[CONTRIBUTION #180 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

1,3,4-TRISUBSTITUTED PIPERIDINE DERIVATIVES FROM MANNICH BASES

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Received April 29, 1949

In a previous communication (1) the Mannich reaction involving acetophenone, methylamine hydrochloride, and formaldehyde was discussed. From the reaction mixture β-benzoylethylmethylamine (IV) and bis-(β-benzoylethyl)-methylamine (VIII) could be isolated directly as hydrochlorides. It was shown that when either of these compounds was treated with alkali, a third cyclic compound (XV) could be obtained in excellent yield (1, 2).

In the course of our work it appeared desirable to prepare substantial quantities of other cyclic ketones of the general formula III. With this goal in mind the Mannich reaction was varied, first, by replacing methylamine with other primary amines and secondly, by replacing acetophenone with some of its phenyl-substituted derivatives. Table I lists the compounds prepared.

The condensation was brought about with alcohol as a solvent and in certain cases without a solvent. When no solvent was used, the reaction became extremely vigorous and was complete in a few minutes. Large scale runs might very well lead to uncontrollable reactions, and for this reason they are not recommended.

In the original reaction, when two moles of acetophenone, two moles of formaldehyde, and one mole of methylamine hydrochloride was used, the main product was the bis compound VIII. The monoketoneamine IV was obtained in much smaller amounts with difficulty. However, in two cases the situation was reversed. Despite the fact that two moles of acetophenone and two moles of formaldehyde were allowed to react with isopropylamine hydrochloride only the monoketoneamine V was isolated. It was obtained in a yield of 43% whereas the diketoneamine was not isolated at all. When this same ratio was used with benzylamine hydrochloride the monoketoneamine VI was obtained in about 50% yield.

Although the conversion of the hydrochloride of bis-(β-benzoylethyl)methylamine (VIII) into the piperidine base (XV) was proved earlier (1) beyond doubt, it was necessary to demonstrate that alkali would cause the same conversion of other diketoneamines of type II into piperidine derivatives. This isomerization was established in four other cases by the fact that in each case the melting point of the original diketoneamine hydrochloride is different from the melting point of the hydrochloride of the piperidine base, obtained by treatment with alkali. The isomeric pairs are listed horizontally in Table II along with their melting points.

When the hydrochlorides of type II are stirred with alkali, the bases thus precipitated are at first oily or gummy but they slowly solidify on prolonged

stirring. The minimum time required for maximum solidification varies with the compound and depends to a great degree on the efficiency of stirring.

The conversion of monoketoneamines of type I into III by means of alkali has already been discussed (1, 2) in the case of the N-methyl derivative (IV). The

TABLE I

LIST OF COMPOUNDS

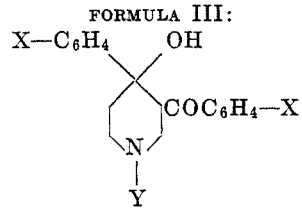
	DERIVATIVE	X	Y
FORMULA I: $X\text{-}C_6H_4COCH_2CH_2NH\text{-}Y$	IV	H	CH_3
	V	H	$CH(CH_3)_2$
	VI	H	$CH_2C_6H_5$
	VII	H	$n\text{-}C_4H_9$
FORMULA II: $(X\text{-}C_6H_4COCH_2CH_2)_2N\text{-}Y$	VIII	H	CH_3
	IX	$m\text{-}OCH_3$	CH_3
	X	$p\text{-}OCH_3$	CH_3
	XI	H	$n\text{-}C_4H_9$
	XII	p-Cl	CH_3
	XIII	$p\text{-}CH_3$	CH_3
	XIV	H	C_2H_5
FORMULA III: 	XV	H	CH_3
	XVI	H	$CH(CH_3)_2$
	XVII	H	$CH_2C_6H_5$
	XVIII	H	$n\text{-}C_4H_9$
	XIX	$m\text{-}OCH_3$	CH_3
	XX	p-Cl	CH_3
	XXI	$p\text{-}CH_3$	CH_3
	XXII	H	C_2H_5

TABLE II

MELTING POINTS OF HYDROCHLORIDES OF DIKETONEAMINES (II) AND PIPERIDINE DERIVATIVES (III)

DIKETONEAMINES		PIPERIDINE DERIVATIVES	
Hydrochloride of	M.P., °C	Hydrochloride of	M.P., °C
XI	77–80[a]	XVIII	182–184
XII	160–162	XX	192–193
XIII	159–160	XXI	195–197
XIV	138–139	XXII	206–208

[a] Contains solvent of crystallization.

reaction was now found to be quite general. Thus the N-isopropyl (V), the N-butyl (VII), and the N-benzyl (VI) derivatives undergo this reaction in the same way as the N-methyl derivative (IV). There is no doubt that the reaction involves decomposition into phenyl vinyl ketone and the primary amine, which recombine in a different ratio to give a base of type II, as first pointed out by Blicke and Burckhalter (2). The latter product then undergoes isomerization into III.

In the reaction of *m*-methoxyacetophenone with methylamine hydrochloride and formaldehyde in alcohol, it was not possible to isolate a product directly. Instead the alcohol was removed and the neutral organic matter was extracted with ether. Treatment of the residue with alkali liberated the organic bases which were quickly extracted with ether and converted into the oxalate. It is not likely that this short treatment with alkali was sufficient to convert the bis compound (IX) into the piperidine derivative XIX, so that we can presume that we are dealing with the oxalate of IX. Conversion of the oxalate into the piperidine base XIX was effected by prolonged treatment with alkali.

The situation was somewhat different with *p*-methoxyacetophenone. Here again it was not possible to isolate any product directly from the Mannich condensation. The base was converted into an oxalate and into a sulfate, which presumably are salts of X, since only a very short contact with alkali was allowed. However, in this case prolonged treatment with alkali did not result in the formation of a solid base in contrast to the behavior of the other ketoneamines reported in this paper.

Acknowledgment. We are indebted to Dr. A. Steyermark for microanalyses and to Mr. P. Bevilacqua for technical assistance.

EXPERIMENTAL

PART I. MONOKETONEAMINES—$XC_6H_4COCH_2CH_2NHY$

A. *β-Benzoylethylisopropylamine* (*V*). A mixture of 120 g. of acetophenone, 48 g. of iso propylamine hydrochloride, and 32 g. of paraformaldehyde was heated to 80° in a 2-liter beaker. After the initial vigorous reaction (1), 200 cc. of ethyl acetate was added and the mixture allowed to crystallize. A yield of 49 g. (43%) of the crude hydrochloride was obtained. Crystallization from ethanol gave the product melting at 174–176°.

Anal. Calc'd for $C_{12}H_{17}NO \cdot HCl$: C, 63.28; H, 7.97.
Found: C, 63.38; H, 7.86.

B. *β-Benzoylethylbenzylamine* (*VI*). The hydrochloride was prepared in 55% yield by Mannich and Hieronimus (3), who used equimolar amounts of reagents. The preparation was essentially repeated by us except that approximately two moles of acetophenone and two moles of formaldehyde were used with one mole of benzylamine hydrochloride. The monoketoneamine compound was obtained in approximately the same yield as that reported by Mannich and Hieronimus. Part of the product was converted into the *oxalate* which after crystallization from ethanol melted at 194–195°.

Anal. Calc'd for $C_{16}H_{17}NO \cdot C_2H_2O_4$: C, 65.64; H, 5.81; N, 4.25.
Found: C, 65.67; H, 5.39; N, 4.33.

C. *β-Benzoylethyl-n-butylamine* (*VII*). A mixture of 111 g. of acetophenone, 28 g. of paraformaldehyde, 50 g. of butylamine hydrochloride, and 250 cc. ethanol was refluxed with stirring for approximately two hours. The solvent was removed *in vacuo* below 60°, and the residue was stirred with 500 cc. of ether. The precipitated solid was filtered, and the filtrate was treated with more water and ether until after shaking two distinct phases were present. The ether phase was extracted several times with normal hydrochloric acid until the acid extract no longer gave a precipitate with sodium hydroxide. The combined aqueous phase and acidic extracts were made alkaline and the organic base extracted with ether. Addition of an ethereal solution of oxalic acid gave a crude compound which yielded 21 g. of the pure *oxalate* of β-benzoylethyl-*n*-butylamine, m.p. 177–179°, after crystallization from ethanol.

Anal. Calc'd for $C_{13}H_{19}NO \cdot C_2H_2O_4$: C, 61.00; H, 7.17; N, 4.74.
Found: C, 60.79; H, 6.99; N, 4.83.

PART II. DIKETONEAMINES—$(XC_6H_4COCH_2CH_2)_2NY$

A. *Bis-(β-benzoylethyl)-n-butylamine* (*XI*). A mixture of 55 g. of *n*-butylamine hydrochloride, 120 g. of acetophenone, and 30 g. of paraformaldehyde was treated as in Part I A. After the reaction the crude mixture was stirred for 1.5 hours with 700 cc. of water. The white precipitate was filtered and crystallized from ethyl acetate. The yield of crystalline hydrochloride, m.p. 77–80°, amounted to 42%. It contained solvent of crystallization.

Anal. Calc'd for $C_{22}H_{27}NO_2 \cdot HCl \cdot 1/2\ H_2O$: C, 69.00; H, 7.63.

Found: C, 68.85; H, 7.73.

B. *Bis-(β-m-methoxybenzoylethyl)methylamine* (*IX*). A mixture of 75 g. of *m*-methoxyacetophenone, 17 g. of methylamine hydrochloride, 15 g. of paraformaldehyde, and 80 cc. of ethanol was refluxed for two hours after which an additional 15 g. of paraformaldehyde was added. After 4.5 hours of refluxing the solvent was removed *in vacuo* and the residue was shaken with water and ether. The aqueous layer was separated, made alkaline, and the bases were extracted with ether. Addition of oxalic acid in ether gave the crude oxalate. After digestion with hot acetone and a hot filtration, it weighed 52 g. Crystallization from water gave the purified *oxalate*, m.p. 117–119° with sintering at 111°.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot C_2H_2O_4$: Neut. equiv., 223. Found: Neut. equiv., 224.

C. *Bis-(β-p-methoxybenzoylethyl)methylamine* (*X*). By essentially the same method as in Part II B starting with *p*-methoxyacetophenone, a yield of 19% of the *oxalate*, m.p. 154–157° was obtained after a previous digestion with hot ethanol.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot C_2H_2O_4$: Neut. equiv., 223. Found: Neut. equiv., 229.

When the base prepared from the oxalate was treated in ether with sulfuric acid, a *sulfate* was obtained. Crystallization from acetone yielded a product melting at 92–96°. Crystallization from water gave a product melting at 99–104° containing one molecule of water of crystallization.

Anal. Calc'd for $C_{21}H_{25}NO_4 \cdot H_2SO_4 \cdot H_2O$: C, 53.48; H, 6.20.

Found: C, 53.46; H, 6.07.

D. *Bis-(β-p-chlorobenzoylethyl)methylamine* (*XII*). The preparation of this compound was carried out by the procedure described in Part I A, using *p*-chloroacetophenone instead of acetophenone. The crystalline cake was stirred with acetone to give an 82% yield of the *hydrochloride*. Crystallization from ethanol gave a product melting at 160–162°. The compound could not be purified satisfactorily.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2 \cdot HCl$: C, 56.94; H, 5.03.

Found: C, 57.78; H, 5.22.

E. *Bis-(β-p-toluylethyl)methylamine* (*XIII*). When 125 g. of *p*-methylacetophenone, 28 g. of paraformaldehyde, and 31 g. of methylamine hydrochloride were reacted in the manner described in Part I A, a crude hydrochloride was obtained, which on crystallization from ethanol gave a 38% yield of practically pure *hydrochloride* of m.p. 159–160°.

Anal. Calc'd for $C_{21}H_{25}NO_2 \cdot HCl$: C, 70.08; H, 7.28.

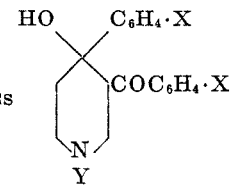
Found: C, 70.00; H, 7.34.

F. *Bis-(β-benzoylethyl)ethylamine* (*XIV*). The reaction of 120 g. of acetophenone, 20 g. of paraformaldehyde, and 41 g. of ethylamine hydrochloride according to Part I A yielded a crude *hydrochloride* which was crystallized from ethyl acetate and from ethanol. An 85% yield of material of m.p. 127–131° was obtained. Another crystallization from alcohol gave the pure compound of m.p. 138–139°.

Anal. Calc'd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99.

Found: C, 69.73; H, 6.75.

PART III. PIPERIDINES



A. *1-Isopropyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVI*). A suspension of 138 g. of crude β-benzoylethylisopropylamine hydrochloride (Part I A) was stirred for about an hour with 20 g. of sodium hydroxide and 1200 cc. of water and allowed to stand until solidification was complete. The solid was crystallized from methanol and acetone in a yield of 85%. The pure compound melts at 123–124°.

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.
Found: C, 77.88; H, 7.65.

B. *1-Benzyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVII*). β-benzoylethylbenzylamine hydrochloride was stirred for 4 hours at 50–60° with excess dilute sodium hydroxide. The crude base was crystallized from ethanol to give a 78% yield of the cyclic base. After crystallization from ethanol it melted at 116–119°. The compound was first isolated as a by-product by Mannich and Hieronimus (3) who reported approximately the same melting point.

Anal. Calc'd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77.
Found: C, 80.45; H, 6.81; N, 3.86.

The *hydrochloride*, prepared by passing hydrogen chloride gas through the ether solution of the base, melts at 193–194°.

C. *1-n-Butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XVIII*). The crude mixture from Part II A was stirred with 30 g. of sodium hydroxide and 750 cc. of water for several hours. After standing overnight the crude base was crystallized from methanol to give a 50% yield of product melting at 94–96°. The pure product obtained by recrystallization from methanol melted at 97–99°.

Anal. Calc'd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.07.
Found: C, 78.18; H, 7.65.

The same base was obtained when the oxalate of β-benzoylethylbutylamine (XI) from Part I C was stirred with alkali. The *hydrochloride* was crystallized from acetone; m.p. 182–184°.

Anal. Calc'd for $C_{22}H_{27}NO_2 \cdot HCl$: Cl, 9.49. Found: Cl, 9.36.

D. *1-Methyl-3-m-methoxybenzoyl-4-hydroxy-4-m-methoxyphenylpiperidine* (*XIX*). A mixture of 122 g. of bis-(β-*m*-methoxybenzoylethyl)methylamine oxalate from Part II B was stirred 2.5 hours with 20 g. of sodium hydroxide and 1200 cc. of water. After standing overnight the crude base was crystallized from dilute methanol in 90% yield. Recrystallization from methanol gave the pure compound, melting at 105–106°.

Anal. Calc'd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09.
Found: C, 71.47; H, 6.97.

E. *1-Methyl-3-p-chlorobenzoyl-4-hydroxy-4-p-chlorophenylpiperidine* (*XX*). To 100 cc. of boiling water was added with stirring 10 g. of bis-(β-chlorobenzoylethyl)methylamine hydrochloride and 30 cc. of 10% sodium hydroxide. The mixture was allowed to cool with stirring, and the crude base was crystallized from benzene. The yield of pure compound melting at 156–159° was 32%.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2$: C, 62.64; H, 5.26.
Found: C, 62.39; H, 5.24.

The *hydrochloride* was crystallized from acetonitrile; m.p. 192–193°.

Anal. Calc'd for $C_{19}H_{19}Cl_2NO_2 \cdot HCl$: Cl (ionic), 8.86. Found: Cl, 8.78.

F. *1-Methyl-3-p-toluyl-4-hydroxy-4-p-tolylpiperidine* (*XXI*). A mixture of 67 g. of the bis-(β-*p*-toluylethyl)methylamine from Part II E, 10 g. of sodium hydroxide, and 540 cc. of water was stirred vigorously for an hour. After standing until solidification was complete, the crude base was crystallized from 70% ethanol; yield, 68%. Recrystallization from methanol gave crystals, melting at 140–143°.

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.
Found: C, 78.01; H, 7.43.

The *hydrochloride* was crystallized from alcohol-ether; m.p. 195–197°.

Anal. Calc'd for $C_{21}H_{25}NO_2 \cdot HCl$: Cl, 9.87. Found: Cl, 9.66.

G. *1-Ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine* (*XXII*). A mixture of 147 g. of bis-(β-benzoylethyl)ethylamine (Part II F), 20 g. of sodium hydroxide, and 1200 cc. of water was stirred for 3 hours. After standing overnight and with additional stirring the base solidified;

it was crystallized from methanol or dilute methanol to give a 74% yield of the piperidine derivative. Recrystallization from acetone or dilute methanol gave a product melting at 100–102°.

Anal. Calc'd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49.
Found: C, 77.79; H, 7.09.

The *hydrochloride* was crystallized from ethanol, m.p. 206–208°.

Anal. Calc'd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99.
Found: C, 69.60; H, 7.17.

SUMMARY

Mannich condensations between acetophenone and its ring substituted derivatives with formaldehyde and primary amines yield secondary and tertiary amines. Both products are converted by alkali into 1,3,4-trisubstituted piperidine derivatives.

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