43. *Experiments on the Synthesis of Physostigmine (Eserine). Part III. Synthesis of Desethoxydehydroeseretholemethine.*

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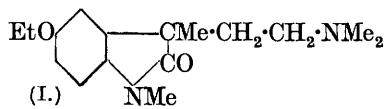
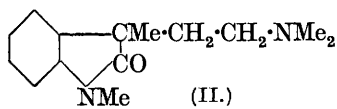
BY the oxidation of eseretholemethine, Stedman and Barger (J., 1925, **127**, 247) obtained dehydroeseretholemethine (I) : the synthesis of this substance would obviously be of interest, since the quaternary carbon group of physostigmine occurs unmodified in the derivative. The present communication describes the method which has been devised for the preparation of a simpler base, which, however, is closely related to (I), being, in fact, its desethoxy-derivative (II).



(I.)

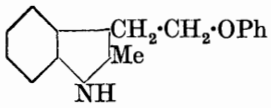


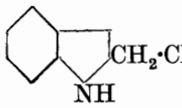
(II.)

γ-Phenoxypropylacetone was obtained by an application of the acetoacetic ester synthesis, and its phenylhydrazone, heated with alcoholic sulphuric acid, furnished an *indole* derivative (III or IV).

The colour reactions do not indicate the presence of a free position in the pyrrole nucleus, so (III) is probably correct; a further argument is that, in the later stages, (IV) would lead to products with

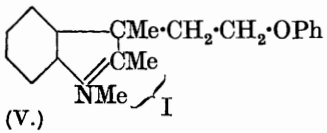
an additional methylene group, and this is not indicated by the analyses.

(III.) 

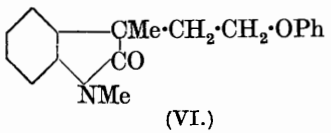


(IV.)

The indole derivative (III) was heated with methyl iodide and methyl alcohol at 120° in an autoclave and 1 : 2 : 3-*trimethyl*-3-β-*phenoxyethylindoleninium iodide* (V) was obtained. The related base was oxidised by potassium permanganate in acetone solution with formation of the syrupy *indolinone* (VI), of which a crystalline *dinitro*-derivative was prepared.



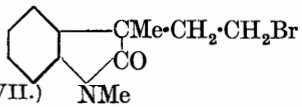
(V.)



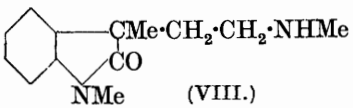
(VI.)

The action of fuming hydrobromic acid on (VI) furnishes the *bromoethyl* derivative (VII), and substituted amino-groups can be introduced into the side chain by treatment of the bromide with amines; for instance, the action of dimethylamine yields (II), and methylamine the base (VIII).

We are of the opinion that it should be possible to effect the ring closure of substances of type (VIII), but this has not yet been investigated.



(VII.)



(VIII.)

EXPERIMENTAL.

γ-Phenoxypropylacetone.—Powell and Adams (*J. Amer. Chem. Soc.*, 1920, **42**, 651) mentioned this ketone and stated that a description would follow, but we have been unable to find further details in the literature.

Ethyl acetoacetate (108 g.) and then β-phenoxyethyl bromide (182 g.; compare "Organic Syntheses," IX, 73) were added to a solution of sodium ethoxide (19 g. of sodium in 420 c.c. of alcohol), and the mixture refluxed for 12 hours. The crude product was isolated and agitated with aqueous sodium hydroxide (700 c.c. of 5%) for 5 hours; it then passed almost completely into solution. The aqueous layer was separated, carefully mixed with sulphuric acid (100 g. of 50%), and distilled in steam. The *ketone* separated from the distillate in colourless leaflets (50 g.), m. p. 51—53°. The

substance crystallised from light petroleum in thin colourless plates, m. p. 55° (Found: C, 73·8; H, 7·9. $C_{11}H_{14}O_2$ requires C, 74·2; H, 7·9%).

The *semicarbazone* separated from alcohol in colourless plates, m. p. 140° (Found: N, 18·2. $C_{12}H_{17}O_2N_3$ requires N, 17·9%).

2-*Methyl*-3-β-*phenoxyethylindole* (III).—The phenylhydrazone of γ-phenoxypropylacetone was not isolated. The ketone (45 g.), phenylhydrazine (30 g.), and alcohol (100 c.c.) were refluxed for 1 hour. Sulphuric acid (18 g.) was gradually added with cooling, and the mixture heated for 2 hours. Considerable darkening occurred and, on cooling, the solution deposited ammonium sulphate. Addition of water caused separation of a reddish oil, which was taken up with ether and washed with aqueous sodium bicarbonate. After drying and removal of the ether, the residue was distilled as a thick yellow oil (40 g.), b. p. 225/1 mm. This solidified on standing and then crystallised from alcohol in stout colourless needles, m. p. 71° (Found: C, 81·0; H, 6·6; N, 5·7. $C_{17}H_{17}ON$ requires C, 81·3; H, 6·8; N, 5·6%), moderately readily soluble in most organic solvents. When the *indole* is warmed with *p*-dimethylaminobenzaldehyde in aqueous-alchoolic hydrochloric acid solution, a fine blue colour is produced, which disappears on cooling: this change may be repeated as often as desired.

1 : 2 : 3-*Trimethyl*-3-β-*phenoxyethylindoleninium Iodide* (V).—2-Methyl-3-β-phenoxyethylindole (50 g.) was heated in an autoclave with methyl iodide (250 g.) and methyl alcohol (100 g.) at 120° for 8 hours. The product was a light yellow solid (70 g.) which after one crystallisation from alcohol had m. p. 221—223° (decomp.) (Found: C, 55·9; H, 5·6; N, 3·4; I, 29·9. $C_{19}H_{22}ONI$ requires C, 56·0; H, 5·4; N, 3·4; I, 31·2%). This *salt* is moderately readily soluble in warm alcohol and acetone, sparingly soluble in ethyl acetate, and insoluble in benzene and ether. A deep red colour is produced when it is heated with diphenylformamidine in acetic anhydride solution.

1 : 3-*Dimethyl*-3-β-*phenoxyethyl*-2-*indolinone* (VI).—1 : 3-Dimethyl-3-β-phenoxyethyl-2-methyleneindoline was obtained from the iodide by interaction with 20% sodium hydroxide solution. A mixture of the iodide (66 g.), ether (100 c.c.), and sodium hydroxide (300 c.c. of 20%) was shaken mechanically for 7 hours and the reddish ethereal layer was separated and washed with water. Removal of the solvent gave a thick reddish oil (45 g.); this was not purified, but converted into the indolinone by oxidation.

The base (45 g.) was dissolved in acetone (300 c.c.) and cooled in ice-water; finely powdered potassium permanganate (90 g.) was then gradually added with stirring. After 9 hours the solution was kept

for 12 hours at room temperature, the excess of permanganate decomposed with methyl alcohol, and the solvents evaporated. The residue, purified by solution in ether, was a yellow oil (33 g.), which was obtained as an almost colourless syrup by distillation in a high vacuum (b. p. 190—195°/1 mm.) (Found : C, 76·5; H, 6·8; N, 5·5. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%).

A *dinitro*-derivative of this *indolinone* was obtained by dissolving the substance in nitric acid (*d* 1·42) at 0°, and allowing the temperature to remain at 20° for 1 hour. The dark brown solution, when poured into water, deposited a greenish solid, from which, by extraction with light petroleum in a Soxhlet apparatus and subsequent crystallisation from alcohol, the dinitro-compound was obtained in light yellow, hexagonal plates, m. p. 169—171° (Found : C, 58·3; H, 4·8; N, 11·4. $C_{18}H_{17}O_6N_3$ requires C, 58·2; H, 4·6; N, 11·3%). Doubtless the nitro-groups are in the *p*-positions to nitrogen and oxygen.

1 : 3-*Dimethyl*-3-β-*bromoethyl*-2-*indolinone* (VII).—By heating the phenoxy-indolinone with hydrobromic acid (*d* 1·7) for 12 hours under reflux, replacement of the phenoxy-group by bromine was effected. The product was a dark-coloured oil, the solution of which in ether was washed with sodium hydroxide in order to remove phenol. The *bromide* was a thick syrup, which did not crystallise, b. p. 155—160°/1 mm. (Found : C, 55·6; H, 5·3; N, 5·0; Br, 27·2. $C_{12}H_{14}ONBr$ requires C, 53·7; H, 5·2; N, 5·3; Br, 29·9%). These figures indicate that the bromide contained a little of the phenoxy-compound, as shown by the high carbon and low bromine contents. From the phenoxy-compound (20 g.), 13 g. of redistilled bromide were obtained. The residues consisted of unchanged material, which was again treated with hydrobromic acid.

1 : 3-*Dimethyl*-3-β-*dimethylaminoethyl*-2-*indolinone* (II).—A clear solution of the bromide (3·8 g.) in methyl alcohol (10 c.c.) was heated together with aqueous dimethylamine (33% w/v) (14 c.c.) in a sealed tube at 170—180° for 10 hours. The methyl alcohol was evaporated, and the residue acidified with dilute hydrochloric acid. A small quantity (0·4 g.) of insoluble oil was taken up with ether, and the clear aqueous layer basified. The ethereal extract of the precipitated oil was dried and evaporated, leaving a colourless oily base (2·3 g.). Addition of methyl iodide gave a semi-solid methiodide, which was difficult to purify. The filtered aqueous solution of this substance was mixed with aqueous picric acid, giving a flocculent precipitate of the *quaternary picrate*, which crystallised from alcohol in flat yellow needles, m. p. 153—155° (Found : C, 53·3; H, 5·5; N, 14·6. $C_{21}H_{25}O_8N_5$ requires C, 53·1; H, 5·3; N, 14·7%).

6-*Nitro*-1 : 3-*dimethyl*-3-β-*dimethylaminoethylindolinone*.—The base

(II) (2·4 g.) was added to nitric acid (10 c.c., *d* 1·46), and the temperature maintained at −10°. Darkening, but only partial solution, took place and the temperature was then allowed to reach 20°; after 1 hour, the base had completely dissolved. Ice was added and the solution was filtered from a little insoluble matter and basified with ammonia; the nitro-base separated as a reddish oil, which was taken up with ether, washed, and dried. Removal of the ether gave a reddish syrup (1·3 g.), an alcoholic solution of which, treated with picric acid, gave a crystalline *picrate*, m. p. 222° (Found: C, 47·4; H, 4·5; N, 16·9. $C_{20}H_{22}O_{10}N_6$ requires C, 47·4; H, 4·4; N, 16·6%). An ethereal solution of the nitro-base with methyl iodide gave a methiodide, which was twice purified from alcohol and had m. p. 167—169°.

1 : 3-*Dimethyl*-3-β-*methylaminoethyl*-2-*indolinone* (VIII).—The bromide (2·8 g.), aqueous methylamine solution (33% w/v) (15 c.c.), and methyl alcohol (10 c.c.) were heated in a sealed tube at 170—180° for 10 hours. The resulting secondary base was isolated in the usual manner, and 1·3 g. of a colourless oil were obtained. On addition of a solution of anhydrous oxalic acid in dry ether to a similar solution of the base, the *hydrogen oxalate* was precipitated. Twice crystallised from alcohol, it was obtained as colourless plates, m. p. 204° (decomp.) (Found in material dried at 110°; C, 58·1; H, 6·6; N, 9·2. $C_{15}H_{20}O_5N_2$ requires C, 58·4; H, 6·5; N, 9·1%).

The authors wish to thank the Royal Commissioners for the Exhibition of 1851 for a Fellowship awarded to one of them.

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