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SYNTHESIS OF NEW DERIVATIVES OF 2,5-DIHYDRO-2-OXOFURANS

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New derivatives of 2,5-dihydro-2-oxofurans were synthesized by the interaction of 3-acetyl-4,5,5-trimethyl-2,5-dihydro-2-oxofuran with *N*-nucleophiles containing aromatic and heterocyclic substituents.

Keywords: 3-acetyl-4,5,5-trimethylfuran-2,5-dihydro-2-oxofuran, *N*-nucleophile, antibacterial activity.

Introduction. 2,5-Dihydro-2-oxofuran derivatives are a large family of heterocycles that include synthetically useful compounds, several natural products [1–14], and a number of drugs with diverse biological activities such as antifungal, antibacterial, and anti-inflammatory properties [15–19]. Thus, there has been a continuous interest in the development of efficient and convenient methods for the preparation of these heterocycles and in their applications [10–14, 20–22].

For the purpose of making a synthesis of 2,5-dihydro-2-oxofuran new derivatives and finding biologically active compounds among the synthesized structures, we studied synthetic capabilities of 3-acetyl-4,5,5-trimethylfuran-2,5--dihydro-2-oxofuran (**1**) [23], viz., the interaction with *N*-nucleophiles containing aromatic and heterocyclic substituents. The reactions reported herein proceed under mild conditions, and the starting materials are readily available.

Material and Methods. We studied the interaction of 3-acetyl-4,5,5--trimethylfuran-2,5-dihydro-2-oxofuran (**1**) with benzohydrazide (**2 a**), isonico-tinohydrazide (**2 b**), 4-aminobenzohydrazide (**2 c**), aromatic (**3 a–c**) and heterocyclic (**3 d,e**) amines. As aromatic amines were taken aniline (**3 a**), anestezine (**3 b**), sulphadimezine (**3 c**), and as heterocyclic amines – 4-amino-1,5-dimethyl-2-phenyl--1H-pyrazole-3(2H)-one (**3 d**) and 5-amino-1-*sec*-butyl-1H-pyrazol--3(2H)-one (**3 e**) (see Scheme).

All obtained compounds are identified and characterized by spectroscopic methods. The IR, ^{1}H NMR spectroscopic data are in agreement with the proposed structures.

Compounds **4 a–c** and **5 a–e** were tested for antibacterial activity at the chemotherapy laboratory, A. L. Mndzhoyan Institute of Fine Organic Chemistry of

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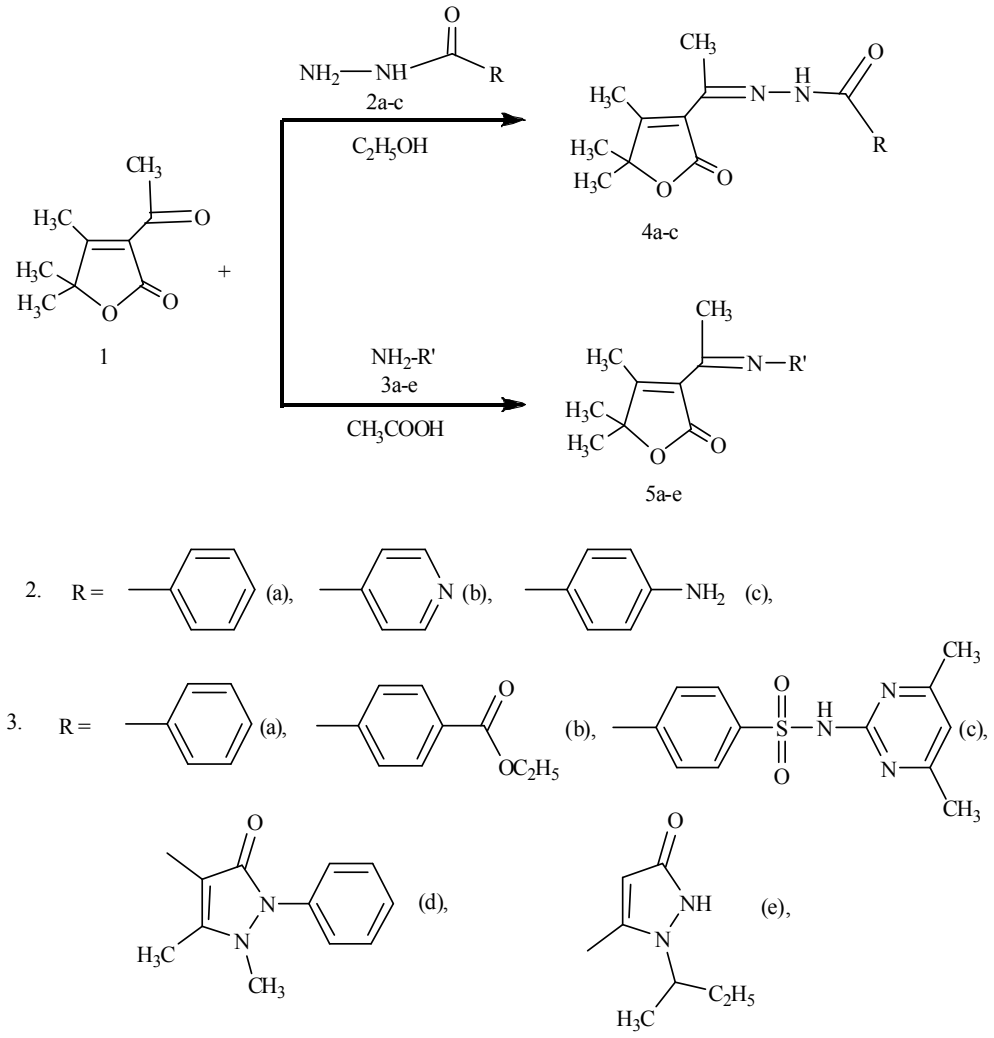
Scientific-Technological Center of Organic and Pharmaceutical Chemistry, NAS of the Republic of Armenia. The test strains were Gram-positive *Staphilococcus aureus* (209p, 1, 93) and Gram-negative *Sh. Dysenteriae flexneri* 6858, *E-coli* 0–55. Compounds **4 a–c** and **5 c** showed a moderate antibacterial activity *in vitro*, making it expedient to conduct further investigations in this area.

Experimental Part. All solvents were dried by standard methods. Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were recorded on a Specord 75 IR spectrometer with samples dispersed in mineral oil. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6/CCl_4 (1:3) solutions on a Varian Mercury-300 VX spectrometer at 300 and 75 *MHz* respectively. The homogeneity and purity of synthesized compounds was tested by means of thin-layer chromatography with TLC on Silufol UV-254 plates, eluent acetone/benzene (1:2), visualization with iodine vapors.



Scheme.

Compound **1** was synthesized by using a published procedure [23].

General Procedure for 4 a–c. A mixture of compound **1** (0.42 *g*, 2.5 *mmol*) and hydrazides **2 a–c** (2.5 *mmol*) in anhydrous ethanol (10 *mL*) was boiled for 7–8 *h*. The solvent was removed under reduced pressure and water was poured to the residue. The precipitated solid was filtered, washed with water and crystallized.

*N'-(1-(4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)benzohydrazide (**4 a**)*. This compound was obtained as a white solid.

Yield 94%; mp 168–169^0C (from hexane); R_f=0.56; IR spectrum, ν, cm^{-1}: 1500–1600 (arom.), 1620 (C=C), 1640 (C=N), 1680 (C=O), 1760 (C=O lactone), 3280 (NH); ^{1}H NMR spectrum, δ, *ppm*: 1.48 bs (6H, $2CH_3$); 2.25 bs (6H, $2CH_3$); 7.38–7.54 m (3H) and 7.78–7.92 bs (2H, C_6H_5); 10.6 bs (1H, NH).

*N'-(1-(4,5,5-Trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)isonicotinohydrazide (**4 b**)*. This compound was obtained as a white solid.

Yield 96%, mp 153–154^0C (from benzene); R_f=0.56; IR spectrum, ν, cm^{-1}: 1500–1600 (arom.), 1620 (C=C), 1640 (C=N), 1680 (C=O), 1760 (C=O lactone), 3280 (NH); ^{1}H NMR spectrum, δ, *ppm*: 1.38–1,54 bs (6H, $2CH_3$); 1.79; 2.25 and 2.31 bs (1H; 3.5H; 1.5H; $2CH_3$); 7.43–7.82 bs (2H, arom. $H_{2,6}$) and bs (2H, arom. $H_{3,5}$); 10.79–11.13 bs (1H, NH).

*4-Amino-N'-(1-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene)-benzohydrazide (**4 c**)*. This compound was obtained as a white solid.

Yield 83%, mp 185–186^0C (from xylene); R_f=0.55; 1500–1600 (arom.), 1620 (C=C), 1640 (C=N), 1680 (C=O), 1760 (C=O lactone), 3260 (NH), 3280 (NH); ^{1}H NMR spectrum, δ, *ppm*: 1.48 bs (6H, $2CH_3$); 2.25 s (6H, $2CH_3$); 7.34 d (2H, arom. $H_{2,6}$); 7.45 d (2H, arom. $H_{3,5}$); 10.6 bs (1H, NH); 11.2 bs (2H, NH).

General Procedure for 5 a–e. A mixture of **1** (0.42 *g*, 2.5 *mmol*) and amines **3 a–e** (2.5 *mmol*) in glacial acetic acid (10 *mL*) in the presence of catalytic amount of conc. sulfuric acid was boiled for 9–11 *h*. The solvent was removed under reduced pressure and water was poured to the residue. The precipitated solid was filtered, washed with water and crystallized.

*4,5,5-Trimethyl-3-(1-(phenylimino)ethyl)-2,5-dihydro-2-oxofuran (**5 a**)*. This compound was obtained as a pale yellow solid.

Yield 85%; mp 94–95^0C (from heptane); R_f=0.59; IR spectrum, ν, cm^{-1}: 1500–1600 (arom.), 1620 (C=C), 1640 (C=N), 1760 (C=O lactone); ^{1}H NMR spectrum, δ, *ppm*: 1,48 bs (6H, $2CH_3$); 2.25 s (6H, $2CH_3$); 6.95–7.55 m (5H, C_6H_5).

*Ethyl 4-(1-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylideneamino)-benzoate (**5 b**)*. This compound was obtained as a white solid.

Yield 88%; mp 88–90^0C (from heptane); R_f=0.58; IR spectrum, ν, cm^{-1}: 1500–1600 (arom.), 1620 (C=C), 1640 (C=N), 1680 (C=O), 1760 (C=O lactone). ^{1}H NMR spectrum, δ, *ppm*: 1,35 t (3H, $CH_2\underline{CH_3}$); 1.48 bs (6H, $2CH_3$); 2.25 s (6H, $2CH_3$); 4.30 k (2H, $\underline{CH_2}CH_3$); 6.85–7.55 m (5H, C_6H_4).

*N-(4,6-Dimethylpyrimidin-2-yl)-4-(1-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran--3-yl)ethylideneamino)benzenesulfonamide (**5 c**)*. This compound was obtained as a white solid.

Yield 85%; mp 137–138^0C (from xylene); R_f=0.56; ^{1}H NMR spectrum, δ, *ppm*: 1.48 bs (6H, $2CH_3$); 2.25 bs (6H, $2CH_3$); 2.71 s (6H, $2CH_3$); 6.74 s (1H, arom. H_4); 7.34 d (2H, arom. $H_{2,6}$); 7.45 d (2H, arom. $H_{3,5}$); 8.6 bs (1H, NH).

*1,5-Dimethyl-2-phenyl-4-(1-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethyl-ideneamino)-1H-pyrazol-3(2H)-one (**5 d**)*. This compound was obtained as a white solid.

Yield 88%; mp 188–189^0C (from toluene); R_f=0.57; ^{1}H NMR spectrum, δ, *ppm*: 1.48 bs (6H, $2CH_3$); 2.25 bs (6H, $2CH_3$); 2.65 s (3H, CH_3); 3,15 s (3H, CH_3); 7.38–7.54 m (3H) and 7.78–7.92 bs (2H, C_6H_5).

*1-Sec-butyl-5-(1-(4,5,5-trimethyl-2-oxo-2,5-dihydrofuran-3-yl)ethylidene-amino)-1H-pyrazol-3(2H)-one (**5 e**)*. This compound was obtained as a white solid.

Yield 87%, mp 158–159^0C (from ethyl acetate); R_f=0.58; ^{1}H NMR spectrum, δ, *ppm*: 0,95 t (3H, $CH_2\underline{CH_3}$); 1.15 d (3H, $CH\underline{CH_3}$); 1.28 kd (2H, $\underline{CH_2}CH_3$); 1.48 s (6H, $2CH_3$); 2.25 s (6H, $2CH_3$); 2.80 kt (1H, $\underline{CH}CH_3$); 8.2 bs (1H, NH).

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