Hydroxytryptamines. Part III. Synthesis of an Azepindole Derivative by Molecular Rearrangement.*

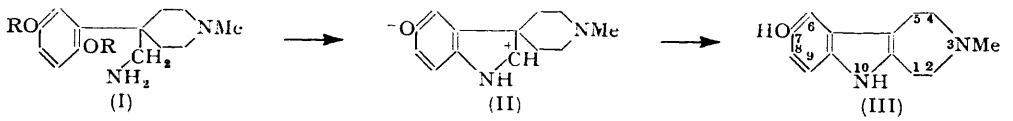
By JOHN HARLEY-MASON and A. H. JACKSON.

[Reprint Order No. 5748.]

Oxidation of 4-aminomethyl-4-(2 : 5-dihydroxyphenyl)-1-methylpiperidine gives 1 : 2 : 3 : 4 : 5 : 10-hexahydro-7-hydroxy-3-methylazep[4, 5-*b*]-indole † (III) by molecular rearrangement.

IN extension of earlier work* on the synthesis of hydroxytryptamine derivatives of physiological interest, 4-aminomethyl-4-(2 : 5-dihydroxyphenyl)-1-methylpiperidine was oxidised in an attempt to prepare a hydroxy*spiro*indolenine related to the oxindole derivatives obtained earlier by Kretz, Müller, and Schlittler (*Helv. chim. Acta*, 1952, **35**, 520).

2 : 5-Dimethoxybenzyl cyanide was alkylated with di-(2-chlorethyl)methylamine (cf. Eisleb, *Ber.*, 1941, **74**, 1433) to give 4-cyano-4-(2 : 5-dimethoxyphenyl)-1-methylpiperidine which was then reduced to 4-aminomethyl-4-(2 : 5-dimethoxyphenyl)-1-methylpiperidine (I; R = Me). Demethylation with hydrobromic acid gave the dihydroxy-amine (I; R = H). Oxidation with potassium ferricyanide gave a product isolated in high yield which had the composition of the expected indolenine. However, its properties were at variance with this type of structure; in particular it remained unchanged after prolonged



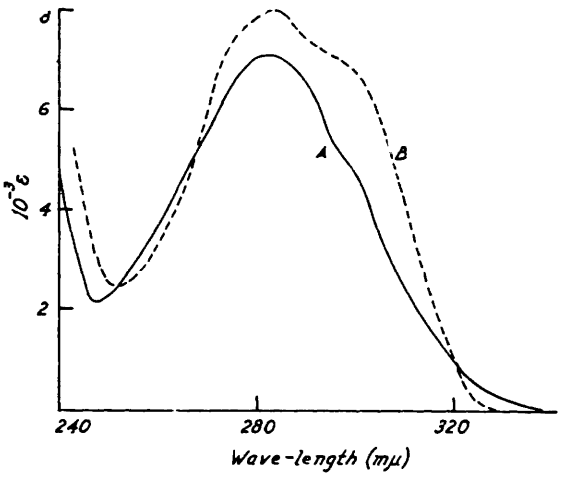
(I) (II) (III)

treatment with acid, and the alkaline solution showed little tendency to undergo autoxidation. The ultra-violet absorption spectrum (Figure) was clearly that of an indole and not an indolenine, and was in fact very similar to that of 5-hydroxy-2 : 3-dimethylindole prepared for comparison. Evidently therefore rearrangement had occurred, analogous to the Plancher rearrangement of 3 : 3-disubstituted indolenines in hot acid, and the product was 1 : 2 : 3 : 4 : 5 : 10-hexahydro-7-hydroxy-3-methylazep[4, 5-*b*]indole † (III). The unusual feature in the present case is that the rearrangement occurred in cold neutral solu-

* Parts I and II, *J.*, 1954, 1165, 3651.

† The name and state of hydrogenation accord with Ring Index principles (cf. R.I. no. 1788).

tion. It is suggested that a quinone imine intermediate is first formed (cf. Cromartie and Harley-Mason, *J.*, 1952, 2525); an oxidation–reduction rearrangement of this would lead to an intermediate (II) having an electron-deficient carbon atom at the indole 2-position, giving a favourable situation for rearrangement at the quaternary carbon atom, possibly further facilitated by electron release from the piperidine nitrogen atom. It is noteworthy that a similar situation arises in the intermediate obtained in the synthesis of (±)-eseroline (Part II, *loc. cit.*): in this earlier case, however, rearrangement of the carbon skeleton does not occur since the electron deficiency at the indole 2-position is satisfied by reaction with the second nitrogen atom giving another ring, a possibility which is on steric grounds absent in the presumed intermediate (II).



Ultra-violet absorption spectra of (*A*) 1 : 2 : 3 : 4 : 5 : 10-*hexahydro*-7-*hydroxy*-3-*methylazep*[4, 5-b]*indole* and (*B*) 5-*hydroxy*-2 : 3-*dimethylindole in* 95% *ethanol.*

Experimental

4-*Cyano*-4-(2 : 5-*dimethoxyphenyl*)-1-*methylpiperidine.*—Liquid ammonia (100 ml.) contained in a flask fitted with stirrer, condenser, and dropping funnel was treated with a small crystal of ferric nitrate followed by sodium (0·1 g.). When dissolution was complete, more sodium (2·3 g.) was added in small pieces and the solution stirred until all had dissolved. Dry ether (50 ml.) was then added and the ammonia was allowed to evaporate at room temperature. The ethereal suspension was treated with a solution of 2 : 5-dimethoxybenzyl cyanide (8·0 g.) (Part I, *loc. cit.*) in dry xylene (100 ml.), and the temperature raised slowly to 100°, the ether being distilled off. Heating and stirring were continued for a further 3 hr. until evolution of ammonia had ceased.

Meanwhile a solution of di-(2-chlorethyl)methylamine hydrochloride (9·0 g.) in water (20 ml.) was treated with 2N-sodium hydroxide (22 ml.) with stirring at 0°. The resulting solution was immediately saturated with solid potassium carbonate and extracted with xylene (3 × 50 ml.), and the extracts were dried (K_2CO_3). This solution was added slowly to the deep red suspension prepared as above. The well-stirred mixture was heated at 100° for 5 hr. After cooling, it was extracted with dilute hydrochloric acid (2 × 150 ml.), and the combined extracts were basified with aqueous sodium hydroxide, saturated with potassium carbonate, and extracted with ether (3 × 100 ml.). The ethereal extracts were dried (K_2CO_3), the ether was removed, and the residue distilled, yielding 4-*cyano*-4-(2 : 5-*dimethoxyphenyl*)-1-*methylpiperidine* (5·1 g., 45%) as a colourless highly viscous oil, b. p. 160—165°/0·7 mm. The *hydrochloride* formed prisms, m. p. 233—234° (decomp.; darkening above 220°), from ethanol–ether (Found: C, 60·4; H, 7·3; N, 9·6. $C_{15}H_{20}O_2N_2$,HCl requires C, 60·3; H, 7·1; N, 9·4%).

4-*Aminomethyl*-4-(2 : 5-*dihydroxyphenyl*)-1-*methylpiperidine* (I; R = H).—A solution of the amino-cyanide (4·5 g.) in ethanol (100 ml.) saturated with ammonia at 0° was hydrogenated over Raney nickel at 100°/80 atm. for 5 hr. The catalyst was filtered off, the solvent removed, and the residual oil taken up in ethanol and treated with ethereal hydrogen chloride. The amorphous precipitate formed at first, slowly crystallised, and after two recrystallisations from ethanol–ether yielded 4-*aminomethyl*-4-(2 : 5-*dimethoxyphenyl*)-1-*methylpiperidine dihydrochloride* (3·5 g., 60%) as prisms, m. p. 245—246° (decomp.) (Found: C, 50·2; H, 7·7; N, 8·0. $C_{15}H_{24}O_2N_2$,2HCl,H_2O requires C, 50·6; H, 7·9; N, 7·9%).

The dihydrochloride (3·0 g.) was refluxed with redistilled hydrobromic acid (*d* 1·49; 20 ml.) for 45 min. and the resulting solution diluted with water and evaporated to dryness on the water-bath under reduced pressure of hydrogen. The last traces of water and hydrobromic acid were removed by storage in a vacuum-desiccator over phosphoric oxide and sodium hydroxide, leaving the dihydroxy-diamine dihydrobromide as a light greenish-brown hygroscopic glass which did not crystallise.

1 : 2 : 3 : 4 : 5 : 10-*Hexahydro-7-hydroxy-3-methylazep*[4, 5-*b*]*indole* (III).—To a solution of the dihydroxy-diamine dihydrobromide (0·85 g.) in water (75 ml.), potassium ferricyanide (1·32 g.) and sodium hydrogen carbonate (0·67 g.) in water (75 ml.) were added slowly with stirring. After 10 min. a little sodium dithionite was added and after saturation with salt the light brown solution was extracted continuously with peroxide-free ether (200 ml.) under nitrogen for 2 days. During the extraction the product partly crystallised. After removal of the ether, the residue was extracted with boiling ethyl acetate (3 × 50 ml.), and these extracts on cooling slowly deposited the *azepindole* as colourless platelets. A further quantity was obtained by addition of light petroleum (b. p. 60—80°) to the ethyl acetate mother-liquors, the total yield being 0·34 g. (75%). A portion was sublimed at 150°/10 ^{4} mm., giving colourless prisms, m. p. 204—205° (Found: C, 72·1; H, 7·4; N, 13·0. $C_{13}H_{16}ON_2$ requires C, 72·3; H, 7·4; N, 13·2%). No reaction was given with Ehrlich's reagent or in the Hopkins–Cole glyoxylic acid test, indicating a 2 : 3-disubstituted indole. The ultra-violet absorption spectrum is recorded in the Figure, together with that of 2 : 3-dimethyl-5-hydroxyindole. The *dipicrate* formed orange prisms, m. p. 201—203° (decomp.), from aqueous ethanol (Found: C, 44·7; H, 3·8; N, 16·4. $C_{13}H_{16}ON_2,2C_6H_3O_7N_3$ requires C, 44·6; H, 3·3; N, 16·6%).

5-*Hydroxy*-2 : 3-*dimethylindole*.—5-Ethoxy-2 : 3-dimethylindole (Keimatsu and Sugasawa, *J. Pharm. Soc. Japan*, 1928, **48**, 348) (1 g.) was refluxed with hydrobromic acid (*d* 1·49; 15 ml.) for 40 min. After addition of water (50 ml.) the dark solution was boiled with charcoal, filtered, and extracted with ethyl acetate. The crude product remaining after removal of the solvent was purified by sublimation at 110°/10^{-4} mm., giving 5-*hydroxy*-2 : 3-*dimethylindole* as needles, m. p. 154—155° (Found: C, 74·3; H, 7·2; N, 9·2. $C_{10}H_{11}ON$ requires C, 74·5; H, 6·8; N, 8·9%).

One of us (A. H. J.) thanks the Department of Scientific and Industrial Research for a maintenance grant.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, September 22nd*, 1954.]