ether units. The same action caused the loss of at least 0.16 mole of primary tosyl or hydroxyl positions (structures II and III).

TABLE III

ARBITRARY DISTRIBUTION OF SUBSTITUENT IN AN ALKALI-SOLUBLE HYDROXYETHYLCELLULOSE

Sample	Moles CH_2CH_2O per glucose unit: Primary position, Monomer	Primary position, Dimer	Secondary position, Monomer	Secondary position, Dimer	Total	Primary OH
Original	0.02	0.05	0.12	0.10	0.44	1.22
				Found	.44	1.22[a]
Three-hour tosylate	.02	.04	.12	.08	.38	1.06[b]
				Found	.39	1.00
Twenty-day tosylate	.02	.0	.12	.0	.14	0.86[b]
				Found	.15	0.82

[a] By extrapolation of tosylation rate plot. [b] All tosylated monomers (0.02 + 0.12 mole) assumed to have become alkylated at primary hydroxyl positions, with elimination of the tosyl group.

Acknowledgments.—The authors are greatly indebted to Dr. R. T. K. Cornwell, of the Sylvania Division, American Viscose Corporation (formerly the Sylvania Industrial Corporation) for literature references, for several valuable suggestions, and for his sustained interest in the work. One of us (C. W. T.) also wishes to thank the same organization for the Fellowship, and the Canadian Pulp and Paper Association for the summer stipend, awarded to him for the period of the research (1946–1947).

Summary

1. A commercial alkali-soluble hydroxyethylcellulose of substitution 0.44 was esterified at 25° with excess *p*-toluenesulfonyl chloride in pyridine. The rapid initial reaction was attributed to a primary hydroxyl content of 1.22 moles per glucose residue and in consequence at least 0.22 mole of the hydroxyethyl substituent was tentatively assigned to secondary positions in the cellulose.

2. When the tosylation was prolonged for twenty to forty days, only 0.14 mole of hydroxyethyl group remained in the product. The elimination of 0.30 mole might be a measure of the polyethylene oxide units originally present as even-membered chains. The residual 0.14 mole might be attached to the cellulose directly, either as a monomer or as the initial unit of an odd-membered polyethylene oxide chain.

3. Partial replacement of tosyloxy groups by halogen, using sodium iodide or pyridine hydrochloride, had little effect on the hydroxyethyl substitution, but decreased the combined tosyl plus halogen substitution by 0.13 mole. Iodine, 1.0 mole per glucose unit, was introduced into one sample and 0.82 mole of chlorine into another, the substitution in both cases presumably occurring in the primary alcohol positions remaining in the two samples. Possible causes for the apparent decrease from the original 1.22 moles of primary alcohol units were suggested.

MONTREAL, P. Q., CANADA RECEIVED AUGUST 4, 1948

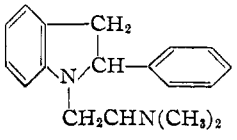
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Histamine Antagonists. IV. Indole and Carbazole Derivatives

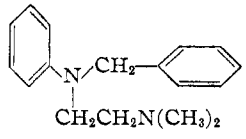
BY JOHN B. WRIGHT

In conjunction with a broad study of histamine antagonists under way in this Laboratory a number of 1-(dialkylaminoethyl)-indole and 9-(dialkylaminoethyl)-carbazole derivatives have been prepared and tested for antihistaminic activity.

A degree of similarity of structure exists between certain of these derivatives, such as 1-dimethylaminoethyl-2-phenylindoline (I), and N,-N - dimethyl - N′ - benzyl - N′ - phenylethylenediamine ("Antergan") (II). Because of this resemblance and the comparative ease with



I



II

which indole and carbazole derivatives may be prepared by means of the Fischer synthesis it seemed of interest to investigate compounds of this type. In this work β-(1-pyrrolidyl)-ethyl and β-dimethylaminoethyl were chosen as substituting groups in the indole or carbazole nucleus. The former grouping was chosen because of the promise that it has shown with other nuclei.[1,2]

The preparation of these compounds was carried out by forming the sodium salt of the indole or carbazole derivative by heating with either sodium or sodium amide in toluene or xylene solution, followed by heating of the resulting mixture under reflux with the dialkylaminoethyl chloride, either as the free base or as the hydrochloride salt. The yields ranged from 34–96%. The method of preparation outlined is essentially that of Eisleb[3] who prepared 9-(β-diethylaminoethyl)-carbazole and 1-(β-diethylaminoethyl)-2-methylindole by this method.

The indole and carbazole nuclei that were used in this work were indole, indoline, 2-phenylindole,

(1) Wright, Kolloff and Hunter, THIS JOURNAL, **70**, 3098 (1948).
(2) Reid, Wright, Kolloff and Hunter, *ibid.*, **70**, 3100 (1948).
(3) Eisleb, *Ber.*, **74B**, 1433 (1941).

2-phenylindoline, carbazole,[4] 1,2,3,4-tetrahydrocarbazole and 1,2,3,4,10,11-hexahydrocarbazole.

Preliminary pharmacological tests[5] indicate that these compounds possess weak to moderate antihistaminic activity. The results of these tests are indicated in Table I.

TABLE I

ANTIHISTAMINE ACTIVITY

Name of compound[a]	Activity[b]
1-[β-(1-Pyrrolidyl)-ethyl]-indole	[c]
1-[β-(1-Pyrrolidyl)-ethyl]-indoline	1/100–1/10
1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindole	1/100–1/10
1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindoline	*ca.* 1/2
1-(β-Dimethylaminoethyl)-2-phenylindoline	1/8–1/2
9-[β-(1-Pyrrolidyl)-ethyl]-carbazole	1/100–1/10
9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole	1/100–1/10
9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole	1/6–1/3

[a] The pharmacological tests in all cases were carried out on aqueous solutions of the hydrochloride salts. [b] Activity is expressed in terms of β-dimethylaminoethyl benzhydryl ether hydrochloride as the unit of activity. These tests were carried out on isolated guinea pig small intestine. [c] Pharmacological results not yet available.

Experimental[6,7]

1-[β-(1-Pyrrolidyl)-ethyl]-indole.—A mixture of 29.3 g. (0.25 mole) of indole and 5.76 g. (0.25 mole) of sodium was heated for two hours, with stirring, in an oil-bath at 180–200°. The mixture was allowed to cool somewhat, 100 cc. of dry xylene was added to the very viscous dark material and the mixture stirred and heated under reflux for fifteen minutes. The mixture was allowed to cool and 33.4 g. (0.25 mole) of β-(1-pyrrolidyl)-ethyl chloride[1] was added all at once. The mixture was stirred and heated under reflux for six hours. After the mixture had cooled to room temperature, the sodium chloride was filtered and washed with a small amount of xylene. The salt was dissolved in water and the aqueous solution extracted with about 250 cc. of xylene. The combined xylene solutions were extracted with a 3% hydrochloric acid solution, the acid extracts basified by the addition of solid potassium carbonate and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled *in vacuo* through a Vigreux column. There was obtained 29.9 g. (56%) of a colorless liquid, boiling at 128–129° (0.25 mm.), which darkened on standing.

The picrate, after two recrystallizations from ethyl acetate, consisted of reddish-orange flat needles melting at 142–142.5°.

Anal. Calcd. for $C_{14}H_{18}N_2 \cdot C_6H_3N_3O_7$: C, 54.17; H, 4.77; N, 15.80. Found: C, 54.34; H, 4.51; N, 15.62.

1-[β-(1-Pyrrolidyl)-ethyl]-indoline.—Sodamide was prepared from 1.9 g. (0.083 mole) of sodium according to the method of Vaughn, Vogt and Nieuwland.[8] To a mixture of the sodamide in 75 cc. of dry toluene was added, dropwise, 8.93 g. (0.075 mole) of indoline.[9] The mixture was stirred and heated under reflux for two and one-half hours. After cooling somewhat, 10.0 g. (0.075 mole) of β-(1-pyrrolidyl)-ethyl chloride was added and the mixture stirred and heated under reflux for fifteen hours. The mixture was filtered and the precipitate dissolved in 100 cc. of water and the aqueous phase extracted with toluene. The toluene extracts were combined with the toluene filtrate and the solution dried over anhydrous magnesium sulfate. The toluene was removed at atmospheric pressure and the residue distilled *in vacuo* through a Vigreux column. After a small amount of forerun, the main fraction boiled at 102–105° (0.2 mm.); yield, 11.3 g. (70%). The free base when freshly distilled is colorless but turns yellow slowly on standing.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 78.03; H, 9.05; N, 12.89.

1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindole.—The procedure given above for 1-[β-(1-pyrrolidyl)-ethyl]-indoline was followed using 5.06 g. (0.22 mole) of sodium, 19.3 g. (0.1 mole) of 2-phenylindole[10] and 17.0 g. (0.1 mole) of β-(1-pyrrolidyl)-ethyl chloride hydrochloride.[1] Xylene was used as the solvent in place of toluene. The reaction mixture was filtered, the precipitate dissolved in water and the resulting solution extracted with xylene. The combined xylene extracts and filtrate were extracted with a 3% hydrochloric acid solution. The acid extract was basified with potassium carbonate and the resulting mixture extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate, the solvent removed and the residue distilled *in vacuo* through a short Vigreux column. There was obtained 19.1 g. (66%) of a light-yellow viscous oil boiling at 187–189° (0.9 mm.). Upon standing the distillate solidified. Two recrystallizations of the crude product from methanol gave colorless needles melting at 78–78.5°.

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.71; H, 7.64; N, 9.65. Found: C, 83.04; H, 7.36; N, 9.71.

2-Phenylindoline was prepared by the reduction of 2-phenylindole[10] with zinc dust and hydrochloric acid, according to the method of Fischer and Schmitt.[11] From 17.1 g. (0.087 mole) of 2-phenylindole there was obtained 14.4 g. (83%) of 2-phenylindoline boiling at 148–149° (1.4 mm.) and melting at 46–47.5°.

1-[β-(1-Pyrrolidyl)-ethyl]-2-phenylindoline Hydrochloride.—The procedure given for 1-[β-(1-pyrrolidyl)-ethyl]-2-phenylindole was followed with the exception that the crude undistilled product of the reaction was heated on a steam-bath for one hour with an excess of acetic anhydride. The solution, when cool, was poured into water. When the excess acetic anhydride had hydrolyzed completely the solution was neutralized with potassium carbonate and extracted with ether. The ethereal solution was extracted with dilute (3%) hydrochloric acid solution, the aqueous phase basified by the addition of solid potassium carbonate and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, the ether removed and the residue distilled *in vacuo* through a short Vigreux column. The product was obtained as a light-yellow viscous liquid boiling at 162–165° (0.2 mm.); yield, 34%.

The hydrochloride was prepared by adding the theoretical amount of a 2.96 *N* alcoholic hydrogen chloride solution to a solution of the free base in anhydrous ethanol and then adding an excess of anhydrous ether to precipitate the hydrochloride salt. Four recrystallizations of the crude material from an isopropyl alcohol–ethyl acetate mixture (1:1) gave clusters of small needles melting at 189.5–191.5°.

Anal. Calcd. for $C_{20}H_{24}N_2 \cdot HCl$: C, 73.04; H, 7.66; N, 8.52; Cl, 10.78. Found: C, 72.99; H, 7.48; N, 8.56; Cl, 10.88.

(4) 9-(β-Dimethylaminoethyl)-carbazole has recently been tested for antihistaminic activity by Freese, Hambourger and Michiels [*Federation Proc.*, **7**, 219 (1948)]. This compound has been reported also by Viaud [*Technologie Produits Pharmaceutiques*, **2**, 53 (1947)].

(5) For these results grateful acknowledgment is made to Dr. Milton J. VanderBrook of the Division of Pharmacology and Endocrinology of these laboratories.

(6) All melting points are corrected.

(7) For the analyses reported in this paper we are indebted to Mr. Harold C. Emerson and his staff of our Microchemical Division.

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

(9) King, Barltrop and Walley, *J. Chem. Soc.*, 280 (1945).

(10) "Organic Syntheses," **22**, 98 (1942).

(11) Fischer and Schmitt, *Ber.*, **21**, 1075 (1888).

1-(β-Dimethylaminoethyl)-2-phenylindoline Hydrochloride.—The procedure described above was employed, using an equivalent amount of β-dimethylaminoethyl chloride hydrochloride. From 12.9 g. (0.66 mole) of 2-phenylindoline there was obtained 12.6 g. (71.5%) of the free base. The free base is a colorless liquid boiling at 183–184° at 3.8 mm. The hydrochloride, prepared as described above, after four recrystallizations from absolute ethanol consisted of fine colorless needles melting at 210.5–212.5°.

Anal. Calcd. for $C_{18}H_{22}N_2 \cdot HCl$: C, 71.38; H, 7.65; N, 9.25. Found: C, 71.38; H, 7.50; N, 9.00.

9-[β-(1-Pyrrolidyl)-ethyl]-carbazole.—Sodamide[8] was prepared from 3.8 g. (0.17 mole) of sodium. A mixture of sodamide, 150 cc. of dry xylene and 25.1 g. (0.15 mole) of carbazole was stirred and heated in an oil-bath at 130° for three hours. To the mixture was added 20.0 g. (0.15 mole) of β-(1-pyrrolidyl)-ethyl chloride and the mixture stirred and heated under reflux for eight hours. The mixture was filtered and the precipitate washed with about 200 cc. of xylene. The xylene filtrate was extracted with dilute hydrochloric acid, the acid extracts made basic by the addition of a cold solution of sodium hydroxide, whereupon a light brown precipitate formed. This was filtered and dried in air. The weight of crude product was 38.4 g. (96%); m. p. 80–81°. Two recrystallizations from petroleum ether (Skelly B) after treatment with charcoal gave light yellow needles melting at 80.5–81.0°.

Anal. Calcd. for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.60. Found: C, 81.80; H, 7.47; N, 10.51.

9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4-tetrahydrocarbazole Hydrochloride.—The procedure given above for 9-[β-(1-pyrrolidyl)-ethyl]-carbazole was followed using 25.6 g. (0.15 mole) of 1,2,3,4-tetrahydrocarbazole.[12] The product, which separated as an oil, was taken up in ether and the ethereal solution dried over anhydrous magnesium sulfate. The drying agent was filtered off and the hydrochloride precipitated by bubbling dry hydrogen chloride through the solution. The yield of crude product, melting at 211–220°, was 38.1 g. (83%). Three recrystallizations from an ethyl acetate–absolute ethanol mixture (3:1) using decolorizing carbon gave light yellow needles melting at 232.5–233.0°.

Anal. Calcd. for $C_{18}H_{24}N_2 \cdot HCl$: C, 70.91; H, 8.27; N, 9.19. Found: C, 70.74; H, 8.01; N, 9.42.

9-[β-(1-Pyrrolidyl)-ethyl]-1,2,3,4,10,11-hexahydrocarbazole Hydrochloride.—The procedure given above for 1-[β-(1-pyrrolidyl)-ethyl]-2-phenylindoline was followed using the appropriate quantity of 1,2,3,4,10,11-hexahydrocarbazole.[13] The free base was obtained as a light yellow, slightly fluorescent liquid boiling at 147–149° (0.5 mm.); yield 62%.

The hydrochloride was prepared as described in the same procedure. The crude product, upon five recrystallizations from ethyl acetate, in the presence of decolorizing charcoal, gave light yellow needles melting at 135–137.5°. The hydrochloride darkens upon standing.

Anal. Calcd. for $C_{18}H_{26}N_2 \cdot HCl$: C, 70.45; H, 8.87; N, 9.13; Cl, 11.55. Found: C, 70.40; H, 8.67; N, 9.07; Cl, 11.55.

Summary

1. Four new 1-[β-(1-pyrrolidyl-ethyl]-indole derivatives, three new 9-[β-(1-pyrrolidyl)-ethyl]-carbazole derivatives, and 1-β-(dimethylaminoethyl)-2-phenylindoline hydrochloride have been prepared.

2. The results of preliminary pharmacological tests on these compounds for antihistaminic activity is reported.

(12) Rogers and Corson, THIS JOURNAL, **69**, 2910 (1947).

(13) Borsche, Witte and Bothe, *Ann.*, **359**, 70 (1908).

KALAMAZOO, MICHIGAN RECEIVED SEPTEMBER 20, 1948

[CONTRIBUTION FROM THE LABORATORIES OF GORDON A. ALLES, PH.D.]

Characterization of Certain Alkaloids from *Fagara coco*

BY C. ERNST REDEMANN, BURNETT B. WISEGARVER AND GORDON A. ALLES

Stuckert[1] and co-workers in 1925 began the isolation and separation of the alkaloids of *Fagara coco* (Gill.) Engl. Six alkaloids were listed, only four of which, α-, β-, γ-, and δ-fagarine, were sufficiently well characterized to be considered discrete compounds. Merck and Company of Darmstadt subsequently carried out the isolation of the fagara alkaloids on a large scale and reported only two alkaloids, designated fagarine I, m.p. 163°, and fagarine II, m.p. 202°. Fagarine I is to be identified with α-fagarine, but fagarine II appears to be a new alkaloid. Later Deulofeu[2] and co-workers isolated α-, β-, and γ-fagarine from a sample of *Fagara coco* supplied by Stuckert. β-Fagarine has been identified[2] as skimmianine[3,4] and γ-fagarine as 8-methoxydictamnine.[5]

The structure of α-fagarine has been of interest since the report of Stuckert and Sartori[6] that it exerts a depressant action upon cardiac function, and the subsequent finding of Moisset de Espanés[7] that it raises the threshold for both auricular and ventricular fibrillation arising from faradic stimulation. It has more recently been reported as a superior substitute[8] for quinidine for controlling cardiac arrythmias. Stuckert[1] arrived at the empirical formula $C_{19}H_{22}NO_4$ for α-fagarine, while Merck[1] gave $C_{19}H_{23}NO_5$. Deulofeu[2,8,9] and co-workers concluded that the empirical formula is $C_{19}H_{23}NO_4$ and suggest a provisional structure.

Dried ground leaves and twigs of *Fagara coco* were extracted by the method of Deulofeu.[2]

(1) "Investigaciones del Laboratorio de Química Biológica, Cordoba, Argentina," Vol. I 1933, and Vol. II, 1938.

(2) Deulofeu, Labriola and de Langhe, THIS JOURNAL, **64**, 2326 (1942).

(3) Honda, *Arch. exp. Path. Pharmakol.*, **52**, 83 (1904).

(4) Asahina and Inubuse, *Ber.*, **63**, 2052 (1930).

(5) Berinzaghi, Muruzabal, Labriola and Deulofeu, *J. Org. Chem.*, **10**, 181 (1945).

(6) Stuckert and Sartori, *Rev., Univ. Nac. Cordoba, Argent.*, **19**, 12 (1932).

(7) Moisset de Espanés and Navarro, *Rev. Soc. Arg. Biol.*, **12**, 137 (1936); **13**, 112 (1937); **13**, 259 (1937).

(8) Deulofeu, Labriola, Orias, Moisset de Espanés and Taquini, *Science*, **102**, 69 (1945).

(9) Deulofeu, Labriola and Berinzaghi, *J. Org. Chem.*, **12**, 217 (1947).