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Synthesis of *N*-Aryl- and *N*,*N*-Diethyl-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamides

V. L. Gein,[a]* T. M. Zamaraeva[a], N. A. Buzmakova[a], M. V. Dmitriev[b], O. E. Nasakin[c], and M. I. Kazantseva[c]

[a] *Perm State Pharmaceutical Academy, ul. Polevaya 2, Perm, 614990 Russia*
**e-mail: geinvl48@mail.ru*

[b] *Perm National State Research University, ul. Bukireva 15, Perm, 614990 Russia*

[c] *I.N. Ul'yanov Chuvash State University, Moskovskii pr. 15, Cheboksary, 428015 Russia*

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Abstract—*N*-Aryl- and *N*,*N*-diethyl-3-oxobutanamides reacted with salicylaldehyde and *N*-phenylthiourea in ethanol in the presence of sodium hydrogen sulfate as catalyst to give the corresponding N-substituted 2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamides.

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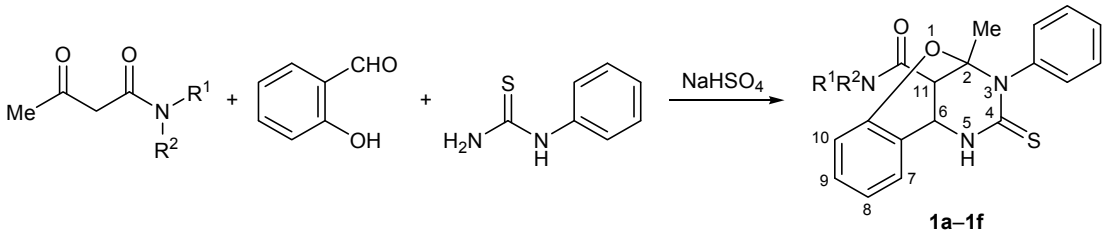
It is known that some N-substituted dihydropyrimidin-2-ones and -thiones exhibit a higher biological activity than their N-unsubstituted analogs [1]. Cardiovascular agents promising as antihypertensive drugs and vasodilators were found among 3-substituted dihydropyrimidines, in particular 3-alkyl, 3-acyl [2, 3], and 3-sulfanyl derivatives [4]. 3-Phenacyl-substituted dihydropyrimidines showed anti-inflammatory activity [5], and 3-carbamoyl derivatives were reported to exhibit high antimalarial activity [6]. 1-Alkyl-substituted dihydropyrimidines are known as antitumor and antiviral agents [7–10], while 1-aryl- [11] and 1-methyl derivatives [12] displayed antimycobacterial activity. Although a large number of compounds possessing practically important properties have been found in the series of N-substituted dihydropyrimidines, the synthesis of new potentially biologically active representatives of this class of compounds remains topical.

Cheng et al. [13, 14] described the three-component reaction of acetylacetone (β-keto esters) with salicylaldehyde and *N*-phenylurea in the presence of $NaHSO_4$, which afforded 9-methyl-10-phenyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene derivatives (2-methyl-4-oxo-3-phenyl-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocines). While continuing studies in this line we examined the three-component condensation of *N*-aryl- and *N*,*N*-diethyl-3-oxobutanamides with salicylaldehyde and *N*-phenylthiourea. The reactions were carried out by heating the reactants in boiling ethanol for 1 h in the presence of $NaHSO_4$ as catalyst. The only products were N-substituted 2-methyl-3-phenyl-4-sulfanyli-

Scheme 1.



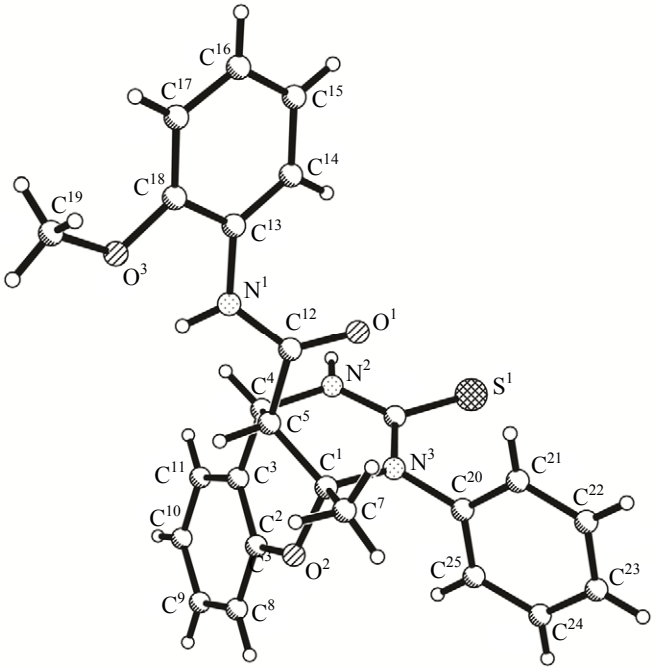
1a–1f

R^1 = H, R^2 = Ph (**a**), 2-MeC_6H_4 (**b**), 2,4-$Me_2C_6H_3$ (**c**), 2-$MeOC_6H_4$ (**d**), 2-ClC_6H_4 (**e**); R^1 = R^2 = Et (**f**).

dene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamides **1a**–**1f** (Scheme 1).

Compounds **1a**–**1f** were isolated as colorless or weakly colored crystalline solids which were soluble in DMF, DMSO, acetic acid, and acetone and insoluble in water. The IR spectra of **1a**–**1f** contained absorption bands due to stretching vibrations of the amide carbonyl group (1664–1680 cm^{-1}), N–H bonds (3150–3392 cm^{-1}), and C=C bonds (1588–1600 cm^{-1}). Apart from signals of protons in the aromatic rings and substituents therein, compounds **1a**–**1f** characteristically showed in the ^{1}H NMR spectra a singlet at δ 1.35–1.45 ppm from the 2-methyl group, a multiplet signal at δ 3.50–3.74 ppm from 11-H, a doublet of doublets at δ 4.42–4.75 ppm (J = 1.0–2.7, 1.8–3.8 Hz) from 6-H, a doublet at δ 9.13–9.37 ppm (J = 2.8–5.6 Hz) from 5-H, a singlet at δ 9.12–9.85 ppm from the amide NH proton (**1a**–**1e**), and multiplet signals at about δ 1.11 and 3.41 ppm due to ethyl groups on the amide nitrogen atom of **1f**. Compounds **1a**–**1f** showed a negative color test for enolic hydroxy group on treatment with a solution of iron(III) chloride. In the mass spectrum of **1e** we observed the molecular ion peak with m/z 450, which is consistent with the proposed structure.

The structure of **1d** in crystal was unambiguously determined by X-ray analysis of its single crystal obtained by slow crystallization from a solution in ethanol (see figure). Compound **1d** crystallized in centrosymmetric space group belonging to the monoclinic crystal system with a unit cell containing four crystallographically independent molecules. Figure shows one independent molecule; atoms of the other molecules are numbered with an additional index, *A*, *B*, or *C*. The pyran and pyrimidine rings in all independent molecules adopt a conformation intermediate between *sofa* and *half-chair*. The C^5 and C^1 atoms deviate from the plane formed by the other four atoms of the pyran ring by 0.63–0.67 and 0.15–0.18 Å, respectively, in opposite directions. Likewise, the pyrimidine atoms C^5 and C^4 deviate from the $C^1N^1C^6N^2$ plane by 0.52–0.56 and 0.24–0.29 Å, respectively, in opposite directions. The phenyl substituent is turned through an angle of ~90° with respect to the pyrimidine ring plane. The arylcarbamoyl substituents are not planar: the absolute values of the torsion angle $C^{12}N^3C^{13}C^{14}$ which characterize rotation of the methoxyphenyl group with respect to the carbamoyl fragment range from 39 to 43°. Molecules **1d** in crystal are linked to form infinite two-dimensional networks parallel to the (001) plane through a developed



Structure of the molecule of *N*-(2-methoxyphenyl)-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (**1d**) according to the X-ray diffraction data.

N–H···S and N–H···O intermolecular hydrogen bond system.

The X-ray diffraction data for compound **1d** were deposited to the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk; CCDC entry no. 1479266).

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 on a Waters Acquity UPLC I-Class instrument coupled with a Xevo TQD detector (electrospray ionization, positive ion detection, capillary voltage 3500–4000 V, cone voltage 20–80 V, temperature 150°C; samples were introduced as solutions in water–acetonitrile–formic acid, 49.95:50.00:0.05). The elemental compositions were determined with a Perkin Elmer 2400 analyzer. The melting points were measured on an M-565 melting point apparatus.

The X-ray diffraction data for compound **1d** were acquired on an Xcalibur R single crystal diffractometer (monochromatized MoK_α radiation, ω-scanning) from

a fragment of a colorless plate crystal using CrysAlisPro software package [15]. Monoclinic crystal system, space group $P2_1/n$; $C_{25}H_{23}N_3O_3S$; unit cell parameters: a = 20.986(3), b = 18.1649(17), c = 25.727(3) Å; β = 110.099(15)°; V = 9210(2) Å^3; M 445.52; d_{calc} = 1.285 g/cm^3; Z = 16. Total of 69535 reflection intensities were measured, including 22602 independent reflections and 12265 reflections with $I > 2\sigma(I)$. A correction for absorption was applied empirically by the SCALE3 ABSPACK algorithm [15]. 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 of the NH groups were localized from the difference Fourier maps, and their positions were refined independently in isotropic approximation. The other hydrogens were refined according to the riding model in isotropic approximation. All calculations were performed using SHELXL [16] and OLEX2 [17]. Final divergence factors: R_1 = 0.0688, wR_2 = 0.1492 [reflections with $I > 2\sigma(I)$]; R_1 = 0.1395, wR_2 = 0.1942 (all independent reflections); goodness of fit S = 1.028.

Compounds 1a–1f (*general procedure*). A mixture of 10 mmol of acetoacetamide, 10 mmol of salicylaldehyde, and 15 mmol of *N*-phenylthiourea in 15 mL of ethanol containing 8 mmol of sodium hydrogen sulfate was heated for 1 h under reflux. After cooling, the precipitate was filtered off and recrystallized from ethanol.

2-Methyl-*N*,3-diphenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1a). Yield 3.49 g (84%), mp 210–212°C. IR spectrum, ν, cm^{-1}: 3304, 3200 (NH), 1672 (C=O), 1596 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.41 s (3H, 2-CH_3), 3.71 m (1H, 11-H), 4.66 d.d (1H, 6-H, J = 1.8, 3.8 Hz), 6.89–8.08 m (14H, H_{arom}), 9.32 d (1H, 5-H, J = 5.6 Hz), 9.59 s (1H, CONH). Found, %: C 69.25, 69.50; H 5.00, 5.17; N 10.00, 10.24. $C_{24}H_{21}N_3O_2S$. Calculated, %: C 69.38; H 5.09; N 10.11.

2-Methyl-*N*-(2-methylphenyl)-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1b). Yield 3.48 g (81%), mp 226–228°C. IR spectrum, ν, cm^{-1}: 3328, 3240 (NH), 1680 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.45 s (3H, 2-CH_3), 2.25 s (3H, C**H**$_3$C$_6$H$_4$), 3.55 m (1H, 11-H), 4.75 d.d (1H, 6-H, J = 2.7, 2.8 Hz), 6.82–7.47 m (13H, H_{arom}), 9.37 d (1H, 5-H, J = 5.5 Hz), 9.54 s (1H, CONH). Found, %: C 69.80, 70.02; H 5.31, 5.50; N 9.66, 9.91. $C_{25}H_{23}N_3O_2S$. Calculated, %: C 69.91; H 5.40; N 9.78.

***N*-(2,4-Dimethylphenyl)-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1c).** Yield 3.50 g (79%), mp 230–232°C. IR spectrum, ν, cm^{-1}: 3272, 3150 (NH), 1664 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.42 s (3H, 2-CH_3), 2.21 s and 2.25 s (3H each, **Me**$_2$C$_6$H$_3$), 3.50 m (1H, 11-H), 4.70 d.d (1H, 6-H, J = 1.8, 1.0 Hz), 6.87–7.23 m (12H, H_{arom}), 9.29 d (1H, 5-H, J = 2.8 Hz), 9.42 s (1H, CONH). Found, %: C 70.29, 70.52; H 5.60, 5.77; N 9.36, 9.60. $C_{26}H_{25}N_3O_2S$. Calculated, %: C 70.40; H 5.68; N 9.47.

***N*-(2-Methoxyphenyl)-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1d).** Yield 3.38 g (76%), mp 214–215°C. IR spectrum, ν, cm^{-1}: 3392, 3200 (NH), 1680 (C=O), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.39 s (3H, 2-CH_3), 3.79 s (3H, CH_3O), 3.74 m (1H, 11-H), 4.65 d.d (1H, 6-H, J = 2.8, 1.8 Hz), 6.83–8.05 m (13H, H_{arom}), 9.28 d (1H, 5-H, J = 4.6 Hz), 9.56 s (1H, CONH). Found, %: C 67.29, 67.52; H 5.12, 5.29; N 9.31, 9.56. $C_{25}H_{23}N_3O_3S$. Calculated, %: C 67.40; H 5.20; N 9.43.

***N*-(2-Chlorophenyl)-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1e).** Yield 4.00 g (89%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3384, 3190 (NH), 1680 (C=O), 1588 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.43 s (3H, 2-CH_3), 3.64 m (1H, 11-H), 4.74 d.d (1H, 6-H, J = 2.7, 1.9 Hz), 6.82–7.77 m (13H, H_{arom}), 9.35 d (1H, 5-H, J = 4.6 Hz), 9.85 s (1H, CONH). Found, %: C 63.95, 64.18; H 4.38, 4.57; N 9.22, 9.47. $C_{24}H_{20}ClN_3O_2S$. Calculated, %: C 64.06; H 4.48; N 9.34.

***N*,*N*-Diethyl-2-methyl-3-phenyl-4-sulfanylidene-3,4,5,6-tetrahydro-2*H*-2,6-methano-1,3,5-benzoxadiazocine-11-carboxamide (1f).** Yield 2.46 g (62%), mp 196–198°C. ^{1}H NMR spectrum, δ, ppm: 1.11 m (6H, C**H**$_3$CH$_2$), 3.41 m (4H, CH$_3$C**H**$_2$), 1.35 s (3H, 2-CH_3), 3.59 m (1H, 11-H), 4.42 d.d (1H, 6-H, J = 1.7, 2.1 Hz), 6.87–7.27 m (9H, H_{arom}), 9.13 d (1H, 5-H, J = 3.8 Hz). Found, %: C 66.36, 66.59; H 6.77, 6.94; N 10.46, 10.70. $C_{22}H_{27}N_3O_2S$. Calculated, %: C 66.47; H 6.85; N 10.57.

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