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Acetylbenzoyl reacted with dimethylamine hydrochloride and benzaldehyde in primary isoamyl alcohol under reflux conditions to form 1,4-diphenyl-3-butene-1,2-dione, compound I, which melted at 56-57°C.

Compound I formed a quinoxaline derivative, compound II, which melted at 152.5-153°C.

Compound I was cleaved by hydrogen peroxide to form cinnamic acid, compound III, which melted at 133°C.

Acetylbenzoyl reacted with dimethylamine hydrochloride and benzaldehyde in glacial acetic acid under reflux conditions to form 1,4,5-triphenyl-1,2,5-pentane-trione, compound IV, which melted at 192-193°C.

Compound IV formed an oxime derivative, compound V, which melted at 232-233°C.
Benzylidene-bis-piperidine, prepared from benzaldehyde and piperidine, reacted with acetylbenezoyl in ethanol at room temperature to form compound VI, which melted at 203°C.
CONDENSATION REACTIONS OF CERTAIN ALDEHYDES
AND AMINES WITH ACETYLBNZOYL

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CONDENSATION REACTIONS OF CERTAIN ALDEHYDES
AND AMINES WITH ACETYL BENZOYL

INTRODUCTION

The family of reactions which involve the condensation of a primary or secondary amine, usually in the form of the hydrochloride, with an aldehyde and a compound containing at least one active hydrogen atom are generally brought together under the name of the Mannich reaction (5). In the Mannich-type condensation, the three components react in such a way so that the net result of the reaction is the replacement of the active hydrogen atom or atoms by substituted amino groups. The active hydrogen atoms are usually those of methyl or methylene groups alpha to the carbonyl function of a ketone, aldehyde, ester, or acid. Acetophenone, for example, reacts with formaldehyde and dimethylamine hydrochloride as follows (16):

\[
\text{O}^\text{O} \text{C-CH}_3 + \text{HCH=O} + (\text{CH}_3)_2\text{NH\cdotHCl} \rightarrow \text{O}^\text{O} \text{C-CH}_2\text{CH}_2\text{N(\text{CH}_3)_2}
\]

Historical.

Although the Mannich reaction was first recognized as a general reaction in about 1917, it has only been within the last twenty years that the mechanism of the reaction
has been established. It was at first thought that the primary step of the Mannich reaction was either the addition of the amine to formaldehyde to form an alkylaminomethanol,

\[ R_2NH + HCH=O \rightarrow R_2NCH_2OH \]

or the addition of the ketone to formaldehyde to form the methylol (5, p. 306).

\[ \overset{O}{R-C-CH_3} + HCH=O \rightarrow \overset{O}{R-C-CH_2CH_2OH} \]

However, in 1933, Bodendorf and Koralewski (6) showed that under alkaline conditions dimethylaminomethanol reacted with antipyrine to give a much poorer yield of condensation product than that obtained from the reaction of antipyrine with formaldehyde and dimethylamine.

\[ \overset{O}{HCH=O} + (CH_3)_2NH + \overset{CH_3}{N-C-CH_3} \rightarrow \overset{CH_3}{N-C-CH_3} \]

They also found that the methylol formed from antipyrine
and formaldehyde does not react at all with dimethylamine. These observations suggested that neither of the two proposed mechanisms represented the primary step of a Mannich-type condensation.

In 1949, Alexander and Underhill (1) conducted a thorough kinetic study of the reaction between ethylmalonic acid, formaldehyde, and dimethylamine.

\[
\text{CH}_3\text{CH}_2-\text{CH(COOH)}_2 + \text{HCH=O} + (\text{CH}_3)_2\text{NH} \quad \downarrow \quad \text{COOH} \\
\text{CH}_3\text{CH}_2-\text{C-CH}_2-\text{N(CH}_3)_2 \quad \text{COOH}
\]

They found that under acidic conditions the reaction followed third order kinetics, first order in each of the three components. However, smooth third order curves were only obtained if the amine and formaldehyde were first mixed and allowed to stand for twelve hours before the addition of the ethylmalonic acid. Also, if the amine and formaldehyde were replaced by dimethylaminomethanol, the reagents could be mixed at once, and the kinetics were unchanged. This suggested that the methylol derivative formed by reaction of the amine and formaldehyde acted as an intermediate in the Mannich reaction. The investigators repeated and verified Bodendorf and Koralewski's
(6) experiments with antipyrine, and concluded that although they did not understand the significance of these results to base-catalyzed transformations, it was clear that they had no bearing on reactions carried out in acidic solutions.

Liberman and Wagner (14), in 1949, suggested that methylene-bis-amines may serve as intermediates in the Mannich reaction. These compounds may be easily formed from the corresponding amines and formaldehyde.

\[
2 \text{R}_2\text{NH} + \text{HCH}=\text{O} \rightarrow (\text{R}_2\text{N})_2\text{CH}_2 + \text{H}_2\text{O}
\]

The suggestion is plausible since Feldman and Wagner (9) obtained Mannich bases by the interaction of phenols with methylene-bis-amines, as well as with amines and formaldehyde. Liberman and Wagner (14) postulated that the Mannich reaction involves dual catalysis in an amphoteric system in which the cation \((\text{R}_2\text{NCH}_2)^+\) is formed from a methylene-bis-amine, and combines finally with the anion of the active hydrogen compound.

They showed experimentally that in reactions between methylene-bis-amines and active hydrogen compounds, the same normal Mannich bases in approximately the same yields were obtained as from the corresponding amines, formaldehyde, and active hydrogen compounds. Thus, 4-piperidino-methylantipyrine, was prepared in the same yield from
methylene-bis-piperidine and antipyrine, as from formaldehyde, piperidine, and antipyrine.

Further evidence was supplied by Butler (8), in 1956, who showed that methylene-bis-N-phenylpiperazine could be substituted for formaldehyde and N-phenylpiperazine in the Mannich reaction with 2-nitropropane. The function of the methylol derivative of the amine in the Mannich reaction may be clarified, if one assumes that an equilibrium exists between it and the methylene-bis-amine.

\[
(R_2N)_2CH_2 + H_2O \rightleftharpoons R_2NCH_2OH + R_2NH
\]

Studies by Logan, Huston, and Dorward (15) on the Mannich reaction of acetophenone, dimethylamine hydrochloride and C\textsuperscript{14}-labeled paraformaldehyde showed that there is no transposition of the carbon atoms during the formation of the Mannich base. This is in agreement with the
Mannich mechanism as it has so far been elucidated.

**Condensation reactions of 1,2-diketones.**

Little work has been done concerning Mannich-type condensations with an aldehyde, amine, and 1,2-diketone. The use of benzylidene-bis-piperidine, prepared from benzaldehyde and piperidine, was made by Leonard, Little, and Kresge (12) for condensations with cyclic 1,2-diketones. These workers found that the principal product of such condensations with up to 11-membered ring diketones was the unsaturated dibenzylidenediketone rather than the diaminodiketone. They concluded that under the conditions of the reaction the diaminodiketone was initially formed but was very easily deaminated to form the dibenzylidinediketone.

![Chemical structure](attachment:diagram.png)

However, high yields of the diaminodiketone intermediates were obtained when 12 to 14-membered ring diketones were utilized in the reaction. This was attributed not to a greater stability of such compounds, but rather to the low solubility of the larger ring diaminodiketone.
diketones so that the final deamination did not occur as readily.

Leonard, Little, and Kresge (12) also pointed out that piperidine or piperidinium acetate has long been known to be effective in promoting condensations between 1,2-diketones and aromatic aldehydes. The use of basic catalysts stronger than piperidine frequently promotes the decomposition of the dibenzylidene products and in some cases encourages the self-condensation of the cyclic 1,2-diketones. This latter behavior was first reported by Müller and von Peckmann (19) in 1889 and later by Levine, and Stephens (13) in the two-fold aldol condensation of acetylbenzoyl in dilute sodium hydroxide to form 2,5-diphenylquinone.

\[
2 \begin{array}{c}
\text{C-C-CH}_3 \\
\text{O} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{O} \\
\text{SO} \\
\text{SO}
\end{array} + 2 \text{H}_2\text{O}
\]

In addition to the deamination of a Mannich base, which easily occurs at elevated temperatures and in many cases at room temperature, the unsaturated product may undergo further reaction. Bachman, Bryant, and Atwood (2) described the preparation of various \(\gamma\)-dinitroparaffins by the condensation of aliphatic nitroparaffins with formaldehyde and amine catalysts. They postulated the initial
formation of the Mannich base followed by deamination and a subsequent Michael condensation between the nitroalkene product and nitroparaffin starting material.
Selection and preparation of starting materials.

In order to study the Mannich-type condensations of 1,2-diketones, it was decided to limit the research activities around the reactions of a typical diketone, similar in structure to ketones which successfully undergo the Mannich reaction. For this purpose acetylbenzoyl was selected. The compound is structurally similar to acetophenone, which reacts with dimethylamine hydrochloride and formaldehyde to form the Mannich base in a 60% yield (16). The phenyl group at one end of the molecule limits the site of the reaction to the single methyl group, thus avoiding the formation of too many products, and allowing the course of the reaction to be studied with greater ease.

Acetylbenzoyl was prepared in two steps from propiophenone. Propiophenone was allowed to react with methyl nitrite in the presence of hydrogen chloride to form isonitrosopropiophenone (4, p. 363-364). The isonitrosopropiophenone was then steam distilled from dilute sulfuric acid solution to yield the 1,2-diketone, acetylbenzoyl (11, p. 20-22).
Reaction of acetylbenzoyl with dimethylamine hydrochloride and formaldehyde in ethanol.

The initial attempt to prepare the Mannich adduct involved the reaction of acetylbenzoyl with dimethylamine hydrochloride and formaldehyde. The three components were refluxed for periods up to six hours in 95% ethanol acidified with hydrochloric acid, but no reaction occurred. This was an unusual and unforeseen circumstance as the reaction proceeds quite readily and in high yield with aceto-phenone.

Bellamy (3, p. 141) points out that there appear to be only very slight interaction effects between the adjacent carbonyl groups of 1,2-diketones as seen by an examination of the Raman frequency shifts for a number of compounds. This would suggest that the activity of the hydrogen atoms on the alpha methyl group would by no means be diminished by the addition of a second carbonyl function on a beta
carbon atom. However, this is clearly not the case.

The activity of a hydrogen atom covalently attached to carbon is dependent upon being adjacent to an unsaturated unit containing carbon and the more electronegative oxygen. A lack of activity of the hydrogen atom might be attributed to the absence of such an unsaturated carbonyl structure. An explanation might be suggested by consideration of the possibility of keto-enol tautomerism occurring in acetyl-benzoyl. Moureu (18) found in a similar compound, 1,3-diphenyl-1,2-propanedione, that in the liquid state 60% of the diketone exists in the enol form.

\[
\text{\begin{tikzpicture}
  \draw (-1,-1) -- (1,-1) -- (1,1) -- (-1,1) -- cycle;
  \draw (-1,-0.5) -- (-0.5,-1);
  \draw (-0.5,0) -- (0.5,1);
  \draw (0.5,-1) -- (1,-0.5);
  \draw (-1,0) -- (-0.5,1);
  \draw (0.5,-1) -- (1,0);
  \node at (0,-0.5) {$\text{H}$};
  \node at (-0.5,0) {$\text{O}$};
  \node at (0.5,0) {$\text{O}$};
  \node at (0,1) {$\text{C}$};
  \node at (0,-1) {$\text{C}$};
  \node at (0,0) {$\text{C}$};
  \node at (0,0.5) {$\text{C}$};
  \node at (0,-0.5) {$\text{C}$};
  \node at (0,1.5) {$\text{H}$};
  \node at (0,-1.5) {$\text{H}$};
  \node at (0,2) {$\text{H}$};
  \node at (0,-2) {$\text{H}$};
\end{tikzpicture}}
\]

Therefore, acetylbenzoyl might also be represented by the tautomeric forms,

\[
\text{\begin{tikzpicture}
  \draw (-1,-1) -- (1,-1) -- (1,1) -- (-1,1) -- cycle;
  \draw (-1,-0.5) -- (-0.5,-1);
  \draw (-0.5,0) -- (0.5,1);
  \draw (0.5,-1) -- (1,-0.5);
  \draw (-1,0) -- (-0.5,1);
  \draw (0.5,-1) -- (1,0);
  \node at (0,-0.5) {$\text{H}$};
  \node at (-0.5,0) {$\text{O}$};
  \node at (0.5,0) {$\text{O}$};
  \node at (0,1) {$\text{C}$};
  \node at (0,-1) {$\text{C}$};
  \node at (0,0) {$\text{C}$};
  \node at (0,0.5) {$\text{C}$};
  \node at (0,-0.5) {$\text{C}$};
  \node at (0,1.5) {$\text{H}$};
  \node at (0,-1.5) {$\text{H}$};
  \node at (0,2) {$\text{H}$};
  \node at (0,-2) {$\text{H}$};
\end{tikzpicture}}
\]

in which a substantial proportion of the enol form would be expected to account for the low reactivity observed. Infrared spectra of acetylbenzoyl (5% in carbon tetrachloride) show the presence of two carbonyl groups absorbing at 1670 and 1710 cm\(^{-1}\), and in the OH stretching region,
two weak bands are also observed at 3330 and 3410 cm$^{-1}$.

Reaction of acetylbenzoyl with dimethylamine hydrochloride
and benzaldehyde in isoamyl alcohol.

In cases of reduced reactivity of components in the
Mannich reaction, van de Kamp and Mosettig (23) have rec-
ommended the use of a higher-boiling solvent such as
isoamyl alcohol. There is, however, a much greater possi-
bility of unwanted side reactions which are associated with
the instability of many aminoketone salts at elevated
temperatures (20).

Dimethylamine hydrochloride and benzaldehyde were
stirred together for 45 minutes in primary isoamyl alcohol
solvent (b.p. 132°C.). Acetylbenzoyl was then added and
the mixture heated under reflux for two hours, after which
stirring at room temperature was continued for an addi-
tional eight hours. During the reflux period the reaction
mixture turned a deep red color. The reaction mixture was
extracted with water which had been acidified with several
drops of concentrated hydrochloric acid in order to remove
the unreacted amine. Removal of the isoamyl alcohol sol-
vent and unreacted acetylbenzoyl was facilitated by steam
distillation of the organic phase.

A red syrupy liquid remained behind after steam
distillation, which crystallized into a red oily solid
over a period of several days at room temperature. The
material was slowly recrystallized from aqueous ethanol, and after refrigeration for two days yielded yellow plates, I, melting at 56-7°C.

An infrared spectrum, obtained by the KBr pellet technique, showed a broad absorption with four principal peaks at 1670, 1635, 1610, and 1590 cm$^{-1}$. Since the two absorption bands in the spectrum of acetylbenzoyl, at 1670 and 1710 cm$^{-1}$, correspond respectively to an aryl ketone and a saturated aliphatic ketone, a comparison of the two spectra indicated that if the 1,2-diketone structure was retained in compound I, the band at 1670 cm$^{-1}$ remains that of an aryl ketone. The band at 1635 cm$^{-1}$, however, corresponds to that of a ketone adjacent to a conjugated unsaturated aliphatic structure. The two bands appearing at 1610 and 1590 cm$^{-1}$ are most likely associated with the carbon-carbon stretching vibrations of an unsaturated system.

In addition, the yellow color of compound I suggested that the 1,2-dicarbonyl relationship was retained. Generally, the presence of twinned carbonyl groups confers color on the molecule (22). The presence of the 1,2-dicarbonyl function may be established by its reaction with o-phenylenediamine to form a substituted quinoxaline as in the case of the synthesis of 2,3-diphenylquinoxaline from benzil (7).
The yellow product I was found to undergo reaction with o-phenylenediamine to produce a quinoxaline derivative, II, which melted at 152.5-3°C.

The ease of cleavage of 1,2-diketones by hydrogen peroxide, as in the case of the formation of benzoic acid from benzil, has been used as a further test for the presence of the dicarbonyl structure (10, p. 237). An alcoholic solution of compound I became decolorized after boiling for several minutes with 30% hydrogen peroxide. Upon cooling, colorless crystals separated from the solution and were removed by filtration. They were recrystallized from water giving fine crystals, III, with a melting point of 133°C. and possessing the pleasant odor characteristic of cinnamic acid.

The presence of unsaturation in compound I was determined by the ease in which decolorization of bromine in carbon tetrachloride occurred. A qualitative test for the presence of nitrogen was found to be negative. Carbon and hydrogen data corresponded to the empirical formula $\text{C}_{16}\text{H}_{12}\text{O}_{2}$. 
These reactions established the structure of compound I as being 1,4-diphenyl-3-butene-1,2-dione and confirmed the following reaction sequence:

\[
\begin{align*}
\text{O} & \text{-C-CH}_3 + \text{-CH=O} + (\text{CH}_3)_2\text{NH-HCl} \\
& \xrightarrow{1) \text{ reflux in isoamyl alcohol}} \xrightarrow{2) \text{ steam distillation}} \\
\text{O} & \text{-C-CH=CH-} \\
\end{align*}
\]

\[
\begin{align*}
\text{I} + \text{-NH}_2 + \text{-NH}_2 & \rightarrow \text{II} \\
\text{I} + \text{H}_2\text{O}_2 & \rightarrow \text{-COOH} + \text{-CH=CHCOOH} \\
\end{align*}
\]

Compound I was also prepared by Ruggli and coworkers (21) by refluxing acetylbenzoyl, benzaldehyde, piperidine, and glacial acetic acid in absolute ether solvent for seven hours. Additional ether was added and the reaction mixture was washed with dilute hydrochloric acid, followed
by aqueous sodium bicarbonate. After drying over sodium sulfate, the ether was removed by distillation, and the product fractionated under a high vacuum. A few drops of the yellow oil fraction boiling at 135-40°C. at 0.02 mm. was recrystallized from petroleum ether, yielding yellow prisms which melted at 55-6°C. The yellow oil obtained from the fractionation was allowed to react with o-phenylenediamine and yielded pale yellow prismatic plates of the quinoxaline derivative, which melted at 144.5-5.5°C.

These workers had previously attempted the reaction with acetylbenzoyl and benzoaldehyde using sodium hydroxide as a condensing agent. However, they were unsuccessful. Reaction of acetylbenzoyl with dimethylamine hydrochloride and benzoaldehyde in glacial acetic acid.

It was decided to try to effect condensation of acetylbenzoyl with an aldehyde and amine by utilization of glacial acetic acid as the reaction solvent. Glacial acetic acid boils at 118°C., which is considerably lower than the previously used isoamyl alcohol. However, it does provide a more acidic environment which might promote the reaction.

Dimethylamine hydrochloride and benzoaldehyde in glacial acetic acid were stirred together at room temperature for a period of four hours. Acetylbenzoyl was then added, the mixture stirred for an additional hour, and then
refluxed for three hours. During the reflux period, the reaction mixture turned from a light yellow to a red-orange color. The reaction mixture was poured into a petri dish and evaporated to dryness overnight before a warm fan. The resulting red crystalline solid and oily liquid were extracted with diethyl ether and a small quantity of water, yielding a yellow crystalline substance. This material was recrystallized twice from aqueous acetone to obtain fine yellow crystals, IV, which melted at 192-3°C.

The presence of the dicarbonyl group in compound IV was confirmed by its decolorization upon being heated to boiling with 30% hydrogen peroxide in acetone. The material failed to decolorize bromine, which indicated a saturated structure. The quinoxaline derivative could not be obtained. However, compound IV did react with a solution of hydroxylamine hydrochloride in ethanol and pyridine to form the oxime derivative V, which melted at 232-3°C.

Carbon and hydrogen determinations of compound IV gave an empirical formula of C23H18O3. An infrared spectrum was obtained by the KBr pellet technique. Examination of the carbonyl stretching region of the spectrum showed three absorption bands at 1660, 1690, and 1715 cm.⁻¹. Comparison of this spectrum with that obtained from acetyl-benzoyl indicated that the bands at 1660 and 1715 cm.⁻¹ correspond to the two carbonyl groups in the 1,2-diketone structure.
The absorption band at 1690 cm\(^{-1}\) represents a third carbonyl group in the molecule, which is not part of a diketone structure. Since the carbonyl absorption at 1690 cm\(^{-1}\) is below the frequency range Bellamy assigns to aliphatic ketones (3, p. 132), it may be deduced that the structure in question is that of an aryl ketone, in which the carbonyl group is adjacent to a phenyl group.

A structure for compound IV, which satisfies the requirements of the infrared spectrum and corresponds to the empirical formula is that of 1,4,5-triphenyl-1,2,5-pentanetrione. However, this is mechanistically impossible.

The reaction sequence is as follows:

\[
\text{C}_{6}\text{H}_{5}-\text{C}-\text{C}-\text{CH}_3 + \text{C}_{6}\text{H}_{5}-\text{CH} = \text{O} + (\text{CH}_3)_2\text{NH}\cdot\text{HCl} \xrightarrow{\text{reflux in glacial acetic acid}} \text{C}_{6}\text{H}_{5}-\text{C}-\text{C}-\text{CH}_2\text{CH}-\text{C} \quad \text{(IV)}
\]

IV + H\(_2\)NOH•HCl \rightarrow Dioxime

V
Effect of prolonged heating of reactants in isoamyl alcohol

In order to determine the effect of more prolonged heating at elevated temperatures, acetylbenzoyl, benzaldehyde, and dimethylamine hydrochloride were refluxed together in primary isoamyl alcohol solvent for a period of six hours. The reaction mixture was allowed to stand for several days, during which time a quantity of yellow crystals precipitated. They were removed by filtration and recrystallized from aqueous ethanol. The melting point was 192-3°C., and the infrared spectrum was found to be identical with that of 1,4,5-triphenyl-1,2,5-pentanetrione, compound IV.

Reaction of acetylbenzoyl with piperidine hydrochloride and paraformaldehyde in several solvents.

The cyclic secondary amine, piperidine, has often been used as the amine component in the Mannich reaction. Mannich and Lammering (17) obtained the adduct phenyl-β-piperidino-ethyketone hydrochloride in 90% yield from piperidine hydrochloride, formaldehyde, and acetophenone.

Because of the ease with which the reaction proceeds with acetophenone, the condensation was attempted using acetylbenzoyl, piperidine hydrochloride, and paraformaldehyde. The solvent was varied from ethanol to glacial acetic acid, but even with the extended reflux periods, only small quantities of any sort of product could be
obtained. This material was characterized by being a red amorphous or semi-plastic tar, and generally appeared to be hygroscopic as well. The products resisted all attempts at further purification.

**Condensations of cyclic 1,2-diketones with benzylidine-bis-piperidine.**

Not only has piperidine been found effective in promoting aromatic aldehyde condensations with ketones, but Leonard and co-workers (12) demonstrated the reactivity of benzylidene-bis-piperidine with cyclic 1,2-diketones to yield a diaminodiketone product. Benzylidene-bis-piperidine was initially prepared by mixing benzenaldehyde and piperidine in a 1:2 molar ratio in cyclohexane solvent, followed by removal of the water with a Dean-Stark trap.

\[
\text{C}_6\text{H}_5-\text{C}-\text{CH}=\text{O} + 2 \text{HN} \rightarrow \text{C}_6\text{H}_5-\text{CH(N)}_2 \quad \text{-H}_2\text{O}
\]

An example of the condensation was the formation of 3,10-dibenzylidene-1,2-cyclodecanedione (80%) and 3,10-di-(phenyl-1'-(piperidylmethyl))-1,2-cyclodecanedione (1%) from sebacil and benzylidene-bis-piperidine in ethanol at room temperature over a period of three weeks.
The dicarbonyl system in the dibenzylidine derivative was found to be practically inert to carbonyl reagents and o-phenylenediamine.

**Reaction of acetylbenzoyl with benzylidine-bis-piperidine in ethanol.**

In view of the extremely mild reaction conditions afforded by the condensation of diketones with benzylidine-bis-piperidine at room temperature, it was hoped that reaction with acetylbenzoyl might be effected without the deamination which apparently had previously occurred.

Benzylidine-bis-piperidine was prepared by refluxing a 1:2 molar ratio of benzaldehyde and piperidine with cyclohexane solvent in a Dean-Stark trap. When all of the water had been removed, the cyclohexane solvent was removed.
by vacuum distillation. The colorless crystalline product was dissolved in absolute ethanol and acetylbenzoyl was added. The solution was transferred to a flask, stoppered, and allowed to remain at room temperature. Over a period of about a week, the originally light yellow reaction mixture had gradually developed a wine red coloration. Four months later a precipitated condensation product was observed in the solution. The material was removed by filtration, giving a quantity of shiny black plates, VI, with a melting point of 203°C.

An elemental analysis for carbon, hydrogen, and nitrogen corresponds most closely to an empirical formula of C_{14}H_{17}O_{2}N.

An infrared spectrum showed the presence of a carbonyl absorption band at 1620 cm.$^{-1}$, which was lower in frequency than any observed previously. This in conjunction with the black color (yellow in very dilute solution) indicated a conjugated structure such as that which might arise from the presence of the enol tautomeric form of an amino-diketone.

The presence of the dicarbonyl structure was verified by the decolorization of compound VI with 30% hydrogen peroxide due to cleavage of the twinned carbonyl groups. The reaction, however, took several hours at room temperature.
The structure of compound VI cannot be determined from the limited information available.

However, the high melting point and dark color suggests a compound of a rather high molecular weight. The overall reaction sequence may be postulated as follows:

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]

\[
\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
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\text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_3 + \text{O} \quad \text{O} \quad \text{C} - \text{C} - \text{CH}_2^- \quad \text{CH(N)}_2 \quad \text{CH} \quad \text{CH}_2^- \\
\text{4 months in absolute ethanol at room temperature}
\]
EXPERIMENTAL

Preparation of isonitrosopropiophenone.

Methyl nitrite, prepared by slowly dropping 100 ml. of 6N sulfuric acid on a mixture of 75 g. sodium nitrite, 48 g. methanol, and 40 ml. water, together with anhydrous hydrogen chloride were bubbled, with stirring, through a solution of 108.3 g. (0.807 mole) of propiophenone in 500 ml. anhydrous diethyl ether for a period of 3 hours, at which time the flow of methyl nitrite stopped. Stirring and the addition of hydrogen chloride was continued for an additional half hour.

The reaction mixture was allowed to stand overnight, and then was extracted 8 times with 100 ml. portions of a 10% sodium hydroxide solution. The basic extract was slowly poured, with stirring, into a mixture of 350 ml. concentrated hydrochloric acid and 400 g. of crushed ice.

The resultant precipitate of isonitrosopropiophenone was filtered, washed with 200 ml. of cold water, and air dried, yielding 103.9 g. (79%) of the light tan product, m.p. 113-114°C.

Preparation of acetylbenzoyl.

To 1 liter of 2N sulfuric acid was added 104 g. (0.64 mole) of isonitrosopropiophenone, and the mixture was steam distilled for approximately 6 hours until a total volume of 6 liters of distillate had been collected. The
distillate was saturated with calcium chloride and then 1 liter quantities were each extracted 3 times with 100 ml. portions of diethyl ether. The combined ether extracts were evaporated on a steam bath followed by vacuum distillation, giving 60.7 g. (64%) of yellow acetylbenzoyl, b.p. 116°C. at 20 mm.

The infrared spectrum (2% in CCl₄) showed maxima at 1670 (C=O) and 1710 cm.⁻¹ (C=O).

Preparation of 1,4-diphenyl-3-butene-1,2-dione, compound I.

To 30 ml. of redistilled primary isoamyl alcohol (b.p. 132°C.) was added 4.5 g. (0.055 mole) of dimethylamine hydrochloride and 5.0 g. (0.047 mole) of benzaldehyde. The mixture was stirred for 45 minutes, and 5.0 g. (0.034 mole) of acetylbenzoyl was added. The resulting mixture was heated under reflux for 2 hours, after which stirring at room temperature was continued for 8 hours.

The reaction mixture was extracted 3 times with acidified water, and then steam distilled leaving behind a water insoluble liquid. After a period of several days this material crystallized into a red oily solid. This material was recrystallized from aqueous ethanol by refrigeration for 2 days, yielding approximately 1 g. of large yellow plates, m.p. 56-57°C., reported (21), 55-56°C. Anal. Calcd. for C₁₆H₁₂O₂: C, 81.3; H, 5.12

Found: C, 80.9; H, 5.35

The infrared absorption spectrum (KBr pellet) showed
maxima at 1670 (C=O), 1635 (C=O), 1610 (C=C), and 1590 cm.⁻¹ (C=C).

Preparation of the quinoxaline of 1,4-diphenyl-3-butene-1,2-dione, compound II.

This compound was obtained by heating the diketone with a 10% molar excess of o-phenylenediamine in absolute ethanol under reflux for 4 hours. The product was purified by recrystallization from 95% ethanol to give fine yellow needles, m.p. 152.5-153°C., reported (21) 144.5-145.5°C.

Anal. Calcd. for C₂₂H₁₆N₂: C, 85.7; H, 5.23
Found: C, 85.2; H, 4.99

Preparation of cinnamic acid, compound III.

This compound was obtained from the peroxide cleavage of 1,4-diphenyl-3-butene-1,2-dione. The reaction was effected by heating an ethanolic solution of the diketone with several ml. of 30% hydrogen peroxide for 5 minutes. Upon cooling, crystals separated out which were purified by recrystallization from water giving fine colorless crystals, m.p. 133°C. (lit. 133°C.).

The melting point was not depressed upon being mixed with an authentic sample of cinnamic acid.

Preparation of 1,4,5-triphenyl-1,2,5-pentanetrione, compound IV.

To 40 ml. of glacial acetic acid (b.p. 118°C.) was added 9.0 g. (0.110 mole) of dimethylamine hydrochloride
and 10.0 g. (0.094 mole) of benzaldehyde. The mixture was stirred for 4 hours at room temperature, and 10.0 g. (0.068 mole) of acetylbenzoyl was added. The resulting mixture was heated under reflux for 3 hours, after which it was evaporated before a warm fan overnight. The resulting red oily residue was extracted with 5 ml. water and 100 ml. diethyl ether, and the insoluble solid subsequently recrystallized twice from aqueous acetone to yield 0.64 g. (2.9%) of fine yellow plates, m.p. 192-193°C.

Anal. Calcd. for C_{23}H_{18}O_{3}: C, 80.7; H, 5.27

Found: C, 80.6; H, 5.32

The infrared absorption spectrum (KBr pellet) showed maxima at 1660 (C=O), 1690 (C=O), and 1715 cm.\(^{-1}\) (C=O).

Preparation of the oxime of 1,4,5-triphenyl-1,2,5-pentanetrione, compound V.

This compound was obtained by heating the triketone with an excess of hydroxylamine hydrochloride in a mixture of ethanol and pyridine under reflux for 2 hours. The solvents were removed by evaporation, and the residue was washed with cold water and filtered. The oxime product was recrystallized from aqueous ethanol to give fine colorless crystals, m.p. 232-233°C.

Anal. Calcd. for C_{23}H_{20}N_{2}O_{3}: C, 74.2; H, 5.41

Found: C, 74.5; H, 5.84

The infrared absorption spectrum (KBr pellet) showed a C=O maximum at 1680 cm.\(^{-1}\).
Preparation of compound VI.

To 50 ml. of cyclohexane in a Dean-Stark trap was added 3.82 g. (0.036 mole) of benzaldehyde and 6.13 g. (0.072 mole) of piperidine. The mixture was refluxed for 2 hours until no more water could be removed. The cyclohexane solvent was removed by vacuum distillation, and 50 ml. of absolute ethanol was added to the colorless solid, benzylidine-bis-piperidine.

To the resulting clear solution was added 5.0 g. (0.034 mole) of acetylbenzoyl. The mixture was transferred to a flask, stoppered, and allowed to stand at room temperature for 4 months. The precipitated product was removed by filtration and washed with a small quantity of cold absolute ethanol to yield 0.27 g. (3.4%) of small black plates, m.p. 203°C.

Anal. Calcd. for C₁₄H₁₇O₂N:  C, 72.7; H, 7.41; N, 6.06

Found:  C, 74.0; H, 7.23; N, 6.21

The infrared absorption spectrum (KBr pellet) showed a C=O maximum at 1620 cm⁻¹.
SUMMARY

Propiophenone was reacted with methyl nitrite and hydrogen chloride to form isonitrosopropiophenone. The isonitrosopropiophenone was steam distilled in dilute sulfuric acid to yield acetylbenzoyl, a 1,2-diketone.

Acetylbenzoyl failed to react with dimethylamine hydrochloride and benzaldehyde in ethanol under reflux conditions.

Acetylbenzoyl was condensed with dimethylamine hydrochloride and benzaldehyde in primary isoamyl alcohol under reflux conditions to form 1,4-diphenyl-3-butene-1,2-dione. The unsaturated diketone was reacted with o-phenylenediamine to produce a quinoxaline derivative. The unsaturated diketone was next heated with hydrogen peroxide which resulted in cleavage of the dicarbonyl group to form cinnamic acid.

Acetylbenzoyl was condensed with dimethylamine hydrochloride and benzaldehyde in glacial acetic acid under reflux conditions to form 1,4,5-triphenyl-1,2,5-pentane-trione. The triketone failed to form a quinoxaline derivative, but reacted with hydroxylamine hydrochloride to form an oxime derivative. The triketone product was also prepared from the same reactants by prolonged heating in primary isoamyl alcohol under reflux conditions.
Acetylbenzoyl was condensed with piperidine hydrochloride and paraformaldehyde in several solvents under reflux conditions, but yielded an amorphous tar which resisted all attempts at purification.

Benzylidene-bis-piperidine was prepared from benzaldehyde and piperidine. It was subsequently allowed to react with acetylbenzoyl in absolute ethanol to form a compound of undetermined structure. The product crystallized from solution after four months at room temperature.


23. Van de Kamp, Jacob and Erich Mosettig. Phenanthrene series. Part XI. Propanolamines of the type C_{14}H_{9}-CH(OH)CH_{2}CH_{2}NR_{2}. Journal of the American Chemical Society 58:1568-1570. 1936.