34. *Contributions to the Chemistry of Pyridine. Part II. 3- and 5-Hydroxy-2-methylpyridine, and the Condensation of 5-Hydroxy-2-methylpyridine with Formaldehyde in Alkaline Medium.*

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" β-Hydroxy-α-picoline ", obtained by the sulphonation of 2-methylpyridine and subsequent alkali fusion, has been shown to be 5-hydroxy-2-methylpyridine. 3-Hydroxy-2-methylpyridine has been prepared from 3-hydroxy-2-hydroxymethylpyridine. 5-Hydroxy-2-methylpyridine reacts with formaldehyde to yield 5-hydroxy-2-methyl-6-hydroxymethylpyridine.

" β-Hydroxy-α-picoline " was first prepared by Wulff (G.P. 541,681/1928, F.P. 685,583/1930) by alkali fusion of 2-methylpyridine-3-sulphonic acid (obtained according to G.P. 541,036/1928 and F.P. 685,062/1930 by sulphonation of 2-methylpyridine). Wulff did not establish the structure of his product and suggested the 3- and the 5-position as alternatives for the hydroxyl group. Later, Graf (*J. pr. Chem.*, 1932, **133**, 35) prepared 5-hydroxy-2-methylpyridine from 6-methylnicotinic acid. Finally, Aso (*Bull. Inst. Phys. Chem. Res. Tokyo*, 1939, **18**, 182; *J. Agric. Chem. Soc. Japan*, 1940, **16**, 249) isolated 5-hydroxy-2-methylpyridine from the products of reaction between hexoses or 5-methylfurfuraldehyde and ammonium salts.

All these authors gave practically the same m. p. of the substance, varying from 164° to 167°. Aso also prepared from his compound the picrate, m. p. 202—203°. The present author has found the same m. p. 202° for the picrate of " β-hydroxy-α-picoline " prepared by the method of Wulff. The identity of all these m. ps. suggests that the product by Wulff's method is identical with those of Graf and Aso. No final evidence, however, exists as to the structure of Wulff's hydroxypicoline, and some statements in the literature suggest it to be 3-hydroxy-2-methylpyridine.

From the resinous products of the oxidising fusion of " β-hydroxy-α-picoline " with potassium hydroxide, the known 5-hydroxypicolinic acid (Bellman, *J. pr. Chem.*, 1884, **29**, 7) has now been isolated. This is evidence that Wulff's product is 5-hydroxy-2-methylpyridine.

The same acid has been isolated in a larger quantity from the by-products of the alkali fusion of 2-methylpyridine-3-sulphonic acid. It is evidently formed from 2-methylpyridine-5-sulphonic acid through 5-hydroxy-2-methylpyridine.

A further proof of the structure of this compound has been obtained by preparing 3-*hydroxy*-2-*methylpyridine*, the parent substance of pyridoxine, by reduction of 3-hydroxy-2-bromomethylpyridine (Part I, *J.*, 1946, 1104) by means of zinc dust.

5-Hydroxy-2-methylpyridine reacts with formaldehyde to form 5-*hydroxy*-2-*methyl*-6-*hydroxymethylpyridine*. To establish the position of the hydroxymethyl group, the substance was oxidised to the corresponding acid. Because of the phenolic character of 3-hydroxy-derivatives of pyridine, it was necessary to methylate the substance before oxidation. The oxidation with potassium permanganate in alkaline medium led to the formation of 3-*methoxy*-6-*methylpicolinic acid* which on demethylation with hydrobromic acid gave 3-*hydroxy*-6-*methylpicolinic acid*.

Experimental.

5-Hydroxypicolinic Acid.—(*a*) " β-Hydroxy-α-picoline " (2 g.) prepared according to Wulff (*loc. cit.*) was fused with potassium hydroxide (5 g.) in a nickel crucible for 2 hours at 240—260°. The melt was dissolved in water, neutralised with hydrochloric acid, acidified with acetic acid, and filtered, and the 5-hydroxypicolinic acid was precipitated as its cupric salt. This was collected and decomposed with hydrogen sulphide, and the solution of the acid was evaporated to dryness. A few mg. of 5-hydroxypicolinic acid were isolated; crystallised from water it had m. p. 260° (Bellmann, *loc. cit.*, gives 258°).

(*b*) The ammonium salt of 2-methylpyridine-3-sulphonic acid (75 g.) was fused with potassium hydroxide as described by Wulff. The mass was dissolved in water (200 c.c.), neutralised (phenolphthalein) with hydrochloric acid, and acidified (litmus) with acetic acid. 5-Hydroxy-2-methylpyridine was collected. The filtrate was treated with cupric acetate, boiled, and the precipitate of cupric salt collected. The salt was decomposed with hydrogen sulphide, and the filtrate evaporated to dryness. The resinous product crystallised on standing. The crystals were washed with a small amount of cold water, dissolved in hot water, and acidified with acetic acid, and the silver salt was precipitated with silver acetate. It was collected, decomposed with hydrogen sulphide, and the filtrate evaporated. The crystalline solid residue was recrystallised from water (twice) and then had m. p. 263—264°, mixed m. p. with 5-hydroxypicolinic acid prepared as in (*a*), 260°. Yield 0·4 g. (Found: N, 9·1. Calc. for $C_6H_5O_3N,H_2O$: N, 8·9%). A small sample decomposed by heating with calcium oxide gave a distillate of 3-hydroxypyridine; after resublimation this had m. p. 120° alone or in admixture with an authentic specimen.

3-*Hydroxy*-2-*methylpyridine*.—3-Hydroxy-2-hydroxymethylpyridine hydrochloride (2 g.) (Part I, *loc. cit.*) was dissolved in 60% hydrobromic acid (20 c.c.) and boiled under reflux for ½ hour. The resulting solution of 3-hydroxy-2-bromomethylpyridine hydrobromide was cooled below — 10° and zinc dust (8 g.) and 30% hydrobromic acid (30 c.c.) were added in small portions during 2 days, the temperature being kept below — 5°. On the third day the mixture was warmed on a water-bath until all the zinc had dissolved. The solution was cooled, made alkaline with 10% sodium carbonate (phenolphthalein), filtered from the precipitate, neutralised with dilute sulphuric acid, evaporated, and extracted with acetone. The extract was evaporated and extracted with hot ethyl acetate. 3-*Hydroxy*-2-*methylpyridine* crystallised on cooling in white needles. Yield, 0·95 g. (70%). After two sublimations under reduced pressure it had m. p. 160—161° (Found: C, 66·2; H, 6·7; N, 12·7. C_6H_7ON requires C, 66·1; H, 6·4; N, 12·8%). It was soluble in hot water, insoluble in chloroform, carbon tetrachloride, or benzene; more soluble in ether, acetone, or ethyl or amyl acetate than was 5-hydroxy-2-methylpyridine. It gave with ferric chloride a wine-red colour which differed slightly from the reddish-brown colour given by 5-hydroxy-2-methylpyridine. The *picrate* crystallised from water as light yellow needles, m. p. 192° (Found: N, 16·4. $C_{12}H_{10}O_8N_4$ requires N, 16·6%).

5-*Hydroxy*-2-*methyl*-6-*hydroxymethylpyridine*.—5-Hydroxy-2-methylpyridine (5·45 g., 0·05 mol.) was dissolved in 10% aqueous sodium hydroxide (22 c.c.) and 36% formaldehyde solution (13·6 c.c., 0·15 mol.). The solution was refluxed on the water-bath for 1½ hours. After cooling it was acidified with glacial acetic acid (4·5 c.c.) and evaporated. The residue was extracted with acetone (*ca.* 500 c.c.), the acetone distilled off, and the free 5-hydroxy-2-methyl-6-hydroxymethylpyridine crystallised out. After recrystallisation from water (yield, 5·2 g.; *ca.* 75%) and then from alcohol it formed plates, m. p. 154°. It was readily soluble in hot water, alcohol, or acetone, and gave a cherry-red colour with ferric chloride (Found: C, 60·4; H, 6·3; N, 10·1. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%). The hydrochloride was prepared by rubbing the base in a mortar with hydrochloric acid. After two recrystallisations from aqueous acetone it had m. p. 162° (Found: N, 7·7; Cl, 19·7. $C_7H_9O_2N,HCl$ requires N, 8·0; Cl, 20·3%). The picrate, precipitated from an alcoholic solution and washed with alcohol, had m. p. 173—174° (Found: N, 15·0. $C_{13}H_{12}O_9N_4$ requires N, 15·2%).

5-*Hydroxy*-2-*methyl*-6-*bromomethylpyridine Hydrobromide*.—5-Hydroxy-2-methyl-6-hydroxymethylpyridine (0·3 g.) was dissolved in 60% hydrobromic acid (20 c.c.) and boiled for 10 minutes under reflux. The resulting solution was evaporated to *ca.* 5 c.c. and cooled. Thick white prisms of 5-*hydroxy*-2-*methyl*-6-*bromomethylpyridine hydrobromide* crystallised out. They were collected, washed with acetone and ether, and dried; m. p. 224° (decomp.). Yield, 0·5 g. (Found: N, 5·0; Br, 56·9. C_7H_8ONBr,HBr requires N, 4·95; Br, 56·5%). When the compound (0·4 g.) was recrystallised from a small quantity of water, white needles of 5-*hydroxy*-2-*methyl*-6-*hydroxymethylpyridine hydrobromide* (0·23 g.) separated; m. p. 164° (Found: N, 6·6; Br, 36·1. $C_7H_9O_2N,HBr$ requires N, 6·4; Br, 36·4%).

5-*Methoxy*-2-*methyl*-6-*methoxymethylpyridine*.—5-Hydroxy-2-methyl-6-hydroxymethylpyridine (5·5 g.) was dissolved in methyl alcohol (50 c.c.) and diazomethane (prepared from 20 g. of nitrosomethylurea) in ether (250 c.c.) was added. Next day the solvents were evaporated. The oily product, 5-methoxy-2-methyl-6-methoxymethylpyridine, solidified on standing. Yield, 6·0 g. The *picrate*, recrystallised twice from water, formed light orange long needles, m. p. 140° (Found: N, 14·0. $C_{15}H_{16}O_9N_4$ requires N, 14·1%).

3-*Methoxy*-6-*methylpicolinic Acid*.—5-Methoxy-2-methyl-6-methoxymethylpyridine (3·4 g.) was dissolved in 1·5% potassium hydroxide solution (150 c.c.) and potassium permanganate (4·3 g.) in water (200 c.c.) was added in the course of 6 hours. The solution was left overnight, filtered, neutralised with sulphuric acid, acidified with acetic acid, and concentrated, and the pale green cupric salts of the products of oxidation were precipitated by addition of cupric acetate. The precipitate was collected, washed with water, decomposed with hydrogen sulphide, and the filtrate evaporated to dryness. Yield, 1·3 g. 3-*Methoxy*-6-*methylpicolinic acid* was extracted with hot light petroleum or chloroform, and crystallised on cooling in long transparent needles which had a faint aromatic smell and became opaque on drying at 90°. It was readily soluble in water, insoluble or sparingly soluble in most organic solvents. Recrystallised from light petroleum or chloroform it had m. p. 104° (Found: C, 57·7; H, 5·5; N, 8·2; equiv. by titration, 165. $C_8H_9O_3N$ requires C, 57·5; H, 5·4; N, 8·4%; equiv., 167).

3-*Hydroxy*-6-*methylpicolinic Acid*.—3-Methoxy-6-methylpicolinic acid (0·25 g.) was boiled under reflux for 3 hours with 60% hydrobromic acid (25 c.c.). The solution was concentrated to *ca.* 5 c.c., neutralised with 10% sodium carbonate solution, and acidified with acetic acid, and the pale-green cupric salt precipitated with cupric acetate. The salt was collected, decomposed with hydrogen sulphide, and the aqueous solution evaporated. The acid, recrystallised from water, had m. p. 228° (decomp.). Yield, 0·06 g. It gave a reddish-yellow colour with ferrous sulphate, and a cherry red with ferric chloride

(Found : C, 55·1 ; H, 4·7 ; N, 8·9. $C_7H_7O_3N$ requires C, 54·2 ; H, 4·5 ; N, 9·15%). When heated above its m. p. it yielded a sublimate of 5-hydroxy-2-methylpyridine, m. p. and mixed m. p. 160°.

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