

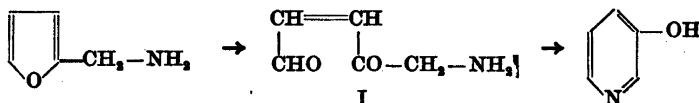
Preparation of 3-Pyridols from Furans

NIELS CLAUSON-KAAS, NIELS ELMING and ZDENĚK TYLE

Centrallaboratoriet, Sadolin & Holmblad A/S, Copenhagen, Denmark

A new method for the preparation of 3-pyridols from 2-(α -aminoalkyl)-furans or their acyl derivatives is described.

Many furans are under certain conditions oxidized to unsaturated 1,4-dicarbonyl compounds or their equivalent¹. When oxidized in this way, furfurylamine should give a dicarbonylamine having the structure I. Since the double bonds in I are *cisoid* one might expect such a compound to condense intramolecularly to yield 3-pyridol.

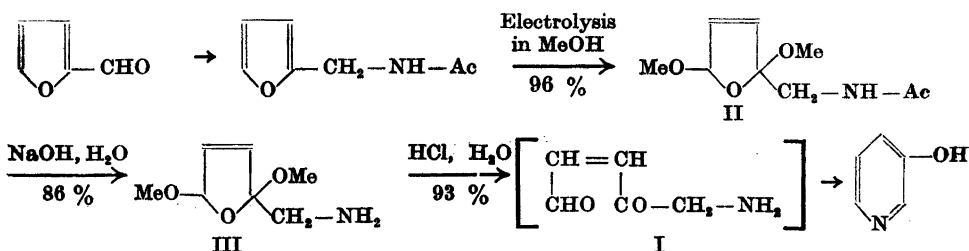


We have indeed found that the transformation of furfurylamine to 3-pyridol is feasible and have worked out reaction conditions, which may be generally used for the preparation of 3-pyridols from 2-(α -aminoalkyl)-furans*. The latter, in turn, are easily obtained by reductive amination of furan-2-carboxaldehydes or furan-2-ketones.

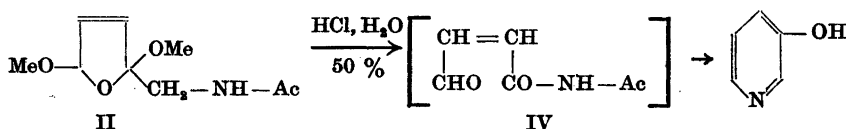
Direct oxidations of furans to unsaturated dicarbonyl compounds are usually difficult to carry out in good yields. If, however, the furans are first electrolytically methoxylated to yield 2,5-dimethoxy-2,5-dihydrofurans and these are subsequently hydrolyzed, yields from 60 to 95 % of dicarbonyl compounds can be obtained.

Electrolytic methoxylation of furfurylamine gave only a low yield of the corresponding dimethoxydihydrofuran (these unsuccessful experiments are not described in the experimental part). Probably the amine group interferes with the methoxylation reaction. But, as has been reported previously², 2-(acetamidomethyl)-furan gives an almost quantitative yield of 2,5-dimethoxy-2-(acetamidomethyl)-2,5-dihydrofuran II. Alkaline hydrolysis of II gave the desired 2,5-dimethoxy-2-(aminomethyl)-2,5-dihydrofuran III, which by boiling with *N* hydrochloric acid was transformed into 3-pyridol (yield 93 %).

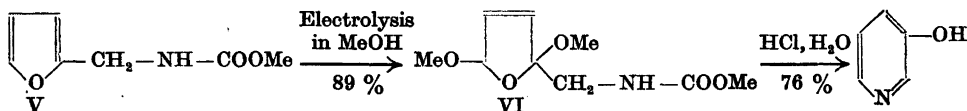
* Patent pending.



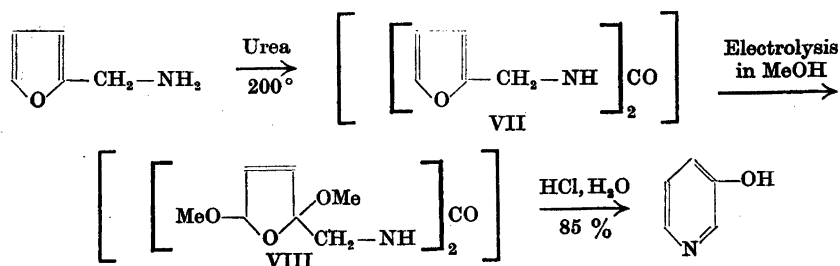
3-Pyridol was also obtained by boiling II with hydrochloric acid, but the yield was only 50 % and the reaction mixture turned dark-red. We believe that the intramolecular condensation of the intermediate dicarbonylamide IV proceeds more slowly than the condensation of the dicarbonylamine I, since the former must hydrolytically lose acetic acid in the course of the condensation. Part of the dicarbonylamide therefore reacts differently due to the prolonged reaction time.



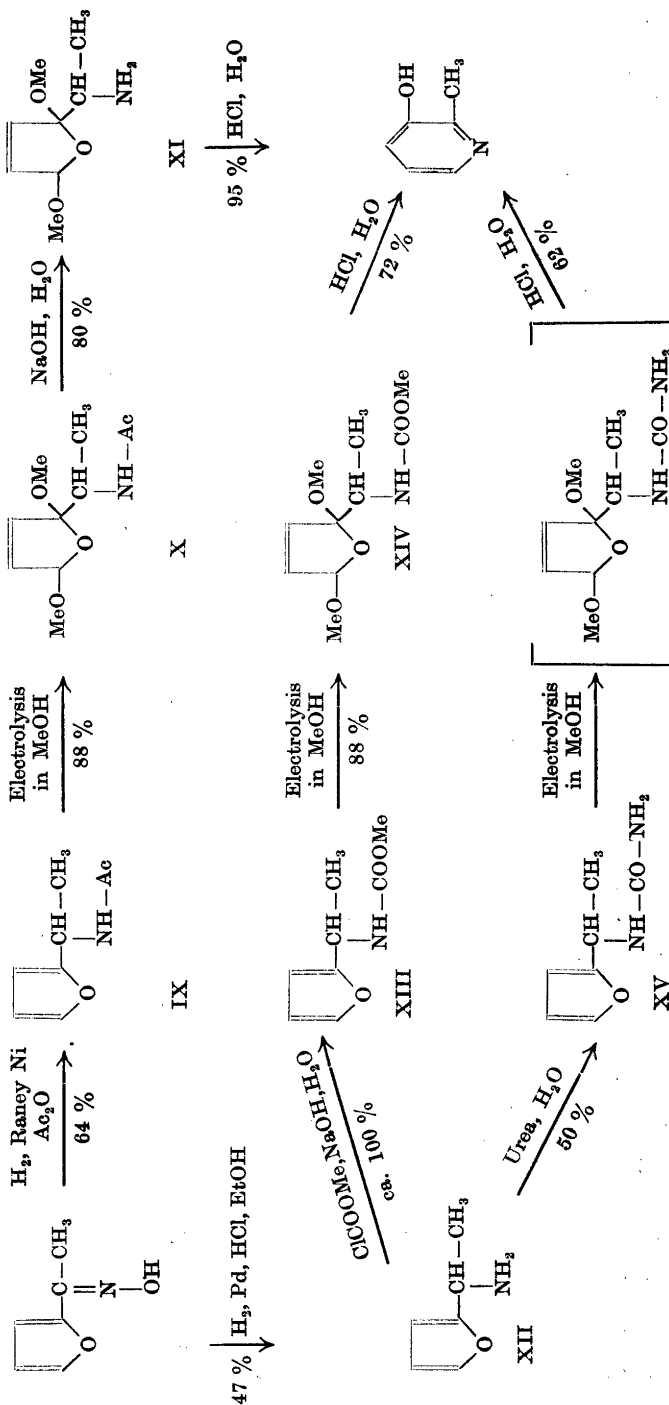
Consistent with this assumption is the fact that an easily hydrolyzed acyl derivative of III, *viz.* the carbamate VI, which was prepared by electrolytic methoxylation of the corresponding furan (V), gave, by boiling with hydrochloric acid, a higher yield of 3-pyridol (76 %).



The above yields of 3-pyridol based upon furfurylamine were 73, 46 and 55 %, respectively. However, by proceeding through *sym*-difurfurylurea VII and the corresponding dimethoxydihydrofuran VIII, an 85 % yield of 3-pyridol was obtained. This reaction sequence, in which the intermediates need not be isolated pure, represents the most convenient way of preparing 3-pyridol from furfurylamine.



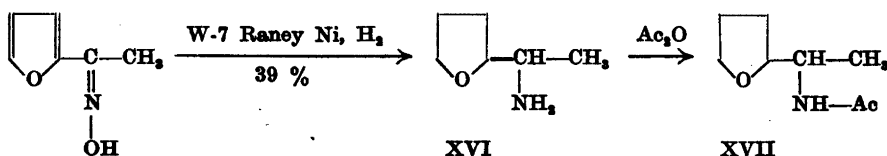
In order to illustrate the general applicability of the new method 2-methyl-3-pyridol was prepared from 2-acetylfuran oxime by the following reactions:



Routes to 2-methyl-3-pyridol from 2-acetylfuran.

The structure of compounds III, V—VI and VIII—XV follows from the methods of their preparation and from analyses. They have all been prepared by known reactions and in only one case, *viz.* the reductive amination of 2-acetylfuran to 2-(α -aminoethyl)-furan (XII) were any difficulties encountered. Under the same conditions as those used for the preparation of furfurylamine from furfural and ammonia, no reaction took place, and attempts to catalytically reduce 2-acetylfuran oxime showed that it was difficult to reduce the oxime group without at the same time reducing the furan nucleus (these experiments are not described in the experimental part). Only when reduced with palladium charcoal in the presence of hydrochloric acid (method of Hartung³) did the oxime give a 47 % yield of the amine. Furthermore it was found that reduction of 2-acetylfuran oxime in acetic anhydride with Raney nickel gave a 64 % yield of 2-(α -acetamidoethyl)-furan (IX), in contradiction to the statement of Adkins and Shriner⁴ that this catalyst cannot be used in acetic anhydride.

2-(α -Aminoethyl)-tetrahydrofuran (XVI) was prepared by catalytic reduction of 2-acetylfuran oxime with the very active W-7 Raney nickel catalyst. Acetylation of XVI gave the expected 2-(α -acetamidoethyl)-tetrahydrofuran XVII. Refractive indices of these compounds were of value in following the course of the above reductions.



EXPERIMENTAL

Microanalyses by E. Boss, K. Glens and G. Cornali

2,5-Dimethoxy-2-(aminomethyl)-2,5-dihydrofuran (III). 2,5-Dimethoxy-2-(acetamidomethyl)-2,5-dihydrofuran (II, mixture of the *cis* and the *trans* isomer as obtained by the synthesis²) (6.96 g, 0.034 mole) was heated under reflux (16 hr) with sodium hydroxide (3 N, 100 ml). The mixture was continuously extracted with ether overnight and the amine distilled. The yield was 4.72 g (86 %) of III (colorless liquid, b.p.₁₂ 95–96°, n_D^{20} 1.4589).

$C_8H_{10}ON(OCH_3)_2$ (159.2)	Calc.	C 52.8	H 8.2	N 8.8	OCH ₃ 39.0
	Found	53.1	8.3	9.0	39.4

3-Pyridol from III. III (1.94 g, 0.012 mole) was heated under reflux (15 min) with hydrochloric acid (N, 22 ml) and the colorless solution evaporated to dryness in a vacuum. The crystalline residue was dissolved in ethanol and the hydrochloride precipitated with ether. The yield was 1.49 g (93 %) of 3-pyridol hydrochloride (almost white crystals, m.p. 105–107° after sintering from 102° (Hershberg apparatus, corr.)).

C_5H_6ONCl (131.6)	Calc.	C 45.6	H 4.6	N 10.7	Cl 27.0
	Found	45.4	4.5	10.7	26.6

Sublimation (150°/0.2 mm) gave perfectly white crystals, m.p. 106–109° (sintering from 102°). 3-Pyridol hydrochloride has previously been prepared by Fischer and Renouf⁵ and by Kao⁶, but no physical constants were reported.

3-Pyridol from II. The crystalline isomer of II (4.04 g, 0.020 mole) was heated under reflux (15 min) with hydrochloric acid (N, 22 ml) and the dark-red solution evaporated to dryness in a vacuum. To the semisolid black residue containing 3-pyridol hydrochloride was added anhydrous potassium carbonate (2.0 g) and so much water, that the total volume was about 10 ml. The resulting suspension was continuously extracted with ether.

Evaporation of the ether and crystallization of the light-brown residue from benzene gave 0.92 g (48 %) of 3-pyridol (m.p. 125–126°). Sublimation did not change the m.p.

C_6H_7ON (95.1)	Calc.	C 63.2	H 5.3	N 14.7
	Found	» 63.3	» 5.3	» 14.4

A similar synthesis starting from the liquid isomer of II gave 0.98 g (52 %) of 3-pyridol (m.p. 125–126°).

Found	C 63.0	H 5.3	N 14.5
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2-(Carbomethoxyamidomethyl)-furan (V). V was prepared from furfurylamine⁹ (9.7 g) according to the directions of Hartman and Brethen⁹. The yield was 12.7 g (82 %) of V (colorless liquid, b.p.₁₀ 122–123°, n_D^{25} 1.4851).

$C_6H_8O_2N(OCH_3)$ (155.2)	Calc.	C 54.2	H 5.9	N 9.0	OCH ₃ 20.0
	Found	» 54.3	» 6.2	» 8.8	» 19.9

2,5-Dimethoxy-2-(carbomethoxyamidomethyl)-2,5-dihydrofuran (VI). VI was prepared from V (31.0 g, 0.20 mole) by electrolytic methoxylation as described previously for the preparation of II² (11.8 amp-hr (110 %) were used). The yield was 38.7 g (89 %) of VI (colorless liquid, b.p._{0.3} 104–107°, n_D^{25} 1.4652).

$C_8H_{10}O_4N(OCH_3)_2$ (217.2)	Calc.	C 49.8	H 7.0	N 6.5	OCH ₃ 42.9
	Found	» 49.5	» 6.8	» 6.9	» 42.3

3-Pyridol from VI. VI (4.34 g, 0.020 mole) was heated under reflux with hydrochloric acid (N, 22 ml) and the light-brown solution worked up as above. The yield was 1.45 g (76 %) of 3-pyridol (m.p. 125–126°).

Found	C 63.1	H 5.3	N 14.4
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3-Pyridol from furfurylamine. Furfurylamine (19.4 g, 0.20 mole) and urea (commercial product, 6.60 g, 0.11 mole) were mixed and heated under reflux (1 hr) in an oil bath (190–210°) (method of Davis and Blanchard¹⁰). Ammonia was evolved. The light-brown crystalline reaction product was dissolved in a solution of ammonium bromide (5.00 g) in methanol (260 ml) and the resulting solution electrolyzed in the usual way³ (11.9 amp-hr (111 %) were used). After electrolysis, the liquid in the cell was almost colorless in the upper part of the cell and yellow near the bottom. The liquid was poured into a solution of sodium methoxide (from 1.20 g of sodium) in methanol (20 ml) and the methanol and the ammonia evaporated in a vacuum. The semisolid residue was heated under reflux (15 min) with hydrochloric acid (N, 240 ml) and the clear yellowish-brown solution evaporated in a vacuum to dryness. Potassium carbonate (22 g) and water (75 ml) were added and the 3-pyridol isolated as above. The yield was 16.1 g (85 %) of 3-pyridol (m.p. 124–127°).

Found	C 63.1	H 5.1	N 14.9
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In separate experiments *sym*-difurfurylurea (VII) and one of the 3 possible stereoisomers of *sym*-(2,5-dimethoxy-2,5 dihydro-2 furfuryl) urea (VIII) were isolated in a pure state.

VII was obtained as white crystals from ethanol (m.p. 129–131°). Further crystallization did not change the m.p. (previously found 128°¹¹).

$C_{11}H_{13}O_3N_2$ (220.2)	Calc.	C 60.0	H 5.5	N 12.7
	Found	» 60.2	» 5.2	» 12.8

VIII was obtained as white crystals from water (m.p. 149–151°). After recrystallization from water the m.p. was raised to 151–152°.

$C_{11}H_{13}O_3N_2(OCH_3)_2$ (344.4)	Calc.	C 52.3	H 7.0	N 8.1	OCH ₃ 36.1
	Found	» 52.4	» 7.1	» 8.4	» 35.3

2-(*a*-Acetamidoethyl)-furan (IX). 2-Acetylfuran oxime (12.5 g) and acetic anhydride (30 ml) were shaken (1 hr) with Raney nickel (1.6 g of a 2 months old sample) under hydrogen (100 atm, 70–80°). The reaction product was isolated by distillation. The yield was 9.8 g (64 %) of IX (pale-yellow liquid, b.p._{0.1} 86–89°, n_D^{25} 1.4922).

$C_8H_9ON(COCH_3)$ (153.2)	Calc.	C 62.7	H 7.2	N 9.1	COCH ₃ 28.1
	Found	» 62.7	» 7.5	» 9.4	» 28.5

IX was also prepared by acetylation of 2-(*a*-aminoethyl)-furan (XII) with acetic anhydride (b.p.₁₂ 143–144°, n_D^{25} 1.4929).

IX crystallized after standing for some time. Crystallization from ether – petroleum ether gave white crystals with the m.p. 52–53°. Another crystallization did not change the m.p.

Found	C 62.4	H 7.2	N 9.3	COCH ₃ 27.6
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2,5-Dimethoxy-2-(α -acetamidoethyl)-2,5-dihydrofuran (X). IX (2.00 g, 0.013 mole) and ammonium bromide (0.30 g, 0.0031 mole) were dissolved in methanol (analytical grade, 20 ml) and the solution electrolyzed in the small cell described previously¹² (temperature of cooling-bath -20°).

Time hr	Current amp	Potential across the cell during electrolysis (volt)	Ampere hours (per cent of theoretical amount)	
0.1	0.8	6.2	0.07	(10 %)
0.3	0.7	6.2	0.25	(36 %)
0.5	0.7	6.2	0.34	(49 %)
1.0	0.6	6.3	0.66	(95 %)
1.2	0.5	6.4	0.77	(110 %)

After electrolysis, the pale-yellow liquid was poured into a solution of sodium methoxide (from 73 mg (0.0032 mole) of sodium) in methanol (3 ml) and the methanol and the ammonia evaporated in a vacuum. Anhydrous ether (50 ml) was added, a precipitate of sodium bromide removed by filtration and the filtrate distilled in a vacuum. The yield was 2.47 g (88 %) of X (colorless, viscous oil, b.p._{0.1} 110–115°, n_D^{25} 1.4739).

$C_8H_{11}ON(OCH_3)_2(COCH_3)$ (215.2) Calc. C 55.8 H 8.0 N 6.5 OCH_3 28.8 $COCH_3$ 20.0
Found » 56.1 » 7.9 » 6.6 » 28.9 » 20.3

2,5-Dimethoxy-2-(α -aminoethyl)-2,5-dihydrofuran (XI). XI was prepared from X (2.15 g) as described for the preparation of III (refluxing time 38 hr). The yield was 1.39 g (80 %) of XI (colorless liquid, b.p.₁₂ 90–92°, n_D^{25} 1.4565).

$C_8H_9ON(OCH_3)_2$ (173.2) Calc. C 55.5 H 8.7 N 8.1 OCH_3 35.8
Found » 55.5 » 9.0 » 8.3 » 35.8

2-Methyl-3-pyridol from XI. This preparation was carried out with XI (1.10 g, 0.0064 mole) as described for the preparation of 3-pyridol from III. The yield was 0.88 g (95 %) of 2-methyl-3-pyridol hydrochloride (white crystals, m.p. 223–224°).

C_8H_9ONCl (145.6) Calc. C 49.5 H 5.5 N 9.6 Cl 24.4
Found » 49.6 » 5.7 » 9.9 » 24.8

The free base was prepared from the hydrochloride in the usual way and obtained as yellowish-white crystals (m.p. 169–170°, previously found 167–168°¹³ and 163–165°¹⁴).

C_8H_9ON (109.1) Calc. C 66.0 H 6.5 N 12.8
Found » 66.2 » 6.6 » 13.0

Sublimation (150°/0.05 mm) gave white crystals (m.p. 169–170°).

2-(α -Aminoethyl)-furan (XII) (directions of Hartung³). 2-Acetylfuran oxime (15.6 g, 0.12 mole) was dissolved in absolute ethanol (200 ml), to which had been added acetyl chloride (26.5 ml, 0.37 mole), and the solution was shaken (4 hr) with palladium charcoal (10 %, 6.5 g) under hydrogen (15 atm). After filtration the solvent was evaporated in a vacuum, the residue made alkaline with sodium hydroxide (50 %) and continuously extracted with ether. Distillation through a short packed column gave 6.5 g (47 %) of XII (colorless liquid, b.p.₇₆₀ 148–149°, n_D^{25} 1.4748).

C_8H_9ON (111.1) Calc. C 64.8 H 8.2 N 12.6
Found » 64.6 » 8.3 » 12.5

Picrate. The m.p. was 184–186° (dec.) after two crystallizations from ethanol.

$C_{12}H_{12}O_8N_4$ (340.3) Calc. C 42.4 H 3.6 N 16.5
Found » 42.4 » 3.7 » 16.8

Phenylthiourea derivative. The m.p. was 101–102° after two crystallizations from ethanol.

$C_{12}H_{14}ON_2S$ (246.3) Calc. C 63.4 H 5.7 N 11.4
Found » 64.0 » 5.7 » 11.2

2-(α -Carbomethoxyamidoethyl)-furan (XIII). 2-Acetylfuran oxime (12.5 g, 0.10 mole) was hydrogenated as described above for the preparation of XII. The reaction mixture was filtered and evaporated to dryness in a vacuum, finally at 0.1 mm (50–55°). The reddish-brown residue was dissolved in water (20 ml), extracted with ether and carbo-

methoxylated with methyl chloroformate (0.10 mole) according to the directions of Hartman and Brethen⁹. The yield was 9.2 g (54 %) of XIII (colorless liquid, b.p._{0.1} 72–75°, n_D^{25} 1.4805).

$C_7H_9O_2N(OCH_3)$ (169.2) Calc. C 56.8 H 6.6 N 8.3 OCH_3 18.3
Found » 57.1 » 7.0 » 8.6 » 18.2

Since the yield, from the reduction of 2-acetylfuran oxime, of actually isolated 2-(α -aminoethyl)-furan was only 47 %, the carbomethoxylation must have been almost quantitative and the carbamate furthermore easier to isolate than the amine.

2,5-Dimethoxy-2-(α -carbomethoxyamidoethyl)-2,5-dihydrofuran (XIV). XIV was prepared from XIII (11.6 g, 0.068 mole) by electrolytic methoxylation as described previously for the preparation of II² (4.1 amp-hr (110 %) were used). The yield was 13.8 g (88 %) of XIV (colorless oil, b.p._{0.2} 98–102°, n_D^{25} 1.4649).

$C_7H_9O_2N(OCH_3)_2$ (231.2) Calc. C 51.9 H 7.4 N 6.1 OCH_3 40.3
Found » 52.2 » 7.7 » 5.9 » 40.5

2-Methyl-3-pyridol from XIV. XIV (2.31 g, 0.010 mole) and hydrochloric acid (N, 100 ml) were heated under reflux (1.5 hr). After decantation from a small amount of an insoluble oil the mixture was evaporated in a vacuum to dryness. The residue was dissolved in methanol (about 5 ml) and the hydrochloride precipitated with ether (100 ml). The yield was 1.23 g (85 %) of crude 2-methyl-3-pyridol hydrochloride (light-brown powder). 200 mg of this product was purified by sublimation (195°/0.05 mm). The yield was 170 mg (72 %) of almost white crystals (m.p. 223–225°).

Found C 49.6 H 5.5 N 9.3 Cl 24.7

2-(α -Ureidoethyl)-furan (XV¹⁰). XII (6.12 g, 0.055 mole) was dissolved in hydrochloric acid (5.8 N, 9.5 ml, 0.055 mole) under cooling, a solution of urea (3.45 g, 0.057 mole) in water (16 ml) was added and the mixture heated under reflux (16 hr). After cooling, the crystalline precipitate was removed by filtration, washed twice with water and dried. The yield was 4.24 g (50 %) of crude XV (light-brown powder, m.p. 91–103°). 200 mg was crystallized from ethyl acetate-ether, yielding 140 mg (35 %) of XV (white crystals, m.p. 114–116°). Sublimation did not change the m.p.

$C_7H_{10}O_2N_2$ (154.2) Calc. C 54.5 H 6.5 N 18.2
Found » 54.5 » 6.5 » 18.2

2-Methyl-3-pyridol from XV. XV (340 mg, 0.0022 mole) and ammonium bromide (150 mg, 0.0015 mole) were dissolved in methanol (analytical grade, 10 ml) and the mixture electrolyzed in the small cell described previously¹² (6.4–6.6 v, 0.4 amp, 0.35 hr). 0.13 amp-hr (0.0024 faraday) was passed through the cell. After electrolysis the pale-yellow liquid was poured into a solution of sodium methoxide (from 37 mg of sodium (0.0016 mole)) in methanol (3 ml) and the solvent evaporated in a vacuum. The residue was heated under reflux (15 min) with hydrochloric acid (N, 22 ml) and the pyridol isolated as described for the preparation of 3-pyridol from II. The crude methylpyridol was converted to the hydrochloride by addition of concentrated hydrochloric acid and evaporation in a vacuum to dryness. The hydrochloride was then purified by precipitation from ethanol – ether (yield 210 mg) followed by sublimation (190°/0.05 mm). The yield was 200 mg (62 %) of 2-methyl-3-pyridol hydrochloride (m.p. 225–227°).

Found C 49.4 H 5.2 N 9.6 Cl 24.7

2-(α -Aminoethyl)-tetrahydrofuran (XVI). 2-Acetylfuran oxime (6.0 g) was dissolved in methanol (50 ml) and the solution was shaken (16 hr) with W-7 Raney nickel catalyst¹⁵ (1 g) under hydrogen (100–50 atm). After filtration the solvent was distilled through a short packed column and the residue distilled further in a vacuum without the column. The yield was 2.17 g (39 %) of XVI (colorless liquid, b.p.₁₃ 47–48°, n_D^{25} 1.4489).

$C_6H_{11}ON$ (115.2) Calc. C 62.6 H 11.4 N 12.2
Found » 62.6 » 11.5 » 12.0

Phenylthiourea derivative. The m.p. was 111–115° after two crystallizations from ethanol.

$C_{13}H_{18}ON_2S$ (250.4) Calc. C 62.4 H 7.3 N 11.2
Found » 62.5 » 7.3 » 11.4

Acetyl derivative (XVII). XVII was obtained as a colorless liquid (b.p._{0.4} 97–101°, n_D^{25} 1.4722).

$C_6H_{11}ON(COCH_3)$ (157.2) Calc. C 61.1 H 9.6 N 8.9 $COCH_3$ 27.4
Found » 61.5 » 9.7 » 8.6 » 26.8

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* *Editor's note:* On the request of the authors the publication of this and the following six papers by the same group has been postponed.