[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

PAPAVERINE ANALOGS. IV. 1-CYCLOALIPHATIC-6,7-DIMETHOXYISOQUINOLINES

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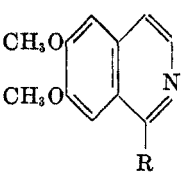
In extending our examination of compounds formally related to papaverine, we have prepared several new 1-cycloaliphatic-6,7-dimethoxyisoquinolines in order to examine them for their coronary dilator action.

The analogs were prepared in a manner similar to that previously reported (1), as were their intermediate amides. Preliminary examination indicated that several of the isoquinoline bases could not be crystallized, and for this reason the isolation was modified to give the more tractable salts.

Bockmühl and Hermann (2) have reported that the 1-cyclohexyl and 1-cyclohexenyl compounds (I, a and b) are more active than papaverine as antispasmodics.



Ia, R = cyclohexyl

Ib, R = 1-cyclohexenyl

Although our results do not substantiate their finding, they are likewise not discordant since our studies have employed methacholine stimulation of the guinea pig intestine as against barium chloride stimulation generally used in earlier pharmacological investigations.

A tentative conclusion that 1-cycloaliphatic isoquinolines appear to have about the same range of antispasmodic and coronary dilator actions as the corresponding 1-benzyl compounds seems justified. However, preliminary studies have shown that toxicity in the 1-cycloaliphatic group is much more pronounced. The second, third, and last compounds (Table I) are only slightly less toxic than papaverine hydrochloride by the intravenous route in mice.

EXPERIMENTAL

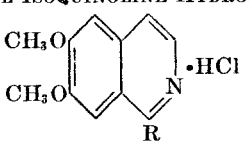
All boiling points are uncorrected. The melting points were determined on a Fisher-John's block.

Intermediates. Homoveratrylamine was supplied by the Monsanto Chemical Company. *Cyclohexanecarboxylic acid* and *β-cyclohexylpropionic acid* were commercial samples that were purified by distillation.

Cyclopentanecarboxylic acid was prepared from 1,4-dichlorobutane and ethyl malonate in 58% yield essentially according to the method of Haworth and Perkin (3). Similarly, cyclopentyl bromide yielded 72% of *cyclopentylacetic acid* following the general methods described by Verwey (4), and Shonle, Keltch, and Swanson (5). The *ethyl ester*, b.p. 76–78°

TABLE I

1-CYCLOALKYL ISOQUINOLINE HYDROCHLORIDES



R	FORMULA	YIELD, %	M.P., °C.	ANALYSES				C.D.[a]	A.[a]
				C		H			
				Calc'd	Found	Calc'd	Found		
Cyclopentyl	$C_{16}H_{19}NO_2$•HCl	64	194–196.5	65.41	65.12	6.86	6.87	0.9	1.25
Cyclopentylmethyl	$C_{17}H_{21}NO_2$•HCl•½H_2O	74	200–202	64.44	64.32	7.32	7.20	.6	0.6
β-Cyclopentylethyl	$C_{18}H_{23}NO_2$•HCl•½C_2H_6O[b]	57	158–162.5	66.17	66.38	7.89	7.62	.5	1.0
Cyclohexyl	$C_{17}H_{21}NO_2$•HCl•½H_2O	41	166–168	64.44	64.55	7.32	7.12	.8	1.0
β-Cyclohexylethyl	$C_{19}H_{27}NO_2$•HCl	56	203–204	67.94	67.66	7.80	7.82	1.1	0.3

[a] Coronary Dilator and Antispasmodic activities, relative to papaverine hydrochloride as unity.

[b] Ethanol of solvation.

(11 mm.) was obtained in 86% yield by first treating the acid with thionyl chloride and then reacting the crude acid chloride with absolute ethanol.

β-Cyclopentylethanol. Ethyl cyclopentylacetate (120 g.) in an equal volume of ether was stirred into a suspension of 20 g. of lithium aluminum hydride in 100 ml. of ether during the course of 1 hour. After an additional hour of stirring, the excess hydride was decomposed with alcohol. The reaction mixture was poured into excess dilute hydrochloric acid and extracted with ether. The ether layer was washed with water and with dilute sodium bicarbonate solution. Distillation gave the alcohol (6), b.p. 94–95° (23 mm.), in 72 g. (82%) yield.

β-Cyclopentylethyl bromide. The preceding alcohol (72 g.) was treated with excess anhydrous hydrogen bromide. The temperature spontaneously rose to 100–120°, where it was then maintained as a slow stream of hydrogen bromide was continually passed through the liquids for 30 minutes after saturation. The mixture was then decomposed on ice and water, extracted with hexane, and the hexane layer was washed with cold dilute sodium bicarbonate solution. Distillation yielded 111.0 g. (99%) of the bromide (6), b.p. 76–78° (19 mm.).

β-Cyclopentylpropionitrile. β-Cyclopentyl bromide (111 g.) was added to a solution of 62 g. of sodium cyanide in 125 ml. of water and 250 ml. of Methyl Cellosolve[1] in the course of 30 minutes under stirring and refluxing. The stirring and refluxing were continued for six hours after the addition of the bromide was completed. On cooling and diluting the reaction mixture, the product was extracted with ether. The ether layer was washed with water and distilled twice to yield 62.4 g. (80%) of the nitrile, b.p. 98–100° (19 mm.); n_D^{25} 1.4490.

Anal. Calc'd for $C_8H_{13}N$: C, 77.99; H, 10.63.
Found: C, 77.50; H, 10.64.

β-Cyclopentylpropionic acid. A mixture of 40 g. of the preceding nitrile and 300 ml. of 25% sodium hydroxide solution was refluxed for 12 hours. The cooled reaction mixture was diluted with water and extracted with ether. The aqueous layer was then acidified with excess hydrochloric acid and the product was recovered by three ether extractions. Distillation of the combined ether solutions yielded 42.7 g. (92%) of the acid, b.p. 134–136° (14 mm.) (7).

N-Homoveratrylcyclopentanecarboxamide. A mixture of 36.2 g. (0.2 mole) of homoveratrylamine and 22.8 g. (0.2 mole) of cyclopentanecarboxylic acid was heated at 190–200° (internal temperature) for 1 hour in an open flask. The product was isolated by crystallizing the cooled reaction mixture from benzene-hexane, followed by recrystallizing from 50% (vol.) methanol. There was thus obtained 40.4 g. (73%) of colorless amide, m.p. 95.5–96.5°.

Anal. Calc'd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.35; N, 5.05.
Found: C, 69.44; H, 8.49; N, 4.99.

The following amides were prepared in a similar manner:

N-Homoveratrylcyclopentylacetamide. M.p. 88–89°; yield, 90%.

Anal. Calc'd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65.
Found: C, 70.16; H, 8.60.

N-Homoveratryl-β-cyclopentylpropionamide. M.p. 89–90°; yield, 85%.

Anal. Calc'd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91.
Found: C, 70.52; H, 9.05.

N-Homoveratrylcyclohexanecarboxamide. M.p. 111.5–112.5°; yield, 84% (2).

N-Homoveratryl-β-cyclohexylpropionamide. M.p. 94.5–95.5°; yield, 77%.

Anal. Calc'd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15.
Found: C, 71.09; H, 9.31.

The amides were converted to the corresponding isoquinolines according to the methods previously described (1). Since the isoquinoline bases were not easily crystallized, they were converted to the corresponding hydrochlorides and were crystallized twice from alcohol-ether solutions. The chemical and pharmacological data are presented in Table I.

[1] Trade name for 2-methoxyethanol.

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SUMMARY

A group of 1-cycloaliphatic isoquinolines related to papaverine has been prepared for pharmacological evaluation. Although their antispasmodic and coronary dilator actions are consonant with the data previously presented for the corresponding 1-benzyl isoquinilines, they are comparatively much more toxic.

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