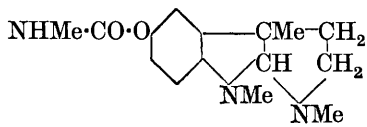
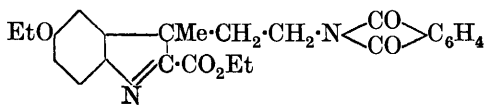
42. *Experiments on the Synthesis of Physostigmine (Eserine). Part II. Synthesis of a Base which is believed to be* dl-*Noreserethole.*

By Robert Robinson and Harusada Suginome.

In extending the scope of the synthesis of indolenines, described in the preceding communication, so as to include the preparation of bases closely allied to eserine (I) it was necessary to obtain intermediates with an appropriately situated and protected amino-



(I.)



(VII.)

group. To this end, acetaldoloxime was reduced in aqueous solution by means of amalgamated aluminium with formation of

γ-hydroxy-*n*-butylamine, $CH_3 \cdot CH(OH) \cdot CH_2 \cdot CH_2 \cdot NH_2$ (II), and this base furnished *phthalo-γ-hydroxybutylimide*,

$$CH_3 \cdot CH(OH) \cdot CH_2 \cdot CH_2 \cdot N{:}(CO)_2{:}C_6H_4 \text{ (III)},$$

when heated with phthalic anhydride.

The related *phthalo-γ-bromobutylimide*,

$$CH_3 \cdot CHBr \cdot CH_2 \cdot CH_2 \cdot N{:}(CO)_2{:}C_6H_4 \text{ (IV)},$$

was always prepared from the alcohol by the action of hydrogen bromide, but it was also obtained in poor yield by the condensation of αγ-dibromobutane and potassium phthalimide.

The bromo-compound and ethyl sodioacetoacetate afforded *ethyl δ-phthalimido-α-acetyl-β-methylvalerate*,

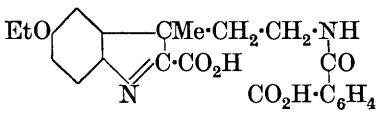
$$C_6H_4{:}(CO)_2{:}N \cdot CH_2 \cdot CH_2 \cdot CHMe \cdot CH(COMe) \cdot CO_2Et \text{ (V)},$$

and when this ester was coupled with *p*-ethoxybenzenediazonium chloride in alkaline solution the acetyl group was eliminated and *ethyl δ-phthalimido-α-keto-β-methylvalerate* p-*ethoxyphenylhydrazone*, $C_6H_4{:}(CO)_2{:}N \cdot CH_2 \cdot CH_2 \cdot CHMe \cdot C(CO_2Et){:}N_2H \cdot C_6H_4 \cdot OEt$ (VI), formed. The indolenine ring-closure was effected by means of ethyl-alcoholic hydrogen chloride and gave *ethyl 5-ethoxy-3-methyl-3-β-phthalimidoethylindolenine-2-carboxylate* (VII) in moderately satisfactory yield.

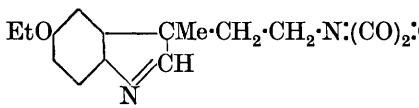
The next stage in the synthesis was the replacement of the carbethoxy-group by a hydrogen atom. This was attempted by a great variety of methods, none of which was entirely successful, although the desired base (IX) was ultimately obtained in about 7% yield.

If the phthalimido-group was first removed, cyclic lactams (see below) were produced, and these resisted further degradation; on the other hand, the carbethoxy-group could not be hydrolysed without affecting the phthalimido-group. Attempts to improve matters by working with the metho-salts of the indolenine ester (VII) were also fruitless.

Hydrolysis of (VII) by means of ethyl-alcoholic potassium hydroxide gave the dicarboxylic acid (VIII) in nearly theoretical amount. When this was heated in boiling xylene solution, it gave



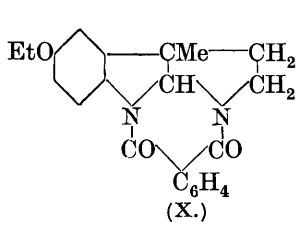
(VIII.)



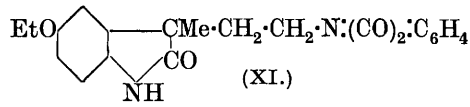
(IX.)

the indolenine (IX); the chief product, however, was a neutral substance which we regard as NN′-*phthaloyldinoreserethole* (X). The latter is a very stable substance and resists hydrolysis even by means

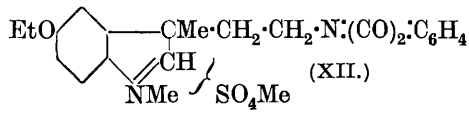
of powerful reagents. When the dicarboxylic acid was heated alone, it gave the same products, and, in addition, a small relative amount of 5-ethoxy-3-methyl-3-β-phthalimidoethylindolinone (XI) was obtained as the result of oxidation.



(X.)

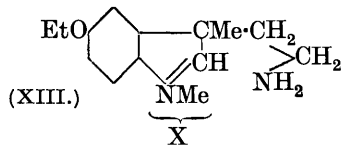


(XI.)

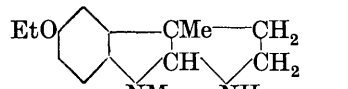


(XII.)

The transformation of the indolenine base (IX) into *dl*-noreserethole (XIV) proceeds smoothly; the methosulphate (XII) of (IX) was treated successively with hydrazine in alcoholic solution and with hydrochloric acid.



(XIII.)



(XIV.)

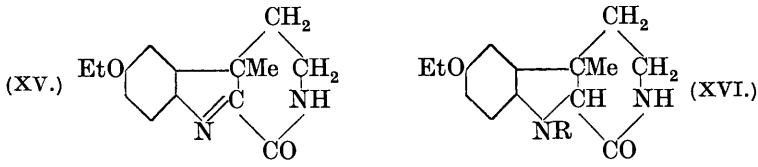
An intermediate product of the form (XIII) doubtless undergoes ring-closure by addition of the side-chain amine group to the indoleninium unsaturated system, the process being entirely analogous to a condensation of cotarninium hydroxide or to the formation of a cyclic acetal from a hydroxy-carbonyl compound, for example, α- or β-glucose from the open-chain hexose.

The base (XIV) is an oil but has been characterised by means of the *hydrochloride*, the *picrate*, and the *chloroplatinate*. It is significant that the substance is mono-acid towards hydrochloric and picric acids but behaves as a di-acid base towards chloroplatinic acid.

On treatment with dry methyl sulphate in benzene solution, the secondary amino-group is methylated and a syrup having the composition and properties anticipated for *dl*-eserethole is obtained; a description of this part of the investigation is reserved for a future communication.

The action of hydrazine, followed by hydrochloric acid, on the indolenine ester (VII) furnishes the *ketoethoxymethyltetrahydro-ψ-carboline* (XV), which is easily reduced to a dihydro-derivative (XVI, R = H). The ψ-carboline yields a methosulphate which can

be reduced with formation of an ethoxyketodimethylhexahydrocarboline (XVI, R = Me).



In order to avoid some of the difficulties mentioned above we projected the preparation of the indolenine base (IX) directly from the appropriate ethoxyphenylhydrazone,

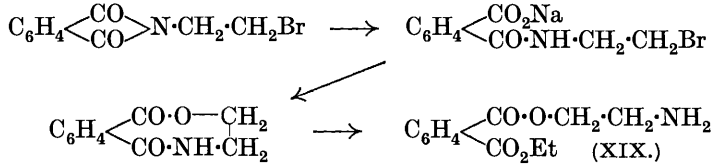
$$EtO\cdot C_6H_4\cdot NH\cdot N{:}CH\cdot CHMe\cdot CH_2\cdot CH_2\cdot N{:}(CO)_2{:}C_6H_4.$$

This investigation has not yet been completed, but a description of the preparation of γ-phthalimido-α-methylbutyric acid,

$$C_6H_4{:}(CO)_2{:}N\cdot CH_2\cdot CH_2\cdot CHMe\cdot CO_2H \text{ (XVII)},$$

is appended in order to draw attention to an interesting side reaction.

The condensation of phthalo-β-bromoethylimide and ethyl sodiomethylmalonate with formation of ethyl methyl-β-phthalimidoethylmalonate, $C_6H_4{:}(CO)_2{:}N\cdot CH_2\cdot CH_2\cdot CHMe(CO_2R)_2$ (XVIII, R = Et), proceeds smoothly in dry benzene solution, but in alcoholic solution, following Aschan (*Ber.*, 1890, **23**, 3692), the yield was poor and a base, $C_{12}H_{15}O_4N$, was isolated as a picrate. This base, on hydrolysis with boiling aqueous sodium hydroxide, gave rise to sodium phthalate and ethyl alcohol, so its constitution must be represented by (XIX). Its formation by the action of alcoholic sodium ethoxide on phthalo-β-bromoethylimide may be represented by the following scheme :



In the series of indolenine derivatives containing a quaternary group and an ethoxyl group it was found that the elementary analyses frequently gave a low value for the carbon content (0·5—0·8). By using a specially hot furnace and slow combustion, normal results were obtained in two typical cases of this kind, and the low results are doubtless due to loss of a simple hydrocarbon from the ethoxyl or quaternary carbon group.

Experimental.

*γ-Hydroxy-*n*-butylamine* (II).—The chloroaurate of this base has been described by Levene and Haller (*J. Biol. Chem.*, 1926, **69**,

573), who obtained it by an application of the Curtius method, but the free base does not appear to have been previously obtained.

Acetaldoloxime (compare Wegscheider and Späth, *Monatsh.*, 1910, **31**, 1023) was prepared in the following manner and, as it could not be distilled undecomposed, the crude substance was employed for reduction.

A fresh solution of aldol (88 g.) in alcohol (170 c.c.) was added to one of hydroxylamine hydrochloride (88 g.) in water (264 c.c.), and potassium hydroxide (70·4 g.) dissolved in alcohol was introduced in the cold. The mixture was heated at 40—50° for 30 minutes and kept for 12 hours, and the solvent then removed under diminished pressure at 40°. The oxime was isolated by means of ether as a colourless syrup (79 g. or 77%).

Amalgamated aluminium foil (120 g.) was added to a solution of acetaldoloxime (103 g.) in water (2500 c.c.) cooled in running water. After 48 hours the filtrate and washings from the aluminium hydroxide along with hydrochloric acid (100 c.c., *d* 1·16) were concentrated under diminished pressure and the viscous brownish residue was dried as completely as possible at 60° in a vacuum. It was then mixed with powdered potassium hydroxide (120 g.) and the base was distilled, then dried over solid potassium hydroxide, and distilled over anhydrous barium oxide (*ca.* 30 g.) (yield, 47—53 g.; b.p. 165—175°). Such a specimen was pure enough for our purposes; redistilled over barium oxide, the base had b. p. 172°/755 mm.

The *chloroplatinate*, prepared by mixing concentrated solutions of the hydrochloride and platinic chloride, crystallised from methyl alcohol in orange-yellow plates, m. p. 206° (decomp.) (Found: Pt, 33·0. $C_{16}H_{24}O_2N_2Cl_6Pt$ requires Pt, 33·2%).

The *picrate* crystallised from alcohol in stout yellow prisms, m. p. 122° (Found: C, 37·8; H, 4·0; N, 17·7. $C_{10}H_{14}O_8N_4$ requires C, 37·7; H, 4·4; N, 17·6%).

Phthalo-γ-hydroxybutylimide (III).—When powdered phthalic anhydride (148 g.) and the butanolamine (89 g.) were mixed, an exothermic reaction set in; the process was completed by heating (oil-bath at 210°) until no further separation of water occurred. The dark brown product was employed directly for the conversion into bromide. A portion was dissolved in a large volume of light petroleum and after concentration the substance crystallised in colourless stellate clusters of needles, m. p. 47—48° (Found: C, 65·2; H, 5·9; N, 6·3. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 5·9; N, 6·4%). The substance is freely soluble in most organic solvents.

Phthalo-γ-bromobutylimide (IV).—The crude hydroxy-compound (from 89 g. of the butanolamine), mixed with hydrobromic acid (200 g., saturated at 0°), was heated on the steam-bath for an hour.

The *bromo*-compound was isolated by means of ether as a crystalline cake (245 g.) and was recrystallised from 75% alcohol (yield, 164—172 g.; *ca.* 60% on the butanolamine), forming colourless needles, m. p. 56·5—57°, readily soluble in most organic solvents (Found : C, 51·1; H, 4·0; N, 5·4; Br, 27·8. $C_{12}H_{12}O_2NBr$ requires C, 51·1; H, 4·3; N, 5·0; Br, 28·3%).

When a smaller proportion (*e.g.*, 1·5 mols.) of hydrobromic acid was employed in this preparation, the yield was diminished owing to the simultaneous formation of *methyl-β-phthalimidoethylcarbinyl hydrogen phthalate*, $C_6H_4(CO)_2N\cdot CH_2\cdot CH_2\cdot CHMe\cdot O\cdot CO\cdot C_6H_4\cdot CO_2H$. This by-product was isolated from the sodium carbonate washings of the bromo-compound. It crystallised from benzene in colourless, thick, rhombic plates, m. p. 101° (Found : N, 4·0. $C_{20}H_{17}O_6N$ requires N, 3·8%), easily soluble in the simple alcohols, acetone, ethyl acetate, chloroform and benzene, less readily soluble in ether, and sparingly soluble in light petroleum.

The constitution of the substance was proved by the following experiment. The by-product (14·7 g.) was heated with 80% hydrobromic acid (37 c.c.) for 1 hour on the steam-bath; it was then possible to isolate phthalo-γ-bromobutylimide (10·7 g.; almost theoretical yield), m. p. 57°, and phthalic acid (6·5 g.), yielding the anhydride, m. p. 128°.

Ethyl δ-Phthalimido-α-acetyl-β-methylvalerate (V).—Phthalo-γ-bromobutylimide (282 g.) and sodium iodide (3·0 g.) were added to a solution of ethyl potassioacetoacetate (47 g. of potassium, 350 c.c. of ethyl alcohol, and 170 g. of ethyl acetoacetate), and the mixture refluxed for 22 hours with protection from carbon dioxide and moisture. After neutralisation by means of acetic acid the materials volatile in steam were removed and the product was isolated by means of ether (276—314 g. or 83—95%) and purified by continuous extraction with light petroleum (yield, 242—248 g. or 73—75%). The *ester* so obtained was a colourless syrup which was pure enough for most purposes; a specimen was distilled, b. p. 215—217°/1 mm. (Found : C, 65·6; H, 6·5; N, 4·4. $C_{18}H_{21}O_3N$ requires C, 65·2; H, 6·4; N, 4·2%). The preparation of this substance does not proceed so conveniently in the absence of an iodide, or if sodium is used instead of potassium.

Ethyl δ-Phthalimido-α-keto-β-methylvalerate p-*Ethoxyphenylhydrazone* (VI).—Crystallised sodium acetate (20 g.) was added to an ice-cold solution of *p*-ethoxybenzenediazonium chloride [from 27·4 g. of *p*-phenetidine, 40 c.c. of hydrochloric acid (*d* 1·16), 14·2 g. of sodium nitrite, and 90 c.c. of water] and this solution was gradually introduced, below 0°, into one of ethyl phthalimidoacetylmethylvalerate (66·2 g.) in alcoholic sodium ethoxide (400 c.c.; 4·6 g. of

sodium). After the addition of much water the dark reddish-brown oil was collected, preferably on a large moistened filter-paper, dissolved as far as possible in ether, and freed from acidic impurities by washing with aqueous sodium carbonate. The residue, after removal of the solvent, crystallised after being kept in the ice-chest. The *hydrazone* was washed with a little alcohol (yield, 9·5—10·3 g.) and crystallised from alcohol or ethyl acetate, forming orange-yellow rosettes, m. p. 108—109° (Found: C, 65·6; H, 6·1; N, 9·8. $C_{24}H_{27}O_5N_3$ requires C, 65·9; H, 6·2; N, 9·6%), readily soluble in most organic solvents, somewhat sparingly soluble in ether, and very sparingly soluble in light petroleum.

The conditions for the preparation of this substance were studied by conversion of the crude product into the readily crystallised indolenine ester (see below). In the presence of various reagents the yields of indolenine ester from phthalimido-ester were the following: alcoholic sodium ethoxide, 15—19; sodium hydroxide, 10; sodium carbonate, 6; sodium acetate, 2%.

Hydrolysis of the crude hydrazone-ester gave no crystalline acid and the oil gave no trace of an indolenine derivative on appropriate treatment. This is doubtless due to the opening of the phthalimide ring and recalls the experience of Manske, Perkin, and Robinson (J., 1927, 9) that indole ring-closure, possible with a phthalimide derivative, did not occur with the related phthalamic acid.

Ethyl 5-Ethoxy-3-methyl-3-(β-phthalimidoethyl)indolenine-2-carboxylate (VII).—A suspension of the pure ethoxyphenylhydrazone (8·7 g.) in alcohol (80 c.c.) was saturated with hydrogen chloride with cooling, and the mixture refluxed for 5 minutes and then concentrated under diminished pressure. Sodium carbonate solution was added to the viscous reddish residue until this was alkaline to litmus and, on keeping in the ice-chest, a pasty mass of crystals was obtained; this was stirred with ether and the solid collected (3·4—3·8 g., or 41—45%). The substance crystallised from alcohol (charcoal) in nearly colourless prisms, m. p. 132—133° (Found: C, 68·1; H, 5·6; N, 6·6. $C_{24}H_{24}O_5N_2$ requires C, 68·5; H, 5·8; N, 6·7%). It is freely soluble in chloroform, moderately easily soluble in the alcohols, acetone, acetic acid, ethyl acetate and benzene, but sparingly soluble in ether and light petroleum. The solution in concentrated hydrochloric or sulphuric acid is orange and becomes colourless on the addition of water. The over-all yield from phthalimido-ester was only 9—11%, but this was increased to 15—18·5% by omitting the purification of the *p*-ethoxyphenylhydrazone. The crude product from phthalimido-ester (66·2 g.) was dissolved in alcohol (200 c.c.) and worked up as before (yield, 12·6—15·6 g.).

Methosulphate. A mixture of the indolenine ester (1·05 g.), methyl sulphate (0·5 g.), and dry benzene (2 c.c.) was heated for 6 minutes; a heavy layer then separated. Ether was added, the upper layer decanted, and the residue washed with ether; on keeping, it crystallised (1·2 g., m. p. 50—60°) (Found: S, 6·3. $C_{26}H_{30}O_9N_2S$ requires S, 5·9%), but recrystallisation was not feasible. The salt dissolves in water, acetic acid or even many neutral organic solvents, to a solution that exhibits an intense bluish-green fluorescence; on the addition of concentrated hydrochloric acid the fluorescence disappears and the solution becomes lemon-yellow. An attempt to oxidise this compound in acetone solution by means of potassium ferricyanide in the presence of potassium hydroxide appeared to proceed normally and potassium ferrocyanide separated after an exothermic reaction. The product was isolated by extraction with benzene and crystallised from alcohol, forming pale buff-coloured rhombohedra, m. p. 116° (decomp.) (Found: C, 66·3; H, 6·3; N, 6·2. $C_{25}H_{28}O_6N_2$ requires C, 66·4; H, 6·2; N, 6·2%). The substance appears to be the *methohydroxide*; it is soluble in acetic acid to a bluish-green fluorescent solution and in dilute hydrochloric acid to a lemon-yellow non-fluorescent solution.

5-Ethoxy-3-methyl-3-(β-o-carboxybenzamidoethyl)indolenine-2-carboxylic Acid (VIII).—A solution of potassium hydroxide (5·0 g.) in water (2·5 c.c.) and alcohol (30 c.c.) was added to a suspension of the indolenine ester (16·8 g.) in 95% alcohol (30 c.c.) with cooling in ice-water and occasional shaking; after 2 hours the mixture was homogeneous and shortly afterwards a potassium salt separated and water (60 c.c.) was added. After 12 hours' keeping at room temperature the alcohol was removed in a vacuum, the residue dissolved in water, and the acid precipitated by means of hydrochloric acid as a flocculent mass which became more definitely crystalline on keeping; it was then collected and dried (15·6 g. or 95%). On heating, this acid decomposes gradually from 90—150°; it is soluble in concentrated hydrochloric acid to a greenish-yellow solution, in concentrated sulphuric acid to an orange-yellow solution, and in acetic acid to a green solution; all the colours are discharged on the addition of water.

The acid could not be recrystallised, but its *dipotassium* salt separated from alcohol in colourless prisms, m. p. 290° with softening at 283° (Found in air-dried material: C, 51·7; H, 4·5; N, 5·8; loss at 105° in a high vacuum over phosphoric anhydride, 3·6.

$$C_{22}H_{20}O_6N_2K_2,H_2O$$

requires C, 52·4; H, 4·4; N, 5·6; H_2O, 3·6%).

The mother-liquor from the preparation of the dicarboxylic acid deposited a second colourless substance (0·5 g.) in crystals, m. p.

270° (decomp.). This is an acid, soluble in aqueous sodium carbonate and precipitated by hydrochloric acid, but it was not further investigated.

5-Ethoxy-3-methyl-3-(β-phthalimidoethyl)indolenine (IX).—Dry xylene (65 c.c.) in which the indoleninedicarboxylic acid (VIII) (2·5 g.) was suspended was refluxed for 3 hours; the evolution of carbon dioxide had then ceased. The indolenine base was extracted by shaking with several small volumes of dilute hydrochloric acid and the filtered combined extracts were basified with sodium carbonate, causing the precipitation of the desired product in a crystalline condition (0·14—0·18 g. or 6·6—8·5%). The *base* crystallised from alcohol in needles, m. p. 123—124° (Found: C, 71·6; H, 5·7; N, 8·0; EtO, 13·4. $C_{21}H_{20}O_3N_2$ requires C, 72·4; H, 5·7; N, 8·0; EtO, 12·9%), freely soluble in most organic solvents but sparingly soluble in light petroleum. The *picrate* crystallised from alcohol in orange-yellow rosettes, m. p. 156—157° (Found: C, 56·3; H, 4·4; N, 12·3. $C_{27}H_{23}O_{10}N_5$ requires C, 56·2; H, 4·0; N, 12·1%).

The *methosulphate* (XII) was prepared by heating a mixture of the base (0·5 g.), pure methyl sulphate (0·3 g.), and benzene (2 c.c.) for 2 minutes; on cooling, the viscous oil that had separated crystallised and it was then collected and washed with ether (yield, 0·61 g.). The derivative crystallised from alcohol–ether in stellate clusters of colourless needles, m. p. 153—154° (Found: S, 6·7. $C_{23}H_{26}O_7N_2S$ requires, S, 6·8%).

NN'-Phthaloyldinoreserethole (X) *and 5-Ethoxy-3-methyl-3-(β-phthalimidoethyl)indolinone* (XI).—The xylene solution from which, as described in the last section, the indolenine base had been removed by means of dilute hydrochloric acid was washed with aqueous sodium carbonate, some chloroform being added to dissolve solid that separated during the process; the aqueous layer afforded 0·3 g. of an acid, decomp. 170°. The chloroform–xylene solution was dried, the solvent removed, and the residue triturated with methyl alcohol. The solid thus obtained (0·91 g., m. p. 215—216°) crystallised from much alcohol or ethyl acetate in stout colourless prisms, m. p. 218—219° (Found: C, 71·6, 71·7; H, 6·2, 6·1; N, 8·2, 8·1, 8·1; EtO, 12·6. $C_{21}H_{20}O_3N_2$ requires C, 72·4; H, 5·7; N, 8·0; EtO, 12·9%). This neutral substance is readily soluble in chloroform, moderately readily soluble in hot alcohol, acetone, ethyl acetate or acetic acid, and sparingly soluble in ether and light petroleum. The solution in sulphuric acid is lemon-yellow, becoming colourless on addition of water.

The unchanged substance was recovered after refluxing with alcoholic potassium hydroxide for 24 hours. Boiled under reflux with a mixture of equal volumes of acetic acid and concentrated

hydrochloric acid, it afforded equal amounts of a base, the investigation of which is not complete, and of the indolinone derivative, m. p. 168—169°, mentioned below.

In the course of attempts to improve the yield of indolenine base the thermal decomposition of the dicarboxylic acid (VIII) was investigated under a variety of conditions and the following example is selected for description.

The dicarboxylic acid (7·1 g.) was gradually heated (oil-bath) to 190° during 20 minutes; the production of water, carbon dioxide, and phthalic anhydride was then observed. When the decomposition ceased, the residue was cooled and treated with a small volume of methyl alcohol. The NN'-*diphthaloyldinoreserethole* (2·37 g., m. p. 214—216°) was thus isolated as a solid and after crystallisation from ethyl acetate had m. p. 218—219°. The mother-liquor from these crystals was evaporated in an evacuated desiccator over sulphuric acid, the dark brown residue (3·96 g.) taken up in benzene, and the extract washed with aqueous sodium carbonate and with water and dried. The solvent was again removed under diminished pressure, and the residue dissolved in a little methyl alcohol and kept in the ice-chest; a yellow crystalline substance which separated (0·6 g., m. p. 168°) was recrystallised from ethyl acetate, forming large yellow rhombohedra, m. p. 169—170° (Found: C, 68·4; H, 5·5; N, 7·9; EtO, 12·1. $C_{21}H_{20}O_4N_2$ requires C, 69·2; H, 5·5; N, 7·7; EtO, 12·4%).

The substance is considered to be 5-*ethoxy*-3-*methyl*-3-(β-*phthalimidoethyl*)*indolinone* (XI); it is much more readily soluble in most organic solvents than the compound, m. p. 218—219°, described above, but it is very sparingly soluble in ether and light petroleum. The solution in concentrated sulphuric acid is dark green.

The final mother-liquor furnished a small, unworkable quantity of the indolenine base (IX).

Similar results were obtained when the dicarboxylic acid was heated in a vacuum with the use of a nitrobenzene-vapour bath.

The action of acetic anhydride on the dicarboxylic acid (VIII) in boiling benzene solution gave a small yield (*ca.* 3%) of a substance that crystallised from much alcohol in colourless rhombohedra, m. p. 228° (Found: C, 66·5; H, 5·1; N, 6·8%). This unidentified neutral substance gives a lemon-yellow solution in sulphuric acid and, on the addition of water, it is precipitated unchanged from a colourless liquid. The action of acetic anhydride alone on the dicarboxylic acid (VIII) did not afford this compound and the acid was decomposed with formation of phthalic anhydride in quantitative amount; the other products could not be purified.

dl-*Noreserethole* (XIV).—A solution of the methosulphate (XII)

(0·3 g.) and hydrazine hydrate (0·3 g.) in alcohol (3 c.c.) was boiled for 5 minutes; woolly crystals then separated, and after acidification with hydrochloric acid the phthalhydrazide was collected. The filtrate was evaporated in an evacuated desiccator over sulphuric acid, the crystalline residue dissolved in water, and the base liberated by potassium hydroxide and isolated by means of ether (yield, 0·13 g. or 89%). The syrup is a strong base (litmus) and it could not be crystallised. The *hydrochloride* was obtained by concentrating a solution (which on keeping became blue) of the base in dilute hydrochloric acid in an evacuated desiccator and crystallising the residue from absolute alcohol. The faintly bluish-grey needles had m. p. 191—192° (Found in air-dried material: C, 61·8, 61·7; H, 7·7, 8·1; N, 10·4; Cl, 13·8. $C_{14}H_{20}ON_2$,HCl requires C, 62·6; H, 7·8; N, 10·4; Cl, 13·2%).

The *chloroplatinate* crystallised from aqueous solution in small yellowish-brown prisms, which darkened at 185° and charred gradually above this temperature but did not melt (Found in an air-dried specimen: loss at 130° in a vacuum over phosphoric anhydride, 4·0. Found in anhydrous salt: Pt, 30·5.

$C_{14}H_{20}ON_2,H_2PtCl_6,1\frac{1}{2}H_2O$

requires $1\frac{1}{2}H_2O$, 4·0. $C_{14}H_{20}ON_2,H_2PtCl_6$ requires Pt, 30·4%).

The *picrate*, prepared in ethereal solution, crystallised from alcohol in reddish-orange prisms, m. p. 180—181° (Found: C, 52·1; H, 5·3; N, 15·1. $C_{20}H_{23}O_8N_5$ requires C, 52·1; H, 5·0; N, 15·2%).

dl-*Eserethole.*—*dl*-Noreserethole (0·7 g.) was dissolved in ethyl acetate (0·5 c.c.), benzene (2 c.c.), and dry neutral methyl sulphate (0·4 g.) and kept in the ice-chest; the precipitated syrup crystallised. The substance was washed with ether and dissolved in water, and the base rendered to ether. The ethereal solution was dried over solid potassium hydroxide and distilled. The pale yellow oily base distilled without decomposition near 200°/1 mm., but the boiling point was not determined owing to the small quantity available (Found: C, 72·9; H, 9·0. $C_{15}H_{22}ON_2$ requires C, 73·2; H, 8·9%). Unlike the majority of the analyses recorded in this memoir, this was a macro-analysis (0·0921 g.) carried out slowly in a long, hot, lead chromate tube. It is hoped that a further description of this base and its derivatives may be submitted to the Society in a short time.

It is probable that the same substance was obtained by the action of aqueous formaldehyde and formic acid on the noreserethole at 135—165° in a sealed tube (compare Hess and Leibbrandt, *Ber.*, 1917, **50**, 1385). The product, isolated after 7 hours' heating, was an oily base, differing from the initial material, but not yielding characteristic salts.

3-*Keto*-10-*ethoxy*-7-*methyl*-3 : 4 : 5 : 6-*tetrahydro*-4-*ψ*-*carboline* (XV). —A solution of the indolenine ester (VII) (2·1 g.) in alcohol (5 c.c. of 95%) containing hydrazine hydrate (0·16 g.) was boiled for 5 minutes; an insoluble crystalline substance then separated. This was decomposed by addition of hydrochloric acid (3 c.c., *d* 1·16) and heating, the phthalhydrazide separated, and the filtrate concentrated in an evacuated desiccator and again filtered from a deposit. The clear orange-yellow solution was basified; the *lactam*, precipitated as an oil which soon crystallised (0·5 g. or 41%), was recrystallised from alcohol, forming colourless needles, m. p. 194—195° (Found: C, 68·7; H, 6·7; N, 15·5; EtO, 17·8. $C_{14}H_{16}O_2N_2$ requires C, 68·8; H, 6·6; N, 15·5; EtO, 18·4%). The substance is sparingly soluble in the common organic solvents and its alcoholic solution has a blue fluorescence. It is soluble in dilute acids to orange-yellow solutions.

When the indolenine ester (2·1 g.) was decomposed with hydrazine hydrate (2 c.c.) under similar conditions of reaction and isolation, another substance (1·0 g.) was obtained which formed faintly brownish prisms, m. p. 111—112°, from alcohol (Found: C, 65·7; H, 7·8; N, 10·2%).

Methosulphate of (XV). When a mixture of the lactam (0·4 g.), pure methyl sulphate (0·4 g.), and benzene (2 c.c.) was heated, the *derivative* separated in the course of a few minutes. It crystallised on cooling and the greenish-yellow substance (0·56 g.) was collected and washed with ether. It separated from alcohol in greenish-yellow rhombohedra which darkened at 145° and decomposed at 162° (Found: S, 8·4. $C_{16}H_{22}O_6N_2S$ requires S, 8·6%). The derivative could also be prepared in alcoholic solution, but the yield was inferior.

3-*Keto*-10-*ethoxy*-7-*methyl*-3 : 4 : 5 : 6 : 7 : 2-*hexahydro*-4-*carboline* (XVI, R = H).—This substance was obtained by reducing the lactam (XV) in the manner described below for its methosulphate; the yield was theoretical. It crystallised from alcohol in colourless needles, m. p. 192—193·5° (Found: C, 67·9; H, 7·3; N, 11·8. $C_{14}H_{18}O_2N_2$ requires C, 68·2; H, 7·3; N, 11·4%). The substance is soluble in acids to colourless solutions and it is moderately readily soluble in most organic solvents but is sparingly soluble in light petroleum.

3-*Keto*-10-*ethoxy*-1 : 7-*dimethyl*-3 : 4 : 5 : 6 : 7 : 2-*hexahydro*-4-*carboline* (XVI, R = Me).—Zinc dust (1·2 g.) was added to a solution of the methosulphate of the lactam base (XV) (0·5 g.) in hydrochloric acid (5 c.c., *d* 1·16): reduction occurred at once with evolution of heat. The filtered solution was rendered strongly alkaline by means of potassium hydroxide; the solid *base* crystallised from alcohol in

colourless prisms, m. p. 148—149° (Found: C, 68·8; H, 7·7; N, 10·8. $C_{15}H_{20}O_2N_2$ requires C, 69·2; H, 7·7; N, 10·8%). The substance is soluble in acids to colourless solutions; it is sparingly soluble in ether and in light petroleum but readily soluble in most other organic solvents.

Ethyl Methyl-β-phthalimidoethylmalonate (XVIII, R = Et).—Ethyl methylmalonate (75 g.) was gradually introduced into a suspension of sodium (8·2 g., granulated with toluene) in benzene (200 c.c.), and the formation of the sodio-compound completed by heating for 2 hours on the steam-bath. Powdered phthalo-β-bromoethylimide (68 g.) and sodium iodide (2·0 g.) were then added and the mixture was refluxed for 24 hours. The reaction product was neutralised with acetic acid and subjected to distillation in steam, and the product isolated from the non-volatile portion by means of ether. The crystals, obtained by cooling below 0°, were triturated with a mixture of alcohol (1 vol.) and light petroleum (5 vols.), collected, and washed (yield, 34·8—40 g. or 40—46%). The *ester* crystallised from light petroleum in stout colourless prisms, m. p. 72·5—73° (Found: C, 62·2; H, 5·9; N, 4·2. $C_{18}H_{21}O_6N$ requires C, 62·2; H, 6·1; N, 4·0%).

The *methyl* ester (XVIII, R = Me), obtained in a like manner, crystallised from light petroleum in colourless prisms, m. p. 85—85·5° (Found: C, 60·4; H, 5·6; N, 4·5. $C_{16}H_{17}O_6N$ requires C, 60·2; H, 5·4; N, 4·4%).

β-Aminoethyl Ethyl Phthalate (XIX).—When the condensation of phthalo-β-bromoethylimide with ethyl sodiomethylmalonate was effected in alcoholic solution, a side-reaction occurred and the product was difficult to crystallise and was obtained in inferior yield (compare Aschan, *loc. cit.*). The crude product (from 33 g. of phthalo-β-bromoethylimide) was dissolved in ether, and ethereal picric acid added until no more yellow precipitate was formed. The *picrate* (14·6 g.) crystallised from alcohol in yellow needles, m. p. 155—156° (Found: N, 12·3. $C_{18}H_{18}O_{11}N_4$ requires N, 12·0%).

The oily base from the picrate could not be crystallised, but the *hydrochloride* crystallised from alcohol–ether in colourless plates, m. p. 113° (Found: C, 52·7; H, 5·8; N, 5·4; Cl, 13·2. $C_{12}H_{15}O_4N$,HCl requires C, 52·6; H, 5·9; N, 5·1; Cl, 13·0%).

A boiling 5% solution of sodium hydroxide quickly dissolved the base and the solution was distilled; alcohol was recognised in the distillate and, on acidification of the residue, phthalic acid was precipitated and readily identified.

Methyl-β-phthalimidoethylmalonic Acid (XVIII, R = H).—The ethyl ester was hydrolysed by boiling hydrochloric acid (20 vols., *d* 1·16) for 3 hours, any loss of the acid being made good, and the

clear colourless solution was concentrated on the steam-bath. The residue was diluted with water, and the solid *acid* collected (yield, 90%); it was already pure after being washed and dried (Found: C, 58·0; H, 4·7; N, 4·4. $C_{14}H_{13}O_6N$ requires C, 57·7; H, 4·5; N, 4·8%). In a similar manner the hydrolysis of the methyl ester was complete in 45 minutes and the yield of acid was 95%.

γ-Phthalimido-α-methylbutyric Acid (XVII).—The methylphthalimidoethylmalonic acid decomposed at 170—180° (cymene-bath) in 5 minutes. The product crystallised from benzene–light petroleum in colourless stellate groups, m. p. 112—113° (Found: C, 63·2; H, 5·1; N, 5·6. $C_{13}H_{13}O_4N$ requires C, 63·1; H, 5·3; N, 5·7%).

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