# *Studies on the Mannich Reaction. I. On the Formation of Piperidine Derivatives (1)*

By Norito UCHINO

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The Mannich reaction of acetophenone with ammonium chloride and formaldehyde[1-3] gives hydrochlorides of mono-(β-benzoylethyl)-amine (I), bis-(β-benzoylethyl)-amine (II), tris-(β-benzoylethyl)-amine (III) and a small quantity of 4-hydroxy-4-phenyl-5-benzoyl-1-(β-benzoylethyl)-piperidine (IV). The last compound is an isomer of the normal product III·HCl. The melting points of the hydrochlorides are 125, 175, 145 and 199~200°C, respectively.

$$C_6H_5COCH_3 + HCHO + NH_4Cl \longrightarrow$$

$C_6H_5COCH_2CH_2NH_2\cdot HCl$ (I·HCl)

$(C_6H_5COCH_2CH_2)_2NH\cdot HCl$ (II·HCl)

$(C_6H_5COCH_2CH_2)_3N\cdot HCl$ (III·HCl)

(IV·HCl)

In general, this cyclic by-product, having a piperidine ring, is obtained by treating compound III·HCl with alkali[2]. It is not considered that compound III·HCl may be converted into the piperidine derivative IV·HCl in the acidic medium which is the usual condition of the Mannich reaction. Therefore, we can regard compounds I·HCl, II·HCl and III·HCl as the normal products in the Mannich reaction, but it is considered plausible that the piperidine derivative IV·HCl may be produced in some different reactions.

Compound II·HCl or III·HCl undergoes decomposition readily when it is heated in the presence of water to give phenyl vinyl ketone[2]. Therefore, at least a small portion of the products in this Mannich reaction will decompose to give phenyl vinyl ketone, because the reaction is carried out in an aqueous medium at 100°C.

$$(C_6H_5COCH_2CH_2)_3N\cdot HCl \xrightarrow{\text{in water}} (C_6H_5COCH_2CH_2)_2NH\cdot HCl + C_6H_5COCH:CH_2$$

(III·HCl) (II·HCl)

It is well known that phenyl vinyl ketone has a great reactivity to amines[4]. So, it is probable that the phenyl vinyl ketone produced may take part in this Mannich reaction.

The reaction of phenyl vinyl ketone with compound II·HCl was carried out, on trial, under the same conditions as those in the Mannich reaction to give a good yield of compound III·HCl and a small quantity of piperidine derivative IV·HCl. During the reaction, however, the temperature was kept at 40~45°C to avoid the polymerization of the phenyl vinyl ketone. This result shows that the above reaction gives the same products as those in the usual Mannich reaction. The same result was obtained, when aqueous alcohol was used instead of water as the medium. Phenyl vinyl ketone also reacted with compound I·HCl to give compound III·HCl and a small quantity of an unknown substance. In this case, piperidine derivative IV·HCl failed to be isolated.

In view of these facts, phenyl vinyl ketone may be thought to have some concern with the main reaction. But phenyl vinyl ketone failed to react with ammonium chloride under the same conditions. At a higher temperature, only the phenyl vinyl ketone polymerized. On the other hand, acetophenone and formaldehyde reacted with compound I·HCl, II·HCl or ammonium chloride to give compound III·HCl and a small quantity of compound IV·HCl.

These facts show that the Mannich reaction of acetophenone, formaldehyde and ammonium chloride proceeds step by step to give compounds III·HCl and IV·HCl, and that phenyl vinyl ketone has no concern with the main reaction. But it is thought the phenyl vinyl ketone may have some concern with the side reaction,

1) C. M. van Marle and B. Tollens, *Ber.*, **36**, 1351 (1903); H. Schäfer and B. Tollens, ibid., **39**, 2181 (1906).

2) C. Mannich and S. M. Abdullah, ibid., **68**, 113 (1935).

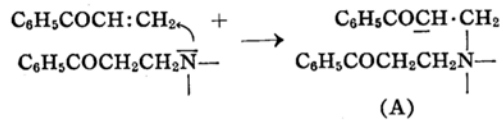
3) Cf. F. F. Blicke, "Organic Reactions", Vol. 1, John Wiley & Sons, Inc., New York (1942), p. 303; E. R. Alexander and E. J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949); S. V. Liebermann and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949); K. Bodendorf and G. Koralewski, *Arch. Pharm.*, **271**, 101 (1933).

4) E. P. Kohler, *Am. Chem. J.*, **42**, 375 (1909).

and that the benzoylethyl group of compound I·HCl or II·HCl plays an important role in the reaction with phenyl vinyl ketone.

In the reaction between phenyl vinyl ketone and compound II·HCl, IV·HCl was also obtained as in the Mannich reaction. But it was not probable that this IV·HCl was produced by intramolecular aldol-condensation of compound III·HCl, because compound III·HCl did not undergo isomerization, and gave no piperidine derivative IV·HCl, even when it was heated to 45°C in water. Compound III·HCl was recovered quantitatively after the treatment.

Since compound III·HCl or IV·HCl is stable and does not isomerize, it must be considered that neither of them is the secondary product but the primary one. Thus the mechanism of the reaction may be assumed as follows. The primary step of the reaction is the combination of the β-carbon atom of phenyl vinyl ketone with the nitrogen atom of compound II·HCl.




(A)

The intermediate A catches a proton to give compound III·HCl. When the intermediate A undergoes aldol-condensation intramolecularly, it gives compound IV·HCl. More detailed mechanism will be discussed in later papers.

## Experimental

**Reaction of Phenyl Vinyl Ketone with Bis-(β-benzoylethyl)-amine Hydrochloride (II·HCl).**—A mixture of 1.5 g. of compound II·HCl, 1.5 g. of phenyl vinyl ketone and 15 ml. of water was heated with vigorous stirring at 40~45°C for 1.5 hr. A greater part of compound II·HCl dissolved better in the phenyl vinyl ketone than in water, and a crystalline matter was produced as the reaction proceeded. After being cooled for one hour, the crystals were filtered off, washed with water, and dried; yield, 2.0 g.

The crystals were treated with 8 ml. of alcohol with gentle warming, and the soluble matter was extracted. The insoluble residue (about 0.2 g.) was recrystallized from alcohol, giving compound IV·HCl; m. p. and mixed m. p., 199~201°C[5].

*Anal.* Found: C, 71.44; H, 6.54; N, 3.07. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

The alcohol extract was evaporated under reduced pressure, and 1.0 g. of compound III·HCl was obtained; m. p. and mixed m. p., 143~144°C (after drying in vacuo at 78°C).

*Anal.* Found: C, 72.29; H, 6.20; N, 3.39. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

The same result was obtained when aqueous alcohol was used in place of water as the medium.

**Reaction of Phenyl Vinyl Ketone with Mono-(β-benzoylethyl)-amine Hydrochloride (I·HCl).**—A mixture of 2.1 g. of compound I·HCl, 1.5 g. of phenyl vinyl ketone, 5 ml. of water and 5 ml. of alcohol was heated with stirring at 40~45°C for two hours. The mixture was allowed to stand overnight. The crystals produced were filtered off, washed successively with benzene and alcohol-ether mixture, and dried at room temperature; yield, 1.5 g. The crystals were recrystallized from alcohol, giving compound III·HCl; m. p. and mixed m. p., 142~144°C (after drying in vacuo at 78°C).

*Anal.* Found: C, 71.84; H, 6.55; N, 3.10. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

The filtrate from compound III·HCl was slightly evaporated to give 0.2 g. of crystals. The crystals were recrystallized from acetone; m. p. 162~164°C. The crystals melted at 174~176°C after repeated recrystallizations. The melting point nearly coincided with that of compound II·HCl (175°C), but the melting point on admixture with an authentic sample depressed exceedingly showing the crystals not to be compound II·HCl. This is further supported by the great solubility of the crystals in alcohol, for the solubility of compound II·HCl is not so great. But it was impossible to make clear whether the crystals were an unknown compound or a mixture of some known compounds, because the yield was too small for the crystals to be identified.

The filtrate from the unknown substance was evaporated under reduced pressure until dry, and 0.5 g. of a residue was obtained. The residue was recrystallized from a mixture of alcohol and acetone; m. p., 121~122°C. The crystals were very soluble in water, and were considered as the starting material I·HCl (m. p., 122~123°C). The melting point on admixture with compound I·HCl did not depress.

**Reaction of Bis-(β-benzoylethyl)-amine Hydrochloride (II·HCl) with Acetophenone and Formaldehyde.**—A mixture of 3.0 g. of compound II·HCl, 1.2 g. of acetophenone and 1.4 g. of 30% formalin was heated on a steam bath with stirring for 1.5 hr. On cooling, 2.8 g. of crystals were produced. The crystals were filtered off, washed with a mixture of alcohol and ether, and recrystallized from a mixture of alcohol and ether, giving compound III·HCl; m.p. and mixed m. p., 145°C (after drying in vacuo at 78°C).

*Anal.* Found: C, 71.81; H, 6.18; N, 3.47. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

The residual mother liquor and washings were concentrated to a syrup under reduced pressure and allowed to stand for about two days to give 0.2 g. of crystals. The crystals were recrystallized from alcohol, giving compound IV·HCl;

5) The melting point of β-benzoylethylamine hydrochloride varies with heating speed because of its instability towards heat.

m. p. and mixed m. p. 199～200°C.

*Anal.* Found: C, 72.01; H, 6.44; N, 3.03. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

**Reaction of Mono-(β-benzoylethyl)-amine Hydrochloride (I·HCl) with Acetophenone and Formaldehyde.**—A mixture of 1.5 g. of compound I·HCl, 2.0 g. of acetophenone and 1.6 g. of 30% formalin was heated on a steam bath with stirring for 1.5 hr. After being cooled for a while, 1.2 g. of crystals were obtained. The crystals were recrystallized from alcohol, giving compound III·HCl; m. p. and mixed m. p., 145°C (after drying in vacuo at 78°C).

*Anal.* Found: C, 71.41; H, 6.33; N, 3.33. Calcd for $C_{27}H_{28}O_3NCl$: C, 72,06; H, 6.27; N, 3.11%.

The residual mother liquor was allowed to stand for a few days to give 0.1 g. of crystals. The crystals were recrystallized from alcohol, giving compound IV·HCl; m. p. and mixed m. p., 200～201°C.

*Anal.* Found: C, 70.71; H, 6.32; N, 2.81. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

**Reaction of Phenyl Vinyl Ketone with Ammonium Chloride.** — To 10 ml. of water were added 0.25 g. of ammonium chloride and 2.0 g. of phenyl vinyl ketone. The mixture was heated with stirring at 40～45°C for three hours, and was allowed to stand overnight at room temperature to give a resinous matter which was the polymerization product of the phenyl vinyl ketone. The aqueous layer was evaporated until dry under reduced pressure. The residue was confirmed as ammonium chloride by analysis.

Aqueous alcohol (5 : 5 v/v) was used in place of water as the solvent to give the same result. In the case of the higher temperature, the polymerization of phenyl vinyl ketone only was facilitated.

**Isomerization of Tris-(β-benzoylethyl)-amine Hydrochloride (III·HCl).** — To 7 ml. of water was added 0.5 g. of compound III·HCl, and the mixture was heated with stirring at 45°C for 1.5 hr. On cooling, a crystalline matter was filtered off; yield, 0.5 g. It was recrystallized from alcohol and dried at 78°C in vacuo, giving the starting material III·HCl; m. p., 142～143°C, mixed m. p. on admixture with an authentic sample (143～144°C), 143～144°C.

## Summary

1) In the reaction of acetophenone with formaldehyde and ammonium chloride, tris-(β-benzoylethyl)-amine hydrochloride (III·HCl) and 4-hydroxy-4-phenyl-5-benzoyl-1-(β-benzoylethyl)-piperidine hydrochloride (IV·HCl) were produced via bis-(β-benzoylethyl)-amine hydrochloride (II·HCl) after mono-(β-benzoylethyl)-amine hydrochloride (I·HCl).

2) Phenyl vinyl ketone readily reacted with compound I·HCl or II·HCl to give compounds III·HCl and IV·HCl.

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*Chemical Laboratory of Textile Fibres*
*Kyoto University of Industrial Arts*
*and Textile Fibres*
*Kita-ku, Kyoto*