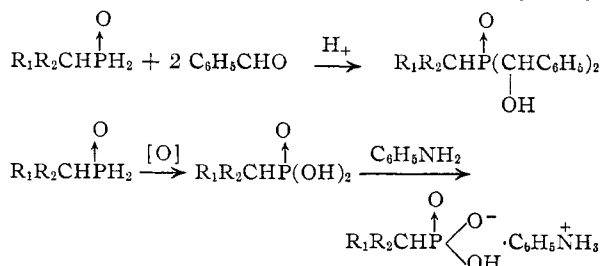


The reactions were conducted by allowing solutions of the ketones in concentrated hydrochloric acid to react with phosphine until no more of the latter was absorbed. Examination of the resulting solutions by n.m.r. spectroscopy in the phosphorus region indicated that a mixture of the corresponding primary phosphine oxide and hydroxy secondary phosphine oxide was formed in all cases.<sup>5</sup> These ketones are ranked in the order of increasing amounts of primary phosphine oxides obtained in reaction with phosphine: cyclohexanone < cyclopentanone < acetone < 2-pentanone < 2-heptanone < 3-pentanone < acetophenone < 4-heptanone. Thus, the relative amounts of the two products obtained is determined largely by steric effects, which govern the extent to which the second reaction takes place.

Some of the primary phosphine oxides were isolated as low melting solids but proved to have poor stability. These substances were, therefore, converted to their benzaldehyde adducts and phosphonic acid oxidation products (isolated as aniline salts) for characterization. The hydroxy

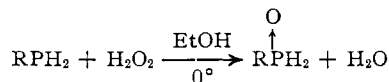


secondary phosphine oxides were obtained as stable crystalline solids in several cases. As an illustration, reaction of phosphine with acetone gave both the primary and secondary oxides. Isopropylphosphine oxide was identified by its conversion to bis-( $\alpha$ -hydroxybenzyl)-isopropylphosphine oxide, m.p. 162–163° (*Anal.* Calcd. for  $C_{17}H_{21}O_3P$ : C, 67.09; H, 6.96; P, 10.18. Found: C, 66.73; H, 7.17; P, 9.89); and to the aniline salt of isopropylphosphonic acid, m.p. 175–177° (*Anal.* Calcd. for  $C_9H_{15}NO_3P$ : C, 49.76; H, 7.43; P, 14.26. Found: C, 49.34; H, 7.21; P, 14.07). The other product was (1-hydroxy-1-methylethyl)-isopropylphosphine oxide, m.p. 71–72.5° (*Anal.* Calcd. for  $C_6H_{15}O_2P$ : C, 47.99; H, 10.07; P, 20.63. Found: C, 47.73; H, 9.78; P, 20.19).

A more widely applicable method of preparing primary phosphine oxides was found in the con-

(5) We wish to express our appreciation to Dr. J. E. Lancaster for the n.m.r. studies. Hydroxy secondary phosphine oxides gave a 1-1 doublet centered near -60 p.p.m. (referred to 85%  $H_3PO_4$ ) while the primary oxides gave a 1-2-1 triplet centered near -15 p.p.m. The splittings (P-H coupling) were about 28 p.p.m., which is in good agreement with those of other organic compounds having the  $>P(O)H$  structure which have been studied in this laboratory. The doublet indicates one hydrogen attached to P; the triplet indicates two.

trolled oxidation of primary phosphines. Several primary phosphine oxides were obtained in this way in good yields using stoichiometric amounts of hydrogen peroxide. These substances were



$$R = C_6H_5, i-C_4H_9, n-C_8H_{17} \text{ and } CNCH_2CH_2$$

characterized by n.m.r. spectroscopy and by the preparation of derivatives as in the case of the phosphine-ketone products. Octylphosphine oxide was isolated as a crystalline solid of limited stability, m.p. 46–48°. It was much more stable in solution and could be heated at 75° in ethanol for a period of several hours without appreciable decomposition. Treatment with acrylonitrile and a trace of sodium methoxide gave bis-(2-cyanoethyl)-octylphosphine oxide, m.p. 66–68°, identical with a specimen obtained by an alternate route.<sup>6</sup> Treatment with benzaldehyde in HCl solution gave bis-( $\alpha$ -hydroxybenzyl)-octylphosphine oxide, m.p. 127–129°. *Anal.* Calcd. for  $C_{22}H_{31}O_3P$ : C, 70.56; H, 8.35; P, 8.27. Found: C, 70.63; H, 8.21; P, 8.18.

The chemistry of primary phosphine oxides will be described in greater detail in a forthcoming publication.

(6) M. M. Rauhut, unpublished work. The material was prepared by reaction of 1-octene and bis-(2-cyanoethyl)-phosphine oxide using a free-radical initiator.

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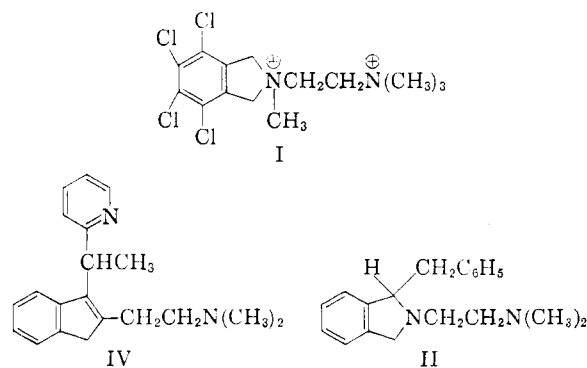
SHELDON A. BUCKLER  
MARTIN EPSTEIN

RECEIVED FEBRUARY 27, 1960

#### A NEW CLASS OF HIGHLY ACTIVE ANTIHISTAMINICS

Sir:

Since 1952 our laboratory has been interested in isoindolines and related substances derived by the reduction of cyclic imides. One outcome of this work was the ganglionic blocking drug, chlorisondamine (I). Among a large number of widely



related substances, 1-benzyl-2-(2-dimethylaminoethyl)-isoindoline (II) (*Anal.* Found for  $C_{19}H_{24}N_2 \cdot 2HCl \cdot 0.5H_2O$ : C, 63.28; H, 7.79; N, 7.64), m.p. 200–201°, was prepared by the sequence to be given. Benzalphthalide was treated with dimethylaminoethylamine to give 3-benzylidene-2-(2-dimethylaminoethyl)-phthalimidine

(*Anal.* Found for  $C_{19}H_{20}N_2O \cdot HCl$ : C, 69.59; H, 6.58; N, 8.52), m.p. 225–226°, which was reduced catalytically to the 3-benzylphthalimidine, then reduced with lithium aluminum hydride to II. II showed an interesting wide spectrum of pharmacological activity. It is a moderately active antihistaminic, a potent local anesthetic, has an antiinflammatory effect in the rat dextran edema test and shows a marked tranquilizing effect on mice.

In exploring variations in the structure of II, compounds obtained by the replacement of the nitrogen of the isoindoline nucleus by carbon, *i.e.*, indenenes, were investigated. Such analogs were prepared as follows. 2-(Dimethylaminoethyl)-indane-1-one, (III), b.p. 132° at 1.7 mm. (*Anal.* Found: C, 76.36; H, 8.53; N, 7.12), prepared by a modification of the method by Hoffmann, *et al.*,<sup>1</sup> for similar basic indanones, was treated with Grignard reagents or organolithium compounds. The intermediate amino alcohols dehydrated easily by warming in dilute aqueous acid to give the desired indenenes. A large number of compounds were prepared by varying the different structural elements of such indenenes. Reaction of III with the organolithium derivative generated by the action of phenyllithium on 2-ethylpyridine and dehydration gave *dl*-2-[1-[2-(2-dimethylaminoethyl)-3-indenyl]-ethyl]-pyridine IV (*Anal.* as the maleate,  $C_{21}H_{22}N_2 \cdot C_2H_4O_4$ . Found: C, 69.81; H, 6.67; N, 7.16), m.p. 159–161°, the most active antihistaminic of the series.<sup>2</sup> Resolution of IV via the tartrate salts was accomplished. The activity resides chiefly in the levo rotating isomer. This substance as the maleate in the standard *in vivo* guinea pig assay is about four times as potent (oral  $ED_{50}$ -31  $\gamma \pm 3.5 \gamma/kg.$ )<sup>3</sup> as dextro-chloropheniramine maleate, the hitherto most active antihistamine reported.<sup>4</sup>

(1) H. J. Schmid, A. Hunger and K. Hoffmann, *Helv. Chim. Acta*, **39**, 607 (1956).

(2) The generic name is dimethylpyridene.

(3) These compounds were investigated pharmacologically by Drs. W. Barrett and A. Plummer.

(4) F. Roth and W. M. Govier, *J. Pharm. and Exp. Ther.*, **124**, 347 (1958).

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RECEIVED MARCH 3, 1960

## THE ISOLATION AND CHARACTERIZATION OF THE CHICK EDEMA FACTOR

Sir:

The agent responsible for an edema condition in broiler type chicks has been traced<sup>1</sup> to certain lots of feed grade animal fat. This toxic factor has been further restricted<sup>2</sup> to the non-saponifiable portion of the tallow. We wish to report here the isolation of the edema-producing substance in crystalline form and its preliminary characterization.

(1) Anon., *Feedstuffs*, **30**, No. 14, 1 (1958).

(2) S. C. Schmitt, H. M. Edwards and D. Morris, *J. Am. Vet. Med. Assoc.*, **132**, 216 (1958).

A three-week assay involving quantitative measurement of the degree of hydropericardium produced in chicks on a test diet containing the materials to be tested was used to guide the purification of the factor. The details of the biological studies will be reported elsewhere.<sup>3</sup>

The toxic tallow was refluxed in aqueous methanolic sodium hydroxide solution and the neutral, non-saponifiable fraction separated by extraction with ethylene dichloride to yield an active (20 $\times$ ) concentrate.<sup>4</sup> This was dissolved in hexane and chromatographed on alumina (load/adsorbent ratio 1:4). The bulk of the inert material passed through the column and the activity was eluted with 10% ether in hexane. The oily product (500 $\times$ ) was separated from carbonyl-containing impurities by chromatography on Decalso (1:100) using hexane as the developing and eluting solvent. The product (5,000 $\times$ ) was again chromatographed on alumina (1:30) to give a 30,000 $\times$  concentrate. Finally, this high potency preparation was chromatographed on a high-ratio alumina column (1:1000) using iso-octane as the developing and eluting agent.

The final chromatogram yielded partly crystalline peak fractions. These were triturated with iso-octane to remove oily impurities and the residues were crystallized from a benzene-hexane mixture. After recrystallization to constant properties, the toxic fat factor was obtained as colorless needles which did not melt on the hot stage but sublimed slowly above 225°, rapidly at 245°. It was homogeneous when examined by reverse-phase chromatography on silanated paper. In 1:1 dimethylformamide-iso-octane, a single spot was observed at  $R_f$  0.88. In iso-octane solution, the factor was characterized by absorption maxima at 244  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  1441) and 312  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  117), and a shoulder at 238  $m\mu$  ( $E_{1\%}^{1\text{cm}}$  1138). No absorption maxima were observed in the infrared below 6.3  $\mu$ , indicating the absence of carbonyl and hydroxyl groups. In the chick assay, this crystalline toxic factor produced marked hydropericardium at a dose of 0.1 mg./kg. of diet, and was assigned a potency of approximately one million times that of the crude toxic fat.

The small quantity (less than 1 mg.) of crystalline toxic factor isolated to date has not permitted structural studies, even to the extent of elementary analysis. The infrared absorption spectrum is notably lacking in structural implications, but does suggest absence of functional groups containing oxygen. Until the last step in the isolation, it was not possible to correlate any chemical or physical property with the active factor; complete dependence on the chick assay was required.

Other groups studying the toxic principle have used purification methods similar to those outlined here and have suggested that the factor might possess a steroidal<sup>5</sup> or other polynuclear structure.<sup>6,7</sup>

(3) W. H. Ott, *et al.*, to be published.

(4) Activities are expressed as multiples of the toxicity of the original tallow.

(5) W. B. Brew, J. D. Dore, J. H. Benedict, G. C. Potter and E. Sipos, *J. Assoc. Offic. Agr. Chemists*, **42**, no. 1, 120 (1959).

(6) L. Friedman, D. Firestone, W. Horwitz, D. Baner, M. Anstead and G. Shue, *ibid.*, **42**, no. 1, 129 (1959).

(7) J. C. Wootton and J. C. Alexander, *ibid.*, **42**, no. 1, 141 (1959).