[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DEPAUW UNIVERSITY]

# Studies in the Indole Series. V. The Complete Synthesis of Physostigmine (Eserine)

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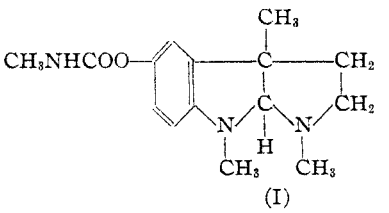
Physostigmine (I), the principal alkaloid of the Calabar bean, and long used as a drug, has, since its isolation by Jobst and Hesse[1] seventy years ago, been the subject of numerous investigations. The determination of its constitution was rendered particularly difficult since its peculiar chemical structure found no analog in other plant products of known composition.



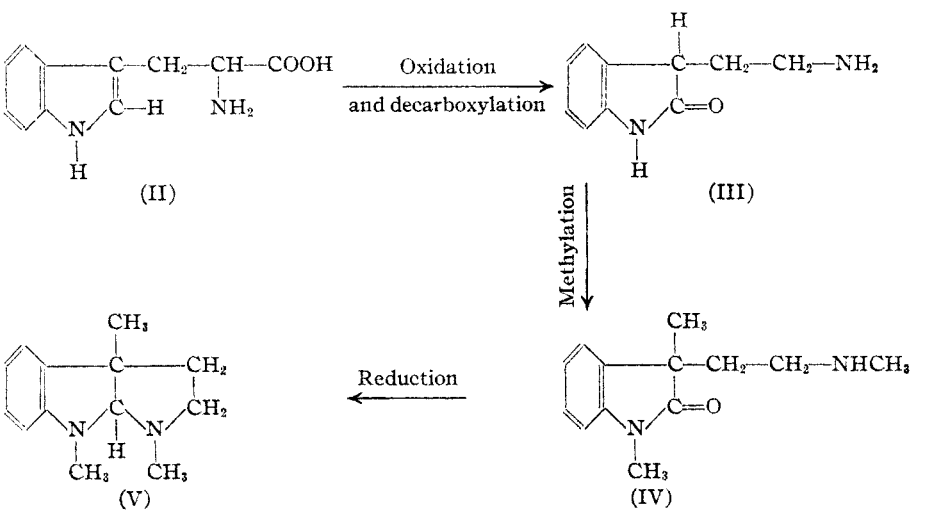
(I)

Thus it stood out as the only known naturally occurring derivative of 5-hydroxyindole until quite recently when Bufotenine, one of the toad poisons, was shown through synthesis[2] to be 5-hydroxyindolylethyldimethylamine. The most convincing work on the constitution of eserine, that from Barger's laboratory,[3] left one important gap unfilled, namely, the synthesis of oxindole derivatives secured as degradation products.

In the fall of 1931 we began experiments on the preparation of certain homoamines and homoacids; our interest centered particularly on these derivatives in the oxindole series.[4] The first objective was oxytryptamine (III), for it seemed to us at that time that the basic structure for physostigmine suggested to Barger and his coworkers by Robinson[5] might be built up by the plant from oxytryptophan in a manner indicated by the formulas (II) ⟶ (V).

Indeed such an hypothesis received much support in Kotake's work[6] on the metabolism of tryptophane in the animal organism, wherein it is suggested that in its transformation to kynurenine, tryptophan (II) is oxidized to oxytryptophan. Many years ago Abderhalden[7] had expressed the belief that oxytryptophan was present along with tryptophan in the amino acids isolated from casein.

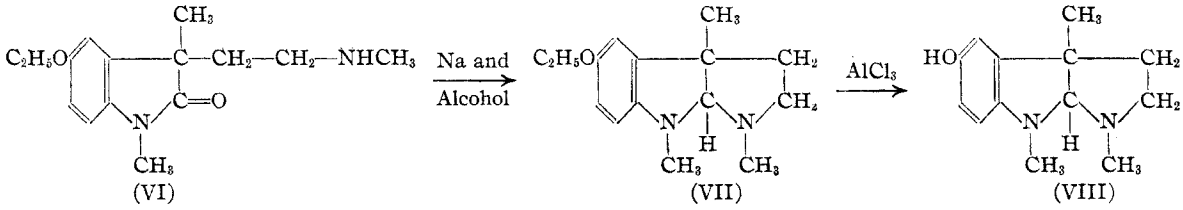
Shortly after promising experiments in the direction of the preparation of the amine (III) were under way, and we were convinced of the probably successful outcome of the methylation indicated in (III) ⟶ (IV)—details of which will appear in a separate communication—the work had to be interrupted and could only be resumed recently. In the meantime the first of a series of ten papers dealing with the synthesis of physostigmine, by Robinson and his collabora-




(II) (III) (IV) (V)

(1) Jobst and Hesse, *Ann.*, **129**, 115 (1864).
(2) Wieland, Konz and Mittasch, *ibid.*, **513**, 1 (1934).
(3) Stedman and Barger, *J. Chem. Soc.*, 247 (1925).
(4) Julian and Sturgis, partly reported at the fall meeting of the American Chemical Society, Chicago, 1933.
(5) Stedman and Barger, *J. Chem. Soc.*, 248 (1925).
(6) Kotake, *Z. physiol. Chem.*, **195**, 139 (1931).
(7) Abderhalden and Kempe, *ibid.*, **52**, 212 (1907).

tors[8] appeared and seemingly proved convincingly that the reduction suggested in formulas (IV) ⟶ (V) could not be realized in practice.[9] Our experiments, nevertheless, were continued and led to the discovery that not only was methylation of (III) in the 3-position of the oxindole nucleus feasible, owing to the decided acidity of the hydrogen atom in that position, but that also the reduction indicated in (IV) ⟶ (V) proceeded in more than 80% yield with sodium and alcohol.[10] This led to the successful synthesis of *d,l*-eserethole (VII) by reduction of 1,3-dimethyl-5-ethoxy-3-β-dimethylaminoethyloxindole (VI)[8]




(VI) (VII) (VIII)

To our surprise, our product (VII) exhibited entirely different properties from those of a compound synthesized by Robinson and his coworkers and called *d,l*-eserethole. Likewise were all derivatives different. Inasmuch as our inactive material, subjected to characteristic reactions of eserethole of natural origin, yielded perfectly analogous results, we expressed the belief that our product was the real *d,l*-eserethole and that that of the English chemists must be assigned another constitution. This is now proved conclusively by synthesis of *l*-eserethole, identical with the product of natural origin.

After some attempts to resolve *d,l*-eserethole into its optical antipodes with *d*-camphorsulfonic and *d*-tartaric acids, the only reagents at our disposal, had failed to yield satisfactory results, resolution of the amine (VI) was attempted. By successive action of *d*-camphorsulfonic acid and *d*-tartaric acid, this amine was resolved into its optical isomers in excellent yield. The *d*-amine-*d*-camphorsulfonate first separated and the mother liquors yielded with *d*-tartaric acid the *l*-amine-*d*-hydrogen tartrate. The free *l*-base (VI) recovered from the latter, yielded on reduction with sodium and alcohol *l*-eserethole in excellent quantity. No trace of racemization could be detected. Its picrate and tartrate were identical with those of eserethole of natural origin.

(8) For references see Julian and Pikl, THIS JOURNAL, **57**, 563 (1935).

(9) See particularly King and Robinson, *J. Chem. Soc.*, 1434 (1932).

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

Conversion of our synthetic *l*-eserethole into *l*-eseroline (VIII) was effected smoothly by gently boiling its petroleum ether solution in which anhydrous aluminum chloride was suspended. The *l*-eseroline (VIII) obtained in this way was likewise identical in every respect with that of natural origin. Since Polonovski and Nitzberg[11] have described conversion of *l*-eseroline into *l*-physostigmine by treatment of the former with methyl isocyanate, our synthesis represents a complete synthesis of the alkaloid physostigmine.[12] Moreover, we believe that the route we have taken presents in its essential stages the phytochemical mechanism for the production of this substance.

Of interest for the cheap production of *d,l*-eserethole in any desired quantity, is a further simplification of our synthesis. Treatment of the sodium salt of 1,3-dimethyl-5-ethoxyoxindole with ethylene dibromide and subsequent heating with methyl alcoholic methylamine at 100° leads in good yield to the amine (VI).

## Experimental Part

**Resolution of 1,3-Dimethyl-5-ethoxyoxindolylethylmethylamine (VI).**—In a preliminary experiment equimolecular quantities of the amine (VI) and *d*-camphorsulfonic acid were brought together in acetone diluted with ether. There soon separated bundles of needles of a salt melting at 78°, which yielded with picric acid the picrate of racemic amine, and was therefore in all probability the *d*-camphorsulfonate of racemic amine. Along with the needles there separated, however, on several days of standing in a cool place, small, ball-like aggregates of crystals, much less soluble in acetone than the 78° compound. After several recrystallizations from acetone, they melted at 160°. Determination of rotation indicated that these represented *d*-amine-*d*-camphorsulfonate. Accordingly 18.2 g. of the amine (VI) was dissolved in 100 cc. of acetone, and 16.17 g. of *d*-camphorsulfonic acid was added. The solution was seeded with some pure 160° compound and allowed to stand. Soon the *d*-amine-*d*-camphorsulfonate separated. It was taken up in a large amount of boiling acetone, from which on concentration,

(11) Polonovski and Nitzberg, *Bull. soc. chim.*, [iv] **19**, 33 (1916).

(12) Since this paper was submitted, a request has come to us for a sample of *d,l*-pphsostigmine for pharmacological experiments. In connection with its preparation (to be described elsewhere), we have repeated the reaction of Polonovski and Nitzberg on our synthetic *l*-eseroline and secured *l*-physostigmine, identical in all respects with the natural drug. The title of this communication is therefore completely justified.

17.1 g. of salt, 140–150° separated. Recrystallized twice more from acetone, it melted at 160°. Ten grams of highly pure salt was obtained.

*Anal.* Calcd. for $C_{25}H_{38}O_6N_2S$: C, 60.73; H, 7.75. Found: C, 61.08; H, 7.75.

The combined mother liquors from the first separation and the first recrystallization out of acetone were basified and 8.62 g. of impure *l*-amine recovered on distillation. This was taken up in 10 cc. of methyl alcohol and treated with a solution of 4.92 g. of *d*-tartaric acid in 10 cc. of methyl alcohol. The solution was diluted with 200 cc. of acetone and sufficient ether added to produce slight turbidity. On standing 8.0 g. of *l*-amine-*d*-hydrogen tartrate, m. p. 175–176°, separated. The melting point was not altered on recrystallization. From the mother liquors, 3.9 g. more of *l*-amine tartrate could be obtained, after removal of *d*-amine as *d*-camphorsulfonate (2.2 g.).

*Anal.* Calcd. for $C_{19}H_{28}O_8N_2$: C, 55.31; H, 6.84. Found: C, 55.55; H, 7.09.

The *l*-amine (VI) was recovered from the tartrate, yield 7.6 g., 83% of the theoretical based on original quantity of racemic amine employed. Determination of rotation gave the results:[13]

For *l*-amine: $[\alpha]^{28}D$ −30.1 ± 0.5° (in alcohol)
For *d*-amine: $[\alpha]^{28}D$ + 30.2 ± 0.5° (in alcohol)

The picrates of both *d*- and *l*-amine melted at 175° and mixed melting point of equal quantities was 192°, the value recorded for the racemic amine picrate.[8]

**Reduction of *l*-Amine (VI) to *l*-Eserethole (VII).**—This reduction was carried out in exactly the same manner as described for *d,l*-eserethole:[8] 6.8 g. of *l*-1,3-dimethyl-5-ethoxyoxindolylethyl-methylamine yielded 5.1 g. of *l*-eserethole. The picrate melted at 135° and showed with the picrate of eserethole of natural origin no depression.

*Anal.* Calcd. for $C_{21}H_{25}O_8N_5$: C, 53.03; H, 5.30. Found: C, 52.86; H, 5.58.

The *d*-hydrogen tartrate of our synthetic eserethole melted at 168° and gave with the same salt from natural eserethole no depression of melting point.

Determination of rotation of *l*-eserethole gave $[\alpha]^{28}D$ −81.6° ± 0.5°. *d*-Eserethole was likewise prepared in similar manner. Mixtures of equal quantities of the picrates of *d*- and *l*-eserethole melted at 155°, value recorded for the racemic picrate.[8]

**Conversion of *l*-Eserethole into *l*-Eseroline (VIII).**—2.6 grams of synthetic *l*-eserethole was dissolved in 20 cc. of petroleum ether (b. p. 70–77°) and 4 g. of anhydrous aluminum chloride added. The mixture was heated on the water-bath overnight. At first a gum formed on the bottom of the flask, which after some time becomes a hard crystalline mass. The petroleum ether was poured off, the crystalline mass broken up and decomposed with ice. From the solution, on rendering alkaline with sodium bicarbonate, the base was recovered. Working at low temperature, the solution barely turns red, even after several shakings, provided sodium bicarbonate is used. On evaporation of the ether, the base was distilled in high vacuum; temperature of air-bath 160°; yield 2.1 g.; recrystallized from ether–petroleum ether, m. p. 128°; mixed with *l*-eseroline of natural origin it showed no depression of melting point. Likewise were the benzoates of synthetic and natural eseroline identical, m. p. 156°. *d*-Escroline was prepared in exactly the same fashion, m. p. 128°. Mixed with *l*-eseroline in equal quantities, the melting point was 139°.

*d,l*-Eseroline was obtained from *d,l*-eserethole in the same manner as described for the active antipodes. It melted at 139°.

*Anal.* Calcd. for $C_{13}H_{18}ON_2$: C, 71.52; H, 8.30. Found: C, 71.36; H, 8.36.

**Preparation of the Amine (VI) from 1,3-Dimethyl-5-ethoxyoxindole and Ethylene Dibromide.**—The reaction between the sodium salt of the oxindole and ethylene dibromide was carried out in similar fashion as described earlier for the unethoxylated analog.[10] The bromide boiled at 175–185°, 0.5 mm.; 30 grams of it was sealed in with excess of 35% methyl alcoholic methylamine and allowed to stand overnight, then heated at 100° for two hours. Excess alcohol and methylamine were distilled off, the residue taken up in 3% hydrochloric acid and benzene, and separated in this manner from less basic material. The amine (VI) obtained in the usual manner was identical in all respects with that already described.

In acknowledging a generous grant from the Rosenwald Fund, the senior author respectfully dedicates this finished project to the memory of Julius Rosenwald, who has made possible innumerable cultural contributions on the part of young negroes to his country's civilization. And he is none the less grateful to Dean W. M. Blanchard, Senior Professor of Chemistry, without whose courageous support this work would have been impossible.

## Summary

1. By successive action of *d*-camphorsulfonic acid and *d*-tartaric acid, 1,3-dimethyl-5-ethoxyoxindolylethyl-methylamine has been resolved into its optical antipodes.

2. Reduction of the *l*-modification of this amine with sodium and alcohol yielded *l*-eserethole, identical with eserethole of natural origin.

3. Heating of *l*-eserethole with anhydrous aluminium chloride at 70–77° resulted in formation of *l*-eseroline, identical with the product from natural sources.

4. The first and complete synthesis of the alkaloid physostigmine is herewith recorded.

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(13) Unfortunately our polarimeter could not be relied upon for the most accurate results. Calibration against known substances indicated the error recorded above.