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Histamine Antagonists. I. Alkamine Ethers

BY JOHN B. WRIGHT, H. G. KOLLOFF AND JAMES H. HUNTER

Recent reports[1-8] indicate that certain alkamine ethers, particularly β-dimethylaminoethyl benzhydryl ether hydrochloride, possess a high order of antihistaminic activity. Antispasmodic properties have also been claimed for compounds of this general structure.[9] In view of the diversified activities of these alkamine ethers, an investigation of related ethers of this type was undertaken.

The compounds listed in Table I were prepared either by reaction of the disubstituted methyl bromides (I) with the requisite amino alcohols (II) in the presence of anhydrous potassium carbonate (Procedure A), or by treatment of the sodium (lithium) salt of the disubstituted carbinol (III) with the appropriate aminoalkyl chloride (IV) (Procedure B).

$$\underset{\text{I}}{R^1R^2CHBr} + \underset{\text{II}}{HOCH_2CH_2N(R^3)_2} \longrightarrow R^1R^2CHOCH_2CH_2N(R^3)_2 \longleftarrow \underset{\text{IV}}{(R^3)_2NCH_2CH_2Cl} + \underset{\text{III}}{Na(Li)OCHR^1R^2}$$

Procedure A was used in the case in which R^1 and R^2 were phenyl; in all other instances, recourse was had to the indicated procedure B or variations thereof.

In the preparation of these ethers according to Procedure B, the use of one equivalent of β-dimethylaminoethyl chloride resulted in low yields. This may be attributed to the ease with which β-dimethylaminoethyl chloride forms a cyclic piperazinium salt.[10] The use of a large excess (Procedure C) of β-dimethylaminoethyl chloride did not improve the yield materially; however, satisfactory results were obtained by treatment of III with one equivalent of β-dimethylaminoethyl chloride hydrochloride in the presence of an additional equivalent of sodium or lithium amide to liberate the dimethylaminoethyl chloride from its salt (Procedure D).

TABLE I

ALKAMINE ETHERS, $RR'CHOCH_2CH_2X$

R	R'	X	Procedure	B. p. °C.	Mm.	Yield, %
Phenyl	Phenyl	1-Pyrrolidyl	A	161–165	0.7	57
Phenyl	Phenyl	1-Pyrrolidyl	..	.....		..
Phenyl	Phenyl	1-(4-Methylpiperazyl)	A	[a]		67
Phenyl	α-Thienyl	Dimethylamino	B(C)(D)	132–134	0.25	0(18)(67)
Phenyl	α-Thienyl	Dimethylamino	..	.....		..
Phenyl	α-Thienyl	1-Pyrrolidyl	B	180–182	0.5	63
Phenyl	Cyclohexyl	Dimethylamino	D[b]	120–125	0.25	15[b]
Phenyl	Cyclohexyl	1-Pyrrolidyl	B	[c]		60
Phenyl	Benzyl	Dimethylamino	D	130–132	0.35	69
Phenyl	Benzyl	1-Pyrrolidyl	B	196–197	0.7	73
n-Butyl	*n*-Butyl	1-Pyrrolidyl	B	124–127	2.3	42
p-MeO-phenyl	*p*-MeO-benzyl	1-Pyrrolidyl	B	218–220	0.35	51

Results of preliminary tests[11] of antihistaminic potency of salts of these alkamine ethers are summarized in Table I. Since it has been reported recently by Winder, *et al.*,[12] that quaternary derivatives of β-dimethylaminoethyl benzhydryl ether are effective antihistaminic and antispasmodic agents, the methiodide salts of several of the alkamine ethers were examined pharmacologically. The hydrochloride and methiodide of β-pyrrolidylethyl benzhydryl ether exhibited an antihistaminic activity greater than that of β-dimethylaminoethyl benzhydryl ether hydrochloride; in all other instances, the activity was considerably weaker.

Experimental[13,14]

β-(1-Pyrrolidyl)-ethyl Chloride Hydrochloride.—The procedure described is a modification of the method of Smith.[15] A mechanically stirred solution of 119.3 g. (1.038 moles) of β-(1-pyrrolidyl)-ethanol[16] in 400 cc. of dry chloroform was chilled in an ice-salt-bath and 136 g. (1.142 moles) of thionyl chloride added dropwise. After standing overnight at room temperature excess thionyl

(1) *Proc. Staff Meetings Mayo Clinic*, **20**, 417 (1945).
(2) Loew, Kaiser and Moore, *J. Pharmacol. Exptl. Therap.*, **83**, 120 (1945).
(3) Friedlander and Feinberg, *J. Allergy*, **17**, 129 (1946).
(4) Levin, *ibid.*, **17**, 145 (1946).
(5) Rieveschl, U. S. Patent 2,421,714.
(6) McGavack, Elias and Boyd, *Am. J. Med. Sci.*, **213**, 418 (1947).
(7) Rieveschl, U. S. Patent 2,427,878.
(8) Loew, *Physiol. Rev.*, **27**, 542 (1947).
(9) Martin, Häfliger, Gätzi and Grob, U. S. Patent 2,397,799.
(10) *Cf.* Knorr, *Ber.*, **37**, 3507 (1904).
(11) For conducting these tests, grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Department of Pharmacology and Endocrinology. Details of these tests will be reported elsewhere by Dr. Vander Brook.
(12) Winder, *et al.*, *J. Pharmacol. Exptl. Therap.*, **87**, 121 (1946).
(13) Appreciation is expressed to Mr. Harold Emerson and his staff for analyses reported.
(14) All melting points are corrected.
(15) W. T. Smith, Jr., private communication.
(16) v. Braun, Braunsdorf and Räth, *Ber.*, **55**, 1673 (1922).

chloride was decomposed by addition of 25.0 g. of absolute methanol and the solvent distilled, the last traces of solvent being removed *in vacuo*. The residue was triturated with a mixture of ether and ethyl acetate (1:1), the insoluble portion collected and washed repeatedly with the same solvent mixture; yield of crude product, 165.8 g. (94%). One crystallization from isopropanol–isopropyl ether using decolorizing charcoal, followed by two recrystallizations from this mixed solvent, gave large glistening plates melting at 173.5–174°.

Anal. Calcd. for $C_6H_{12}NCl\cdot HCl$: C, 42.37; H, 7.70; N, 8.24. Found: C, 42.60; H, 7.72; N, 8.30.

β-(1-Pyrrolidyl)-ethyl Chloride.—β-(1-Pyrrolidyl)-ethyl chloride hydrochloride was dissolved in a minimum volume of water and the solution basified with solid potassium carbonate. β-(1-Pyrrolidyl)-ethyl chloride was isolated as a colorless liquid boiling at 90° at 56 mm.; yield, 88%. The product gradually became yellow on standing and precipitated a solid considered to be the cyclic dimer.

a nine-inch modified Widmer column; yield, 50.3 g. (87.5%) of a colorless liquid which slowly became yellow on standing; b. p. 73–75° at 3.0 mm.

The **dihydrochloride** crystallized from ethanol as prisms; m. p. 208.5–209.5°.

Anal. Calcd. for $C_7H_{16}N_2O\cdot 2HCl$: C, 38.72; H, 8.35; N, 12.90. Found: C, 38.62; H, 8.34; N, 13.29.

Procedure A. β-(1-Pyrrolidyl)-ethyl Benzhydryl Ether Hydrochloride.—The procedure used was essentially that of Rieveschl,[5] for the preparation of benzhydryl alkamine ethers. With mechanical stirring, a mixture of 494 g. (2.0 moles) of benzhydryl bromide,[20] 345 g. (3.0 moles) of β-(1-pyrrolidyl)-ethanol and 250 g. of finely ground anhydrous potassium carbonate was heated under an atmosphere of nitrogen for four hours in an oil-bath at 150–170°. The mixture was allowed to cool to room temperature, poured into 4 liters of water, and extracted with ether.[21] The ether extracts were combined and extracted twice with 5% hydrochloric acid and once with

TABLE I (*Continued*)

Molecular formula	M. p., °C.[14]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Activity[k]
$C_{19}H_{23}NO\cdot HCl$[d]	132–132.5	71.80	71.81	7.61	7.89	4.41	4.43	1.5–2
$C_{19}H_{23}NO\cdot CH_3I$[e]	164.5	56.74	56.88	6.19	6.37	3.31	3.57	1–1.3
$C_{26}H_{28}N_2O\cdot 2HCl$[f]	190–190.5	62.66	62.63	7.36	7.41	7.31	7.33	0.1
$C_{15}H_{19}NOS\cdot HCl$[g]	119–121	60.49	60.40	6.77	6.59	4.70	4.87	0.4
$C_{15}H_{19}NOS\cdot CH_3I$[g]	176.5–177	47.64	47.90	5.50	5.32	3.47	3.42	0.3
$C_{17}H_{21}NOS\cdot CH_3I$[g]	133–134	50.53	50.65	5.63	5.48	3.26	3.83[l]	0.14–0.25
$C_{17}H_{27}NO\cdot HCl$[h]	137–139	68.55	68.55	9.47	9.21	4.70	4.78	0.06
$C_{19}H_{29}NO\cdot HCl$[d]	152.5–153.5	70.45	70.44	9.34	9.38	4.33	5.01	0.07–0.14
$C_{18}H_{23}NO\cdot HCl$[i]	132–133	70.68	70.85	7.91	7.79	4.58	4.88	0.04
$C_{26}H_{25}NO\cdot HCl$[j]	113.5–114.5	72.38	72.43	7.90	7.44[m]	4.22	4.12	0.03
$C_{15}H_{31}NO$	.....	74.62	74.77	12.94	12.70	5.80	5.68	0.3[n]
$C_{22}H_{29}NO_3\cdot CH_3I$[g]	143–145	55.53	55.30	6.49	6.40	2.82	2.84	0.07

[a] The crude free base was a solid (m. p. 50–53°) and was converted directly to the dihydrochloride without distillation. [b] Lithium amide was substituted for sodamide. [c] When the reaction was worked up the product dissolved in the benzene layer rather than in the acidic aqueous layer. The hydrochloride was obtained by adding ether to the benzene solution. [d] Recrystallized from isopropanol–ethyl acetate (1:20). [e] Recrystallized from absolute ethanol–isopropyl ether. [f] Recrystallized from acetone–isopropanol. [g] Recrystallized from absolute ethanol. [h] Recrystallized from ethyl acetate–isopropyl ether (2:1). [i] Recrystallized from acetone. [j] Recrystallized from ethyl acetate. [k] Activity is expressed in terms of β-dimethylaminoethyl benzhydryl ether hydrochloride as the unit of activity. These experiments were carried out on isolated guinea pig small intestine. [l] Calcd. for S, 7.47; found, 7.57. Calcd. for I, 29.56; found, 29.70. [m] Calcd. for Cl, 10.68; found, 10.60. [n] This compound was tested as the hydrochloride, which was prepared by adding the theoretical amount of an aqueous hydrochloric acid solution.

β-(4-Methyl-1-piperazine)-ethanol.[17]—A solution of 13 g. (0.1 mole) of 1-piperazineethanol[18] and 24 cc. (approx. 0.3 mole) of 40% aqueous formaldehyde in 100 cc. of ethanol was reduced with Raney nickel at an initial pressure of fifty pounds. The reaction products from four such runs were combined, the catalyst removed by filtration and the green filtrate concentrated, first at atmospheric pressure and finally *in vacuo*. The residue was dissolved in 200 cc. of ether and the ethereal solution extracted with 300 cc. of a very dilute solution of potassium carbonate. Concentration of the ethereal extract gave no residue. The green-colored potassium carbonate was extracted again with 200 cc. of ether and the ethereal extract discarded. The potassium carbonate extract was then concentrated to dryness *in vacuo*. The residue was treated with 200 cc. of ether and the insoluble material separated by filtration. The insoluble material was washed with ether and the washings added to the ethereal filtrate. The green ethereal solution was dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo* under nitrogen[19] through

(17) An alternate method of synthesis for this compound is described by Northey and Hultquist in U. S. Patent 2,419,366. These authors, however, give no physical constants.

(18) Kitchen and Pollard, *J. Org. Chem.*, **8**, 338 (1943).

(19) Smith and Adkins, THIS JOURNAL, **60**, 657 (1938).

water. The aqueous extracts were basified by the addition of solid potassium carbonate and the resulting mixture extracted with ether. The combined ethereal extract was dried and the solvent removed. The residue was distilled under reduced pressure through a short Vigreux column. The free base slowly turned yellow on standing.

The hydrochloride salt was prepared by bubbling dry hydrogen chloride into an ethereal solution of the free base.

Procedure B.[22] **β-(1-Pyrrolidyl)-ethyl 1,2-Diphenylethyl Ether Hydrochloride.**—Sodamide was prepared from 1.44 g. (0.0625 gram atom) of sodium according to the method of Vaughn, Vogt and Nieuwland.[23] To a stirred suspension of the sodamide in 62 cc. of dry benzene was added, dropwise, a solution of 12.9 g. (0.065 mole) of benzylphenylcarbinol[24] in 62 cc. of dry benzene. The

(20) Courtot, *Ann. chim.*, [9] **5**, 80 (1916).

(21) A small amount of a dark tarry material was present which would dissolve in neither the aqueous nor the ether layer.

(22) This procedure is a modification of that described in U. S. Patent 2,397,799.

(23) Vaughn, Vogt and Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(24) We are indebted to Mr. E. H. Lincoln of this Laboratory for the preparation of this carbinol and certain other intermediates used in this study.

mixture was heated, with stirring, in an oil-bath at 60–70° for two hours; when cool, 9.0 g. (0.0675 mole) of β-(1-pyrrolidyl)-ethyl chloride was added and the mixture stirred and heated in an oil-bath at 90–95° for eighteen hours. The cooled reaction mixture was poured into water and acidified with hydrochloric acid. The benzene layer was separated, washed once with water and the aqueous extract combined with the dilute acid extract. The resulting aqueous solution was extracted once with ether and the ethereal extract discarded. The aqueous solution was basified by the addition of solid potassium carbonate and extracted with ether. The combined ethereal extract was dried, the solvent removed and the residue distilled under reduced pressure. The hydrochloride salt was prepared as described in Procedure A.

Procedure C. 2-Dimethylaminoethyl α-Thienylphenylmethyl Ether Hydrochloride.—Procedure B was followed except that the amount of β-dimethylaminoethyl chloride used in the reaction was increased ten-fold. The hydrochloride salt was prepared by adding the theoretical amount of a 1.93 *N* methanolic hydrochloric acid solution to the free base and removing the methanol in a current of dry air. Ether was added to the residue and crystallization induced by scratching.

Procedure D. β-Dimethylaminoethyl 1,2-Diphenylethyl Ether Hydrochloride.—Procedure B was modified in that one equivalent of β-dimethylaminoethyl chloride *hydrochloride* was used instead of β-dimethylaminoethyl chloride and the amount of sodamide used was doubled.

Summary

1. The hydrochloride and methiodide salts of ten disubstituted methyl alkamine ethers have been prepared and tested for antihistaminic activity. Preliminary tests indicate the hydrochloride of β-(1-pyrrolidyl)-ethyl benzhydryl ether, as well as the corresponding methiodide, to be more effective than β-dimethylaminoethyl benzhydryl ether hydrochloride.

2. The preparation of β-(1-pyrrolidyl)-ethyl chloride hydrochloride and β-(4-methyl-1-piperazine)-ethanol dihydrochloride has been described.

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Histamine Antagonists. II. N-(Pyrrolidylalkyl)-phenothiazines

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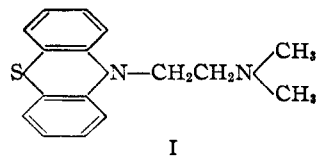
In 1946 Halpern and Ducrot[1] reported on the antihistaminic activity of N-(2-dimethylaminoethyl)- (I) and N-(2-dimethylaminopropyl)-thiodiphenylamine (II).



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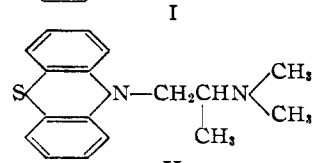

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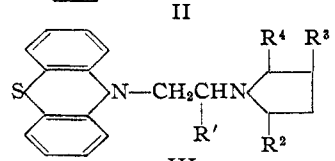

III

In conjunction with other phases of a broad study of histamine antagonists in progress in this Laboratory,[2] several N-pyrrolidylalkylphenothiazines of type III (R^{1-4} = H, CH_3) have been synthesized.

On the basis of preliminary assays,[3] using 2-dimethylaminoethyl benzhydryl ether hydrochloride as a standard, N-pyrrolidylethylphenothiazine (III, R^{1-4} = H) was shown to possess a higher level of antihistaminic activity than the other members of this series. The pharmacologic properties of these phenothiazine derivatives is the subject of another report from this Laboratory.

Pyrrole and its dimethyl homologs were hydrogenated over Raney nickel, the resulting pyrrolidines treated with the appropriate alkylene chlorohydrin and the N-pyrrolidylalkanols thus formed converted into the corresponding N-pyrrolidylalkyl chlorides hydrochloride by means of thionyl chloride.

N-Alkylation of phenothiazine with the N-pyrrolidylethyl chlorides in the presence of sodium amide proceeded smoothly. Alkylation with the homologous propyl chlorides in certain instances occasioned some difficulties in the isolation of the product. These difficulties were not unexpected in view of several recorded instances[4] in which isomers have been isolated from alkylations with dimethylaminopropyl chlorides; however, in the present work only one product was isolated in each case. Recently Charpentier[5] has shown that the product obtained when phenothiazine is alkylated with 1-dimethylamino-2-chloropropane in the presence of sodium amide has the structure represented by II above. This suggests that the N-(pyrrolidylpropyl)-phenothiazine (III, R^1 = CH_3; R^{2-4} = H) and its homologs (Table II) have a similar structure, *i.e.*, it seems reasonable to assume that they are the 2-pyrrolidyl-1-propyl rather than the 1-pyrrolidyl-2-propyl phenothiazines.

(1) Halpern and Ducrot, *Compt. rend. soc. biol.*, **140**, 361 (1946).

(2) Wright, Kolloff and Hunter, THIS JOURNAL, **70**, 3098 (1948).

(3) Grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Pharmacology Department for conducting these assays.

(4) (a) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188 (1947). (b) Brode and Hill, *ibid.*, **69**, 724 (1947).

(5) Charpentier, *Compt. rend.*, **225**, 306 (1947).