

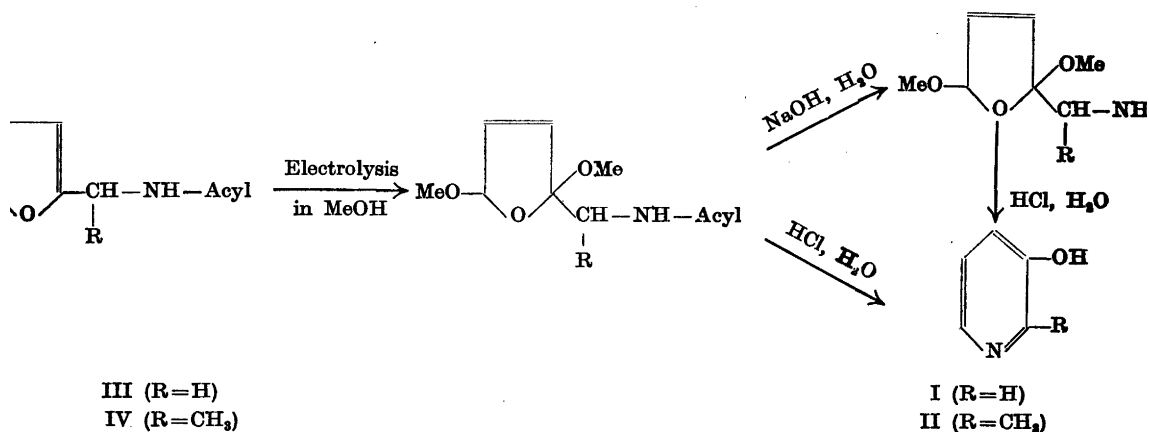
## A New Synthesis of Pyridoxine

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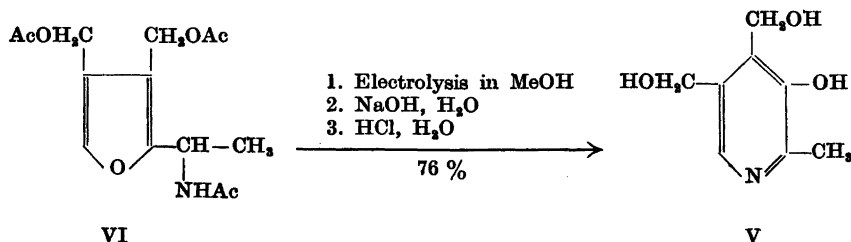
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A new synthesis of pyridoxine from 2-( $\alpha$ -acetamidoethyl)-3,4-bis(acetoxymethyl)-furan is described.

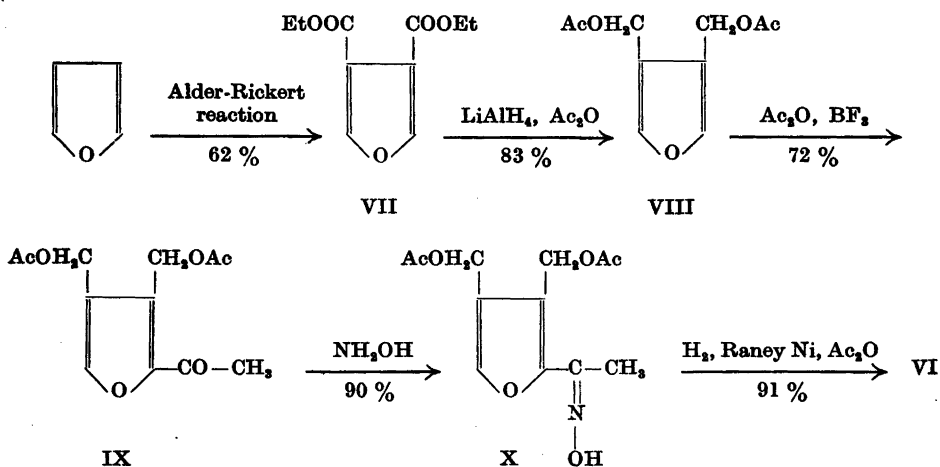
A new method for the preparation of 3-pyridols from N-acyl derivatives of 2-( $\alpha$ -aminoalkyl)-furans has recently been described<sup>1</sup>. The furan was first electrolytically methoxylated to the corresponding 2,5-dimethoxy-2,5-dihydrofuran and the latter was then heated under reflux with dilute hydrochloric acid to give the desired 3-pyridol. In order to obtain a good yield of the pyridol certain acyl derivatives required alkaline hydrolysis of the amide group prior to treatment with hydrochloric acid. The method was used for the preparation of 3-pyridol (I) and 2-methyl-3-pyridol (II) from various acyl derivatives of furfurylamine (III) and 2-( $\alpha$ -aminoethyl)-furan (IV).



We have used the above method for a synthesis of pyridoxine (2-methyl-4,5-bis(hydroxymethyl)-3-pyridol) (V) from 2-( $\alpha$ -acetamidoethyl)-3,4-bis(acetoxymethyl)-furan (VI). The overall yield of the three-step synthesis without isolation of the intermediate dimethoxydihydrofurans was 76 %.



VI was prepared from furan by the sequence of standard reactions shown below. The structure of compounds VI and VIII—X follows from their method of preparation and from analyses.



### EXPERIMENTAL

Microanalyses by Ernst Boss and Kirsten Glens

*3,4-Dicarbethoxyfuran (VII)*<sup>2</sup>. Furan (13.0 g, 0.19 mole) and diethyl acetylenedicarboxylate (29.0 g, 0.17 mole) were mixed and heated (100°, 18 hr) under hydrogen (about 140 atm). After cooling acetone (120 ml) and 10 % palladium charcoal (0.22 g) were added and the mixture shaken (1 hr) under hydrogen (15–20 atm). The catalyst was removed by filtration and the filtrate distilled in a vacuum, whereby a pale-yellow liquid (28 g, b. p.<sub>18–15</sub> 158–198°) was obtained. Redistillation through a short packed column gave 22.4 g (62 %) of VII (colorless liquid, b. p.<sub>13</sub> 154–157°,  $n_D^{25}$  1.4690, previously found<sup>2</sup> b. p.<sub>11</sub> 140–165°). (Found: C 56.8; H 6.0; OC<sub>2</sub>H<sub>5</sub> 42.2. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>5</sub>(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub> (212.2): C 56.6; H 5.7; OC<sub>2</sub>H<sub>5</sub> 42.5).

*3,4-Bis(acetoxymethyl)-furan (VIII)*. 3,4-Dicarbethoxyfuran (3.18 g, 0.015 mole) in dry ether (15 ml) was added dropwise (10 min) to a stirred mixture of lithium aluminum hydride (0.69 g, 0.018 mole) and dry ether (20 ml). Stirring was continued for 5 minutes. Acetic anhydride (20 ml) was added during 5 minutes. The reaction flask was placed in an oil-bath and the temperature of the bath gradually raised to 110° whereby the ether distilled. The temperature of the bath was then maintained at 115–120° for 3 hours. After cooling, ether (40 ml) was added, the mixture filtered and the ether distilled. Distillation of the residue gave 2.63 g (83%) of VIII (as a colorless liquid, which crystallized on cooling (b. p.<sub>0.1</sub> 88–90°,  $n_D^{25}$  1.4672, m. p. 29–31° (Hershberg apparatus, corr.)). (Found: C 56.9; H 5.9; COCH<sub>3</sub> 40.0. Calc. for C<sub>6</sub>H<sub>8</sub>O<sub>5</sub>(COCH<sub>3</sub>)<sub>2</sub> (212.2): C 56.6; H 5.7; COCH<sub>3</sub> 40.6).

After crystallization from ether the m. p. was raised to 30–32°.

*2-Acetyl-3,4-bis(acetoxymethyl)-furan (IX)*<sup>3</sup>. VIII (22.0 g) was dissolved in acetic anhydride (25 ml) and a solution of boron fluoride etherate (1.3 ml) in acetic anhydride (20 ml) was added in one portion with stirring. The temperature rose to 40°. The mixture was heated to 85–90° and maintained at this temperature for 10 minutes. After cooling, water (40 ml) was added and stirring continued for 10 minutes. The dark-brown mixture was extracted with 80 ml and then with 50 ml of ether. The ethereal extracts were washed with water, potassium hydrogen carbonate (2 M), water and dried. Distillation gave 18.9 g (72%) of IX (almost colorless liquid, b. p.<sub>0.1</sub> 127–129°, m. p. 48–51°). (Found: C 56.9; H 6.0; COCH<sub>3</sub> 32.2. Calc. for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>(COCH<sub>3</sub>)<sub>2</sub> (254.2): C 56.7; H 5.6; COCH<sub>3</sub> 33.9). After crystallization from ether the m. p. was raised to 51–53°.

*2-Acetyl-3,4-bis(acetoxymethyl)-furan oxime (X)*. IX (18.5 g), anhydrous sodium acetate (8.2 g) and hydroxylamine hydrochloride (6.2 g) were mixed and heated under reflux (5 h) with ethanol (80 ml). The hot mixture was filtered and the ethanol evaporated in a vacuum. There remained an almost colorless liquid, which crystallized to a white solid after addition of water and cooling. Filtration, washing with water and drying gave 17.6 g (90%) of X (m. p. 78–81°). (Found: C 53.6; H 5.9; N 5.4; COCH<sub>3</sub> 32.4. Calc. for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>N(COCH<sub>3</sub>)<sub>2</sub> (269.3): C 53.5; H 5.6; N 5.2; COCH<sub>3</sub> 32.0). After crystallization from ether the m. p. was 79–81°.

*2-(α-Acetamidoethyl)-3,4-bis(acetoxymethyl)-furan (VI)*. X (2.50 g) and acetic anhydride (20 ml) were shaken (1 hr) with Raney nickel (0.4 g) under hydrogen (100 atm, 70–80°). After filtration, the solvent was evaporated in a vacuum, finally under 0.1 mm at 60–70°. The residue was shaken with anhydrous ether (20 ml) whereupon white crystals were formed. About 10 ml of ether was distilled, the crystals were removed by filtration, washed twice with ether and dried. The yield was 2.52 g (91%) of 2-(α-acetamidoethyl)-3,4-bis(acetoxymethyl)-furan (white crystals, m. p. 92–94°). (Found: C 56.3; H 6.4; N 4.5; COCH<sub>3</sub> 42.5. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>5</sub>N(COCH<sub>3</sub>)<sub>2</sub> (297.3): C 56.6; H 6.4; N 4.7; COCH<sub>3</sub> 43.4).

After crystallization from benzene-ether the m. p. was raised to 95–96°.

In another experiment the reaction product was isolated by distillation (yield 79%, b. p. 170–190° at about 0.1 mm). The pale-yellow liquid crystallized after standing for some days. Crystallization of 500 mg from ether gave 350 mg of white crystals, m. p. 65–68°, which were readily soluble in ether. (Found: C 56.5; H 6.6; N 4.7; COCH<sub>3</sub> 42.4). Another crystallization from ether gave 280 mg, m. p. 66–68°.

An ethereal solution of this product was seeded with the product from the first experiment (m. p. 95–96°) whereupon white crystals, m. p. 95–96°, which were slightly soluble in ether, were obtained.

VI may thus crystallize in two forms, of which the higher melting, slightly soluble form is apparently the one usually obtained.

*Pyridoxine (V)*. VI (2.50 g) and ammonium bromide (300 mg) were dissolved in methanol (20 ml) and the solution electrolyzed with the set-up described previously<sup>4</sup> (temperature of cooling-bath –21°).

Time hr	Current amp	Potential across the cell during electrolysis volt	Ampere hours (per cent of theoretical amount)
0.1	0.7	6.2	0.07 (16 %)
0.3	0.7	6.3	0.20 (44 %)
0.6	0.7	6.3	0.30 (67 %)
0.8	0.5	6.5	0.50 (110 %)

After electrolysis, the liquid in the cell was yellow. The liquid was poured into a solution of sodium methoxide (from 458 mg of sodium) in methanol (5 ml) and the methanol and the ammonia evaporated in a vacuum. Sodium hydroxide (3 N, 8.5 ml) was added, the mixture heated under reflux (21 hr) and then continuously extracted with ether (48 hr). The ether was evaporated in a vacuum and the residue heated under reflux (20 min) with hydrochloric acid (N, 15 ml). The mixture was evaporated to dryness in a vacuum and the residue was crystallized from 99 % ethanol. The yield was 1.19 g (69 %) of pyridoxine hydrochloride (white crystals, m. p. and mixed m. p. with authentic pyridoxine hydrochloride 207–209° (dec.)). The product was further characterized by the infrared absorption spectrum, which was identical over the whole range with that of pyridoxine hydrochloride. (Found: C 46.9; H 6.0; N 6.8; Cl 17.4. Calc. for  $C_8H_{11}O_2NCl$  (205.6): C 46.7; H 5.9; N 6.8; Cl 17.2).

From the mother liquor a further 100 mg of pyridoxine hydrochloride (6 %) was obtained (almost white crystals, m. p. 206–208° (dec.)). (Found: C 46.8; H 5.9; N 6.8; Cl 17.3).

The extraction with ether was continued for 24 hours and the extract worked up as above. The yield was 20 mg (1 %) of pyridoxine hydrochloride (white crystals, m. p. 207–209° (dec.)). (Found: C 47.0; H 5.9; N 6.6; Cl 17.3).

The total yield of pyridoxine hydrochloride was thus 1.31 g (76 %).

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