[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

2-(BENZHYDRYLOXYMETHYL)IMIDAZOLINE, A NEW HISTAMINE ANTAGONIST

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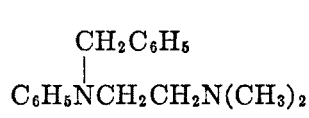
Most of the recently published work on antihistaminic drugs centered on preparing a variety of compounds derived from N,N-dimethylethylenediamine (1, 2) and β-dimethylaminoethanol (3), which resulted in the discovery of therapeutically active drugs such as Antergan (I) (1), Pyribenzamine (II) (2) and Benadryl (III) (3).



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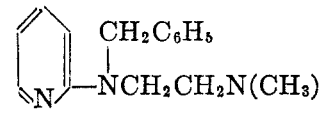

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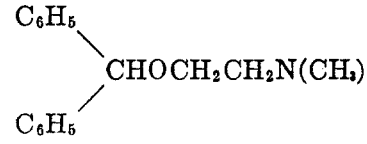
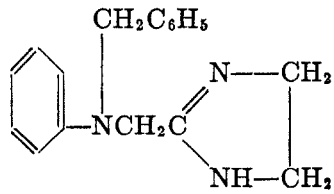


III

Miescher, Klarer, and Urech (4) were able to show, however, that the dimethylaminoethyl moiety is not entirely essential for antihistaminic activity, since 2-N-benzyl-N-phenylaminomethyl)imidazoline (Antistine) (IV) has strong histaminolytic properties and differs from Antergan (I) only in the nature of the side chain. Recently (5), we have extended the scope of this observation by preparing imidazoline and amidine analogs of phenolic ethers, such as F929 (V), which have been synthesized in Fourneau's laboratory and which were among the first specific histamine antagonists (6). We found the 2-(thymoxymethyl)-imidazoline (VI) to be at least as active as V and therefore we have continued our work on the replacement of the dialkylaminoethyl side chain of various pharmacologically active compounds by other substituents such as the 2-methylimidazoline group.



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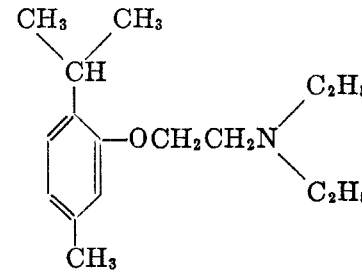

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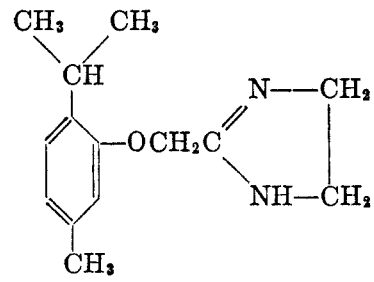
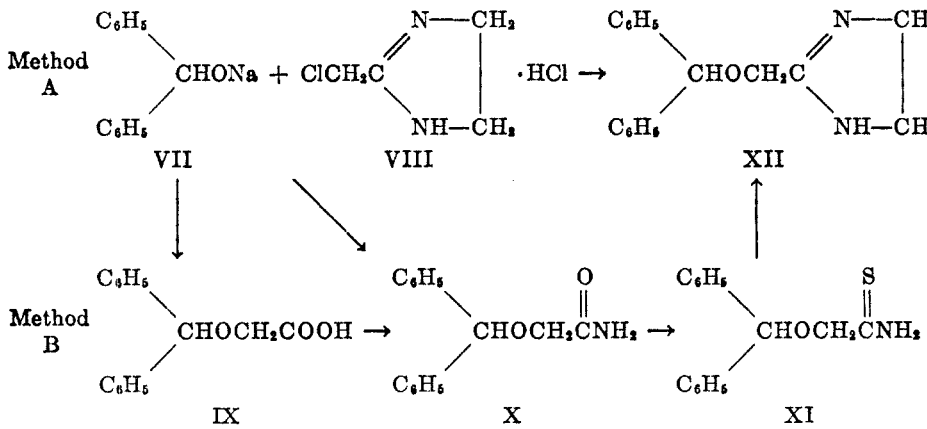


VI

On applying this approach to β-dimethylaminoethyl benzhydryl ether (III) (3), we have synthesized 2-(benzhydryloxymethyl)imidazoline (XIII) and have found it to be a strong histamine antagonist. The present paper, which deals with the synthesis of this compound, is prompted by the appearance of a preliminary note by Cavallini and Mazzuchi (7) who reported some of the physical constants and pharmacological data of this substance, but did not record the method of synthesis.

Of a number of syntheses which have been studied, the following two have proved to be the most satisfactory. Method A involved the direct condensation of sodium benzhydrolate (VII) and 2-(chloromethyl)imidazoline hydrochloride (VIII) (8) in toluene suspension, while Method B employed as the key intermediate benzhydryloxyacetamide (X), which after Kindler conversion (9) to the thioamide (XI) and reaction with ethylenediamine according to Forssel (10) afforded the desired imidazoline XII. The melting points of the base, its picrate and hydrochloride agree well with the values reported by the Italian workers (7).

Since the submission of this paper, an article by Dahlbom and Sjögren (11) has come to our attention in which the preparation of the imidazoline XII by method A is described.



The detailed pharmacological results on this imidazoline derivative XII will be published by Dr. B. N. Craver and co-workers from our Division of Macro-

biology. Briefly, compound XII was about one-half as toxic as Pyribenzamine (II) (2) in rats ($L.D._{50}$ intravenous = 23 mg./kg.) and demonstrated antihistaminic and antianaphylactic properties *in vitro* and in guinea pigs, comparable to those of Benadryl and Pyribenzamine. Contrary to the action of some antihistaminic drugs, this substance *per se* relaxes the bronchiolar muscles of the guinea pig.

EXPERIMENTAL[1]

2-(Benzhydryloxymethyl)imidazoline (XII). Method A. Since our procedure is essentially the same as that of the Swedish investigators (11), the experimental details are not repeated here except for the following physical constants:

2-(Benzhydryloxymethyl)imidazoline (XII) was obtained as colorless needles from hexane-acetone and melted at 102–103° [lit. (7, 11): 102–103°].

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.52. Found: N, 10.56.

The *hydrochloride* formed colorless, non-hygroscopic crystals from a mixture of ethanol and methyl ethyl ketone and showed the m.p. 207–208° [reported (7): 204–205°; (11): 203–205°].

Anal. Calc'd for $C_{17}H_{19}ClN_2O$: N, 9.25; HCl, 12.32.
Found: N, 9.39; HCl, 12.27.

The *picrate* crystallized from acetone as bright yellow prisms, m.p. 204–205° [lit. (7); 205°; (11): 202–204°; no analysis was given].

Anal. Calc'd for $C_{23}H_{21}N_5O_8$: C, 55.75; H, 4.27; N, 14.14.
Found: C, 55.66; H, 4.34; N, 14.00.

Benzhydryloxyacetic acid (IX). The apparatus consisted of a ground-joint, three-necked flask equipped with mercury seal, Hershberg stirrer, combined gas inlet tube, and dropping-funnel, and in the third side arm a Vigreux column with sealed-on condenser set downward for distillation. A solution of 3.4 g. of sodium in 60 cc. of methanol was treated in a current of nitrogen while stirring with a solution of 27.6 g. of benzhydrol in 120 cc. of dry toluene. The clear solution was immersed in an oil-bath maintained at *ca.* 140–150° so that a moderate rate of distillation was achieved. Sodium benzhydrolate started to appear after a short time and dry toluene was added from time to time so as to keep the reaction mixture fluid until the temperature in the Vigreux column had reached 90°. The column was then replaced by a reflux condenser and 10.4 g. of bromoacetic acid was added followed by 70 cc. of toluene. After refluxing with stirring under nitrogen for one and one-half hours, water was added, the solution made alkaline and the toluene was removed by steam distillation. The residue was extracted with ether to recover unreacted benzhydrol (15.5 g.), and the alkaline solution acidified and again extracted with ether. The ether solution was washed until neutral, dried, evaporated, and the residue recrystallized from hexane-acetone to yield 11.5 g. (63%) of colorless crystals of the acid IX melting at 77–79°.

Anal. Calc'd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82; neut. equiv. 242.
Found: C, 74.18; H, 5.87; neut. equiv. 244.

A sample of the acid on treatment with ethereal diazomethane solution, evaporation, and crystallization from hexane gave *methyl benzhydryloxyacetate* melting at 37–39°.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29.
Found: C, 74.70; H, 5.93.

The *ethyl ester*, prepared from sodium benzhydrolate and ethyl bromoacetate, was obtained as a heavy oil, b.p. 170–180° at 1 mm., n_D^{20} 1.5500.

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71.
Found: C, 75.80; H, 6.68.

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[1] All melting points are corrected. The microanalyses were carried out by Mr. Joseph Alicino, Metuchen, N. J. The Misses Helen Dudek and Jean Rogers assisted capably in the experimental work.

Benzhydryloxyacetamide (*X*). A solution of 4.8 g. of the acid IX in 30 cc. of benzene was refluxed with 4 cc. of thionyl chloride and two drops of pyridine for one-half hour and excess thionyl chloride was removed by repeated addition of benzene and distillation to dryness under reduced pressure. The residue was redissolved in benzene and added to an ethanolic ammonia solution. After removal of the solvent, the material was taken up in acetone, filtered, and hexane was added, whereupon the amide crystallized as colorless needles, m.p. 135.5–136°; yield 3.8 g. (76%). Recrystallization from ethanol did not change the melting point. The same product was obtained by shaking a suspension of methyl or ethyl benzhydryloxyacetate with concentrated aqueous ammonium hydroxide solution overnight, or by condensing sodium benzhydrolate (VII) with chloroacetamide.

Anal. Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81.
Found: C, 74.69; H, 6.28; N, 6.02.

2-(Benzhydryloxymethyl)imidazoline (*XII*). *Method B.* The Kindler reaction (9) was carried out by stirring 2.4 g. of the amide X, 0.9 g. of phosphorus pentasulfide, 0.62 g. of powdered anhydrous sodium sulfide, and 10 cc. of toluene until a homogeneous paste was obtained, and then heating with stirring at 80–90° for one-half hour. The mixture was cooled, the supernatant liquid was decanted and the residue stirred with 10 cc. of toluene at 80° for fifteen minutes and the process repeated. The combined toluene solutions were concentrated and diluted with hexane to yield 2.74 g. of material melting at 96–104° (turbid); on dissolving in acetone, filtering, and adding hexane, the crystals melted at 102–105° and represented an approximately 1:1 mixture (Found: S, 6.99) of *thioamide* XI and amide X. This crop was subjected directly to the Forssel procedure (10) by refluxing with a slight excess of anhydrous ethylenediamine (based on total amide mixture) in toluene solution for three hours. After working up as in method A by extracting with acid, there was obtained a nearly quantitative yield of recovered amide X from the neutral fraction, while the basic fraction gave 57–68% of 2-(benzhydryloxymethyl)imidazoline (XII) characterized as the hydrochloride and picrate.

SUMMARY

Two methods for the preparation of a new histamine antagonist, 2-(benzhydryloxymethyl)imidazoline (XII), have been described. Preliminary pharmacological data are included.

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REFERENCES

(1) VIAUD, *Produits Pharm.*, **2**, 53 (1947).
(2) HUTTRER, DJERASSI, BEEARS, MAYER, AND SCHOLZ, *J. Am. Chem. Soc.*, **68**, 1999 (1946).
(3) RIEVESCHL AND HUBER, A.C.S. Meeting, Atlantic City, April, 1946, paper 41, Division of Medicinal Chemistry.
(4) As quoted by MEIER AND BUCHER, *Schweiz. Med. Wochschr.*, **76**, 294 (1946).
(5) DJERASSI AND SCHOLZ, *J. Am. Chem. Soc.* **69**, 1688 (1947).
(6) STAUB, *Ann. Inst. Pasteur*, **63**, 400, 485 (1939).
(7) CAVALLINI AND MAZZUCHI, *Farm. sci. e tec.* (Pavia), **2**, 273 (1947); *Chem. Abstr.*, **42**, 1664 (1948).
(8) KLARER AND URECH, *Helv. Chim. Acta*, **27**, 1762 (1944).
(9) KINDLER, *Ann.*, **431**, 187 (1923).
(10) FORSSEL, *Ber.*, **25**, 2132 (1892).
(11) DHALBOM AND SJÖGREN, *Scand. Chem. Acta*, **1**, 777 (1947).