[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

Histamine Antagonists. 1-*p*-Chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butene[1]

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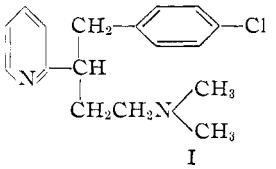
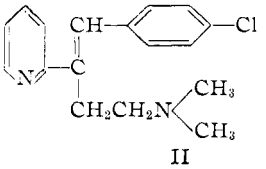
Dehydration of crude 1-*p*-chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butanol with hot sulfuric acid yielded a mixture of *cis*- and *trans*-1-*p*-chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butenes. The *cis* and *trans* isomers were separated by fractional crystallization of the maleates and the position of the double bond was established by ozonolysis. The assignment of the configurations was based on a comparison of the ultraviolet absorption spectra of the isomers with those of *cis*- and *trans*-stilbene and *trans*-α-methylstilbene.

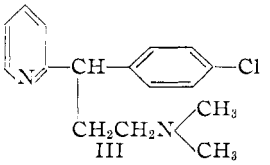
As part of our studies on histamine antagonists not derived from either ethanolamine or ethylenediamine,[2] it was of interest to prepare 4-*p*-chlorophenyl-3-(2′-pyridyl)-N,N-dimethylbutylamine (I) and 1-*p*-chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butene (II) for pharmacological comparison with the potent antihistaminic agent, 3-*p*-chlorophenyl-3-(2′-pyridyl)-N,N-dimethylpropylamine[3] (III). While this work was in progress the synthesis of a series of antihistaminic agents re-



I



II



III

lated to II was reported.[4] Recently a patent of 1-*p*-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-butenes appeared[5] in which one isomer, 1-*p*-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-2-butene diphosphate, has been reported to be an effective antihistaminic agent both in animals[6] and in man.[7]

The synthesis of I was effected by the alkylation of 3-(2′-pyridyl)-N,N-dimethylpropylamine (IV) with potassium amide and *p*-chlorobenzyl chloride.

(1) Presented before the Division of Medicinal Chemistry, 128th Meeting of the American Chemical Society, Minneapolis, Minnesota, September 13, 1955.

(2) (a) N. Sperber and R. Fricano, THIS JOURNAL, **75**, 2986 (1953); (b) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *ibid.*, **73**, 5752 (1951).

(3) "Chlor-Trimeton" registered trademark of the Schering Corporation.

(4) E. Rohrmann, U. S. Patent 2,485,662 (1949), described the preparation of a series of α-(β-dialkylaminoalkyl)-stilbenes by the dehydration of the corresponding 1,2-diphenyl-4-(N,N-dialkylamino)-2-butanol with hydrochloric acid. Although there was a possibility of obtaining either Δ_1- or Δ_2-butenes, the author considered these compounds to be Δ_1-butenes, W. G. Stoll, Ch. J. Morel and Ch. Frey, *Helv. Chim. Acta*, **33**, 1194, 1208 (1950), prepared the corresponding Δ_1- and Δ_2-butenes and proved their structures. It was established that the compounds described in Rohrman's patent were not Δ_1-butenes (stilbenes) but were the isomeric Δ^2-butenes.

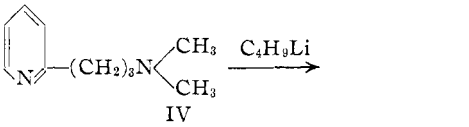
(5) J. Mills, U. S. Patent 2,655,509 (1953), reported that the dehydration of 1-*p*-chlorophenyl-2-phenyl-4-(N-pyrrolidino)-2-butanol yielded Δ_1- or Δ_2-butenes; however, the location of the double bond was not established.

(6) H. M. Lee, R. C. Anderson and P. N. Harris, *Proc. Soc. Exp. Biol. Med.*, **80**, 458 (1952).

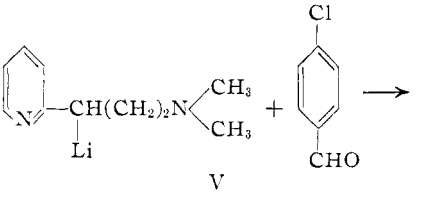
(7) M. H. Mothersill, J. Mills, H. M. Lee, R. C. Anderson and P. N. Harris, *Ann. Allergy*, **11**, 754 (1953).

Attempts to prepare II from I, *via* the introduction of a bromine atom on the carbon atom alpha to the pyridine ring, followed by dehydrohalogenation were unsuccessful. In another approach to II, IV was treated with *p*-chlorobenzaldehyde and acetic anhydride, employing the usual procedure for the preparation of α-stilbazoles.[8] However none of the desired product was obtained.

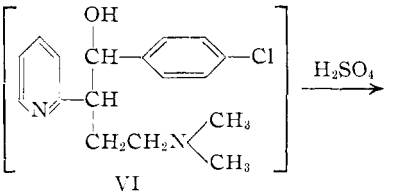
The synthesis of II was achieved by the reaction of 3-(2′-pyridyl)-N,N-dimethylpropylamine (IV) with butyllithium to obtain the corresponding lithio salt, V. The latter was treated with *p*-chlorobenzaldehyde and yielded a viscous carbinol



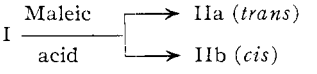
IV



V



VI



VI which could not be obtained crystalline and decomposed upon distillation. The dehydration of crude VI was achieved after several different methods were studied. When VI was heated with thionyl chloride in benzene a tar separated. The carbinol resisted dehydration both with iodine in refluxing xylene and with 40 or 85% sulfuric acid solutions at 100°. However, when a solution of IV in 85% sulfuric acid was heated at 170–185° for 20–30 minutes, a 58% yield of a yellow oil was obtained which analyzed for the dehydrated product II. An ultraviolet absorption spectrum of the oil in ethanol gave a maximum at 258 mμ and a shoulder at 280–290 mμ. Extensive fractionation of the oil yielded cuts with sharper ultraviolet absorption spectra; however, complete separation of

(8) M. Chiang and H. Hartung, *J. Org. Chem.*, **10**, 21 (1945).

the components could not be effected by distillation.

Although it was assumed that dehydration of VI would result in the formation of the Δ_1-butene, the possibility existed of a shift of the double bond to the Δ_2-position. When a sample of II was ozonized, there was obtained a small quantity of *p*-chlorobenzaldehyde (as the semicarbazone) and a 50% yield of *p*-chlorobenzoic acid. When a solution of II in hot isopropyl acetate reacted with an equivalent amount of maleic acid, a salt, IIa, separated which melted at 133–134° after a recrystallization from ethyl acetate. Upon concentration of the mother liquor a small quantity of solid IIb was obtained which melted at 123–124° after several recrystallizations from ethyl acetate. However, when II was treated with oxalic acid in alcohol only one oxalate, melting at 159–160°, was obtained. Ozonolysis of the maleate IIb and the free base liberated from IIa yielded *p*-chlorobenzoic acid, thus establishing that both isomers possessed a double bond in the 1,2-position.

The purity of IIa and IIb was determined by a solubility analysis study[9] and a comparison of the ultraviolet absorption spectra. It was established that IIa possessed a purity of 96% and exhibited a maximum at 290 mμ while IIb was 90% pure and showed a maximum at 258 mμ.

The assignment of the configuration of the isomers was based on a comparison of IIa and IIb with *cis*- and *trans*-stilbene and *trans*-α-methylstilbene (Table I). *trans*-Stilbene exhibited a maximum at 295 mμ (ε 27,000) while *cis*-stilbene had a maximum at 280 mμ (ε 13,500). The replacement of one of the alpha hydrogens of *trans*-stilbene with a methyl group resulted in a hypsochromic shift of 25 mμ (λ_{max} 270 mμ, ε 18,000).[10] For comparison purposes 4′-chloro-α-stilbazole was prepared[11] and found to have a maximum at 315 mμ (ε 31,000), which appeared to be the *trans* form. The replacement of the alpha hydrogen of 4′-*p*-chloro-α-stilbazole with a β-dimethylaminoethyl group IIa resulted in a hypsochromic shift of 25 mμ. The position of maximum absorption of the *trans* and *cis* forms of stilbene differed by 15 mμ, while the *trans* and *cis* forms of II differed by 32 mμ. The magnitudes of the hypsochromic shifts in the case of *trans*- and *cis*-stilbene and of IIa and IIb were empirically of the same order. From these data it would appear that IIa was the *trans* form and IIb the *cis* form.[12]

A preliminary pharmacological evaluation of the antihistaminic potency of I, II, IIa and IIb showed a low order of activity.[2b] No activity was observed *in vivo* at 24 mg./kg. for any of these compounds. The *in vitro* activity of I was one third and the remaining substances less than one tenth of 3-phenyl-3-(2′-pyridyl)-N,N-dimethylpropylamine.

(9) W. Tarpley and M. Yudis, *Anal. Chem.*, **25**, 121 (1953).

(10) E. A. Braude, *J. Chem. Soc.*, 1902 (1949).

(11) J. M. Smith, Jr., H. W. Stewart, B. Roth and E. H. Northey, THIS JOURNAL, **70**, 3997 (1948).

(12) D. W. Adamson, P. A. Barrett, J. W. Billinghurst, A. F. Green and T. S. G. Jones, *Nature*, **168**, 204 (1951), have described an analogous example of *cis–trans* isomerism resulting from the dehydration of 1-*p*-chlorophenyl-1-(2′-pyridyl)-3-(N-pyrrolidino)-1-propanol to 1-*p*-chlorophenyl-1-(2′-pyridyl)-3-(N-pyrrolidino)-1-propene. However, no assignment of *cis–trans* configuration could be made.

TABLE I

COMPARISON OF SPECTRA OF STILBENES AND STILBAZOLES

Compound	λ_{max}, mμ	ϵ_{max}
cis-Stilbene[10]	280	13,500
trans-Stilbene[10]	295	27,000
trans-α-Methylstilbene[10]	270	18,000
IIb	258	13,800
IIa	290	18,200
4′-Chloro-α-stilbazole	315	31,000

Experimental

4-*p*-Chlorophenyl-3-(2′-pyridyl)-N,N-dimethylbutylamine (I).—To a solution of potassium amide (from 8 g. of potassium) in 500 ml. of liquid ammonia, there was added 33 g. (0.2 mole) of 3-(2′-pyridyl)-N,N-dimethylpropylamine.[2b] After 10 minutes, 32.2 g. (0.2 mole) of *p*-chlorobenzyl chloride was added followed by the addition of 300 ml. of anhydrous ether. The reaction mixture was stirred for seven hours at room temperature, decomposed with water, the ether layer separated and extracted with dilute hydrochloric acid. The acid extracts were made basic with dilute sodium hydroxide solution, the resulting oil extracted with ether, the ether extracts dried, concentrated and the residual oil fractionated; yield 22 g. (38%), b.p. 161–168° (2 mm.), $n^{28}D$ 1.5461.

Anal. Calcd. for $C_{17}H_{21}N_2Cl$: N, 9.70. Found: N, 9.48.

1-*p*-Chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butene (II).—To a cold (0°) solution of phenyllithium (from 3.5 g. of lithium shot and 40 g. (0.25 mole) of bromobenzene in 500 ml. of ether), there was added 31 g. (0.19 mole) of 3-(2′-pyridyl)-N,N-dimethylpropylamine. After stirring for 20 minutes at 0°, a solution of 28 g. (0.2 mole) of *p*-chlorobenzaldehyde in 100 ml. of ether was added dropwise and the mixture was stirred for eight hours at room temperature. The reaction mixture was decomposed with cold, dilute ammonium chloride solution, the ether layer separated, extracted with cold, dilute hydrochloric acid and the acid extracts made basic with dilute sodium hydroxide solution. The oily layer was extracted with ether and the ether extracts dried and concentrated to a residue. Attempted high vacuum distillation of the red viscous oil resulted in decomposition. *The crude 1-p-chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butanol* was dehydrated directly in the following manner. A solution of 11 g. of the crude carbinol in 65 ml. of 85% sulfuric acid was heated at 170–180° for 20 minutes.[2b] The dark reaction mixture was poured on ice, made basic with 50% sodium hydroxide solution and extracted with ether. The ether extracts were dried, concentrated and the residual oil distilled; yield 6 g. (58%), b.p. 161–165° (1 mm.), $n^{28}D$ 1.5890.

Anal. Calcd. for $C_{17}H_{19}N_2Cl$: C, 71.16; H, 6.67. Found: C, 70.85; H, 6.41.

Ozonolysis of II.—A solution of 2 g. of the free base in 70 ml. of carbon tetrachloride was ozonized for two hours at −40°. The stirred mixture was cooled, treated with 30% acetic acid followed by 5 g. of zinc dust, and heated on a steam-bath until all of the carbon tetrachloride had distilled. The residue was acidified with concentrated hydrochloric acid, extracted with ether and the ethereal layer extracted with dilute sodium carbonate solution. The organic layer was concentrated, the residual oil was dissolved in ethanol, treated with 1 g. of semicarbazide hydrochloride, 1 g. of sodium acetate and heated on the steam-bath for 10 minutes. Upon cooling a small amount of solid separated which melted at 238–239° after two recrystallizations from methanol. The latter did not depress the melting point of an authentic sample of *p*-chlorobenzaldehyde semicarbazone (m.p. 240–241°).

Acidification of the basic aqueous phase with concentrated hydrochloric acid gave 0.55 g. (50%) of a white solid, m.p. 238–244°. After one recrystallization from ethanol the solid melted at 240–241° and did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid (m.p. 241–242°).

1-*p*-Chlorophenyl-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butene Maleates (IIa and IIb).—To a solution of 20 g. of II in 150 ml. of isopropyl acetate there was added a solution of 9.5 g. of maleic acid in 100 ml. of isopropyl acetate. Upon cooling 15.3 g. of a pale green solid separated which melted at 116–121°. From the filtrates there was obtained an

additional 6.0 g. of green solid melting at 107–110°. The combined solids were recrystallized from ethyl acetate and 10 g. of a white solid which melted at 127–129° was obtained. After several recrystallizations from ethyl acetate the maleate (IIa) melted at 133–134° and exhibited a maximum at 290 mμ.

Anal. Calcd. for $C_{21}H_{23}O_4N_2Cl$: N, 6.95. Found: N, 6.65.

From the ethyl acetate filtrate there was obtained a second crop of 6.0 g. of a white solid which melted at 110–114°. After several recrystallizations from ethyl acetate, the maleate IIb melted at 123–124° and exhibited a maximum at 258 mμ. The melting point of a mixture of IIa and IIb was depressed (m.p. 111–113°).

Anal. Calcd. for $C_{21}H_{23}O_4N_2Cl$: N, 6.95. Found: N, 6.62.

The residual ethyl acetate filtrates were concentrated and the free base liberated from the oily maleate salt with a dilute sodium hydroxide solution. Upon fractional distillation there was obtained 4.5 g. of a yellow oil, b.p. 163–167° (1 mm.), $n^{26}D$ 1.5838, maximum at 256 mμ in ethanol.

1-(*p*-Chlorophenyl)-2-(2′-pyridyl)-4-N,N-dimethylamino-1-butene Oxalate.—A solution of 1.45 g. of II dissolved in a minimum of absolute ethanol was treated with an alcoholic solution of 0.45 g. of oxalic acid. Upon cooling 0.7 g. of a yellow solid separated which melted at 143–146°. After two recrystallizations from ethanol, the colorless solid melted at 159–160° and exhibited a maximum at 290 mμ in ethanol.

Anal. Calcd. for $C_{19}H_{21}O_4N_2Cl$: N, 7.43. Found: N, 7.49.

Ozonolysis of IIa.—A solution of 0.95 g. of the maleate IIa in 50 ml. of ethyl acetate was ozonized at −40° for three hours. The mixture was decomposed with dilute acetic acid and concentrated *in vacuo*. The brown residue was made basic with sodium carbonate solution, extracted with ether, the aqueous portion acidified with dilute hydrochloric acid and filtered. The crude solid when recrystallized from ethanol–water melted at 242–243° and did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid (m.p. 241–242°).

Ozonolysis of IIb.—A solution of 4.0 g. of the free base (liberated from the maleate IIb, m.p. 120–123°), in 100 ml. of chloroform was ozonized at −40° for three hours. The mixture was decomposed with dilute acetic acid, the aqueous acidic layer separated and discarded. The chloroform layer was extracted with dilute sodium hydroxide solution, the basic layer separated, acidified with dilute hydrochloric acid and filtered. The crude solid, 0.72 g., after recrystallization from ethanol–water, melted at 239–240°, and did not depress the melting point of an authentic sample of *p*-chlorobenzoic acid.

Acknowledgment.—The authors wish to express their appreciation to Mr. Edwin Connor and his staff for the microanalyses and ultraviolet absorption spectra reported in this paper. We are grateful to Dr. William Tarpley[13] and Mr. Edward Townley for the solubility analysis studies.

(13) Aeroprojects, Inc., West Chester, Pennsylvania.

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, CO., INC., RAHWAY, NEW JERSEY]

Studies on Carcinolytic Compounds. VI. Substituted 2-(*Aldo*-Polyhydroxyalkyl)-benzimidazoles

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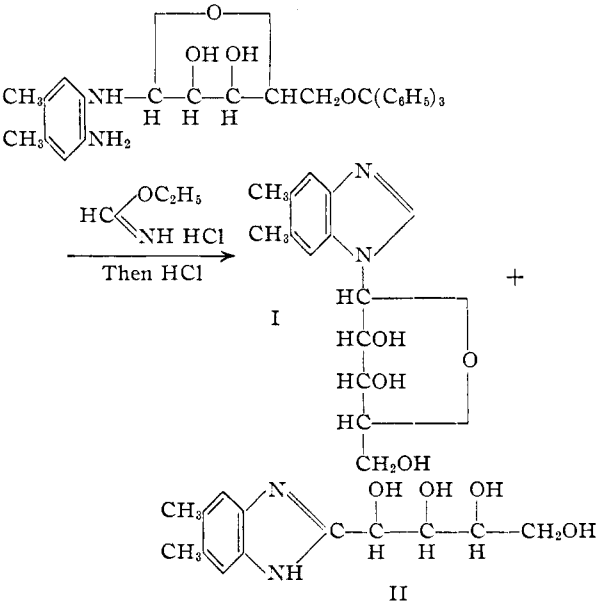
A series of 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles with chlorine or methyl substituents in the benzene ring has been prepared. Several of these compounds have been tested for activity against a lymphosarcoma in mice. The activity which was observed could be considered only a weak effect.

Several 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles have been isolated as a result of side reactions in the use of imino ether hydrochlorides as ring closing agents in the formation of 1-glycosides of benzimidazoles from N-glycosides of 2-aminoanilines. Such a side reaction occurs under certain conditions during the synthesis of 1-α-D-ribofuranosyl-5,6-dimethylbenzimidazole (I), and 5,6-dimethyl-2-D-ribobenzimidazole (II) is also formed.[1] One of the 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles was found to enhance the regression of a lymphosarcoma in mice. Consequently, a series of these compounds was synthesized and tested for carcinolytic activity.

Descriptions of compounds of this type have appeared in the literature in a number of publications including a review article.[2] Almost all of the benzimidazoles described in this paper have substituents in the benzene ring from among the following groups: 5-methyl, 5,6-dimethyl, 5-chloro and 5,6-dichloro. These 2-(*aldo*-polyhydroxyalkyl)-benzimidazoles are best prepared by the method of Moore and Link[3] and Dimler and Link[4] in which



(1) F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, J. B. Lavigne and K. Folkers, THIS JOURNAL, **74**, 4521 (1952).

(2) N. K. Richtmyer, *Advances in Carbohydrate Chem.*, **6**, 175 (1951).

(3) S. Moore and K. P. Link, *J. Biol. Chem.*, **133**, 293 (1940).

(4) R. J. Dimler and K. P. Link, *ibid.*, **150**, 345 (1943).