ACTION OF AMMONIA ON γ-BENZOYLBUTYRIC ESTER

THE ACTION OF AMMONIA ON γ-BENZOYLBUTYRIC ESTER.

A Thesis.

by

William L. Ball.

Submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

McGill University.

April, 1935

Acknowledgment.

The author wishes to take this opportunity of expressing his very sincere appreciation of the unfailing wealth of advice and information which Dr. C. F. H. Allen, under whom this research was undertaken, has so cheerfully given.

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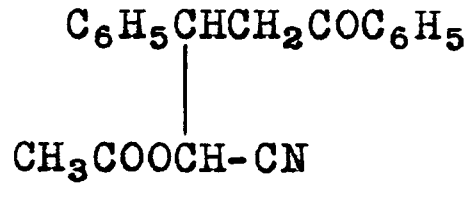
THE ACTION OF AMMONIA ON γ-BENZOYLBUTYRIC ESTER.

Historical Introduction.

All δ-ketonic nitriles investigated up to the present time have been highly substituted.

The following may be cited as examples:



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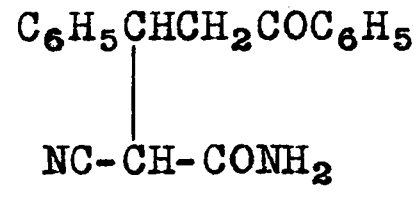

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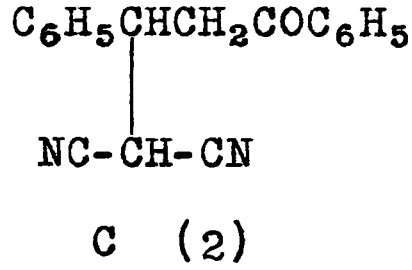
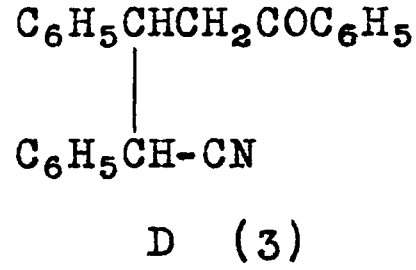
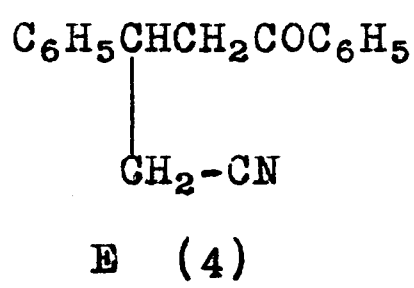


C (2)



D (3)



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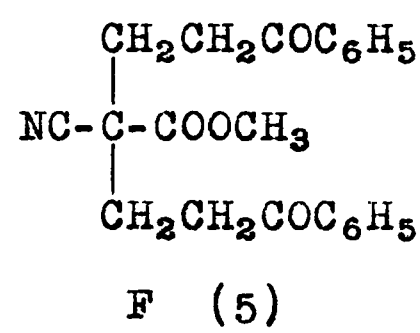

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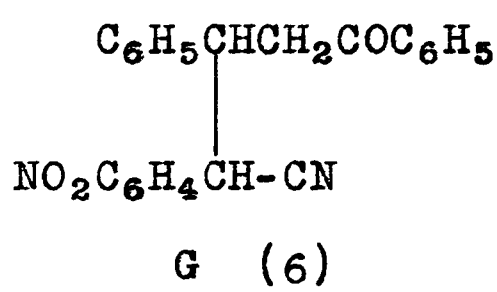
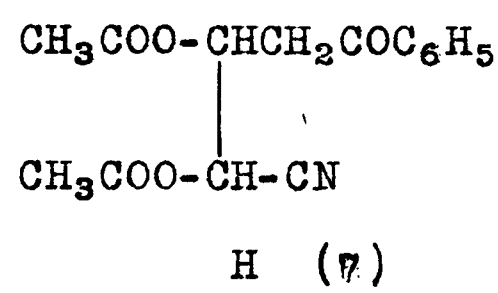
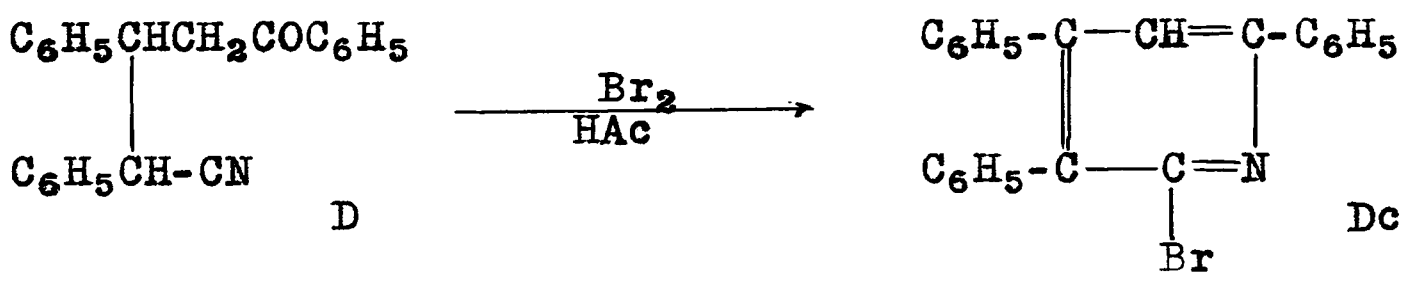


G (6)

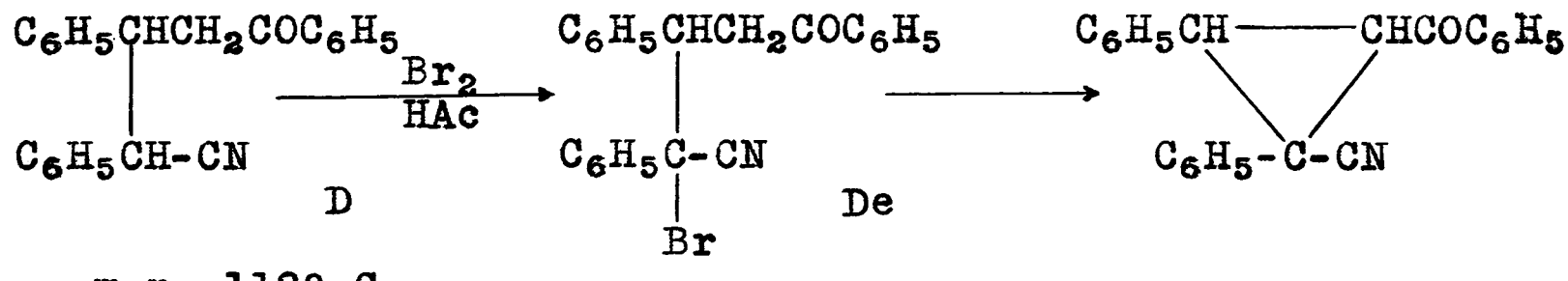


H (7)

It was of interest to prepare and study the simplest member of the series, γ-benzoylbutyronitrile (I) and to learn what connection, if any, there was between the degree of substitution and the course of the reaction. Nitriles A and D, for example, on bromination gave either bromopyridines (six membered rings) or open chain substitution products that readily lost the elements of hydrogen bromide to yield cyclopropanes (three membered rings). This indicates that there is some relation between chemical properties and configuration. In the only cases (D, G) where both of the possible stereoisomers are known, one form gave exclusively pyridines and the other only cyclopropanes.



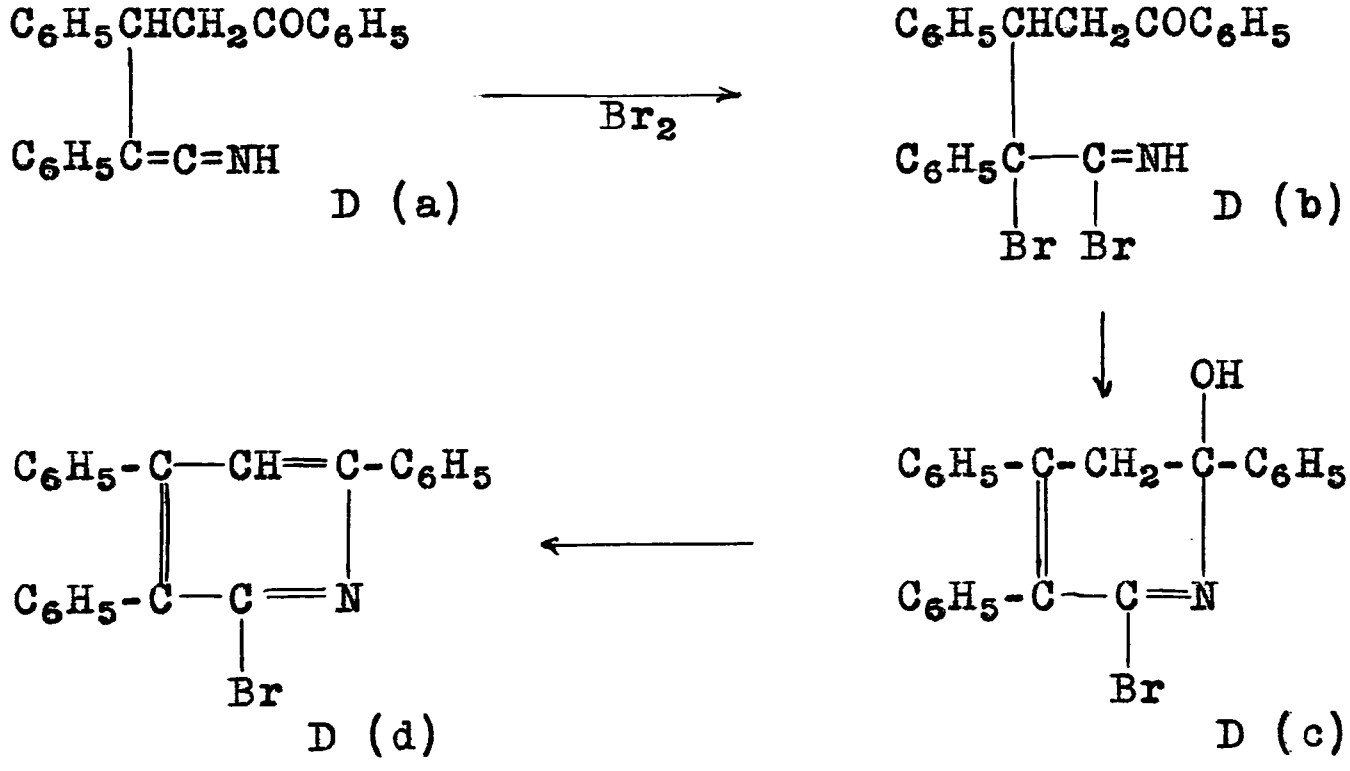
m.p. 109° C



m.p. 118° C.

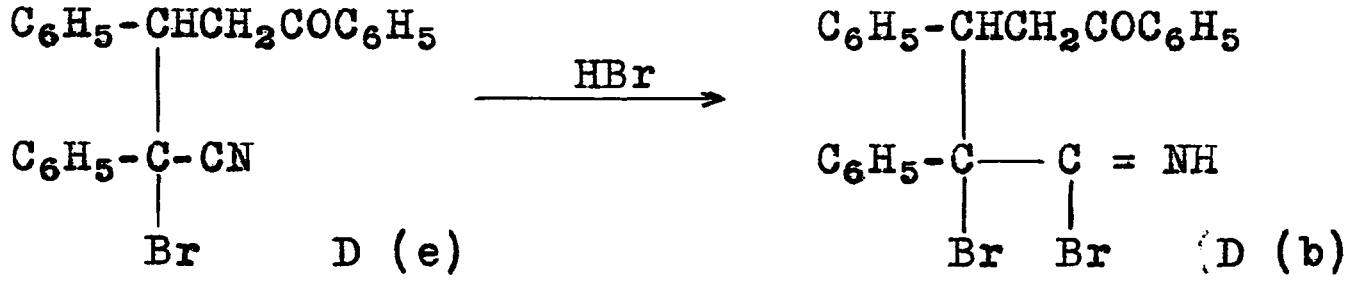
All the other types studied gave exclusively pyridines, but in none of these instances was more than one of the possible stereoisomers available for study.

Kohler and his students have described two characteristic reactions of δ-ketonic nitriles (8). The first is the formation of pyridines on bromination, as indicated above. The mechanism is as follows: bromine first adds to a tautomeric imino form of the nitrile D (a). The dibromide D (b) thus formed then loses hydrogen bromide to give the hydroxybromopyridine D (c) which itself loses the elements of water to yield the bromopyridine D (d).

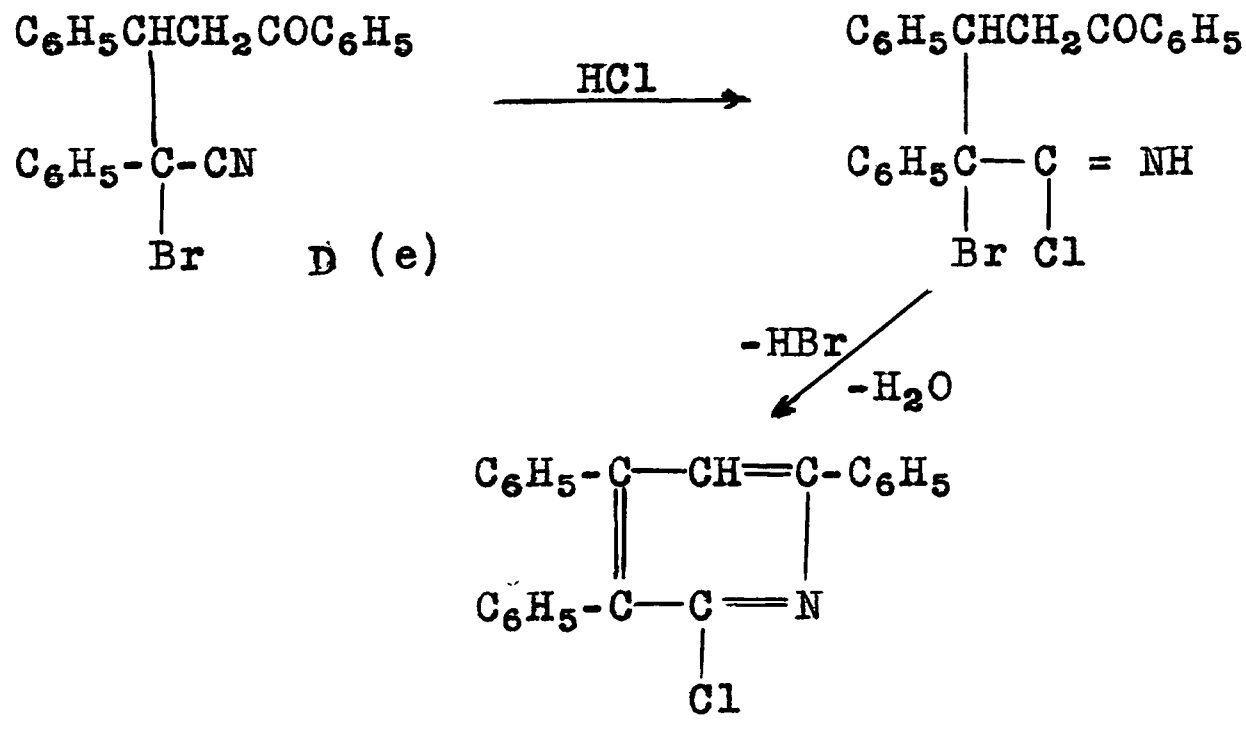


The intermediate hydroxy bromide D (c) was actually isolated, proving definitely that the last step was the loss of water (3).

The same bromopyridine may also be obtained by the action of hydrogen bromide on the open chain bromo compound D (e), resulting from the bromination of the higher melting form of the nitrile D. The first step in the mechanism of the reaction is, presumably, the addition of hydrogen bromide to the C≡N linkage of the nitrile with the resultant formation of the dibromide D (b), the remaining steps being the same as above.

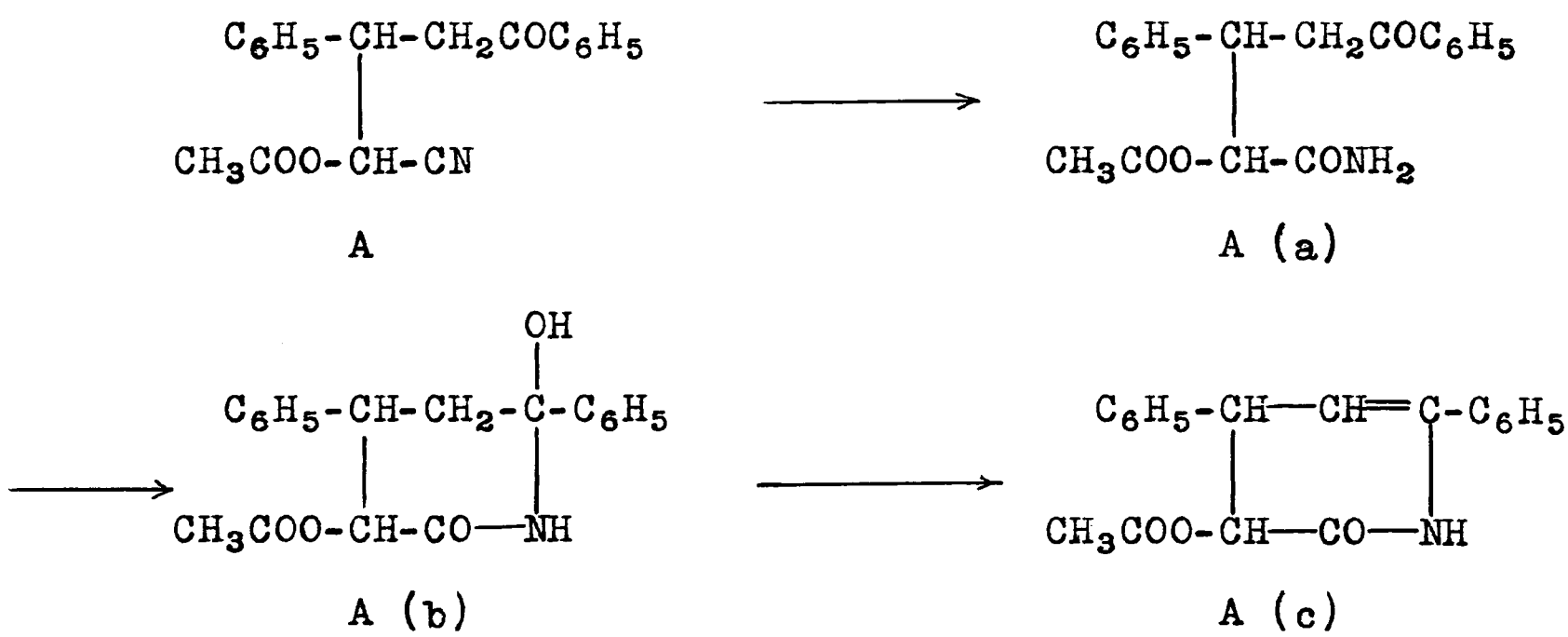


The correctness of this assumption is shown by the substitution of hydrogen chloride for hydrogen bromide, when the corresponding <u>chloro</u>pyridine is formed.



The other characteristic reaction of these nitriles is the formation of tetrahydropyridines on treatment with mineral acids in inert solvents. In chloroform, hydrogen bromide sometimes forms loose addition products with the nitriles, the so-called "amide bromides". These substances are very unstable and readily lose hydrogen bromide with the regeneration of the original nitrile or formation of a tetrahydropyridine which is isomeric with the nitrile. Whether or not they are intermediates has not been determined.

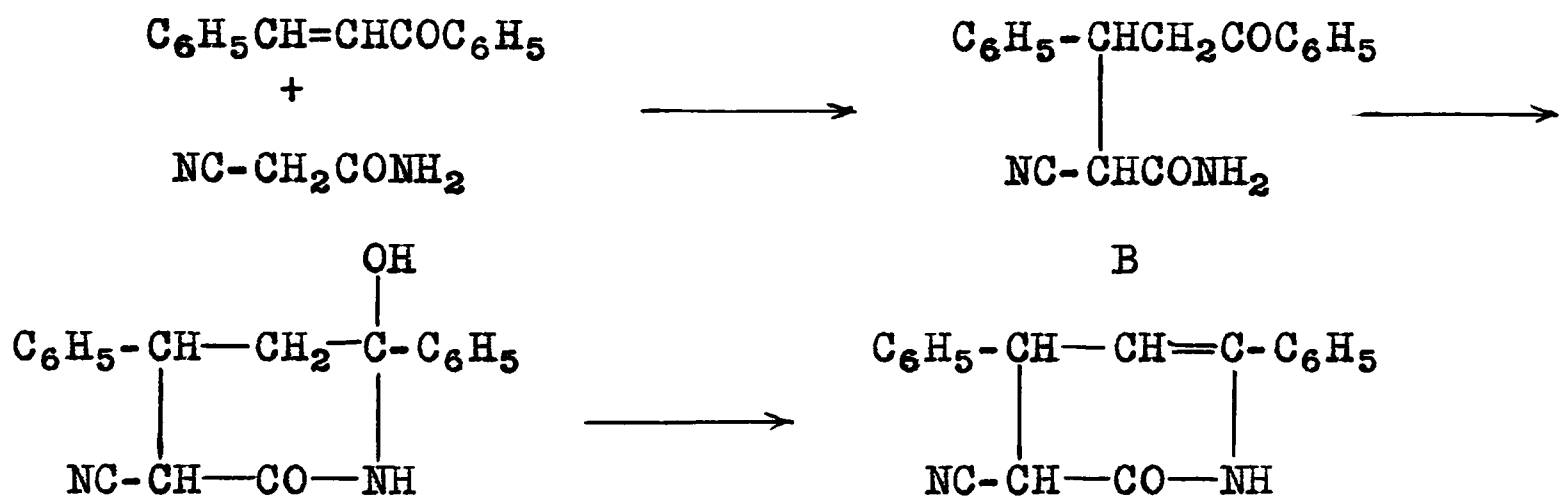
The mechanism of hydropyridine formation from δ-ketonic nitriles has been shown to be the addition of water to form an amide, followed by the elimination of water in another way to yield the cyclic compound (1).



In support of this mechanism Kohler and Souther (2) in 1922 found that when cyanoacetamide was used as an addend

to benzalacetophenone and the product B treated with hydrogen bromide, a cyanohydropyridine B (a) resulted. Ring formation, therefore, involved the $CONH_2$ group and not the CN group.

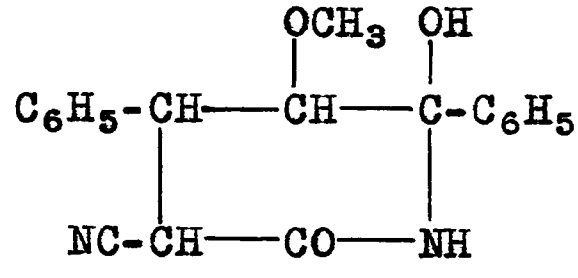
From a study of a series of similar compounds, Barat (9) concluded that Kohler and Souther had really obtained compound B (a), the hydroxy compound, since it showed none of the reactions of the carbonyl group.



B (a) B (b)

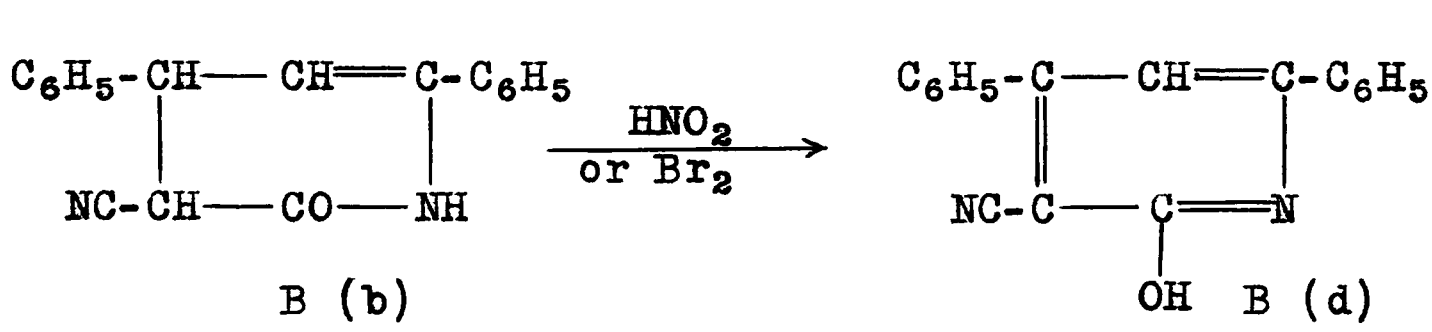
The formation of the tetrahydropyridine in this instance would then be simple dehydration. Allen (6) had already shown this by dehydrating the hydroxypyridine B (a) with acetyl chloride and obtaining B (b). The same investigator also isolated the intermediate amide by treatment of the addition product G (p-nitrobenzyl cyanide and benzalacetophenone) with concentrated sulfuric acid (6). Prolonged treatment with sulfuric acid gave the same tetrahydropyridine as was obtained from the original nitrile by the action of hydrogen bromide.

An homologous addition product J has been prepared by Scarrow (10) in this laboratory and also found to be cyclic. In this case cyanoacetamide was added to benzal-α-methoxy-acetophenone.



J

These reduced pyridine derivatives were easily dehydrogenated to the corresponding pyridines, a characteristic reaction in this series.

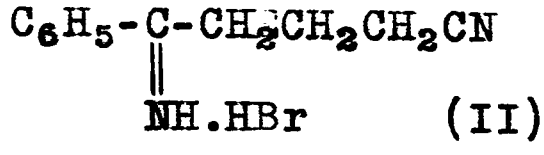


B (b) B (d)

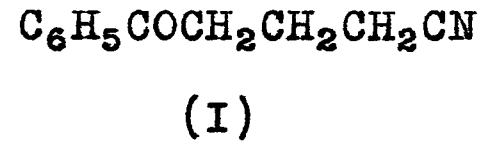
A complete summary of the chemistry of all the known δ-ketonic nitriles has been given in a thesis presented to the Faculty of Graduate Studies and Research of McGill University by Dr. A. C. Bell (1934) and need not be duplicated here.

In 1923 Bruylants (11) found that the action of two moles of phenyl magnesium bromide on glutaronitrile gave the ketimine hydrobromide (II); ammonium hydroxide at 50° C. hydrolysed this substance to a compound melting at 158° C.

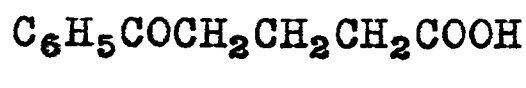
and analyzing for $C_{11}H_{11}ON$. Since it was hydrolyzed to the known γ-benzoylbutyric acid (III) it was accordingly represented as γ-benzoylbutyronitrile (I).



(II)

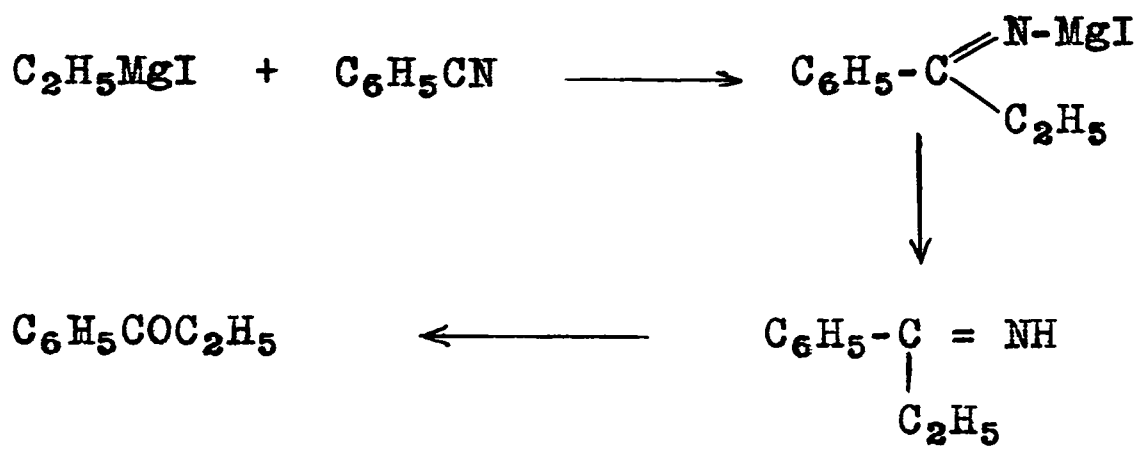


(I)



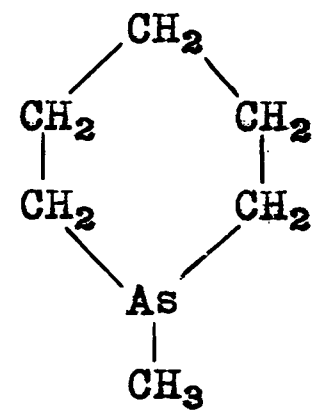
(III)

This is in accord with the usual action of Grignard reagents with nitriles, which is to form imides ~~xxxxxx~~, that on hydrolysis yield the corresponding ketone (12).

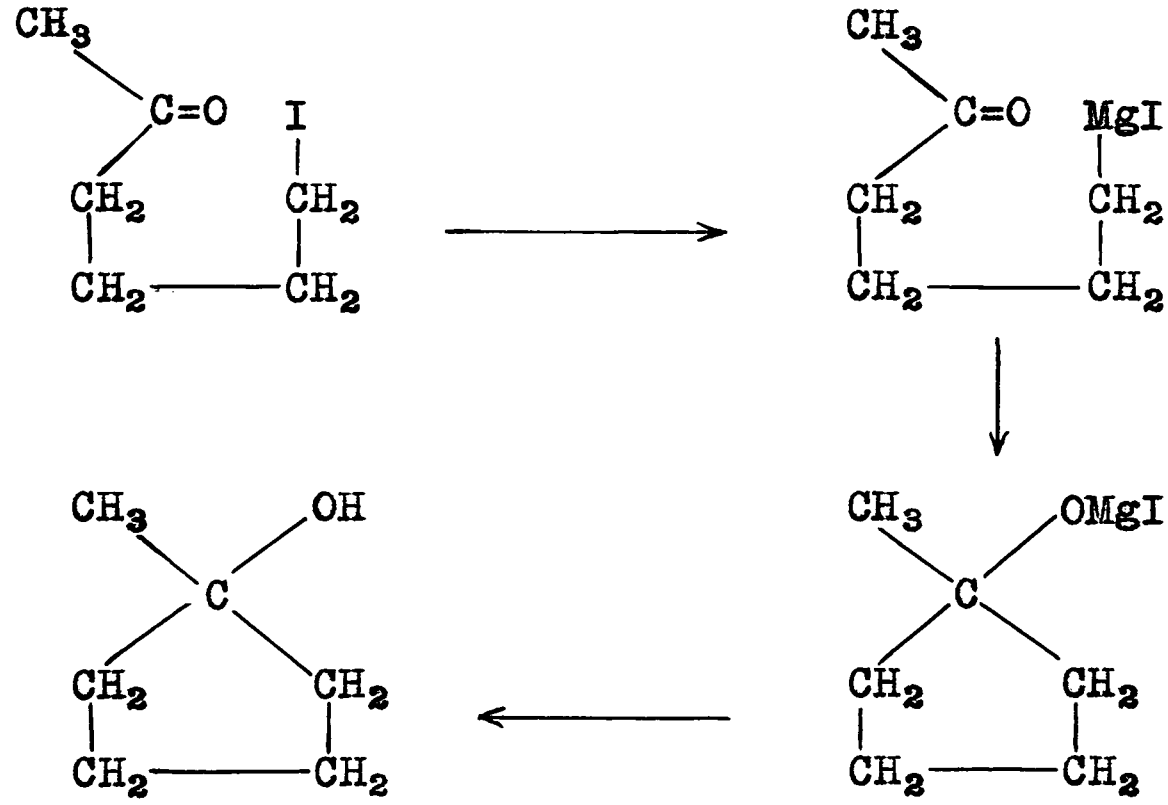


Grignard reagents may, however, bring about ring closure in suitably constituted cases. This has been observed in the synthesis of carboxylic acids; for example, 1,5-dibromopentane forms the di-magnesium compound which on treatment with carbon dioxide yields cyclohexanone and pimelic acid (13).

In another case the Grignard reagent obtained from 1,5-dibromopentane was allowed to react with CH_3AsCl_2 and the product obtained was methylcyclopentamethylenearsine (14):



The Grignard reaction has also been used to effect ring closure in the case of the preparation of 1-methyl-1-hydroxycyclopentane (15).



Another case of ring formation has been described under a German patent (16) covering the preparation of cyano-ketones to be used as perfume intermediates. Nitriles of

the general formula $NC-(CH_2)_n-CN$, when treated with condensing agents of the form RR'N-M where R and R' are aryl, alkyl etc. and M is a metal such as an alkali earth, magnesium or aluminium, are said to yield cyano-ketimides of the general formula $NC-\overline{CH-(CH_2)_{n-1}C}=NH$, which on saponification with mineral acids yield the corresponding cyanoketones.

In his first paper in 1921 Bruylants (17) described the action of certain other Grignard reagents on glutaronitrile. In each instance he has represented the resulting compound as a ketonitrile. Although Methyl magnesium iodide evolved only methane, (*) ethyl magnesium bromide gave, besides ethane, a small amount of a substance which he has represented as the ketonitrile (V), since on hydrolysis it gave the corresponding acid. The main product, only 3% in

$$C_2H_5-CO-CH_2-CH_2-CH_2-CN \qquad (V)$$

this case, was the same whether methyl, ethyl or propyl magnesium halides were used. It analysed for $C_{10}H_{11}ON_3$ and the molecular weight was between 100 and 110. It reacted with

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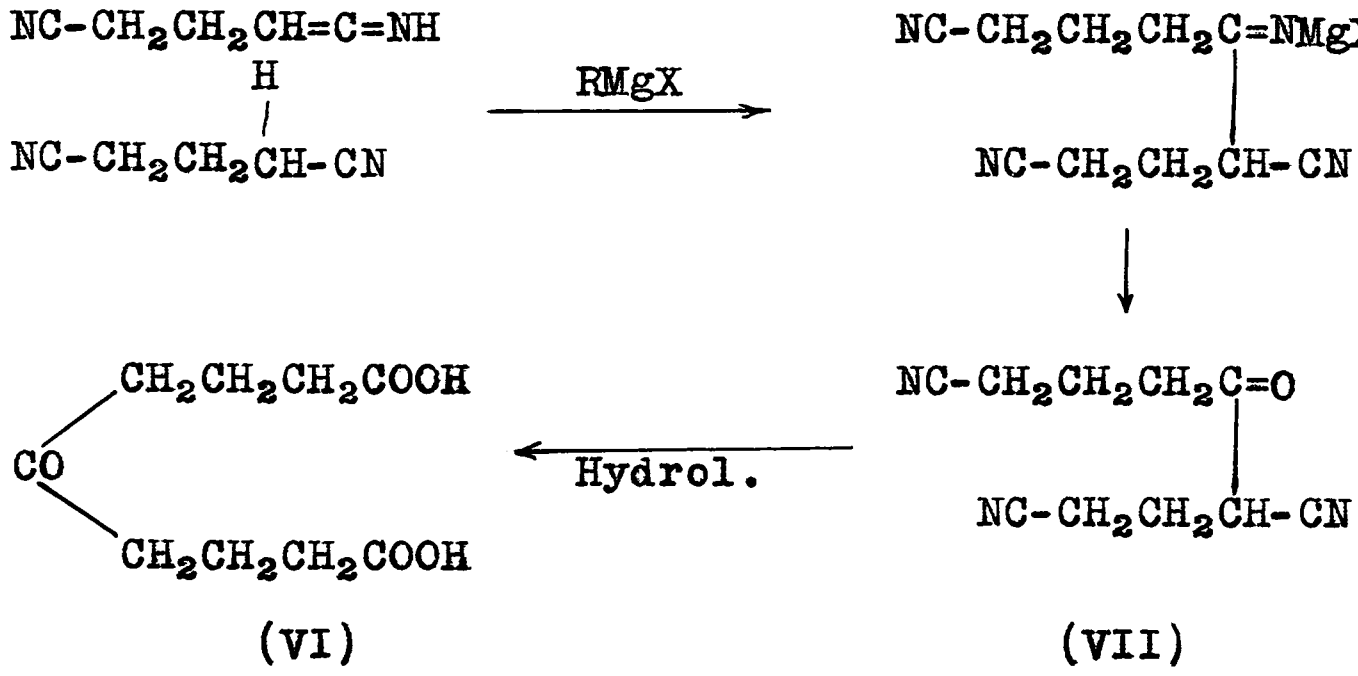
(*) As these nitriles always evolved some hydrocarbon with Grignard reagents, Bruylants concluded that the reaction involved the tautomeric imide.

$$RCH_2C{\equiv}N \rightleftarrows RCH=C=NH \rightleftarrows RCH=C=N-MgBr$$

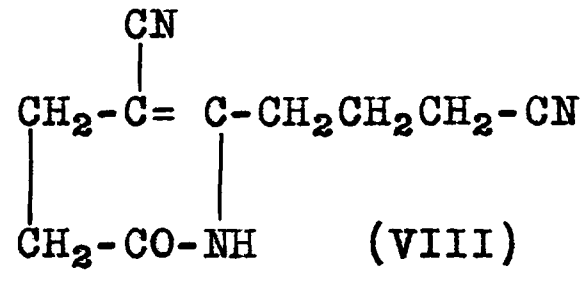
one mole of bromine and evolved a mole of hydrogen bromide. On hydrolysis with concentrated hydrochloric acid it formed the dibasic acid (VI). Bruylants at first considered that it was a four membered ring, but later decided that it was the straight chain compound (VII). Since it gave no oxime or semicarbazone, but reacted with bromine, he stated that it was the enolic form and that such a compound might be formed by the partial hydrolysis of the dimer of the nitrile.

The course of the reaction would then be as follows:



(VI) (VII)

The substance described as a trinitrile (VII) could equally well be represented as a tetrahydropyridine (VIII), formed by partial hydrolysis of the ketonic nitrile and subsequent ring closure.

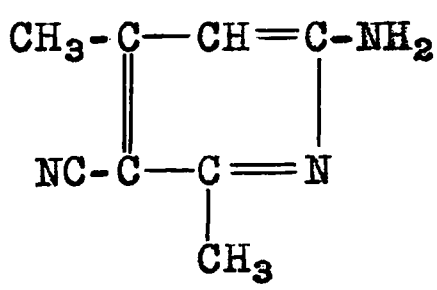


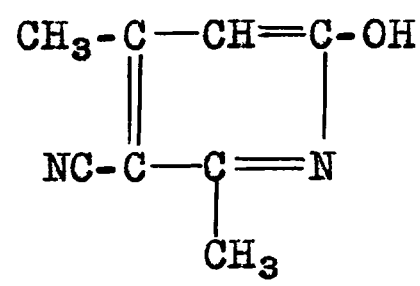
(VIII)

Such a compound would yield no oxime or semicarbazone, but would evolve one mole of hydrogen bromide with one mole of bromine. Upon hydrolysis the ring would open to give the same ketonic acid as the straight chain compound. Bruylants obtained three moles of ammonium chlȯride when he hydrolysed his compound with concentrated hydrochloric acid. The same result would be obtained with the cyclic compound. Thus, although the evidence agrees better with the second structure, it was not considered by Bruylants.

The same author has also described the action of an excess of methyl and ethyl magnesium halides on acetonitrile (18). Here again one mole of hydrocarbon was evolved and on working up the reaction mixture a variety of products was obtained, among these CH_3COCH_2CN and the products resulting from the interaction of two molecules, but no trace of methyl ethyl ketone, i.e. the Grignard reagent had brought about condensation of the acetonitrile.

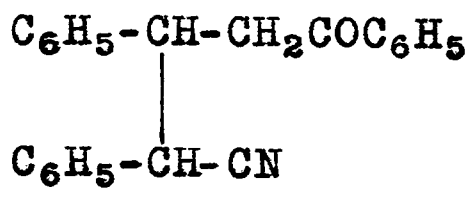
The following products were isolated:





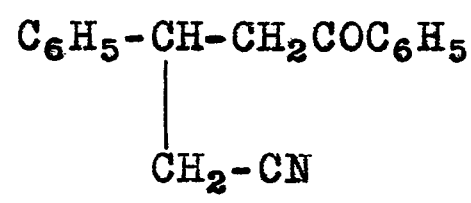
A small amount of a base, $C_7H_7N_2$ (main product).

It is interesting to compare the reported γ-benzoyl-butyronitrile (I) with its known phenyl homologues D and E.



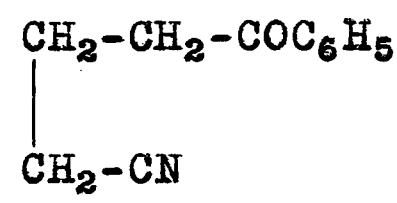
D

m.p. 109°
118°



E

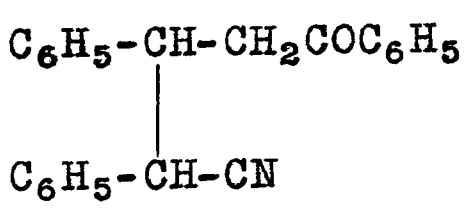
m.p. 76°



(I)

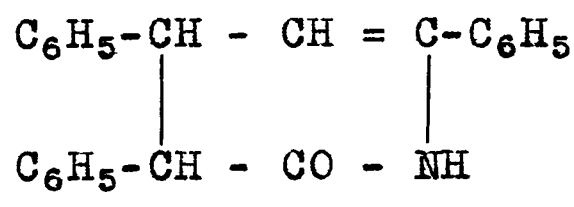
m.p. 158°

Since the presence of phenyl groups always raises the melting point in a series such as this, it seemed illogical that the simplest member should have the highest melting point. If a phenyl group causes a difference of 35° in the melting points (compare D and E) then the melting point of (I), if it is the nitrile as Bruylants has postulated, should be in the range 35°- 40° C. δ-Ketonic nitriles are readily transformed to the isomeric tetrahydropyridines when acted on by basic and acid reagents. Thus, as was shown previously, nitrile D on treatment with hydrobromic acid in acetic acid readily yields the tetra-hydropyridine D (d).



D

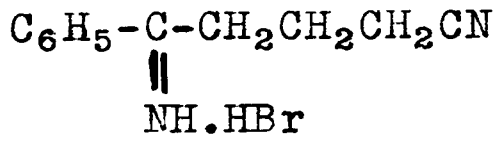
m.p. 109° C.
118° C.



D (d)

m.p. 170° C.

The melting point 158° C. given by Bruylants would seem to indicate that this substance might well be in the same series as compound D (d) since it has been shown in previous investigations on these compounds that the melting points of the cyclic members are always higher than those of their corresponding open chain isomers. As the cyclic compounds are isomeric with those having a straight chain, they could not be distinguished by analyses. On hydrolysis the ring would be opened, so that the same acid would be obtained from the closed chain compound as from the corresponding open chain isomer. Further, each reacts with one mole of bromine and liberates one mole of hydrogen bromide. The cyclic substance may, however, add two atoms of bromine to the unsaturated linkage and should show none of the reactions of the carbonyl group unless the ring is opened. Bruylants has not described the formation of a derivative which would indicate the presence of an active carbonyl group. His observations, therefore, do not exclude the formation of a compound having the structure (IV).



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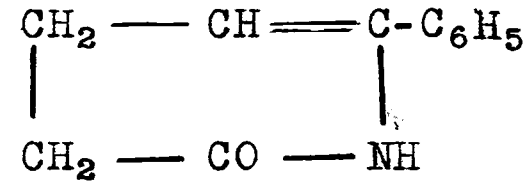


(IV)

There is a possibility that the ring may have been closed during the hydrolysis of the ketimine hydrobromide (II),

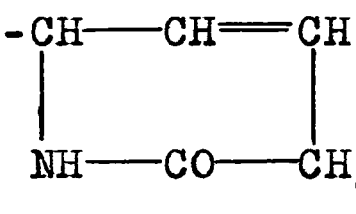
by ammonium hydroxide, since Biedermann (19) found that in many attempts to form the amides of ketonic acids the action of ammonia on the esters yielded only cyclic compounds.

Discussion of the Problem.

The main object of this work has been to synthesize γ-benzoylbutyronitrile in an unambiguous manner, to study its reactions and, incidentally, to show that the compound obtained by Bruylants was not the nitrile (I) but the cyclic isomer (IV).

$C_6H_5-CO-CH_2CH_2CH_2CN$

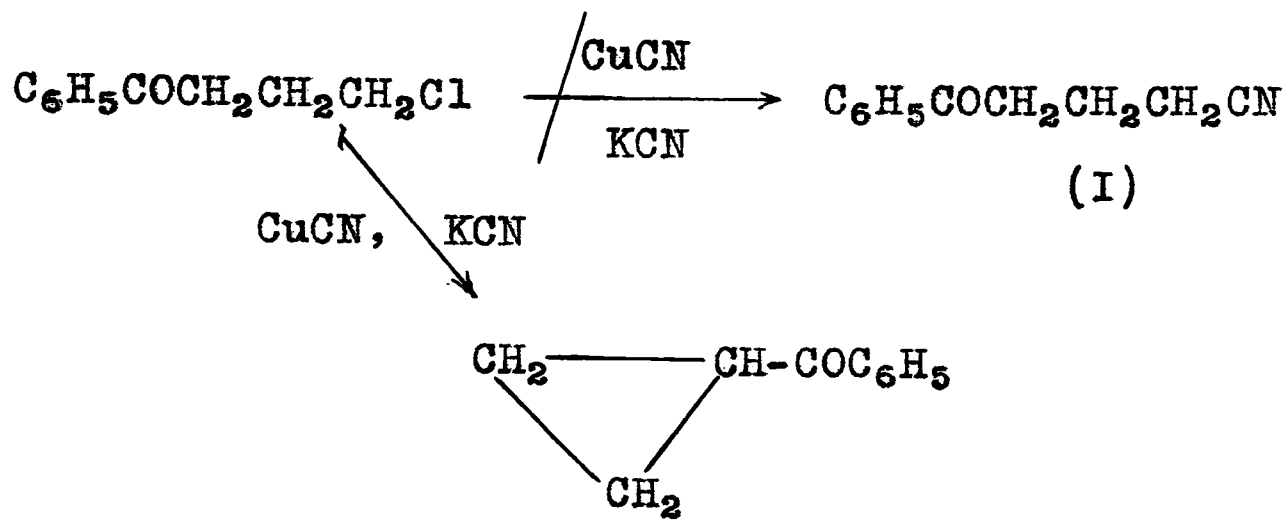
(I)



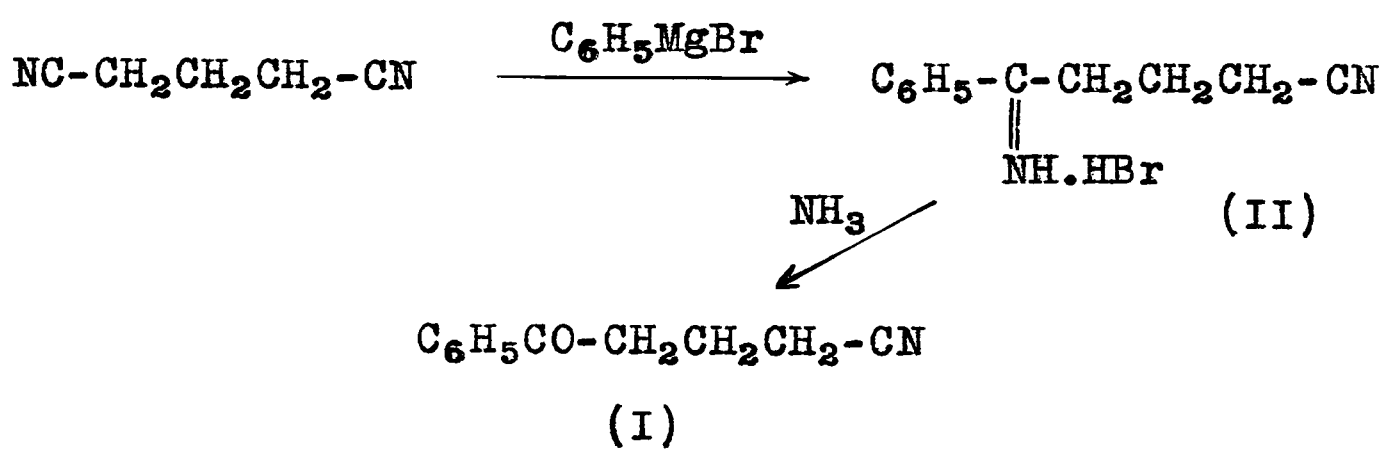
(IV)

Various methods which might possibly give the desired nitrile are as follows:

(a) Replacement of chlorine by the cyanide radical was at first considered to be the most feasible procedure. Boyer, working in this laboratory, treated γ-chlorobutyrophenone with potassium cyanide, but obtained no trace of the nitrile (I). An excellent yield of benzoylcyclopropane was obtained however (20). The same substance resulted when the alkali cyanide was replaced by copper cyanide.



(b) The next most logical procedure appeared to be the treatment of glutaronitrile with phenyl magnesium bromide, as described by Bruylants, the expected course of the reaction being as follows:



As will be shown, however, the compound formed is the tetrahydropyridine (IV).

(c) A third possible preparation was the Friedel-Crafts reaction of γ-cyanobutyryl chloride on benzene. This was rejected because of the inaccessibility of the acid and the lack of analogous cases involving nitriles.

(d) The fourth method involved the dehydration of the corresponding amide (IX).

$$C_6H_5COCH_2CH_2CH_2CONH_2 \xrightarrow{-\ H_2O} C_6H_5COCH_2CH_2CH_2CN$$

(IX) (I)

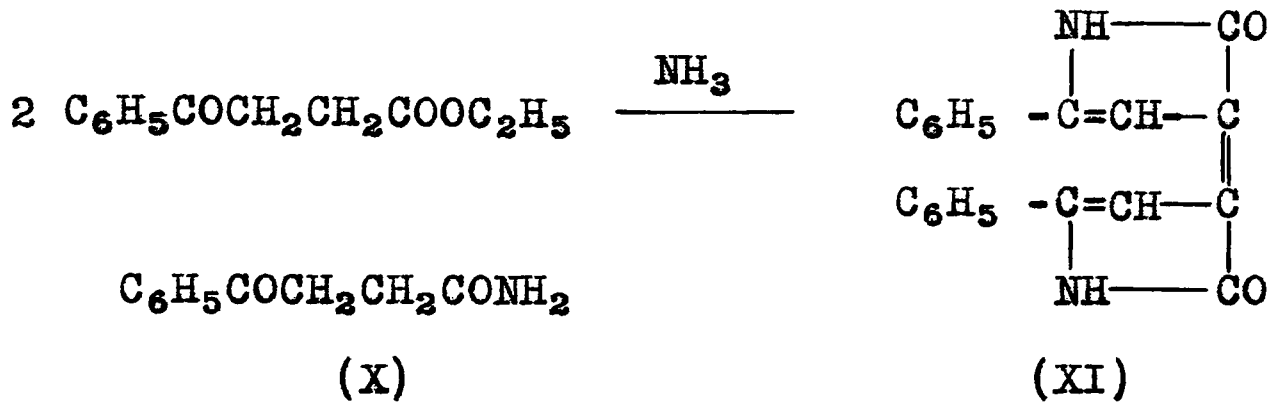
The preparation of the amide which was finally adopted, i.e., the action of ammonia on the corresponding ester, was very similar to one employed by Kugel (21) in an attempt to prepare β-benzoylpropionamide (X). Since Biedermann had shown that the action of ammonia on certain ketonic esters gave cyclic compounds it was thought that this method would be inapplicable; however, when tried as a last resource it proved successful.

. . . . . .

Kugel's observations are interesting since they are very closely paralleled by certain ones made in the present investigation. He heated β-benzoylpropionic ester and alcoholic ammonia in a sealed tube at 100° C. The solution was observed to become blue, then wine red. Cooling the tube after the reaction had proceeded for some time caused the precipitation of a bronze substance and on opening the tube and allowing the contents to stand a yellow product was obtained. The yields of these products were very small and too prolonged heating gave intractable mixtures. On purification the yellow product melted at 233° C. and analysed for $C_{10}H_9ON$. It dissolved in concentrated sulfuric acid and was reprecipitated by the addition of water. The compound was not β-cyano-

propiophenone which has been obtained in another investigation in this laboratory (22).

The bronze substance, while showing no melting point, sublimed on ignition. Under a microscope it appeared as fine blue leaves. It analysed for $C_{10}H_7ON$ and he assigned the following formula (XI) to it.



$$2\ C_6H_5COCH_2CH_2COOC_2H_5 \xrightarrow{NH_3} C_6H_5COCH_2CH_2CONH_2$$

(X)

(XI)

It gave a blue solution in phenol and was precipitated from sulfuric acid, in which it was readily soluble, by the addition of water. In alcoholic potassium hydroxide the blue color disappeared and yellow plates were precipitated. The residue, which comprised the main part of the product, came out of the wine red solution by the addition of water. It could not be further purified.

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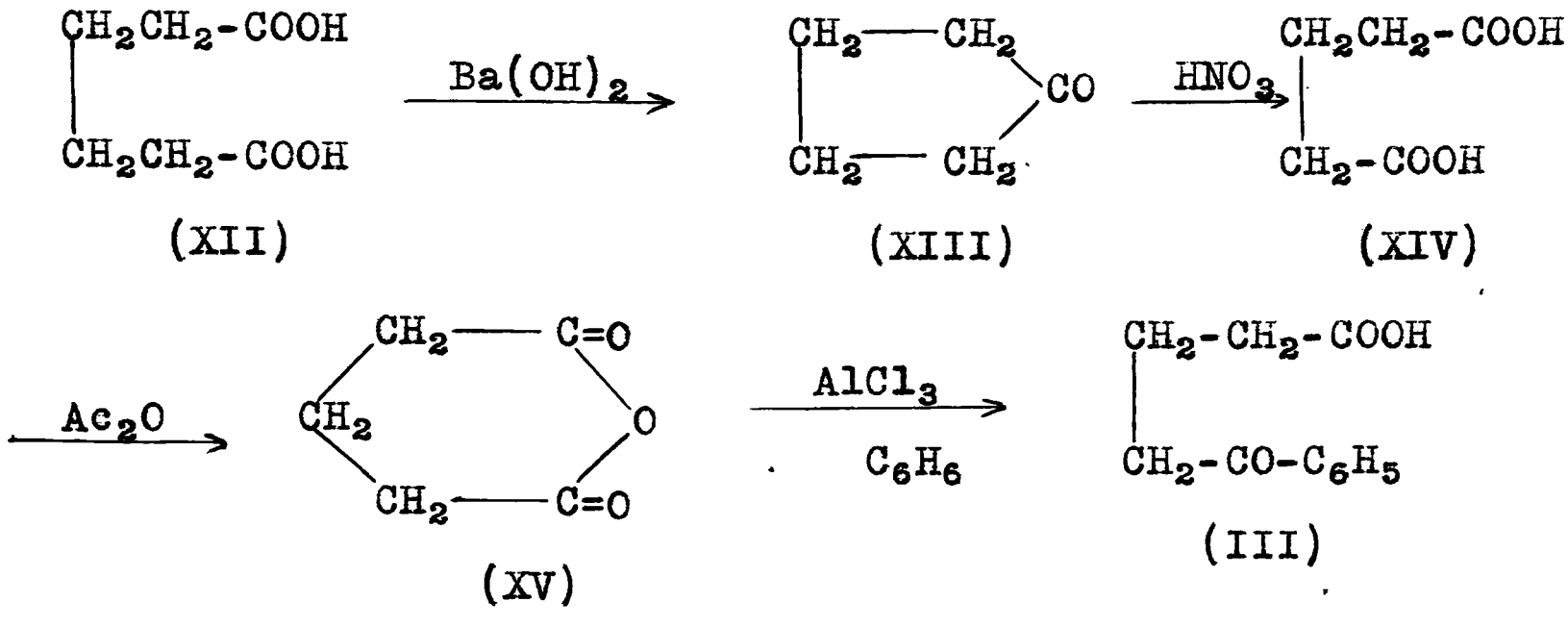
In the present investigation, the amide was prepared by the following series of steps:



On passing anhydrous ammonia into a methyl alcohol solution of γ-benzoylbutyric ester (XVI) and heating the solution in a sealed tube at 100° C., practically the same color changes were observed as Kugel had described as occuring from this treatment of the lower member. A yellow product separated on allowing the solution to evaporate, but it could not be further purified by recrystallization.

If the reaction were allowed to stand for a week at room temperature, the solution became wine red at first, deepening to purple. A metallic appearing product, having properties similar to Kugel's "bronze" substance, precipitated

in small amount. On allowing the alcoholic solution to evaporate, a white product was isolated. This analysed for $C_{11}H_{16}O_2N_2$, that is, the amide (IX) plus a molecule of ammonia. This product, on standing or heating in solvents, readily lost ammonia, and yielded the desired amide.

In the hope of obtaining this amide Somerville (23) of this laboratory, passed anhydrous ammonia into molten γ-benzoylbutyric acid. The product he obtained has been shown in this investigation to be the tetrahydropyridine (IV).

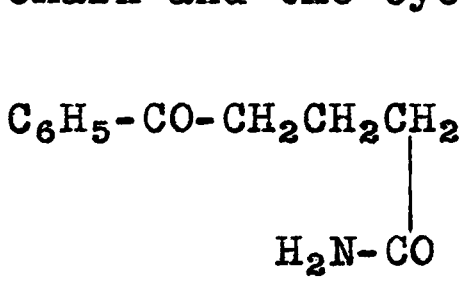
The nitrile (I), which was readily prepared by dehydrating the amide (IX) with acetic anhydride, was isolated by distillation in vacuo. It came over as a viscous oil which solidified at room temperature to a white solid melting at 37-38° C. In most preparations it was accompanied by a small amount of the higher melting isomer (IV).

The nitrile was converted to γ-benzoylbutyramide (IX) by the action of anhydrous hydrogen bromide in chloroform. On hydrolysis with mineral acids both the nitrile and the amide gave γ-benzoylbutyric acid. The ease of hydrolysis was so marked that it was only by working very carefully that the reaction could be stopped before the formation of the acid.

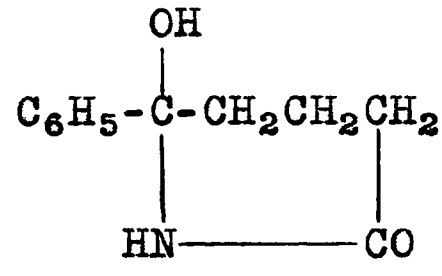
In various attempts to isomerize the nitrile to the tetrahydropyridine, by the action of anhydrous hydrogen bromide in acetic acid, hydrolysis to the acid usually took place,

unless the reagents were extremely dry. With this precaution the reaction could be stopped at the formation of the intermediate amide (IX). Apparently the small amount of moisture in the apparatus was sufficient to convert the small amount of nitrile (in most runs less than one gram) to the amide.

In the first attempt to obtain γ-benzoylbutyronitrile (I) by dehydrating the amide, use was made of acetyl chloride. The product which resulted, however, was the tetrahydropyridine (IV). This proved to be identical with the substance obtained by a repetition of the work in which Bruylants attempted to prepare the nitrile(I). Heating the amide in air also brought about dehydration, the cyclic compound again being formed. These reactions may possibly indicate that the amide exists as a mobile equilibrium mixture of the open chain and the cyclic forms.



(IX)



In accord with a tetrahydropyridine structure (IV) it was found that the substance decolorized bromine instantly and a bromide-bromate titration indicated that 106% of the theoretical amount of bromine had been absorbed, calculated

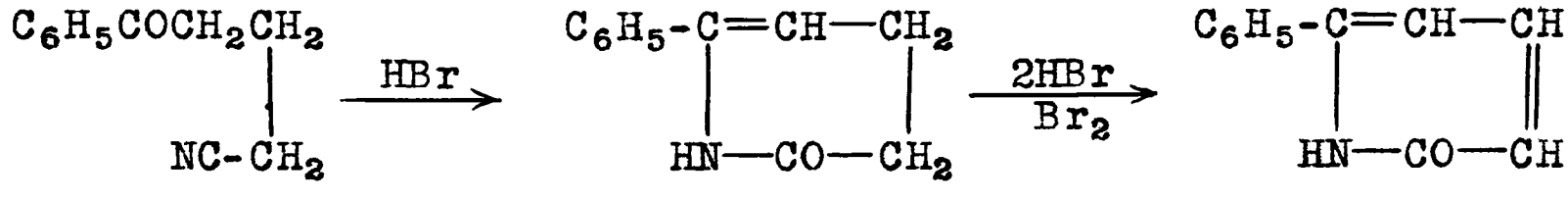
on the basis of one mole of bromine per mole of substance. No pure substance could be isolated from the oily mass that resulted from the action of bromine. Hydrogen bromide was evolved after about two-thirds of the theoretical amount of bromine had been added.

An unexpected development was the formation of a dinitrophenylhydrazone, which proved to be identical with the one prepared from the amide. Clearly the ring must have been opened and water added. However, it is well known that the tetrahydropyridine rings are readily opened by acids to yield open chain compounds (8), and in this case it is necessary to use an acid catalyst. Bruylants also noticed the ease with which this substance was hydrolysed to γ-benzoylbutyric acid. Young, in this laboratory, has found that 2,5-dimethylpyrrol almost instantly gives the mono-2,4-dinitrophenylhydrazone of acetonyl acetone (24), a comparable instance of ease of ring opening.

From the frequency with which it has occurred and from the widely divergent procedures that have resulted in its formation, it may be concluded that the tetrahydropyridine is considerably more readily formed than its straight-chain isomer, the nitrile.

The action of bromine on the nitrile in chloroform caused the evolution of hydrogen bromide and yielded an oily

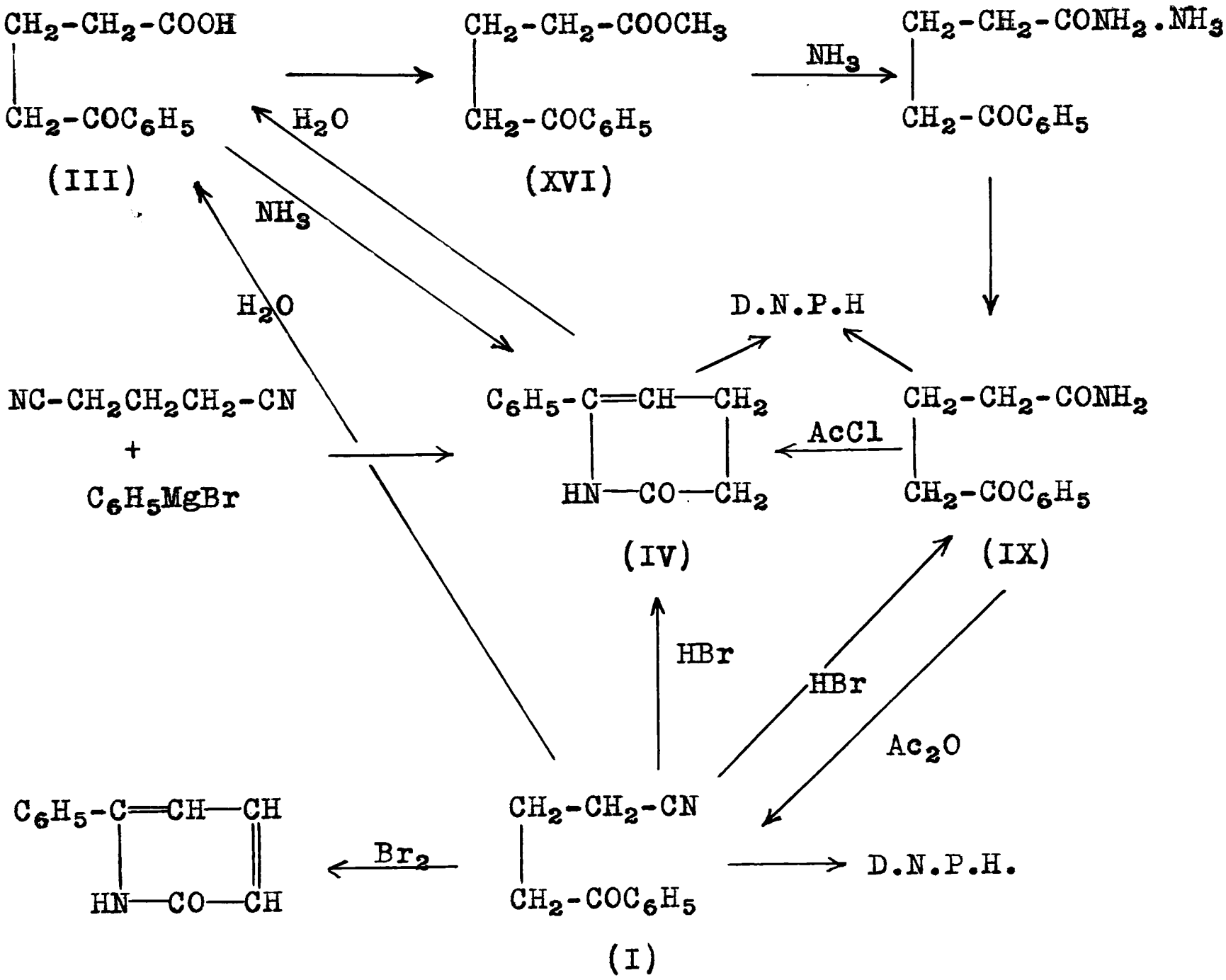
product containing a trace of a solid having chemical and physical properties corresponding to those of α-phenylpyridone (XVII)(*), the formation of which may be accounted for by assuming that a trace of hydrogen bromide was present or generated and isomerized the nitrile to the tetrahydropyridine and that the bromine then removed the two hydrogen atoms. Dehydration by bromine is characteristic of tetrahydropyridines.



(I) (IV) (XVII)

These reactions may be conveniently summarized in the flow sheet on the following page.

(*) Since this thesis was written, Mr. J.C. Evans in this laboratory has synthesized some α-phenylpyridone by the directions given in the literature, and found it to be identical with that described here.



D.N.P.H. = 2,4-dinitrophenylhydrazone.

Experimental.

The Preparation of Starting Materials.

Cyclopentanone (XIII) was prepared by heating adipic acid (XII) with barium hydroxide (25).

Glutaric Acid (XIV).

This was easily and cheaply prepared by the oxidation of cyclopentanone with nitric acid. The oxidation needs careful control since if the temperature rises too high the reaction gets out of hand and a considerable part of the cyclopentanone is converted into succinic acid.

In a 2-liter round bottom 3-necked flask fitted with a stirrer and two large bore condensers were placed 200 cc. of 50% nitric acid and 0.25 g. of vanadium pentoxide. The flask was heated to 65-70° C. in a water bath (thermometer in the water) and 1 cc. of cyclopentanone added to start the reaction. Oxidation is indicated by the production of the brown fumes of nitric oxide. When this was observed the water bath was removed and the remainder of 42 g. of the cyclic ketone added from a dropping funnel through one of

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Note: This preparation has been published in Organic Syntheses, Vol. XIV, p. 90.

the condensers at the rate of a drop every 3 seconds. This rate of addition maintained the reaction temperature at about 70° C. If the temperature was allowed to drop, oxidation ceased, when ketone accumulated and on heating the reaction might proceed explosively. In such a case or if the temperature was allowed to rise much above 70° C. succinic acid was formed in considerable amount. After addition had been completed, the water bath was replaced and heated to boiling. The contents of the flask were then poured into an evaporating dish and the volume reduced to half on a steam bath in a fume cupboard. When cold the acid was filtered, the filtrate again evaporated down and a new crop of crystals obtained. This last product was yellowish, but on washing with dilute hydrochloric acid most of the color was removed. If it was suspected that much succinic acid had been formed, this was almost entirely removed by allowing the solution to cool before evaporating, when the acid crystallized out. The crude glutaric acid was almost pure white in color. In several runs, yields of 50-55 g. (80-85%) were obtained, m.p. 92-4° C. It was found more convenient to allow the mother liquor from several runs to accumulate and work them up together. From each run 2-3 more g. of glutaric acid could be obtained in this way. Further purification was brought about if necessary by the use of the original directions for the preparation of glutaric acid (26).

The acid as prepared above, although containing traces of nitric acid, was satisfactory for conversion into the anhydride. In the absence of the catalyst the yield was decreased by about 10%.

Glutaric Anhydride (XV).

This was prepared by heating a mixture of 50 g. of glutaric acid and 100 g. of acetic anhydride under a reflux condenser for 5 hours and then distilling under diminished pressure (27). The anhydride boiled at 145-150° C. at 12 mm. and was obtained in 95% yield (41 g.). On cooling, it solidified to a white solid, m.p. 56-57° C.

γ-Benzoylbutyric acid. (III)

This acid was prepared from glutaric anhydride and benzene in the presence of aluminium chloride according to a method developed in this laboratory (28).

γ-Benzoylbutyric Ester (XVI).

The methyl ester of γ-benzoylbutyric acid was prepared by treating the acid in methyl alcohol with anhydrous hydrochloric acid. It was readily obtainable in 85-90% yields.

B. The Action of Ammonia on γ-Benzoylbutyric Ester.

The action of ammonia in various media was investigated.

Gaseous ammonia was led into a solution of 25 g. of ester in 75 cc. of methyl alcohol in a glass-stoppered flask until the solution was saturated. The flask was then closed and allowed to stand for a week. The solution slowly became a wine-red color which deepened to purple. On pouring into a beaker and allowing to evaporate, a white product separated around the edge of the beaker. This, when removed and washed with ether, melted at 110-115° C. This solid was dissolved in a slight excess of chloroform and ether (1:1 mixture), the solution warmed until the ether boiled and then allowed to cool slowly in a beaker covered with a watch glass. Rosettes of white needles melting at 118-120° precipitated, while the solution from which they were obtained remained purple. On being allowed to stand over night, the product melted at 115-122° C., with decomposition to a blue liquid. After having been twice recrystallized from benzene, the product melted at 120-121° C. Heating of this product caused the evolution of ammonia. The yield was small due to the formation of a large amount of a brown oily product. The product melting at 121° decolorized bromine in carbon tetrachloride only on warming and a solution of potassium permanganate containing it became brown only on warming also. The bromine addition

product obtained in the first test was more soluble in water than in carbon tetrachloride. Evaporation of the water layer yielded a small amount of a product melting at 100-105°, but no further investigation of this latter substance was made.

The addition of ether to the original alcohol filtrate caused the precipitation of more of the compound melting at 121°, the total yield being 8.5 g. (34%).

On warming in benzene, chloroform and carbon tetrachloride this compound dissolved forming a reddish solution, the color of which became lighter on cooling. If heating had been continued for some time, cooling resulted in the precipitation of colorless needles of melting point 140-142°. These on being recrystallized once from benzene melted at 143-4°, the product coming down as plate-like rods.

Boiling the compound melting at 121° in water and recrystallizing from carbon tetrachloride also yielded the product melting at 144°. Heating the lower melting compound in air resulted in the evolution of ammonia and water, with the formation of a product melting at 150°. This was subsequently identified as the tetrahydropyridine (IV) obtained by Bruylants.

Anal: of the compound which melted at 121° ($C_6H_5COCH_2CH_2CH_2CONH_2.NH_3$)

Calc'd. for $C_{11}H_{16}O_2N_2$: C, 63.5; H, 7.7; N, 13.5.

Found: C, 63.9; H, 7.6; N, 13.9, 13.8.

γ-Benzoylbutyramide (IX).

(a) To 5 g. of γ-benzoylbutyric ester in a glass-stoppered flask were added 50 cc. of ammonium hydroxide and 10 cc. of ethyl alcohol. Mechanical shaking was continued for 4 hours and the contents of the flask allowed to stand over night. On pouring into a beaker and evaporating, a white product, melting over the range 110-125°, came down almost instantly. The melted product was purple and recrystallization from benzene yielded the amide, melting at 144°. The yield was 3.7 g. or 80% of the theoretical.

Anal. Calcd. for $C_{11}H_{13}O_2N$: C, 69.1; H, 6.8; N, 7.3.

Found: C, 69.4; H, 6.8; N, 7.3.
C, 69.6; H, 6.8; N, 7.2.

In another investigation no alcohol was added to the ammonium hydroxide. In this case the ester and ammonia did not form a solution and it was necessary to shake for a much longer time before an appreciable amount of the amide was formed. The final yield was approximately the same, however.

(b) As shown previously, heating the ammonia addition product yielded a substance melting at 144°. The latter was also isolated in considerable quantity from the oily residue left on evaporation of the filtrate from the lower melting compound, by the following procedure: the residue was shaken mechanically for several hours in an excess of ammonium hydroxide and the olive green, somewhat oily solid thus produced

filtered and dissolved in boiling water. A quantity of an oily black substance that floated on the surface of the water, solidified on cooling and was removed. From the remaining solution a light yellow product melting at 135° precipitated and was proved to be the amide. The black solid gave a red solution in benzene. Animal charcoal was added and after boiling for 5 minutes and filtering, the red solution deposited more of the yellow product melting at 135°. By thus working up the residues, 8 g. of relatively pure amide were obtained. The total yield was 70% of the theoretical.

Derivatives.

The 2,4-dinitrophenylhydrazone was prepared by adding 0.5 g. of the amide in 15 cc. of warm ethyl alcohol to a solution of 1 g. of 2,4-dinitrophenylhydrazine and 2 cc. of concentrated sulfuric acid in 15 cc. of alcohol. On cooling, a light orange product separated, and, after recrystallization from carbon tetrachloride or chloroform, melted at 182-184° C. Recrystallization from ethyl alcohol and ethyl acetate raised the melting point to 184-186°. From methyl alcohol and ethyl acetate clusters of orange rods with square ends were obtained, m.p. 195-6°.

Anal. Calcd. for $C_{17}H_{17}O_5N_5$: N, 18.8. Found: N, 18.6.

An attempt to prepare the semicarbazone by the usual procedure yielded long needles which melted over the range 135-140° C. All attempts at further purification were unsuccessful and an analysis for nitrogen was low.

The amide was readily hydrolysed to γ-benzoyl-butyric acid by boiling its chloroform solution with a few drops of hydrochloric acid.

The Metal-like Compound.

In an attempt to obtain a better yield of the amide by the second method described (action of anhydrous ammonia on the ester in methyl alcohol) the contents of the flask were allowed to stand stoppered for 3 weeks. At the end of this time it was noted that a small amount of a black crystalline solid had separated. This did not melt at 320°, but when heated on a spatula, it sublimed in brown fumes. It was readily soluble in concentrated sulfuric acid with a blue color but was reprecipitated by the addition of water. In acid it gave a blue solution and in base a colorless one. Its properties were thus very similar to the "bronze substance" of Kugel (21).

The filtrate, when treated as previously (see section on the action of ammonia on the ester) yielded first the compound melting at 121° and then the amide melting at 144°.

Unsuccessful Attempts to Prepare the Amide.

(a) Anhydrous ammonia was passed into an ethereal solution of the ester. A small amount of a product came down immediately. This melted at 105-110° C. Evaporation of the filtrate yielded the unchanged ester, however.

(b) Five g. of the ester were placed in a sealed tube with 15 cc. of methyl alcohol which had been saturated with anhydrous ammonia. The tube was then heated to 100° for 2 hours. During this time the solution became red, rather than purple as before. On allowing the solution to evaporate, a yellow amorphous product, which could not be further purified, separated.

C. The Tetrahydropyridine (IV).

This was obtained by several widely different methods during the course of this investigation.

(a) The amide (IX) was refluxed with acetyl chloride for 30 minutes and the white solid that separated was filtered and washed with ether. The melting point was 155° C. Evaporation of the filtrate left an oily residue which, when distilled under 10 mm. pressure, boiled at 170°. On cooling the distillate solidified and proved to be the same as the product obtained above.

(b) On heating the amide (IX) in a test tube the mass became first blue, then red and finally brown. Recrystallization from ethyl alcohol and animal charcoal yielded a product melting at 150°, which proved again to be the tetrahydropyridine. (IV)

(c) A third method by which the tetrahydropyridine resulted is taken from a report by Mr. L. F. Somerville of this laboratory (23). Briefly, dry ammonia was bubbled through molten γ-benzoylbutyric acid in a test tube, heated to a temperature of 160-170° in an oil bath for 9 hours. A white solid was obtained which when recrystallized from benzene melted at 146-150°. In the present investigation recrystallization from carbon tetrachloride raised the melting point to 151-153°. Further attampts at purification tended to cause the product to become oily. A mixed melting point with a sample prepared according to Bruylants directions for preparing the nitrile showed no depression.

(d) The last method was by a repetition of Bruylants' work (11). Outlined briefly, this was as follows: in 100 cc. of dry ether 5 g. of magnesium and 38 g. of bromobenzene were allowed to react. This, when filtered, constituted solution A. In another flask were placed 9.4 g. of glutaronitrile and 12 cc. of toluene. Solution A was then added with cooling. The reaction mixture was decomposed by pouring on

ice,and allowed to stand. The ether layer, when evaporated, left an oily residue which, on vacuum distillation and recrystallization, yielded a solid melting at 174° C. This product, when dissolved in water and treated with ammonia at 50°, gave the tetrahydropyridine which, even after several recrystallizations from methyl alcohol, melted over the range 145-150° C.

Bromide-bromate Titration.

A sample of the pyridine weighing 0.2 g. was dissolved in 10 cc. of carbon tetrachloride and 25 cc. of water added. An excess of standard bromide-bromate solution was added and back titrated with standard sodium thiosulfate.

Theoretical amount of bromine for one double bond = 0.185 g.

Amount of bromine used = 0.195 g.

Action of Nitrous Acid.

A sample of the pyridine was dissolved in acetic acid, an excess of sodium nitrite added, and the mixture allowed to stand over night. Evaporation of the solvent left an oil from which no solid product could be obtained.

The 2,4-Dinitrophenylhydrazone.

This derivative was prepared as previously described (page 31). On purification it was found to be identical to

the former one by a mixed melting point. The 2,4-dinitrophenylhydrazones from both these compounds showed a marked depression of melting points on the admixture of 2,4-dinitrophenylhydrazine. It may be noted that the melting point, 196° is very close to that of the reagent.

The Semicarbazone.

This was prepared in the usual manner and crystallized as rods melting over the range 145-152° C. Since it could not be further purified, no analysis was made.

D. γ-Benzoylbutyronitrile (I).

A solution of 5 g. of the amide (IX) in 25 cc. of acetic anhydride was allowed to stand in a closed flask over night. On removal of the solvent by evaporation at room temperature under reduced pressure the amide was recovered unchanged. The solution was made up to its original volume again and refluxed for 1 hour. When the product was distilled under 10 mm. it boiled at 135-140° C. and nearly all solidified on standing. Some of the solid, when spread on porous plate and washed with ether, melted at 37-38° C.

In several runs using 5 g. of starting material the yields varied between 3.5 and 4.0 g. (82-94% of the theoretical).

If impure amide was used, the acetic anhydride solution took on a deep red color and the distillate itself was reddish in color. This color disappeared when the product was allowed to stand for some days. Unless very pure the nitrile would not solidify at room temperature.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.3; H, 6.4.

Found: C, 76.2; H, 6.4.
C, 76.0; H, 6.5.

The 2,4-Dinitrophenylhydrazone.

To a solution of 0.5 g. of 2,4-dinitrophenylhydrazine in 15 cc. of ethyl alcohol containing 2 cc. of concentrated sulfuric acid were added 0.25 g. of the nitrile in 10 cc. of warm alcohol. On cooling, a slightly gummy mass came down. It was only sparingly soluble in ethyl alcohol but more readily so in ethyl acetate. When recrystallized from a mixture of one part of ethyl alcohol to two parts of ethyl acetate, reddish-brown plates were obtained, m.p. 173-175° C.

Anal. Calcd. for $C_{17}H_{15}O_4N_5$: N, 19.9; Found: N, 19.5.

The Semicarbazone.

To 25 cc. of ethyl alcohol were added 1 g. of the nitrile, 2 g. of semicarbazide hydrochloride and 4 g. of potassium acetate. The mixture was heated to boiling,

allowed to cool and the sodium chloride filtered off. The filtrate was set aside for about 12 hours when thick needles of a product melting at 165-176° C. were precipitated. Recrystallization from ethyl alcohol raised the melting point to 173-176°. From a 1:1 mixture of chloroform and carbon tetrachloride well-defined monoclinic plates melting at 176-177° C. were obtained.

Anal. Calcd. for $C_{12}H_{14}ON_4$: N, 24.3; Found: N, 24.1.

E. Reactions of the Nitrile.

In many attempts to convert the nitrile to the isomeric tetrahydropyridine (IV) by the action of mineral acids, hydrolysis to γ-benzoylbutyric acid (III) resulted. In no case was the pyridine obtained directly, but the intermediate amide (IX) was isolated and could be converted to the pyridine by several different methods as seen before.

A solution of 0.6 g. of the nitrile in 35 cc. of chloroform was saturated with hydrogen bromide and allowed to stand stoppered over night. The solution became green and on allowing the chloroform to evaporate, a semi-solid brownish mass precipitated. When pressed out on a piece of porous plate and washed with ether, a white solid resulted, which melted to a red liquid at 205-210° C. It was probably an "imide bromide". It was not obtained in a pure state but

when taken up in ethyl alcohol it yielded γ-benzoylbutyric acid.

A similar procedure was carried out with acetic acid as the solvent. The acid was distilled under vacuo and the residue boiled with water. On cooling a large amount of a white product, which proved to be γ-benzoylbutyric acid again, was precipitated.

Formation of the Amide from the Nitrile.

The same procedure was prepeated, using chloroform as the solvent, but in this case care was taken to have the reagents dry. The product left on evaporation of the chloroform was taken up in absolute ethyl alcohol and 1 g. of potassium acetate added. The solution was then evaporated to dryness, the residue taken up in benzene and the inorganic material filtered off. On evaporation of the filtrate and recrystallization of the product from carbon tetrachloride, the amide (IX) was obtained. It was identified by a mixed melting point with an authentic sample.

The Action of Bromine on the Nitrile.

To 1 g. of the nitrile in 20 cc. of acetic acid was added an excess of bromine. On warming, the color at first decreased, but later became very dark. When the flask was opened fumes of hydrogen bromide came off. The solution

was poured into water containing sodium bisulfite and the black oily mass which came down was extracted with ether. Sodium bicarbonate was added to the ether solution and the mixture allowed to stand. The inorganic material was filtered off and the ether filtrate allowed to evaporate. The oily product thus precipitated did not solidify even on standing for several weeks.

The same experiment was carried out using chloroform as solvent. Darkening of the solution and evolution of hydrogen bromide were observed as before. In this case the chloroform was allowed to evaporate off and the residue taken up with ether and treated as before. No better result was obtained.

These somewhat rough investigations having proved unsuccessful, the problem was now undertaken more carefully.

To 3 g. of nitrile in 50 cc. of chloroform were added 3 g. of bromine in 50 cc. of the same solvent. The color of the bromine continued to disappear until about three quarters had been added, when the evolution of hydrogen bromide was observed. On standing the solution became almost black. The solvent was then mostly evaporated off on a steam bath and the residue distilled under reduced pressure. At 20 mm. the first fraction came over at 180° C. and the second, which mainly solidified, at 190° C.

On being recrystallized from methyl alcohol, a product melting at 190-193° C. was obtained as a mat of flat rods with square ends. It was very soluble in chloroform and quite soluble in benzene and carbon tetrachloride. While apparently crystallizing well from 80-90° petroleum ether, the melting point of the product so obtained was 180-185° C. It was soluble in hot water but insoluble in cold. A qualitative test showed no indication of halogen.

Some of the product obtained above was dissolved in concentrated hydrochloric acid and the acid evaporated off under reduced pressure. An oily solid melting at 95-100° remained, which, on pressing out on a piece of porous plate and washing with ether, melted at 101-103° C.

The properties of the higher melting compound agree well with those reported for α-phenylpyridone (29) (XVII). This substance is reported to melt at 195° C., act in solvents as did the one described above, and yield a hydrochloride melting at 104° C. The yield was so small, however, that the product could not be sufficiently purified for analysis.

Attempted Preparations of α-Phenylpyridone (XVII).

This substance was required for a mixed melting point with the substance prepared in the last investigation.

Two methods which should theoretically have yielded this product, but which failed due to experimental difficulties, will be outlined below.

(a) An investigator in this laboratory (5) has prepared phenylpropargyl aldehyde (XVIII) from cinnamic aldehyde by a series of already published procedures.

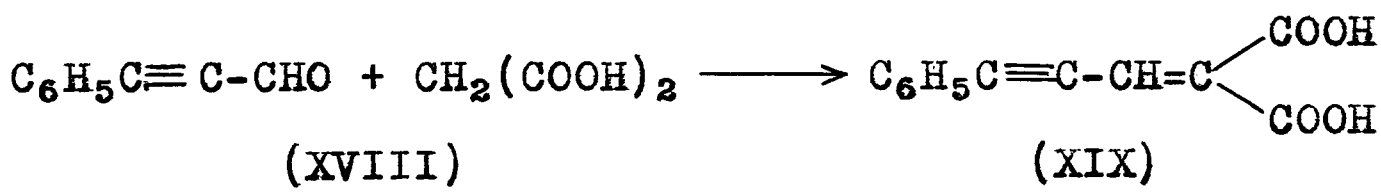
Beginning with phenylpropargyl aldehyde, the steps which were expected to lead to the formation of phenylpyridone are outlined as follows:

Phenylpropargyl aldehyde (XVIII) + Malonic acid

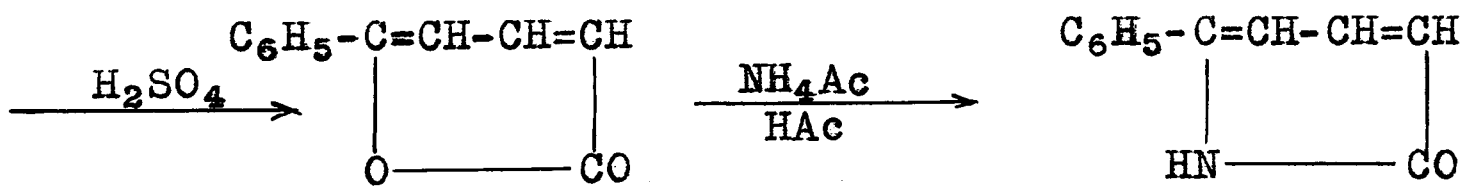
↓

Phenylpropargylidene malonic acid (XIX)

⟶ Phenyl Coumalin (XX) ⟶ Phenylpyridone (XVII)



(XVIII) (XIX)



(XX) (XVII)

Phenyl coumalin has been prepared (30) by the steps outlined above but the yields reported were only 10-15% of the theoretical even when samples as large as 5 g. were used.

In the present investigation only about 4 g. of the diacid were available in all, and in only one case was any phenyl coumalin isolated. This was not obtained in sufficient quantity to be used in the next step.

Phenylpropargylidine Malonic Acid (XIX)

Equimolecular quantities of phenylpropargyl aldehyde and malonic acid in 1.5 times their weight of acetic acid were heated on a water bath for 4 hours. The yellow product which came down, when washed with acetic acid and water and dried, melted at about 210° C. The pure product is reported to melt at 218° C.

Phenyl Coumalin (XX)

The product obtained above was boiled with 49% sulfuric acid for 4 hours, the insoluble matter filtered from the cooled solution and the filtrate diluted with an equal volume of water. After standing at 0° C. for 24 hours, one run yielded a few crystals of a substance melting at 65°. The melting point of the pure product is reported as 68° C.

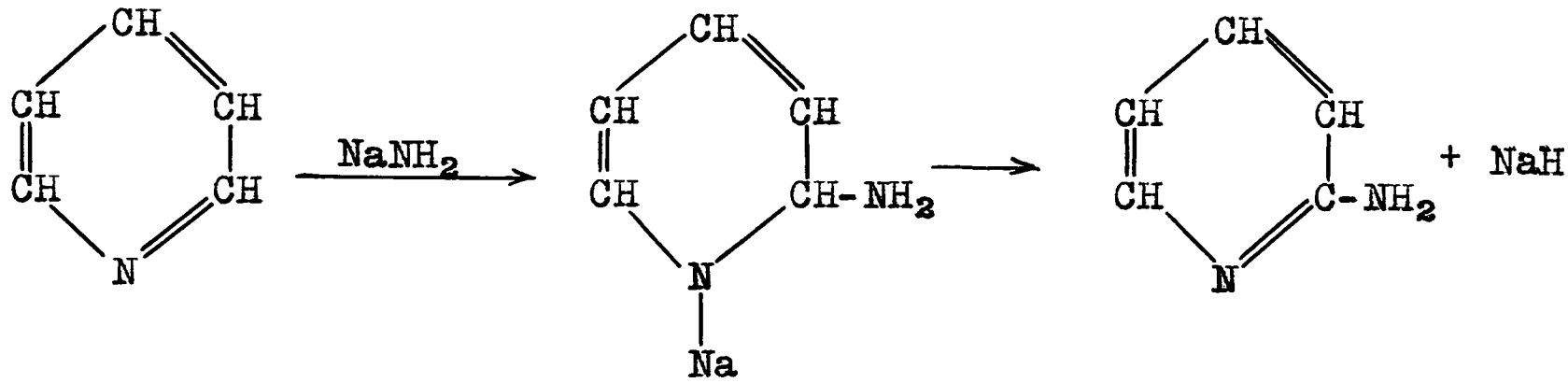
Attempt to Prepare Phenylpyridone (XVII)

In several runs in the previous preparation, the addition of water to the acid solution precipitated a small

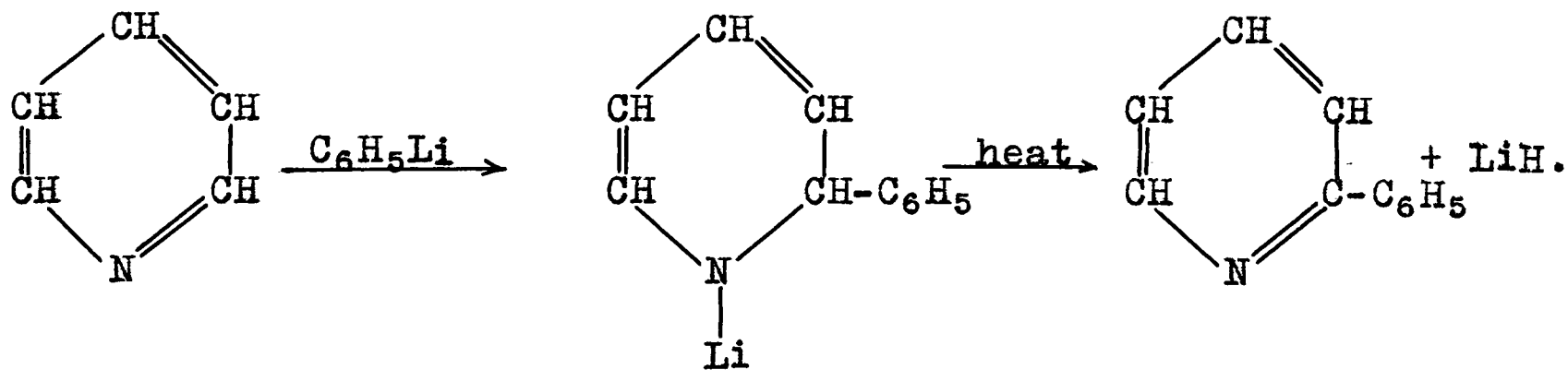
amount of a yellow product. This was treated according to the directions for the preparation of phenylpyridone (29) but no product with its properties was isolated.

(b) Another method which should theoretically lead to the formation of phenylpyridone was suggested by a summary of the chemistry of pyridine by Maier-Bode (31).

Aminopyridine has been prepared as outlined below (32):

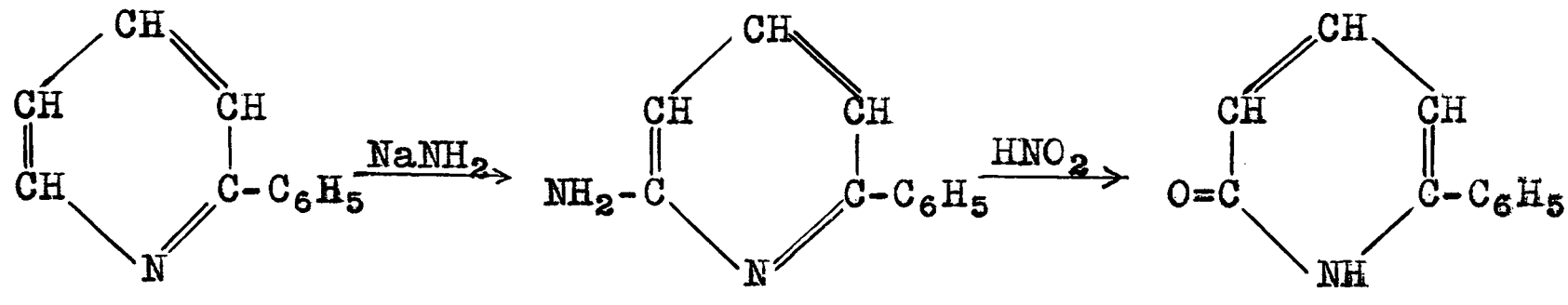


α-Phenylpyridone has been prepared as follows (33):



Now by a combination of the two foregoing steps, it should be possible to synthesize α-phenyl- α'aminopyridine. This product could then be oxidized to α-phenylpyridone (XVII).

This procedure could be outlined as shown below:



(XVII)

Phenylpyridine was obtained, but in several attempts, no trace of phenylaminopyridine could be isolated. (*)

2-Phenylpyridine.

Phenyllithium was obtained by a repetition of the instructions of Ziegler and Colonius (34).

To 0.35 g. of metallic lithium in 25 cc. of very dry ether were added through a dropping funnel 8.75 g. of bromobenzene in the same solvent. The reaction started almost immediately. When it had ceased, the flask was allowed to stand stoppered for 24 hours, the ether solution of the lithium alkyl was then decanted off from the lithium bromide.

(*) Another worker in this laboratory has carried on a more complete investigation of this reaction since this thesis was completed, and found that the action of sodium amide on 2-phenylpyridine gives high molecular weight products with no evidence of any of the 2'-amino derivative desired.

A slight excess of pyridine (dried over barium oxide) in benzene was added and a considerable evolution of heat occurred. When the vigorous reaction had ceased, the mixture was heated on a steam bath of 30 minutes. The product was then distilled in vacuo. The yields reported in the literature(*) were not duplicated, but a picrate derived from the product in the usual way melted at 175° C., as given in the literature.

(*) It has since been found that the yields are greatly improved if the pyridine is refluxed over quicklime.

Summary.

(1) The course of the reaction of ammonia on γ-benzoylbutyric ester has been determined. The final product has been shown to be γ-benzoylbutyramide.

(2) On dehydration with acetic anhydride this amide forms γ-benzoylbutyronitrile.

(3) The latter is readily hydrolysed, through the amide (which may be isolated), to γ-benzoylbutyric acid.

(4) The behaviour of the nitrile with halogen acids is like that of other δ-ketonic nitriles, but the action of bromine could not be definitely determined.

(5) The isomeric tetrahydropyridine has been obtained by the dehydration of the amide with acetyl chloride, by the action of anhydrous ammonia on γ-benzoylbutyric acid and by treating glutaronitrile with phenyl magnesium bromide and ammonia.

(6) This cyclic compound shows the reactions which are typical of tetrahydropyridines and is readily converted into open chain compounds.

(7) Bruylants' supposed γ-benzoylbutyronitrile is in reality this cyclic tetrahydropyridine.

References.

1. Kohler, Graustein and Merrill, J.A.C.S., 44, 2536 (1922).
2. Kohler and Souther, J.A.C.S., 44, 2903 (1922).
3. Kohler and Allen, J.A.C.S., 46, 1522 (1924).
4. Lowry, Dissertation, Harvard University (1924).
5. Allen and Bell, Can. J. Research, 11, 40 (1934).
6. Allen, J.A.C.S., 49, 1112 (1927).
7. Corson, Dissertation, Harvard University (1924).
8. Kohler and Others, See 1, 2 and 3, above.
9. Barat, J. Indian Chem. Soc., 7, 321 (1930).
10. Allen and Scarrow, Can. J. Research, 11, 395 (1934).
11. Bruylants, Bull. Soc. chim. Belg., 32, 307 (1923).
12. Blaise, Compt. rend., 132, 38; 133, 299 (1901).
13. Grignard and Vignon, Compt. rend., 144, 1358 (1907).
14. Gorski, Schpanski and Muljar, Ber., 67B, 730 (1934).
15. Zelinsky and Moser, Ber., 35, 2684 (1902).
16. Schering Kahlbaum, German Patent 591,269.
17. Bruylants, Bull. sci. Acad. roy. Belg., (5) 7, 252 (1921).
18. Bruylants, Bull. sci. Acad. roy. Belg., (5) 8, 7 (1923).
19. Biedermann, Ber., 24, 4074 (1891).
20. Allen and Boyer, Can. J. Research, 9, 159 (1933).
21. Kugel, Ann., 299, 63 (1897).
22. Young, Unpublished work.

23. Somerville, Report, (1932).

24. Allen and Young, Can. J. Research, 10, 771 (1934).

25. Organic Syntheses, Coll. Vol. I, p. 187.

26. Organic Syntheses, Vol. X, p. 58.

27. Sircar, J.C.S., 902 (1928).

28. Organic Syntheses, Vol. XIII, p. 13.

29. Leben, Ber., 29, 1678 (1896).

30. Kalff, Rec. Trav. Chim., 46, 594 (1927).

31. Maier-Bode, Zeit. ang. Chem., 49 (1931).

32. Tschitschibabin and Seide, J. Russ. Chem. Ges., 46, 1216 (1914).

33. Ziegler and Zeiser, Ber., 63, 1847 (1930).

34. Ziegler and Colonius, Ann., 479, 135 (1930).

DIHYDRO-p-TOLUALDEHYDE.

Introduction.

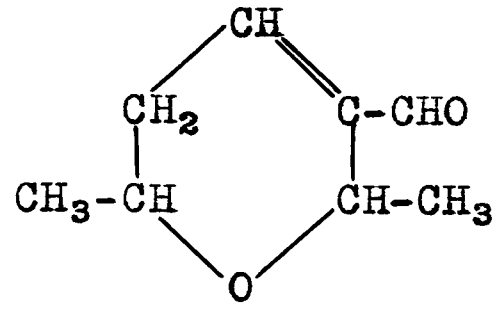
Crotonaldehyde is prepared commercially in large amounts by the condensation of acetaldehyde with itself in the presence of acidic catalysts. After the product has been distilled, an oil remains in the stills. This accumulates in considerable amounts in the large tonnages involved. On distillation in vacuo, several fractions, which appear to be more or less homogeneous, may be collected.

The purpose of this investigation has been to identify one or more of the principal constituents of this residue.

The literature contains a number of references to the formation of condensation products from crotonaldehyde. In 1892 Kekule (1) condensed crotonaldehyde with acetaldehyde by the action of zinc chloride and obtained hexadienal. Doebner in 1900 (2) further condensed this latter compound with malonic acid, obtaining octatrienic acid. This reaction was brought about in pyridine solution.

Note: This work has been published in the Canadian Journal of Research, 9, 169-174 (1933).

Delepine (3) prepared what he has described as a dimer of crotonaldehyde by the action of concentrated sulfuric acid on paraldehyde. This compound analyzed for $C_8H_{12}O_2$. He assigned the following formula to it.



It was a liquid with properties similar to those of the oils obtained as by-products in the commercial preparation of crotonaldehyde.

While working on the determination of the cause of color in unsaturated hydrocarbons, Kuhn (4) made a number of polyenes by starting with unsaturated aldehydes of the type of some met with in the present investigation. In further researches (5,6) he found that by condensing acetaldehyde with itself in the presence of piperidine and then the crotonaldehyde so formed with more acetaldehyde, he obtained first hexadienal and then octatrienal. That this last compound could not be formed from pure crotonaldehyde he showed by carefully drying and purifying a sample of crotonaldehyde. It then would not condense with itself under

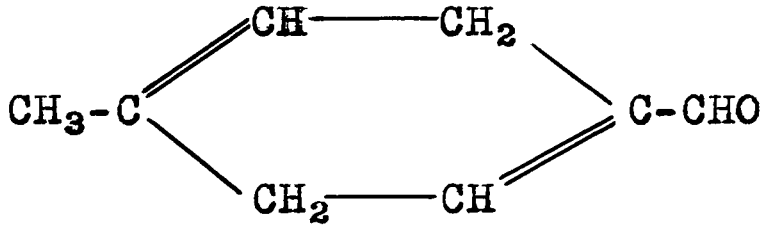
the above mentioned conditions, the unchanged aldehyde being recovered in all cases. The presence of a very small amount of water caused the hydrolysis of the crotonaldehyde to acetaldehyde, and this then reacted with the remaining crotonaldehyde, the reaction continuing until all the croton-aldehyde had reacted. Both hexadienal and octatrienal were found to add much less than the calculated amount of bromine. As they were difficult to separate by distillation, separation was finally effected by utilizing the differences in the solubilities of their bisulfite addition products.

Discussion of the Work.

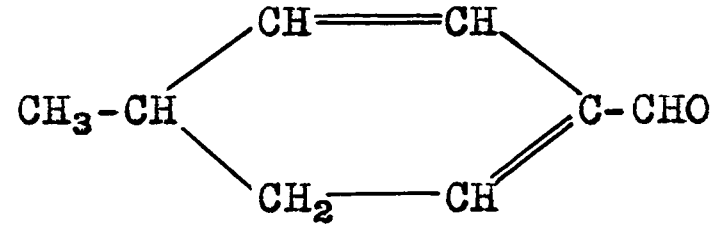
Several samples of the residual oils, obtained as by-products in the commercial preparation of crotonaldehyde, were received in this laboratory from the Shawinigan Chemicals Company.

They were all found to be rather viscous yellow oils which decolorized bromine and permanganate readily and gave addition products with sodium bisulfite. This indicated the presence of an unsaturated aldehyde or methyl ketone. When submitted to slow fractionation under reduced pressure, two main fractions were obtained, A (b.p. 68° C. at 10 mm.) and B (b.p. 77° C. at 10 mm.). Both of these decolorized bromine instantly, but in a short time evolved hydrogen

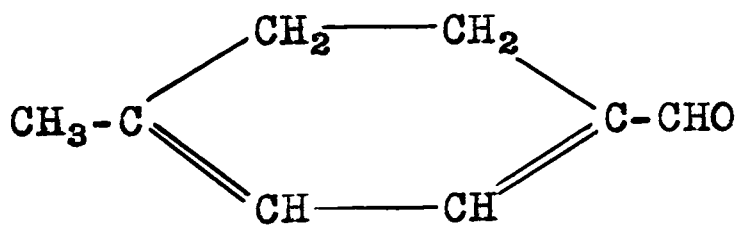
bromide. They reduced permanganate readily, formed addition products with sodium bisulfite and reduced Fehling's solution. With semicarbazide, 2,4-dinitrophenylhydrazine, hydrazine and cyanoacetic acid, they both gave the same derivatives. These derivatives differed in all cases from the corresponding ones of p-tolualdehyde. Upon oxidation with nitric acid, both gave p-toluic acid; with permanganate, the oxidation proceeded to terephthalic acid. In view of these properties, the substances would seem to be aldehydes and derivatives of dihydrobenzene, having a methyl group in the position para to the aldehyde group. Five structures for dihydro-p-tolualdehydes are thus possible, as shown below:



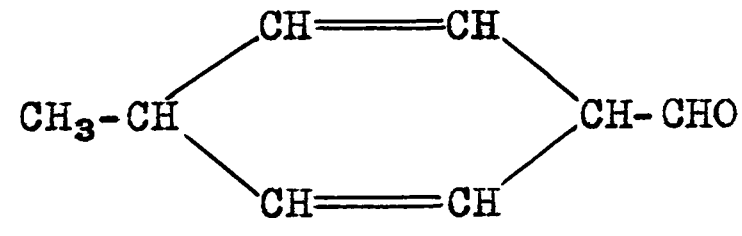
(I)



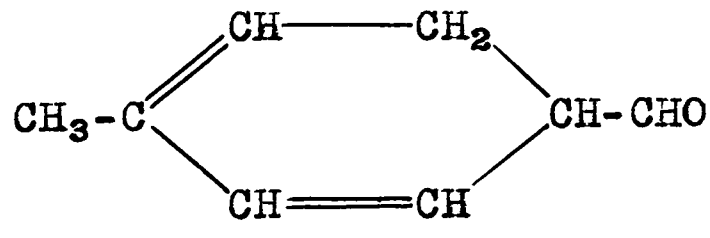
(II)



(III)



(IV)



(V)

Since structures (II, III and V) contain a conjugated system, a study of the addition products with maleic anhydride or α-naphthaquinone was expected to give a clue as to the nature of the substance. Neither fraction reacted, however, the anhydride or quinone being recovered unchanged. The aldehydes did not add 1,4-diphenylbutadiene. These facts cannot be used to exclude the three structures, for it is only when the Diels-Alder reaction is positive that it is of value in the determination of structure (7).

Ozone slowly oxidized both fractions, but the product was p-toluic acid. Fractions A and B were distinguished entirely by their physical properties, since in every instance they gave the same derivatives. The identities of these latter were established by melting points, mixed melting points, solubilities and crystallographic properties (*). The reactions yielding these derivatives were very rapid. In all cases investigated, however, A reacted somewhat more slowly and the yields were smaller. Both A and B were completely soluble in a saturated aqueous solution of sodium bisulfite, but when the

---

(*) These were determined by Professor R.P.D. Graham of the Department of Mineralogy, to whom the author expresses his indebtedness.

aldehyde was regenerated, B alone was found, (b.p. determination), but its physical properties were somewhat different. B was also regenerated from the semicarbazone, This would indicate that A contained some other substance. Although fraction A apparently reacted completely with sodium bisulfite, on washing the filtered bisulfite addition product with ether, evaporation of the wash left an oil of penetrating odor, which, on standing, resinified. No pure chemical compound could be isolated from this residue.

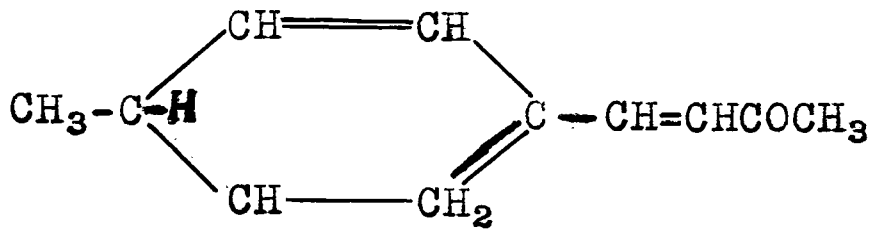
The physical properties of dihydro-p-tolualdehyde, as determined, are shown in Table I, along with those of p-tolualdehyde and hexadienal for comparison.

Table I

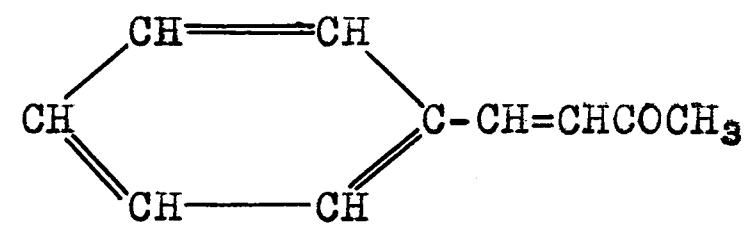
Substance	Boiling point, °C.		Density d_4^{20}	η_D^{20}	Molecular refraction
	At 10 mm.	At 760 mm.			
A	68	195	1.0035	1.5182	36.854
B	77		1.0150	1.5279	37.006
Regenerated from $NaHSO_3$ compound	77	202	1.0176	1.5408	37.661
p-Tolualdehyde	95	203	1.0297	1.5465	37.546
Hexadienal	64-6/11	173-4/754	0.9807_4^{22}	1.5372_D^{22}	

Octatrienal is a solid, m.p. 55° C., that polymerizes in a few hours (5).

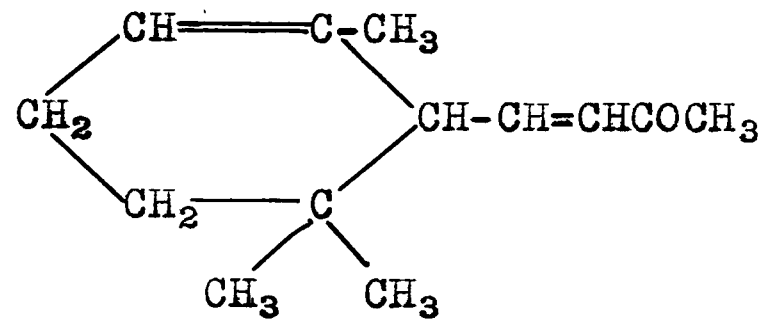
On condensing the aldehyde with acetone, a product (VI) was obtained which had an odor more like benzalacetone (VII) than like ionone (VIII).



(VI)

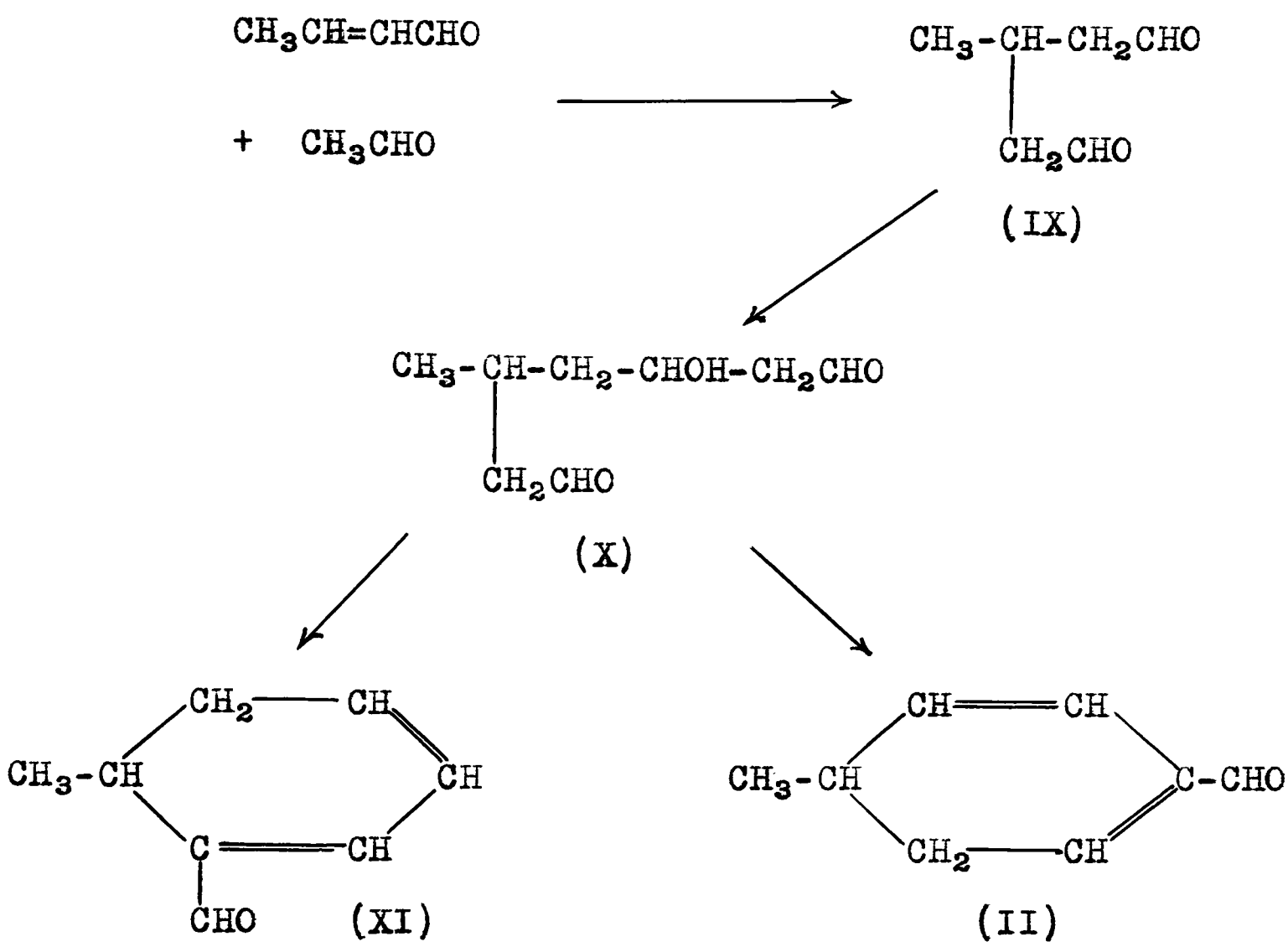


(VII)



(VIII)

A plausible mechanism which may explain the formation of both dihydro-p-tolualdehyde and the ortho-isomer is given below. The assumption has been made that acetaldehyde is always present, either initially or is produced by hydrolysis of crotonaldehyde. A molecule of acetaldehyde adds to the conjugated system of croton-aldehyde and the dialdehyde (IX) then adds a second molecule of acetaldehyde to form (X). This latter may condense with itself in two ways to form either the ortho- or para-isomer (II).



The location of the double bonds is not certain but one pair is probably conjugated with the carbonyl group in the side chain, since the molecular refraction shows an exaltation. Because of the ease of removal of two hydrogens, formula (I) may be favored.

While this work was in progress, a paper by Bernhauer in which he described the preparation of dihydro-o-tolualdehyde from crotonaldehyde, became available. He also described an aldehyde which from the meager details

given may have been dihydro-p-tolualdehyde. Bernhauer was first led into this field while attempting to prepare unsaturated compounds of the terpene-carotenoid type by condensing crotonaldehyde with itself in the presence of unstated organic bases. He obtained oily mixtures of open chain and cyclic unsaturated aldehydes. The first of these he isolated proved to be octatrienal (XII) (8). This substance was present only to a very slight extent in the higher-boiling fractions of the oil. It was identified by oxidation to octatrienic acid. Later (9) he obtained two liquid aldehydes of which the boiling points were determined as 71-3° C (A) and 97-8° C. (B) at 12 mm. Heating A in nitrogen gave an isomeric aldehyde (C). Oxidation of aldehyde B with silver oxide gave 1,2-dihydro-o-toluic acid which on dehydrogenation with bromine in a sealed tube, gave o-toluic acid. This proved definitely that the aldehyde was dihydro-o-tolualdehyde (XI). Aldehyde (C) was a slightly yellow oil of penetrating odor and painful to the eyes.

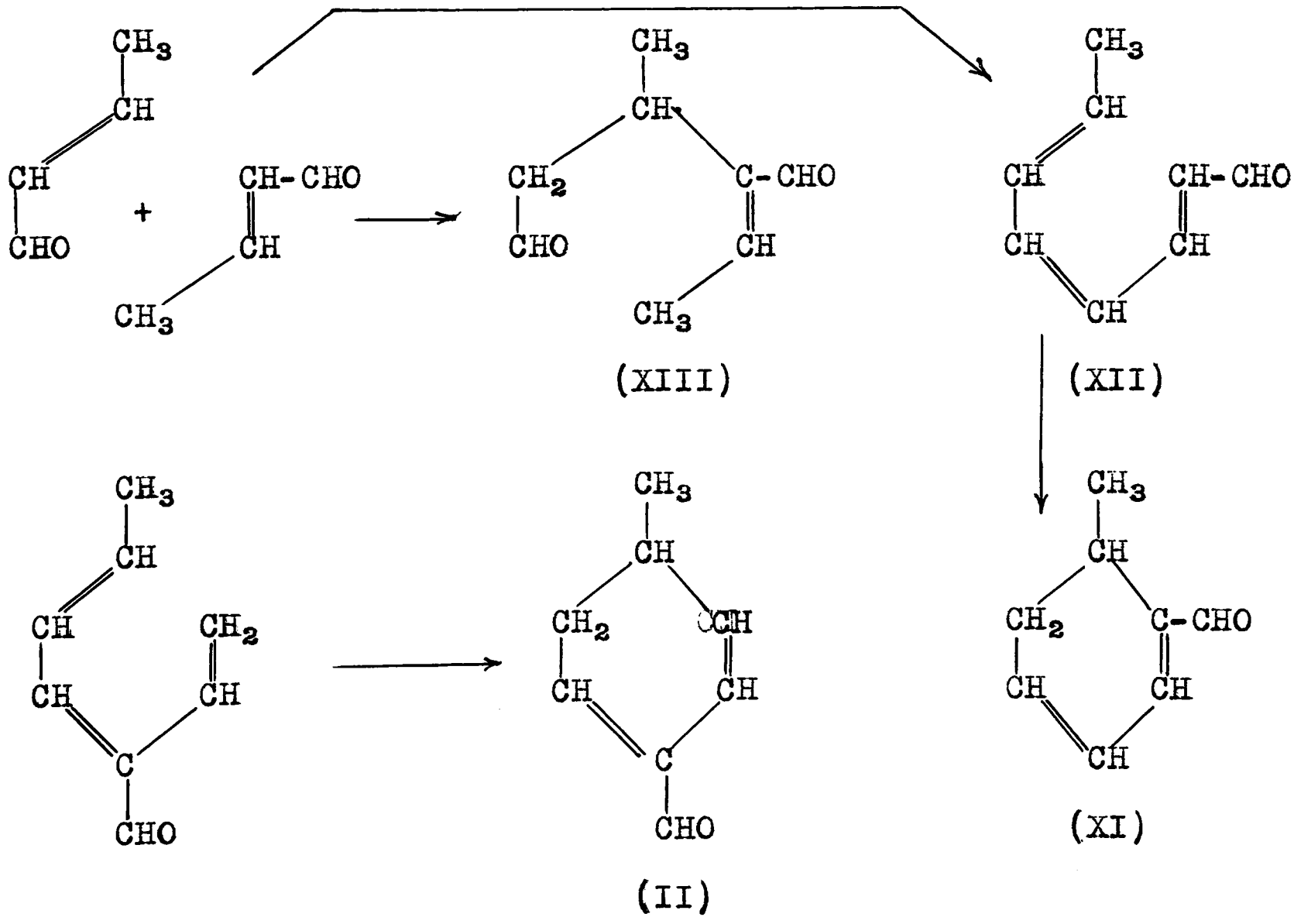
In a further investigation (10) a new aldehyde with a boiling point intermediate to the two previous ones (A and B) was isolated. This, on oxidation with silver

oxide, yielded p-toluic acid. He claims the fact that no intermediate hydrogenated aldehyde could be isolated was to be expected, since such a compound could readily lose two atoms of hydrogen.

Along with octatrienal in the higher boiling fraction he eventually obtained certain hydroxy aldehydes and also dicrotonic aldehyde (XIII) which was identified by oxidation to the known dicrotonic acid.

To sum up, he obtained, in order of boiling points: dihydro-o-tolualdehyde, dihydro-p-tolualdehyde (possibly), dicrotonic aldehyde and octatrienal.

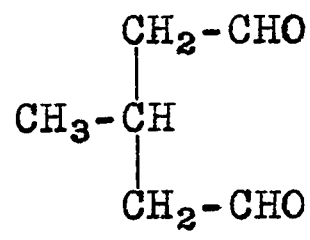
To explain the formation of these compounds Bernhauer has proposed the following mechanisms:



He was apparently unaware of Kuhn's work (5) where the latter, as stated above, has shown that pure crotonaldehyde will not condense with itself. Also the mechanism is highly speculative, since unsaturated aldehydes of the type to which crotonaldehyde belongs tend to add across the double bond rather than to condense.

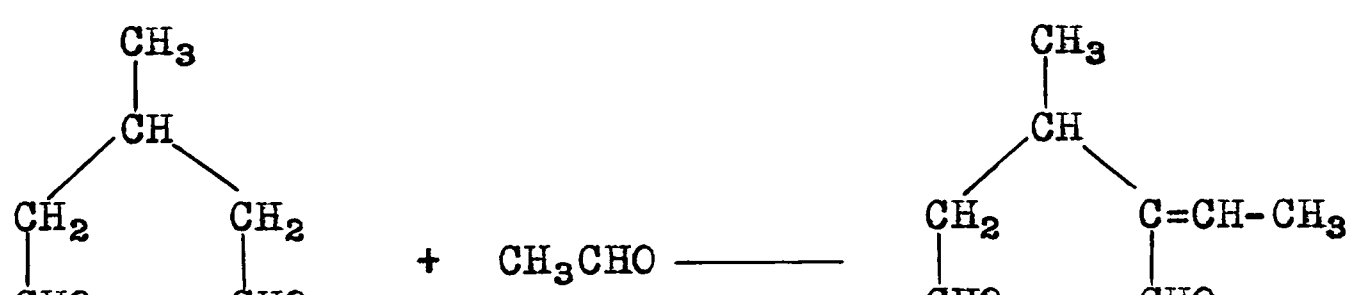
Kuhn has shown that octatrienal is obtained from the condensation of crotonaldehyde with acetaldehyde in the presence of piperidine. This mechanism readily explains the presence of octatrienal in the oils obtained by Bernhauer.

The presence of dicrotonaldehyde (XIII) may be explained by some work done by Riban (12) in 1872. This investigator heated acetaldehyde with zinc dust and water in a sealed tube. He obtained a mixture of crotonaldehyde, aldol and a new product which analysed for $C_6H_{10}O_2$. It decomposed on distillation at ordinary pressure, yielding water and oils, and gave a crystalline bisulfite addition profuct. He states that the formula probably is



(XIV)

Meerwein's work (13) in 1918 in which he prepared a number of 1,5 dialdehydes containing phenyl groups by the same method as Riban used, lends support to the latter's formula. Now if the dialdehyde which Riban thought he had obtained were formed as a condensation product among the oils being investigated by Bernhauer, the simple condensation of another molecule of acetaldehyde would yield dicrotonaldehyde (XIII) as shown below:



(XIV) (XIII)

Experimental.

Three different fractions of oil labelled "Dicroton" were obtained from the Shawinigan Chemicals Company. The boiling points were stated to be 78°, 87° and 125° C. at 10 mm. A fourth sample, of which the boiling point was said to be 195° C. at 760 mm., proved to be the same as the fraction of b.p. 87° C. at 10 mm.

These samples of oil were all further fractionated at 10 mm. in a continuous distillation apparatus kept filled with carbon dioxide. A partial condenser containing technical n-butyraldehyde was used to prevent high boiling material from distilling over. That superheating was very pronounced was shown by the fact that the rate of distillation had a marked effect on the boiling point as registered by the thermometer. The containing flask was heated by a water bath at such a rate that four drops of distillate every five seconds were collected at the end of the condenser.

On distilling the sample labelled b.p. 87° C. at 10 mm. under the above conditions, 75% of the distillate came over at 77° C. (B). The final product boiled at 125° C. at 10 mm.

The refractive index of the main portion was 1.5279^{20}_{D} and the density 1.0150^{20}_{4}.

A semicarbazone prepared in the usual manner was obtained in 95% yield.

The sample of which the boiling point was stated to be 78° C. at 10 mm. was now investigated. On distilling 100 g. of the oil under the above stated conditions, the following fractions were obtained:

1st fraction,	b.p. 61-68° C.	=	22 g.
2nd "	" 68° (A)	=	66 g.
3rd "	(residue in flask)	=	8 g.
		Total =	96 g.

The density of the main fraction (A) was 1.035^{20}_{4} and the refractive index 1.5182^{20}_{D}.

The same semicarbazone resulted from the 61-68° fraction. It was obtained in 50% yield and precipitated much less readily than that from the 77° fraction. On precipitation and purification, it proved to be identical to the former one by a mixed melting point and comparison of the crystalline structures.

The main fraction also gave the same semicarbazone in 75% yield.

Both fractions A and B were shaken with a saturated aqueous solution of sodium bisulfite and the precipitated addition product filtered and washed thoroughly with ether. Fraction A left an oily residue which had a very penetrating odor and became resinous on standing. Fraction B, however, all reacted with the bisulfite. In each case the addition product was decomposed by mixing with slightly more than the calculated amount of potassium carbonate in water and steam distilled. The aldehyde was extracted with ether, the extract dried with potassium carbonate and after removal of the solvent, distilled under diminished pressure. The distillate was a very highly refractive, colorless liquid possessing a sweet, pleasant odor somewhat resembling that of p-tolualdehyde. The penetrating odor of the original samples is apparently due to the impurity. The boiling point was 77° C. at 10 mm., 202° C. at 760 mm. The density was 1.0176^{20}_{4}; refractive index 1.5408^{20}_{D}; the molecular refraction (M_D) = 37.661; calculated M_D for (I) = 36.954.

The same constants were obtained with a sample regenerated from the semicarbazone.

Anal. Calcd. for $C_8H_{10}O$: C, 78.6; H, 8.2.

Found: C, 78.6; H, 8.0.

Dihydro-p-tolualdehyde is not appreciably soluble in water, dilute acids or alkalis, but is easily miscible with the usual organic solvents. It is charred by concentrated sulfuric acid and becomes dark brown in the presence of alkalis. It may readily be steam distilled, the distillate being about one-seventh aldehyde. It gives no color with Schiff's reagent but reduces Fehling's solution easily, especially in the presence of a little alcohol. It dissolves completely in an aqueous solution of sodium bisulfite and the addition product separates from the saturated solution in lustrous plates.

Although the aldehyde readily undergoes auto-oxidation, the process may be inhibited by the addition of a little hydroquinone. It instantly decolorizes bromine but in the presence of a large amount of bromine, hydrogen bromide is evolved. This is not observed when p-tolualdehyde is subjected to the same reaction. The aldehyde consumes far less than the calculated amount of bromine.

Kuhn (6) has found this to be true of many polyene aldehydes. In this investigation the amount of bromine absorbed varied somewhat with slight variations in operating; e.g., assuming that one mole of bromine is absorbed by one mole of aldehyde (100%) the following values were obtained (bromide-bromate procedure or direct titration): 52.95, 34.47, 50.59, 41.43, 33.53. Pure p-tolualdehyde gave only 0.43.

It was unchanged on heating in an inert atmosphere for several hours. There was no reaction with maleic anhydride or α-naphthaquinone, even when the mixture was heated for several hours, the anhydride or quinone being recovered unchanged on cooling.

The 2,4-dinitrophenylhydrazone was prepared in the usual manner. It was found to be very soluble in hot xylene or p-cymene, sparingly soluble in hot butyl alcohol, and insoluble in the other usual solvents. Xylene is the best medium for purification. The product forms brick red plates with square ends, m.p. 239° C.

Anal. Calcd. for $C_{14}H_{14}O_4N_4.H_2O$: N, 17.5. Found: N, 17.7, 17.9, 17.6.

The 2,4-dinitrophenylhydrazone of p-tolualdehyde

when prepared in the same way, for comparison, crystallized from xylene in pointed rods that melted at 206° C.

The semicarbazone was also prepared in the usual manner, i.e.: to 2 parts of the semicarbazide hydrochloride and 4 parts of sodium acetate in ethyl alcohol was added 1 part by weight of the aldehyde. It formed long transparent needles with square ends. It is moderately soluble in ethyl alcohol but is more so in ethyl acetate. In a capillary melting point tube it shrinks slightly at about 215° C. and melts to a clear liquid at 219° C. A mixed melting point with the semicarbazone of p-tolualdehyde, while showing no marked depression, shrank at 214° C. and melted over a range 217-219° C. The crystal structure, size of crystals and other properties, however, were entirely different.

Anal. Calcd. for $C_9H_{13}ON_3$: N, 23.6. Found: N, 23.4.

The p-nitrophenylhydrazone was an amorphous substance and could not be crystallized.

The Cyano Acid; $C_7H_9CH=C(CN)COOH$.

A solution of 2 g. of sodium hydroxide, 30 cc.

of water, and 4 g. of cyanoacetic acid was made slightly alkaline to litmus by adding aqueous sodium hydroxide. A stirrer was introduced and 5 g. of the aldehyde added. The reaction was complete after warming and stirring for three minutes and the condensation product was precipitated by the addition of concentrated hydrochloric acid. When filtered and recrystallized from dilute alcohol, the solid formed pale yellow needles and rods of melting point 212-213° C.

Anal. Calcd. for $C_{11}H_{11}O_2N$: N, 7.4. Found: N, 7.3.

The Aldazine. $C_7H_9CH=N-N=CHC_7H_9$.

A mixture of 5 g. of hydrazine sulfate, 10 g. of potassium acetate and 50 cc. of hot water was slightly cooled and 50 cc. of alcohol added. To the filtrate from the precipitated salt, 10 g. of aldehyde was added, and the product which separated filtered cold. When recrystallized from n-propyl alcohol, in which it is very soluble when hot but practically insoluble when cold, it precipitated as pale yellow, wedge-shaped prisms of m.p. 157° C. It is insoluble in the cold alcohols and only sparingly soluble in hot ethyl alcohol, but dissolves readily in

ether or hot propyl alcohol. It slowly goes into solution in concentrated sulfuric acid with the formation of a bright yellow color.

Anal. Calcd. for $C_{16}H_{20}N_2$: N, 11.7. Found: N, 11.6.

A cinchoninic acid prepared from the aldehyde, α-naphthylamine and pyruvic acid was obtained in such poor yield that it was not deemed worth while purifying it.

Action of Oxidizing Agents.

(A) Nitric Acid.

To 5 g. of the aldehyde in a 250 cc. three-necked flask fitted with a stirrer and reflux condenser were added 100 cc. of dilute acid prepared by adding 25 cc. of acid (sp. gr. 1.42) to 75 cc. of water. Refluxing was continued for an hour on the steam bath. The p-toluic acid which separated on cooling weighed 3.5 g. (64%) and melted at 176-177° C.; a mixed melting point with an authentic sample, 176-177° C.

(B) Potassium Permanganate.

In the apparatus described above were placed 40 cc. of acetone, 30 cc. of water and 10 g. of the aldehyde. The whole was brought to gentle boiling and 50 g. of permanganate were added in 10 g. portions as rapidly

as the course of the reaction permitted. After an hour the oxidation was considered complete, though traces of toluic acid were found later. When the oxides of manganese had been filtered and extracted with boiling water, acidification of the filtrate resulted in the precipitation of terephthalic acid. It was dissolved in aqueous sodium bicarbonate and reprecipitated by hydrochloric acid. The yield was 8 g. or 66%. For the purpose of identification a sample was converted into the dimethyl ester by the usual procedure. The melting point was 135-137° C. and the mixed melting point with a known sample 136-137° C.

(C) Ozonization.

This was not done quantitatively. After four hours there was still some unchanged aldehyde present, as was shown by the removal with sodium bisulfite and formation of the dinitrophenylhydrazone. The alkaline extract of the ethereal solution gave p-toluic acid on acidification.

(D) Autoxidation.

A sample which was left open to the atmosphere on a watch glass became nearly solid on standing for three days. The solid was identified as p-toluic acid.

A similar sample containing hydroquinone was apparently unchanged after the same length of exposure.

The Condensation with Acetone. ($C_7H_9CH=CHCOCH_3$).

A mixture of 50 g. of the aldehyde, 100 cc. of acetone and 500 cc. of water containing 10 g. of barium hydroxide was shaken mechanically for 14 hours, acidified and steam distilled. The residual oil was taken up in ether and benzene, the extract dried, and after the removal of the solvent, the unsaturated ketone was distilled in an atmosphere of carbon dioxide. The boiling point was 177-185° C. at 25 mm. Owing to the fact that much high-boiling product and tar was obtained the yield was low (15.3 g. or 23%). The odor of the pure product resembled that of benzalacetone. The semicarbazone, when prepared as usual, crystallized in white rods from ethyl acetate. In a capillary tube it shrank at 196° C. and melted at 206-210° C. with decomposition.

Anal. Calcd. for $C_{12}H_{17}ON_3$: N, 19.2. Found: N, 18.5.

This unsaturated ketone gives a bright red color with concentrated sulfuric acid.

Summary.

In the condensation of acetaldehyde to crotonaldehyde, dihydro-p-tolualdehyde is obtained as a by-product. The determination of its structure, its properties and some of its reactions have been described.

References.

1. Kekulé, Ann., 162, 105 (1872).
2. Doebner, Ber., 33, 2140 (1900).
3. Delépine, C. r., 150, 395. Ann. ch., (8) 20, 396.
4. Kuhn and Winterstein, Ber., 63, 1489 (1930).
5. Kuhn and Hoffer, Ber., 63, 2164 (1930).
6. Kuhn and Hoffer, Ber., 64, 1977 (1931).
7. Coffman and Carothers, J.A.C.S., 55, 2040 (1933).
8. Bernhauer and Woldan, Biochem. Z., 249, 199 (1932).
9. Bernhauer and Neubauer, Biochem. Z., 251, 173 (1932).
10. Bernhauer and Irrgang, Biochem. Z., 254, 434 (1932).
11. Bernhauer and Drobnick, Biochem. Z., 266, 197 (1933).
12. Riban, Bull. Soc. chim., (2) 18, 62 (1872).
13. Meerwein, J. prak. Chem., 97, 225 (1918).

STUDIES IN THE DIPHENYL SERIES.

Historical Introduction and Discussion.

The original purpose of this section of the work was to find a suitable method for preparing the methyl ether (II) of phenacyl carbinol (I); all the usual procedures for methylating that have been tried being unsuccessful. Diazomethane had never been used and since it is the most powerful methylating agent known, and yet acts in the absence of solvents and catalysts, it seemed possible that its use might lead to the desired result.

$$C_6H_5COCH_2OH + CH_2N_2 \longrightarrow C_6H_5COCH_2OCH_3 + N_2$$

(I) (II)

A second object of this work was to prepare certain hitherto unknown derivatives of diphenyl, to be used as reference compounds for the determination of the structures of other substances being investigated in this laboratory.

Note: This work has been published in the Canadian Journal of Research, Vol. 7, 643-5 (1932).

The preparation of keto alcohols of the type of phenacyl carbinol (benzoyl carbinol) (I) is usually brought about by the action of dilute aqueous alkali on the corresponding acetate.

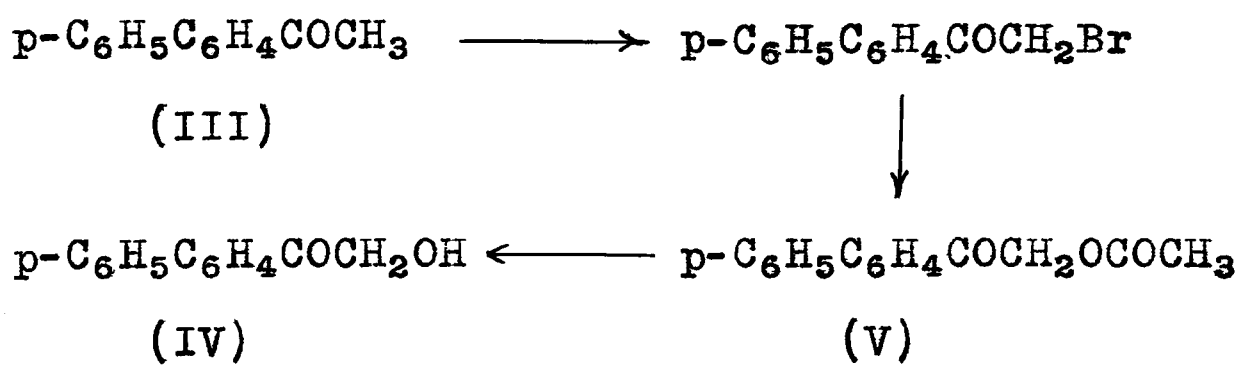
Phenacyl carbinol was first obtained by Graebe (8). Fischer and Busch (7) have greatly improved the yield by the hydrolysis of the acetate in aqueous solution with barium carbonate. Judefind and Reid (9), using the same procedure, obtained the p-chloro- and p-bromophenacyl alcohols in good yields.

Since this method gave no carbinol with p-phenylphenacyl acetate, various other previously reported preparations were resorted to. These also failed to yield the desired alcohol. Among the methods used was that of the Eastman Kodak Company (14) in which p-nitrobenzyl carbinol was prepared by the action of 15% sodium hydroxide on the corresponding acetate in methyl alcohol solution. More recently Madelung and Oberwegner (10) prepared β-naphthoyl carbinol by refluxing the acetate with barium hydroxide.

No references were found in the literature to the use of acid reagents for the hydrolysis of acetates of this type to the corresponding alcohols.

Phenacyl carbinol has the undesirable properties of a low melting point, great solubility in the common solvents, and of separation with water of crystallization; further it is prepared by a series of reactions in which all the intermediate products are low-melting and very soluble (10). Hoping to avoid these experimental difficulties by selecting a suitable derivative, p-phenylacetophenone (III) was chosen (6). The introduction of a phenyl group often raises the melting point and decreases the solubility (6) (12).

In the preparation of p-phenylphenacyl carbinol (IV) the steps through the acetate (V) were known (7) and it only remained to determine the most suitable conditions for hydrolysis.



This proved to be more difficult than was anticipated; the usual methods, using basic reagents, leading to colored mixtures from which no carbinol could be isolated. Eventually it was found that the carbinol could be pre-

pared by the hydrolysis of the acetate using mineral acids.

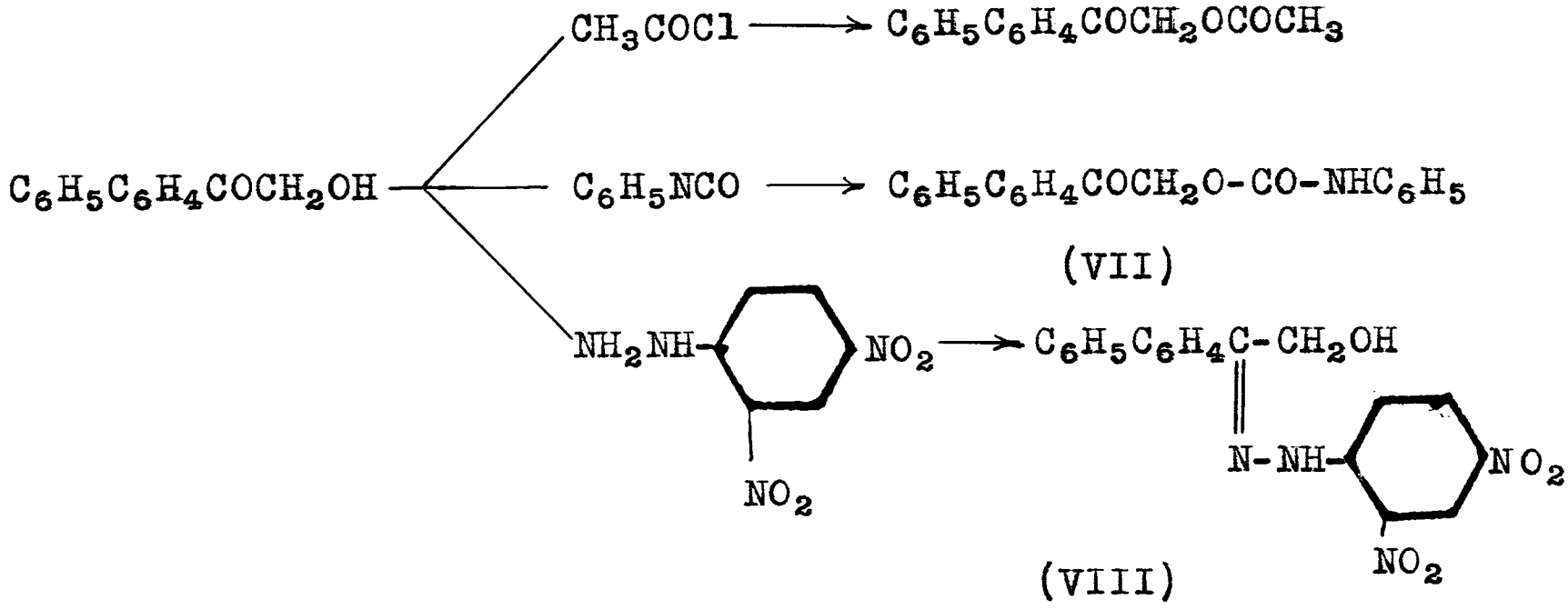
Clibbons and Nierenstein (4) reported that diazomethane was without action on benzoyl carbinol. Meerwein and Hinz (11), however, have found that although aliphatically bound hydroxyl groups react to a very slight extent or not at all with diazomethane, polar or easily polarized groups greatly increase the reactivity. Arndt and Martius (2) have shown that the more acidic or ionized the hydrogen of the hydroxyl the greater is the reaction with diazomethane.

Meerwein and Hinz further investigated the action of diazomethane and found in the case of such an alcohol as tolualcohol ($C_6H_5CH_2OH$) that although the methyl ether was formed to a small extent, further reaction was inhibited by this product. In the case of acetol (CH_3COCH_2OH), however, a new type of product was obtained. Although some of the methyl ether was formed, the main product was found to be the isomeric keto alcohol, methyl acetol ($CH_3CH_2COCH_2OH$). Phenacyl alcohol was found to yield exclusively phenyl acetyl carbinol (VI) with diazomethane.

$$C_6H_5COCH_2OH + CH_2N_2 \longrightarrow C_6H_5CH_2COCH_2OH \quad \text{(VI)}$$

As a result of this last discovery, work on this subject was discontinued after the preperties and proof of structure of the phenylphenacyl carbinol had been determined.

This alcohol showed one active hydrogen by the Zerewitanoff method, with acetyl chloride regenerated the acetate, and readily formed a phenylurethane (VII) and a 2,4-dinitrophenylhydrazone (VIII). The reactions of the carbinol are summarized in the following flow sheet.



Since diphenyl has only recently become commercially available, there are still many phases of its chemistry uninvestigated.

p-Phenylacetophenone (III) was condensed with benzaldehyde to form benzal-p-phenylacetophenone (IX) (6) which on the addition of bromine yielded the dibromide (X) which in turn was converted into benzoyl-p-phenylbenzoylmethane (XI). This diketone gave a red color with ferric chloride and formed a copper derivative, showing the presence of the enolic modification.

Although β-diketones may theoretically enolize both ways, up to 1927 no case had been found in which both forms were proved to be present at the same time. It was originally though that the way in which a diketone enolized would be determined from the structure of the isoxazole derived from it. Weygand (15) has shown that this method is not infallible. The way in which enolization proceeded was usually determined by ozonization and identification of the products.

Weygand concludes that only one enol should be expected of an unsymmetrical diketone such as $C_6H_5COCH_2COCH_3$ since phenyl and methyl are so different chemically. He found, however, that on ozonization of diketones he obtained all the possible products, indicating that both keto groups had been enolized to some, if not equal extent.

From the foregoing it must be assumed that diketones may enolize both ways, but at different rates. Thus in chemical reactions we get derivatives of only one form.

To determine the configuration of the isoxazol (XII) prepared from the diketone (XI) it was compared with the isoxazol (XIII) prepared from benzal-p-phenyl-acetophenone dibromide (X). Melting point and mixed melting point proved these compounds to be different. The structure of the latter is known by its method of preparation (15).

The reactions of the ketone are conveniently summarized in the following flow sheet.

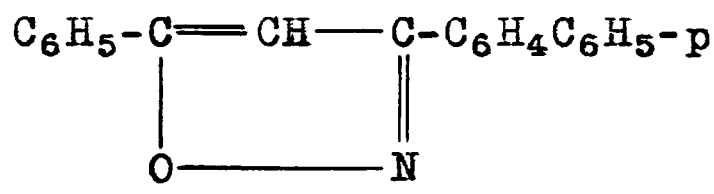
$C_6H_5C_6H_4COCH_3$ + C_6H_5CHO $\xrightarrow{NaOH}$ $C_6H_5CH{=}CH{-}CO{-}C_6H_4C_6H_5$-p

(III) (IX)

$C_6H_5CHBrCHBrCOC_6H_4C_6H_5$-p

(X)

$NH_2OH.HCl$



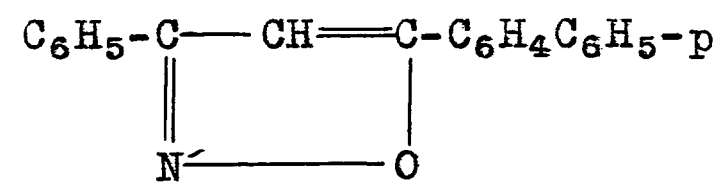
(XIII)

$NaOCH_3$

$C_6H_5COCH_2COC_6H_4C_6H_5$-p

(XI)

$NH_2OH.HCl$



(XII)

The work was now turned to a different series starting with trans di-p-phenylbenzoylethylene (XIV)(13). Though this substance had been previously reported and the unsaturated ketone was readily obtainable, the directions for the preparation of the dibromide (XV) were inadequate and only traces of it could be obtained. After using various solvents in which to carry out the bromination, without success, the study of the substance was abandoned. Several attempts at bromination resulted in a white substance melting at about 246° C. and containing bromine. Oddy (13) has reported the dibromide as melting at 218° C.

Certain interesting facts were observed. On standing in sunlight in a chloroform solution, no change was noticed in the ketone even after several days. Exposure to ultra-violet rays had no effect either. However, on exposure to sunlight in the solid state, the yellow product became white in one or two hours. All attempts to isolate the white substance resulted in reconversion to the yellow isomer.

$$\underset{\text{(XIV)}}{p\text{-}C_6H_5C_6H_4COCH{=}CHCOC_6H_4C_6H_5} \rightarrow \underset{\text{(XV)}}{p\text{-}C_6H_5C_6H_4COCHBrCHBrCOC_6H_4C_6H_5\text{-}p}$$

Experimental. (A).

The Preparation of Starting Materials.

p-Phenylacetophenone was prepared by the method of Drake and Bronitsky (6). It was found advisable to leave enough of the carbon disulfide in the flask to keep the mass liquid,as complete evaporation of the solvent made the solid difficult to remove. The melting point of the crude product was 118° C. and yields of 90-95% were obtained. The product was recrystallized from ethyl alcohol, using animal charcoal, and obtained as white powdery substance melting at 120° C.

The corresponding bromide was prepared by the same authors as an agent for identifying acids. Yields of 65-70% were obtained; the light product melted at 123° C. After recrystallization from ethyl alcohol, with the use of animal charcoal, it formed a white product melting at 125.5° C. Addition of water to the acetic acid filtrate brought down a yellow product of indefinite composition.

p-Phenylphenacyl Acetate.

Potassium acetate (10 g.) was dissolved in

150 cc. of 60% alcohol and 10 g. of the bromide added. The solution was acidified with acetic acid; (the addition of acid prevents the formation of coloured by-products.) On cooling, white leaflets were precipitated and after one recrystallization from ethyl alcohol, melted at 111° C. Butyl alcohol was not as satisfactory. When impure bromide was used, the reaction did not go to completion but on filtering off the product and refluxing again, a second crop of less pure acetate was obtained. Total yields of 8.3-8.5 g. (90-95%) were easily obtainable. The product is also very soluble in acetone and ethyl acetate.

The preparation of p-Phenylphenacyl carbinol (III).

The acetate (5 g.) in 50 cc. of ethyl alcohol was refluxed with 1 cc. of concentrated sulfuric acid for three hours, the flask cooled in an ice and salt mixture and the product filtered off. Three and eight-tenths grams were obtained (91%). The product was recrystallized from ethyl alcohol, boiled with animal charcoal and filtered hot. It separated out in the form of white leaflets which melted over the range 123.5-128.5° C. No amount of recrystallization or use of

different solvents resulted in a sharp melting substance. It is also soluble in acetone, ethyl acetate and chloroform.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.4; H, 5.66.
Found: C, 79.1; H, 5.75.

Many unsuccessful attempts to prepare the carbinol were made. Among these were methodsfor the preparation of phenacyl carbinol using barium carbonate (8), that for p-bromophenacyl carbinol (9), and the Eastman Kodak preparation of p-nitrobenzyl alcohol (14). No alkaline reagent brought about the desired hydrolysis. Among those tried were sodium bicarbonate, sodium carbonate, potassium carbonate, and sodium hydroxide which gave colored products from which no carbinol could be isolated. Hydrogen chloride was bubbled through an alcohol solution of the acetate which was then allowed to stand for a day stoppered. A distinct odor of ethyl acetate was observed on opening the flask, indicating that reaction had taken place. No carbinol was isolated however. In the first attempt using sulfuric acid the solution was refluxed for eight hours. A 1:1 mixture

of carbinol and a red insoluble product melting at 225° C. resulted. This substance was insoluble in alcohol and decomposed on prolonged standing in sunlight.

Reactions.

(a) The number of active hydrogens was determined by the Zerewitanoff method, using methyl magnesium iodide. Theoretical number of cc. of methane evolved under the conditions of the experiment for one active hydrogen: 22.5; number of cc. observed: 23.8.

(b) Regeneration of the Acetate:

The carbinol (0.1 g.) was dissolved in a minimum amount of acetyl chloride and the excess solvent allowed to evaporate. The recrystallization product melted at 111° C. and a mixed melting point with the acetate showed no depression.

(c) Phenyl Urethane:

The carbinol (0.5 g.) and 0.7 g. of phenyl isocyanate were placed in a small test tube and heated in a beaker of hot water for a few minutes. The mixture solidified

on cooling and recrystallization from ethyl alcohol yielded a white powdery substance melting at 186-187° C.

Anal. Calcd. for $C_{14}H_{17}O_3N$: N, 4.2. Found: N, 4.1.

(d) 2,4-dinitrophenylhydrazone.

2,4-dinitrophenylhydrazine (1.0 g.) was dissolved in 2 cc. of sulfuric acid and 15 cc. of ethyl alcohol and 1.06 g. (0.02 mol.) carbinol in warm alcohol were added. A deep red precipitate came down immediately. It was practically insoluble in methyl alcohol, ethyl alcohol, chloroform, and benzene. It was, however, fairly soluble in ethyl acetate and was recrystallized from a solution of three parts of ethyl acetate to one of ethyl alcohol. The product came out as scarlet red crystals melting at 222-223° C. with decomposition. Wool-like,deep red needles may be obtained if the proportion of solvent and the rate of crystallization be somewhat varied.

Anal. Calcd. for $C_{20}H_{16}O_5N_5$: N, 14.3. Found: N, 14.1.

Experimental (B).

Benzal-p-phenylacetophenone was prepared by the method of Dilthey (5). p-Phenylacetophenone (2 g.) was made into a paste with 1.2 g. of pure benzaldehyde and mixed with 60 cc. of hot ethyl alcohol. The solution was made basic with 1 cc. of 50% potassium hydroxide, allowed to stand ten minutes and heated on a water bath for half an hour under a reflux condenser. On cooling, a yellow product came down which, on recrystallization from ethyl alcohol, formed yellow crystals melting at 156° C. A yield of 2.7 g. (93%) was obtained. It is interesting to compare this yield with that obtained by Bergmann and Wolff (3) by the action of cinnamoyl chloride on diphenyl. They obtained 70 g. (63.5%) of the unsaturated ketone from 60 g. of diphenyl. By the two step procedure shown above, 60 g. of diphenyl will yield 100 g. (90%) of the ketone.

Benzal-p-phenylacetophenone Dibromide.

The chalcone (2.84 g. (0.01 mol.)) was dissolved in 30 cc. of carbon disulfide and cooled to room temperature, 1.6 g. of bromine in 20 cc. of carbon disulfide were then added with stirring and after allowing

the mixture to stand at room temperature for ten minutes with occasional shaking, it was cooled in an ice and salt bath, filtered and washed with an aqueous sodium bisulfite solution. The yield was 3.0 g. and on evaporation of the filtrate, 0.5 g. more was obtained (75% of the theoretical, approximately). Recrystallization from benzene yielded a chalky white substance melting at 189° C. If alcohol is used for recrystallization, a reaction takes place, resulting in an unstable brown product.

Anal. Calcd. for $C_{21}H_{16}OBr_2$: Br, 36.0. Found: Br, 36.1.

p-Phenyldibenzoylmethane was prepared by the method of Allen, Abell and Normington for dibenzoylmethane (1). Benzal-p-phenylacetophenone dibromide (4.44 g. (0.01 mol.)) was reacted with 4.6 g. of sodium methylate. The yellow product which separated on the addition of hydrochloric acid was filtered, washed with water, and recrystallized from ethyl alcohol, from which solvent it came down as yellow crystals melting at 112° C. The yield was 2.4 g. (80%).

Anal. Calcd. for $C_{21}H_{16}O_2$: C, 84.0; H, 5.33.
Found: C, 83.7; H, 5.15.

The Formation of the Copper Derivative.

The diketone was dissolved in ether and shaken with an excess of a saturated aqueous solution of copper acetate in a separatory funnel. A light, olive-green, powdery product, insoluble in ether, alcohol and benzene was precipitated. On washing with water and alcohol, the melting point was approximately 290° C. with decomposition. The substance was ignited to copper oxide and the percentage of copper determined.

Anal. Calcd. for $C_{42}H_{30}O_4Cu$: Cu, 9.6. Found: Cu, 9.4.

3-Xenyl-5-phenylisoxazol (XII).

To 1 g. of hydroxylamine hydrochloride in 15 cc. of acetic acid was added with shaking 2 g. of potassium acetate, the potassium chloride was filtered off and to the filtrate was added 1 g. of the benzoyl p-phenylbenzoylmethane. After refluxing for two hours water was added to dissolve any inorganic material, the solution cooled, the product filtered, and recrystallized from benzene. The characteristic mother-of-pearl lustre of an isoxazol was observed, the product melting at 182-183° C. The yield was 0.8 g. (70%).

Anal. Calcd. for $C_{21}H_{15}ON$: N, 4.7. Found: N, 4.5.

The Preparation of 3-phenyl-5-xenylisoxazol (XIII) (15).

Benzal-p-phenylacetophenone dibromide (2 g.) and 1 g. of hydroxylamine hydrochloride in 50 cc. of ethyl alcohol were refluxed for half an hour with 4 cc. of 40% sodium hydroxide. The solution turned yellow, and on cooling, white crystals came down. The product, on recrystallization from benzene, melted at 195° C. Yields of 0.6-0.7 g. (40-50%) were obtained.

Anal. Calcd. for $C_{21}H_{15}ON$: N, 4.7. Found: N, 4.9.

Oxime Formation in Acid Solution.

Attempts to form the oxime of benzal-p-phenyl-acetophenone by the method of Blatt and Stone (16) were unsuccessful.

Trans di-p-phenylbenzoylethylene (13).

A mixture of 8 g. of fumaryl chloride, 12 g. of diphenyl and 20 g. of aluminium chloride in 60 cc. of benzene was allowed to stand at room temperature for one day, decomposed by pouring into an ice and hydrochloric acid mixture and the solvent and excess diphenyl steam distilled. A yellow mass resulted which, on recrystal-lization from benzene, melted at 248° C. The product was

also soluble in acetic acid and chloroform to some extent. Other solvents tried were ethyl bromide, cellosolve acetate and ether, nitrobenzene and ethylene bromide. Of these the last two mentioned were the best solvents, but proved difficult to get rid of. The product was practically insoluble in ethyl acetate and ether. Yields of 9 g. (60%) were obtained.

The dibromide was formed by adding bromine to a chloroform solution of the diketone, evaporating off the solvent and recrystallizing from acetone. A trace of a white product melting at 218° C. was obtained. Using ethylene bromide as solvent and allowing the solution to stand for several days, a 50% yield of a white substance melting at 246° C. and containing bromine was obtained on recrystallization from benzene. As Oddy had reported the dibromide as melting at 218° C. it was assumed that this was not the desired product and further work along this line was abandoned.

Summary.

1. p-Phenylphenacyl carbinol may be prepared by acid hydrolysis of the acetate. It decomposes at the melting point but otherwise shows the reactions of keto alcohols.

2. Phenyldibenzoylmethane has been prepared and the structure of its isoxazol determined by comparison with the isoxazol of benzal-p-phenylacetophenone dibromide.

References.

1. "Organic Syntheses", John Wiley & Sons, Inc., New York, Coll. Vol. 1, p. 199.
2. Arndt and Martius, Ann., 499, 228-287 (1932).
3. Bergmann and Wolff, J.A.C.S., 54, 1644-7 (1932).
4. Clibbons and Nierenstein, J.C.S., 107, 1491 (1915).
5. Dilthey, J. prakt. Chem., 101, 177-206 (1921).
6. Drake and Bronitsky, J.A.C.S., 52, 3715-20 (1930).
7. Fischer and Busch, Ber., 24, 2680 (1891).
8. Graebe, Ber., 4, 35 (1871).
9. Judefind and Reid, J.A.C.S., 42, 1043 (1920).
10. Madelung and Oberwegner, Ber., 65, 931 (1932).
11. Meerwein and Hinz, Ann., 484, 1-25 (1930).
12. Morgan and Pettet, J.C.S., 1125 (1923).
13. Oddy, J.A.C.S., 45, 2160 (1923).
14. Private Communication, W.W. Hartman, Eastman Kodak Co.
15. Weygand, Ann., 459, 99 (1927).
16. Blatt and Stone, J.A.C.S., 53, 1133-41 (1931).

GRIGNARD REAGENTS FROM ALKYL DIHALIDES.

Introduction and Discussion.

The preparation of Grignard reagents from alkyl dihalides was originally attempted as these compounds were to be used in the preparation of unsymmetrical heterocyclic compounds in which one of the atoms forming part of the ring was arsenic.

All unsymmetrical dibromides studied, however, lost hydrogen bromide so readily that no Grignard reagent could be prepared from them. As a result of this, the work was abandoned.

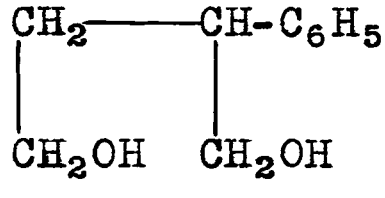
Up to the time this work was commenced, only one unsymmetrical dibromide had been recorded in the literature, namely, methyltetramethylene dibromide (VIII). Harries and Neresheimer (1) claim to have obtained it in 86% yield from methyltetramethylene glycol.

This method was used in the present investigation but the yields reported could not be duplicated. This dibromide has also been made in the active form by Von Braun and Jostes (2) by a long series of reactions from pulegone.

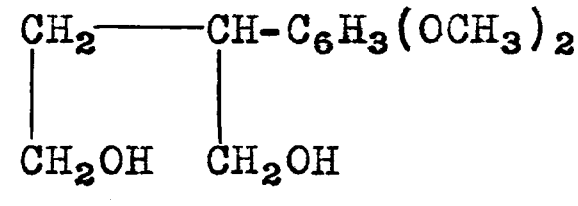
Note: This work has been published in the Canadian Journal of Research, 9, 432-435 (1933).

β-phenylbutanediol-1,4 (I) has been prepared by a procedure (3) almost identical with one developed in this laboratory by Wilson (4). Wilson has also prepared the 2,4-dimethoxy homologue (II).

Of these only the β-methylated glycol (VII) gave a dibromide which could be isolated in the pure state, the tendency to elimination of hydrogen bromide and dehydration being too great in the others.



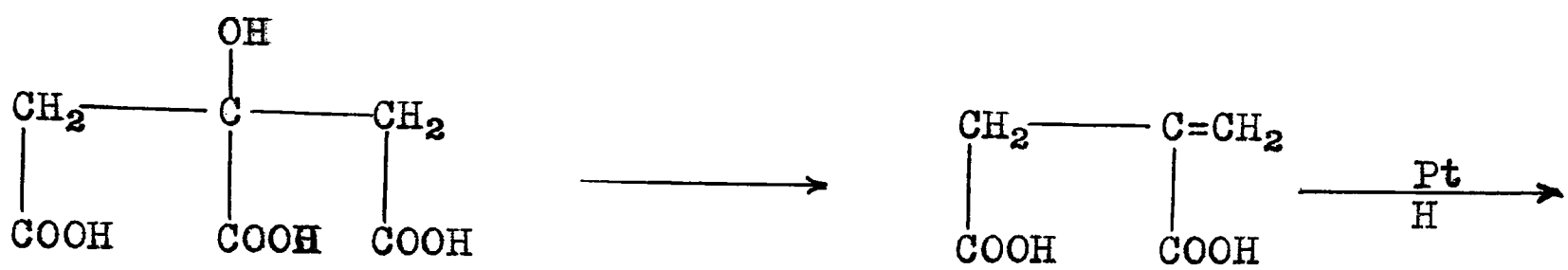
(I)



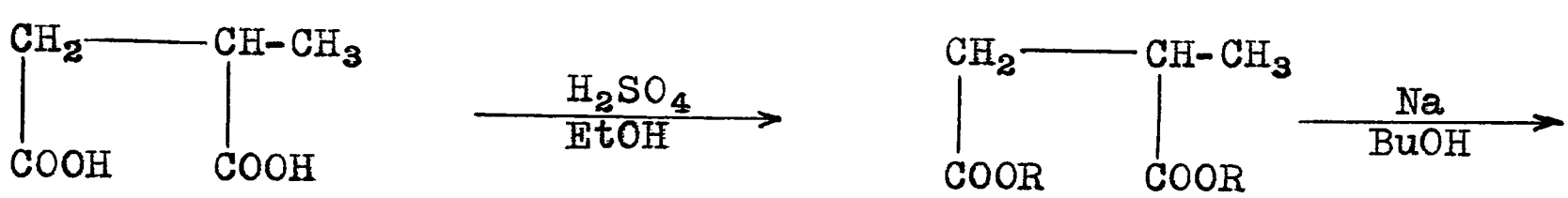
(II)

β-methylbutanediol-1,4 had previously been known (1) but the method of preparation was long and tedious, the yields low and the starting material expensive. A cheaper method was devised but the final yield was no better. The final step was a modification of the method for cetyl alcohol (5). The steps to the dibromide were as follows:

Citric acid (III) → itaconic acid (IV) → methylsuccinic acid (V) → methylsuccinic ester (VI) → β-methylbutanediol-1,4 (VII) → β-methylbutanedibromide (VIII).



(III) (IV)



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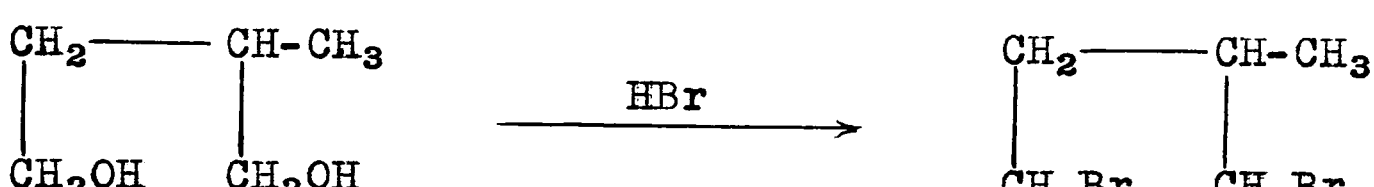


(VII) (VIII)

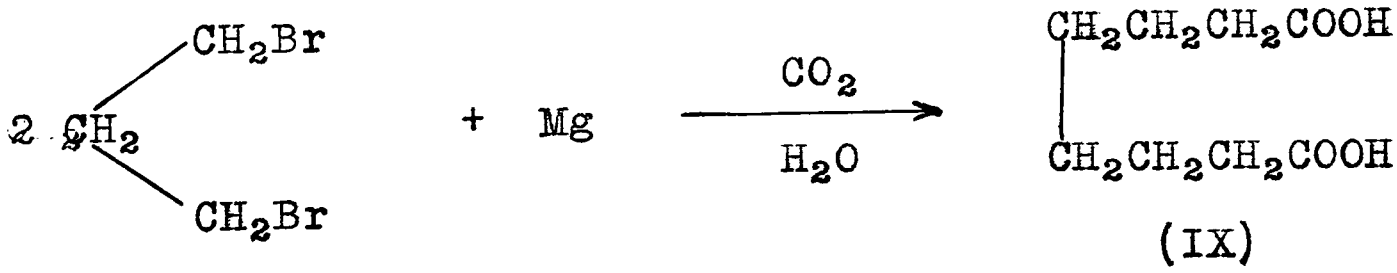
β-methyltetramethylene dibromide-1,4 reacted with magnesium but no detectable amount of Grignard reagent could be obtained. The only product which was isolated proved to be magnesium bromide etherate ($MgBr_2.2C_4H_{10}O$) which, on treatment with water, gave magnesium bromide hexahydrate ($MgBr_2.6H_2O$).

Tissier and Grignard (18) have reported magnesium bromide etherate as resulting from the action of magnesium on an etheral solution of ethylene bromide.

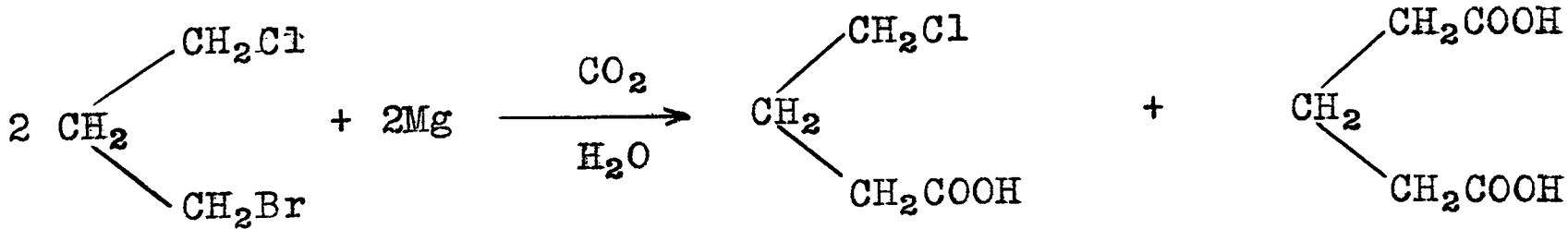
No quantitative study of the formation of Grignard reagents from dihalides has yet been made, but based on the yields of products obtained, the tetra- and pentamethylene dibromides must have yielded between 25 and 40% of the theoretical amount of Grignard reagent (2,6,7,8,9).

Ethylene dibromide and magnesium are said to yield ethylene exclusively (10). Trimethylene dibromide gave a large amount of cyclopropane and only about 1% of Grignard reagent (10). On formation of the acid by passing in carbon dioxide and then adding water, suberic acid (IX) was obtained instead of the expected glutaric acid.

In this investigation, use was made of trimethylene chlorobromide in the hope that the less active chlorine might allow the formation of a Grignard reagent. The addition of carbon dioxide and water to the reaction mixture resulted in the formation of about 10% of the theoretical amount of a mixture of γ-chlorobutyric acid (X) and glutaric acid (XI)



(IX)



(X) (XI)

Gilman's color test for Grignard reagents (11) was negative, in spite of the proven presence of a Grignard reagent.

From the foregoing results it may be suggested that possibly the higher mixed dihalides may give better yields of Grignard reagents than the yields reported for the dibromides.

Experimental. (A).

(a) The Preparation of Starting Materials.

Itaconic acid was obtained by the distillation of citric acid, use being made of a method developed in this laboratory (12).

Esterification of Itaconic Acid.

To 21 g. of itaconic acid in 50 cc. of ethyl alcohol (95%) were added 15 cc. of concentrated sulfuric acid and the mixture refluxed for six hours. Most of the alcohol was distilled off under vacuum, the residue in the flask extracted with benzene, and the extract neutralized with sodium bicarbonate. The inorganic matter was filtered off and the benzene distilled under vacuum. The boiling point of the ester so obtained was 160° C. at 20 mm. The yield was 15 g. or 67% of the theoretical.

Methylsuccinic Ester.

The itaconic diethyl ester obtained above was reduced by Adam's method (13) to methylsuccinic ester. A 95% conversion to a product boiling at 105-110° C. at

10 mm. was obtained.

The distillate from the reduction of itaconic ester was judged completely reduced when it failed to decolorize 10% bromine in carbon tetrachloride or reduce potassium permanganate in acetone.

On refluxing 1 g. of reduced ester in 10 cc. of 10% sodium hydroxide for half an hour and precipitating by means of hydrochloric acid, the benzene extract yielded a white product melting at 105-110° C. This melting point was not depressed by the admixture of an authentic sample of methylsuccinic acid.

The reduction of itaconic acid to methylsuccinic acid proceeded more readily than the reduction of the ester, but the acid could not be converted in as large runs and presented more difficulty in recovery.

Attempted reductions of itaconic acid with sodium amalgam proved unsatisfactory.

Methyltetramethylene glycol (β-methylbutanediol-1,4) (VII).

This glycol was prepared from methyl succinate by a modification of the method used for the preparation of cetyl alcohol (5).

In a 2-l. r.b. three-necked flask fitted with a wide bore condenser were placed 400 cc. of pure, dry

butyl alcohol containing 38 g. (0.2 mol) of methylsuccinic ester. To this were added 30 g. of metallic sodium in large pieces. Cooling of the reaction flask was necessary. When most of the sodium had reacted, the solution was refluxed until no more sodium was visible (2 hours), 20 cc. of water added through the condenser slowly and the refluxing continued for an additional half hour. The total time of the reaction was 2.5 hours.

The reaction mixture was allowed to cool and carefully neutralized with concentrated hydrochloric acid. The solid which precipitated was filtered off and washed with ether. Most of the butyl alcohol was distilled under reduced pressure and the combined filtrate and the residue extracted with ether.

The extract was filtered into a Claisen distilling flask, the ether removed, and the remainder distilled in vacuo.

The yield was 10 g. (48%) of a product boiling at 112-114° C. at 10 mm. A second fraction boiling at 160° was obtained.

On redistillation of the first fraction at 8 mm. two-thirds of the product came over at 100-110° C. and the remainder at 135° C.

Shepard and Johnson (14) have reported 2-methylbutenediol-1,4 as boiling at 128° C. at 7 mm. with a

refractive index of 1.4815^{20}_{d}. The refractive index of the substance obtained in this laboratory was 1.4322^{20}_{d}.

A diphenylurethane of the fraction boiling at 100-110° was prepared and melted at 99-100° C. This is the melting point reported by Harries and Neresheimer for the diurethane of the glycol they have described (1).

Preparation of Methyltetramethylene dibromide (VIII).

The procedure described by Harries and Neresheimer was used (1).

To 10 g. of glycol were added three times their volume of fuming hydrobromic acid (60%) and the reaction mixture heated in a sealed tube for 3 hours at 100° C. The tube was allowed to cool and opened. The contents were poured into a beaker and neutralized with a slight excess of potassium hydroxide, extracted with ether, most of the ether removed and the remainder dried over potassium carbonate. The carbonate was then filtered off, the ether driven off on a steam bath, and the residue vacuum distilled. It gave 4.5 g. of an oil boiling at 70-80° C. at 8 mm. and 5.5 g. of an oil boiling at 120-170° C. at 8 mm.

In another attempt, 5 g. of glycol in 10 g. of acetic anhydride were saturated with gaseous hydrobromic acid, (a total weight of 4 g. of acid being absorbed)

allowed to stand for two days and worked up in the same way. It gave 6 g. of an oil b.p. 90° C. at 8 mm.

(b) Attempted Preparation of a Grignard Reagent from Methyltetramethylene Dibromide.

To 1.5.g. of magnesium turnings covered with 10 cc. of dry ether were added 6 g. of the dibromide in 20 cc. of dry ether. No reaction was observed even on heating, but the addition of a crystal of iodine caused a slow reaction to take place. The addition of a small amount of Gilman's activated copper-magnesium alloy (15) caused a more vigorous reaction.

When the action had ceased (1 hour) the whole was refluxed for an additional hour. A sample of the ether solution was withdrawn but gave a negative test for the presence of Grignard reagent with Michler's ketone (11). The ether solution was then filtered off and the remaining solid weighed (3.85 g.). This solid also gave a negative color test. On washing with water the substance dissolved with considerable hissing and the evolution of an inflammable vapour. The dried residue, on the filter paper weighed 1.00 g.

On allowing the reaction mixture from another run to stand overnight, a number of large colorless crystals were observed. These turned white on exposure

to the atmosphere and reacted vigorously with water. On allowing the ether to evaporate off, the mass became syrupy owing to the hygroscopic nature of the solid.

These crystals apparently had the same structure as those of magnesium bromide etherate ($MgBr_2.2C_4H_{10}O$) which was prepared by allowing hydrobromic acid in ether to react on magnesium turnings. This compound was also prepared by adding bromine in dry ether to magnesium (17) and besides similar crystalline structure, the action with water was similar.

Some of the white crystalline solid obtained above was washed with water and the filtrate evaporated to dryness on a steam bath. A white product melting at 162° C. was obtained. The melting point of magnesium bromide hexahydrate ($MgBr_2.6H_2O$) is given in the literature as 162° C.

Most of the ether filtrate from the above reaction was allowed to stand stoppered for several weeks, when a gummy residue separated which was of an elastic nature and on ignition smelled very strongly of rubber. This, however, may have resulted from the extraction of the stopper used. The remainder of the ether solution (5 cc.) was used in an attempt to prepare a mercury derivative (16). The ether solution was poured into an excess of mercuric

bromide and the reaction mixture warmed and shaken for five minutes. It was then evaporated to dryness, the residue boiled with 20 cc. of 95% alcohol, filtered into 10 cc. of cold water and allowed to stand for some days. No mercury derivative was obtained.

At the completion of a reaction of magnesium and the dibromide, dry carbon dioxide was passed into the flask and then dilute hydrochloric acid added. The ether solution was filtered and dried over potassium carbonate. No crystalline product was obtained from the ether solution.

Experimental. (B).

The Grignard Reagent from Trimethylene Chlorobromide.

To 0.48 g. (0.02 mol) of magnesium turnings in dry ether were added 3.15 g. (0.02 mol) of trimethylene chlorobromide in 25 cc. of ether. No reaction was observed on warming, but the addition of a crystal of iodine produced immediate action which continued for an hour. Refluxing was continued for an extra hour. A large quantity of white powder was formed and some unchanged magnesium was left in the flask. A sample of the ether layer gave a negative test with Michler's ketone and the addition of water caused no evolution of gas.

The white solid also gave no color test but dissolved in water with much hissing and considerable evolution of an inflammable vapour (ether). The mixture from the flask was filtered, dried and weighed. (3.25 g.).

On placing 1.08 g. of the dry solid in the Zerewitanoff apparatus and adding water, 40 cc. of gas were evolved. (760 mm. and 22° C.) The addition of hydrochloric acid evolved a further 16 cc. No conclusions may be drawn from the first finding, since part of the volume measured is probably due to the liberation of ether of crystal-

lization. Theoretically, 16 cc. of hydrogen at 760 mm. and 22° C. indicate 0.017 g. of magnesium; therefore, of the total magnesium added, 0.048 g., or one-tenth, did not react.

In another investigation, to 3 g. of magnesium in 20 cc. of ether were added slowly 15.75 g. (0.1 mol) of trimethylene chlorobromide in 60 cc. of ether. The reaction started without the addition of iodine on gentle warming. At the end of an hour the reaction had practically ceased; refluxing was continued for another hour. Solid carbon dioxide in a flask was allowed to vaporize, and, passing into a U-tube containing calcium carbonate and phosphorus pentoxide, was led into the reaction mixture with stirring. The flask was allowed to stand stoppered overnight and the product decomposed with dilute hydrochloric acid. It was extracted five times with ether and the total extract neutralized with sodium bicarbonate solution. The water layer was separated, evaporated down to a small volume, acidified and extracted with ether. On evaporation, the ether solution first obtained yielded 0.2 g. of an oil. The acid ether solution, on evaporation, yielded 1.3 g. of an oil having the characteristic odor of chlorobutyric acid. On adding a few cc. of benzene and allowing the solution to stand, rosettes of a solid, which on recrystallization melted at 96-97° C., separated. A mixed melting point proved this product to be glutaric acid.

Summary.

1. Branched chain aliphatic dibromides are too unstable to yield Grignard reagents.

2. Trimethylene chlorobromide was found to give better yields of Grignard reagent than the corresponding dibromide.

References.

1. Harries and Neresheimer, Ann., 383, 167-175 (1911).
2. von Braun and Jostes, Ber., 59, 1091-6 (1926).
3. Manske, J.A.C.S., 53, 3153-59 (1931).
4. Allen, Wilson and Ball, Can. J. Research, 9, 432-5 (1933).
5. Private Communication, Reid, Cockerville, Meyer, Cox and Ruhoff.
6. Grüttner and Wiernik, Ber., 48, 1473-86 (1915).
7. Grüttner and Krause, Ber., 49, 437-44 (1916).
8. Steinkopf, Schubart and Roch, Ber., 65, 409-412 (1932).
9. von Braun and Sobecki, Ber., 44, 1918-31 (1911).
10. Zelinsky and Gutt, Ber., 40, 3049-50 (1907).
11. Gilman and Schulze, J.A.C.S., 47, 2002-5 (1925).
12. Wilson and Allen, "Organic Syntheses", Vol. XIII, p. 111.
13. Adams, "Organic Syntheses", Coll. Vol. I, p. 452.
14. Shepard and Johnson, J.A.C.S., 54, 4385-91 (1932).
15. Gilman and Harris, J.A.C.S., 49, 1825-28 (1927).
16. Marvel, Gauerke and Hill, J.A.C.S., 47, 3010 (1925).
17. Menschutkin, Z. anorg. Chem., 49, 34-45 (1906).
18. Tissier and Grignard, Compt. rend., 132, 835-7 (1901).