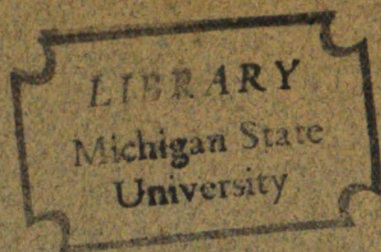


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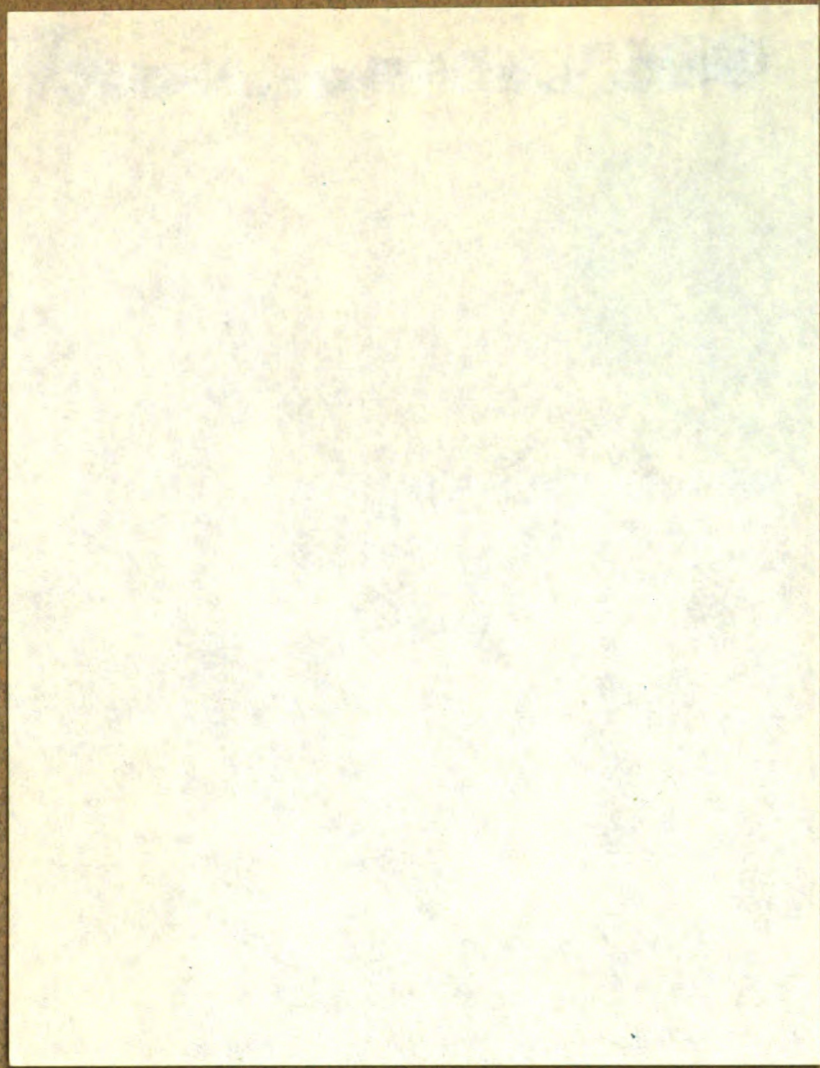
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SUPPLEMENTARY
MATERIAL
IN BACK OF BOOK

CONDENSATIONPRODUCTS OF ACETONE
AND SOME OF THEIR DERIVATIVES

CONDENSATION PRODUCTS OF ACETONE
AND SOME OF THEIR DERIVATIVES

by

Herbert Ernst Ungnade

Thesis

Submitted to the faculty of Michigan
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Master of Science.

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A C K N O W L E D G M E N T

The writer wishes to express his sincere appreciation to Dr. R.C. Huston and Dr. Otto Ungnade for the counsel and assistance given him in the completion of this work.

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Historical Data

Historical Data

The scope of this thesis is limited to a small group of condensation products of acetone which are obtained by the action of alkali. From the latter we want to consider mainly the primary compound diacetone alcohol and the two unsaturated homologs mesityloxide and isophorone.

Isophorone was first isolated by Fittig (Annalen, 110, 23, 1859) from the products of the alkaline condensation of acetone. Previous to Fittig acetone had been condensed by means of potassium and potassium hydroxide by Weidmann and Schweizer (Poggendorffs Annalen, 43, 48, 50, 265), and by Loewig and Weidmann (Journ. f. pract. Chem., 21, 54). In these earlier investigations the authors obtained mainly two products, a resin and an oil, named "xylitoel". The latter was recognized by Voelckel (Annalen 80, 306, 82, 63) as a mixture of substances. Voelckel and Schweizer both obtained xylitoil by the treatment of acetone with calcium oxide, and defined it as an oil boiling at 200-220° , with the composition $C_{12}H_{18}O$.

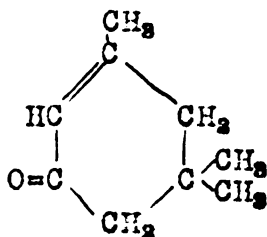
Fittig, working with calcium oxide as well as with sodium, proved in his reaction also the formation of mesityloxide and pinacone. For the substance boiling at 210-220° he found the correct composition $C_9H_{14}O$, he suspected it to be identical with campherphorone.

Liquid phorone was later isolated from the products of the reaction of zincalkyls with acetone, by Rieth and Beilstein (Annalen, 126, 245--1836) and by Pawlow (Annalen,

188.130--1877). Louise observed it in the condensation of acetone with aluminum chloride (Berichte, 15, 2732--1862). Freer obtained liquid phorone when he investigated the reaction of sodium upon acetone (Annalen 278, 130--1894), and Brecht finally proved that identical products are obtained whether sodium alcoholate or calcium oxide is used as a condensing agent. (Annalen, 239, 10--1896)

The name of isophorone was given to the liquid phorone $C_9H_{14}O$, which was obtained by condensation of acetone with sodium ethylate, by Kerp in his article "Zur Kenntniss des Kampherphorons, des Isophorons und des Mesityloxyds" (Annalen, 290, 127--1896). Kerp definitely proved that isophorone and campherphorone are two different substances by preparing reduction products, oxydation products and derivatives.

The constitution of isophorone was established by Knoevenagel (Annalen, 297, 185--1897) as trimethyl-1-3-3-cyclohexenone-5

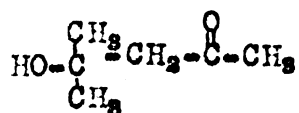


Knoevenagel synthesized isophorone by condensation of mesityloxyde and ethyl acetate with metallic sodium. This product was identical with Kerp's isophorone from acetone. However, while Kerp encountered considerable difficulties in the purification of his substance, Knoevenagel's syn-

thesis yielded almost a pure product. Kerp and Mueller, in a later article (Annalen, 299, 211, --1898), starting from acetone, purified their product by treating the mixture with sodium bisulphite which combines more readily with mesityloxide than with isophorone. Other investigators isolated the isophorone from its oxime.

A good yield of isophorone is obtained by treating acetone with sodium amide (Hoechst Farbwerke, D.R.P. 134,982, C. 1902 II, 1164), the biproducts in this case are mesityloxide, and xylitone, in presence of benzene the products are mesityloxide, phorone and isophorone.

Diacetone alcohol, the primary product in all alkaline condensations of acetone, was discovered in 1873 by Heintz as an impurity in commercial acetone of unknown source (Annalen, 169, 114). Shortly later Heintz synthesized diacetone alcohol from diacetone amine (Annalen 178, 342--1875). The oxalic acid salt of diacetone amine was dissolved in water and the solution treated with potassium nitrite. This reaction gave a better yield, enabling Heintz to establish the structure of diacetone alcohol, which was found to be 4-methyl-4-hydroxy-pentanone-2



The compound was identical with the substance found previously in the acetone.

Emmerling, prior to the work of Heintz, claimed to

have discovered diacetone alcohol (Berichte, 6, 24--1873). His substance was obtained from the treatment of bromacetone with silveroxide. The author found that he could not separate the two substances obtained after steamdistillation of the mixture. He states however that the aqueous solution tastes sweet, and reduced Fehling solution, which latter properties he attributed to diacetone alcohol. As a matter of fact, diacetone alcohol does not taste sweet and, according to later research, has only very slight reducing properties, for which reasons the work of Emmerling is rather doubtful.

The condensation mechanism, and the equilibrium existing between acetone and diacetone alcohol was studied by Koelichen (Zeitschrift f. Phys. Chem. 33, 129--1900). The latter prepared diacetone alcohol by allowing acetone to react with alkali solutions for certain periods of time, then removing the alkali by passing in CO₂ gas, and distilling. Distillation in the presence of alkali must be avoided because it leads to the formation of mesityloxide.

Koelichen found that the condensation of acetone and the decomposition of the formed alcohol are reversible reactions which lead to an equilibrium between the two substances.



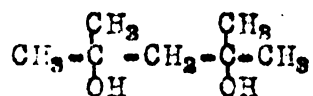
Both reactions are catalysed by OH ions. The equilibrium between acetone and the alcohol can be expressed by

the following formula, provided that the solutions are not too concentrated.

$$\frac{C(\text{diacetone alcohol})}{C^2(\text{acetone})} = K$$

The summary of the experimental data of formation and decomposition of diacetone alcohol by means of alkali gives direct proof for the law of the independance of a chemical reaction from the quantity of the catalyst. The equilibrium is greatly dependant upon the temperature, diacetone alcohol being favoured at lower temperatures. The speed of reaction is in either direction a function of the concentration of the hydroxyl ions. Deviations in the case of weak bases can be traced to secondary reactions.

Joseph Lemaire (Recueil des trav. chim., 29, 69, Chem. Zentralblatt, 1909, I, 1982) obtained diacetone alcohol and mesityloxide by treating beta-oxy-isovaleric acid nitrile with magnesium methyl bromide, he quotes however that diacetone alcohol is easier to prepare by the method of Heintz. When diacetone alcohol was allowed to react with magnesium methyl bromide, it was converted to 2-4-dimethyl-pentandiol-2-4



The preparation of diacetone alcohol from acetone by the action of alkali was first described by Koelichen, and modified by Kuester and Heberlein (Zeitschrift f. An. Chem., 43, 67--1905). The method consists in treating acetone with

solid alkali and not enough water to dissolve all the alkali, shaking for two days, allowing to stand for two days in a freezing mixture, removing the alkali by CO_2 , and finally distilling the mixture of acetone and diacetone alcohol.

A more efficient method is described by Hoffman (Journ. Am. Chem. Soc. 31, 723--1909). A round-bottomed flask is connected with a soxhlet extractor, and the latter with a reflux condenser in such a way that the condensed acetone flows continuously through the extractor back into the flask. The thimble of the extractor is filled with calcium oxide, and the acetone brought to boil. Since the condensation products of acetone boil considerably higher than acetone itself, their vapors are thus prevented from coming in contact with the condensing agent, while the acetone circulates until most of it is converted. The product in this case is almost entirely mesityloxide, with a trace of higher condensation products and a trace of diacetone alcohol.

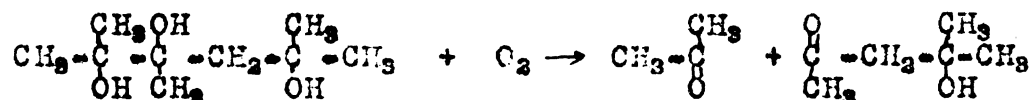
Since the earlier work had shown that alkali hydroxides form diacetone alcohol, the next experiments were carried out with calcium hydroxide in the thimble. The product in this case was diacetone alcohol with some unchanged acetone.

To prove that diacetone alcohol was the primary product, chemically pure, dry calcium oxide was heated in a sealed tube with pure, dry acetone. While there was no reaction in the first case, a trace of calcium hydroxide caused a thick

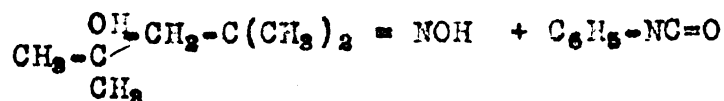
syrup of condensation products to be formed. Thus Hoffman definitely proved that diacetone alcohol is the primary condensation product of acetone upon treatment of the latter with alkali.

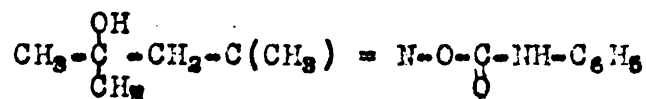
Heintz's method of preparation of diacetone alcohol from diacetone amine was slightly improved by Zelinsky and Zelikow (B. 34, 2857--1901).

Diacetone alcohol can be obtained by careful oxidation of 2-3-5-trimethyl-hexanetriol-2-3-5 with chromic oxide in acetic acid solution. (Bouveault and Locquin, Annales de chimie (8) 21, 415--1910)

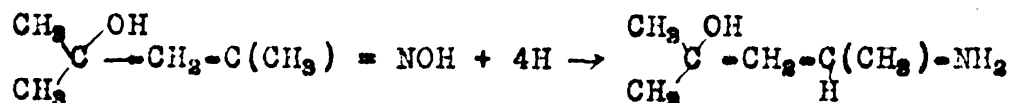


Diacetone alcohol is also formed in small amounts by the action of sodium acetylene upon acetone, along with 3-methylbutinol, mesityloxide, isophorone and isophorone acetylene. (Hess and Munderloh, B. 51, 382--1918), by the action of magnesium amalgam on acetone in the presence of waterfree ether or benzene (Bouveault and Locquin), and by the reduction of benzoylacetone with sodium and alcohol (Bauer, Comptes rendus 145, 1093--1907). Bauer proved the diacetone alcohol by converting it into the oxime which reacted with phenylisocyanate to give a carbanilide oxime $\text{C}_{13}\text{H}_{18}\text{O}_3\text{N}_2 + \text{H}_2\text{O}$, which melts at $104 - 105^\circ\text{C}$.





The oxime of diacetone alcohol was first prepared by Kohn and Lindauer (Monatshefte f. Chemie, 23, 755--1902) The oxime, 2-methyl-pentanol-2-oxime-4 was found to melt at 57.5-58.5°. Upon reduction it yielded beta-oxy-isohexyl-amine.

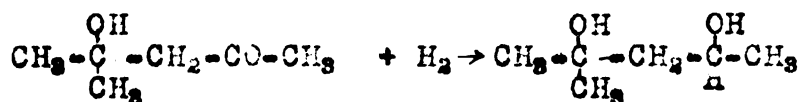


Kyriakides improved the preparation of diacetone alcohol of Hoffman by using barium hydroxide instead calcium hydroxide, a small amount of tartaric acid was added to the acetone in order to neutralize any barium hydroxide which might be carried down (Am. Chem. Soc. 36, 534--1915) -Hoffmans process is protected by D.R.P. 229,678. The patent is referred to in C. 1911, I, 275)

A new separation of diacetone alcohol is covered by the British patent 402,788 of Ernest E. Conolly (1933). The inventor claims the addition of water (about 10%) to the mixture, subsequent distillation of the mixture under atmospheric pressure, and final distillation under vacuum.

A modification of the Koelichen method of preparation of the alcohol was used by Oestling (Soc. 101, 469--1912). The reaction mixture was kept cold (in an ice chest) causing the alkali to solidify. The acetone solution was poured off, neutralized, the acetone distilled off, and poured

back on the solid mass. The alcohol thus obtained was reduced with 3 % sodium amalgam to give 2-methyl-pentandiol-2-4. This same reduction product was also obtained by Zelinsky and Zelikow (B. 34,2858--1901).



The patents of the French Société des Destilleries des deux Sèvres, Henri Guinot inventor, claim the preparation of diacetone alcohol by the action of alkali in alcohol solution (several patents). Other patents require a certain pH for this reaction.

Properties of Diacetone Alcohol.

Diacetone alcohol is a colorless and almost odorless liquid.

Bp = 163.5-164.5° Bp₃₅ = 77-80° Bp₁₁ = 63-64°

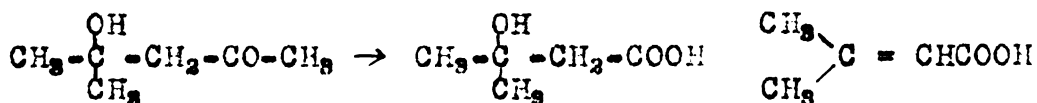
Bp₁₇ = 75-80° (different investigators)

D₂₀ = 0.9555 D₂₅ = 0.9306

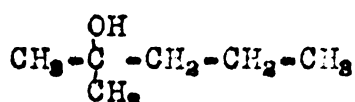
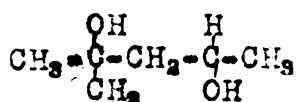
It is miscible in all proportions with water, alcohol, and ether. It decomposes slightly upon boiling under atmospheric pressure. From the aqueous solution it is separated by means of KOH, NaOH or K₂CO₃. With alkali it is partially split into acetone, the reaction being reversible. When heated with a little alkali hydroxide solution or alkali carbonate, it decomposes even below 100° into acetone.

Diacetone alcohol is oxidized by NaOBr to give beta-oxy-valeric acid (Kohn, M. 24,767--1903). The latter acid, being a beta hydroxy acid, splits off water with the formation of

beta-dimethyl-acrylic acid according to the following equation:



The electroreduction of diacetone alcohol was carried out by R.R. Read and F.A. Fletcher (trans. Am. Electrochem. Soc. 47,--1925). Their investigations show that efficient reduction takes place when the alcohol is reduced with lead electrodes ⁱⁿ dilute sulfuric acid at a low current density. The products of such reduction are 2-methyl-pentandiol-2-4 and 2-methyl-pentanol-2

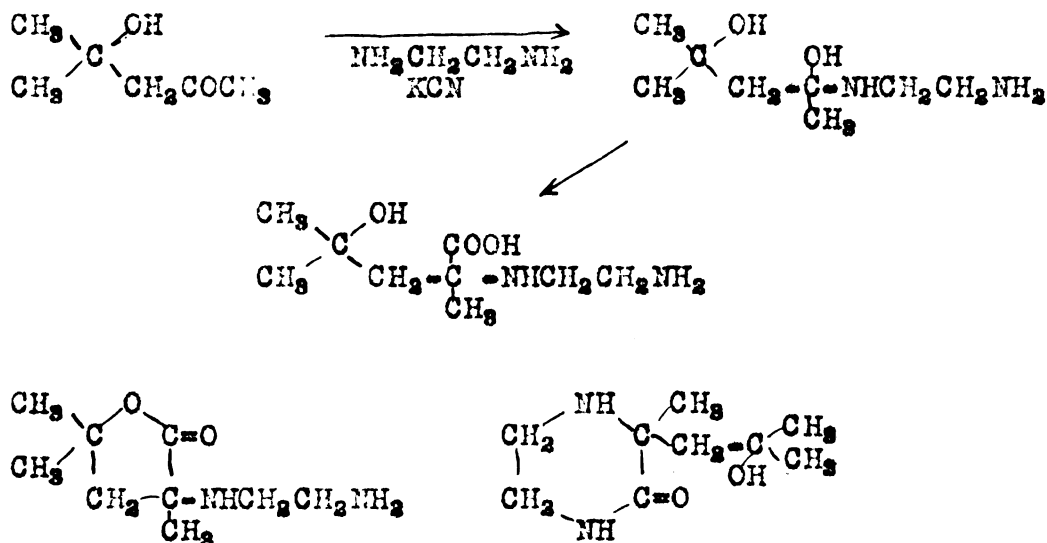


The work of Bacon and Freer (Am. Chem. Journ. 38/374--1907) shows that diacetone alcohol may be partially reconver-
ted into acetone by the action of sodium, which is due to the primary formation of sodium hydroxide by dehydration of the alcohol. In an atmosphere of nitrogen a yellow sodium salt could be isolated, in both cases, however, the bulk of the products consisted of condensation products.

Upon dissolving in concentrated sulfuric acid diacetone-alcohol decomposes into water and mesityloxide (Heimtz). This same reaction is brought about by small amounts of concentrated or even 20 % sulfuric acid, phosphorus pentoxide, zinc chloride, or iodine, on heating. (Ref. Kohn, D. R. P.

208,635 , C. 1909,I,1282,Hibbert,Am.Soc. 37,1755--1915).

Treatment of diacetone alcohol with one mole each of the following, ethylene diamine hydrochloride, KCN and KOH at 60° and following concentration with fuming hydrochloric acid, gives the anhydride of the compound $(CH_3)_2C(OH)CH_2C(CH_3)(COOH)NHCH_2CH_2NH_2$. (Kohn and Osterseizer M. 34,783--1893). The authors did not decide for either one of the two more probable structures.

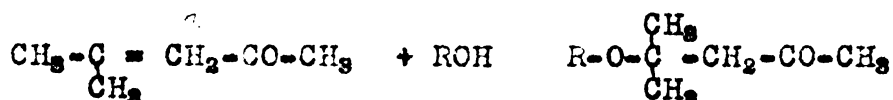


The reducing power of diacetone alcohol, glycols and a number of similar compounds was studied quantitatively by Mylius and Schoorl (R. 36,360--1917,C. 1916,II,396) A series of common reagents was used, and the amount of reduction determined by iodometric titration. Diacetone alcohol had the smallest reducing power from all substances tested, and from all reagents tested only Fehling solution was reduced. The experiments were carried out in order to find the

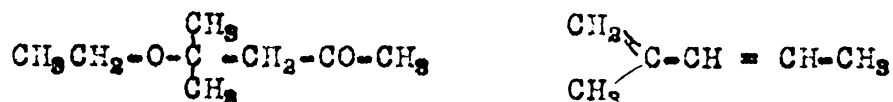
groups responsible for the reducing power of sugars.

Goesta Åkerloef studied the velocity of the decomposition of diacetone alcohol in a number of different salt solutions. He concludes that the velocity of a catalysed reaction in acid-salt solution and in alkaline solution is always a function of the activity of the ion catalysing the reaction. The velocity curves plotted for the different salt solutions are nearly all of the same form, independantly of the nature of the anion of the salt.

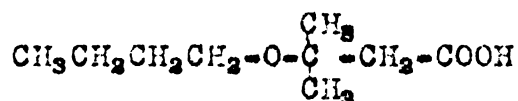
The ethers of diacetone alcohol were discovered by Alfred Hoffman in 1927 (J. Am. Chem. Soc. 49, 530). They were exceptionally prepared by the action of the corresponding alcohol upon mesityloxide.



The mixture of the alcohol and mesityloxide was allowed to stand with sulfuric acid for ten days, the yield being 20-25 %. In this way the methyl, ethyl, propyl, butyl, isobutyl, isoamyl and benzyl ethers were prepared. The oxime was prepared from the ethyl ether, and the semicarbazone from all ethers. Upon reduction with sodium in alcohol containing boric acid the ethyl ether gave 4-ethoxy-4-methyl-pentan-2-ol, which gave 4-methyl-2-pentadiene with sulfuric acid.



Oxidation of the butylether with sodium hypobromide gives beta-butoxy-isovaleric acid



According to U.S. Patent 1,823,704 (1923) the ethers of diacetone alcohol can also be prepared by the action of alkali on a mixture of mesityloxide and the corresponding alcohol.

D.R.P. 246,967 (Doerfflinger C.1912,I,--1928) protects the use of diacetone alcohol as a solvent for acetyl-cellulose. It is also used as a solvent for-nitro cellulose.

Peter Maitland and Atanley Tucker condensed fluorene with acetone and alkali, and obtained $\text{C}_{19}\text{H}_{20}\text{O}$. On the basis of this experiment they condensed diacetone alcohol with 9-fluorenyl-magnesium-bromide. The following compounds were isolated: fluorene, difluorenyl, $\text{C}_{19}\text{H}_{18}$, 9-iso-propylidene-fluorene, alpha-9-fluorenyl-alpha, gamma, gamma, trimethyl-trimethylene glycol.

Definition of Problem

Definition of Problem

The present problem was the isolation and identification of a mixture of high-boiling compounds obtained along with the unsaponifiable fraction of vegetable oils. The oils, such as cotton-seed oil were saponified with alcoholic KOH in the presence of an equal amount of acetone by refluxing for three hours.

Another method to obtain the unsaponifiable matter consisted in saponifying the oil with alcoholic potassium hydroxide, removal of the alcohol, and extracting the soap with acetone.

In both cases a high-boiling fraction remained after evaporation of the solvent, which could be separated from the unsaponifiable matter by distillation under vacuum.

Extracting the soap with acetone by the soxhlet principle resulted in the formation of diacetone alcohol. This reaction can be explained by the catalytic effect of the free alkali in the soap.

Saponification in the presence of hot acetone results in the formation of a mixture of compounds. The extraction of the unsaponifiable matter in this case being more complete, the obtained mixture may contain volatile substances which are known to occur in the unsaponifiable fraction. Substances of that kind are ketones, and their isolation would meet difficulties since the acetone condensation-products which are also formed in this case are also ketones.

The simplest way for the separation seemed to be the fractional distillation although earlier research on this field shows that such separation is extremely difficult and unsatisfactory.

This separation was successfully accomplished. However, there was no indication of ketones originating in the unsaponifiable matter.

Among the products was diacetone alcohol. Upon experimenting with it, the acetyléster was discovered by chance. Research in this direction showed that other esters could be prepared. The second part of this thesis deals with the esters and their derivatives.

Experimental Data.

I. Separation and identification of mesityloxide, diacetone alcohol and isophorone.

The mixture of compounds obtained along with the unsaponifiable matter of vegetable oils by saponification with alcoholic KOH in the presence of acetone constitutes an amber colored oil of peppermint-like odor. When distilled, even under vacuum, it darkens indicating oxidation. It dissolves rubber, thus making the distillation still more difficult. Only in the presence of inert gases can the mixture be heated without decomposition.

To meet all these requirements the distilling apparatus for its separation must contain no rubber stoppers on places where they may come in contact with the vapors. It must be free from leaks to prevent air from oxidizing the substance, and it must separate with a high efficiency. Furthermore it must have devices to introduce inert gas into the apparatus, free from air and impurities.

Experiments in this line showed that all-glass connections are advisable to maintain a good vacuum. A distilling-column according to Podbialniak is the most efficient, its height and diameter can be found by experiment and analogy.

Difficulties were encountered only in the introduction of the inert gas. When the vacuum inside the apparatus is allowed to draw the gas from the tank by suction, there is always a danger of air coming in, because valves and connections cannot be made entirely leak-proof. Therefore the gas

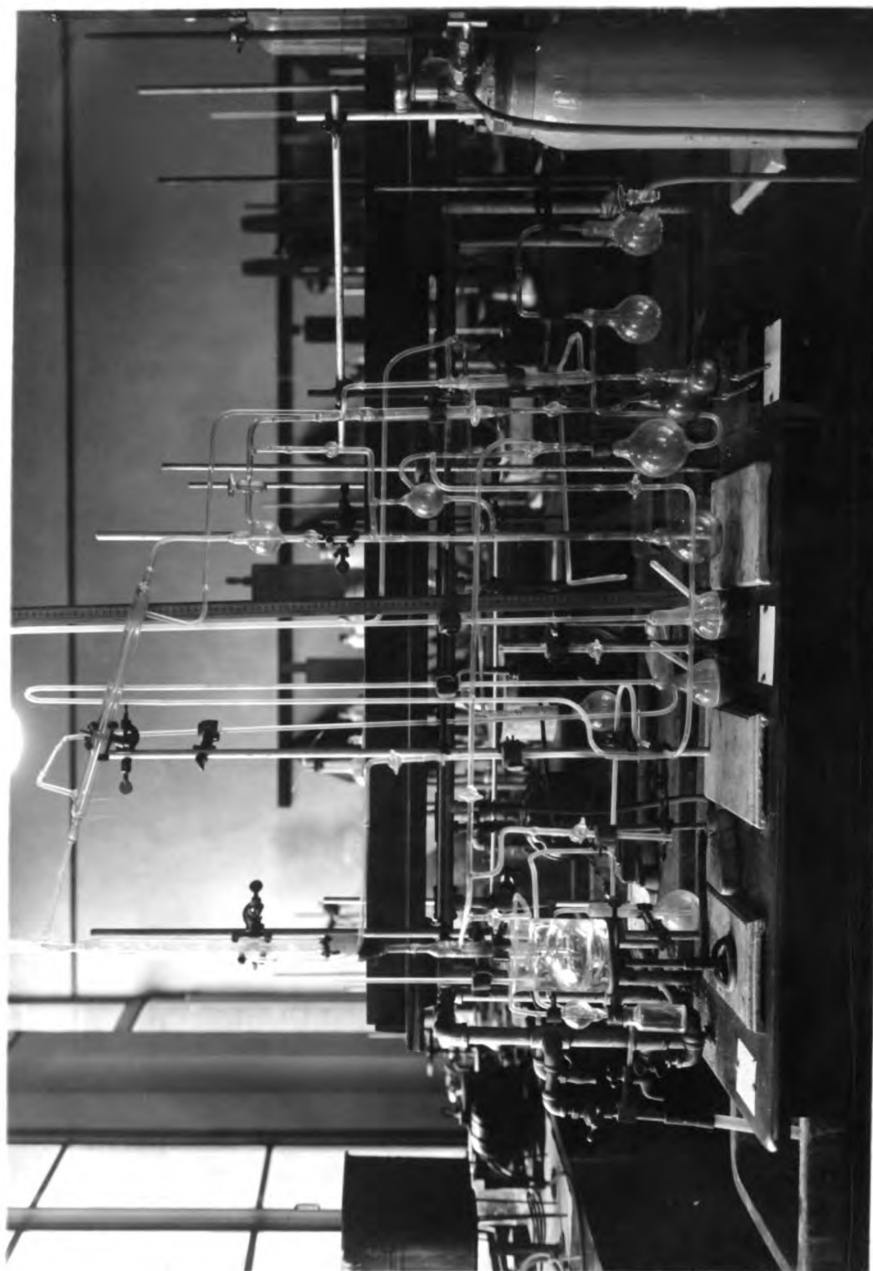
was filled directly from the tank through a membrane reducing valve into a container, which was first swept several times with the gas, under a suitable pressure. From this container the gas could be drawn without danger of contamination by air, the only precaution necessary being to keep the container under pressure, which can easily be observed on a double gauge (see blue print).

For continuous distillation a fractionating device was built in, which allows the withdrawal of fractions during the distillation. The substances are introduced and the residues are emptied by vacuum since the distilling flask is not removable.

The inert gas is introduced through a capillary into the boiling flask, heated in an oil bath. Another line enters the fractionating device to allow removal of the fractions under inert gas. The gas is first washed by sulfuric acid or another appropriate absorbant.

It was found difficult to trap all the vapors, especially with low-boiling substances, therefore a special condenser was inserted in behind the fractionating part. The water-cooled trap delivers its condensate to a bulb. A stopcock allows to shut off the bulb, when the low-boiling substances are all removed, because its content, having a high vapor pressure would otherwise lower the vacuum.

To read the temperature an Anschuetz thermometer is suspended from a ground stopper on a platinum wire.



Distilling Apparatus
(later modifications are given in the blue-print)

A photograph of the apparatus in the experimental stage is shown on page 13. The drawing of the apparatus after completion is attached in the back.

The distilling column offered another problem because the inner and outer jackets have different temperatures , and due to the different expansion , crack at the joints. To eliminate this trouble an elastic seal was used, which was first applied by Helmut Gootemoot (M.S.C.), consisting of asbestos, liquid rubber and De Kotansky cement.

Directions for the use of the distilling apparatus (referred to the blue-print)

To introduce the sample close 2,4,8,10 and open 14,9 and 12. Start pump 1. Draw the sample through 3. Then slowly heat the oil bath in which the distilling flask C is immersed. Open 5, close 1,6 and 7, and start pump 2.

Close 13, open 7 and 11. Through 13 flood with nitrogen, evacuate again, and keep the reservoir Q under a pressure of about 200 mm of mercury. Adjust 4 so that a slow but steady stream of gas enters the distilling flask, through the capillary. Open 8 and 10 and close 9. Then the cooling water is turned on, and the beaker T may be filled with ice.

According to the material handled the flasks M and N may be filled with some washing liquid, to remove impurities from the inert gas.

J is only an expansion flask, A and O are traps to prevent oil from sucking back into the apparatus.

P is a manometer and vacuum gauge for the gas system.

When the apparatus is in operation the temperature of the oil bath is slowly raised, in such a way that the difference in temperature between the oil bath and the distilling column is not more than 20°.

To remove a fraction, stopcocks 8 and 10 are closed, 9 is opened and the pressure is equalized by opening 11 slowly. Inert gas is then added through 13 to maintain the pressure. When atmospheric pressure is reached, 11 and 13 are closed, and the receiver is taken off. During this procedure the distillate collects in G, a new receiver is attached, and evacuated by opening 7 while 5 is closed. When equal pressure is reached 7 is closed, 8 and 10 are opened, and 9 is closed.

When the last fraction is to be removed, the flame is taken off, 14 is closed, and the pressure equalized through 11. The residue is removed by opening 1 and then 2. Through 7, 11 and 1 the flask B can also be filled with inert gas.

R and S are the manometer bulbs, filled with mercury, the pressure is read by means of adjustable scales. The pumps used are Cenco Hyvac pumps, which produce in the described apparatus a vacuum better than 1 mm. The glass used was pyrex.

Vacuum fractionation of the mixture.

After two distillations the mixture could be separated into three main fractions;

	n_{20}°
1. 22-30° / 1mm	1.4418
2. 30-40° / 1mm	1.4290
3. 50-60° / 1mm	1.4630

Fraction 1 is a volatile compound of strong, honey-like odor. It was converted into the oxime which was identical with mesityloxime (preparations and constants see later). Therefore fraction 1 consists largely of mesityloxide. The fraction was accordingly distilled under atmospheric pressure, and gave in one distillation pure mesityloxide, boiling at 123-129° (atm. pressure) $Bp_2 = 22-22.5^{\circ}$

$$n_D^{20} = 1.4439$$

Fraction 2 was found to be water-soluble, and was therefore suspected to be diacetone alcohol, the odor indicated mesityloxide as an impurity. The liquid was diluted with one fourth of its volume of water, and then distilled under vacuum. Mesityloxide and water come over first, and finally the pure diacetone alcohol was obtained boiling at 36-37°/1mm

$$n_D^{20} = 1.4240$$

The last fraction was examined by treating a small fraction with semicarbazide hydrochloride and sodium acetate. The product upon recrystallization was found to be a pure substance and not a mixture. M.P. 193-194°. Hence the third

fraction must be considered as one substance with small amounts of impurities present. Fraction 3 was then redistilled under high vacuum until a constant boiling fraction was obtained, boiling at 55-56° / 1mm. This substance, a yellow oil of agreeable odor, was analysed as follows:

$$D_{19.5}^{19.5} = 0.9136$$

$$\text{B.P.} = 200-201^{\circ}$$

$$n^{20} = 1.4800$$

Elementary analysis

	Carbon	Hydrogen
found	77.56%	10.34%
found	77.61%	10.31%
calculated for $\text{C}_9\text{H}_{14}\text{O}$	78.26%	10.14%

Molecular weight by boiling point elevation

found	151.0	146.1
calculated for $\text{C}_9\text{H}_{14}\text{O}$	138.1	

Qualitative tests indicated that the substance was unsaturated. It added rapidly bromine. The bromide however was very unstable. - Analysis of the bromide

found	44.47 %	44.01 %
calculated for $\text{C}_9\text{H}_{14}\text{OBr}_2$	53.66 %	

Addition of bromine corresponding to two and more equivalents caused decomposition of the substance, hydrogen bromide being given off. Analysis of the resulting compounds revealed even lower bromine content of the residues.

It is obvious therefore that bromine added in excess of one molecular equivalent does not add, but decomposes the compound. The bromide obtained is so unstable that it decomposes when in contact with the air only for a short time. This accounts for the low values obtained by the parr bomb determination. The result seems to indicate that the compound had only one double bond, which allows the conclusion that the compound contains one ring.

Comparison with Beilstein revealed that the compound was isophorone, corresponding with its properties in all details.

II. Diacetone Alcohol.

1. Preparation.

In a two liter round bottomed flask are placed 1500 cc of commercial acetone with a few boiling chips. The flask is fitted with a rubber stopper carrying a soxhlet extractor. Two paper thimbles are placed in the extractor, one above the other. The lower one is filled nearly full, the top one is filled three quarter full of barium hydroxide, and the remainder of the space is filled with glass wool.

The flask is heated on a steam bath or in an oil bath. The heat is so regulated that the acetone refluxes back into the extractor rather rapidly. As the reaction proceeds the temperature in the bath has to be raised. After 95-100 hours the reaction is finished. The crude diacetone alcohol is distilled first under atmospheric pressure until all the acetone is removed, the temperature on top of the column being 70° when the process is complete. The residual liquid is transferred to a Claisen flask and distilled under reduced pressure. Yield 850 g.

Ref. Kyriakides, J. Am. Chem. Soc. 36, 534.

The pure diacetone alcohol is collected at 60 to 63° / 6 mm. The refractive index of this product is

$$n_D^{20} = 1.4240$$

The diacetone alcohol thus obtained was used for all of the following experiments.

According to the literature, diacetone alcohol can

be dehydrated by means of small amounts of sulfuric acid, iodine, phosphorus pentoxide or zinc chloride at high temperatures.

It was interesting to see whether also HCl gas would give that dehydrating reaction. One hundred grams of diacetone alcohol were placed in a round-bottomed flask, immersed in an ice bath. Hydrochloric acid gas, dried over sulfuric acid, was passed into the cooled alcohol. The reaction mixture turned yellow, and the color deepened as the reaction proceeded. The deep red solution still absorbed HCl gas with liberation of heat. After the rate of absorption decreased the flask was removed, and allowed to stand for 24 hours. Then the mixture was poured into ice water and washed thoroughly. The raw oil was neutralized with carbonate solution and finally with some lead carbonate to remove the last traces of acid. Then it was dried over night and distilled. The reaction produced almost a quantitative yield of mesityloxide. The yield of pure product was 80 % and better.

Constants of the mesityloxide obtained:

	found	literature
Boiling point	Bp ₇₄₃ = 126-127	129-130 (corr.)
Density	D ₂₅ ²⁵ = 0.8560	D ₂₅ ²⁵ = 0.8548
Refractive index	n _D ²⁰ = 1.4433	n _D ²⁰ = 1.4439

In order to prove the identity of the mesityloxide it was converted to the oxime as follows:

One hundred grams of mesityloxide were dissolved in one liter of alcohol, and to this solution was added a solution of 70 g hydroxylamine hydrochloride, in the smallest possible amount of water. The solution was made alkaline by adding solid crystalline sodium carbonate in small portions to avoid increase in temperature. After 5-8 days the alcohol was removed by distilling from the water bath, and the separated oil was washed with twice its volume of water, extracted with ether and fractionated.

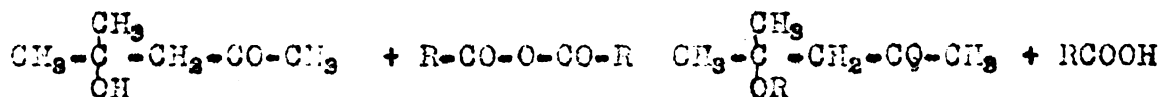
The oil obtained agreed in all properties with the data given in the literature. (Harries, *Annalen* 330, 192).

Mesityloxime, 2-methyl-pentene-2-oxime-4.

	found	literature
Boiling point	183-190°(dec.)	180-190°(dec.)
Bp ₂₅	100°C	
Density	$D_{25}^{25} = 0.9443$	$D_4^{21} = 0.9417$
Refractive index	$n_D^{21} = 1.4910$	$n_D^{21} = 1.4908$

A qualitative test showed that diacetone alcohol can also be dehydrated by the action of acetic anhydride. In a quantitative study of this reaction it was found that there was a high boiling fraction although all unreacted diacetone alcohol had been removed by washing. This latter fraction had a definite boiling point and properties different from those of either mesityloxide or diacetone alcohol. The qualitative analysis showed that the compound must be an ester since it

hydrolysed in the presence of aqueous alkali. The saponification number proved it to be an ester of diacetone alcohol. The general reaction for this esterification, which was found to take place also with other fatty acid anhydrides, is as follows:



The mesityloxide obtained as main product in this reaction is a rather pure product and does not darken in contrast with the product obtained by other dehydrating agents.

Esters of Diacetone Alcohol.

1. Preparation.

The acetyléster of diacetone alcohol can be prepared by the action of acetic anhydride ^{or acetic acid} on diacetone alcohol.

I. Acetic acid.

Two hundred and thirty-two grams of diacetone alcohol freshly distilled and water-free, are mixed with 120 g of glacial acetic acid. Boiling chips are added, and the mixture is refluxed for three hours. Then the liquid is allowed to cool to room temperature. The cold substance is poured into an equal volume of ice water and shaken thoroughly, in a separatory funnel, whereby unreacted diacetone alcohol and acetic acid are removed.

Both the water-layer and the oily layer are then neutralized against litmus with sodium carbonate or better bicarbonate solution. The oily layers are combined, and washed

again with water. The neutral oil at this stage is around 170 g, it is amber colored, the odor being mainly that of mesityloxide. With a 300-400 mm fractionating column or modified Claisen flask the latter compound can be removed almost quantitatively. Pure mesityloxide comes over at 20-40° at 2-5 mm, a small amount of a mixture distills at 40-50° at 5 mm, and the pure ester is obtained at 60-62° / 5 mm.

The yield of 12 g can be slightly increased by increasing the time of heating.

When 164 g of anhydrous sodium acetate is added to the mixture of 252 g diacetone alcohol and 120 g acetic acid, and then refluxed, and treated in the same manner as above, only 60 -65 g of the crude oil are obtained which yield 50-55 g of mesityloxide and 10 g of the acetate.

II. Acetic anhydride.

The best method for the preparation of the new acetyléster is the acetylation by means of acetic anhydride.

Four hundred and sixty-four grams of diacetone alcohol are mixed with 204 g of acetic anhydride in a three liter round-bottomed flask. Boiling stones are added, and the mixture refluxed for three hours, cooled to room temperature, neutralized, separated and dried as directed as above.

Around 350 g of crude oil are obtained in this manner and yield upon distillation about 270 g of mesityloxide and 30 g of the ester.

Properties of the ester.

The acetyléster of diacetone alcohol is a colorless liquid with slight but agreeable odor. It is insoluble in water, soluble in ether, benzene and acetone. It boils at $171-173^{\circ}$ / 742 mm. $Bp_5 = 60-62^{\circ}$ $Bp_{10} = 72-73^{\circ}$ At atmospheric pressure the compound boils with only a small amount of decomposition.

Density: $D_{25}^{25} = 0.9811$

Refractive index: $n_D^{20} = 1.4239$

The saponification number gives the following results:

percent acetic acid	found	37.82 - 38.07 %
calculated for $C_8H_{14}O_3$		37.97 %

The ester reacts with phenylhydrazine and semicarbazide.

Preparation of the semicarbazone:

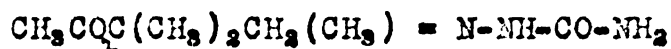
Dissolve one part of semicarbazide hydrochloride in the smallest possible amount of distilled water. Then add one part of the ester. To bring about the reaction, add slowly, with stirring a saturated alcoholic solution of potassium ^{acetate} ~~carbonate~~ until a homogeneous solution results. The semicarbazone crystallizes in a short time in bundles of needles. If potassium chloride should crystallize out, it is necessary to filter.

The semicarbazone crystallizes in colorless needles melting at $137.5-138^{\circ}C$. It is insoluble in water but soluble in alcohol. A 50 % alcoholic solution is used for its recrystallization.

Nitrogen in the semicarbazone:

found	calculated for $C_9H_{17}O_3N_3$
19.49 %	19.53 %
19.33 %	

giving it the structure:



The acetyleser of diacetone alcohol undergoes Claisen condensation by treatment with sodium. This reaction will be discussed later in detail.

Yields of the acetyleser of diacetone alcohol obtained by different acetylating agents.

1. Glacial acetic acid

diacetone alcohol used	Yield ing	Yield in % of the theory
232 g acetate	12 g	3.7 %
mesityloxide	158 g	73.7 %

2. Glacial acetic acid plus sodium acetate

diacetone alcohol used	Yield ing	Yield in % of the theory
232 g acetate	10 g	3.1 %
mesityloxide	52 g	24.3 %

3. Acetic anhydride

diacetone alcohol used	Yield in g	Yield in % of the theory
464 g acetate	90 g	14.2 %
mesityloxide	300 g	70.1 %

Influence of mesityloxiide on the esterification

When a small amount of mesityloxiide is present in the diacetone alcohol used for the preparation of the ester, the resulting ester shows some difference in its properties. There is for instance a marked difference in the reactivity toward sodium. While the product obtained from pure diacetone alcohol reacts vigorously with freshly cleaned, metallic sodium, the ester obtained from impure alcohol does not react in the cold. Only when heated, a small amount of hydrogen is generated, and the pieces of sodium are soon covered with a reaction product which prevents it from further reaction. Obviously the ester is impure, although it does not change properties upon distillation.

In order to investigate the effect of mesityloxiide one tenth of a mole of mesityloxiide was added to the reaction-mixture as follows:

Two hundred and thirty-two grams of diacetone alcohol are mixed with 204 g of acetic anhydride and 20 g mesityloxiide. The mixture was refluxed for six hours and treated as previously described.

The same experiment was repeated using an initial quantity of one molecular equivalent of mesityloxiide.

Two hundred and thirty-two grams of diacetone alcohol are mixed with 102 g acetic anhydride and 196 g of mesityloxiide. The mixture was again refluxed and treated like the above.

Results:

Time of heating	3 hrs	6 hrs	6 hrs
Mesityloxiide (initial)	none	19.6 g	196 g
Yield of the ester	90 g	93 g	27 g
n_{20}^D	1.4229	1.4232-1.4246	1.4253
percent acetic acid	37.8 %	34.60 %	---- (not determined)

The results indicate that mesityloxiide enters the reaction, forming a compound which has a boiling point close to that of the ester. In another experiment mesityloxiide was allowed to react with one molecular equivalent of acetic anhydride. The product was a mixture of compounds which were obtained in small yield. The following fraction were distilled off:

	n_{20}^D
1. 30-35° / 10 mm	1.4430
2. 35-45° / 10 mm	1.4465
3. 45-57° / 10 mm	1.4542
4. 55-60° / 10 mm	1.4482

The three last fractions constitute the wanted compound (or mixture), however the yield is so small that the identity could not be established. Possibly the mixture contains acetylmesityloxiide, which was prepared by Fittig (Berichte, 22, 1013) by the action of sodium on a mixture of mesityloxiide and ethyl acetate.

Diacetone alcohol propionyl ester.

The propionyl ester of diacetone alcohol is obtained

analogous to the acetyléster from the alcohol and propionic anhydride.

Four hundred sixty-four grams of diacetone alcohol are mixed with 260 g of propionic anhydride, and the mixture is refluxed for 10 hours. After cooling to room temperature the solution is poured into an equal volume of ice-water, neutralized with sodium bicarbonate, and dried over calcium chloride.

The propionylester, $C_9H_{16}O_3$ boils at $182-184^\circ / 742 \text{ mm.}$
 $Bp_s = 80-81^\circ$

Density	$D_{25}^{25} = 0.9680$
Refractive index	$n_D^{20} = 1.4256$
Percent propionic acid	found 42.99-43.20 %
	calc. 42.99 %

Diacetone propionic ester reacts with semicarbazide analogous to the acetyl ester. The semicarbazone is however much more difficult to prepare. The recrystallized compound melts at $144.51-145^\circ$. It crystallizes in plates from alcohol (95%) and in needles from 50 % alcohol.

Nitrogen	found	18.52 %	calculated for $C_{10}H_{18}O_3N_2$
		18.40 %	18.34 %

The butyryl ester of diacetone alcohol is obtained in the same way as the above from diacetone alcohol and butyric anhydride.

Four hundred sixty-four grams of diacetone alcohol and

three hundred sixteen grams of butyric anhydride yield 250 g crude oil ,from which a 90 g yield of the ester can be obtained.

The propionylester and butyrylester both are more difficult to prepare than the acetylester,because the sodium salts of the acids are more insoluble and occlude some of the oily layer during neutralization.

Both the propionyl and the butyrylester are colorless oils of agreeable odor.What is true for the acetylester in regard to initially present mesityloxiide is also true for the higher esters.It is impossible to separate the impurities by distillation.

Properties of the butyrylester.

Boiling point 192-193° / 742 mm , Bp₁₂ = 97-98°

Density D₂₀²⁵ = 0.9536

Refractive index n_D²⁰ = 1.4270

Percent butyric acid found calculated for

47.31 % C₁₀H₁₈O₃

47.43 % 47.23

The semicarbazone crystallizes in silky needles from 50 % alcohol.It melts at 110.4 - 110.8 °

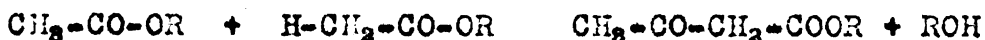
Nitrogen in the semicarbazone:

found	17.00 %	calculated for C ₁₁ H ₂₁ O ₃ N ₃
found	16.82 %	17.24 %

Following the preparation of the above esters that of the valeryl, caproyl and benzoyl esters was attempted. In the case of the former two not sufficient chemicals were on hand to investigate them thoroughly. It was observed, however, that the difficulties during neutralization become greater as the molecular weight of the fatty acids increases. The limit for this method of preparation is rather close since the higher fatty acids cannot be converted into the sodium salts anymore by sodium^{bi}carbonate or even carbonate, stronger alkali however cannot be used since it would probably hydrolyse the esters. The benzoyl ester could not be obtained by the above method from benzoic anhydride, the products being mesityloxide and benzoic acid.

IV. Derivatives of the Esters.

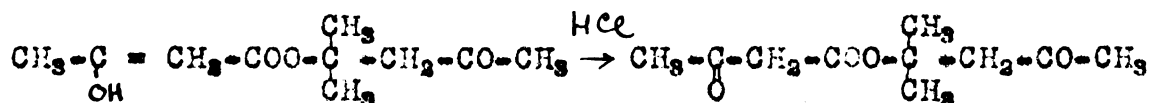
Pure acetyléster of diacetone alcohol reacts with sodium metal vigorously with the liberation of hydrogen. The reaction is analogous to Claisens Ester Condensation, which follows the general scheme:



As mentioned before this reaction does not take place when the ester is impure.

Molecular equivalents of the ester and sodium are allowed to react, either directly or in anhydrous ether. The reaction mixture has to be cooled in the beginning, and is finished

by warming on the water bath. In order to convert the enol form of the resulting ester into the keto form, one equivalent of concentrated HCl is added;



Then the mixture is poured into ice-water, acidified with hydrochloric acid. The ether solution is washed with water, dried over calcium chloride and distilled under diminished pressure. The aceto-acetic ester obtained boils between 80 and 90 ° at 6 - 8 mm.

Refractive index $n_D^{20} = 1.4363$

Bp₇₂₈ = 189.0° (micro determ.)

The ester was saponified qualitatively with dilute alkali, and the solution was tested for aceto-acetic acid. The color test with ferric chloride was positive as well as the iodo-acetone test.

Saponification numbers:

one hour saponified	19.2 %	acetoacetic acid
one " "	22.9 %	"
24 " "	36.3 %	"
calculated	55.4 %	"

The obtained ester was a yellow liquid, and apparently still impure. There was not enough substance however to purify it further or to run other determinations. The fact that it has

a pronounced phorone odor which still persists after saponification and that it is colored indicates that it contains probably the latter compound as an impurity, which would be sufficiently explained by the action of some sodium on the diacetone alcohol formed during the condensation.

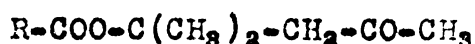
Reactions of the esters with aldehydes.

Ketones can only react with aldehydes when they contain methyl or methylene groups directly attached to the carbonyl group. Such condensations are effected by means of dilute alkali, sodium ethylate or hydrochloric acid. The reaction is being used as a qualitative test for methyl and methylene groups in positions such as the required. The reaction-products are benzylidene compounds or there may be ring closure with the formation of hydropyrones.

In ketones of the formula $R-CH_3-CO-CH_3$ the methyl group is more reactive than the methylene group when alkaline condensing agents are used. When however hydrochloric acid gas is used, the methylene group is more reactive, and in this case only the methylene group can react, so that only one benzylidene group can be introduced.

References on these condensations are given in Hans Meyer, *Analyse und Konstitutionsermittlung Organischer Verbindungen*.

According to the above, it is obvious that diacetone esters having the general formula



can react with only one molecule of aldehyde when HCl is used as condensing agent. Aqueous alkali cannot be used because it would hydrolyse the esters. After reaction with one molecule of the aldehyde, which would enter the methylene group, there is a possibility of introducing another molecule of the aldehyde by means of alkaline condensation.

The work of Mostanecki and G. Rossbach however shows that the alkaline condensation does not always consist of the simple interaction of two molecules, but may lead to high-molecular compounds. An example for this is the condensation between benzaldehyde and acetophenone. In the cold this reaction results in the formation of benzalacetophenone. When higher temperatures are used, benzaldiacetophenone is formed. Higher temperatures and stronger alkali cause the formation of dibenzaltriacetophenone.

In the case of the benzalderivative of diacetone alcohol acetyléster the first product isolated, using weak alkali, and room temperature was a compound containing one molecule benzaldehyde and two molecules of the benzalderivative of diacetone alcohol acetyl ester.

Condensations.

A mixture of 15.3 g of diacetone alcohol acetyléster and 10.6 g of benzaldehyde is cooled in an ice bath, and hydrochloric acid gas, dried over sulfuric acid passed in. When the rate of absorption decreases, the solution has a brilliant red color. The mixture is then allowed to stand for

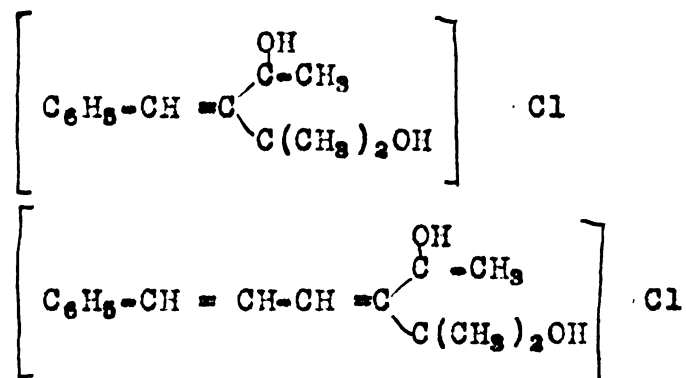
ten to twelve hours. At the end of this period it is poured into ice water. Then the oil is washed with water and with carbonate solution, and dried over calcium ^{chloride} ~~(carbonate)~~. The oil is then distilled under the vacuum of a water - pump (to keep corrosive vapors from the electric pump) until all the unchanged aldehyde is removed. A heavy oil is then collected at 145-147° / 6 mm. Yield around 4 g.

One molecular equivalent of diacetone alcohol acetyl-ester is condensed with 13.2 g of cinnamic aldehyde. The color in this case is blue-green. In this condensation however the condensation product is difficult to isolate. The product consists of bright yellow crystals which appear on the neck of the distilling flask. The product coming over however is phenyl ethylene indicating decomposition.

The condensation with benzaldehyde was carried out with the acetyl, propionyl and butyryl esters of diacetone alcohol, with modified quantities and duration of condensation. In all cases the yield was around 3.2-4.0 g per one tenth of a mole, of the diacetone ester. (Better yields are obtained with larger amounts of chemicals.)

The color formation in these reactions is explained by the research of Pfeiffer who found that color occurs among the compound R-CO-A in which R = phenyl, oxyphenyl, methoxyphenyl, cinnamyl and furyl, and A = H, CH₃, OH, OC₂H₅, NH₂. He found that all these compounds add tin tetrachloride and tin tetrabromide to give compounds of the composition

$\text{SnX}_4 \cdot 2\text{RCO-A}$. The appearance of Halochromism is attributed by Pfeiffer to changes in the affinity relationships which take place when the components add to each other. As the number of ethylene groups increases as for instance in the cinnamyl derivative in comparison with the benzal derivative the carbonyl carbon atom becomes more unsaturated, and the color deepens. The salts of the particular compound which we deal with can be expressed as :

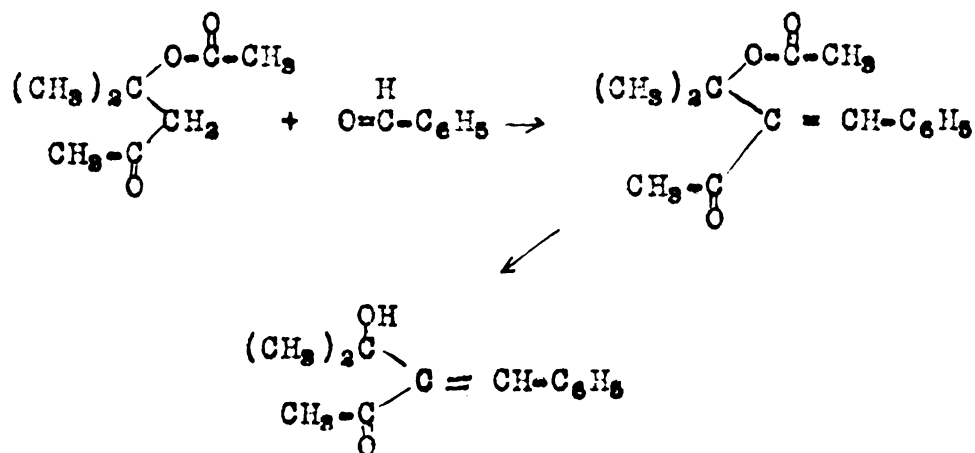


Ref. Pfeiffer, Organische Molekuelverbindungen.

All compounds obtained by the above condensations of benzaldehyde with the three esters were found to be identical. Furthermore upon saponification they were found to be, not esters, but alcohols.

This however can only be the case if the fatty acid groups were hydrolysed off during the procedure of the condensation. This assumption is confirmed by the fact that the fatty acids could be proved in the water after the reaction-mixture had reacted for ten hours. The hydrolysis must take place after the methylene group has reacted with the aldehyde because diacetone alcohol with hydrochloric acid gas

yields mesityloxide as shown previously. In these reactions however no mesityloxide was formed.



2-acetyl-2-benzal-1-1-dimethyl-ethanol.

Boiling point 145-147° / 5 mm

$D_{25}^{25} = 1.0099$

Refractive index $n_{20}^D = 1.6123$

The yellow oil crystallizes in the refrigerator but is liquid at room temperature. It is insoluble in water, soluble in alcohol, ether and benzene.

The alcohol reacts rapidly with bromine in carbon disulphide. The dibromide is obtained as a yellow oil which darkens and decomposes on the air. It cannot be distilled without decomposition. In the refrigerator it crystallized after three days, but it could not be recrystallized so far, because it is too soluble in most solvents, or comes down as an oil.

A solution of 10.2 g of the alcohol in carbon disulphide is immersed in an ice bath and 3 g bromine are added

slowly, with stirring from a dropping funnel. The carbon disulphide is removed under diminished pressure with very little heat. The viscous yellow oil is analysed for bromine by the parr bomb method.

bromine found	33.53 %	calculated for $C_{13}H_{16}O_2Br_2$
	33.31 %	43.92 %

Molecular weight determination in the alcohol by the boiling-point elevation method.

found	203.1	calculated for $C_{13}H_{16}O_2$
found	200.0	204

The benzal derivative having a methyl group directly attached to the carbonyl group, is still capable of reacting with another molecule of benzaldehyde.

Sixteen grams of the benzal derivative and 3 g benzaldehyde were dissolved in 100 cc of alcohol. To this solution was added 20 g of 10 % NaOH with stirring. The reaction mixture was then stirred for two hours. At the end of this time a red colored solid mass had settled at the bottom of the beaker. The substance was extracted with ether, the ether extract washed with water and dried. Then the ether was distilled off. The residue was purified by dissolving in alcohol and precipitating with water. The amorphous, orange-yellow compound melted at 98-100° with decomposition.

Analysis

	found	calculated for $C_{33}H_{36}O_4$
Carbon	81.23 %	80.23 %
Hydrogen	6.87 %	7.03 %

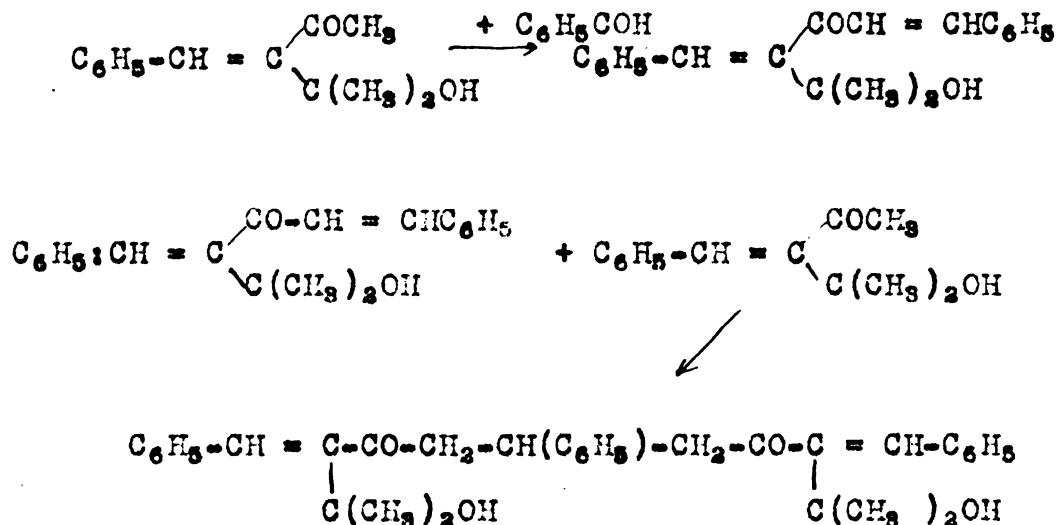
Molecular weight determination
by boiling-point elevation

found	497.5	510.2	calc.	490.0
			for $C_{33}H_{36}O_4$	

Since in the above reaction some unreacted benzaldehyde was found among the reaction product, there is an indication that only one molecular equivalent of the benzaldehyde reacted with two molecular equivalents of the benzal derivative. Accordingly the structure of the compound should be:

2-10-dimethyl-3-9-benzal-4-8-diketo-6-phenyl-undecandiol-2-10

The formation of the compound is given by the following equation:



The compound was not quite pure, however the results are sufficient to establish the above structure.

Physical Constants.

The densities of diacetone alcohol and the three esters were calculated for 20°C referred to water of 4°C. These calculations were based on the change in molecular volume, which amounts to 0.11 cc per degree change. With the values thus obtained and the refractive index taken at 20°C the molecular refractions were calculated according to the formula

$$M = \frac{n^2 - 1}{n^2 + 2} \cdot \frac{m}{d}$$

and the values obtained were compared with those calculated according to Eisenlohr.

1. Diacetone alcohol.

$$D_4^{20} = 0.9347 \text{ (according to W. L. L. L.)}$$

$$n_D^{20} = 1.4242$$

$$M_D = 31.68$$

$$\text{calc. } M_D = 31.56$$

2. Acetyl ester

$$D_4^{20} = 0.9853$$

$$n_D^{20} = 1.4229$$

$$M_D = 40.85$$

$$\text{calc. } M_D = 40.80$$

3. Propionylester

$$D_4^{20} = 0.9698$$

$$n_D^{20} = 1.4256$$

$$M_D = 45.42$$

$$\text{calc. } M_D = 45.42$$

3. Butyrylester.

$$D_4^{20} = 0.9581$$

$$n_D^{20} = 1.3270$$

$$M_D = 50.04$$

$$\text{calc. } M_D = 50.04$$

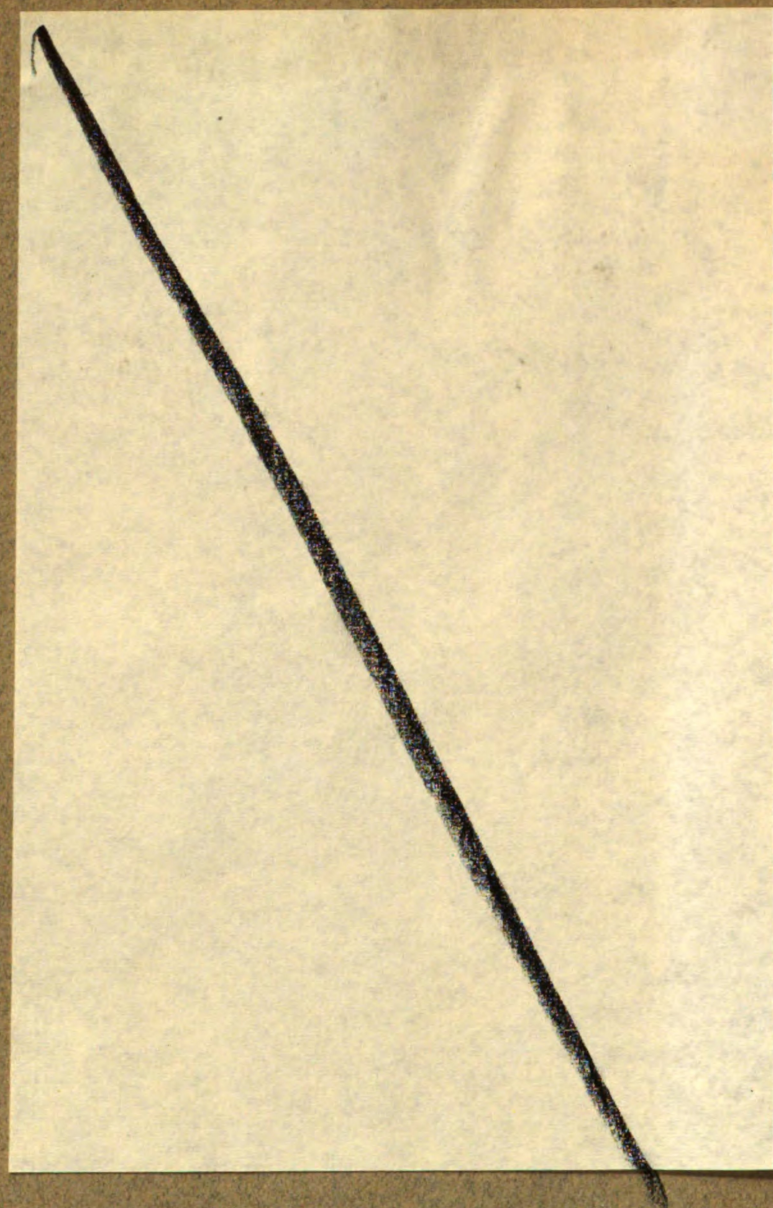
Summary

1. Isophorone was separated from mesityloxi~~de~~ and diacetone alcohol by distillation and the compounds were identified.
2. Diacetone alcohol was dehydrated by hydrochloric acid, fatty acids and their anhydrides.
3. Three esters of diacetone alcohol were prepared and definitely proven.
4. The esters were condensed with aldehydes and the products identified.
5. Some physical constants were determined and calculated.

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acetone & some of their
derivatives.

7-1-4



University of Minnesota
Minneapolis , Minnesota
April 5 , 1935.

Miss Jean O'Brien
327 Hillcrest
East Lansing , Michigan

Dear Miss O'Brien ,

I was very glad to hear about the progress on the subject of my former problem . According to your letter I take it that you carried out the alkaline condensation without getting the desired product , or else were in doubt about the procedure .

I looked up my original notebook on the particular reaction as well as the literature , and found that there is apparently a mistake in the procedure as outlined in the thesis (page 43) , the discrepancy being in the strength of the alkali . The error is due to the fact that I obtained the compound the first time by means of 10 % alkali, was however unable to reproduce the reaction, and thus had to use stronger alkali . The correct procedure is as follows : Dissolve 16 g of the benzalderivative and 8 g benzaldehyde in 100 cc of ethyl alcohol . To this solution add 20 g of 40 % NaOH (aqueous) , slowly, with stirring . The reaction is carried out in a beaker at room temperature , the stirring is best accomplished by means of a motor . The product separates out after 10 or 20 minutes . Stirring is continued for a while , and then the orange precipitate separated by decanting . The substance is insoluble in most solvents . It

can be purified by dissolving in a large volume of alcohol and precipitating with water . It is somewhat soluble in chloroform .

The method is by no means original with me but was adapted from the condensation of benzaldehyde with acetophenone by Kostanecki and Rossbach , B. 29,1488-1497 .

The reaction mechanism is discussed in some detail in the above paper to which I had like to refer you .

I am very interested to hear about the physical constants of benzalmesityloxy since they are not known in the literature . I wonder whether it also crystallizes in the refrigerator ?

In regard to the derivatives I would like to make a few suggestions , although , of course , I do not know which derivatives you are working on , and may thus propose some which you have already tried out . We use here in similar cases semicarbazide in preference to hydrazines , and if the former should yield non-crystallizable oils , substituted hydrazines such as p-nitro-phenylhydrazine or 2-4-dinitro-phenylhydrazine may be used with advantage . In fact those latter two compounds hardly ever fail . If you should have difficulties to obtain those reagents , I would be very glad to get them for you .

Your observation in regard to partial crystallization of the benzal compound almost suggests a mixture of isomers does it not ? This in term would explain very nicely the fact that the high-molecular condensation product did not analyse

correctly . Assuming that we deal with a mixture of isomers the problem would then consist in the purification of the partially crystallized compound , or of some derivative, which may be easier to accomplish .

I hope that my suggestions may be helpful to you , and that you obtain solid derivatives some of these days . If you should lack other information please let me know , I shall be very glad to give you suggestions.

Please give my compliments to Dr. Huston .

I wish you success and remain

Yours very truly ,

Herbert Ernst Ungnade.

H.E. Ungnade
University of Minnesota
Minneapolis , Minnesota



Miss Jean O'Brien

327 Hillcrest

East-Lansing , Michigan

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SUPPLEMENTARY
MATERIAL

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THS
Suppl 2

School of Chemistry
University of Minnesota
Minneapolis, Minn.

April 20, 1935

Miss Jean O'Brien
327 Hillcrest St.
East Lansing, Mich.

Dear Miss O'Brien,

I am mailing to you to-day two one-gram-samples of p-nitro-phenylhydrazine and 2-4 dinitrophenylhydrazine respectively.

In the following I would like to give you some references about those derivatives.

Reaction with 2-4-dinitrophenylhydrazine

" Kamm, Edition 1932, page 170

(Analyst 51, 77 and J.A.C.S. 52, 2955).

According to the experience in this Department it is advisable to use 5 cc of a 1% solution of the hydrazine and 1 or two drops of the Ketone in 5 cc alcohol, and repeat this procedure several times rather than using large amounts.

For p-nitrophenylhydrazine, with which I have less experience you find numerous references in:
Haus Meyer, Analyse u. Konstitution Org. Verb. d. page 428.

For your particular problem 2-4 dinitrophenylhydrazine is most appropriate.

If I can be of any further help to you, don't hesitate to call on me.

Yours very truly,

Herbert Ernst Ungnade.

Herbert E. Ungnade
School of Chemistry
University of Minnesota
Minneapolis, Minn.

November, 15. 1934.

Dear Art,

Thank you very much for your letter and for sending the sample of my compound. I guess you have received the sample back by this time. I have written down the analyses together with other data which I collected and which I believed to be necessary in order to make the work complete. As you see the compound you sent did not quite correspond to the structure that I assumed it to be.

This fact, of course, led me to an investigation of the next higher product using the above as a starting material.

The compound you sent up here ~~now~~ is an isomer of Claisen's benzal-mesityloxide. I prepared a small amount of the latter compound and I am sending it to you in the near future. I wonder if it might be possible for one of your prep. students to prepare a larger amount of the substance and determine its constants which Claisen did not determine. The values could then be compared with the values which I found for my substance.

The preparation is relatively easy, the reference is given at the end of the enclosed supplement of the thesis.

I am very glad that your research is coming fine, and I hope that you are all through by now with your prelims.

Please excuse typing and other errors which are due to the fact that I have to hurry because I have still much to do this evening.

Remember me to your wife please and receive best wishes and good luck for your research and otherwise

your

Herbert.

Please give my best regards to Dr. Hurler, Dr. Harpport and Mr. Ball.

S U P P L E M E N T

to the thesis

CONDENSATION PRODUCTS OF ACETONE
AND SOME OF THEIR DERIVATIVES

by

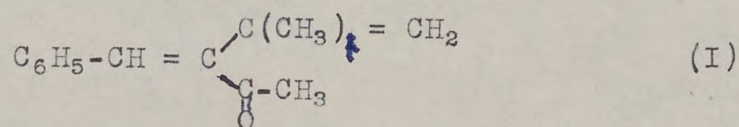
Herbert Ernst Ungnade

The compound assumed to be 2-acetyl-2-benzal-1-1-dimethyl-ethanol was analysed for Carbon and Hydrogen and the following values were obtained:

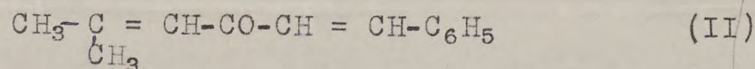
	H	C
found	7.60%	83.95%
calculated for $C_{13}H_{14}O$	7.58%	83.82%
calculated for $C_{13}H_{16}O_2$	7.84%	76.47%

Accordingly we deal not as assumed with $C_{13}H_{16}O_2$ but with $C_{13}H_{14}O$. In agreement with the latter formula are the molecular weight determinations, which are within 10% of the theory.

Assuming that the primary step in the synthesis of the compound $C_{13}H_{14}O$ is the combination of one molecule of benzaldehyde with one molecule of the acetyler of diacetone alcohol the structure of the compound would be:



If however, we assume that the ester is first decomposed with the formation of mesityloxide, the resulting compound should be benzal-mesityloxide, which is isomeric with the above.



It is obvious that the physical properties of the two possible structures cannot be very different. Their odor, color, B.P. etc would most likely not allow a differentiation. It should, however, be possible to differentiate them by their reactivity towards benzaldehyde. Structure (I) has a methyl group adjacent to the carbonyl group which is capable to react with one molecule of benzaldehyde, while the structure (II) does not have any such group.

In the previous work the obtained compound $C_{13}H_{14}O$ was submitted to alkaline condensation with benzaldehyde, and the isolated product analysed. On the basis of this analysis and the assumption of the 2-acetyl-2-benzal-1-1-dimethyl-ethanol structure its formula was found to be " $C_{33}H_{36}O_4$ ".

Difficulties were encountered in the analysis though in as far as little substance was available, and the latter in an amorphous state.

A new preparation of the compound, subsequent purification and analysis showed contradicting values

found	H	C	M.W.
	6.85 %	84.23 %	84.20%
calc. for $C_{33}H_{36}O_4$	7.03 %	80.23%	496
calc. for $C_{33}H_{32}O_2$	6.95 %	86.08 %	460
calc. for $(C_{20}H_{18}O)_2$	6.57 %	87.59 %	548

The mere fact that a higher condensation product with benzaldehyde was formed would indicate that we deal with structure (I) as mentioned above.

As to the structure of the condensation product the analytical results exclude a simple condensation of two molecules, one each of the ketone and the aldehyde. The molecular weight of that particular compound would be 274 ($C_{20}H_{18}O$) Its dimer does not agree with the results of the C, H analysis.

The previously assumed $C_{33}H_{36}O_4$ is out of question because the assumption of the ketone-alcohol structure of the starting material did not verify. Therefore we must assume the structure to be $(C_{33}H_{32}O_2)$:

3-9-benzal-2-10-methylene-4-8-diketo-6-phenyl-undecan.

The final proof cannot be brought until the compound can be crystallized from some suitable solvent, or purified by some other method than precipitation.

The proof forwarded for the structure (I) of $C_{13}H_{14}O$ would be insufficient, however, unless it were proven that the structure (II) does not react with benzaldehyde.

Correspondingly the benzal-mesityloxiide was prepared according to Claisen by treating a mixture of benzaldehyde and mesityloxiide in an ice bath with dry HCl gas. The product formed as in the case of the product from diacetone alcohol acetyloster forms a molecular compound with hydrochloric acid, giving rise to a deep red color.

The pure yellow liquid was treated in the cold with benzaldehyde and 10% alkali. There was no reaction in the cold. On prolonged heating the liquid droplets darkened but remained liquid.

It might be interesting to compare the two isomers as far as physical properties and derivatives are concerned. Claisen gives only the boiling point and the C, H, analysis.

Ref. Claisen, ~~14~~

Berichte, 14, 349

Melting - Point of

2-Acetyl-2-benzylidene-1-1-dimethyl-ethanol.

17°C

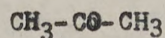
H. E. Ungnade

Synthesis of Isophorone (Mesityloxiide, Diacetone alcohol and Xylitone)

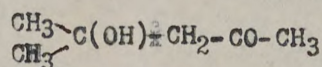
- Raw material
Acetone 800cc.
Methanol 200 cc.
Sod.hydroxide 25 gm.
- Reflux 1 hour per day for 10 days
- Neutralize with CO_2 and filter the sodium bicarbonate off.
- Distil the filtrate under atmospheric pressure. About 650 cc. of acetone and 200 cc. of alcohol are obtained before the temp. reaches 66.6° at which point the distillation is stopped.
- The residue is distilled under a reduced pressure of 15 mm. (aspirator) and the folowing obtained:

Diacetone alcohol	$n = 1.427$
Mesityloxiide	$n = 1.446$
Water	
- The residue is distilled under high vacuum in the presence of an inert gas after drying with CaCl_2 . The following are obtained:

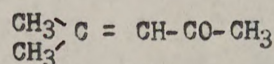
Mesityl oxide	$n = 1.4389$	B.p. 60-90/4 mm.
Isophorone	$n = 1.4780$	B.p. 90-100/4mm., 198/atmos.
	$D = .09228$	at 20°
Xylitone	$n = 1.5$	B.p. 120/4mm.



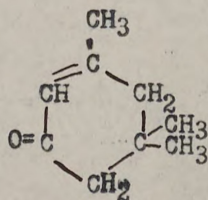
Acetone



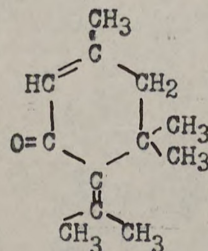
Diacetone alcohol



Mesityloxiide



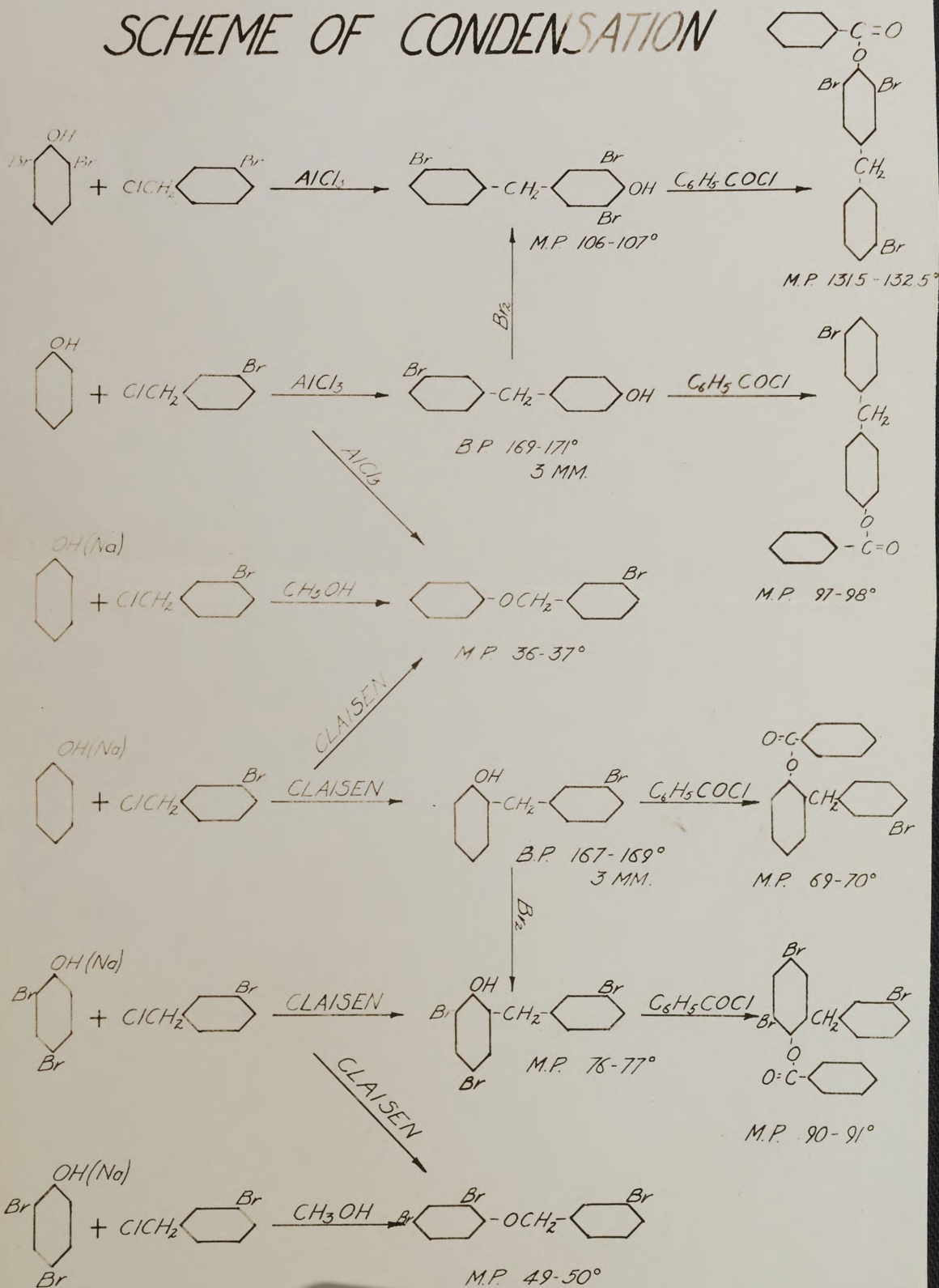
Isophorone



Xylitone

- | | | |
|-------------------|---|---------------|
| 2 acetone - 1 HOH | → | Mesityl oxide |
| 3 acetone - 2 HOH | → | Isophorone |
| 4 acetone - 3 HOH | → | Xylitone |

SCHEME OF CONDENSATION



Esters of Diacetone Alcohol and Some Derivatives.

by Ralph C. Huston and Herbert E. Ungnade

The lower esters of diacetone alcohol were discovered as bi-products in the dehydration of diacetone alcohol by fatty-acid anhydrides.

A yield of 80 % (of the theory) of mesityloxide was obtained by treating with anhydrous hydrochloric acid. When fatty acid anhydrides were used the yield dropped to 70 %, with a 15 % of ester as biproduct.

The esters obtained by treatment with acetic, propionic and butyric anhydride were isolated and identified.

The acetyléster upon treatment with sodium underwent Claisens Condensation.

All three esters could be condensed with benzaldehyde by hydrochloric acid. The esters were hydrolysed during this reaction, giving rise to only one alcohol:

2-benzal-2-acetyl-1-1-dimethyl-ethanol

The latter alcohol was again condensed with benzaldehyde by cold, aqueous alkali. The reaction product was found to be :

2-10-dimethyl-3-9-benzal-4-8-diketo-6-phenyl-undecandiol-2-10

Experimental.

Diacetone alcohol esters.

The acetyléster of diacetone alcohol was prepared refluxing a mixture of 464 g of diacetone alcohol and 204 g acetic anhy-

dride for three hours on a sand bath. The reaction mixture after cooling was poured into an equal volume of ice water and neutralized with sodium bicarbonate. The oily layer was washed with H_2O , separated, dried and fractionated under reduced pressure. Three hundred and fifty grams of the crude oil gave 270 g of mesityloxide and 80 g of the ester. The ester was obtained as an oil boiling at $171-173^\circ / 742 \text{ mm.}$

Bp ₅ = $60-62^\circ$	Bp ₁₀ = $72-73^\circ$
Density	$D_{25}^{20} = 0.9811$
Refractive index	$n_D^{20} = 1.4229$
Saponification	percent HAc found $37.82-38.07 \%$
	calculated for $C_8H_{14}O_3$ 37.97%

The propionyl and butyryl esters were obtained analogously from the alcohol and the corresponding anhydrides.

Constants:

1. propionylester:

Bp ₇₄₂ = $182-184^\circ$	Bp ₈ = $80-81^\circ$
Density	$D_{25}^{25} = 0.9680$
Refractive index	$n_D^{20} = 1.4256$
Saponification	percent propionic acid
	found $42.99-43.20 \%$
	calculated for $C_9H_{16}O_3$ 42.99%

2. Butyrylester.

Bp ₇₄₂ = $192-193^\circ /$	Bp ₁₂ = $97-98^\circ$
Density	$D_{25}^{25} = 0.9536$
Refractive index	$n_D^{20} = 1.4270$
Saponification	percent butyric acid
	found $47.31-47.28 \%$
	calculated for $C_{10}H_{18}O_3$ 47.28%

Semicarbazones.

All three esters react with semicarbazide hydrochloride giving crystalline semicarbazones. The semicarbazones were obtained as follows:

Dissolve one part of semicarbazide hydrochloride in the smallest possible amount of distilled water. Then add one part of the ester. Add a saturated alcoholic solution of KAc. until a homogeneous solution results.

The semicarbazones of the three esters crystallize best from 50 % alcohol.

$C_9H_{17}O_3N_3$	M.P.	137.5-138 °
$C_{10}H_{19}O_3N_3$	M.P.	144.5-145°
$C_{11}H_{21}O_3N_3$	M.P.	110.4-110.8 °

Nitrogen in semicarbazones	calc.	found
$C_9H_{17}O_3N_3$	19.53 %	19.49 %
		19.33 %
$C_{10}H_{19}O_3N_3$	18.34 %	18.52 %
		18.40 %
$C_{11}H_{21}O_3N_3$	17.24 %	17.00 %
		16.82 %

The densities of the esters were then calculated for 20°C referred to water at 4°C. The following values were obtained:

Diacetone alcohol	$D_4^{20} = 0.9347$
Acetylēster	0.9347 0.9853
Propionylester	0.9698
Butyrylēster	0.9551

From these values the molecular refractions were calculated according to the formula:

$$M = \frac{n^2 + 1}{n^2 - 1} \frac{m}{d}$$

and the obtained results were compared with those calculated according to Eisenlohr's atomic figures.

	M (found)	M (calculated)
Diacetone alcohol	31.68	31.56
Acetyléster	40.85	40.80
Propionylester	45.42	45.42
Butyryléster	50.04	50.04

	V (found)	V(calculated)
Molecular volumes		
Diacetone alcohol	124.14	152.00
Acetyléster	160.45	197.20
Propionylester	177.46	219.20
Butyryléster	193.80	241.20

Condensations of diacetone alcohol esters with benzaldehyde.

A mixture of 15.8 g of diacetone alcohol and 10.6 g of benzaldehyde was cooled in an ice bath and hydrochloric acid dried over H_2SO_4 was passed in. The deep red colored solution was allowed to stand for 10 hours. Then it was poured into ice water, washed with water and carbonate solution, dried and distilled under reduced pressure. A heavy yellow oil was collected at 145-147°C / 6 mm. The yield was 4 g.

Identical products were obtained with the homologous esters.

When cinnamic aldehyde was used instead of benzaldehyde a deep blue-green color resulted upon condensation with HCl. The ~~color~~ ^{colored addition product} formation is due to the particular structure of the obtained keto-alcohols, their structure being identical with those investigated by Pfeiffer.

The condensation product in the case of cinnamic aldehyde could not be isolated because it decomposed upon distillation. The obtained product was phenylethylene.

The benzaldehyde condensation product boiled at 145-147°/5 mm.

$$D_{25}^{25} = 1.0099$$

Refractive index $n_D^{20} = 1.6128$

Melting point 17°C

The compound added readily bromine, the dibromide however decomposed on the air, giving off HBr.

Molecular weight determined in the benzal compound by boiling-point elevation method.

found	203.1	calculated for $\text{C}_{12}\text{H}_{16}\text{O}_2$
found	200.0	204.0

The benzal derivative was condensed again with benzaldehyde by dissolving 8 g benzaldehyde and 16 g of the benzal derivative in 100 cc of alcohol. To this solution was added 20 g of 10 % NaOH, with stirring. The amorphous, orange yellow product was dissolved in alcohol and reprecipitated by adding water. The dry precipitate melted at 98-100°.

Carbon	^{found} 81.23 %	^{calculated} 80.23 %
Hydrogen	6.87 %	7.03 %

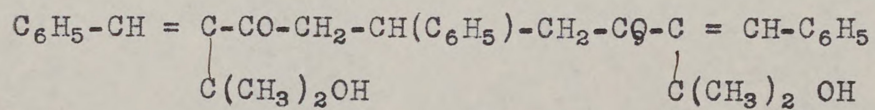
for $\text{C}_{33}\text{H}_{36}\text{O}_4$.

Molecular weight by boilingpoint elevation.

found 497.5 510.2 calc. 490.0

for $C_{33}H_{36}O_4$

formula



Molecular Volume of the diacetone alcohol esters.

$$V = \frac{M}{d}$$

	V_1	V_2	$V_1 - V_2$
Diacetone alcohol	152.00	124.14	27.86
Diacetone acetyléster	197.20	160.45	36.75
Diacetone propionylester	219.20	177.46	42.74
Diacetone butyryléster	241.20	193.80	47.40

V_1 = molecular volume calculated from the atomic values.

V_2 = molecular volume calculated from density and molecular weight.

Constants used for the calculation:

	D_4^{20}	M
Diacetone alcohol	0.9347	116.0
Diacetone acetyléster	0.9853	158.1
Diacetone propionylester	0.9698	172.1
Diacetone butyryléster	0.9551	186.1

Atomic values:

Carbonyl oxygen	12.2 cc
ether oxygen	7.8 cc
hydrogen	5.5 cc
carbon	11.0 cc

H. E. Huganade.

Molecular Volume of the diacetone alcohol esters.

$$V = \frac{M}{d}$$

	V_1	V_2	$V_1 - V_2$
Diacetone alcohol	152.00	124.14	27.86
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Atomic values:

Carbonyl oxygen	12.2 cc
ether oxygen	7.8 cc
hydrogen	5.5 cc
carbon	11.0 cc

H. E. McGuade.

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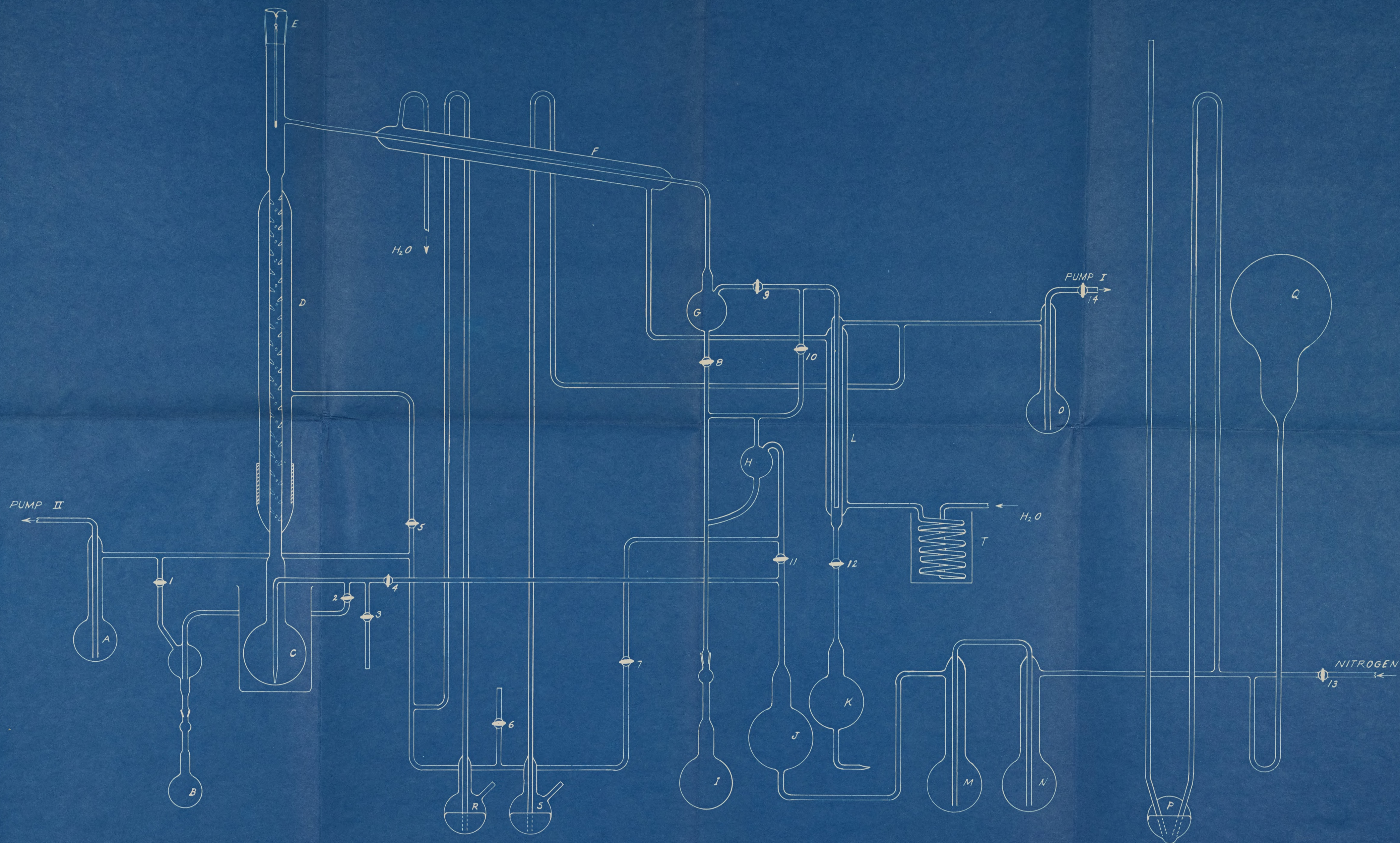
Otto Ungnade 518 W Ash St Mason Mich

Kollenstoff 84,23 Wasserstoff 6,87 Stockstoff 19,41 Stickstoff 18,46
Stickstoff 16,91

Dr Friedrich Fischer

532 PM

Analysis of semicarbazones (nitrogen) and CH for highest Cond. Prod.
with Echo.



SCALE:- 1" = 3"

