[CONTRIBUTION FROM THE RESEARCH DIVISION, LAKESIDE LABORATORIES, INC., AND THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF WASHINGTON]

A New Class of Potent Monoamine Oxidase Inhibitors. Chemistry and Structure-Activity Relationships of Aminoalkylhydrazines

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A series of (*N*,*N*-disubstituted)aminoalkylhydrazines was prepared *via* hydrazinolysis of the corresponding aminoalkyl halides or reductive hydrazinolysis of the appropriate aminoaldehyde or ketone. The latter route was the method of choice in the synthesis of compounds with substituents on the terminal hydrazino nitrogen. The aralkylaminoalkylhydrazines were potent monoamine oxidase inhibitors equal in activity to the previously described aralkyl hydrazines. Substitution on the phenyl ring often enhanced that activity, while substituents on the hydrazino nitrogen generally decreased or abolished the monoamine oxidase inhibitory activity of the parent compounds.

The potent monoamine oxidase inhibitory properties of a series of aralkylhydrazines[1,2,3] and the subsequent demonstration of the clinical usefulness of one of the compounds (α-methylphenethylhydrazine[4]) by various investigators[5-12] in the treatment of mental depression, angina pectoris, arthritis, and essential hypertension prompted the evaluation of a series of aminoalkylhydrazines as potential monoamine oxidase inhibitors:

$$Am—CH_2CH_2NH—Am_1$$

The compounds, where Am represented a dialkylamino or heterocyclic amino group and Am_1 an amino, dialkylamino, or heterocyclic amino moiety, were described previously from the standpoint of synthesis, as well as their chemical and hypotensive properties.[13] As monoamine oxidase inhibitors they were subsequently found inactive.[14] However, those compounds in which Am was arylamino, aralkylamino, or aralkyl alkylamino proved to be highly effective inhibitors of monoamine oxidase and the series was therefore extended to establish possible structure-activity relationships.

Two preparative methods were employed for the synthesis of the above compounds: In the case of

$$Am—C_2H_4Cl + H_2N—Am_1 \quad (1)$$

$$\downarrow$$

$$AmC_2H_4NHAm_1$$

$$AmCH_2CHO + H_2N—Am_1 \longrightarrow \uparrow LiAlH_4$$

$$AmCH_2CH{=}N—Am_1 \quad (2)$$

$Am_1 = NH_2$, method 1 was preferred. The aminoalkyl halide reacted with a 400% excess of hydrazine hydrate in ethanol. The large excess of hydrazine prevented the formation of disubstitution products. In the case where Am_1 was a mono- or disubstituted amino group, only method 2 was applicable, in order to achieve symmetrical substitution. Alkylation of a mono- or unsymmetrically disubstituted hydrazine will usually occur on the most fully substituted nitrogen and is therefore of no avail when symmetrical substitution is desired.[15]

The mono(aminoalkyl)hydrazines were quite unstable in the form of their bases evolving nitrogen on distillation and standing at room temperature. Their crystalline salts, however, were stable and could be stored for an indefinite period of time without decomposition. The *N*,*N*′-disubstituted hydrazines, on the other hand, were quite stable and their bases could be assayed successfully. Two compounds having a branched alkylene chain separating the amino from the hydrazine moiety did not form crystalline salts: 1-(*N*-methyl-*N*-3-chlorobenzyl)amino-2-hydrazinopropane, as well as the unsubstituted benzyl derivative.

N-Methyl-*N*-aralkylaminoalkanols were prepared by treating ethylene chlorohydrin with the

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(11) L. Gillespie, L. T. Terry, and A. Sjoerdsma, *Am. Heart J.*, **58**, 1 (1959).

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(13) J. H. Biel, A. E. Drukker, and T. F. Mitchell, *J. Am. Chem. Soc.*, **82**, 2204 (1960).

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(15) C. C. Clark, *Hydrazine*, 1st ed., Mathieson Chemical Corp., Baltimore, Md., 1953, p. 30.

TABLE I

$RC_6H_4—CH_2N(CH_3)—CH_2CH(R')—OH$

R	R′	B.P./mm.	n_D^{20}	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2,6-Cl_2	H	100/0.15	1.5527	$C_{10}H_{13}Cl_2NO$[a]	5.98	5.88
3-Cl	H	103/0.55	1.5407	$C_{10}H_{14}ClNO$[b]	7.02	7.10
4-Cl	H	108/0.7	1.5402	$C_{10}H_{14}ClNO$[c]	7.02	6.90
3,4-O_2CH_2	H	130/0.4	1.5423	$C_{11}H_{15}NO_3$	6.69	6.53
3-OCH_3	H	118/0.95	1.5316	$C_{11}H_{17}NO_2$	7.17	7.22
2-CH_3	H	95/0.6	1.5250	$C_{11}H_{17}NO$	7.81	7.70
3-Cl	CH_3	100/0.4	1.5249	$C_{11}H_{16}ClNO$[d]	6.57	6.83
H	CH_3	90/1.2	1.5103	$C_{11}H_{17}NO$	7.83	7.81
4-F	H	81/0.1	1.5083	$C_{10}H_{14}FNO$	7.64	7.58

[a] Calcd.: Cl, 30.29. Found: Cl, 29.91. [b] Calcd.: Cl, 17.76. Found: Cl, 18.07. [c] Calcd.: Cl, 17.76. Found: Cl, 17.81. [d] Calcd.: Cl, 16.59. Found: Cl, 16.83.

TABLE II

$RC_6H_4—CH_2N(CH_3)—CH_2CHCl(R')\cdot HCl$

R	R′	M.P.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Ionic Halide Calcd.	Ionic Halide Found
2,6-Cl_2	H	151–153	$C_{10}H_{13}Cl_4N$	4.85	4.76	12.27	12.16
4-F	H	165	$C_{10}H_{14}Cl_2FN$	5.88	5.90	14.90	14.77
2-Cl	H	193–195	$C_{10}H_{14}Cl_3N$	5.50	5.45	13.95	13.90
4-Cl	H	186–189	$C_{10}H_{14}Cl_3N$	5.50	5.45	13.95	13.99
2-CH_3	H	193–195	$C_{11}H_{17}Cl_2N$	5.98	5.88	15.14	15.10
3-Cl	CH_3	134–136	$C_{11}H_{16}Cl_3N$	5.21	5.18	13.20	13.44
H	CH_3	177–179	$C_{11}H_{17}Cl_2N$	5.98	6.03	15.14	15.06
3-OCH_3	H	128–130	$C_{11}H_{17}Cl_2NO$	5.60	5.62	14.17	14.14
4-OCH_3	H	152–154	$C_{11}H_{17}Cl_2NO$	5.60	5.64	14.17	14.24

TABLE III

$RC_6H_4—CH_2N(CH_3)C_2H_4NHNH_2$

R	Formula	Salt	Salts: Nitrogen, % Calcd.	Salts: Nitrogen, % Found	Salts: Anion, % Calcd.	Salts: Anion, % Found	M.P.
H	$C_{10}H_{17}N_3$	Dimaleate	10.21	10.24			124–125
		2 HCl	16.68	16.65	28.12	28.03	189
		2 H_3PO_4	11.19	11.12	52.23	52.98	152
2-CH_3	$C_{11}H_{19}N_3$	2 HCl	15.79	15.67	26.64	26.33	182–185
2-OCH_3	$C_{11}H_{19}N_3O$	Difumarate	9.50	9.78			125–128
3-OCH_3	$C_{11}H_{19}N_3O$	2 HCl	14.88	15.09	25.13	25.06	189–191
4-OCH_3	$C_{11}H_{19}N_3O$	2 HCl	14.88	15.00	25.13	25.01	188–190
3,4-O_2CH_2	$C_{11}H_{17}N_3O_2$	2 HCl	14.19	14.15	23.94	23.92	189–191
2-SCH_3	$C_{11}H_{19}N_3S$	Dimaleate	9.19	9.03	7.01[a]	7.07	103–105
2-Cl	$C_{10}H_{16}ClN_3$	2 HCl	14.66	14.38	24.74	25.20	166–169
3-Cl	$C_{10}H_{16}ClN_3$	2 HCl	14.66	14.53	24.74	24.78	203–204
4-Cl	$C_{10}H_{16}ClN_3$	2 HCl	14.66	15.03	24.74[b]	24.66	187–189
4-F	$C_{10}H_{16}FN_3$	2 HCl	15.55	15.50	26.25	26.42	191–192

[a] Sulfur assay. [b] Total chloride, Calcd.: 37.11. Found: 37.23.

N-methylaralkylamines,[16] by the Eschweiler-Clark methylation of the *N*-aralkylaminoalkanols[17] or by reaction of an alkylene oxide with an *N*-methylaralkylamine.[18] The only exception was *N*-methyl-*N*-(2-thiomethyl)benzylaminoethanol, which was prepared by the lithium aluminum hydride reduction of *N*-methyl-*N*-(2-thiomethyl)benzoylaminoethanol. Compounds not previously reported in the literature are listed in Table I.

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(17) W. Wilson, *J. Chem. Soc.*, 3524 (1952).

(18) W. H. Horne and R. L. Shriner, *J. Am. Chem. Soc.*, **54**, 2925 (1932).

The *N*-methyl-*N*-aralkylaminoalkyl chlorides were synthesized from the corresponding alcohols by treatment with thionyl chloride.[19] Compounds not previously reported are listed in Table II.

The *in vitro* and *in vivo* data relative to the monoamine oxidase inhibitory properties of the aminoalkylhydrazines are listed in Table IV. The methods

TABLE IV

$RC_6H_4-(CH_2)_nN(CH_3)C_2H_4NHNH_2$

	R	*In Vivo*[b] Potency (Iproniazid = 1)	*In Vitro* Potency $10^{-5}M$	*In Vitro* % inhibition $10^{-6}M$
1	H	12		70
2	2-CH_3	20	82	60
3	2-OCH_3	4		
4	3-OCH_3	8	100	30
5	4-OCH_3	20	97	89
6	3,4-O_2CH_2	20	89	41
7	2-SCH_3	4	100	100
8	2-Cl	20		
9	3-Cl	16	100	13
10	4-Cl	20	100	40
11	4-F	20		
12	H	40	100	65

[a] $n = 1$ except for compound 12 where $n = 0$. [b] Drug administered to mice (i.p.) 2 hr. prior to the administration of 5.0 mg./kg. (i.p.) of reserpine.

of evaluation were identical to those employed for the aralkylhydrazines.[2] This series generally afforded compounds with potent enzyme inhibitory activities. In contrast to the aralkylhydrazines, the aralkylamino derivatives showed improved potency when the phenyl ring was substituted with an alkyl, halogen, 4-methoxy or 3,4-methylenedioxy group. Furthermore, these compounds did not display the potent amphetamine-like effects (direct central stimulation and pressor action) exhibited, for instance, by α-methyl-phenethylhydrazine.[2] Di- or trisubstitution of the hydrazine moiety as well as replacement of the arylamino or aralkylamino moiety by dialkylamino or heterocyclic amino groups resulted in complete loss of activity. The most potent compound (no. 12) was an arylaminoalkylhydrazine with an *in vivo* potency equal to α-methylphenethylhydrazine.

EXPERIMENTAL

N-Methylaralkylamines were prepared by reduction of the Schiff's bases, obtained from *N*-methylamine and aromatic aldehydes, with either Raney nickel[20] or sodium borohydride.[21] Compounds not previously listed in the literature are:

2-Methoxybenzaldehyde-N-methylimide, b.p. 105° (10 mm.)

Anal. Calcd. for $C_9H_{11}NO$: N, 9.39. Found: N, 9.34.

3-Methoxybenzaldehyde-N-methylimide, b.p. 107° (12 mm.), n_D^{20} 1.5575.

Anal. Calcd. for $C_9H_{11}NO$: N, 9.39. Found: N, 9.23.

3-Chlorobenzaldehyde-N-methylimide, b.p. 104° (14 mm.).

Anal. Calcd. for C_8N_8ClN: N, 9.12. Found: N, 9.02.

2,6-Dichlorobenzaldehyde-N-methylimide, m.p. 56–60°.

Anal. Calcd. for $C_8H_7Cl_2N$: Cl, 37.71. Found: Cl, 37.58.

N-Methyl-2-methylbenzylamine, b.p. 80° (11 mm.), n_D^{20} 1.5235.

Anal. Calcd. for $C_9H_{13}N$: N, 10.36. Found: N, 10.33.

N-Methyl-3-chlorobenzylamine, b.p. 97° (6.6 mm.).

Anal. Calcd. for $C_8H_{10}ClN$: N, 8.99. Found: 9.03.

N-Methyl-2,6-dichlorobenzylamine, b.p. 67° (0.4 mm.), n_D^{20} 1.5589.

Anal. Calcd. for $C_8H_9Cl_2N$: N, 7.37; Cl, 37.31. Found: N, 7.34; Cl, 37.43.

N-Methyl-N-2-thiomethylbenzoylaminoethanol. To a refluxing solution of 100 g. (1.33 moles) of *N*-methylaminoethanol in 550 cc. of dry benzene was added in 1 hr. a solution of 53 g. (0.28 mole) of 2-thiomethylbenzoylchloride[22] in 200 cc. of benzene. After a 5-hr. reflux period the benzene layer was extracted with water, the aqueous extracts were saturated with potassium carbonate and extracted with tetrahydrofuran. The extracts were dried over potassium carbonate, filtered and the solvent was removed by distillation. Residual methylaminoethanol was removed at high vacuum. A residue of 54.4 g. (88%) dark oil remained.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: N, 6.22; S, 14.23. Found: N, 6.18; S, 14.26.

N-Methyl-N-2-thiomethylbenzylaminoethanol. To a suspension of 9.5 g. (0.25 mole) of lithium aluminum hydride in 500 cc. of tetrahydrofuran was added in 25 min. a solution of 52 g. (0.231 mole) of crude *N*-methyl-*N*-2-thiomethylbenzoylaminoethanol in 150 cc. of tetrahydrofuran. After stirring for 20 hr. at room temperature the reduction complex was decomposed with aqueous potassium hydroxide, filtered and the solution was dried over potassium carbonate. After removing the solvent by distillation we obtained 36.4 g. (74.6%), b.p. 110°/0.04 mm., n_D^{20} 1.5730.

Anal. Calcd. for $C_{11}H_{17}NO_2$: N, 6.63; S, 15.17. Found: N, 6.50; S, 15.17.

N-Methyl-N-2-chlorobenzylaminoacetaldehyde diethylacetal. A solution of 155.5 g. (1 mole) of *N*-methyl-2-chlorobenzylamine, 197 g. (1 mole) of bromoacetal, and 101 g. (1 mole) of triethylamine in 1 l. of toluene was refluxed for 12 hr. The amine hydrochloride was removed by filtration, and the toluene was removed by distillation. Fractionation of the residue yielded 205.5 g. of product (75%), boiling at 110°/0.4 mm., n_D^{20} 1.4995.

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: N, 5.15. Found: 5.22.

N-[2-(N-methyl-N-2-chlorobenzylamino)ethylidenyl]aminopyrrolidine. To 250 g. of 38% aqueous hydrochloric acid was added 66 g. (0.242 mole) of *N*-methyl-*N*-2-chlorobenzylaminoacetaldehyde diethylacetal while cooling with ice water. After 2 hr. the excess of hydrochloric acid was removed by distillation *in vacuo* using a 60° water bath and the residue was taken up in 250 cc. of water. The excess of free hydrochloric acid was neutralized with dilute alkali and to the solution was added dropwise a solution of 24.4 g. (0.26 mole) of *N*-aminopyrrolidine in 250 cc. of water. After standing at room temperature for 24 hr. the solution was saturated with potassium hydroxide and the hydrazone was extracted repeatedly with ether. The etheral extracts were dried over potassium carbonate, filtered and the ether removed by distillation; b.p. 130°/0.3 mm., n_D^{20} 1.5576.

Anal. Calcd. for $C_{14}H_{20}ClN_3$: N, 15.81. Found, N, 15.75.

The following previously unknown compounds were prepared by the same method:

(19) J. B. Wright, E. H. Lincoln, R. V. Heinzelmann, and J. H. Hunter, *J. Am. Chem. Soc.*, **72**, 3536 (1950).

(20) A. R. Surrey, A. J. Olivet, and J. O. Hoppe, *J. Am. Chem. Soc.*, **76**, 4920 (1953).

(21) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22**, 1068 (1957).

(22) E. W. McClelland and L. A. Warren, *J. Chem. Soc.*, 2625 (1929).

N-[2-(N-methyl-N-2-chlorobenzylamino)ethylidenyl]-aminomorpholine. b.p. 161°/0.06 mm., n_D^{20} 1.5547.

Anal. Calcd. for $C_{14}H_{20}ClN_3O$: N, 14.91; Cl, 12.58. Found: N, 14.89; Cl, 12.67.

N-Dimethyl-N'-2-(N-methyl-N-2-chlorobenzylamino)-ethylidenylhydrazine, b.p. 115°/0.4 mm., n_D^{20} 1.5435.

Anal. Calcd.for $C_{12}H_{18}ClN_3$: N, 11.68. Found: N, 11.66.

N-[2-(N-methyl-N-2-chlorobenzylamino)ethyl]aminopyrrolidine. A solution of 50.5 g. (0.189 mole) of *N*[2-(*N*-methyl-*N*-2-chlorobenzylamino)ethylidenyl]aminopyrrolidine in 500 cc. of ethyl ether was added dropwise to a slurry of 6.4 g. (0.168 mole) of lithium aluminum hydride in 500 cc. of dry ether. After the addition was completed, the solution was refluxed for an additional 4 hr., after which was added dropwise a 40% aqueous potassium hydroxide solution. The ethereal solution was decanted, dried over potassium carbonate, and subjected to distillation; yield 39.3 g. (77.8%), b.p. 135°/0.45 mm., n_D^{20} 1.5389.

Anal. Calcd. for $C_{14}H_{22}ClN_3$: N, 15.69; Cl, 13.24. Found: N, 15.66; Cl, 13.27.

Dimaleate salt. m.p. 129–131°.

Anal. Calcd. for $C_{22}H_{30}ClN_3O_8$: N, 8.40; Cl, 7.09. Found: N, 8.46; Cl, 7.24.

The following hydrazines were prepared by the same method:

N-[2-(N-methyl-N-2-chlorobenzylamino)ethyl]aminomorpholine, b.p. 158°/0.065 mm., n_D^{20} 1.5368.

Anal. Calcd. for $C_{14}H_{22}N_3O$: N, 14.80; Cl, 12.49. Found: N, 14.85; Cl, 12.77.

Dimaleate salt, m.p. 124°.

Anal. Calcd. for $C_{22}H_{30}ClN_3O_9$: N, 8.15; Cl, 6.87. Found: N, 8.18; Cl, 7.12.

N-Dimethyl-N'-2-(N-methyl-N-2-chlorobenzylamino) ethylhydrazine, b.p. 111°/0.7 mm., n_D^{20} 1.5215.

Anal. Calcd. for $C_{12}H_{20}ClN_3$: N, 17.39. Found: N, 17.37.

2-(N-methyl-N-substituted benzyl)aminoethylhydrazines—General method. To a stirred refluxing solution of 6 equivalents of 85% hydrazine hydrate in 500 cc. of alcohol was added dropwise in 3 hr. a solution of 1 equivalent of 2-(*N*-methyl-*N*-substituted benzyl)aminoethylchloride hydrochloride in 500 cc. of ethanol. After another hour of reflux, the ethanol and excess hydrazine hydrate were removed by distillation and the residue was poured into 500 cc. of water. The aqueous solution was saturated with potassium hydroxide and next extracted with ether. After the etheral solution had been dried over potassium carbonate, the solvent was removed by distillation and the product isolated by fractional distillation. The results are tabulated in Table III.

2-(N-Methyl-N-phenyl)aminoethylhydrazine. To a refluxing solution of 77.8 g. (1.32 moles) of 85% hydrazine hydrate in 150 cc. of ethanol was added dropwise in 3 hr. a solution of 44 g. (0.26 mole) of 2-(*N*-methyl-*N*-phenyl)aminoethylchloride[23] in 200 cc. of ethanol. After the addition was completed the solution was refluxed for another 3 hr. The alcohol was removed by distillation, 100 cc. water was added and the aqueous solution was saturated with potassium hydroxide. The base was extracted with ether, dried over potassium carbonate, filtered, and the ether was removed by distillation. Fractionation of the residue yielded 40.3 g. (98%) b.p. 105°/0.2 mm., n_D^{20} 1.5827.

Anal. Calcd. for $C_9H_{15}N_3$: N, 25.43. Found: N, 25.70.

The *maleate salt* was prepared in ethanol, m.p. 90–91°.

Anal. Calcd. for $C_{13}H_{19}N_3O_4$: N, 14.94. Found: N, 15.08.

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(23) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 489 (1944).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

Sterically Hindered Amines. II. α-Amino Ketones and Alcohols[1]

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Twelve acetylenic amines, $R^1R^2C(NHR^3)—C{\equiv}CH$, were converted in good yields to the α-amino ketones, $R^1R^2C(NHR^3)—COCH_3$, and thence, by reduction with lithium aluminum hydride or sodium borohydride, to the α-amino alcohols, $R^1R^2C(NHR^3)—CH(OH)CH_3$.

The facile synthesis of sterically hindered acetylenic amines $R^1R^2C(NR^3R^4)—C{\equiv}CH$ described earlier[3,4] and the subsequent finding[5] that many of these and their hydrogenation products have notable hypotensive properties, prompted a study of the preparation of methyl ketones (B) and the corresponding alcohols (C) from the acetylenic compounds (A).

$$R^1R^2C(NHR^3)—C{\equiv}CH \xrightarrow[Hg^{++};\ H^+]{H_2O} R^1R^2C(NHR^3)—COCH_3 \xrightarrow{LiAlH_4} R^1R^2C(NHR^3)—CH(OH)CH_3$$

(A) (B) (C)

The hydration reaction,[6] catalyzed by mercuric ion, consistently gave good yields of the ketones when carried out with purified amine along with three equivalents of sulfuric acid in aqueous methanol. The ketones proved to be stable to distillation and yielded nicely crystalline nonhygroscopic hydrochloride salts.

(1) Paper No. 76 on substituted acetylenes; previous paper G. F. Hennion and A. P. Boisselle, *J. Org. Chem.*, **26,** 2677 (1961).

(2) Eli Lilly Co. Fellow, 1959–61. Abstracted from a portion of the Ph.D. Dissertation of P. E. B.

(3) G. F. Hennion and K. W. Nelson, *J. Am. Chem. Soc.*, **79,** 2142 (1957).

(4) G. F. Hennion and R. S. Hanzel, *J. Am. Chem. Soc.*, **82,** 4908 (1960).

(5) Nelson R. Easton, Abstracts of Papers Presented at New York, N. Y., Meeting of the American Chemical Society, Sept. 11–16, 1960, p. 46-O.

(6)(a) I. G. Farbenindustrie, British Patent **510,876** (1939); *Chem. Abstr.*, **34,** 5673 (1940). (b) J. D. Rose and B. C. L. Weedon, *J. Chem. Soc.*, 782 (1949). (c) G. F. Hennion and A. C. Perrino, *J. Org. Chem.*, **26,** 1073 (1961).