

# Syntheses of Some New Mannich Bases Using 2,6-Dimethylmorpholine as Amine Moiety

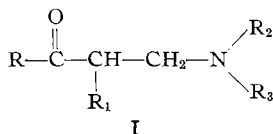
By K. K. KHULLAR and L. G. CHATTEN

The use of 2,6-dimethylmorpholine as an amine moiety in Mannich reaction has been investigated. Nine new Mannich bases have been synthesized using nine different ketones. The salts of  $\beta$ -amino esters have also been synthesized by Mannich reaction using *p*-nitrophenylacetic acid, formaldehyde solution (37 per cent), and three different amines (2,6-dimethylmorpholine, piperidine, and 4-methylpiperidine) followed by esterification. The structures of these compounds have been established by infrared spectra, mass spectra, and elemental analyses.

IN THEIR studies on the synthesis of anti-spasmodics by Mannich reaction (1), Denton and co-workers (2) observed that the most effective amino group in their series from a pharmacological standpoint was piperidyl.

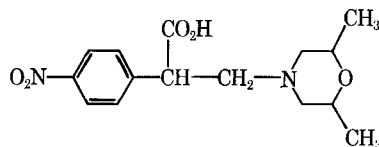
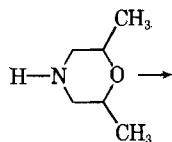
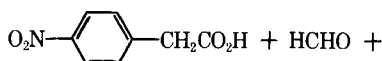
Compounds containing this amine moiety possessed outstanding properties when the acyl group belonged to the propiophenone series which possessed no ring or side chain substituents. In addition, piperidyl was as effective as any other amino group in the propionaphthone series. On the other hand, morpholinyl derivatives generally were the least active. The changes in activity which resulted from structural variations prompted the investigation of the use of substituted morpholines in the Mannich reaction to determine whether the resulting compounds possessed improved activity.

Although Mannich bases containing the morpholine ring as in structure I are known to possess low activity (2), their basic esters have pronounced antispasmodic activity and in general are less toxic than their diethylamine analogs (3). Synthesis of the  $\beta$ -amino acid (Scheme I) has been successfully attempted by Mannich reaction of *p*-nitrophenylacetic acid, formaldehyde (37%), and 2,6-dimethylmorpholine in aqueous medium (4), and the salt of the  $\beta$ -amino ester has been synthesized (Scheme II) by esterification of the appropriate acid by thionyl chloride and methanol (5).



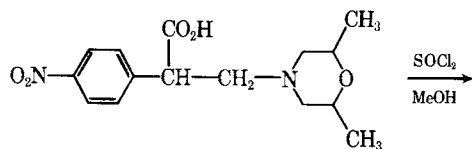
For the purpose of comparison of pharmacological activities, salts of  $\beta$ -amino esters have also been synthesized using piperidine and 4-methylpiperidine as amine moieties.

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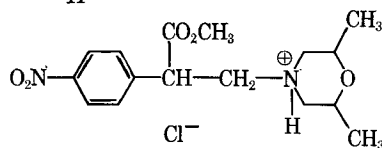


II

Scheme I



II



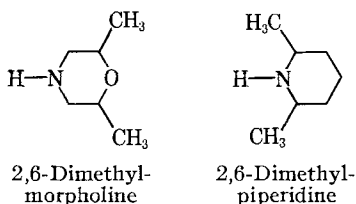
III

Scheme II

## DISCUSSION

2,6-Dimethylmorpholine, b.p. 144–146°/758 mm., was converted into its hydrochloride by passing dry hydrogen chloride gas through a solution of 2,6-dimethylmorpholine in ether. The Mannich bases of type I were obtained by Method A (6) (see under *Experimental*). Where a solid product did not separate on cooling, the solvent and unreacted acetone were removed on the evaporator. The resulting residue was recrystallized from acetone. These reactions, in addition to their use in the preparation of compounds which may have antispasmodic activity, will permit speculation on the steric requirements of the Mannich reaction. It is noteworthy that, whereas the reaction proceeds easily and gives crystalline products with sharp melting points with 2,6-dimethylmorpholine, the reactions

fail with 2,6-dimethylpiperidine under similar conditions.

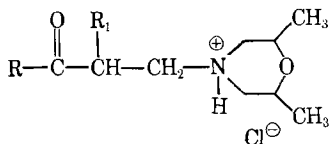


Furthermore, as illustrated by Scheme III, it is intended to convert the morpholino Mannich bases into compounds of type IV by stirring the Mannich base with potassium cyanide and piperidine hydro-

chloride at room temperature (7). The resulting compounds would appear to possess interesting possibilities as antiperistaltic agents (8) and/or analgesics (9).

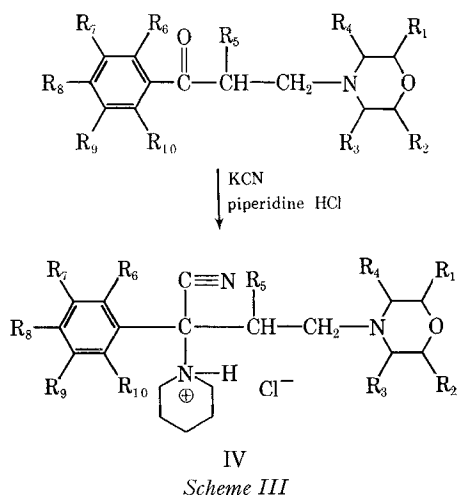
Mass spectra of the salts of Mannich bases of type I, recorded by direct probe introduction method using the MS9 mass spectrometer, permit ready elucidation of their structure. In addition, it is hoped to be able to correlate mass spectral data of these bases with their structure-activity relationship as antispasmodics. Since more information is required to substantiate our viewpoint, this report will appear at a later date.

Infrared spectra (10) of the salts of Mannich bases of type I performed on a Perkin-Elmer instrument using Nujol mull appear in Table I. The

TABLE I—MANNICH BASES TYPE I<sup>a</sup>

Compd. I	R	R <sub>1</sub>	Yield, %	M.p., °C.	Formula	Anal.		Infrared
						Calcd.	Found	
1	Phenyl	H	70	195-196.5	C <sub>15</sub> H <sub>21</sub> NO <sub>2</sub> ·HCl	C, 63.48 H, 7.81 N, 4.93	63.11 7.69 4.95	ν <sub>max</sub> 2870 (—CH str), 2670, 2530, 2450 O + (NH), 1690, (Ph—C—), 1600, 1580 (phenylgr.), 1460, 747, 695 (monosub. ben. ring), 1087 (=CH—O—CH<) cm. <sup>-1</sup> .
2	<i>p</i> -Nitrophenyl	H	61	203-204	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C, 54.79 H, 6.44 N, 8.52	54.95 6.02 8.79	ν <sub>max</sub> 2900 (—CH str), 2670, 2530, 2450 O (NH <sup>+</sup> ), 1700 (Ph—C—), 1610 (phenylgr.), 1530, 1350 (=C—NO <sub>2</sub> ), 1087 (>CH—O—CH<), and 860-800 (1:4 disub. ben. ring) cm. <sup>-1</sup> .
3	Methyl	H	42	156-157	C <sub>10</sub> H <sub>19</sub> NO <sub>2</sub> ·HCl	C, 54.17 H, 9.09 N, 6.32	54.22 9.09 6.50	ν <sub>max</sub> 2900 (—CH str), 2670, 2550, 2410 (NH <sup>+</sup> ), 1720 (carbonyl gr), 1087 (>CH—O—CH<) cm. <sup>-1</sup> .
4	Naphthyl	H	55	221-223	C <sub>19</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	C, 68.36 H, 7.25 N, 4.19	68.27 6.97 4.02	ν <sub>max</sub> 2900 (—CH str), 2670, 2530, 2450 O (NH <sup>+</sup> ), 1680 (ph—C—), 1600, 1575 (α-sub. naphthalene ring), 1100-1070 (>CH—O—CH<), 798-770, 770 (4 adj. H atoms on aro. ring) cm. <sup>-1</sup> .
5	Phenyl	CH <sub>3</sub>	68	187-188.5	C <sub>15</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	C, 64.52 H, 8.12 N, 4.70	64.53 8.18 4.50	ν <sub>max</sub> 2900 (—CH str), 2700, 2570 (NH <sup>+</sup> ), O 1680 (carbonyl-Ph—C—), 1600, 1587 (phenylgr.), 1455, 765, 704 (monosub. ben. ring), and 1087 (>CH—O—CH<) cm. <sup>-1</sup> .
6	<i>p</i> -Methoxyphenyl	H	60	203-205	C <sub>16</sub> H <sub>22</sub> NO <sub>2</sub> ·HCl	C, 61.23 H, 7.70 N, 4.46	60.98 7.70 4.39	ν <sub>max</sub> 2900 (—CH str.), 2680, 2560, 2480 O (NH <sup>+</sup> ), 1680 (Ph—C—), 1605, 1578 (phenylgr.), 1265 (=C—O—), 1087 cm. <sup>-1</sup> (>CH—O—CH<), 850-800 (1:4 disub. ben. ring) cm. <sup>-1</sup> .
7	<i>p</i> -Chlorophenyl	H	63	203.5-204.5	C <sub>15</sub> H <sub>21</sub> NO <sub>2</sub> Cl·HCl	C, 56.61 H, 6.65 N, 4.40	56.47 6.69 4.33	ν <sub>max</sub> 2910 (—CH str.), 2690, 2570, 2490 O (NH <sup>+</sup> ), 1695 (Ph—C—), 1595, 1577 (phenylgr.), 1095 (>CH—O—CH<), 860-800 (1:4 disub. ben. ring) cm. <sup>-1</sup> .
8	<i>p</i> -Methylphenyl	H	80	207-208	C <sub>15</sub> H <sub>23</sub> NO <sub>2</sub> ·HCl	C, 64.64 H, 8.08 N, 4.71	64.63 8.29 4.49	ν <sub>max</sub> 2900 (—CH str), 2680, 2550, 2470 O (NH <sup>+</sup> ), 1690 (Ph—C—), 1613, 1580 (phenylgr.), 1090 (>CH—O—CH<), 860-798 (1:4 disub. ben. ring) cm. <sup>-1</sup> .
9	<i>m</i> -Nitrophenyl	H	53	196-197	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> ·HCl	C, 54.79 H, 6.40 N, 8.52	54.55 6.60 8.58	ν <sub>max</sub> 2900 (—CH str.), 2560, 2430, 2360 O (NH <sup>+</sup> ), 1700 (Ph—C—), 1620, 1590, (phenylgr.), 1537, 1350 (=C—NO), 1093 (>CH—O—CH<), 804, 790, 697 (metasub. ben. ring) cm. <sup>-1</sup> .

<sup>a</sup> Prepared by Method A.

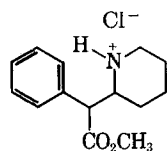


Mannich bases of type II were obtained by *Method B* (see under *Experimental*) (4). Infrared spectra of this type of compound are reported in Table II.

The  $\beta$ -amino acids formed from *p*-nitrophenylacetic acid through the Mannich reaction (type II) are insoluble in water and most organic solvents. These compounds exist as zwitterions, and since zwitterions are usually rather inert pharmacologically, no special attempt was made to purify these amino acids.

The salts of the  $\beta$ -amino esters (type III) were prepared from the amino acids by *Method C* (see under *Experimental*) (5). (Table III.) This type of compound, in addition to being antispasmodic, may also have mild psychomotor stimulant properties for minor neuroses, psychoneuroses, psychoses, and also for narcolepsy, as indicated by its structural similarity to methylphenidate HCl.

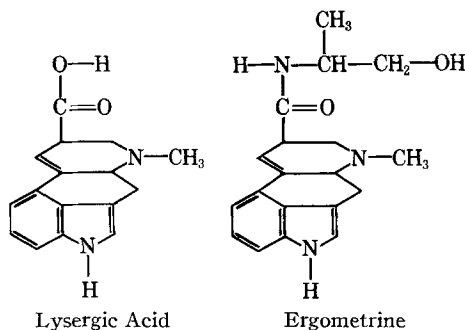
The  $-\text{NO}_2$  group may increase the toxicity, but the compound without the nitro group may easily



Methylphenidate HCl

be obtained by using phenylmalonic acid in place of *p*-nitrophenylacetic acid.

All the naturally occurring ergot alkaloids are derivatives of lysergic acid. They have been widely

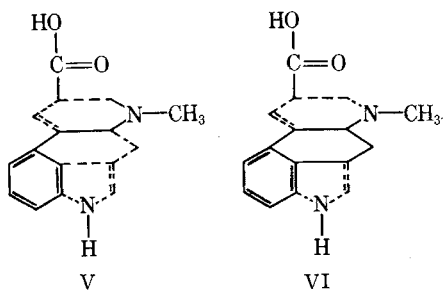


used as oxytocics, vasoconstrictors, and sympatholytics (11). Bovet and his co-workers (12), through the ingenious design of a series of analogs utilizing the method of disjunction, have provided an answer to the very important and interesting question—whether the three actions of these alkaloids depend on a single pharmacomorph moiety or whether there are distinct moieties responsible for each type of action. According to them, these actions are indeed separable. They visualized the presence of a sympathomimetic amine structure embedded in the lysergic acid nucleus as in V and VI.

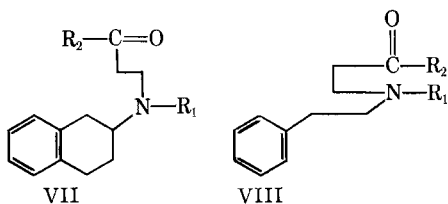
TABLE II—MANNICH BASES TYPE II<sup>a</sup>

Compd.	R	Yield, %	M.p., °C.	Formula	Infrared <sup>c</sup>
1 <sup>b</sup>	Piperidyl	58	136	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub>	$\nu_{\text{max}}$ . 2900 ( $-\text{CH}$ str.), 2500–2000 ( $^+\text{NH}$ ), 1630 $\begin{array}{c} \text{O}^- \\   \\ (-\text{C}=\text{O}), 1605 \text{ (phenylgr.)}, 1515, 1330-150 \\ (= \text{C}-\text{NO}_2), 843 \text{ cm.}^{-1}. \end{array}$
2	4-Methyl-piperidyl	56	143	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub>	$\nu_{\text{max}}$ . 2900 ( $-\text{CH}$ str.), 2500–2100 ( $^+\text{NH}$ ), 1625 $\begin{array}{c} \text{O}^- \\   \\ (-\text{C}=\text{O}), 1600 \text{ (phenyl gr.)}, 1515, 1350 (= \text{C}- \\ \text{NO}_2), 860-800 \text{ (1:4 disubst. benzene ring)}, 740, \\ 695 \text{ cm.}^{-1}. \end{array}$
3	2,6-Dimethyl-morpholinyl	88	142–143	C <sub>15</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub>	$\nu_{\text{max}}$ . 2900 ( $-\text{CH}$ str.), 2500–1800 ( $^+\text{NH}$ ), 1640 $\begin{array}{c} \text{O}^- \\   \\ (-\text{C}=\text{O}), 1605 \text{ (phenylgr.)}, 1520, 1340 (= \text{C}- \\ \text{NO}_2), 1095 (> \text{CH}-\text{O}-\text{CH} <), 770-680 \text{ cm.}^{-1}. \end{array}$

<sup>a</sup> Prepared by *Method B*. Converted to ester; hence acids not submitted for elemental analysis. <sup>b</sup> Compound 1 has been synthesized previously in literature (6). <sup>c</sup>  $\nu_{\text{max}}$ . 2900  $\text{cm.}^{-1}$  may be due to Nujol as well.

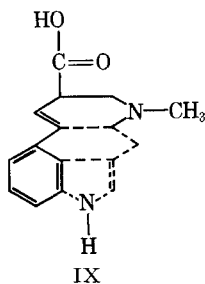


On the basis of this type of reflection, various series of products were designed, synthesized, and evaluated for the above-mentioned activities. These series included the types of disjunction analogs shown in VII and VIII.

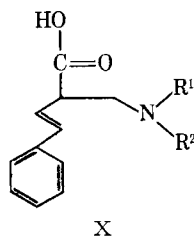


where  $R_1$  = various alkyl, and  
 $R_2$  = various alkylamide groups.

Careful examination of the structure of lysergic acid shows the presence of another type of structure (IX).

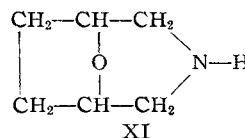


Upon writing the delineated portion separately (X),



it is observed to be a simple vinylog of the type of  $\beta$ -amino acid II which has been synthesized in this laboratory. It is intended to convert this acid into amide derivatives of various ethanol and propanolamines which may be of special interest (as found in ergometrine).

The successful use of substituted morpholines in Mannich reaction would pave a way for the use of 8-oxa-3-azabicyclo[3.2.1]octane (13) which has fused tetrahydrofuran and morpholine rings (XI).



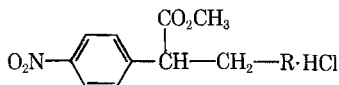
This would provide an interesting addition to the study of co-relating the structure of Mannich bases with antispasmodic activity.

Additional modifications to these Mannich bases, some of which may incorporate suggestions by other authors (14-18), will be reported in subsequent publications, together with the results of pharmacological screening.

## EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 21. Elemental analyses were performed by Dr. G. Weiler, Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, England. All the yields reported were calculated on the basis of amine used. All the chemicals used were

TABLE III—SALTS OF BASIC ESTERS<sup>a</sup>



Compd.	R	Yield, %	M.p., °C.	Formula	Anal.		Infrared
					Calcd.	Found	
1	Piperidyl	Quan.	211	$C_{16}H_{20}N_2O_4 \cdot HCl$	C, 54.79 H, 6.44 N, 8.52	54.68 7.21 8.44	$\nu_{max}$ . 2900 (—CH str.), 2570, 2470 (NH <sup>+</sup> ), 1730 (—C—), 1600 (phenylgr.), 1530, 1345 (=C—NO <sub>2</sub> ), 862-837 cm. <sup>-1</sup> .
2	4-Methyl-piperidyl	Quan.	148.5-149.5	$C_{16}H_{22}N_2O_4 \cdot HCl$	C, 56.14 H, 6.72 N, 8.19	56.29 6.72 8.19	$\nu_{max}$ . 2900 (—CH str.) 2600, 2440, 2375 (NH <sup>+</sup> ), 1750 (carbonyl group), 1612, 1605 (phenyl gr.), 1520 1350 (=C—NO <sub>2</sub> ), 860-800 (1:4 disubst. benzene ring), 735, 685 cm. <sup>-1</sup> .
3	2,6-Dimethyl-morpholinyl	68	150-152	$C_{16}H_{22}N_2O_5 \cdot HCl$	C, 53.56 H, 6.46 N, 7.80	53.73 6.67 7.62	$\nu_{max}$ . 2900 (—CH str.) 2400 (NH <sup>+</sup> ), 1737 (—C—), 1600 (phenylgr.), 1530, 1343 (=C—NO <sub>2</sub> ), 1082 (>CH—O—CH<), 860, 930 cm. <sup>-1</sup> .

<sup>a</sup> Prepared by Method C.

obtained from commercial sources unless otherwise reported.

**Method A**—A mixture of a ketone (0.10 mole), 2,6-dimethylmorpholine hydrochloride (0.10 mole), paraformaldehyde (0.20 mole), and concentrated hydrochloric acid (0.50 ml.) in 50 ml. of absolute ethanol was heated under reflux. After refluxing for 3 hr., another 0.10 mole of paraformaldehyde was added and refluxing continued for an additional 6 hr. Boiling acetone (200 ml.) was added to the hot mixture with shaking. The resulting solution was allowed to cool overnight, and then in the refrigerator for 3 hr. The crystalline product thus precipitated was filtered. Ethanol-acetone is a suitable solvent pair for crystallization.

**Method B**—The  $\beta$ -amino acids were prepared according to the procedure of Mannich and Stein (4). A white solid started separating after about 4 hr. The crystalline product thus precipitated after 24 hr. was filtered. The residue was washed twice with absolute ethanol (50-ml. portions) and dried. Some of these acids turn red on standing, probably due to air oxidation.

**Method C**—Thionyl chloride (20 ml.) was added to the  $\beta$ -amino acid (0.025 mole) dropwise with cooling and shaking. After the completion of addition, the mixture was allowed to stand at room temperature for about 16 hr. During this period, the entire solid went into solution. The unreacted thionyl chloride then was removed on the evaporator. The residue then was taken up in carbon tetrachloride (100 ml.), methanol (20 ml.) was added

slowly, and the resulting mixture was refluxed on a steam bath. After about 6 hr., the solvent and unreacted methanol were removed on the evaporator, and a portion of the resulting residue was recrystallized from acetone.

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# Stability of Metal Complexes of Salicylic Acid Derivatives and Analogs III

## 3,6-Dialkyl Derivatives and Pyridine Analogs

By WILLIAM O. FOYE, MARTIN D. BAUM, and DAVID A. WILLIAMS

Stability constants are reported for the complexation of a series of 3,6-dialkylsalicylic acids and pyridine analogs of salicylic acid with Cu (II), Fe (III), and Al (III) ions. These compounds were selected in an attempt to increase the affinity of salicylates for ferric ion. The 3,6-dialkyl substituents lowered metal complex stabilities, but the presence of a ring-nitrogen adjacent to the phenolic group increased complex stabilities considerably. The 3,6-dialkylsalicylic acids revealed somewhat greater analgesic effects than salicylic acid, but less anti-inflammatory action.

THE AVIDITY of salicylic acid for complex formation with transition metals has suggested that some, if not all, of the biological effects of salicylates may be due to complexation of metalloenzymes (1). Ample evidence may be found in the literature that salicylic acid or its derivatives become involved in enzymatic reactions; some references of this nature were cited in a

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previous paper (1), and other examples have appeared since (2-6). Since salicylates apparently affect cellular oxidations, salicylate derivatives which show a greater affinity for iron might be expected to show enhanced biological effects. Increased affinity for iron could be realized in two ways. Introduction of bulky substituents in the 3,6-positions of salicylic acid would tend to crowd the chelating groups together and thus provide a better fit for the ferric ion, which is a relatively small ion (7). Or the introduction of nitrogen into the ring in positions adjacent to the chelating groups might also provide molecules