3.84; N, 26.90; S, 15.36. Found: C, 46.09; H, 3.94; N, 25.73; S, 14.81.

Summary

Synthesis of several mercaptopteridines in good yields has been described. The ultraviolet absorption spectra of their alkaline solutions and their solubility in phosphate buffer solution has been measured.

BERKELEY, CALIFORNIA RECEIVED NOVEMBER 30, 1949

[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Syntheses in the Oxindole Series[1]

BY E. C. HORNING AND M. W. RUTENBERG[2]

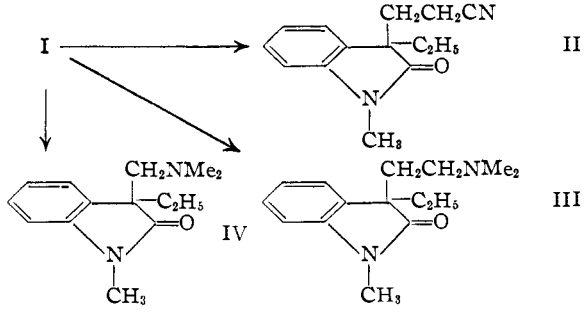
Consideration of the structures of morphine derivatives and synthetic analgesics (Demerol and Amidone series) reveals certain structural features which are common to all; the most important of these appear to be a quaternary carbon atom attached to an aromatic ring) with an amino nitrogen in a beta relationship to it. This might be considered the "essential" structural feature for this type of physiological activity.

In connection with the general problem of the relationship between chemical structure and physiological activity of morphine-type compounds, it has been suggested that compounds containing the "essential" structural features with a nitrogen atom in a position corresponding to the bridge oxygen of morphine would lead to similar physiological effects. It has been postulated[3] that drug molecules adhere to cell surfaces at the site of action by means of specific chemical groups. The possible attachment points of the morphine molecule may be at the basic amino nitrogen and at the oxygen atom of the furan ring (which may form an attachment by hydrogen bonding). A nitrogen atom, replacing the oxygen, would also have free electrons available for hydrogen bonding. Studies of carbazole derivatives, in which nitrogen is in a position corresponding to the bridge oxygen of morphine, have been reported.[4,5] Although these compounds did not show a high order of activity, it was noted that a substituent (methyl, ethyl or acetyl) on the bridge nitrogen led to increased effectiveness with respect to analgesic activity. Oxindoles have been prepared in connection with the synthesis of physostigmine,[6,7] but no record of analgesic activity has been found.

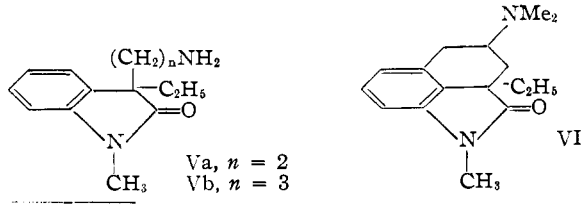
1-Methyl-3-ethyloxindole (I) was prepared by the Stolle method.[8] By employing the Bruson[9] cyanoethylation procedure, the cyanoethyloxindole (II) was prepared. Hydrolysis of the nitrile yielded the corresponding acid, from which a formamide was obtained by the Curtius procedure. This compound was alkylated with a mixture of formic acid and formalin[10] to yield the desired dimethylaminoethyloxindole (III). Alkylation of the oxindole with dimethylaminoethyl chloride gave the same product, in more direct fashion.

For purposes of obtaining information about structure and activity in this series, a group of related amines was prepared. These compounds were designed to test the effect of variation in chain length between the quaternary carbon atom and the amino nitrogen, as well as the effect of substitution on the amino nitrogen.

1-Methyl-3-ethyl-3-dimethylaminomethyloxindole (IV) was prepared by the Mannich reaction. Primary amines of the general structure V were prepared by reduction of appropriate nitriles. In general, reduction with palladium–carbon and platinum catalysts gave mixtures of primary and secondary amines. The next higher homolog of III, 1-methyl-3-ethyl-3-(γ-dimethylaminopropyl)-oxindole



was prepared by methylation of the corresponding primary amine with formic acid and formalin. A



(1) From the dissertation of M. W. Rutenberg, presented to the faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy, April, 1949.

(2) Bristol Laboratories Fellow, 1947–1949.

(3) C. C. Pfeifer, *Science*, **107**, 94 (1948); *The Modern Hospital*, **71**, no. 6, 88 (Dec., 1948).

(4) Eddy, *J. Pharmacol. Exp. Therap.*, **65**, 294, 308 (1939).

(5) Ruberg and Small, THIS JOURNAL, **63**, 736 (1941).

(6) Robinson, *et al.*, *J. Chem. Soc.*, 317 (1932).

(7) Julian and Pikl, THIS JOURNAL, **57**, 2026 (1935).

(8) Stolle, *J. prakt. Chem.*, [2] **128**, 1 (1930); Julian and Pikl, THIS JOURNAL, **57**, 563 (1935).

(9) Bruson and Riener, *ibid.*, **65**, 23 (1943).

(10) E. C. Wagner and E. Staple, *J. Org. Chem.*, **14**, 559 (1949).

second series of compounds was obtained by application of the Oxley–Short[11] method for the preparation of imidazolines. In this case the basic nitrogen atom is incorporated in a ring system, while the distance to the quaternary carbon atom is varied.

The synthesis of a tetralin analog VI was attempted without success. It was anticipated that difficulties might be encountered in the proposed cyclization, by analogy with recent work directed to the synthesis of tetralin lactones.[12] The required acid chloride did not undergo cyclization, although normal reactivity of the carbonyl chloride group was indicated by intermolecular acylation with benzene–aluminum bromide. Attempted cyclization of a formyl derivative was also unsuccessful. The results of the pharmacological studies will be reported elsewhere.

Acknowledgment.—The authors are indebted to Mrs. Sarah M. Woods for the analytical data.

Experimental[12a]

1-Methyl-3-ethyloxindole (I) was prepared in 81% yield by the method of Stolle.[8]

1-Methyl-3-ethyl-3-(β-cyanoethyl)-oxindole (II).—The cyanoethylation procedure of Bruson,[9] when applied to I, gave a 71% yield of product. Recrystallization from cyclohexane provided a colorless sample, m. p. 84–85°.

Anal. Calcd. for $C_{14}H_{16}ON_2$: C, 73.66; H, 7.07. Found: C, 73.92; H, 6.87.

1-Methyl-3-ethyl-3-(β-carboxyethyl)-oxindole.—A solution of 7.3 g. (0.03 mole) of 1-methyl-3-ethyl-3-(β-cyanoethyl)-oxindole (II) in 20 ml. of glacial acetic acid, 20 ml. of concd. hydrochloric acid and 20 ml. of water was heated under reflux for ten hours. Isolation of the product yielded 7.0 g. (96%) of a viscous, yellow oil. A small portion (1.0 g.) was evaporatively distilled to yield 0.6 g. of very viscous, almost colorless oil.

Anal. Calcd. for $C_{14}H_{17}O_3N$: C, 68.00; H, 6.93. Found: C, 67.97; H, 6.88.

1-Methyl-3-ethyl-3-(β-dimethylaminoethyl)-oxindole (III). A. Curtius Method.—1-Methyl-3-ethyl-3-(β-carboxyethyl)-oxindole was converted by the "wet method"[13] to the corresponding acid azide. The azide was converted to a formamide with formic acid (98–100%) and methylation of the formamide was carried out with formic acid–formaldehyde. A 38% (over-all) yield of the desired amine was obtained.

B. **Alkylation Method.**—The alkylation of 17.5 g. (0.1 mole) of I was effected in toluene solution with sodamide (from 3.15 g., 0.14 mole of sodium) and β-dimethylaminoethyl chloride (from 26.4 g., 0.19 mole of hydrochloride). A 65% yield of the amine was obtained, b. p. 119–126° (0.4 mm.). Redistillation at 114–116° (0.3 mm.) provided an analytical sample.

Anal. Calcd. for $C_{15}H_{22}ON_2$: C, 73.13; H, 9.00. Found: C, 72.96; H, 8.95.

The **hydrochloride** was prepared in ether with dry hydrogen chloride, and purified by recrystallization from methyl isobutyl ketone; m. p. 190–191°.

Anal. Calcd. for $C_{15}H_{22}ON_2 \cdot HCl$: C, 63.70; H, 8.20. Found: C, 63.90; H, 8.18.

1-Methyl-3-ethyl-3-dimethylaminomethyloxindole (IV).—To a mixture of 8.9 g. (0.1 mole) of 36% formaldehyde solution and 18.4 g. (0.1 mole) of 25% aqueous dimethylamine cooled to 8° there was added a solution of 17.5 g. (0.1 mole) of I. The reaction mixture remained at room temperature for twenty-four hours. Then 40 ml. of 10% hydrochloric acid was added and the mixture extracted with ether. The aqueous layer was poured into a solution of 24 g. of sodium hydroxide in 120 ml. of water, with cooling. The alkaline mixture was extracted with ether; the extract was dried and evaporated to yield 17.3 g. of viscous oil. Distillation yielded 15.2 g. (66%) of product, collected at 104–105° (0.5 mm.), crystallizing to a colorless solid melting at 49–55°. An analytical sample was obtained by recrystallization from acetone (Dry Ice), m. p. 53.5–55°.

Anal. Calcd. for $C_{14}H_{20}ON_2$: C, 72.37; H, 8.68. Found: C, 72.46; H, 8.77.

1-Methyl-3-ethyl-3-cyanomethyloxindole.—The alkylation of 36.2 g. (0.21 mole) of I with 31.6 g. (0.42 mole) of chloroacetonitrile was carried out in dry ethanol with sodium ethoxide prepared from 5.48 g. (0.24 mole) of sodium. Excess alcohol was removed by distillation, and from the residue there was isolated by ether extraction 31.1 g. (70%) of product, b. p. 138–144° (0.5 mm.).

Anal. Calcd. for $C_{13}H_{14}ON_2$: C, 72.87; H, 6.59. Found: C, 72.77; H, 6.54.

Reduction of 1-Methyl-3-ethyl-3-cyanomethyloxindole.—The reduction of 11.0 g. of 1-methyl-3-ethyl-3-cyanomethyloxindole in 36 ml. of acetic acid with 0.56 g. of Adams catalyst required one and one-half hours. Evaporative distillation of the basic product (some neutral material (1.3 g.) was also obtained) yielded 7.9 g. (69%) of nearly colorless, viscous oil, collected at 80–120° (0.2 mm.). This was the expected primary amine, **1-methyl-3-ethyl-3-(β-aminoethyl)-oxindole.**

Anal. Calcd. for $C_{13}H_{18}ON_2$: C, 71.52; H, 8.31. Found: C, 71.69; H, 8.16.

The colorless **benzenesulfonamide** was recrystallized from ethanol; m. p. 149–150.5°.

Anal. Calcd. for $C_{19}H_{22}O_3N_2S$: C, 63.66; H, 6.19. Found: C, 63.60; H, 6.07.

When a 5% palladium–carbon catalyst (Hartung catalyst) was employed for reduction in acetic acid solution at 65°, the product was a mixture of primary amine (30%) and secondary amine (36%).

Di-[β-(1-methyl-3-ethyloxindolyl-3)-ethyl]-amine was a colorless solid, m. p. 144–145.5°.

Anal. Calcd. for $C_{26}H_{33}O_2N_3$: C, 74.43; H, 7.93. Found: C, 74.49; H, 7.79.

Reduction of 1-Methyl-3-ethyl-3-(β-cyanoethyl)-oxindole.—The reduction of 8.6 g. of II in 30 ml. of acetic acid with 0.60 g. of Adams catalyst required one and one-half hours. Evaporative distillation of the basic product (0.5 g. of neutral material was also obtained) provided 5.27 g. (60%) of primary amine, **1-methyl-3-ethyl-3-(γ-aminopropyl)-oxindole,** collected at 80–118° (0.1–0.3 mm.).

Anal. Calcd. for $C_{14}H_{20}ON_2$: C, 72.37; H, 8.68. Found: C, 72.31; H, 8.50.

A similar reduction with a 5% palladium–carbon catalyst yielded only 11% of the primary amine. The major product was a high boiling material which could not be purified, but which was evidently the secondary amine.

1-Methyl-3-ethyl-3-(γ-dimethylaminopropyl)-oxindole.—A methylation of 5.0 g. of 1-methyl-3-ethyl-3-(γ-aminopropyl)-oxindole was carried out with 5.5 g. of formic acid (90%) and 5 ml. of formaldehyde solution (36%), with a heating period of seven hours. The tertiary amine was evaporatively distilled at 90–128° (0.2 mm.), as a colorless oil, in 3.0 g. (54%) yield.

Anal. Calcd. for $C_{16}H_{24}ON_2$: C, 73.80; H, 9.29. Found: C, 73.96; H, 9.12.

1-Methyl-3-ethyl-3-(γ-cyanopropyl)-oxindole.—The alkylation of 37.1 g. (0.21 mole) of 1-methyl-3-ethyloxindole with 45.2 g. (0.44 mole) of γ-chlorobutyronitrile was carried out in toluene with sodamide prepared from 5.81 g. (0.25 mole) of sodium. A yield of 26.7 g. (52%, or 75% based on unrecovered starting material) of prod-

(11) Oxley and Short, *J. Chem. Soc.*, 497 (1947).

(12) Horning and Schock, THIS JOURNAL, **70**, 2941 (1948).

(12a) All melting points are corrected.

(13) "Organic Reactions," Vol. III, p. 387 (1946).

uct was obtained; b. p. 158–165° (0.5 mm.). An analytical sample was collected at 160–161° (0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49. Found: C, 74.61; H, 7.33.

1-Methyl-3-ethyl-3-(2'-dihydroimidazolylmethyl)-oxindole.—By application of the fusion procedure of Oxley and Short[11] to 1-methyl-3-ethyl-3-cyanomethyloxindole the corresponding imidazoline was obtained (42%) by evaporation distillation at 95–130° (0.3 mm.) as a viscous oil which solidified on long standing, m. p. 93–97°.

Anal. Calcd. for $C_{15}H_{19}ON_3$: C, 70.01; H, 7.44. Found: C, 70.10; H, 7.41.

The picrate was recrystallized from ethanol; m. p. 181–182.5°.

Anal. Calcd. for $C_{15}H_{19}ON_3 \cdot C_6H_3O_7N_3$: C, 51.85; H, 4.56. Found: C, 52.15; H, 4.90.

1-Methyl-3-ethyl-3-[β-(2'-dihydroimidazolyl)-ethyl]-oxindole was prepared in the same way from the corresponding nitrile in 50% yield. The solid product, m. p. 178–180.5°, could not be obtained in analytical purity, but a **picrate**, m. p. 142.5–143.5°, served for identification.

Anal. Calcd. for $C_{16}H_{21}ON_3 \cdot C_6H_3O_7N_3$: C, 52.80; H, 4.83. Found: C, 52.83; H, 5.00.

1-Methyl-3-ethyl-3-[γ-(2'-dihydroimidazolyl)-propyl]-oxindole was prepared in the same way (76% yield): m. p. 101–103.5°, identified as the **picrate**, m. p. 177–178°.

Anal. Calcd. for $C_{17}H_{23}ON_3 \cdot C_6H_3O_7N$: C, 53.59; H, 5.28. Found: C, 53.57; H, 5.10.

Cyclization Experiments.—Attempts were made to carry out a cyclization of an acid chloride derived from 1-methyl-3-ethyl-3-(β-carboxyethyl)-oxindole with stannic chloride, aluminum chloride and aluminum bromide in various solvents. These were unsuccessful, although normal reactivity of the acid chloride was indicated by the fact that use of aluminum bromide and benzene gave a ketonic product, m. p. 87.5–89°, resulting from reaction with the solvent.

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 78.15; H, 6.89. Found: C, 78.01; H, 7.01.

The orange **2,4-dinitrophenylhydrazone** melted at 157–158°.

Anal. Calcd. for $C_{26}H_{25}O_6N_6$: C, 64.05; H, 5.17. Found: C, 63.92; H, 4.99.

A different cyclization procedure, applied to the formyl derivative obtained from the Claisen condensation of ethyl formate with the methyl ester of 1-methyl-3-ethyl-3-(β-carboxyethyl)-oxindole, was also unsuccessful.

These experiments were extended to the homologous acid, **1-methyl-3-ethyl-3-(γ-carboxypropyl)-oxindole**, m. p. 115–116.5° (*Anal.* Calcd. for $C_{15}H_{19}O_3N$: C, 68.94; H, 7.33. Found: C, 68.96; H, 7.21), without success.

Summary

The synthesis of 1-methyl-3-ethyl-3-(β-dimethylaminoethyl)-oxindole and related amines and imidazolines is described.

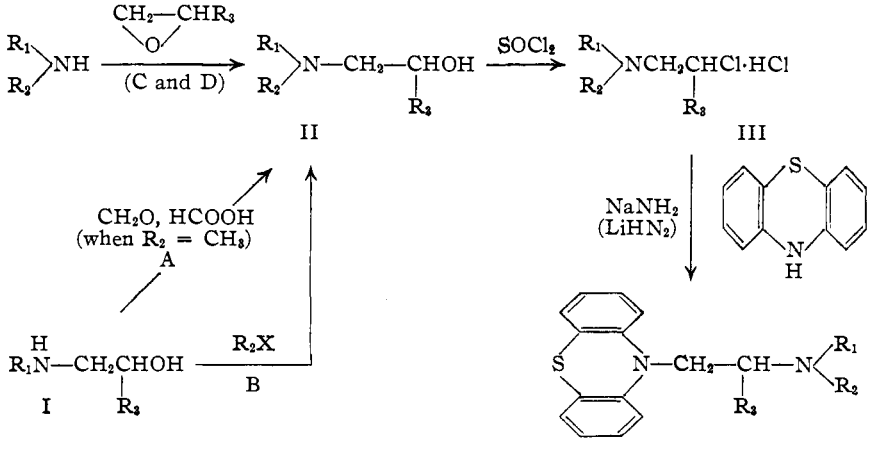
PHILADELPHIA, PENNA. RECEIVED JANUARY 29, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Histamine Antagonists. VII. Phenothiazine Derivatives[1]

BY JOHN B. WRIGHT, EDWARD H. LINCOLN, RICHARD V. HEINZELMANN AND JAMES H. HUNTER

A review[2–4] of the literature of antihistamine drugs reveals that the most active compounds possess the N-(β-dimethylaminoethyl) grouping.



Although such variations as N-(β-diethylaminoethyl), N-(β-piperidinoethyl), N-(β-morpholinoethyl), N-(β-pyrrolidinoethyl) and N-[(2-imidazolyl)-methyl] have been reported, it seemed to us that a systematic study was necessary to reveal the relationship between antihistaminic activity and this type of chemical structure. Therefore, a series of N-disubstituted aminoalkylphenothiazine derivatives has been prepared. These compounds, together with the results[5] of the screening for antihistaminic activity, are listed in Table III.

The amino alcohols (II) used in this work were prepared either by treatment of secondary amines with epoxides[6] (Procedures C and D) or from secondary aminoalcohols (I) by (a) reductive alkylation[7] (Procedure A); (b) alkyla-

(1) For previous papers in this series see Lincoln, Heinzelmann and Hunter, THIS JOURNAL, **71**, 2902 (1949).

(2) Huttrer, *Ensymologia*, **12**, 277 (1948).

(3) Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947).

(4) Bovet and Bovet-Nitti, "Medicaments du Systeme Nerveau Vegetative," S. Karger, New York, N. Y., 1948, p. 741.

(5) For conducting these tests, grateful acknowledgment is made to Dr. Milton J. Vander Brook of our Department of Pharmacology and Endocrinology.

(6) Horne and Shriner, THIS JOURNAL, **54**, 2928 (1932).

(7) Clarke, Gillespie and Weisshaus, *ibid.*, **55**, 4571 (1933).