

New Method for the Preparation of Quaternary 3-Hydroxypyridinium Chlorides

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Oxidation of *N*-monosubstituted 2-(α -aminoalkyl)furans with chlorine in water gives quaternary 3-hydroxypyridinium chlorides. This new reaction has been exemplified by the preparation of ten quaternary compounds, seven of which are new. Quaternary chlorides of 3-hydroxypicolinamide decompose into this compound and alkyl chloride at 250–270°.

The method of preparing 3-pyridinols by oxidation of 2-(α -aminoalkyl)-furans with chlorine in aqueous solution^{1,2} has been extended to include oxidation of *N*-monosubstituted 2-(α -aminoalkyl)furans. Quaternary 3-hydroxypyridinium chlorides are hereby formed. The reaction is pictured below. Yields are given in Table 1.

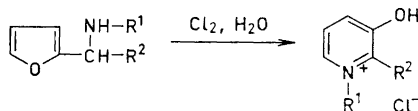
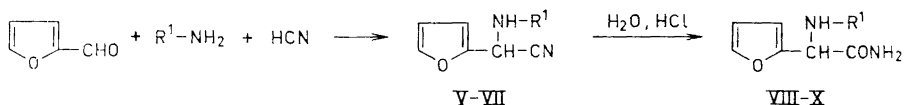


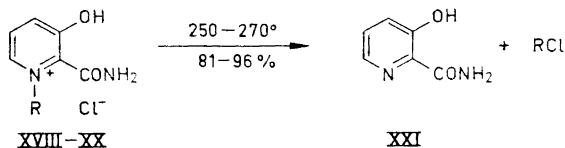
Table 1. Quaternary 3-hydroxypyridinium chlorides from furans. New compounds are marked with an asterisk.

R ¹	R ²	Furan compound	Quaternary compound	Yield %
CH ₃	H	I	XI	99
C ₂ H ₅	H	II	XII *	63
CH ₂ C ₆ H ₅	H	III	XIII	61
C ₆ H ₅	H	IV	XIV	31
CH ₃	CN	V *	XV *	32
C ₂ H ₅	CN	VI *	XVI *	33
CH ₂ C ₆ H ₅	CN	VII *	XVII *	29
CH ₃	CONH ₂	VIII *	XVIII *	95
C ₂ H ₅	CONH ₂	IX *	XIX *	87
CH ₂ C ₆ H ₅	CONH ₂	X *	XX *	64

Of the starting materials the *N*-substituted furfurylamines (I–IV) are known. The derivatives of α -amino-2-furanacetonitrile (V–VII) were prepared from furfural by a Strecker type reaction and these were hydrolysed to the corresponding amides (VIII–X).



Thermal decomposition of the three 1-alkyl-2-carbamoyl-3-hydroxypyridinium chlorides (XVIII–XX) afforded in each case 3-hydroxypicolinamide (XXI) in high yield.



The structures of all new compounds follow from the syntheses and from the analyses. The quaternary compounds give an orange color with an aqueous solution of ferric chloride as has been found previously³ for other quaternary 3-hydroxypyridines.

EXPERIMENTAL

α -(Methylamino)-2-furanacetonitrile (V). A mixture of furfural (38.4 g, 0.400 mole) and acetic acid (24.0 g, 0.400 mole) was added to a well-stirred solution of sodium cyanide (19.6 g, 0.400 mole) in water (140 ml) at 0–5° over a period of about 15 min. Efficient cooling was required. Methylamine (31.0 g of a 40% aqueous solution, 0.400 mole) was added in one portion to the resulting light brown emulsion of cyanohydrin, the temperature of the reaction mixture rising to 20°. The emulsion was stirred for 2 h at room temperature; a suspension of canary-yellow crystals of V was obtained. Scratching is sometimes necessary to induce crystallization. After cooling to 0° the crystals were isolated by filtration, washed with three 50 ml portions of water of 0°, and dried (25°, 10 mm). V (48.4 g; 89%) was obtained as yellow crystals, m.p. 39–40°. Crystallization from methylocyclohexane gave white crystals with constant m.p. (40–41°). [Found: C 61.7; H 6.0; N 20.5. Calc. for C₇H₈N₂O (136.2): C 61.8; H 5.9; N 20.6].

V deteriorates on standing. The hydrochloride of V, which is stable, may be prepared by treatment of V with an equimolar amount of concentrated hydrochloric acid, evaporation to dryness on the water bath (100°) under reduced pressure, and trituration and washing of the resulting crystalline residue with acetone. The hydrochloride of V melts at 127–128°.

α -(Ethylamino)-2-furanacetonitrile (VI) hydrochloride. An emulsion of furfural cyanohydrin was prepared as described above. Ethylamine (25.7 g, 70% aqueous solution, 0.400 mole) was added, the mixture stirred for 2 h, and the resulting emulsion of VI extracted with three 100 ml portions of ether. The combined ethereal extracts were extracted with 3 N hydrochloric acid (150 ml, 0.45 mole), and the acid phase was evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline

residue was triturated in a mortar with acetone, isolated by filtration, washed with acetone, and dried in a hood at 100°. The hydrochloride of VI (52.7 g; 71 %) was obtained as white crystals, m.p. 127–129° (decomp.). A sample crystallized from ethanol had m.p. 125–128° (decomp.). [Found: C 51.4; H 6.0; Cl⁻ 19.0; N 15.0. Calc. for C₈H₁₁ClN₂O (186.6): C 51.6; H 5.9; Cl⁻ 19.0; N 15.0].

α-(Benzylamino)-2-furanacetonitrile (VII) hydrochloride. An emulsion of furfural cyanohydrin was prepared as described above. Benzylamine (42.9 g, 0.400 mole) was added, the emulsion stirred for 2 h at room temperature, and then poured into 6 N hydrochloric acid (150 ml) with efficient stirring. The resulting grey crystalline precipitate was isolated by filtration, washed with three 50 ml portions of 3 N hydrochloric acid and with acetone, and then dried in a hood at 50°. The hydrochloride of VII (80.0 g; 80 %) was obtained, m.p. 128–129° (decomp.). A sample crystallized from 99 % ethanol had the same m.p. [Found: C 62.8; H 5.3; Cl⁻ 14.3; N 10.9. Calc. for C₁₃H₁₃ClN₂O (248.7): C 62.8; H 5.3; Cl⁻ 14.3; N 11.2].

α-(Methylamino)-2-furanacetamide (VIII) hydrochloride. A suspension of canary-yellow crystals of V was prepared as described above, and extracted with three 50 ml portions of ether. The combined ethereal extracts were dried over magnesium sulfate and evaporated to dryness on the water bath (30°) under reduced pressure. The resulting tea-colored oily or semisolid residue of crude V was poured slowly into concentrated hydrochloric acid (150 ml) at 0–10° with efficient stirring, forming a precipitate of the hydrochloride of V. The temperature was allowed to rise to 25° and was kept there for 4 h. The resulting thick dark suspension of the hydrochloride of VIII was cooled to 0°, and the precipitate isolated by filtration, washed with acetone on the filter (without stirring), and dried at 100°. The hydrochloride of VIII (61.6 g; 81 %) was obtained as slightly grey crystals, m.p. 263° (decomp.). A sample crystallized from water had the same m.p. [Found: C 44.2; H 5.9; Cl⁻ 18.7; N 14.5. Calc. for C₇H₁₁ClN₂O₂ (190.6): C 44.1; H 5.8; Cl⁻ 18.6; N 14.7].

α-(Ethylamino)-2-furanacetamide (IX). An emulsion of VI was prepared as described above, and added with stirring to concentrated hydrochloric acid (800 ml). The resulting clear solution was left standing at room temperature for 21 h. The dark solution now containing the hydrochloride of IX, was evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline residue was dissolved in 3 N sodium hydroxide (500 ml). Addition of 40 % aqueous sodium hydroxide (150 ml) caused an oil to separate. Extraction with three 150 ml portions of ether and evaporation of the combined ethereal extracts on the water bath (100°) under reduced pressure gave a light brown oil (35.0 g), which crystallized on scratching. Crystallization from carbon tetrachloride (100 ml) gave IX (31.0 g; 46 %) as fine yellow crystals, m.p. 72–76°. Recrystallization from toluene to constant m.p. gave white crystals, m.p. 75–77°. [Found: C 57.2; H 7.4; N 16.5. Calc. for C₈H₁₂N₂O₂ (168.2): C 57.1; H 7.2; N 16.7].

α-(Benzylamino)-2-furanacetamide (X). An emulsion of VII was prepared as described above. The emulsion was extracted with ether (100 ml) and the ethereal extract dissolved in concentrated hydrochloric acid (800 ml) with stirring. The resulting dark solution was left standing overnight at room temperature. Evaporation on the water bath (100°) under reduced pressure gave a thick dark residue, which after boiling with acetone (300 ml) was converted into a brown crystalline paste. On filtration, washing with acetone, and drying at room temperature, a brown crystalline product was obtained. This was dissolved in hot 99 % ethanol (175 ml) and precipitated with hot acetone (175 ml). The crystalline precipitate was isolated by filtration, washed with acetone, and dried at room temperature to give white impure hydrochloride of X (78.0 g), m.p. 198–200° (decomp., softening from 107°). Stirring with 0.7 N sodium hydroxide (535 ml) precipitated crude crystalline X. It was filtered off, dissolved in methanol (150 ml), and precipitated with water (400 ml). Upon filtration, washing with water, and drying (50°, 10 mm) X (30.6 g; 33 %) was obtained as white crystals, m.p. 70–72°. A sample was recrystallized from carbon tetrachloride to constant m.p. (71–72°). [Found: C 67.6; H 6.0; N 12.2. Calc. for C₁₃H₁₄N₂O₂ (230.3): C 67.8; H 6.1; N 12.2].

3-Hydroxy-1-methylpyridinium chloride (XI). *N*-Methylfurfurylamine (I) (22.2 g, 0.200 mole) was dissolved in N hydrochloric acid (200 ml, 0.200 mole). Chlorine (14.9 g, 0.210 mole) was passed into the solution at 75–80° over a period of about 20 min with efficient stirring. The resulting light brown solution was evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline residue was crushed rapidly

in a mortar under acetone. Filtration, washing with acetone, and drying (100°, 10 mm) gave XI (28.7 g; 99 %) as light brown, extremely hygroscopic crystals, m.p. 157–162°. 5.00 g of this material was dissolved in 99 % ethanol (10 ml), precipitated with acetone (30 ml), and isolated as above. XI (4.14 g; 82 %) was obtained, m.p. 161–162°. Repetition of this procedure gave white crystals, m.p. 162–164° (reported⁴ m.p. 158°). Further purification did not change the m.p. [Found: C 48.2; H 5.9; Cl⁻ 24.5; N 9.4. Calc. for C₈H₈ClNO (145.6): C 49.5; H 5.5; Cl⁻ 24.4; N 9.6]. The carbon-hydrogen values should be judged in view of the strong hygroscopicity of XI.

A mixed m.p. determination and infrared spectroscopy (in KBr) proved this sample to be identical with a sample prepared by conversion of 3-hydroxy-1-methylpyridinium iodide⁵ into XI with moist silver oxide and hydrochloric acid.

1-Ethyl-3-hydroxypyridinium chloride (XII). *N*-Ethylfurfurylamine (II) (3.76 g, 30.0 mmole) was dissolved in 0.75 N hydrochloric acid (40.0 ml, 30.0 mmole). Chlorine (2.2 g, 31 mmole) was passed into the solution at 70–80° over a period of about 20 min with efficient stirring. The resulting light brown solution was evaporated to dryness on the water bath (100°) under reduced pressure. The dark brown, oily residue crystallized after shaking with acetone for 30 min. Filtration, washing with acetone, and drying (100°, 0.1 mm) gave XII (3.00 g; 63 %) as greyish, very hygroscopic crystals, m.p. 108–111°. A sample crystallized from ethanol-acetone had the same m.p. [Found: C 50.6; H 6.9; Cl⁻ 22.5; N 8.5. Calc. for C₈H₁₀ClNO (159.6): C 52.7; H 6.3; Cl⁻ 22.3; N 8.8].

The carbon-hydrogen values should be judged in view of the strong hygroscopicity of XII. XII is a new compound, but the corresponding bromide is known.⁶

1-Benzyl-3-hydroxypyridinium chloride (XIII). *N*-Benzylfurfurylamine (III) hydrochloride⁷ (2.24 g, 10.0 mmole) was dissolved in water (40 ml) at 70°. Chlorine (0.7 g, 10 mmole) was passed into the solution at 70° over a period of about 20 min with efficient stirring. The resulting light brown solution was evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline residue was boiled with acetone, isolated by filtration, washed with acetone, and dried (100°, 0.1 mm) Crude XIII (1.59 g, m.p. 146–156°) thus obtained was dissolved in 99 % ethanol (10 ml), precipitated with ether, and isolated as described above. XIII (1.35 g; 61 %) was obtained as greyish crystals, m.p. 159–161°. Repetition of this procedure gave white crystals, m.p. 160–161°, (reported⁸ m.p. 160°). Further purification did not change the m.p. [Found: C 65.0; H 5.6; Cl⁻ 15.9; N 6.2. Calc. for C₁₃H₁₂ClNO (221.7): C 64.8; H 5.5; Cl⁻ 16.0; N 6.3].

3-Hydroxy-1-phenylpyridinium chloride (XIV). *N*-Phenylfurfurylamine⁹ (IV) hydrochloride (4.19 g, 20.0 mmole) was suspended in 9 N hydrochloric acid (40 ml). Chlorine (1.4 g, 20 mmole) was passed into the suspension at 15–25° over a period of about 20 min with efficient stirring. The resulting almost clear green solution was evaporated to dryness on the water bath (100°) under reduced pressure. The thick, dark green oily residue was treated with acetone (50 ml) and filtered in order to remove some crystalline impurity. A large volume of ether was added to the filtrate. The resulting precipitate was isolated by filtration, washed with ether, and dried (100°, 0.1 mm). Crude XIV (1.27 g; 31 %) was obtained as a brown powder, m.p. 203–205°. Three crystallizations from propanol gave white crystals with constant m.p. (214–215°, reported¹⁰ m.p. 212–214°). [Found: C 63.6; H 4.9; Cl⁻ 17.2; N 6.8. Calc. for C₁₁H₁₀ClNO (207.7): C 63.5; H 4.9; Cl⁻ 17.1; N 6.7].

2-Cyano-3-hydroxy-1-methylpyridinium chloride (XV). V (4.09 g, 30.0 mmole) was dissolved in 8 N hydrochloric acid (30 ml). Chlorine (2.2 g, 31 mmole) was passed into the solution at 15–25° with efficient stirring over a period of about 20 min. The resulting light yellow solution was evaporated to dryness on the water bath (100°) under reduced pressure and the reddish crystalline residue was washed on a filter with 99 % ethanol (two 10 ml portions) and acetone, and dried (100°, 1 mm). XV (1.62 g; 32 %) was obtained as white crystals, m.p. 204–213° (decomp.). Crystallization from 99 % ethanol (130 ml) gave 1.13 g, m.p. 209–213° (decomp.). [Found: C 49.1; H 4.3; Cl⁻ 20.6; N 16.3. Calc. for C₇H₇ClN₂O (170.6): C 49.2; H 4.1; Cl⁻ 20.8; N 16.4].

2-Cyano-1-ethyl-3-hydroxypyridinium chloride (XVI). The hydrochloride of VI (9.33 g, 50.0 mmole) was dissolved in 4 N hydrochloric acid (90 ml) at 50°. Chlorine (3.9 g, 55 mmole) was passed into the solution at 50–55° with efficient stirring over a period of about 20 min. The tea-colored reaction mixture was evaporated to dryness on the water bath (100°) under reduced pressure. The resulting brown crystalline residue was crystallized from 99 % ethanol (250 ml). XVI (3.07 g; 33 %) was obtained as white

crystals, m.p. 220–223° (decomp.). [Found: C 51.8; H 5.0; Cl⁻ 19.1; N 15.1. Calc. for C₈H₉ClN₂O (184.6): C 52.0; H 4.9; Cl⁻ 19.2; N 15.2].

1-Benzyl-2-cyano-3-hydroxypyridinium chloride (XVII). The hydrochloride of VII (12.44 g, 50.0 mmole) was suspended in 4 N hydrochloric acid (90 ml) at 50°. Chlorine (3.9 g, 55 mmole) was passed into the suspension at 50–55° with efficient stirring over a period of about 20 min. The resulting yellow suspension was filtered in order to remove some unchanged starting material. The filtrate, which turned red during filtration, was evaporated to dryness on the water bath (100°) under reduced pressure. The brown semicrystalline residue was treated with acetone, filtered, and washed with acetone and 99 % ethanol. XVII (3.55 g; 29 %) was obtained as grey crystals, m.p. 158–160°. Crystallization from 99 % ethanol (40 ml) gave white crystals (2.20 g) with constant m.p. (162–164°). [Found: C 63.1; H 4.6; Cl⁻ 14.3; N 11.3. Calc. for C₁₃H₁₁ClN₂O (246.7): C 63.3; N 4.5; Cl⁻ 14.4; N 11.4].

2-Carbamoyl-3-hydroxy-1-methylpyridinium chloride (XVIII). Crude hydrochloride of VIII (19.1 g, 0.100 mole) was dissolved in water (200 ml). Chlorine (7.5 g, 0.106 mole) was passed into the solution at 20–30° with efficient stirring over a period of about 45 min. The resulting faintly yellow solution was evaporated to dryness on the water bath (100°) under reduced pressure and the crystalline residue was triturated with acetone. The crystals were isolated by filtration, washed with two 15 ml portions of ethanol and with acetone, and dried at 100°. XVIII (17.9 g; 95 %) was obtained as grey crystals, m.p. 265° (decomp.).

5.00 g of this product was dissolved in hot 3 N hydrochloric acid (5.0 ml). Acetone (30 ml) was added and the mixture cooled to 0°. The precipitate was isolated by filtration, washed with acetone, and dried at 100°. XVIII (4.70 g; 89 %) was obtained as white crystals, m.p. 269° (decomp.). [Found: C 44.6; H 4.9; Cl⁻ 19.0; N 14.9. Calc. for C₇H₉ClN₂O₂ (188.6): C 44.6; H 4.8; Cl⁻ 18.8; N 14.9].

XVIII (1.00 g) was placed in a test tube (I.D. 30 mm) mounted at an angle. The tube was heated carefully with a flame, until no more gas was evolved. A small dark residue remained at the bottom of the tube. 3-Hydroxypicolinamide (XXI) (0.70 g; 96 %) was scratched off the upper end of the tube, partly as a white sublimate, and partly as greenish-white solidified distillate; m.p. after homogenization 191–197° (reported¹¹ m.p. 194°). Washing with methanol (1 ml), water (1 ml), and again with methanol (1 ml), and drying gave 0.66 g; m.p. and mixed m.p. with an authentic sample 196–198°.

Heating of XVIII in a m.p. tube showed that decomposition takes place at about 270°.

2-Carbamoyl-1-ethyl-3-hydroxypyridinium chloride (XIX). IX (5.04 g, 30.0 mmole) was dissolved in 0.75 N hydrochloric acid (40.0 ml). Chlorine (2.3 g, 32 mmole) was passed into the solution at 20–30° with efficient stirring over a period of about 20 min. The colorless reaction mixture was decanted from a small amount of a sticky by-product and evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline residue was boiled with acetone, isolated by filtration, and dried (100°). XIX (5.28 g; 87 %) was obtained as white crystals, m.p. 249° (decomp.). Crystallization from ethanol did not change the m.p. [Found: C 47.6; H 5.6; Cl⁻ 17.4; N 13.9. Calc. for C₈H₁₁ClN₂O₂ (202.6): C 47.4; H 5.5; Cl⁻ 17.5; N 13.8].

XIX (150 mg) was kept in a sublimation tube at 270° for 15 min. The sublimate formed was washed as described above for the decomposition of XVIII. XXI (83 mg; 81 %) was obtained, m.p. 194–197°.

1-Benzyl-2-carbamoyl-3-hydroxypyridinium chloride (XX). X (6.90 g, 30.0 mmole) was dissolved in 1.5 N hydrochloric acid (40 ml). Chlorine (2.3 g, 32 mmole) was passed into the solution at 25–35° with efficient stirring over a period of about 20 min. The resulting slightly yellow reaction mixture was decanted through a filter to remove a small quantity of solid material and evaporated to dryness on the water bath (100°) under reduced pressure. The crystalline residue was triturated with acetone, isolated by filtration, washed with two 10 ml portions of 99 % ethanol and with acetone, and dried (100°). XX (5.04 g; 64 %) was obtained as white crystals, m.p. 224° (decomp.). A sample was recrystallized from propanol to constant m.p. [225° (decomp.)]. [Found: C 58.7; H 5.0; Cl⁻ 13.4; N 10.5. Calc. for C₁₃H₁₃ClN₂O₂ (264.7): C 58.9; H 5.0; Cl⁻ 13.4; N 10.6].

XX (100 mg) was placed in a test tube (I.D. 8 mm) and the tube inserted in an oil bath at 250° for 3 min. Some sublimate was formed. The tube was then evacuated (0.2

mm) and the material in the tube (sublimate and residue) sublimed at 200°. XXI (50 mg; 96 %) was obtained, m.p. 194–198°.

Ferric chloride reactions. Compounds XI–XX each gave an orange color with ferric chloride in aqueous solution. The color is distinctly different from the red color given by non-quaternary 3-pyridinols.

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Received November 4, 1968.