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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.

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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[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 Ducrot¹ reported on the antihistaminic activity of N-(2-dimethylamino-ethyl)- (I) and N-(2-dimethylaminopropyl)-thio-diphenylamine (II).



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

- (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. 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 instances4 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 Charpentier⁵ 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-(pyrrolidy|propy|)-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.

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

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



				B, p, ^a		Yield.		М. р.		anal	
Rı	R:	R	R4	°C.	Mm.	%	Salt	°C.	Formula	Calcd.	Found
CH₃	H	н	н	90-91	107	54	HC1	189.5-190.5	C7H14NCl·HCl	7:61	8.19 ^e
CH3	Н	CH3	CH3	117-119	98	71.2	Picrate	115 - 117	$C_9H_{18}NCl \cdot C_6H_8N_8O_7$	13.85	13.72
CH3	CH3	Н	CH_3	107-108	51	88	CH₃I	188.5 (dec.)	C ₉ H ₁₈ NCl·CH ₈ I	4.41	4.40
H	н	CH3	CH_3	116	98	73.4	HCl	201.5 - 202.5	C ₈ H ₁₆ NCl·HCl	7.07	6.55^{f}
н	CH ₈	H	CH₃	9697	40	67	HC1	141–2	C ₈ H ₁₆ NCl·HCl	7.07	7.33
	R1 CH3 CH3 CH3 CH3 H H	R ₁ R ₃ CH ₃ H CH ₃ H CH ₃ CH ₃ H H H CH ₃	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	R_1 R_3 R_4 R_4 CH_3 H H CH_3 H CH_3 CH_3 CH_3 H CH_3 CH_3 H H H CH_3 H	R_1 R_3 R_4 $^{\circ}C.$ $^{\circ}C.$ CH_3 H H 90-91 CH_3 H CH_3 CH_3 117-119 CH_3 CH_3 H CH_3 107-108 H H CH_3 CH_3 116 H CH_8 H CH_3 96-97	R1 R3 R4 $^{\text{B. p.}^{\circ}}$ Mm. CH3 H H 90-91 107 CH3 H CH3 CH3 117-119 98 CH3 H CH3 CH3 107-108 51 H H CH3 107-108 51 H H CH3 CH3 107-108 51 H H CH3 CH3 116 98 H CH3 H CH3 96-97 40	R1 R3 R4 B. p. a Yield, % CH3 H H 90-91 107 54 CH3 H CH3 CH3 117-119 98 71.2 CH3 CH3 H CH3 107-108 51 88 H H CH3 CH3 116 98 73.4 H CH3 H CH3 96-97 40 67	R1 R3 R4 $^{\circ}C.$ Mm. Yield, % Sait CH3 H H 90-91 107 54 HCl CH3 H CH3 CH3 117-119 98 71.2 Picrate CH3 CH3 H CH3 107-108 51 88 CH3I H H CH3 CH3 116 98 73.4 HCl H CH3 H CH3 96-97 40 67 HCl	R1R3R4 $^{\text{B. p.}a}$ $^{\text{Min.}}$ $^{\text{Yield,}}$ $^{\text{M. p.}}$ CH3HH90-9110754HCl189.5-190.5CH3HCH3CH3117-1199871.2Picrate115-117CH3CH3HCH3107-1085188CH3I188.5 (dec.)HHCH3CH31169873.4HCl201.5-202.5HCH3HCH396-974067HCl141-2	R1 R3 R4 ${}^{\text{B. p.}}_{\text{C.}}$ ${}^{\text{Yield}}_{\text{Salt}}$ ${}^{\text{M. p.}}_{\text{Sc.}}$ Formula CH3 H H 90-91 107 54 HCl 189.5-190.5 C_7H_{14} NCl·HCl CH3 H CH3 CH3 117-119 98 71.2 Picrate 115-117 C_9H_{18} NCl· C_8H_8 NgO7 CH3 H CH3 107-108 51 88 CH3I 188.5 (dec.) C_9H_{18} NCl·CH3I H H CH3 CH3 116 98 73.4 HCl 201.5-202.5 C_8H_{16} NCl·HCl H CH3 H CH3 96-97 40 67 HCl 141-2 C_8H_{16} NCl·HCl	R1 R3 R4 $^{\circ}$ C. Mm. $^{\circ}$ Vield, $^{\circ}$ C. M. p. $^{\circ}$ C. Formula Calcd. CH3 H H 90-91 107 54 HCl 189.5-190.5 C ₇ H ₁₄ NCl·HCl 7:61 CH3 H CH3 CH3 117-119 98 71.2 Picrate 115-117 C9H18NCl·C6H3N8O7 13.85 CH3 CH3 H CH3 107-108 51 88 CH3I 188.5 (dec.) C9H18NCl·CH3I 4.41 H H CH3 CH3 116 98 73.4 HCl 201.5-202.5 C3H16NCl·HCl 7.07 H CH3 H CH3 96-97 40 67 HCl 141-2 C3H16NCl·HCl 7.07

^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	TI
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		N	I-(Pyrro	olidylalkyl)-pi	IENOTHI	AZINES S	J—CH₂-	-CH-N R ₁	\mathbb{R}_{4}	CH CH R 3		
R1	R:	R:	R4	M. p., °C. hydrochloride	Vield, %	Formula	с	Caled. % H	N	C Fo	ound, % H	N
н	н	н	\mathbf{H}	196-197	51	C ₁₈ H ₂₀ N ₂ S·HCl	64.94	6.36	8.42	65.10	6.18	8.57
н	н	CH ₈	CH3	160-162	61	$C_{20}H_{24}N_2S \cdot HCl$	66.55	6.98	7.76	67.00^{b}	6.91	7.78
Н	CH ₈	H	CH ₃	1946	36	$C_{20}H_{24}N_2S \cdot HCl$	66.55	6.98	7.76	66.59	6.95	8.00
CH ₈	H	н	н	192.5 - 194.0	45	C ₁₉ H ₂₂ N ₂ S·HCl	65.78	6.68	8.08	65.56	6.41	8.39
CH ₃	н	CH3	CH3	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 ₈	н	CH₃	a	87.5	$\mathrm{C_{21}H_{26}N_{2}S}$	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-dimethylpyrrole³ 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 pentane¹⁰ and distilled through a 20-cm. Widmer column. The fraction boiling at $110-111^{\circ}$ at atmospheric pressure represented 110.7 g. (47.3%)

(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.

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-dimethylpyrrole¹¹ 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 re-action 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

(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 $116-117^{\circ}$ at 110 mm. By the same general procedure the alkanols reported in Table I were prepared. 1-(1-Pyrrolidyl)-2-chloropropane.—Twenty-five and

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 almost completely and then 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 $90-91^{\circ}$ at 107mm. (54%). By the same general procedure as given above the chloro compounds reported in Table I were prepared.

N-[2-(1-Pyrrolidy])-ethyl]-phenothiazine Hydrochlo-ride.—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 chloride² 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 mag-nesium 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]-phenothi-

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%).

hydrochloride, after two crystallizations from isopropanol, melted at $160-162^\circ$; yield 19.8 g. (61%). N - [2 - (1 - (2, 4 - Dimethyl) - pyrolidyl) - propyl] - phenothiazine Hydrochloride.—This compound was prepared from0.2 molar amounts of phenothiazine, sodium amide and 1-<math>(2, 4-dimethylpyrrolidyl) - 2-chloropropane as described forthe preparation of N-[2-(1-pyrrolidyl) - ethyl] - phenothiazine hydrochloride with the exception of the purificationprocedure. When the solution was extracted with dilutehydrochloric acid a brown oil separated, which was dissolved in 1.51. 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-(1pyrrolidyl)-ethyl]-phenothiazine hydrochloride wasfollowed. After recrystallization from isopropanol-isopropyl ether the product melted at 194–196° (36%).

 \tilde{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°.

chloride was purified by crystallization from acetone-isopropyl ether, m.p. 192.5-194.0°. **N-[2-(1-(2,5-Dimethyl)-pyrrolidyl)-propyl]-phenothia**zine.—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-(2,5dimethyl)-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 1pyrrolidylpropanols 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.

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