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THE REACTION OF ACETOPHENONE WITH FORMALDEHYDE AND METHYLAMINE HYDROCHLORIDE

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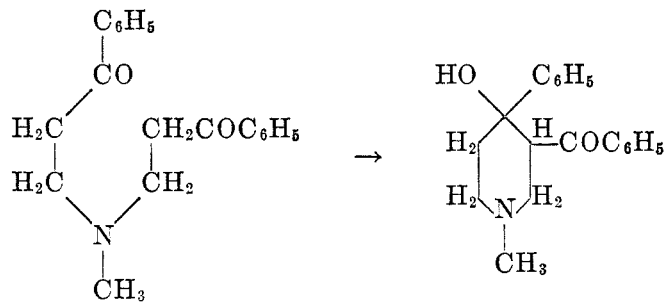
Mannich and Heilner (1) were the first to investigate the reaction of acetophenone, formaldehyde, and methylamine hydrochloride. They found that these reagents reacted readily in alcoholic solution, according to the following equations:

(A) $C_6H_5COCH_3 + CH_2O + CH_3NH_2 \cdot HCl \rightarrow C_6H_5COCH_2CH_2NHCH_3 \cdot HCl$ (I)

(B) $2C_6H_5COCH_3 + 2CH_2O + CH_3NH_2 \cdot HCl \rightarrow (C_6H_5COCH_2CH_2)_2NCH_3 \cdot HCl$ (II)

A yield of 31% of bis-(β-benzoylethyl)methylamine hydrochloride (II) and an undetermined amount of I were obtained when the reagents were mixed in the proportions shown in equation B. When the reagents were mixed in equimolar quantities in the sense of equation A, Blicke and Burckhalter (2) obtained a 34% yield of I and a 29% yield of II.

Warnat (3) repeated the work of Mannich and Heilner but reported an additional compound (III),[1] whose formation he explained as an isomerization of II, according to the following scheme.



Base II → III

Several years later Mannich and Hieronimus (5) confirmed the isolation of compound III without giving experimental details.

Apparently both Mannich and Warnat regard compound III as a component of the reaction mixture obtained after refluxing the alcoholic solution of the three reagents. It will be subsequently shown that this assumption is not very likely and that compound III is very probably formed at a later stage during the isolation procedure.

In their study of the reaction Blicke and Burckhalter report that when compound I is treated with alkali, a dissociation into phenyl vinyl ketone and methyl-

[1] A piperidine base of similar structure, 1,4-dimethyl-3-acetyl-4-hydroxypiperidine, had been isolated previously by Mannich and Ball (4) from the interaction of acetone, formaldehyde, and methylamine hydrochloride.

amine occurs, which recombine in a different ratio to give the base of compound II in the sense of the following equations

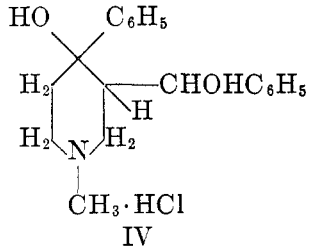
(C) $C_6H_5COCH_2CH_2NHCH_3 \rightarrow C_6H_5COCH{=}CH_2 + NH_2CH_3$

(D) $2C_6H_5COCH{=}CH_2 + NH_2CH_3 \rightarrow (C_6H_5COCH_2CH_2)_2NCH_3$
Base II

There is no doubt that this mechanism is correct for the most part. However, these authors actually isolated the piperidine base (III) instead of the base of compound II, as they reported. It will be observed that the melting point reported by Blicke and Burckhalter agrees with that reported by Warnat for the cyclic base (III).

In testing the mechanism depicted in equations (C) and (D), Blicke and Burckhalter allowed equimolar amounts of methylamine and phenyl vinyl ketone to react. They claimed that the base of compound II was formed by this process. Again the melting point given for their base agrees substantially with that of the piperidine base (III). There is no doubt in our minds that again they were dealing with the piperidine base (III).

Because we needed substantial amounts of the piperidine base (III), which hitherto has been regarded only as a by-product in the Mannich condensation, we turned our attention to the possibility that this base might be formed as a result of treatment of compound II with alkali. This was actually found to be the case. When compound II was stirred with aqueous alkali at room temperature, an oily base was first formed. On continued stirring the oil hardened and the resulting solid could be filtered off and crystallized from methanol. The crystals melted very approximately at the temperature reported by Warnat for the piperidine base (III). The yield was excellent. The melting point of the hydrochloride was essentially that reported by Warnat. Its solubility in water was of the order of fifty percent, whereas the hydrochloride of compound II was only slightly soluble. The presence of a hydroxyl group was established by the preparation of an acetate and a propionate. Hydrogenation of the hydrochloride of III gave a dihydroxy compound (IV), distinctly different from the dihydroxy compound (V) described by Külz and Rosenmund (6).



IV

$(C_6H_5CHOHCH_2CH_2)_2NCH_3 \cdot HCl$
V

The easy conversion of compound II into the piperidine base (III) in the presence of alkali necessitates a re-interpretation of the results of Blicke and Burckhalter. In the light of new knowledge the reactions proceed in the following manner. The monosubstituted methylamine derivative (I) yields the piperidine base (III) by treatment with alkali. Any compound II, which might be conceived as an intermediate, would not be stable under these conditions.

The reaction of phenyl vinyl ketone and methylamine under the conditions employed by Blicke and Burckhalter yields the piperidine base (III). The alkalinity produced by the use of excess methylamine (100% excess) is sufficient to cause an isomerization of any intermediate base (II) into the piperidine base (III).

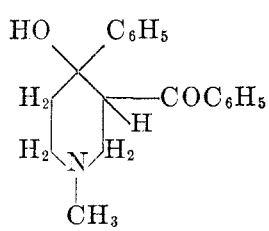
It can also be pointed out that Warnat, and also Mannich and Hieronimus, had obtained the piperidine base (III) as a secondary product because at some stage in working up their reaction mixtures they had used alkali. The use of alkali is not specifically mentioned by the above authors, but since they describe conversion of the hydrochlorides to the free bases, it is obvious they must have used alkali to liberate them.

In the course of our investigation we examined the behavior of the piperidine base (III) towards heat. When it was placed in a distillation flask, and subjected to an initial pressure of 0.2 mm., it was noticed that as distillation progressed, the pressure rose to 4 mm. When the distillation ceased, the pressure decreased to the initial value. This behavior is indicative of the loss of some very volatile material. Moreover, distillation occurred at 125–130°, a temperature considerably below that expected as the boiling point of the piperidine base (III). When hydrogen chloride was passed into an ether solution of the distillate, β-chloropropiophenone and bis-(β-benzoylethyl)methylamine hydrochloride (II) were obtained.

It can be concluded from the foregoing that distillation yielded phenyl vinyl ketone and methylamine. A considerable portion of the latter substance escaped through the oil-pump and was responsible for the increase in pressure, but some of it recombined with phenyl vinyl ketone in some part of the distillation apparatus to give the base of compound II.

There can be no doubt that we were dealing in this instance with the base of compound II and not the cyclic base. Treatment with hydrogen chloride gave the hydrochloride (II) directly. It was characterized by its analysis and by comparison of its properties with a known sample of bis-(β-benzoylethyl)methylamine hydrochloride (II). The melting points and the solubility in water were substantially the same. It was also possible to convert it into the piperidine base (III) by treatment with sodium hydroxide.

It can be argued that perhaps the piperidine base (III) might also, as a result of ring opening, form bis-(β-benzoylethyl)methylamine hydrochloride (II) on treatment with hydrogen chloride. To eliminate this possibility an authentic sample of the piperidine base (III) was treated with hydrogen chloride. A totally different hydrochloride was obtained. Thus the behavior of the piperidine base (III) on distillation can be represented by the scheme below:



III

$$\xrightarrow{\text{Distn.}} 2C_6H_5COCH{=}CH_2 + CH_3NH_2 \rightarrow (C_6H_5COCH_2CH_2)_2NCH_3$$

Base II

It is seen from the above discussion that 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine is not a primary product of the Mannich condensation. However, it becomes readily available when the primary products (I) and (II), particularly II, are treated with alkali.

In view of this fact, the Mannich condensation was studied further with the object of improving the yield of II. The reaction of methylamine hydrochloride, acetophenone, and paraformaldehyde could be carried out in various solvents other than alcohol. At first it was thought that some entraining agent, which removed water from the reaction continuously, would lead to improved yields. Thus benzene and alcohol, carbon tetrachloride, tetrachloroethane, and excess acetophenone were used as solvents with varying results. Mr. H. Weinhagen of our laboratory found subsequently, however, that even water can be used as a solvent for the reaction. Finally we succeeded in carrying out the condensation with no solvent at all. The reaction in this instance is extremely vigorous and is complete in 15–20 minutes with the formation of a solid cake. Because of the extreme vigor of the reaction large scale experiments are not recommended.

The investigations reported in this paper have led to an elucidation of the behavior of Mannich bases of the types $RCOCH_2CH_2NHR'$ and $(RCOCH_2CH_2)_2NR'$. The newly gained knowledge permits the preparation of certain 3,4-disubstituted piperidine derivatives in high yields.

Acknowledgment. We are indebted to Dr. A. Steyermark for microanalyses.

EXPERIMENTAL

PART I. THE CONDENSATION OF ACETOPHENONE WITH FORMALDEHYDE AND METHYLAMINE HYDROCHLORIDE

BIS-(β-BENZOYLETHYL)METHYLAMINE HYDROCHLORIDE (II)

(A) *In alcohol.* The reaction in alcohol has been adequately described by Mannich and Heilner (1), Warnat (3), and Blicke and Burckhalter (2).

(B) *In benzene–alcohol.* A mixture of 136 g. of methylamine hydrochloride, 130 g. of paraformaldehyde, 480 cc. of acetophenone, 240 cc. of ethanol, and 240 cc. of benzene was stirred and heated in a water-bath at 80–83°. A homogeneous solution resulted, the internal temperature rose to 3–7° above the bath temperature, and refluxing began. A trap in the path of the condensate separated the water in the distillate and permitted the return of the organic solvents. The bath temperature was raised finally to 90° and the material was refluxed for 6–8 hours until 80–100 cc. of the aqueous phase had separated. The mixture was cooled, and the crystals were filtered and washed with about 100 cc. of ethanol. The yield of bis-(β-benzoylethyl)methylamine hydrochloride (II), m.p. 150–155°, amounted to 63–68%. The yield can be improved by 15–20% by utilization of the mother liquor from the original reaction mixture as the solvent medium for the next batch of reagents. The crude product was satisfactory for our purposes, but it could be crystallized with an 85% recovery from 30 volumes of ethanol. The crystals thus obtained melted at 166–169°.

(C) *In tetrachloroethane.* Acetophenone (364 g.) was added to a suspension of 190 g. of paraformaldehyde, 208 g. of methylamine hydrochloride, and 700 cc. of tetrachloroethane. The mixture was heated. When the temperature reached 70°, an exothermic reaction took place. With the aid of a cold-water bath the temperature was maintained at 70–80° until all of the material had dissolved. In a vacuum of 50–70 mm., a mixture of tetrachlorethane and water was then slowly distilled off, while simultaneously an additional 362 g. of acetophenone was added to the reaction mixture. The distillate was collected in a separator

which permitted retention of the water and return of the tetrachlorethane. The mixture was maintained at 65–72° throughout the distillation, which was allowed to continue until 92 cc. of water was collected. The entire process required about one hour. Towards the end of the reaction the bis-(β-benzoylethyl)methylamine hydrochloride (II) began to precipitate. The mixture was cooled to room temperature, 900 cc. of acetone was added, and the whole was filtered in a centrifuge basket. The product, m.p. 156°, weighed 662 g. (66%). It was not pure but was satisfactory for the preparation of the piperidine base (III).

(D) *In carbon tetrachloride.* The reaction was carried out in essentially the same fashion. Only a very slight reduced pressure was applied to the system to permit a temperature of 70°. However, a reaction time of about 2.5 hours was required for complete removal of the water. The yield was 48%.

(E) *In excess acetophenone.* A mixture of 16.9 g. of methylamine hydrochloride and 242 cc. of acetophenone was stirred and heated to 80° and to it was added every four minutes 2 g. of paraformaldehyde until a total of 16 g. had been added. The thick suspension was cooled and filtered. The precipitate was digested with Skellysolve B, and then with hot alcohol. The yield of bis-(β-benzoylethyl)methylamine hydrochloride (II), m.p. 159°, amounted to 85%.

(F) *In water.* A mixture of 480 g. of acetophenone, 150 g. of methylamine hydrochloride, 306 cc. of 36% formalin, and 300 cc. of 10% hydrochloric acid was heated in a bath with stirring at 90° for 40–60 minutes until homogeneous solution resulted and then for an additional 15 minutes. The bath was removed and the mixture allowed to cool and crystallize with stirring during 15 hours. The crystals were filtered and washed with about 300 cc. of ice-cold ethanol. After drying at 40–50°, the bis-(β-benzoylethyl)methylamine hydrochloride (II) weighed 360–380 g. (54–57%) and melted at 162–163°. This preparation was first carried out by Mr. H. Weinhagen of this laboratory.

(G) *Without solvent.* A mixture of 120 g. of acetophenone, 32 g. of paraformaldehyde, and 34 g. of methylamine hydrochloride was placed in a 2-liter beaker and heated on a hot plate to about 80° with stirring. A vigorous reaction soon occurred and it was necessary to discontinue heating and stirring to avoid overflow. The solid mass of crystals thus obtained was ground in a mortar in the presence of 200 cc. of ethanol. On drying, the crystals weighed 116 g., (70%) and melted at 160–161°.

PART II. 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (III)

(A) *Base.* A suspension of 1440 g. of bis-(β-benzoylethyl)methylamine hydrochloride in 16 liters of water was stirred and treated with a solution of 320 g. of sodium hydroxide in 3200 cc. of water during 30 minutes at room temperature. After about an hour the oily base, which was first obtained, solidified and the solid was filtered and crystallized from 7 liters of methanol. After standing overnight 760 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, m.p. 135–136°, was obtained. The filtrate was diluted with an equal volume of water and the resulting precipitate was crystallized from 2600 cc. of acetone. An additional 272 g. of the piperidine derivative, m.p. 135–136° was thus obtained. By repetition of the dilution process 56 g. more of the piperidine derivative was obtained, m.p. 134–135°. The total yield thus amounted to 1088 g. (85%). Crystallization from methanol raised the melting point to 138–140° which is approximately that reported by Warnat (3).

(B) *Hydrochloride.* A solution of 2.0 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenlypiperidine in 175 cc. of ether was treated with gaseous hydrogen chloride. The hydrochloride weighed 1.6 g. and melted at 194–196°. The melting point depends somewhat on the rate of heating. The substance can be dissolved in water to form a 50% solution.

PART III. ACYL DERIVATIVES OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (III)

(A) *1-Methyl-3-benzoyl-4-acetoxy-4-phenylpiperidine oxalate.* A mixture of 75 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, 375 cc. of acetic anhydride, and 4 drops

of concentrated sulfuric acid was shaken occasionally during 24 hours. The crystals dissolved gradually. The solvent was removed under reduced pressure below 55°. To the cooled residue was added a solution of 60 g. of sodium carbonate monohydrate in 300 cc. of water and the mixture was stirred until effervescence had ceased. The gummy solid was taken up in 500 cc. of ether and the solution washed twice with 100-cc. portions of water. After drying with sodium sulfate the ether solution was treated with an ethereal solution of oxalic acid until no further precipitate was obtained (about 32 g. of oxalic acid). The precipitated *oxalate* was crystallized from 1100 cc. of alcohol to give 63 g. of the acetoxy derivative, m.p. 154–155°. An additional 6.8 g., m.p. 153–154° was obtained by reducing the filtrate to one-half of the original volume. The pure substance obtained by further crystallization from alcohol melted at 160–161°.

Anal. Calc'd for $C_{23}H_{25}NO_7$: C, 64.62; H, 5.90.
Found: C, 64.88; H, 5.90.

Alternatively the ether solution after drying with sodium sulfate can be distilled to dryness. Under these conditions the crude *acetoxy base*, m.p. 106–107° can be obtained. The base distilled in the presence of 2% powdered potassium carbonate at 200–203° at 0.7 mm.

(B) *1-Methyl-3-benzoyl-4-propionoxy-4-phenylpiperidine. 1. Oxalate.* A mixture of 26.2 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine, 12.5 cc. of propionyl chloride, and 500 cc. of toluene was allowed to stand overnight at room temperature. The precipitate (18.8 g.) was dissolved in 100 cc. of water, treated with 65 cc. of 0.972 *N* sodium hydroxide and allowed to stand in the ice-bath. The supernatant aqueous layer was decanted from the gummy precipitate which had settled to the bottom and along the sides of the container. The gummy precipitate was crystallized from 80 cc. of methanol to give 4.5 g. of unchanged starting material. The filtrate was distilled to dryness *in vacuo* and the residue was leached 4 times with 100 cc. of ether. About 1.1 g. of material remained undissolved. To the combined ether solutions, a solution of 7 g. of oxalic acid in ether was added. After standing in the refrigerator overnight, the supernatant ether was decanted from the insoluble precipitate, which was crystallized from 75 cc. of ethyl alcohol. In this manner 5.7 g. of the oxalate of 1-methyl-3-benzoyl-4-propionoxy-4-phenylpiperidine, m.p. 179–180° was obtained. Apparently the melting point depends on the rate of heating since the compound melted at 173–174° after two crystallizations.

Anal. Calc'd for $C_{22}H_{25}NO_3 \cdot C_2H_2O_4$: C, 65.29; H, 6.17; N, 3.17.
Found: C, 65.10; H, 6.35; N, 3.26.

2. Phosphate. A solution of 4 g. of the oxalate in 280 cc. of water was treated with 183 cc. of 0.1000 *N* sodium hydroxide and extracted twice with 200 cc. of ether. After adding 400 cc. of additional ether to the combined extracts, 16 cc. of 85% syrupy phosphoric acid was added with stirring. In this manner 4.45 g. of the *phosphate salt*, m.p. 178–179° was obtained.

Anal. Calc'd for $C_{22}H_{25}NO_3 \cdot 2H_3PO_4$: Neutral equivalent, 137.
Found: Neutral equivalent, 136.

PART IV. HYDROGENATION OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE HYDROCHLORIDE

1-Methyl-3-(α-hydroxybenzyl)-4-hydroxy-4-phenylpiperidine hydrochloride (IV). A mixture of 0.45 g. of platinum oxide catalyst, 115 cc. of ethanol, and 25 cc. of 1.18 *N* hydrochloric acid was shaken for a few minutes to reduce the catalyst. Then 8.7 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine was introduced, and hydrogenation was continued at room temperature for 24 hours. About 0.05 mole of hydrogen was absorbed. The mixture was filtered, and the insoluble precipitate was digested with 110 cc. of boiling water and filtered. From the filtrate 3.1 g. of 1-methyl-3-(α-hydroxybenzyl)-4-hydroxy-4-phenylpiperidine hydrochloride (IV), m.p. 267–268° (d), was obtained on cooling.

Anal. Calc'd for $C_{19}H_{23}NO_2 \cdot HCl$: C, 68.35; H, 7.24; N, 4.20.
Found: C, 68.07; H, 7.12; N, 4.20.

PART V. BEHAVIOR OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE TOWARDS DISTILLATION

When 25 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (III) was distilled under an initial pressure of 0.2 mm., it was noticed that as distillation progressed, the pressure rose to 4 mm. When the distillation ceased, the pressure returned to approximately the initial value. At 120–130°, 16.1 g. of distillate was collected. The residue weighed 6.5 g. A small sample of the distillate titrated electrometrically with 0.1 *N* hydrochloric acid gave a neutral equivalent of 620. The remainder of the distillate was stirred with 150 cc. of ether, and the mixture filtered from a small amount of insoluble material. Hydrogen chloride was passed through the filtrate. The precipitate of bis-(β-benzoylethyl)-methylamine hydrochloride weighed 8.6 g. and melted at 157–159°. Crystallization from alcohol gave the pure compound, m.p. 169–171°. Its solubility in water was 0.100 g. in 17 cc.

Anal. Calc'd for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.76; H, 6.68; N, 4.22;
Found: C, 68.55; H, 6.79; N, 4.66.

Treatment with sodium hydroxide gave a base which was crystallized from methanol to give crystals melting at 135–136° which is the m.p. of the piperidine base (III).

β-Chloropropiophenone. The ethereal filtrate after the precipitation of the hydrochloride was evaporated to dryness *in vacuo* to give 8.6 g. of β-chloropropiophenone, m.p. 48–49°. After crystallization from cyclohexane it melted at 50–53°. To identify the compound positively, 1.0 g. of the crystallized product was dissolved in 5 cc. of ethanol and then treated with 3 drops of acetic acid and 1.2 cc. of phenylhydrazine. After completion of the reaction, the precipitate was filtered and digested in 70 cc. of hot ethanol containing 0.5 cc. of 40% sodium hydroxide. The mixture was filtered hot and the filtrate allowed to crystallize. In this manner 0.81 g. of *1,3-diphenylpyrazoline* (7) m.p. 153–155° was obtained in the form of yellow crystals. A similar procedure was utilized by Blicke and Burckhalter (2) to identify phenyl vinyl ketone.

SUMMARY

Discrepancies in the literature, concerning the products of the condensation of acetophenone, methylamine hydrochloride, and formaldehyde have been clarified. A method is described for the preparation of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine.

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