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CRYSTAL STRUCTURE OF ETHYL 9-METHYL-10-PHENYL-11-THIOXO-8-OXA-10,12-DIAZATRICYCLO[7.3.1.0^{2,7}] TRIDECA-2(7),3,5-TRIEN-13-CARBOXYLATE

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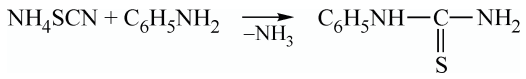
Three-component condensation of N1-phenylthiocarbamide with salicylaldehyde and with the ether of acetoacetic acid in the presence of trifluoroacetic acid provides a productive synthesis of ethyl 9-methyl-10-phenyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-13-carboxylate **I**. Single crystal XRD is used to determine the crystal structure of **I** and to identify the conformation properties of the structures.

Keywords: single crystal X-ray diffraction, crystal structure, ethyl 9-methyl-10-phenyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-13-carboxylate, N1-phenylthiocarbamide.

It is known from the literature that the simplest and most convenient synthesis of 3,4-dihydropyrimidine-2(1H)thiones is based on three-component condensation of aldehydes, methylene active compounds, and thiocarbamides [1-4] in the acid medium by the Biginelli reaction.

Based on the fact that dihydropyrimidinthiones have a broad pharmacological [5] activity, their optimal synthesis is always in the focus of researchers. With regard to the above, we synthesized N1-phenylthiocarbamide as a precursor by the interaction of ammonium rhodanide with aniline without solvents.



In order to investigate the effect of the hydroxyl group in the 4-aryl radical on the structural parameters of biologically active dihydropyrimidinthiones, we studied the one-stage three-component reactions of N-phenylthiocarbamide, acetoacetic ether with calycilaldehyde in the presence of trifluoroacetic acid. This line of the research has lead to unexpected results. The three-component reaction produced ethyl 9-methyl-10-phenyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2(7),3,5-trien-13-carboxylate **I** with a 65% yield.

This paper presents the results of single crystal X-ray diffraction of compound **I**.

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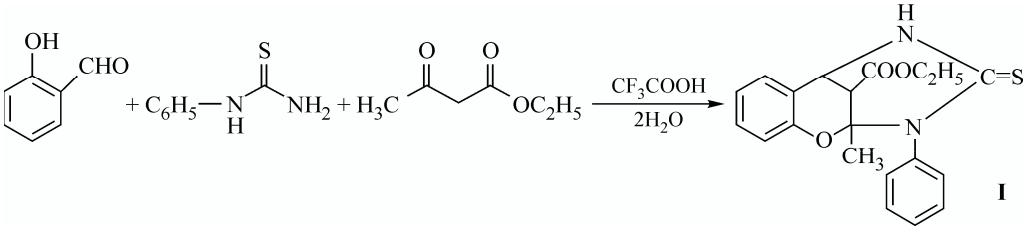

TABLE 1. Selected Values of the Bond Lengths (*d*, Å) and Bond Angles (ω, deg) in the Structure of **I**

Bond	*d*	Bond	*d*	Bond	*d*	Bond	*d*
S(1)–C(7)	1.685(4)	N(2)–C(7)	1.358(4)	S(2)–C(25)	1.677(4)	N(4)–C(25)	1.371(4)
O(1)–C(1A)	1.372(4)	N(2)–C(1)	1.500(4)	O(4)–C(19A)	1.372(4)	N(4)–C(19)	1.489(4)
O(1)–C(1)	1.434(4)	C(1)–C(8)	1.510(5)	O(4)–C(19)	1.420(4)	C(19)–C(26)	1.519(5)
N(1)–C(7)	1.337(4)	C(5A)–C(6)	1.492(5)	N(3)–C(25)	1.335(4)	C(23A)–C(24)	1.505(4)
N(1)–C(6)	1.470(4)	C(6)–C(8)	1.519(4)	N(3)–C(24)	1.456(4)	C(24)–C(26)	1.525(4)

Angle	ω	Angle	ω	Angle	ω
C(1A)–O(1)–C(1)	118.1(3)	N(1)–C(6)–C(8)	106.2(3)	O(4)–C(19)–C(26)	112.4(3)
C(7)–N(1)–C(6)	122.6(3)	C(5A)–C(6)–C(8)	109.8(3)	N(4)–C(19)–C(26)	107.9(3)
C(7)–N(2)–C(1)	123.4(3)	N(1)–C(7)–N(2)	118.2(3)	O(4)–C(19A)–C(23A)	122.7(3)
O(1)–C(1)–N(2)	108.1(3)	C(1)–C(8)–C(6)	106.8(3)	C(19A)–C(23A)–C(24)	120.2(3)
O(1)–C(1)–C(8)	112.3(3)	C(19A)–O(4)–C(19)	117.1(3)	N(3)–C(24)–C(23A)	112.1(3)
N(2)–C(1)–C(8)	107.5(3)	C(25)–N(3)–C(24)	122.5(3)	N(3)–C(24)–C(26)	105.5(3)
O(1)–C(1A)–C(5A)	122.5(3)	C(25)–N(4)–C(19)	123.5(3)	C(23A)–C(24)–C(26)	109.4(3)
C(1A)–C(5A)–C(6)	119.6(4)	O(4)–C(19)–N(4)	108.7(3)	N(3)–C(25)–N(4)	117.7(3)
N(1)–C(6)–C(5A)	111.3(3)			C(19)–C(26)–C(24)	106.1(3)

Experimental. Crystals for XRD were obtained by double crystallization of compound **I** from ethanol. Single crystal X-ray diffraction of compound **I** was carried out on a Bruker APEX II CCD diffractometer ($T = 296$ K, λMoK_α radiation, graphite monochromator, φ- and ω-scanning, $2\theta_{max} = 46°$).

The crystals of compound **I** ($C_{20}H_{20}N_2O_3S$, $M_r = 368.44$) were colorless, $T_m = 232°C$, prismatic, 0.20×0.10×0.10 mm, and monoclinic: $a = 12.627(2)$ Å, $b = 13.649(2)$ Å, $c = 21.574(3)$ Å, $\beta = 96.498(3)°$, $V = 3694.1(10)$ Å^3, $P2_1/c$ space group, $Z = 8$, $d_x = 1.325$ g/cm^3, $\mu = 0.197$ mm^{-1}. We measured the intensities of 24,457 reflections (4985 independent reflections, $R_{int} = 0.095$), for which we introduced a semi-empirical absorption correction using the SADABS program [11].

The structure of compound **I** was solved by the direct method and refined by LSM in an anisotropic approximation for non-hydrogen atoms. Hydrogen atoms of the amino groups were objectively identified in Fourier difference syntheses and included into the refinement with fixed positions and thermal parameters ($U_{iso}(H) = 1.2U_{eq}(N)$). The coordinates of the other hydrogen atoms were calculated from geometrical considerations and refined with fixed positions (the riding model) and thermal parameters ($U_{eq}(H) = 1.5U_{eq}(C)$ for CH_3 groups and $U_{eq}(H) = 1.2U_{eq}C$) for all the other groups). The final values of the divergence factors are $R_1 = 0.051$ for 2748 independent reflections with $I > 2\sigma(I)$ and $wR_2 = 0.093$ for all independent reflections. All the calculations were made using the SHELXTL program package [12].

The structure of **I** has been deposited with the Cambridge Crystallographic Data Centre (No. CCDC 768016).

Results and Discussion. The structure and crystal packing of compound **I** are shown in Figs. 1 and 2; the selected values of bond lengths and bond angles are given in Table 1. The crystal of compound **I** contains two crystallographically independent molecules that are different only in the conformation of the carboxylate substituent with respect to the central bicyclic fragment (the (Me)C–C–C=O torsion angles in these molecules are –22.8(6)° and 162.8(3)°, Fig. 1).

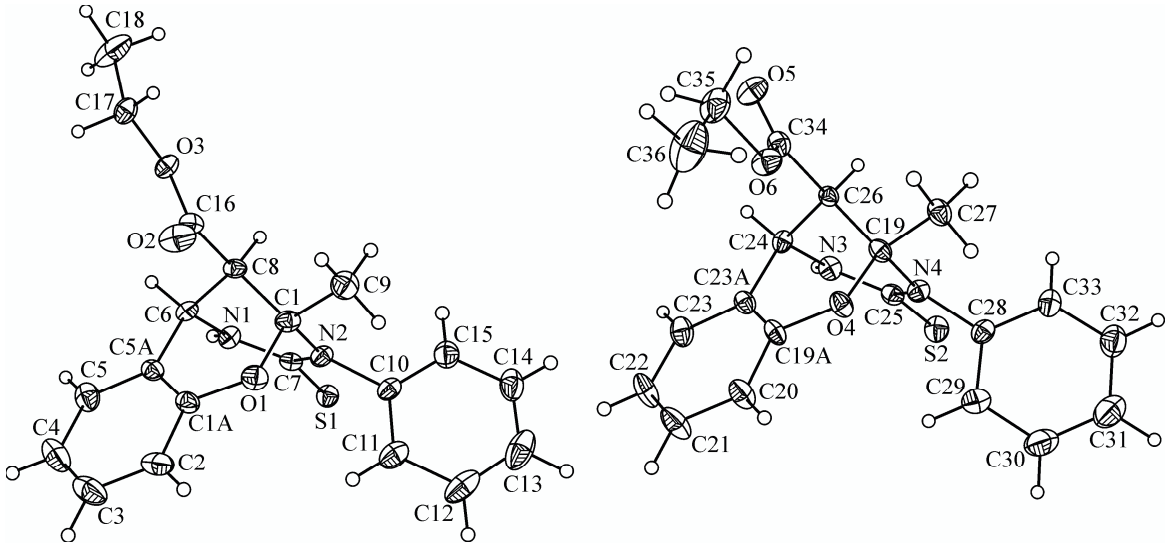

Fig. 1. Molecular structure of compound **I**. The figure presents two crystallographically independent molecules.

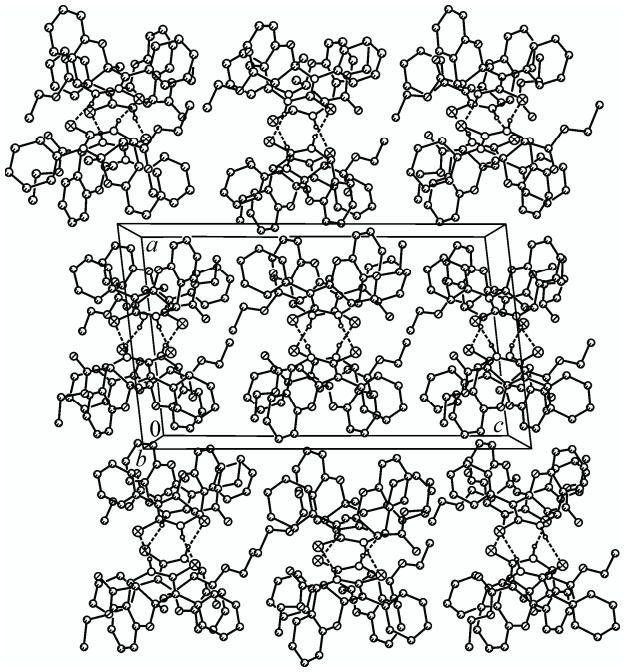

Fig. 2. Packing of the molecules of **I** in the crystal along the ***b*** axis. Hydrogen bonds are shown by dashes.

The molecule of **I** contains a rigid tricyclic system consisting of conjugated hexahydropyrimidine, dihydropyran, and benzene rings (Fig. 1). The hexahydropyrimidine and dihydropyran rings in the bicyclic fragment adopt asymmetric *half-chair* conformations (deviations of the C(6)/C(24), C(8)/C(26) and C(1)/C(19), C(8)/C(26) atoms in two crystallographically independent molecules from the central planes drawn through the other atoms of the rings are –0.169/–0.236 Å, 0.643/0.622 Å and –0.086/–0.157 Å, 0.649/0.611 Å respectively). At the same time, the benzene ring is practically perpendicular to the of the hexahydropyrimidine plane (the angle between the respective planes is 76.9° and 78.5° for the two crystallographically independent molecules). Nitrogen atoms of the hexahydropyrimidine ring have a planar trigonal configuration (sums of the bond angles at N(1), N(2), N(3), and N(4) atoms of the two crystallographically independent

TABLE 2. Parameters of H-Bonds (Å and deg) in the Structure of **I**

H-Bond Type	D*–H	H…A*	D…A	∠(D–H…A)
N(1)–H(1N)…S(1) [–*x*+1, –*y*+1, –*z*+1]	0.91	2.61	3.496(4)	166
N(3)–H(3N)…S(2) [–*x*+1, –*y*, –*z*+1]	0.91	2.44	3.345(4)	170

*D is the proton donor; A is the proton acceptor.

molecules are 360.1°, 359.8°, 360.0°, and 359.8° respectively). A similar conformation of the central tricyclic fragment was observed in related compounds studied previously [6-9]. The carboxylate substituent is planar with a *trans*-configuration of the C–C and O–C bonds (the C–C–O–C torsion angle is 172.9(3)° and 167.6(3)° in the two crystallographically independent molecules) and is in the equatorial position with respect to the hexahydropyrimidine ring and the axial position with respect to the dihydropyran ring. The terminal phenyl substituent is turned at an angle of 78.8° and 81.6° in the two crystallographically independent molecules with respect to the planar fragment of the hexahydropyrimidine ring.

Table 1 shows that the bonds of the thioured fragment in the molecule of **I** are conjugated: the N(1)–C(7), C(7)–N(2) and N(3)–C(25), C(25)–N(4) bond lengths are shortened, and the C(7)=S(1) and C(25)=S(2) lengths are elongated as compared to the average statistical values for the length of the ordinary C–N and double C=S bonds respectively [10]. At the same time, the values of the *endo*-cyclic bond angles in the hexapyrimidine ring at the nitrogen atoms are below the ideal value of 120° for sp^2-hybridized atoms, and those at the carbon atoms are larger than the ideal value of 109.5° for sp^3-hybridized atoms (Table 1). Moreover, the values of the *endo*-cyclic bond angles in the hexapyrimidine ring appear to affect the distribution of the *endo*-cyclic bond angles in the dihydropyran ring through the geometry of the adjacent bridging C–C–C fragment. Thus, the values of the *endo*-cyclic bond angles in the dihydropyran cycle at oxygen atoms are less than the ideal value of 120°, and those at carbon atoms bonded to the oxygen atom are larger than the ideal values of 120° and 109.5° for sp^2- and sp^3-hybridized atoms respectively (Table 1).

Compound **I** is a diastereomer with three asymmetric centers at C(1)/C(19), C(6)/C(24) and C(8)/C(26) carbon atoms. The crystal of the studied compound is a racemate with the relative configuration of the chiral atoms — *rac*-1/19***R****,6/24***R****,8/26***R****.

In the crystal, the enantiomers form centrosymmetric dimers by means of intermolecular H-bonds N–H…S (Fig. 2, Table 2). The dimers are packed in stacks along the ***b*** axis (Fig. 2).

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