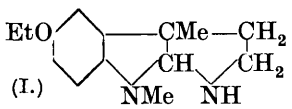
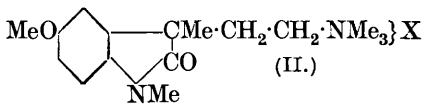
191. *Experiments on the Synthesis of Physostigmine (Eserine). Part VI. A Synthesis of* dl-*Esermethole Methopicrate.*

By FREDERICK ERNEST KING and ROBERT ROBINSON.

RECENTLY (this vol., pp. 298—336) two distinct syntheses of eserine-like bases have been described. Ring closure of the requisite indolenine (*loc. cit.*, Part II, p. 304) led to a small quantity of a base believed to be *dl*-noreserethole (I); on the other hand, the resolution of a synthetic indolinone (II) to yield a degradation product of physostigmine (see Part V, p. 326) confirmed the constitution of the alkaloid and also indicated a second route for its synthesis.

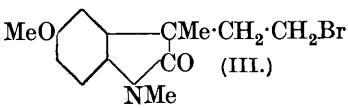


(I.)

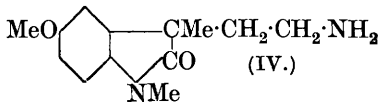


(II.)

The production of the tricyclic system (I), the basis of the eserine structure, from the secondary base related to (II) is theoretically feasible after reduction to the indoleninium salt, a transformation which might be difficult to effect in practice. With a primary amine of this type, however, apart from such a procedure, a direct ring



(III.)

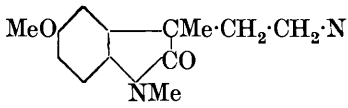


(IV.)

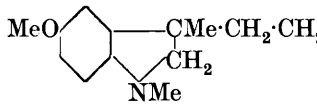
closure appears practicable; a further quantity of the methoxyindolinone bromide (III), an intermediate in the earlier synthesis

(*loc. cit.*, p. 333), was therefore prepared with a view to its conversion into 5-*methoxy*-1 : 3-*dimethyl*-3-β-*aminoethyl*-2-*indolinone* (IV).

When the compound (III) was heated under pressure with an excess of saturated alcoholic ammonia, a small amount of a crystalline solid was produced, but it proved to be a secondary base formed from two molecules of the indolinone bromide and one of ammonia. The indolinone bromide and potassium phthalimide reacted with formation of a *phthalimidoethylindolinone* (V), from which the liquid amine (IV) was derived by combination with hydrazine hydrate and subsequent hydrolysis. The dimethyl-methiodide and the methopicrate of this base were identical with the respective salts of *dl*-dehydroesermetholemethine (*loc. cit.*, p. 333); in addition a crystalline *picrolonate* and a *picrate* have been prepared.



(V.)

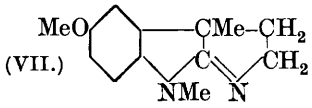


(VI.)

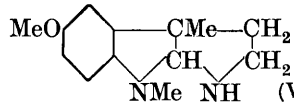
From an attempt to prepare *dl*-dinoresermetholemethine by electrolytic reduction, the compound (IV) was recovered unchanged, and the action of sodium in boiling amyl alcohol resulted in complete reduction of the carbonyl group to furnish 5-*methoxy*-1 : 3-*dimethyl*-3-β-*aminoethylindoline* (*dl*-dihydronoresermethole) (VI), an oily base which was characterised by means of a crystalline *picrolonate* and a *picrate*. The more remote alternative, that the product was *dl*-noresermethole (VIII), formed by reduction of the indolinone (IV) to a carbinol with subsequent elimination of water, was rejected after comparison of the foregoing products with authentic specimens of *dl*-noresermethole and its picrolonate. In view of the more successful outcome of attempts to promote direct ring closure of the indolinone (IV) to the base (VII), the reduction experiments were discontinued.

The substance (VII) being essentially an amidine, efforts were made to prepare it by Hofmann's method, but boiling phosphorus trichloride was without action on the amine (IV). The latter was dehydrated, however, by phosphoric oxide in boiling xylene (compare Sen and Ray, J., 1926, 646): the uncrystallisable product was not homogeneous, but was, indeed, mainly the amidine (VII). When it was treated with boiling alcoholic picrolonic acid, the primary base (IV) was regenerated and good yields of the picrolonate were thus isolated. The methiodide, which was amorphous, did

not absorb hydrogen, but the crude amidine, when catalytically reduced in a non-hydroxylic solvent, very slowly absorbed approximately 80% of the theoretical quantity of hydrogen, yielding crude *noresermethole* (VIII). This formed a crystalline *picrolonate*, but the methiodide and methosulphate were syrups which reacted with picric acid to form a crystalline quaternary salt, dl-*esermethole methopicrate* (IX), closely resembling the natural salt in properties (*loc. cit.*, p. 334).

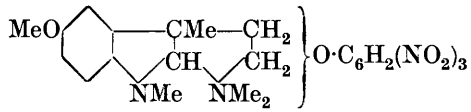


(VII.)



(VIII.)

(IX.)



An attempt to resolve this salt is in progress.

EXPERIMENTAL

Di-(5-methoxy-1 : 3-dimethyl-2-indolinone-3-β-ethyl)amine.—The methoxy-bromide (III) (4 g.) was heated under pressure at 150° for 3 hours with a large excess (20 c.c.) of saturated methyl-alcoholic ammonia. The oil which remained after evaporation of the alcohol was shaken with dilute hydrochloric acid, and the sticky residue removed by ether; on addition of ammonia to the aqueous solution, an oil (2·5 g.) was precipitated, and this was isolated by repeated extraction with ether and distilled in a high vacuum, giving a straw-coloured resin (1·7 g.), b. p. 250—260°/1 mm. It dissolved freely in organic solvents except light petroleum and eventually crystallised from acetone–light petroleum in tiny fan-shaped clusters of colourless needles, the pure substance (0·25 g.) having m. p. 166—168° (Found: C, 68·9; H, 7·5; N, 9·5. $C_{26}H_{33}O_4N_3$ requires C, 69·2; H, 7·3; N, 9·3%). Its methiodide was easily produced and crystallised from boiling alcohol in pale cream, voluminous, tiny needles, m. p. 122—125°.

5-Methoxy-1 : 3-dimethyl-3-β-phthalimidoethyl-2-indolinone (V).—The bromide (III) (10 g.) and potassium phthalimide (10 g.) were heated together (oil-bath at 170°) for an hour; boiling water was then added to extract the potassium salts. The plastic amorphous residue of the *phthalimido-base* crystallised from *iso*amyl alcohol in bright yellow, thick, rectangular plates (9—9·5 g.), m. p. 108—109° after being washed with light petroleum (Found: C, 69·3; H, 5·5; N, 8·0. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·7%).

5-Methoxy-1 : 3-dimethyl-3-β-aminoethyl-2-indolinone (IV).—An

alcoholic solution (25 c.c.) of the phthalimido-base (9 g.), heated under reflux on a steam-bath with hydrazine hydrate (1·5 g.), set to a pasty mass after 10—15 minutes; water (30 c.c.) and concentrated hydrochloric acid (30 c.c.) were then added, the mixture refluxed for 30 minutes, the alcohol removed under diminished pressure, and after several hours the phthalhydrazide * (4 g.) collected. Excess of sodium hydroxide added to the filtrate liberated the primary amine, which was isolated by means of chloroform and distilled as a colourless syrup (4·8 g.), b. p. 160—165°/1 mm. This, warmed with methyl iodide in ethereal solution, gave a methiodide, which crystallised from alcohol in long rectangular plates, m. p. 156—158° (dried in a vacuum), unaffected by admixture with a specimen of the quaternary salt prepared from the corresponding tertiary base (II). The methopicrates were likewise identical, having m. p. 193—195°, either alone or in mixture. The *picrolonate* readily crystallised from alcoholic solutions of the two components in flocks of lemon-yellow needles, m. p. 250° (decomp.) (Found: C, 55·8; H, 5·5; N, 16·8. $C_{13}H_{18}O_2N_2$,$C_{10}H_8O_5N_4$ requires C, 55·4; H, 5·2; N, 16·9%), very sparingly soluble in alcohol but freely in acetone. The *picrate* crystallised from a small volume of methyl alcohol in stout, pointed, bright yellow prisms, softening at 80—82°. After drying in a vacuum at room temperature, the crystals became opaque and then had m. p. 161—162° (Found for the dried specimen: C, 49·5; H, 4·5; N, 15·0. $C_{13}H_{18}O_2N_2$,$C_6H_3O_7N_3$ requires C, 49·2; H, 4·5; N, 15·1%).

5-*Methoxy*-1 : 3-*dimethyl*-3-β-*aminoethylindoline* (VI).—The indolinone base (1·6 g.) in 25% sulphuric acid (100 g.) was submitted to electrolytic reduction at a lead cathode for 3½ hours by means of a current of 0·15 amp./cm.^{2}. The solution, basified with ammonia after elimination of most of the acid as barium sulphate, gave an oil (1·5 g., isolated by means of chloroform), the picrolonate of which, m. p. 248—250° (decomp.) after the first crystallisation, was identical (mixed m. p.) with that of the starting material.

The base (1·5 g.) in boiling *iso*amyl alcohol (15 g.) was reduced with sodium (0·8 g.), added during 1 hour. Water (15 c.c.) and then concentrated hydrochloric acid (6—7 c.c.) were added to the cold solution, the alcoholic layer was washed with very dilute acid, and the combined aqueous solutions were basified with ammonia. A dried chloroform extract of the turbid liquid was evaporated, leaving a red-brown oil (1·3 g.) which gave, in alcoholic solution, an impure picrolonate, m. p. 200—205° (decomp.). The crude *base* (1 g.) was distilled, and an almost colourless oil (0·79 g.) obtained, b. p. 113—116°/1 mm. (oil-bath at 150°) (Found: C, 70·5; H,

* An attempt to nitrate phthalhydrazide gave a quantitative yield of phthalic acid.

8·2; N, 12·3; MeO, 13·9. $C_{13}H_{20}ON_2$ requires C, 70·9; H, 9·1; N, 12·7; MeO, 14·1%). The *picrolonate* prepared from the purified indoline had m. p. 214—215° (decomp.). After three crystallisations from alcohol, in which it was moderately easily soluble, the salt was obtained in light brown, tiny, crystalline aggregates, m. p. 220° (decomp.) (rapidly heated) (Found: C, 57·0; H, 5·8; N, 17·4. $C_{13}H_{20}ON_2,C_{10}H_8O_5N_4$ requires C, 57·4; H, 5·4; N, 17·4%). With alcoholic picric acid the base yielded a deep red *picrate*, crystallising from methyl alcohol in long rhombic plates, m. p. 159° (Found: C, 51·2; H, 4·8; N, 15·6. $C_{13}H_{20}ON_2,C_6H_3O_7N_3$ requires C, 50·8; H, 5·1; N, 15·6%).

Product containing Dehydronoresermethole (VII).—A solution of the amine (IV) (5·5 g.) in dry xylene (20 c.c.) was heated under reflux with phosphoric oxide (oil-bath at 170°) for 6 hours. The xylene was then decanted, and the solid residue dissolved in ice-water, shaken with ether, and basified with sodium hydroxide. The precipitated oil, isolated and dried in chloroform, distilled as a straw-coloured gum (4·2 g.), b. p. *ca.* 145—155°/1 mm. (Found: C, 69·9; H, 7·3; N, 12·4. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%. $C_{13}H_{18}O_2N_2$ requires C, 66·6; H, 7·7; N, 12·0%). This base gave with methyl iodide a white amorphous powder, readily soluble in alcohol, acetone, and chloroform. With hot alcoholic picrolonic acid, a lemon-yellow picrolonate was obtained in 70—75% yield, m. p. 250° (decomp.) alone or mixed with the picrolonate of the parent base, 5-methoxy-1:3-dimethyl-3-β-aminoethyl-2-indolinone.

dl-*Noresermethole* (VIII).—The crude dehydronoresermethole (VII) (1 g.) in ethyl acetate (10 c.c.), in a suspension of platinum (produced from 0·1 g. of platinum oxide) in the same solvent (10 c.c.) absorbed only 10 c.c. of hydrogen after 16 hours. The experiment was repeated with a sample of catalyst reduced in the presence of the base: hydrogen was steadily absorbed (5 c.c./hour), reduction ceasing when 83 c.c. had disappeared (theory requires 103·7 c.c.). The filtered solution was warmed with alcoholic picrolonic acid, and the yellow crystalline *picrolonate* of *dl*-noresermethole precipitated (1·9 g.) was purified by extraction with alcohol in a Soxhlet apparatus; it had m. p. 227° (decomp.), was very sparingly soluble in boiling alcohol, acetone, and chloroform, and crystallised in yellow diamond-shaped plates (Found: C, 56·4, 55·9; H, 5·0, 5·5; N, 17·1, 16·7. $C_{13}H_{18}ON_2,C_{10}H_8O_5N_4,\frac{1}{2}H_2O$ requires C, 56·4; H, 5·5; N, 17·1%). The picrolonate (1·9 g.) was suspended in methyl alcohol (10 c.c.) and warmed with concentrated hydrochloric acid (2 c.c.). After 12 hours' keeping in the ice-chest, the picrolonic acid (1 g.) was collected, and the filtrate and aqueous washings were warmed to

50° under diminished pressure to eliminate alcohol. A further very small precipitate was then removed, and the solution basified with ammonia. By chloroform extraction a reddish liquid (0·86 g.) was recovered which distilled in a high vacuum, giving an almost colourless oil (0·76 g.), b. p. 130—132° (bath temperature, 170°) (Found: C, 70·1; * H, 8·2; N, 12·6. $C_{13}H_{18}ON_2$ requires C, 71·6; H, 8·2; N, 12·8%). The methosulphate, prepared by heating under reflux a benzene solution of the base and excess of methyl sulphate, and the methiodide, from a concentrated alcoholic solution of the base and methyl iodide, separated as almost colourless, viscous syrups. With alcoholic picric acid, they each formed a reddish-yellow gum which crystallised from alcohol (charcoal) in tiny red leaflets. The *methopicrate* (IX) dissolved in alcohol to a light yellow solution and after three crystallisations was obtained in bright red, irregular, hexagonal leaflets, m. p. 183—184° (Found: C, 53·0; H, 5·3; N, 15·0. $C_{21}H_{25}O_8N_5$ requires C, 53·1; H, 5·3; N, 14·7%). At the melting point the crystals shrink, then wet the sides of the capillary tube, and subsequently quickly darken and decompose. Therefore we consider that decomposition follows, and does not precede, fusion.

A mixture of this *dl*-picrate with the natural active picrate (*loc. cit.*), m. p. 194°, has m. p. 183—184° whether the proportion is 1 : 1 or 1 : 3; there is certainly no depression of the m. p. of the inactive picrate.

The methopicrate which was the subject of the synthesis described in Part V (*loc. cit.*) is available in active and inactive forms, m. p. 132—133° and 193—195°, respectively, and in this case identity of constitution is established.

All mixtures of these salts at least soften at the lower temperature (132°), and not below. We do not put forward these observations as proof of the identity of our new methopicrate with the salt of natural origin, but, considering the great resemblance of the active and inactive salts in their general properties, we are of the opinion that the title of this communication will be justified in the sequel.

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* Compare Part II, this vol., p. 304, for a discussion of similar low figures for carbon content.