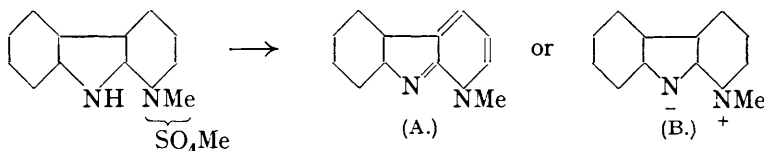


381. Some Derivatives of 3-Carboline.

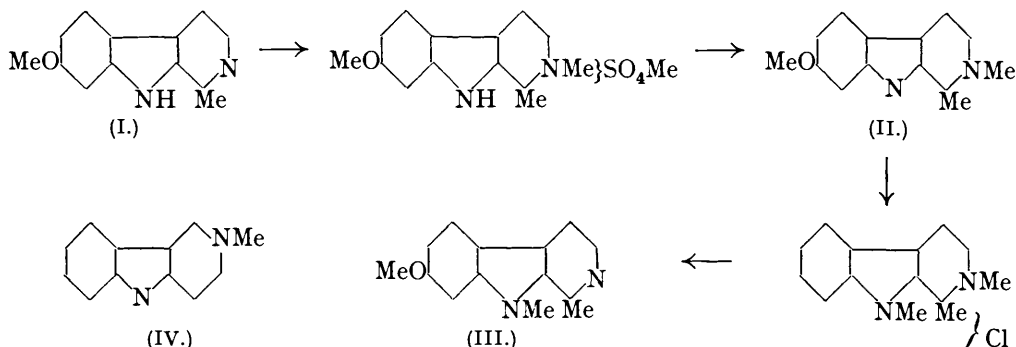
By R. H. FREAK and ROBERT ROBINSON.

The method of preparation of 3-carboline has been improved, and the behaviour of the base on alkylation studied. 1-2'-Pyridyl-1 : 2 : 3-benzotriazole is decomposed with formation of 3-carboline when it is heated in syrupy phosphoric acid solution. The metho-salts of the colourless base are decomposed by alkalis with formation of yellow 3-methyl-3-isocarboline.



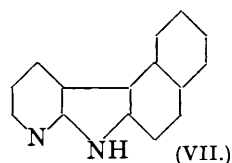
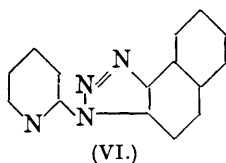
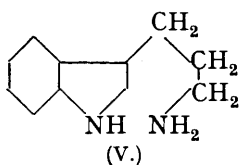
Alkylation of methylisocarboline involves attack of the centrally situated nitrogen atom and the sequence is analogous to that observed in the glyoxaline, pyrazole, and harmine series. Methylisocarboline is a typical anhydronium base and, as suggested by Armit and Robinson (J., 1925, 127, 1604), the constitutions of all such substances are not to be expressed by either of the formulæ types (A) and (B), but by an intermediate form, in fact by what is now termed a resonance hybrid. The opposing tendencies resulting in a compromise are clear enough in these cases; they are the tendency of (A) to render the heterocyclic nuclei aromatic and the tendency of (B) to effect neutralisation of the betaine charges by electromeric displacements.

ACCORDING to the current theory of heterocyclic aromatic nuclei (cf. J., 1917, 111, 964; 1918, 113, 640; 1919, 115, 943; 1921, 119, 1607; 1922, 121, 437, 827) the tertiary nitrogen atom of pyrazole and glyoxaline is of pyridine nitrogen function and is the seat of the basic character; alkylation, for example, occurs at this point and is not a substitution reaction of the imino-groups. The same view applies when the aza- and imino-centres are in separate nuclei as in the carbolines. In the case of harmine (I) precise experimental proof is available showing that the following scheme is valid (Kermack, Perkin, and Robinson, J., 1922, 121, 1872; Iyer and Robinson, J., 1934, 1636) :



Methylharmine (II) is a yellow base, quite different in character from harmine, but *ind-N*-methylharmine (III) resembles the parent substance. Methylation of 5-carboline also affords a yellow base of the *iso*-series (IV) (Robinson and Thornley, J., 1924, 125, 2169) and we have now found that 3-carboline behaves in the same way (formulæ in the summary above). So far as we are aware, 6-carboline has not yet been prepared, but quindoline is a derivative of it and this also is alkylated under neutral conditions at the tertiary nitrogen atom. (In the presence of strong bases quindoline is alkylated at the secondary nitrogen, but this is probably consequent on the removal of a proton.) Thus all the carbolines behave in a similar fashion on alkylation. The two nitrogen atoms of 3-carboline are alkylated successively, because two different methylethyl-3-carbolinium iodides are

produced depending on the order of introduction of the methyl and ethyl groups. On reduction with sodium and butyl alcohol 3-carboline affords 3- γ -aminopropylindole (V) along with other products.



2-Chloropyridine and 1 : 2-diaminonaphthalene condense with formation of an aminonaphthylaminopyridine and it is assumed that the β -amino-group of the naphthylene-diamine has entered into the reaction. This is very probable because β -naphthylamine is a stronger base than α -naphthylamine and moreover the α -amino-group is the more subject to "hindrance." The corresponding isotriazole is (VI), and when this is heated with phosphoric acid, 9 : 10-benzo-3-carboline (VII) is obtained.

EXPERIMENTAL.

3-Carboline.—The following method was indicated by Robinson and Thornley (J., 1924, 125, 2169), but no details were given. 1-2'-Pyridyl-1 : 2 : 3-benzotriazole (5 g.), mixed with syrupy phosphoric acid (25 c.c., *d* 1.8), was heated until the vigorous evolution of nitrogen ceased; the mixture was then allowed to cool. A hot solution of picric acid (10 g.) in alcohol (150 c.c.) and then hot water (50 c.c.) were added and, after cooling, the precipitated picrate was collected and washed with warm water. It was decomposed by heating with aqueous sodium hydroxide (250 c.c. of 8%), the base collected and dissolved in a little dilute hydrochloric acid, and the filtered solution kept for a few hours. The hydrochloride, which crystallised, was collected, dissolved in water, and basified with ammonia. The 3-carboline crystallised from alcohol or toluene in colourless needles (1 g.), m. p. 211°.

3-Carboline Methosulphate.—A solution of pure methyl sulphate (2.0 g., b. p. 74—76°/13 mm.) in pure dry toluene (10 c.c.) was gradually added to one of 3-carboline (1.0 g.) in hot dry toluene (50 c.c.). The salt, which separated, crystallised from hot acetone (50 c.c.), to which just sufficient methyl alcohol had been added to bring about complete solution, in flat, nearly square, prisms, m. p. 204—205°. Long prismatic needles were obtained from the mother-liquor (m. p. 201—202°; mixed m. p., 199—203°). On one occasion this form was deposited first and changed into the flat prisms in contact with the solvent (Found in material dried at 105° in a vacuum : C, 53.5; H, 4.8. $C_{13}H_{14}O_4N_2S$ requires C, 53.1; H, 4.8%).

The *methiodide*, formed by the action of sodium iodide on the methosulphate in aqueous solution, crystallised from water in long needles, which were dried at 100° and then had m. p. 208° (Found in material dried for a long time at 120° in a high vacuum : C, 46.6; H, 3.9; N, 9.0. $C_{12}H_{11}N_2I$ requires C, 46.5; H, 3.5; N, 9.0%).

3-Methyl-3-isocarboline (A).—Addition of sodium hydroxide to an aqueous solution of the methosulphate precipitated a yellow oil, which crystallised on trituration. It was found best to isolate the substance by means of ether, in which, however, it was rather sparingly soluble. The base separated in bright yellow crystals on slow evaporation of its solution in acetone; m. p. 138—139° after softening from 135° (Found in material dried at 100° without loss of weight : C, 79.1; H, 5.5. $C_{12}H_{10}N_2$ requires C, 79.1; H, 5.5%).

3-Methyl-1-ethylcarbolinium Iodide.—This salt was formed by the union of 3-methyl-3-isocarboline and ethyl iodide (excess) in hot benzene solution. It separated from alcohol in almost colourless, prismatic needles, m. p. 195° (Found in material dried at 120° : C, 49.7, 49.4; H, 4.9, 4.8; N, 8.0. $C_{14}H_{15}N_2I$ requires C, 49.7; H, 4.4; N, 8.3%). Treatment of an aqueous solution of this salt with sodium hydroxide affords no base soluble in benzene, ether or ethyl acetate. In the preparation of this substance, a small quantity of a much more sparingly soluble salt was obtained, m. p. 232° (Found : C, 49.6; H, 4.7%). The constitution of this iodide has not been ascertained.

3-Carboline ethosulphate, prepared like the methosulphate, ethyl sulphate being used, crystallised from acetone in long prisms, m. p. 114—115° (Found : C, 55.6; H, 5.6. $C_{13}H_{18}O_4N_2S$ requires C, 55.9; H, 5.6%).

3-Ethyl-3-isocarboline, obtained from the ethosulphate by the action of sodium hydroxide in aqueous solution, was a bright yellow substance, readily soluble in alcohol, acetone, benzene

and chloroform. It crystallised in flat square plates, m. p. 102°, from chloroform–light petroleum (Found: C, 79.4; H, 6.4; N, 13.6. $C_{13}H_{13}N_2$ requires C, 79.6; H, 6.1; N, 14.3%). The base dissolved readily in dilute sulphuric acid and the addition of sodium iodide precipitated 3-carboline ethiodide, which was also obtained from the above ethosulphate in a similar manner. The salt crystallised from water or alcohol in long prisms, m. p. 199–200° (Found: C, 48.1; H, 4.1; N, 8.5. $C_{13}H_{13}N_2I$ requires C, 48.3; H, 4.0; N, 8.6%).

1-Methyl-3-ethylcarbolinium Iodide.—3-Ethyl-3-carboline was brought into reaction with methyl sulphate (2 mol.) in hot dry toluene solution and the product, which was easily soluble in water and methyl alcohol, was directly converted into the iodide in the usual way. This was crystallised four times from water, a coloured by-product separating first. The larger crystals of the salt had a somewhat higher m. p. than the smaller ones; the highest value observed was 209.5° (sharp) (Found: C, 49.5; H, 4.7; N, 8.2. $C_{14}H_{16}N_2I$ requires C, 49.7; H, 4.4; N, 8.3%).

Reduction of 3-Carboline. Formation of 3- γ -Aminopropylindole.—A number of experiments on the reduction of the base by means of sodium (excess) and butyl alcohol were conducted in test-tubes, and the products combined. The solutions, which became yellow and then colourless, a stage which was taken to indicate the completion of the reaction, were rendered acid by means of dilute hydrochloric acid and extracted with benzene–ether. The extract was found by the Ehrlich test to contain a neutral indole derivative, probably 3-propylindole. The aqueous solutions were concentrated in a vacuum and basified, and the base isolated by means of ether; it gave a strong Ehrlich reaction. The oily product, when heated with an approximately equal weight of phthalic anhydride, afforded phthalo- γ -3'-indolylpropylimide, which was washed with ether, crystallised from alcohol, and obtained in plates, m. p. 132° alone or mixed with a specimen prepared by the method of Jackson and Manske (*J. Amer. Chem. Soc.*, 1930, 52, 5029).

1:2-Diaminonaphthalene.—The method of Bamberger and Schieffelin (*Ber.*, 1889, 22, 1376) has been modified as follows. Aniline (90 g.) was diazotised, and the product coupled with β -naphthylamine in aqueous alcoholic solution in the presence of sodium acetate. The moist azo-compound, pressed as far as possible, weighed 400 g. This product (40 g.) was dissolved in boiling acetic acid (1000 c.c. of 20%), and zinc dust added until a clear golden-yellow solution resulted and dark oily drops had disappeared. The filtered solution was mixed with dilute sulphuric acid, the separated sulphate basified with aqueous sodium hydroxide (150 c.c. of 10%) in the presence of a little sodium hyposulphite, and the base distilled; b. p. 150–170°/1 mm., m. p. 95–96°.

3-2'-Pyridyl- β -naphthaisotriazole (VI).—A mixture of 2-chloropyridine (38 g.) and 1:2-naphthylenediamine (53 g.) was heated (oil-bath at 140–150°) under 100 mm. for 9 hours; the mass then became viscous. After cooling, the clear brittle solid was dissolved in alcohol, concentrated hydrochloric acid (50 c.c.) added, and sodium nitrite (20 g.), dissolved in a little water, gradually introduced with stirring. The precipitate (50 g.) was collected, washed with alcohol, and dried. The isotriazole crystallised from alcohol in pale brownish, thick needles, m. p. 159° (Found: C, 73.3; H, 4.4; N, 22.9. $C_{15}H_{10}N_4$ requires C, 73.2; H, 4.0; N, 22.8%).

9:10-Benzo-3-carboline (VII).—A mixture of the above pyridynaphthaisotriazole (5 g.) and phosphoric acid (30 c.c., previously concentrated by heating until the temperature of the liquid reached 220°) was heated at 160–170°/12 mm. Owing to frothing the pressure had to be increased towards the end of the operation. The product was cooled, a hot solution of picric acid (8 g.) in alcohol (200 c.c.) added, and the yellow picrate collected; after three crystallisations from nitrobenzene, it had decomp. 300° (Found: C, 56.6; H, 3.1; N, 15.8. $C_{15}H_{10}N_2C_6H_3O_7N_3$ requires C, 56.4; H, 2.9; N, 15.7%). The picrate was decomposed with aqueous sodium hydroxide at 90°, and the base isolated; it crystallised from alcohol and from toluene in colourless needles, m. p. 256° (Found: C, 82.2; H, 4.9; N, 13.0. $C_{15}H_{10}N_2$ requires C, 82.6; H, 4.6; N, 12.8%). The hydrochloride was a pale yellow, microcrystalline powder; the hydrogen oxalate crystallised from alcohol in long thin prisms; the hydrogen tartrate crystallised from alcohol in bunches of feathery crystals consisting of irregular elongated prisms.

The reduction of the base with sodium and butyl alcohol was investigated, but no pure compounds could be isolated. Evidence was obtained that neutral and basic naphthindole derivatives were formed.