[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

Studies in the Indole Series. IV. The Synthesis of *d,l*-Eserethole

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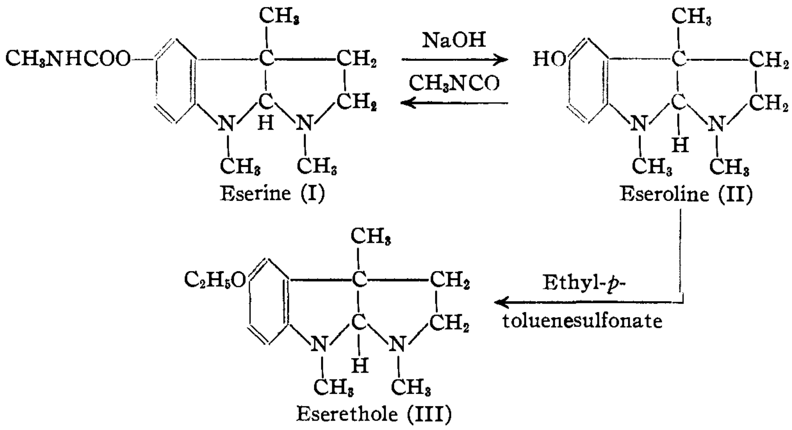
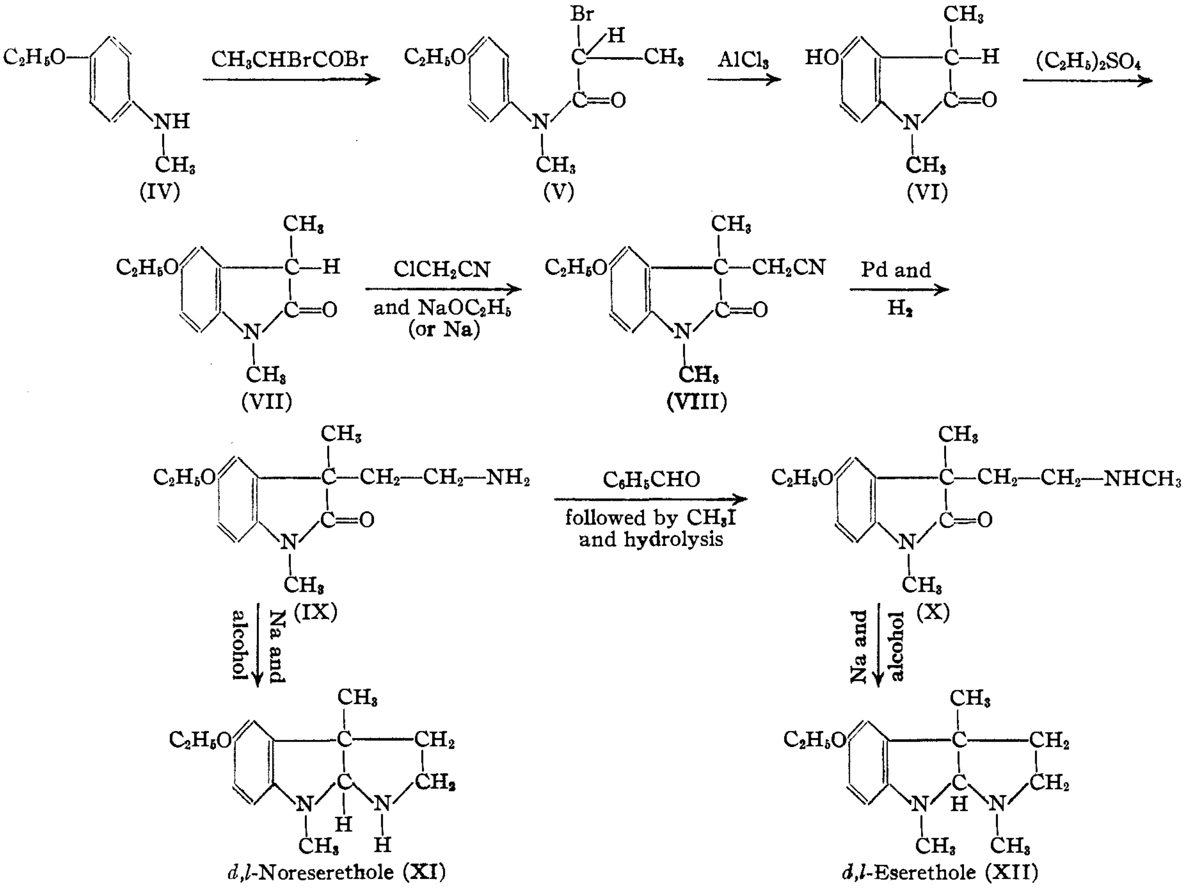
Recently an improved synthesis of substances containing the basic ring structure of the alkaloid, physostigmine (eserine) has been reported,[1] and the reactions of these substances shown to run exactly parallel with those of natural physostigmine. This work has now been extended to include the synthesis of *d,l*-noreserethole (XI) and *d,l*-eserethole (XII). A synthesis of eserethole represents a complete synthesis of physostigmine (I) since eseroline (II) easily obtained from physostigmine by treatment with alkali, is reconverted into eserine on reaction with methyl isocyanate.



Our method of synthesis follows in the main the course indicated in previous communications on this subject.[1,2] N-Methylphenetidine (IV) is treated with α-bromopropionyl bromide to yield



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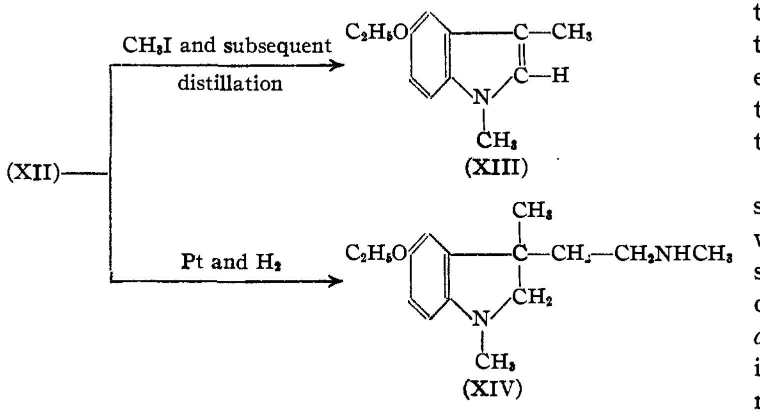
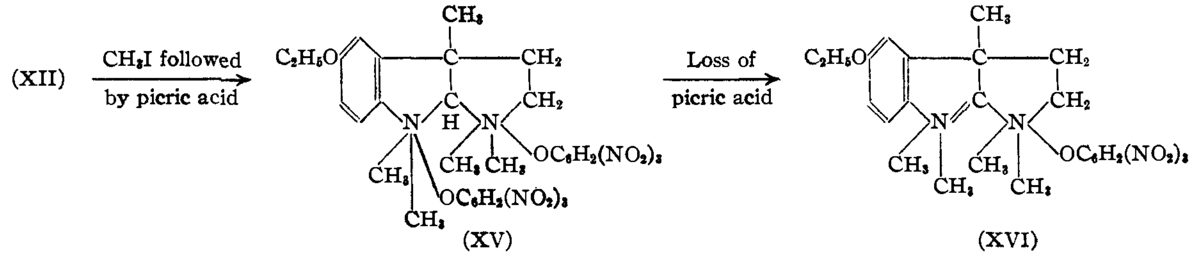
(1) Julian and Pikl, THIS JOURNAL, **57**, 539 (1935).

(2) Julian, Pikl and Boggess, *ibid.*, **56**, 1797 (1934).

the anilide (V). On treatment with an excess of aluminum chloride, the ethoxyl group in (V) is cleaved smoothly, subsequent heating and working up of the mass leading to 1,3-dimethyl-5-hydroxyoxindole (VI) in excellent yield. The latter on ethylation with one mole of ethyl sulfate yields 1,3-dimethyl-5-ethoxyoxindole (VII). From this point the steps are exactly similar to those already outlined[1,2] as is indicated in the formulas just given.

The yields at every stage are excellent, thus rendering *d,l*-eserethole a readily accessible substance, since the materials employed are inexpensive and the reactions require relatively little time. Our *d,l*-eserethole has been obtained, moreover, in crystalline form and found to be identical in its reactions with eserethole of natural origin. Thus distillation of the product secured on treatment of (XII) with methyl iodide gives the ethyl ether of physostigmol (XIII), identical with that secured from eserethole of natural origin.[3] Also, like *l*-eserethole,[4] our *d,l*-eserethole takes up two atoms of hydrogen on catalytic reduction yielding 1,3-dimethyl-3-β-methylaminoethyl-5-ethoxy-2,3-dihydroindole (XIV).





For reasons which will appear in the sequel, the action of methyl iodide on eserethole deserves special attention. In most of the literature on physostigmine it has been assumed that this reaction results always in addition of only one mole of methyl iodide, and to the more basic of the two nitrogen atoms, namely, that of the pyrrolidine nucleus. In methyl alcohol solution with an excess of methyl iodide, *d,l*-eserethole seems to add two moles of methyl iodide, as indicated by examination of the picrate (XV) made in the cold from the product with alcoholic picric acid. The yellow diquaternary picrate (XV) loses very readily in alcoholic solution, even on attempted recrystallization, a mole of picric acid, passing over into the red monopicrate (XVI).

In a series of ten beautiful papers[5] Robinson and his co-workers have described syntheses of compounds which they call "*d,l*-eserethole" and "*d,l*-esermethole." Their "*d,l*-eserethole" is not the compound (XII) described in this communication as *d,l*-eserethole, and the constitution of which can hardly be questioned. We believe that the English authors are in error, that the compound they describe as *d,l*-eserethole is not the substance, and that we are describing for the first time the real *d,l*-eserethole.

Indeed, this conclusion finds strong support in the reactions of eserethole with methyl iodide, which we have described above. The English authors depend upon methylation of their *d,l*-noreserethole (which seems to be identical with our product (XI)) with methyl *p*-toluenesulfonate and at times methyl sulfate. This could well lead to a substance whose structure is represented by (XVII). A substance with this formula assigned to it has been obtained by Hoshino and Kobayashi[6] through methylation by various procedures

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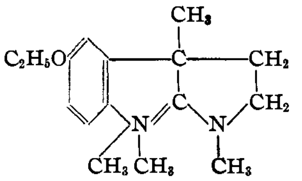
[3] Späth and Brunner, *Ber.*, **58**, 518 (1925); Stedman, *J. Chem. Soc.*, 1373 (1924).

[4] Barger and Stedman, *ibid.*, 249 (1925).

[5] Robinson and Suginome, *ibid.*, 298, 304 (1932); Boyd-Barrett and Robinson, *ibid.*, 317 (1932); Boyd-Barrett, *ibid.*, 321 (1932); King and Robinson, 326, 1433 (1932); 270 (1933); King, Robinson and Suginome, 1472 (1933); King, Liguori and Robinson, 1475 (1933); 1416 (1934).

[6] Hoshino and Kobayashi, *Proc. Imp. Acad.* (Tokyo), **10**, 99–102 (1934).



(XVII)

of dinoreserethole. Its melting point appears to be identical with the "*d,l*-eserethole" of Robinson and his co-workers and likewise the melting points of the two picrates seem identical. The English authors, themselves, express the opinion "that reinvestigation will show that the bases are identical," but "that action of alkali on trimethyldinoreserethole iodide results in the loss of a methyl group." Our results tend to substantiate, however, the claim of the Japanese chemists.

Final proof that we have completed the synthesis of physostigmine will be forthcoming when resolution experiments now in progress are completed.

Experimental Part

Preparation of N-Methylphenetidine (IV).—Since a cheap and convenient method for preparation of this substance could not be found in the literature, we devised the following procedure: 716 g. (4 moles) of acetylphenetidine was added all at once to a 5-liter flask containing 92 g. of sodium powder under 2 liters of xylene. Soon reaction sets in, assisted if necessary by gentle warming, and the xylene is heated to boiling. To complete the reaction, the mass is heated on the water-bath for one hour with occasional stirring by means of a large spatula or glass rod; 320 g. of dimethyl sulfate was dropped in, at first at such a rate as to keep the xylene gently boiling, the flask shaken now and then. After all was added, heating on the water-bath was continued for a half hour and the xylene then removed under diminished pressure. To the residue a solution of 560 g. of potassium hydroxide in a mixture of 2 liters of alcohol and 200 cc. of water was added, and the flask heated on the water-bath for thirty-six hours. After removal of the alcohol under diminished pressure, enough water is added to dissolve the inorganic salts and the N-methylphenetidine extracted with ether. The product is pure on first distillation in vacuum, b. p. 138°, 18 mm.; yield 96% of the theoretical.

1,3-Dimethyl-5-hydroxyoxindole (VI).—To a solution of 302 g. of N-methylphenetidine in 750 cc. of dry benzene, well cooled in a freezing mixture, 217 g. of α-bromopropionyl bromide was rapidly run in. Heating on the water-bath for one-half hour was sufficient to ensure completion of the reaction. 500 cc. of water was added and the benzene layer separated. To remove traces of unchanged phenetidine the benzene solution was shaken several times with 1.5% hydrochloric acid to which some sodium chloride had been added to diminish tendency to form an emulsion. The benzene solution was transferred to a 3-liter flask and the benzene removed completely under diminished pressure. To the residue 250 g. of sublimed aluminum chloride was added. After a few seconds reaction set in, becoming rather vigorous with copious evolution of ethyl chloride, the mass setting solid; 200 g. more of sublimed aluminum chloride was added, the flask provided with a mechanical stirrer, connected to the flask most conveniently by means of a loose stopper. The flask with contents was then heated for an hour in a metal bath at 180–185°, stirring being begun as soon as the mass liquefied sufficiently. The homogeneous melt is poured while hot onto a marble slab, this procedure being strongly recommended, since the material otherwise can be removed from the flask only by prolonged heating with water, causing production of dark colored tarry substances and diminishing the yield and purity of the final product to a great extent. On cooling, the mass is now very easily pulverized and decomposition with 1 kg. of crushed ice gives a colorless product, m. p. 203–208°, yield 92% of the theoretical, containing but a trace of inorganic material. For the next step in the synthesis, no further purification is necessary. For analysis a small quantity was crystallized from alcohol, m. p. 219°.

Anal. Calcd. for $C_{10}H_{11}O_2N$: C, 67.76; H, 6.27. Found: C, 67.80; H, 6.51.

1,3-Dimethyl-5-ethoxyoxindole (VII).—To a filtered solution of 88.5 g. of crude 1,3-dimethyl-5-hydroxyoxindole (VI) in 670 cc. of 5% potassium hydroxide, 90 g. of diethyl sulfate was dropped in under stirring, at room temperature. After warming for a half hour on a water-bath, keeping alkaline all the while, with subsequent cooling, the ethoxylated oxindole crystallized out. It was taken up in ether, the aqueous solution also extracted with ether, and the oxindole distilled, b. p. 192–194°, 18 mm.; recrystallized from ether–petroleum ether, m. p. 78°; yield, 70 g.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.21; H, 7.36. Found: C, 70.33; H, 7.60.

1,3-Dimethyl-5-ethoxyoxindolyl-3-acetonitrile (VIII).—This substance was prepared from 78 g. of oxindole, 84 g. of chloroacetonitrile and 5% ethylate from 25 g. sodium in essentially the same manner as already described for the unethoxylated analog.[2] The main portion of the nitrile crystallized from the ether and was filtered off. It boils at 226–228°, 17 mm.; yield 84% of the theoretical of pure crystallized product; recrystallized from ether–petroleum ether, m. p. 109°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.82; H, 6.60. Found: C, 68.87; H, 6.96.

1,3-Dimethyl-3-β-aminoethyl-5-ethoxyoxindole (IX).—The catalytic reduction of the nitrile (VIII) to the amine (IX) likewise was carried out in essentially the same manner as described for the unethoxylated analog in a recent communication.[1] The yield was considerably better, however, 91% of theoretical. The same catalyst was used over and over again and speed of reduction increased with age of catalyst; b. p. 216°, 13 mm.

Anal. Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.69; H, 8.14. Found: C, 67.84; H, 8.23.

The lemon-yellow picrate melted at 184°. The Schiff base, made from equivalent quantities of the amine (IX) and benzaldehyde, melted at 81°, recrystallized from ether–petroleum ether.

Anal. Calcd. for $C_{21}H_{24}O_2N_2$: C, 74.96; H, 7.20. Found: C, 74.76; H, 7.32.

***d,l*-Noreserethole (XI).**—The reduction of amine (IX) to (XI) was effected in similar manner as for desoxynoreseroline[1] from 8 g. of amine, 800 cc. of absolute alcohol and 50 g. of sodium; yield 5.3 g., b. p. 187–192°, 12 mm. The red picrate melted at 182–183°, slightly higher than that recorded by Robinson and his co-workers,[7] and by Hoshino and Kobayashi.[6]

Anal. Calcd. for $C_{20}H_{23}O_8N_5$: C, 52.04; H, 5.03. Found: C, 52.12; H, 5.28.

The picrolonate melted at 221°. The benzoyl derivative made in the usual fashion melted at 108°.

Anal. Calcd. for $C_{21}H_{24}O_2N_2$: C, 74.96; H, 7.20. Found: C, 75.15; H, 7.40.

The free base examined in the Grignard machine showed one active hydrogen and consumed one mole of reagent.

1,3-Dimethyl-3-β-methylaminoethyl-5-ethoxyoxindole (X).—The amine (IX) was monomethylated as already described for the unethoxylated substance,[1] the hydroiodide in this case crystallizing out on addition of ether to the alcoholic solution after hydrolytic cleavage of the methiodide of the Schiff base. From 38.5 g. of amine (IX), 52 g. of crystalline hydroiodide of the N-methylamine was obtained; recrystallized from absolute alcohol, m. p. 188°.

Anal. Calcd. for $C_{15}H_{23}O_2N_2I$: C, 46.13; H, 5.95. Found: C, 46.47; H, 6.38.

From the ether–alcohol filtrate, 2 g. more of amine could be obtained. It boils at 212–213°, 14.5 mm., is appreciably soluble in water, difficultly soluble in ether, and was best extracted with chloroform.

Anal. Calcd. for $C_{15}H_{22}O_2N_2$: C, 68.65; H, 8.47. Found: C, 68.48; H, 8.64.

Its picrate, yellow in color, melted at 192°.

***d,l*-Eserethole (XII).**—Again the procedure for this reduction follows the course laid down for its unethoxylated relative.[1] From 17.5 g. of amine (X), 95 g. of sodium and 1500 cc. of absolute alcohol, 16.2 g. of *d,l*-eserethole was obtained, b. p. 181–183°, 12 mm. Overnight the distillate crystallized in needles almost 1 cm. in length, very soluble in all of the usual organic solvents, even in cold, low-boiling petroleum ether (30°); it had to be recrystallized from ether–petroleum ether gradually cooled down in a mixture of solid carbon dioxide and acetone, m. p. 38°. For analysis these crystals were distilled in high vacuum.

Anal. Calcd. for $C_{15}H_{22}ON_2$: C, 73.11; H, 9.02. Found: C, 73.07; H, 9.15.

The picrate was orange-yellow, m. p. 155°.

Anal. Calcd. for $C_{21}H_{25}O_8N_5$: C, 53.03; H, 5.30. Found: C, 53.17; H, 5.41.

Picrates of Product from *d,l*-Eserethole and Methyl Iodide.—A mixture of 0.65 g. of *d,l*-eserethole, 5 cc. of methyl alcohol and 2 g. of methyl iodide was allowed to stand overnight at room temperature. The excess methyl iodide was removed in vacuum at room temperature, and a solution of 1.5 g. of picric acid in 30 cc. of alcohol added to the residue. The lemon-yellow dipicrate separated and could only be purified by recrystallization from acetone and water to which some picric acid had been added, m. p. 169–171°.

Anal. Calcd. for $C_{29}H_{32}O_{15}N_8$: C, 47.52; H, 4.41. Found: C, 47.15; H, 4.37.

On attempted recrystallization from pure alcohol, the yellow dipicrate lost picric acid, passing over into the red monopicrate (XVI), m. p. 194° with decomposition.

Anal. Calcd. for $C_{23}H_{29}O_8N_5$: C, 54.8; H, 5.8. Found: C, 54.5; H, 6.2.

Physostigmole Ethyl Ether from *d,l*-Eserethole.—The methyl iodide addition product prepared as indicated above was subjected to distillation in high vacuum. 1,3-Dimethyl-5-ethoxyindole sublimed in beautiful colorless crystals, and was identical with the same product secured in like fashion from *l*-eserethole, m. p. 85°; mixed melting point showed no depression.

Catalytic Reduction of *d,l*-Eserethole.—The procedure was the same as employed for desoxyeseroline.[1] Also like the reduction product of desoxyeseroline, the 1,3-dimethyl-3-β-methylaminoethyl-5-ethoxy-2,3-dihydroindole gave a yellow dipicrate, m. p. 166°, and an orange-red monopicrate, m. p. 140°. The monopicrate was analyzed.

Anal. Calcd. for $C_{21}H_{27}O_8N_5$: C, 52.81; H, 5.7. Found: C, 52.64; H, 5.78.

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Summary

1. *d,l*-Eserethole has been synthesized it is believed for the first time.

2. The "*d,l*-eserethole" described by other workers in this field is thought to have another constitution than that ascribed to it.

3. The synthesis of the alkaloid physostigmine is hereby completed except for resolution of *d,l*-eserethole into the optically active antipodes.

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(7) King Liguori and Robinson, *J. Chem. Soc.*, 1416 (1934).