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Chemistry

CONVENIENT APPROACH TO SYNTHESIS OF ALKALOID CERPEGIN DERIVATIVES

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A convenient method for obtaining pyridine alkaloid cerpegin and its various new C-1 and N-5 derivatives in high yields has been developed. Starting enaminolactones, synthesized by means of various tertiary keto-alcohols, have been condensed with primary aliphatic, aromatic or heterocyclic amines for a pyridine cycle formation. Bromine derivatives of furo[3,4-c]pyridinenones are obtained as well.

Keywords: cerpegin, pyridinealkaloid, 2-oxo-2,5-dihydrofuran, furo[3,4-c]-pyridine-3,4-dione.

Introduction. Our studies focus on the development of synthetic methodologies and their utilization towards the syntheses of biologically important natural products and new artificial biomolecules.

Pyridine alkaloid cerpegin, isolated from the widely used in popular medicine plant *Ceropegia juncea*, possesses tranquilizer, anti-inflammatory, analgesic and anti-ulcer properties. Its structure is established as 1,1,5-trimethylfuro-[3,4-c]pyridine-3,4(1H,5H)-dione [1, 2]. Apart from some metabolites of pyridoxal [3] to our knowledge cerpegin is the only naturally occurred example of bicyclical furo[3,4-c]pyridine ring system.

Recent investigations on furo[3,4-c]pyridine fused systems biological activities present that they can be used for treating hypertension [4]; sexual disfunction [5]; as preventives or remedies for various autoimmune diseases [6]; they also possess antibacterial activity [7].

Dihydrofuro[3,4-c]pyridinones are the first class of small molecules reported to inhibit cytolytic effects of lymphocyte toxin perforin [8]. Furopyridines are useful for inhibiting protein tyrosine kinases [9]; for treating and preventing tumors and cancers [10]; as inhibitor of activated blood coagulation factor X [11].

Several reports on the complete synthesis of cerpegin and norcerpegin and their synthetic analogues were published [12–18]. It should be mentioned that quite a number of these compounds possess biological activity. All described methods could be devised into two groups, those based on chemical transformations of pyridone cycle [12–15] and 2-oxo-2,5-dihydrofurans [16–18].

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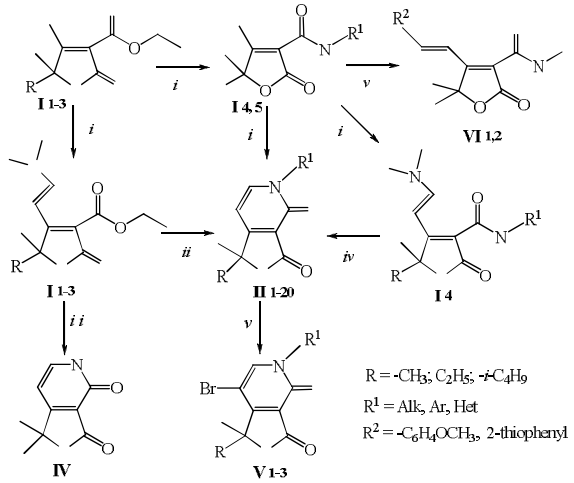
The majority of these methods, employing three to six synthetic steps with sophisticated reaction conditions (temperature lower than –78°*C*, use of lithium reagents, etc.) exhibit relatively low total yields up to 34% [16]. This paper is a continuation of our previous work [19–23] and reports on a simple and convenient method for obtaining cerpegin and its derivatives with various substituents at C-1 and N-5 positions.

The proposed method is based on employment of C-4 mobile methyl group reactivity of ethyl 4,5-dimethyl-5-alkyl-2-oxo-2,5-dihydrofuran-3-carboxylates (**I 1–3**) [24]. Being condensed with DMFDMA, it forms corresponding β-dimethyl-aminovinyl derivatives (**II 1–3**) with yields up to 90%. Obtained **II 1–3**, when refluxed with primary amines (bp >100°*C*) in anhydrous xylene form targeted 1-methyl-1-alkyl-1H,5H-furo[3,4-c]pyridine-3,4-dione N-derivatives (**III 1–18**) in good yields. For synthesis of cerpegin and analogues in the case of amines with low boiling points (bp <100°*C*), we chose a different approach: instead of ethyl 2-oxo-2,5-dihydrofuran-3-carboxylates (**I**) the corresponding amides **I 4**,**5** were used in the reaction with DMFDMA. In this case it became possible to isolate both intermediate dimethylaminovinyl derivative **II 5** and final product **III 19**,**20** in high yields depending on time of heating in xylene (3 to 15 *h* respectively). The cyclic condensation of compound **II 4** also could be realized by heating without solvent or by refluxing in DMFA.



Reagents and conditions: (*i*) [25]; (*ii*) **I 1–3**, DMFDMA, xylene, reflux; (*iii*) **I**, NH_2R, xylene, reflux 15*h*; (*iv*) xylene, reflux 12 *h*, 91–92% yield; (*v*) **III**, bromine, CCl_4, reflux 12*h*, 82–96% yield; (*vi*) **I 4**,**5**, R–CH=O, NaOH, ethanol.

The condensation of **II 1** with urea in the abovementioned conditions with attended 1,1- dimethyl - 3,4-dioxo -3,4-dihydrofuro[3,4-c]pyridine-5(1H)-carboxamide synthesis does not occur, the starting compounds were unchanged. Realization of the same processes in glacial acetic acid in the molar ratio of the initial compounds 1:2 lead to nor-cerpegin, due to elimination of carboxamide group in the reaction conditions.

With the purpose of forming a conjugated system analogous to structure of compound **II**, that can be interesting from the point of view of biological activities, amide **I 4** was condensed with several aldehydes with formation of targeted **VI 1**,**2**.

The interaction was carried out using starting compounds molar ratio 1:1.1 in the reflux conditions in anhydrous ethanol in the presence of sodium hydroxide with high yields.

The bromine derivatives **V 1–3** were obtained by interaction of **III 2**,**7**,**19** with bromine in carbon tetrachloride. Generally for piridones the reaction with bromine occurs at ortho- and para-positions to carbonyl group [26]. In the case of furopyridinones reaction occurs with formation of C-7 derivatives in accordance with general rule. Unlike chlorine derivatives, bromine derivatives didn't react with primary amines in similar conditions of reflux in xylene.

We have demonstrated the utility of proposed method that allows to introduce substituents at the position C-5 of a 2-oxo-2,5-dihydrofuran cycle and at nitrogen atom of pyridinone cycle for synthesizing novel potential biologically active furo[3,4-c]pyridines and bromine derivatives. Conjugated furanone-contained systems were synthesized as well.

Experimental Part. Mps were determined on a SMP-10 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian Mercury 300 spectrometer operating at 300 *MHz* with TMS as internal standard in DMSO-d_6 solution at 303 *K*. TLC analysis was performed on Silufol-254 UV plates, eluent acetone/benzene (1:3) and iodine vapors. The elemental analyses matched the calculated composition.

Ethyl 4,5-dimethyl-5-alkyl-2-oxo-2,5-dihydrofuran-3-carboxylates (**I 1–3**) were synthesized according to the method from [24]; **I 4**,**5** was synthesized from **I 1**,**2** *via* reaction with methylamine [25].

General Procedure for the Synthesis of 4-[2-(Dimethylamino)vinyl]-5,5--dialkyl-2-oxo-2,5-dihydrofuran-3-carboxylic Acids Ethyl Esters (II 1–3) and Methylamide (II 4). A mixture of compound **I 1–4** (10 *mmol*) and DMFDMA (12 *mmol*) in an anhydrous xylene (12 *mL*) was refluxed for 3 *h*, cooled to room temperature; 5 *mL* of light petroleum was added. The precipitated crystals were filtered, washed with ether, dried.

*Ethyl 4-[2-(dimethylamino)vinyl]-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3--carboxylates (**II 1**)*. Yield 86.2%; mp 168°*C*. ^{1}H NMR, *δ*, *ppm*: 7.72 d (*J*=13.7 *Hz*, 1H, =CHN); 6.06 d (*J*=13.7 *Hz*, 1H, =CH); 4.18 q (*J*=7.1 *Hz*, 2H, OCH_2); 3.26 br (3H, NCH_3); 3.01 br (3H, NCH_3); 1.55 s (6H, CH_3); 1.32 t (*J*=7.1 *Hz*, 3H, CH_3).

*Ethyl 4-[2-(dimethylamino)vinyl]-5-ethyl-5-methyl-2-oxo-2,5-dihydrofuran--3-carboxylates (**II 2**)*. Yield 74.3%; mp 142°*C*. ^{1}H NMR, *δ*, *ppm*: 7.71 d (*J*=13.6 *Hz*, 1H, =CH); 6.08 d (*J*=13.6 *Hz*, 1H, =CH); 4.17 q (*J*=7.1 *Hz*, 2H, OCH_2); 3.25 br (3H, NCH_3); 3.00 br (3H, NCH_3); 1.79–1.97 m (2H, CH_2); 1.52 s (3H, CH_3); 1.32 t (*J*=7.1 *Hz*, 3H, CH_3); 0.76 t (*J*=7.1 *Hz*, 3H, CH_3).

*Ethyl 4-[2-(dimethylaminovinyl)-5-isobutyl-5-methyl-2-oxo-2,5-dihydrofuran-3-carboxylate (**II 3**)*. Yield 86.9%; mp 118°*C*. ^{1}H NMR, *δ*, *ppm*: 7.72 d (*J*=13.7 *Hz*, 1*H*); 6.06 d (*J*=13.7 *Hz*, 1H); 4.18 q (*J*=7.1 *Hz*, 2H); 3.26 br (3H); 3.01 br (3H); 2.31–2.24 m (1H); 1.73–1.54 m (2H); 1.51 s (3H); 1.32 t (*J*=7.1 *Hz*, 3H); 0.92 d (*J*=6.6 *Hz*, 3H); 0.83 d (*J*=6.6 *Hz*, 3H).

*4-[2-dimethylamino-vinyl]-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-carboxylic acid methyllamide (**II 4**)*. Yield 71.0; mp 167°*C*. ^{1}H NMR, *δ*, *ppm*: 8.14–8.28 m (2H, CH, NH); 6.14 d (1H, CH); 2.94–3.28 m (9H, CH_3); 1.54 s (6H, CH_3).

General procedure for the synthesis of cerpegin N-substituted derivatives III 1–18. In a flask fitted with a reflux **II 1–3** (10 *mmol*) and the corresponding starting amine (40 *mmol*) were mixed in an anhydrous xylene atmosphere (7 *mL*).

The mixture was boiled for 15 *h* (extra 2 *h* after cessation of dimethylamine isolation), cooled to room temperature; 5 *mL* of light petroleum was added. The precipitated crystals were filtered, washed with ether and dried. Yields and physical data of the obtained compounds are given below:

5-Cyclopentyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 1)***. Yield 75.1%; mp 240°*C*. ^{1}H NMR, *δ*, *ppm*: 8.00 d (*J*=6.9 *Hz*, 1H, =CHN); 6.47 d (*J*=6.9 *Hz*, 1H, =CH); 5.17 kv (*J*=8.1 *Hz*, 1H, CH); 2.12 m (2H, CH_2); 1.85–1.96 m (2H, CH_2); 1.7 m (4H, CH_2); 1.58 s (6H, CH_3).

5-Cyclohexyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 2)***. Yield 44.2%; mp > 300°*C*. ^{1}H NMR, *δ*, *ppm*: 8.01 d (*J*=6.9 *Hz*, 1H, =CHN); 6.46 d (*J*=6.9 *Hz*, 1H, =CH); 4.77 tt (J_1=11.5; J_2=3.6 *Hz*, 1H, NCH); 1.74–1,96 m (5H, CH_2); 1.58 s (6H, CH_3); 1.45–1.67 m (4H, CH_2); 1.30 br.m (1H, CH_2).

5-Cycloheptyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 3)***. Yield 82.4%; mp 197°*C*. ^{1}H NMR, *δ*, *ppm*: 7.98 d (*J*=6.8 *Hz*, 1H, =CHN); 6.45 d (*J*=6.8 *Hz*, 1H, =CH); 4.89 tt (J_1=10.5 *Hz*; J_2=3.8 *Hz*, 1H, =NCH); 1.51–1.94 m (12H, CH_2); 1.57 s (6H, CH_3).

5-Dodecyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 4)***. Yield 79.7%; mp 125°*C*. ^{1}H NMR, *δ*, *ppm*: 8.03 d (*J*=6.7 *Hz*, 1H, =CHN); 6.43 d (*J*=6.7 *Hz*, 1H, =CH); 3.94 m (2H, CH_2N); 1.68 m (2H, $\underline{CH_2}CH_2N$); 1.57 s (6H, CH_3); 1.22–1.37 m (18H, CH_2); 0.89 m (3H, CH_3).

1,1-Dimethyl-5-octadecylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 5)***. Yield 53.6%; mp 124°*C*. ^{1}H NMR, *δ*, *ppm*: 8.00 d (*J*=6.7 *Hz*, 1H, =CHN); 6.41 d (*J*=6.7 *Hz*, 1H, =CH); 3.94 t (*J*=7.3 *Hz*, 2H, CH_2N); 1.69 br.kv (*J*=7.3 *Hz*, 2H, CH_2); 1.57 s (6H, CH_3); 1.24–1.37 m (30H, $\underline{CH_2}$); 0.98 t (*J*=6.8 *Hz*, 3H, CH_3).

5-(2-Ethylaminoethyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 6)***. Yield 92.7%; mp 136°*C*. ^{1}H NMR, *δ*, *ppm*: 8.01 d (*J*=6.7 *Hz*, 1H, =CHN); 6.39 d (*J*=6.7 *Hz*, 1H, =CH); 4.03 t (*J*=6.0 *Hz*, 2H, NCH_2); 2.85 t (*J*=6.0 *Hz*, 2H, $NHCH_2$); 2.65 br (1H, NH); 2.61 q (*J*=7.1 *Hz*, 2H, $NHCH_2$); 1.58 s (6H, CH_3); 1.05 t (*J*=7.1 *Hz*, 3H, CH_3).

5-Benzyl-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 7)***.Yield 97.7 %; mp 202°*C*. ^{1}H NMR, *δ*, *ppm*: 8.18 d (*J*=6.7 *Hz*, 1H); 7.43–7.22 m (5H); 6.47 d (*J*=6.7 *Hz*, 1H); 5.18 s (2H); 1.57 s (6H).

5-(3,3-Diethoxypropyl)-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 8)***. Yield 87.1%; mp 100°*C*. ^{1}H NMR, *δ*, *ppm*: 7.99 d (*J*=6.7 *Hz*, 1H); 6.41 d (*J*=6.7 *Hz*, 1H); 4.55 t (*J*=5.3 *Hz*, 1H); 4.01 t (*J*=7.0 *Hz*, 2H); 3.67–3.35 m (4H); 1.97 dd (*J*=12.5 *Hz*; 6.9 *Hz*, 2H); 1.57 s (6H); 1.15 t (*J*=7.0 *Hz*, 6H).

5-(2,2-Dimethoxyethyl)-1-isobutyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)--dione ***(III 9)***. Yield 54.0%; mp 130°*C*. ^{1}H NMR, *δ*, *ppm*: 7.92 d (*J*=6.8 *Hz*, 1H); 6.39 d (*J*=6.8 *Hz*, 1H); 4.57 t (*J*=5.3 *Hz*, 1H); 4.04 dd (*J*=5.3 *Hz*; 3.8 *Hz*, 2H); 3.38 s (6H); 1.91 dd (*J*=14.4; 5.3 *Hz*, 1H); 1.64 ddd (*J*=18.8; 13.5; 6.5 *Hz*, 2H); 1.54 s (3H); 0.93 d (*J*=6.5 *Hz*, 3H); 0.84 d (*J*=6.5 *Hz*, 3H).

5-(2-Ethylaminoethyl)-1-isobutyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)--dione ***(III 10)***. Yield 81.4%; mp 112°*C*. ^{1}H NMR, *δ*, *ppm*: 8.00 d (*J*=6.7 *Hz*, 1H); 6.35 d (*J*=6.7 *Hz*, 1H); 4.13–3.94 m (2H); 2.86 t (*J*=6.0 *Hz*, 2H); 2.60 q (*J*=7.1 *Hz*, 2H); 2.31–2.24 m (1H); 1.90 dd (*J*=14.4; 5.6 *Hz*, 1H); 1.75–1.55 m (2H); 1.53 s (3H); 1.04 t (*J*=7.1 *Hz*, 3H); 0.93 d (*J*=6.5 *Hz*, 3H); 0.85 d (*J*=6.5 *Hz*, 3H).

5-(3-Imidazol-1-yl)propyl)-1-isobutyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)--dione ***(III 11)***. Yield 25.8%; mp 159°*C*. ^{1}H NMR, *δ*, *ppm*: 8.03 d (*J*=6.7 *Hz*, 1H),

7.56 s (1H); 7.07 m (1H); 6.86–6.82 m (1H); 6.40 d (*J*=6.7 *Hz*, 1H); 4.15–3.87 m (4H); 2.21 p (*J*=7.1 *Hz*, 2H); 1.89 dd (*J*=14.5; 5.8 *Hz*, 1H); 1.78–1.54 m (2H); 1.53 s (3H); 0.92 d (*J*=6.6 *Hz*, 3H); 0.85 d (*J*=6.6 *Hz*, 3H).

5-(3,4-Dimethoxyphenethyl)-1-isobutyl-1-methylfuro[3,4-c]pyridine-3,4(1H, 5H)-dione ***(III 12)***. Yield 62.8%; mp 105°*C*. ^{1}H NMR, *δ*, *ppm*: 7.72 d (*J*=6.7 *Hz*, 1H); 6.76–6.63 m (3H); 6.27 d (*J*=6.7 *Hz*, 1H); 4.25–4.09 m (2H); 3.76 s (3H); 3.75 s (3H); 2.93 t (*J*=7.2 *Hz*, 2H); 1.88 dd (*J*=14.5; 5.9 *Hz*, 1H); 1.72–1.52 m (2H); 1.51 s (3H); 0.92 d (*J*=6.6 *Hz*, 3H); 0.82 d (*J*=6.6 *Hz*, 3H).

5-(4-Hydroxyphenethyl)-1-isobutyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)- -dione ***(III 13).*** Yield 86.5%; mp 81°*C*. ^{1}H NMR, *δ*, *ppm*: 8.85 s (1H); 7.69 d (*J*=6.7 *Hz*, 1H); 6.95–6.90 m (2H); 6.66–6.60 m (2H); 6.27 d (*J*=6.7 *Hz*, 1H); 4.23–4.01 m (2H); 2.94–2.81 m (2H); 1.88 dd (*J*=14.6; 5.9 *Hz*, 1H); 1.68 dd (*J*=14.6 *Hz*; 6.2 *Hz*, 2H); 1.51 s (3H); 0.92 d (*J*=6.6 *Hz*, 3H); 0.83 d (*J*=6.6 *Hz*, 3H).

1-Ethyl-5-(2-hydroxyethyl)-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 14)***. Yield 62.5%; mp 108°*C*. ^{1}H NMR, *δ*, *ppm*: 7.97 d (*J*=6.7 *Hz*, 1H); 6.36 d (*J*=6.7 *Hz*, 1H); 4.69 s (1H); 4.12–3.94 m (2H); 3.68 t (*J*=5.2 *Hz*, 2H); 2.04–1.78 m (2H); 1.55 s (3H); 0.80 t (*J*=7.4 *Hz*, 3H).

1-Ethyl-5-(2-hydroxy-2-phenylethyl)-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)- -dione ***(III 15)***. Yield 70.5%; mp 98°*C*. Two diastereoisomers 1:1. ^{1}H NMR, *δ*, *ppm*: 7.94; 7.92 d (^{3}*J*=6.7 *Hz*, 0.5H, 0.5H, NCH); 7.46–7.21 m (5H, C_6H_5); 6.35, 6.34 d (^{3}*J*=6.7 *Hz*, 0.5H, 0.5H, =CH); 5.49 d (^{3}*J*=6.7 *Hz*, 0.5H, 0.5H, OH); 4.89 m (1H, OCH); 4.41, 4.38 dd (^{2}*J*=12.9 *Hz*, ^{3}*J*=3.2 *Hz*, 0.5H, 0.5H, NCH_2); 3.69, 3.65 dd (^{2}*J*=12.9 *Hz*, ^{3}*J*=9.0 *Hz*, 0.5H, 0.5H, NCH_2); 2.04–1.80 m (2H, CH_2CH_3); 1.57, 1.55 s (1.5H, 1.5H, CH_3); 0.83, 0.79 t (^{3}*J*=7.4 *Hz*, 1.5H, 1.5H, CH_3CH_2).

1-Ethyl-1-methyl-5-(pyridin-3-ylmethyl)-furo[3,4-c]pyridine-3,4(1H,5H)- -dione ***(III 16)***. Yield 83.2%; mp 204°*C*. ^{1}H NMR, *δ*, *ppm*: 8.64 d (*J*=2.1 *Hz*, 1H); 8.46 dd (*J*=4.8; 1.7 *Hz*, 1H); 8.32 d (*J*=6.8 *Hz*, 1H); 7.79 dt (*J*=7.8; 2.1 *Hz*, 1H); 7.31–7.25 m (1H); 6.45 d (*J*=6.7 *Hz*, 1H); 5.21 q (*J*=14.1 *Hz*, 2H); 2.04, 1.74 m (2H); 1.54 s (3H); 0.79 t (*J*=7.4 *Hz*, 3H).

1-Ethyl-1-methyl-5-phenethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 17)***. Yield 86.5%; mp 145°*C*. ^{1}H NMR, *δ*, *ppm*: 7.82 d (*J*=6.7 *Hz*, 1H); 7.30–7.12 m (5H); 6.26 d (*J*=6.7 *Hz*, 1H); 4.28–4.11 m (2H); 3.00 t (*J*=7.2 *Hz*, 2H); 1.97 dq (*J*=14.6; 7.4 *Hz*, 1H); 1.83 dq (*J*=14.6; 7.4 *Hz*, 1H); 1.53 s (3H); 0.77 t (*J*=7.2 *Hz*, 3H).

5-Benzyl-1-ethyl-1-methylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 18)***. Yield 92.8%; mp 165°*C*. ^{1}H NMR, *δ*, *ppm*: 8.17 d (*J*=6.7 *Hz*, 1H); 7.40–7.22 m (5H), 6.42 d (*J*=6.7 *Hz*, 1H); 5.18 q (*J*=14.1 *Hz*, 2H); 2.04–1.78 m (2H); 1.55 s (3H), 0.80 t (*J*=7.4 *Hz*, 3H).

1,1-Dimethyl-1H,5H-furo[3,4-c]pyridine-3,4-dione ***(IV,*** *Norcerpegin)* was obtained in the reaction of **II**, **1** with urea in glacial acetic acid. Yield 64.2%; mp 260°*C*. ^{1}H NMR, *δ*, *ppm*: 12.19 br (1H, NH); 7.68 d (*J*=6.5 *Hz*, 1H, =CHN); 6.39 d (*J*=6.5 *Hz*, 1H, =CH); 1.57 s (6H, CH_3).

General Procedure for the Synthesis of Cerpegin and 1-R-Analogues (III 25,26). In a flask fitted with a reflux **I** **4**,**5** (5 *mmol*) and DMFDMA (5.5 *mmol*) were mixed in an anhydrous xylene atmosphere (10 *mL*). The mixture was boiled about 15 *h* (extra 2 *h* after cessation of dimethylamine isolation), cooled to room temperature; then 5 *mL* of light petroleum was added. The precipitated crystals were filtered, washed with ether and dried.

1,1,5-Trimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(III 19****, Cerpegin)* was obtained from N,4,5,5-tetramethyl-2-oxo-2,5-dihydrofuran-3-carboxamide (**I 4**). Yield 92.6%; mp 270°*C*. ^{1}H NMR, *δ*, *ppm*: 8.08 d (*J*=6.7 *Hz*, 1H); 6.42 d (*J*=6.7 *Hz*, 1H); 3.55 s (3H); 1.57 s (6H).

1-Ethyl-1,5-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-dione ***(II 20)*** was obtained from 5-ethyl-N,4,5-trimethyl-2-oxo-2,5-dihydro-furan-3-carboxamide (**I 5**). Yield 96.1%; mp 195°*C*. ^{1}H NMR, *δ*, *ppm*: 8.10 d (*J*=6.7 *Hz*, 1H, NCH=); 6.37 d (*J*=6.7 *Hz*, 1H, =CH); 3.55 s (3H, NCH_3); 1.96 dq (*J*=14.4; 7.4 *Hz*, 1H, CH_2CH_3); 1.86 dq (*J*=14.4; 7.4 *Hz*, 1H, CH_2CH_3); 1.54 s (3H, CH_3); 0.78 t (*J*=7.4 *Hz*, 3H, CH_2CH_3).

Synthesis of 5-R-7-Bromo-1,1-dimethylfuro[3,4-c]pyridine-3,4(1H,5H)-diones (V 1 and 2). A mixture of corresponding 1,1-dimethyl-5-R-furo[3,4-c]pyridine--3,4(1H,5H)-dione **(III 19**,**7**,**2)** (10 *mmol*) and bromine 0.59 *mL* (11.5 *mmol*) in anhydrous carbon tetrachloride (17 *mL*) was refluxed for 2 *h* and left to cool. The solid product, so formed, was filtered and crystallized (ethanol).

7-Bromo-1,1,5-trimethyl-furo[3,4-c]pyridine-3,4(1H,5H)-dione ***(V 1)***. From **III 19**. Yield 82.7%; mp 235°*C*. ^{1}H NMR, *δ*, *ppm*: 8.47 s (1H, =CHN); 3.56 s (3H, NCH3); 1.71 s (6H, CH_3).

5-Benzyl-7-bromo-1,1-dimethyl-furo[3,4-c]pyridine-3,4(1H,5H)-dione ***(V 2)***. From **III 7**. Yield 83.0%; mp 164°*C*. ^{1}H NMR, *δ*, *ppm*: 8.56 s (1H, =CHN); 7.24–7.45 m (5H, arom.); 5.19 s (2H, CH_2); 1.71 s (6H, CH_3).

7-Bromo-5-cyclohexyl-1,1-dimethyl-furo[3,4-c]pyridine-3,4(1H,5H)-dione ***(V 3)***. From **III 2**. Yield 96.6%; mp 207°*C*. ^{1}H NMR, *δ*, *ppm*: 8.22 s (1H, =CHN); 4.74 m (1H, CH, C_6H_{11}); 1.72 s (6H, CH_3); 1.64–1.96 m (2H, C_6H_{11}); 1.43–1.58 m (7H, C_6H_{11}); 1.31 m (1H, C_6H_{11}).

Synthesis of 5,5-Dimethyl-2-oxo-4-(2-R-vinyl)-2,5-dihydro-furan-3-carboxylic Acid Methylamide (VI 1,2). Ethanol solution of **I 4** and corresponding aldehyde in molar ratio 1:1.1 in the presence of catalytic amount of sodium hydroxide was refluxed 7 *h*. Hydrochloric acid solution (1:1) was added till pH 6, the precipitated crystals were filtered, washed by cold ethanol and diethyl ether, then crystallized from ethanol.

4-(4-Methoxystyryl]-N,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-carboxamide ***(VI 1)***. Condensation with 4-methoxy-benzaldehyde. Yield 75%; mp 82°*C*. ^{1}H NMR (C_6D_6), *δ*, *ppm*: 8.32 d (*J*=17.3 *Hz*, 1H); 8.24 q (*J*=4.4 *Hz*, 1H); 7.70–7.54 m (2H); 7.31 d (*J*=17.3 *Hz*, 1H); 7.01–6.88 m (2H); 3.85 s (3H); 2.87 d (*J*=4.8 *Hz*, 3H); 1.73 s (6H).

N,5,5-Trimethyl-2-oxo-4-(2-(thiophen-2-yl)-vinyl)-2,5-dihydrofuran-3-carboxamide ***(VI 2)***. Condensation with thiophene-2-carbaldehyde. Yield 89.8%; mp 218°*C*. ^{1}H NMR (DMSO-d_6/CCl_4), *δ*, *ppm*: 8.23 q (^{3}*J*=4.8 *Hz*, 1H, NH); 8.19 d (^{3}*J*=17.0 *Hz*, 1H); 7.58 d (^{3}*J*=17.0 *Hz*, 1H); 7.55 d (^{3}*J*=5.1 *Hz*, 1H); 7.46 d (^{3}*J*=3.7 *Hz*, 1H); 7.10 dd (^{3}*J*=5.1; 3.7 *Hz*, 1H); 2.87 d (^{3}*J*=4.8 *Hz*, 3H); 1.72 s (6H).

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