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Synthesis of *N*-Aryl- and *N*,*N*-Diethyl-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamides

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Abstract—Three-component condensation of *N*-aryl- and *N*,*N*-diethyl-3-oxobutanamides with salicylaldehyde and thiourea in ethanol in the presence of sodium hydrogen sulfate afforded *N*-aryl- and *N*,*N*-diethyl-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamides. Reaction of the same compounds in the absence of a catalyst under solvent-free conditions gave *N*-aryl-6-(2-hydroxyphenyl)-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamides.

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It is known that dihydropyrimidinones(thiones) possessing an aryl substituent with a hydroxy group in the *ortho* position can be converted into tricyclic structures with an oxygen bridge connecting the heterocycle and the aryl substituent [1–4]. The formation of 9-methyl-11-oxo(sulfanylidene)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene derivatives together with 4-(2-hydroxyphenyl)pyrimidines in reactions of β-ketoesters with salicylaldehyde and urea (thiourea) in the presence of $NaHSO_4$ was reported [5]. Three-component condensation of acetylacetone with salicylaldehyde and urea (thiourea) in the presence of $NaHSO_4$ under microwave irradiation or on heating in boiling ethanol in the presence of $MnCl_2$ as catalyst led to the formation of 13-acetyl-9-methyl-11-oxo(sulfanylidene)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trienes as the only products [6, 7].

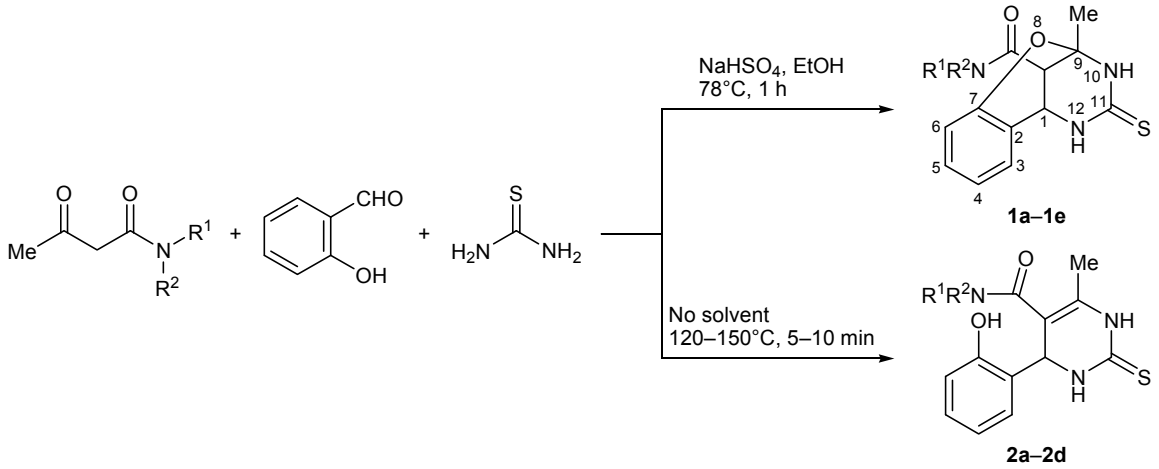
Biological screening of 9-methyl-11-oxo(sulfanylidene)-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene derivatives showed prospects of using them as calcium channel blockers with prolonged antiarrhythmic and antianginal effects on cardiac muscle and antihypertensive and spasmolytic effects on brain vessels [1, 8]. Therefore, synthesis of new potentially biologically active compounds of this series seems to be important.

N-Aryl- and *N*,*N*-diethyl-3-oxobutanamides were not involved in analogous three-component condensations. In some cases, *N*-aryl-3-oxobutanamides behave differently from 3-oxobutanoic acid esters and acetylacetone in multi-component reactions [9]. Furthermore, amide group is a pharmacophoric fragment [10].

While continuing studies in this line, *N*-aryl- and *N*,*N*-diethyl-3-oxobutanamides were brought into three-component condensation with salicylaldehyde and thiourea on heating in ethanol (reaction time 1 h) in the presence of sodium hydrogen sulfate as catalyst. As a result, we isolated *N*-aryl- and *N*,*N*-diethyl-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo-[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamides **1a**–**1e** (Scheme 1). When the reaction was carried out under the conditions described in [11, 12], we isolated *N*-aryl-6-(2-hydroxyphenyl)-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamides **2a**–**2d**. We failed to isolate analogous *N*,*N*-diethyl derivative in the reaction with *N*,*N*-diethyl-3-oxobutanamide.

Compounds **1a**–**1e** and **2a**–**2d** are colorless or slightly colored crystalline substances soluble in DMF, DMSO, acetic acid, and acetone and insoluble in water. Unlike **2a**–**2d**, compounds **1a**–**1e** showed a negative color test for enolic hydroxy group on treatment with an alcoholic solution of iron(III) chloride.

Scheme 1.



R^1 = H, R^2 = Ph (**a**), 2-MeC_6H_4 (**b**), 2-$MeOC_6H_4$ (**c**), 2-ClC_6H_4 (**d**); R^1 = R^2 = Et (**e**).

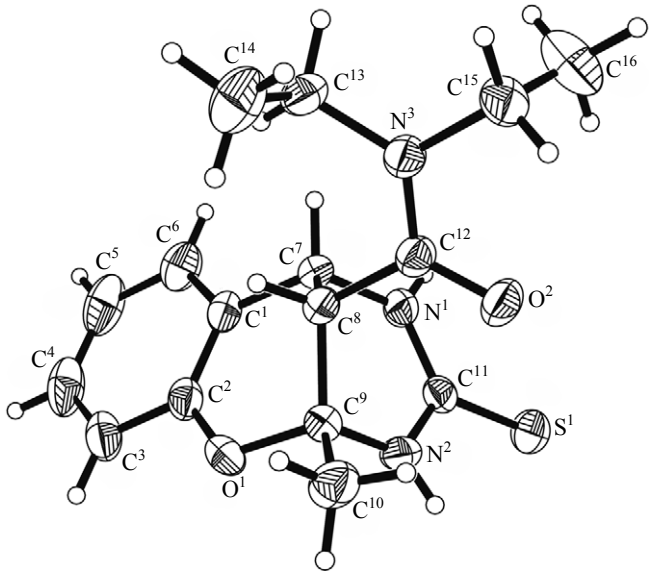
The mass spectra of **1a**–**1d** contained the molecular ion peaks with *m*/*z* values consistent with the proposed structures (see Experimental).

The structure of **1e** was determined by X-ray analysis of a single crystal which was obtained by slow crystallization from ethanol (see figure). Compound **1e** crystallized in centrosymmetric space group belonging to the monoclinic crystal system. All bond lengths and bond angles in molecule **1e** are close to the corresponding reference values. The dihydropyran and hexahydropyrimidine rings appear in *sofa* conformation. The dihedral angle formed by the two planar fragments $C^7C^1C^2O^1C^9$ and $C^7N^1C^{11}N^2C^9$ is 69.6°, and the angles between the $C^7N^1C^{11}N^2C^9$ and $C^7C^8C^9$ planes and between the $C^7C^1C^2O^1C^9$ and $C^7C^8C^9$ planes are 52.4 and 58.2°, respectively. Molecules **1e** in crystal are linked through intermolecular hydrogen bonds N^1–$H^1\cdots O^2$ [*x*, 0.5 – *y*, 0.5 + *z*; N^1–H^1 0.82(2), $N^1\cdots O^2$ 2.805(2), $H^1\cdots O^2$ 2.16(2) Å, $\angle N^1H^1O^2$ 136(2)°] to form infinite chains along the *c* crystallographic axis. The X-ray diffraction data for compound **1e** were deposited to the Cambridge Crystallographic Data Centre (entry no. CDDC 1 453 995) and are available at *www.ccdc.cam.ac.uk*.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord M-80 spectrometer. The ^{1}H NMR spectra were measured on a Bruker 500 instrument at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra were obtained using a Waters Acquity UPLC I-Class instrument equipped with a Xevo TQD detector; samples were introduced as solutions in water–acetonitrile–formic acid (49.95 : 50 : 0.05); electrospray ionization, positive ion detection; 150°C; capillary voltage 3500–4000 V; cone voltage 20–80 V. The elemental analyses were obtained on a Perkin Elmer 2400 analyzer. The melting points were determined on an M-565 melting point apparatus.

The X-ray diffraction data for compound **1e** were acquired on an Xcalibur R diffractometer with a CCD detector [MoK_α radiation, 295(2) K, ω-scanning with a step of 1°] according to standard procedure [13].



Structure of the molecule of *N*,*N*-diethyl-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene-13-carboxamide (**1e**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

A correction for absorption was applied by the SCALE3 ABSPACK algorithm [13]. Monoclinic crystal system, space group $P2_1/c$; unit cell parameters: a = 9.6764(13), b = 18.556(3), c = 9.1490(13) Å; β = 95.519(13)°; V = 1635.1(4) Å^3; Z = 4. The structure was solved by the direct method and was refined by the full-matrix least-squares method in anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were placed in geometrically calculated positions and were refined according to the riding model in isotropic approximation with dependent thermal parameters, except for NH hydrogens which were refined independently in isotropic approximation. The structure was solved and refined using SHELXS and SHELXL packages [14]. Final divergence factors: R_1 = 0.0419, wR_2 = 0.1101 [3267 reflections with $I > 2\sigma(I)$]; R_1 = 0.0502, wR_2 = 0.1157 (3845 independent reflections); goodness of fit S = 1.049; Δρ = 0.285/–0.341 $\bar{e}$Å^{-3}.

9-Methyl-*N*-phenyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamide (1a). A mixture of 0.01 mol of 3-oxo-*N*-phenylbutanamide, 0.01 mol of salicylaldehyde, 0.01 mol of thiourea, and 0.008 mol of sodium hydrogen sulfate in 15 mL of ethanol was refluxed for 1 h. After cooling, the precipitate was filtered off and recrystallized from ethanol. Yield 2.98 g (88%), mp 214–216°C. IR spectrum, ν, cm^{-1}: 3312, 3208 (NH), 1672 (C=O), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, 9-CH$_3$), 3.17 m (1H, 13-H), 4.60 d.d (1H, 1-H, J = 2.8, 3.1 Hz), 6.74–7.54 m (9H, H$_{arom}$), 8.97 s (1H, 10-H), 8.92 d (1H, 12-H, J = 2.7 Hz), 10.06 s (1H, CONH). Mass spectrum, m/z: 339 $[M]^+$, 262 $[M - Ph]^+$. Found, %: C 63.57, 63.82; H 4.97, 5.14; N 12.24, 12.51. $C_{18}H_{17}N_3O_2S$. Calculated, %: C 63.70; H 5.05; N 12.38.

Compounds **1b**–**1e** were synthesized in a similar way.

9-Methyl-*N*-(2-methylphenyl)-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamide (1b). Yield 3.00 g (85%), mp 262–264°C. IR spectrum, ν, cm^{-1}: 3200, 3296, 3280 (NH), 1664 (C=O), 1580 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, 9-CH$_3$), 2.21 s (3H, C**H**$_3$C$_6$H$_4$), 3.35 m (1H, 13-H), 4.61 d.d (1H, 1-H, J = 2.7, 3.1 Hz), 6.74–7.39 m (8H, H$_{arom}$), 8.95 s (1H, 10-H), 9.02 d (1H, 12-H, J = 2.7 Hz), 9.41 s (1H, CONH). Mass spectrum: m/z 353 $[M]^+$. Found, %: C 64.46, 64.69; H 5.34, 5.52; N 11.76, 12.02. $C_{19}H_{19}N_3O_2S$. Calculated, %: C 64.57; H 5.42; N 11.89.

***N*-(2-Methoxyphenyl)-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamide (1c).** Yield 2.98 g (81%), mp 200–202°C. IR spectrum, ν, cm^{-1}: 3300, 3270, 3200 (NH), 1670 (C=O), 1608 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.75 s (3H, 9-CH$_3$), 3.38 m (1H, 13-H), 3.74 s (3H, CH$_3$O), 4.46 d.d (1H, 1-H, J = 2.8, 2.7 Hz), 6.66–7.15 m (8H, H$_{arom}$), 8.90 s (1H, 10-H), 9.04 d (1H, 12-H, J = 2.7 Hz), 9.25 s (1H, CONH). Mass spectrum: m/z 369 $[M]^+$. Found, %: C 61.66, 61.89; H 5.08, 5.26; N 11.25, 11.50. $C_{19}H_{19}N_3O_3S$. Calculated, %: C 61.77; H 5.18; N 11.37.

***N*-(2-Chlorophenyl)-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamide (1d).** Yield 3.39 g (91%), mp 239–240°C. IR spectrum, ν, cm^{-1}: 3352, 3250, 3200 (NH), 1672 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.75 s (3H, 9-CH$_3$), 3.37 m (1H, 13-H), 4.60 d.d (1H, 1-H, J = 2.8, 3.0 Hz), 6.72–7.42 m (8H, H$_{arom}$), 8.94 s (1H, 10-H), 9.67 d (1H, 12-H, J = 2.8 Hz), 9.70 s (1H, CONH). Mass spectrum: m/z 373 $[M]^+$. Found, %: C 57.72, 57.96; H 4.22, 4.40; N 11.12, 11.37. $C_{18}H_{16}ClN_3O_2S$. Calculated, %: C 57.83; H 4.31; N 11.24.

***N*,*N*-Diethyl-9-methyl-11-sulfanylidene-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxamide (1e).** Yield 2.05 g (64%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3300, 3280 (NH), 1670 (C=O), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.06 t and 1.13 t (3H each, C**H**$_3$CH$_2$, J = 6.8 Hz), 3.38 m (4H, CH$_3$C**H**$_2$), 1.69 s (3H, 9-CH$_3$), 3.28 m (1H, 13-H), 4.40 d.d (1H, 6-H, J = 2.0, 3.2 Hz), 6.83–7.19 m (4H, H$_{arom}$), 9.05 s (1H, 10-H), 9.10 d (1H, 12-H, J = 2.8 Hz). Found, %: C 60.04, 60.29; H 6.54, 6.70; N 13.03, 13.28. $C_{16}H_{21}N_3O_2S$. Calculated, %: C 60.16; H 6.63; N 13.15.

6-(2-Hydroxyphenyl)-4-methyl-*N*-phenyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamide (2a). A mixture of 0.01 mol of acetoacetanilide, 0.01 mol of salicylaldehyde, and 0.01 mol of thiourea was heated for 5–10 min at 120–150°C until gas no longer evolved. The mixture was cooled and treated with ethanol, and the precipitate was filtered off and recrystallized from ethanol. Yield 2.58 g (76%), mp 261–263°C. IR spectrum, ν, cm^{-1}: 3290, 3200 (NH), 3150 (OH), 1670 (C=O), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.75 s (3H, 4-CH$_3$), 4.60 d (1H, 6-H, $J_{1,6}$ = 2.8 Hz), 6.74–7.53 m (10H, H$_{arom}$, OH), 8.88 d (1H, 1-H, $J_{1,6}$ = 2.8 Hz), 8.94 s and 8.95 s (1H, 3-H, 2-SH), 10.03 s (1H, CONH). Found, %: C 63.57,

63.83; H 4.95, 5.13; N 12.26, 12.49. $C_{18}H_{17}N_3O_2S$. Calculated, %: C 63.70; H 5.05; N 12.38.

Compounds **2b**–**2d** were synthesized in a similar way.

6-(2-Hydroxyphenyl)-4-methyl-*N*-(2-methylphenyl)-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamide (2b). Yield 2.58 g (73%), mp 260–262°C. IR spectrum, ν, cm^{-1}: 3400, 3380, 3210 (NH), 3096 (OH), 1664 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, 4-CH_3), 2.21 s (3H, C**H**$_3$C$_6$H$_4$), 4.63 d (1H, 6-H, $J_{1,6}$ = 2.8 Hz), 6.75–7.41 m (9H, H_{arom}, OH), 8.93 d (1H, 1-H, $J_{1,6}$ = 2.8 Hz), 8.95 s and 8.96 s (1H, 3-H, 2-SH), 9.40 s (1H, CONH). Found, %: C 64.44, 64.68; H 5.33, 5.50; N 11.77, 12.00. $C_{19}H_{19}N_3O_2S$. Calculated, %: C 64.57; H 5.42; N 11.89.

6-(2-Hydroxyphenyl)-*N*-(2-methoxyphenyl)-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamide (2c). Yield 2.58 g (70%), mp 247–249°C. IR spectrum, ν, cm^{-1}: 3390, 3340, 3200 (NH), 3150 (OH), 1672 (C=O), 1590 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.73 s (3H, 4-CH_3), 3.78 s (3H, CH_3O), 4.51 d (1H, 6-H, $J_{1,6}$ = 2.1 Hz), 6.73–7.96 m (9H, H_{arom}, OH), 8.92 d (1H, 1-H, $J_{1,6}$ = 2.1 Hz), 8.94 s and 8.96 s (1H, 3-H, 2-SH), 9.41 s (1H, CONH). Found, %: C 61.65, 61.87; H 5.10, 5.28; N 11.24, 11.49. $C_{19}H_{19}N_3O_3S$. Calculated, %: C 61.77; H 5.18; N 11.37.

***N*-2-(Chlorophenyl)-6-(2-hydroxyphenyl)-4-methyl-2-sulfanylidene-1,2,3,6-tetrahydropyrimidine-5-carboxamide (2d).** Yield 2.94 g (79%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3360, 3280, 3200 (NH), 3025 (OH), 1680 (C=O), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, 4-CH_3), 4.62 d (1H, 6-H, $J_{1,6}$ = 1.9 Hz), 6.75–7.71 m (9H, H_{arom}, OH), 8.93 d (1H, 1-H, $J_{1,6}$ = 1.9 Hz), 8.95 s and 8.96 s (1H, 3-H, 2-SH), 9.69 s (1H, CONH). Found, %: C 57.70, 57.94; H 4.23, 4.41; N 11.11, 11.36. $C_{18}H_{16}ClN_3O_2S$. Calculated, %: C 57.83; H 4.31; N 11.24.

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