118. *The Constitution of Yohimbine and Related Alkaloids. Part VI.* The Synthesis of* 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro-2-ketoindolo*-(2 : 3-a)*pyridocoline and* 1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline.*†

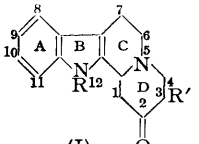
By L. H. Groves and G. A. Swan.

The compounds (I; R = R′ = H) and (II), named in the title, have been synthesised as a step towards further synthetic work in the field of the indole alkaloids. Both of these compounds have been converted into 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydroindolo(2 : 3-*a*)pyridocoline.

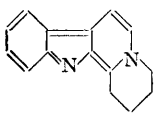
After the synthesis of yohimbone (Part IV, *J.*, 1950, 1534), synthesis of yohimbine requires also the introduction of the carbomethoxy-group. From Birch's work (*J.*, 1950, 1551) on the methyaltion of 2 : 5-dihydroanisole it appeared that this might be done *via* the potassium salt of 3″-methoxy-3 : 4 : 6 : 9*b* : 1″ : 4″-hexahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)pyridocoline. Accordingly, attempts were made first to introduce the carbethoxy-group into 2 : 5-dihydroanisole by Birch's method except that the methyl iodide was replaced by ethyl carbonate or chloroformate; but these attempts were unsuccessful.

At this stage we were also interested in obtaining *m*-methoxyphenylalanine in quantity, for the preparation of 6-methoxyl*iso*quinoline-3-carboyxlic acid, since the introduction of a (potential) carbomethoxy-group into position 5 of this compound (as opposed to its 1 : 2 : 3 : 4-tetrahydro-derivative) seemed feasible. We also investigated two further methods for the preparation of *m*-methoxyphenylalanine; and these are described in the Experimental section, although the yields obtained are no better than those recorded in Part IV.

Even before these failures, attention was also turned to other synthetic routes and it seemed likely that ketones of type (I) might be useful starting materials for the synthesis, not only of yohimbine, but also of certain other alkaloids and degradation products thereof:



(I)



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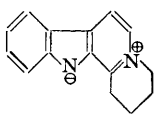


(IIa)

recent work on corynantheine (Karrer, Schwyzer, and Flam, *Helv. Chim. Acta*, 1951, **34**, 993; Janot, Goutarel, and Prelog, *ibid.*, p. 1207), serpentine (Schlittler and Schwarz, *ibid.*, 1950, **33**, 1463), and the alstonia alkaloids (Karrer and Enslin, *ibid.*, p. 100; Elderfield and Gray, *J. Org. Chem.*, 1951, **16**, 506) has emphasised the importance of this ring system. We now describe preliminary experiments which have led to the syntheses of (I; R = R′ = H) and (I; R = Me, R′ = H) by methods which might allow extension to products in which R′ is some other group. In the case of serpentine and the alstonia alkaloids, ring c has the less reduced form as in (II), and we describe also a synthesis of this compound.

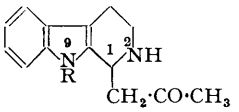
Tryptamine hydrochloride condensed with αγ-diketovaleric acid in water at 45°, or with formylacetone dimethyl acetal at room temperature, to give 1-acetonyl-1 : 2 : 3 : 4-tetrahydro-β-carboline ‡ (III; R = H). 1-Methyltryptamine similarly yielded (III; R = Me). Attempts to cyclise these compounds to (I; R = R′ = H) and (I; R = Me, R′ = H), respectively, by treatment with formaldehyde failed, so (IV; X = OMe and Cl) were synthesised. The latter, 1-(4-chloro-2-ketobutyl)-1 : 2 : 3 : 4-tetrahydro-β-carboline,

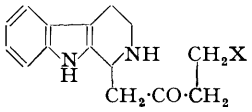
* Part V, *J.*, 1950, 1539.

† Ring Index numbering and names (no. 2420) are used, except that pyridocoline is used in place of quinolizine.

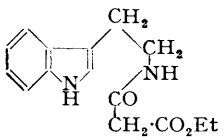
‡ Ring Index numbering for carboline will be used in this and succeeding papers of this series.

was obtained as the hydrochloride in mediocre yield by condensing tryptamine with 2-chloroethyl 2-chlorovinyl ketone, and, on subsequent treatment with alkali, yielded a yellow resin. The action of sodium methoxide (2 mols.) in methanol on this ketone afforded 2 : 2-dimethoxyethyl 2-methoxyethyl ketone, which condensed smoothly with tryptamine hydrochloride, to give 1 : 2 : 3 : 4-tetrahydro-1-(2-keto-4-methoxybutyl)-β-carboline (IV; X = OMe). Attempts to cyclise this to (I; R = R′ = H) gave only resins.


(III)


(IV)

Next, the synthesis of 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetic acid (VI; R = R′ = H) was investigated. Tryptamine and carbethoxyacetyl chloride gave the amide (V) as a gum which was cyclised by phosphoric oxide in xylene to the ethyl ester (VI; R = H, R′ = Et) of the required acid in low yield. Condensation of tryptamine with ethyl ethoxymethylenemalonate yielded a crystalline product, the analysis of which agreed with that for the expected derivative (VII). Attempts to convert (VII) into (VI; R = R′ = H) were unsuccessful, the compound being readily hydrolysed to tryptamine by alkali or acid. A condensation product of similar properties was also obtained from 2-phenylethylamine and ethyl ethoxymethylenemalonate. Finally, 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetic acid was obtained in satisfactory yield by condensing tryptamine hydrochloride with oxaloacetic acid in water at 40°, and was converted into the ethyl ester (VI; R = H, R′ = Et) by ethanolic hydrogen chloride. Similar condensation of tryptamine hydrochloride and carbethoxypyruvic acid afforded a mixture of the acid (VI; R = R′ = H) and its ester in combined yield greater than that of the acid obtained above, so this is the preferred method of preparation.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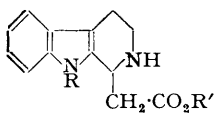
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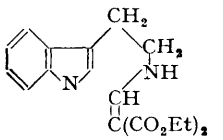

(VII)

Condensation of the ester (VI; R = H, R′ = Et) with vinyl cyanide and with ethyl acrylate afforded respectively ethyl 2-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate and diethyl 1 : 2 : 3 : 4-tetrahydro-β-carboline-1-acetate-2-β-propionate (VIII; R = H, R′ = CN or CO_2Et, respectively), the latter in higher yield. Attempts to effect a similar condensation with ethyl β-chloro- or β-bromo-propionate were futile. The ester (VI; R = H, R′ = Et) condensed with ethyl ethoxymethylenemalonate, but hydrogenation of the product in ethanol in presence of Adams's catalyst caused fission to the original monoester. When the ester (VIII; R = H, R′ = CO_2Et) was subjected to a Dieckmann reaction and the product was hydrolysed with dilute hydrochloric acid, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydro-2-ketoindolo(2 : 3-*a*)pyridocoline (I; R = R′ = H) was obtained.

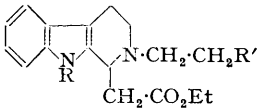
It seemed that, in an application of a reaction first used by du Feu, McQuillin, and Robinson (*J.*, 1937, 53), the action of 4-diethylaminobutan-2-one methiodide on the sodium salt of (I; R = R′ = H) might yield "base D" and/or "base E" described in Part IV. If this could be effected, a further extension might afford a synthesis of yohimbine. Experiments to bring about the Mannich base condensation were, however, unsuccessful, possibly on account of the presence of the acidic hydrogen atom of the indole nucleus. Attempts to acetylate (I; R = R′ = H) at this position were not encouraging, so the synthesis of (I; R = Me, R′ = H) was investigated.

1-Methyltryptamine and carbethoxypyruvic acid yielded ethyl 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline-1-acetate (VI; R = Me, R′ = Et). This with vinyl cyanide gave only a low yield of ethyl 2-2′-cyanoethyl-1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline

(VIII; R = Me, R′ = CN), and a similar reaction with ethyl acrylate produced a product which failed to crystallise either as the base or as the hydrochloride. However, Dieckmann cyclisation and hydrolysis of this crude product afforded the desired ketone (I; R = Me, R′ = H) in low yields which have not allowed further work.

With a view to the synthesis of de-ethylcoryline or coryline (alstyrine), the preparation of (I; R = H, R′ = Et) was also attempted. The reaction between (VI; R = H, R′ = Et) and ethyl α-ethylacrylate did not proceed smoothly as with ethyl acrylate; so condensation with ethyl α-formylbutyrate, followed by hydrogenation of the product, as used in an analogous case by Battersby and Openshaw (*Experientia*, 1950, **6**, 378), was investigated. Dr. Openshaw kindly communicated to us, before their publication, details of the experimental conditions employed in the latter work; but, even using these conditions, we were unable to isolate the required products from (VI; R = H or Me, R′ = Et).

Concurrently with the above work, synthesis of (II) was carried out. Tryptamine hydrochloride condensed with δ-hydroxyvaleraldehyde in water at 45°, to give 1-4′-hydroxybutyl-1 : 2 : 3 : 4-tetrahydro-β-carboline (IX) in good yield. This was smoothly dehydrogenated in presence of palladium black at 160° to give (X; X = OH), which reacted with hydrobromic acid to form the hydrobromide of 1-4′-bromobutyl-β-carboline (X; X = Br).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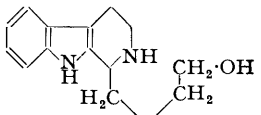
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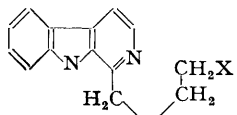
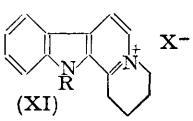

(X)

The base (X; X = Br) liberated from the above hydrobromide by the action of 1 equivalent of sodium carbonate very rapidly underwent internal quaternisation to give the colourless 1 : 2 : 3 : 4-tetrahydro-12*H*-indolo(2 : 3-*a*)pyridocolinium bromide (XI; R = H, X = Br). Treatment of the latter with excess of sodium hydroxide yielded a yellow crystalline base, $C_{15}H_{14}N_2,H_2O$. This might be the quaternary hydroxide (XI; R = H, X = OH), a *pseudo*-base, *e.g.*, (XII), or a hydrate of the anhydro-base (II). Attempts to dehydrate the base over phosphoric oxide *in vacuo* at 70° gave a product which differed in melting point, solubility properties, absorption spectrum, and analytical results, the last suggesting that oxidation had taken place; so subsequent work was carried out on the product dried *in vacuo* at room temperatue. As seen from the figure, the ultra-violet absorption spectra of the bromide and the base in ethanol are not significantly different, except that the extinction coefficients are higher for the former. On the addition of sodium hydroxide, however, the three absorption maxima are all displaced bathochromically. These results are, on the whole, in good agreement with those recorded by Schwarz and Schlittler in the case of *N*-methylnorharman, serpentinine, serpentine, and *N*-methylyobyrine (*Helv. Chim. Acta*, 1951, **34**, 629). The yellow base is readily soluble in methanol and is not precipitated from the resulting solution by the addition of water; if, however, sodium hydroxide solution is added to the diluted solution, precipitation occurs. It may,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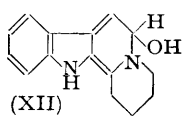
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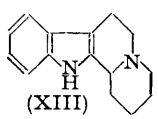
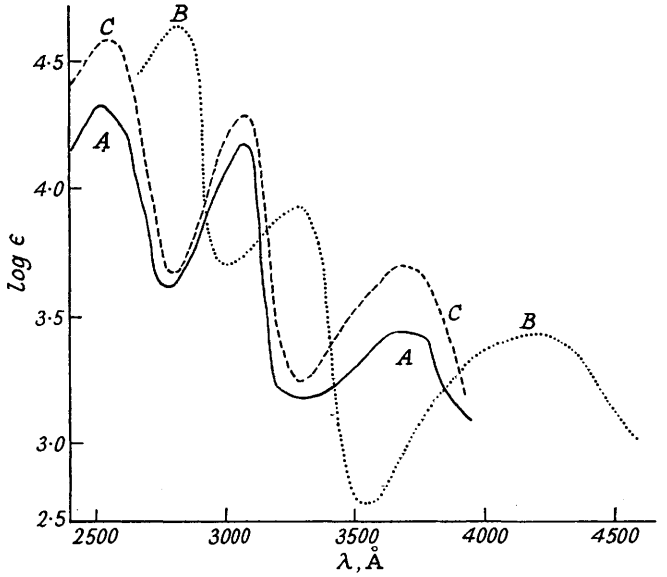

(XIII)

therefore, be concluded that in alcoholic solution the base exists largely as the quaternary hydroxide (XI; R = H, X = OH), but in presence of sodium hydroxide is transformed into the anhydro-base, which will exist as a resonance hybrid involving structures (II) and (II*a*). Treatment of the base with methyl iodide afforded a product formulated as the iodide (XI; R = Me, X = I). The ultra-violet absorption spectrum of this iodide is not appreciably changed in presence of sodium hydroxide, and is essentially the same as that of (XI; R = H, X = Br). These observations exclude the *pseudo*-base structure (XII) for the yellow base; for if this were correct, the absorption maxima of (XI; R = Me, X = I)

should be displaced bathochromically in presence of alkali, as in the case of the methyl-free compound.

Hydrogenation of (II) in ethanol in presence of Adams's catalyst yielded a colourless base, 1 : 2 : 3 : 4 : 6 : 7 : 12 : 12*b*-octahydroindolo(2 : 3-*a*)pyridocoline (XIII), recognised as a derivative of 1 : 2 : 3 : 4-tetrahydro-β-carboline by its ultra-violet absorption spectrum which is similar to that of yohimbine, and by the characteristic colour reaction with concentrated sulphuric acid in presence of an oxidising agent (Part I, *J.*, 1946, 617). This colour reaction was given generally by the various compounds represented in this paper as derivatives of 1 : 2 : 3 : 4-tetrahydro-β-carboline. Those substances, however, in which the indole-nitrogen atom is methylated, gave an extremely transient reddish-purple colour (instead of blue), changing to olive-green in a few seconds. The test failed in the case of 1 : 2 : 3 : 4-tetrahydro-9-methyl-β-carboline itself.

The hydroxyl group of (IX) was replaced by bromine on treatment of the substance with hydrobromic acid, the yield being very low. When (IX) was treated with hydrogen



A, 1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline in ethanol.*
B, *The same in* 0·015N-*ethanolic sodium hydroxide.*
C, 1: 2 : 3 : 4-*Tetrahydro*-12H-*indolo*(2 : 3-a)*pyridocolinium bromide in ethanol.*

chloride and triphenyl phosphite (cf. Landauer and Rydon, *Chem. and Ind.*, 1951, 313) and the product was basified with sodium hydroxide, (XIII) was obtained in low yield. The ketone (I; R = R′ = H) has also been converted into this substance by the Wolff–Kishner reduction, although the yield obtained was low, the main product being another base, the structure of which is uncertain. However, the identity of the product obtained in this way and by hydrogenation of (II) was established. The formation of the other product in the Wolff–Kishner reduction is not unexpected in view of the known instability of β-amino-ketones under alkaline conditions. It was thought that the action of Raney nickel on a thioketal of (I; R = R′ = H) might afford a better method of conversion. As a model, the reaction was tried on yohimbone, but the action of Raney nickel in boiling ethanol left its thioketal largely unchanged.

The reduction of 3-carbamylindole with lithium aluminium hydride was investigated as a possible preparative method for tryptamine, but the yield obtained was too low to be of value. Attempts to prepare γ-aminobutaldehyde phenylhydrazone (which can be cyclised to tryptamine) by the condensation of nitrosobenzene with 1 : 4-diaminobutane failed, although acetaldehyde phenylhydrazone was obtained from nitrosobenzene and ethylamine.

Experimental

M. p.s are uncorrected

1-*Acetonyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline* (III; R = H).—(*a*) A solution of tryptamine hydrochloride (0·5 g.) and αγ-diketovaleric acid (0·75 g.) (Lehninger and Witzemann, *J. Amer. Chem. Soc.*, 1942, **64**, 874) in water (7·5 ml.) was heated at 45° for 2 days, cooled, basified (sodium hydroxide solution), and extracted with ether. The extract was dried (K_2CO_3), acidified with methanolic hydrogen chloride, and cooled in ice. The *hydrochloride* (0·59 g.) was collected, washed with ether, and recrystallised from ethanol as colourless, felted needles (0·45 g.), still unmelted at 320° (Found: C, 63·3; H, 6·75. $C_{14}H_{17}ON_2Cl$ requires C, 63·5; H, 6·45%). A solution of this in water was basified (sodium hydroxide solution) and extracted with ether; the extract was dried (K_2CO_3) and the solvent was removed, leaving the *base* as a gum which eventually crystallised. This separated from light petroleum (b. p. 60—80°) as pale yellow crystals, m. p. 102—103° (Found: C, 73·65; H, 7·25. $C_{14}H_{16}ON_2$ requires C, 73·75; H, 7·0%). The *picrate* separated from ethanol as light orange prisms, m. p. 164—165° (decomp.) (Found: C, 52·65; H, 4·0. $C_{14}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 52·5; H, 4·15%). The *semicarbazone hydrochloride* separated from ethanol as cream-coloured prisms, m. p. 241—242° (decomp.) (Found: C, 55·9; H, 6·2. $C_{15}H_{20}ON_5Cl$ requires C, 56·0; H, 6·2%). The *benzoyl* derivative, prepared by the Schotten–Baumann method in presence of ether, separated from light petroleum (b. p. 80—100°) as colourless prisms, m. p. 133° (Found: C, 75·6; H, 5·8. $C_{21}H_{20}O_2N_2$ requires C, 75·9; H, 6·0%). (*b*) A solution of tryptamine hydrochloride (0·3 g.) in water (5 ml.) was treated with formylacetone dimethyl acetal (0·5 g.) (Price and Pappalardo, *J. Amer. Chem. Soc.*, 1950, **72**, 2613) and the mixture kept at room temperature for 2 days. Isolation as in (*a*) gave the hydrochloride (0·2 g.).

1-*Acetonyl*-1 : 2 : 3 : 4-*tetrahydro*-9-*methyl*-β-*carboline* (III; R = Me).—A solution of 1-methyltryptamine (0·2 g.) (Späth and Lederer, *Ber.*, 1930, **63**, 2102) and αγ-diketovaleric acid (0·45 g.) in water (3 ml.), treated as in (*a*) above, afforded the *hydrochloride* (0·13 g.) which separated from ethanol as colourless crystals, m. p. 240° after sintering at 168—170° (Found: C, 64·5; H, 6·9. $C_{15}H_{19}ON_2Cl$ requires C, 64·65; H, 6·8%).

Reaction between (III; R = H) *and Formaldehyde.*—(*a*) A solution of the hydrochloride of (III; R = H) (100 mg.) in methanol (20 ml.) was treated with paraformaldehyde, and the mixture was heated for 2 days at 45°, then for 8 hours on the water-bath. The methanol was removed and the residue treated with water and filtered. The filtrate was basified (sodium hydroxide solution) and extracted with ether, and the extract dried (Na_2SO_4) and acidified with methanolic hydrogen chloride. The precipitated hydrochloride was recrystallised from methanol, forming colourless needles (20 mg.), and under Schotten–Baumann conditions in presence of ether yielded a *benzoyl* derivative, m. p. 171—172° [from light petroleum (b. p. 80—100°)] (Found: C, 73·2; H, 6·2. $C_{22}H_{22}O_3N_2$ requires C, 72·85; H, 6·1%).

(*b*) A 0·8% formaldehyde solution (4 ml.; 1·5 mols.) was added to a solution of the hydrochloride of (III; R = H) (0·2 g.) in a phosphate buffer solution of pH 6 (5 ml.). After a few minutes the solution became turbid and deposited a yellow, flocculent solid, which was collected at the end of 1 hour. This solid was shaken with a mixture of benzene and 10% sodium hydroxide solution until all was in solution, the benzene layer was dried (Na_2SO_4), and the solvent was removed, leaving a yellow base, m. p. 213—215° (decomp.), which could not be purified.

(*c*) Treatment of (III; R = H) with methylal and concentrated hydrochloric acid yielded only black, polymeric products.

2-*Chloroethyl* 2-*Chlorovinyl Ketone.*—By the general procedure of Catch, Elliot, Hey, and Jones (*J.*, 1948, 278), without the use of a solvent, β-chloropropionyl chloride (13 g.) and aluminium chloride (15 g.) absorbed acetylene (1·3 g.) during 6 hours and afforded the ketone (9·2 g.), b. p. 88—94°/16 mm. (Found: C, 39·3; H, 4·3. Calc. for $C_5H_6OCl_2$: C, 39·25; H, 3·95%) [cf. D.R.-P. 642 147 (*Chem. Abs.*, 1937, **31**, 3501) and Yakubovich and Merkulova, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 55 (*Chem. Abs.*, 1947, **41**, 91)].

2 : 2-*Dimethoxyethyl* 2-*Methoxyethyl Ketone.*—A solution of sodium (0·62 g.) in methanol (10 ml.) was added dropwise to a stirred, ice-cold solution of the foregoing ketone (2 g.) in methanol (10 ml.). The mixture was set aside for 2 hours at room temperature and filtered from sodium chloride. The filtrate was evaporated at 30—35° under reduced pressure, the residue dissolved in chloroform, and the solution washed with dilute sodium hydrogen carbonate solution and dried (Na_2SO_4). The chloroform was removed at 30° under reduced pressure and the residue distilled giving 2 : 2-*dimethoxyethyl* 2-*methoxyethyl ketone* as a colourless oil (0·85 g.), b. p.

103—104°/14 mm. (Found: C, 54·3; H, 9·2; MeO, 51·6. $C_8H_{16}O_4$ requires C, 54·55; H, 9·1; MeO, 51·8%).

When the amount of sodium used was halved, the *product* was a colourless oil (0·6 g.), b. p. 70—74°/13 mm. (Found: C, 48·3; H, 6·3; MeO, 21·2. C_6H_9OCl requires C, 48·5; H, 6·1; MeO, 20·9%). This failed to condense with tryptamine hydrochloride. A solution containing this product (0·6 g.) and dimethylamine (1 g.) in methanol (15 ml.) was kept at room temperature overnight. The methanol was removed, the residue shaken with ether and sodium hydroxide solution, the ethereal layer separated, and the aqueous layer extracted with ether. The residue from the dried (Na_2SO_4) extract distilled as a pale yellow oil (0·42 g.), b. p. 123—127°/2 mm. (Found: C, 61·4; H, 9·6. $C_8H_{15}O_2N$ requires C, 61·15; H, 9·55%). When a solution containing this *substance* (0·1 g.) and methyl iodide (0·2 g.) in dry benzene (1 ml.) was kept overnight at 8°, a *salt* separated which after recrystallisation from methanol formed colourless needles, m. p. 183—184° (decomp.) (Found: C, 38·5; H, 6·25. $C_{10}H_{20}O_2NI$ requires C, 38·35; H, 6·4%).

1-(4-*Chloro*-2-*ketobutyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline* (IV; X = Cl).—A mixture of tryptamine (0·24 g.), benzene (5 ml.), and 10% sodium carbonate solution (5 ml.) was cooled in ice and stirred vigorously while a solution of 2-chloroethyl-2-chlorovinyl ketone (0·24 g.) in benzene (5 ml.) was added during 15 minutes, and then stirred for 30 minutes longer. The benzene layer was separated and the aqueous layer was extracted with chloroform. The combined organic extracts were dried (Na_2SO_4) and evaporated, leaving a gummy residue which was dissolved in acetone and acidified with methanolic hydrogen chloride. A tar was precipitated, followed, slowly, by 1-(4-*chloro*-2-*ketobutyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline hydrochloride* and this was separated from the tar by decantation and recrystallised from methanol–acetone (charcoal), giving colourless crystals (0·1 g.) m. p. > 300° (Found: C, 57·1; H, 5·95. $C_{15}H_{18}ON_2Cl_2$ requires C, 57·5; H, 5·75%).

1 : 2 : 3 : 4-*Tetrahydro*-1-(2-*keto*-4-*methoxybutyl*)-β-*carboline* (IV; X = OMe).—Tryptamine hydrochloride (0·85 g.) was condensed with 2 : 2-dimethoxyethyl-2-methoxyethyl ketone (1·1 g.) in water (15 ml.), as in the preparation of (III; R = H) by method *b*, and yielded a crude *hydrochloride* (0·75 g.) which, after recrystallisation from methanol–acetone, afforded colourless needles, m. p. >300° (Found: C, 62·9; H, 7·05; OMe, 9·9. $C_{16}H_{21}O_2N_2C$ lrequires C, 63·05; H, 6·9; OMe, 10·0%). The base failed to crystallise, but the *benzoyl* derivative separated from light petroleum (b. p. 80—100°) as short, colourless needles, m. p. 152—153° (Found: C, 73·1; H, 6·7. $C_{23}H_{24}O_3N_2$ requires C, 73·4; H, 6·4%).

Condensation of Tryptamine with Ethyl αγ-Diketovalerate.—When a solution of tryptamine (50 mg.) in benzene (3 ml.) was treated with ethyl αγ-diketovalerate (50 mg.) (*Org. Synth.*, **6**, 40), a semi-solid mass separated almost immediately. The mixture was diluted with light petroleum (b. p. 40—60°) and cooled and the *substance* (0·1 g.) produced recrystallised from benzene as colourless crystals, m. p. 106—107° (decomp.) (Found: C, 63·9; H, 6·7. $C_{17}H_{22}O_4N_2$ requires C, 64·2; H, 6·9%).

A similar reaction with 2-phenylethylamine (0·5 g.) and ethyl αγ-diketovalerate (0·66 g.) yielded a *substance* as colourless, felted needles (1 g.), m. p. 124° (decomp.) (Found: C, 64·7; H, 7·85. $C_{15}H_{21}O_4N$ requires C, 64·5; H, 7·55%). Attempted dehydration of the material with magnesium sulphate in boiling benzene yielded a gum; and it was readily hydrolysed by dilute hydrochloric acid (water-bath) to 2-phenylethylamine.

3-2′-(2″ : 2″-*Dicarbethoxyvinylamino*)*ethylindole* (VII).—A mixture of tryptamine (1 g.) and ethyl ethoxymethylenemalonate (1·36 g.) was heated for 1 hour on the water-bath and then cooled in ice with stirring, whereupon it solidified. The *indole* derivative produced was stirred with light petroleum and recrystallised first from dilute ethanol, then from light petroleum (b. p. 60—80°), affording colourless prisms (1·4 g.), m. p. 93·5—94·5° (Found: C, 65·45; H, 7·1. $C_{18}H_{22}O_4N_2$ requires C, 65·45; H, 6·7%).

Ethyl 2′-*Phenylethylaminomethylenemalonate.*—The reaction between 2-phenylethylamine (0·48 g.) and ethyl ethoxymethylenemalonate (1 g.) (3 hours; water-bath) afforded a colourless, viscous *ester* (0·8 g.), b. p. 206—208°/2 mm. (Found: C, 65·8; H, 7·1. $C_{16}H_{21}O_4N$ requires C, 66·0; H, 7·2%). The same product (0·7 g.) was obtained by shaking the reactants suspended in water (10 ml.) for 24 hours at room temperature.

1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetic Acid* (VI; R = R′ = H).—(*a*) A solution of carbethoxyacetyl chloride (0·24 g.) in benzene (4 ml.) was added during 20 minutes to a vigorously stirred mixture of tryptamine (0·25 g.), benzene (9 ml.), and 0·5N-sodium hydroxide (3 ml.). After being stirred for a further 20 minutes, the mixture was basified (sodium hydroxide solution), the benzene layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed successively with 2N-sodium hydroxide, 2N-hydrochloric

acid, and 2N-sodium hydroxide, and dried (K_2CO_3). Evaporation of the organic solvents yielded a gum (0·22 g.) which was dissolved in xylene (10 ml.). The boiling solution, in an atmosphere of nitrogen, was treated with phosphoric oxide (2·5 g.) during 45 minutes. The mixture was heated under reflux for 1 hour longer, cooled, and treated with dilute hydrochloric acid (to give a clear solution), and the aqueous layer was extracted with ether, then basified (sodium hydroxide), and again extracted with ether. The last extract was dried (K_2CO_3) and acidified with ethanolic hydrogen chloride. The crude hydrochloride thus precipitated was hydrogenated immediately in ethanol in presence of palladium–charcoal, at ordinary temperature and pressure. The filtered solution on evaporation yielded the *ethyl* ester *hydrochloride*, which separated from ethanol as colourless needles (20 mg.), m. p. 240° (decomp.) (Found: C, 61·25; H, 6·5. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·05; H, 6·75%).

(*b*) A solution of tryptamine hydrochloride (0·75 g.) and oxaloacetic acid (0·75 g.) (Heidelberger and Hulbert, *J. Amer. Chem. Soc.*, 1950, **72**, 4704) in water (10 ml.) was heated at 45° for 1½ hours, then cooled, and the *acid* filtered off, washed with water, and boiled with methanol to remove impurities, whereupon colourless crystals (0·49 g.), m. p. 223—224° (decomp.), remained (Found: C, 62·7; H, 6·1. $C_{13}H_{14}O_2N_2,H_2O$ requires C, 62·9; H, 6·45%). A mixture of this acid (2 g.) and ethanol (40 ml.) was saturated at 0° with hydrogen chloride and then heated under reflux overnight. The solution was concentrated to a small volume, then cooled, and the ethyl ester hydrochloride (2 g.) was collected, washed with acetone, and recrystallised from ethanol as colourless needles, m. p. 240° (decomp.) (Found: C, 61·1; H, 6·45. $C_{15}H_{19}O_2N_2Cl$ requires C, 61·05; H, 6·75%). The *ethyl* ester *picrate* separated from ethanol as orange needles, m. p. 204—205° (decomp.) (Found: C, 51·55; H, 4·4. $C_{15}H_{18}O_2N_2,C_6H_3O_7N_3$ requires C, 51·75; H, 4·3%). The *ethyl* ester *benzoyl* derivative formed colourless needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 180° (Found: C, 72·5; H, 6·1. $C_{22}H_{22}O_3N_2$ requires C, 72·9; H, 6·1%). The ethyl ester (VIII; R = H, R′ = Et) liberated by alkali from the hydrochloride formed a gum. The *methyl* ester *hydrochloride* separated from methanol–acetone as colourless needles, m. p. 225° (decomp.) (Found: C, 59·5; H, 5·7. $C_{14}H_{17}O_2N_2Cl$ requires C, 59·9; H, 6·05%). The *methyl* ester *picrate* separated from ethanol as orange needles, m. p. 197—197·5° (Found: C, 50·35; H, 4·2. $C_{14}H_{16}O_2N_2,C_6H_3O_7N_3$ requires C, 50·75; H, 4·0%).

(*c*) Carbethoxypyruvic acid was prepared by a modification of Wislicenus's method (*Annalen*, 1888, **246**, 306). A mixture of diethyl sodio-oxaloacetate (10 g.), water (75 ml.), and 1 equiv. of sodium hydroxide (48 ml.; 0·872N.) was shaken for 3 minutes, then acidified with 4N-sulphuric acid and extracted with ether (6 × 60 ml.). The solvent was removed (finally in a vacuum) from the dried (Na_2SO_4) extract, and the residue washed with a little ice-cold carbon tetrachloride, affording carbethoxypyruvic acid, m. p. 98—100° (Wislicenus and Endres, *Annalen*, 1902, **321**, 372, give m. p. 102—103°), the yield varying from 1·5 to 3·1 g.

A solution of tryptamine hydrochloride (0·8 g.) and the above acid (0·9 g.) in water was heated at 40° for 15 hours. The acid (VI; R = R′ = H) (0·43 g.) was collected and the filtrate basified (sodium hydroxide solution) and extracted with ether. The dried (Na_2SO_4) extract was acidified with methanolic hydrogen chloride, giving the ethyl ester hydrochloride (0·47 g.).

Ethyl 2-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate* (VIII; R = H, R′ = CN).—A mixture of the ester (VI; R = H, R′ = Et) (0·17 g.) and vinyl cyanide (0·8 g.) was heated under reflux overnight, the excess of vinyl cyanide removed, the residue dissolved in ether, and the solution acidified with methanolic hydrogen chloride. The precipitated gum was triturated with a little acetone, and the resulting *hydrochloride* was recrystallised from methanol–acetone, forming colourless plates, m. p. 179·5—180·5° (80 mg.) (Found: C, 62·35; H, 6·4. $C_{18}H_{22}O_2N_3Cl$ requires C, 62·2; H, 6·35%).

Diethyl 1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetate*-2-*propionate* (VIII; R = H, R′ = CO_2Et).—A mixture of the ester (VI; R = H, R′ = Et) (3 g.) and ethyl acrylate (20 ml.) was heated in a sealed tube at 130° for 15 hours. The excess of ethyl acrylate was removed by distillation under reduced pressure and the residue was dissolved in ether and acidified with methanolic hydrogen chloride. The precipitated gum solidified when stirred with acetone (7 ml.), giving the diester *hydrochloride* (3 g.) which was filtered off and washed with acetone–ether (2 : 1). This separated from methanol–ether as colourless crystals, m. p. 147—148° (decomp.) (Found: C, 60·55; H, 6·85. $C_{20}H_{27}O_4N_2Cl$ requires C, 60·85; H, 6·85%). Basification gave the *diester* which separated from light petroleum (b. p. 40—60°) as colourless crystals, m. p. 77·5—78·5° (Found: C, 67·1; H, 7·4. $C_{20}H_{26}O_4N_2$ requires C, 67·05; H, 7·3%).

Ethyl 2-(2 : 2-*Dicarbethoxyvinyl*)-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*-1-*acetate*.—The ester (VI; R = H, R′ = Et) (0·5 g.) and ethyl ethoxymethylenemalonate (0·42 g.) were heated together on the water-bath for 2 hours. Trituration with light petroleum (b. p. 40—60°) then yielded a

light brown solid (0·55 g.; m. p. 111—118°), which was recrystallised first from benzene–light petroleum (b. p. 60—80°) and then from dilute ethanol, affording the *triester* as colourless crystals (0·45 g.), m. p. 134—134·5° (Found : C, 64·2; H, 6·9. $C_{23}H_{28}O_6N_2$ requires C, 64·5; H, 6·55%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro*-2-*ketoindolo*(2 : 3-a)*pyridocoline* (I; R = R′ = H).—A solution of the diester (VIII; R = H, R′ = CO_2Et) (1·2 g.) in benzene (10 ml.) was added with cooling to sodium ethoxide (from sodium, 0·11 g.), and the mixture was heated under reflux overnight. After the addition of 10% hydrochloric acid (30 ml.), the mixture was heated on the water-bath for 6 hours, and then evaporated to dryness in a vacuum. The residue was dissolved in water, and the resulting solution was basified (sodium hydroxide solution) and extracted with ether. The extract was dried (Na_2SO_4) and the ether was removed. The residue (0·55 g.) was recrystallised from a small volume of benzene, affording the *ketone* (0·4 g.) as colourless prisms, m. p. 180—180·5° (Found : C, 75·1; H, 7·1; N, 11·7. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 12·25%). The 2 : 4-*dinitrophenylhydrazone hydrochloride* separated from acetic acid as orange crystals, m. p. 243° (decomp.) (Found : C, 52·25; H, 4·95. $C_{21}H_{21}O_4N_6Cl,1·5H_2O$ requires C, 52·15; H, 4·75%). The *semicarbazone* separated from ethanol as colourless crystals, m. p. 213—214° (decomp.) (Found : C, 61·25; H, 7·0. $C_{16}H_{19}ON_5,H_2O$ requires C, 60·95; H, 6·7%).

1 : 2 : 3 : 4-*Tetrahydro*-9-*methyl*-β-*carboline*-1-*acetic Acid* (VI; R = Me, R′ = H).—A solution of 1-methyltryptamine hydrochloride (1·85 g.) and carbethoxypyruvic acid (3 g.) in water (25 ml.) was kept at 40—45° for 2 days. The products were isolated as for (VI; R = R′ = H), the combined yield of the hydrochlorides of the acid and ester being about 1·3 g.; the former was esterified as before. The *ethyl* ester *hydrochloride* separated from methanol–acetone as colourless needles, m. p. 217° (Found : C, 62·05; H, 7·1. $C_{16}H_{21}O_2N_2Cl$ requires C, 62·2; H, 6·8%). The *acid hydrochloride*, crystallised from methanol, had m. p. 157—158° (Found : C, 59·85; H, 6·2. $C_{14}H_{17}O_2N_2Cl$ requires C, 59·9; H, 6·05%). The ethyl ester formed a gum.

Ethyl 2-2′-*Cyanoethyl*-1 : 2 : 3 : 4-*tetrahydro*-9-*methyl*-β-*carboline*-1-*acetate* (VIII; R = Me, R′ = CN).—A mixture of the foregoing ester (0·1 g.) and vinyl cyanide (1 ml.), heated for 20 hours at 115° in a sealed tube, afforded the *hydrochloride* (10 mg.), m. p. 116—117°, of the cyano-compound (Found : C, 61·25; H, 7·2. $C_{20}H_{26}O_2N_3Cl$ requires C, 61·0; H, 7·1%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydro*-2-*keto*-12-*methylindolo*(2 : 3-a)*pyridocoline* (I; R = Me, R′ = H).—The gum (0·3 g.) obtained by heating a mixture of (VI; R = Me, R′ = Et) (0·25 g.) and ethyl acrylate (2 ml.) for 18 hours at 130—135° in a sealed tube was heated for 12 hours on the water-bath with benzene (3 ml.) and sodium ethoxide (from sodium, 40 mg.). Hydrolysis and working up as for (I; R = R′ = H) yielded a gum (80 mg.) which slowly solidified in the cold. This product was washed with light petroleum (b. p. 40—60°) and passed through a column of alumina. Elution with benzene containing ethanol (2%) afforded a fraction which on evaporation yielded the *ketone* (10 mg.) as colourless crystals, m. p. 124—125°, after recrystallisation from benzene–light petroleum (b. p. 60—80°) (Found : C, 75·5; H, 7·05. $C_{16}H_{18}ON_2$ requires C, 75·6; H, 7·1%).

Reaction between Ethyl 1 : 2 : 3 : 4-*Tetrahydro*-β-*carboline*-1-*acetate and Ethyl* α-*Formylbutyrate*.—A solution of (VI; R = H, R′ = Et) (100 mg.) and ethyl α-formylbutyrate (70 mg.) in dry ether (1 ml.) was kept at room temperature for 48 hours. The solid *substance* (100 mg.) left after evaporation was recrystallised twice from benzene–light petroleum (b. p. 60—80°), then from a small volume of ether, and formed colourless crystals, m. p. 116—117° (Found : C, 62·7; H, 7·5. $C_{22}H_{29}O_5N_2,H_2O$ requires C, 62·85; H, 7·6%). This material did not absorb hydrogen in presence of Adams's catalyst and was hydrolysed to (VI; R = H, R′ = Et) by warming it for 2 minutes on the water-bath with N-hydrochloric acid. Attempts to dehydrate it gave no new crystalline product. The same product was obtained after condensation and hydrogenation under the conditions used by Battersby and Openshaw. The latter conditions were also applied in the case of (VI; R = Me, R′ = Et); but here the product obtained was a gum which failed to crystallise even after being chromatographed and, when this gum was subjected to the treatment used in the Dieckmann cyclisation, a small amount of a product which failed to form a 2 : 4-dinitrophenylhydrazone resulted.

1 : 2 : 3 : 4-*Tetrahydro*-9-*methyl*-β-*carboline* (cf. Späth and Lederer, *loc. cit.*).—A solution of 1-methyltryptamine (0·2 g.) in 4% formaldehyde solution (2·2 ml.) kept at 40—45° for 1 day yielded the *hydrochloride* (0·18 g.), m. p. 273° (from methanol), of the carboline (Found : C, 64·7; H, 7·0. $C_{12}H_{15}N_2Cl$ requires C, 64·7; H, 6·75%). The *picrate* separated from ethanol as deep yellow crystals, m. p. 242° (decomp.) (Found : C, 52·0; H, 4·3. $C_{12}H_{14}N_2,C_6H_3O_7N_3$ requires C, 52·05; H, 4·1%).

1 : 2 : 3 : 4-*Tetrahydro*-1-4′-*hydroxybutyl*-β-*carboline* (IX).—A solution of tryptamine hydrochloride (1 g.) and δ-hydroxyvaleraldehyde (1 g.) in water (20 ml.) was kept at 45° for 2 days, and the product isolated as for the preparation of (III; R = H). The *hydrochloride* (1 g.) was precipitated as a gum which solidified on trituration with acetone and then separated from methanol–acetone as colourless needles, m. p. 192—193° (Found: C, 63·95; H, 7·65. $C_{15}H_{21}ON_2Cl$ requires C, 64·15; H, 7·5%). The *carboline* base had m. p. 154° (from benzene) (Found: C, 73·5; H, 8·35. $C_{15}H_{20}ON_2$ requires C, 73·75; H, 8·2%). The *picrate* separated from ethanol as orange crystals, m. p. 198—199° (Found: C, 53·1; H, 5·15. $C_{15}H_{20}ON_2,C_6H_3O_7N_3$ requires C, 53·25; H, 4·9%). The *picrolonate* separated from ethanol as yellow needles, m. p. 238—239° (Found: C, 58·75; H, 5·85. $C_{15}H_{20}ON_2,C_{10}H_8O_5N_4$ requires C, 59·05; H, 5·5%). When the hydrochloride (0·5 g.) was warmed on the water-bath for a few minutes with acetic acid (15 ml.), and the solution then allowed to cool, 1-4′-*acetoxybutyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline hydrochloride* (0·5 g.) separated; from methanol–acetone this formed colourless needles, m. p. 214° (Found: C, 63·05: H, 7·05. $C_{17}H_{23}O_2N_2Cl$ requires C, 63·25; H, 7·1%). The corresponding *picrolonate* separated from ethanol as yellow crystals, m. p. 197° (Found: C, 58·85; H, 5·8. $C_{17}H_{22}O_2N_2,C_{10}H_8O_5N_4$ requires C, 58·9; H, 5·5%).

1-4′-*Hydroxybutyl*-β-*carboline* (X; X = OH).—A mixture of (IX) (1·4 g.) and palladium black (0·5 g.) was heated at 160°/10 mm. until hydrogen evolution ceased and for 10 minutes thereafter. The residue was extracted with methanol, and the filtrate was evaporated, leaving the *base* (1·3 g.; m. p. 165—169°), which separated from dilute methanol as colourless, glistening plates, m. p. 173° (1 g.) (Found: C, 75·0; H, 7·15. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7%). The dehydrogenation of (IX) or of 1 : 2 : 3 : 4-tetrahydro-β-carboline itself was not satisfactorily brought about by lead tetra-acetate in acetic acid or by chloranil or Raney nickel in xylene.

1-4′-*Bromobutyl*-β-*carboline* (X; X = Br) *Hydrobromide*.—A solution of the foregoing compound (0·35 g.) in concentrated hydrobromic acid (20 ml.) was heated under reflux for 30 minutes, then evaporated to dryness in a vacuum. The residue was dissolved in methanol, and the resulting solution diluted with acetone. A small amount of flocculent material was removed and the filtrate was concentrated and diluted with ether, to precipitate the *bromo*-compound *hydrobromide* (0·5 g.) which separated from methanol–ether as colourless needles, m. p. 168—169° (Found: C, 47·05; H, 4·4. $C_{15}H_{16}N_2Br_2$ requires C, 46·9; H, 4·2%).

1 : 2 : 3 : 4-*Tetrahydroindolo*(2 : 3-a)*pyridocoline* (II).—An aqueous solution of the foregoing hydrobromide (100 mg.) was briefly shaken with chloroform and sodium carbonate (13·8 mg., 1 equiv.), and the chloroform layer was then rapidly separated and cooled to 0°, whereupon it deposited crystals within a few minutes. These crystals (47 mg.) were removed and the filtrate was concentrated, a further crop (10 mg.) being obtained. This, 1 : 2 : 3 : 4-*tetrahydro*-12H-*indolo*(2 : 3-a)*pyridocolinium bromide* (XI; R = H, X = Br), separated from methanol–acetone as fine, colourless needles, m. p. 280° (decomp.) (Found: C, 59·5; H, 5·2. $C_{15}H_{15}N_2Br$ requires C, 59·4; H, 4·95%). Light absorption in ethanol: $\lambda_{max.}$ 2540, 3060, and 3660 Å (log ε = 4·57, 4·27, and 3·67), $\lambda_{min.}$ 2790 and 3300 Å (log ε = 3·65 and 3·22). When an aqueous solution of this salt was basified with sodium hydroxide solution, the *base* (II) separated as yellow, felted needles, m. p. 80—81° after drying for 4 hours over potassium hydroxide in a vacuum-desiccator (Found: C, 74·5; H, 6·7. $C_{15}H_{14}N_2,H_2O$ requires C, 75·0; H, 6·7%). Light absorption in ethanol: $\lambda_{max.}$ 2510, 3070, and 3660 Å (log ε = 4·31, 4·16, and 3·43), $\lambda_{min.}$ 2780 and 3290 Å (log ε = 3·6 and 3·17). Light absorption in 0·015N-ethanolic sodium hydroxide solution: $\lambda_{max.}$ 2830, 3280, and 4200 Å (log ε = 4·63, 3·92, and 3·41), $\lambda_{min.}$ 3000 and 3540 Å (log ε = 3·69 and 2·75). Treatment of this base with methyl iodide produced 1 : 2 : 3 : 4-*tetrahydro*-12-*methylindolo*(2 : 3-a)*pyridocolinium iodide* (XI; R = Me, X = I) which separated from methanol as pale brown needles, m. p. 276—277° after sintering at 263° (Found: C, 52·8; H, 5·2. $C_{16}H_{17}N_2I$ requires C, 52·75; H, 4·7%). Light absorption in ethanol: $\lambda_{max.}$ 2610, 3080, and 3775 Å (log ε = 4·49, 4·27, and 3·68), $\lambda_{min.}$ 2860 and 3330 Å (log ε = 3·90 and 3·11). Light absorption in 0·015N-ethanolic sodium hydroxide solution: $\lambda_{max.}$ 2600, 3080, and 3775 Å (log ε = 4·51, 4·16, and 3·63), $\lambda_{min.}$ 2860 and 3330 Å (log ε = 3·90 and 3·11).

1-4′-*Bromobutyl*-1 : 2 : 3 : 4-*tetrahydro*-β-*carboline*.—A solution of (IX) (40 mg.) in acetic acid (9 ml.) and concentrated hydrobromic acid (1 ml.) was heated under reflux for 1 hour, then evaporated to dryness in a vacuum. A solution of the residue in methanol was diluted with acetone, and the precipitate removed. The filtrate was concentrated and diluted with ether, giving the *hydrobromide* (5 mg.) as almost colourless crystals, m. p. 190—191° after sintering at 180° (Found: C, 45·65; H, 5·8. $C_{15}H_{20}N_2Br_2,0{\cdot}5H_2O$ requires C, 45·35; H, 5·3%).

1 : 2 : 3 : 4 : 6 : 7 : 12 : 12b-*Octahydroindolo*(2 : 3-a)*pyridocoline* (XIII).—(*a*) A solution of the yellow base (II) (50 mg.) in ethanol (5 ml.) was shaken in presence of Adams's catalyst (20 mg.)

in an atmosphere of hydrogen at room temperature and pressure for 3 days. The filtered solution was evaporated to dryness, and the residue was dissolved in ether and acidified with methanolic hydrogen chloride. The *hydrochloride* (45 mg.) which separated as colourless crystals, after recrystallisation from ethanol, had m. p. 311—312° (Found : C, 64·5; H, 7·2. $C_{15}H_{19}N_2Cl,H_2O$ requires C, 64·2; H, 7·5%). The *base* separated from light petroleum (b. p. 60—80°) as colourless crystals, m. p. 147—147·5° (Found : C, 79·5; H, 8·2. $C_{15}H_{18}N_2$ requires C, 79·65; H, 8·0%). Light absorption in ethanol : $\lambda_{max.}$ 2790 Å (log ε = 3·89), $\lambda_{min.}$ 2470 Å (log ε = 3·33).

(*b*) A mixture of the base (IX) (0·1 g.), triphenyl phosphite (0·5 g.), and benzene (2 ml.) was saturated with dry hydrogen chloride at 0° and shaken overnight at room temperature; it was then basified (sodium hydroxide solution) and extracted with chloroform. The solvent was removed from the dried (Na_2SO_4) extract, and the residue was dissolved in acetone and acidified with methanolic hydrogen chloride. Dilution with ether afforded the *hydrochloride* (20 mg.), m. p. 311—312° after recrystallisation from ethanol, not depressed by admixture with the product from (*a*).

(*c*) A mixture of the ketone (I; R = R′ = H) (0·12 g.) and 90—95% hydrazine hydrate (1 ml.) was heated for 1 hour on the water-bath, cooled, and extracted with chloroform. The residue left after evaporation of the dried (Na_2SO_4) extract was heated with a solution of sodium (80 mg.) in ethanol (1·5 ml.) in a sealed tube for 18 hours at 165—175°. The mixture was then acidified with 2N-hydrochloric acid and evaporated to dryness in a vacuum. A solution of the residue in water was basified (sodium hydroxide solution), and extracted with ether, the extract dried (Na_2SO_4), and the solvent removed. Fractional crystallisation of the residue from benzene afforded two bases A and B, the latter being the more soluble. *Base A* (50 mg.) formed colourless crystals, m. p. 244° (decomp.), which gave the colour test for a 1 : 2 : 3 : 4-tetrahydro-β-carboline derivative [Found : C, 72·1, 72·55, 72·2; H, 8·1, 7·6, 7·9%; *M* (Rast) 255] and gave a colourless hydrochloride, m. p. 278° (from ethanol). Base B (10 mg.) was identical with (XIII) obtained as in (*a*) and admixture caused no depression of the m. p.

Reaction between Yohimbone and Ethanethiol.—A mixture of (−)-yohimbone (50 mg.), acetic acid (1 ml.), ethanethiol (0·1 g.), and a trace of hydrochloric acid was kept at room temperature overnight, *yohimbone diethyl thioketal hydrochloride* (50 mg.) separating as lustrous prisms, m. p. 290—292° after sintering at 250° (Found : C, 63·0; H, 7·6. $C_{23}H_{33}N_2S_2Cl$ requires C, 63·2; H, 7·6%).

3-*Carbamylmethylindole.*—A solution of 3-carboxymethylindole (1 g.) (Snyder and Pilgrim, *J. Amer. Chem. Soc.*, 1948, **70**, 3770) in methanol (20 ml.) was treated with one of diazomethane (0·25 g.) in ether (25 ml.), kept for 1 hour at 0°, washed with sodium hydrogen carbonate solution, and dried (Na_2SO_4). The solvents were removed, the residue was dissolved in a small volume of ether and mixed with aqueous ammonia (*d* 0·88; 12 ml.), and the whole was saturated at 0° with ammonia, then shaken in a stoppered bottle for 2 days at room temperature. Saturation and shaking were repeated twice, and the amide (0·83 g.) (m. p. 145—147°) collected and recrystallised from ethanol–light petroleum (b. p. 40—60°); it had m. p. 152—153°. Snyder and Pilgrim (*loc. cit.*) give m. p. 153°.

Tryptamine.—A solution of the above amide (0·5 g.) in dry tetrahydrofuran (6 ml.) was added dropwise in an atmosphere of nitrogen to one of lithium aluminium hydride (0·3 g.) in ether (30 ml.) and heated under reflux for 15 minutes. Water and dilute sulphuric acid were added and the organic layer was extracted with dilute sulphuric acid. The combined acid extracts were washed with chloroform, then basified (40% sodium hydroxide solution), and extracted again with chloroform. The latter extract was dried (K_2CO_3), the solvent removed, and the residue was dissolved in acetone, acidified with methanolic hydrogen chloride, and cooled in ice. The tryptamine hydrochloride, after being washed with acetone and recrystallised from methanol–acetone, had m. p. 248—249° (0·12 g.).

The bulk of the tryptamine used was prepared by the method of Schöpf and Steuer (*Annalen*, 1947, **558**, 124), the necessary β-cyanopropaldehyde diethyl acetal being made by Wohl's method (*Ber.*, 1906, **39**, 1951), although, in order to obtain the highest yield, it was found necessary to employ 0·5M-amounts of potassium iodide. Reduction to δ-aminobutaldehyde diethyl acetal by Wohl's method (*Ber.*, 1901, **34**, 1914) was effected in 70% yield.

Reaction between Nitrosobenzene and Ethylamine.—A solution of nitrosobenzene (2 g.) and ethylamine (1·4 g.) in benzene (10 ml.) was kept at room temperature for 4 days, then fractionated, yielding a yellow oil (0·7 g.), b. p. 70—73°/20 mm. (Bamberger and Pemsel give the b. p. of benzeneazoethane as 60—62°/12 mm.; *Ber.*, 1903, **36**, 53), and a brown oil (0·9 g.), b. p. 160°/2 mm. (Found : C, 75·2; H, 6·0%). The former fraction was heated for 3 minutes on the water-bath with a solution of sodium (0·18 g.) in ethanol (8 ml.), and the mixture then

poured into ice-water (25 ml.). The precipitated solid on recrystallisation from light petroleum (b. p. 60—80°) afforded light brown crystals (0·2 g.), m. p. 100—102°, not depressed on admixture with an authentic specimen of acetaldehyde phenylhydrazone, m. p. 102°.

m-*Methoxybenzyl Chloride.*—*m*-Methoxybenzyl alcohol was prepared from the aldehyde, by the general method of Carothers and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1675). Thionyl chloride (5·3 g.) was added dropwise to a mixture of the alcohol (5·1 g.) and dry pyridine (3·2 g.) in benzene (5 ml.) which was then kept overnight at room temperature, treated with water, and extracted with ether. The extract was washed thrice with sodium carbonate solution, dried (Na_2SO_4), and distilled, yielding the chloride (4·7 g.), b. p. 98—102°/4 mm.

Ethyl α-*Formamido*-α-m-*methoxybenzylmalonate.*—To a solution of sodium (0·28 g.) in absolute ethanol (20 ml.), ethyl formamidomalonate (2·47 g.) (Galat, *J. Amer. Chem. Soc.*, 1947, **69**, 965) and then a solution of *m*-methoxybenzyl chloride (1·85 g.) in ethanol (10 ml.) were added. The mixture was kept for 18 hours at room temperature, heated under reflux for 8 hours, and filtered. The bulk of the ethanol was removed in a vacuum and the residue was treated with water and extracted with chloroform. The extract was washed with water, then dried ($CaCl_2$), and the solvent was removed, leaving a gum, which crystallised on trituration with light petroleum (b. p. 40—60°). *Ethyl* α-*formamido*-α-m-*methoxybenzylmalonate* separated from dilute ethanol as colourless needles, m. p. 96—97° (1·8 g.) (Found : C, 59·4; H, 6·65. $C_{16}H_{21}O_6N$ requires C, 59·4; H, 6·5%).

This ester (0·8 g.) was heated under reflux for 45 minutes with a solution of potassium hydroxide (0·8 g.) in ethanol (8 ml.), then diluted with water (35 ml.), extracted with ether, cooled in ice, acidified (dilute hydrochloric acid), and again extracted with ether. The solvent was removed from the dried (Na_2SO_4) extract, and the residual gum solidified on cooling, yielding the colourless *acid* (0·42 g.), m. p. 128° (decomp.) (Found : C, 53·75; H, 4·6. $C_{12}H_{13}O_6N$ requires C, 53·9; H, 4·85%).

N-*Formyl*-β-m-*methoxyphenylalanine.*—The dibasic acid was decarboxylated at 100°/18 mm. (45 minutes); the product separated from water as colourless prisms, m. p. 156° (Found : C, 59·25; H, 6·2. Calc. for $C_{11}H_{13}O_4N$: C, 59·2; H, 5·8%). Chakravarti and Rao (*J.*, 1938, 172) give m. p. 156°.

β-m-*Methoxyphenylalanine.*—The *N*-formyl derivative (0·52 g.) was heated (water-bath) with 5% hydrochloric acid (7 ml.) for 4 hours in an atmosphere of nitrogen. The mixture was evaporated to dryness in a vacuum, and a solution of the residue in water (1·5 ml.) was adjusted to pH 5 with aqueous ammonia. After being kept overnight at 0°, the product (0·29 g.) was collected and formed colourless needles, m. p. 214—215° (decomp.).

m-*Methoxybenzyl Toluene*-p-*sulphonate.*—A mixture of *m*-methoxybenzyl alcohol (1 g.) and toluene-*p*-sulphonyl chloride (1·38 g.) in dry ether (8 ml.) was cooled in a freezing mixture and stirred vigorously while finely powdered potassium hydroxide (1·51 g.) was added in small portions, the temperature being kept below 4°. The mixture was stirred for 3 hours longer, shaken overnight at room temperature, treated with water, and extracted with chloroform. The extract was washed with water, then dried ($CaCl_2$), the solvent was removed, and the *ester* (1·4 g.) was recrystallised from benzene–light petroleum (b. p. 60—80°), giving colourless crystals, m. p. 83·5—84·5° (Found : C, 61·9; H, 5·7. $C_{15}H_{16}O_4S$ requires C, 61·65; H, 5·5%).

The yield of ethyl α-formamido-α-*m*-methoxybenzyl malonate obtained by condensation of ethyl formamidomalonate with this ester (1 g.) was only 0·38 g., *i.e.*, lower than with *m*-methoxybenzyl chloride.

m-*Methoxybenzylidenerhodanine.*—Anhydrous sodium acetate (5·45 g.) was added to a solution of *m*-methoxybenzaldehyde (5 g.) and rhodanine (4·9 g.) in acetic acid (14·5 ml.), and the mixture was boiled for 30 minutes with occasional shaking and poured into water (72 ml.). The *product* (8·45 g.; m. p. 225—227°) was collected, washed well with water, then with a little ethanol and ether. It separated from acetic acid as golden-yellow needles, m. p. 227° (Found : C, 52·45; H, 3·9. $C_{11}H_9O_2NS_2$ requires C, 52·7; H, 3·6%).

α-*Hydroxyimino*-β-m-*methoxyphenylpyruvic Acid.*—The above (2·9 g.) was heated on the water-bath for 5 minutes with 15% sodium hydroxide solution (15 ml.). The solution was cooled in a freezing mixture and acidified rapidly with 10% hydrochloric acid. The crude β-*m*-methoxyphenyl-α-thiopropionic acid (2·6 g.) was collected and washed with water.

A warm solution of hydroxylamine hydrochloride (5·16 g.) in water (5 ml.) was added to a solution of sodium (1·7 g.) in ethanol (50 ml.), and the precipitated sodium chloride removed by filtration. The above thio-acid was heated under reflux for 3 hours with this hydroxylamine solution, and the mixture then evaporated to dryness in a vacuum. The residue was dissolved in 5% sodium hydroxide solution (7 ml.), and the solution was centrifuged to remove sulphur,

cooled in ice, and acidified with 10% hydrochloric acid (12 ml.). The *hydroxyimino-acid* (1·85 g.), m. p. 130—135°, separated and after recrystallisation from water afforded colourless plates (1·4 g.), m. p. 138—140° (Found : C, 57·7; H, 5·2. $C_{10}H_{11}O_4N$ requires C, 57·45; H, 5·25%). Difficulty was experienced in attaining reproducible yields in this preparation, the initial 5 minutes' reaction time with sodium hydroxide being very critical.

β-m-*Methoxyphenylalanine.*—A solution of the hydroxyimino-acid (1·4 g.) in 10% sodium hydroxide solution (10 ml.) was warmed on the water-bath and, to it, 4% sodium amalgam (28 g.) was added during 15 minutes. After being cooled, the mercury was separated and the mixture was adjusted to pH 6 with acetic acid, boiled with charcoal, filtered, and concentrated to a small volume. The crude product which separated was purified *via* the copper salt, the yield then being 0·5 g., and the m. p. 215° (decomp.).

The light absorption data were determined by use of a Hilger Medium Quartz Spectrograph.

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