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Antihistamine Agents

II. 2-Imidazolinylmethyl Ethers of Carbocyclic Carbinols

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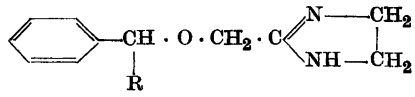
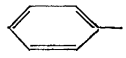
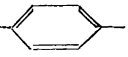
In a recent communication[1] the syntheses of 2-[(diphenylmethoxy)-methyl]-imidazoline (I) was described. As this compound exhibited promising properties as an antispasmodic and antihistamine agent, it seemed to be of interest to investigate some further compounds of this group.

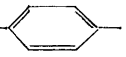
The present paper deals with the preparation of some modifications of the parent imidazoline (I), one phenyl group of which has been substituted or exchanged for another carbocyclic group (II—V). Some compounds containing substituents of a heterocyclic nature will be described later.

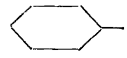
The new imidazolines were prepared by treating two moles of the sodium salt of the corresponding carbinol with one mole of 2 (chloromethyl)-imidazoline hydrochloride. The reaction product was isolated by precipitation with hydrogen chloride.

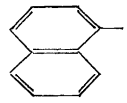


I. R = 

II. R = CH_3— 

III. R = CH_3O— 

IV. R = 

V. R = 

These imidazolines were rather sensitive especially to acids. Addition of strong acids to the aqueous solutions of their salts caused cleavage of the molecule at the ether linkage, the corresponding carbinol and salts of 2-(hydroxymethyl)-imidazoline being formed.

The bases could be precipitated from the aqueous solutions of their salts by sodium carbonate and ammonia but not by sodium bicarbonate. They could not be distilled without decomposition even at 10^{-3} mm Hg.

Results of preliminary tests* of the antihistaminic and antispasmodic potency of the hydrochlorides of the imidazolines are summarized in the following table. The tests were carried out on isolated guinea pig ileum. Activity is expressed in terms of β-dimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) as the unit of activity.

Table 1. Effect of 2-imidazolinylmethyl ethers.

Compound	Effect in reducing the spasm produced by		
	Histamine	$BaCl_2$	Acetylcholine
I	0.5	0.9	0.7
II	0.6	0.8	0.3
III	0.2	0.3	0.1
IV	0.07	1.6	0.7
V	0.05	1.5	0.8
Benadryl	1	1	1

EXPERIMENTAL

2-[(*p*-Methyldiphenylmethoxy)-methyl]-imidazoline

p-Methylbenzohydrol was prepared in 94 % yield from *p*-methylbenzophenone by reduction with aluminium isopropoxide following the procedure given for the preparation of benzohydrol in *Organic reactions*[3]. *p*-Methylbenzohydrol (35.0 g) was dissolved in toluene (150 ml), powdered sodium (4.0 g) was added, and the mixture allowed to stand at room temperature overnight. Next day, 2-(chloromethyl)-imidazoline[3] (13.5 g) was added and the mixture warmed at 60° for 30 minutes with vigorous stirring. After cooling, the separated sodium chloride was filtered off, and the toluene solution precipitated with dry hydrogen chloride in ether. In order to remove sodium and ammonium chlorides the precipitate was dried in air and dissolved in water, whereupon the solution was made alkaline with sodium carbonate.

The resulting oil was extracted with ether, and dry hydrogen chloride in ether was added to the dried ether layer. The hydrocloride (8.1 g) was collected and washed with light petroleum. M. p. 180—184°. After two purifications by dissolving in acetone and precipitating with light petroleum, it melted at 188—189°.

* For these tests acknowledgment is made to Dr. S. Wiedling of our Department of Biology. Details will be reported elsewhere.

$C_{18}H_{20}N_2O \cdot HCl$ (318.8) Calc. N 8.9 Cl 11.2
Found » 9.0 » 11.3

The free base was obtained by dissolving the hydrochloride in water and precipitating with sodium carbonate solution. This yielded an oil, which soon crystallised. After recrystallisation from ether the free imidazoline melted at 98—99°.

$C_{18}H_{20}N_2O$ (280.4) Calc. N 10.0 Eq. wt. 280.4
Found » 10.1 » » 281.2 (titr. with 0.1 *N* H_2SO_4 with methyl red as indicator.)

With picric acid the base gave a picrate with m.p. 166—168°.

2-[(*p*-Methoxydiphenylmethoxy)-methyl]-imidazoline

p-Methoxybenzohydrol was prepared from the corresponding ketone by reduction with aluminium isopropoxide in the same way as the preceding carbinol. Yield 91 %. The reaction between *p*-methoxybenzohydrol (21.4 g), sodium (2.3 g) and 2-(chloromethyl)-imidazoline hydrocloride (7.75 g) was carried out as in the preceding experiment. The precipitated oily hydrochloride was boiled with acetone and insoluble salts were filtered off. On cooling and diluting with light petroleum, white crystals (6.5 g) with the m.p. 145—148° separated. After purification in the same way the hydrochloride melted at 150—151°.

$C_{18}H_{20}N_2O_2 \cdot HCl$ (332.8) Calc. Cl 10.65 N 8.4
Found » 10.7 » 8.4

It was impossible to obtain the base in crystalline form. For further characterisation of the base, its bioxalate was prepared by adding a solution of oxalic acid in ether to an ether solution of the base. After recrystallisation from water the bioxalate melted at 152—152.5°.

$C_{18}H_{20}N_2O_2 \cdot (COOH)_2$ (386.4) Calc. C 62.2 H 5.7
Found » 62.1 » 5.8

With picric acid a picrate melting at 143—145° was obtained.

2-[(Cyclohexylphenylmethoxy)-methyl]-imidazoline

This compound was prepared from cyclohexylphenylcarbinol[4] (28.9 g), powdered sodium (3.45 g), and 2-(chloromethyl)-imidazoline hydrochloride (11.6 g) in the usual way. The crude hydrochloride was boiled with acetone, and the acetone filtered and diluted with light petroleum. After cooling, white crystals (5.9 g) melting at 172—174° were collected. Repeated recrystallisations from acetone-light petroleum raised the m. p. to 180—180.5°.

$C_{17}H_{24}N_2O \cdot HCl$ (308.9) Calc. N 9.1 Cl 11.5
Found » 9.1 » 11.6

Addition of alkali to an aqueous solution of the hydrochloride gave the crystalline base, which after recrystallisation from light petroleum melted at 86—87°.

$C_{17}H_{24}N_2O$	(272.4)	Calc.	N	10.3	Eq.wt. 272.4
		Found	»	10.5	» 273.1

The base gave a bioxalate melting at 144—146°, recrystallised from ethyl acetate.

$C_{17}H_{24}N_2O \cdot (COOH)_2$	(362.4)	Calc.	C	63.0	H	7.2
		Found	»	63.1	»	7.1

The picrate melted at 131—132°.

2-[(α-Naphthylphenylmethoxy)-methyl]-imidazoline

This imidazoline was prepared in the usual way with some slight modifications. The reaction between α-naphthylphenylcarbinol[5] (29.0 g) and sodium (2.85 g) was rather slow and the mixture was therefore refluxed for four hours before the 2-(chloromethyl)-imidazoline hydrochloride (9.7 g) was added. The mixture was then stirred at 60° for 45 minutes. The precipitated, semi-solid hydrochloride was separated from inorganic salts by dissolving in acetone and diluting with light petroleum. The crude hydrochloride (5.8 g), m. p. 176—180°, obtained in this way was purified by repeated recrystallisations from ethanol-light petroleum. M. p. 204—205°.

$C_{21}H_{20}N_2O \cdot HCl$	(316.4)	Calc.	N	7.9	Cl	10.1
		Found	»	8.1	»	10.0

The free base was obtained as an oil, which did not crystallise. From the solution of the base in ether the bioxalate was prepared. M. p. 126—128° after recrystallisation from a mixture of ethyl acetate and light petroleum.

$C_{21}H_{20}N_2O \cdot (COOH)_2$	(406.4)	Calc.	C	68.0	H	5.45
		Found	»	67.8	»	5.35

SUMMARY

The preparation of four 2-imidazolinylmethyl ethers of carbocyclic carbinols is described. Results from preliminary pharmacological tests are reported.

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