Studies on the Mannich Reaction. III. On the Formation of Piperidine Derivatives (3)

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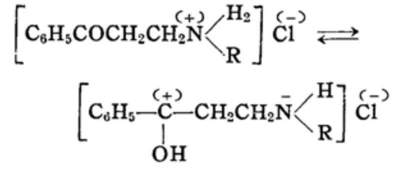
In the previous papers of this series[1], tautomerism of the Mannich compound involving prototropy was proposed as indicated below.



$$\left[C_6H_5COCH_2CH_2\overset{(+)}{N}\begin{smallmatrix}H_2\\R\end{smallmatrix}\right]\overset{(-)}{Cl} \rightleftarrows$$

$$\left[C_6H_5-\underset{OH}{\overset{(+)}{C}}-CH_2CH_2\overset{-}{N}\begin{smallmatrix}H\\R\end{smallmatrix}\right]\overset{(-)}{Cl}$$

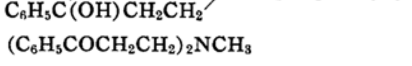
$R=H,\ CH_3,\ C_6H_5COCH_2CH_2$

The present experiment shows a fact which seems to support the above scheme.

The β-benzoylethylamines[2-4] used are: bis-(β-benzoylethyl)-amine(II), tris-(β-benzoylethyl)-amine(III), 4-oxy-4-phenyl-5-benzoyl-1-(β-benzoylethyl)-piperidine(IV), bis-(β-benzoylethyl)-methylamine(VI) and 4-oxy-4-phenyl-5-benzoyl-1-methyl-piperidine(VII).

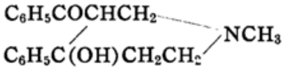
$(C_6H_5COCH_2CH_2)_2NH$ (II)

$(C_6H_5COCH_2CH_2)_3N$ (III)



(IV)

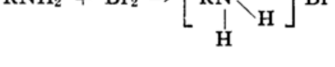
$(C_6H_5COCH_2CH_2)_2NCH_3$ (VI)



(VII)

When bromine water was added to an aqueous solution of hydrochloride of the above Mannich base, yellow precipitates were produced almost quantitatively. The precipitates thus obtained had an irritative odor, probably that of bromine originated from the compounds. The bromine as molecule was also partly removed by washing with water.

In general, bromine may add to a free amine as the following scheme:



$$RNH_2 + Br_2 \rightarrow \left[\underset{H}{\overset{(+)}{RN}}\begin{smallmatrix}Br\\H\end{smallmatrix}\right]\overset{(-)}{Br}$$

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

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

[3] J. T. Plati and W. Wenner, *J. Org. Chem.*, **14**, 543 (1949).

[4] C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922); F. F. Blicke and J. H. Burckhalter, *J. Am. Chem. Soc.*, **64**, 451 (1942).

In the present study, such an addition of bromine seems impossible, because the amine is treated as a hydrochloride. Substitution in a benzene nucleus or addition to a double bond which is formed by enolization of a carbonyl group is not probable, considering the ease of evolution of bromine from the addition products and negative ferric chloride test regarding II·HCl or III·HCl.

The bromine compound from the hydrochloride of the Mannich base could be recrystallized from alcohol if the recrystallization was carried out within a little while, bright yellow crystals being obtained which were of an indistinct melting point. When the crystals were heated to a higher temperature, they decomposed and melted to a dark-brown liquid. The recrystallized addition compound still had a smell of bromine, and reduced potassium iodide.

The acid value, the halogen content and the oxidizing power of the recrystallized bromine addition product of II·HCl are summarized in Table I.

TABLE I. ANALYTICAL RESULTS OF BROMINE ADDITION PRODUCT OF II·HCl

	Found ml./g.	Calcd. ml./g.
Acid value (N/10-NaOH)	50.7	21.0[c)]
Oxidizing power[a)] (N/10-$Na_2S_2O_3$)	24.1	42.0[d)]
Halogen content[b)] (N/10-$AgNO_3$)	52.6	63.0[d)]

a) The bromine addition product was dissolved in alcohol, and potassium iodide was added to the solution. Iodine produced was titrated with sodium thiosulfate solution.

b) Bacon's method was used.

c) Theoretical value of N/10-NaOH consumed for hydrochloric acid which is present as hydrochloride of the addition compound of one mole of bromine with one mole of II·HCl.

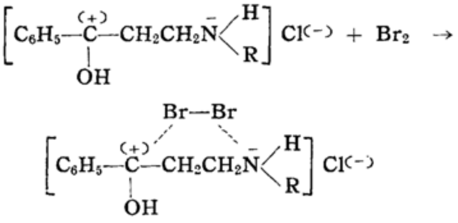
d) Theoretical value for the addition compound of one mole of bromine with one mole of II·HCl.

From the above results, it is considered that at least one mole of bromine is added to one mole of the hydrochloride.

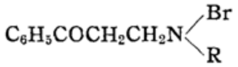
The yellow color of the product from II·HCl or III·HCl disappeared on refluxing the alcoholic solution. On cooling, compound II·HCl was recovered from the solution. When the addition product of II·HCl or III·HCl was treated with alcoholic alkali, base IV was obtained[5)]. To obtain the free base of the bromine compound by the alkali treatment, a suspension in water of the additional product of II·HCl or III·HCl was rapidly treated with alkali and the assumed free base produced was immediately extracted with ether. However, the colorless crystals formed proved to be the hydrobromide of II (II·HBr).

The compound II·HCl or III·HCl, however, gave no crystals on the brief treatment with alkali; the ether solution was evaporated to give base IV[5)].

On the brief treatment of the bromine addition compound with alkali, a free base containing bromine thus dissolves in ether, and the bromine is partially removed from the original addition product, because the yellow color disappears. Thus the mechanism of the addition of bromine is considered as the following scheme:



The bromine links, in the form of linking astride, on the carbonium ion and on the lone pair of electrons of the nitrogen atom, both of which are formed by the prototropy. When the product is treated with alkali for a little while, the hydrogen chloride and the hydrogen bromide are removed. The free base thus produced may be *N*-bromo-β-benzoylethylamine.



$$C_6H_5COCH_2CH_2N{<}^{Br}_{R}$$

The compound of *N*-halogenamine type seems to have an oxidizing power. In the present case, the unstable *N*-bromo-bis-(β-benzoylethyl)-amine oxidizes contaminants in the solvent (ether), changing into base II. Base II combines with hydrobromic acid produced, and separates as a hydrobromide.

In order to isolate the unstable *N*-bromoamine, extraction with ether, benzene or carbontetrachloride was attempted without success; the only product obtained was the reduced one II·HBr.

Bromine likewise adds to the free Mannich base. For example, the yellow precipitates readily formed on addition of excessive bromine to an ether solution of base II or III. This product on brief treatment with alkali also yielded the colorless compound II·HBr.

It is known that an amine yields an *N*-bromoamine on treatment with sodium

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[5)] Even if base II or III is produced by the alkali treatment, it changes into base IV; cf. Ref. 2.

hypobromite⁶⁾. Here, compound II·HCl was treated with sodium hypobromite to give II·HBr. This fact also shows the existence of the unstable *N*-bromo-β-benzoylethylamine.

The bromine addition product of III·HCl also gives II·HBr on brief treatment with alkali, probably because of the unstability of the *N*-bromoamine derivative.

Experimental

Addition of Bromine to the Salt of the Mannich Base.—One gram of compound II·HCl or III·HCl was dissolved in 200~300 ml. of water. To the solution was added 500 ml. of bromine water. The yellow precipitates were filtered and dried in vacuo at room temperature in the presence of phosphorous pentoxide; 1.3 g. of bromine addition product of II·HCl or 1.2 g. of that of III·HCl was obtained.

Recrystallization of the Bromine Addition Product.—The bromine addition product, which was obtained from 2.0 g. of II·HCl, was recrystallized from alcohol within a little while to give yellow crystals; yield, 1.5 g. The crystals were analyzed after vacuum-drying at room temperature in the presence of phosphorous pentoxide (Table I).

Decomposition of the Bromine Addition Product by Alcohol.—In boiling alcohol was dissolved 1.5 g. of bromine addition product of II·HCl, and the solution was refluxed for thirty minutes. After being cooled, 1.2 g. of colorless crystals were obtained, which were recrystallized from alcohol acidified with hydrochloric acid to give II·HCl; m. p. and mixed m. p. 173°C.

Anal. Found: C, 67.80; H, 6.52; N, 4.47. Calcd. for $C_{18}H_{20}O_2NCl$: C, 68.02; H, 6.34; N, 4.40%.

The bromine addition product obtained from 1.0 g. of III·HCl was also treated with alcohol giving 0.5 g. of II·HCl; m. p. and mixed m. p. 171~173°C.

Treatment of the Bromine Addition Product with Alcoholic Alkali.—The bromine addition product obtained from 1.0 g. of II·HCl was dissolved in hot alcoholic sodium hydroxide, and the solution was poured into a great volume of water. The aqueous solution which became turbid was allowed to stand for one day. The turbid matter coagulated to a resinous matter. The product was dissolved in hot alcohol, and the free base was converted into hydrochloride by adding hydrochloric acid. After being cooled, the hydrochloride was separated by adding a little ether, filtered, and washed with ether. Yield, 0.1 g. The hydrochloride was recrystallized twice from alcohol giving compound IV·HCl; m. p. and mixed m. p. 196~198°C.

Anal. Found: C, 71.79; H, 6.05; N, 3.18. Calcd. for $C_{27}H_{28}O_3NCl$: C, 72.06; H, 6.27; N, 3.11%.

The bromine addition product obtained from 1.0 g. of III·HCl was also treated with alcoholic alkali to give 0.2 g. of IV·HCl; m. p. and mixed m. p. 197~199°C. The residual alcohol solution was evaporated giving only a dark-brown resinous matter.

Short Treatment of the Bromine Addition Product with Alkali. — The bromine addition product obtained from 2.0 g. of III·HCl was suspended in 100 ml. of water, and an excess of dilute solution of sodium hydroxide was added. The colorless matter produced was quickly extracted with 400 ml. of ether. The organic layer was kept at room temperature; colorless crystals began to separate from the solution. After one day, the crystals were filtered and washed with ether; yield, 0.8 g.; m. p. 166~167°C (from alcohol). The crystals showed a remarkable flame reaction of halogen, and gave precipitates of silver bromide with silver nitrate.

Anal. Found: C, 60.30; H, 5.86; N, 3.88. Calcd. for $C_{18}H_{20}O_2NBr$(II·HBr): C, 59.67; H, 5.56; N, 3.86%.

The crystals were converted into hydrochloride by repeated recrystallization from alcoholic hydrogen chloride to give II·HCl; m. p. and mixed m. p. 172~173°C. From these results, the crystals separated from the ether solution were confirmed to be II·HBr.

The residual ether solution was evaporated only to give a dark-brown resinous matter which could not be distilled at the usual reduced pressure. The resinous matter decomposed at a higher temperature.

The bromine addition product obtained from 2.0 g. of II·HCl gave 1.5 g. of II·HBr in the same way as above; m. p. 166~167°C.

Anal. Found: C, 60.80; H, 5.72; N, 3.89. Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.67; H, 5.56; N, 3.86%.

In the above reaction, ether, benzene or carbontetrachloride was used as an extracting solvent. All these solvents were sufficiently purified just before use. In this case, compound II·HBr was also separated from the solvent, and the yields were 0.8, 0.2 and 0.3 g., respectively.

Reaction of the Salt of the Mannich Base with Alkali.—To 200 ml. of water was added 2.0 g. III·HCl, and an excess of solution of sodium hydroxide. The free base produced was extracted with ether. No crystals separated even when the ether solution was allowed to stand. When the ether solution was evaporated, an oily matter was obtained which solidified after a while. Recrystallization from alcohol gave 1.5 g. of base IV; m. p. and mixed m. p. 149~150°C.

Anal. Found: C, 78.63; H, 6.75; N, 3.65. Calcd. for $C_{27}H_{27}O_3N$: C, 78.42; H, 6.58; N, 3.38%.

Two grams of II·HCl gave 1.1 g. of base IV in the same way as above; m. p. and mixed m. p. 149~150°C.

The Bromine Addition Product of the Free Mannich Base.—To an ether solution of free base III, which was obtained by treating 3.0 g. of III·HCl with a dilute solution of sodium hydroxide for a little while, was added 1.1 g. of bromine.

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6) Cf. R. Willstätter and V. Hottenroth, *Ber.*, **37**, 1783 (1904); F. Rashig, *Ann.*, **230**, 223 (1885).

Yellow precipitates produced were filtered, washed, and dried to give 3.5 g. of yellow powder which emitted an irritating odor of bromine. The bromine content of the precipitates was 26.0% [Theoretical $(C_6H_5COCH_2CH_2)_3NBr_2$, 27.9%]. One gram of this addition product was suspended in ether, and an excess of dilute solution of sodium hydroxide was added with shaking. The bromine addition product turned colorless, and dissolved in ether. The ethereal portion was allowed to stand to give 0.2 g. of II·HBr; m. p. 168~169°C (from alcohol).

Anal. Found: C, 59.43; H, 5.63; N, 3.59. Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.67; H, 5.56; N, 3.86%.

The residual ether solution was evaporated to give 0.7 g. of base IV; m. p. and mixed m. p. 149~150°C (from alcohol).

A bromine addition product of base II was produced by the same process as the above one. The bromine content was 44.1% [Theoretical $(C_6H_5COCH_2CH_2)_2NH\cdot Br_2$, 36.2%]. From 0.2 g. of this addition product was obtained 0.1 g. of II·HBr; m. p. 169~170°C (from alcohol).

Anal. Found: C, 59.84; H, 5.68; N, 4.08. Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.67; H, 5.56; N, 3.86%.

In the case of bromine addition product of base VI, the results were somewhat different from those of the above reaction. The bromine addition product of base VI, which was obtained from 5.0 g. of VI·HCl, was suspended in ether, and an excess of dilute solution of sodium hydroxide was added to the suspension with shaking. The addition product turned somewhat pale-yellow, but it was hardly soluble in ether. The pale-yellow matter was filtered and dried; yield, 3.5 g. Its bromine content was 27.5%, which is lower than the theoretical value of $(C_6H_5COCH_2CH_2)_2\cdot NCH_3\cdot Br_2$ (35.1%), and higher than that of VI·HBr (21.2%). Two grams of the above matter was dissolved in 50 ml. of alcohol and refluxed for one hour to give 1.4 g. of VI·HBr; m. p. 188~189°C (from alcohol). The mother liquor was slightly condensed to give an additional amount (0.2 g.) of VI·HBr.

Anal. Found: C, 60.65; H, 6.03; N, 3.79. Calcd. for $C_{19}H_{22}O_2NBr$: C, 60.64; H, 5.89; N, 3.72%.

The above crystals were converted into VI·HCl by repeated recrystallization from alcoholic hydrogen chloride; m. p. and mixed m. p. 169~170°C.

The ether layer, which was separated from the bromine addition product, was kept at room temperature to give the same product VI·HBr; m. p. 188~189°C; yield, 0.1 g.

Anal. Found: C, 60.36; H, 6.14; N, 3.89. Calcd. for $C_{19}H_{22}O_2NBr$: C, 60.64; H, 5.89; N, 3.72%.

Reaction of Bis-(β-benzoylethyl)-amine Hydrochloride (II·HCl) with Sodium Hypobromite.—One gram of II·HCl was added to 100 ml. of water. To this solution was added a solution of sodium hypobromite which was prepared by adding excessive sodium hydroxide to bromine water. The free base produced was extracted with ether. The ether solution was left to stand to produce crystals; yield, 1.0 g. The crystals were recrystallized from alcohol giving II·HBr; m. p. 170°C.

Anal. Found: C, 59.96; H, 5.65; N, 3.76. Calcd. for $C_{18}H_{20}O_2NBr$: C, 59.67; H, 5.56; N, 3.86%.

Summary

i) The addition of bromine to β-benzoylethylamine hydrochloride was studied. It was concluded that bromine molecule was added to β-benzoylethylamine hydrochloride in the form linking astride to the carbionium ion and the lone pair of electrons of the nitrogen atom, both of which were formed by prototropy.

ii) The bromine addition product of β-benzoylethylamine hydrochloride was treated with alkali for a little while to give *N*-bromo-β-benzoylethylamine which was very unstable and decomposed to give β-benzoylethylamine hydrobromide.

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