

## 17. 5-Hydroxyindole.

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5-Hydroxyindole has been synthesised by debenylation and decarboxylation of 5-benzyloxyindole-2-carboxylic acid, prepared from 2-nitro-5-hydroxytoluene and the corresponding phenylpyruvic acid.

ALTHOUGH hydroxyindoles are the parent compounds of a number of physiologically important substances, such as bufotenine, physostigmine and harmine, simple 5-hydroxyindoles have not yet been synthesised. For this reason, it also being borne in mind that these or the corresponding indolines may play an important part in adrenaline metabolism, 5-hydroxyindole has now been prepared by adapting the method used by Blaikie and Perkin (J., 1924, 125, 296) for the preparation of 5-methoxyindole-2-carboxylic acid to the preparation of the corresponding 5-benzyloxyindole-2-carboxylic acid.

2-Nitro-5-hydroxytoluene was benzyliated in the usual manner to give 2-nitro-5-benzyloxytoluene, which when condensed with ethyl oxalate in the presence of potassium ethoxide, followed by hydrolysis of the crude product, yielded 2-nitro-5-benzyloxyphenylpyruvic acid. Although not itself obtained analytically pure, the pyruvic acid formed a phenylhydrazone which gave correct analytical figures. The crude 2-nitro-5-benzyloxyphenylpyruvic acid on reduction with ferrous sulphate and ammonia yielded 5-benzyloxyindole-2-carboxylic acid.

An attempt to decarboxylate this substance not proving very successful, the benzyl group was first removed by catalytic hydrogenation, palladium-charcoal being used, giving 5-hydroxyindole-2-carboxylic acid, which on decarboxylation by heating with copper powder yielded the desired 5-hydroxyindole. The yields at all stages of this synthesis were very good until the final one, the hydroxyindole being obtained in only 10% yield from the carboxylic acid. The methyl ester of 5-hydroxyindole-2-carboxylic acid also was prepared by catalytic hydrogenation of the corresponding benzyloxy-compound.

## EXPERIMENTAL.

2-Nitro-5-benzyloxytoluene.—To a solution of sodium ethoxide (sodium, 3 g.; absolute alcohol, 100 c.c.), 2-nitro-5-hydroxytoluene (20 g.) and benzyl chloride (16.6 g.) were added, and the mixture refluxed on the water-bath for 8 hours. The alcohol was then distilled off, and the residue dissolved in ether and washed with water and dilute sodium hydroxide solution. From these aqueous solutions starting material (5 g.) was recovered. The washed ethereal solution yielded 2-nitro-5-benzyloxytoluene, m. p. 70–71° after two recrystallisations from light petroleum (b. p. 60–80°). Yield, 95% (Found: N, 5.8.  $C_{14}H_{13}O_3N$  requires N, 5.8%).

2-Nitro-5-benzyloxyphenylpyruvic Acid.—To potassium ethoxide, prepared from potassium (5.3 g.) in ether (150 c.c.) and absolute ethyl alcohol (6.2 g.), freshly distilled ethyl oxalate (19.6 g.) was gradually added, a clear yellow solution being formed. 2-Nitro-5-benzyloxytoluene (32.4 g.), dissolved in ether, was then added, the mixture left at room temperature for 60 hours, 4% sodium hydroxide solution (200 c.c.) added, and the whole shaken vigorously, left for 1 hour, and acidified. The red ethereal solution was repeatedly extracted with 4% sodium hydroxide solution, and the combined extracts washed once with ether, freed from ether, and acidified, 23.4 g. of 2-nitro-5-benzyloxyphenylpyruvic acid being precipitated. Starting material (5 g.) was recovered from the ethereal extracts. The crude acid could not be readily obtained pure by recrystallisation, the m. p. being always very vague (100–105°). The phenylhydrazone after recrystallisation from aqueous methyl alcohol had m. p. 152–153° (Found: N, 10.1.  $C_{22}H_{19}O_5N_3$  requires N, 10.4%).

5-Benzyloxyindole-2-carboxylic Acid.—The preceding acid (3.8 g.) was dissolved in 24 c.c. of a solution made from 17 c.c. of aqueous ammonia (d 0.880), a hot solution of ferrous sulphate (22 g.) in water (24 c.c.) added, and the mixture refluxed and shaken for 1 hour. The iron hydroxide was repeatedly extracted with hot dilute aqueous ammonia; the combined filtrates on acidification gave 5-benzyloxyindole-2-carboxylic acid, m. p. 193–194° after recrystallisation from dilute acetic acid. Yield, 70% (Found: N, 5.2.  $C_{16}H_{15}O_3N$  requires N, 5.2%).

Methyl 5-Benzyloxyindole-2-carboxylate.—(1) The acid (4 g.) was refluxed with 100 c.c. of 6% methyl-alcoholic hydrogen chloride for 4 hours, some of the alcohol distilled off, and water added. The methyl ester, which separated, had m. p. 150–151° after recrystallisation from methyl alcohol.

(2) The ester was also obtained by the action of an ethereal solution of diazomethane on the acid (Found: N, 4.8.  $C_{17}H_{15}O_3N$  requires N, 4.9%).

Methyl 5-Hydroxyindole-2-carboxylate.—25% Palladium-charcoal (0.4 g.), suspended in methanol (30 c.c.), was saturated with hydrogen and shaken with methyl 5-benzyloxyindole-2-carboxylate (1 g.) in methanol (100 c.c.) under slight pressure of hydrogen for 6 hours; 90 c.c. of hydrogen were absorbed (calc., 85 c.c.). The methanolic solution was filtered and concentrated; the product had m. p. 146–147° after recrystallisation from benzene. It gave a faint red colour on heating with the Ehrlich reagent, the colour disappearing on cooling. Yield, 80% (Found: N, 7.1.  $C_{10}H_9O_3N$  requires N, 7.3%).

5-Hydroxyindole-2-carboxylic Acid.—Palladium-charcoal (0.4 g.), suspended in methyl alcohol (50 c.c.), was saturated with hydrogen and shaken with a solution of 5-benzyloxyindole-2-carboxylic acid (1 g.) in methyl alcohol (100 c.c.) as described above, the theoretical amount of hydrogen being absorbed (90 c.c. in 40 minutes). The solution was filtered and evaporated to dryness in a vacuum, and the residue crystallised from water; it had m. p. 246° (decomp.). Yield, 70% (Found: N, 7.7.  $C_9H_7O_3N$  requires N, 7.9%).

5-Hydroxyindole.—5-Hydroxyindole-2-carboxylic acid (0.5 g.) was mixed with copper powder (0.5 g.) and heated at 250° for 10 minutes in an atmosphere of nitrogen. The product was distilled in a high vacuum, heating being carried out in an air-bath. At 200–220° an oil came over which rapidly solidified. When larger quantities than 0.5 g. were used, the yield was poorer. The average yield from five experiments was 0.08 g. After two recrystallisations from benzene-light petroleum (b. p. 60–80°), the pure product was obtained, m. p. 107–109°. Yield, 0.28 g. from 2.5 g. of starting material (Found: C, 72.6; H, 5.2; N, 11.0.  $C_8H_7ON$  requires C, 72.2; H, 5.3; N, 10.5%).