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

Antispasmodics. I[1]

BY F. F. BLICKE AND EZRA MONROE[2]

The adoption of papaverine as a therapeutic agent followed soon after the discovery of its antispasmodic action. Papaverine is obtained as a by-product during the isolation of morphine from opium but due to the restrictions placed on the manufacture of morphine it seemed that the amount of papaverine available from a natural source would be inadequate to supply clinical demands.

The fact that papaverine can be synthesized in the laboratory led to the hope that a relatively inexpensive commercial process might be found for this alkaloid. This expectation has not been realized but a number of synthetic compounds which closely resemble papaverine in constitution and pharmacological activity have been adopted or suggested for clinical use.[3]

During recent years a number of synthetic compounds have been discovered which exhibit antispasmodic activity. Many of these products are simpler in structure than the naturally-occurring antispasmodics papaverine and atropine and a few of them have appeared on the market as substitutes for these alkaloids.[4]

In this paper the preparation of a number of secondary and tertiary amines has been described many of which conform to the general types $RN(H)(CH_2)_xR'$ and $RN[(CH_2)_xR']_2$ in which R = alkyl and R′ = cycloalkyl.

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

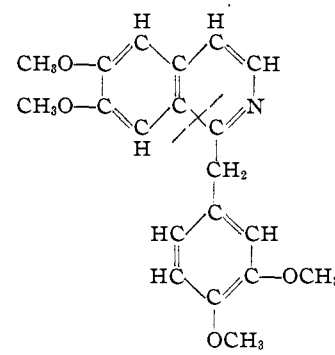
(2) Frederick Stearns and Company Fellow.

(3) Eupaverine (1-(3′,4′-methylenedioxybenzyl)-3-methyl-6,7-methylenedioxyisoquinoline), British Patent 348,956, *Chem. Zentr.* **102**, II, 1196 (1931); perparin (1-(3′,4′-diethoxybenzyl)-6,7-diethoxyisoquinoline), French Patent 719,638, *Chem. Zentr.*, **103**, II, 740 (1932); neupaverine (1-(2′,4′-methylenedioxyphenyl)-3-methyl-6,7-methylenedioxyisoquinoline), German Patent 613,005, *C. A.*, **29**, 5604 (1935); octaverine (1-(3′,4′,5′-triethoxyphenyl)-6,7-dimethoxyisoquinoline), Ellinger, Koschara and Seerar, *Klin. Wochschr.*, **13**, 411 (1934), French Patent 760,825, *C. A.*, **28**, 4178 (1934).

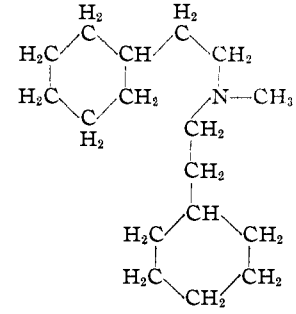
(4) 3-Keto-4-benzyl-3,4-dihydrobenzoxazine-1,4. British Patent 370,350, *Brit. Chem. Abstracts*, **B**, 786 (1932); syntropan (the tropic acid ester of 3-diethylamino-2,2-dimethylpropanol-1), Fromherz, *Arch. exptl. Path. Pharmakol.*, **173**, 86 (1933); ethyldi-(β-phenylethyl)-amine, U. S. Patent 2,006,114, *C. A.*, **29**, 5602 (1935); octin (the acid tartrate or hydrochloride of N,1,5-trimethylhexenyl-(4)-amine, German Patent 617,536, *C. A.*, **30**, 731 (1936); trasentin (the diphenylacetic acid ester of β-diethylaminoethanol), Meier, *Klin. Wochschr.*, **15**, 1403 (1936); jucundal (tributylacetamide) Junkmann, *Arch. exptl. Path. Pharmakol.*, **186**, 552 (1937); sestron (the hydrochloride of ethyldi-(γ-phenylpropyl)-amine), Külz and Rosenmund, *Klin. Wochschr.*, **17**, 345 (1938).

Several of them, especially methyldi-(β-cyclohexylethyl)-amine, proved to be strong antispasmodics. The compounds were tested primarily on isolated sections of small intestine of the rabbit according to the method of Magnus by Dr. C. W. Geiter in the Frederick Stearns and Company Laboratories. In most instances the amines were tested in the form of their hydrochlorides.

Although these compounds are distinctly different from papaverine in structure, nevertheless, a relationship between some of them, for example methyldi-(β-cyclohexylethyl)-amine, and a completely hydrogenated papaverine can be established if the isoquinoline ring is ruptured as shown in the accompanying formula.



Papaverine



Methyldi-β-cyclohexylethyl-amine

A discussion of the relationship between structure and antispasmodic action, as far as the compounds prepared by us are concerned, will be reserved for our next paper.

Experimental Part

The secondary and tertiary amines were prepared by interaction of the primary amines mentioned in Table I and

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The amine hydrochlorides were recrystallized in the following manner: compounds 1, 2, 3, 4, 7, 8, 10, 11, 14, 15, 17, 18, 19, 21, 23, 24, 26, 27, 28, 29 and 30 were recrystallized from ethyl acetate; compound 6 from absolute alcohol; compound 9 from dilute alcohol; compound 22 from a mixture of benzene and ether; compound 25 from a mixture of benzene and petroleum ether (30–40°); compounds 12, 13 and 20 were precipitated from an ethyl acetate solution by addition of dry ether and compounds 5 and 16 were precipitated from absolute alcohol solution by addition of dry ether.

	Amine (secondary)	Anti-spasmodic activity	Prepared from	B. p. of fraction used, °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	Found
1	Methyl-β-cyclohexylethyl	Weak	Methylamine	89–90	14	169–170	$C_9H_{20}NCl$	19.96	19.88
2	Ethyl-β-cyclohexylethyl	Weak	Ethylamine	100–105	21	231–232	$C_{10}H_{22}NCl$	18.50	18.68
3	Butyl-β-cyclohexylethyl	Weak	Butylamine	120–123	17	262–263	$C_{12}H_{26}NCl$	16.14	16.22
4	Allyl-β-cyclohexylethyl	Weak	Allylamine	114–116	18	235–236	$C_{11}H_{22}NCl$	17.42	17.29
5	Cyclohexyl-β-cyclohexylethyl	Active[i]	Cyclohexylamine	174–177	35	197–198	$C_{14}H_{28}NCl$	14.40	14.17
6	Benzyl-β-cyclohexylethyl	Weak	Benzylamine	187–189	20	227–228	$C_{15}H_{24}NCl$	13.98	14.03
7	Ethyl-β-phenylethyl	Inactive	Ethylamine	107–110	20[a]	181–182[b]	.....	...	...
8	Allyl-β-phenylethyl	Inactive	Allylamine	123–126	19	176–177	$C_{11}H_{16}NCl$	17.95	17.75
9	N,N'-Di-(β-phenylethyl)-ethylenediamine	Weak	Ethylenediamine	235–240	19	306–307	$C_{18}H_{26}N_2Cl_2$[j]	20.79	20.89
10	Methyl-β-(α-naphthyl)-ethyl	Weak	Methylamine	175–177	20	164–165	$C_{13}H_{16}NCl$	16.00	15.84
11	Methyl-γ-cyclohexylpropyl	Weak	Methylamine	105–108	20	167–168	$C_{10}H_{22}NCl$	18.50	18.27
12	Methyl-δ-cyclohexylbutyl	Weak	Methylamine	110–112	20	143–144	$C_{11}H_{24}NCl$	17.24	17.09
13	Ethyl-δ-cyclohexylbutyl	Weak	Ethylamine	131–134	19	202–203	$C_{12}H_{26}NCl$	16.14	16.31
14	Butyl-δ-cyclohexylbutyl	Active	Butylamine	150–156	20	232–233	$C_{14}H_{30}NCl$	13.99	13.80
15	Methyl-β-cyclopentylethyl	Weak	Methylamine	.....	..	159–160	$C_8H_{18}NCl$	21.67	21.99
16	Methyl-γ-phenoxypropyl	Weak	Methylamine	137–140	19[c]	156–157[d]	$C_{10}H_{16}ONCl$	17.58	17.60
	Amine (tertiary)								
17	Dimethyl-β-cyclohexylethyl	Weak	Dimethylamine	93–94	28	238–239	$C_{10}H_{22}NCl$	18.52	18.75
18	Dimethyl-δ-cyclohexylbutyl	Weak	Dimethylamine	131–132	38	196–197	$C_{12}H_{26}NCl$	16.14	15.86
19	Dimethyl-β-cyclopentylethyl	Weak	Dimethylamine	79–81	32	219–220	$C_9H_{20}NCl$	19.96	19.73
20	Diethyl-β-cyclopentylethyl	Weak	Diethylamine	108–110	37	121–122	$C_{11}H_{24}NCl$	17.24	16.94
21	Methyldi-β-cyclohexylethyl	Active	Methylamine	188–190	23	257–258	$C_{17}H_{34}NCl$	12.32	12.20
22	Ethyldi-β-cyclohexylethyl	Active	Ethylamine	195–197	21	132–133	$C_{18}H_{36}NCl$	11.76	11.99
23	Methyldi-γ-cyclohexylpropyl	Weak	Methylamine	200–204	20	214–215	$C_{19}H_{38}NCl$	11.23	11.09
24	Methyldi-δ-cyclohexylbutyl	Weak	Methylamine	225–227	36	189–190	$C_{21}H_{42}NCl$	10.22	10.05
25	Ethyldi-δ-cyclohexylbutyl	Weak	Ethylamine	230–236	19	134–135	$C_{22}H_{44}NCl$	9.91	9.91
26	Methyldi-β-phenylethyl	Active	Methylamine	192–193	18[e]	158–159[f]	$C_{17}H_{22}NCl$	12.86	12.71
27	Methyldi-β-cyclopentylethyl	Weak	Methylamine	.....	..	240–241	$C_{15}H_{30}NCl$	13.66	13.64
28	Methyldi-γ-phenoxypropyl	Active	Methylamine	245–250	21	125–126	$C_{19}H_{26}O_2NCl$	10.56	10.35
29	Methyldi-β-benzoylethyl	Weak	Methylamine	(M. p. 141–142°)[g]		191–192[h]	$C_{19}H_{22}O_2NCl$	10.69	10.43
30	N-(β-Cyclohexylethyl)-piperidine	Inactive	Piperidine	139–140	18	255–256	$C_{13}H_{26}NCl$	15.31	15.07

[a] Von Braun [*Ber.*, **43**, 3215 (1910)] reported 99–100° (13 mm.) while Kindler [*Ann.*, **431**, 217 (1923)] found 99° (14 mm.). [b] Kindler [*ibid.*, **431**, 217 (1923)] reported 182°. [c] Cowan and Marvel [THIS JOURNAL, **58**, 2278 (1936)] found 133–138° (23 mm.). [d] Cowan and Marvel [*ibid.*, **58**, 2278 (1936)] reported the m. p. of the hydrobromide. [e] Wieland, Schöpf and Hermsen [*Ann.*, **444**, 681 (1925)] found 188° (13 mm.). [f] The picrate was described by Wieland, Schöpf and Hermsen, *ibid.*, **444**, 68 (1925). [g] Mannich and Heilner [*Ber.*, **55**, 362 (1922)] found 142° while Bermejo and Blas [*Chem. Zentr.*, **101**, I, 554 (1930)] reported 143°. [h] Mannich and Heilner [*Ber.*, **55**, 362 (1922)] reported 162°; the same m. p. was found by Bermejo and Blas [*Chem. Zentr.*, **101**, I, 554 (1930)]. [i] In this table the term active is used to denote that the compound is a strong antispasmodic. [j] Dihydrochloride.

the following bromides[5]: β-cyclohexylethyl,[a] γ-cyclohexylpropyl,[a] δ-cyclohexylbutyl,[a] β-cyclopentylethyl,[b] β-(α-naphthyl)-ethyl,[c] β-phenylethyl,[d] and γ-phenoxypropyl bromide.[e]

The following general procedure was used. In those instances in which the primary amine boiled below 55°, 0.1 mole of the latter was dissolved in 50 cc. of alcohol and 0.1 mole of the required bromide added. In some instances 0.05 mole of anhydrous sodium carbonate was added to the mixture. After two to six days[5a] at ordinary temperature the solvent was removed, the residue treated with excess 10% hydrochloric acid and the unchanged bromide extracted with ether. The aqueous acidic layer was made alkaline and the mixture of amines extracted with ether. The ether solution was dried with fused sodium sulfate, the solvent removed and the secondary and tertiary amines separated by distillation.

If the primary amine boiled above 55°, twice the quantity of bromide mentioned above was used and the mixture heated on a steam-bath for one to two days. However, if the primary amine boiled at a relatively high temperature the solvent was omitted and the mixture was heated in an oil-bath at 140–145° for four hours.

Methyldi-(β-cyclohexylethyl)-amine (Compound 21).—A mixture of 12.4 g. of methylamine, dissolved in 60 cc. of alcohol, 152.8 g. of β-cyclohexylethyl bromide and 84.8 g. of anhydrous sodium carbonate was heated in an autoclave at 145–150° for about six hours. The alcohol was removed, sodium hydroxide solution added, the amines extracted with ether and fractionated. There was obtained 37 g. of methyldi-(β-cyclohexylethyl)-amine, b. p. 180–

(5) (a) Hiers and Adams, THIS JOURNAL, **48**, 1091, 2388 (1926); (b) Yohe and Adams, *ibid.*, **50**, 1505 (1928); (c) Haworth and Mavin, *J. Chem. Soc.*, 1014 (1933); (d) Rupe, *Ann.*, **395**, 114 (1913); (e) "Organic Syntheses," Coll. Vol. I, p. 425.

(5a) This time can be shortened to a few hours if an autoclave is used.

184° (19 mm. pressure), and 23 g. of methyl-β-cyclohexylethylamine, b. p. 89–90° (14 mm. pressure).

In a second procedure 56.4 g. of methyl-β-cyclohexylethylamine, 76.4 g. of β-cyclohexylethyl bromide and 42.4 g. of anhydrous sodium carbonate was heated in an oil-bath at 145–150° for twenty hours; yield of methyldi-(β-cyclohexylethyl)-amine 45 g.

The hydrochlorides were obtained by treatment of an ether solution of the base with hydrogen chloride; in the case of compound 31 the base was dissolved in carbon tetrachloride.

Some of the amine hydrochlorides, such as those of compounds 5, 9, 23, 30 and 31, are not very soluble in water.

The nitrate of methyldi-(β-cyclohexylethyl)-amine precipitated in crystalline form when the calcd. amount of concd. nitric acid was added to the base dissolved in ether; m. p. 158–159° after recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_{17}H_{34}O_3N_2$: N, 8.92. Found: N, 8.84.

Upon addition of gold chloride solution to an aqueous solution of methyldi-(β-cyclohexylethyl)-amine hydrochloride the yellow, crystalline chloroaurate precipitated; m. p. 166–167° after recrystallization from dilute alcohol.

Anal. Calcd. for $C_{17}H_{33}N\cdot HCl\cdot AuCl_3$: Au, 33.35. Found: Au, 33.37.

Methyldi-(β-benzoylethyl)-amine (Compound 29).—By a slight modification of the procedure of Mannich and Heilner,[6] namely, interaction of acetophenone, trioxymethylene and methylamine hydrochloride, the yield of the desired amine was increased from 31 to 58%.

(6) Mannich and Heilner, *Ber.*, **55**, 362 (1922).

After removal of the alcohol from the reaction mixture the residue was heated on a steam-bath for twelve hours, the mixture of crystals and oil treated with ether and the undissolved, crystalline hydrochloride washed with alcohol; the hydrochloride weighed 32.3 g. The combined ether and acetone solutions were placed in an evaporating dish, the solvents removed on a steam-bath and the residue heated for twelve hours. The mixture of oil and crystals was washed with ether and acetone as described above; an additional 6.2 g. of amine hydrochloride was obtained.

Treatment of the salt, dissolved in dilute alcohol, with sodium hydroxide yielded the oily base which soon crystallized; m. p. 141–142°.[7]

The hydrochloride precipitated when the base, dissolved in carbon tetrachloride, was treated with hydrogen chloride. The base may also be dissolved in benzene, hydrogen chloride passed into the solution and the hydrochloride precipitated by the addition of dry ether; m. p. 191–192°.[8]

Anal. Calcd. for $C_{19}H_{22}O_2NCl$: Cl, 10.69. Found: Cl, 10.43.

Summary

A number of new secondary and tertiary amines which contain a cycloalkylalkyl or an arylalkyl group have been described.

It was found that most of the amines exhibit antispasmodic activity to some extent and that several of them are very potent in this respect.

(7) Mannich and Heilner [*ibid.*, **55**, 362 (1922)] reported 142°.

(8) Mannich and Heilner (Ref. 7) as well as Bermejo and Blas (*Chem. Zentr.*, **101**, I, 554 (1930)) reported 162°.

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

Antispasmodics. II[1]

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Since no extensive, systematic study seems to have been published which might permit some conclusion to be reached relative to a relationship between chemical structure and antispasmodic activity, we have prepared a large number of amines which have been tested pharmacologically, usually in the form of their hydrochlorides, by Dr. C. W. Geiter in the Frederick Stearns and Company Laboratories.

It cannot be stressed too emphatically that no trustworthy, broad generalization can be drawn except on the basis of data obtained from the examination of hundreds of compounds. However, as far as the amines described in this and the preceding paper[3] are concerned, the following statements may be made from the data now available.

An examination of the cyclohexylalkyl compounds of the series $CH_3N[(CH_2)_x\text{-}C_6H_{11}]_2$ in which x = 1, 2, 3 or 4 showed that all of the compounds appear to be weak in activity except methyldi-β-cyclohexylethylamine, $CH_3N[(CH_2)_2\text{-}C_6H_{11}]_2$, which is a strong antispasmodic.

A second series may be represented by the general formula $RN(CH_2\text{-}CH_2\text{-}C_6H_{11})_2$ in which R = hydrogen, methyl, ethyl, propyl, isopropyl, butyl, amyl, heptyl, phenyl, β-cyclohexylethyl, allyl, cyclohexyl, benzyl or β-hydroxyethyl. The first five compounds in this group were found to be

(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.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Monroe, THIS JOURNAL, **61**, 91 (1939).