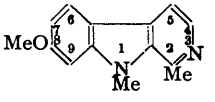
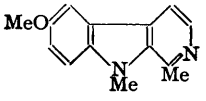
269. *The Chemistry of the* Mitragyna *Genus. Part II. Synthesis of 7-Methoxy-2-methyl- and 7-Methoxy-1 : 2-dimethyl-β-carboline.*

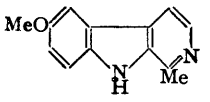
By J. W. Cook, J. D. Loudon, and P. McCloskey.

5-Methoxyindole and its 1-methyl derivative have been converted *via* the corresponding derivatives of gramine and tryptophan into 7-methoxy-2-methyl- (III) and 7-methoxy-1 : 2-dimethyl-β-carboline (II). Of these two end-products, the latter (II) was also prepared from the former (III) and was shown, by direct comparison, to be distinct from the base, $C_{14}H_{14}ON_2$, obtained by Ing and Raison (*J.*, 1939, 986) from degradation of mitragynine.

By distilling mitragynine from zinc dust Ing and Raison (*J.*, 1939, 986) obtained a base, $C_{14}H_{14}ON_2$, which contained one methoxyl group, one methylimino-group and one reactive methylene group (*p*-nitrobenzylidene derivative). Despite highly significant similarities it was shown conclusively that this base was not identical with *ind*-*N*-methylharmine (I) nor—as was indeed less likely—with the isomeric *pyr*-*N*-methylharmine. The possibility remains that the base is a β-carboline derivative substituted in a manner different from (I). Partly with the object of preparing the compound (II) for specific comparison and partly with the more general purpose of making available close analogues of harmine, we have now synthesised a number of harman derivatives methoxylated at position 7.

(I.) 

 (II.)



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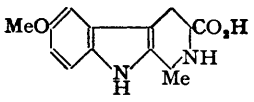

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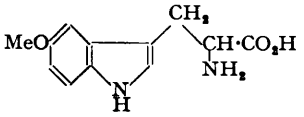

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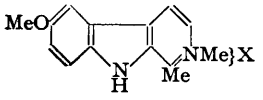
Späth and Lederer (*Ber.*, 1930, **63**, 2102) have already described a synthesis of 7-methoxy-2-methyl-β-carboline (III), which proceeds from *p*-methoxyphenylhydrazine and the diethyl acetal of γ-amino-*n*-butaldehyde to 5-methoxytryptamine and its *N*-acetyl derivative, the latter being cyclised and the resulting dihydrocarboline dehydrogenated. We have preferred the alternative " gramine method " of synthesis with 5-methoxytryptophan (V) as intermediate. 5-Methoxygramine (cf. Bell and Lindwall, *J. Org. Chem.*, 1948, **18**, 547) was condensed with ethyl sodio-acetamidomalonate in presence of methyl sulphate according to the procedure of

Albertson, Archer, and Suter (*J. Amer. Chem. Soc.*, 1945, **67**, 36) and the product was hydrolysed first (with decarboxylation) to α-acetamido-β-(5-methoxy-3-indolyl)propionic acid and then to the trytophan (V). Acetaldehyde condensed smoothly with (V) in aqueous solution at ordinary temperature, the tetrahydrocarboline-4-carboxylic acid (IV) crystallising as the reaction progressed. This acid appeared to homogeneous but the mother-liquor contained traces of a by-product which may represent the second of the two possible (±)-forms. Dehydrogenation and simultaneous decarboxylation of (IV), yielding (III), were effected by heating a solution of the acid and potassium dichromate in aqueous acetic acid.

Following the principle by which Iyer and Robinson (*J.*, 1934, 1635) prepared *ind-N*-methylharmine from harmine, the base (III) was converted *via* the methosulphate (VI; X = $MeSO_4$) into the methohydroxide (VI; X = OH) whence, by heating to form the anhydronium base (VII) and subsequent addition of methyl iodide, there was obtained 7-methoxy-1 : 2 : 3-trimethyl-β-carbolinium iodide (VIII). When this salt was heated at 300—320° methyl iodide was eliminated and 7-methoxy-1 : 2-dimethyl-β-carboline (II) was produced.

Confirmation of the structure assigned to this product was next sought in an alternative but similar synthesis in which methylation of the indole nitrogen was effected at an early stage. The requisite 5-methoxy-1-methylindole (IX) was prepared by two methods, namely (*a*) by thermal decomposition of 5-methoxy-1-methylindole-2-carboxylic acid and (*b*) together with a small quantity of the corresponding indoline (cf. Julian and Printy, *J. Amer. Chem. Soc.*, 1949, **71**, 3206) by reducing 5-methoxy-1-methyloxindole with lithium aluminium hydride. Both methods afforded the indole (IX) as a well-defined crystalline substance and its previous description as an oil (Bell and Lindwall, *loc. cit.*) is thereby amended. The subsequent stages



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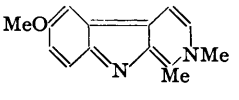

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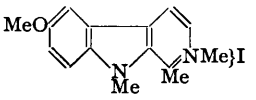

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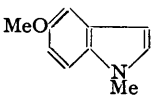

(IX.)

of the synthesis—through the 5-methoxy-1-methyl derivatives of gramine and tryptophan to the *ind-N*-methyl derivatives of (IV) and (III)—followed with minor variations on the lines described for (III) and afforded the product (II) identical in all respects with that obtained by the first method of synthesis.

Through the kindness of Dr. H. R. Ing, whom we warmly thank for placing his specimens at our disposal, direct comparison between the mitragynine degradation product and the base (II) was made possible. This comparison, which was extended to include the picrates and *p*-nitrobenzylidene derivatives, conclusively showed that the respective compounds of the two series are not identical. We hope to compare the degradation product with other harman derivatives of which the syntheses are now in hand.

Experimental.

M. p.s are corrected unless otherwise stated.

5-Methoxyindole was prepared from 5-methoxy-2-nitrotoluene (Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074) *via* 5-methoxyindole-2-carboxylic acid as described by Blaikie and Perkin (*J.*, 1924, **125**, 296).

3-*Dimethylaminomethyl-5-methoxyindole* (*5-Methoxygramine*).—Acetic acid (11·5 c.c.) was added to aqueous dimethylamine (33%; 11·5 c.c.), cooled in a freezing mixture, so that the temperature did not exceed 5°. Formalin (37%; 5·75 c.c.) was then added and the whole was poured, with shaking, into 5-methoxyindole (11·3 g.). Heat was evolved and the resulting light-brown solution was set aside at room temperature for 20 hours, during which some deposition occurred. The mixture was poured into aqueous sodium hydroxide (10%; 200 c.c.) and after 2 hours at 0° the solid was collected, washed with water, powdered, and treated with N-hydrochloric acid (200 c.c.) and ether (50 c.c.). After being freed from some insoluble material the solvent layers were separated, and the aqueous layer was washed with ether (30 c.c.) and was just made alkaline whereby a crude initial precipitate was formed and could be removed by adherence to a stirring rod. Subsequent addition of dilute alkali to the mother-liquor afforded 5-methoxygramine (12·2 g.) as almost white needles of m. p. 124—125° (from benzene) (Bell and Lindwall, *loc. cit.*, give m. p. 127·5—128°) (Found: C, 70·55; H, 7·4; N, 13·8. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·8; N, 13·7%). The *picrate* formed amber-coloured prisms, m. p. 164—165°, from benzene–ethanol (Found: C, 49·8; H, 4·7; N, 15·9. $C_{12}H_{16}ON_2,C_6H_3O_7N_3$ requires C, 49·9; H, 4·4; N, 16·2%); Wieland and Hsing (*Annalen*, 1936, **526**, 188) give m. p. 168°, without analytical results.

Ethyl α-Acetamido-α-carbethoxy-β-(5-methoxy-3-indolyl)propionate.—Ethyl acetamidomalonate (11·0 g.) was added with mechanical stirring and rigid exclusion of moisture to a cold solution of sodium ethoxide (from 1·15 g. of sodium) in dry ethanol (100 c.c.). 5-Methoxygramine (10·2 g.) was then added, followed, when dissolution was complete, by gradual addition of methyl sulphate (8·3 c.c.) during 25 minutes. The rise in temperature, incurred in the last step, was controlled at 40° (thermometer bulb in reaction

mixture) by occasional external cooling. The mixture was then stirred for 1 hour and left overnight at room temperature. The solid resulting from addition to water (300 c.c.) and cooling in ice (1 hour), was collected, washed with water, and dissolved in benzene (150 c.c.), the solution being washed with N-hydrochloric acid (3 × 50 c.c.), again with water, dried, and concentrated under reduced pressure. The residual glass-like mass was dissolved in ethanol and readily afforded the solid *ester* (17·1 g.) when the solution was poured into cold water. The ester in this form was sufficiently pure for subsequent experiments but was obtained as colourless needles or rods, softening at 126°, m. p. 128—129°, from ethanol–water (1 : 1) (Found : C, 60·7; H, 6·2; N, 7·1. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·45%).

α-Acetamido-β-(5-methoxy-3-indolyl)propionic Acid.—The above ester (18·8 g.) was heated under reflux for 1½ hours with a solution of sodium hydroxide (8 g.) in water (80 c.c.). The filtered solution was cooled in ice and acidified, affording a reddish oil which solidified overnight at 0°. The powdered, washed, and air-dried solid (14·6 g.)—probably the malonic acid derivative—had m. p. 156—160° (efferv.) and slowly acquired a purplish colour on exposure to air and light. This acid (14 g.), when heated under reflux with water (100 c.c.), dissolved with gradual evolution of carbon dioxide which was apparently complete after 6 hours. On cooling, *α-acetamido-β-(5-methoxy-3-indolyl)propionic acid* separated as an oil which solidified overnight to a mixture of a hydrated and an anhydrous form. The *hydrate*, colourless rods of m. p. 115—120° (efferv.) from water (Found : C, 57·0; H, 6·2; N, 9·3. $C_{14}H_{16}O_4N_2,H_2O$ requires C, 57·1; H, 6·1; N, 9·5%), resolidified on continued heating and re-melted at 182—183°, *i.e.*, at the m. p. of the anhydrous form which, as small warty nodules, sometimes accompanies the hydrate from aqueous solution and usually changes to the hydrate on recrystallisation. A sample of the hydrate after being heated at 120—125°/18 mm. for 1 hour until effervescence ceased gave the analytical figures : C, 61·1; H, 6·1 ($C_{14}H_{16}O_4N_2$ requires C, 60·9; H, 5·8%). A persistent colour in the crude hydrate was best removed by shaking the hot filtered aqueous solution until the oil which formed began to solidify, whereupon rapid filtration gave an almost colourless solution and a colourless second crop.

α-Amino-β-(5-methoxy-3-indolyl)propionic Acid (*5-Methoxytryptophan*) (V).—A solution of the foregoing acid (2·5 g.) in 10% aqueous sodium hydroxide (25 c.c.) was heated at 100° for 6 hours before being cooled and treated dropwise with acetic acid. Gelatinous silica separated during this last stage. When 2·8 c.c. of acetic acid had been added and the solution was still slightly alkaline, the product suddenly separated as a fine crystalline precipitate which was collected, washed with cold water, dissolved in hot ethanol–water (1 : 1; 50 c.c.), and filtered from silica. Concentration of the filtrate, preferably under reduced pressure, gave 5-methoxytryptophan (1·13 g.), and a further quantity (0·4 g.) was obtained from the combined reaction—and mother—liquors. These were made faintly acid with acetic acid, then slightly alkaline with aqueous ammonia, and concentrated almost to dryness. The residue was dissolved in hot ethanol–water (1 : 1; 10 c.c.), the cooled solution was filtered from sodium acetate, and the filtrate was seeded. *5-Methoxytryptophan* formed slender, colourless rods, m. p. 254—256° (decomp.) with previous softening at 245°, from ethanol–water (1 : 1). For analysis the compound was dried at 100°/15 mm. for 3½ hours over phosphoric oxide (Found : C, 61·3; H, 6·2; N, 11·8. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

2 : 3 : 4 : 5-*Tetrahydro-7-methoxy-2-methyl-β-carboline-4-carboxylic Acid* (IV).—5-Methoxytryptophan (0·5 g.) was dissolved in warm water (50 c.c.), and the solution was rapidly cooled and treated with freshly distilled acetaldehyde (1 c.c.). After 3 hours at room temperature the mixture was gently warmed on the water-bath for an hour, cooled and left overnight at 0°. The crystalline product, augmented by a small second crop (total, 0·48 g.) from the concentrated mother-liquor, afforded the *acid* as masses of tiny needles, m. p. *ca.* 240—245° with sintering at 235°, from hot water (charcoal) (Found : C, 56·7; H, 6·8; N, 9·3. $C_{14}H_{16}O_3N_2,2H_2O$ requires C, 56·8; H, 6·8; N, 9·5%). When the combined mother-liquors from several preparations were evaporated and the residue was crystallised from water, a first crop, consisting of the above product, was followed by a small second crop of material which had m. p. 253—255° (decomp.) (from water) and mixed m. p. 238° with 5-methoxytrytophan. This may have been a stereoisomer of (IV) but was too small in quantity for further investigation.

7-Methoxy-2-methyl-β-carboline (*7-methoxyharman*) (III) was prepared from the above acid by the procedure described for analogous cases (Jacobs and Craig, *J. Biol. Chem.*, 1936, **113**, 759; cf. Harvey and Robson, *J.*, 1938, 97). The acid (0·5 g.), dissolved in boiling water (120 c.c.), was oxidised with 10% aqueous potassium dichromate (25 c.c.) followed by acetic acid (5 c.c.). The whole was boiled for 3 minutes and the cooled mixture, in which a yellow solid had separated, was treated with an excess of aqueous sodium sulphite and then with a saturated solution of sodium carbonate. After 2 hours at 0° the solid was collected (and was slightly augmented by material recovered from an ethereal extract of the filtrate—total yield, 0·255 g.) and afforded 7-methoxyharman as pale straw-coloured prisms, m. p. 275—276°, from methanol (Späth and Lederer, *loc. cit.*, give m. p. 273°) (Found : C, 73·7; H, 5·8; N, 12·9. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7; N, 13·2%). 7-Methoxyharman gives a yellow solution in dilute hydrochloric acid; addition of ethanol produces a pale yellow-green fluorescence.

7-Methoxy-2 : 3-dimethyl-β-carbolinium Methosulphate and Hydroxide (VI; X = $MeSO_4$ and OH).—When a suspension of the base (III) (0·25 g.) in benzene (6 c.c.) and methyl sulphate (0·25 c.c.) was heated under reflux for 1 hour the mixture became pasty and light yellow in colour. After 12 hours at room temperature, removal of the solvent afforded the crude *methosulphate* which crystallised in slender yellow needles, m. p. 210—211° (from methanol), containing a molecule of solvent (Found, after drying at 100°/15 mm. for 3 hours : C, 52·0; H, 5·8. $C_{14}H_{15}ON_2,MeSO_4,MeOH$ requires C, 51·9; H, 5·9%). By repeated crystallisation or by warming with dilute sulphuric acid the methosulphate was changed to a *salt*, possibly the hydrogen sulphate, which had a strongly acid reaction and formed greenish-yellow rods of m. p. 276—278° (uncorr.) from methanol, again retaining a molecule of solvent (Found : C, 50·8; H, 5·3. $C_{14}H_{15}ON_2,HSO_4,MeOH$ requires C, 50·6; H, 5·6%). Addition of dilute aqueous sodium hydroxide to a solution of the methosulphate (0·15 g. of m. p. 210°) in water (3 c.c.) caused

precipitation of the ***hydroxide*** which formed tufts of yellow needles (from water), losing water at *ca.* 100°, softening above 210° and gradually melting to a dark brown liquid at *ca.* 225° [Found, (i) after drying at 20°/18 mm. for 2 days: C, 68·5; H, 6·5; N, 11·2; (ii) after drying at 100—110°/18 mm. for 7 hours: C, 74·0; H, 5·85. $C_{14}H_{14}ON_2,H_2O$ requires C, 68·85; H, 6·6; N, 11·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2%].

7-Methoxy-1 : 2 : 3-trimethyl-β-carbolinium Iodide (VIII).—The foregoing hydroxide (0·2 g.), after being heated at 100°/15 mm. for 30 minutes, cooled, and suspended in dry benzene (2 c.c.), was treated with methyl iodide (1 c.c.) and the mixture was warmed under reflux at 45—50° for 3 hours. After 12 hours at room temperature the solvent was removed, affording the ***methiodide*** which formed slender yellow needles, m. p. *ca.* 320° (decomp.), from water (Found: C, 49·0; H, 4·7; N, 7·4. $C_{14}H_{14}ON_2,CH_3I$ requires C, 48·9; H, 4·6; N, 7·6%).

7-Methoxy-1 : 2-dimethyl-β-carboline (II).—The above methiodide (50 mg.) was heated in a sublimation tube at 300—310°/15 mm., affording a yellowish sublimate (30 mg.) which, after renewed sublimation at 135—140°/15 mm., gave the ***carboline*** (II) as almost colourless lustrous plates of m. p. 80—81°, resolidifying and re-melting at 130—131° (from ethanol–water) (Found, after drying at 100°/15 mm. for 3 hours: C, 74·2; H, 6·1; N, 12·4. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%). The compound (II) was readily soluble in dilute acid giving a yellow solution which fluoresced pale green-yellow on addition of ethanol. The *picrate* formed yellow needles, m. p. 277—278° (decomp.) with softening at 260°, from ethanol (Found: C, 52·7; H, 3·45. $C_{14}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 52·75; H, 3·7%). For conversion into the *p*-nitrobenzylidene derivative, the base (II) (10 mg.) was heated with *p*-nitrobenzaldehyde (50 mg.) for 5 minutes at 250—255°. The cooled mixture was then treated with benzene and dilute hydrochloric acid, affording an insoluble hydrochloride which was filtered off, washed with benzene, and decomposed by rubbing it with cold dilute sodium hydroxide. The resulting powder was washed with water and extracted with hot benzene from which, on cooling, the p-*nitrobenzylidene* derivative separated as brick-red needles, m. p. 230—231° after further crystallisation (Found: C, 69·8; H, 4·5. $C_{21}H_{17}O_3N_3$ requires C, 70·2; H, 4·7%).

as-p-Methoxyphenylmethylhydrazine, b. p. (uncorr.) 134—138°/10 mm., was prepared by reduction of *N*-nitroso-*N*-methyl-*p*-anisidine, using zinc and acetic acid essentially as described by Späth and Brunner (*Ber.*, 1925, **58**, 522) but the following points were noted: (*a*) the use of partially oxidised (" aged ") zinc dust is preferable to that of fresh zinc powder since the latter reagent produces a greater proportion of *N*-methyl-*p*-anisidine: (*b*) aluminium amalgam in moist ether gives good results: (*c*) prolonged boiling during vacuum-distillation is to be avoided since decomposition to *N*-methyl-*p*-anisidine occurs (cf. Chattaway and Aldridge, *J.*, 1911, **99**, 404). For characterisation *as-p*-methoxyphenylmethylhydrazine was converted into its *benzylidene* derivative, pale yellow plates of m. p. 130—131° (from ethanol), which is formed when a solution of the hydrazine in acetic acid is mixed with one of benzaldehyde in ethanol (Found: N, 11·3. $C_{15}H_{16}ON_2$ requires N, 11·7%).

5-Methoxy-1-methylindole-2-carboxylic Acid.—*as-p*-Methoxyphenylmethylhydrazine (50 g.) was treated under cooling with a solution of pyruvic acid (29 g.) in water (15 c.c.). After 12 hours the supernatant liquid was decanted from the oily hydrazone, the latter was dissolved in a solution of concentrated sulphuric acid (25 g.) in ethanol–water (1 : 1, 150 c.c.), and the whole was warmed until reaction occurred whereby the temperature rose to 75°. The product (14 g.) separated on cooling and storage and formed pale yellow leaflets, m. p. 219—220° (decomp.), from ethanol (Found: C, 64·15; H, 5·3; N, 6·7. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%): Kermack and Tebrich (*J.*, 1940, 314) give m. p. 216°.

5-Methoxy-1-methylindole (IX).—(*a*) 5-Methoxy-1-methylindole-2-carboxylic acid (10 g.) was heated in a Claisen flask at 760 mm. and 220—225° (bath-temp.). When frothing had subsided the pressure was gradually reduced to 20 mm. and the *product* distilled (7·3 g.). After purification by sublimation, it formed white lustrous plates, m. p. 103—104°, from ethanol (Found: C, 74·6; H, 6·7; N, 9·1. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%) and afforded a *picrate* as dark red needles of m. p. 111—112° from ethanol (Found: C, 49·5; H, 3·6; N, 14·5. $C_{10}H_{11}ON,C_6H_3O_7N_3$ requires C, 49·2; H, 3·6; N, 14·4%). (*b*) 5-Methoxy-1-methyloxindole (1 g.) of m. p. 96—97° (cf. Porter, Robinson, and Wyler, *J.*, 1941, 620, who give m. p. 92°) was dissolved in ether (10 c.c.) and treated with a solution of lithium aluminium hydride (0·15 g.) in ether (6 c.c.), which was added with stirring during 10 minutes. Stirring was continued for a further 10 minutes, then water (2·5 c.c.) followed by 4% hydrochloric acid (2·5 c.c.) was cautiously added. After renewed washing the ether solution was separated and evaporated. The residue was distilled in steam and the distillate was extracted with ether from which the indole (0·36 g.), m. p. 103—104° [from light petroleum (b. p. 60—80°)], was recovered and was identified with the product from (*a*) by mixed m. p. and formation of the picrate.

The acid washings from (*b*) on basification and recovery from ether afforded a small quantity of oil which when treated with a solution of picric acid in ethanol yielded the *picrate* of 5-methoxy-1-methylindoline as yellow prisms, softening at 165° and melting at 171—173° (decomp.) (from methanol) (Found: C, 49·2; H, 4·2; N, 14·1. $C_{10}H_{13}ON,C_6H_3O_7N_3$ requires C, 49·0; H, 4·1; N, 14·3%).

3-Dimethylaminomethyl-5-methoxy-1-methylindole (*5-methoxy-1-methylgramine*) was prepared from 5-methoxy-1-methylindole by the method described above for 5-methoxygramine (cf. Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703). When precipitated, by means of 10% aqueous sodium hydroxide from its solution in ice-cold N-hydrochloric acid, it formed an almost colourless crystalline powder which, in a vaccum-desiccator, first liquefied, then re-solidified and thereafter crystallised as colourless prisms, m. p. 43—45°, from light petroleum (b. p. 60—80°) (Found: C, 71·3; H, 8·2; N, 12·95. $C_{13}H_{18}ON_2$ requires C, 71·6; H, 8·3; N, 12·8%). The base appeared to form both a dipicrate and a *monopicrate*. The former, which was rather unstable, separated as dark-red rectangular slabs of purple lustre and m. p. 129—130° when the base was treated with a concentrated solution of picric acid in benzene–ethanol (Found: C, 45·3; H, 3·5; N, 15·8 and 16·15. Calc. for $C_{13}H_{18}ON_2,2C_6H_3O_7N_3$: C, 44·4; H, 3·55; N, 16·6%) and, on attempted recrystallisation from benzene–ethanol, dissociated into the well-defined

monopicrate, orange needles of m. p. 143—144° (decomp.) (Found: C, 51·3; H, 4·9; N, 15·9. $C_{13}H_{18}ON_2,C_6H_3O_7N_3$ requires C, 51·0; H, 4·7; N, 15·7%). The *methiodide* of the base was formed when its components were mixed in ethanol at 0°, and was collected after 10 hours. It crystallised from ethanol as colourless prisms which sintered at *ca.* 180° and decomposed gradually above 200° (Found: C, 47·0; H, 5·7; N, 7·9. $C_{14}H_{21}ON_2I$ requires C, 46·7; H, 5·8; N, 7·8%).

Ethyl α-Acetamido-α-carbethoxy-β-(5-methoxy-1-methyl-3-indolyl)propionate.—The method which was successful in the analogous preparation (cf. above) from 5-methoxygramine miscarried when applied to 5-methoxy-1-methylgramine but the following procedure based on that of Snyder and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 350; cf. Snyder and Eliel, *ibid.*, 1949, **71**, 663) proved to be effective: 5-Methoxy-1-methylgramine methiodide (3·0 g.) was added to a solution of ethyl acetamidomalonate (1·8 g.) in ethanol (17 c.c.) containing sodium ethoxide (from 0·19 g. of sodium), and the whole was heated under reflux for 32 hours by which time evolution of trimethylamine had practically ceased. After filtration and partial concentration the solution was added to cold water (120 c.c.), the precipitated gum readily becoming solid (2·8 g.). It was purified for analysis by passage of a solution in benzene through a column of alumina, the recovered *ester* being obtained as colourless prisms, m. p. 122—123°, from benzene–light petroleum (b. p. 60—80°) and then from ethanol–water (Found: C, 61·5; H, 7·0; N, 7·6. $C_{20}H_{26}O_6N_2$ requires C, 61·5; H, 6·7; N, 7·2%).

α-Acetamido-β-(5-methoxy-1-methyl-3-indolyl)propionic Acid.—According to the general procedure of Albertson (*J. Amer. Chem. Soc.*, 1950, **72**, 1396) the above crude ester (2·5 c.c.) was heated under reflux with a solution of sodium carbonate (2·5 g.) in water (25 c.c.) for 17 hours, after which only a small quantity of a dark oil remained undissolved. The mixture was extracted with ether, and the separated aqueous layer was acidified and set aside at 0°. The solid acid (1·7 g.) was collected and crystallised as leaflets, m. p. 211—212°, from ethanol–water (1 : 2) (Found: C, 62·3; H, 6·2; N, 9·5. $C_{15}H_{18}O_4N_2$ requires C, 62·1; H, 6·2; N, 9·65%).

α-Amino-β-(5-methoxy-1-methyl-3-indolyl)propionic Acid (*5-Methoxy-1-methyltryptophan*).—The above acetyl derivative (1·1 g.) was heated (6 hours) with water (15 c.c.) in a sealed tube at 200° (for procedure cf. Rinderknecht and Niemann, *J. Amer. Chem. Soc.*, 1948, **71**, 2296). The solid obtained by filtration and some recovery from the concentrated mother-liquor (total, 0·84 g.) gave *5-methoxy-1-methyltryptophan* as colourless needles, m. p. 264—265° (decomp.), from ethanol–water (1 : 2) (Found: C, 62·7; H, 6·5; N, 11·5. $C_{13}H_{16}O_3N_2$ requires C, 62·9; H, 6·45; N, 11·3%).

2 : 3 : 4 : 5-*Tetrahydro-7-methoxy-1* : 2-*dimethyl-β-carboline-4-carboxylic acid* was prepared, as described for (IV), from 5-methoxy-1-methyltryptophan (0·5 g.), the product, however, separating only after the reaction solution had been concentrated from 50 c.c. to 10 c.c. under reduced pressure. The crude acid (0·5 g.) was separated by fractional crystallisation from ethanol into (i) a main fraction consisting of colourless needles, m. p. 268—269° (decomp.) (Found: C, 64·9; H, 6·25. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6%), and (ii) a second smaller fraction of pointed leaflets, m. p. 244—245° (decomp.) (Found: C, 64·95; H, 6·2%). These two fractions appeared to be distinct and the compounds are possibly stereoisomers although mixed m. p. determinations gave inconclusive results; moreover, admixture of the second fraction with the distinct acid (IV) again produced no depression of m. p. The difficulty in obtaining satisfactory analytical figures for this type of compound has been experienced previously (cf. Snyder *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 219).

Conversion into 7-methoxy-1 : 2-*dimethyl-β-carboline* (II). The above acid yielded (II) when oxidised as described in the preparation of (III) from (IV). The product, recovered in ether from the reaction mixture and purified on alumina with benzene–light petroleum (1 : 1) as solvent, crystallised as colourless, glistening needles, m. p. 130—131°, from ethanol–water (1 : 1) or as plates, m. p. 80—81°, re-solidifying and re-melting at 130—131°, from a more aqueous solvent. This melting behaviour was unaffected by admixture with the previous specimen of 7-methoxy-1 : 2-dimethyl-β-carboline. Both samples gave the same picrate and *p*-nitrobenzylidene derivative.

A hydrochloride, yellow needles of m. p. 286—287° (decomp.), and a nitrate, yellow needles of m. p. 210—211° (sharp decomp.), were prepared but were not analysed.

The following table shows the results of m. p. and mixed m. p. determinations on the degradation products (A) from mitragynine and their isomers (B) of the 7-methoxy-1 : 2-dimethyl-β-carboline type:

	A.	B.	A + B.
Base	softens 120°; m. p. 129—134°	m. p.s 80—81° and 130—131°	m. p. 92—102°
Picrate	decomp. 260—262°	decomp. 277—278°	decomp. 256°
p-Nitrobenzylidene derivative	m. p. 260—261°	m. p. 230—231°	m. p. 227—228°

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