The Hypotensive Activity of N-Cyclohexyl and N-Methyl Derivatives of Alkylenediamines[1]

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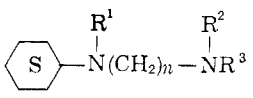
A series of N-cyclohexylalkylenediamines, $C_6H_{11}R^1N(CH_2)_nNR^2R^3$ (R^1, R^2, R^3 = H, CH_3, or C_6H_{11}; n = 2, 3, 4, 5, 6, or 10), has been investigated for hypotensive activity. Since N-cyclohexyl-1,3-propanediamine appeared to be the most active, further work was restricted to derivatives of this compound. The amino hydrogens were progressively substituted with methyl and cyclohexyl groups, and quaternary salts were prepared from the bis-tertiary amines. The most potent hypotensive agent among this group of compounds proved to be the dimethiodide salt of N-cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine (Table I, **11a**). Pharmacological data are presented.

Through routine screening of compounds for hypotensive activity it was discovered that N-cyclohexyl-1,3-propanediamine (Table I, **2**) showed significant activity. It was compared with a series of homologous alkylenediamines (I, $R^1 = R^2 = R^3 = H$) where $n = 2, 4, 5, 6$, and 10. They were prepared by reductive alkylation of the appropriate alkylenediamines with cyclohexanone (method A). Since none of the five



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additional compounds showed any marked increased in activity over the original lead, further work was restricted to derivatives of 1,3-propanediamine. Our goal was to substitute methyl and cyclohexyl groups for the amine hydrogen atoms.

If only one cyclohexyl group is present, two monomethyl derivatives, two dimethyl derivatives, and one trimethyl derivative are possible. Reduction of 3-(N-cyclohexyl-N-methylamino)propionitrile gave N-cyclohexhyl-N-methyl-1,3-propanediamine (Table I, **7**), while N-cyclohexyl-N′-methyl-1,3-propanediamine (Table I, **8**) and the two dimethyl derivatives (Table I, **9, 10**) were obtained by method A from cyclohexanone and the appropriate diamine. The trimethyl compound (Table I, **11**) was prepared from N-cyclohexyl-N′,N′-dimethyl-1,3-propanediamine by methylation with formaldehyde-formic acid (method B).

Reaction of 1,3-propanediamine with an excess of cyclohexanone gave N,N′-dicyclohexyl-1,3-propanediamine (Table I, **12**). Only one monomethyl derivative (Table I, **13**), and one dimethyl derivative (Table I, **14**), of this compound are possible. The former was prepared by method A, and method B was used to obtain the latter.

The isomeric unsymmetrical dicyclohexyl compounds could not be prepared by method A. They could, however, be synthesized by alkylation of the appropriate amine with 3-dicyclohexylaminopropyl chloride (method C).

Reaction of 3-dicyclohexylaminopropyl chloride with ammonia, methylamine, and dimethylamine gave the desired three unsymmetrical dicyclohexyl derivatives (Table I, **15, 16, 17**). The two tricyclohexyl compounds (Table I, **18, 19**), as well as N,N,N′,N′-tetracyclohexyl-1,3-propanediamine (Table I, **20**), were also prepared by method C. Attempts to prepare the latter from dicyclohexylamine and 1,3-dibromopropane failed.

Several quaternary salts were prepared from the fully alkylated diamines. N-Cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine and N,N′-dicyclohexyl-N,N′-dimethyl-1,3-propanediamine formed bisquaternary salts, while N,N-dicyclohexyl-N′,N′-dimethyl-1,3-propanediamine and N-methyl-N,N′,N′-tricyclohexyl-1,3-propanediamine formed only monoquaternary salts.

Reaction of N-cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine with cyclohexyl bromide did not lead to formation of any quaternary compound, but gave the dihydrobromide salt of the starting amine.

Pharmacology

Methods.—Normotensive cats, unselected as to size or sex, were anesthetized with 30 mg./kg. i.p. of pentobarbital. Mean arterial blood pressure responses were recorded from an exposed carotid artery on a Grass Model 5 polygraph *via* a Statham pressure transducer (Model P23AC). Respiration and heart rate were also recorded. Drugs were dissolved in saline and injected intravenously in doses of 1.25, 2.5, and 5.0 mg./kg. body weight. The dose administered refers to milligrams of free base for the amines and to milligrams of cation for the quaternary compounds.

It is recognized that the magnitude and duration of a depressor response are dependent on many factors, but a method is employed here wherein the observed blood pressure response *per se* is used as a basis of comparison of hypotensive activity of this large group of compounds. A "hypotensive index" for each compound was calculated using the formula

$$\frac{(\text{sum of decreases in pressure in mm.})(\text{sum of durations of responses in min.})}{\text{sum of administered doses in mg./kg.}}$$

Results.—Blood pressure responses to each of the compounds were obtained and a "hypotensive index" was calculated for each compound. Our most active compound, **11a**, caused a mean reduction of 105 mm. of

(1) This work was presented before the Division of Medicinal Chemistry at the 144th National Meeting of the American Chemical Society, Los Angeles, California, April, 1963.

TABLE I

$$C_6H_{11}-N(CH_2)_nNR^3$$
(with R^1 on the ring nitrogen and R^2 on the chain nitrogen)

	Compound[a] R¹	R²	R³	n	Method[b]	Yield, %	Free base B.p., °C. (mm.)	Free base $n^{25}D$	Salt M.p., °C.	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
1	H	H	H	2	A	84	102-104[c] (20)	1.4785								
	Dihydrochloride								212-214[d]	$C_8H_{18}N_2 \cdot 2HCl$	44.65	44.55	9.37	9.34	13.02	13.18
2	H	H	H	3	A	63	117-120[e] (15)	1.4792								
	Dihydrochloride								205-206[d]	$C_9H_{20}N_2 \cdot 2HCl$	47.16	46.90	9.67	9.59	12.22	12.30
3	H	H	H	4	A	84	130-131 (11)	1.4788		$C_{10}H_{22}N_2$	70.53	70.37	13.02	12.81	16.45	16.44
	Dihydrochloride								249-250[d]	$C_{10}H_{22}N_2 \cdot 2HCl$	49.38	49.54	9.95	10.27	11.52	11.31
4	H	H	H	5	A	82	142-147[f] (11)	1.4766								
	Dihydrochloride								239-240[d,u]							
5	H	H	H	6	A	87	105-116[f] (0.5)	1.4756								
	Dihydrochloride								234[d]	$C_{12}H_{26}N_2 \cdot 2HCl$	53.13	53.03	10.40	10.61	10.57	10.40
6	H	H	H	10	A	77	159-162 (1.0)	1.4736		$C_{16}H_{34}N_2$	75.52	75.47	13.47	13.56	11.01	10.83
	Dihydrochloride								220[d]	$C_{16}H_{34}N_2 \cdot 2HCl$	58.70	58.45	11.08	11.09	8.56	8.79
7	CH_3	H	H	3	[g]	87	133-135[h] (24)	1.4783								
	Dihydrochloride								193.5-195.5[i]	$C_{10}H_{22}N_2 \cdot 2HCl$	49.37	49.39	9.95	9.87	11.52	11.57
8	H	CH_3	H	3	A	58	100 (0.6)	1.4725		$C_{10}H_{22}N_2$	70.53	70.86	13.02	12.46	16.45	16.86
	Dihydrochloride								282.5-284.5[d]	$C_{10}H_{22}N_2 \cdot 2HCl$	49.37	49.38	9.95	9.70	11.52	11.42
9	CH_3	CH_3	H	3	A	52	132-134 (20)	1.4711		$C_{11}H_{24}N_2$	71.68	71.92	13.13	13.22	15.20	15.39
	Dihydrochloride								192.5-194.5[j]	$C_{11}H_{24}N_2 \cdot 2HCl$	51.35	51.49	10.19	10.28	10.89	11.05
10	H	CH_3	CH_3	3	A	98	103-113 (10-11)	1.4620		$C_{11}H_{24}N_2$	71.68	71.49	13.13	13.24	15.20	15.39
	Dihydrochloride								235-236[d]	$C_{11}H_{24}N_2 \cdot 2HCl$	51.35	51.50	10.19	10.39	10.89	10.66
11	CH_3	CH_3	CH_3	3	B	80	70-72 (0.5)	1.4643		$C_{12}H_{26}N_2$	72.66	72.91	13.21	13.51	14.12	14.22
	Dihydrochloride								287-288[d]	$C_{12}H_{26}N_2 \cdot 2HCl$	53.13	53.34	10.40	10.37	10.33	10.08
11a	Dimethiodide								229-230[k]	$C_{14}H_{32}I_2N_2$	34.86	34.95	6.69	6.84	5.81	5.88
11b	3,4-Dichlorobenzyl chloride								194.5-195.5	$C_{19}H_{31}Cl_3N_2$	57.95	57.68	7.93	7.76	7.11	6.88
12	H	C_6H_{11}	H	3	A	90	[l]									
	Dihydrochloride								287-287.5[d]	$C_{15}H_{30}N_2 \cdot 2HCl$	57.87	57.91	10.36	10.41	9.00	9.17
13	CH_3	C_6H_{11}	H	3	A[m]	81	193 (15)	1.4883		$C_{16}H_{32}N_2$	76.12	76.19	12.78	12.81	11.10	11.09
	Hydrochloride								155-155.5[i]	$C_{16}H_{32}N_2 \cdot HCl$	66.51	66.78	11.51	11.32	9.69	9.76
14	CH_3	C_6H_{11}	CH_3	3	B	85	138-142 (1.0)	1.4880		$C_{17}H_{34}N_2$	76.62	76.60	12.86	12.65	10.51	10.72
	Dihydrochloride								220-221[n]	$C_{17}H_{34}N_2 \cdot 2HCl$	60.16	60.24	10.69	10.82	8.25	8.40
14a	Dimethiodide								235-235.5	$C_{19}H_{40}I_2N_2$	41.46	41.48	7.33	7.14	5.09	5.16
14b	Diethiodide								206-206.5[o]	$C_{21}H_{44}I_2N_2$	43.60	43.73	7.67	7.70	4.64	4.85
14c	Bis-(2-bromobenzyl bromide)								175.5-176.5[o]	$C_{31}H_{46}Br_4N_2$	48.58	48.59	6.05	6.01	3.66	3.80
15	C_6H_{11}	H	H	3	C	46	114 (0.2)	1.4962		$C_{15}H_{30}N_2$	75.56	75.39	12.68	12.86	11.75	11.70
16	C_6H_{11}	CH_3	H	3	C	50	125-126 (1.2)	1.4922		$C_{16}H_{32}N_2$	76.12	75.70	12.78	13.03	11.10	11.45
	Dihydrochloride								202-204	$C_{16}H_{32}N_2 \cdot 2HCl$	59.10	59.11	10.52	10.65	8.61	8.76
17	C_6H_{11}	CH_3	CH_3	3	C	74	147-148[p] (2.4)	1.4856		$C_{17}H_{34}N_2$	76.62	76.69	12.86	12.75	10.51	10.54
	Dihydrochloride								198-199[o]	$C_{17}H_{34}N_2 \cdot 2HCl$	60.16	60.06	10.69	10.80	8.25	8.48
17a	Ethobromide								179.5-180.5[q]	$C_{19}H_{39}BrN_2$[r]	60.78	60.21	10.47	10.36	7.46	7.45
17b	4-Bromobenzyl bromide								159-160	$C_{24}H_{40}Br_2N_2$	55.82	55.80	7.81	8.05	5.43	5.52
18	C_6H_{11}	C_6H_{11}	H	3	C	74	214-222 (4.5)	1.4760		$C_{21}H_{40}N_2$	78.68	78.85	12.58	12.72	8.74	8.86
	Hydrochloride								156-158[q]	$C_{21}H_{40}N_2 \cdot HCl$	70.65	70.50	11.58	11.68	7.85	7.91
19	C_6H_{11}	C_6H_{11}	CH_3	3	C	80	193-195 (0.5)	1.5001		$C_{22}H_{42}N_2$	78.97	78.90	12.65	12.83	8.37	8.51
	Dihydrochloride								162-164[o]	$C_{22}H_{42}N_2 \cdot 2HCl$	64.84	64.56	10.89	10.99	6.88	6.88
19a	Methioide								170.5-171.5	$C_{23}H_{46}IN_2$	57.97	57.91	9.52	9.78	5.88	5.93
19b	2,4-Dichlorobenzyl chloride								143-144	$C_{29}H_{47}Cl_3N_2$	65.71	65.36	8.94	8.95	5.29	5.20
20	C_6H_{11}	C_6H_{11}	C_6H_{11}	3	C	18	230-245[s] (1.5)	1.5022		$C_{27}H_{50}N_2$	80.53	80.27	12.52	12.44	6.96	6.96

[a] C_6H_{11} = cyclohexyl. [b] Methods A, B, and C refer to the procedures described in the Experimental section. [c] Pearson, Jones, and Cope, ref. 4, report b.p. 101-102° (14 mm.); $n^{25}D$ 1.4800. [d] Recrystallized from ethanol. [e] Tarbell, Shakespeare, Claus, and Bunnett, ref. 6, report b.p. 80° (0.5 mm.); $n^{20}D$ 1.4820. [f] A. R. Surrey, *J. Am. Chem. Soc.*, **71**, 3354 (1949) reports b.p. 111–118° (0.7–0.8 mm.); $n^{25}D$ 1.4756. [g] For method of preparation, see Experimental. [h] J. Corse, J. T. Bryant, and H. A. Shonle, *J. Am. Chem. Soc.*, **68**, 1907 (1946), report b.p. 122–124° (24 mm.). [i] Recrystallized from 2-propanol. [j] Recrystallized from ethanol–isopropyl ether. [k] Recrystallized from 1-propanol. [l] The product solidified and melted at 43–44° after recrystallization from Skellysolve C. The recorded m.p. is 33°: J. A. Harpham, R. J. J. Simpkins, and A. F. Wright, *J. Am. Chem. Soc.*, **72**, 343 (1950). [m] Prepared from cyclohexanone and N-cyclohexyl-N-methyl-1,3-propanediamine (**7**). [n] Recrystallized from 2-propanol–methyl ethyl ketone. [o] Recrystallized from acetone–ethanol. [p] This compound slowly solidified, m.p. 26–29°. [q] Recrystallized from acetone. [r] Br: Calcd., 21.28; Found: 21.38. [s] The distillate solidified and was recrystallized from Skellysolve B to give a white solid which melted at 73–73.5°. [t] The reported b.p. is 98–99° (1.0 mm.), $n^{20}D$ 1.4805, according to J. M. Stewart, *J. Am. Chem. Soc.*, **76**, 3229 (1954). [u] The recorded m.p. is 246–248°, according to Stewart, see ref. *t*.

mean arterial blood pressure for an average of 100 min. at a dose of 1.25 mg./kg. Since **11a** had the highest index, it was arbitrarily assigned a value of 100 and the activity of all the other compounds was expressed as a fraction of this value. These data are summarized in Table II. The quaternary salts showed the greatest effect on the blood pressure. These compounds are probably exerting their effect through ganglionic blockade. Very few of the amines showed significant activity.

Experimental

3-Dicyclohexylaminopropyl Chloride.—A solution of 90 g. (0.38 mole) of 3-dicyclohexylamino-1-propanol[2] in 450 ml. of chloroform was added dropwise, with stirring, to a solution of 90 g. (0.76 mole) of thionyl chloride in 500 ml. of chloroform. The flask was cooled intermittently in an ice bath. The reaction mixture was heated under reflux for 4 hr. and then stripped. The residue was dissolved in 400 ml. of chloroform and washed three times with 100 ml. of 10% sodium carbonate solution and water. The chloroform solution was dried over magnesium sulfate, and, after removing the drying agent and solvent, the residue was subjected to vacuum distillation. A viscous, light yellow oil distilled at 109–117° (0.3 mm.), $n^{25}D$ 1.4972. The yield was 78.5 g. (80%).

(2) W. H. Yanko, H. S. Mosher, and F. C. Whitmore, *J. Am. Chem. Soc.*, **67**, 666 (1945).

TABLE II

RELATIVE HYPOTENSIVE ACTIVITY

Compound[a]	Relative activity[b]	Compound	Relative activity	Compound	Relative activity
11a	100	**12**	1.5	**7**	0.6
19a	26	**3**	1.5	**8**	0.5
17b	23	**5**	1.4	**14a**	0.4
2	18	**13**	1.3	**17**	0.4
14c	10	**14**	0.9	**10**	0.3
19b	10	**16**	0.8	**14b**	0.2
6	9	**15**	0.7	**9**	0.2
17a	4	**19**	0.7	**11**	0.1
4	4	**18**	0.7	**1**	0
20	3	**11b**	0.6		

[a] The numbers refer to the compounds in Table I. [b] The most active compound has been assigned a value of 100, and the activities of all the other compounds are expressed as a fraction of this value.

Anal. Calcd. for $C_{15}H_{28}ClN$: C, 69.88; H, 10.95; N, 5.43. Found: C, 69.84; H, 10.84; N, 5.57.

Preparation of Diamines. Method A.—A mixture of 0.2 mole of cyclohexanone and 0.4 mole of the appropriate amine was allowed to stand for 1 hr.[3] An exothermic reaction occurred and the temperature rose to 50–60°. If little or no heat was evolved, the mixture was warmed gently. The imine was dissolved in 100 ml. of dry ethanol, and 1.0 g. of reduced platinum oxide was added. Hydrogenation was carried out at 2–3 atm. pressure. In many cases, uptake was completed in 2 hr. or less, while some required as long as 18 hr. The catalyst and solvent were removed and the residue was subjected to vacuum distillation. The products are described in Table I (**1–6, 8–10, 12, 13**). This procedure is essentially that of Pearson, *et al.*[4]

Method B.—The methylation reactions were carried out with formaldehyde and formic acid using the procedure described by Icke, *et al.*[5] The two compounds prepared in this manner are described in Table I (**11** and **14**).

Method C.—To a solution of 0.1 mole of 3-dicyclohexylaminopropyl chloride in 200 ml. of ethanol was added 50 ml. of 28% ammonia water or 0.2–0.5 mole of the appropriate amine. The resulting solution was heated under reflux overnight. Most of the solvent was removed, the residue was dissolved in 200 ml. of water, and 30 ml. of 50% sodium hydroxide solution was added. The free base was taken up in ether and dried over magnesium sulfate. The drying agent and solvent were removed and the residue was subjected to vacuum distillation. The compounds obtained by this method are described in Table I (**15–20**).

N-Cyclohexyl-N-methyl-1,3-propanediamine.—A mixture of 114 g. (0.685 mole) of 3-(N-cyclohexyl-N-methylamino)propionitrile,[6] 100 ml. of methanol, 100 ml. of liquid ammonia, and 23 g. of 5% rhodium-on-alumina was hydrogenated at room temperature under 80–90 atm. for 2 hr. The catalyst and solvent were removed and the residue was subjected to vacuum distillation (Table I, **7**).

Reaction of N-Cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine with Cyclohexyl Bromide.—A mixture of 6.0 g. (0.03 mole) of N-cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine and 16 g. (0.1 mole) of cyclohexyl bromide was heated at 150° for several hours until a solid resulted. The solid was taken up in 200 ml. of boiling ethanol and chilled to give 7.3 g. of white crystalline solid, m.p. 260–261°. Recrystallization from ethanol raised the m.p. to 262°. It proved to be identical with an authentic sample of N-cyclohexyl-N,N′,N′-trimethyl-1,3-propanediamine dihydrobromide.

Anal. Calcd. for $C_{12}H_{26}N_2 \cdot 2HBr$: C, 40.01; H, 7.84; Br, 44.37; N, 7.78. Found: C, 40.29, 40.17; H, 7.83, 7.65; Br, 44.57; N, 7.65, 7.78.

Acknowledgment.—The microanalytical results were provided by Mr. Elmer Shelberg, Mr. Orville Kolsto, and staff of the Abbott Microanalytical Laboratory.

(3) In order to obtain N,N′-dicyclohexyl-1,3-propanediamine, 0.4 mole of cyclohexanone was allowed to react with 0.2 mole of the amine. Equimolar amounts of cyclohexanone and N-cyclohexyl-N-methyl-1,3-propanediamine were used to obtain N,N′-dicyclohexyl-N-methyl-1,3-propanediamine.

(4) D. E. Pearson, W. H. Jones, and A. C. Cope, *J. Am. Chem. Soc.*, **68**, 1227 (1946).

(5) R. N. Icke, B. B. Wisegarver, and G. A. Alles, "Organic Syntheses," Col. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 723.

(6) D. S. Tarbell, N. Shakespeare, C. J. Claus, and J. F. Brunett, *J. Am. Chem. Soc.*, **68**, 1218 (1946).