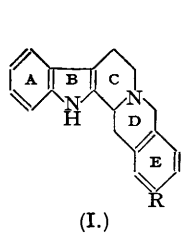
318. *The Constitution of Yohimbine and Related Alkaloids. Part IV. A Synthesis of Yohimbone.*

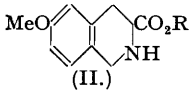
By G. A. Swan.

A compound having the structure (I; R = OMe) has been synthesised by two independent methods. By reduction of this with sodium and *tert.*-butanol in liquid ammonia and treatment of the product with acid, followed by catalytic hydrogenation, a racemic base (X) has been obtained. Resolution of this gave a (−)-base, identical with yohimbone.

The present paper describes experiments which have been carried out to synthesise yohimbone, the Oppenauer oxidation product of yohimbine (Witkop, *Annalen*, 1943, **554**, 83), bearing in mind the future extension to the synthesis of yohimbine itself.



(I.)



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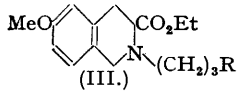

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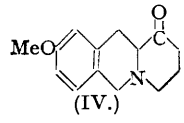

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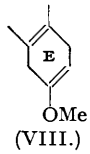

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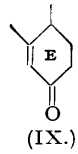
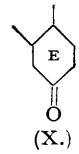


(IX.)



(X.)

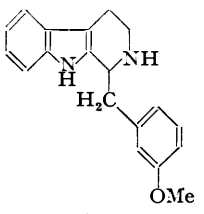
The synthesis of (I; R = H) has already been described (Part I, *J.*, 1946, 617; Part III, *J.*, 1949, 1720) and that of (I; R = OMe) is now recorded. Earlier work resulted in the preparation of this compound by an extension of the method described for (I) in Part I; although the yield was low, it appeared possible to use a similar route to obtain a product in which ring E was hydrogenated. *m*-Methoxyphenylalanine was condensed with formaldehyde in alkaline solution at 37° to give 6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylic acid (II; R = H) (the strongly acidic conditions used in Part I are unsuitable on account of the possibility of hydrolysis of the methoxyl group). The ethyl ester (II; R = Et) was condensed with

γ-bromobutyronitrile to give ethyl 6-methoxy-2-3′-cyanopropyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (III; R = CN) which was converted into ethyl 6-methoxy-2-3′-carbethoxypropyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (III; R = CO_2Et). This diester was subjected to the Dieckmann reaction, giving 9-keto-2′-methoxy-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline (IV), the phenylhydrazone of which underwent the Fischer indole reaction giving 3″-methoxy-3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2′ : 3′-1 : 2)-pyridocoline (I; R = OMe).

The dehydrogenation of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate with sulphur in tetralin (cf. G.P. 674,400) gave ethyl *iso*quinoline-3-carboxylate. In a similar manner, ethyl 6-methoxy*iso*quinoline-3-carboxylate was prepared.

It was hoped that a more convenient synthesis of (I; R = OMe) would be the methylation of (I; R = OH), obtained by the condensation of *m*-hydroxyphenylpyruvic acid with tryptamine, and cyclisation of the product with formaldehyde (Hahn and Hansel, *Ber.*, 1938, **71**, 2194). Unfortunately attempted methylation (*e.g.*, with diazomethane in ether–methanol or ether–dioxan) gave only traces of the required product. The preparation of *m*-hydroxyphenylpyruvic acid by Hahn and Werner's method (*Annalen*, 1935, **520**, 130) gives poor yields; by the use of aceturic acid in place of hippuric acid (cf. MacDonald, *J.*, 1948, 376), α-acetamido-*m*-acetoxycinnamic acid azlactone was obtained in 62% yield, and this was hydrolysed to *m*-hydroxyphenylpyruvic acid in 75% yield. In contrast, for the preparation of *m*-methoxyphenylpyruvic acid (see below), the azlactone derived from *m*-methoxybenzaldehyde and hippuric acid (Pschorr, *Annalen*, 1912, **391**, 44) was preferred to α-acetamido-*m*-methoxycinnamic acid azlactone, as the latter could be obtained only in low yield by the aceturic acid condensation.

Finally, a convenient synthesis of (I; R = OMe) was found in the condensation of *m*-methoxyphenylpyruvic acid with tryptamine to give 2-*m*-methoxybenzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline (V) followed by reaction with formaldehyde in aqueous solution at 40—45°.



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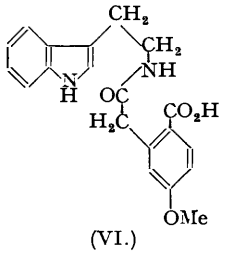

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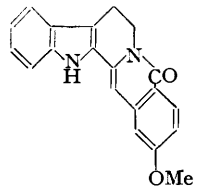

(VII.)

In another possible route to (I; R = OMe), tryptamine was condensed with 5-methoxyhomophthalic anhydride (obtained by the action of acetyl chloride on the acid) to give *N*-2′-3″-indolylethyl-2-carboxy-5-methoxyphenylacetamide (VI). This was esterified with diazomethane and the product treated with phosphoryl chloride in an attempt to prepare (VII); but only a very small amount of what appeared to be the required product was isolated. Further attempts to convert (VII) into (I; R = OMe) by reduction first with lithium aluminium hydride, then catalytically, were therefore abandoned.

With a view to the synthesis of derivatives of (I; R = OMe) in which ring E is hydrogenated, attempts were made to hydrogenate (II; R = Et) to ethyl 6-methoxydecahydro*iso*quinoline-3-carboxylate; but difficulty was experienced in preventing further action on the carbethoxy-group. Hydrogenation could be accomplished in acetic acid solution with platinum at 6 atmospheres' pressure; or in ethanol with nickel on kieselguhr (Covert, Connor, and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 1651) at 155—160° and 80 atmospheres. The latter catalyst is already known to be preferable to Raney nickel for the hydrogenation of anisole derivatives, as it is less liable to cause hydrogenolysis of the ether linkage (Duzee and Adkins, *J. Amer. Chem. Soc.*, 1935, **57**, 147). The reduced ester was treated as for the conversion of (II; R = Et) into (IV), and gave a gum which was probably a mixture of stereoisomeric forms of (IV) in which the benzene ring is hydrogenated; but no crystalline derivatives could be obtained.

The hydrogenation of the ketone (IV) has also been investigated. With platinum and acetic acid at room temperature and atmospheric pressure, 1 mol. of hydrogen was rapidly absorbed, and from the product two crystalline compounds, ' base *A* ' and ' base *B*,' were isolated. The analytical results agreed with the empirical formula $C_{14}H_{19}O_2N$ in each case, suggesting that these were the two possible racemic forms of (IV; CH·OH instead of CO). The same products

were also obtained by the Ponndorf–Meerwein reduction of (IV). The acetylated bases *A* and *B* (prepared by using acetic anhydride) had the empirical formula $C_{16}H_{21}O_3N$. Attempts to oxidise the bases back to the original ketone by chromic acid, the Oppenauer method (by using aluminium phenoxide and *cyclo*hexanone in xylene), or the modification of the latter due to Woodward, Wendler, and Brutschy (*J. Amer. Chem. Soc.*, 1945, **67**, 1425) failed.

Finally, a successful synthesis of yohimbone was achieved by the following process in which the asymmetric centres are introduced one at a time so that at no stage should more than two racemates be produced. The compound (I; R = OMe) was reduced to ' base *C*,' presumably 3''-methoxy-3 : 4 : 6 : 9 : 1'' : 4''-hexahydro-7 : 8-benzindolo-(2' : 3'-1 : 2)pyridocoline (VIII), by the action of sodium and *tert.*-butanol in liquid ammonia (cf. Birch, *J.*, 1944, 430). When ' base *C* ' was treated with aqueous methanolic hydrochloric acid, it yielded ' base *D*,' together with a small amount of ' base *E*,' presumably the two racemic forms of (IX). ' Base *D* ' was hydrogenated in the presence of Adams's catalyst in glacial acetic acid; the hydrogen uptake slowed down after the absorption of 1 mole so the hydrogenation was interrupted, and a keto-base, m. p. 266° (decomp.), isolated. This must be the previously unknown (±)-yohimbone as it was resolved through the salt with (−)-camphor-10-sulphonic acid [the (−)-base-(−)-acid salt being the less soluble in ethanol] and the resulting (−)-base, m. p. 305—306° (decomp.), $[\alpha]_D^{18}$ −106°, proved identical with yohimbone obtained from yohimbine by the Oppenauer oxidation. No depression of m. p. was observed on admixture of the two bases or of their methiodides.

Thus structure (X) for yohimbone is considered to be established synthetically, the only uncertain feature being the configurations of the asymmetric centres. This confirms the nuclear structure and the position of the hydroxyl group of yohimbine itself.

Experimental.

Unless otherwise stated, the light petroleum used had b. p. 60—80°. All m. p.s are uncorrected.

Ethyl iso*Quinoline-3-carboxylate.*—A mixture of ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (1·2 g.), flowers of sulphur (0·5 g.), and tetralin (4 c.c.) was heated for 4 hours at 160—165°. The cooled product was diluted with benzene, and the filtered solution extracted with dilute hydrochloric acid. The acid extract was basified (sodium carbonate solution) and extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled, giving a colourless oil (0·5 g.; b. p. 165—170°/2 mm.). This yielded a crude *picrate*, m. p. 154—157°; when recrystallised from ethanol this formed a yellow powder, m. p. 157° (Found: C, 50·25; H, 3·3. $C_{12}H_{11}O_2N,C_6H_3O_7N_3$ requires C, 50·25; H, 3·25%). The picrate (1 g.) was ground with hydrochloric acid (20%), the resulting picric acid removed by filtration, and the filtrate basified (Na_2CO_3) and extracted with ether. The extract was dried (K_2CO_3), the ether removed, and the *base* (0·3 g.; b. p. 165—170°/2 mm.) distilled as a colourless oil which soon set to a white solid (after being washed with light petroleum) (0·29 g.; m. p. 40—46°) (Found: C, 71·65; H, 5·45. $C_{12}H_{11}O_2N$ requires C, 71·65; H, 5·45%).

α-Acetamido-m-*acetoxycinnamic Acid Azlactone.*—The temperature of a mixture of *m*-hydroxybenzaldehyde (7·15 g.), aceturic acid (8·1 g.), acetic anhydride (23 c.c.), and triethylamine (6·5 c.c.) was raised from 15° to 70° during 5 days, then kept at 0° for 1 day. The resulting solid was collected, washed with aqueous ethanol, and dried (8·85 g.; m. p. 118—120°). Recrystallised twice from ethanol this afforded the *azlactone* as pale-yellow crystals, m. p. 120—121° (Found: C, 62·5; H, 5·2. $C_{13}H_{11}O_4N,\frac{1}{2}C_2H_6O$ requires C, 62·7; H, 5·2%).

m-*Hydroxyphenylpyruvic Acid.*—The azlactone (0·9 g.) was heated under reflux for 2½ hours with a mixture of concentrated hydrochloric acid (1·1 c.c.) and water (12 c.c.). The solution was cooled and after the addition of aqueous sodium hydrogen sulphite (40%; 6 c.c.) it was extracted with ether, strongly acidified (concentrated hydrochloric acid) and evaporated (water-bath) to dryness under reduced pressure. The residue was extracted with ethyl acetate, the extract evaporated, and the resulting yellow solid washed with light petroleum, affording the acid (0·5 g.), m. p. 163° (decomp.).

α-Acetamido-m-*methoxycinnamic Acid Azlactone.*—(*a*) A mixture of *m*-methoxybenzaldehyde (Chakravarti and Nair, *J. Indian Chem. Soc.*, 1932, **9**, 580) (1·02 g.), aceturic acid (0·59 g.), acetic anhydride (1·2 c.c.), and fused sodium acetate (0·3 g.) was heated under reflux for 1 hour, and cooled, and the *azlactone* collected, washed with aqueous ethanol, and dried (0·65 g.; m. p. 99—100°). Recrystallised from ethanol this formed pale yellow crystals, m. p. 103—104° (Found: C, 64·95; H, 5·8. $C_{12}H_{11}O_3N,\frac{1}{2}C_2H_6O$ requires C, 65·0; H, 5·85%).

(*b*) The temperature of a mixture of *m*-methoxybenzaldehyde (1·36 g.), aceturic acid (1·17 g.), acetic anhydride (4·1 c.c.), and triethylamine (1 c.c.) was raised from 30° to 65° during 5 days, then kept at 0° for 2 days, giving the crude azlactone, as above (0·5 g.; m. p. 98—101°).

Ethyl 6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*iso*quinoline-3-carboxylate* (II; R = Et).—*m*-Methoxyphenylalanine was prepared by Chakravarti and Rao's method (*J.*, 1938, 172) except that it was purified through the copper salt. However, the intermediate *N*-benzoyl-*β*-*m*-methoxyphenylalanine (for which these authors quote m. p. 144°) after crystallisation first from methanol then from benzene formed colourless plates or prisms, m. p. 129° (Found: C, 68·2; H, 5·65. Calc. for $C_{17}H_{13}O_4N$: C, 68·65; H, 5·6%). The overall yield of *m*-methoxyphenylalanine from the azlactone was 30%.

Formalin (7 c.c.; 40 %) was added to a solution of *m*-methoxyphenylalanine (10 g.) in 0·5N-sodium hydroxide solution (100 c.c.). The solution was kept at room temperature for 4 hours, then heated in a water-bath at 37° for 15 hours, evaporated to half of its original volume (water-bath; reduced pressure),

acidified (Congo-red) by the addition of concentrated hydrochloric acid (about 7 c.c.) and then evaporated to complete dryness (water-bath; reduced pressure), the last traces of water being removed by the addition and distillation of a little absolute ethanol. The residue was treated with absolute ethanol (120 c.c.), and the cooled mixture saturated with dry hydrogen chloride and heated under reflux (water-bath) for 2½ hours. The bulk of the ethanol was removed by distillation (water-bath), the residue was dissolved in a small volume of cold water, and the solution was saturated with sodium carbonate and extracted with ether. The ether was removed from the dried (K_2CO_3) extract, and the residue distilled, the fraction, b. p. 155—165°/2 mm. (6·5 g.), being collected. The crude *picrate*, m. p. 183—186°, on being twice recrystallised from ethanol, formed pale yellow needles, m. p. 187—188° (Found: C, 49·45; H, 4·2. $C_{13}H_{17}O_3N,C_6H_3O_7N_3$ requires C, 49·15; H, 4·3%). The pure picrate was decomposed by treatment with cold 2N-sodium hydroxide solution, the base extracted with ether, the extract dried (K_2CO_3), the ether removed and the residue distilled, giving the *ester* as a pale yellow, viscous liquid, b. p. 160°/2 mm. (Found: C, 66·3; H, 7·25. $C_{13}H_{17}O_3N$ requires C, 66·4; H, 7·25%).

Methyl 6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline-3-*carboxylate*.—This was prepared similarly and gave a *picrate* forming pale yellow needles from methanol, m. p. 185° (Found: C, 48·25; H, 4·1. $C_{12}H_{15}O_3N,C_6H_3O_7N_3$ requires C, 48·0; H, 4·0%).

6-*Methoxy*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline-3-*carboxylic Acid* (II; R = H).—Sodium hydroxide (1·1 g.) in water (1·1 c.c.) was added to the ethyl ester (1·1 g.) in 95% ethanol (13 c.c.). The mixture was heated under reflux (water-bath) for 7 hours, the ethanol distilled off, the residue dissolved in water, and the solution neutralised with dilute acetic acid. The crude acid (0·47 g.) separated; recrystallised from water, it formed colourless leaflets, m. p. 302° (decomp.) (Found: C, 62·9; H, 6·35. Calc. for $C_{11}H_{17}O_3N$: C, 63·7; H, 6·3%). Chakravarti and Rao, *loc. cit.*, quote m. p. 263—264° (decomp.) for this acid.

Ethyl 6-*Methoxy*isoquinoline-3-*carboxylate*.—Ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (0·6 g.) was dehydrogenated with sulphur (0·24 g.) in tetralin (3 c.c.) as described for ethyl 1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate. The product was not distilled, but was crystallised from benzene–light petroleum (yield: 0·23 g.; m. p. 98—102°); when recrystallised this afforded the *ester* as very pale-yellow prisms, m. p. 104—105° (Found: C, 67·95; H, 5·6. $C_{13}H_{13}O_3N$ requires C, 67·55; H, 5·6%). The *picrate* separated from ethanol as bright-yellow crystals, m. p. 181—182° (Found: C, 47·75; H, 3·7. $C_{13}H_{13}O_3N,C_6H_3O_7N_3,H_2O$ requires C, 47·7; H, 3·75%).

m-*Methoxyphenylalanine Ethyl Ester*.—*m*-Methoxyphenylalanine (0·5 g.) was heated under reflux with ethanolic hydrogen chloride for 1½ hours (water-bath), the bulk of the ethanol removed by distillation, the residue dissolved in cold water, the solution saturated with sodium carbonate and extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled, yielding the ester (0·2 g.) as a liquid, b. p. 140°/2 mm. The *picrate* separated from ethanol as bright-yellow crystals, m. p. 159—160° (Found: C, 47·95; H, 4·6. $C_{12}H_{17}O_7N,C_6H_3O_7N_3$ requires C, 47·8; H, 4·45%).

Ethyl 6-*Methoxy*-2-3′-*cyanopropyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline-3-*carboxylate* (III; R = CN).—A mixture of ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate (5·2 g.), γ-bromobutyronitrile (4·1 g.), and anhydrous potassium carbonate (1·8 g.) was heated, with occasional stirring, for 6 hours in the water-bath. After cooling, water (50 c.c.) was added, the mixture extracted with ether, the extract dried (K_2CO_3), the ether removed, and the residue distilled (5·2 g.; b. p. 190—220°/2 mm.). On redistillation this yielded the *nitrile* as a pale-yellow, viscous liquid, b. p. 210°/2 mm. (Found: C, 67·2; H, 7·1. $C_{17}H_{22}O_3N_2$ requires C, 67·5; H, 7·25%).

Ethyl 6-*Methoxy*-2-3′-*carbethoxypropyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline-3-*carboxylate* (III; R = CO_2Et).—The nitrile (III; R = CN) (5·2 g.) was converted into the diester as described for the preparation of ethyl 2-3′-carbethoxypropyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline-3-carboxylate in Part I (*loc. cit.*); the *ester* was obtained as a pale-yellow, viscous liquid (4·8 g.; b. p. 200°/2 mm.) (Found: C, 65·0; H, 7·9. $C_{19}H_{27}O_5N$ requires C, 65·3; H, 7·75%).

9-*Keto*-2′-*methoxy*-1 : 4 : 6 : 7 : 8 : 9-*hexahydro*-2 : 3-*benzpyridocoline* (IV).—The diester (III; R = CO_2Et) (4·8 g.) was subjected to the Dieckmann reaction as described in Part I for the preparation of 9-keto-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline, except that the subsequent hydrolysis was by heating of the mixture on the water-bath for 6 hours with hydrochloric acid (150 c.c.; 10%). The dried (K_2CO_3) ether extract obtained after evaporation and basification was concentrated to a very small volume, decanted from a little gummy material, and allowed to cool, whereupon the crude *ketone* (1·3 g.; m. p. 110—115°) crystallised. Recrystallisation, first from ether, then from benzene–light petroleum afforded orange-yellow plates (0·5 g.), m. p. 123—124° (Found: C, 72·1; H, 7·35. $C_{14}H_{17}O_2N$ requires C, 72·7; H, 7·40%). The *hydrochloride* separated from methanol–acetone as yellow tablets, m. p. 195—196° (Found: C, 62·1; H, 6·3. $C_{14}H_{18}O_2NCl$ requires C, 62·8; H, 6·7%). The *oxime* was prepared by heating under reflux a solution of the crude ketone (50 mg.), hydroxylamine hydrochloride (50 mg.), and fused sodium acetate (0·1 g.) in methanol (2 c.c.) for 2½ hours; the product (20 mg.) separated from methanol as almost colourless prisms, m. p. 223—224° (Found: C, 68·45; H, 7·25. $C_{14}H_{18}O_2N_2$ requires C, 68·3; H, 7·3%). The *phenylhydrazone* was prepared by heating a solution of the ketone (0·28 g.) in absolute ethanol with phenylhydrazine (0·14 g.) for 4 hours on the water-bath; from methanol (charcoal) it separated as very pale yellow prisms (0·33 g.), m. p. 88—90° after sintering at 75° (Found: C, 70·8; H, 7·65. $C_{20}H_{23}ON_3,CH_4O$ requires C, 71·4; H, 7·65%).

Catalytic Hydrogenation of the Ketone (IV).—The ketone (0·646 g.) in glacial acetic acid (10 c.c.) was hydrogenated at room temperature and atmospheric pressure, 1 mol. of hydrogen being absorbed during 30 minutes when Adams's catalyst (0·19 g.) was used. The filtered solution was evaporated to dryness (water-bath; reduced pressure), the residue dissolved in water and basified (Na_2CO_3), the solution extracted with chloroform, the extract dried (K_2CO_3), the chloroform distilled off, and the residue crystallised from methanol, giving a solid (0·225 g.; m. p. 161—165°); on concentration the mother-liquors afforded a further crop (0·13 g.; m. p. 155—164°). These two solids were combined ('crude A'). The methanol was distilled off from the mother-liquors, and the residue recrystallised from benzene–light petroleum, giving 'crude B' (0·13 g.; m. p. 122—132°). 'Crude A' was recrystallised first from methanol (giving 0·23 g.; m. p. 165—166°) and finally from benzene, yielding '*base* A' as colourless

crystals, m. p. 166° (Found: C, 72·2; H, 8·2. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·15%). A mixture of base *A'* (15 mg.) and acetic anhydride was warmed on the water-bath for 35 minutes, cooled, treated with water, and basified (NH_4OH), and the resulting white solid (13 mg.) washed with water, dried, and recrystallised from benzene–light petroleum, affording '*acetylated base* A' as colourless needles, m. p. 118° (Found: C, 69·75; H, 7·55. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·65%). Solutions of 'base *A*' (20 mg.) and of picric acid (30 mg.) in ethanol were mixed, the solution concentrated, and diluted with ether. The precipitate was recrystallised from a small volume of ethanol, gives '*base A picrate*' as yellow prisms (27 mg.), m. p. 144—145° after sintering at 141° (Found: C, 52·05; H, 5·2. $C_{14}H_{19}O_2N,C_6H_3O_7N_3$ requires C, 51·95; H, 4·8%). 'Crude *B*' was recrystallised twice from benzene–light petroleum, giving '*base* B' as colourless prisms, m. p. 138—140° (Found: C, 71·9; H, 8·35. $C_{14}H_{19}O_2N$ requires C, 72·1; H, 8·15%). This (22 mg.) was acetylated as for 'base *A*' and the product isolated by extraction with ether, removing the ether from the dried (K_2CO_3) extract and recrystallising the residue from light petroleum (b. p. 40—60°), giving '*acetylated base* B' as colourless crystals (9 mg.) m. p. 86—87° (Found: C, 69·4; H, 7·3; N, 5·1. $C_{16}H_{21}O_3N$ requires C, 69·8; H, 7·65; N, 5·1%).

Reduction of the Ketone (IV) *by the Ponndorf–Meerwein Method.*—The ketone (0·23 g.) was treated with aluminium *iso*propoxide (0·2 g.) and *iso*propyl alcohol dropped in during the slow distillation (total volume, 7 c.c.). The solvent was finally removed on the water-bath under reduced pressure, the residue treated with water and sodium hydroxide solution and extracted with chloroform, the extract dried (K_2CO_3), and the solvent removed, leaving an oil which soon solidified. A benzene solution of the resulting solid was boiled with charcoal, filtered, concentrated, and diluted with light petroleum. The resulting solid was recrystallised first from methanol and finally from benzene–light petroleum, giving a product (40 mg.), m. p. 165—166° not depressed by admixture with 'base *A*.' The methanol mother-liquors on evaporation gave a residue which when recrystallised twice from benzene–light petroleum afforded a product, m. p. 138—140° not depressed by admixture with 'base *B*.'

2-m-*Methoxybenzyl*-2 : 3 : 4 : 5-*tetrahydro*-β-*carboline* (V).—Solutions of *m*-methoxyphenylpyruvic acid (2·6 g.) in water (60 c.c.) and of tryptamine hydrochloride (2·45 g.) in water (30 c.c.) were mixed and heated for 2 days on the water-bath. After being cooled, the resulting solid was collected, washed with water, and dried (3·55 g.). Recrystallised from 95% ethanol, this afforded the hydrochloride as colourless crystals (2·45 g.), m. p. 270° (decomp.). A portion was shaken with a mixture of dilute sodium hydroxide solution and ether until solution was complete, the ethanol layer was dried (K_2CO_3) and evaporated, and the residue was recrystallised from benzene–light petroleum, giving the *base* as colourless needles, m. p. 124° (Found: C, 78·6; H, 6·8. $C_{19}H_{20}ON_2$ requires C, 78·1; H, 6·85%).

3''-*Methoxy*-3 : 4 : 6 : 9-*tetrahydro*-7 : 8-*benzindolo*(2' : 3'-1 : 2)*pyridocoline* (I; R = OMe).—(*a*) 9-Keto-2'-methoxy-1 : 4 : 6 : 7 : 8 : 9-hexahydro-2 : 3-benzpyridocoline phenylhydrazone (0·5 g.) was added to ice-cooled absolute ethanol (15 c.c.), previously saturated with hydrogen chloride. After 1 hour at 0°, the mixture was heated under reflux for 7 hours on the water-bath, the bulk of the ethanol removed by distillation, and the residue treated with water. The hydrochloride (0·3 g.) was collected, washed with water, and shaken vigorously with a mixture of dilute sodium hydroxide solution and ether until all was dissolved. The ethanol layer was dried (K_2CO_3), the ether removed, and the residue recrystallised from benzene–light petroleum (charcoal), affording the *base* as colourless plates (0·2 g.), m. p. 168° after sintering at 150° (Found, in material dried for 1 hour at 100°/1 mm.: C, 78·7; H, 6·6. $C_{20}H_{20}ON_2$ requires C, 78·95; H, 6·6%).

(*b*) 2-*m*-Methoxybenzyl-2 : 3 : 4 : 5-tetrahydro-β-carboline hydrochloride (2·45 g.) was dissolved in boiling water (1,100 c.c.), the solution cooled to 40° and treated with formalin (36·5 c.c.; 40%). The solution was kept at 40—45° for 3 days, basified (40% sodium hydroxide solution), and cooled, and the resulting white solid collected, washed with water, dried in a vacuum desiccator, and recrystallised first from a small volume of benzene (charcoal), then from benzene–light petroleum, giving the base (1·15 g.) as colourless plates, m. p. 169° after sintering at 150° (Found, in material dried for 1 hour at 100°/1 mm.: C, 79·2; H, 6·75. $C_{20}H_{20}ON_2$ requires C, 78·95; H, 6·6%). Mixed m. p., with product from (*a*), 169°.

5-*Methoxyhomophthalic Anhydride.*—5-Methoxyhomophthalic acid (Chakravarti and Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 101) (1·4 g.) was heated under reflux for 2 hours with acetyl chloride (7 c.c.), the mixture evaporated to dryness (water bath; reduced pressure), and the residue recrystallised from benzene (charcoal), giving the *anhydride* (1·1 g.) as creamy white plates, m. p. 171° (Found: C, 62·6; H, 3·85. $C_{10}H_8O_4$ requires C, 62·5; H, 4·15%).

N-2'-3''-*Indolylethyl*-2-*carboxy*-5-*methoxyphenylacetamide* (VI).—A solution of tryptamine (1·06 g.) in pure dry chloroform (25 c.c.) was added to one of the above anhydride (1·25 g.) in chloroform (45 c.c.). The mixture was heated under reflux for 8 hours, concentrated to 25 c.c., and allowed to cool. The *acid* was collected, washed with chloroform, and dried (2 g.; m. p. 169—170°); recrystallised from methanol, this afforded colourless crystals, m. p. 170—171° (Found: C, 67·6; H, 6·0. $C_{20}H_{20}O_4N_2$ requires C, 68·2; H, 5·7%).

Attempted Synthesis of the Hexahydro-Derivative of (IV).—Ethyl 6-methoxy-1 : 2 : 3 : 4-tetrahydro*iso*-quinoline-3-carboxylate (4·76 g.) in ethanol (100 c.c.) was hydrogenated for 7 hours at 155—160° in the presence of freshly reduced nickel–kieselguhr catalyst (0·95 g.), the initial hydrogen pressure being 80 atmospheres at room temperature. The ethanol was removed from the filtered solution, and the residue distilled at 2 mm. pressure giving (*a*) a liquid (0·45 g.), b. p. 137—150°; (*b*) a liquid (3·8 g.), b. p. 150—157° (mainly 155°) (Found: C, 67·7; H, 8·7. $C_{13}H_{23}O_3N$ requires C, 64·75; H, 9·55%). When treated with γ-bromobutyronitrile as described for the preparation of (III; R = CN), (*b*) yielded a gum (1·72 g.), b. p. 140°/2 mm. On treatment with ethanolic hydrogen chloride, this gave another gum, which was subjected to the Dieckmann reaction, giving, after distillation, a red gum (0·27 g.) (Found: C, 71·0; H, 8·8. $C_{14}H_{23}O_2N$ requires C, 70·9; H, 9·7%). Attempts to prepare a crystalline oxime or semicarbazone from this failed; and no crystalline picrate could be obtained from this or from the intermediate products.

When the hydrogenation was carried out at higher temperatures, the reduced ester had a lower b. p., and the analysis (C, 70; H, 10%) indicated that extensive hydrogenation and/or hydrogenolysis had occurred. Hydrogenation at atmospheric pressure of the ester (1 g.) in acetic acid in the presence of

Adams's catalyst (0·1 g.) gave a product (0·5 g.) apparently similar to the above (Found : C, 66·7; H, 9·8%).

Reduction of 3''-Methoxy-3 : 4 : 6 : 9-tetrahydro-7 : 8-benzindolo(2' : 3'-1 : 2)pyridocoline.—The base (1·2 g.) was dissolved in liquid ammonia (ca. 300 c.c.) contained in an un-silvered Dewar vessel. Sodium (2·5 g.) and *tert.*-butanol (9 c.c.) were added with occasional stirring alternately each in 6 equal portions during 1 hour. After a further 1 hour, more sodium (0·6 g.) was added; an hour later, methanol was added dropwise until the solution was colourless. The solution was then poured into a beaker, the ammonia allowed to evaporate, and the residue treated with ice and water. The resulting solid was collected, washed with water, and dried in a vacuum desiccator; it (1·05 g.) had m. p. 179—183°. Recrystallised from benzene, this gave '*base* C ' as shining, colourless leaflets (0·95 g.), m. p. 183—184° (Found, in material dried at 100°/1 mm. for ½ hour : C, 78·6; H, 7·3. $C_{20}H_{22}ON_2$ requires C, 78·45; H, 7·2%).

A solution of this (0·95 g.) in methanol (55 c.c.) was treated with 2N-hydrochloric acid (19 c.c.), heated on the water-bath for 1¼ hours, and diluted with hot water (25 c.c.). The bulk of the methanol was removed by distillation from the water-bath, and the residue was basified (2N-sodium hydroxide solution) and cooled; the resulting solid was washed with water and dried in a vacuum desiccator (0·88 g.). Recrystallised four times from methanol this gave '*base* D,' as long, yellow needles, m. p. 260—261° (decomp.) (Found : C, 77·8; H, 6·95. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·85%). Light absorption in ethanol : $\lambda_{max.}$ 2710 A.; log ε 3·97.

The mother-liquors from the first recrystallisation of ' base *D* ' on concentration gave a small amount of ' *base* E ' which, after recrystallisation from methanol, formed yellow plates, m. p. 211—212° (Found : C, 77·85; H, 6·85. $C_{19}H_{20}ON_2$ requires C, 78·05; H, 6·85%).

(±)-*Yohimbone.*—' Base *D* ' (0·469 g.) in glacial acetic acid (15 c.c.) was hydrogenated at room temperature and pressure in the presence of previously reduced Adams's catalyst (70 mg.), and the hydrogenation was interrupted after the uptake of 1 mole of hydrogen in 38 minutes. The solvent was removed from the filtered solution, the residue dissolved in warm water, cooled, and basified (N-sodium hydroxide solution), and the precipitate collected, washed with water, dried, and crystallised from methanol (charcoal) giving the base (0·35 g.; m. p. 242—244°). After being twice recrystallised from methanol the (±)-*yohimbone* formed long, slender, colourless needles, m. p. 266° (decomp.) after darkening and sintering at 263° (Found : C, 77·6; H, 7·9. $C_{19}H_{22}ON_2$ requires C, 77·55; H, 7·5%). Light absorption in ethanol : $\lambda_{max.}$ 2780 A.; log ε 3·91. The *dinitrophenylhydrazone hydrochloride* separated from methanol as orange-red crystals which became black at ca. 280°, but did not melt below 320° (Found : C, 57·8; H, 5·4. $C_{25}H_{26}O_4N_6,HCl,\frac{1}{2}H_2O$ requires C, 57·75; H, 5·4%).

Resolution of (±)-*Yohimbone.*—Fractional crystallisation of the (+)-tartrate gave little resolution. The (+)-camphor-10-sulphonate of (±)-yohimbone (0·53 g.) was recrystallised six times from ethanol and a base (25 mg.), m. p. 299—301° (decomp.), $[\alpha]_D^{18}$ +93°, recovered. The final resolution was therefore carried out as follows : A solution of (±)-yohimbone (0·77 g.) in hot ethanol was treated with one of (−)-camphor-10-sulphonic acid (0·74 g.), and the mixture concentrated to a small volume and kept overnight in a refrigerator. The resulting solid (0·8 g.) was recrystallised nine times from ethanol, giving the (−)-base-(−)-camphorsulphate (0·16 g.) as colourless crystals, m. p. 294—296° (decomp.). A solution of this in hot water (40 c.c.) was cooled and basified (N-sodium hydroxide solution), the precipitate taken up in chloroform, the solution dried (K_2CO_3), the solvent removed, and the residue recrystallised from methanol, giving (−)-yohimbone (70 mg.) as long, slender, colourless needles; m. p. 305—306° (decomp.) after darkening at 285°, not depressed by admixture with natural yohimbone of m. p. 304—305° (decomp.) (Found : C, 77·8; H, 7·9. $C_{19}H_{22}ON_2$ requires C, 77·55; H, 7·5%). It had α_D^{18} −1·371° (in pyridine, *c*, 2·585, *l*, 0·5, *d* 0·9922), $[\alpha]_D^{18}$ −106° (Witkop, *loc. cit.*, gives −103·9° and −105·8° for *c*, 0·8565 and 0·652, respectively). The picrate of the synthetic (−)-base, prepared as described by Witkop for that of yohimbone, had m. p. 169° (Witkop gives 171°). For yohimbone methiodide Witkop gives m. p. 290° (decomp.) and m. p. 286° (decomp.); when prepared as he describes, however, it was found to have m. p. 296—297° (decomp.). The methiodide of the synthetic (−)-base had m. p. 297—298°, not changed by recrystallisation from methanol–acetone, and not depressed by admixture with the above.

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