The Decomposition of Quaternary Ammonium Salts and the Syntheses of Some Cyclic Ketones.

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THE DECOMPOSITION OF QUATERNARY AMMONIUM SALTS

AND

THE SYNTHESES OF SOME CYCLIC KETONES

by

Samuel J. Nelson, Jr.

A DISSERTATION

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the Degree of

Doctor of Philosophy

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1951

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Samuel J. Nelson Jr.

Samuel J. Nelson, Jr.

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

4 June 1951
Date

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Accepted, 6 June 1951
Date

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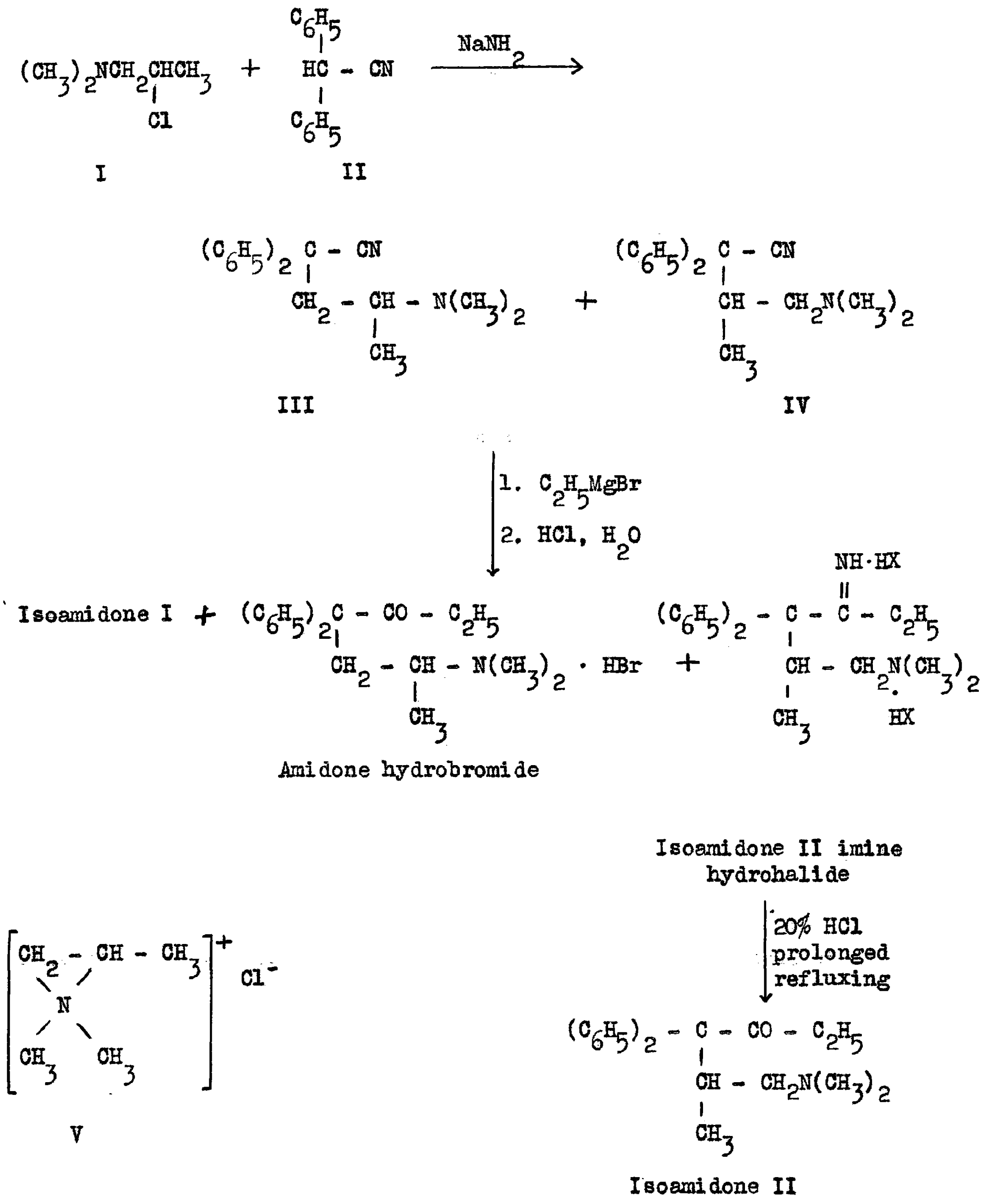
I. INTRODUCTION

The work described in this thesis arose from studies of the synthetic analgesic Amidone and its isomers. It would therefore be well to review briefly the chemistry of these compounds.

Amidone, which has been renamed Methadon by the U. S. Department of Public Health, was first prepared by Bockmuhl and Ehrhart, and was used in Germany during World War II. Their work was originally described in the Office of the Publication Board Report PB-981 (29), and has since been published by these authors (6).

Shortly after the publication of PB-981 studies on compounds of the Amidone type were begun in this country. It was soon discovered that the structure of Amidone did not correspond to the one that should be obtained according to the method of synthesis. The course of this reaction was clarified through an independent synthesis of Amidone by Easton, Gardner and Stevens (15), and through an examination of the intermediate nitriles by Schultz, Robb, and Sprague (32). The results of their findings are outlined in the series of reactions below.



NOTE: The isomers of amidone are named according to Easton, Gardner, and Stevens (13).

When diphenylacetonitrile (II) was alkylated with 1-dimethylamino-2-chloropropane (I) the latter compound appeared to react through an intermediate ethylenimonium ion (V) (16, 32). This gave rise to approximately equal amounts of two isomeric aminonitriles, (III and IV), both of which have been isolated (32). The rearranged product III, eventually yields Amidone. When the mixed nitriles were treated with ethyl magnesium bromide, and the reaction mixture decomposed with aqueous hydrochloric acid three products were obtained (13, 14). The hydrobromide of Amidone, along with Isoamidone I separated as an oil (which slowly crystallized), insoluble in water and benzene, while the imine of Isoamidone II remained in the acidic aqueous layer. Amidone was liberated when the hydrobromide was neutralized. The free base thus obtained was dissolved in absolute alcohol. The hydrochloride precipitated when dry hydrogen chloride was added to this solution. When the mother liquor was concentrated and oxalic acid added, the oxalate of Isoamidone I precipitated in relatively small quantity. This compound was isomeric with the other two, but its structure is still undetermined. The ketimine of Isoamidone II was obtained by treating the aqueous layer with sodium hydroxide and extracting with ether. This imine was remarkably stable, and was only partially hydrolyzed by boiling for five hours with 20% hydrochloric acid (14).

It is interesting to note that the difference in the rate of hydrolysis of the imines of Amidone and Isoamidone II can be readily explained through

Newman's "six number" concept of steric hindrance (28). The six number of the imine of Amidone is three, while that of the imine of Isoamidone II is six.

In an early effort to establish the structures of Amidone and its isomers, exhaustive methylations were carried out on each compound (12) and it is in these experiments that this thesis has its origin.

In an exhaustive methylation the quaternary ammonium halide or, more usually, the hydroxide, is thermally decomposed to give an olefin. When an iodide, for example, is decomposed two reactions are possible.

$$[RCH_2CH_2NR_3]^+ I^- \xrightarrow[\text{heat}]{} RCH = CH_2 + NR_3 + HI$$

$$R_4N^+ I^- \xrightarrow[\text{heat}]{} R_3N + RI$$

The first reaction yields the olefin, which is usually the desired product. Under some conditions, however, the second reaction predominates. The conditions under which these reactions occur will be discussed more extensively in Section II.

Upon pyrolyzing the quaternary ammonium iodide of Amidone, Isoamidone I and Isoamidone II the following products were obtained (12):

(1) Amidone yielded a solid compound that on bromination formed a monobromo derivative with the liberation of hydrogen bromide, and did not react with potassium permanganate in acetone.

(2) Isoamidone I similarly gave a solid product which was unreactive to potassium permanganate, and formed a monobromo derivative with the liberation of hydrogen bromide.

(3) Isoamidone II, upon pyrolysis of the methiodide, gave a liquid product that reacted with bromine to give a dibromide.

The products obtained upon pyrolysis of the methiodide of Amidone and Isoamidone I thus did not show the characteristics generally attributed to unsaturated compounds. Furthermore, no solid products were isolated from the pyrolysis of the quaternary hydroxides (12).

In order to explain these anomalous reactivities, three possibilities were advanced, particularly with respect to Amidone, the compound of known structure.

(1) Unsaturation occurred in the normal manner, but the product, because of steric or other factors, was not reactive to the usual reagents. Initially, this did not seem too likely, since there appeared to be nothing in the structure that would hinder the addition of bromine or oxidation with permanganate.

(2) The compound rearranged to a sterically hindered system. Migration of a phenyl group, followed by elimination of a proton, could produce a stilbene derivative. Stilbene itself reacts very slowly with bromine (34), and although it reacts with permanganate, the addition of further groups might confer unreactivity to the oxidizing agent. Stilbene derivatives are also usually solid, as was the pyrolysis product of Amidone methiodide.

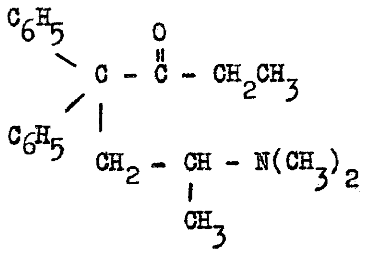
(3) Upon elimination of the quaternary nitrogen, the compound

cyclized to a cyclopentanone. This would very readily explain the failure to behave as an olefin. Since the cyclic structure is more compact, the product could be expected to crystallize. This would account for the fact that it was a solid, while the pyrolysis product of the quaternary hydroxides, giving the normal olefins, might be liquids. This last possibility seemed particularly attractive in view of the known alkylation of active methylene groups with quaternary ammonium salts.

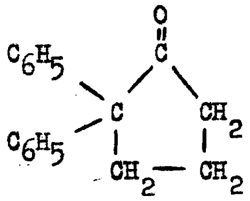
These possibilities will be discussed in more detail in Section IV.

The problem, then, was to determine the structure of these compounds and the nature of the reaction that produced them. Since these amino-ketones have been classified as narcotics it was impossible to use the compounds just described. However, it was possible and, in fact, desirable to use simpler models to carry out this work.

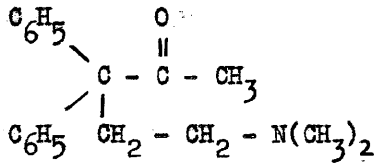
In the development of this problem the preparation of some cyclic ketones was necessary. In addition it was felt that certain derivatives of these cyclic ketones might show analgesic activity. By comparing the structure of Amidone with that of 2,2-diphenylcyclopentanone (VI) it can be seen that the latter compound contains most of the carbon skeleton of Amidone in cyclized form. Structure VII, 5-dimethylamino-3,3-diphenyl-2-pentanone, is, except for the dimethylamino group, the exact open chain analogue of VI. Compound VII has analgesic activity, though less than Amidone.



Amidone



VI



VII

It has been frequently found that open chain and cyclic analogues of physiologically active compounds are similar in their effects, although it cannot be said that either has a general superiority.

II. REACTIONS OF QUATERNARY AMMONIUM COMPOUNDS

The thermal decomposition of quaternary ammonium compounds has long been known, and has had much use, particularly in the preparation of olefins and in the degradation of complicated natural products. While it was known that the olefin was not always produced in the pyrolysis of these salts, especially when the quaternary halide was used instead of the quaternary hydroxide, it was not until 1927 that an extensive investigation was begun by Ingold and his coworkers into the factors affecting the mode of decomposition (20) and into the mechanisms of elimination reactions in general. (For a review of these reactions see references 10 and 24).

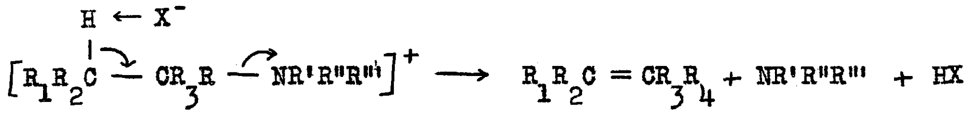
The two most common reactions of these compounds have been described by Hughes, Ingold and Patel through the following equations (25).

$$\text{(A)}\quad [R_1R_2CHCR_2R_3NR'R''R'']^+\ X^- \longrightarrow R_1R_2C = CR_3R_4 + NR'R''R''' + HX$$

$$\text{(B)}\quad [RNR'R''R''']^+\ X^- \longrightarrow RX + NR'R''R'''$$

In these reactions, R_1, R_2, R_3, and R_4 may be hydrogen atoms, and X^- any basic ion, including the halogens.

Upon decomposition, reaction A can occur through three mechanisms.

(A2) 

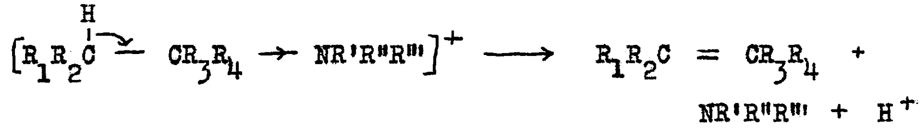
$$\left[R_1R_2\overset{\overset{H \leftarrow X^-}{|}}{C} - CR_3R - NR'R''R'''\right]^+ \longrightarrow R_1R_2C = CR_3R_4 + NR'R''R''' + HX$$

The first and most common of these is represented by the equation A2, (the numbers after the letters "A" and "B" are used to show the order of the reactions), a bimolecular reaction in which the basic group, X$^-$, coordinates with a hydrogen atom on the carbon β to the quaternary nitrogen, and the electron pair forms a double bond with the α carbon, releasing the nitrogen atom. An example of a compound that decomposes through this mechanism is β-phenylethyltrimethylammonium hydroxide (23).

$$\left[C_6H_5 - CH_2 - CH_2 - N(CH_3)_3\right]^+ OH^- \longrightarrow C_6H_5CH = CH_2 + N(CH_3)_3 + H_2O$$

This reaction was found to be first order with respect to both the hydroxide ion and the ammonium ion, and therefore a second order reaction.

A first order reaction that gives a product of the same type occurs when the β hydrogen is highly activated, and the basic ion is so weak that it does not assist in the removal of the proton. This is illustrated by reaction A1.

(A1) 

$$\left[R_1R_2\overset{\overset{H}{|}}{C} - CR_3R_4 \rightarrow NR'R''R'''\right]^+ \longrightarrow R_1R_2C = CR_3R_4 + NR'R''R''' + H^+$$

$$X^- + H^+ \longrightarrow HX$$

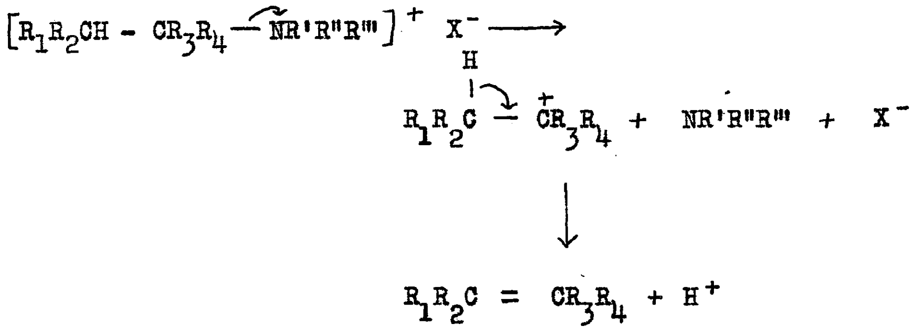
The existence of this mechanism was shown by kinetic studies of the decomposition of β-p-nitrophenylethyltrimethylammonium iodide in water (23).

$$[p - NO_2 - C_6H_4 - CH_2CH_2N(CH_3)_3]^+ I^- \longrightarrow p - NO_2 - C_6H_4 - CH = CH_2 + N(CH_3)_3 + HI$$

The reaction was found to be unaffected by iodide ion and other neutral salts, but accelerated by alkalis and retarded by acids. The reaction was also retarded when isopropyl alcohol was used on the solvent instead of water. Although this reaction is first order, it must still be considered a bimolecular process and essentially the same as A2, since the solvent takes over the function of the base.

A third possible process for olefin formation is illustrated by A'1.

(A'1)



$$[R_1R_2CH - CR_3R_4 - \overset{+}{N}R'R''R''']^+ X^- \longrightarrow R_1R_2\overset{H}{C} - \overset{+}{C}R_3R_4 + \dot{N}R'R''R''' + X^-$$

$$\downarrow$$

$$R_1R_2C = CR_3R_4 + H^+$$

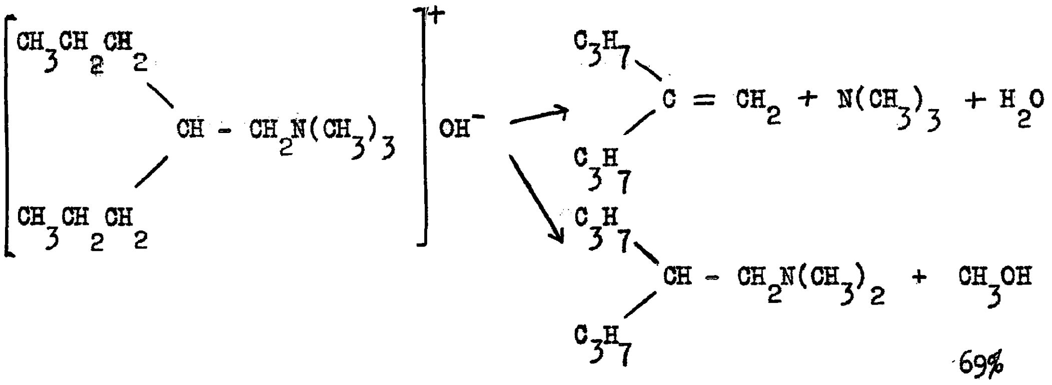
This would be a first order and unimolecular process, insensitive to the presence of added base. While it has not yet been demonstrated for quaternary ammonium compounds, it has been shown to exist in eliminations of sulfonium groups, the halogens and sulfuric acid esters, (10) and probably occurs with ammonium salts (23). This reaction is closely related to mechanism B1, described below.

Mechanism B has two paths, one of which is first order, and the other second, the first order reaction proceeding as illustrated in B1.

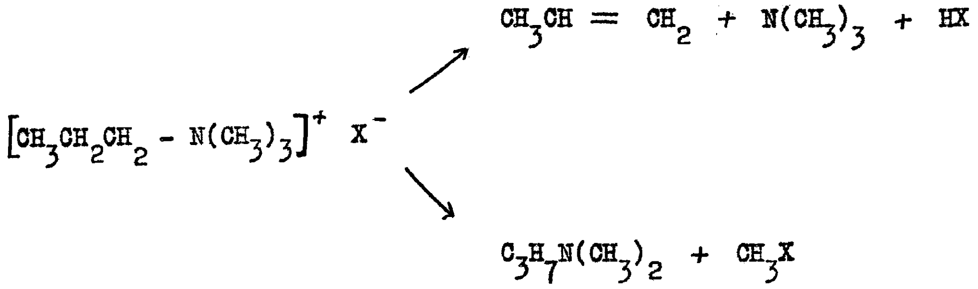
$$\text{(B1)}\quad [R \overset{\curvearrowright}{-} NR'R''R''']^{+}\ X^{-} \longrightarrow R^{+} + NR'R''R''' + X^{-}$$

$$R^{+} + X^{-} \longrightarrow RX$$

This reaction proceeds when there are no β hydrogens, or when the β carbon has election releasing groups which inhibit the removal of a proton. Frequently, mechanism A2 and B1 occur together, and, with a given anion, the extent of reaction B1 depends upon the negative charge on the β carbon. For example, ethyltrimethylammonium hydroxide yields ethylene exclusively, while β-*n*-propyl-*n*-amyltrimethylammonium hydroxide, shown below, yields 69% of methyl alcohol (20).



Data have been also obtained on the effect of the basicity of the negative ion on the ratio of reactions A2 and B1 using various trimethyl-n-propylammonium salts (20).



$$[CH_3CH_2CH_2 - N(CH_3)_3]^+ \; X^- \nearrow CH_3CH = CH_2 + N(CH_3)_3 + HX$$

$$[CH_3CH_2CH_2 - N(CH_3)_3]^+ \; X^- \searrow C_3H_7N(CH_3)_2 + CH_3X$$

The salts compared, among others, were the hydroxide, phenoxide, m-nitrophenoxide, chloride and iodide. The hydroxide gave 19% methyl alcohol, the phenoxide 65% anisole, and the m-nitrophenoxide 89% of m-nitroanisole.

$$\begin{tikzcd}
 & CH_3CH = CH_2 + N(CH_3)_3 + H_2O \\
{[CH_3CH_2CH_2 - N(CH_3)_3]^+ \; OH^-} \arrow[ur] \arrow[dr] & \\
 & CH_3CH_2CH_2N(CH_3)_2 + CH_3OH \\
 & 19\%
\end{tikzcd}$$

$$\begin{tikzcd}
 & CH_3CH = CH_2 + N(CH_3)_3 + C_6H_5OH \\
{[C_3H_7N(CH_3)_3]^+ \; \bar{O}-C_6H_5} \arrow[ur] \arrow[dr] & \\
 & CH_3CH_2CH_2N(CH_3)_2 + CH_3-O-C_6H_5 \\
 & 65\%
\end{tikzcd}$$

$$\begin{tikzcd}
 & CH_3CH = CH_2 + N(CH_3)_3 + mNO_2-C_6H_4OH \\
{[C_3H_7N(CH_3)_3]^+ \; \bar{O}-C_6H_4-NO_2-m} \arrow[ur] \arrow[dr] & \\
 & CH_3CH_2CH_2N(CH_3)_2 + CH_3O-C_6H_4-NO_2-m \\
 & 89\%
\end{tikzcd}$$

The chloride and iodide gave results similar to those with the m-nitrophenoxide, but this was attributed to the possibility that the halide ions, in the non-aqueous fusion system used in these particular experiments, might be as strongly basic as m-nitrophenoxide ion.

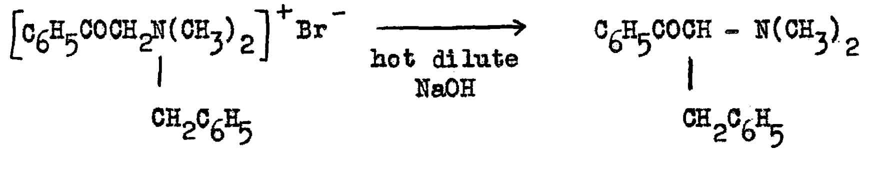
The second order decomposition B2 can be described by the following equation:

(B2) 

$$\left[R'R''R'''\overset{\overset{R \leftarrow X^-}{\curvearrowleft}}{N}\right]^+ \longrightarrow R'R''R'''N + RX$$

This mechanism can operate when the carbon atom being attacked is at least as positive as the carbon of the methyl group, and when the base is as strong or stronger than the hydroxide ion. It has been observed as a side reaction in the formation of olefins (23), and along with another alcohol when none of the R groups held a β hydrogen (22).

Rearrangement can occur when no β hydrogen is present. These have been studied extensively by Stevens (38) and are of the following type:



$$\left[C_6H_5COCH_2\underset{\underset{CH_2C_6H_5}{|}}{N}(CH_3)_2\right]^+ Br^- \xrightarrow[\text{NaOH}]{\text{hot dilute}} C_6H_5CO\underset{\underset{CH_2C_6H_5}{|}}{CH} - N(CH_3)_2$$

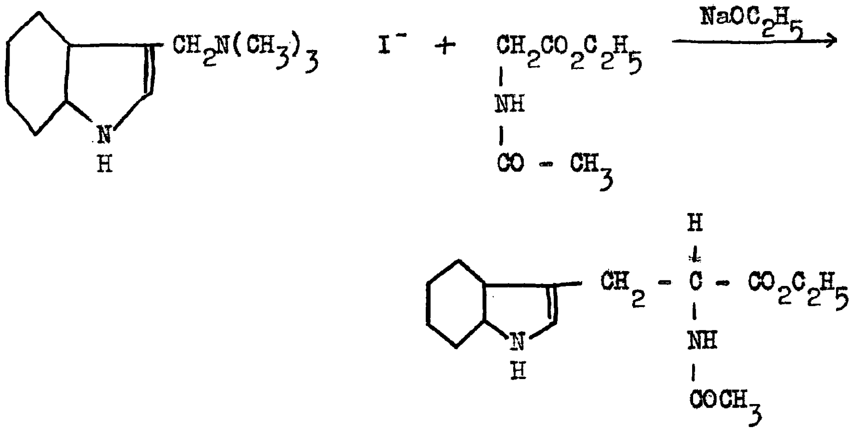
This was interpreted by Hughes and Ingold to be a removal of a proton from the α carbon, followed by stabilization through migration of the benzyl group.

A final reaction of quaternary ammonium salts should be described, since, at least initially, it had considerable bearing upon this work. This is the alkylation of compounds containing active methylene groups, such as malonic ester, with quaternary ammonium salts. The following reaction is typical (36).

$$[C_6H_5CH_2N(CH_3)_2C_6H_5]^+ Cl^- + CH_2(CO_2C_2H_5)_2 \xrightarrow{NaOC_2H_5}$$

$$C_6H_5CH_2CH(CO_2C_2H_5)_2 + C_6H_5N(CH_3)_2$$

A similar reaction has been carried out with the methiodide of gramine in the preparation of tryptophan (37).

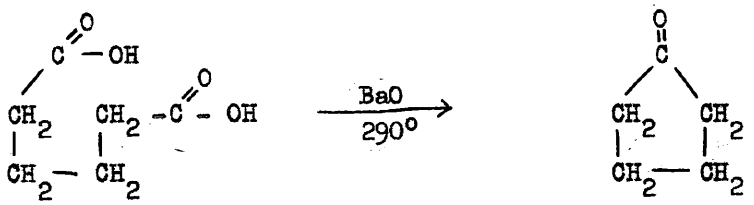


It was later found that gramine would condense with nitroacetic acid in the absence of any catalyst other than gramine itself (27).

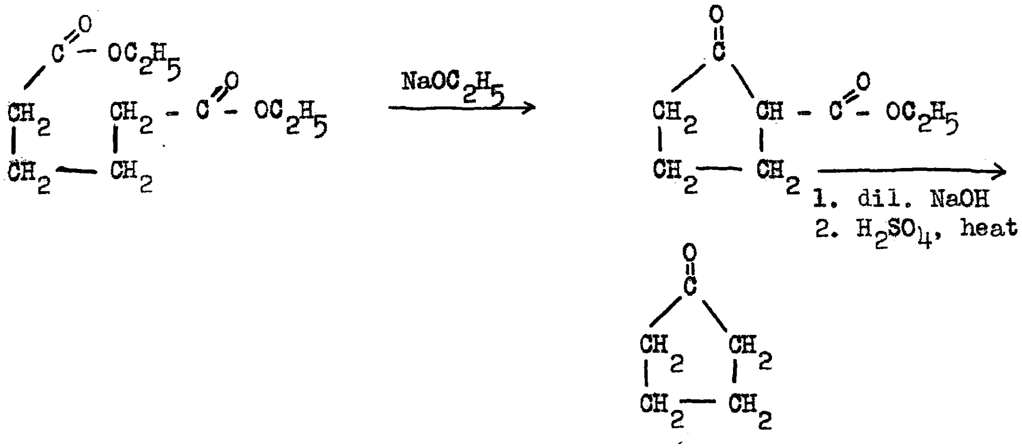
III. THE FORMATION OF CYCLIC KETONES

Although it is not possible to generalize completely with respect to the formation of alicyclic compounds containing a keto group, there are three well known, general and somewhat similar reactions for the formation of cyclic ketones from linear compounds. These are:

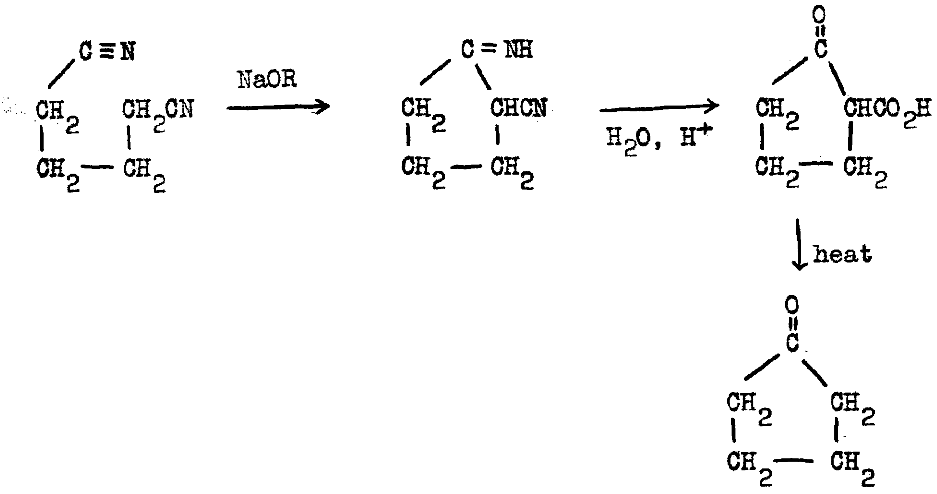
(1) The pyrolysis of metallic salts of dibasic acids. This can be illustrated by the formation of cyclopentanone from adipic acid.



(2) The Dieckmann reaction, which is an internal Claisen condensation of the ester of a dibasic acid. The product is a beta-ketonic ester which can be hydrolyzed and decarboxylated to give the desired ketone.



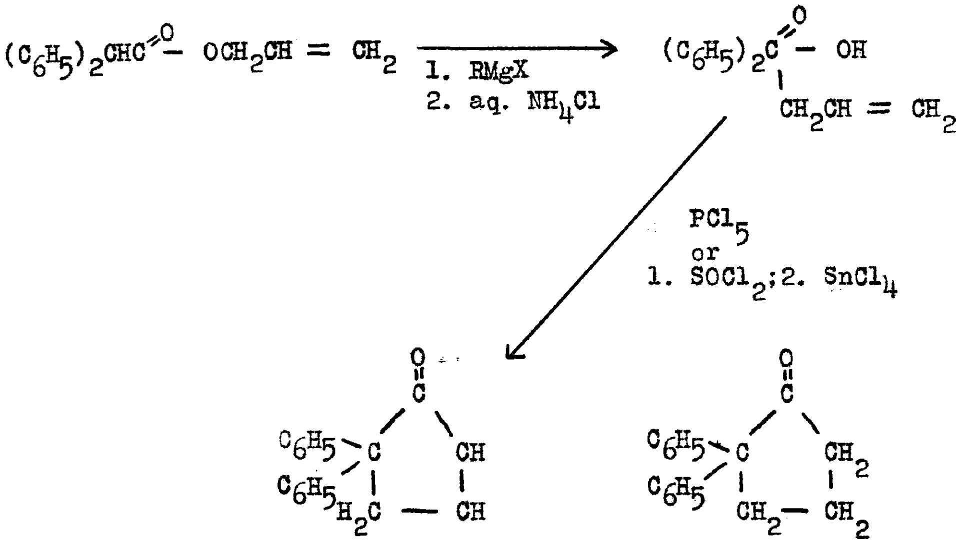
(3) The Thorpe reaction, which is carried out on the nitrile of a dibasic acid, and gives a cyclic imino-nitrile that can be hydrolyzed to the keto-acid and decarboxylated to the ketone.



All of the above reactions give satisfactory yields. However, the Dieckmann is most generally used.

In this work it was necessary to prepare some 2,2-diphenylcyclopentanones, and although it is a general rule that alkyl groups, and particularly gem-dimethyl groups increase the yield of cyclic product in these reactions (17), the effect of gem-diphenyls in the alpha position was quite uncertain.

The unsaturated compound, 5,5-diphenyl-2-cyclopentanone (VIII) has been prepared (9) starting with the rearrangement of allyl diphenylacetate (5). The yield of cyclic product in this series of reactions is not very good.



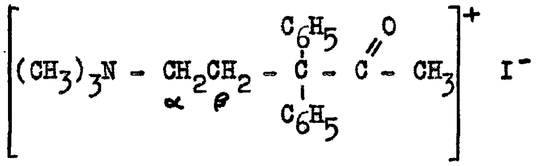
VIII　　　　VI

The saturated compound, 2,2-diphenylcyclopentanone (VI) has been prepared (8) but the method of synthesis has not been published.

IV. DISCUSSION AND RESULTS

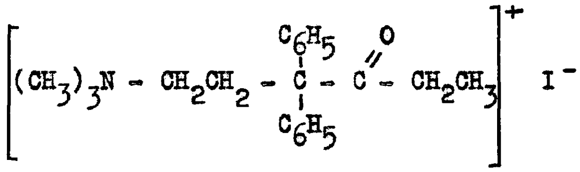
A. The Structure of the Pyrolysis Products of 5-Dimethylamino-3,3-Diphenylpentan-2-One Methiodide and 6-Dimethylamino-4,4-Diphenyl-Hexan-3-One Methiodide.

As mentioned in Part I, the methiodides of compounds modeled after Amidone were used in this work. These compounds were 5-dimethylamino-3,3-diphenylpentan-2-one methiodide (IX) and 6-dimethylamino-4,4-diphenylhexan-3-one methiodide (X).



$$\left[(CH_3)_3N - \underset{\alpha}{CH_2}\underset{\beta}{CH_2} - \overset{C_6H_5}{\underset{C_6H_5}{C}} - \overset{O}{\overset{/\!/}{C}} - CH_3\right]^+ I^-$$

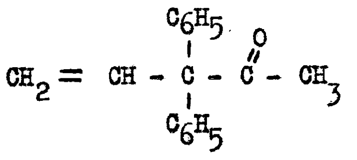
IX



$$\left[(CH_3)_3N - CH_2CH_2 - \overset{C_6H_5}{\underset{C_6H_5}{C}} - \overset{O}{\overset{/\!/}{C}} - CH_2CH_3\right]^+ I^-$$

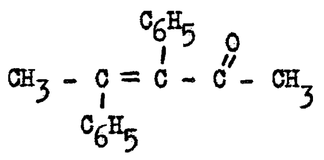
X

Considering the methiodide of the methyl ketone, IX, from the point of view of the discussion in Sections I and II, three compounds could conceivably be obtained upon pyrolysis. These are 3,3-diphenyl-4-penten-2-one (XI), 3,4-diphenyl-3-penten-2-one (XII) and 2,2-diphenylcyclopentanone (VI).



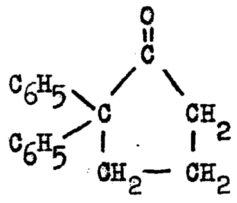
$$CH_2=CH-\overset{C_6H_5}{\underset{C_6H_5}{C}}-\overset{O}{\overset{\|}{C}}-CH_3$$

XI



$$CH_3-\underset{C_6H_5}{C}=\overset{C_6H_5}{C}-\overset{O}{\overset{\|}{C}}-CH_3$$

XII

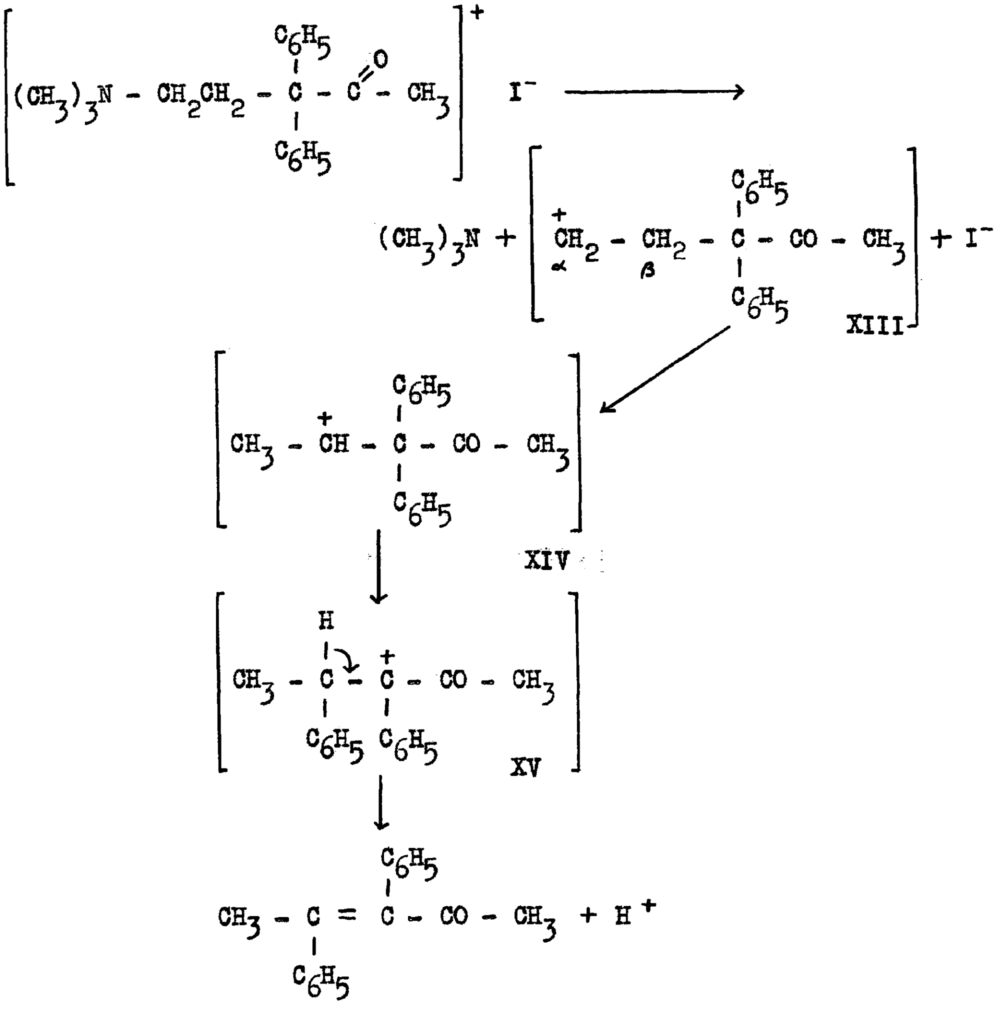


VI

The normal olefin, XI, would be produced either by mechanism A2 or A'1 described in Secton II, and requires no further discussion.

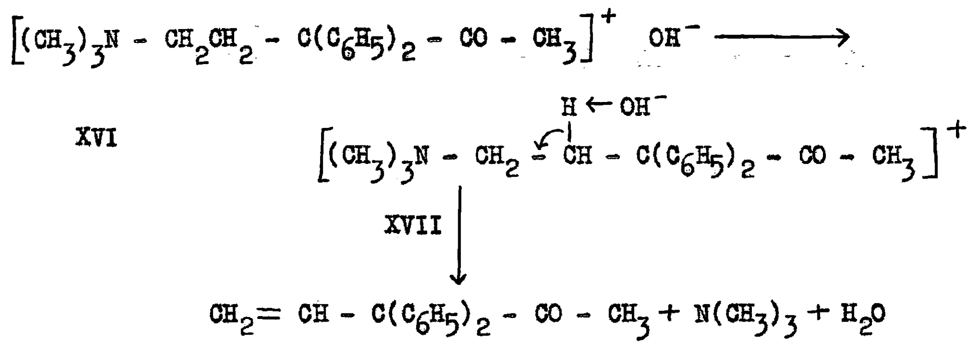
A rearranged product such as 3,4-diphenyl-3-penten-2-one (XII) was at the outset considered quite remote, but the possibility of its formation was not entirely discarded since such a compound would fairly well explain the properties of the pyrolysis product obtained, and would also aid, better than either of the other possibilities, in explaining the apparent difference between the pyrolysis products of the iodide and hydroxide obtained in the original work (12). Assuming that different products were to be formed from the iodide IX and the hydroxide XVI, as was the case with Amidone, an explanation could be found through the alternative mechanisms illustrated below with the quaternary salts of the amino-ketone IX which was used in this work.

The formation of compound XII could be initialed in the manner of reactions A'1 and B1 of Section II.



XII

The intermediate carbonium ion XIII could lead to the normal olefin XI through elimination of a proton from the carbon (mechanism A'1). This would seem to be the most likely course of reaction. However, it could also conceivably pass through the intermediates XIV and XV to give the stilbene derivative, XII. This would readily explain the difference, if any were obtained, between the pyrolysis products of the quaternary iodide and hydroxide of Amidone. The iodide ion being a very feeble base, would be much less likely to attack the β hydrogen (indicated in formula IX) than the strongly basic hydroxide ion. This would lead to the intermediate XII with iodide, and XVII with the hydroxide, and account for two different final products.



$$\left[(CH_3)_3N - CH_2CH_2 - C(C_6H_5)_2 - CO - CH_3\right]^+ \; OH^- \longrightarrow$$

XVI

$$\left[(CH_3)_3N - CH_2 - \overset{H \leftarrow OH^-}{CH} - C(C_6H_5)_2 - CO - CH_3\right]^+$$

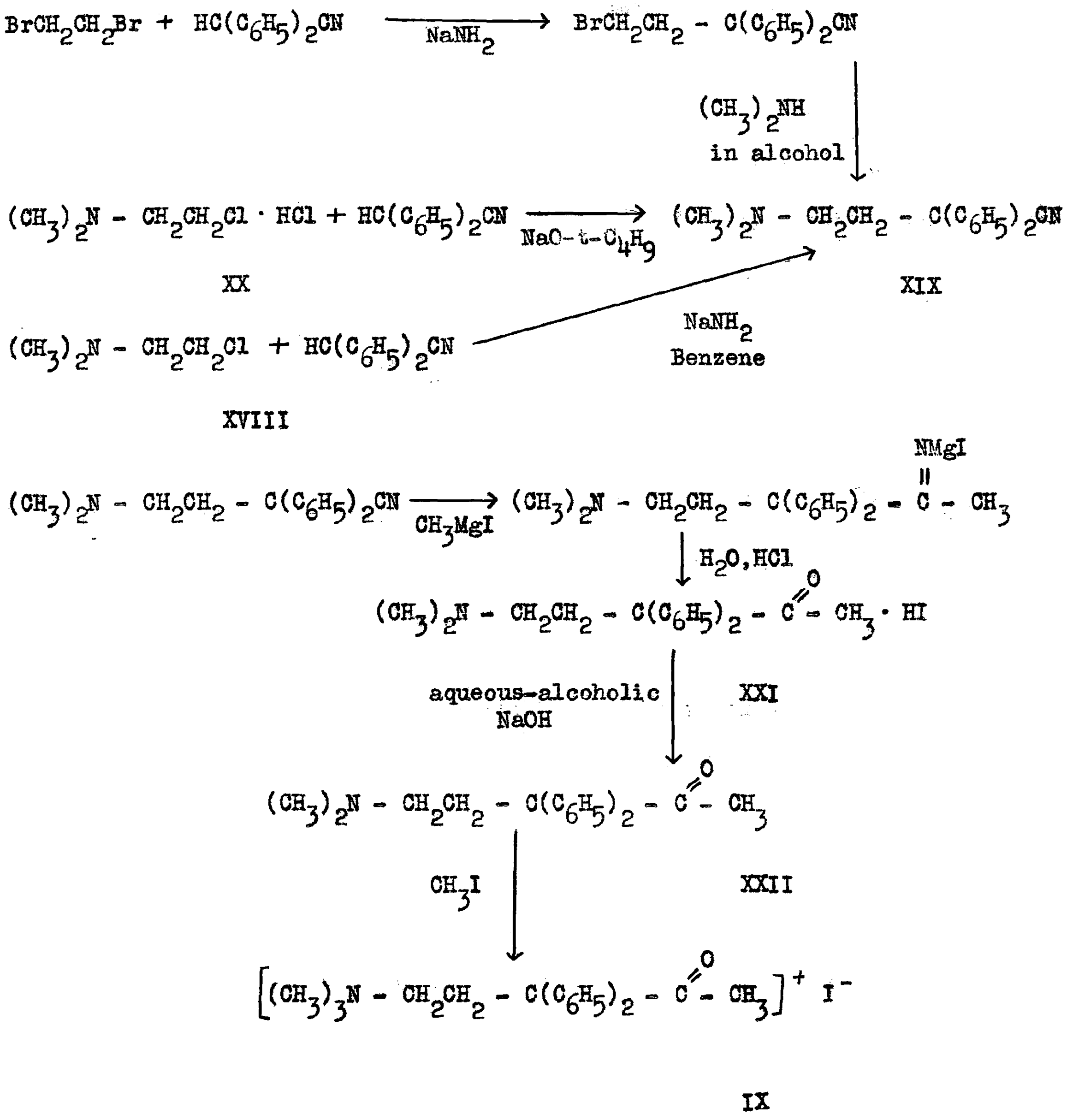
$$\Big\downarrow \text{XVII}$$

$$CH_2{=}\,CH - C(C_6H_5)_2 - CO - CH_3 + N(CH_3)_3 + H_2O$$

XI

The third possibility, cyclization to the 2,2-diphenylcyclopentanone, would follow the same path as the alkylations of active methylene compounds with quaternary ammonium salts described in Section II. This is presumably a displacement of the quaternary nitrogen with a carbanion, and in the case of compound IX, would apparently mean removal of a proton from the methyl group, and attack of the resulting negative ion on the α carbon of IX. While the base is weak, and the methyl hydrogens are not nearly as activated as those of malonic ester or nitroacetic ester, it was felt that the conditions of pyrolysis might be sufficiently drastic to permit the reaction to proceed. The cyclic structure would best account for the properties of the pyrolysis products obtained in the previous work. However, it would seem that some of the same product should be obtained upon pyrolysis of the hydroxide XVI.

With these possibilities in mind, the methiodide of 5-dimethylamino-3,3-diphenylpentan-2-one (IX) was prepared through the following reactions. The intermediate, 4-dimethylamino-2,2-diphenylbutanenitrile (XIX) was prepared by three methods (11, 33, 29) shown below. This was converted to 5-dimethylamino-3,3-diphenylpentan-2-one (XXII), and then to the quaternary iodide (XXIII).



$$BrCH_2CH_2Br + HC(C_6H_5)_2CN \xrightarrow[NaNH_2]{} BrCH_2CH_2 - C(C_6H_5)_2CN$$

$$\Big\downarrow \begin{matrix}(CH_3)_2NH \\ \text{in alcohol}\end{matrix}$$

$$(CH_3)_2N - CH_2CH_2Cl \cdot HCl + HC(C_6H_5)_2CN \xrightarrow[NaO\text{-}t\text{-}C_4H_9]{} (CH_3)_2N - CH_2CH_2 - C(C_6H_5)_2CN$$

XX XIX

$$(CH_3)_2N - CH_2CH_2Cl + HC(C_6H_5)_2CN \xrightarrow[\text{Benzene}]{NaNH_2} \text{XIX}$$

XVIII

$$(CH_3)_2N - CH_2CH_2 - C(C_6H_5)_2CN \xrightarrow[CH_3MgI]{} (CH_3)_2N - CH_2CH_2 - C(C_6H_5)_2 - \overset{\overset{NMgI}{\|}}{C} - CH_3$$

$$\Big\downarrow H_2O, HCl$$

$$(CH_3)_2N - CH_2CH_2 - C(C_6H_5)_2 - \overset{\overset{O}{/\!/}}{C} - CH_3 \cdot HI$$

XXI

$$\Big\downarrow \begin{matrix}\text{aqueous-alcoholic} \\ NaOH\end{matrix}$$

$$(CH_3)_2N - CH_2CH_2 - C(C_6H_5)_2 - \overset{\overset{O}{/\!/}}{C} - CH_3$$

XXII

$$\Big\downarrow CH_3I$$

$$\left[(CH_3)_3N - CH_2CH_2 - C(C_6H_5)_2 - \overset{\overset{O}{/\!/}}{C} - CH_3\right]^+ I^-$$

IX

Alkylation of diphenylacetonitrile to give 4-bromo-2,2-diphenylbutanenitrile followed by amination with dimethylamine (11)

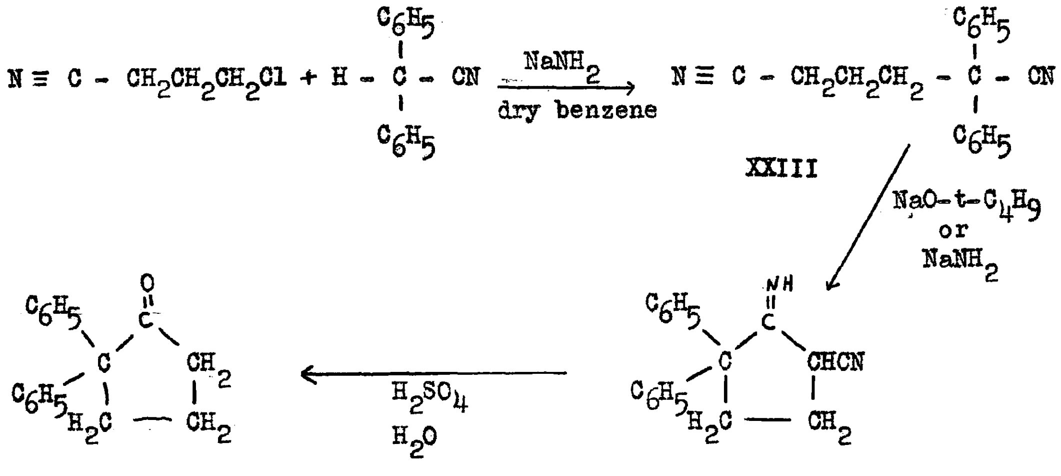
proved, in general, to be the most convenient method for the preparation of the amino-nitrile XIX. The ketone was prepared by reaction of the nitrile with methyl magnesium iodide in ether-xylene solution, followed by hydrolysis in 10% hydrochloric acid. The resulting hydroiodide of 5-dimethylamino-3,3-diphenyl-pentan-2-one (XXI) was treated with aqueous-alcoholic sodium hydroxide to obtain the free base XXII, which was purified by distillation at reduced pressure, or alternatively by recrystallization of the oxalate followed by conversion to the free base. The methiodide IX was prepared by the reaction of methyl iodide and the amino-ketone in absolute alcohol.

The methiodide of 5-dimethylamino-3,3-diphenyl-2-pentanone was decomposed under vacuum by heating it in a distilling flask with a free flame. The product was distilled from the flask and condensed in the receiver as it was formed. The brownish oil was purified by dissolving in benzene, extraction with dilute hydrochloric acid, and finally distillation at reduced pressure.

The product which analyzed for $C_{17}H_{16}O$, was a colorless oil that darkened slowly in air. It did not react with potassium permanganate in acetone and reacted with bromine with the liberation of hydrogen bromide. This was in accord with the previous results with Amidone methiodide, except for the fact that the decomposition product of compound IX was a liquid, while that from Amidone methiodide was a solid. Because of the inactivity to permanganate and bromine, the olefinic structure XI (page 20) was initially considered unlikely, unless for some reason the double bond should be unreactive.

The pyrolysis product also formed a 2,4-dinitrophenylhydrazone melting at 194.0 - 194.5°, and an oxime melting at 171.0 - 172.0°. Both of these derivatives retained a molecule of water that could not be removed when dried in an Abderhalden apparatus over boiling acetone, and under a vacuum of 1 mm. or less. The 2,4-dinitrophenylhydrazone was not very stable, and was purified with difficulty. Analyses were consequently not too good.

The cyclic structure VI was eliminated by the synthesis of 2,2-diphenylcyclopentanone (XXV). It was prepared in good yield through the following reactions:



XXV

XXIV

Diphenylacetonitrile was alkylated with γ-chlorobutyronitrile using sodium amide as the catalyst to give yields of about 50% of α,α-diphenyladiponitrile (XXIII), which was a solid melting at 66 - 67°. There was sometimes obtained, in addition to the linear product, the cyclic 5-cyano-2,2-diphenylcyclopentanone imine (XXIV) which melted at 149 - 150°, and this was sometimes the only isolatable product. It is reasonable that some of the cyclic product should be formed, since the cyclization would be catalyzed by the presence of sodium amide or perhaps diphenylacetonitrile anion, even if present in very small excess. A facile method for separation of some of the cyclic product in very pure form was to evaporate the benzene and dilute the oily residue with about five volumes of ether. The cyclic product crystallized upon standing overnight. The material remaining in solution appeared to be a mixture of the cyclic and linear compounds, and in spite of the great difference in melting points, they were almost impossible to separate. However, the mixture could be converted entirely to cyclic product by the procedure described below for the preparation of α,α-diphenyladiponitrile.

When sodium tertiary butoxide was used as the catalyst in this reaction only diphenylacetamide was isolated.

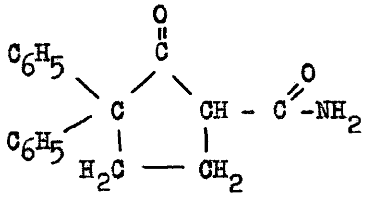
The imino-nitrile XXIV was prepared from the linear compound through the Thorpe reaction in yields of 90% using catalytic amounts of sodium t-butoxide in absolute t-butyl alcohol, or with sodium amide in dry benzene. The former system gave a much cleaner reaction, and gave none of the heavy, reddish tar obtained when sodium amide was used.

Hydrolysis and decarboxylation of 5-cyano-2,2-diphenylcyclopentanone imine (XXIV) to 2,2-diphenylcyclopentanone (XXV) was carried out in 91% yield by dissolving the cyclic product in 88% sulfuric acid on the steam bath, diluting with water, and stirring at reflux for at least 18 hours. The product was a crystalline solid melting at 89 - 90°, and formed a 2,4-dinitrophenylhydrazone that melted at 182.0 - 182.5°.

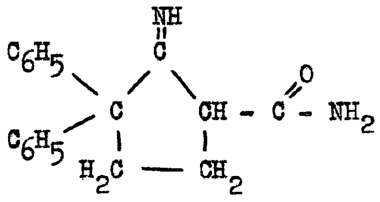
This product was quite obviously different from the pyrolysis product of 5-dimethylamino-3,3-diphenylpentan-2-one methiodide, which was a liquid and formed a 2,4-dinitrophenylhydrazone melting at 194.0 - 194.5°.

When shorter reflux times (8 - 10 hours) were used in the hydrolysis and decarboxylation of 5-cyano-2,2-diphenylcyclopentanone imine, the amide of 2,2-diphenylcyclopentanone-5-carboxylate XXVI, melting at 132 - 133° was isolated. This could be converted to 2,2-diphenylcyclopentanone by refluxing and stirring with dilute sulfuric acid.

Under the same conditions, the amide of 2,2-diphenylcyclopentanone imine-5-carboxylate (XXVII) was sometimes isolated. This compound melted at 229 - 232°. It was also obtained through basic hydrolysis of 5-cyano-2,2-diphenylcyclopentanone imine.



XXVI



XXVII

With the possibility of a cyclic compound eliminated it was necessary to distinguish between structures XI and XII, or some other rearranged product. Since any rearrangement would almost certainly involve the phenyl group it is apparent that strong oxidation would give the desired information. Accordingly, the pyrolysis product of the methiodide IX was oxidized with chromic anhydride in acetic acid. No benzoic acid was isolated, but a neutral material was obtained which, upon treatment with semicarbozide yielded a crystalline derivative. The derivative was identified as benzophenone by means of a melting point and mixed melting point. It was therefore concluded that structure XI was the correct one. The reaction can then be written in the following manner:

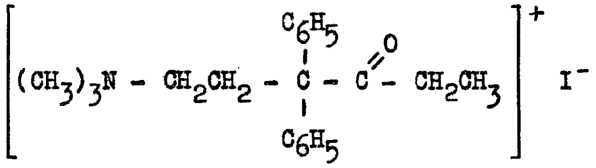
$$\left[(CH_3)_3N - CH_2CH_2 - C(C_6H_5)_2 - CO - CH_3\right]^+ I^-$$

$$\Big\downarrow \text{heat}$$

$$CH_2 = CH - C(C_6H_5)_2 - CO - CH_3 + (CH_3)_3N + HI$$

XI

These results were confirmed through the pyrolysis of 6-dimethylamino-4,4-diphenylhexan-3-one methiodide (X).



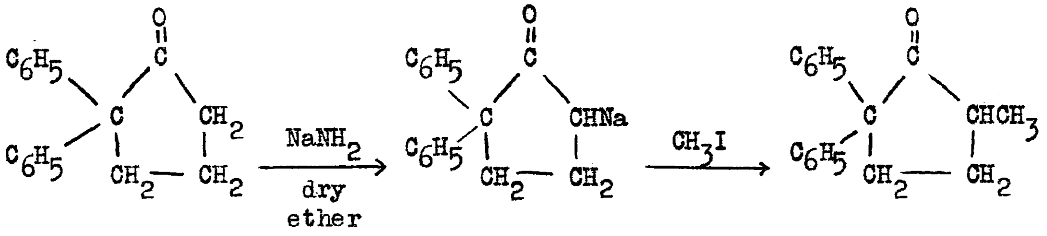
$$\left[(CH_3)_3N - CH_2CH_2 - \overset{C_6H_5}{\underset{C_6H_5}{C}} - \overset{O}{\overset{\|}{C}} - CH_2CH_3\right]^+ I^-$$

X

This compound was prepared in a manner exactly analogous to that for the methyl ketone IX, using ethyl magnesium iodide instead of methyl magnesium iodide.

The methiodide X was decomposed by heating under reduced pressure as before. The product distilled from the reaction flask into the receiver, where it quickly crystallized. After recrystallization from alcohol it melted at 104.5 - 105.5. It analyzed for $C_{18}H_{18}O$, and formed a 2,4-dinitrophenylhydrazone melting at 124.5 -126.0°

In order to check again the possibility of cyclization, 2,2-diphenyl-5-methyl-cyclopentanone (XXIX) was prepared through the following reactions (40):



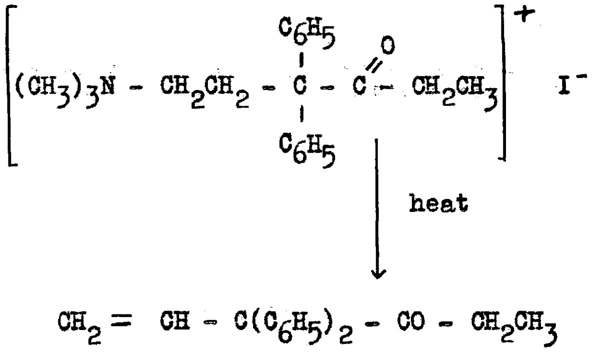
XXIX

This compound melted at 54.0-56.5° again eliminating the possibility of cyclization. It also formed a 2,4-dinitrophenylhydrazone melting at 84 - 87°.

The pyrolysis product of compound XXX was also oxidized with chromic oxide. A small amount of benzoic acid was obtained in this oxidation, but most of the recovered product was benzophenone which was identified as the semicarbazone.

In order to check the source of the benzoic acid obtained in the oxidation a sample of benzophenone was oxidized in the same way. A similar proportion of benzoic acid was recovered. An ether solution of the benzophenone used was shaken with 5% potassium hydroxide. Acidification of the extract yielded no organic acid.

It was therefore concluded that in this case too, the phenyl group had not migrated and that the product of pyrolysis was 4,4-diphenyl-5-hexen-3-one (XXX).



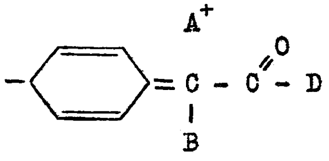
$$\left[(CH_3)_3N - CH_2CH_2 - \overset{C_6H_5}{\underset{C_6H_5}{C}} - \overset{O}{\overset{/\!/}{C}} - CH_2CH_3\right]^+ I^- \xrightarrow{\text{heat}} CH_2 = CH - C(C_6H_5)_2 - CO - CH_2CH_3$$

XXX

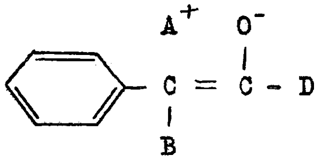
In addition, quaternary hydroxides were prepared from 5-dimethylamino-3,3-diphenylpentan-2-one methiodide (IX) and 6-dimethylamino-4,4-diphenylhexan-3-one methiodide (X). Upon thermal decomposition, each yielded the same compound as was obtained from the corresponding iodide. This strongly confirms the olefin structure since, in the absence of an attack by the base on a hydrogen alpha to the carbonyl group to give the cyclized product, it should attack beta to the quaternary nitrogen to give the elimination product.

While these reaction are entirely normal for quaternary ammonium halides and hydroxides, it leaves unexplained the failure of the products to react with reagents that usually attack olefinic linkages.

An explanation of such anomalous reactivities can be found through the spectroscopic studies of Kumler, Strait and Alpen (3, 26). These authors examined the ultra violet absorption spectra of a number of α-phenylcarbonyl compounds. The anticipated spectrum for an α-phenylaldehyde or ketone would have a peak at about 260 mμ due to absorption by the phenyl group, and a second peak at 270 - 280 mμ with a molecular extinction coefficient of 15 - 25, representing absorption by the carbonyl group. They found, instead, that with α-phenylaldehydes and ketones the second peak was at 295 mμ with a molecular extinction coefficient of 100 - 400. In addition, the second peak showed considerable fine structure, which is not usually found for carbonyl absorption. This was interpreted to mean that, contrary to the general rule that chromophores separated by a saturated carbon atom absorb independently, the phenyl and carbonyl groups interact through the saturated carbon, and that no bond resonance formulas such as XXXI and XXXII make a significant contribution to the structure of the molecule.



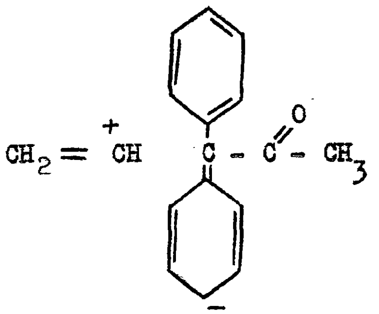
XXXI



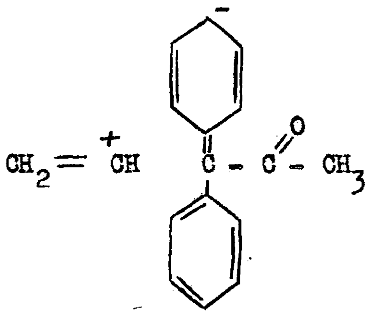
XXXII

It was also observed that if the group D had an unshared pair of electrons so that it could interact with the carbonyl oxygen, the 295 mμ peak disappeared, as would be expected. Phenylacetic acid and diphenylacetic acid showed no 295 mμ bond.

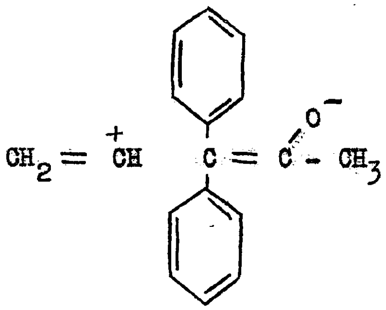
Applying these results to 3,3-diphenyl-4-penten-2-one, if such structures as XXXIII, XXXIV and XXXV were to contribute to the structure of the molecule, the vinyl group would have a relatively high positive charge.



XXXIII



XXXIV



XXXV

This would then account for the inactivity of the double bond. Addition of bromine to a double bond is an electrophilic process (1), and the high positive charge on the vinyl group makes reaction so slow that the methyl or methylene group adjacent to the carbonyl is brominated.

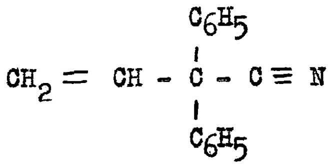
A reduction in the electron density of a vinyl group is known to reduce reactivity to bromine. The rate of addition of bromine to vinyl bromide is very slow compared with ethylene (4). The allyl grouping, which normally adds bromine rapidly, is unreactive when attached to a quaternary nitrogen as in XXXVI (31).

$$CH_2 = CH - CH_2\overset{+}{N}R_3$$

XXXVI

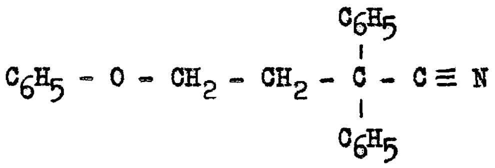
The reason for failure of the double bond to react with permanganate under test conditions for an olefinic linkage is similar. Oxidizing agents are electrophilic, and apparently the supply of electron in the area of the double bond has been depleted sufficiently to make difficult the attack of neutral permanganate at room temperature.

Further confirmation of this point of view was obtained through 2,2-diphenylbutenenitrile (XXXVII) and 4 -phenoxy-2,2-diphenylbutanenitrile (XXXVIII), which will be described more fully later.



$$CH_2=CH-\overset{\displaystyle C_6H_5}{\underset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}-C\equiv N$$

XXXVII

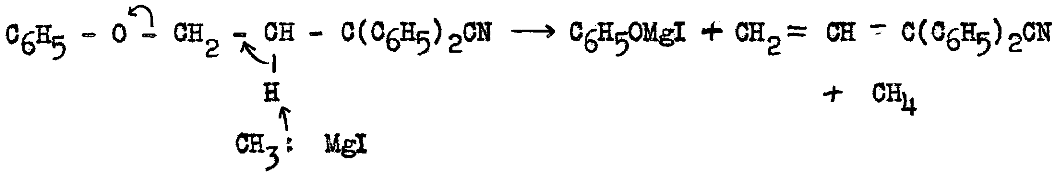


$$C_6H_5-O-CH_2-CH_2-\overset{\displaystyle C_6H_5}{\underset{\displaystyle C_6H_5}{\overset{|}{\underset{|}{C}}}}-C\equiv N$$

XXXVIII

Both of these compounds would be expected to have no bond resonance structures similar to those of α-phenylcarbonyl compounds. The unsaturated nitrile (XXXVII) which cannot react with bromine by substitution, did not add bromine in carbon tetrachloride at room temperature to any visible extent over a period of 48 hours. With 4 -phenoxy-2,2-diphenylbutanenitrile it appears that an unusual reaction occurred. When this compound was treated with methyl magnesium iodide in an effort to convert it to 5-phenoxy3,3-diphenyl-

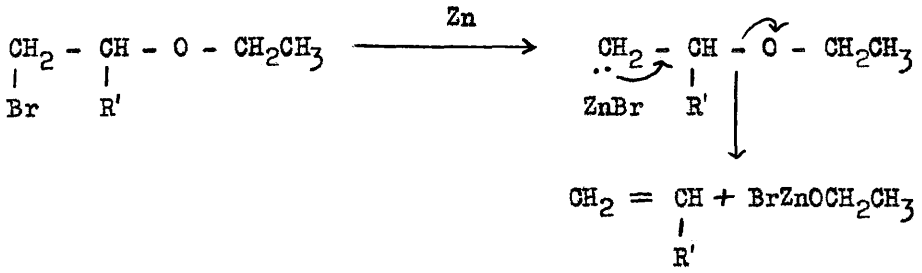
2-pentanone, phenol was isolated from the reaction mixture. The presence of phenol could be accounted for by an attack of the methyl anion of the Grignard reagent on a hydrogen β to the phenoxy group, resulting in the elimination of phenol. This could occur if a relatively strong positive charge was developed on the β carbon, as would be the case if hyperconjugation similar to that of α-phenylketones occurred. In the presence of the strongly basic Grignard reagent, and at the high temperature at which this reaction was carried out, it appears that the attack of the anion occurred at a β hydrogen.



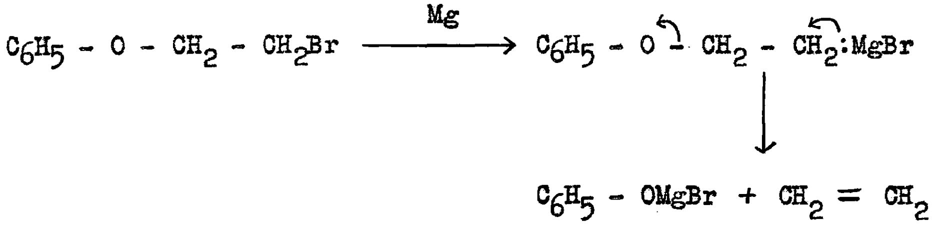
$$C_6H_5-O-CH_2-\underset{\underset{\underset{CH_3:\ MgI}{\uparrow}}{H}}{\underset{|}{CH}}-C(C_6H_5)_2CN \longrightarrow C_6H_5OMgI + CH_2=CH-C(C_6H_5)_2CN + CH_4$$

Since phenol was the only product identified, the above reaction has not been definitely demonstrated, but it does account for the presence of phenol, and a non-ketonic product which was also obtained.

Similar eliminations of an ether group occur in the Boord synthesis, in which a β-bromo ether is treated with zinc to give an olefin, and in the reaction of β-phenoxyethyl bromide with magnesium to give phenoxymagnesium bromide and ethylene (19).



$$\underset{\mathrm{Br}}{\mathrm{CH_2}} - \underset{\mathrm{R'}}{\mathrm{CH}} - \mathrm{O} - \mathrm{CH_2CH_3} \xrightarrow{\mathrm{Zn}} \underset{\mathrm{ZnBr}}{\ddot{\mathrm{C}}\mathrm{H_2}} - \underset{\mathrm{R'}}{\mathrm{CH}} - \mathrm{O} - \mathrm{CH_2CH_3} \longrightarrow \mathrm{CH_2} = \underset{\mathrm{R'}}{\mathrm{CH}} + \mathrm{BrZnOCH_2CH_3}$$



$$\mathrm{C_6H_5 - O - CH_2 - CH_2Br} \xrightarrow{\mathrm{Mg}} \mathrm{C_6H_5 - O - CH_2 - CH_2{:}MgBr} \longrightarrow \mathrm{C_6H_5 - OMgBr + CH_2 = CH_2}$$

In both of these reactions, a carbanion is formed β to the group eliminated, as would be the case for the suggested reaction of methyl magnesium iodide with 4-phenoxy-2,2-diphenylbutanenitrile.

The inactivity of the double bond of 3,3-diphenyl-4-penten-2-one, and 2,2-diphenylbutanenitrile, along with the elimination of phenol from 4-phenoxy-2,2-diphenylbutanenitrile constitute chemical evidence for the no bond resonance structures of α-phenylketone suggested by Kumler, Strait and Alpen from spectroscopic data.

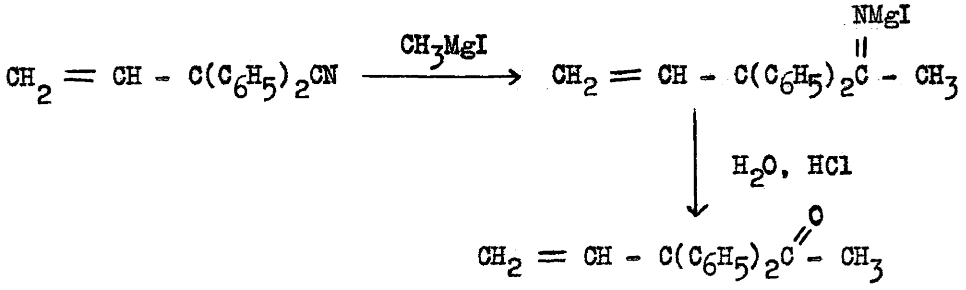
B. Attempted Syntheses of 3,3-Diphenyl-4 -Penten-2-One.

Although the above evidence as to the structures of compounds XI and XXX seemed quite conclusive, a direct synthesis was desirable. Unfortunately, this was not achieved, although several attempts were made. These efforts are described below.

1. The reaction of 2,2-diphenylbutenenitrile (XXXVI) and methyl magnesium iodide.

$$\mathrm{BrCH_2CH_2-C(C_6H_5)_2CN \xrightarrow{\substack{NaOCH_3\\ in\\ CH_3OH}} CH_2=CH-C(C_6H_5)_2CN}$$

XXXVI



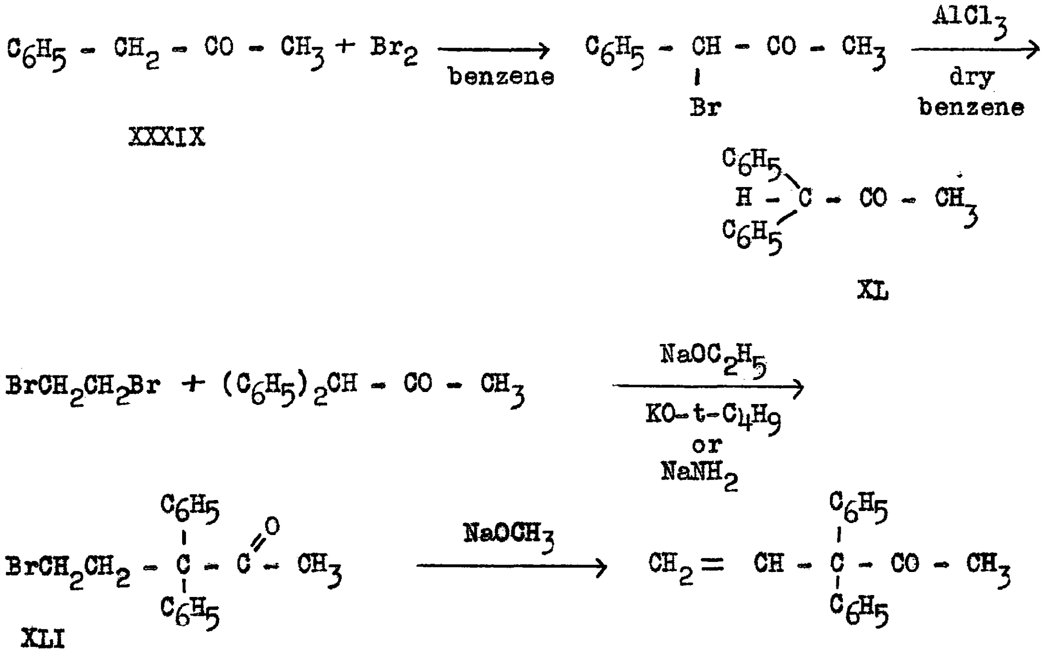
$$\mathrm{CH_2=CH-C(C_6H_5)_2CN \xrightarrow{CH_3MgI} CH_2=CH-C(C_6H_5)_2\overset{NMgI}{\overset{\|}{C}}-CH_3 \xrightarrow{H_2O,\ HCl} CH_2=CH-C(C_6H_5)_2\overset{O}{\overset{\|}{C}}-CH_3}$$

XI

The 2,2-diphenylbutenenitrile was readily prepared by the action of sodium methoxide or potassium hydroxide in methyl alcohol on 4 -bromo-2,2-diphenylbutanenitrile. However, when this compound was treated with methyl magnesium iodide no ketone could be isolated. Depending upon reaction conditions, various proportions of tar and starting nitrile were obtained. When the reaction mixture was refluxed using a mixture of ether and xylene as the solvent, as in the preparation of 5-dimethylamino-2,2-diphenyl-pentan-3-one, only tar was obtained. The results were similar with an ether-benzene solvent. The reaction was also run at room temperature using ether alone as the solvent. When the reaction mixture was decomposed and the organic material distilled, most of the starting nitrile was recovered, and the remainder was a tarry residue in the distilling flask.

(2). The dehydrohalogenation of 5-bromo-3,3-diphenyl-pentan-2-one (XLI)

Since it is known that α,α-diphenylacetone alkylates on the α carbon (39), a synthesis was attempted through the alkylation of this ketone with ethylene bromide using sodium ethoxide, potassium t-butoxide and sodium amide as the condensing agents. The reactions attempted are indicated below.



$$C_6H_5-CH_2-CO-CH_3+Br_2 \xrightarrow[\text{benzene}]{} C_6H_5-\underset{\underset{\displaystyle Br}{|}}{CH}-CO-CH_3 \xrightarrow[\text{dry benzene}]{AlCl_3} H-C(C_6H_5)_2-CO-CH_3$$

XXXIX

XL

$$BrCH_2CH_2Br+(C_6H_5)_2CH-CO-CH_3 \xrightarrow[\text{KO-t-}C_4H_9 \text{ or } NaNH_2]{NaOC_2H_5}$$

$$BrCH_2CH_2-\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{NaOCH_3} CH_2=CH-\overset{\overset{\displaystyle C_6H_5}{|}}{\underset{\underset{\displaystyle C_6H_5}{|}}{C}}-CO-CH_3$$

XLI

The preparation of α,α-diphenylacetone (XXXIX) is described in Organic Syntheses (40). By varying this procedure at two points, the yield was increased from 53 - 57% to 70%. In Organic Syntheses, the hydrogen bromide resulting from the bromination of phenylacetone (XXXIV) was removed with a stream of dry nitrogen, and the subsequent Friedel-Crafts reaction was carried out at the boiling point of benzene. In this work the hydrogen bromide was removed by extraction with water and the solution dried with anhydrous magnesium sulfate. The Friedel-Crafts reaction was run, for the most part at room temperature, and was followed by a period of refluxing. The latter change is probably the most important.

The reaction between ethylene bromide and diphenyl acetone using sodium ethoxide in absolute alcohol appeared to go smoothly enough, with sodium bromide precipitating in the manner to be expected, but upon working up the reaction mixture only diphenyl acetone was obtained. During another attempt using potassium t-butoxide as the catalyst it was noticed that an organic vapor, presumably vinyl bromide, escaped through the condenser. It was concluded that this type of catalyst offered little hope.

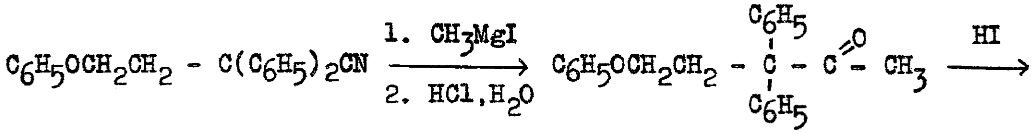
A final attempt to produce the desired reaction was made using sodium amide in dry benzene. It was also unsuccessful. The product of the attempted alkylation was an oil which yielded derivatives of α,α-diphenylacetone. Treatment of the oil with sodium methoxide in methyl alcohol, followed by distillation did not yield the desired product.

(3) The preparation of 5-phenoxy-3,3-diphenylpentan-2-one XLII, cleavage of the ether linkage, and dehydrohalogenation.

The following reactions were used.

$$C_6H_5ONa + BrCH_2CH_2Br \longrightarrow C_6H_5 - O - CH_2CH_2Br$$

$$C_6H_5OCH_2CH_2Br + (C_6H_5)_2CHCN \xrightarrow[\text{dry benzene}]{NaNH_2}$$



$$C_6H_5OCH_2CH_2 - C(C_6H_5)_2CN \xrightarrow[2.\ HCl, H_2O]{1.\ CH_3MgI} C_6H_5OCH_2CH_2 - \overset{C_6H_5}{\underset{C_6H_5}{C}} - \overset{O}{\overset{\|}{C}} - CH_3 \xrightarrow{HI}$$

XXXVIII XLII

$$ICH_2CH_2C(C_6H_5)_2COCH_3 \xrightarrow[\text{alcohol}]{KOH} CH_2 = CH - C(C_6H_5)_2 - CO - CH_3$$

β -Phenoxyethyl bromide was prepared by the method of "Organic Syntheses" (27A). This compound was used to alkylate diphenylacetonitrile to give 4 -phenoxy-2,2-diphenylbutanenitrile (XXXVIII). This reaction proceeded easily. Upon reaction of the nitrile with methyl magnesium iodide, however, the compound appeared to decompose, yielding phenol; a non-ketonic portion distilling at 140 - 150° at 1 mm., and a small amount of a crystalline substance that melted at 326 - 329° with decomposition after recrystallization from alcohol. The crystalline material was nearly insoluble in the usual organic solvents and water.

The presence of phenol and the non-ketonic substance has been accounted for in the previous discussion of this reaction. The high melting material was probably a product of the reaction of the nitrile group with methyl magnesium iodide, but analysis did not reveal its structure.

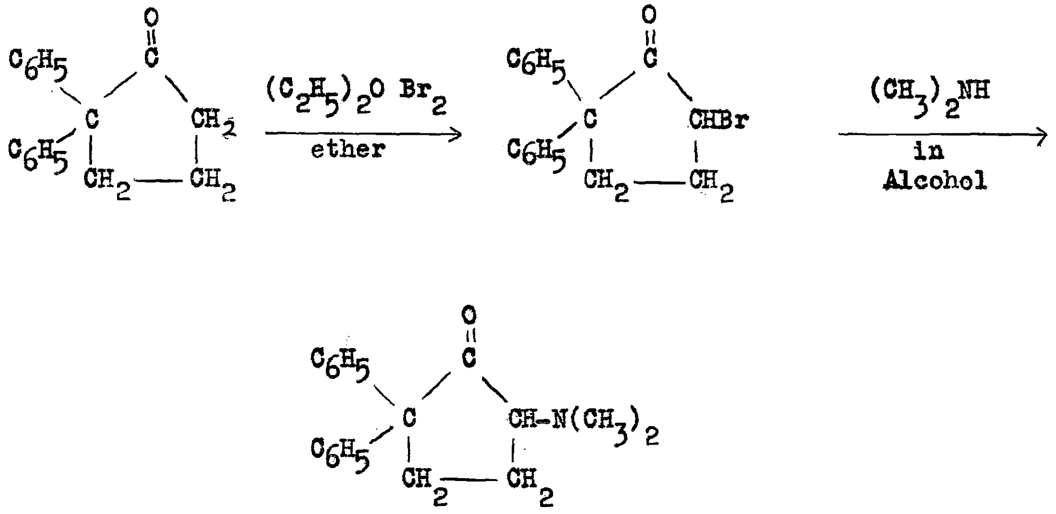
(4) The reaction of 4-bromo-2,2-diphenylbutanenitrile and methyl magnesium bromide.

$$\begin{tikzcd}
BrCH_2CH_2C(C_6H_5)_2CN \arrow[r, "1.\ CH_3MgI", "2.\ H_2O{,}HCl"'] & BrCH_2CH_2C(C_6H_5)_2CO - CH_3 \arrow[d, "KOH\ alcohol"] \\
 & CH_2 = CH - C(C_6H_5)_2COCH_3
\end{tikzcd}$$

An attempt was made to recover some ketonic product from this tarry reaction mixture using Girard's Reagent T. This was, however, unsuccessful. An oil which was not a ketone and which did not give a Beilstein test for halogen was obtained. There was also a high melting solid similar to that obtained from 4-phenoxy-2,2-diphenylbutanenitrile. It is possible that this reaction followed a course similar to that of the 4-phenoxy-2,2-diphenylbutanenitrile.

C. Further Derivatives of 2,2-Diphenylcyclopentanone

Further reactions were carried out with 2,2-diphenylcyclopentanone to make 5-dimethylamino-2,2-diphenylcyclopentanone XLIII which will be tested for analgesic properties. This was prepared through the 5-bromo compound.



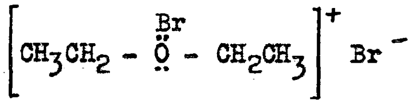
XLIII

The bromination of 2,2-diphenylcyclopentanone proved to be a particularly interesting reaction. When bromine was added to a solution of the ketone in ether or carbon tetrachloride a high melting by-product was obtained along with the normal bromination product. This product was impossible to separate from the desired one except through the tedious process of fractional crystallization. When finally obtained, it appeared from analysis to be a dibromide, but it decomposed upon recrystallization and was not obtained in pure form.

If, however, the ketone was brominated using the so-called

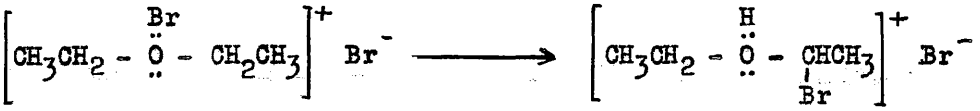
"Schutzenbergers bromide"(33A) the reaction gave the monobromo product in excellent yield, and without difficulty.

Recent literature indicates that the compound formed between an ether and bromine is a bromooxonium bromide, illustrated below with ethyl ether.



$$\left[CH_3CH_2-\overset{Br}{\ddot{\underset{\cdot\cdot}{O}}}-CH_2CH_3\right]^+ Br^-$$

This compound is an oily liquid, deep red in color (probably because of the presence of free bromine), freezing at 7°C, and only slightly soluble in ether. It can be formed by addition of bromine to an excess of ether, or by the addition of ether to bromine. In either case, the resulting reaction was quite exothermic, and when ether was added to bromine it was carried out in an ice bath and the temperature followed closely with a thermometer. The resulting compound was used at once, since it gradually decomposed, presumably in the following manner.



$$\left[CH_3CH_2-\overset{Br}{\ddot{\underset{\cdot\cdot}{O}}}-CH_2CH_3\right]^+ Br^- \longrightarrow \left[CH_3CH_2-\overset{H}{\ddot{\underset{\cdot\cdot}{O}}}-\underset{Br}{CHCH_3}\right]^+ Br^-$$

The compound formed between bromine and diisopropyl ether appeared to be especially unstable (unpublished data from this laboratory).

The reason for the superiority of this reagent is not known with certainty, but it is probably milder in its action than free bromine. It is well known for example, that bromination proceeds more slowly in pyridine and ethyl alcohol than in the usual non-polar solvents.

Another recent article describes the bromination of various compounds using dioxane dibromide (43) which is a solid. Excellent yields were obtained in the bromination of ketones and other compounds with active methylene groups.

The amination of 5-bromo-2,2-diphenylcyclopentanone was carried out in benzene at 0°C and in 95% alcohol at 40°C. Only very small yields of amine could be obtained in benzene. In alcohol the yield was 33% of amine. It is possible that dehydrohalogenation occurred to give 2,2-diphenyl-4-pentenone (VIII) and that the dimethylamine went into the 4 position through 1,4-addition to the conjugated system rather than the 2 position through substitution. However, it was found by Craig and Witt that it was impossible (at least under normal conditions) to form derivatives of VIII using reagents for the carbonyl group (9). These reagents, such as 2,4-dinitrophenylhydrazone, hydroxylamine, and semicarbazide will react by 1,4 addition to α, β-unsaturated ketones (21A). Since this did not occur, it is felt that dimethylamine reacted by substitution with the saturated bromide rather than by addition to the unsaturated compound, particularly since the conditions under which the reaction was carried out were quite mild.

V. EXPERIMENTAL DETAILS

4-Dimethylamino-2,2-diphenylbutanenitrile (XIX)

Method A. From dimethylaminoethyl chloride (XVIII) and diphenylacetonitrile)Procedure of PB-981) (29).

In a 3-neck flask equipped with a dropping funnel, stirrer, and reflux condenser were placed 200 ml. of chloroform and 40 grams (0.449 moles) of β-dimethylaminoethyl alcohol (obtained from the Carbide and Carbon Chemicals Corporation). To this 48 ml. (78.5 grams, 0.66 moles) of thionyl chloride was added fairly rapidly through a dropping funnel. The solution was stirred vigorously. The temperature was allowed to rise, and the contents of the flask were at reflux throughout most of the addition. After the thionyl chloride was added, the solution was refluxed for 4 hours.

The chloroform and excess thionyl chloride were distilled under reduced pressure, leaving β-dimethylaminoethyl chloride hydrochloride XX as a solid crystalline residue. This was recrystallized from 200 ml. of absolute alcohol. The product was dried at room temperature, and then in an oven at 80°. The yield was 50.9 grams or 79.0% of theory. The product melted at 203 - 205°, compared with literature values of 201° (35) and 206 - 207° (18).

By evaporation of the mother liquor a second crop of crystals of slightly lower melting point was obtained. This weighed

8.9 grams for a total yield of 59.8 grams, or 92%.

The free base was obtained by dissolving 23.6 grams of the β-dimethylaminoethyl chloride hydrochloride in a small quantity of water, and adding a saturated solution of sodium carbonate at 10-15° until the amine solution was strongly basic. The liquid that separated was taken up in ether, and the salt-water layer extracted several times with ether. The solution was dried over magnesium sulfate, and after evaporation of the ether the residue was distilled in vacuo. There was obtained 17.6 grams, 67% of theory, of an oil distilling at 30 - 45° under a pressure of 90 mm. This product, dimethylaminoethyl chloride (XVIII) is very unstable, and it is best to use it immediately.

4-Dimethylamino-2,2-diphenylbutanenitrile was then prepared. To a suspension of 4.2 grams (0.108 moles) of sodium amide in 20 ml. of benzene, there was added 18.8 grams (0.0975 moles) of diphenylacetonitrile over a period of 15 minutes at a temperature of 40 - 45°. The temperature was then held at 40 - 45° for 1½ hours. During this time a deep red color developed. The mixture was cooled, and 10.5 grams (0.0975 moles) of β-dimethylaminoethyl chloride added in 20 minutes. There was a slight temperature rise during the next ¾ hour. The mixture was held at 40 - 45° for ½ an hour, and then refluxed for one hour.

The reaction mixture was poured into water, and the organic layer separated. The benzene solution was extracted with 5% HCl, and the aqueous layer made basic with solid NaOH. The amine was taken up in ether, and purified either by distillation under reduced pressure or by recrystallization of the hydrochloride from isopropyl alcohol. Upon distillation a colorless oil boiling at 160 - 170° at 1 mm pressure was obtained. The yield of 4-dimethylamino-2,2-diphenylbutanenitrile was 16.0 grams, or 60% of theory.

An attempt to prepare this compound using the amine hydrochloride instead of the free base resulted in a yield of only 11.5%.

Method B. Alkylation using sodium t-butoxide.

This is similar to the method of Shultz, Robb, and Sprague (32). The amine hydrochloride was used instead of the free base, and the sodium salt of t-butyl alcohol was used instead of the potassium salt.

Sodium metal (15.0 grams, 0.65 moles) was converted to sodium sand by shaking with hot xylene, and added to 600 ml. of t-butyl alcohol in a 1-liter 3-neck flask. The tertiary butyl alcohol had been dried for several days with a hydrous magnesium sulfate, and was then distilled from sodium. The alcohol mixture was then refluxed with stirring for 3 hours. The sodium only partially dissolved. To this was added 50.0 grams (0.259 moles) of diphenylacetonitrile, and the mixture refluxed with stirring for 2 hours longer. More sodium went into solution, and a dark color appeared. The reaction mixture was cooled, and 37.1 grams (0.259 moles) of β dimethylaminoethyl chloride hydrochloride was added, and the reaction mixture refluxed for 3 hours. The mixture was poured into water, and the oily layer taken up in benzene. The benzene solution was extracted three times with 5% HCl. A crystalline solid separated upon evaporation of the hydrochloric acid solution at reduced pressure. After two recrystallizations from isopropyl alcohol there was obtained 51.0 grams of 4-dimethylamino-2,2-diphenylbutanenitrile hydrochloride. An additional 5.5 grams was recovered from the mother liquors for a total yield of 56.5 grams, 71% of theory. A sample purified for analysis melted at 198 - 200°.

Analysis. Calculated for $C_{18}H_{21}N_2Cl$: Cl, 10.80; N, 9.32.

Found: Cl, 11.90; N, 9.42.

Method C. By the amination of 4-bromo-2,2-diphenyl-butanenitrile.

4-Bromo-2,2-diphenylbutanenitrile was prepared by the method of Dupre et al (11).

In a 2-liter, 3-neck flask equipped with a condenser and Hershberg stirrer were placed 900 ml. of benzene (dried over sodium), 22.6 grams (0.578 moles) of finely powdered $NaNH_2$, and 106.5 grams (0.552 moles) of diphenylacetonitrile. The solution was refluxed with vigorous stirring. It first became deep red in color and in the course of 1 to 3 hours, a white precipitate appeared which made stirring difficult. This reaction was sometimes mildly exothermic with rapid evolution of ammonia, so initial heating was cautious. The flask was cooled in ice to about 15°, and 95 ml. (207 grams, 1.10 moles) of ethylene bromide added all at once. The ice bath was removed, but kept nearby, as the reaction was sometimes excessively energetic. When a rapid increase in temperature was noticed, the bath was applied to the flask again. After the initial reaction was over, the mixture was heated to reflux for 3 hours. During this period, finely divided sodium bromide precipitated.

The reaction mixture was transferred to a 2 liter separatory funnel, and extracted with water. The benzene and excess ethylene bromide were distilled, reduced pressure and a steam bath being used for the final stage. The oily residue crystallized upon trituration with petroleum ether. After air drying it weighed 144 grams, 87% of theory. The melting point of this crude material varied from 60 to 68°. It could be recrystallized from methyl alcohol to give a product melting at 69 - 70°. Literature: 68.5-70 (11), 70-71 (6). Yields, including material melting at 63 - 66°, recovered from the mother liquors, were 65 - 77%. During the recrystallization, 3 - 5 grams of $\alpha, \alpha, \alpha', \alpha'$-tetraphenyladiponitrile, m.p. 204 -206 (11) was recovered.

The bromo compound was converted to the desired amine by placing 144 grams (0.36 moles) of the crude bromo-nitrile and 400 ml. of 95% alcohol in a 28 oz. soda bottle. The bottle was cooled in ice, and about 100 grams (2.2 moles) of dimethyl amine condensed in it. It was then capped and placed in a water bath at 45° for 4 days. The contents of the bottle were agitated mechanically with end-over-end rotation. A solid remained suspended during this period. The bottle was cooled in ice and opened. The solid was filtered off, and identified by melting point as $\alpha, \alpha, \alpha', \alpha'$-tetraphenyladiponitrile. The solution was evaporated on the steam bath, transferred to a 1-liter separatory funnel, and water and benzene added. The water was drawn off, and the resulting benzene layer washed with water until neutral (3 times). It was then extracted with one 500 ml. portion and two 200 ml. portions of 5% HCl. The combined aqueous extracts were made basic with solid sodium hydroxide, and the oil taken up in ether. The ether solution was dried over a mixture of anhydrous magnesium sulfate and potassium carbonate.

The ether was removed by distillation, and the residual oil distilled from a 250 ml. Claisen flask under 1 mm. pressure. Most of the 4-dimethylamino-2,2-diphenylbutanenitrile came over at 160-170°. It weighed 93.5 grams, for a yield of 76% based on the crude bromo compound or 64.5% based on the original diphenylacetonitrile.

4-Dimethylamino-2,2-diphenylbutanenitrile methiodide.

A few grams of the amino-nitrile was dissolved in twice its volume of absolute alcohol, and a 50% excess of methyl iodide added. After the initial exothermic reaction was over, the solution was refluxed for 15 minutes. Anhydrous ether was added, and the methiodide crystallized upon scratching. After several recrystallizations from absolute alcohol and ether it melted at 223.0 - 224.5°.

Analysis. Calculated for $C_{19}H_{23}N_2I$: N, 6.90.

Found: N, 6.71.

5-Dimethylamino-3,3-diphenylpentan-2-one (XXII)

This compound was prepared according to the German procedure for Amidone (29).

In a 250 ml. 3-neck flask fitted with a condenser, stirrer and dropping funnel a Grignard reagent was prepared from 7.36 grams (0.303 moles) of magnesium and 18.9 ml. (43.1 grams, 0.303 moles) of methyl iodide in 50 ml. of ether. The methyl iodide was added through the dropping funnel rapidly enough to keep the ether refluxing. After all of the iodide was added, the mixture was refluxed for ½ hour.

To the Grignard reagent a solution of 40 grams (0.151 moles) of 4 - dimethylamino-2,2-diphenylbutanenitrile in 32 ml. of dry xylene was added. A mildly exothermic reaction occurred. The reaction mixture was refluxed gently for 3 hours. During this time, a grayish green precipitate appeared. The resulting mixture, while still hot, was poured into a solution of 170 ml. of water and 70 ml. of concentrated hydrochloric acid. A violent reaction (probably caused by the excess Grignard reagent) occurred, and most of the solvent was evaporated. Benzene was added with stirring to the milky suspension. Three layers resulted. An oily lower layer, which was the hydroiodide of the amino ketone (XXI), a middle aqueous layer, and the benzene layer on top. The hydroiodide crystallized within 5 - 10 hours. The crude product was filtered and was found to be virtually a quantitative yield of 62.0 grams.

The hydroiodide was dissolved in a mixture of alcohol and water, and the solution made strongly basic with solid sodium hydroxide. The liberated amine was taken up in ether, dried with magnesium sulfate, and purified by distillation at 155 - 165° under 1 mm. pressure. The yields varied from 27 - 34 grams or 64 - 80% of theory. This product could also be purified by recrystallization of the oxalate.

The hydroiodide as obtained from the reaction mixture originally melted at 74 - 78°. Upon recrystallization from water or from benzene it melted at 77 - 79° and 79 - 81° respectively. Further recrystallization from benzene gave a product melting at 90 - 91°. After one recrystallization from absolute alcohol and ether this product melted at 121 - 122°, and after a second at 140 - 141°. Further recrystallization did not change the melting point. The highest melting product analyzed correctly for the amino-ketone hydroiodide, but the low melting product was low in nitrogen. This compound was possibly a hydrate.

<u>Analysis</u>. Calculated for $C_{19}H_{24}ONI$: N, 3.42

Found: N, 3.32

Oxalate of 5-dimethylamino-3,3-diphenylpentan-2-one

To a solution of 5.0 grams of the amino-ketone in 20 ml. of absolute alcohol there was added 4.0 grams of oxalic acid. Upon the addition of ether, the oxalate precipitated. The crude product melted at 160 - 162°, and after several recrystallizations from absolute alcohol melted at 163.0-163.5°.

In one case, when the oxalate was prepared in 95% alcohol, the product melted at 142 - 144° for several recrystallizations from absolute alcohol and ether, but finally melted at the higher temperature. It is not certain whether this was another crystalline form, a hydrate, or contained a different ratio of oxalic acid.

Analysis. Calculated for $C_{19}H_{23}ON\ C_2H_2O_4$:
C, 67.90; H, 6.79; N, 3.77

Found: C, 67.88; H, 6.92; N, 3.73, 3.76

5-Dimethylamino-3,3-diphenylpentan-2-one methiodide (IX)

A few grams of 5-dimethlyamino-3,3-diphenyl-2-pentanone was dissolved in twice its volume of absolute alcohol, and a 50% excess of methyl iodide was added. After the initial exothermic reaction was over, the mixture was refluxed for 15 minutes. Upon the addition of ether an oil separated that crystallized with cooling and scratching. The solid melted at 144 - 148°.

A sample purified for analysis by repeated crystallization from absolute alcohol and ether melted at 151.5 - 152°.

Analysis. Calculated for $C_{20}H_{26}ONI$: N, 3.32
Found: N, 3.26

3,3-Diphenyl-4-penten-2-one (XI)

A. By pyrolysis of the methiodide of 5-dimethylamino-3,3-diphenylpentan-2-one.

In a 50 ml. distilling flask equipped with a receiver and thermometer was placed 23 grams of the methiodide (IX). The system was evacuated to 13 mm. using an aspirator, and the flask gently heated with a direct flame. The solid melted to a viscous yellowish liquid. In the course of about 15 minutes, 8.7 grams of a viscous liquid distilled over, for the most part at 190°. The flask was cooled and a second receiver attached. A second distillate was obtained at 205 - 270° at 13 mm., weighing 2.2 grams. A tarry residue remained in the distilling flask. These distillates darkened upon standing.

The viscous liquids were dissolved in benzene. A small amount of white solid was filtered from each. The benzene solutions were extracted with 5% HCl, washed with water, and redistilled. The first fraction distilled at 188 - 192° at 12 mm., and weighed 7.4 grams. The second fraction distilled at 195 - 203° at 16 mm. Upon standing overnight in an ice bath, a few tenths of a gram of a crystalline solid appeared in fraction 2. This was removed by filtration. After recrystallization from petroleum ether and sublimation it melted at 75 - 78°. It was not investigated further. The remainder of fraction 2 was, upon preparation of the 2,4-dinitrophenylhydrazone, shown to be identical with the first fraction.

Similar results were obtained when the methiodide was decomposed using an oil bath for heat.

This oil did not react with potassium permanganate in acetone except on long standing, and reacted with bromine in carbon tetrachloride with the liberation of hydrogen bromide. The tests were used as described in Shriner and Fuson (34).

Analysis. Calculated for $C_{17}H_{16}O$; C, 86.40; H, 6.84
Found: C, 86.26, H, 6.90

B. By the pyrolysis of the quaternary ammonium hydroxide of 5-dimethylamino-3,3-diphenylpentan-2-one.

To a solution of 7.4 grams of 5-dimethylamino-3,3-diphenylpentan-2-one methiodide in 15 ml. of water and 35 ml. of alcohol was added the silver oxide paste from 4.5 grams of silver nitrate (mole ratio of quaternary iodide to Ag_2O 1:1.5). The mixture was shaken vigorously for a few minutes. After settling, a sample of the supernatant liquid did not give a precipitate after acidification with nitric acid and the addition of silver nitrate solution. The solid was filtered and washed with water, and the solution evaporated to a syrup under aspirator vacuum over a water bath. It finally solidified.

The solid was transferred to a test tube, and heated with an oil bath. In the course of 30 minutes the temperature was raised to 230°. There was some sodium hydroxide present because of incomplete washing of the silver oxide paste.

The organic product was taken up in ether and distilled. There was obtained 1.3 grams of material distilling at 190 - 200° at 17 mm. A 2,4 -dinitrophenylhydrazone was prepared, and found to be identical with that obtained by the pyrolysis of the methiodide.

2,4 -Dinitrophenylhydrazone of 3,3-diphenyl-4 -pentene-2-one.

A 2,4 -dinitrophenyl hydrazone was prepared in the usual manner (34). The product was a finely divided light yellow powder. After several recrystallizations from a mixture of benzene and petroleum ether it melted at 194.0 - 194.5° with decomposition. This product was not particularly stable, and was difficult to purify. The analysis, although it was not too good, indicated that a molecule of water was present. Further drying at pressures less than 1 mm. did not change the analysis.

Analysis. Calculated for $C_{23}H_{20}O_4N_4 \cdot H_2O$:
C 63.58; H, 5.11; N, 12.90

Found: C, 63.96, 64.11; H, 5.12, 5.28;
N 12.72, 12.75

Oxime of 3,3-diphenyl-4 -penten-2-one

An oxime was prepared in the usual manner (34). After several recrystallizations from alcohol the product melted at 168 - 170.5°, and after drying in the Abderhalden apparatus (under aspirator vacuum and at the temperature of boiling acetone) for 2 hours, it melted at 171 - 172°. This derivative also appeared to retain a molecule of water.

Analysis. Calculated for $C_{17}H_{17}ON \cdot H_2O$:
C 75.80; H 7.11; N 5.20

Found: C 75.94, 75.83; H 6.93, 7.03;
N 5.20, 5.24

Oxidation of 3,3-diphenyl-4-penten-2-one with CrO_3

A solution of 5 grams of chromic anhydride in 3.5 ml. of water and 3.5 ml. of glacial acetic acid was added slowly to 1 gram of ketone dissolved in 5 ml. of glacial acetic acid. The temperature rose rapidly. About one-half of the CrO_3 solution was added. The test tube, in which the reaction was carried out, was placed in a water bath at 90 - 100° for 6 hours. During this time, the remainder of the CrO_3 solution was added so that there was always an excess.

The oxidation mixture was diluted with water to approximately 200 ml., and extracted several times with small portions of benzene. The combined benzene extracts were extracted with a 5% sodium bicarbonate solution. Acidification of the bicarbonate solution did not cause the precipitation of an organic acid.

Evaporation of the benzene solution left a small amount of a neutral oil. From this, a semicarbazone was prepared. After recrystallization it melted at 163 - 166°. The melting point was not depressed by mixing with an authentic sample of benzophenone semicarbazone. Literature values for the melting point of benzophenone semicarbazone are 164 (34) and 167 (21).

6-Dimethylamino-4,4-diphenylhexan-3-one

This was prepared in the same way as the methyl ketone.

To the Grignard reagent prepared from 7.36 grams (0.303 moles) of magnesium and 47.2 grams (0.303 mole) of ethyl iodide (B.P. 72-73°) in 50 ml. of dry ether was added 40 grams of 4-dimethylamino-2,2-diphenylbutanenitrile in 32 ml. of xylene. The reaction mixture was refluxed with stirring for 3 hours. A greenish gray precipitate appeared in the dark solution. The suspension was poured while hot into a solution of 70 ml. of concentrated hydrochloric acid and 170 ml. of water. After the violent reaction subsided, benzene was added and the mixture stirred. An oil separated that started to crystallize immediately. After standing overnight crystallization of the hydroiodide was complete. It melted at 161 - 173°, and weighed 60.0 grams for a nearly quantitative yield of crude product, calculated as the hydroiodide.

The hydroiodide was dissolved in alcohol and water, and solid sodium hydroxide added until the solution was strongly basic. More water was added, and the oil that separated was extracted with ether. This solution was dried with magnesium sulfate. The ether was removed by distillation and the product distilled from a Claisen flask at about 170° under 1 mm. pressure.

Oxalate of 6-dimethylamino-4,4-diphenyl-3-hexanone

The oxalate was prepared in absolute alcohol. It was purified for analysis by repeated crystallization from absolute alcohol. It melted at 161.5 - 163°.

Analysis. Calculated for $C_{20}H_{25}NO\ C_2H_2O_4$:
N, 3.65. Found: N, 3.60

Methiodide of 6-dimethylamino-4,4 -diphenyl-3-hexanone

The methiodide which was prepared in absolute alcohol in the usual manner melted at 193 - 196°. After several recrystallizations from absolute alcohol it melted at 199.5 - 200.5°.

Analysis. Calculated for $C_{21}H_{28}NOI$: N, 3.20
Found: N, 3.17, 3.10

4,4 -Diphenyl-5-penten -3-one (XXX)

A. By the pyrolysis of 6-dimethylamino-4,4 -diphenyl-3-hexanone methiodide.

In a 10 ml. Claisen flask fitted with a side arm test tube as a receiver was placed 3.7 grams of the methiodide of 6-dimethylamino-4,4 -diphenyl-3-hexanone. The system was evacuated to about 15 mm. pressure, and the flask gently heated with a free flame. The methiodide first melted, and a clear liquid that rapidly solidified distilled as decomposition took place. This product weighed 2.0 grams. After one recrystallization from alcohol it melted at 101 - 104°.

An analytical sample melting at 104.5 - 105.5° was obtained after two more recrystallizations from alcohol.

Analysis. Calculated for $C_{18}H_{18}$: C, 86.36; H, 7.24
Found: C, 86.43; H, 7.25

B. By the pyrolysis of the quaternary hydroxide.

To an aqueous-alcoholic solution of 6-dimethylamino-4,4-diphenyl-3-pentanone methiodide was added the silver oxide paste from 1.16 grams of silver nitrate (50% excess). The silver oxide paste was prepared by adding a dilute sodium hydroxide solution to an aqueous solution of the silver nitrate, filtering the precipitated oxide and washing with water until the filtrate was neutral.

The suspension was shaken vigorously for 15 minutes, and the solid allowed to settle overnight. A test with silver nitrate showed the liquid to be free of iodide ion. The suspension was filtered, the precipitate washed and the combined filtrate and washings concentrated, with the final evaporation taking place in a 10 ml. distilling flask. After the water was removed, a receiver was put in place on the flask, the system evacuated, and the residue heated slowly with a micro burner. The hydroxide decomposed with much foaming, and a slightly yellow oil, which crystallized upon standing for a short time, distilled. The oil was recrystallized twice from alcohol. It melted at 104.5 - 106.0, and its melting point was not depressed by the addition of the compound obtained by the pyrolysis of the methiodide.

2,4 -Dinitrophenylhydrazone of 4,4 -diphenyl-5-penten-3-one

A 2,4 -dinitrophenyl hydrazone was prepared. It melted at 123.0 - 125.0 after two recrystallizations from alcohol and ethyl acetate.

Oxidation of 4,4-diphenyl-5-hexen-3-one with CrO_3

To a solution of 0.9 grams of the ketone in 5 ml. of glacial acetic acid was added 3.5 grams of chromic anhydride in 3.5 ml. of water and 3.5 ml. of acetic acid. The solution became quite warm as the oxidizing agent was added. After the addition was complete, the test tube in which the reaction was carried out was heated at 95 - 100° for 7 hours.

The reaction mixture was diluted with water to 50 ml. and extracted twice with benzene and three times with ether. The combined extracts were then extracted with an amount of 5% potassium carbonate solution sufficient to neutralize partially the acetic acid. Two extractions with 20 ml. of 5% potassium hydroxide were made. Upon acidification an organic acid, or mixture of acidic products was liberated. This melted at 130 - 133°. The neutral layer was evaporated, finally at 100°under reduced pressure, leaving a residue of 0.46 grams. This appeared to consist of an oil and a crystalline solid. By dilution with ether and decantation the solid was separated. It melted at 74 - 79°.

Since these products appeared to be the result of partial oxidation, they were reoxidized as before using 5 grams of chromic anhydride, and heating on the steam bath for 9 hours. The resulting solution, which contained an excess of oxidizing agent, was diluted with water and extracted with benzene and ether as before. The extracts were washed several times with water, and then extracted with a 5% potassium hydroxide solution. Upon acidification, a turbidity appeared. The solution was made basic again, evaporated to a volume of 5 ml., and again acidified. A precipitate, identified as benzoic acid by melting point and mixed melting point, appeared. It weighed 29 mg.

The benzene-ether solution was evaporated, leaving a residue weighing 0.11 grams. From this a semicarbazone was prepared. Upon recrystallization from dilute alcohol and after drying on a porous plate, it melted at 161 - 164. An authentic sample of benzophenone semicarbazone did not depress the melting point.

Oxidation of benzophenone with CrO_3

In order to check the source of benzoic acid obtained above, an 0.5 grams sample of benzophenone was similarly oxidized, using 5 grams of CrO_3 in 5 ml. of water-acetic acid solution. No heat was evolved when the oxidizing agent was added to the ketone solution. The solution was placed on the steam bath for 9 hours.

When the reaction mixture was worked up as before 24 mg. of benzoic acid and 0.33 grams of a neutral oil, presumably benzophenone, were obtained.

2,2-Diphenylbutenenitrile (XXXVII)

In a 100 ml. 3-neck flask were placed a solution of 12 grams of potassium hydroxide in 40 ml. of methyl alcohol, and 10 grams of 4-bromo-2,2-diphenylbutanenitrile. The solution was refluxed for 1 hour with stirring. The reaction mixture was poured into water, and the water solution extracted three times with benzene. The benzene was evaporated, and the 2,2-diphenylbutenenitrile distilled at 178 - 185° under a pressure of 11 - 12 mm. The product weighed 6.95 grams for a yield of 95%. n_D^{20} 1.5800.

This compound was completely inert to bromine in carbon tetrachloride, and did not react with potassium permanganate in acetone except on long standing.

Analysis. Calculated for $C_{16}H_{13}N$: N, 6.39
Found: N, 6.20

Reaction of 2,2-diphenylbutenenitrile with methyl magnesium iodide.

A Grignard reagent was prepared from 4.44 grams (0.183 mole) of magnesium and 11.4 ml. (25.9 grams, 0.183 mole) of methyl iodide in 50 ml. of ether. The flask was cooled to room temperature, and 10.0 grams (0.46 mole) of 2,2-diphenylbutenenitrile in 10 ml. of ether was added. The temperature rose a few degrees. The reaction mixture was then stirred at room temperature for 7 hours. It was poured into a solution of 100 ml. of water and 40 ml. of concentrated hydrochloric acid and the organic material recovered with three extractions with ether. The ether layer was shaken once with a dilute sodium bisulfate solution and twice with water, and then dried with anhydrous magnesium sulfate.

The ether was evaporated and the product distilled. Three fractions were cut, all of which were slightly yellow in color.

Fraction 1: B.p. 120 - 135° at 1.5 mm. Weight, 1.95 g.
n_D^{20}: 1.5816

Fraction 2: B.p. 125 - 130° at 0.5 mm. Weight, 3.59 g.
n_D^{20}: 1.5812

Fraction 3: B.p. 130° at 0.5 mm. Weight, 1.48 g.
n_D^{20}: 1.5817

A tarry residue remained in the flask.

A comparison of these refractive indices with that of the starting material, and comparison with the refractive indices of of benzyl cyanide and phenyl acetone indicate that the desired reaction has not occurred, and that the distillate was starting material. These refractive indices are:

$C_6H_5CH_2CN$: n_D^{20} 1.5242; density (20°C) 1.018
$C_6H_5CH_2COCH_3$: n_D^{20} 1.5168; density (20°) 1.028

This distillate furthermore, did not give a derivative with 2,4-dinitrophenylhydrazine.

When this reaction was carried out under the conditions used for the preparation of 5-dimethylamino-3,3-diphenylpentan-2-one, only tar was obtained, as was also the case when an intermediate temperature was used.

Reaction of 2,2-diphenylbutenenitrile with ethyl magnesium iodide.

This reaction was carried out in the same manner as with methyl magnesium iodide, and with the same results. A 2,4-dinitrophenylhydrazone could not be formed from the product.

β -Phenoxyethyl bromide

β -Phenoxyethyl bromide was prepared by the method of Organic Syntheses (27A) from sodium phenoxide and ethylene bromide.

4 -Phenoxy-2,2-diphenylbutanenitrile (XXXVIII)

In a 1-liter 3-neck flask fitted with a stirrer and condenser were placed 500 ml. of dry benzene, 14.0 grams (0.359 moles) of sodium amide and 70 grams (0.362 moles) of diphenylacetonitrile. The mixture was heated at reflux with stirring for three hours. During this time much of the sodium salt of diphenylacetonitrile had precipitated, and it was difficult to stir the contents of the flask. The flask was cooled to room temperature and 72 grams (0.358 moles) of β -phenoxyethyl bromide was added through a dropping funnel in the course of 40 minutes. The temperature rose appreciably during the addition, but the reaction was not difficult to control. The reaction mixture was refluxed with stirring for 5 hours.

The cooled solution, along with the suspended sodium bromide, was transferred to a 1-liter separatory funnel, and washed with water. The benzene was evaporated, on a water bath under reduced pressure. The product, 4 -phenoxy-2,2-diphenylbutanenitrile, crystallized upon the addition of petroleum ether and with scratching. After filtering and washing with petroleum ether it melted at 85 - 87°, and weighed

76.5 grams, 68% of theory.

An analytical sample was prepared by recrystallizing twice from ethyl alcohol. It melted at 87 - 88.5°.

Analysis. Calculated for $C_{22}H_{19}ON$: N, 4.47

Found: N, 4.44

Reaction of 4-phenoxy-2,2-diphenylbutanenitrile with methyl magnesium iodide

In a 500-ml. 3-neck flask fitted with a stirrer, condenser and addition funnel, a Grignard reagent was prepared from 7.76 grams (0.333 moles) of magnesium and 21 ml. (47.8 grams, 0.337 moles) of methyl iodide in 160 ml. of dry ether. To this 50 grams (0.16 moles) of 4-phenoxy-2,2-diphenylbutanenitrile dissolved in about 65 ml. of xylene was added dropwise, after which the reaction mixture was refluxed for 3 hours with stirring. The reaction mixture was decomposed with a solution of 200 ml. of water and 80 ml. of concentrated hydrochloric acid. The organic material was taken up in benzene, layers separated, and the aqueous layer washed with benzene. The benzene solution was washed with water, and some of the benzene evaporated under vacuum. A white solid appeared. It was filtered off and found to melt with decomposition at about 310°. It weighed 2.0 grams.

From the concentrated solution, 17.5 grams of 4-phenoxy-2,2-diphenylbutanenitrile, melting at 86 - 88°, crystallized. It was filtered off, and the filtrate placed in the refrigerator for a few days.

A second crop of the nitrile was filtered off and washed with ice cold methanol. It weighed 5.0 grams. The solvent was finally removed by heating on a water bath under reduced pressure. This reddish oil weighed 23.0 grams.

A small quantity of this oil (5-6 grams) was distilled from a 10 ml. Claisen flask. Three fractions were obtained:

Fraction 1 distilled at 85 - 140° at 15 mm., with nearly all of it distilling near the lower temperature.

Fraction 2 distilled at 140 - 150° at 1 mm.

Fraction 3 distilled at 200 - 210° at 1 mm.

The first fraction came over as a liquid but soon solidified. The solid was very hygroscopic and had a strong odor of phenol. It melted at 36 - 40°, compared with a literature value of 42° (34).

The second fraction which distilled for the most part at 146 - 148° at 1 mm. remained a liquid and did not form a 2,4 -dinitrophenylhydrazone.

The third fraction, which weighed 0.3 grams proved upon crystallization to be starting nitrile.

The 2.0 grams of high melting material which was filtered from the benzene solution was sparingly soluble in the usual organic solvents and water. It burned with a smoky flame, leaving a residue. After 3 recrystallizations from absolute alcohol it melted at 326 - 329° with decomposition and previous darkening. Analysis did not reveal its structure. Found: C, 68.24; H, 5.36; N, 4.54. When samples were digested for the Kjeldahl analysis, violet vapors appeared which indicated the presence of iodine, although C - H values appear to be too high for this. This compound was not investigated further.

α, α -Diphenylacetone (XL)

This was prepared, for the most part, according to the Organic Syntheses procedure (33).

A. α -Bromo- α ,-phenyl acetone

A 1-liter 3-neck flask was fitted with a stirrer, dropping funnel, and a condenser set for distillation. In the flask was placed 500 ml. of thiophene free benzene, and 150 ml. was distilled off to dry it. A second portion of 150 ml. was distilled for use later in the experiment, leaving 200 ml. in the flask. The flask was cooled, the condenser set for reflux, and an inverted U tube with one end in a beaker of water placed at the top of the condenser. Phenylacetone (37 grams, 0.276 mole) was then added.

The phenylacetone was obtained from the Swope Oil and Chemical Co., and purified by distillation. The product distilling at 96 - 100° at 15 mm. was used.

To the stirred reaction mixture 14.42 ml. (45 grams, 0.28 moles) of bromine was added dropwise with stirring over a period of one hour. The bromination was carried out at room temperature.

The resulting solution of α-bromo- α-phenyl acetone was poured into a 1-liter separatory funnel, and washed with water (4 times) until the water layer was neutral. It was dried over anhydrous magnesium sulfate overnight.

B. α, α-Diphenylacetone.

The equipment was the same as that used for the bromination.

Anhydrous aluminum chloride (80 grams, 0.60 moles) and about 100 ml. of dry benzene were placed in the flask. The stirrer was started, and the solution of α-bromo- α-phenylacetone added through a dropping funnel at room temperature in the course of one hour. The liberated HBr was absorbed as before. After the addition was complete, the dark solution that resulted was refluxed for one hour.

The cooled solution was poured with stirring into 500 grams of ice and 100 ml. of concentrated HCl. It became light yellow in color. The mixture was transferred to a separatory funnel and the water layer drawn off. The water layer was then extracted three times with 50 ml. of ether. The combined extracts were washed once with water and once with 100 ml. of a saturated sodium bicarbonate solution, and dried over 70 grams of anhydrous sodium sulfate.

The diphenylacetone solution was concentrated by flash distillation in a 125 ml. Claisen flask, and finally heated with an oil bath to 185° under 15 mm. pressure. A small amount of yellow oil, probably phenylacetone, distilled. A new receiver was put in place on the Claisen flask, and the product distilled rapidly at 150 - 160° at 2 mm.

It weighed 49.0 grams. The liquid was transferred to an erlenmeyer flask, and crystallization induced by scratching. The crystals were triturated with petroleum ether, cooled to 0°, filtered with suction, and washed with a few ml. of ice cold petroleum ether.

The product was purified by dissolving in 350 ml. of petroleum ether (solution was not too good) and cooling overnight in the refrigerator. The crystals were filtered and washed. The weight of diphenylacetone, when dry, was 58.0 grams, of a product melting at 60 - 61°. This is 70% of theory, compared with a maximum of 57% of material of the same melting point obtained by the Organic Syntheses procedure.

2,4 -dinitrophenylhydrazone of α, α -diphenylacetone

A 2,4 -dinitrophenylhydrazone of α, α-diphenyl acetone was prepared and purified in the usual manner. It melted at 143.0 - 144.0. Literature 142.5 - 143.0 (7).

Analysis. Calculated for $C_{21}H_{18}O_4N_4$: C, 64.60; H, 4.65

Found: C, 64.48; H, 4.65

Reaction of α, α -diphenylacetone with ethylene bromide

A. Using sodium ethoxide as the condensing agent.

Into a 100 ml. 3-neck flask fitted with a condenser and stirrer 32 ml. of absolute alcohol, dehydrated with sodium and diethyl phthalate (41) was distilled. To this was added 1.05 grams (0.0456 moles) of sodium metal. After it had reacted, 10.0 grams (0.0476 moles) of α, α-diphenylacetone was dissolved in the sodium ethoxide solution and 8.5 ml. (18.5 grams, 0.98 moles) of ethylene bromide added, a precipitate appeared immediately. The reaction mixture was neutral to litmus after refluxing for 30 minutes.

Upon working up the reaction mixture only diphenylacetone was obtained.

B. Using potassium t-butoxide as the catalyst.

This was similar to the previous reaction except for the use of potassium t-butoxide in t-butyl alcohol as the catalyst.

To 30 ml. of anhydrous tertiary butyl alcohol in a 100 ml. 3-neck flask fitted with a stirrer and condenser was added 1.86 grams of potassium metal. The metal was dissolved by refluxing and stirring. The t-butyl alcohol was obtained from the Eastman Kodak Co., and had been dried over magnesium sulfate for several days. It was finally distilled from sodium. α, α-Diphenylacetone (10.0 grams, 0.0476 moles) was added to the cooled solution. After it was dissolved, 7.2 ml. (15.7 grams, 0.0835 moles) of ethylene bromide was added. There was an immediate formation of a precipitate, and it was noticed than an organic vapor was escaping through the condenser. This was presumably vinyl bromide, which has a boiling point of 15°. After refluxing for 30 minutes the reaction mixture was neutral. Most of the α, α-Diphenylacetone was recovered.

C. Using sodium amide.

In a 100 ml. 3-neck flask fitted with a stirrer and condenser were placed 10 grams (0.476 moles) of diphenyl acetone, 1.90 grams (0.487 moles) of finely powdered sodium amide and 65 ml. of dry benzene. The mixture was stirred at reflux for 2½ hours. Ammonia was evolved, and a green color appeared which gradually became weaker as refluxing proceeded. A small amount of precipitate also appeared.

The flask was cooled and 7.2 ml. (15.7 grams, 0.835 mole) of ethylene bromide was added. The reaction mixture was refluxed for 5 hours. The benzene solution was washed with water, dried over anhydrous magnesium sulfate and the benzene evaporated under vacuum. An oily residue, weighing 9.0 grams resulted. Efforts to crystallize it were not successful beyond the recovery of some diphenyl acetone. Attempts to prepare the oxime and 2,4-dinitrophenylhydrazone gave derivatives of the starting ketone.

Similar results were obtained when the reaction time of the ketone with sodium amide was shortened in order to minimize condensation reactions of the ketone with itself.

γ-Chlorobutyronitrile

γ-chlorobutyronitrile was prepared by the reaction of trimethylene chlorobromide and sodium cyanide according to the method of Organic Syntheses (2). The yield was 48%.

α, α-Diphenyladiponitrile

In a 250 ml. 3-neck flask fitted with a stirrer, condenser, and dropping funnel were placed 110 ml. of benzene that had been dried over sodium metal, 18.4 grams (0.0953 moles) of diphenylacetonitrile and 3.90 grams (0.100 mole) of finely powdered sodium amide. The mixture was refluxed rapidly with stirring until the contents of the flask became too viscous to stir (45 minutes). The flask was cooled, and 10 grams (0.0965 moles) of γ-chlorobutyronitrile in 20 ml. of benzene was added in ½ hour. The temperature rose slowly, the semi-solid mass dissolved, and a precipitate of sodium chloride appeared. Refluxing was continued for six hours.

The reaction mixture was transferred to a separatory funnel and washed twice with water. The benzene was distilled and the oily residue allowed to stand overnight in ice. The oil crystallized, and after two recrystallizations from methyl alcohol, melted at 65 - 67°. The product, α,α-diphenyladiponitrile, weighed 12.3 grams for a yield of 51% of theory.

In this preparation the cyclized product described below is also likely to be formed.

A sample was prepared for analysis by sublimation. The melting point was 66 - 67°.

<u>Analysis</u>. Calculated for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76

Found: C, 82.61; H, 6.09; N, 10.82

In an attempt to use sodium t-butoxide in anhydrous t-butyl alcohol as the catalyst for this reaction diphenylacetamide was produced in good yield. No other products were isolated.

5-Cyano-2,2-diphenylcyclopentanone imine

This compound was obtained in the preparation of α,α-diphenyladiponitrile, and by the subsequent cyclization of this linear compound.

A. By the reaction of γ-chlorobutyronitrile and α,α-diphenylacetonitrile.

In a 2-liter, three neck flask equipped with a Hershberg stirrer, condenser and dropping funnel were placed 1200 ml. of dry thiophene free benzene, 32.8 grams (0.84 mole) of sodium amide and 162.3 grams of diphenylacetonitrile (m.p. 74.0 - 75.5). The sodium salt of diphenylacetonitrile was formed as before in about 2 hours, after which 87 grams (0.84 mole) of γ-chlorobutyronitrile in an equal volume of dry benzene was added to the cooled suspension over a period of 45 minutes. The flask was then heated to reflux for 2½ hours. At this time titration of an aliquot showed the reaction to be about 95% complete.

The contents of the flask were transferred to a 2-liter separatory funnel and washed twice with water. The benzene was evaporated on the water bath under reduced pressure. The oily residue, which was light orange-red in color, was diluted with ether to a volume of one liter. From this, 5-cyano-2,2-diphenylcyclopentanone imine crystallized in quite pure form. After the solid was filtered and washed with a small volume of ether it melted at 148 - 150°, and weighed 22.8 grams.

A second crop of cyclic compound was obtained by evaporation of the ether, and dilution of the residue with methyl alcohol to a volume of 300 ml., and allowing crystallization to take place in the refrigerator. After filtering and washing 24.9 grams of cyclic compound of slightly lower purity was obtained.

The solvent was removed from the mother liquors obtained from the above crystallizations, and the residual oil distilled under reduced pressure. The following fractions were obtained:
Fraction 1: B.P. 125 - 165° at 1-2 mm; Weight, 48.0 grams.
Fraction 2: B.P. 165 - 210° at 1 mm; Weight, 23.0 grams.
Fraction 3: B.P. 210 - 235° at 1 mm; Weight, 61.2 grams.

The first fraction, which was mostly crystalline was recrystallized from methylcyclohexane. It yielded 36.3 grams of diphenylacetonitrile melting at 73.5 - 75.5°. The second and third fractions were oils which were dissolved in methyl alcohol and crystallized. These products melted roughly in the range 60 - 135°, and appeared to be mixtures of the cyclic and linear compounds with a higher proportion of the cyclic compound in the third fraction. Although a painstaking effort was made to separate these compounds through fractional recrystallization from methyl alcohol, only a small amount of reasonably pure linear compound was obtained. The cyclic compound could not be obtained pure by crystallization from this mixture, but conversion of all of the material to the cyclic compound could be accomplished by the procedure below.

By the use of a 10% excess of sodium amide, the entire recoverable product was cyclic but a large amount of a deep red tar was formed.

B. By the cyclization of α, α-diphenyladiponitrile.

A condenser with a drying tube was attached to a 500 ml. single neck flask containing 27.9 grams of α, α-diphenyladiponitrile and 200 ml. of anhydrous t-butyl alcohol in which 0.20 grams of sodium metal had previously been dissolved. The dinitrile was dissolved with heating and swirling, and the resulting solution refluxed for 3½ hours. The t-butyl alcohol was distilled off, initially at atmospheric pressure and finally under reduced pressure with gentle heating. The flask was cooled and the residue crystallized forming a solid cake of grayish color. The cake was broken up, removed from the flask, and dried. The melting point was 136 - 146°.

A sample, purified for analysis by three recrystallizations from methyl alcohol, melted at 149 - 150°.

Analysis. Calculated for $C_{18}H_{16}N_2$: C, 83.04; H, 6.20; N, 10.76.

Found: C, 83.32; H, 6.13; N, 10.80

2,2-Diphenylcyclopentanone (VI, XXV)

To a solution of 48 ml. of water and 14 ml. of concentrated sulfuric acid was added 27.5 grams of the crude, finely powdered 5-cyano-2,2-diphenylcyclopentanone imine. The imine was added slowly with manual stirring to give a smooth dispersion. The resulting paste was heated on the steam bath until the imino-nitrile was all dissolved, and then for 15 minutes more. The flask was cooled in ice, and 250 ml. of water added all at once. The mixture was then refluxed for 18 hours with good stirring, preferably using a Hershberg stirrer.

Benzene was added to the still warm mixture, and the two layers transferred to a separatory funnel. The water layer was drawn off and extracted twice with small amounts of ether. These were combined with the benzene solution, the solvents were evaporated, and the product distilled rapidly from a Claisen flask at a temperature of about 150° and 1 mm. pressure. The melting point of the product was 87.5 - 89.5, and it weighed 20.1 grams for a yield of 81% based on the initial α, α-diphenyladiponitrile.

A product of superior purity was obtained by evaporating the benzene solution to a small volume and allowing the product to crystallize. It was filtered, washed with a small amount of cold methyl alcohol, and distilled as before. The melting point was 89.5 - 90.0°, and the yield was 72%. Distillation of the mother liquor gave an additional quantity melting at 84 - 89°. The total yield was 91% based on the cyclic imino-nitrile.

<u>Analysis</u>. Calculated for $C_{17}H_{16}O$; C, 86.40; H, 6.84

Found: C, 86.71; H, 6.84

2,4 -dinitrophenylhydrazone of 2,2-diphenylcyclopentanone

A 2,4 -dinitrophenylhydrazone was prepared in the usual manner. It was recrystallized by suspending about 0.3 grams in 4 - 5 ml. of benzene, and adding alcohol dropwise to the hot suspension until solution was obtained. After three recrystallizations it melted at 182.0 - 182.5°. A value of 182.0 - 182.5 has been previously obtained (8).

Analysis. Calculated for $C_{23}H_{20}O_4N_4$:
C, 66.33; H, 4.84

Found: C, 66.64; H, 5.00

Amide of 2,2-diphenylcyclopentanone-5-carboxylate (XXVI)

With shorter reflux times (8-10 hours) were used in the hydrolysis and decarboxylation reaction of 5-cyano-2,2-diphenylcyclopentanone imine, the flask from which the final distillation was conducted contained a non-volatile residue. This residue contained two compounds which were separated on the basis of their solubility in hot benzene. The hot benzene solution of the residue was filtered leaving a white powder described below. By evaporation of the solvent and cooling a second compound, the amide of 2,2-diphenylcyclopentanone-5-carboxylate was obtained. It melted at 125 - 127.5°, and after several recrystallizations from methyl alcohol melted at 132 - 133°.

This compound was converted to 2,2-diphenylcyclopentanone by refluxing with stirring in dilute acid.

Analysis. Calculated for $C_{18}H_{17}O_2N$: C, 77.39;
H, 6.14; N, 5.02

Found: C, 77.63; H, 6.26; N, 4.88

Amide of 2,2-cyclopentanone imine-5-carboxylate (XXVII)

The benzene insoluble powder filtered from the soluble portion of the residue obtained upon distillation of the partially hydrolyzed 5-cyano-2,2-diphenylcyclopentanone imine was a high melting compound insoluble in the most organic solvents. It was recrystallized twice from glacial acetic acid, (m.p. 218 - 222) and finally sublimed at 175° and a pressure of 1 mm. or less. It was a white powder with a slight yellowish cast melting at 229 - 232° with darkening.

Analysis. Calculated for $C_{18}H_{18}ON_2$: C, 77.67; H, 6.52; N, 10.07

Found: C, 77.65; H, 6.60; N, 10.08

This compound was also obtained from an attempted basic hydrolysis of 5-cyano-2,2-diphenylcyclopentanone imine.

5-Methyl-2,2-Diphenylcyclopentanone (XXIX)

This preparation, for the most part, followed the Organic Syntheses procedure for 2-allylcyclohexanone (40).

In a 100 ml. 3-neck flask fitted with a condenser, stirrer and addition funnel were placed 5 grams (0.0212 moles) of 2,2-diphenylcyclopentanone and 35 ml. of absolute ether. The solid was dissolved by stirring under reflux. The flask was cooled to room temperature (with a soda lime drying tube in the condenser) and 0.820 grams (0.0210 moles) of finely powdered sodium amide added. The suspension was refluxed for 4 hours with vigorous stirring. At this time, the evolution of ammonia had virtually ceased, and most of the suspended sodium amide had reacted. A tube was introduced through the condenser to a point just above the surface of the ether solution, and the remaining ammonia flushed from the flask with dry nitrogen.

The flask was cooled to 0°, and 3.05 grams (0.0215 moles) of methyl iodide in 5-10 ml. of dry ether was added rapidly through a small addition funnel. The reaction mixture was warmed slowly. When reflux began, the flow of nitrogen was stopped. It was briefly turned on a few times during the reaction period to sweep out any additional ammonia that was liberated. Shortly after warming began a precipitate appeared. The reaction mixture was refluxed with stirring for 6 hours.

The suspended sodium iodide was filtered. A nearly quantitative recovery was obtained. The ether was evaporated, and the residue allowed to crystallize. The crude 5-methyl-2,2-diphenylcyclopentanone melted at 54 - 58°. After one recrystallization from methyl alcohol it melted at 56 - 59.5° and weighed 4.46 grams. Further recrystallization from methyl alcohol resulted in concentration of the higher melting starting material, 2,2-diphenylcyclopentanone. A 2,4-dinitrophenylhydrazone was prepared with some difficulty. It melted at 84 - 87°. A sample melting at 64 - 66° was obtained through fractional recrystallization.

<u>Analysis</u>. Calculated for $C_{18}H_{18}O$: C, 86.36; H, 7.25
Found: C, 86.66, 86.21; H, 7.40, 7.11

This sample analyzed with difficulty, and the analysis was obtained only through modification of the apparatus.

5-Bromo-2,2-diphenylcyclopentanone

In a 100 ml. 3-neck flask were placed 5 grams (0.0211 mole) of 2,2-diphenylcyclopentanone and 50 ml. of ether. The ketone was dissolved with stirring and gentle heating.

The bromooxonium bromide of ethyl ether was prepared from 3.56 grams (0.222 moles) of bromine. The bromine was weighed into a test tube and cooled in an ice bath. Dry ether was added very slowly, and the temperature, which was observed by means of a thermometer placed in the test tube, was not permitted to rise above 20°. Ether was added until it formed a second layer above the dark red ether insoluble oil that resulted. This material was used immediately, since the available bromine decreased upon standing.

The ether-bromine reaction product was transferred to a small separatory funnel and added in 15 minutes to the rapidly stirred solution of the ketone, which was at room temperature. Vigorous stirring was necessary to keep the heavy, insoluble oil in suspension. The faintly yellow solution was evaporated on the steam bath. The product, 5-bromo-2,2-diphenylcyclopentanone, crystallized upon cooling. It was recrystallized from about 50 ml. of methyl alcohol, filtered, and washed with a few ml. of cold methyl alcohol. It melted at 97.5 - 99.5°, and weighed 5.1 grams, for a yield of 76%. An additional quantity of less pure material was obtained upon evaporation of the mother liquor.

A sample was purified for analysis by five recrystallizations from methyl alcohol, from which it was obtained as brilliant needles melting at 99.5 - 100.5°.

<u>Analysis</u>. Calculated for $C_{17}H_{15}OBr$: C, 64.77; H, 4.80

Found: C, 64.62; H, 4.87

Bromination of 2,2-diphenylcyclopentanone with bromine itself always resulted in the presence of a higher melting impurity that could not be separated even after several recrystallizations. It was present after bromination in carbon tetrachloride or ether solution, after bromination at 10°, and even when only 70% of the theoretical amount of bromine was used. The product usually melted in the range of 95 - 115°, and the melting point could not be improved upon recrystallization. A fractional crystallization was carried out on the combined products of several experiments. From a total 5.5 grams of 2,2-diphenylcyclopentanone were obtained 0.5 grams of starting ketone, 4.5 grams of monobromide, and 0.8 grams of a compound melting at 121.0 - 124.5. Repeated recrystallization of the high melting compound from methyl alcohol raised the melting point to 125 - 130, but it appeared to be too unstable to be obtained readily in pure form. Analysis indicated that it was a dibromide. Values found were C, 55.11 and H, 3.98, compared with C, 51.80 and H, 3.58 for the formula $C_{17}H_{14}OBr_2$.

5-Dimethylamino-2,2-diphenylcyclopentanone XLIII

In a 100 ml. 3-neck flask fitted with a stirrer and condenser were placed 50 ml. of 95% alcohol and 5.1 grams of 5-bromo-2,2-diphenylcyclopentanone. The ketone was dissolved, and the solution cooled rapidly in ice with stirring. The ketone then precipitated in finely divided form, and in the resulting paste 5.8 grams (0.064 moles) of dimethyl amine was absorbed. The flask was heated slowly with stirring to 40°, and was held at this temperature for 2½ hours. The ketone dissolved, and the alcohol solution slowly developed a greenish fluorescence. After the period of heating was over the solution was allowed to stand overnight at room temperature.

The alcohol was evaporated under reduced pressure, and water added. A brown oil separated that was taken up in benzene. The mixture was transferred to a separatory funnel, and the water layer removed. The benzene solution was shaken with 5% HCl. A short time after the two layers formed, the amine hydrochloride crystallized from the aqueous layer. The crystals were filtered and washed with 5% HCl, and benzene. When dry, the product weighed 1.7 grams (33%) and melted at 201 - 204° with decomposition.

When the amination was carried out in benzene at room temperature or 0°C. the same product was obtained in very low yield.

A sample was recrystallized from absolute alcohol and ether. It melted at 201 - 204° with decomposition.

Analysis. Calculated for $C_{19}H_{21}ON\ HCl$: N, 4.43

Found: N, 4.40

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