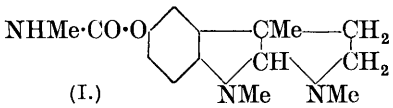
45. *Experiments on the Synthesis of Physostigmine (Eserine). Part V. A Synthesis of Dehydroesermetholemethine.*

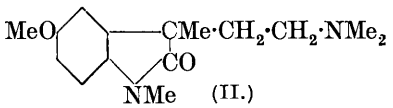
By FREDERICK ERNEST KING and ROBERT ROBINSON.

METHOXYLATED aromatic substances often surpass their ethoxylated analogues in crystallising power, so, in continuing the investigation of the promising lines developed in Part III (see p. 317), we decided to prepare dehydroesermetholemethine (II) from physostigmine (I)



(I.)

in the hope that the substance might be a solid. Like the dehydroeseretholemethine of Stedman and Barger (J., 1925, **127**, 247), it is, however, a syrup characterised by crystalline derivatives.



(II.)

The synthesis of (II) has been effected and the related methosalt has been resolved and identified with the corresponding substance from physostigmine. Thus the main features of the constitution of this alkaloid have been established by a synthetical method.

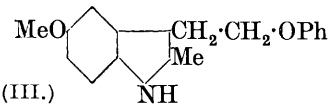
When one of us originally suggested (compare Stedman and Barger, *loc. cit.*, p. 248) the formula (I), the whole basis of the fused pyrroline–pyrrolidine ring system and the quaternary carbon group was a hypothesis of biogenesis from a hydroxytryptophan. It was thought probable that methylation of an indole nucleus might take a course in a phytochemical synthesis similar to that which occurs when methyl iodide is allowed to interact with indole or its derivatives. The peculiar constitution of physostigmine affords powerful support to such a hypothesis apart from the justification by successful prediction.

It is now appropriate to reflect that the vegetable methylating agent is generally considered to be formaldehyde or an equivalent and the *C*-alkylation of indoles has not, so far as we are aware, been accomplished by such means.

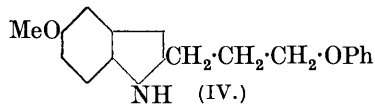
Nevertheless, formaldehyde can be used to methylate amines, and the hetero-enoid systems (N—C=C) contain carbon atoms which are analogous in quality of reactivity to the nitrogen atom of amines; there is every probability, therefore, that the *C*-methyl-

ation of indoles by means of formaldehyde could be experimentally realised. An attempt to find the correct conditions will be made.

The synthesis of dehydroesermetholemethine was accomplished in the following manner. The action of boiling alcoholic sulphuric acid on the *p*-methoxyphenylhydrazone of γ-phenoxypropylacetone induced indole ring-closure with great facility and the product might have the constitution (III) or (IV).



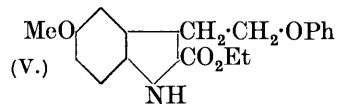
(III.)

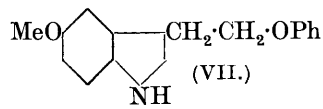


(IV.)

In order to obtain evidence that the product was actually the desired compound (III), the *p*-methoxyphenylhydrazone of ethyl α-keto-δ-phenoxyvalerate, prepared from *p*-methoxybenzenediazonium chloride and ethyl α-acetyl-δ-phenoxyvalerate by the application of the Japp–Klingemann reaction, was similarly converted into an indole. In this reaction no alternative course is possible and *ethyl 5-methoxy-3-β-phenoxyethylindole-2-carboxylate* (V) is undoubtedly the product.

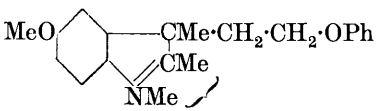
(V.)



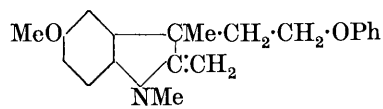


(VII.)

Hydrolysis of (V) in alcoholic solution by means of alkali gave *5-methoxy-3-β-phenoxyethylindole-2-carboxylic acid* (VI), and the latter when heated above its melting point evolved carbon dioxide with formation of *5-methoxy-3-β-phenoxyethylindole* (VII). Of the four related indoles (III) (or IV), (V), (VI), and (VII) thus obtained, only compound (VII) developed, with Ehrlich's reagent in the cold, the intense colour characteristic of an indole with a free position in the pyrrole nucleus. Indole cyclisation of γ-phenoxypropylacetone-*p*-methoxyphenylhydrazone thus appears to give *5-methoxy-2-methyl-3-β-phenoxyethylindole* (III). When this is methylated



(VIII.) I



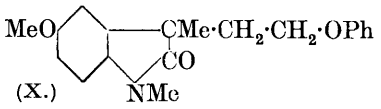
(IX.)

with methyl iodide in an autoclave *5-methoxy-1 : 2 : 3-trimethyl-3-β-phenoxyethylindoleninium iodide* (VIII) is produced, whereas (IV) would give an iodide containing a further methylene group which would readily be detected by analysis especially in the further stages. The methylation of (VII) was considered as an alternative method

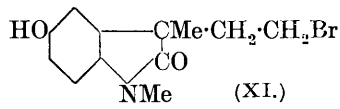
for the preparation of (VIII), but the product was highly impure and scarcely any indication of the formation of the required iodide was obtained. With silver chloride, the iodide (VIII) gave a deliquescent chloride, which was not purified but converted into a *quaternary picrate*.

When the iodide (VIII) was shaken with cold aqueous sodium hydroxide the solid *methylene-indoline* (IX) was obtained, and the latter was oxidised by means of potassium permanganate in acetone solution to the indolinone (X). This compound is a syrup, but a solid *trinitro*-derivative was readily prepared (compare trinitroeserethole; Stedman and Barger, *loc. cit.*, p. 256).

When treated for 12 hours with boiling fuming hydrobromic acid, the phenoxy-group of the indolinone (X) was replaced by bromine, but demethylation at position 5 occurred simultaneously



(X.)



(XI.)

and the solid product was 5-*hydroxy*-1 : 3-*dimethyl*-3-β-*bromoethyl-indolinone* (XI), characterised by an *acetyl* derivative. When (XI) was methylated with methyl sulphate under special conditions, a viscous *methyl* ether was obtained, and this reacted with methyl-alcoholic dimethylamine under pressure with formation of the tertiary base (II), convertible into a *methiodide* and a *methopicrate*, m. p. 193—195°.

Esermethole was prepared from physostigmine by the action of sodium ethoxide in alcoholic solution, followed by methyl *p*-toluene-sulphonate. This method was found very satisfactory by Polonovski (*Bull. Soc. chim.*, 1915, **17**, 235) for the preparation of the ethyl ether of eseroline, but the yields of the new base are poor. The methochloride, obtained in the usual stages, furnished dehydroesermetholemethine (II) on oxidation with alkaline potassium ferricyanide solution. The *methopicrate* had m. p. 132—133° and the d-*bromocamphorsulphonate* had m. p. 245—248° and $[\alpha]_D^{19^\circ}$ + 28·0°.

The resolution of the methiodide of the synthetic base (II) was effected by fractional crystallisation of the mixed *d*-bromocamphorsulphonates. The latter were obtained as a gum, which was dissolved in a small quantity of acetone. On standing, approximately half of the product separated, and this was recrystallised from acetone; it had m. p. 166—167° and $[\alpha]_D^{18^\circ}$ + 77·0° and was therefore the d-*base* d-*acid*. The remainder of the substance was precipitated from the acetone solution with ether and, after several recrystallisations from a mixture of these solvents and drying in

a vacuum, had $[\alpha]_D^{18°}$ + 27·8° and m. p. 245—248°, alone or mixed with the *d*-bromocamphorsulphonate of the natural base. The *picrate* had m. p. 132—133°, alone or mixed with the salt of natural origin.

The synthetic *d*-base *d*-acid likewise gave a *picrate*, m. p. 132—133°, which is the optical antipode of that obtained from the *l*-base *d*-acid. When mixed with either the synthetic or the natural enantiomorph, it had m. p. 193—195°, alone or mixed with the picrate from the synthetic methiodide.

Finally, the racemic and the optically active bases of formula (II) were regenerated by thermal decomposition of the methochlorides and their identity was established by reconstitution of the methiodides.

EXPERIMENTAL.

5-Methoxy-2-methyl-3-β-phenoxyethylindole (III).—A solution of γ-phenoxypropylacetone (compare Part III, p. 318) (50 g.) and *p*-methoxyphenylhydrazine (40 g.) in 95% alcohol (110 c.c.) was refluxed on a steam-bath for an hour. The hydrazone was not isolated, but sulphuric acid (20 g.) was cautiously added to the cooled solution; on warming, it began to boil vigorously and this proceeded for an appreciable time without external heating; meanwhile ammonium sulphate was precipitated. After completion of the reaction by further refluxing, the hot liquid was poured into water, and the brown solid collected and crystallised from alcohol. After one crystallisation the product (67 g.) had m. p. 113—114°, and it was finally obtained in colourless rectangular leaflets, m. p. 115°, easily soluble in all the usual organic solvents (Found: C, 76·6; H, 6·8; N, 4·8. $C_{18}H_{19}O_2N$ requires C, 76·8; H, 6·8; N, 5·0%). With *p*-dimethylaminobenzaldehyde in aqueous-alcoholic hydrochloric acid the *indole* gives a faint blue-green colour and on boiling this changes to an intense blue, which fades as the solution cools.

5-Methoxy-1 : 2 : 3-trimethyl-3-β-phenoxyethylindoleninium Iodide (VIII).—When heated in an autoclave at 120° for 6—8 hours with methyl iodide (230 g.) and methyl alcohol (95 g.), the indole derivative (50 g.) gave a dark semi-solid mass (55—60 g.) of the *iodide*. This crystallised from methyl alcohol in light brown, stout, rectangular prisms, m. p. 200° to a deep purple liquid (Found: C, 55·0; H, 5·1; N, 3·2; I, 29·1; OMe, 6·6. $C_{20}H_{24}O_2NI$ requires C, 54·9; H, 5·5; N, 3·2; I, 29·1; OMe, 7·1%). The salt is moderately easily soluble in warm alcohol, but practically insoluble in most other solvents. By heating it for 10 minutes in aqueous-alcoholic solution with silver chloride on a steam-bath, the chloride was

formed; this was isolated, by evaporation of the solvents under diminished pressure, as a reddish gum. In contact with acetone it solidified and when washed with this solvent was obtained as a white solid, very freely soluble in alcohol and water and difficult to purify because of its deliquescence. It was therefore dissolved in water and converted into the *quaternary picrate*, which crystallised from alcohol in bright yellow, rectangular tablets, m. p. 128—130° (Found: C, 57·9; H, 4·9; N, 10·0. $C_{20}H_{24}O_2N,C_6H_2O_7N_3$ requires C, 58·0; H, 4·8; N, 10·4%).

Ethyl α-Acetyl-δ-phenoxyvalerate.—A solution of sodium (10·5 g.) in absolute alcohol (250 c.c.), containing ethyl acetoacetate (120 g.) and γ-phenoxypropyl bromide (105 g.), was heated under reflux on a steam-bath for 6 hours. The precipitated sodium bromide and the alcohol were then removed and the ethereal solution of the residual oil was washed with water, dried, and distilled, finally under diminished pressure; the fraction (75—80 g.), b. p. 198—203°/15 mm., was collected (Found: C, 68·3; H, 7·6. Calc. for $C_{15}H_{20}O_4$: C, 68·2; H, 7·5%) (compare Manske, *Canad. J. Res.*, 1931, **4**, 591).

Ethyl 5-Methoxy-3-β-phenoxyethylindole-2-carboxylate (V).—To a cooled solution of ethyl α-acetyl-δ-phenoxyvalerate (26·4 g.) in 95% alcohol (100 c.c.), aqueous sodium hydroxide (50 c.c. of 20%) was added, followed by a solution of *p*-methoxybenzenediazonium chloride prepared from *p*-anisidine (12·4 g.), concentrated hydrochloric acid (30 c.c.), water (50 c.c.), and a solution (30 c.c.) of sodium nitrite (6·8 g.). The orange-coloured solution at once began to deposit a dark red oil, which, after the addition of an excess of dilute acid, was taken up in ether (150 c.c.). Evaporation of the ether left the crude ethyl α-keto-δ-phenoxyvalerate *p*-methoxyphenylhydrazone, and this was converted into the indole (V) by heating under reflux on a steam-bath for 2 hours in alcoholic solution (75 c.c.) containing sulphuric acid (11 g.). By the addition of water *ethyl 5-methoxy-3-β-phenoxyethylindole-2-carboxylate* was obtained as a sticky mass (17—18 g.), which crystallised from alcohol, in which it was moderately easily soluble, in colourless short needles, m. p. 179° (Found: C, 71·0; H, 6·0; N, 4·1. $C_{20}H_{21}O_4N$ requires C, 70·8; H, 6·2; N, 4·1%). The ester is soluble in the usual organic solvents with the exception of light petroleum. No colour is developed with Ehrlich's reagent unless the solution is boiled; then a faint blue-green colour ultimately appears.

5-Methoxy-3-β-phenoxyethylindole-2-carboxylic Acid (VI).—This was obtained by heating the ester (9 g.) under reflux on a steam-bath with alcoholic sodium hydroxide (3 g. in 40 c.c. of alcohol). The ester was only partly dissolved by the quantity of alcohol employed, but in the course of 15 minutes a clear orange solution was obtained.

This was poured into water (150 c.c.), and the product precipitated by hydrochloric acid. It was moderately easily soluble in benzene and crystallised from this solvent in white flocks of microcrystalline needles, m. p. 179—180° (Found: C, 69·9; H, 5·4; N, 4·8. $C_{18}H_{17}O_4N$ requires C, 69·5; H, 5·5; N, 4·5%). The acid was not appreciably soluble in light petroleum, water, or sodium carbonate solution. No colour was produced by the addition of concentrated hydrochloric acid to an alcoholic solution of the indole and *p*-dimethylaminobenzaldehyde, but, when boiled, the solution acquired a faint olive-green colour which became permanently red-purple.

5-*Methoxy*-3-β-*phenoxyethylindole* (VII).—When heated in the air above its melting point (*ca.* 200°), the acid (VI) evolved carbon dioxide, affording 5-*methoxy*-3-β-*phenoxyethylindole*, but some charring occurred. A cleaner product was obtained if the heating was carried out in a vacuum. The product was purified by crystallisation from ethyl alcohol, in which it was very soluble, or from ligroin containing some benzene. It formed clusters of almost colourless needles, m. p. 89°, freely soluble in most organic solvents (Found: C, 76·2; H, 6·6; N, 5·1. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2%). With Ehrlich's reagent an intense red-purple colour was immediately produced in the cold, and this turned to deep blue on heating.

When (VII) was heated with methyl iodide and methyl alcohol under the conditions employed for the methylation of 5-methoxy-2-methyl-3-β-phenoxyethylindole, only an unworkable tar was obtained. The conditions were therefore modified and 5-methoxy-3-β-phenoxyethylindole (4 g.), methyl iodide (20 g.), and methyl alcohol (10 c.c.) were heated in a sealed tube at 100° for 4 hours. On cooling, no product crystallised and the contents appeared unchanged, but after further heating at 120° for 2 hours, the liquid separated into two layers. The upper, almost colourless layer was miscible with both water and ether and was discarded. By the addition of ether to the dark liquid residue, most of the product was obtained as a tarry precipitate. The product was fractionally precipitated from alcohol, and a very small amount of a brown crystalline substance, m. p. 190—194° to a deep purple liquid, was obtained (compare 5-methoxy-1 : 2 : 3-trimethyl-3-β-phenoxyethylindoleninium iodide).

5-*Methoxy*-1 : 3-*dimethyl*-3-β-*phenoxyethyl*-2-*methyleneindoline* (IX).—The indoleninium iodide (50 g.), ether (100 c.c.), and aqueous sodium hydroxide (250 c.c. of 20%) were mixed and shaken mechanically for 8 hours. The ethereal, deep purple layer was separated and washed with water, and the solvent evaporated. An oil remained which solidified to a purplish solid (33·5 g.). It crystallised from alcohol in short pointed rods which acquired a

purple tint in the air; the pure substance was colourless and had m. p. 65° (Found: C, 77·4; H, 7·3; N, 4·8. $C_{20}H_{23}O_2N$ requires C, 77·6; H, 7·4; N, 4·5%).

5-*Methoxy*-1 : 3-*dimethyl*-3-β-*phenoxyethyl*-2-*indolinone* (X).—An acetone solution (160 c.c.) of the methylene-indoline (25 g.) was treated at 0° with finely powdered potassium permanganate (45 g.), added in small amounts during 9 hours. When oxidation was complete the excess of permanganate was destroyed by boiling with methyl alcohol, and the manganese dioxide separated. The red-brown oil which remained after evaporation of the acetone was distilled in a high vacuum, and the indolinone (X) was obtained as a straw-coloured syrup (16 g.), b. p. 238—243°/1 mm.

A *trinitro*-derivative was prepared by the addition of concentrated nitric acid, dissolved in acetic anhydride, to a solution of the indolinone in the same solvent at 18°. After an hour water was added, and the deep yellow precipitate purified by extraction in a Soxhlet apparatus with 95% alcohol, in which the trinitroindolinone is only sparingly soluble. It was recrystallised from small quantities of ethyl acetate containing ligroin and separated in bright yellow prisms, m. p. 192—193° (Found: C, 51·2; H, 4·2; N, 12·4. $C_{19}H_{18}O_9N_4$ requires C, 51·1; H, 4·0; N, 12·6%), soluble in most organic solvents except light petroleum.

5-*Hydroxy*-1 : 3-*dimethyl*-3-β-*bromoethyl*-2-*indolinone* (XI).—The indolinone (15 g.) was heated for 12 hours with an excess of fuming hydrobromic acid (*d* 1·7) in a Geissler flask, in an oil-bath at 150°. When cool, the mixture, which had a strong odour of phenol, was poured into water; the heavy brown oil slowly solidified. The solid (13·5 g.) was washed with large quantities of water to remove the phenol and acid, and crystallised from aqueous alcohol. Recrystallised from 95% alcohol, it was obtained as colourless rectangular prisms, m. p. 199—200°, readily soluble in dilute alkali (Found: C, 51·1; H, 4·7; N, 4·9; Br, 28·0. $C_{12}H_{14}O_2NBr$ requires C, 50·7; H, 4·9; N, 4·9; Br, 28·1%).

An *acetyl* derivative was prepared by boiling the hydroxy-bromide for 2 hours with acetic anhydride containing a small amount of hydrobromic acid. When poured into water, the product very slowly solidified; after drying, it was purified by extraction with light petroleum in a Soxhlet apparatus. The acetate was deposited in aggregates of large colourless prisms, m. p. 66—68°, but was contaminated with a viscous impurity. It was therefore further purified by distillation in a high vacuum, the colourless syrupy product having b. p. 190—192°/1 mm.; it readily solidified in contact with light petroleum and then had m. p. 71—72° (Found: N, 4·4; Br, 24·3. $C_{14}H_{16}O_3NBr$ requires N, 4·3; Br, 24·5%).

5-*Methoxy*-1 : 3-*dimethyl*-3-β-*bromoethyl*-2-*indolinone*.—Methyl sulphate (10 g.) was added drop by drop to a vigorously stirred solution of the hydroxy-bromide (10 g.) in aqueous sodium hydroxide (75 c.c. of 5%). The temperature was maintained at 15° and the operation required 1½ hours, during which time a further 75 c.c. of 5% alkali were added. The precipitated oil was taken up in ether, and the solution dried with anhydrous sodium sulphate. Distillation in a high vacuum gave the pure *methyl* ether, b. p. 170—175°/1 mm., as a very viscous, straw-coloured oil (7 g.) (Found : N, 5·0; Br, 26·7. $C_{13}H_{16}O_2NBr$ requires N, 4·7; Br, 26·8%). From the alkaline solution, 1·5 g. of unchanged hydroxy-bromide were recovered by precipitation with dilute acid.

dl-5-*Methoxy*-1 : 3-*dimethyl*-3-β-*dimethylamino*-2-*indolinone* (II).—The methoxy-bromide (6·7 g.), dissolved in a solution of dimethylamine (5 g.) in 95% methyl alcohol (25 c.c.), was heated in a sealed tube at 150° for 4—6 hours. The alcohol was evaporated on a steam-bath, and the residual oil treated with dilute hydrochloric acid. A small quantity of an oil (0·8 g.) remained and this was removed by extraction with ether. The acid solution was basified with ammonia, and the precipitated oil taken up with ether. The solution was dried over anhydrous sodium sulphate, filtered, and evaporated, leaving a light brown oil (4·6 g.). This in dry ether, with methyl iodide, gave a *methiodide* (6 g.), which crystallised from methyl alcohol in colourless rectangular plates, m. p. 130—135° when rapidly heated. After being dried in a vacuum, the pure compound had m. p. 157—158° (Found : N, 6·7, 6·8; I, 31·1. $C_{16}H_{25}O_2N_2I$ requires N, 6·9; I, 31·4%). The salt was not very stable and, on keeping, it acquired a yellow colour and melted at a lower temperature. When it was warmed with alcoholic picric acid, an orange-yellow *quaternary picrate* was obtained, sparingly soluble in cold alcohol and crystallising from this solvent in bright yellow, irregular leaflets, m. p. 193—195° (Found : N, 13·9. $C_{16}H_{25}O_2N_2,C_6H_2O_7N_3$ requires N, 13·9%).

Esermethole from Physostigmine.—A solution of sodium (0·9 g.) in absolute alcohol (50 c.c.), in a flask fitted with a reflux condenser and an inlet tube passing dry oxygen-free nitrogen, was boiled to expel air. An alcoholic solution (50 c.c.) of physostigmine (10 g.), previously boiled, was then added, followed by a solution of methyl *p*-toluenesulphonate (7·5 g. in 30 c.c.); the nearly colourless solution soon became cloudy with the deposition of finely crystalline sodium *p*-toluenesulphonate. After 24 hours the reaction was completed by refluxing the solution on a steam-bath, a slow stream of nitrogen preventing access of air. The solution was then diluted with water (75 c.c.) and acidified with hydrochloric acid, and the alcohol

evaporated. After two extractions with ether, the solution was basified with aqueous caustic soda, which produced a deep red colour, and the crude esermethole was removed by repeated extraction with ether; the ethereal solution was dried over anhydrous sodium sulphate and evaporated, and the reddish oil distilled under diminished pressure. The pure base (2·3 g.) distilled at 164—167°/12 mm. The *methiodide* was prepared by the addition of methyl iodide to an ethereal solution of the base, and was crystallised by the addition of ethyl acetate to a concentrated solution in absolute alcohol. It was then obtained in squat rectangular prisms with pointed ends, m. p. 169—170° (Found: N, 7·7; I, 34·0. $C_{15}H_{23}ON_2I$ requires N, 7·5; I, 34·0%). Alcoholic picric acid converted the iodide into a *quaternary picrate*, which crystallised from alcohol in bright orange-red, diamond-shaped plates, m. p. 194° (Found: N, 14·4. $C_{15}H_{23}ON_2,C_6H_2O_7N_3$ requires N, 14·7%).

Dehydroesermetholemethine (II).—Esermethole methiodide (2·5 g.), dissolved in alcohol (10 c.c.) and water (50 c.c.), was heated on a steam-bath for 10 minutes with an excess of silver chloride (10 g.). The filtered solution was evaporated under diminished pressure, leaving a straw-coloured gum which readily solidified in the presence of acetone. The methochloride was not purified, but was dissolved in alcohol (10 c.c.) and heated to boiling with a solution of potassium ferricyanide (5 g.) and potassium hydroxide (7·5 g.) in water (60 c.c.). To prevent the precipitation of inorganic salts, water (100 c.c.) was then added, and the free base was extracted with ether. By evaporation of the ethereal solution, dried over anhydrous sodium sulphate, the optically active dehydroesermetholemethine was obtained as a nearly colourless oil (1·6 g.), which readily gave a *methiodide* (2·3 g.), crystallising from methyl alcohol in colourless, long, rectangular prisms, m. p. 142° when rapidly heated. When dried in a vacuum, however, the crystals became opaque, and the pure substance had m. p. 186—187° (Found: N, 6·9; I, 31·8. $C_{16}H_{25}O_2N_2I$ requires N, 6·9; I, 31·4%). The addition of an excess of aqueous picric acid to the methiodide (0·8 g.) in alcohol (2·5 c.c.) and water (10 c.c.) precipitated the *quaternary picrate* as an orange oil, which rapidly solidified in the presence of ether. It dissolved freely in cold alcohol and crystallised from acetone, on addition of ether, in clusters of orange-yellow needles, m. p. 132—133° (Found: C, 51·8; H, 5·5; N, 13·5. $C_{16}H_{25}O_2N_2,C_6H_2O_7N_3$ requires C, 52·3; H, 5·3; N, 13·9%).

The d-*bromocamphorsulphonate* was prepared from the methiodide (1 g.) in aqueous alcohol and an aqueous solution (20 c.c.) of silver *d*-bromocamphorsulphonate (1·1 g.). The solution, filtered from silver iodide, was evaporated under diminished pressure to a small

bulk and cooled in ice. A semi-solid mass of fine needles was obtained, but owing to the great solubility of the salt in water it was isolated by evaporating the solution to dryness. A specimen of the colourless gum which remained was dissolved in alcohol, and an excess of ether added. On standing, crystals appeared which served to inoculate the remainder of the product. The salt is very soluble in alcohol and chloroform, moderately easily soluble in acetone, scarcely soluble in ethyl acetate, and insoluble in benzene, toluene, and ether. It is best crystallised from acetone by addition of ether until a permanent turbidity appears; the pure salt is then obtained in clusters of long hexagonal leaflets, softening above 65° and melting at 245—248°. After being dried in a vacuum, it has m. p. 245—248° without previous softening (Found in material dried in a vacuum over phosphoric anhydride for 12 days: C, 53·4; H, 6·3; Br, 13·4. $C_{16}H_{25}O_2N_2,C_{10}H_{14}O_4BrS$ requires C, 53·2; H, 6·6; Br, 13·6%). A solution of the *d*-bromocamphorsulphonate (0·2212 g.) in absolute alcohol (10·0 c.c.) in a 1 dcm. tube had α + 0·62°, whence $[\alpha]_D^{18°}$ + 28·0°.

The Resolution of Synthetic Dehydroesermetholemethine Methiodide.—The iodide (2·3 g.) in alcohol (15 c.c.) was diluted with water (25 c.c.) and mixed with an aqueous solution (30 c.c.) of silver *d*-bromocamphorsulphonate (2·5 g.). When the solution, filtered from silver iodide, was evaporated under reduced pressure, a viscous syrup (3·2 g.) remained, and this was dissolved in boiling acetone (10 c.c.). On standing for an hour in the ice-chest, a mass of crystals (1·5 g.) was obtained, m. p. 157—160°; from the acetone mother-liquor a further quantity (1·6 g.), m. p. 200—220° after softening above 65°, was precipitated by ether. The first fraction was the d-*base* d-*bromocamphorsulphonate* and after two recrystallisations from acetone the pure salt (1 g.) was obtained in clusters of colourless rectangular plates, m. p. 166—167° (Found: C, 51·6; H, 7·0; Br, 13·2; N, 4·3. $C_{16}H_{25}O_2N_2,C_{10}H_{14}O_4BrS,H_2O$ requires C, 51·6; H, 6·8; Br, 13·2; N, 4·6%). A solution of the salt (0·230 g.) in absolute alcohol (10·0 c.c.) in a 1 dcm. tube had α + 1·77°, whence $[\alpha]_D^{18°}$ + 77·0°. The second fraction (m. p. 200—220°), by repeated fractional crystallisation from acetone–ether, eventually gave the pure l-*base* d-*bromocamphorsulphonate* (0·4 g.) in long, rectangular, hexagonal plates, softening above 65°, but, when dried in a vacuum, having m. p. 245—248°, alone or mixed with a specimen of the salt of natural origin (Found: C, 51·3; H, 6·8; Br, 13·5; N, 4·2. $C_{16}H_{25}O_2N_2,C_{10}H_{14}O_4BrS,H_2O$ requires C, 51·6; H, 6·8; Br, 13·2; N, 4·6%) [0·2264 g. in 10 c.c. of alcohol (*l*, 1 dcm.) gave α + 0·63°, whence $[\alpha]_D^{18°}$ + 27·8°]. This specimen was not intensively dried.

Synthetic l-*Base Methopicrate.*—The *l*-base *d*-bromocamphor-

sulphonate (0·4 g.), dissolved in water (5 c.c.) acidified with hydrochloric acid, was mixed with aqueous picric acid. The orange oil which separated solidified on standing. Crystallised from acetone by addition of ether, the *picrate* (0·2 g.) was obtained in clusters of orange-yellow needles, m. p. 132—133°, alone or mixed with a specimen of the picrate prepared from the alkaloid degradation product (Found: C, 51·6; H, 5·6; N, 13·5. $C_{16}H_{25}O_2N_2,C_6H_2O_7N_3$ requires C, 52·3; H, 5·3; N, 13·9%).

d-*Base Methopicrate*.—The *d*-base *d*-bromocamphorsulphonate (0·75 g.) was converted through the chloride into the *picrate* of the *d*-base, which separated as an orange oil (0·5 g.). In contact with ether it solidified to an orange-yellow solid, which crystallised from acetone, diluted with ether, in needles, m. p. 132—133° (Found: C, 51·8; H, 5·6; N, 13·7%).

Mixtures of equal amounts of the picrates (m. p. 132—133°) of the *d*-base and the synthetic or natural *l*-base had m. p. 193—195°, *i.e.*, the melting point of the picrate prepared from the unresolved dehydroesermetholemethine methiodide. The addition of an authentic specimen of the latter picrate did not affect the melting point of the mixtures of the two isomerides.

Preparation of the Optically Active Tertiary Base (II).—The picrate from the *l*-base *d*-bromocamphorsulphonate (0·5 g.) of synthetic origin was dissolved in acetone (2—3 c.c.), and the solution diluted with water (20 c.c.). The solution was acidified with concentrated hydrochloric acid, and the free picric acid removed by five extractions with ether. The aqueous solution was evaporated under diminished pressure and the methochloride was obtained as a viscous gum which could not be crystallised. It was therefore transferred to a small distilling flask in solution in methyl alcohol (2 c.c.) and, after evaporation of the solvent, heated in a vacuum. At 150—200° (bath temperature) bubbles of gas were evolved and at 260—300° a small quantity of an oil distilled which gave a solid methiodide (0·14 g.) crystallising from methyl alcohol in long rectangular prisms, m. p. 142°. Dried in a vacuum, it had m. p. 185—187° and did not affect the m. p. of the pure natural substance, m. p. 186—187°, when mixed with it.

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