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.

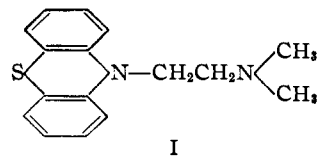
KALAMAZOO 99, MICHIGAN RECEIVED MAY 6, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

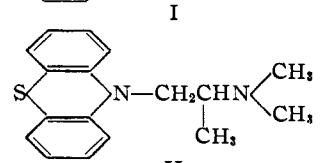
Histamine Antagonists. II. N-(Pyrrolidylalkyl)-phenothiazines

BY WM. BRADLEY REID, JR., JOHN B. WRIGHT, H. G. KOLLOFF AND JAMES H. HUNTER

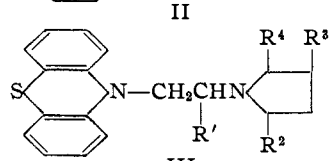
In 1946 Halpern and Ducrot[1] reported on the antihistaminic activity of N-(2-dimethylaminoethyl)- (I) and N-(2-dimethylaminopropyl)-thiodiphenylamine (II).



I



II



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).

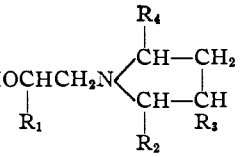
(3) Grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Pharmacology Department for conducting these assays.

(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).

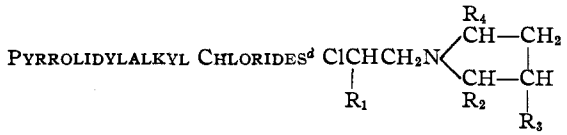
TABLE I

PYRROLIDYLALKANOLS



R_1	R_2	R_3	R_4	B. p.[a] °C.	Mm.	Yield, %	Formula	Nitrogen analyses, % Calcd.	Found
CH_3	H	H	H	116–117	110	77	$C_7H_{15}NO$	10.84	10.84
CH_3	H	CH_3	CH_3	118–119	83	76.5	$C_9H_{19}NO$	8.92	8.76
CH_3	CH_3	H	CH_3	107–108	50	81	$C_9H_{19}NO$	8.92	8.74
H	H	CH_3	CH_3	117	73	78	$C_8H_{17}NO$	15.05[b]	15.04[b]
H	CH_3	H	CH_3	113–116	62	74.5	$C_8H_{17}NO$	15.05[c]	15.03[c]

PYRROLIDYLALKYL CHLORIDES[d]

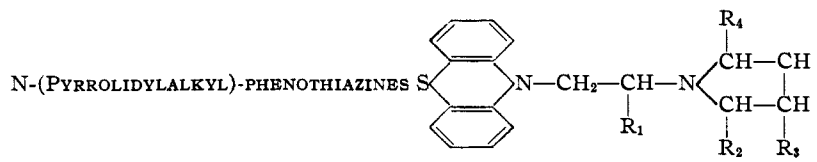


R_1	R_2	R_3	R_4	B. p.[a] °C.	Mm.	Yield, %	Salt	M. p. °C.	Formula	Nitrogen analyses, % Calcd.	Found
CH_3	H	H	H	90–91	107	54	HCl	189.5–190.5	$C_7H_{14}NCl\cdot HCl$	7:61	8.19[e]
CH_3	H	CH_3	CH_3	117–119	98	71.2	Picrate	115–117	$C_9H_{18}NCl\cdot C_6H_3N_3O_7$	13.85	13.72
CH_3	CH_3	H	CH_3	107–108	51	88	CH_3I	188.5 (dec.)	$C_9H_{18}NCl\cdot CH_3I$	4.41	4.40
H	H	CH_3	CH_3	116	98	73.4	HCl	201.5–202.5	$C_8H_{16}NCl\cdot HCl$	7.07	6.55[f]
H	CH_3	H	CH_3	96–97	40	67	HCl	141–2	$C_8H_{16}NCl\cdot HCl$	7.07	7.33

[a] Observed. [b] As picrate; m. p. 90–91.5°. [c] As picrate; m. p. 104–105°. [d] 2-(1-Pyrrolidyl)-ethyl chloride and its hydrochloride salt have been reported previously.[2] [e] Calcd. for Cl, 38.52; found, 38.89. Calcd. for C, 45.66; found, 45.90. Calcd. for H, 8.21; found, 8.17. [f] Hygroscopic, cannot be dried due to instability; picrate is an oil.

TABLE II

N-(PYRROLIDYLALKYL)-PHENOTHIAZINES



R_1	R_2	R_3	R_4	M. p., °C. hydrochloride	Yield, %	Formula	Calcd. % C	H	N	Found, % C	H	N
H	H	H	H	196–197	51	$C_{18}H_{20}N_2S\cdot HCl$	64.94	6.36	8.42	65.10	6.18	8.57
H	H	CH_3	CH_3	160–162	61	$C_{20}H_{24}N_2S\cdot HCl$	66.55	6.98	7.76	67.00[b]	6.91	7.78
H	CH_3	H	CH_3	194–6	36	$C_{20}H_{24}N_2S\cdot HCl$	66.55	6.98	7.76	66.59	6.95	8.00
CH_3	H	H	H	192.5–194.0	45	$C_{19}H_{22}N_2S\cdot HCl$	65.78	6.68	8.08	65.56	6.41	8.39
CH_3	H	CH_3	CH_3	249–250	28.5	$C_{21}H_{26}N_2S\cdot HCl$	67.26	7.25	7.47	67.17	7.24	7.33
CH_3	CH_3	H	CH_3	[a]	87.5	$C_{21}H_{26}N_2S$	74.51	7.74	8.28	74.66	7.53	8.36

[a] The free base melts at 102.5–103.5°. [b] Calcd. for S, 8.88; Cl, 9.82. Found: S, 9.15; Cl, 9.82.

Experimental[6,7]

2,4-Dimethylpyrrolidine and 2,5-Dimethylpyrrolidine.—Two hundred twenty-five grams (2.36 moles) of freshly distilled 2,4-dimethylpyrrole[8] was hydrogenated at an initial pressure of 3500 p. s. i. at 150° using 15 g. of Raney nickel catalyst. During the course of three hours only 58–60% of the hydrogen required was absorbed,[9] at which time the bomb was cooled and the product filtered, carefully washed with pentane[10] and distilled through a 20-cm. Widmer column. The fraction boiling at 110–111° at atmospheric pressure represented 110.7 g. (47.3%) of pure 2,4-dimethylpyrrolidine. From the residue a total of 69 g. of 2,4-dimethylpyrrole was obtained. The yield based on recovered pyrrole was 68.2%. By the same procedure 225 g. (2.36 moles) of 2,5-dimethylpyrrole[11] yielded 100 g. (43%) of pure 2,5-dimethylpyrrolidine boiling at 104–105° at atmospheric pressure. There was recovered 81.5 g. of 2,5-dimethylpyrrole. The yield based on recovered pyrrole was 66.8%.

1-(1-Pyrrolidyl)-propanol-2.—Seventy-seven grams (0.82 mole) of propylene chlorohydrin was added dropwise to a mechanically stirred solution of 106.7 g. (1.5 moles) of pyrrolidine in 220 ml. of water containing 35 g. (0.875 mole) of sodium hydroxide. The temperature of the reaction mixture was kept at 40° during the addition of the propylene chlorohydrin. After stirring for an additional two hours, the mixture was allowed to stand for eighteen hours. To the reaction mixture was then added 50 g. of solid sodium hydroxide and solution was effected by stirring. When cool, the upper layer of the crude

(6) All melting points are corrected, unless otherwise stated.

(7) Analyses by Mr. Harold Emerson and Staff of our Microanalytical Laboratory.

(8) "Organic Syntheses," Coll. Vol. II, 1943, p. 217.

(9) Previous experience has shown that further treatment destroys the unreacted pyrroles.

(10) Pentane is better than ether, since a cleaner fractionation is obtained whence a larger amount of unreacted pyrrole is recovered.

(11) "Organic Syntheses," Coll. Vol. II, 1943, p. 219.

amino alcohol was separated and dried over solid sodium hydroxide.[12] Distillation through a Widmer column gave 54 g. of a colorless liquid boiling at 116–117° at 110 mm. By the same general procedure the alkanols reported in Table I were prepared.

1-(1-Pyrrolidyl)-2-chloropropane.—Twenty-five and eight-tenths grams (0.2 mole) of 1-pyrrolidylpropanol-2 was added to 57 ml. of dry benzene containing 30 g. (0.252 mole) of thionyl chloride. A thick black precipitate resulted. The mixture was heated under reflux for two hours and during this time the precipitate dissolved almost completely and then the hydrochloride of the chloro compound precipitated. The mixture was allowed to stand for sixteen hours, after which time the crude pyrrolidylalkyl chloride hydrochloride was filtered, washed with dry benzene, dry acetone and finally dried *in vacuo*. The material was dissolved in a minimal amount of water, filtered from insoluble matter and the residue washed with water. The combined aqueous solutions were basified with 50% sodium hydroxide solution and the resulting free chloro compound extracted with several portions of ether. After drying the combined ether extracts with solid potassium hydroxide, the ether was removed and the residue distilled under reduced pressure. There was obtained 15.9 g. of a colorless oil boiling at 90–91° at 107 mm. (54%). By the same general procedure as given above the chloro compounds reported in Table I were prepared.

N-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine Hydrochloride.—To a mechanically stirred suspension of 4.29 g. (0.11 mole) of sodium amide in 100 ml. of dry toluene was added 19.9 g. (0.1 mole) of purified phenothiazine. After refluxing for two hours the suspension of yellow sodium salt was cooled to room temperature and a solution of 13.36 g. (0.1 mole) of 2-pyrrolidylethyl chloride[2] in 50 ml. of dry toluene was added dropwise. When the mixture had stirred and refluxed for fifteen hours, the toluene layer was extracted several times with dilute hydrochloric acid and the acid layer made alkaline with dilute sodium hydroxide. The resulting brown oil was extracted with ether and the ether layer dried over anhydrous magnesium sulfate. The dry ether solution was treated with anhydrous hydrogen chloride and the resulting semi-solid mass scratched to induce crystallization. The hydrochloride was filtered, washed with ether and twice recrystallized from absolute isopropanol yielding 17 g. (51.2%) of white cubes, m. p. 200–201°.

N-[2-(1-(2,4-Dimethyl)-pyrrolidyl)-ethyl]-phenothiazine Hydrochloride.—In a manner identical with that described for N-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride, 19.9 g. (0.1 mole) of phenothiazine, 4.29 g. (0.11 mole) of sodium amide and 16.15 g. (0.1 mole) of 2-[1-(2,4-dimethyl)-pyrrolidyl]-ethyl chloride were refluxed for a total of eighteen hours. The resulting hydrochloride, after two crystallizations from isopropanol, melted at 160–162°; yield 19.8 g. (61%).

N-[2-(1-(2,4-Dimethyl)-pyrrolidyl)-propyl]-phenothiazine Hydrochloride.—This compound was prepared from 0.2 molar amounts of phenothiazine, sodium amide and 1-(2,4-dimethylpyrrolidyl)-2-chloropropane as described for the preparation of N-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride with the exception of the purification procedure. When the solution was extracted with dilute hydrochloric acid a brown oil separated, which was dissolved in 1.5 l. of water and extracted with ether to remove any ether soluble material. On warming the aqueous phase on a steam cone to remove the dissolved ether a white crystalline material precipitated. After filtering, air drying and recrystallization from isopropanol a total of 10.7 g. of N-[2-(1-(2,4-dimethyl)-pyrrolidyl)-propyl]-phenothiazine hydrochloride was obtained; m.p. 249–250° with sintering at 247° (28.5%).

The remaining aqueous layers were combined, made alkaline, extracted with ether and the ether layers dried. However, all attempts to isolate any remaining isomer by the use of dry hydrogen chloride or oxalic acid failed and in either case the only material obtained was a dark green oil.

N-[2-(1-(2,5-Dimethyl)-pyrrolidyl)-ethyl]-phenothiazine Hydrochloride.—The procedure given for N-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride was followed. After recrystallization from isopropanol–isopropyl ether the product melted at 194–196° (36%).

N-[2-(1-Pyrrolidyl)-propyl]-phenothiazine Hydrochloride and Oxalate.—The procedure given for N-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride was followed except that the crude free base was purified by distillation in a Hickman-type pot still at a pressure of 0.2 mm. The light yellow, viscous distillate was dissolved in anhydrous ether and to this solution was added a saturated solution of oxalic acid in ether. The gummy semi-solid mass was triturated with acetone to induce crystallization. The yield of crude oxalate melting at 181° (dec.) was 18.2 g. (45%) and further recrystallization from absolute ethanol did not change the melting point.

Anal. Calcd. for $C_{19}H_{22}N_2S \cdot H_2C_2O_4$: C, 62.98; H, 6.04; N, 7.00. Found: C, 63.09; H, 6.09; N, 6.97.

The hydrochloride salt was prepared from the oxalate salt by dissolving 8.1 g. of the oxalate in water and basifying with sodium hydroxide. The free base was extracted with ether and the ether solution dried with anhydrous magnesium sulfate. Then dry hydrogen chloride was added to the filtered ether solution. The resulting crude hydrochloride was purified by crystallization from acetone–isopropyl ether, m.p. 192.5–194.0°.

N-[2-(1-(2,5-Dimethyl)-pyrrolidyl)-propyl]-phenothiazine.—The procedure given for N-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride was followed using 6.44 g. (0.165 mole) of sodium amide, 29.9 g. (0.15 mole) of phenothiazine and 26.35 g. (0.15 mole) of 1-[1-(2,5-dimethyl)-pyrrolidyl]-2-chloropropane. The free base upon scratching crystallized. The yield of crude free base was 44.3 g. (87.5%). Recrystallization from methanol, after treatment with Darco G-60, followed by two recrystallizations from absolute ethanol yielded colorless needles, m.p. 102.5–103.5°.

Summary

1. Several 2-(1-pyrrolidyl)-ethanols and 1-pyrrolidylpropanols containing methyl groups in the pyrrolidyl nucleus have been prepared, as well as their corresponding chlorides.

2. Six alkylpyrrolidylalkyl phenothiazines have been prepared by the reaction between the above mentioned chlorides and phenothiazine in the presence of sodium amide.

KALAMAZOO 99, MICHIGAN RECEIVED MAY 14, 1948

(12) The last traces of water are very effectively removed by the careful addition of calcium carbide.