Some Methyl Derivatives of β-Carboline.

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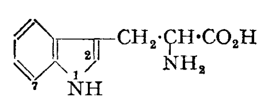
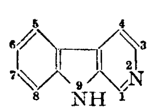
8-Methyl-, 8 : 9-dimethyl-, 1 : 8-dimethyl-, and 1 : 8 : 9-trimethyl-β-carboline and 1 : 7-dimethyltryptophan are synthesised.

7-METHYLTRYPTOPHAN (I) (Rydon, *J.*, 1948, 705) was converted by established methods into 8-methyl-, 8 : 9-dimethyl-, 1 : 8-dimethyl- and 1 : 8 : 9-trimethyl-β-carbolines (see II). The second and fourth of these products were also obtained from 1 : 7-dimethyltryptophan which was itself synthesised from 1 : 7-dimethyloxindole *via* the corresponding indole and gramine.

(I)





(II)

Comparisons of recorded properties show that the base, $C_{12}H_{10}N_2$ (m. p. 176—183°), obtained from calycanthine (Barger, Madinaveitia, and Streuli, *J.*, 1939, 510) is not identical with 8-methyl-β-carboline and that " Base F," $C_{13}H_{12}N_2$ (m. p. 78—81°), obtained from alstonine (Leonard and Elderfield, *J. Org. Chem.*, 1942, **7**, 556) is not identical with either 8 : 9- or 1 : 8-dimethyl-β-carboline.

EXPERIMENTAL

N-*Methylchloroacet*-o-*toluidide*.—Benzenesulphon-*o*-toluidide was methylated in an excess of aqueous sodium hydroxide by methyl sulphate. The resultant N-*methylbenzenesulphon*-o-*toluidide*, m. p. 78° (from ethanol) (Found : C, 64·3; H, 5·7. $C_{14}H_{15}O_2NS$ requires C, 64·4; H, 5·8%), was hydrolysed when heated (45 min.) with a mixture of water and sulphuric acid (1 : 2, v/v). *N*-Methyl-*o*-toluidine (yield 40% from *o*-toluidine) was recovered in steam from the basified solution. Chloroacetyl chloride (3·3 g.) was slowly added to a solution of the base (3·6 g.) in benzene (25 c.c.) and pyridine (2·4 g.), and after 2 hr. N-*methylchloroacet*-o-*toluidide*, m. p. 46° [from light petroleum (b. p. 60—80°)], was recovered from the acid-washed benzene solution (yield, 85%) (Found : C, 60·6; H, 6·2. $C_{10}H_{12}ONCl$ requires C, 60·8; H, 6·1%).

1 : 7-*Dimethylindole*.—A mixture of *N*-methylchloroacet-*o*-toluidide (7·5 g.), aluminium chloride (7·5 g.), and sodium chloride (1·5 g.) was heated at 180—185° for 1 hr. and the cooled, powdered product was added to ice and extracted with benzene. After purification on alumina 1 : 7-*dimethyloxindole* was recovered and had m. p. 119—120° [from light petroleum (b. p. 60—80°)] (Found : C, 74·7; H, 6·9; N, 8·9. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·7%). To a stirred suspension of this oxindole (3·5 g.) in anhydrous ether (35 c.c.) lithium aluminium hydride (1·2 g.) was slowly added. After further stirring (10 min.), water (10 c.c.) and then hydrochloric acid (10 c.c., 4%) were added and the ethereal layer was washed with acid (1 : 7-dimethylindoline was recoverable in steam from the basified acid solutions), dried, and evaporated. A solution of the residue in light petroleum (b. p. 60—80°) was passed through an alumina column, and elution with the same solvent gave 1 : 7-*dimethylindole* as needles (1·5 g.), m. p. 78° [from light petroleum (b. p. 40—60°)] (Found : C, 82·5; H, 7·7; N, 9·6. $C_{10}H_{11}N$ requires C, 82·7; H, 7·6; N, 9·7%), whereas subsequent elution with benzene afforded unchanged 1 : 7-dimethyloxindole (1 g.).

1 : 7-*Dimethyl*-3-*dimethylaminomethylindole* (1 : 7-*Dimethylgramine*).—To an aqueous solution of dimethylamine (3 c.c.; 33%), maintained below 5°, acetic acid (3 c.c.) and then formaldehyde (1·5 c.c.; 40%) were added and the whole was poured upon 1 : 7-dimethylindole (2·9 g.) which dissolved when the mixture was shaken at room temperature. After 16 hr. the solution was

basified and extracted with ether. Since the base did not readily crystallise, a portion of the ethereal solution was treated with a solution of picric acid in ether, affording 1 : 7-*dimethylgramine picrate* as orange needles, m. p. 142° (from ethanol) (Found : C, 53·0; H, 5·0; N, 16·4. $C_{13}H_{18}N_2,C_6H_3O_7N_3$ requires C, 52·9; H, 4·9; N, 16·2%). To the rest of the ethereal solution methyl iodide was added and the precipitated salt was dried *in vacuo* for use in the following experiment.

α-*Amino*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionic Acid* (1 : 7-*Dimethyltryptophan*).—A solution of the foregoing salt (0·86 g.) and ethyl acetamidomalonate (0·54 g.) in anhydrous ethanol (10 c.c.) containing sodium ethoxide (from 0·056 g. of sodium) was heated under reflux for 26 hr. Addition to water (200 c.c.) afforded *ethyl* α-*acetamido*-α-*ethoxycarbonyl*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionate*, m. p. 162° (after softening at 158°) (from ethyl acetate) (Found : C, 64·5; H, 7·2. $C_{20}H_{26}O_5N_2$ requires C, 64·2; H, 7·0%). It (3·5 g.) was heated under reflux for 18 hr. with a solution of sodium carbonate (3·5 g.) in water (35 c.c.) and, after some oil was removed in ether, the acidified solution afforded α-*acetamido*-β-(1 : 7-*dimethyl*-3-*indolyl*)*propionic acid*, m. p. 181° (from ethyl acetate) (Found : C, 65·4; H, 6·7. $C_{15}H_{18}O_3N_2$ requires C, 65·7; H, 6·6%). The acetamido-compound (1 g.) and water (50 c.c.) were heated at 200° for 6 hr. The solid obtained was extracted with dilute sulphuric acid from which 1 : 7-*dimethyltryptophan* was precipitated at pH 7 by dilute sodium hydroxide and formed colourless needles, m. p. 218°, from water (Found : C, 66·9; H, 7·1. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·95%).

8-*Methyl*-β-*carboline*.—Formaldehyde (1 c.c.; 40%) was added to a solution of 7-methyltryptophan (0·1 g.) in water (15 c.c.) and after 3 hr. at ordinary temperature the whole was heated (2 hr.) at 100° until the ninhydrin test was negative. Aqueous potassium dichromate (5 c.c.; 10%) and acetic acid (1 c.c.) were added and the solution was boiled for 3 min. Residual dichromate was reduced by addition of sodium sulphite, and the carboline was precipitated by aqueous sodium carbonate and recovered in ether. After sublimation at 150°/1 mm., 8-*methyl*-β-*carboline* formed needles, m. p. 229—230°, from benzene (Found : C, 78·9; H, 5·5; N, 15·4. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). Light absorption in ethanol : $\lambda_{\text{max.}}$ 3500, 3360, 2880, 2380 Å; log ε 3·69, 3·69, 4·17, 4·58.

1 : 8-*Dimethyl*-β-*carboline*, needles, m. p. 213° (from benzene), was obtained by using acetaldehyde (0·3 c.c.) in place of formaldehyde as in the preceding experiment (Found : C, 79·3; H, 6·4; N, 14·4. $C_{13}H_{12}N_2$ requires C, 79·5; H, 6·2; N, 14·3%). Light absorption in ethanol : $\lambda_{\text{max.}}$ 3520, 3400, 2900, 2370 Å; log ε 3·63, 3·64, 4·19, 4·57.

8 : 9-*Dimethyl*-β-*carboline*.—(*a*) The condensate of 1 : 7-dimethyltryptophan and formaldehyde was prepared and oxidised as described for 8-methyl-β-carboline. 8 : 9-*Dimethyl*-β-*carboline*, after sublimation and crystallisation from methanol, melted at 68—70°, then solidified and re-melted at 96° (Found : C, 72·8; H, 6·7. $C_{13}H_{12}N_2,H_2O$ requires C, 73·1; H, 6·5%).

(*b*) A suspension of 8-methyl-β-carboline in benzene was heated under reflux with methyl sulphate for 1 hr. and, after 16 hr. at room temperature, 2 : 8-*dimethyl*-β-*carbolinium methosulphate* was collected. It formed yellow needles, m. p. 228°, from methanol (Found : C, 54·4; H, 5·2. $C_{14}H_{16}O_4N_2S$ requires C, 54·5; H, 5·2%) and when treated in aqueous solution with sodium hydroxide afforded hydrated 2 : 8-*dimethyl*-β-*carbolinium hydroxide* as yellow needles (from water), m. p. 165° re-solidifying and decomposing above 230° (Found : C, 60·35; H, 7·5. $C_{13}H_{14}ON_2,3H_2O$ requires C, 60·0; H, 7·7%). The hydroxide was heated at 100°/15 mm. for 1 hr., then suspended in dry benzene and heated with methyl iodide at 45° for 3 hr. After 12 hr. at room temperature removal of the solvent gave 2 : 8 : 9-*trimethyl*-β-*carbolinium iodide* as needles, decomp. above 320° (from water) (Found : C, 49·8; H, 4·3. $C_{14}H_{15}N_2I$ requires C, 49·7; H, 4·5%). The sublimate obtained when this iodide was heated at 300°/15 mm. was re-sublimed, affording 8 : 9-dimethyl-β-carboline (from methanol) with the same m. p. and mixed m. p. behaviour as the sample from (*a*).

1 : 8 : 9-*Trimethyl*-β-*carboline* was obtained by the foregoing methods, *viz.*, (*a*) from 1 : 7-dimethyltryptophan and acetaldehyde, and (*b*) from 1 : 8-dimethyl-β-carboline through 1 : 2 : 8-trimethyl-β-carbolinium methosulphate (m. p. 218°) and hydroxide (hydrate, m. p. 165°, re-solidifying and decomposing above 230°) and 1 : 2 : 8 : 9-tetramethyl-β-carbolinium iodide (m. p. 310°). It formed needles, m. p. 168—169°, from benzene, after sublimation at 150°/15 mm. (Found : C, 80·1; H, 6·9. $C_{14}H_{14}N_2$ requires C, 80·0; H, 6·7%).

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