[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. III[1]

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It has been found that methyldi-β-cyclohexylethylamine, $CH_3N(CH_2—CH_2—C_6H_{11})_2$, and certain other closely related cycloalkylalkylamines are strong antispasmodics.[3,4] Since the cyclohexyl group is aliphatic rather than aromatic in character we wished to determine whether or not antispasmodic activity might be found among the saturated, strictly aliphatic amines, particularly in such a compound as methyldi-*n*-octylamine since this substance contains two saturated carbon chains which correspond to those which would be formed if the cyclohexyl rings in methyldi-β-cyclohexylethylamine were ruptured between the ring carbon atoms 1 and 2. Consequently, there was prepared methyldi-*n*-octylamine, methyldi-*n*-hexylamine and also methyldi-2-ethylhexylamine and methyldi-2-ethylbutylamine (Table I). Methyldi-*n*-octyl- and methyldi-*n*-hexylamine proved to be weak in activity while the other two amines exhibited such a low order of potency that they have been listed as inactive.

It was of interest to prepare and compare the activity of the four compounds ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyldi-β-cyclopentylethylamine with the corresponding four cyclohexylamines which have been described previously, namely, ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyldi-β-cyclohexylethylamine. In the cyclopentyl series only the *n*-amyl compound was found to be a strong antispasmodic, whereas among the cyclohexyl compounds only the ethyl and propyl derivatives exhibited strong activity.

No active antispasmodics were found among the seven heterocyclic amines which contained the morpholine, piperazine or α-furfuryl ring.

Methyldi - 2 - methylcyclohexylmethyl- and methyldi-3-cyclohexylmethylamine, two closely related isomers of methyldi-β-cyclohexylethylamine, were prepared (Table II). The 2-methylcyclohexylmethyl compound proved to be a weak antispasmodic and the 3-methylcyclohexylmethylamine possessed so little activity that it has been described as inactive.

The next higher homolog of the last mentioned amine, that is, methyldi-β-3-methylcyclohexylethylamine, proved to be active; methyldi-β-4-methylcyclohexylethylamine also was found to be an active amine.

Since ethyl- and propyldi-β-phenylethylamine, as well as ethyl- and propyldi-β-cyclohexylethylamine, are strong antispasmodics, it can be seen that, at least in some instances, phenyl can be substituted for cyclohexyl without loss of activity. Another illustration of this is found in the strong antispasmodic ethyl-β-cyclohexylethyl-β′-phenylethylamine.

Ethyl - β - cyclohexylethylcyclohexylmethylamine, an isomer of methyldi-β-cyclohexylethylamine, is an active compound.

By the introduction of methyl and β-cyclohexylethyl groups into ethylenediamine and trimethylenediamine (compounds 17 and 18, Table II) these two diamines were converted into substances which possessed marked antispasmodic properties.

Experimental Part

Alcohols.—2-Methylcyclohexylmethyl,[5] b. p. 76–77° at 18 mm., 3-methylcyclohexylmethyl,[5] b. p. 75–76° at 6 mm., β-(3-methylcyclohexyl)-ethyl, b. p. 86–88° at 5 mm. and β-(4-methylcyclohexyl)-ethyl alcohol, b. p. 85–87° at 6 mm., were prepared by treatment of the substituted cyclohexylmagnesium bromide with formaldehyde or ethylene oxide according to a slight modification[6] of the method used by Hiers and Adams[7] for the preparation of β-cyclohexylethyl alcohol.

α-Cyclohexylethyl alcohol was obtained from cyclohexylmagnesium bromide and acetaldehyde.[8]

Cyclopentanol was prepared by reduction of cyclopentanone with sodium and a mixture of one part of methyl alcohol, one part of ether and two parts of water.[9] It is claimed that methyl alcohol reduces the amount of

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

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(3) (a) Blicke and Monroe, THIS JOURNAL, **61**, 91 (1939); (b) Blicke and Zienty, *ibid.*, **61**, 93 (1939).

(4) All of the pharmacological data have been determined by Dr. C. W. Geiter in the Laboratories of Frederick Stearns and Company.

(5) This alcohol has been obtained by a different procedure by Skita and Schonfelder, *Ann.*, **431**, 20, 29 (1923).

(6) Ref. 3 (b).

(7) Hiers and Adams, THIS JOURNAL, **48**, 1091 (1926); see also "Organic Syntheses," Coll. Vol. I, 1932, p. 182.

(8) Bouveault (*Bull. soc. chim.*, [3] **29**, 1050 (1903)) and Zelinsky, (*ibid.*, [4] **2**, 1122 (1907)) used cyclohexylmagnesium chloride.

(9) Nenitzescu and Ionescu, *Bull. soc. chim. Romania*, **14**, 65 (1932); *C. A.*, **27**, 1329 (1933).

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 1, 2, 3, 4 and 17 from acetone; compounds 10, 11 and 24 from alcohol; compounds 7, 13 and 15 from 1,4-dioxane; compound 25 and the chloroaurates of compounds 19 and 20 from dilute alcohol; compound 26 from methyl alcohol; compounds 18, 27 and 28 and the chloroaurate of compound 14 were precipitated from an acetone solution by the addition of dry ether; compound 12 was precipitated from a carbon tetrachloride solution by the addition of dry ether; compound 23 was precipitated from a chloroform solution by the addition of acetone.

	Amine (secondary)	Anti-spasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	% Cl Found
1	Methylhexyl	Inactive	Methylamine	140–142	735	178–179	$C_7H_{18}NCl$	23.39	23.51
2	Methyl-2-ethylbutyl	Inactive	Methylamine	128–129	742	201–202	$C_7H_{18}NCl$	23.39	23.49
3	Methyl-2-ethylhexyl	Inactive	Methylamine	73–75	15	185–186	$C_9H_{22}NCl$	19.73	19.58
4	Methyloctyl	Weak	Methylamine	78–79	14	180–181	$C_9H_{22}NCl$	19.73	19.70
5	Methyl-2-octyl	Weak	Methylamine	70–71	14	Oil	$C_9H_{21}N$	N, 9.78	9.64
6	Ethyl-β-cyclopentylethyl	Inactive	Ethylamine	73–74	13	197–198	$C_9H_{20}NCl$	19.96	20.24
7	Propyl-β-cyclopentylethyl	Inactive	Propylamine	72–74	5	251–253	$C_{10}H_{22}NCl$	18.50	18.36
8	Butyl-β-cyclopentylethyl	Inactive	Butylamine	106–107	13	278–279	$C_{11}H_{24}NCl$	17.24	17.26
9	Amyl-β-cyclopentylethyl	Inactive	Amylamine	98–100	4	284–285	$C_{12}H_{26}NCl$	16.14	16.28
10	Dicyclohexyl	Weak	.....	.....	...	326–327[a]	.....	...	...
11	β-Cyclohexylethyl-γ′-cyclohexylpropyl	Weak	β-Cyclohexylethylamine[b]	150–156	6	322–323	$C_{17}H_{34}NCl$	12.32	12.34
	Amine (tertiary)								
12	Methyldihexyl	Weak	Methylamine	121–122	19	144–145	$C_{13}H_{30}NCl$	15.04	15.00
13	Methyldi-2-ethylbutyl	Inactive	Methylamine	100–101	13	154–155	$C_{13}H_{30}NCl$	15.04	14.87
14	Methyldi-2-ethylhexyl	Inactive	Methylamine	113–114	6	103–104*	$C_{13}H_{38}NCl_4Au$	Au, 33.12	33.15
15	Methyldioctyl	Weak	Methylamine	136–138	5	149–150	$C_{17}H_{38}NCl$	12.15	12.18
16	Methyldi-β-hydroxyethyl	(Stimulant)	Methylamine	141–142	18[c]	.....	.....	...	...
17	Methyldi-β-chloroethyl	Inactive	Compound 16	.....	...	113–114[d]	$C_5H_{12}NCl_3$	55.26	55.14
18	Ethyldi-β-cyclopentylethyl	Weak	Ethylamine	140–145	7	115–116	$C_{16}H_{32}NCl$	12.95	13.42
19	Propyldi-β-cyclopentylethyl	Weak	Propylamine	147–150	7	145–146*	$C_{17}H_{34}NCl_4Au$	Au, 33.35	33.37
20	Butyldi-β-cyclopentylethyl	Weak	Butylamine	153–158	6	133–134*	$C_{18}H_{36}NCl_4Au$	Au, 32.58	32.66
21	Amyldi-β-cyclopentylethyl	Active	Amylamine	163–168	5	Oil	$C_{19}H_{37}N$	N, 5.02	4.77
22	N-Butylmorpholine	(Stimulant)	Morpholine	67–68	10	213–214	$C_8H_{18}ONCl$	19.74	19.59
23	N-Cyclohexylmorpholine[e]	(Stimulant)	Morpholine	111–112	12	254–255	$C_{10}H_{20}ONCl$	17.24	17.07
24	N-β-Cyclohexylethylmorpholine	(Stimulant)	Morpholine	132–134	12	260–261	$C_{12}H_{24}ONCl$	15.17	15.09
25	Methyldi-β-N-morpholylethyl	Inactive	Morpholine and compound 17	161–164	8	277–278[f]	$C_{13}H_{30}O_2N_3Cl_3$	29.01	29.30
26	N,N′-Di-β-cyclohexylethylpiperazine	Weak	β-Cyclohexylethylamine	.....	...	325–326[g]	$C_{20}H_{40}N_2Cl_2$	18.70	18.73
27	Methylcyclohexylmethyl-α-furfuryl	Weak	Methyl-α-furfurylamine[h]	103–105	5	107–108	$C_{13}H_{22}ONCl$	14.55	14.49
28	Methyl-β-cyclohexylethyl-α-furfuryl	Weak	Methyl-α-furfurylamine	121–123	5	163–164	$C_{14}H_{24}ONCl$	13.68	13.78

[a] Willstätter and Hatt (*Ber.*, **45**, 1476 (1912)) stated that the compound sublimes at 300–315°. Winans and Adkins (THIS JOURNAL, **54**, 310 (1932)) reported the melting point to be 333°. [b] Coleman and Adams, *ibid.*, **54**, 1983 (1932). [c] Knorr and Matthes (*Ber.*, **31**, 1069 (1898)) reported the boiling point to be 246–248°. [d] Prelog and Stepan (*Coll. Czech. Chem. Comm.*, **7**, 93 (1935); *C. A.*, **29**, 4013 (1935)) stated the melting point to be 116–117°. [e] This compound is mentioned in the French Patent 711,560, *Chem. Zentr.*, **103**, I, 2998 (1932); in the English Patent 362,061, *Chem. Zentr.*, **103**, I, 3502 (1932), and by Carswell and Morrill, *Ind. Eng. Chem.*, **29**, 1248 (1937), but the analysis and properties were not recorded. [f] Trihydrochloride. [g] Dihydrochloride. [h] Schwabbauer, *Ber.*, **35**, 410 (1902); von Braun and Köhler, *ibid.*, **51**, 86 (1918). * M. p. of chloroaurate.

pinacol formed in the ordinary reduction procedure in which alcohol is not used.[10]

Bromides.—The 2-, 3- and 4-methylcyclohexylalkyl bromides were prepared by the action of phosphorus tribromide (20% excess) on the corresponding alcohols: 2-methylcyclohexylmethyl bromide, b. p. 74–76° at 10 mm.; 3-methylcyclohexylmethyl bromide, b. p. 71–73° at 7 mm.; β-(3-methylcyclohexyl)-ethyl bromide, b. p. 79–81° at 5 mm.; β-(4-methylcyclohexyl)-ethyl bromide, b. p. 78–79° at 8 mm.

α-Cyclohexylethyl bromide was obtained when dry hydrogen bromide was passed into 372 g. of α-cyclohexylethyl alcohol, dissolved in 200 cc. of benzene, until no further formation of water was evident. After several hours the benzene layer was separated, dried with calcium chloride, the solvent removed and the residue distilled. The distillate was shaken twice with 100-cc. portions of concd. sulfuric acid and then distilled again; b. p. 94–96° under 26 mm. pressure; yield 330 g. or 59% of the calcd. amount.

Anal. Calcd. for $C_8H_{15}Br$: Br, 41.83. Found: Br, 41.87.

Amines.—The amines were synthesized by the general methods outlined previously.[11]

All of the amine hydrochlorides listed in Table I were

(10) In the attempted reduction of dimethyl sebacate with sodium, water and ether almost all of the ester was recovered unchanged. However, when the ester was treated with sodium in the presence of a mixture of water and ether which contained 15–20% of methyl alcohol a 65% yield of decamethylene glycol was obtained.

(11) Ref. 3a.

TABLE II

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 1, 2, 3, 4, 9, 10, 12 and 13 from acetone; compounds 5, 17 and 18 from absolute alcohol; compound 6 from dilute alcohol; compounds 7 and 8 from 1,4-dioxane; compounds 15 and 16 from carbon tetrachloride; compounds 11 and 14 were precipitated from acetone solution by the addition of dry ether.

	Amine (secondary)	Antispasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	Found
1	Methyl-2-methylcyclohexylmethyl	Inactive	Methylamine	57–61	7	230–231	$C_9H_{20}NCl$	19.96	20.25
2	Methyl-3-methylcyclohexylmethyl	Inactive	Methylamine	58–60	6	182–184	$C_9H_{20}NCl$	19.96	19.96
3	Methyl-β-3-methylcyclohexylethyl	Inactive	Methylamine	74–75	8	162–163	$C_{10}H_{22}NCl$	18.50	18.42
4	Methyl-β-4-methylcyclohexylethyl	Weak	Methylamine	81–82	9	162–163	$C_{10}H_{22}NCl$	18.50	18.64
5	N-β-Cyclohexylethylethylenediamine	(Stimulant)	Ethylenediamine	115–120	8	About 305[a] (dec.)	$C_{10}H_{24}N_2Cl_2$	29.16	29.11
6	N,N′-Di-β-cyclohexylethylethylenediamine	Weak	Ethylenediamine	195–200	8	319–320[a]	$C_{18}H_{38}N_2Cl_2$	20.07	19.97
	Amine (tertiary)								
7	Methyldi-2-methylcyclohexylmethyl	Weak	Methylamine	.....	..	188–189	$C_{17}H_{34}NCl$	12.32	12.35
8	Methyldi-3-methylcyclohexylmethyl	Inactive	Methylamine	135–140	7	205–206	$C_{17}H_{34}NCl$	12.32	12.37
9	Methyldi-β-3-methylcyclohexylethyl	Active	Methylamine	158–161	7	228–229	$C_{19}H_{38}NCl$	11.23	11.14
10	Methyldi-β-4-methylcyclohexylethyl	Active	Methylamine	166–170	9	241–242	$C_{19}H_{38}NCl$	11.23	11.23
11	Ethyldi-β-phenylethyl	Active	Ethylamine	176–178	7[b]	136–137[c]	.....	...	...
12	Propyldi-β-phenylethyl	Active	Propylamine	170–172	6	158–159	$C_{19}H_{26}NCl$	11.68	11.79
13	Butyldi-β-phenylethyl	Weak	Butylamine	194–195	9	140–141	$C_{20}H_{28}NCl$	11.16	11.13
14	Ethyl-β-cyclohexylethyl-cyclohexylmethyl	Active	Ethylcyclohexylmethylamine[d]	146–149	5	116–117	$C_{17}H_{34}NCl$	12.32	12.42
15	Ethyl-β-cyclohexylethyl-β′-phenylethyl	Active	Ethyl-β-phenylethylamine[e]	163–168	7	117–118	$C_{18}H_{30}NCl$	11.99	11.75
16	Butyl-β-cyclohexylethyl-β′-phenylethyl	Weak	Butyl-β-phenylethylamine[f]	180–182	6	128–129	$C_{20}H_{34}NCl$	10.96	11.02
17	N,N′-Dimethyl-N,N′-di-β-cyclohexylethylethylenediamine	Active	Methyl-β-cyclohexylethylamine[g]	180–182	9	276–277[a]	$C_{20}H_{42}N_2Cl_2$	18.60	18.73
18	N,N′-Dimethyl-N,N′-di-β-cyclohexylethyltrimethylenediamine	Active	Methyl-β-cyclohexylethylamine	190–195	5	294–295[a]	$C_{21}H_{44}N_2Cl_2$	17.95	17.86

[a] Dihydrochloride. [b] Külz and Rosenmund (German Patent 623,593, *Chem. Zentr.*, **107**, II, 1025 (1936)) reported 180–182° (2 mm.). [c] Külz and Rosenmund (ref. *b*) found 134° but in U. S. Patent 2,006,114 (*C. A.*, **29**, 5602 (1935)) reported as 137°. [d] Blicke and Zienty, THIS JOURNAL, **61**, 774 (1939). [e] Von Braun, *Ber.*, **43**, 3215 (1910). [f] Winans and Adkins, THIS JOURNAL, **54**, 310 (1932). [g] Blicke and Monroe, *ibid.*, **61**, 91 (1939).

prepared by treatment of an ether solution of the amine with hydrogen chloride except compounds 1, 2, 3, 4, 12, 13 and 15; in these instances the amine was dissolved in petroleum ether (30–40°).

The hydrochlorides of five of the amines in Table I were obtained as oils, hence in the case of compound 5 and compound 21 the corresponding bases were analyzed for nitrogen. The oily hydrochlorides of compounds 14, 19 and 20 were dissolved in water and excess hydrochloric acid added; upon addition of 5% gold chloride solution the chloroaurates precipitated. If the latter separated in an oily state they became crystalline after a short time.

In order to prepare the amine hydrochlorides mentioned in Table II, ether was used as a solvent for the bases except in the case of compound 14 and compound 16; petroleum ether was used for the former and a mixture of ether and petroleum ether for the latter.

Summary

Forty-six secondary and tertiary amines have been described. Many of the amines contain alkyl and cycloalkylalkyl or arylalkyl groups. Nine of these substances proved to be strong antispasmodics.

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