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# 3-Hydroxypicolinaldehyde

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3-Hydroxypicolinaldehyde triacetate was obtained by rearrangement of 2-hydroxymethyl-3-pyridinol-1-oxide. Hydrolysis of this compound gave pure 3-hydroxypicolinaldehyde.

The following derivatives of 3-hydroxypicolinaldehyde were prepared: the diethyl acetal, the dimethyl acetal, the aldoxime, the 2,4-dinitrophenylhydrazone hydrochloride and the hydrochloride.

As part of an investigation of oximes of the pyridine series Ginsburg and Wilson [1] prepared 3-hydroxypicolinaldehyde and certain of its derivatives. Starting from 2-acetoxymethyl-3-acetoxypyridine (obtained from 3-pyridinol after Stempel and Buzzi [2]) they prepared the 1-oxide which was transformed into 3-hydroxypicolinaldehyde triacetate (method of Boekelheide and Linn [3]). The triacetate was then hydrolyzed to 3-hydroxypicolinaldehyde. The intermediate products were not isolated. The aldehyde was obtained in a 12 % yield as an oil which was not analyzed.

In connection with other experiments in the 3-pyridinol field 3-hydroxypicolinaldehyde has been prepared by a modification of the route used by Ginsburg and Wilson. Better yields were obtained and all intermediate products and derivatives were isolated pure. The reactions carried out are summarized below.

## EXPERIMENTAL

Microanalyses by K. Glens and P. Hansen

*2-Hydroxymethyl-3-pyridinol (II).* 2-Acetoxymethyl-3-acetoxypyridine (I) (prepared from 3-pyridinol after Stempel and Buzzi [2]) (2.09 g, 0.010 mole) and 1 N potassium hydroxide in ethanol (40 ml, 0.040 mole) were mixed and heated under reflux for 2 h. Water (15 ml) was added and the ethanol evaporated in a vacuum. The solution was neutralized by adding conc. hydrochloric acid, solid potassium carbonate was added and the mixture then continuously extracted with ether overnight. The ether was evaporated and the residue washed twice with ether and dried. The yield was 1.02 g (81 %) of II [yellowish-white crystals; m.p. 136—139° (Hershberg apparatus, corr.), previously found [4] 132°]. (Found: N 11.0. Calc. for $C_6H_7NO_2$ (125.1): N 11.2).

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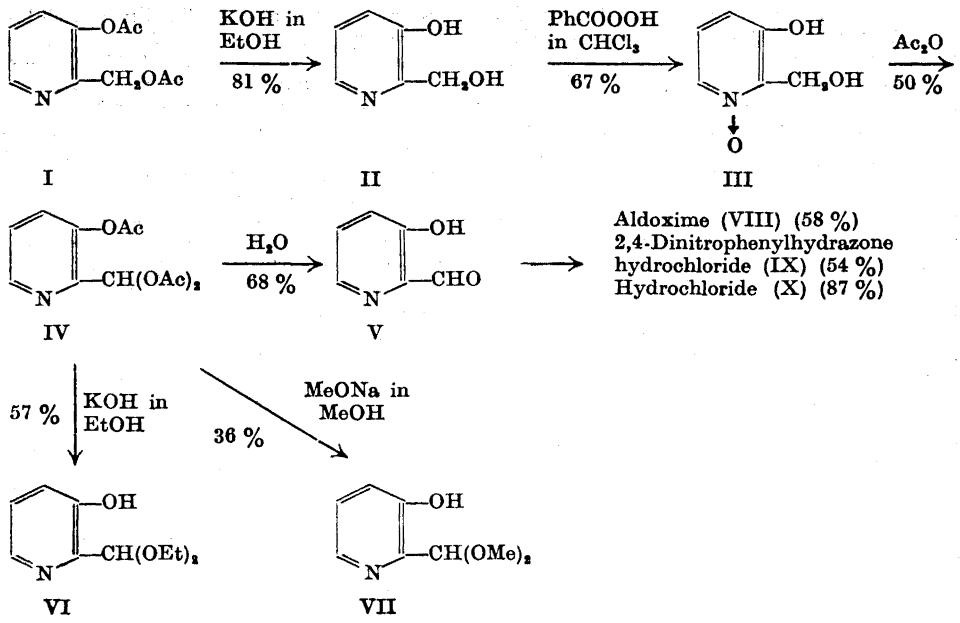


Sublimation (110—125°/0.05 mm) gave white crystals, m.p. 137—139°.

In another experiment I (2.09 g, 0.010 mole) and conc. hydrochloric acid (20 ml) were mixed and refluxed for 12 h. The solution was evaporated to dryness in a vacuum, dissolved in water and solid potassium carbonate added. Continuous extraction with ether overnight gave 0.91 g (73 %) of II (yellowish-white crystals, m.p. 136—139°).

*2-Hydroxymethyl-3-pyridinol hydrochloride.* II (125 mg, 0.0010 mole) was dissolved in N hydrochloric acid (5 ml) and the solution evaporated to dryness in a vacuum. Dissolution of the residue in 99 % ethanol and precipitation with ether gave 148 mg (92 %) of 2-hydroxymethyl-3-pyridinol hydrochloride (white crystals; the m.p. was not sharp, but the compound darkened at 209—211°; previously found [4] m.p. 206°). (Found: N 8.8; Cl 22.9. Calc. for $C_6H_8ClNO_2$ (161.6): N 8.7; Cl 21.8).

*2-Hydroxymethyl-3-pyridinol-1-oxide (III).* II (8.00 g, 0.064 mole) was dissolved in methanol (32 ml) and chloroform (60 ml) was added. A solution of perbenzoic acid (13.8 g, 0.10 mole) in chloroform (180 ml) was added and the mixture left standing at room temperature overnight. The solution was concentrated to about 100 ml in a vacuum, the precipitate removed by filtration, washed with chloroform and dried. Crystallization from methanol gave 6.00 g (67 %) of III [white crystals; m.p. 175—177°). (Found: C 50.9; H 5.2; N 9.8. Calc. for $C_6H_7NO_3$ (141.1): C 51.1; H 5.0; N 9.9).

III gave a red color with aqueous ferric chloride.

*3-Hydroxypicolinaldehyde triacetate (IV).* III (6.30 g) was dissolved in acetic anhydride (63 ml) and the solution heated under reflux for 30 min. Distillation gave 8.0 g of a pale yellow liquid ($b.p._{0.1}$ 140—145°), which crystallized completely on standing. Crystallization from ether gave 5.9 g (50 %) of III [white crystals; m.p. 79—81° (Hershberg apparatus, corr.)]. (Found: C 53.7; H 5.0; N 5.2; $COCH_3$ 49.1. Calc. for $C_6H_4NO_3(COCH_3)_3$ (267.2): C 53.9 ;H 4.9; N 5.2; $COCH_3$ 48.3). IV gave no color reaction with aqueous ferric chloride.

*3-Hydroxypicolinaldehyde (V).* IV (1.34 g) and water (25 ml) were heated under reflux overnight. The crystalline reaction product sitting in the reflux condenser was dissolved in ether (the remaining solution in the flask was made alkaline with potassium carbonate and continuously extracted with ether for 5 h, whereby only 40 mg of an oil was obtained), washed with a little 2 M potassium hydrogen carbonate and dried with magne-

sium sulfate. Evaporation gave 0.53 g of a yellow crystalline residue. Sublimation (40—50°/0.05 mm) gave 0.42 g (68 %) of V (yellowish-white crystals, m.p. 81—82°). Crystallization from ether followed by sublimation did not change the m.p. (Found: C 58.1; H 4.4; N 11.1. Calc. for $C_6H_5NO_2$ ((123.1): C 58.5; H 4.1; N 11.4). V gave a red color with aqueous ferric chloride. When V is placed on the skin a persistent green color develops.*

*3-Hydroxypicolinaldehyde diethyl acetal (VI).* IV (0.67 g, 0.0025 mole) and 0.5 N potassium hydroxide in 96 % ethanol (30 ml, 0.015 mole) were mixed, heated under reflux for 1.5 h and then evaporated in a vacuum to about 10 ml. A little water was added, the solution neutralized under cooling with acetic acid and then made alkaline by adding potassium carbonate. The solution was extracted twice with ether, the ether extract washed with a little water and dried with magnesium sulfate. Evaporation gave 0.34 g of a white crystalline residue. Sublimation (75°/0.05 mm) gave 0.28 g (57 %) of VI (white crystals; m.p. 82—83°). Crystallization from ether followed by sublimation did not change the m.p. (Found: C 61.0; H 7.7; N 7.1; $OC_2H_5$ 44.4. Calc. for $C_6H_5NO(OC_2H_5)_2$ (197.2): C 60.9; H 7.7; N 7.1; $OC_2H_5$ 45.7). VI gave a red color with aqueous ferric chloride.

*3-Hydroxypicolinaldehyde dimethyl acetal (VII).* IV (1.34 g, 0.0050 mole) was dissolved in methanol (10 ml) and sodium methoxide in methanol [prepared from 0.24 g of sodium (0.011 mole) and methanol (5 ml)] was added. After 30 min at room temperature the reaction mixture was worked up essentially as described above for the preparation of VI. The yield after sublimation (90°/0.1 mm) was 0.30 g (36 %) of VII (white crystals; m.p. 104—105°). Crystallization from ether followed by sublimation did not change the m.p. (Found: C 56.4; H 6.3; N 8.5; $OCH_3$ 36.4. Calc. for $C_6H_5NO(OCH_3)_2$ (169.2): C 56.8; H 6.6; N. 8.3; $OCH_3$ 36.7). VII gave a red color with aqueous ferric chloride.

*3-Hydroxypicolinaldehyde aldoxime (VIII).* V (0.37 g, 0.0030 mole) was dissolved in a mixture of pyridine (6 ml) and 99 % ethanol (6 ml). Hydroxylamine hydrochloride (0.33 g, 0.0048 mole) was added, the mixture heated under reflux for 1 h and then evaporated. Ether (50 ml) was added to the residue and the mixture heated under reflux for 10 min. The ether extract was washed with water, dried with magnesium sulfate and evaporated. The crystalline residue was sublimed (120°/0.05 mm). The yield was 0.24 g (58 %) of VIII (white crystals; m.p. 173—174°; previously found [5] 170°). Crystallization from ether followed by sublimation did not change the m.p. (Found: C 52.2; H 4.4; N 20.0. Calc. for $C_6H_6N_2O_2$ (138.1): C 52.2; H 4.4; N 20.3).

*3-Hydroxypicolinaldehyde 2,4-dinitrophenylhydrazone hydrochloride (IX).* V (10 mg) was dissolved in water (2 ml) and 15 ml of a 0.2 % solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid was added. A yellow precipitate was formed at once. After 1 h the precipitate was removed by filtration, washed with water and dried. The yield was 15 mg (54 %) of IX [orange-red crystals; m.p. 305—310° (decomp.); previously found [6] 219—221° (decomp.)] (Found: C 42.5; H 3.1; N 19.7. Calc. for $C_{12}H_{10}ClN_5O_5$ (339.7): C 42.4; H 3.0; N 20.6).

IX was also obtained from IV after hydrolysis (1 h) as described above for the preparation of V. Crystallization from 96 % ethanol gave 50 % of IX, m.p. 305—310° (decomp.).

*3-Hydroxypicolinaldehyde hydrochloride (X).* V (40 mg) was dissolved in anhydrous ether (10 ml), gaseous hydrogen chloride was passed into the solution, the white precipitate was removed by filtration, washed with ether and dried. The yield was 45 mg (87 %) of X (white crystals, m.p. 218—221°). (Found: N 8.6; Cl 21.9. Calc. for $C_6H_6ClNO_2$ (159.6): N 8.8; Cl 22.2).

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* *Note added in proof:* Mathes, W. and Sauermilch, W. (*Chem. Ber.* **90** (1957) 758), have prepared V(m.p. 83°) by gas phase oxidation of 2-methyl-3-pyridinol. The yield of crude product was 26.5 %.

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