophenacyl ester

One gram of the acid was neutralized with 10% sodium hydroxide solution. A few drops of the acid were added till the solution was just acid to litmus. One gram of p-bromophenacyl bromide dissolved in 15 ml. of ethanol was added and the mixture refluxed for one hour. On cooling brown leaves were obtained. These were dissolved in alcohol and poured into an equal volume of water. Pure white shiny leaves melting at 83.5-84 degrees were obtained. Experimental; C, 49.35%, H, 3.88%: Theoretical for $C_{13}H_{13}O_4Br$; C, 49.84%, H, 4.15%.

2) p-Nitrobenzyl ester

The same procedure as above was followed. Recrystallization from ethanol-water yields white shiny leaves melting at 52-53 degrees. Experimental; C, 58.07%, H, 5.27%: Theoretical for $C_{12}H_{13}O_5N$; C, 57.37%, H, 5.17%.

3) p-Phenylphenacyl ester

The same procedure to produce the derivatives was followed. Recrystallization from ethanol water produced white crystals (M.P. 84 degrees). Experimental; C, 73.47%, H, 5.92%; Theoretical for $C_{17}H_{12}O_4$; C, 73.54%, H, 5.80%.

4) Phenylhydrazide

One gram of the acid was boiled with 2 ml. of phenylhydrazine for 30 minutes. The mixture was chilled and 10 ml. of benzene added which brings out brown crystals. These were recrystallized from hot benzene yielding pure white needles of melting point 135 degrees. Experimental; C, 63.88%, H, 7.44%; Theoretical for $C_{11}H_8O_2N_2$; C, 64.07%, H, 6.79%.

5) Water-Ether Partition Coefficient

Two grams of tetrahydrofuroic acid were dissolved in 50 ml. of distilled water. Ten ml. of this solution were titrated with standardized sodium hydroxide solution, phenolphthalein being used as the indicator. The exact normality of the original acid solution was calculated and a portion of it diluted with distilled water to make

the solution 0.100 N. Fifty ml. of this solution were transferred to a 200 ml. separatory funnel and 50 ml. of water-saturated ether added. The mixture was shaken for five minutes, the layers separated and each titrated against the standard sodium hydroxide solution. The ratio of the concentration in water to that of ether was found to be 4.12.

S U M M A R Y

The following derivatives have been prepared and proved by combustion analysis or melting point checks. In the case of previously prepared compounds, references are given.

<u>Tetrahydrofurfural</u>	M.P.
2,4-dinitrophenylhydrazone (5),(7),(6)	129°
2,4-dinitrophenylosazone (6)	241-42°
p-Nitrophenylhydrazone (6)	146-47°
p-Nitrophenylosazone	246° d
Benzylphenylhydrazone (3),(6)	74°
Methone	158°
Cyclized methone	195°
Phenylsemicarbazone	230°
m-Tolylsemicarbazone	231-32°

Tetrahydrofuroic acid

p-Bromophenacyl ester	83.5-84°
p-Nitrobenzyl ester	52-53°
p-Phenylphenacyl ester (11)	84°
Phenylhydrazide	135°

Water-ether partition coefficient	4.12
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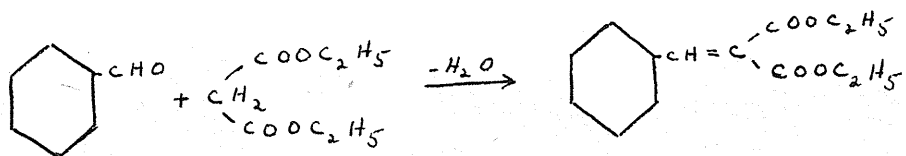
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PART 111

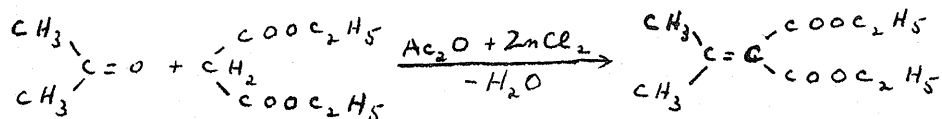
THE PREPARATION OF SOME UNSATURATED MALONIC ESTERS
AND BARBITURATES

INTRODUCTION

Many substituted unsaturated malonic esters have been made by a Knoevenagel reaction with aldehydes of the type:

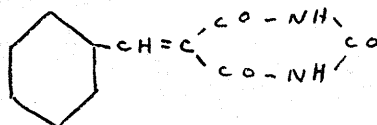


This type of compound has also been made from ketones using acetic anhydride:



but very few of this type have been reported.

Although some unsaturated barbiturates have been made, for example, benzylidene barbituric acid,

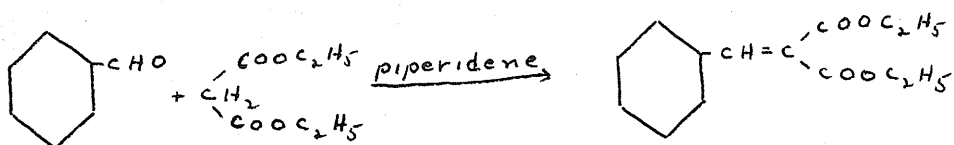


directly from the aldehyde plus barbituric acid, no attempts have been reported to put the unsaturated malonic esters into barbiturate condensations. Nor have any ketones been combined directly with barbituric acid.

It was the aim of this work to fill in some of the gaps in the unsaturated malonic ester and barbituric acid series. These barbiturates could be tested by the Medical Research Department for possible physiological activity.

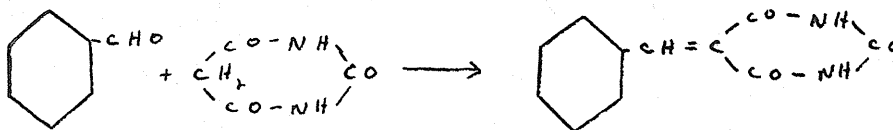
LITERATURE SURVEY

The Knoevenagel reaction is the condensation of aldehydes or ketones with a compound containing an active methylene group in the presence of piperidine or other primary or secondary amines or ammonia as condensing agent.

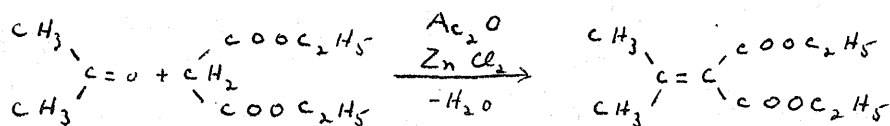


Many reactions of this type had been carried out before but Knoevenagel (9) was the first to generalize the condensation. His work was concerned only with aldehydes.

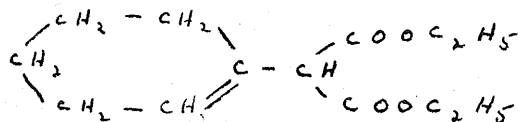
No attempts were made to put the substituted malonic esters so produced into barbiturate condensations. However Conrad and Reinbach (4) produced the barbiturates directly from the aldehyde plus barbituric acid, by heating a water mixture of the two on a water bath.



Meyenberg (13) produced the same type of unsaturated malonic ester from acetone. However, his method did not involve a Knoevenagel type condensing agent. He used acetic anhydride and zinc chloride to react the ketone with malonic ester, giving rise to isopropylidene malonic ester.



Cope and Hancock (5) used Meyenberg's method to produce 1-methylpropylidene malonate from methyl ethyl ketone. Cyclopentylidene malonate was produced by Kon and Speight (10) from cyclopentanone by the same method, but using cyclohexanone the only product isolated was ethyl Δ' -cyclohexenyl-1-malonate.



Barbituric acid itself was made by Blitz and Wittik (2) from urea and malonic acid using acetic anhydride as the dehydrating agent. Phosphorous

oxychloride was also used as a condensing agent to form barbituric acid from malonic acid and urea (14). Attempts to produce substituted malonic acids in the Knoevenagel manner, invariably resulted in decarboxylation to give a monobasic acid (1), (7), (12), so this method of obtaining substituted malonic acids and hence substituted barbiturates is not feasible.

The standard method of synthesizing barbiturates is that using sodium ethylate for the condensing agent between urea and the malonic ester. This method had never been applied to unsaturated malonic esters. The double bond may possibly be reduced by the action of sodium ethylate.

A summary of the unsaturated malonic esters and barbiturates described in the literature appears in Table 1.

TABLE I

<u>Carbonyl compound</u>	<u>Malonic Ester</u>	<u>Barbiturates</u>
Formaldehyde	methylenebis (8)	
Acetaldehyde	ethylidenebis-B.P.198-200/15mm (9)	
Isobutaldehyde	isobutylidenebis-B.P.198/12mm (9)	
Isoamylaldehyde	isoamylidenebis-B.P.210-15/25mm (9)	
Heptaldehyde	heptylidenebis-B.P.195/16mm (9)	
Propionaldehyde	propylidenebis-B.P.195-205/12mm (11)	
Benzaldehyde	benzylidene-B.P.185-86/1mm (9)	M.P.256 (14)
Cumaldehyde	cumylidene-B.P.205-208/11mm (9)	
p-Nitrobenzaldehyde	p-nitrobenzylidene (9)	
Anisaldehyde	anisylidene-B.P.200-207/14mm (9)	
Methylsalicylic (aldehyde)	methylsalicylidene B.P.193-95/14mm (9)	
Piperonal	piperonylidene-B.P.216-19/11mm (9)	
Furfural	furfurylidene-B.P.168/11mm (9)	M.P.280 (4)
o-Nitrobenzaldehyde		M.P.250 (d) (4)
o-Aminobenzaldehyde		yellow-red powder (4)
Cinnamaldehyde		M.P.226-28 (d) (4)
Salicylic aldehyde		M.P.260 (d) (4)
Acetone	isopropylidene-B.P.140-41/20mm (13)	
Methyl ethyl ketone	1-methylpropylidene-B.P.134-36/22mm (5)	
Cyclopentanone	cyclopentylidene-B.P.140/10mm (10)	
m-Nitrobenzaldehyde	m-nitrobenzylidene-(11)	
Butyraldehyde	butylidene-B.P.144/25mm (3)	

DISCUSSION OF RESULTS

A) MALONIC ESTERS FROM ALDEHYDES

The only work done with aldehydes was a repetition of the benzaldehyde and acetaldehyde condensations carried out by Knoevenagel (9) to produce benzylidene and ethylidene bis-malonic esters respectively. The work on aldehydes has been done rather exhaustively and further work on this was felt to be unnecessary.

B) MALONIC ESTERS FROM KETONES

Knoevenagel's method, using piperidine was tried on acetone with no results at all. Meyenberg's method (13) was the only one which would condense the ketones. The condensation seems to be selective. All the aliphatic and cyclic aliphatic ketones tried condensed quite well. Acetophenone was the only aliphatic-aromatic ketone tried and it reacted but only in very low yield. Benzophenone condensed very easily in good yield, yet fluorenone, an exactly similar compound except for the bridge between the two rings, failed to

condense at all. Benzil also would not react. These were all the ketones available in this laboratory.

C) MALONIC ACIDS FROM ESTERS

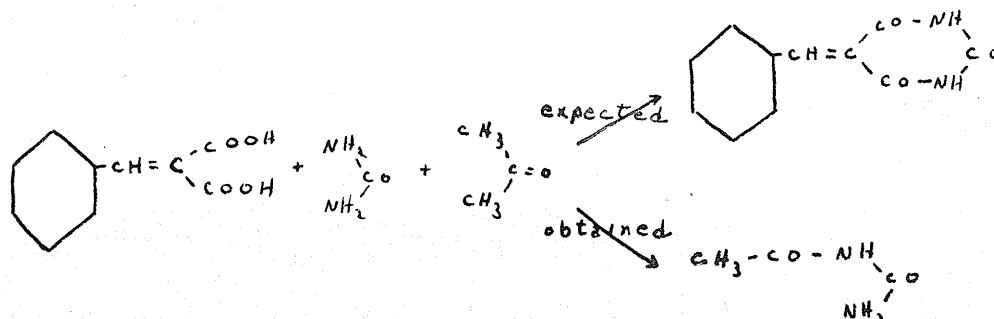
Biltz and Wittk (2) report a method of making barbituric acid from malonic acid and urea using acetic anhydride as a dehydrating agent. It was thought that if the malonic esters previously produced could be saponified to substituted malonic acids, these could be condensed with urea to produce substituted barbiturates.

Potassium hydroxide saponification works quite smoothly with benzylidene malonic ester, but with the isopropylidene ester it yields an unidentified product with a melting point far below that of the acid.

D) BARBITURATES FROM MALONIC ACIDS

Barbituric acid itself may be made by the method outlined in the experimental section (see part G) but for some reason the substituted malonic acids will

not react in this manner, yielding only acetyl urea.



Since this was the only product obtained further attempts at saponification of the esters were discontinued.

E) BARBITURATES FROM ESTERS

The standard method for the preparation of barbiturates from malonic esters using sodium ethylate as condensing agent was tried in this section. In the case of benzylidene malonic ester a brown powder was obtained which did not have the melting point of benzylbarbituric (206 degrees) or benzylidene barbituric (256 degrees) but an intermediate one of 225 degrees. Isopropylidene and benzophenylidene malonic esters yielded only gums which had no definite melting point and could not be made to crystallize.

F) BARBITURATES FROM BARBITURIC ACIDS

Since ketones react with malonic ester under the influence of acetic anhydride and zinc chloride, it was thought that they might react similarly with barbituric acid. Attempts to produce unsaturated barbiturates in this manner led only to the same white powder from every ketone. A blank run, using only barbituric acid, acetic anhydride, and zinc chloride produced the same white powder melting at 302 degrees. Since these are the only starting materials, the most likely product is either 5-acetyl or 5,5-diacetyl barbituric acid. A comparison of the theoretical and experimental combustion results proves the compound to be 5-acetylbarbituric acid.

Experimental	C, 42.29%, H, 3.40%
Theoretical for monoacetylbarbituric	C, 42.35%, H, 3.53%
$C_6H_6O_4N_2$	
Theoretical for diacetylbarbituric	C, 45.28%, H, 3.77%
$C_8H_8O_5N_2$	

The monoacetyl derivative is listed in Beilstein but no melting point or other physical constants are given and the original paper was not available.

G) PRODUCTION OF BARBITURIC ACID

The two methods used for the production of barbituric acid were the standard sodium ethylate method and that of Biltz and Wittik (2) using malonic acid, urea, and acetic anhydride. Of the two, the latter is more satisfactory both in regard to yield and ease of preparation.

As far as could be seen by this worker, all possible avenues of approach to this problem of producing unsaturated barbiturates from ketones have been exhausted. However, further work could be done on the products resulting from the sodium ethylate treatment of the ester and urea (Part E). Also possibly a modification of the Meyenberg method on barbituric acid might produce some results. Due to lack of time, these lines of research could not be carried on by this worker.

EXPERIMENTAL

(A) MALONIC ESTERS FROM ALDEHYDES

The method of Knoevenagel (9) was used for these condensations.

Ethyl malonate (100 g., 0.62 mole), previously fractionated from anhydrous sodium sulphate, was mixed with 70 g. of freshly distilled benzaldehyde (0.66 mole) in a thick walled 200 ml. flask. Piperidine (2 g.) was added gradually at room temperature and allowed to stand for 2 days in a well corked condition. Then it was heated for 12 hours on a water bath. The condensation products were taken up in ether, washed with acid and water, dried over anhydrous sodium sulphate, and vacuum distilled. There was about 70% yield of benzylidene malonic ester boiling at 185-86 degrees at 11 mm.

(B) MALONIC ESTERS FROM KETONES

The method of Meyenberg (13) later modified by Cope and Hancock (5) was used.

A mixture of 100 g. of ethyl malonate (0.62 mole)

54 g. of acetone (0.93 mole), 80 g. of acetic anhydride (0.78 mole) and 12 g. of freshly fused zinc chloride were heated together under reflux at 110 degrees for 24 hours. The mixture was cooled and taken up in 80 ml. of benzene. The black solution was washed with four 50 ml. portions of water. The water washings were extracted with 10 ml. portions of benzene which were added to the main volume. The product was vacuum distilled and the ester came over at 60-125 degrees at 18 mm. On redistillation the ethyl isopropylidene malonate boils at 111-113 degrees at 9 mm.

This method was used in attempts to prepare substituted malonates from the following ketones.

- (i) Acetone (5), (13) -27.6 g. (22% yield) of mobile water-bright liquid B.P.110-117 degrees/14mm.
- (ii) Methyleneethyl ketone (6)-5.1 g.(5% yield) of pale yellow oil B.P.120-130 degrees/14mm., results from 60 hours heating of the reactants.
- (iii) Diethyl ketone- 7.5 g.(11% yield) of pale green mobile liquid B.P.103-107 degrees/20mm results from 50 hours heating of the reactants.

- (iv) Cyclohexanone- 35 g. (47% yield) of yellow-orange oil B.P. 152 degrees/14mm.
- (v) Acetophenone- 6 g. (7% yield) of green oil B.P. 167-170 degrees/16mm.
- (vi) Benzophenone- 10.7 g. (39% yield) of mobile water-bright liquid B.P. 170-72 degrees/16mm.
- (vii) Benzil- no reaction
- (viii) Fluorenone- no reaction

C) MALONIC ACIDS FROM ESTERS

Ethyl benzylidene malonate (25 g., 0.1 mole) was mixed with 100 ml. of 35 percent potassium hydroxide solution and boiled under reflux until solution was complete (about four hours). The solution was neutralized with hydrochloric acid and the white powder filtered off. After recrystallization from ether-petroleum ether it had a melting point of 198 degrees. Knoevenagel (9) reports the melting point as 195-96 degrees. The yield amounted to 46 g., a 24 percent yield.

The work was repeated using ethyl isopropylidene malonate. Prolonged boiling would not completely

dissolve the ester layer. The aqueous layer was separated and acidified. White needles were obtained melting about 112 degrees. Isopropylidene malonic acid melts at 170-71 degrees (13).

D) BARBITURATES FROM MALONIC ACIDS

Benzylidene malonic acid (4.2 g., 0.022 mole) and 1.2 g of urea (0.02 mole) were dissolved in 10 ml. of glacial acetic acid at 60-70 degrees. Acetic anhydride (5 g.) was dropped in over a period of one half hour at this temperature. The temperature was raised to 90 degrees and maintained for six hours. On cooling pink crystals melting at 215 degrees were obtained which on recrystallization melted at 218 degrees and proved to be monoacetylurea. Addition of water forced out the unreacted benzylidene malonic acid. No barbituric acid was formed.

E) BARBITURATES FROM ESTERS

Benzylidene malonic ester was used since it is easily prepared and the benzylidene barbituric

acid is known.

In a dry 250 ml. distilling flask with the thermometer bulb nearly touching the bottom of the flask, was placed 2.6 g. of sodium (0.11 mole) and 70 ml. of superdry ethanol added. After the sodium had dissolved, 12 g. of benzylidene malonate (0.05 mole) and 3.5 g. of dry urea (0.06 mole) were added. The mixture was heated to slowly distill the alcohol and the temperature gradually raised to 110 degrees where it was kept for four hours. Fifty ml. of hot water were added to dissolve the solid. Another 50 ml. of water containing 3.5 ml. of concentrated sulphuric acid were added. The solution fizzed a great deal and a red gum separated. The gum was dissolved in glacial acetic acid and precipitated with ethanol. A brown powder separates having a melting point of 225 degrees.

F) BARBITURATES FROM BARBITURIC ACID

In a 100 ml. 2-necked flask was placed 7.7 g. of barbituric acid (0.06 mole), 5.4 g. of acetone

(0.09 mole), 1.2 g. of freshly fused zinc chloride, and 50 ml. of acetic anhydride. The mixture was heated at 110 degrees for 24 hours. The solids dissolved and after a few hours a brown solid began to separate. At the end of the 24 hours period the mixture was cooled and filtered. The solid was dissolved in 5% sodium hydroxide solution, decolorized with animal charcoal, and reprecipitated with dilute hydrochloric acid. A fawn powder was obtained which melted at 296 degrees. This was dissolved in 25-fold volume of boiling water, decolorized and cooled. White plates of melting point 302 degrees were obtained.

Three other ketones, methylethyl, diethyl, and benzophenone were tried in a similar procedure. The results in every case were a white powder melting at 302 degrees.

A blank was run using all the reactants except the ketone. The brown powder obtained, on recrystallization from water melted at 302 degrees. Combustion analysis gave C.42.29%, H,3.40%.

G) PRODUCTION OF BARBITURIC ACID

In a 500 ml. 2-necked flask was placed 5.8 g. of sodium (0.25 mole). To this was added 125 ml. of "superdry" ethyl alcohol. When the reaction had ceased, 20 g. of ethyl malonate (0.125 mole) and 15 g. of dry urea (0.25 mole) in 70 ml. of superdry ethyl alcohol were added. The mixture was refluxed for 7 hours, during which time a white solid separated. At the end of this time 70 ml. of hot water were added and then concentrated hydrochloric acid to free the barbituric acid from its sodium salt. The filtered solution was chilled overnight and the white solid filtered and dried. It has a melting point of 243 degrees and amounts to 7.0 g., a 56% yield.

The method of Biltz and Wittek (2) was also used. Urea (6 g., 0.1 mole) and 12 g. of malonic acid (0.11 mole) were dissolved in 25 ml. of glacial acetic acid. The temperature was maintained at 60-70 degrees while 25 ml. of acetic anhydride were dropped in over a period of one half hour with frequent shaking. The temperature was raised to 90% and maintained for six hours. By cooling 7.5 g. of rose colored crystals

separated. A further 1 gram was obtained by evaporating the filtrate and triturating with water. It was recrystallized from a 25-fold volume of water using animal charcoal and had a melting point of 245 degrees. Yield was 66%.

S U M M A R Y

The following unsaturated malonic esters were produced from ketones by the Meyenberg method, those with references having been made before:

- 1) Isopropylidene malonate from acetone (5), (13) a water bright liquid B.P.110-117 degrees/14mm.
- 2) Methylpropylidene malonate from methylethyl ketone (6)-yellow oil B.P.120-130 degrees/14mm.
- 3) 1-Ethylpropylidene malonate from diethyl ketone-green mobile liquid B.P.103-107 degrees/20mm.
- 4) Δ' -Cyclohexenyl malonate from Cyclohexanone-yellow orange oil, B.P.152 degrees/14mm.
- 5) 1-Phenylethylidene malonate from acetophenone-green oil B.P.167-170 degrees/16mm.

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