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1-Alkoxy-7-hydroxy-1,3-dihydrofuro[3,4-*c*]pyridinium Salts

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Abstract—New salt structures have been synthesized from pyridoxal and various organic and inorganic acids.

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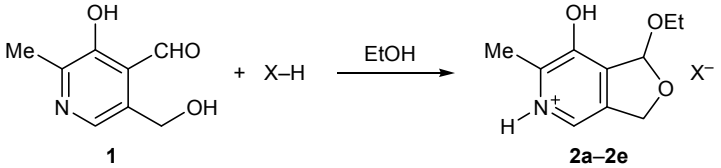
Pyridoxal (3-hydroxy-5-hydroxymethyl-2-methylpyridine-4-carbaldehyde) is a form of vitamin B_6; it plays an important role in biochemical processes occurring in living organisms. Its catalytically active (coenzyme) form, pyridoxal phosphate, is involved in many reactions. Pyridoxal is a polyfunctional compound possessing reactive phenolic, pseudo alcohol, and formyl groups together with basic pyridine nitrogen atom which is capable of forming salt structures. Pyridoxal is fairly unstable and is therefore commercially produced as pyridoxal hydrochloride. Analogous salt structures are formed in many reactions. We previously studied alkylation of a series of phenols and polyphenols with pyridoxal. The reactions were carried out in the presence of HCl, and the products were the corresponding hydrochlorides [1]. Pyridoxal reacted with dialkyl hydrogen phosphites to give inner salts [2]. Ammonium moiety often constitutes a necessary structural unit of potentially biologically active compounds [3–5].

In this work we made an attempt to obtain onium salts from pyridoxal (**1**) and some mineral, carboxylic, and phosphorus acids. The reaction of pyridoxal with such strong acids as sulfuric, trifluoromethanesulfonic, and trifluoroacetic in alcohol afforded alkoxyfuropyridinium salts **2a**–**2c** (Scheme 1). The structure of **2a**–**2e** was confirmed by elemental analyses and IR, ^{1}H and ^{13}C NMR, and mass spectra. According to the ^{1}H NMR data, compounds **2a**–**2e** contained an ethoxy group, protons of the endocyclic methylene group (3-H) resonated as two doublets with fairly similar chemical shifts (J = 13.10–14.10 Hz), and the OCHO signal (1-H) was a singlet. The 4-H signal was observed in a weaker field than the corresponding signal of free pyridoxal, and the OH signal appeared as a broadened singlet. The IR spectra of **2a**–**2e** showed a number of absorption bands in the region 1800–2500 cm^{-1}, which are typical of N^+–H group. The salt structure of **2a**–**2e** is indirectly supported by their solubility in water.

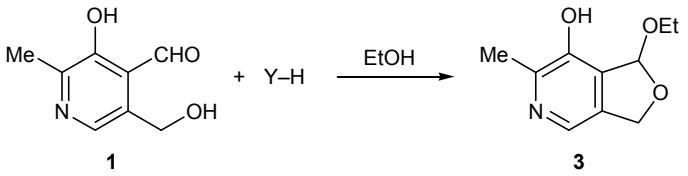
The reaction of **1** with weaker acids, such as acetic acid or phenol, gave a different result. In these cases, the product was neutral acetal **3** (Scheme 2), and acetic acid or phenol acted as catalyst. No alkoxyfuropyridines were formed in the absence of acid catalyst. Compound **1** could be expected to react with dicarboxylic acids to give 2 : 1 adducts; however, these

Scheme 1.



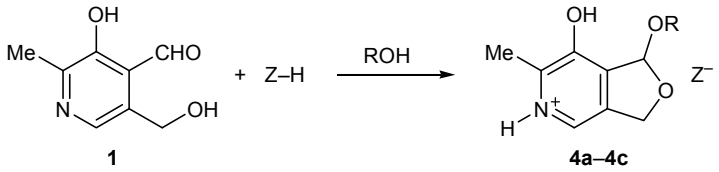
2, X = HSO_4^- (**a**), $CF_3SO_2^-$ (**b**), CF_3COO^- (**c**), $HOC(O)C(O)O^-$ (**d**), $HOC(O)CH{=}CHC(O)O^-$ (**e**).

Scheme 2.



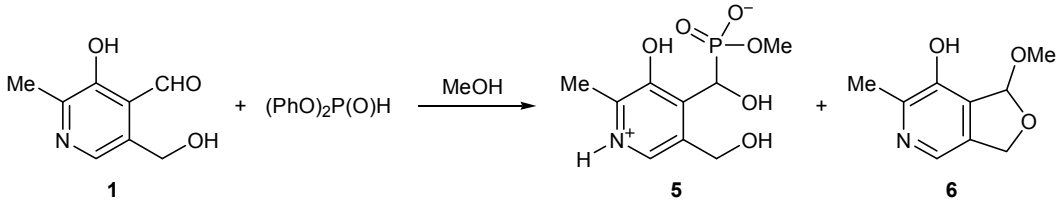
Y–H = PhOH, AcOH.

Scheme 3.



4, R = Et, Z = $(ClCH_2)_2P(O)O$ (**a**), $(HO)_2P(O)C(Me)(OH)P(O)(OH)O$ (**b**); R = Me, Z = $(ClCH_2)_2P(O)O$ (**c**).

Scheme 4.



reactions involved only one carboxy group with formation of 1:1 acid salts **2d** and **2e** (Scheme 1).

We previously showed that pyridoxal forms salt structures with phosphorous acid; the reactions were carried out in alcohols, and pyridoxal was converted to the corresponding acetal, alkoxyfuropyridine [6]. Bis(chloromethyl)phosphinic and 1-hydroxyethane-1,1-diylphosphonic acids reacted with pyridoxal (**1**) in ethanol or methanol to give alkoxyfuropyridinium salts **4a**–**4c** (Scheme 3). The structure of **4a** was proved by X-ray analysis (Fig. 1). The bond lengths in molecule **4a** conform to the corresponding standard values. The pyridine heterocycle is planar, and the dihydrofuran ring has an *O-envelope* conformation with the $C^1C^8C^9C^3$ fragment planar within 0.024(6) Å and the O^1 atom deviating from that plane by 0.320(3) Å; the ethoxy group occupies the axial position.

The reaction of pyridoxal with a weak phosphorus acid, diphenyl hydrogen phosphite, in methanol gave a mixture of inner salt **5** and acetal **6**. Presumably, compound **5** is formed as a result of replacement of phenoxy groups on the phosphorus by methoxy and addition of phosphorus to the carbonyl carbon atom with formation of dialkyl α-hydroxyphosphonate which (as shown in [2]) is very readily hydrolyzed to α-hydroxyphosphonate **5**.

EXPERIMENTAL

The IR spectra (400–3600 cm^{-1}) were recorded in KBr on a Bruker Tensor-27 spectrometer. The ^1H, ^{13}C, and ^{31}P NMR spectra were measured on a Bruker Avance 400 spectrometer at 400.13, 100.61, and 161.98 MHz, respectively. The mass spectra (MALDI-TOF) were obtained on a Bruker Ultraflex III TOF/TOF instrument using 4-nitroaniline as matrix.

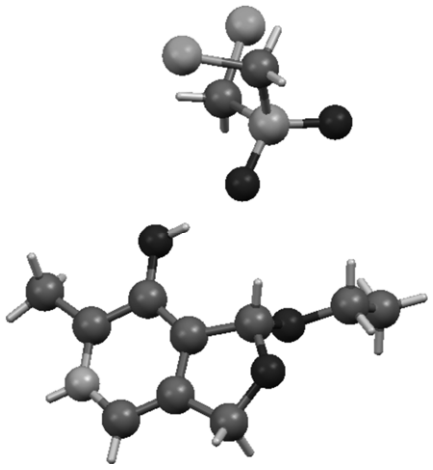


Fig. 1. Structure of the molecule of 1-ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-5-ium bis(chloromethyl)phosphinate (**4a**) according to the X-ray diffraction data.

The X-ray diffraction study of a single crystal of **4c** was performed at the Diffraction Methods Laboratory (Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences). Monoclinic crystal system, space group $C2/c$; $C_{10}H_{14}NO_3 \cdot C_2H_4Cl_2O_2P$, M 358.14; unit cell parameters (296 K): a = 18.4814(16), b = 9.9639(7), c = 19.9972(17) Å; β = 115.096(4)°; V = 3334.8(5) Å^3; Z = 8; d_{calc} = 1.427 g/cm^3; μ = 0.503 mm^{-1}; $F(000)$ = 1488. The data were obtained on a Bruker Smart APEX II CCD automated diffractometer (Mo K_α radiation, λ 0.71073 Å, graphite monochromator; ω-scanning, 2θ < 52°). Total of 14222 reflection intensities were measured, including 3264 independent reflections (R_{int} = 0.094) and 1682 reflections with $I > 2\sigma(I)$. Final divergence factors: R = 0.0539, wR_2 = 0.1602; goodness of fit 1.01; 138 variables. A correction for absorption was applied using SADABS program [7]. The structure was solved by the direct method (SIR [8]) and was refined first in isotropic and then in anisotropic approximation (SHELXL-97 [9]). All hydrogen atoms were placed in geometrically calculated positions which were refined according to the riding model. All calculations were carried out using WinGX [10] and APEX2 [11]. The X-ray diffraction data for compound **4c** were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1813446) and are available at *http://www.ccdc.cam.ac.uk*.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium hydrogen sulfate (2a). A mixture of 0.72 g (4 mmol) of pyridoxal (**1**) and 0.42 g (4 mmol) of sulfuric acid in 20 mL of anhydrous ethanol was refluxed for 2 h. The solvent was removed, the residue was treated with 20 mL of diethyl ether, and the precipitate was filtered off and dried under reduced pressure. Yield 1.17 g (97%), mp 110–112°C. IR spectrum, ν, cm^{-1}: 3074 (OH), 2600–2500 (NH$^+$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.15 t (3H, CH_3, J = 7.0 Hz), 2.58 s (3H, CH_3), 3.74 m (2H, OCH_2), 5.12 d and 5.16 d (1H each, 3-H, J = 14.0 Hz), 6.43 s (1H, 1-H), 8.35 s (1H, 4-H). Found, %: C 40.75; H 5.06; N 4.44; S 11.12. $C_{10}H_{15}NO_7S$. Calculated, %: C 40.94; H 5.16; N 4.78; S 10.93.

Compounds **2b**–**2e** and **4a**–**4c** were synthesized in a similar way.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium trifluoromethanesulfonate (2b). Yield 1.26 g (85%), mp 123–126°C. IR spectrum, ν, cm^{-1}: 3154 (OH), 2750–2600 (NH$^+$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.15 t (3H, CH_3, J = 7.0 Hz), 2.51 s (3H, CH_3), 3.73 m (2H, OCH_2), 5.11 d and 5.17 d (1H each, 3-H, J = 14.0 Hz), 6.42 s (1H, 1-H), 8.34 s (1H, 4-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 15.26, 15.63, 64.02, 70.01, 103.87, 126.07, 138.66, 138.87, 143.93, 149.34. Found, %: C 37.99; H 4.24; N 3.99; S 9.11. $C_{11}H_{14}F_3NO_6S$. Calculated, %: C 38.26; H 4.09; N 4.06; S 9.28.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium trifluoroacetate (2c). Yield 1.02 g (87%), mp 110–113°C. IR spectrum, ν, cm^{-1}: 3063 (OH), 2549–2104 (NH$^+$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.14 t (3H, CH_3, J = 7.0 Hz), 2.53 s (3H, CH_3), 3.70 m (2H, OCH_2), 5.07 d and 5.13 d (1H each, 3-H, J = 13.7 Hz), 6.40 s (1H, 1-H), 8.24 s (1H, 4-H). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 15.67, 16.10, 63.82, 70.02, 104.06, 127.50, 137.00, 138.14, 144.42, 148.87, 159.09. Found, %: C 46.54; H 4.27; N 4.43. $C_{12}H_{14}F_3NO_5$. Calculated, %: C 46.60; H 4.57; N 4.53.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium carboxymethanoate (2d). Yield 0.83 g (77%), mp 149°C. IR spectrum, ν, cm^{-1}: 3063 (OH), 2552–2112 (NH$^+$), 1726 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 2.41 s (3H, CH_3), 3.65 m (2H, $C\mathbf{H}_2CH_3$), 4.95 d and 5.05 d (1H each, 3-H, J = 13.1 Hz), 6.29 s (1H, 1-H), 8.00 s (1H, 4-H), 9.53 br.s (2H, OH). Mass spectrum: m/z 195 [M – HOCOCOOH]$^+$. Found, %: C 50.45; H 5.34; N 4.64. $C_{12}H_{15}NO_7$. Calculated, %: C 50.53; H 5.26; N 4.91.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium 3-carboxyprop-2-enoate (2e). Yield 0.60 g (47%), mp 139°C. IR spectrum, ν, cm^{-1}: 3061 (OH), 2591–2122 (NH$^+$), 1694 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, $CH_2C\mathbf{H}_3$, J = 7.0 Hz), 2.43 s (3H, CH_3), 3.65 m (2H, $C\mathbf{H}_2CH_3$), 4.98 d and 5.07 d (1H each, 3-H, J = 13.2 Hz), 6.19 s (2H, CH=CH), 6.31 s (1H, 1-H), 8.06 s (1H, 4-H), 9.53 br.s (1H, OH). Mass spectrum: m/z 195 [M – HOC(O)CH=CHC(O)OH]$^+$. Found, %: C 53.90; H 5.38; N 4.24. $C_{14}H_{17}NO_7$. Calculated, %: C 54.19; H 5.16; N 4.52.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-7-ol (3). *a*. A mixture of 0.69 g (4 mmol) of pyridoxal (**1**) and 0.25 g (4 mmol) of acetic acid in 20 mL of anhydrous ethanol was refluxed for 2 h. The mixture was cooled, the solvent was removed, the residue was treated with 20 mL of anhydrous diethyl ether, and the precipitate was filtered off. Yield 0.55 g (69%), mp 118–121°C [2].

^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, CH_3, J = 7.1 Hz), 2.37 s (3H, CH_3), 3.65 m (2H, OCH_2), 4.93 d and 5.03 d (1H each, 3-H, J = 12.9 Hz), 6.27 s (1H, 1-H), 7.93 s (1H, 4-H).

b. When the reaction was carried out with phenol, the yield of **3** was 0.65 g (81%), mp 118–120°C.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium bis(chloromethyl)phosphinate (4a). Yield 1.29 g (87%), mp 135–137°C. IR spectrum: ν 2353–2086 cm^{-1} (NH^+). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, CH_3, J = 7.0 Hz), 2.47 s (3H, CH_3), 3.68 d (4H, $ClCH_2$, J = 8.0 Hz), 5.00 d and 5.08 d (1H each, 3-H, J = 13.3 Hz), 6.37 s (1H, 1-H), 8.08 s (1H, 4-H). ^{31}P NMR spectrum (DMSO-d_6): δ_P 26.85 ppm. Found, %: C 39.99; H 4.21; Cl 20.09; N 3.93; P 8.62. $C_{11}H_{16}Cl_2NO_5P$. Calculated, %: C 40.24; H 4.40; Cl 19.79; N 3.91; P 8.65.

1-Ethoxy-7-hydroxy-6-methyl-1,3-dihydrofuro-[3,4-*c*]pyridin-5-ium hydrogen (1-hydroxy-1-phosphonoethyl)phosphonate (4b). Yield 1.32 g (85%), mp 171–173°C. IR spectrum: ν 2520–2151 cm^{-1} (NH^+). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, CH_3, J = 7.1 Hz), 1.44 t (3H, CH_3, J = 15.6 Hz), 2.42 s (3H, CH_3), 3.65 m (2H, CH_2), 4.76 s (4H, OH), 4.97 d and 5.06 d (1H each, 3-H, J = 13.1 Hz), 6.29 s (1H, 1-H), 8.01 s (1H, 4-H). ^{31}P NMR spectrum (DMSO-d_6): δ_P 20.65 ppm. Found, %: C 35.76; H 5.32; N 3.82; P 15.43. $C_{12}H_{21}NO_{10}P_2$. Calculated, %: C 35.91; H 5.29; N 3.49; P 15.44.

7-Hydroxy-1-methoxy-6-methyl-1,3-dihydrofuro[3,4-*c*]pyridin-5-ium bis(chloromethyl)phosphinate (4c). Yield 1.17 g (83%), mp 138–141°C. IR spectrum: ν 2349–2082 cm^{-1} (NH^+). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.44 s (3H, CH_3), 3.35 s (3H, OCH_3), 3.64 d (4H, CH_2, J = 8.0 Hz), 5.00 d and 5.08 d (1H each, 3-H, J = 13.3 Hz), 6.26 s (1H, 1-H), 8.06 s (1H, 4-H). ^{31}P NMR spectrum (DMSO-d_6): δ_P 28.09 ppm. Found, %: C 38.19; H 4.61; Cl 20.29; N 3.93; P 8.82. $C_{11}H_{16}Cl_2NO_5P$. Calculated, %: C 38.37; H 4.70; Cl 20.60; N 4.07; P 9.00.

Methyl [hydroxy(3-hydroxy-5-hydroxymethyl-2-methylpyridin-1-ium-4-yl)methyl]phosphonate (5). A mixture of 0.4 g (2 mmol) of pyridoxal, 0.56 g (2 mmol) of diphenyl hydrogen phosphite, and 10 mL of anhydrous methanol was refluxed for 3 h. The mixture was left to stand for 24 h, and the precipitate was filtered off and washed with diethyl ether. Yield 0.16 g (25%), mp 300°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.43 s (3H, CH_3), 3.56 d (3H, CH_3, J = 10.1 Hz), 4.66 d and 4.76 d (1H each, 5-CH_2, J = 14.4 Hz), 5.05 d (1H, PCH, J = 16.5 Hz), 7.94 s (1H, 6-H). ^{31}P NMR spectrum (DMSO-d_6): δ_P 18.51 ppm. Mass spectrum: m/z 263 $[M]^+$. Found, %: C 41.13; H 5.34; N 5.72. $C_9H_{14}NO_6P$. Calculated, %: C 41.06; H 5.32; N 5.32.

1-Methoxy-6-methyl-1,3-dihydrofuro[3,4-*c*]-pyridin-7-ol (6) was isolated from the filtrate. Yield 0.21 g (48%), mp 167–170°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.42 s (3H, CH_3), 3.34 s (3H, OCH_3), 4.98 d and 5.06 d (1H each, 3-H, J = 13.3 Hz), 6.27 s (1H, 1-H), 8.01 s (1H, 4-H). Mass spectrum: m/z 181 $[M]^+$. Found, %: C 59.44; H 6.16; N 7.57. $C_9H_{11}NO_3$. Calculated, %: C 59.67; H 6.08; N 7.73.

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