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SHORT COMMUNICATIONS

Synthesis and Hydrolysis of Bicyclic 2-Imino-2,5-dihydrofurans Fused to a Pyridine Ring

A. A. Avetisyan†, L. V. Karapetyan, and M. D. Tadevosyan

Erevan State University, ul. Aleka Manukyana 1, Erevan, 0025 Armenia
e-mail: lousine_karapetyan@yahoo.com

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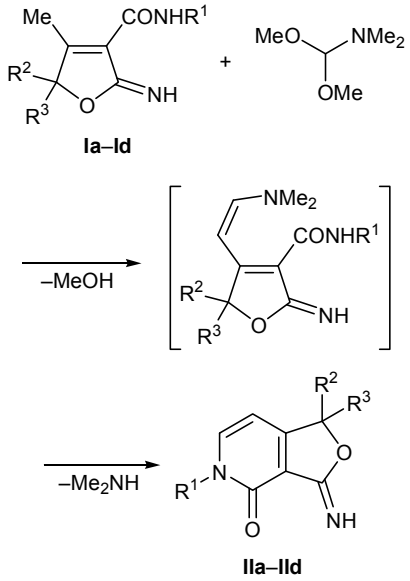
Numerous fused pyridine derivatives are widely used in medicine as cardiotonics [1] and antiphlogistic agents [2]. Functionally substituted derivatives of unsaturated γ-lactones are widespread in nature, and they often exhibit pronounced biological activity. Apart from monocyclic unsaturated γ-lactones, derivatives of spiro and fused bicyclic systems are present in natural sources [3–6]. Taking into account that nitrogen-containing analogs of various oxygen-containing biologically active compounds often possess equally useful properties, we continued studies in this field with a view to synthesize new derivatives of functionally substituted 2-imino-2,5-dihydrofurans [7]. For this purpose, 2-imino-2,5-dihydrofurans **Ia**–**Id** were brought into reaction with *N*,*N*-dimethyl(dimethoxy)-methanamine (*N*,*N*-dimethylformamide dimethyl acetal), and optimal conditions were found for this reaction. The best results were obtained by heating a mixture of 2-imino-2,5-dihydrofuran **I** and dimethylformamide dimethyl acetal at a ratio of 1 : 1.1 in boiling anhydrous benzene. Presumably, the reaction involves intermediate formation of enamine with elimination of two methanol molecules and subsequent cyclization to furanopyridines **IIa**–**IId** with liberation of dimethylamine which was detected in the reaction mixture on a qualitative level (Scheme 1).

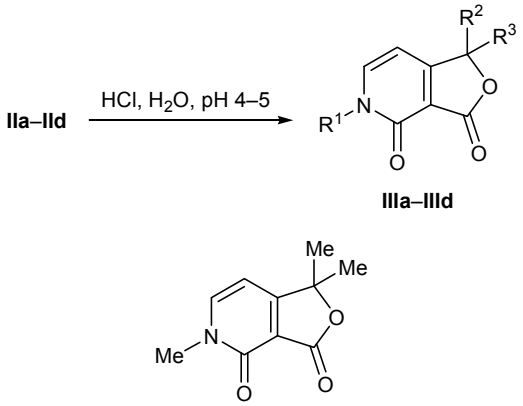
Scheme 1.



R^1 = H (**a**, **c**), Me (**b**, **d**); $R^2 = R^3$ = Me (**a**, **b**); $R^2R^3 = (CH_2)_5$ (**c**, **d**).

Fused furanopyridine derivatives **IIa**–**IId** readily underwent acid hydrolysis (pH 4–5, 85–90°C, 2 h), yielding the corresponding furo[3,4-*c*]pyridine-3,4(1*H*,5*H*)-diones **IIIa**–**IIId** which may be regarded as analogs of natural alkaloid cerpegin (Scheme 2).

Scheme 2.



† Deseased.

The structure of the isolated compounds was confirmed by their IR and ^{1}H NMR spectra and elemental analyses.

3-Iminofuro[3,4-*c*]pyridin-4(5*H*)-ones IIa–IId (*general procedure*). A mixture of 1 mmol of 2-imino-2,5-dihydrofuran **Ia–Id** and 1.1 mmol of *N*,*N*-dimethylformamide dimethyl acetal in 20 ml of anhydrous benzene was heated for 30–35 h under reflux until dimethylamine no longer evolved. The solvent was removed under reduced pressure, the residue was treated with diethyl ether, and the precipitate was filtered off and washed with water.

3-Imino-1,1-dimethylfuro[3,4-*c*]pyridin-4(5*H*)-one (IIa). Yield 90%, mp 168–170°C. IR spectrum, ν, cm^{-1}: 3360, 3180 (NH); 1680 (C=O); 1640 (C=N); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.42 s (6H, CH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d.d (1H, 6-H, J = 4.9, 5.6 Hz), 7.23 s (1H, =NH), 9.36 d (1H, NH, J = 4.9 Hz). Found, %: C 60.91; H 5.87; N 15.89. $C_9H_{10}N_2O_2$. Calculated, %: C 60.66; H 5.66; N 15.72.

3-Imino-1,1,5-trimethylfuro[3,4-*c*]pyridin-4(5*H*)-one (IIb). Yield 87%, mp 123–124°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1680 (C=O); 1640 (C=N); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.42 s (6H, CH_3), 3.4 s (3H, NCH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d (1H, 6-H, J = 7.9 Hz), 7.23 s (1H, NH). Found, %: C 62.64; H 6.44; N 14.77. $C_{10}H_{12}N_2O_2$. Calculated, %: C 62.49; H 6.29; N 14.57.

3-Imino-1,1-pentamethylenefuro[3,4-*c*]pyridin-4(5*H*)-one (IIc). Yield 87%, mp 201–203°C. IR spectrum, ν, cm^{-1}: 3360, 3180 (NH); 1680 (C=O); 1640 (C=N); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.58–1.88 m (10H, (CH_2), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d.d (1H, 6-H, J = 4.9, 5.6 Hz), 7.23 s (1H, =NH), 9.36 d (1H, NH, J = 4.9 Hz). Found, %: C 66.35; H 6.64; N 12.97. $C_{12}H_{14}N_2O_2$. Calculated, %: C 66.04; H 6.47; N 12.84.

3-Imino-5-methyl-1,1-pentamethylenefuro[3,4-*c*]-pyridin-4(5*H*)-one (IId). Yield 85%, mp 128–130°C. IR spectrum, ν, cm^{-1}: 3240 (NH); 1680 (C=O); 1640 (C=N); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.56–1.86 m (10H, (CH_2), 3.4 s (3H, NCH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d (1H, 6-H, J = 7.9 Hz), 7.24 s (1H, NH). Found, %: C 67.44; H 7.14; N 12.27. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.22; H 6.94; N 12.06.

Furo[3,4-*c*]pyridine-3,4(1*H*,5*H*)-diones IIIa–IIId (*general procedure*). A mixture of 1 mmol of compound **IIa–IId** and 5 ml of water was acidified to pH 4–5 with hydrochloric acid and was heated for 3 h at 85–90°C. The mixture was cooled and extracted with diethyl ether (3 × 5 ml), the extract was dried over magnesium sulfate, the solvent was distilled off, and the residue was recrystallized from appropriate solvent.

1,1-Dimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (IIIa). Yield 90%, mp 257–260°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 3280 (NH); 1760, 1670 (C=O); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.42 s (6H, CH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.68 d.d (1H, 6-H, J = 4.9, 5.6 Hz), 9.36 d (1H, NH, J = 4.9 Hz). Found, %: C 60.59; H 5.34; N 7.97. $C_9H_9NO_3$. Calculated, %: C 60.33; H 5.06; N 7.82.

1,1,5-Trimethylfuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (cerpegin, IIIb). Yield 89%, mp 268–270°C (from CH_2Cl_2–EtOH). IR spectrum, ν, cm^{-1}: 1760, 1670 (C=O); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.42 s (6H, CH_3), 3.4 s (3H, NCH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d (1H, 6-H, J = 7.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 24.18 (CH_3), 37.75 (NCH_3), 82.51, 98.38, 112.17, 145.96, 157.90, 166.88, 170.86. Mass spectrum (70 eV), m/z (I_{rel}, %): 193 (34.58) $[M]^+$, 178 (100) $[M - CH_3]^+$, 150 (4.79) $[M - CH_3CO]^+$, 136 (3.65), 108 (12.87), 79 (5.79), 42 (49.67). Found, %: C 62.36; H 5.95; N 7.49. $C_{10}H_{11}NO_3$. Calculated, %: C 62.17; H 5.74; N 7.25. M 193.20.

1,1-Pentamethylenefuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (IIIc). Yield 91%, mp 160–161°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 3280 (NH), 1760, 1670 (C=O); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.58–1.88 m (10H, (CH_2), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d.d (1H, 6-H, J = 4.9, J = 5.6 Hz), 9.36 d (1H, NH, J = 4.9 Hz). Found, %: C 65.97; H 6.14; N 6.71. $C_{12}H_{13}NO_3$. Calculated, %: C 65.74; H 5.98; N 6.39.

5-Methyl-1,1-pentamethylenefuro[3,4-*c*]pyridine-3,4(1*H*,5*H*)-dione (IIId). Yield 87%, mp 101–102°C (from hexane). IR spectrum, ν, cm^{-1}: 1760, 1670 (C=O); 1625, 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.56–1.86 m (10H, (CH_2), 3.4 s (3H, NCH_3), 4.86 d (1H, 7-H, J = 4.9 Hz), 5.66 d (1H, 6-H, J = 7.9 Hz). Found, %: C 67.14; H 6.79; N 6.37. $C_{13}H_{15}NO_3$. Calculated, %: C 66.94; H 6.48; N 6.00.

The IR spectra were recorded on a Specord 75IR spectrometer from samples dispersed in mineral oil. The NMR spectra were measured on a Varian Mercury-300 instrument (300 MHz for ^{1}H), using tetramethylsilane as internal reference and DMSO-d_6–CCl_4 (1:3) as solvent. The purity of the products was

checked by TLC on Silufol UV-254 plates using acetone–benzene (1:2) as eluent; development with iodine vapor or under UV light.

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