749. *The Chemistry of the* Mitragyna *Genus. Part III.* Synthesis of a Degradation Product of Mitragynine.*

By J. W. Cook, J. D. Loudon, and P. McCloskey.

Derivatives of 2 : 3-dihydro-3-ketobenz-1 : 4-oxazine were produced by heating α-halogenoacyl-*o*-anisidides with aluminium chloride at 160—190°. At a higher temperature 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine underwent rearrangement, and methylation of the phenolic product afforded a mixture of 4- and 7-methoxy-1-methyloxindoles. These oxindoles were reduced by lithium aluminium hydride to the corresponding indoles, and their structures were established by independent, standard syntheses.

4-Methoxy-1-methylindole was converted *via* the corresponding gramine and tryptophan into 6-methoxy-1 : 2-dimethyl-β-carboline (IX). This was shown to be identical with the degradation product of mitragynine, which Ing and Raison obtained by distillation of the alkaloid from zinc dust (*J.*, 1939, 986).

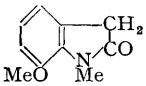
Ing and Raison (*J.*, 1939, 986) pointed out that the base, $C_{14}H_{14}ON_2$, which they obtained by degrading the alkaloid mitragynine, has the properties of a methoxy-*N*-methylharman. They showed, however, that it was not identical with *ind*-*N*-methylharmine (8-methoxy-1 : 2-dimethyl-β-carboline †) and Cook, Loudon, and McCloskey further showed that it was distinct from 7-methoxy-1 : 2-dimethyl-β-carboline (Part II*). None the less the close resemblance of the degradation product to these isomeric bases encouraged the view that the compound is indeed an *ind*-*N*-methylharman and we now present evidence which establishes its structure.

Since the alkaloid vomicine is known to contain an indole fragment which is oxygenated at position-7, corresponding to position-9 of the β-carboline system, and since damascenine (methyl 3-methoxy-2-methylaminobenzoate) might be considered as biogenetically related to a 7-methoxy-1-methylindole, our attention was primarily directed to the synthesis of 9-methoxy-1 : 2-dimethyl-β-carboline. In view of the inaccessibility of 7-methoxyindole the preparation of 7-methoxy-1-methyloxindole (I) by the Stollé method was attempted. This involved heating the chloroacetyl derivative of *N*-methyl-*o*-anisidine with aluminium chloride at 160° and, not unexpectedly, the main product of the reaction was the benzoxazine

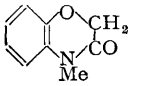
* Part II, *J.*, 1951, 1203. † Numbering as in (IX).

derivative (II). As had been hoped, however, this compound was converted by aluminium chloride at higher temperatures into derivatives of indole. The alkali-soluble rearrangement product was not homogeneous but, after methylation with methyl sulphate and alkali, was converted into two isomeric methoxyoxindoles (A) and (B) of molecular formula $C_{10}H_{11}O_2N$. On reduction with lithium aluminium hydride each compound yielded a corresponding methoxyindole together with a methoxyindoline, but whereas oxindole-A and its reduction products—indole-A and indoline-A—were readily shown to contain each one *N*-methyl group, the *N*-methyl value determined for oxindole-B was fractional and was zero for indole-B and for the picrate of indoline-B. Since Ing and Raison's compound is known to contain one *N*-methyl group, indole-A was here selected for successive conversion into the corresponding gramine, tryptophan, and methoxy-1 : 2-dimethyl-β-carboline by reactions which are more fully described below. The carboline thus synthesised proved to be identical with the mitragynine degradation product.

At this stage, therefore, it seemed highly probable that the degradation product of mitragynine was 9-methoxy-1 : 2-dimethyl-β-carboline although the situation was somewhat anomalous in that the synthesis did not provide unequivocal proof of structure. Nevertheless the remaining ambiguity was now associated with compounds of simpler type and attention was turned to identifying 7-methoxy-1-methylindole by an independent and unambiguous synthesis. Methylation of 7-methoxyindole by the action of methyl iodide and potassium in liquid ammonia afforded a methylated product which was identified as indole-B and, like the original specimen, gave a zero value for *N*-methyl analysis. This result suggested that *C*-methylation had occurred but the compound was then found to be isomeric and not identical with either 7-methoxy-2- or -3-methylindole. These compounds were synthesised by the Fischer method from the *o*-methoxyphenylhydrazones of acetone and propaldehyde respectively. Furthermore *N*-methyl-*o*-anisidine was acylated by oxalyl chloride and the product (III) was smoothly converted into 7-methoxy-1-methylisatin (IV) by aluminium chloride in ethylene dichloride. Reduction of (IV) in two stages gave oxindole-B.



(I)



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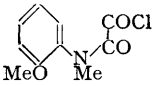

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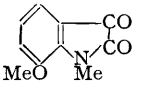


(IV)

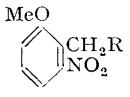
In the light of these findings the conclusion was inescapable that indole-B and oxindole-B are 7-methoxy-1-methyl-indole and -oxindole (cf. I) respectively, and that in consequence Ing and Raison's compound cannot be 9-methoxy-1 : 2-dimethyl-β-carboline. The elimination of the 7-, 8-, and 9-methoxy-1 : 2-dimethyl-β-carboline structures, when considered together with the synthesis of the mitragynine degradation product as outlined above, virtually identifies the compound as 6-methoxy-1 : 2-dimethyl-β-carboline (IX). Confirmation was now sought in an unambiguous synthesis of oxindole-A which, accordingly, should be 4-methoxy-1-methyloxindole. To this end 2-methoxy-6-nitrobenzyl chloride (V; R = Cl) was condensed with potassium cyanide in aqueous ethanol and the nitrile formed was hydrolysed to 2-methoxy-6-nitrophenylacetic acid (V; R = CO_2H). Catalytic reduction of this acid was accompanied by cyclisation of the intermediate amino-acid with formation of 4-methoxyoxindole (VI; R = H) and methylation then yielded 4-methoxy-1-methyloxindole (VI; R = Me) which was found to be identical with oxindole-A.

It follows from the identification of oxindole-A that indole-A is 4-methoxy-1-methylindole (VII; R = H) and its conversion into the mitragynine degradation product may now be described more fully. Condensation of the indole (VII; R = H) with formaldehyde and dimethylamine gave 4-methoxy-1-methylgramine (VII; R = $CH_2{\cdot}NMe_2$) (conveniently characterised as the picrate). In the form of its methiodide, this reacted with ethyl sodioacetamidomalonate, yielding [VII; R = $CH_2{\cdot}C(NHAc)(CO_2Et)_2$] and thence by appropriate stepwise hydrolysis and decarboxylation 4-methoxy-1-methyltryptophan [VII; R = $CH_2{\cdot}CH(NH_2){\cdot}CO_2H$]. The tryptophan was condensed with acetaldehyde, forming 2 : 3 : 4 : 5-tetrahydro-6-methoxy-1 : 2-dimethyl-β-carboline-4-carboxylic acid

(VIII) from which 6-methoxy-1 : 2-dimethyl-β-carboline (IX) was obtained by treatment with potassium dichromate. The carboline (IX) was most easily purified by chromatography and the same treatment was applied to a specimen of the mitragynine degradation product. Both samples, and their picrates and *p*-nitrobenzylidene derivatives, had corresponding melting points which remained undepressed on admixture of the appropriate pairs of compounds.

Although derivatives of 5-, 6-, and 7-hydroxy- and of 5 : 6-dihydroxy-indole have been recognised among naturally occurring compounds (cf. Sir Robert Robinson, *Chem. and Ind.*, 1952, 358) this degradation product of mitragynine is the first representative of the 4-hydroxyindole type to be obtained from a natural source. It is produced, however, by distilling mitragynine with zinc dust and in view of the severity of this treatment its precise significance in respect of the alkaloid's structure requires further investigation.

The formation of oxindole-A (VI; R = Me) by methylation of the phenolic rearrangement products of 2 : 3-dihydro-3-keto-4-methylbenzoxazine (II) indicates that the latter is partly converted into 4-hydroxy-1-methyloxindole during the fusion with aluminium chloride. This involves a change—from *ortho* to *meta*—in the positional relationship between the *O*- and the *N*-atom attached to the benzene ring, and migration of one or other of them must occur. Discussion of the reaction mechanism must await fuller investigation but it may be noted here that the change was confirmed on specially purified material and that by heating 7-methoxy-1-methyloxindole with aluminium chloride, followed by methylation of the phenolic product, there was obtained only the starting compound, thereby eliminating 7-hydroxy-1-methyloxindole as a possible intermediate in the formation of the 4-hydroxy-isomer. Finally, under the conditions effective in rearranging (II), neither 2 : 3-dihydro-3-ketobenz-1 : 4-oxazine nor its 2-methyl derivative yielded appreciable quantities of phenolic material. The last two compounds were prepared by heating chloroacetyl- and α-bromopropionyl-*o*-anisidide respectively with aluminium chloride.



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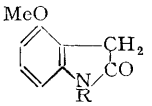

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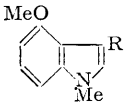

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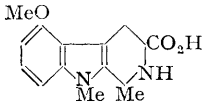

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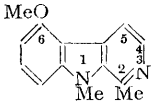

(IX)

The low values obtained in *N*-methyl estimations in the 7-methoxy-1-methylindole series remain unexplained. The infra-red absorption spectra of the oxindoles-A and -B resemble each other and also the corresponding spectrum of an *N*-alkyloxindole : in particular, they show that neither contains a free hydroxyl or imino-group and that a carbonyl group is present in both. It may be added that ready reduction to the corresponding indole, as here effected by lithium aluminium hydride, is more characteristic of an *N*-alkyl- than of an *N*-unsubstituted oxindole (cf. Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206). *N*-Methyl determinations, independently carried out in other laboratories on 7-methoxy-1-methylindole, gave positive but fractional values which were subject to rather wide variation and the conclusion may be drawn that a real analytical difficulty exists. On the other hand it is noteworthy that, as recorded in the following paper, 9-methoxy-1 : 2-dimethyl-β-carboline, which contains the 7-methoxy-1-methylindole structure, gave a satisfactory combined *O*- and *N*-methyl analysis.

Experimental

M. p.s are corrected unless otherwise stated.

N-Methyl-*o*-anisidine was prepared by the action of methyl sulphate (or iodide) on the sodio-derivative of acetyl-*o*-anisidide, followed by removal of the acetyl group by refluxing 50% sulphuric acid (6 hours). It had b. p. 228—230°/760 mm., 138—139·5°/47 mm. (Diepolder, *Ber.*, 1899, **32**, 3515, gives b. p. 141—143°/46—47 mm.; Mülhäuser, *Annalen*, 1881, **207**, 247, gives b. p. 218—220°; Best, *ibid.*, 1889, **255**, 176, gives b. p. 220°). The picrate formed yellow prisms, m. p. 141—142°, from ethanol (Found : C, 45·9; H, 4·0; N, 15·4. Calc. for $C_8H_{11}ON,C_6H_3O_7N_3$: C, 45·9; H, 3·8; N, 15·3%) (Wedekind, *Ber.*, 1906, **39**, 486, gives m. p.

139°). Addition of methyl sulphate (1 mol.) to *o*-anisidine (1 mol.) at 50—60°, with subsequent warming to 80° for 1 hour, yielded, probably, mainly *NN*-dimethyl-*o*-anisidine, b. p. 128—131°/47—48 mm., 210—211°/743 mm. (Mülhäuser, *loc. cit.*, gives b. p. 210—212°). The *picrate* formed yellow prisms, m. p. 144—145°, from ethanol (Found: C, 47·2; H, 4·4; N, 14·8. $C_9H_{13}ON,C_6H_3O_7N_3$ requires C, 47·4; H, 4·2; N, 14·7%).

2 : 3-*Dihydro*-3-*keto*-4-*methylbenz*-1 : 4-*oxazine* (II).—To *N*-methyl-*o*-anisidine (120 g.) in dry benzene (700 c.c.) and pyridine (70 c.c.), freshly distilled chloroacetyl chloride (67·5 c.c.) in dry benzene (300 c.c.) was added slowly with shaking and cooling. The mixture was set aside overnight at room temperature and then heated under reflux for 1 hour at 100°. After cooling, the mixture was treated with water to dissolve precipitated salts, the separated benzene solution was washed with dilute hydrochloric acid and then with water until neutral, dried, and evaporated completely on the water-bath under reduced pressure. The residue (168 g.) was treated with powdered anhydrous aluminium chloride (130 g.) (temperature rise to 130°). Further aluminium chloride (130 g.) was added and the mixture heated, with constant stirring, to 150—160° (bath-temperature) until evolution of gases had diminished (1½ hours). The thick mixture was poured on a tile, allowed to cool, powdered, added, with stirring, to crushed ice (1 kg.), and set aside overnight at 0°. The supernatant liquor was decanted, with filtration, and the sticky brown product was stirred with 7·5% sodium hydroxide solution (750 c.c.) wherein a small proportion dissolved and the remainder gradually became granular. The insoluble material (80 g.) was dissolved in ether, shaken with dilute sodium hydroxide solution, filtered, and washed with water until neutral. After drying and removal of the solvent, the residue was distilled, giving a pale yellowish solid, b. p. 127—129°/3 mm., with a faint, camphor-like odour. This crystallised from light petroleum (b. p. 60—80°), containing a little benzene, as colourless rods, m. p. 57—58° (Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 2188, give m. p. 58—59° for this benzoxazine derivative) (Found: C, 66·4; H, 5·4; N, 8·4; *N*-Me, 8·5. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5; N, 8·6; *N*-Me, 9·2%).

Rearrangement of 2 : 3-*Dihydro*-3-*keto*-4-*methylbenz*-1 : 4-*oxazine*.—Powdered anhydrous aluminium chloride (63·5 g.) was stirred into the molten benzoxazine derivative (31 g.), and the mixture heated (oil-bath) with constant stirring. At 215°, reaction set in and the temperature rose spontaneously to 225°, acid vapours being evolved. Heating at 220° was continued for 1 hour after which the thick brown paste was removed, allowed to cool, powdered, and decomposed by addition to crushed ice (200 g.). Concentrated hydrochloric acid (30 c.c.) was added, and the mixture set aside overnight at 0°. The solid product was then filtered off and washed with cold water, and the acidic material was dissolved in dilute aqueous sodium hydroxide. From the alkaline solution ether removed unchanged 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine (6·7 g.). The aqueous solution was filtered and acidified with concentrated hydrochloric acid. After 3 hours at 0° the precipitated pale brown solid was filtered off, washed with water, and dried (20 g.).

The crude product (19 g.), dissolved in 7·5% sodium hydroxide solution (68 c.c.), was shaken during the gradual addition of neutral methyl sulphate (13·5 c.c.). An oil separated. The reaction was completed on the water-bath (30 minutes), with small additions of sodium hydroxide solution to maintain alkalinity. Next morning, the mixture was neutralised and extracted with ethyl acetate (500 c.c.). The extract was washed with cold water, the solvent removed under reduced pressure on the water-bath, and the residue distilled. The pale yellowish, solid distillate, b. p. 118—123°/0·25 mm. (11·5 g.), was extracted with several portions of cold ether. The undissolved residue formed colourless, stout prisms (4·0 g.) which, recrystallised from hot water, yielded glistening needles or leaflets, m. p. 137—138°, subsequently shown to be 4-*methoxy*-1-*methyloxindole* (Found: C, 67·9; H, 6·0; N, 7·85; OMe, 16·8; *N*-Me, 7·9. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9; OMe, 17·5; *N*-Me, 8·5%). The combined ethereal washings were concentrated by evaporation at room temperature. A further crop, of m. p. 137° (0·3 g.), was obtained, but the remainder of the solute (*ca.* 7·0 g.) consisted of a second product which crystallised from the mother-liquor in well-defined clusters of flat, yellowish needles. These crystals were recrystallised from ether, purified in ether on alumina, and again recrystallised from ether, yielding 7-*methoxy*-1-*methyloxindole* (VI; R = Me) (see below) as long, pointed, colourless leaflets, m. p. 101—102° (Found: C, 67·7; H, 6·2; N, 7·8; OMe, 16·7, 16·9, 17·3; *N*-Me, 7·0, 6·6. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9; OMe, 17·5; *N*-Me, 8·5%).

The experiment was repeated with similar results on specially purified 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine, but neither the 2-methyl nor the methyl-free parent compound yielded appreciable quantities of hydroxyindoles on treatment with excess of aluminium chloride at 220—250° for periods up to 1 hour.

2 : 3-*Dihydro*-3-*keto*-2-*methylbenz*-1 : 4-*oxazine*.—α-Bromopropionyl-*o*-anisidide was heated with aluminium chloride to 160° for 15 minutes and the cooled mixture was decomposed with crushed ice. An almost colourless, lachrymatory solid—probably the α-bromopropionyl-*o*-hydroxyanilide—separated and readily dissolved in dilute aqueous sodium hydroxide. The alkaline solution rapidly deposited crystalline 2 : 3-dihydro-3-keto-2-methylbenz-1 : 4-oxazine which formed colourless needles, m. p. 144·5—145·5°, from aqueous ethanol (Bischoff, *Ber.*, 1900, **33**, 1593, gives m. p. 144—145°) (Found : C, 66·4; H, 5·25; N, 8·6. Calc. for $C_9H_9O_2N$: C, 66·3; H, 5·5; N, 8·6%).

2 : 3-*Dihydro*-3-*ketobenz*-1 : 4-*oxazine*.—Chloroacetyl-*o*-anisidide, heated with four times its weight of aluminium chloride to 175—190° for 1 hour, yielded 2 : 3-dihydro-3-keto-1 : 4-oxazine after decomposition of the cooled reaction mixture with ice, filtration, and treatment with dilute aqueous sodium hydroxide. The product formed colourless leaflets, m. p. 172—173°, from aqueous ethanol (2 : 1) (Jacobs and Heidelberger, *loc. cit.*, give m. p. 173°) (Found : C, 64·3; H, 4·4; N, 9·1. Calc. for $C_8H_7O_2N$: C, 64·4; H, 4·7; N, 9·4%).

7-*Methoxy*-1-*methylisatin*.—Oxalyl chloride (26 g.) in dry benzene (75 c.c.) was mixed with *N*-methyl-*o*-anisidine (13 g.) in dry benzene (25 c.c.), and the clear yellow solution was refluxed for 3 hours. The solvent was then removed under reduced pressure on the water-bath and the oily residue was treated in dry ethylene dichloride (100 c.c.) with powdered aluminium chloride (13 g.), in small portions, with cooling. The dark red mixture was set aside for 25 hours with occasional shaking at room temperature, then poured on ice (250 g.). The organic layer was washed successively with 0·1N-hydrochloric acid (3 × 20 c.c.), water, and dilute aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated on the water-bath under reduced pressure. The semi-solid residue (15 g.) was boiled with aqueous ethanol (charcoal); after filtration and cooling, dark red crystals separated (2 g.) and were filtered off. Dilution of the mother-liquor with water caused the precipitation of a red oil which was not investigated. Recrystallisation of the solid from ethanol yielded blood-red needles of 7-methoxy-1-methylisatin, m. p. 186·5—187° (Kaufmann and Rothlin, *Ber.*, 1916, **49**, 578, give m. p. 187°) (Found : C, 62·7; H, 4·8; N, 7·5. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7; N, 7·3%). An attempt to reduce the isatin by lithium aluminium hydride in ether afforded only a small quantity of a steam-volatile indole and an unidentified, non-volatile material which on passage in ether through alumina changed from green to deep blue and gave tiny purple prisms of m. p. 208—210°.

7-*Methoxy*-1-*methylisatin* β-*Oxime*.—(*a*) 7-Methoxy-1-methylisatin (65 mg.) was heated with hydroxylamine hydrochloride (30 mg.) and crystallised sodium acetate (50 mg.) in water (2 c.c.) on the steam-bath for 1 hour, after which the isatin crystals had been replaced by yellow crystals of the *oxime*. The mixture was cooled and the very sparingly soluble solid filtered off. It separated from water–ethanol (2 : 1) in fine, golden-yellow needles, m. p. 234—235° (decomp.), softening at 225° when the temperature was raised at a rate not greater than 3°/minute. The m. p. varied slightly with the rate of heating (Found : C, 55·2; H, 5·15; N, 12·9; OMe, 14·1; *N*-Me, 3·2. $C_{10}H_{10}O_3N,\frac{1}{2}H_2O$ requires C, 55·8; H, 5·1; N, 13·0; OMe, 14·4; *N*-Me, 6·9%).

(*b*) 7-Methoxy-1-methyloxindole (25 mg., prepared *via* 2 : 3-dihydro-3-keto-4-methylbenz-1 : 4-oxazine) in glacial acetic acid (1 c.c.) was treated with a few drops of concentrated aqueous sodium nitrite. The solution became yellow and was set aside for 1 hour. Dilution with water (6 c.c.) afforded a fine crystalline solid, which was filtered off, washed with water, and crystallised from water–ethanol (2 : 1) as golden-yellow needles, m. p. 230—231° (decomp.), softening at 220°, and m. p. 232—233° (decomp.) on admixture with 7-methoxy-1-methylisatin oxime (above). When 4-methoxy-1-methyloxindole was treated with nitrous acid in glacial acetic acid as described for 7-methoxy-1-methyloxindole, little or no reaction occurred, a good yield of starting material being recovered.

7-*Methoxy*-1-*methyldioxindole*.—Sodium hydrosulphite (dithionite) (0·51 g.) was added in small portions to a gently boiling suspension of 7-methoxy-1-methylisatin (0·39 g.) in water (10 c.c.) (cf. Marschalk, *Ber.*, 1912, **45**, 583). The red crystals of the isatin were rapidly replaced by a colourless solid which dissolved when more water (5 c.c.) was added and boiling continued. After concentration to 5 c.c., the solution was cooled and set aside in a stoppered vessel for 2 hours at 0°. The product, a pale pink solid (0·275 g.), was filtered off and washed with ice-water, and after crystallisation from hot water containing a trace of sodium hydrosulphite formed colourless prisms of 7-*methoxy*-1-*methyldioxindole* which became brown at 150° and melted with decomposition at 170—175° after softening at 160° (Found : C, 61·9; H, 5·3; N, 7·4. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·25%). The compound, in hot aqueous solution, was readily oxidised by air to the isatin.

7-*Methoxy*-1-*methyloxindole* (I).—7-Methoxy-1-methyldioxindole, suspended in dilute aqueous

ethanol, or in dilute acetic acid at 0°, was not readily reduced by 5% sodium amalgam at 0° during passage of carbon dioxide (cf. Marschalk, *loc. cit.*). The reduction was successful under the following conditions (cf. Baeyer and Knop, *Annalen*, 1865, **140**, 29). A solution of 7-methoxy-1-methyldioxindole (50 mg.) in boiling water (5 c.c.) was made weakly acid with dilute sulphuric acid and treated gradually with 5% sodium amalgam, with occasional additions of acid to maintain acidity, until the reddish colour was completely discharged (40 minutes). The hot mixture was then filtered and the filtrate on cooling deposited slender, colourless needles of 7-methoxy-1-methyloxindole, identical with the product, m. p. 101—102°, obtained by rearrangement of the benzoxazine derivative (Found: OMe, 16·5; *N*-Me, 5·1%).

2-*Methoxy*-6-*nitrobenzyl Cyanide* (V; R = CN).—Crude 2-methoxy-6-nitrobenzyl chloride (4·5 g.) (Buehler, Deebel, and Evans, *J. Org. Chem.*, 1941, **6**, 217) in ethanol (4·5 c.c.) was heated under reflux with a solution of potassium cyanide (1·6 g.) in water (1·5 c.c.). After 6 hours the mixture was cooled and extracted with ether in which some dark brown resinous material did not dissolve. The ethereal solution was washed with water, dried, and concentrated, yielding a reddish oil which partly crystallised on being rubbed. 2-*Methoxy*-6-*nitrobenzyl cyanide* crystallised from ethanol–water (1 : 1) (charcoal) as yellow, light-sensitive leaflets of m. p. 78—79° (Found: C, 56·4; H, 4·2; N, 14·3. $C_9H_8O_3N_2$ requires C, 56·25; H, 4·2; N, 14·6%).

2-*Methoxy*-6-*nitrophenylacetic Acid* (V; R = CO_2H).—The above nitrile (4·2 g.; crude) was refluxed with concentrated hydrochloric acid (125 c.c.) for 6 hours, after which a little tar remained undissolved. When the mixture was cooled crystals separated readily and after filtration were stirred and warmed with dilute aqueous sodium carbonate on the steam-bath for 10 minutes. Charcoal was added and stirring continued whilst the mixture cooled. After filtration the solution was acidified and, after an hour at 0°, the straw-coloured solid was filtered off (1·8 g.). 2-*Methoxy*-6-*nitrophenylacetic acid* crystallised from hot water containing a little ethanol as very pale yellow prisms, m. p. 171—172° (Found: C, 51·45; H, 4·1; N, 7·2. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·7%).

4-*Methoxyoxindole* (VI; R = H).—Catalytic hydrogenation (palladium black) of 7-methoxy-6-nitrophenylacetic acid (0·5 g.) in glacial acetic acid (10 c.c.) at room temperature gave 4-methoxyoxindole (0·38 g.), recovered by distillation of the solvent on the water-bath under reduced pressure. The product, crystallised from ethanol–water (1 : 5), formed pale yellow needles, m. p. 196—197° (Found: C, 66·5; H, 5·8; N, 8·7. $C_9H_9O_2N$ requires C, 66·25; H, 5·5; N, 8·6%).

4-*Methoxy*-1-*methyloxindole* (VI; R = Me).—4-Methoxyoxindole (0·326 g.) was dissolved in absolute methanol (4 c.c.) containing sodium methoxide (from 0·046 g. of sodium), and the solution refluxed with methyl iodide (0·284 g.) at 40—45° for 6 hours. The solvent was then distilled from the dark brown solution and the residue, a brown oil, was treated while still warm with 10% aqueous sodium hydroxide (2 c.c.). Crystals immediately separated and, after cooling, were filtered off. They (0·067 g.) were washed with cold water and after recrystallisation from hot water containing a little ethanol formed leaflets or small pale yellow prisms, m. p. 136·5—137° unchanged on admixture with the compound of m. p. 137—138° obtained *via* the benzoxazine derivative.

7-*Methoxy*-1-*methylindole*.—(*a*) Reduction of 7-methoxy-1-methyloxindole with lithium aluminium hydride as described for the 4-methoxy-isomer yielded 7-*methoxy*-1-*methylindole* which, after purification in light petroleum (b. p. 60—80°) on alumina, formed lustrous colourless leaflets, m. p. 54·5—55·5°, from that solvent (Found: C, 74·6; H, 6·8; OMe, 18·45; *N*-Me, nil. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; OMe, 19·25; *N*-Me, 9·3%). The *picrate* formed chocolate-brown needles, m. p. 151°, from ethanol (Found: C, 49·5; H, 3·5. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6%). From the acid washings of the reduction product a small quantity of oily 7-methoxy-1-methylindoline was recovered and was characterised as the *picrate*, yellow prisms, softening at 130°, m. p. 145—148° (uncorrected) (from ethanol) (Found: C, 49·2; H, 4·1; N, 13·9, 14·2; OMe, 7·8; *N*-Me, nil. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires C, 49·0; H, 4·1; N, 14·3; OMe, 7·9; *N*-Me, 3·8%).

(*b*) To a solution of potassium (60 mg.) in liquid ammonia (5 c.c.) containing a small crystal of ferric nitrate was added, dropwise and with stirring, 7-methoxyindole (212 mg.) in dry ether (1 c.c.), and then methyl iodide (0·092 c.c.) also in dry ether (1 c.c.). After 30 minutes the solvents were evaporated and the recovered solid (202 mg.) was purified in light petroleum (b. p. 60—80°) on alumina. The product was obtained as colourless leaflets, m. p. 54—54·5°, from light petroleum (b. p. 60—80°), the m. p. being slightly raised by admixture with the indole prepared as in (*a*) (Found: OMe, 18·4; *N*-Me, nil). The picrate had m. p. and mixed m. p. with the sample from (*a*) 151°.

4-*Methoxy*-1-*methylindole* (VII; R = H).—Finely powdered 4-methoxy-1-methyloxindole

(5 g.), suspended in dry ether (100 c.c.), was treated, with stirring and exclusion of moisture, with powdered lithium aluminium hydride (0·8 g.) in small portions during 20 minutes. The mixture was stirred for a further 20 minutes; then water (25 c.c.) was slowly added, followed by N-hydrochloric acid (50 c.c.). After being thoroughly shaken, the solvent layers were separated and the ethereal solution was washed with N-hydrochloric acid (2 × 25 c.c.). The green ethereal solution was dried (K_2CO_3) and evaporated, and the residue distilled in steam. When the distillation was concluded, unreduced 4-methoxy-1-methyloxindole, which was not appreciably volatile in steam, was recovered on cooling as a crystalline solid (0·5 g.). The distillate was extracted with ether from which *4-methoxy-1-methylindole* (3 g.) was recovered. It crystallised from light petroleum (b. p. 60—80°) containing a little ethanol as colourless, flattened prisms, m. p. 89° (Found: C, 74·4; H, 6·8; N, 8·5; OMe, 18·7; *N*-Me, 8·6. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7; OMe, 19·25; *N*-Me, 9·3%). The *picrate* crystallised as dark red needles (from ethanol), m. p. 153° (Found: 49·3; H, 3·9; N, 14·2. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%). The acid washings from the reduction were made alkaline and extracted with ether. After washing and removal of the ether, 4-methoxy-1-methylindoline (0·72 g.) was distilled as a very pale yellow oil, b. p. (bath-temperature) 95—97° (uncorr.)/10·5 mm., which yielded a *picrate* as yellow crystals (from ethanol), m. p. 163—164° (decomp.), softening at 157° (bath pre-heated to 150°) (Found: C, 48·8; H, 4·4; N, 14·2; OMe, 7·9; *N*-Me, 3·1. $C_{10}H_{13}ON,C_6H_3O_7N$ requires C, 49·0; H, 4·1; N, 14·3; OMe, 7·9; *N*-Me, 3·8%).

7-Methoxy-2-methylindole.—*o*-Methoxyphenylhydrazine (20 g.) was dissolved in glacial acetic acid (20 c.c.) and the mixture diluted with water (30 c.c.). When acetone (11 c.c.) was added to the slightly turbid solution heat was evolved and an oil separated rapidly. After being kept overnight at 0° the mixture was extracted with ether from which the hydrazone was recovered by evaporation on the warm water-bath under reduced pressure. The hydrazone (19 g.) was treated with powdered, anhydrous zinc chloride (19 g.), with good stirring, and the mixture then slowly heated to 110—120°/15 mm. under a reflux air-condenser. After 15 minutes a brief vigorous reaction commenced. Heating at 115° was continued for a further 30 minutes. The cooled mixture was dissolved in boiling, very dilute hydrochloric acid, and distilled in steam. A colourless oil, which gave strongly positive Ehrlich and vanillin reactions, distilled readily and quickly solidified. Periodically a hard cake which formed in the distillation flask was dissolved in a small quantity of ethanol and diluted with an equal volume of hot water, before resumption of the steam-distillation. The distillate was extracted with ether and the recovered *7-methoxy-2-methylindole* (1·53 g.) was purified in light petroleum (b. p. 60—80°) on alumina; from this solvent it crystallised as flat, colourless needles, m. p. 83—83·5°. It showed a tendency to become yellowish in air or in ether (Found: C, 74·7; H, 6·7; N, 8·5. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). The *picrate* formed shining, brownish-red needles, m. p. 157—158°, from ethanol (Found: C, 49·5; H, 3·6; N, 14·0. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%).

7-Methoxy-3-methylindole.—*o*-Methoxyphenylhydrazine (20 g.) was mixed with freshly distilled propaldehyde (15 c.c.) with shaking and cooling. Heat was evolved and the oily hydrazone separated rapidly. After being washed with cold water it was dissolved in a mixture of sulphuric acid (4 c.c.) and ethanol (50 c.c.). The solution immediately became hot and ammonium sulphate separated. The reaction was completed on the water-bath (30 minutes) after which the mixture was cooled, diluted with water (150 c.c.), and extracted with ether. The blue-fluorescent ethereal solution was washed and separated from some insoluble, sticky residue, and after drying (Na_2SO_4) the solvent was removed and the residue of dark oil was distilled in steam. A small quantity (0·5 c.c.) of anisole (b. p. 153°) was isolated from the first fraction of the distillate but the skatole was only sparingly volatile in steam. Accordingly, the undistilled residue was redissolved in ether, dried, and distilled after removal of the solvent. 7-Methoxy-3-methylindole distilled as a pale yellow oil, b. p. 150° (uncorr.)/15 mm. (5—6 g.) (Blaikie and Perkin, *J.*, 1924, **125**, 330, give b. p. 170°/20 mm.), and gave a picrate which crystallised as dark red needles, m. p. 158·5—159°, from ethanol (Blaikie and Perkin, *loc. cit.*, give m. p. 156°) (Found: C, 49·4; H, 3·9; N, 14·2. Calc. for $C_{10}H_{11}ON,C_6H_3O_7N_3$: C, 49·2; H, 3·6; N, 14·4%). The undistilled residue (*ca.* 4 c.c.), a very thick reddish transparent gum, was not investigated.

3-Dimethylaminomethyl-4-methoxy-1-methylindole (*4-Methoxy-1-methylgramine*) (VII; R = $CH_2{\cdot}NMe_2$).—Acetic acid (1 c.c.) was added to aqueous dimethylamine (33%; 1·05 c.c.), cooled in a freezing mixture so that the temperature did not exceed 5°. Aqueous formaldehyde (37%; 0·47 c.c.) was added and the mixture was quickly poured, with shaking, into finely powdered 7-methoxy-1-methylindole (1·07 g.). The mixture became warm and was shaken,

with occasional gentle warming to 40°, for 3 hours and then left at room temperature for 24 hours. The pale-brown mixture was poured into 10% aqueous sodium hydroxide (20 c.c.) and after 3 hours at 0° a yellow-brown gum was collected and treated with N-hydrochloric acid (20 c.c.) and ether (10 c.c.). After being freed from some insoluble material the solvent layers were separated and the aqueous layer was washed with ether and made alkaline at 0°. 4-Methoxy-1-methylgramine, recovered in ether, was an oil (1·1 g.) which solidified on being rubbed at 0° but re-melted at room temperature. The *picrate* formed yellow prisms, m. p. 160—161°, from methanol (Found, after drying *in vacuo* over phosphoric oxide: C, 50·8; H, 4·4; N, 15·7. $C_{13}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 51·0; H, 4·7; N, 15·7%). The *methiodide*, formed from its components in ethanol, crystallised as colourless leaflets from benzene–ethanol but was highly sensitive to atmospheric moisture [Found: (1st specimen) C, 39·9, 40·2; H, 5·3, 6·2: (2nd specimen) C, 41·6; H, 5·9. $C_{14}H_{21}ON_2I,3H_2O$ requires C, 40·6; H, 6·5%].

Ethyl α-Acetamido-α-carbethoxy-β-(4-methoxy-1-methyl-3-indolyl)propionate [VII; R = $CH_2{\cdot}C(NHAc)(CO_2Et)_2$].—4-Methoxy-1-methylgramine methiodide (1·72 g.) was added to a solution of ethyl acetamidomalonate (1·04 g.) in ethanol (11 c.c.) containing sodium ethoxide (from 0·11 g. of sodium), and the mixture was heated under reflux for 24 hours by which time evolution of trimethylamine had practically ceased. The filtered solution was poured into cold water (100 c.c.). The gum obtained rapidly solidified (1·35 g.). It was purified for analysis by passage in benzene through a column of alumina, the recovered *ester* being obtained as colourless prisms, m. p. 144—145°, from benzene–light petroleum (b. p. 60—80°) (1 : 2) (Found: C, 61·7; H, 6·5; N, 7·4. $C_{20}H_{26}O_6N_2$ requires C, 61·5; H, 6·7; N, 7·2%).

α-Acetamido-β-(4-methoxy-1-methyl-3-indolyl)propionic Acid [VII; R = $CH_2{\cdot}CH(NHAc){\cdot}CO_2H$].—The foregoing ester (1·25 g.) was heated under reflux with a solution of sodium carbonate (1·25 g.) in water (12·5 c.c.) for 22 hours after which time only a small quantity of a dark oil remained undissolved. This was removed in ether. Acidification of the carbonate solution afforded the *acid* (0·73 g.) as long pointed leaflets (from ethanol–water, 1 : 2) which when slowly heated softened slightly at 120° and melted at 190—195° but when rapidly heated melted with effervescence at 120—125° (Found: C, 58·35; H, 6·3; N, 9·2. $C_{15}H_{18}O_4N_2,H_2O$ requires C, 58·4; H, 6·5; N, 9·1%).

α-Amino-β-(4-methoxy-1-methyl-3-indolyl)propionic Acid (*4-Methoxy-1-methyltryptophan*).—The foregoing acetyl derivative (0·63 g.) was heated with water (10 c.c.) at 180—190° for 6 hours. The *tryptophan*, recovered from the concentrated solution (charcoal), formed nearly colourless, flat needles, m. p. *ca.* 250° (decomp.), from ethanol–water (1 : 1) (Found: C, 62·7; H, 6·7; N, 11·0. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·45; N, 11·3%).

2 : 3 : 4 : 5-*Tetrahydro-6-methoxy-1 : 2-dimethyl-β-carboline-4-carboxylic Acid* (VIII).—A solution of 4-methoxy-1-methyltryptophan (0·35 g.) in hot water (50 c.c.) was rapidly cooled and treated with freshly distilled acetaldehyde (1 c.c.). After 24 hours at room temperature, during which a slight deposition occurred, the mixture was warmed at 50—70° in a stoppered flask for 12 hours and then left at room temperature overnight. The mixture was evaporated to dryness on the water-bath affording a solid residue (0·38 g.) which gave only a weakly positive ninhydrin reaction, and yielded the *tetrahydrocarbolinecarboxylic acid* as tiny, cream-coloured leaflets, softening at 250°, m. p. 255—257° (decomp.), from hot water (charcoal) (Found: C, 61·6; H, 6·4; N, 9·8. $C_{15}H_{18}O_3N_2,H_2O$ requires C, 61·6; H, 6·8; N, 9·6%).

6-Methoxy-1 : 2-dimethyl-β-carboline (IX) was prepared by treating the foregoing acid (0·28 g.) in hot aqueous solution (170 c.c.) with 10% aqueous potassium dichromate (14 c.c.) and acetic acid (3 c.c.). The whole was boiled for 3 minutes, cooled, and treated with an excess of aqueous sodium sulphite and then with a saturated solution of sodium carbonate. The carboline (0·14 g.), recovered in ether and purified in benzene on alumina, formed very pale yellowish prisms, m. p. 139—140°, from benzene–light petroleum (b. p. 60—80°) (3 : 1) (Found: C, 74·4; H, 5·9; N, 12·15. Calc. for $C_{14}H_{14}O_4N_2$: C, 74·3; H, 6·2; N, 12·4%). The picrate formed masses of tiny yellow needles, m. p. *ca.* 267° (decomp.), from methanol (Found, after drying at 100°/15 mm. for 1 hour over phosphoric oxide: C, 52·9; H, 3·9. Calc. for $C_{14}H_{14}ON_2,C_6H_3O_7N_3$: C, 52·75; H, 3·7%). The *p*-nitrobenzylidene derivative was formed by heating the base (20 mg.) with *p*-nitrobenzaldehyde (100 mg.) at 250—255° for 5 minutes, cooling, extracting the product in benzene, and shaking the benzene solution with dilute hydrochloric acid whereupon the insoluble hydrochloride was formed and was decomposed by treatment with cold dilute aqueous sodium hydroxide. The base formed golden-yellow needles, m. p. 264°, from benzene (Found: C, 70·2; H, 4·9. Calc. for $C_{21}H_{17}O_3N_3$: C, 70·2; H, 4·7%).

The sample (5—8 mg.) of the degradation product of mitragynine, as supplied by Dr. Ing, had m. p. 129—134° (softening at 120°). It was passed in benzene through a column of alumina

and eluted with benzene. The recovered base yielded almost colourless crystals, m. p. 138·5—139·5° from (1 : 4) benzene–light petroleum (b. p. 60—80°). The following table summarises the m. p. and mixed m. p. behaviour of the degradation products (A) from mitragynine and the synthetic samples (B) of the 6-methoxy-1 : 2-dimethyl-β-carboline series :

	A	B	A + B
Base	m. p. 138·5—139·5°	m. p. 139—140°	m. p. 138·5—139·5°
Picrate	decomp. *ca.* 260°	decomp. *ca.* 267°	decomp. *ca.* 265°
p-Nitrobenzylidene derivative ...	m. p. 261°	m. p. 264°	m. p. 263°

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