g., m.p. 302–307°. Recrystallization from water afforded colorless needles, m.p. 302–304°. This material was identical (C, H, I, and N analyses, ultraviolet and infrared spectra) with the sample prepared from 3-(1-pyrrolin-2-yl)indole and methyl iodide.

1-Acetyl-3-(1-acetyl-2-pyrrolin-2-yl)indole (X).[11]—A solution containing 5.2 ml. (0.065 mole) of pyridine and 5.2 ml. (0.051 mole) of acetic anhydride was added to 1.84 g. (0.01 mole) of 3-(1-pyrrolin-2-yl)indole. The mixture was heated on a steam bath for 2 hr. The resulting brown solution was evaporated *in vacuo*. The brown oily residue was dissolved at room temperature in 10 ml. of ethyl acetate and crystallization was induced by scratching and allowed to proceed overnight. The crystals were filtered, washed with ethyl acetate, then with petroleum ether to give 1.4 g. (52%), m.p. 130–144°. Crystallization from pyridine–petroleum ether at room temperature afforded clusters of colorless rods; m.p. 132–144°; ν_{max} 3060, 1708, 1636, 1588, and 1558 cm.$^{-1}$; λ_{max} (in dioxane) 238 mμ (ε 25,850), sh 292 (7250), and 301 (8800).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 72.02; H, 6.20; N, 10.15.

1-Acetyl-3-(2-pyrrolidinyl)indoline Hydrochloride (XI).—A solution of 0.452 g. of VIII in 25 ml. of acetic acid containing 0.1 g. of platinum oxide was shaken on a Parr apparatus at 3 atm. initial pressure. After 20 min. the solution was filtered and evaporated to dryness. The residue was dissolved in water, made basic with sodium bicarbonate, and extracted with ether. The extract was washed with water and saturated salt solution, dried through sodium sulfate, and evaporated to give 0.393 g. of a pale yellow oil. The hydrochloride was prepared in 2-propanol. Two crystallizations from 2-propanol–methanol followed by methanol afforded 0.173 g. (33%); m.p. 259–261°; ν_{max} 2740, 2550, 2520, 2490, 2425, and 1655 cm.$^{-1}$; λ_{max} 252 mμ (ε 15,500), sh 278 (3100), and sh 287 (2200).

Anal. Calcd. for $C_{14}H_{18}N_2O\cdot HCl$: C, 63.03; H, 7.18; Cl, 13.29; N, 10.50. Found: C, 62.80; H, 7.58; Cl, 13.05; N, 10.35.

1-Methyl-3-(1-methyl-2-pyrrolin-2-yl)indole (XII).—A solution of 34 g. (0.1 mole) of VI in 200 ml. of methanol and 300 ml. of methylene chloride was prepared under nitrogen and 600 ml. of 1 *N* sodium hydroxide was added. The mixture was stirred for 2 hr. The organic layer was separated and the aqueous solution was extracted with two 200-ml. portions of methylene chloride. The combined organic solution was washed with saturated salt solution and dried through sodium sulfate. It was evaporated *in vacuo* below 40° to give 27 g. of yellow oil; λ_{max} (in ether) 238 mμ (ε 7450), 293 (6500), and sh 301 (5650); λ_{max} (in methanol) 253 mμ (ε 15,000), sh 270 (8900), and 335 (20,000).

1,1-Dimethyl-2-(1-methylindol-3-yl)-2-pyrrolinium Iodide (XIV and VI) by Alkylation of XII with Methyl Iodide. A. Without Solvent.—Methyl iodide (200 ml.) was added cautiously with cooling to 27 g. of XII, whereupon a suspension resulted. It was refluxed for 15 min., cooled to room temperature, and filtered to give 34.5 g., m.p. 186–206°. Two recrystallizations from methanol afforded 10.4 g. of colorless needles, m.p. 253–254°. This material was identical (mixture melting point, ultraviolet and infrared spectra) with VI. The last filtrate from the above crystallization was concentrated and afforded 9.5 g. of solid, m.p. 180–190°. Six crystallizations from methanol gave 3.16 g. of XIV; m.p. 205–207°; ν_{max} 3070, 1643, 1614, 1575, and 1531 cm.$^{-1}$; λ_{max} 212 mμ (ε 34,000), 243 (12,850), sh 260 (7050), and 303 (12,900). The structure proposed for XIV was supported by the n.m.r. spectrum which showed indole N–CH_3 at 239 c.p.s. (area 3) and pyrrolidine N–CH_3 at 206 c.p.s. (area 6),[13,20] and by the following analysis.

Anal. Calcd. for $C_{15}H_{19}IN_2$: C, 50.85; H, 5.41. Found: C, 50.74; H, 5.98.

B. In Dimethylformamide.—A solution of 27 g. of XII in 100 ml. of dry dimethylformamide was treated during 10 min. with 34 ml. (0.54 mole) of methyl iodide. The temperature was kept at 15–20° by cooling in ice. The suspension was stirred overnight at room temperature and then heated at 55° for 1 hr. It was cooled, filtered, and the solid was washed with cold dimethylformamide and then with ether to give 6 g. of VI, m.p. 254–255°. The solvent was evaporated from the filtrate under a high vacuum below 45° and the resulting oil was crystallized from methanol–ether. Another crystallization afforded 10.1 g. of XIV, m.p. 203–205°. A mixture melting point with XIV obtained previously showed no depression.

(20) The n.m.r. spectrum was run with a Varian D.P. 60 spectrometer and deuterated dimethylformamide as solvent. Frequencies are reported in c.p.s. downfield from internal tetramethylsilane. We thank Dr. G. Slomp and F. A. McKellar for the spectrum and its interpretation.

4-Aminomorpholines[1]

MAX J. KALM

Chemical Research Division of G. D. Searle & Company, Chicago 80, Illinois

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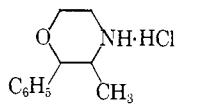
A variety of substituted 4-aminomorpholines has been prepared. The preparation of such hydrazines, in which one nitrogen is part of a cyclic structure, has been investigated and the methods used are discussed. One of these compounds, 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine, has been shown to possess very interesting central nervous system activity. The preparation of some of the optically active isomers of this compound is also discussed.

The substitution of the morpholine radical for other dialkylamine or cyclic amine radicals in biologically active substances has generally resulted in reduction or elimination of activity. A notable exception has been observed in compounds affecting the central nervous system.[2] A morpholine derivative of particular interest has been 3-methyl-2-phenylmorpholine hydrochloride (**1**) which finds use as an appetite inhibitor[3] and has also been shown to affect the central nervous system by producing mild stimulation and euphoria.[4] Such stimulant activity, coupled with the discovery that 2-hydrazino-1-phenylpropane hydrochloride (**2**) is a potent central nervous system stimulant and inhibitor of monoamine oxidase[5] led to the investigation of 4-aminomorpholines related structurally to 3-methyl-2-phenylmorpholine.



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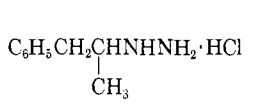

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The unsubstituted 4-aminomorpholines were pre-

(1) Presented in part before the 7th Medicinal Chemistry Symposium, Kingston, R. I., June 21, 1960.

(2) (a) P. A. J. Janssen and A. H. Jageneau, *J. Pharm. Pharmacol.*, **9**, 381 (1957); (b) R. J. Anderson, P. M. Frearson, and E. S. Stern, *J. Chem. Soc.*, 4088 (1956); (c) B. Basil, N. D. Edge, and G. F. Somers, *Brit. J. Pharmacol.*, **5**, 125 (1950).

(3) (a) O. Thomae and H. Wick, *Arch. Exptl. Pathol. Pharmakol.*, **222**, 540 (1954); (b) M. E. Rossman, M. Beyers, and S. Merlis, *N. Y. State J. Med.* **58**, 2394 (1958); (c) C. Ressler, *J. Am. Med. Assoc.*, **165**, 135 (1957.)

(4) (a) R. H. Barnes, *ibid.*, **166**, 898 (1958); (b) J. B. Randell, *Brit. Med. J.*, **2**, 508 (1957).

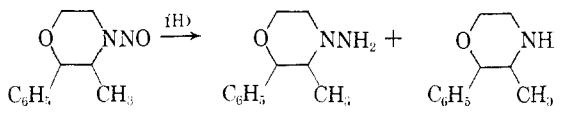
(5) (a) L. G. Etherington and A. Horita, *J. Pharmacol. Exptl. Therap.*, **128**, 7 (1960); (b) S. Spector, P. A. Shore, and B. B. Brodie, *ibid.*, **128**, 15 (1960); (c) A. Horita, *Ann. N. Y. Acad. Sci.*, **80**, 590 (1959).

pared by nitrosation of the desired morpholine[6] followed by reduction of the intermediate N-nitrosamine with lithium aluminum hydride.[6,7] Although lithium aluminum hydride gave excellent yields of hydrazine, other reducing agents were studied using 3-methyl-4-nitroso-2-phenylmorpholine as the reactant. The chemical reducing agents used[8–13] and the results obtained are shown in Table I.

Attempts were also made to reduce 3-methyl-4-nitroso-2-phenylmorpholine (**3**) to 4-amino-3-methyl-2-phenylmorpholine (**4**) by catalytic hydrogenation[14] (see Table I). The conditions used in the catalytic

TABLE I

CHEMICAL REDUCTION OF 3-METHYL-4-NITROSO-2-PHENYLMORPHOLINE



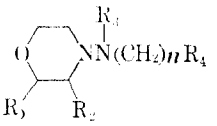
3 **4** **1**

Reducing agent	Result[a]
$LiAlH_4$ in $(C_2H_5)_2O$	Hydrazine **4** (95%)
$NaBH_4$ in C_2H_5OH	No reaction
KBH_4 in C_2H_5OH	No reaction
$H_2NNH_2 \cdot H_2O$ (100%) + Pd/C (10%)[b] (reaction time—5 min.)	No reaction
$H_2NNH_2 \cdot H_2O$ (100%) + Pd/C (10%)[b] (reaction time—1 hr.)	Nitrosamine **3** (85%), amine **1** (5%)
$NaBH_4$–$AlCl_3$ in diethylene glycol dimethyl ether[c]	Amine **1**[c] (83%)[d]
$Na_2S_2O_4$ in NH_4OH[f]	Nitrosamine **3** (89%), amine **1** (5%)
Zn–CH_3CO_2H (50%)[g]	Hydrazine **4** (51%), amine **1** (22%)
Zn–CH_3CO_2H (90%)[g]	Hydrazine **4** (65%), amine **1** (26%)
Zn–CH_3CO_2H (90%) + $HgSO_4$[h]	Hydrazine **4** (69%), amine **1** (22%)
$NaHSO_3$–NaOH[i]	No reaction

[a] Figures in parentheses are yields of pure product isolated. [b] See ref. 12. [c] This product was isolated as the BH_3 salt. [d] This yield constitutes crude material. [e] See ref. 8. [f] See ref. 9. [g] See ref. 10. [h] See ref. 11. [i] See ref. 13.

hydrogenations were platinum oxide and glacial acetic acid in ethanol, pre-reduced ruthenium oxide in ethanol, ruthenium on carbon in benzene, ruthenium on carbon with liquid ammonia in ethanol, rhodium on alumina in ethanol, nickel–chromium[15] in ethanol, palladium on charcoal in ethanol, palladium on charcoal and hydrogen chloride in ethanol, palladium on charcoal and liquid ammonia in ethanol, palladium on charcoal in dibutyl ether, palladium on charcoal and ferrous sulfate in aqueous ethanol, and palladium on calcium carbonate. The reductions were run at room temperature and in most instances low pressures were employed. In every instance, the major product of the reduction was 3-methyl-2-phenylmorpholine (**1**) resulting from cleavage of the –N–N– bond. Increasing the pressure to 1600–1900 p.s.i. (112.5–133.6 kg./cm.^{2}) had no effect in altering the course of the reaction.

The 4-amino-substituted morpholines thus prepared were converted to a variety of N-substituted 4-aminomorpholines which can be represented by the general formula



R_1 = phenyl, 4-methoxyphenyl, cyclohexyl, or 4-methoxycyclohexyl; R_2 = methyl or phenyl; R_3 = H or methyl; R_4 = H, phenyl, methoxyphenyl, phenoxy, phenylcycloalkyl, cycloalkyl, indolyl, furyl, piperidyl, or pyrazinyl; $-(CH_2)_n-$ = unbranched or branched alkylene chain or hydroxyalkylene, where n = 0 or a positive integer.

Synthesis of these compounds was accomplished by reductive alkylation of the appropriate 4-aminomorpholine with a carbonyl compound. No attempt was made to isolate the intermediate hydrazones, except in the case of the reductive alkylation of 4-amino-3-methyl-2-phenylmorpholine (**4**) with benzaldehyde. In this case, isolation and purification of the hydrazone was necessary before saturation of the double bond would take place under catalytic conditions. Reductive alkylations, for the most part, were carried out in the presence of glacial acetic acid at high pressure, these being conditions which gave optimum yields in the reduction of phenylacetone hydrazone.[16]

The only exceptions to the above described method of preparation of N-substituted 4-aminomorpholines were the N-methylated derivatives. Using the procedure of Biel and co-workers,[17] the N-aminomorpholine was formylated with ethyl formate and reduction with lithium aluminum hydride gave the N-methylaminomorpholine. Repeating this sequence of reactions gave good yields of the N,N-dimethylaminomorpholine. An attempt to extend this methylation to other N-substituted 4-aminomorpholines resulted only in the recovery of starting material. It would seem that steric hindrance plays a part in these results, the methyl group being small enough to allow introduction of a second group on the nitrogen atom while higher alkyls effectively block the formylation reaction. Conditions tried for introducing a methyl group into 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine (**5**), in addition to the formylation–reduction procedure, included reaction with methyl iodide in the presence of potassium hydroxide and with sodamide. In each case the only product isolated was the trisubstituted hydrazine.

(6) C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.*, **77**, 4100 (1955).
(7) F. W. Schueler and C. Hanna, *ibid.*, **73**, 4996 (1951).
(8) H. C. Brown and B. C. S. Rao, *ibid.*, **78**, 2582 (1956).
(9) C. G. Overberger, J. G. Lombardino, and R. G. Hiskey, **80**, 3009 (1958).
(10) (a) L. Knorr, *Ann.*, **221**, 297 (1883); (b) A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 514 (1952).
(11) P. F. Derr, U. S. Patent 2,961,467 (Nov. 22, 1960).
(12) M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 2556 (1956).
(13) Laboratories Miguel, S. A., Spanish Patent 262,712 (Dec. 5, 1960); *Chem. Abstr.*, **56**, 11496*h* (1962).
(14) (a) D. R. Levering and L. G. Maury, British Patent 797,483 (July 2, 1958); (b) J. W. Churchill and J. F. Haller, German Patent 1,064,954 (Sept. 10, 1959); (c) K. Klager, E. M. Wilson, and G. K. Helmkamp, *Ind. Eng. Chem.*, **52**, 119 (1960); (d) W. B. Tuemmler and H. J. S. Winkler, British Patent 868,147 (May 17, 1961).
(15) I. Scriabine, J. F. Billau, A. F. S. Bellone, and M. Gaillard, U. S. Patent 2,502,348 (March 28, 1950).
(16) J. H. Biel, A. E. Drukkler, T. F. Mitchell, E. P. Sprengeler, P. A. Nuhfer, A. C. Conway, and A. Horita, *J. Am. Chem. Soc.*, **81**, 2805 (1959).
(17) J. H. Biel, E. Drukker, and T. F. Mitchell, Jr., *ibid.*, **82**, 2204 (1960).

Although 3-methyl-2-phenylmorpholine has two asymmetric carbon atoms, standard methods of synthesis[18] lead to only one of the two possible diastereoisomers. This was verified by the conversion of both norephedrine and norpseudoephedrine to a pair of diastereoisomeric N-β-hydroxyethylnorephedrines and converting them in almost quantitative yield to the same 3-methyl-2-phenylmorpholine. The 3-methyl-2-phenylmorpholine thus prepared has been shown to have the *trans* configuration.[19] The *cis* isomer was successfully prepared by a new synthetic route utilizing 5-methyl-6-phenyl-3-morpholinone as the intermediate.[19]

Conversion of this morpholine (**1**) to an N-substituted 4-aminomorpholine in which the side chain has an additional asymmetric carbon atom results in the possibility of two diastereoisomers or four enantiomorphs. In the case of 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine (**5**), the hydrochloride of the crude free base was separated into two diastereoisomers by crystallization. The higher melting of these two substances (**5A**), which was the major product, is of great interest because of its biological activity, and the two enantiomorphs comprising this material were prepared by stereospecific syntheses.

Using *d*-3-methyl-2-phenylmorpholine,[20] the *d*-4-amino compound was prepared and converted to the *d*-isomer of **5A**. The levorotatory isomer was prepared by the same sequence of reactions from *l*-3-methyl-2-phenylmorpholine, which was synthesized from *d*-norephedrine by reaction with ethylene oxide followed by ring closure with sulfuric acid. A 1:1 mixture of these enantiomorphs was identical with the higher melting racemate (**5A**).

The substituted 4-aminomorpholines prepared from various 2,3-disubstituted 4-aminomorpholines are shown in Table II.

The biological activity of these compounds, with special emphasis on 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine hydrochloride (**5A**), is discussed in detail in the following paper. Discussed are not only the unique central nervous system activity which this substance has shown, but also the marked difference of this activity from those of 3-methyl-2-phenylmorpholine hydrochloride (**1**), 2-amino-1-phenylpropane, and 2-hydrazino-1-phenylpropane (**2**), the structural features of all three compounds being present in this 4-aminomorpholine.

Experimental[21]

***d,l*-3-Methyl-2-phenylmorpholine**[18] (**1**).—To 200 ml. of concentrated sulfuric acid, cooled in an ice bath and stirred slowly, was added, in portions, 200 g. of N-β-hydroxyethylnorephedrine,[22] and the resulting solution was heated at 100° with stirring for 5 hr. The red solution was then cooled in an ice bath and was made alkaline by slow addition of 6 *N* sodium hydroxide. Extraction with ether and drying over anhydrous potassium carbonate gave, after removal of solvent and distillation, 80–90% of **1**, b.p. 87–88° (0.8 mm.), $n^{25}D$ 1.5376 ± 0.0004.

***l*-3-Methyl-2-phenylmorpholine (45).**—A solution of 24.4 g. of *d*-N-β-hydroxyethylnorephedrine (prepared from *d*-norephedrine by the method used for the *dl*-compound)[22] and 100 ml. of 48% hydrobromic acid was heated under reflux for 3 hr. The hydrobromic acid was removed at reduced pressure and the residue was taken up in 50 ml. of water and made alkaline with 6 *N* sodium hydroxide. The product was extracted with ether and the extracts were dried over anhydrous potassium carbonate prior to removal of solvent. Distillation gave a 39% yield of the product, b.p. 90–93° (1.1 mm.), $[\alpha]D$ −21.9° (0.1 *N* HCl).

***d*-3-Methyl-2-phenylmorpholine (46).**—Using the reaction described for the *l*-isomer, *l*-N-β-hydroxyethylnorephedrine[20] was converted in 52.3% yield to *d*-3-methyl-2-phenylmorpholine, b.p. 80° (0.4 mm.), $[\alpha]D$ +22.8° (0.1 *N* HCl).

2,3-Diphenylmorpholine[18] (**47**).—A solution of 212 g. (1.0 mole) of benzoin and 61 g. (1.0 mole) of β-hydroxyethylamine in absolute ethanol was reduced at 3.5–4.2 kg./cm.² of hydrogen pressure using platinum oxide as the catalyst. Filtration of catalyst followed by removal of solvent at reduced pressure gave a product which was purified by conversion to the hydrochloride salt and crystallization from ethanol and ether. Regeneration of the free base gave a 76% yield of 1,2-diphenyl-1-hydroxy-N-(β-hydroxyethyl)ethylamine. This material was cyclized by the procedure described for 3-methyl-2-phenylmorpholine to give **47** which was purified as the hydrochloride. The product, which crystallized from ethanol–ether, had m.p. 272–274° (lit.[18] m.p. 265°).

2-(4-Methoxyphenyl)-3-methylmorpholine[23] (**48**).—Using the procedure described for 1-hydroxy-1-phenyl-2-propanone,[24] 1-hydroxy-1-(4-methoxyphenyl)-2-propanone, b.p. 105–110° (0.1 mm.), was prepared in 70% yield from anisaldehyde. Reductive alkylation of 103 g. (0.572 mole) of this ketone with 36.6 g. (0.6 mole) of β-hydroxyethylamine in 250 ml. of methanol, using 5 g. of platinum oxide catalyst and 3.5–4.2 kg./cm.² of hydrogen pressure gave a 25% yield of 1-hydroxy-N-β-hydroxyethyl-1-(4-methoxyphenyl)-2-propylamine. The cyclization was carried out by refluxing this material for 2 hr. with 135 ml. of concentrated hydrochloric acid. Work-up as described for *l*-3-methyl-2-phenylmorpholine followed by purification as the hydrochloride gave a 52% yield of **48** hydrochloride, which crystallized from ethanol–ether, m.p. 205–208° (lit.,[23] m.p. 207°).

2-Cyclohexyl-3-methylmorpholine (49).—To a solution of 75 g. (0.424 mole) of 3-methyl-2-phenylmorpholine in 500 ml. of glacial acetic acid was added 7.5 g. of rhodium on alumina catalyst and the mixture was reduced at hydrogen pressures of 21.1–49 kg./cm.². The reduction stopped after the theoretical amount of hydrogen had been absorbed and the catalyst was removed by filtration. The solvent was stripped at reduced pressure and the residue was taken up in 200 ml. of water. Neutralization with potassium carbonate, followed by extraction with ether gave, after drying with anhydrous potassium carbonate, the crude product. Distillation gave a colorless oil with b.p. 68–69.5° (0.8 mm.), $n^{25}D$ 1.4855 ± 0.0005. The yield varied between 75 and 90%.

Anal. Calcd. for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.53.

2-(4-Methoxycyclohexyl)-3-methylmorpholine (50).—Reduction of 15.5 g. (0.075 mole) of 2-(4-methoxyphenyl)-3-methylmorpholine (**48**) in 150 ml. of ethanol with 1.5 g. of ruthenium oxide catalyst at 42.2–63.3 kg./cm.² and 60–100° yielded, after removal of catalyst and solvent, a product which was purified by conversion to the hydrochloride salt. Crystallization from ethanol–ether gave an 83% yield of the product, m.p. 205–206°.

Anal. Calcd. for $C_{12}H_{24}ClNO_2$: N, 5.61; Cl, 14.20. Found: N, 5.76; Cl, 14.44.

General Procedure for the Preparation of 2,3-Disubstituted-4-nitrosomorpholines.—A solution of 0.2 mole of the morpholine in 0.206 mole of concentrated hydrochloric acid, diluted with 65 ml. of water, is heated to 75° with stirring. A solution of 0.206 mole of sodium nitrite in 40 ml. of water is added dropwise while the internal temperature is maintained at 75–80°. Stirring at this temperature is continued for 2 hr. after addition has been completed. Extraction with ether or with benzene followed by drying of the extracts over anhydrous potassium carbonate and removal of solvent yields the crude product.

(18) O. Thoma, U. S. Patent 2,835,669 (May 20, 1958).

(19) F. H. Clarke, *J. Org. Chem.*, **27**, 3251 (1962).

(20) Spofa, Sdruženi Podniků Pro Zdravotnickou Výrobu, Belgian Patent 586,516 (Jan. 13, 1960).

(21) In most instances no attempt was made to obtain maximum yields in these syntheses. The yields reported constitute, for the most part, results from a single experiment. All melting points are corrected. Rotations were determined at 26 ± 1° at a concentration of 1.2% in methanol unless otherwise specified.

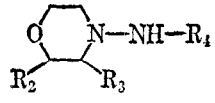
(22) M. J. Kalm, *J. Org. Chem.*, **25**, 1929 (1960).

(23) C. H. Boehringer Sohn, British Patent 862,198 (March 1, 1961).

(24) S. Murahashi and N. Hagihara, *Proc. Japan Acad.*, **23**, 147 (1947); *Chem. Abstr.*, **46**, 932*f* (1952).

TABLE II

4-N-SUBSTITUTED AMINOMORPHOLINES



No.	R_2	R_3	R_4	Formula	Salt	M.p., °C.	Salts — Nitrogen, % Calcd.	Salts — Nitrogen, % Found	Salts — Anion, % Calcd.	Salts — Anion, % Found	Method	Yield, %
8	C_6H_5	CH_3	$-CH(CH_3)_2$	$C_{14}H_{22}N_2O$	HCl	212.5–213.5	10.35	10.64	13.10	13.12	A	54
9	C_6H_5	CH_3	$-CH_2C_6H_5$	$C_{18}H_{22}N_2O$	HCl	156–159	8.79	9.12[a]			B	58
10	C_6H_5	CH_3	$-CH(CH_3)C_6H_5$	$C_{19}H_{24}N_2O$	HBr	205–206.5	7.43	7.18	21.18	21.03	B	22[b]
11	C_6H_5	CH_3	$-CH(CH_3)$–(2-furyl)	$C_{17}H_{22}N_2O_2$	HCl	180–181	8.68	8.60	10.98	10.93	B	32
12	C_6H_5	CH_3	$-CH(C_2H_5)C_6H_5$	$C_{20}H_{26}N_2O$	HCl	221.5–222	8.08	8.59	10.22	10.19	B	27
13	C_6H_5	CH_3	$-CH_2CH_2C_6H_5$	$C_{19}H_{24}N_2O$	HCl	187–188	8.42	8.44	10.65	10.53	A	22
14	C_6H_5	CH_3	$-CH(CH_3)CH_2C_5H_9$	$C_{19}H_{30}N_2O$	HCl	199–202	8.27	8.18	10.46	10.44	B	53
15	C_6H_5	CH_3	$-CH(CH_3)CH_2C_6H_{11}$	$C_{20}H_{32}N_2O$	HCl	208–210			10.05	10.20	B	24
5A						210–211	8.08	7.83	10.22	10.10	B	60[c]
5B						183–189	8.08	7.88	10.22	10.09		
	C_6H_5	CH_3	$-CH(CH_3)CH_2C_6H_5$	$C_{20}H_{26}N_2O$	HCl							
d-5A						225–226.5[d]	8.08	8.01	10.22	10.05	A	39[b]
l-5A						226.5–227.5[e]	8.08	7.88	10.22	10.21	A	33[b]
16	C_6H_5	CH_3	$-CH(CH_3)CH(OH)C_6H_5$	$C_{20}H_{26}N_2O_2$	HCl	158.5–160[f]	7.72	8.08	9.77	10.08	A	30
17	C_6H_5	CH_3	$-CH(CH_3)CH_2$–(3,4-dimethoxyphenyl)	$C_{22}H_{30}N_2O_3$	HCl	216.5–217.5	6.89	6.75	8.71	8.72	B	68
18	C_6H_5	CH_3	$-CH(CH_3)CH_2OC_6H_5$	$C_{26}H_{26}N_2O_2$	HBr	175–179	6.88	7.25	19.62	19.40	B	28
19	C_6H_5	CH_3	$CH(CH_3)CH(C_6H_5)_2$	$C_{26}H_{30}N_2O$	HCl	225–228			8.38	8.39	B	9
20	C_6H_5	CH_3	$-CH(CH_3)CH_2$–(3-indolyl)	$C_{22}H_{27}N_3O$	HCl	207–209	10.89	10.78	9.19	9.23	B	30
21	C_6H_5	CH_3	$-CH(CH_3)CH_2$–(2-pyrazinyl)	$C_{15}H_{21}N_4O$[g]			17.94	17.40[h]			A	58
22	C_6H_5	CH_3	$-CH(CH_3)CH_2CH_2C_6H_5$	$C_{21}H_{28}N_2O$	HCl	233–236	7.76	8.14	9.83	9.77	B	20
23	C_6H_5	CH_3	$-C_5H_9$	$C_{16}H_{24}N_2O$	HCl	206–207.5	9.44	9.71	11.95	11.91	B	45
24	C_6H_5	CH_3	$-C_6H_{11}$	$C_{17}H_{26}N_2O$	HCl	238.5–239.5	9.01	9.33	11.41	11.43	B	54
25	C_6H_5	CH_3	$-C_7H_{13}$	$C_{18}H_{28}N_2O$	HCl	229–230	8.62	8.34	10.92	10.98	B	47
26	C_6H_5	CH_3	$-C_8H_{15}$	$C_{19}H_{30}N_2O$	HCl	197–198.5	8.27	8.19	10.46	10.48	B	31
27	C_6H_5	CH_3	$-C_6H_{10}$–C_6H_5	$C_{23}H_{30}N_2O$	HCl	159–161	7.21	7.15	9.16	9.12	B	21

28	C_6H_5	CH_3		$C_{21}H_{26}N_2O$	HCl	149–152	7.81	7.48		B	49	
30	C_6H_{11}	CH_3	$-CH(CH_3)_2$	$C_{14}H_{25}N_2O$	HCl	166–169			12.81	12.55	A	47
31	C_6H_{11}	CH_3	$-CH(CH_3)C_6H_5$	$C_{19}H_{30}N_2O$	HCl	233.5–234	8.27	8.68	10.46	10.39	B	61
32	C_6H_{11}	CH_3	$-CH(C_2H_5)C_6H_5$	$C_{20}H_{32}N_2O$	HCl	227–228.5	7.94	8.38	10.05	10.40	B	48
33	C_6H_{11}	CH_3	$-CH(CH_3)CH_2C_6H_{11}$	$C_{20}H_{38}N_2O$	HCl	227–229	7.81	7.99	9.88	9.82	B	34
34	C_6H_{11}	CH_3	$-CH(CH_3)CH_2C_6H_5$	$C_{20}H_{32}N_2O$	HCl	213–214.5	7.94	8.14	10.05	9.91	A	51
35	C_6H_{11}	CH_3	$-CH(CH_3)CH(OH)C_6H_5$	$C_{20}H_{32}N_2O_2$	HCl	193–195[i]	7.60	7.76	9.61	9.77	A	35[j]
36	C_6H_{11}	CH_3	$-CH(CH_3)CH_2CH_2C_6H_5$	$C_{21}H_{34}N_2O$	HCl	182.5–184.5	7.64	7.82	9.66	9.78	A	17[k]
37	C_6H_{11}	CH_3		$C_{23}H_{36}N_2O^g$		136.5–138.5	7.86	8.11[k]		B	32	
39	C_6H_5	C_6H_5	$-CH(CH_3)_2$	$C_{21}H_{30}N_2O^l$	HCl	149–151	7.39	7.55	9.36	9.41	A	52
40	C_6H_5	C_6H_5	$-CH(CH_3)CH_2C_6H_5$	$C_{27}H_{34}N_2O^p$			7.52	7.76[m]			A	47
42		CH_3	$-CH(CH_3)CH_2C_6H_5$	$C_{21}H_{28}N_2O_2$	HCl	215–216.5	7.43	7.46	9.41	9.07	B	46
44		CH_3	$-CH(CH_3)CH_2C_6H_5$	$C_{21}H_{34}N_2O_2$	HCl	210–212			9.26	9.14	B	30

[a] *Anal.* Calcd.: C, 67.80; H, 7.27. Found: C, 68.01; H, 7.41. [b] Crystallized from ethanol. [c] Average yield. [d] $[\alpha]_D$ +23.6°. For solvent and concentration of all rotations, see footnote 21. [e] $[\alpha]_D$ −24.3°. [f] *l*-Isomer: $[\alpha]_D$ −39.4°. [g] Free base. [h] *Anal.* Calcd.: C, 69.20; H, 7.75. Found: C, 69.32; H, 7.46. [i] *l*-Isomer: $[\alpha]_D$ −27.0°. [j] Crystallized from 2-propanol–ether. [k] *Anal.* Calcd.: C, 77.48; H, 10.18. Found: C, 77.47; H, 10.09. [l] Monoethanolate. [m] *Anal.* Calcd.: C, 80.61; H, 7.58. Found: C, 81.25; H, 7.76.

(**A**) **3-Methyl-4-nitroso-2-phenylmorpholine** (**3**).—The various isomers were prepared by the above general procedure in crude yields of 90–98%.

(1) **From** *d,l*-**3-Methyl-2-phenylmorpholine.**—The product was a pale yellow solid. Recrystallization from Skellysolve C yielded the pure material, m.p. 66.5–68°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.05; H, 6.84. Found: C, 64.09; N, 6.78.

(2) **From** *d*-**3-Methyl-2-phenylmorpholine.**—This product was not isolated but was used directly in the next step.

(3) **From** *l*-**3-Methyl-2-phenylmorpholine.**—This product was not isolated but was used directly in the next step.

(**B**) **2,3-Diphenyl-4-nitrosomorpholine** (**51**).—Using the general procedure this compound was prepared in 95% yield. The product was not purified but was used directly in the next step.

(**C**) **2-(4-Methoxyphenyl)-3-methyl-4-nitrosomorpholine** (**52**) was prepared by the general procedure, was not isolated, but was used directly in the next step.

(**D**) **2-Cyclohexyl-3-methyl-4-nitrosomorpholine** (**53**).—Using the general procedure, this compound was prepared in 95–100% yield. The product, a pale yellow solid, m.p. 51–55°.

Anal. Calcd. for $C_{11}H_{20}N_2O_2$: C, 62.23; H, 9.50; N, 13.20. Found: C, 61.85; H, 9.26; N, 13.33.

(**E**) **2-(4-Methoxycyclohexyl)-3-methyl-4-nitrosomorpholine** (**54**) was prepared by the general procedure, was not isolated, but was used directly in the next step.

General Procedure for the Preparation of 2,3-Disubstituted-4-aminomorpholines.—A suspension of 0.75 mole of $LiAlH_4$ in 1000 ml. of anhydrous ether is heated under reflux with stirring for 30 min. On removal of the source of heat, 0.5 mole of the appropriate 4-nitrosomorpholine in 750 ml. of ether, benzene, or tetrahydrofuran is added at a rate consistent with the exothermic reaction. On completion of the addition, the mixture is stirred at room temperature for an additional 30 min. followed by heating under reflux for 2.5 hr. The reaction mixture is now cooled in an ice bath while sufficient ethyl acetate is added to decompose the excess $LiAlH_4$. The complex is decomposed by addition of (1) 4 ml. of water per 0.1 mole of $LiAlH_4$ used, (2) 3 ml. of 20% NaOH per 0.1 mole of $LiAlH_4$ used, and (3) 14 ml. of water per 0.1 mole of $LiAlH_4$ used. The inorganic salts are removed by filtration and the filtrate is stripped of solvent at reduced pressure to yield the crude 4-aminomorpholine. Purification *via* the hydrochloride salt is accomplished by acidification of an ethanol solution of the base with hydrogen chloride in 2-propanol and adding anhydrous ether to turbidity. Recrystallization from ethanol–ether gives the pure hydrochloride.

(**A**) **4-Amino-3-methyl-2-phenylmorpholine** (**4**).—The various isomers were prepared by the above procedure. The yields of crude base varied between 90 and 100%.

(1) **From** *d,l*-**3-Methyl-4-nitroso-2-phenylmorpholine.**—The product, a yellow oil, had $n^{25}D$ 1.5454.

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.51. Found: C, 68.55; H, 8.17; N, 14.48.

Hydrochloride salt: m.p. 193–194.5°.

Anal. Calcd. for $C_{11}H_{17}ClN_2O$: N, 12.25; Cl, 15.50. Found: N, 12.63; Cl, 15.34.

(2) **From** *d*-**3-Methyl-4-nitroso-2-phenylmorpholine.**—The product, a pale yellow oil, had $[\alpha]_D$ +36.1°.

Hydrochloride salt: m.p. 187–190°, $[\alpha]_D$ +34° (H_2O).

Anal. Calcd. for $C_{11}H_{17}ClN_2O$: N, 12.25; Cl, 15.50. Found: N, 12.00; Cl, 15.32.

(3) **From** *l*-**3-methyl-4-nitroso-2-phenylmorpholine.**—The product, a yellow oil, had $[\alpha]_D$ −42.3°.

(**B**) **4-Amino-2,3-diphenylmorpholine** (**38**).—Using the general procedure with tetrahydrofuran as solvent for the nitrosamine, this compound was prepared in 97% yield of crude free base. The orange oil was purified as the hydrochloride salt, m.p. 209–211°.

Anal. Calcd. for $C_{16}H_{19}ClN_2O$: Cl, 12.19. Found: Cl, 12.02.

(**C**) **4-Amino-2-(4-methoxyphenyl)-3-methylmorpholine** (**41**).—This compound was prepared by the general procedure, using benzene as the solvent for the nitrosamine. The product, a brown oil, was obtained in 94% yield. Purification as the hydrochloride salt gave a crystalline solid, m.p. 214.5–216°.

Anal. Calcd. for $C_{12}H_{19}ClN_2O_2$: N, 10.83; Cl, 13.70. Found: N, 11.10; Cl, 13.23.

(**D**) **4-Amino-2-cyclohexyl-3-methylmorpholine** (**29**).—Using the general procedure, the crude free base was prepared in 92–

97% yield as a colorless oil. The hydrochloride had m.p. 212–214°.

Anal. Calcd. for $C_{11}H_{23}ClN_2O$: C, 56.27; H, 9.87; N, 11.94. Found: C, 56.22; H, 9.53; N, 11.91.

(E) 4-Amino-2-(4-methoxycyclohexyl)-3-methylmorpholine (43).—Using the general procedure, with benzene as the solvent for the nitrosamine, the crude free base was prepared in 82% yield as an orange oil. The hydrochloride had m.p. 206–208°.

Anal. Calcd. for $C_{12}H_{25}ClN_2O_2$: N, 10.58; Cl, 13.39. Found: N, 10.84; Cl, 13.35.

General Procedure for Reductive Alkylation of 4-Amino-2,3-disubstituted Morpholines. (A) Without Acetic Acid Catalysis.—A mixture of 0.0445 mole of the appropriate 4-aminomorpholine and 0.05 mole of a carbonyl compound is stirred at room temperature until the exothermic reaction from hydrazone formation has subsided.[25] The mixture is then taken up in 150 ml. of methanol, 0.5 g. of platinum oxide catalyst is added, and the mixture is hydrogenated at room temperature at a pressure of 4.2 kg./cm.^{2}. When hydrogen uptake has ceased, representatively 6–11 hr., the catalyst is removed by filtration and solvent is stripped at reduced pressure. The oily residue is dissolved in ethanol and is converted to a salt by addition of hydrogen chloride in 2-propanol or hydrogen bromide in ethanol. Addition of ether induces crystallization and recrystallization from ethanol–ether gives the pure salt.

(B) With Acetic Acid Catalysis.—A mixture of 0.05 mole of the appropriate 4-aminomorpholine and 0.055 mole of a carbonyl compound is stirred at room temperature until hydrazone formation is completed.[25] To this mixture is added 3.0 g. of glacial acetic acid and when the exothermic reaction has subsided the mixture is taken up in 30–50 ml. of ethanol. Addition of 0.25 g. of platinum oxide catalyst is followed by hydrogenation at room temperature and pressures of 77.3–140.6 kg./cm.^{2}.[26] When hydrogen uptake has ceased, representatively 1–6 hr., the catalyst is removed by filtration and solvent is stripped at reduced pressure. The oily residue is suspended in 50 ml. of water and the mixture is made alkaline with 6 *N* sodium hydroxide. The base is extracted with ether and the extracts are dried over anhydrous potassium carbonate. Removal of solvent followed by conversion to the salt as described in part A gives the desired product in pure form.

The compounds shown in Table II were prepared by the above procedures and the methods used and yields obtained are shown in that table.

Aldehydes and Ketones.—All carbonyl compounds used in the above procedures for the preparation of the compounds in Table II were purchased with the exception of the following compounds.

***l*-1-Hydroxy-1-phenyl-2-propanone** was prepared by fermentation of benzaldehyde.[27] The product had b.p. 65–67° (0.4 mm.), $n^{25}D$ 1.5296, $[\alpha]D$ −223.2°; lit.,[27] b.p. 124–125° (12 mm.), $n^{20}D$ 1.5315, $[\alpha]^{23}D$ −181.9° (ethanol).

4-Phenyl-2-butanone was prepared by reduction of benzalacetone,[28] b.p. 56–57° (0.4 mm.), $n^{25}D$ 1.5102; lit.,[28] b.p. 112–113° (12 mm.).

2-Pyrazynylacetone was prepared from 2-methylpyrazine,[29] b.p. 110–113° (8 mm.), $n^{25}D$ 1.5209; lit.,[29] b.p. 113–114° (9 mm.).

2-Phenylcyclohexanone was prepared from 2-chlorocyclohexanone,[30] m.p. 57–60°; lit.,[30] m.p. 59.5–60°.

3-Indolylacetone was prepared by the method of Jones and co-workers.[31] The product had m.p. 109–112°; lit.,[31] m.p. 115–117.5°.

3,4-Dimethoxyphenylacetone was prepared by the method of Stein and co-workers[32] to yield a product, b.p. 102–104° (0.1 mm.); lit.,[32] b.p. 118° (0.4 mm.).

4-N-Formamido-3-methyl-2-phenylmorpholine (55).—A solution of 50 g. (0.26 mole) of 4-amino-3-methyl-2-phenylmorpholine (**4**) in 384 g. (5.2 moles) of ethyl formate was heated under reflux for 4 hr. The excess ethyl formate was removed at reduced pressure to yield an orange solid. Recrystallization from 150 ml. of absolute ethanol gave 41 g. (71.7%) of an off-white solid, m.p. 168–170.5°.

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.72; H, 7.61; N, 12.81.

3-Methyl-4-methylamino-2-phenylmorpholine Hydrochloride (6).—A mixture of 8.1 g. (0.213 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran was heated at 35–40° for 30 min. On removal of the heat, a solution of 41 g. (0.186 mole) of 4-*N*-formamido-3-methyl-2-phenylmorpholine (**55**) in 600 ml. of tetrahydrofuran was added over 1.75 hr. The mixture was now heated under reflux, with stirring, for 4 additional hr. While cooling in an ice bath, the excess hydride was destroyed by addition of ethyl acetate followed by decomposition of the complex with (1) 8.5 ml. of water, (2) 6.4 ml. of 20% sodium hydroxide, and (3) 29.8 ml. of water. The salts were removed by filtration and the residue was stripped of solvent to give 34.6 g. of yellow oil. The free base was converted to the hydrochloride which was crystallized from ethanol and ether. Recrystallization from these solvents gave the product as a white crystalline solid, m.p. 135–137°.

Anal. Calcd. for $C_{12}H_{19}ClN_2O$: N, 11.54; Cl, 14.61. Found: N, 11.72; Cl, 14.56.

4-Dimethylamino-3-methyl-2-phenylmorpholine Hydrochloride (7).—Formylation of 26.6 g. (0.129 mole) of 3-methyl-4-methylamino-2-phenylmorpholine (**6**) was achieved by refluxing in 191 g. (2.58 moles) of ethyl formate for 7 hr. Removal of the solvent yielded 27.9 g. of yellow oil which crystallized on standing. Reduction of the formylamine was achieved by adding a solution of 27.2 g. (0.116 mole) of this material in 200 ml. of tetrahydrofuran to a mixture of 6.61 g. (0.174 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran over 1.5 hr. and refluxing the resulting mixture for 5 hr. Work-up, as described for the monomethylated compound **6**, using (1) 6.96 ml. of water, (2) 5.22 ml. of 20% sodium hydroxide, and (3) 24.4 ml. of water to decompose the complex, gave 23.7 g. of the crude free base. The base was distilled at reduced pressure to yield 17.3 g. of pure material, b.p. 100–101° (0.8 mm.), $n^{25}D$ 1.5230.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.86; H, 9.15. Found: C, 70.68; H, 9.24.

Conversion of this base to the hydrochloride and crystallization from ethanol–ether gave a white granular solid with m.p. 190–191°.

Anal. Calcd. for $C_{13}H_{21}ClN_2O$: N, 10.91; Cl, 13.81. Found: N, 10.54; Cl, 13.94.

4-Benzylamino-3-methyl-2-phenylmorpholine Hydrochloride (9).—A mixture of 10 g. (0.052 mole) of 4-amino-3-methyl-2-phenylmorpholine (**4**) and 5.8 g. (0.055 mole) of benzaldehyde was treated with 3.0 g. of glacial acetic acid. When the exothermic reaction had subsided, the viscous oil was dissolved in 150 ml. of absolute ethanol, 0.5 g. of platinum oxide catalyst was added, and the mixture was hydrogenated at 117.74–131.81 kg./cm.^{2}. Hydrogen uptake stopped after 3 hr. when more than 100% of theory had been absorbed. Removal of catalyst by filtration gave a solution from which a crystalline product was deposited. Recrystallization of this material from methanol yielded colorless needles with m.p. 91.5–94°. Spectral analysis showed the product to be the hydrazone, despite the uptake of hydrogen. The yield was 58%.

Anal. Calcd. for $C_{18}H_{20}N_2O$: C, 77.10; H, 7.19; N, 10.00. Found: C, 76.79; H, 7.05; N, 9.98.

A solution of 7.6 g. (0.0272 mole) of the crystalline hydrazone in 150 ml. of absolute ethanol and 3.0 g. of glacial acetic acid was treated with 0.5 g. of platinum oxide catalyst and was again hydrogenated at 121.3–133.6 kg./cm.^{2}. Hydrogen uptake stopped after 2.5 hr. The catalyst was removed and after distillation of solvent the residue was suspended in 25 ml. of water and was made alkaline with 6 *N* sodium hydroxide. Extraction with ether, followed by drying over anhydrous potassium carbonate and removal of solvent, yielded a yellow oil. Conversion to the hydrochloride and crystallization from ethanol–ether gave a white crystalline solid, m.p. 156–159°. Spectral analysis showed that the double bond had now been saturated.

(25) In some cases there was no observable evidence of hydrazone formation.

(26) Reduction may also be carried out at 3.51–4.22 kg./cm.^{2} in which case 150–200 ml. of ethanol and 0.5 g. of platinum oxide are used.

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Anal. Calcd. for $C_{18}H_{23}ClN_2O$: C, 67.80; H, 7.27; N, 8.79. Found: C, 68.01; H, 7.41; N, 9.12.

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Behavioral and Neuropharmacological Actions of 3-Methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine and Associated 4-Aminomorpholines

DONALD L. KNAPP

Division of Biological Research, G. D. Searle and Company, Chicago 80, Illinois

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A number of substituted 4-aminomorpholines have been examined for their neuropharmacological and behavioral effects. Methods utilized and results obtained with these materials are presented. One of these compounds, 3-methyl-4-(1-phenyl-2-propylamino)-2-phenylmorpholine, was selected for more intensive biological evaluation. A selective effect of this compound upon conditioned behavior is among the findings presented in detail.

Much laboratory work over the period of the last 20 years has been devoted to the synthesis and biological evaluation of compounds bearing either direct or remote configural resemblances to endogenously occurring psychoactive materials, of which the catecholamines represent a prominent example. Numerous derivatives of epinephrine have been studied[1-3] and several clinically useful materials, notably *d*-amphetamine and methamphetamine, have come out of this research. Of the many lines of investigation which have been opened up by this work, two of importance include phenmetrazine, which may be conceived as a cyclized amphetamine, and the hydrazine derivatives of amphetamine. Although perfectly consistent structure–activity relationships are lacking, it would appear that the central nervous stimulant aspect of drug action will survive either type of structural modification,[4,5] while the hydrazine substitution imparts additionally a monoamine oxidase inhibiting property to chemicals so prepared.[5,6] The possibility that compounds possessing structural features which included both the morpholine and hydrazine substituents might reveal important biological activities led to the investigation of a series of substituted 4-aminomorpholines.

A report covering the chemical preparation of some 41 of these compounds has been presented in the preceding paper.[7] In order to promote effective communication, the compound numbering system utilized therein will be preserved in the present report.

Materials and Methods

A list of several compounds selected for preliminary biological screening is given in Table I. It should be mentioned that for the sake of brevity only structures which were found to be "active" in one or more tests are included therein. A comprehensive list of structures tested, including those which were "inactive," can be found by referring to Table II of the preceding chemical paper.[7] The preliminary screening series included tests 1 through 4 described below. Tests 6 through 13 were considered to represent follow-up work on structures with more interesting activities. All compounds were administered as normotonic saline solutions or as microcrystalline suspensions. Physiological saline (0.9%) was the usual dissolving medium, but in some cases ethylene carbonate, propylene carbonate, or these two in equal parts were utilized. Control tests with the various solvents in appropriate concentrations revealed no measurable biological effects. The methods employed for individual tests were as follows.

(A) **Preliminary Screening Tests.** (1) **Four-Hour Mouse Test.**—This test is an adaptation of the mouse screening procedure developed by Irwin.[8] The primary function of this test is to provide as rapidly as possible specific, quantitative data regarding the number and kinds of central and other effects which compounds may induce *in vivo*. To this end, male albino mice are observed and manipulated both before and after intraperitoneal administration of test compounds. A wide variation in dosage is employed, and ratings of both spontaneous and elicited behavior are recorded periodically, in order to provide data relevant to questions of potency and onset, peak, and duration of action. In the present experiments, ratings for dose groups were summed over a 4-hr. period and compared with scores obtained with standard reference materials, such as *d*-amphetamine (stimulant) or thiopropazate (depressant). Compounds achieving scores equal to those produced by the reference materials, whether at doses equal to, 2, or 4 times the minimally active doses of the reference compounds, were considered to be "stimulant" or "depressant." The determination of LD_{50} doses (doses lethal to 50% of mice so treated) was by simple count at the end of the 4-hr. period.

(2) **Four-Hour Cat Test.**—This test combines many of the features of the procedures developed independently by Irwin[8] and S. Norton[9] for the study of the effects of drugs in the cat. In our experiments, testing was carried out in a fully lit laboratory room containing six contiguous wire-mesh observation cages (76.2 × 81.4 × 142.4 cm.), which permitted the cats virtually complete visual access to each other and to the experimenter, as well as providing sufficient floor space to encourage locomotor activity in subjects so inclined. Subjects were of either sex, and no studies involving test drugs were permitted with a given

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