Studies on the Mannich Reaction. II. On the Formation of Piperidine Derivatives (2)

By Norito UCHINO

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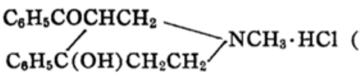
The Mannich reaction of acetophenone with methylamine hydrochloride and formaldehyde gives hydrochlorides of mono-(β-benzoylethyl)-methylamine (V) and bis-(β-benzoylethyl)-methylamine (VI)[1]. The melting points of the hydrochlorides are 139~141°C and 166~169°C, respectively. 4-Hydroxy-4-phenyl-5-benzoyl-1-methyl-piperidine (VII, m. p., 138~140°C) can be obtained by treating compound VI·HCl with alkali, for its isolation is difficult.

$$C_6H_5COCH_3+HCHO+CH_3NH_2\cdot HCl \rightarrow$$

$$C_6H_5COCH_2CH_2NH(CH_3)\cdot HCl \qquad (V\cdot HCl)$$

$$(C_6H_5COCH_2CH_2)_2NCH_3\cdot HCl \qquad (VI\cdot HCl)$$



(VII·HCl)

It has been shown that the reaction of phenyl vinyl ketone with compound V·HCl in aqueous alcohol gives a good yield of VI·HCl together with a small quantity of VII·HCl. When water only was used as the medium, the piperidine base failed to be isolated.

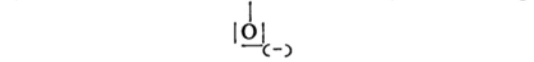
In the reaction of phenyl vinyl ketone with mono-(β-benzoylethyl)-amine hydrochloride (I·HCl), the formation of the isomer of bis-(β-benzoylethyl)-amine hydrochloride (II·HCl) was not certain[2]. But in this case, piperidine derivative VII·HCl could be obtained.

It is necessary to investigate whether or not both of the compounds VI·HCl and VII·HCl were formed at the same time, or whether one of them was formed first and then partly converted into the other. Of course, compound VI·HCl does not isomerize to give compound VII·HCl. Also compound VII·HCl was not converted into compound VI·HCl, under the same conditions as those in the reaction of phenyl vinyl ketone with compound V·HCl.

As the piperidine ring is stable under the above conditions, it is considered that both of the compounds VI·HCl and VII·HCl are primary products of the reaction. The initial step of the reaction may be the combination of the β-carbon atom of phenyl vinyl ketone with the nitrogen atom of compound V·HCl as it has been assumed in the preceding work[2].

If the β-carbon atom of phenyl vinyl ketone can react with the nitrogen atom of β-benzoylethylamine hydrochloride, it seems possible that ammonium chloride or methylamine hydrochloride can also react with phenyl vinyl ketone. Since this is not true, the benzoylethyl group of the amine is likely to play an important role in the reaction.

When a free base of ammonia or methylamine replaced the hydrochloride, it readily reacted with phenyl vinyl ketone to give 4-hydroxy-4-phenyl-5-benzoyl-1-(β-benzoylethyl)-piperidine (IV) or base VII, respectively. The mechanism of this reaction can be considered as follows. The resonance of phenyl vinyl ketone is shown as the following scheme:



$$C_6H_5COCH{:}CH_2 \leftrightarrow C_6H_5\underset{\underset{|\underline{O}|^{(-)}}{|}}{C}{:}CH\overset{(+)}{C}H_2 \leftrightarrow C_6H_5CO\overset{(-)}{C}H\overset{(+)}{C}H_2$$

This positive carbon atom of phenyl vinyl ketone will combine with ammonia or methylamine by attacking the lone pair of electrons of the nitrogen atom, and give tris-(β-benzoylethyl)-amine (III) or base VI, respectively. As a free base III or VI is very unstable, it isomerizes to give piperidine base IV or VII, respectively[1,3].

From the above, it is concluded that phenyl vinyl ketone can react with a nitrogen atom which has a lone pair of electrons. Here, it is also considered that compound I·HCl, II·HCl or V·HCl may react with phenyl vinyl ketone as the free base which is formed by hydrolysis. To show this, it is necessary for β-benzoylethylamines to be weaker bases than

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[1] C. Mannich and C. Heilner, *Ber.*, **55**, 356 (1922); F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942); J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949); cf. C. Mannich and G. Ball, *Arch. Pharm.*, **264**, 65 (1926).

[2] N. Uchino, This Bulletin, **32**, 1009 (1959).

[3] C. Mannich and S. M. Abdullah, *Ber.*, **68**, 113 (1935).

ammonia or methylamine, and to give sufficient free bases by hydrolysis of the salts. As the free base of β-benzoylethylamines are very unstable, the basicity of them can not be measured directly. Therefore, the dissociation constant was calculated from the hydrogen ion concentration of the aqueous solution of the salt. The hydrogen ion concentration was measured with 0.05 or 0.1 N solution at 20°C.

TABLE I. DEGREE OF HYDROLYSIS OF β-BENZOYLETHYLAMINE HYDROCHLORIDE

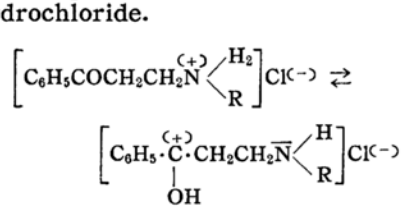
Salt	pH	Dissociation constant of base	Degree of hydrolysis (%)
I·HCl	4.8(0.05 N)	2×10^{-6}	3×10^{-2}
II·HCl	5.0(0.05 N)	5×10^{-6}	2×10^{-2}
V·HCl	5.1(0.1 N)	1×10^{-5}	8×10^{-3}
NH_4Cl		1.79×10^{-5}	
$CH_3NH_2\cdot HCl$		4.38×10^{-4}	

The result of the measurement shows that β-benzoylethylamines are weaker bases than ammonia or methylamine, but their differences are not so great as to elucidate the mechanism of the reaction.

β-Chloropropiophenone was able to react with ammonia to give base IV. As it is well known that phenyl vinyl ketone on being added to hydrogen chloride gives β-chloropropiophenone⁴⁾, it may be considered that β-chloropropiophenone is an intermediate product of the reaction. But this consideration is not correct, because it is difficult for ammonium chloride to hydrolyze to give enough hydrochloric acid. In fact, ammonium chloride did not react with phenyl vinyl ketone.

Already it was concluded that (i) the benzoylethyl group plays an important role in the reaction of phenyl vinyl ketone with compound I·HCl, II·HCl or V·HCl, and that (ii) phenyl vinyl ketone can react readily with a nitrogen atom which contains a lone pair of electrons.

Now, we will assume the following prototropy for β-benzoylethylamine hydrochloride.

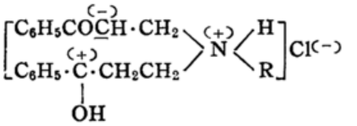


$$\left[C_6H_5COCH_2CH_2\overset{(+)}{N}\!<\!\begin{array}{l}H_2\\R\end{array}\right]Cl^{(-)} \rightleftarrows$$

$$\left[C_6H_5\cdot\underset{OH}{\overset{(+)}{C}}\cdot CH_2CH_2\overline{N}\!<\!\begin{array}{l}H\\R\end{array}\right]Cl^{(-)}$$

R = H, CH_3, $C_6H_5COCH_2CH_2$

Here, it is reasonably considered that the β-carbon atom of phenyl vinyl ketone can combine with the lone pair of electrons appearing as in the above equation and gives an intermediate B. The hydrogen



$$\left[\begin{array}{l}C_6H_5CO\overset{(-)}{C}H\cdot CH_2\\ C_6H_5\cdot\underset{OH}{\overset{(+)}{C}}\cdot CH_2CH_2\end{array}\!>\!\overset{(+)}{N}\!<\!\begin{array}{l}H\\R\end{array}\right]Cl^{(-)} \qquad (B)$$

atom of the hydroxyl group moves to the carbanion as a proton to give the normal product. When the intermediate B undergoes aldol-condensation, it gives the piperidine derivative.

In general, it can be considered that the phenyl vinyl ketone formed by decomposition of the products in the Mannich reaction is concerned with the formation of the piperidine bases which are found in that reaction.

Experimental

Reaction of Mono-(β-benzoylethyl)-methylamine Hydrochloride (V·HCl) with Phenyl Vinyl Ketone.—To a mixture of 5 ml. of water and 3 ml. of alcohol were added 0.5 g. of phenyl vinyl ketone and 0.5 g. of compound V·HCl. The mixture was next heated with stirring at 45~50°C for 2.5 hr. Then the mixture was evaporated until dry under reduced pressure, and washed with benzene to remove the polymerized phenyl vinyl ketone. The residue obtained (0.9 g.) was extracted with a small volume of water, and the insoluble matter (0.8 g.) was recrystallized from alcohol giving compound VI·HCl; m.p. and mixed m. p., 165~167°C.

Anal. Found: C, 68.70; H, 6.83; N, 4.16. Calcd. for $C_{19}H_{22}O_2NCl$: C, 68.76; H, 6.68; N, 4.22%.

The extract was evaporated under reduced pressure. The extraction and evaporation were repeated once more, and the solid matter obtained was recrystallized twice from alcohol giving 0.05 g. of compound VII · HCl; m. p. and mixed m. p., 196~198°C.

Anal. Found: C, 68.71; H, 6.79; N, 4.11. Calcd. for $C_{19}H_{22}O_2NCl$: C, 68.76; H, 6.68; N, 4.22%.

Isomerization of 4-Hydroxy-4-phenyl-5-benzoyl-1-methyl-piperidine Hydrochloride (VII · HCl).—In 5 ml. of water was dissolved 0.2 g. of compound VII·HCl, and the solution was heated to 40~45°C for 1.5 hr. If compound VI·HCl is formed by isomerization, some crystalline matter is expected to appear because of its small solubility. But no crystalline matter appeared. The same result was obtained not only when the temperature of the reaction was kept at 55~60°C, but also when three drops of concentrated hydrochloric acid or a small quantity of alkali was added to the solution, respectively. Removal of the solvent

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4) E. P. Kohler, *Am. Chem. J.*, **42**, 289 (1909).

under reduced pressure gave the starting material VII·HCl; m. p. and mixed m. p., 196～198°C.

Reaction of Phenyl Vinyl Ketone with Methylamine Hydrochloride.—Two grams of methylamine hydrochloride were dissolved in 3 ml. of water, and about 1 g. of phenyl vinyl ketone was added to the solution. The solution was heated with stirring at 50～55°C for five hours. Almost all the phenyl vinyl ketone polymerized. The aqueous solution was evaporated until dry under reduced pressure. The residue was confirmed to be only methylamine hydrochloride, and no β-benzoylethylamine hydrochloride was detected.

Reaction of Phenyl Vinyl Ketone with Ammonia.—A mixture of 1 g. of phenyl vinyl ketone, 0.5 ml. of aqueous ammonia (28%) and 10 ml. of water was heated with shaking at 40°C for two minutes. The greater part of the phenyl vinyl ketone polymerized to become viscous, and the liquid phase became turbid. After standing overnight at room temperature, the crystals produced were picked up with a pincette, and were washed with alcohol. As it was difficult to separate the crystals from the resinous matter, the yield was only 0.1 g. The crystals were recrystallized from alcohol, giving base IV; m. p. and mixed m. p., 147～148°C.

Anal. Found: C, 77.90; H, 6.52; N, 3.73. Calcd. for $C_{27}H_{27}O_3N$: C, 78.42; H, 6.58; N, 3.38%.

Reaction of Phenyl Vinyl Ketone with Methylamine.—A gas of excessive methylamine was passed into a solution of 4.5 g. of phenyl vinyl ketone in ether with ice cooling. Then the solution was evaporated to a syrup, which solidified after a while; yield, 4.7 g. The product was recrystallized from methanol giving 2.0 g. of base VII; m. p. and mixed. m. p., 139～140°C.

Anal. Found: C, 77.20; H, 7.25; N, 4.73. Calcd. for $C_{19}H_{21}O_2N$: C, 77.25; H, 7.16; N, 4.74%.

Reaction of β-Chloropropiophenone with Ammonia.—To a solution of 5 ml. of water and 5 ml. of alcohol were added 1 g. of β-chloropropiophenone and 1 ml. of aqueous ammonia (25%), and the mixture was heated with stirring at 40～45°C for an hour. One gram of a crystalline substance was formed. On cooling, the crystals were filtered off and recrystallized from alcohol giving base IV; m. p. and mixed m. p., 148～149°C.

Anal. Found: C, 78.48; H, 6.62; N, 3.63. Calcd. for $C_{27}H_{27}O_3N$: C, 78.42; H, 6.58; N, 3.38%.

β-Chloropropiophenone could react with ammonia, but not with ammonium chloride.

Summary

1) The mechanism of the reaction of phenyl vinyl ketone with β-benzoylethylamine hydrochloride was discussed.

It was concluded that the β-carbon atom of phenyl vinyl ketone combined with β-benzoylethylamine hydrochloride on attacking the lone pair of electrons which appeared in consequence of prototropy, and gave the same products as those in the Mannich reaction.

2) In the Mannich reaction, piperidine bases are found to be produced.

It was concluded that the phenyl vinyl ketone, which was produced by decomposition of the products in the Mannich reaction, was concerned with the formation of these piperidine bases.

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