243. *Contributions to the Chemistry of Pyridine. Part I. Condensation of β-Hydroxypyridine with Formaldehyde in Alkaline Medium.*

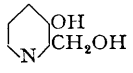
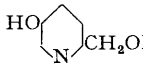
By T. URBAŃSKI.

3-Hydroxypyridine reacts with formaldehyde in the presence of aqueous sodium hydroxide, furnishing 3-*hydroxy*-2-*hydroxymethylpyridine*. The position of the hydroxymethyl group was established by oxidation of the substance to the known 3-hydroxypicolinic acid.

Some derivatives of 3-hydroxy-2-hydroxymethylpyridine have been prepared.

THE fact that 3-hydroxypyridine is related to the vitamin B group (Williams, *J. Ind. Eng. Chem.*, 1921, **13**, 1107; Kuhn *et al.*, *Ber.*, 1939, **72**, 305, 309, 310, 311; Stiller, Keresztesy, and Stevens, *J. Amer. Chem. Soc.* 1939, **61**, 1237; Harris, Stiller, and Folkers, *ibid.*, p. 1242) creates a new interest in this compound. In an investigation of the possibility of the direct introduction of hydroxymethyl groups into 3-hydroxypyridine by the action of formaldehyde, in order to produce a substance similar to pyridoxine, it has been found that 3-hydroxypyridine condenses with one mol. of formaldehyde in presence of sodium hydroxide, forming 3-*hydroxy*-2-*hydroxymethylpyridine* (I) (isolated in the first place as its *hydrochloride*). Oxidation of this compound with sodium permanganate gives 3-hydroxypicolinic acid, identical with that prepared by Kirpal (*Monatsh.*, 1908, **29**, 231) by diazotisation of 3-aminopicolinic acid.

Attempts to esterify 3-hydroxypicolinic acid with methyl alcohol in presence of hydrochloric or sulphuric acid gave negligible yields. Better results were obtained by the action of methyl alcohol on the acid chloride or the action of methyl iodide on the silver salt of the acid. The same ester (m. p. 72—73°) was obtained by either reaction, whether the acid had been made from 3-aminopicolinic acid or by oxidation of 3-hydroxy-2-hydroxymethylpyridine. For this reason, an alternative structure (II) for the hydroxy-hydroxymethylpyridine should be rejected. This structure was ascribed by Aso (*J. Agric. Chem. Soc. Tokyo*, 1939, **15**, 629; 1940, **16**, 249) to one of the products which he obtained from sugars or ethoxymethylfurfuraldehyde and ammonium salts.

(I.)   (II.)

Both hydroxyl groups in 3-hydroxy-2-hydroxymethylpyridine can be esterified with acetic anhydride in presence of sodium acetate. Boiling of (I) with 60% hydrobromic acid yields the *hydrobromide* of 3-*hydroxy*-2-*bromomethylpyridine*. This is easily hydrolysed by heating with water and yields the *hydrobromide* of (I).

EXPERIMENTAL.

3-*Hydroxy*-2-*hydroxymethylpyridine Hydrochloride*.—3-Hydroxypyridine (0·2 mol., 19 g.) was dissolved in 10% aqueous sodium hydroxide (94 c.c.) and 36% formaldehyde (42 c.c., 0·5 mol.). The solution was refluxed on the water-bath for 1½—2 hours, during which time it acquired a ruby colour. After being cooled, it was acidified with glacial acetic acid (19 c.c.) and evaporated. The syrupy residue was extracted with acetone (*ca.* 2 l.). The colour changed to green or bluish-green. (The changes of the colour, *viz.*, red in alkaline and green or blue in the acid medium, are probably due to formation of coloured open-chain products of the type described by Zincke, *Annalen*, 1904, **330**, 361; 1905, **339**, 193, **341**, 365.) The acetone was distilled off, and alcoholic hydrogen chloride was added to the syrupy residue. Crystalline 3-*hydroxy*-2-*hydroxymethylpyridine hydrochloride* was filtered off and washed with acetone (yield 16·5 g.;

51%) (Found : C, 44·3; H, 5·0; N, 8·6; Cl, 22·4. $C_6H_8O_2NCl$ requires C, 44·5; H, 5·0; N, 8·7; Cl, 22·0%). It was purified by dissolving it in aqueous acetone (100 c.c. acetone + 20 c.c. water) and adding more acetone (*ca.* 1·5 l.). Repeated crystallisation gives needles, m. p. 206°. The substance is readily soluble in water, soluble in alcohol, insoluble in most organic solvents. It gives a yellow colour with ferric chloride.

3-*Hydroxy*-2-*hydroxymethylpyridine* (I).—(*a*) The hydrochloride of (I) (1 g.) was dissolved in sufficient 10% sodium carbonate solution to give a neutral solution (litmus), the solution evaporated, and the residue extracted with acetone. Evaporation of the acetone left a syrup which crystallised slowly. The crystals were washed with a small quantity of water and crystallised from water (or acetone); m. p. 132° (0·15 g.). As this method leaves sodium salts in the substance, the following method is preferable. (*b*) The hydrochloride of (I) (1 g.) was dissolved in water and acidified with acetic acid. Freshly precipitated silver oxide was added, and silver chloride filtered off. The solution was saturated with hydrogen sulphide, silver sulphide filtered off, and the filtrate evaporated. The syrupy residue crystallised in a desiccator over potassium hydroxide, and was recrystallised from water; m. p. 130° (0·25 g.). The *substance* (Found : C, 57·3; H, 5·3; N, 11·6. $C_6H_7O_2N$ requires C, 57·6; H, 5·6; N, 11·2%) is soluble in water, alcohol, or hot acetone, insoluble in benzene, ether, methyl acetate, or light petroleum.

The *picrate* crystallised from hot water in light yellow needles, m. p. 208—210° (Found : C, 40·4; H, 3·2; N, 15·9. $C_{12}H_{10}O_9N_4$ requires C, 40·7; H, 2·8; N, 15·8%). The methiodide, prepared as a reddish oil soluble in water or alcohol, insoluble in ether and in methyl iodide, was dissolved in small quantity of alcohol and precipitated with ether, and then crystallised slowly in needles, m. p. 140°. The base formed a platinichloride, hygroscopic, reddish-brown needles.

3-*Hydroxy*-2-*bromomethylpyridine Hydrobromide*.—3-Hydroxy-2-hydroxymethylpyridine hydrochloride (1 g.) was boiled with 60% hydrobromic acid (20 c.c.) for 10 mins. under reflux. The resulting solution was evaporated to *ca.* 10 c.c. and crystallised on cooling. The *hydrobromide* is insoluble in most organic solvents and the bromomethyl group was hydrolysed readily in hot water. It was therefore purified only by washing with small quantity of cold water, acetone, and ether; yield 1·2 g. of needles, m. p. 182—184° (Found : N, 5·1; Br, 60·5. $C_6H_7ONBr_2$ requires N, 5·2; Br, 59·4%). When heated above its m. p., it develops an intense purple colour.

3-*Hydroxy*-2-*hydroxymethylpyridine Hydrobromide*.—(*a*) A solution of the foregoing hydrobromide (1·2 g.) in water (10 c.c.) was evaporated down to 2—3 c.c. on the water-bath; white prisms of the *hydrobromide* of (I) crystallised on cooling (1·0 g.), m. p. 205—207° (Found : N, 6·7; Br, 39·5. $C_6H_8O_2NBr$ requires N, 6·8; Br, 38·8%). It is soluble in water, relatively soluble in acetone, insoluble in most organic solvents. (*b*) 3-Hydroxy-2-hydroxymethylpyridine (0·2 g.) was dissolved in 25% hydrobromic acid (2 c.c.) and left in a vacuum desiccator over potassium hydroxide. Crystals of the hydrobromide of (I) (0·28 g.) resulted; m. p. and mixed m. p. 204—208°.

Acetylation of 3-*Hydroxy*-2-*hydroxymethylpyridine*.—The hydrochloride of (I) (2 g.), acetylated in the normal manner, afforded 3-*acetoxy*-2-*acetoxymethylpyridine* as an oil. It was extracted with ether, dried (Na_2SO_4), and distilled under reduced pressure. A fraction, b. p. 118—122°/4 mm., was collected (1·5 g.) as a colourless, viscous liquid, appreciably soluble in water; $n_D^{20°}$ 1·4881 (Found : Ac, 41·1. $C_{10}H_{11}O_4N$ requires 2Ac, 41·1%).

Oxidation of 3-*Hydroxy*-2-*hydroxymethylpyridine*.—The hydrochloride of (I) (3 g.) was dissolved in water (150 c.c.) and 10% sodium carbonate solution (40 c.c.). A solution of sodium permanganate (7·0 g.) in water (150 c.c.) was added gradually with stirring below 5°. The solution was left overnight at room temperature, oxides of manganese filtered off and washed with water, and the filtrate and washings neutralised with 10% sulphuric acid and concentrated to *ca.* 100 c.c. Acidification with acetic acid and addition of copper acetate precipitated the light green cupric salt of 3-hydroxypicolinic acid. This salt was decomposed with hydrogen sulphide in the usual way, and the filtrate evaporated to dryness. The substance still contained sodium salts and was purified by reprecipitation of the cupric salt; yield 1·2—1·6 g. It crystallises from water, acetone, or light petroleum in white needles or plates, m. p. 205°. It is soluble in hot water, or in alcohol, acetone, xylene, or light petroleum. It gives an intense cherry-red colour with ferrous sulphate and a lighter one with ferric chloride (Found : C, 51·5; H, 3·9; N, 9·7; equiv. by titration, 141. Calc. for $C_6H_5O_3N$: C, 51·8; H, 3·6; N, 10·1%; equiv., 139).

The same acid was prepared from 3-aminopicolinic acid (Suchards, *Ber.*, 1925, **58**, 1727) by diazotisation, decomposition of the diazonium compound, and purification through the copper salt; after recrystallisation from water and from light petroleum, it had m. p. 208° (corr. 216°), and mixed with the acid prepared as above, m. p. 205—208°.

Methyl 3-*Hydroxypicolinate*.—(*a*) Esterification by the Fischer–Speier method afforded the methyl ester, m. p. 65°, in poor yield. (*b*) Conversion of the acid (0·4 g.) into its chloride and thence into the ester afforded white needles (0·03 g.), m. p. 72° after crystallisation from ether. (*c*) Esterification of the acid (0·5 g.) *via* its silver salt and reaction with methyl iodide afforded the *ester* (0·20 g.), m. p. 73° after two crystallisations from ether (Found : C, 54·5; H, 4·6; N, 9·1. $C_7H_7O_3N$ requires C, 54·9; H, 4·6; N, 9·15%). The ester is soluble in alcohol, ether, or chloroform, insoluble in benzene or petroleum. It possesses a characteristic smell of roasted hazel-nuts. It gives a blood-red colour with ferric chloride and a light brown with ferrous sulphate.

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ARMAMENT RESEARCH DEPARTMENT, ROYAL ARSENAL, WOOLWICH. [*Received, January 23rd*, 1946.]