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Some New Cyclic Hydroxamic Acids

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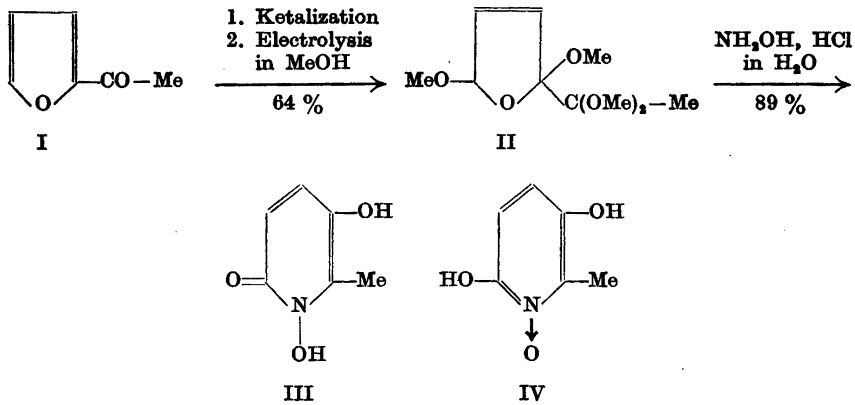
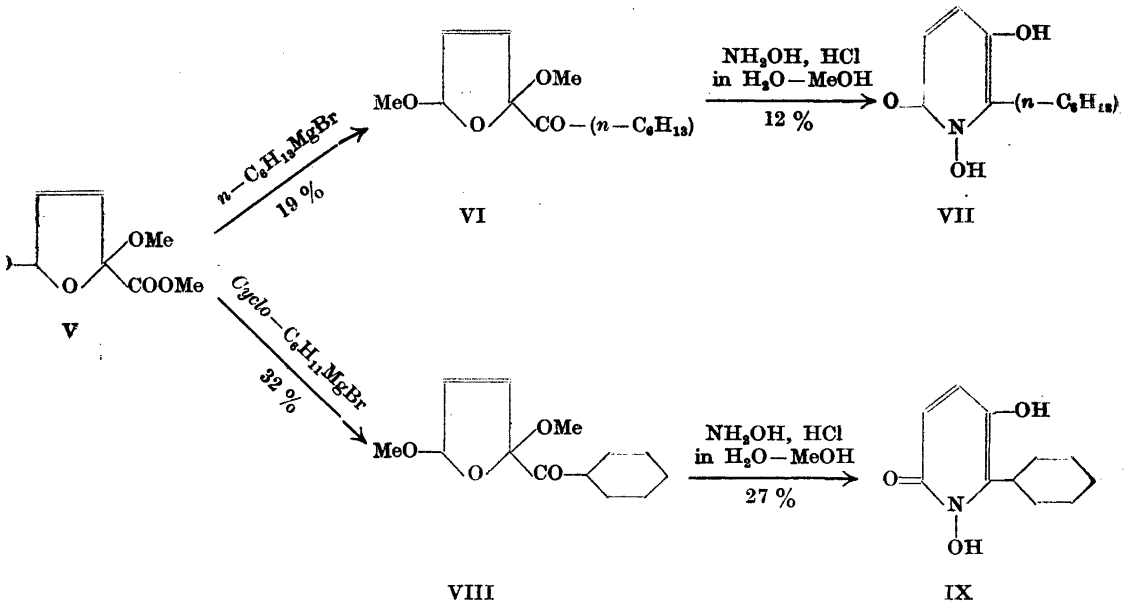
A compound prepared from 2-acetylfuran and previously [1] claimed by us to be 2-methyl-3,6-pyridinediol-1-oxide (IV) we now believe to be the tautomeric hydroxamic acid 1,5-dihydroxy-6-methyl-2-pyridone (III). Three similar cyclic hydroxamic acids have been prepared from methyl furoate (VII and IX) and furfural (XII), respectively.

We have recently found [1] that 2-acetylfuran (I) may be transformed by a two-step reaction into a compound, which was formulated as 2-methyl-3,6-pyridinediol-1-oxide (IV). Having become acquainted with experiments by Shaw, *et al.* [2-5], on certain cyclic hydroxamic acids related to the antibiotic aspergillic acid, we now think that our compound, rather than being a 2-hydroxypyridine-1-oxide, is the tautomeric hydroxamic acid 1,5-dihydroxy-6-methyl-2-pyridone (III).

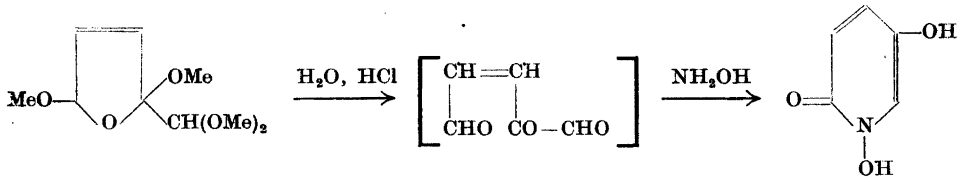


I II III IV

The new reaction has been used for the preparation of two more hydroxamic acids (VII and IX) by the reactions shown below. Compounds VI—IX are new. Their structures follow from the syntheses and from analyses.

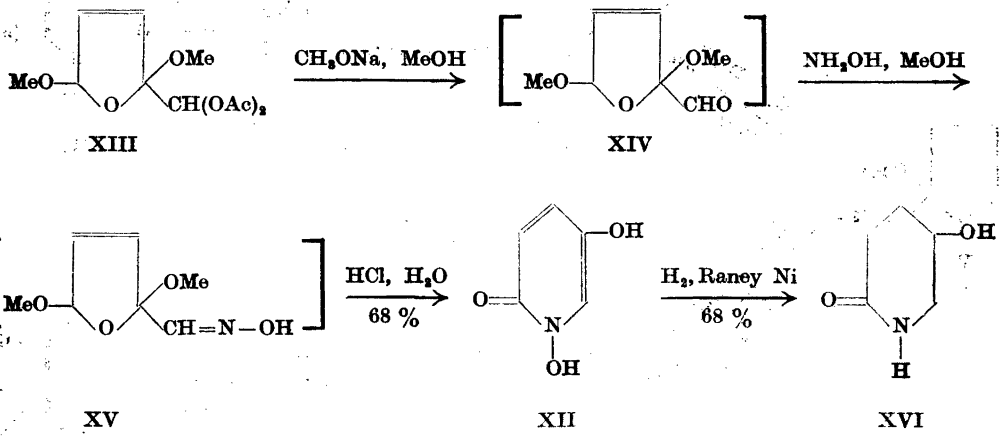


The corresponding unsubstituted hydroxamic acid (1,5-dihydroxy-2-pyridone) (XII) has also been prepared though under somewhat different reaction conditions. One might expect any easily hydrolyzable derivative of 2-*cis*-pentene-1,5-dial-4-one (XI) to react with hydroxylamine hydrochloride to give (XII). 2,5-Dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran [6] (X) gave, however, only a dark reaction mixture, from which no XII could be isolated. The mixture nevertheless gave a strong violet ferric chloride reaction indicating that a small amount of XII actually was formed.



A good yield of XII was obtained by using 2,5-dimethoxy-2,5-dihydrofurfural [7] (XIV) as a starting material. A methanolic solution of this compound was prepared from 2,5-dimethoxy-2-diacetoxymethyl-2,5-dihydrofuran (XIII), the solution treated with hydroxylamine and the reaction product hydrolyzed and condensed to XII. Probably the reaction proceeds through the oxime XV or its equivalent, the initial attachment of the hydroxylamine mole-

cule to the organic molecule thus taking place at one of the ends of the chain of carbon atoms as required for the formation of XII.



XIII XIV XV XII XVI

The structure of the new hydroxamic acid XII was proved by catalytic hydrogenation to the known 5-hydroxy-2-piperidone XVI.

EXPERIMENTAL

Microanalyses by E. Boss and K. Glens

2,5-Dimethoxy-2-(α-oxo-n-heptyl)-2,5-dihydrofuran (VI). An etheral solution of *n*-hexylmagnesium bromide [from *n*-hexyl bromide (36.0 g, 0.22 mole) and 70 ml of ether] was added at −60° to a solution of V[8] (37.6 g, 0.20 mole) in 150 ml of ether. A saturated solution of ammonium chloride (32 ml) was added at 5° and the etheral solution removed by decantation. The residue was extracted twice with 35 ml of ether. Distillation of the combined etheral solutions through a 5 cm column [9] first gave a forerun (13 g, b.p.$_{17}$ 68–157°) consisting mainly of V, and then 9.1 g (19 %) of VI (almost colorless liquid, b.p.$_{17}$ 157–159°, n_D^{25} 1.4483). (Found: C 64.6; H 9.0; OCH_3 25.6. Calc. for $C_{11}H_{16}O_2(OCH_3)_2$ (242.3): C. 64.4; H 9.2; OCH_3 25.6).

About 15 ml of a higher boiling residue, consisting mainly of the corresponding tertiary alcohol, remained in the distillation flask.

1,5-Dihydroxy-6-(n-hexyl)-2-pyridone (VII). VI (1.21 g, 0.0050 mole) was dissolved in methanol (3 ml) and the solution added to a solution of hydroxylamine hydrochloride (0.44 g, 0.0063 mole) in methanol (3 ml) — water (2.5 ml). After standing (17 hr) the light-brown reaction mixture was evaporated to dryness in a vacuum from a water bath (25°). The residue was dissolved in ammonium hydroxide (20 %, 4.0 ml) and continuously extracted with ether. The etheral solution was evaporated to dryness and the residue crystallized from ether. The yield was 126 mg (12 %) of VII [almost white crystals, m.p. 86–88° (Hershberg app., corr)]. The crystals gave a strong violet ferric chloride reaction. (Found: C 62.8; H 8.4; N 6.5. Calc. for $C_{11}H_{17}O_3N$ (211.3): C 62.5; H 8.1; N 6.6).

2,5-Dimethoxy-2-[α-oxo-α-(cyclohexyl)-methyl]-2,5-dihydrofuran (VIII). This compound was prepared from cyclohexyl bromide (24.0 g) and V (25.0 g) as described for the preparation of VI. The yield was 10.2 g (32 %) of VIII (almost colorless liquid, b.p.$_{14}$ 160–162°, n_D^{25} 1.4732). (Found: C 64.8; H 8.2; OCH_3 25.8. Calc. for $C_{11}H_{14}O_2(OCH_3)_2$ (240.3): C 65.0; H 8.4; OCH_3 25.8).

1,5-Dihydroxy-6-cyclohexyl-2-pyridone (IX). This compound was prepared from VIII (1.20 g) as described for the preparation of VII. The crude product was crystallized from methanol-ether. The yield was 286 mg (27 %) of IX (almost white crystals, m.p. 180—182°). The crystals gave a strong violet ferric chloride reaction. (Found: C 62.9; H 7.4; N 6.5. Calc. for $C_{11}H_{15}O_3N$ (209.2): C 63.1; H 7.2; N 6.7).

1,5-Dihydroxy-2-pyridone (XII). XIII (500 mg, 0.0019 mole) was dissolved in methanol (2.0 ml) and the solution added to a solution of sodium methoxide [from 44 mg of sodium (0.0019 mole) in methanol (1.0 ml)]. After standing for 15 minutes a solution of hydroxylamine hydrochloride (0.16 g, 0.0023 mole) and anhydrous sodium acetate (0.050 g) in methanol (2.0 ml) was added, the mixture left standing for 20 minutes and a precipitate of sodium chloride removed by filtration. The almost colorless filtrate was heated under reflux (8 min) and then evaporated in a vacuum from a water bath (30—40°) to about 1 ml. Water (1 ml) and then *N* hydrochloric acid (2.5 ml) were added and the solution left standing for 10 minutes. A precipitate of white crystals of XII was removed by filtration and washed with water, ethanol and ether. The yield was 164 mg (68 %); m.p. in an evacuated tube 216—225° (dec.). Crystallization from ethanol gave 138 mg (57 %), m.p. 215—223°. The product gave a strong violet ferric chloride reaction. (Found: C 47.3; H 4.2; N 10.8. Calc. for $C_5H_5O_3N$ (127.1): C 47.3; H 4.0; N 11.0).

In a similar experiment starting from 2,5-dimethoxy-2,5-dihydrofurfural (XIV) (600 mg) practically the same yield of XII (330 mg = 69 %) was obtained. (Found: C 46.9; H 4.2; N 10.8).

In an attempt to prepare XII from 2,5-dimethoxy-2-dimethoxymethyl-2,5-dihydrofuran (X), X (0.41 g) and hydroxylamine hydrochloride (0.21 g) were dissolved in water (7 ml) and the solution left standing over-night. The next day the dark reaction mixture gave a strong violet ferric chloride reaction but isolation of pure XII failed.

5-Hydroxy-2-piperidone (XVI). XII (0.47 g) and anhydrous methanol (25 ml) were shaken (1 hr) with Raney nickel (0.2 g) under hydrogen (100 atm., 100°). The Raney nickel was removed by filtration and the filtrate evaporated in a vacuum. The crystalline residue was crystallized from methanol-ether. The yield was 0.29 g (68 %) of XVI (almost colorless crystals, m.p. 144—146°, previously found 145—146° [10, 11]). (Found: C 51.9; H 7.7; N 12.0. Calc. for $C_5H_9O_2N$ (115.1): C 52.2; H 7.9; N 12.2.)

Recrystallization from methanol-ether did not change the m.p.

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