3-*Methyl- and* 3-*Ethyl*-2-2′-*pyridylindole.*

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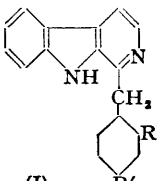
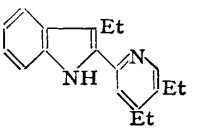
Some preliminary work bearing on the synthesis of alstyrine included the preparation of 3-methyl- and 3-ethyl-2-2′-pyridylindole. The substances resemble alstyrine (corynanthyrine) in ultraviolet absorption and in a new characteristic colour reaction. Before the constitution of alstyrine was known some 2-*cyclo*hexylmethyl-β-carbolines isomeric with that degradation product were synthesised by standard methods.

THE present work was initiated in 1948 (Y.-S. Kao, D.Phil. Thesis, Oxford, 1950) when we were able to examine a specimen of alstyrine kindly provided by Dr. T. M. Sharp of the Wellcome Research Laboratories. This was obtained colourless after chromatography and showed no fluorescence in acid solution. Nevertheless we synthesised certain isomeric 2-*cyclo*hexylmethyl-β-carbolines (I), partly with a view to examining their behaviour in contact with dehydrogenating agents.

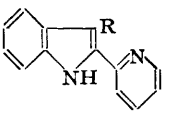
However, in 1949, Karrer and Enslin (*Helv. Chim. Acta*, 1949, **32**, 1390; cf. *idem*, *ibid.*, 1950, **33**, 100) showed that corynanthyrine (= alstyrine) has the constitution (II) and this caused us to consider the preparation of alstyrine by the obvious application of the Fischer indole-derivatives synthesis.



(I)



(II)



(III)

The introduction of the ethyl group into the 4-position of 5-ethyl-2-methylpyridine by an adaptation of Wibaut's methods (*Rec. Trav. chim.*, 1942, **61**, 59; 1947, **66**, 236; 1948, **87**, 545) succeeded, but the yield was very unfavourable. Hence we turned to 5-ethyl-2-methylpyridine itself as a starting point. This could be converted into 5-ethyl-2-styrylpyridine and the latter oxidised to 5-ethylpyridine-2-carboxylic acid (Prostenik and Filipovic, *Arhiv Kemi*, 1946, **18**, 3). Again we were anticipated here by Anderson, Clemo, and Swan (*J.*, 1954, 2962) who synthesised de-ethylalstyrine (alstyrine less the ethyl group in position 4 of the pyridine nucleus), a degradation product of corynantheine. As the yield of 4 : 5-diethyl-2-methylpyridine was unsatisfactory, we have investigated some 2-phenylpyridine derivatives substituted in positions 3 and 4 in such a way that later conversion of the groups into ethyl groups might be feasible. The project was to nitrate the diethylphenylpyridine, reduce the nitro-group, and oxidise the benzene ring to carboxyl.

Difficulties were encountered in implementing this scheme, which was set aside in favour of other work.

The 2-acylpyridines required for the synthesis of (III; R = Me and Et) were made by distillation of the mixed calcium salts of picolinic and propionic (or butyric) acid. The

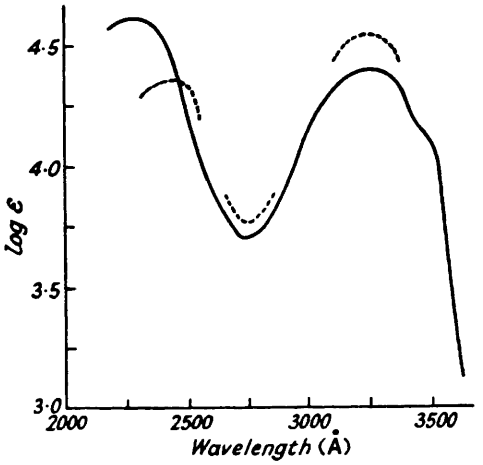
only merit of this process was that it saved time; the alternative adopted by Anderson, Clemo, and Swan (*loc. cit.*) is superior in all other respects.

The ultraviolet absorption spectrum (see Figure) of the 2-2′-pyridylindoles is not much affected by the nature of the alkyl substituents.

At the time of writing the interest taken in these bases in this laboratory has increased, because certain degradation products of ajmaline and its derivatives appear to be substituted 2-2′-pyridylindoles. The synthetical aspect is now being further studied.

Experimental

Alstyrine.—A sample kindly provided by Dr. T. M. Sharp (pale yellow crystals; 0·1 g.) was dissolved in benzene (5 c.c.), adsorbed on an alumina column (6 g.), and eluted with benzene (20 c.c.). The residue obtained on evaporation recrystallised from a little alcohol as colourless plates, m. p. 112—113°. The following colour reaction has been noted. A few crystals of alstyrine were covered with freshly distilled methyl sulphate, and the mixture was gently heated. The yellow product was shaken with benzene and a little water. The aqueous solution gave a red colour on the addition of aqueous sodium hydroxide. The synthetic lower homologues of alstyrine described below gave this characteristic reaction.



Ultraviolet absorption spectra of (—) *3-methyl-2-2′-pyridylindole and* (– – –) *alstyrine.*

3-Methyl-2-2′-pyridylindole (III; R = Me).—Ethyl 2-pyridyl ketone was prepared by the dry distillation of a mixture of crude calcium picolinate and calcium propionate (2 mols.). The ketone, b. p. 202—207° (3·7 g.), in ether (30 c.c.) was mixed with phenylhydrazine (2·5 g.) in ether (5 c.c.). The whole was kept overnight and then heated on the steam-bath for a few minutes. The ether was distilled off until crystallisation commenced and the solution was then cooled. The product (3·7 g.) had m. p. 140—142° after recrystallisation from alcohol (Pinner, *Ber.*, 1901, **34**, 4237, reported the m. p. 140—143°) (Found: C, 74·6; H, 6·2. Calc. for $C_{14}H_{15}N_3$: C, 74·6; H, 6·7%).

A solution of this phenylhydrazone (3 g.) in alcohol (100 c.c.) was saturated with hydrogen chloride at 0°. The mixture was kept at the room temperature for 2 hr., and then refluxed on the steam-bath for 1 hr. The sparingly soluble, yellow hydrochloride, together with ammonium chloride, separated after 20 min. The whole was then concentrated to about 50 c.c. under reduced pressure; abundant separation of long, yellow needles occurred. The solids were washed with alcoholic hydrogen chloride and then with a little alcohol. Concentration of the mother-liquor gave a further crop. The product was dissolved in hot water and the clear yellow, cold solution made alkaline with sodium hydroxide, whereupon the *base* separated as a crystalline mass, an ethereal solution of which was dried and concentrated to about 10 c.c. Long, prismatic needles (0·5 g.), m. p. 104—105°, separated. The mother-liquor afforded 1·4 g. of pale yellow material which, crystallised from alcohol, has m. p. 104—105°. After adsorption on alumina and elution with benzene the m. p. of the colourless, prismatic needles was still 104—105° (Found: C, 80·5; H, 5·8; N, 13·4. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·4%).

The *hydrochloride* crystallised from water and from ethanol as yellow needles, m. p. 250—260°,

giving intense yellow solutions (Found : C, 68·8; H, 5·1. $C_{14}H_{13}N_2Cl$ requires C, 68·7; H, 5·4%). The *picrate* crystallised from ethanol, in which it is sparingly soluble, as elongated, yellow plates, m. p. 206—207° (Found : C, 54·6; H, 3·3. $C_{20}H_{15}O_7N_5$ requires C, 54·9; H, 3·5%). The methiodide was prepared by heating the base and an excess of methyl iodide in a little boiling acetone for several hours. The crystalline residue left after evaporation was recrystallised from methanol and then from ethanol, giving large, orange prisms, m. p. 205—206° (Found : C, 51·8; H, 4·2. $C_{14}H_{12}N_2,CH_3I$ requires C, 51·4; H, 4·3%).

3-*Ethyl*-2-2'-*pyridylindole* (III; R = Et).—Crude propyl 2-pyridyl ketone (3·3 g.; b. p. 217—223°) was prepared by the dry distillation of a mixture of calcium picolinate and calcium butyrate. Without further purification the ketone was mixed with ether (20 c.c.) and phenylhydrazine (2·4 g.). The solution was kept overnight, and then concentrated on the steam-bath and the sides of the vessel rubbed with a glass rod. When crystallisation commenced, the mixture was cooled and filtered and the solid (1·6 g.) washed with ether until almost colourless; it had m. p. 90—92° (Engler and Majmon, *Ber.*, 1891, **24**, 2536, report m. p. 82°); a further 1·3 g. were obtained from the mother-liquor. An alcoholic solution of the phenylhydrazone was saturated with hydrogen chloride at 0°, kept at room temperature for 2 hr., and then refluxed on the steam-bath for 1 hr. The difficultly soluble hydrochloride, together with ammonium chloride, separated after ½ hr. The greater part of the alcohol was removed under diminished pressure and the mixture was cooled and kept until crystallisation was complete. The product was washed with a little alcoholic hydrogen chloride, dissolved in hot water containing a few drops of hydrochloric acid, and made alkaline with sodium hydroxide. The *base* was collected by means of ether and recrystallised twice from ethanol. It formed large prisms, m. p. 75—76° (Found : C, 80·8; H, 6·5; N, 12·7. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·4; N, 12·6%).

The *hydrochloride* crystallised from ethanol in small, yellow needles, m. p. 219—220° (Found : C, 69·1; H, 6·0. $C_{15}H_{15}N_2Cl$ requires C, 69·6; H, 5·8%). It gave yellow solutions which became turbid on dilution with water. The *picrate* crystallised from ethanol in yellow plates, m. p. 205° (Found : C, 55·9; H, 3·6. $C_{21}H_{17}O_7N_5$ requires C, 55·9; H, 3·8%). The *methiodide*, prepared in acetone as above, was thoroughly washed with acetone and crystallised from ethanol as yellow prisms, m. p. 206—207° (decomp.) (Found : C, 52·6; H, 4·5. $C_{15}H_{14}N_2,CH_3I$ requires C, 52·8; 4·7%).

2-*Methyl*-6-*phenylpyridine*-3 : 4-*dicarboxylic Acid*.—(*a*) A solution of ethyl benzoylpyruvate (44 g.) and ethyl β-aminocrotonate (26 g.) in ether (80 c.c.) was kept at 0° for 24 hr. and at room temperature for a further 24 hr. Large crystals were deposited, which were washed with a little ether. The *substance* melted at 113—114° with vigorous decomp. (Found : C, 61·8; H, 6·7; N, 3·8. $C_{18}H_{23}O_6N$ requires C, 61·8; H, 6·6; N, 4·0%). Mumm and Böhme (*Ber.*, 1921, **54**, 726) state that this adduct has m. p. 148°.

On recrystallisation from methanol or ethanol, in which solvents the substance is difficultly soluble, only a small amount of the material, m. p. 142—143° (decomp.), was recovered (Found : C, 61·9; 6·9; N, 3·6%).

From the alcoholic mother-liquor, on concentration, long needles of the condensation product, m. p. 74—75°, were obtained (see below).

The ethereal filtrate, after removal of the adduct, was evaporated to dryness, leaving a semi-crystalline mass (40 g.), which was combined with the addition product and heated at 130° for 1 hr. Smooth separation of water occurred. The residue was cooled and on crystallisation from ethanol gave white, silky rods (25 g.), m. p. 74—75° (Found : C, 69·1; H, 6·3; N, 4·0. Calc. for $C_{18}H_{19}O_4N$: C, 69·0; H, 6·1; N, 4·4%).

(*b*) Ethyl benzoylpyruvate (22 g.) and ethyl β-aminocrotonate (13 g.) were fused together at about 30° and then kept at the room temperature for 24 hr. Some heat was evolved at first; after 4—5 hr., the whole crystallised. A sample washed with a little ethanol had m. p. 113° (decomp.). The solid was ground with a little ethanol, collected, dried, and then heated at 130°. The product (13 g.) had m. p. 74—75°. This ester was hydrolysed with 10% methanolic potassium hydroxide, at just below the b. p. for 2 hr. The sparingly soluble potassium salt separated after 10 min. Next day the solid was collected, washed with methanol and with ether, and dissolved in a little water, and the solution acidified to Congo-red with hydrochloric acid. The white crystalline acid which separated was washed with water and crystallised from aqueous formic acid, giving white, prismatic needles, m. p. 219° (decomp.) (Found : C, 65·1; H, 4·5; N, 5·5. Calc. for $C_{14}H_{11}O_4N$: C, 65·4; H, 4·3; N, 5·4%). When heated with resorcinol an orange-brown melt was produced and this dissolved in aqueous sodium hydroxide to a cherry-red solution, exhibiting an intense green fluorescence.

The *phenylimide* was obtained in quantitative yield by boiling the dicarboxylic acid with

aniline for 10 min. It was crystallised from benzene and then from ethanol, in which it is sparingly soluble, and obtained as long rods, m. p. 192—193° (Found : C, 76·2; H, 4·6. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·5%).

2-Methyl-6-phenyl-3 : 4-di(hydroxymethyl)pyridine.—A solution of ethyl 2-methyl-6-phenylpyridine-3 : 4-dicarboxylate (15 g.) in ether (100 c.c.) was added dropwise with stirring during 2 hr. to an ethereal solution (200 c.c) of lithium aluminium hydride (*ca.* 8·5 g.) (prepared according to Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199) with usual precautions. An insoluble double compound separated as a viscous oil, and heat was evolved. The stirring was continued for a further ½ hr. Then, with external ice-cooling, ether, saturated with water, was added with stirring, followed by water and finally 10% aqueous sodium hydroxide (300 c.c.). The ethereal layer was dried and evaporated (residue, 10 g., chiefly unchanged ester). The filtered aqueous layer was extracted twice with chloroform (200 c.c.). After concentration of the solution slender colourless needles separated, having m. p. about 95° with softening from 80°. The material collected from the aqueous layer was extracted with hot water and, on cooling, long needles separated, and these showed the same behaviour on heating. The substance is soluble in hot water, hot chloroform, alcohol, and dilute hydrochloric acid, and is difficultly soluble in ether. It crystallises from water, aqueous methanol, or benzene–ethyl acetate, in all cases as fine needles, without a sharp m. p. The *picrate* crystallised from methanol as stout, yellow rods, m. p. 174—175° (decomp.) (Found : C, 52·6; H, 4·1; N, 12·4. $C_{20}H_{18}O_9N_4$ requires C, 52·4; H, 4·0; N, 12·2%).

Ethyl 3-Acetyl-2-methyl-6-phenylpyridine-4-carboxylate.—A mixture of ethyl benzoylpyruvate (22 g.) and 4-aminopent-3-en-2-one (10 g.) was kept for 4 days. Alcoholic picric acid (22 g.; 50 c.c.) was then added; large, yellow prisms (7 g.), m. p. 288° (decomp.), consisting of ammonium picrate separated during 2 days (Found : C, 29·6; H, 2·4; N, 22·7. Calc. for $C_6H_6O_7N_4$: C, 29·3; H, 2·4; N, 22·8%). The alcoholic filtrate was concentrated and the residue shaken with aqueous ammonia and ether. The ethereal layer was washed with aqueous ammonia, dried, and evaporated, leaving a residue, which was triturated with a little alcohol. The white needles so obtained had m. p. 65—66°, unchanged on recrystallisation from ethanol (Found : C, 72·0; H, 6·3; N, 4·7. $C_{17}H_{17}O_3N$ requires C, 72·1; H, 6·0; N, 4·9%). A further quantity of the *pyridine derivative* was recovered from the mother-liquor (total, 6·5 g.). It is readily soluble in ether, moderately readily soluble in alcohol and hot light petroleum. A somewhat better yield was obtained when a mixture of the generators was kept for 10 days and anhydrous sodium sulphate added after 4 days.

3-Acetyl-2-methyl-6-phenylpyridine-4-carboxylic Acid.—The foregoing ester (2 g.) was hydrolysed by 10% methanolic potassium hydroxide (8 c.c.). The separated potassium salt (long, white needles) was dissolved in water (5 c.c.), acetic acid (1 c.c.) added, and the mixture extracted with ether. Evaporation of the dried extract left a viscous liquid containing some acetic acid, which was washed with a little water by decantation, and the product crystallised from 50% formic acid, from which it separated very slowly as rhombic needles. The air-dried substance had m. p. 163—164·5° after slight softening (Found : C, 70·1; H, 5·1; N, 5·4. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%). The methanolic mother-liquor was worked up to yield more of the same *acid* (total, 1·0 g.).

An aqueous solution of iodine was added to the keto-acid (0·6 g.) dissolved in dioxan (20 c.c.) and 10% aqueous sodium hydroxide (6 c.c.) until iodine remained in excess. After 3 hours' heating on the steam-bath the solution was concentrated to about 15 c.c., acidified with a slight excess of sulphuric acid (the precipitate formed redissolved), and filtered from a gum. Sodium hydroxide solution was added until the precipitate redissolved, and the solution was carefully acidified until no more turbidity appeared. The product crystallised on concentration of a dried ethereal solution. It was recrystallised from aqueous formic acid, and had m. p. 219° (decomp.) alone or mixed with 2-methyl-6-phenylpyridine-3 : 4-dicarboxylic acid.

1 : 6-Dihydro-3 : 2'-dimethyl-6-oxo-1 : 6'-diphenylpyridino(3' : 4'-4 : 5)pyridazine.—Equivalent quantities of ethyl 3-acetyl-2-methyl-6-phenylpyridine-4-carboxylate and phenylhydrazine were heated in a little ethanol on the steam-bath for ½ hr. After trituration with a little ether the crystals were collected, washed with ether, and recrystallised from benzene and from ethanol; the *base* formed long, white needles, m. p. 182—183°, sparingly soluble in ethanol (Found : C, 77·1; H, 4·8; N, 13·0. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2; N, 12·9%).

Similarly with hydrazine the keto-ester afforded *1 : 6-dihydro-3 : 2'-dimethyl-6-oxo-6'-phenylpyridino(3' : 4'-4 : 5)pyridazine* which is sparingly soluble in most solvents but crystallised from ethanol (0·5 g. in 100 c.c.); it had m. p. 261—262° (Found : C, 7·1; H, 5·0; N, 17·1. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

4 : 5-*Diethyl-2-methyl- and* 4 : 5-*diethyl-2-styrylpyridine Picrates.*—Zinc dust (35 g.) (activated by acid, washed with water and acetone, and dried *in vacuo*) was added during 3 hr. to a mixture of acetic anhydride (170 c.c.) and 5-ethyl-2-methylpyridine (50 g.) which was vigorously stirred at 50°. Acetic acid (35 c.c.) was added, and another portion of zinc (15 g.) was added gradually, after which the solution was refluxed for 2 hr. The basified solution was steam-distilled and a litre of distillate was collected. This was acidified with hydrochloric acid and concentrated to about 150 c.c. The *base* was then set free and isolated by means of ether. About 28 g. of recovered 5-ethyl-2-methylpyridine distilled up to 200°. Further distillation under diminished pressure gave fractions : (3·0 g.) b. p. 74—80°/25 mm., (1·0 g.) b. p. 88—102°/25 mm., and the desired 4 : 5-diethyl derivative (2·5 g.), b. p. 102—104°/25 mm. (Found : 78·8; H, 10·2; N, 9·4. Calc. for $C_{10}H_{15}N$: C, 80·5; H, 10·3; H, 9·4%). The base (0·5 g.) was mixed with picric acid (1 g.) in ethanol (6 c.c.), giving a yellow crystalline *picrate* (0·5 g.) which, recrystallised thrice from ethanol, had m. p. 165—167° (Found : C, 51·2; H, 4·8; N, 14·7. $C_{16}H_{18}O_7N_4$ requires C, 50·8; H, 4·8; N, 14·8%).

A mixture of the crude 4 : 5-diethyl-2-methylpyridine (2·0 g,), benzaldehyde (5 c.c.), and zinc chloride (1 g.) was refluxed under nitrogen for 4 hr. The yellow product (0·5 g.), isolated in the known manner, did not solidify. From alcohol–ether solution it gave a *picrate* which, thrice recrystallised from methanol, formed yellow prisms, m. p. 143—144° with previous softening (Found : C, 59·3; H, 4·8; N, 11·6. $C_{23}H_{22}O_7N_4$ requires C, 59·2; H, 4·8; N, 12·0%).

3-(2-cyclo*Hexylacetamidoethyl*)*indole.*—A mixture of tryptamine hydrochloride (1·0 g.) and powdered potassium carbonate (2·1 g.) was suspended in ether (20 c.c.) and gently refluxed for ½ hr. *cyclo*Hexylacetyl chloride (0·92 g.) in ether (100 c.c.) was then added during an hour and refluxing continued for 8 hr. Evaporation of the ethereal solution left a viscous oil which solidified when rubbed. The solid (1·2 g.) was dissolved in benzene (charcoal), and the filtered solution concentrated to about 5 c.c., whereupon white needles, m. p. 82—83°, were deposited on keeping (0·5 g.). A further portion (0·1 g.) was obtained from the mother-liquor. The *amide* crystallised from aqueous methanol as colourless needles, m. p. 82—83° (Found : C, 75·2, 76·7; H, 8·5, 8·5; N, 9·7. $C_{18}H_{24}ON_2$ requires C, 76·1; H, 8·4; N, 9·9%).

2-cyclo*Hexylmethyl*-4 : 5-*dihydro*-β-*carboline.*—Phosphoric anhydride (7 g.) was gradually added, during 45 min., to a hot solution of 3-(2-*cyclo*hexylacetamidoethyl)indole (0·9 g.) in toluene (40 c.c.). The toluene layer was decanted and treated with another equal quantity of phosphoric anhydride as before. The combined solid residues were decomposed with ice and water, concentrated hydrochloric acid (5 c.c.) was added, and the whole digested on the steam-bath until the aqueous layer became clear. The gum that remained was treated with further dilute hydrochloric acid. The combined acid solution (200 c.c.) was washed with ether and then made strongly alkaline with potassium hydroxide. The mixture was extracted twice with ether, and the ethereal layer dried and concentrated to a small volume; fine needles (50 mg.) separated, m. p. 166—169° to a turbid oil becoming completely clear at 174°. The ethereal mother-liquor was evaporated to dryness, leaving pale yellow crystals (0·1 g,) of the *carboline* which, after two recrystallisations from methanol, had m. p. 172—174° with previous softening (Found : C, 81·0; H, 8·4. $C_{18}H_{22}N_2$ requires C, 81·1; H, 8·3%). A dilute acidic solution exhibited a strong green fluorescence.

The *methiodide* was prepared in acetone. The solution at once developed a green fluorescence and was kept for a day; on slow evaporation, large greenish prisms separated, having m. p. 238—240° (Found : C, 55·8; H, 6·3. $C_{18}H_{22}N_2,CH_3I$ requires C, 55·9; H, 6·2%).

2-cyclo*Hexylmethyl*-β-*carboline* (I; R = R′ = H).—*cyclo*Hexylmethyldihydro-β-carboline (140 mg.) and selenium (70 mg.) were heated together at 300° for 10 min. The light brown melt was extracted repeatedly with ether. The ethereal solution which showed a strong fluorescence was concentrated to about 2 c.c. Four-sided plates, m. p. 195—197° (40 mg.), separated. In order to remove a trace of selenium which caused discoloration, a solution of the crystals in ether (15 c.c.) was filtered through a kieselguhr column and then concentrated to a small volume. The colourless crystals which separated had m. p. 198—199°; and m. p. 200° after recrystallisation from methanol (Found : C, 81·5; H, 7·5; N, 10·4. $C_{18}H_{20}N_2$ requires C, 81·8; H, 7·6; N, 10·6%).

The *picrate* crystallised from ethanol in yellow, prismatic needles, m. p. 250—261° (Found : C, 58·7; H, 4·8. $C_{24}H_{23}O_7N_5$ requires C, 58·4; H, 4·7%). The *methiodide*, prepared in acetone, formed large, yellow prisms which, recrystallised from acetone, had m. p. 260° (decomp.), after softening from 250° (Found : C, 56·9; H, 5·9. $C_{19}H_{20}N_2,CH_3I$ requires C, 56·1; H, 5·7%).

3-[2-(4′-*Methyl*cyclo*hexylacetamido*)*ethyl*]*indole.*—Tryptamine (0·5 g.; m. p. 113°; freshly prepared from its hydrochloride) was intimately mixed with 4-methyl*cyclo*hexylacetic acid

(0·5 g.) and heated at 180—190° for ½ hr. The melt darkened slightly and solidified on cooling. It was crushed and repeatedly triturated with ether. A small amount (0·2 g.) of insoluble crystalline material remained (soluble in water and probably tryptamine methyl*cyclo*hexylacetate) and the ethereal solution was filtered (charcoal) and evaporated to dryness. The residue (0·7 g.) crystallised from benzene as prismatic needles, m. p. 68—75° with softening from 60° and becoming completely clear at 80° (Found: C, 76·3; H, 8·3; N, 9·4. $C_{19}H_{26}ON_2$ requires C, 76·5; H, 8·8; N, 9·4%).

2-(4'-*Methyl*cyclo*hexylmethyl*)-β-*carboline* (I; R = H, R' = Me).—Phosphoric anhydride (15 g.) was added portionwise to a gently boiling solution of 3-[2-(4'-methyl*cyclo*hexylacetamido)-ethyl]indole (1·5 g.) in benzene (40 c.c.), and the solid cake broken up from time to time with a glass rod. After 45 min., the benzene was decanted and the residue washed several times with benzene (a considerable amount of unchanged amide could be recovered from the benzene). The phosphoric complex was decomposed by crushed ice, concentrated hydrochloric acid (5 c.c.) was added, and the whole digested on the steam-bath until a clear solution resulted. The solution was then decanted from the insoluble gum, which was again treated with hydrochloric acid as before. The combined acid solution was washed with ether and made alkaline with potassium hydroxide. The liberated base, isolated by means of ether, crystallised from light petroleum as long, pale yellow needles, m. p. 157—159° with softening from 150°. The substance closely resembled the lower homologue and was submitted to dehydrogenation without further purification.

The dihydro-carboline (0·2 g.) was intimately mixed with selenium (0·1 g.) and heated with stirring at 295—300° for 10 min. The dark cake was broken up and repeatedly triturated with ether. The extract was filtered through kieselguhr to remove colloidal selenium, and then concentrated to a small volume, from which crystals separated (50 mg.). The *compound* recrystallised from a little methanol as colourless prisms, m. p. 204—205° (Found: C, 82·0; H, 8·4. $C_{19}H_{22}N_2$ requires C, 81·9; H, 8·0%). The *picrate* crystallised from ethanol as yellow needles, m. p. 235—236° (Found: C, 58·9; H, 5·0. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0%).

2-*Methyl*cyclo*hexylacetic Acid*.—It was found that ethyl 1-hydroxy-2-methyl*cyclo*hexylacetate (Auwers and Ellinger, *Annalen*, 1912, **397**, 230) was most conveniently dehydrated by treatment with thionyl chloride and pyridine at 0° in ether. The product had b. p. 120—122°/35 mm. The unsaturated ester was hydrogenated over Adams catalyst and hydrolysed. 2-Methyl*cyclo*hexylacetyl chloride (by thionyl chloride) had b. p. 105—106°/35 mm. With ammonia it furnished the amide which crystallised from benzene in glistening needles, m. p. 155—156°, unchanged by recrystallisation. For the amide of this acid (made in a different manner), Wallach (*Annalen*, 1912, **394**, 322) gave m. p. 160—161° and Mousseron and Winternitz (*Bull. Soc. chim. France*, 1946, 604) gave m. p. 149—150°.

3-[2-(2'-*Methyl*cyclo*hexylacetamido*)*ethyl*]*indole*.—This compound was prepared by condensing tryptamine with either 2-methyl*cyclo*hexylacetyl chloride or with the acid itself. The product (crude, m. p. 105—108°), when recrystallised twice from benzene, formed colourless, prismatic needles, m. p. 110—111° (Found: C, 76·1; H, 8·7; N, 9·3. $C_{19}H_{26}ON_2$ requires C, 76·4; H, 8·8; N, 9·4%).

4 : 5-*Dihydro*-2-(2'-*methyl*cyclo*hexylmethyl*)-β-*carboline*.—Phosphoric anhydride (10 g.) was added to a solution of the above tryptamide (1·0 g.) in refluxing benzene (40 c.c.) during 1½ hr., and the whole refluxed for another 2 hr. The *product* was worked up as in the previous examples and eventually crystallised from ether as elongated prisms, m. p. 190—192° (Found: C, 81·0; H, 8·6; N, 10·5. $C_{19}H_{24}N_2$ requires C, 81·4; H, 8·6; N, 10·0%).

2-(2'-*Methyl*cyclo*hexylmethyl*)-β-*carboline* (I; R = Me, R' = H).—The preceding base (0·14 g.) and selenium (70 mg.) were heated at 295—300° for 10 min. with constant stirring. The *product*, isolated as above, crystallised from ethanol as prismatic needles, m. p. 215° (Found: C, 81·9; H, 7·5; N, 10·4. $C_{19}H_{22}N_2$ requires C, 82·0; H, 8·0; N, 10·1%). The acid solutions of this base exhibited the usual blue-violet fluorescence. The *picrate* crystallised from ethanol as greenish-yellow prisms, m. p. 233—234° (Found: C, 59·4; H, 5·1. $C_{25}H_{25}O_7N_5$ requires C, 59·2; H, 5·0%).

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