Antihistamine Agents

III. 2-Imidazolinylmethyl Ethers of Heterocyclic Carbinols

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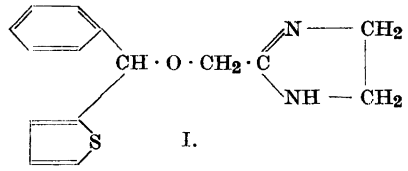
Replacement of a phenyl nucleus of an antihistamine agent by a heterocyclic one often yields compounds with a strongly increased effect. Sometimes, however, the antihistaminic activity is diminished or completely destroyed. For excellent reviews in this field see Loew [1] or Strauss [2].

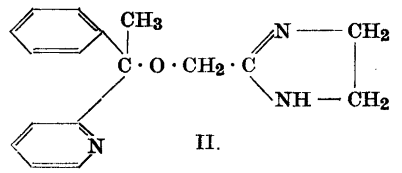
In earlier papers [3, 4] the preparation and the antihistaminic properties of 2-[(diphenylmethoxy)-methyl]-imidazoline and some related compounds have been described. In order to investigate the effect of imidazolinylmethyl ethers of heterocyclic carbinols, the compounds I and II were synthesized and tested. Compound II is an imidazoline analog of Decapryn, a well known histamine antagonist.

The new imidazolines were prepared by condensing equivalent parts of α-thienylphenylcarbinol or phenyl-α-pyridylmethyl-



I.

carbinol with 2-(chloromethyl)-imidazoline in the presence of sodium amide, two equivalents of sodium amide being used to liberate the chloroimidazoline from its hydrochloride. Attempts to use lithium amide or lithium hydride as condensing agents resulted in very poor yields. The compounds were isolated from the reaction mixtures by precipitation with oxalic acid. The free bases could not be obtained in crystalline form and could not be distilled without decomposition even at very low pressures. The bioxalates of the compounds were therefore used in the tests.



II.

Results of preliminary tests of the antihistaminic and antispasmodic activity of the oxalates of these two imidazolines are summarized in Table 1. 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. According to the tests the antihistaminic and antispasmodic activity of these compounds is rather weak.

Table 1. Effect of 2-imidazolinylmethyl ethers.

Compound	Effect in reducing the spasm produced by: Histamine	$BaCl_2$	Acetylcholine
I	0.15	0.55	0.3
II	0.1	0.1	0.05
Benadryl	1	1	1

loses and the open-chain saccharides is reached in a very slow reaction.

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2-[(α-Thienylphenylmethoxy)-methyl]-imidazoline bioxalate. The starting α-thienylphenylcarbinol was prepared from α-benzoylthiophene by reduction with aluminium isopropoxide. After recrystallisation from light petroleum m.p. 57—58°. Yield 88 %. Minnis [5] who prepared this compound by reduction of the ketone with aluminium amalgam reported the same m.p. This carbinol seemed to be rather unstable. On keeping in air or in vacuum it sometimes decomposed into a tarry mass with a strong smell of sulphur dioxide. The carbinol was therefore used immediately after preparation.

To a suspension of sodium amide in toluene (75 ml), prepared from sodium (4.1 g) and liquid ammonia according to Vaughn, Vogt, and Nieuwland [6], a solution of α-thienylphenylcarbinol (16.2 g) in toluene (75 ml) was added. The reaction mixture was stirred at 70—80° for an hour and left overnight at room temperature. Next day, 2-(chloromethyl)-imidazoline [7] (13.2 g) was added and the mixture warmed at 60° for 1.5 hours. After the mixture had been cooled, the inorganic salts were filtered off. The oxalate was precipitated by the addition of a saturated ethereal solution of oxalic acid to the toluene solution. The crude bioxalate was collected and recrystallised from water. Yield 6.1 g, m.p. 155—156,5°.

$C_{15}H_{16}N_2OS \cdot (COOH)_2$ (362.4)

Calc.	C	56.35	H	4.45	S 8.85
Found	»	56.7	»	4.8	» 9.1

With picric acid a picrate was obtained. M.p. 179—179.5° after recrystallisation from ethanol.

$C_{15}H_{16}N_2OS \cdot C_6H_3N_3O_7$ (501.5)

Calc.	C	50.3	H	3.4	N 14.0
Found	»	50.0	»	3.7	» 14.1

2-[(Phenyl-α-pyridylmethylmethoxy)-methyl]-imidazoline bioxalate. This compound was prepared from phenyl-α-pyridylmethylcarbinol [8] (16.4 g) ans 2-(chloromethyl-imidazoline hydrochloride (12.7 g) in the same way as the preceding imidazoline. In order to remove the oxalate of the starting carbinol the crude oxalate was dissolved in water, made alkaline with sodium bicarbonate and extracted with ether.

The imidazoline base was precipitated from the bicarbonate solution by diluted sodium hydroxide. The oily base was extracted with ether and oxalic acid in ether added until no more precipitate was formed. The bioxalate (3.5 g) was recrystallised from acetone-water 3 : 1. M.p. 197—198° with decomposition.

$C_{17}H_{19}N_3O \cdot (COOH)_2$ (371.4)

Calc.	C	61.4	H	5.7	
Found	»	61.6	»	5.7	

With picric acid a dipricrate was obtained. M.p. 203—205° after recrystallisation from ethanol.

$C_{17}H_{19}N_3O \cdot (C_6H_3N_3O_7)_2$ (739.6)

Calc.	C	47.1	H	3.4	
Found	»	46.8	»	3.4	

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