SYNTHESIS OF NEW DERIVATIVES OF 4-AMINO-10-OXA-4-AZATRICYCLO[5.2.1.$0^{2,6}$]DEC-8-ENE-3,5-DIONE

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10-Oxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione derivatives are characterized by various pharmacological actions [1-4].
Imide (**a**) or anhydride (**b**) obtained in Diels-Alder reaction was used as a starting material [5]. Compounds (**a**) or (**b**) in reaction with hydrazine (80% aqueous solution) gave compound **1** [6]. Afterwards the compound **1** was subjected to the reaction with phenyl, 4-methoxyphenyl, ethyl isothiocyanate to be transformed into the corresponding thiourea derivatives. 4-Amino-10-oxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**1**) was used to the reaction with ethyl chloroformate, ethyl bromoacetate and acetic anhydride. Obtained esters (**2** and **5**) were transformed into the corresponding amides.
All final compounds were characterized by ^{1}H NMR spectra which corresponded with the proposed structures. The structure of obtained product (**4**) was confirmed by the X-ray crystallography.
A general synthesis pathway is given in Scheme 1.

Experimental
Chemistry.

Melting points were determined in a Kofler's apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AVANCE DMX400 spectrometer, operating at 400.13 MHz. The chemical shift values are expressed in ppm relative to TMS as an internal standard. Elemental analyses were recorded with a CHN model 2400 Perkin-Elmer. Flash chromatography was performed on Merck silica gel 60 (200-400 mesh) using chloroform/methanol (19:1vol.) mixture as eluent. Analytical TLC was carried out on silica gel F_{254} (Merck) plates (0.25 mm thickness).

The diffraction data were collected at 275 K on a KM-4 diffractomater using the crystal of dimensions $0.22 \times 0.15 \times 0.11$ mm and CuKα radiation. Within the θ range of 5.3 to 72.2°, 2445 reflections were collected. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 (programs SHELXS97 and SHELXL97 [7,8]). The refinement of 175 parameters converged at final R indices: $R_1 = 0.0311$, $wR_2 = 0.0889$ (for 1039 observed reflections, $I > 2\sigma(I)$) and $R_1 = 0.1377$, $wR_2 = 0.1188$ (all data), and Goof = 0.996. The extinction coefficient was 0.0032(3), residual electron density $\Delta\rho(max) = 0.20$ and $\Delta\rho(min) = -0.18$ e A^{-3}.

4-Amino-10-oxa-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (**1**) has been synthesized as described previously [6].
(3,5-Dioxo-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl)-carbamic acid ethyl ester (**2**), *(3,5-dioxo-10-oxa-4-aza-tricyclo[5.2.1.0%2,6&]dec-8-en-4-ylamino)-acetic acid ethyl ester* (**5**), *N-acetyl-N-(3,5-dioxo-10-oxa-4-aza-tricyclo[5.2.1.$0^{2,6}$]dec-4-yl)-acetamide* (**4**).

0.01Mole (1.8g) of the compound **1** 3g of K_2CO_3 and 0.011 mole of ethyl chloroformate (1.1g) or ethyl bromoacetate (1.68g) or acetic anhydride (1.1g) in 100cm^3 acetone were refluxed for 6h. The reaction mixture was filtered and the solvent was removed under a reduced pressure. The residue was crystallized from ethanol. Next it was purified by column chromatography (silica gel) using chloroform/methanol (19:1) as eluent.

2: m.p. 140-141°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (t, 3H, CH_3); 3.1 (s, 2H, CH-C=O); 4.15 (q, 2H, CH_2); 5.17 (s, 2H, CH-O); 6.06 (s, 2H, CH=). For $C_{11}H_{12}N_2O_5$ (252.22) calculated: 52.83 % C, 4.8 % H, 11.11 % N; found: 52.92 % C, 5.16 % H, 10.72 %N.

5: m.p. 144-145 °C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 (t, 3H, CH_3); 3.02 (s, 2H, CH-C=O); 4.15 (q, 2H, CH_2); 4.16 (s, 2H, CH_2); 5.17 (s, 2H, CH-O); 6.06 (s, 2H, CH=). For $C_{12}H_{14}N_2O_5$ (266.24) calculated: 54.13 % C, 5.3 % H, 10.52 % N; found: 54.26 % C, 5.32 % H, 10.62 %N.

4: m.p. 128°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.68 (m, 2H, CH_2); 1.93 (m, 2H, CH_2); 2.11 (s, 3H, CH_3); 2.59 (s, 3H, CH_3); 3.1 (s, 2H, CH-C=O); 4.96 (s, 2H, CH-O. For $C_{12}H_{14}N_2O_5$ (266.25) calculated: 54.13 % C, 5.30 % H, 10.52 % N; found: 54.18 % C, 45.32 % H, 10.72 %N.

Crystal data for (**4**): $C_{12}H_{14}N_2O_5$, *M.W.* = 266.25, crystal system orthorhombic, space group *Pbca* with unit cell dimensions *a* = 6.977(1), *b* = 16.658(3), *c* = 21.361(4) A and *V* = 2482.6(7) A^{-3}; Z = 8, *d*(*calc*) = 1.425 g cm^{-3}, μ = 0.952 mm^{-1}, F(000) = 1120.

(3,5-Dioxo-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-urea (**3**), *2-(3,5-dioxo-10-oxa-4-aza-tricyclo[5.2.1.0^{2,6}]dec-8-en-4-ylamino)-acetamide* (**6**).

100cm^3 of a 25% aqueous ammonia solution was added to a tighly closed vessel containing 0.01 mole of compound **2** (2.5g) or **5** (2.6g). The reaction mixture was kept for one week at room temperature. The obtained products **3** or **6** were collected by filtration and recrystallised from ethanol – water solution (1:1).

3: m.p. 170°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.1 (s, 2H, CH-C=O); 4.20 (s, 2H, NN_2); 5.08 (s, 2H, CH-O); 6.06 (s, 2H, CH=). For $C_9H_9N_3O_4$ (223.18) calculated: 48.43 % C, 4.06 % H, 18.83 % N; found: 48.72 % C, 4.16 % H, 18.72 %N.

6: m.p. 182°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.02 (s, 2H, CH-C=O); 4.16 (s, 2H, CH_2); 4.82 (s, 2H, NH_2); 5.17 (s, 2H, CH-O); 6.06 (s, 2H, CH=). For $C_{12}H_{14}N_2O_5$ (266.24) calculated: 54.13 % C, 5.3 % H, 10.52 % N; found: 54.26 % C, 5.32 % H, 10.62 %N.

1-(3,5-Dioxo-10-oxa-4-aza-tricyclo[5.2.1.0%2,6&]dec-8-en-4-yl)-3-(phenyl)-thiourea (**7**), *1-(3,5-Dioxo-10-oxa-4-aza-tricyclo[5.2.1.0%2,6&]dec-8-en-4-yl)-3-(4-methoxy-phenyl)-thiourea* (**8**), *1-(3,5-Dioxo-10-oxa-4-aza-tricyclo[5.2.1.0%2,6&]dec-8-en-4-yl)-3-(ethyl)-thiourea* (**9**).

A solution of compound **1** (0.01 mole; 1.8g)) in acetonitrile (6 cm^3) was treated with phenyl, 4-metoxyphenyl, ethyl isothiocyanate (0.011mol) and the mixture was refluxed for 6h. The precipitate was filtered and then washed with ether to give compounds **7 - 9**. Next it was purified by column chromatography (silica gel) using chloroform/methanol (19:1) as eluent.

7: m.p. 167-168°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.0 (s, 2H, CH-C=O); 5.21 (s, 2H, CH-O); 6.58 (s, 2H, CH=); 7.2-7.36 (m, 5H, $CH_{arom.}$); 9.93 (s, 1H, NH); 10.34 (s, 1H, NH). For $C_{15}H_{13}N_3O_3S$ (315.33) calculated: 57.13 % C, 4.16 % H, 13.33 % N; found: 57.24 % C, 4.16 % H, 13.24 %N.

8: m.p. 178°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.83 (s, 2H, CH-C=O); 3.79 (s, 3H, OCH_3); 5.21 (s, 2H, CH-O); 6.51 (s, 2H, CH=); 6.81-7.45 (m, 5H, $CH_{arom.}$); 8.31 (s, 1H, NH);

8.5 (s, 1H, NH). For $C_{16}H_{15}N_3O_4S$ (345.37) calculated: 55.64 % C, 4.83 % H, 12.12 % N; found: 55.82 % C, 4.48 % H, 12.16 %N.

9: m.p. 165°C. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.74 (t, 3H, CH_3); 2.13 (q, 2H, CH_2); 3.96 (s, 2H, CH-C=O); 5.15 (s, 2H, CH-O); 6.56 (s, 2H, CH=). For $C_{11}H_{13}N_3O_3S$ (267.3) calculated: 49.43 % C, 4.9 % H, 15.72 % N; found: 49.64 % C, 4.92 % H, 15.78 %N.

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Scheme 1.

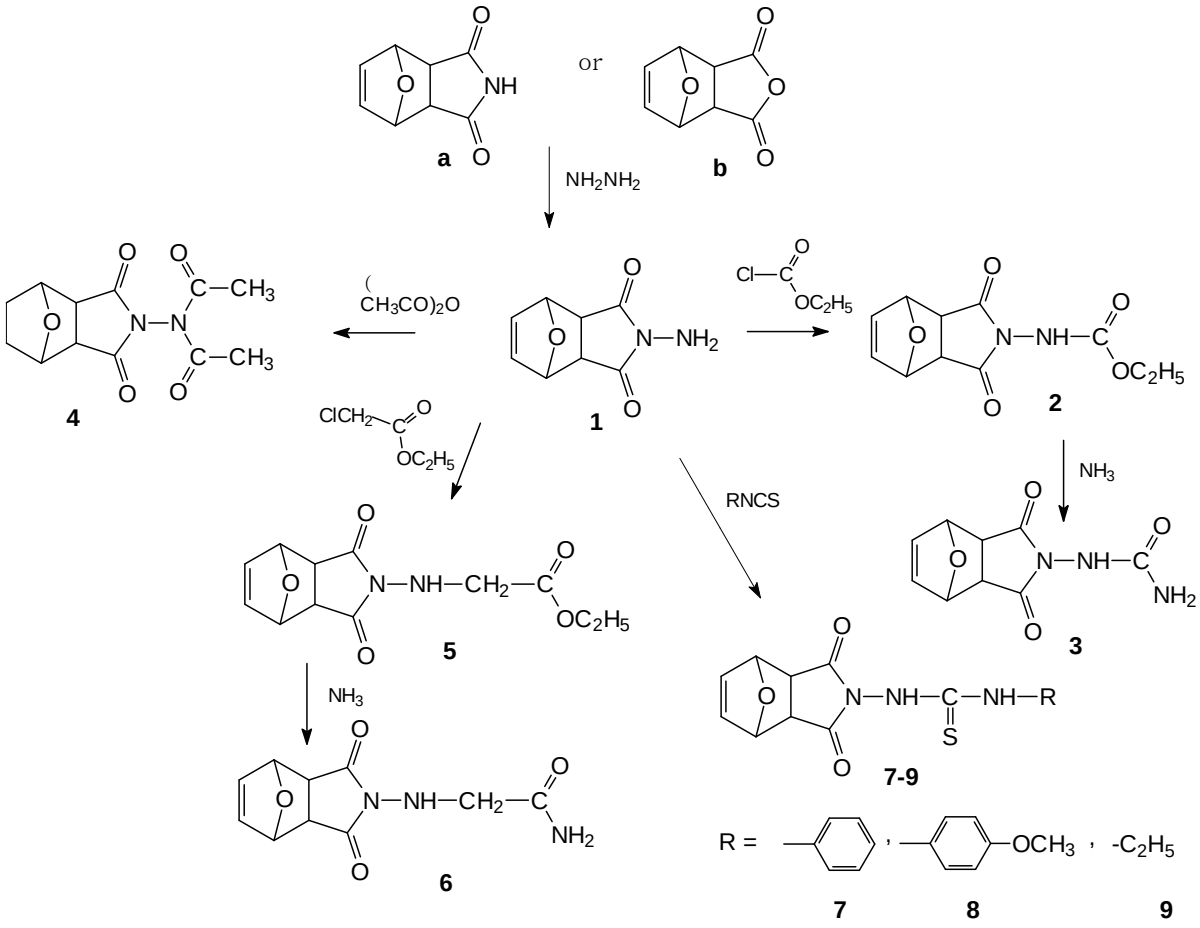

Fig. 1. Perspective view of molecular structure of compound **4**. *Cis*, *exo* configuration at the ring junction (C3–C8); the N,N-diacetyl fragment is planar with perpendicular orientation to the imid ring plane; the C=O bonds of acetyl groups are *anti.*

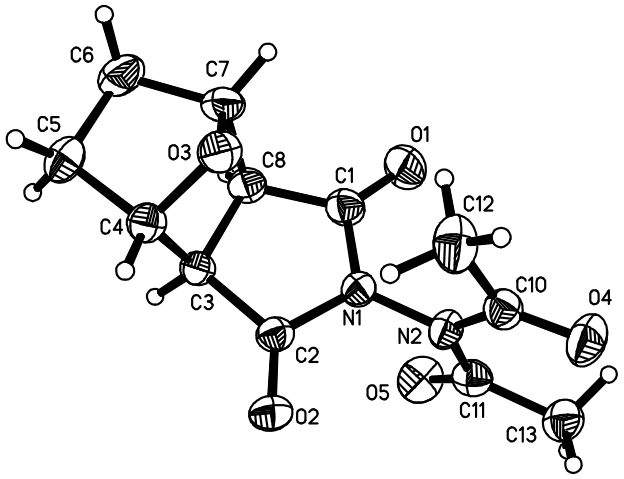

Table 1. Bond lengths (Å).

N(1)-N(2)	1.383(2)	C(3)-C(4)	1.525(3)
N(1)-C(1)	1.393(3)	C(3)-C(8)	1.542(3)
N(1)-C(2)	1.396(3)	C(4)-C(5)	1.529(3)
N(2)-C(10)	1.416(2)	C(5)-C(6)	1.537(3)
N(2)-C(11)	1.420(3)	C(6)-C(7)	1.521(3)
O(1)-C(1)	1.205(3)	C(7)-C(8)	1.542(3)
O(2)-C(2)	1.201(2)	C(10)-C(12)	1.490(3)
O(3)-C(4)	1.440(2)	C(11)-C(13)	1.486(3)
O(3)-C(7)	1.442(3)	N(2)-N(1)-C(1)	122.5(2)
O(4)-C(10)	1.198(2)	N(2)-N(1)-C(2)	123.2(2)
O(5)-C(11)	1.199(2)	C(1)-N(1)-C(2)	114.0(2)
C(1)-C(8)	1.489(3)	C(1)-N(1)-N(2)-C(10)	93.2(2)
C(2)-C(3)	1.508(2)	C(2)-N(1)-N(2)-C(11)	90.6(2)