750. *The Chemistry of the* Mitragyna *Genus. Part IV.* Derivatives of Harman.*

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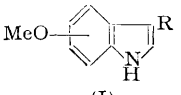
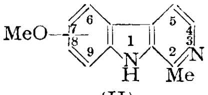
Syntheses of 9-methoxy-, 9-methoxy-1-methyl-, and 6-methoxy-1-methyl-β-carboline complete the set of eight harman derivatives which contain a methoxyl group in the benzene nucleus, with or without a 1-methyl substituent. The ultra-violet absorption spectra of these eight compounds and of 1 : 2-dimethyl-β-carboline are recorded.

THE identification of 6-methoxy-1 : 2-dimethyl-β-carboline as a degradation product of mitragynine (Part III; * cf. Ing and Raison, *J.*, 1939, 986) adds to the growing list of harman derivatives which have a bearing on the chemistry of indole alkaloids (cf. T. A. Henry, "The Plant Alkaloids," Churchill, London, 1949). It was the object of the present work to complete and characterise as reference compounds those derivatives of harman and of *ind-N*-methylharman, which contain a methoxyl substituent in the benzene ring. Five of these compounds were already known (for references, see Experimental section): the remaining three have now been synthesised and the ultra-violet absorption spectra of the eight compounds are here recorded.

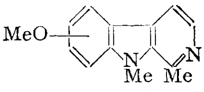
The same general procedure served for the preparation of all of the required compounds (cf. Part II; Cook, Loudon, and McCloskey, *J.*, 1951, 1203; Part III *). From the methoxyindole (I; R = H), the gramine (I; R = $CH_2{\cdot}NMe_2$) and tryptophan [I; R = $CH_2{\cdot}CH(NH_2){\cdot}CO_2H$], and thence, *via* the 2 : 3 : 4 : 5-tetrahydro-2-methylcarboline-4-carboxylic acid, the harman derivative (II) were produced. The methosulphate of (II) was converted into the anhydronium base and thence by addition of methyl iodide into the 1 : 2 : 3-trimethyl-β-carbolinium iodide which on pyrolysis yielded (III). 6-Methoxy-1 : 2-dimethyl-β-carboline, prepared in this way from 6-methoxyharman, was identical with the compound synthesised by the alternative route described in Part III, and 1 : 2-dimethyl-β-carboline (III; H for MeO) was similarly prepared from harman (II; H for OMe).



(I)



(II)



(III)

The ultra-violet absorption spectra of the four methoxyharmans and their 1-methyl derivatives are shown in Figs. 1—4. The spectrum of 1-methylharman is included (Fig. 1) and shows a general resemblance to the spectra of harman (Raymond-Hamet, *Compt. rend.*, 1945, **221**, 387) and 2-ethyl-β-carboline (Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556). Similar resemblances are found in the absorption curves of the methoxylated harmans when compared respectively with those of their 1-methyl derivatives. The

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* Part III, preceding paper.

position of the methoxyl group in the benzene ring has considerable influence on the absorption. The curves of the 6- and the 9-methoxy-compound, with α-methoxy-groups (Figs. 2 and 4), resemble each other, but those of the 7- and the 8-methoxy-compound (Figs. 1 and 3), with β-methoxy-groups, show appreciable differences. We are indebted to Dr. W. F. Short for a specimen of harmine from the collection of the late Dr. F. L. Pyman, F.R.S. For absorption measurements this specimen was purified by passing a solution in benzene through alumina, followed by recrystallisation. The absorption curve (Fig. 1) shows lower maximal intensities and a more pronounced flattening in the region, 320—340 mμ, than does the curve of " Harmin reinst " as given by Pruckner and Witkop (*Annalen*, 1943, **554**, 136).

FIG. 1.

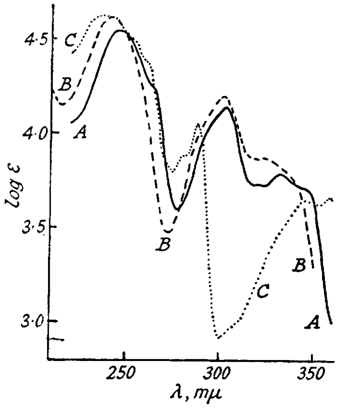

FIG. 2.

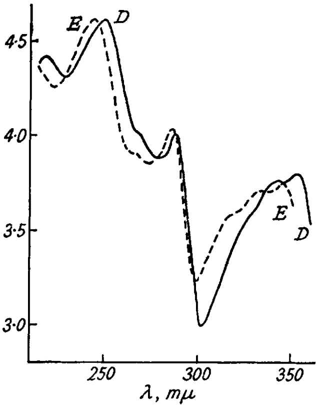

FIG. 1. *A*, 8-*Methoxy*-1 : 2-*dimethyl*-β-*carboline, max. at* 245, 303, *and* 332 mμ, log ε 4·55, 4·15, *and* 3·79.
B, 8-*Methoxy-2-methyl*-β-*carboline, max. at* 242 *and* 301 mμ, log ε 4·62 *and* 4·20.
C, 1 : 2-*Dimethyl*-β-*carboline, max. at* 237, 288, 346, *and* 359 mμ, log ε 4·63, 4·05, 3·65 *and* 3·67.

FIG. 2. *D*, 6-*Methoxy*-1 : 2-*dimethyl*-β-*carboline, max. at* 218, 249, 288, 342, *and* 352 mμ, log ε 4·42, 4·62, 4·01, 3·76, *and* 3·80.
E, 6-*Methoxy-2-methyl*-β-*carboline, max. at* 244, 286, 333, *and* 344 mμ, log ε 4·62, 4·03, 3·72, *and* 3·74.

FIG. 3.

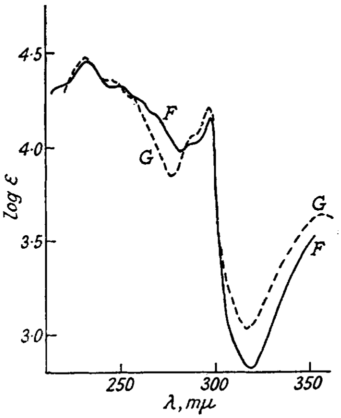

FIG. 4.

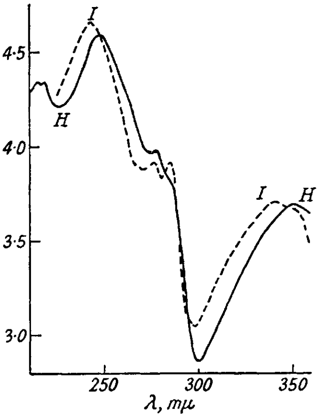

FIG. 3. *F*, 7-*Methoxy*-1 : 2-*dimethyl*-β-*carboline, max. at* 231 *and* 298 mμ, log ε 4·46 *and* 4·16.
G, 7-*Methoxy-2-methyl*-β-*carboline, max. at* 231, 296, *and* 358 mμ, log ε 4·48, 4·21, *and* 3·64.

FIG. 4. *H*, 9-*Methoxy*-1 : 2-*dimethyl*-β-*carboline, max. at* 213, 218, 247, 278, *and* 350 mμ, log ε 4·34, 4·35, 4·59, 3·98 ,*and* 3·69.
I, 9-*Methoxy-2-methyl*-β-*carboline, max. at* 242, 276, 284, *and* 340 mμ, log ε 4·66, 3·92, 3·91, *and* 3·70.

All spectra are for ethanol solutions.

EXPERIMENTAL

4- and 7-Methoxyindole which were required for the synthetic work were prepared essentially as described by Blaikie and Perkin (*J.*, 1924, **125**, 296) from 6-methoxy- and 3-methoxy-2-nitrotoluene respectively, and these were obtained by methylating the corresponding nitrocresols with methyl sulphate and alkali. 3-Hydroxy-2-nitrotoluene was prepared by Haworth and Lapworth's method (*J.*, 1923, **123**, 2993). For the preparation of 6-hydroxy-2-nitrotoluene, 2 : 4 : 6-trinitrotoluene was reduced to 4-amino-2 : 6-dinitrotoluene (Parkes and Farthing, *J.*, 1948, 1275) which was deaminated by diazotisation and treatment with 30% hypophosphorous acid (method : cf. Kornblum, " Organic Reactions," 1944, Vol. II, p. 277). 2 : 6-Dinitrotoluene, so obtained, was reduced by sodium hydrogen sulphide (cf. standard procedure of Hodgson and Ward, *J.*, 1948, 242; 1949, 1316) and the resultant 6-amino-2-nitrotoluene was treated as described by Noelting (*Ber.*, 1904, **37**, 1024).

1 : 2-*Dimethyl*-β-*carboline* (ind-N-*Methylharman*).—Harman, m. p. 238° (corr.) (from benzene), was prepared from (±)-tryptophan (Harvey and Robson, *J.*, 1938, 97). When it (0·2 g.) was heated under reflux with neutral methyl sulphate (0·25 c.c.) in dry benzene (6 c.c.) for 1 hour, it formed the *methosulphate* which was recovered by distillation of the solvent and crystallised as needles, m. p. (decomp.) 262°, from methanol (Found : C, 54·6; H, 5·3; N, 9·0. $C_{14}H_{16}O_4N_2S$ requires C, 54·5; H, 5·2; N, 9·1%). The methosulphate (0·246 g.), treated with N-sodium hydroxide, afforded the anhydronium *base* as yellow needles, m. p. (decomp.) 177—178°, from water, and this was dried for analysis at 140°/20 mm. for 2 hours (Found : C, 79·0; H, 6·5; N, 14·2. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2; N, 14·3%). The base (0·1 g.) and methyl iodide were mixed, and after 18 hours at room temperature were gently heated for 30 minutes and afforded, after evaporation, 1 : 2 : 3-*trimethyl*-3-*carbolinium iodide* as yellow clusters of needles which softened at 270° and melted at 279—281° (Found : C, 49·5; H, 4·3; N, 8·3. $C_{14}H_{15}N_2I$ requires C, 49·7; H, 4·5; N, 8·3%). This salt was heated in a sublimation tube at 290°/0·5 mm. for 1 hour. The sublimate was resublimed and gave *ind-N*-methylharman as colourless platelets, m. p. 102°, from light petroleum (b. p. 60—80°) (Found : C, 79·5; H, 6·3; N, 14·4. Calc. for $C_{13}H_{12}N_2$: C, 79·6; H, 6·2; N, 14·3%). Mukherji, Robinson, and Schlittler record m. p. 102° for *ind-N*-methylharman prepared from harman, potassamide, and methyl iodide in liquid ammonia (*Experientia*, 1949, **5**, 215) ; Späth and Lederer (*Ber.*, 1930, **63**, 2102) prepared it from 1-methyltryptamine and record m. p. 102—103°.

7-Methoxy-2-methyl-β-carboline, m. p. 275—276°, and 7-methoxy-1 : 2-dimethyl-β-carboline, m. p. 130—131°, were prepared as described in Part II (*loc. cit.*). 8-Methoxy-2-methyl-β-carboline (harmine), purified by passage in benzene through a column of alumina, formed colourless needles of m. p. 261—262° from methanol–water. It was converted into 8-methoxy-1 : 2-dimethyl-β-carboline (*ind-N*-methylharmine) essentially as described by Iyer and Robinson (*J.*, 1934, 1935), the product being obtained as needles of (micro-)m. p. 122—123° (anhydrous).

3-*Dimethylaminomethyl*-4-*methoxyindole* (4-*Methoxygramine*).—Acetic acid (3 c.c.) was added dropwise to 25% aqueous dimethylamine (4 c.c.) kept below 5°. Aqueous formaldehyde (40% ; 1·5 c.c.) was then added at the same temperature and the whole was poured into finely ground 4-methoxyindole (3 g.) with stirring. The temperature rose slowly to 25°; the suspended indole became pasty and then emulsified and the mixture was then shaken at room temperature for 1 hour and set aside for 20 hours. The solution, in which some solid was present, was basified with 10% aqueous sodium hydroxide, and the solid precipitate was collected, washed with water, and dissolved in ether (250 c.c.). The base was recovered from the ethereal solution in N-hydrochloric acid (3 × 20 c.c.) and was reprecipitated by alkali from the filtered acid solution. 4-*Methoxygramine* formed prisms, m. p. 142—143°, from benzene (charcoal) and then from ethanol–light petroleum (b. p. 60—80°) (Found : C, 70·6; H, 7·9; N, 14·0. $C_{12}H_{16}ON_2$ requires C, 70·6; H, 7·8; N, 13·7%).

Ethyl α-*Acetamido*-α-*carbethoxy*-β-(4-*methoxy*-3-*indolyl*)*propionate*.—Ethyl acetamidomalonate (5·94 g.) was added with stirring and exclusion of moisture to a cold solution of sodium methoxide (from 0·55 .g of sodium) in dry ethanol (62 c.c.). 4-Methoxygramine (5·5 g.) was added and the whole was then treated dropwise with methyl sulphate (4·45 c.c.) under continuous stirring. After 16 hours at room temperature the reaction mixture was poured into water (200 c.c.), and the resultant solid precipitate was dissolved in chloroform and washed with N-hydrochloric acid (3 × 30 c.c.) and then with water. The *ester*, recovered from the dried chloroform solution, was obtained from ethanol as leaflets, which softened at 158° and melted at 162—163° (Found : C, 60·4; H, 6·4; N, 7·7. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·45%).

α-*Amino*-β-(4-*methoxy*-3-*indolyl*)*propionic Acid* (4-*Methoxytryptophan*).—The foregoing ester (10 g.) was heated under reflux with an aqueous solution (100 c.c.) of sodium carbonate (10 g.) for 18 hours. After filtration and extraction with ether the aqueous layer was acidified and the crude gummy acetamido-acid was collected. It (5·6 g.) was heated in a sealed tube with water (90 c.c.) at 180° for 6 hours, affording a solution which was treated with charcoal, filtered, and concentrated. 4-*Methoxytryptophan* was thereby obtained as prisms, darkening at 230° and m. p. (decomp.) 235—246°, from ethanol–water (1 : 3) (Found : C, 61·4; H, 6·0; 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*-6-*methoxy*-2-*methyl*-β-*carboline*-4-*carboxylic Acid*.—Acetaldehyde (4 c.c.) was added to a cooled solution of 4-methoxytryptophan (1·6 g.) in water (240 c.c.) and after 24 hours at room temperature the solution was gradually heated and finally kept at 100° for 1 hour. The solution was decolorised by heating it with charcoal and, on concentration, afforded the *carboline acid*, m. p. 259—260° (with gas evolution) (from water) (Found : C, 60·2; H, 6·4; N, 10·3. $C_{14}H_{16}O_3N_2,H_2O$ requires C, 60·4; H, 6·5; N, 10·1%).

6-*Methoxy*-2-*methyl*-β-*carboline* (6-*Methoxyharman*).—To a solution of the foregoing acid (1·2 g.) in boiling water (500 c.c.) were added 10% aqueous potassium dichromate followed by acetic acid (12 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 sulphate and then with a saturated solution of sodium carbonate. 6-*Methoxyharman* was recovered in ether and, after purification in chloroform on a column of alumina, formed almost colourless rods of m. p. (decomp.) 246—247° from chloroform–light petroleum (b. p. 60—80°) (Found : C, 73·3; H, 5·4; N, 13·4. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·7; N, 13·2%).

6-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*.—Following the procedure described for 1 : 2-dimethyl-β-carboline (above), 6-methoxyharman was converted into the *methosulphate*, pale yellow needles which softened at 272°, m. p. 285° (decomp.) (from methanol) (Found : C, 53·5; H, 5·4; N, 8·1. $C_{15}H_{18}O_5N_2S$ requires C, 53·4; H, 5·35; N, 8·3%), and thence into the corresponding base which was obtained as prisms, m. p. 234° (decomp.) from water but was not analysed. By reaction with methyl iodide the base afforded 6-*methoxy*-1 : 2 : 3 -*trimethyl*-β-*carbolinium iodide* as brown-stained needles, m. p. 253—254° (decomp.), from aqueous ethanol (Found : C, 46·0, 46·2; H, 4·55, 4·45; N, 7·4. $C_{15}H_{17}ON_2I,H_2O$ requires C, 46·6; H, 4·9; N, 7·25%). Pyrolysis of this iodide gave 6-methoxy-1 : 2-dimethyl-β-carboline which, after sublimation and crystallisation from light petroleum (b. p. 60—80°), had m. p. 138° with softening at 135° and mixed m. p. 137—138° with the sample of m. p. 139—140° synthesised as described in Part III (*loc. cit.*).

9-*Methoxy*-2-*methyl*-β-*carboline* (9-*Methoxyharman*).—7-Methoxygramine, obtained as slender rods of m. p. 112·5° from ethanol–light petroleum (b. p. 60—80°) (Found : C, 70·25; H, 7·8; N, 13·7. Calc. for $C_{12}H_{16}ON_2$: C, 70·6; H, 7·8; N, 13·7%) (Bell and Lindwall, *J. Org. Chem.*, 1948, **13**, 547, give m. p. 105—106°), was prepared from 7-methoxyindole as described for the 4-methoxy-isomer and was similarly condensed with ethyl sodio-acetamidomalonate. *Ethyl* α-*acetamido*-α-*carbethoxy*-β-(7-*methoxy*-3-*indolyl*)*propionate* was thereby obtained as prisms, m. p. 147°, from ethanol (Found : C, 60·6; H, 6·5; N, 7·6. $C_{19}H_{24}O_6N_2$ requires C, 60·6; H, 6·4; N, 7·45%) and was hydrolysed in two stages (cf. 4-methoxy-isomer) to 7-methoxytryptophan, yellowish needles, m. p. (decomp.) about 250° (Found : C, 61·5; H, 5·7. Calc. for $C_{12}H_{14}O_3N_2$: C, 61·5; H, 6·0%) (Marchant and Harvey, *J.*, 1951, 1808, record m. p. 255—264° for an analytically impure specimen of the tryptophan). The reaction solution obtained by condensing 7-methoxytryptophan (4 g.) with acetaldehyde (10 c.c.) in water (600 c.c.) afforded on concentration (charcoal), as first and main fraction, needles (2·35 g.), m. p. 252—253°, and a residue, m. p. 230—244°, which appeared to contain unchanged methoxytryptophan, mixed m. p. 246—250°. Recrystallisation of the needles gave 2 : 3 : 4 : 5-tetrahydro-9-methoxy-2-methyl-β-carboline-4-carboxylic acid, m. p. (decomp.) 255—256°, from water, depressed to *ca.* 230—235° by admixture with the tryptophan (Found : C, 60·0; H, 6·6; N, 10·3. Calc. for $C_{14}H_{16}O_3N_2,H_2O$: C, 60·4; H, 6·5; N, 10·1%) (Marchant and Harvey, *loc. cit.*, give m. p. 256—258° for this monohydrate). Treatment of this carboline acid with potassium dichromate as described for the 6-methoxy-isomer gave 9-methoxyharman, m. p. 239—240°, from methanol (Späth and Lederer, *loc. cit.*, give the same m. p.)(Found : C, 73·6; H, 5·6; N, 13·3. Calc. for $C_{13}H_{12}ON_2$: C, 73·6; H, 5·7; N, 13·2%).

9-*Methoxy*-1 : 2-*dimethyl*-β-*carboline*.—As described for analogous cases, 9-methoxyharman was converted *via* the *methosulphate*, needles, m. p. 245° (from methanol) (Found : C, 53·15; H, 5·1; N, 8·1. $C_{15}H_{18}O_5N_2S$ requires C, 53·4; H, 5·35; N, 8·3%), and the corresponding base [needles, m. p. 167° (decomp.), from water] into 9-*methoxy*-1 : 2 : 3-*trimethyl*-β-*carbolinium* *iodide*, needles, m. p. 294—295° (decomp.) (from much ethanol) (Found : C, 48·9; H, 4·7; N, 7·7. $C_{15}H_{17}ON_2I$ requires C, 48·9; H, 4·6; N, 7·6%). Pyrolysis of the iodide followed by resublimation of the product afforded 9-*methoxy*-1 : 2-*dimethyl*-β-*carboline* as platelets, m. p. 164—165° [from light petroleum (b. p. 60—80°)] (Found: C, 74·45; H, 6·4; N, 12·5. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%. 7·175 Mg. of substance gave 14·37 mg. of silver iodide. Calc. for 1OMe and 1NMe group, 14·92 mg.).

We are indebted to the University of Glasgow for a research grant (to P. McC.) and to Imperial Chemical Industries Limited, Nobel Division, for a supply of 4-amino-2 : 6-dinitrotoluene. Grateful acknowledgment is also made to Professor J. W. Cook, F.R.S., for his interest and advice. Microanalyses were carried out by Mr. J. M. L. Cameron and Miss M. W. Christie.

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[*Received, May* 17*th*, 1952.]