74. *Experiments on the Synthesis of Physostigmine (Eserine). Part VII.*

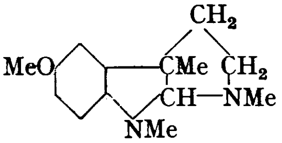
By Frederick E. King and Robert Robinson.

In the earlier parts of this series (J., 1932, 298—336, 1433) synthetic bases closely related to eserole have been described, but attempts to resolve these substances have not yet been entirely successful. Having regard to the resolution of a synthetic indolinone (*loc. cit.*, p. 326) by the use of quaternary salts, we first attempted to achieve our end by the crystallisation of a methopicrate of *dl*-esermethole (I) (*loc. cit.*, p. 1435), but no spontaneous separation occurred. Other metho-salts of the optically active base from natural sources, *e.g.*, the metho-*d*-bromocamphorsulphonate and metho-*d*-camphorsulphonate, were examined, but none of these was suitable for the purpose. Furthermore, in completing the synthesis by way of metho-salts, a necessary stage must be the decomposition of such quaternary salts with simple loss of a methyl group, but, unfortunately, the work of Straus (*Annalen*, 1913, **401**, 350; 1914, **406**, 332) has shown that methiodides of bases of the type (I) suffer thermal decomposition with the formation of derivatives of indole. It was hoped that the employment of methochlorides, heated in high vacua, might overcome this difficulty, but actually the customary degradation to a physostigmole ether (II) ensued.

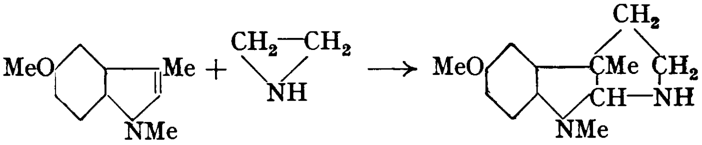
The resolution of the quaternary salts is not likely, therefore, to be a stage in the actual synthesis of eserine, but it would still be a step in the synthetical proof of the constitution of this base.

l-*Esermethole hydrogen* d-*tartrate* has considerable crystallising power; the completion of the synthesis thus appeared to be in reach, but difficulty has been experienced in obtaining an adequate supply of the inactive synthetic esermethole.

The synthesis outlined in Part VI (*loc. cit.*, p. 1433) has not proved satisfactory for the preparation of relatively large quantities of the material necessary for resolution experiments owing to the capricious behaviour, and occasional failure of the catalytic reduction, of crude dehydro*nor*esermethole. Although the expenditure of time and labour will enable us to utilise the methods already recorded, we have made efforts to improve them, and some preliminary investigations in this direction are described in the experimental section. In the first place the direct addition of ethyleneimine to 5-methoxy-1 : 3-dimethylindole failed; this might have constructed the eserine ring-system as follows :—



(I.)



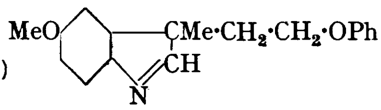
(II.)

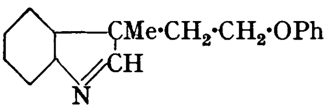
The idea is perhaps worth following up with less highly substituted indoles, because we find that 1-methylated indoles are even difficult to alkylate in the 3-position (*vide infra*).

New experiments along the lines of our earlier work have been directed to the synthesis of the metho-salt of the base (III) and in the first instance we studied the addition of methyl iodide to the more readily accessible analogous indoles. The results, described in the experimental section, showed that addition of methyl to the 3-position without attack of an unsubstituted 2-position is not feasible as a method of preparation if the initial substance is 1-alkylated.

We have, however, been able to prepare an indolenine (IV) and the work is being extended at the present time in this direction in collaboration with Dr. M. Liguori.

(III.)





(IV.)

γ-Phenoxy-α-methylbutyryl chloride (for the acid, see Bentley, Haworth, and Perkin, J., 1896, **69**, 171) could not be reduced by Rosenmund's method, but the related nitrile was reduced following Stephen (J., 1925, **127**, 1874). The aldehyde was not purified, but its phenylhydrazone afforded the indolenine (IV) on treatment with alcoholic hydrogen chloride.

EXPERIMENTAL.

Recrystallisation of dl-*Esermethole Methopicrate.*—Microscopic examination and m. p. determination of salt deposited at various temp. from EtOH solutions of *dl*-esermethole methopicrate seeded with the *l*-base methopicrate afforded no evidence of resolution.

Salts of l-*Esermethole with Optically Active Acids.*—Silver *d*-bromocamphorsulphonate (0·7 g.) in H_2O (5 c.c.) was added to a solution of esermethole methiodide (0·6 g.) in EtOH aq. (9 c.c. of 60%), and the pptd. AgI removed (charcoal). By concn. at 50° under reduced press., esermethole *d*-bromocamphorsulphonate was isolated as a faintly pink gum. The product was sol. in hot org. solvents, except Et_2O and light petroleum, but the cold solutions formed gels containing white flocks of needles which slowly blackened, probably through oxidation of the basic constituent by the grouping ·CO·CHBr· of the camphor acid. The prepn. of esermethole *d*-camphorsulphonate was similar, but the deliquescent product did not crystallise.

Powdered *d*-tartaric acid (0·3 g.) was added to a solution of *l*-esermethole (0·46 g.) in boiling MeOH (4 c.c.). The product (0·65 g.) which separated on cooling was recrystallised from EtOH–EtOAc, forming colourless elongated prisms, m. p. 160—161°. After several days the crystals of *tartrate* began to cohere, and a redetermination of m. p. gave 65—70°. When dried in vac. over P_2O_5, first at room temp. and finally at 100°, the salt again melted at 160—161° (Found : C, 56·3; H, 7·1; N, 7·1. $C_{18}H_{26}O_7N_2$ requires C, 56·5; H, 6·8; N, 7·3%). The salt is readily sol. in H_2O, hot MeOH and EtOH, but is almost insol. in other solvents.

Degradation of l-*Esermethole Methochloride.*—The methochloride (*loc. cit.*, p. 334) from the methiodide (1 g.) and AgCl in EtOH aq. was heated in a high vac. With the oil bath at 160—170°, darkening occurred and a light brown liquid distilled; the expt. was discontinued at 200°. The solid distillate (0·36 g., *ca.* 75%), after crystn. from EtOH, had m. p. 59—60°, undepressed by admixture with 5-methoxy-1 : 3-dimethylindole. With Ehrlich's reagent, the characteristic deep purple colour developed, which later changed to Prussian blue.

Synthesis of 5-*Methoxy*-1 : 3-*dimethylindole.*—The prepn. of *p*-methoxyphenylhydrazine followed the convenient method of Kermack, Perkin, and Robinson (J., 1922, **121**, 1880) for the *m*-isomeride. The intermediate *nitrosomethyl*-p-*anisidine*, described by Späth and Brunner (*Ber.*, 1925, **58**, 522) as a dark red oil, separated during its prepn. in cream-coloured nodules. The compound, recryst. from MeOH, formed pale yellow, rectangular leaflets, m. p. 45—46° (Found : C, 57·6; H, 6·2; N, 16·9. $C_8H_{10}O_2N_2$ requires C, 57·8; H, 6·0; N, 16·9%). Propaldehyde (3—4 g.) and *p*-methoxyphenylmethylhydrazine (5 g.) reacted immediately with evolution of heat, yielding the syrupy hydrazine. When the latter was dissolved in EtOH–H_2SO_4 (15 c.c. of 15%) (cf. Späth and Brunner's use of anhyd. $ZnCl_2$), the solution boiled, depositing $(NH_4)_2SO_4$. The reaction was completed under reflux on a steam-bath, and the indole isolated by means of Et_2O. It was purified by distillation (b. p. 120—122°/1 mm.), and the solid distillate crystallised from EtOH in colourless plates, m. p. 60°.

Ethyleneimine.—The use of a sealed tube in the prepn. of β-bromoethylamine hydrobromide from phthalo-β-bromoethylimide (Gabriel, *Ber.*, 1888, **21**, 566) is unnecessary if stronger acid is employed; with HBr aq. (*d* 1·7) the reaction is complete within 2 hr. Following Gabriel and

Stelzner (*Ber.*, 1895, **28**, 2929), heating the amine hydrobromide with NaOH aq. (33%) yielded a fraction, b. p. 55—60°, and 5-methoxy-1 : 3-dimethylindole (1 g.) was heated with an excess of this base (2 c.c.) in a sealed tube at 120° for 3 hr. The solution was evaporated (b. p. of distillate *ca.* 57°), and the solid residue washed with dil. HCl. The washings were basified and shaken with $CHCl_3$, but nothing was extracted; the neutral residue was the unchanged physostigmol ether.

β-Phenoxyethylamine.—This base was described by Schmidt (*Ber.*, 1889, **22**, 3256), who obtained the hydrochloride by the action of boiling conc. HCl on the phthalamic acid prepared from phthalo-β-phenoxyethylimide and alkali. Phthalo-β-phenoxyethylimide (45 g.) was boiled under reflux with HBr aq. (180 c.c. of *d* 1·7) for 15 hr.; H_2O (100 c.c.) was added, and the solution was filtered from phthalic acid, and evaporated to dryness on a steam-bath. The pink residue, consisting largely of β-phenoxyethylamine hydrobromide (Marckwald and Chain, *Ber.*, 1901, **34**, 1159), was crystallised from a small amount of EtOH and formed colourless short needles, m. p., after sintering, 180—190°, 192—193°.

The colourless base was liberated by NaOH aq. (20%) and extracted with Et_2O; picric acid in EtOH yielded the *picrate*, which separated from a small vol. of EtOH in bright yellow, rhombic tablets, m. p. 167—169° (Found : N, 15·8. $C_8H_{11}ON,C_6H_3O_7N_3$ requires N, 15·3%). Schmidt (*loc. cit.*) records an analysis, but no m. p. The base in EtOH also formed a *picrolonate*, which was moderately sol. in boiling EtOH, and separated, after concn. of the solution, in orange-yellow, pointed, flat prisms, m. p. 216—217° (decomp.) (Found : C, 54·1; H, 4·6; N, 17·2. $C_8H_{11}ON,C_{10}H_8O_5N_4$ requires C, 53·9; H, 4·7; N, 17·5%).

5-*Methoxy*-1 : 2-*dimethyl*-3-β-*phenoxyethylindole.*—A solution of *p*-methoxyphenylmethylhydrazine (5·5 g.) and γ-phenoxypropyl methyl ketone (6 g.) in EtOH (15 c.c.) was heated under reflux on a steam-bath for 30 min. With the addition of conc. H_2SO_4 (3 g.) a vigorous reaction ensued, and $(NH_4)_2SO_4$ was deposited. After a further 20 min. on the steam-bath, the liquid was poured into H_2O, and the red semi-solid material removed in Et_2O, dried over anhyd. K_2CO_3, and distilled in a high vac. The fraction (7·9 g.) of b. p. 215—225°/1 mm. was a straw-coloured syrup, which crystallised from MeOH in colourless, shining, long, rectangular plates, m. p. 67° (Found : C, 77·0; H, 7·2; N, 4·6. $C_{19}H_{21}O_2N$ requires C, 77·3; H, 7·1; N, 4·7%).

The Methylation of Some Indole Derivatives.—(i) 5-*Methoxy*-1 : 3-*dimethylindole.* A solution of physostigmol methyl ether (0·5 g.) in EtOAc (5 c.c.) and MeI (2 c.c.) was heated under reflux on a steam-bath for 9 hr.; the residue obtained on evaporation of the solvents was the original indole, identified by mixed m. p. In another expt., the compound (1 g.) was heated in a sealed tube with MeOH (6 c.c.) and MeI (2 g.) at 100—105° for 2 hr. The non-volatile residue was stirred with Et_2O, which extracted unchanged material (0·7 g., identity from mixed m. p.); the red-brown gummy residue could not be crystallised.

(ii) 5-*Methoxy*-1 : 2-*dimethyl*-3-β-*phenoxyethylindole.* A solution of this indole (1 g.) in EtOAc (10 c.c.) was unchanged by heating with MeI (5 g.) under reflux for 6 hr. The compound (2 g.) was subsequently methylated by heating in a sealed tube at 100—105° for 5 hr. with MeOH (10 c.c.) and MeI (3 g.). A small amount of tar was removed from the boiling solution of the product by filtration (charcoal), and the crude material isolated by evaporation of the solvents and stirring with Et_2O. A light brown solid (1·25 g.) remained, which crystallised from EtOH in short rectangular prisms, m. p. 197—200°, unaffected by addition of 5-methoxy-1 : 2 : 3-trimethyl-3-β-phenoxyethylindoleninium iodide.

γ-Phenoxy-α-methylbutyric Acid.—Bentley, Haworth, and Perkin (*loc. cit.*) prepared this acid by hydrolysis of the condensation products of phenoxyethyl bromide with ethyl α-acetopropionate or ethyl methylmalonate. In the present work, excess of ethyl α-acetopropionate (220 g.) and phenoxyethyl bromide (220 g.) in an abs. EtOH solution (550 c.c.) of NaOEt (24 g. of Na) were heated under reflux on a steam-bath for 9 hr. The resulting oil was isolated by means of Et_2O and distilled, and the fraction (180—190 g.) boiling above 130°/13 mm. collected. Redistillation of a portion gave *ethyl γ-phenoxy-α-methylbutyrate* as a colourless oil with a faint pleasant odour, b. p. 147°/13 mm. (Found : C, 70·1; H, 8·2. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%). The identity of this ester was confirmed by its prepn. from abs. EtOH (5 c.c.) and γ-phenoxy-α-methylbutyryl chloride (5 g.) (*vide infra*). The ester was isolated and distilled, b. p. 147—148°/14 mm. (4·4 g.) (Found : C, 70·2; H, 8·2%).

The crude ester (25 g.) from the foregoing process was dissolved in EtOH–NaOH (60 c.c. of 20%), and heated under reflux on a steam-bath for 30 min. Dilution with H_2O (100 c.c.), and evaporation of EtOH, gave a clear solution, from which γ-phenoxy-α-methylbutyric acid (16 g.) was pptd. by dil. HCl. The dried product was recrystallised from light petroleum, and formed colourless, glistening, rectangular plates, m. p. 79—80° (Found : C, 68·0; H, 7·2. Calc. for $C_{11}H_{14}O_3$: C, 68·0; H, 7·2%).

In a further expt., ethyl α-acetopropionate (120 g.) and phenoxyethyl bromide (155 g.) were condensed in an abs. EtOH solution (250 c.c.) of KOEt (30 g. of K) containing a little NaI (2 g.), by heating under reflux on a steam-bath for 18 hr. On working up, a fraction (103 g.), b. p. 145—151°/1 mm., was collected; on standing, colourless foliated crystals separated, and a further small quantity was obtained as a by-product in the subsequent hydrolysis of the impure ester. The solid (total, 9 g.) crystallised from EtOH in shining leaflets, m. p. 97—98°, alone or mixed with authentic ethylene diphenyl ether.

Phenoxyethyl bromide (40 g.) in EtOH (200 c.c.) was boiled under reflux with KCN aq. (36 g. in 60 c.c.) for 4 hr. The solid product remaining after addition of H_2O and evaporation of EtOH was recrystallised from EtOH and gave ethylene diphenyl ether (9 g.), m. p. 96—98°.

γ-Phenoxy-α-methylbutyryl Chloride.—The substituted butyric acid (45 g.) was dissolved in $SOCl_2$ (60 g.) and heated under reflux on a steam-bath until HCl evolution ceased (20—30 min.). The *acid chloride* was isolated by distillation under reduced press. as a mobile colourless liquid, b. p. 150—152°/15 mm. (Found : C, 62·2; H, 6·0; Cl, 17·0. $C_{11}H_{13}O_2Cl$ requires C, 62·1; H, 6·1; Cl, 16·8%). No HCl was evolved when dry H was passed into a solution of γ-phenoxy-α-methylbutyryl chloride (15 g.) in boiling dry xylene (50 c.c.) containing palladised $BaSO_4$.

γ-Phenoxy-α-methylbutyramide.—The acid chloride (43 g.) was poured into NH_3 aq. (150 c.c. of *d* 0·88 and 100 c.c. H_2O) and vigorously shaken. The white ppt. (36 g.), recryst. from C_6H_6 or EtOH aq., formed tiny rectangular plates, m. p. 102—103·5°, readily sol. in EtOH, EtOAc, acetone, and C_6H_6, sparingly sol. in H_2O and light petroleum (Found : C, 68·3; H, 7·6; N, 7·0. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·3%).

γ-Phenoxy-α-methylbutyronitrile.—A solution of the amide (20 g.) in $SOCl_2$ (30 g.) was heated under reflux on a steam-bath for 30 min. After evaporation of the $SOCl_2$ excess, the straw-coloured liquid was shaken with Na_2CO_3 aq. and extracted by Et_2O, and the extract dried with anhyd. K_2CO_3. By distillation under reduced press., the nitrile (15 g.) was obtained as a colourless oil, b. p. 165°/18—20 mm. (cf. v. Braun and Deutsch, *Ber.*, 1911, **44**, 3706).

γ-Phenoxy-α-methylbutyraldehyde.—Dry HCl was passed into a suspension of anhyd. $SnCl_2$ (25 g.) (Stephen, J., 1930, 2787) in purified Et_2O (120 c.c.) until separation into two liquid layers was complete (1—1·5 hr.). γ-Phenoxy-α-methylbutyronitrile (14 g.) in Et_2O (30 c.c.) was then added with shaking, and the mixture left at room temp. Moisture was rigorously excluded throughout the expt., but contrary to Stephen's experience (J., 1925, **127**, 1874) no stannichloride complex separated, even after 12 hr. The mixture was accordingly heated under reflux on a water-bath; a white solid then appeared, and after 5—6 hrs.' heating, the solution was again saturated with HCl. Much of the ppt. remained, and next day the solid (14 g.) was collected and warmed with H_2O (30 c.c.), whereby a colourless oil was liberated. Its ethereal solution was dried (anhyd. Na_2SO_4) and evaporated; the residue (6·5 g.) possessed a faint aromatic odour, gave a cryst. $NaHSO_3$ compound, and reacted with phenylhydrazine with evolution of heat. Attempted distillation (12 mm.) led to resinification, and the odour of PhOH was apparent; even at 100° the aldehyde acquired a reddish tint and became more viscous.

3-*Methyl*-3-β-*phenoxyethylindolenine* (IV).—The crude aldehyde (1 g.) and phenylhydrazine (1 mol.; 0·6 g.) were dissolved in boiling EtOH (7 c.c.). The solution was saturated with dry HCl at 0°, and later heated under reflux on a steam-bath. A ppt. of NH_4Cl indicated that ring-closure was complete in a few min., and after filtration the reddish solution was evaporated under reduced press. The residual thick syrup was stirred with NaOH aq. (15 c.c. of 7%) and the greyish amorphous solid collected and washed (H_2O). It was dissolved in EtOH (15 c.c.), and picric acid (1·5 g.) added to the boiling solution. On cooling, a picrate (1·45 g., equivalent to 0·76 g. base, or 54%) separated, m. p. 145—148°. It was recrystallised from EtOH, and pure 3-*methyl*-3-β-*phenoxyethylindolenine picrate* obtained as bright yellow clusters of elongated prisms, m. p. 152—153° (Found : C, 57·7; H, 4·2; N, 11·7. $C_{17}H_{17}ON,C_6H_3O_7N_3$ requires C, 57·5; H, 4·2; N, 11·7%). Decomp. of a specimen of the unpurified picrate by NaOH aq. afforded a gummy solid, which dissolved in conc. H_2SO_4 to a pale orange solution, but the amount available was inadequate for further investigation.

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