

### 143. Structure of New 2-Oxo-2,8-dihydro-[1,2,4]oxadiazolo-[2,3-*a*]pyrimidinecarbamates

by **Jean-Claude Muller, Henri Ramuz,**  
Pharmaceutical Research Department

**John Daly and Peter Schönholzer**  
Central Research Units

*F. Hoffmann-La Roche & Co. Ltd., CH-4002 Basle*

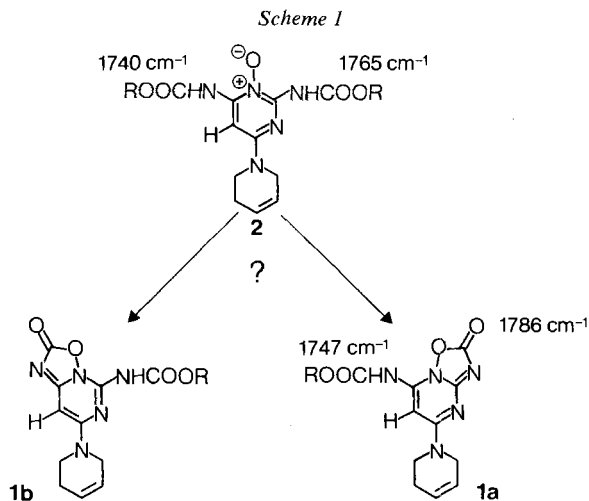
Dedicated to Prof. Dr. *Walter Boguth* on the occasion of his 65th birthday

(11. V. 82)

#### Summary

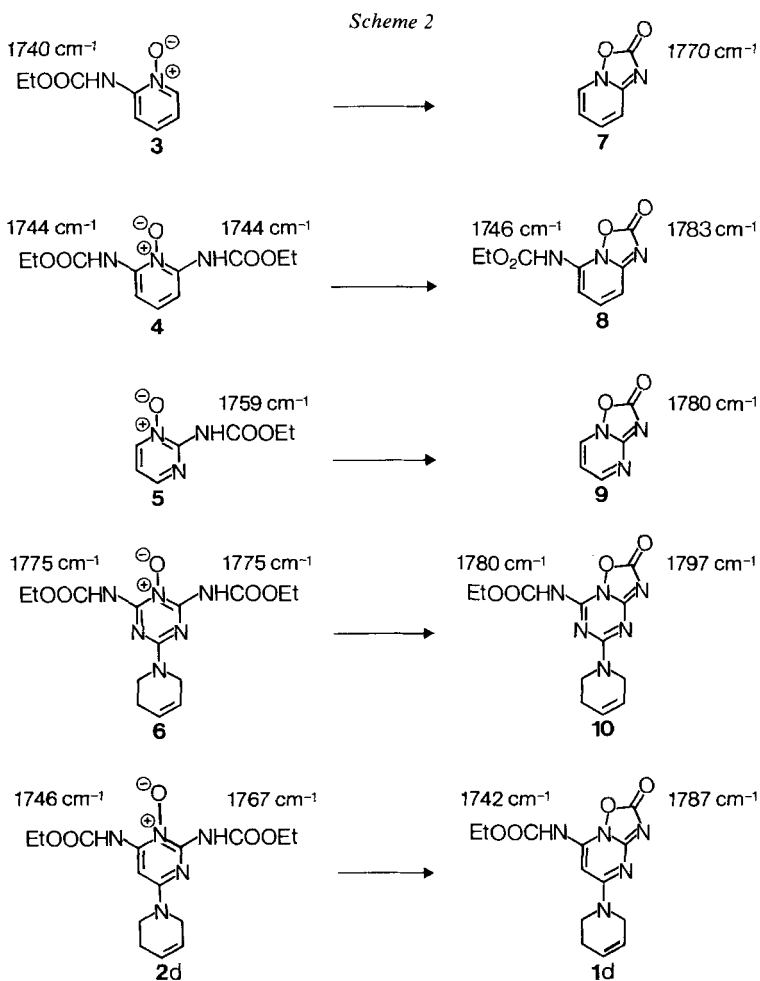
The structure of new 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo-[2,3-*a*]pyrimidinecarbamates **1** was established by correlating the IR. and NMR. data with these of analogous compounds. A X-ray crystallographic analysis of **1c** gave an unequivocal proof of structural assignment.

**Introduction.** – The new 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo [2,3-*a*]pyrimidinecarbamates **1**, potent and long-lasting antihypertensive agents and peripheral vasodilators in experimental animals and man were obtained by regioselective pyrolytic heterocyclization of the bis(acetylamino)pyrimidine *N*-oxide **2** [1]. Since 2



do not possess a symmetry axis, cyclization can occur on one or the other CO-group, leading to structure **1a** or **1b** (Scheme 1). From the physicochemical data of **1** we conclude that *one isomer* was formed and whatever R, it was always the same regioisomer. We now bring proof that the new substances have structure **1a**.

Comparison of the spectra of known fused oxadiazolones [2–5] with those of **1** did not allow us to choose between **1a** and **1b**. The dicarbamates **2** possess two CO-groups with IR. absorption at about 1740 and 1765  $\text{cm}^{-1}$ . We had expected that an analysis of the crystal data of **2** (Fig. 1) would therefore indicate differences between the geometrical parameters of the two CO-functions and thus aid understanding of the high regioselectivity of the cyclization from **2** to **1a** or **1b**. In a survey of X-ray crystallographic analyses of compounds containing nucleophilic moieties and CO-groups, Bürgi *et al.* [6] demonstrated a close relation between the non-planarity of the CO-group and the direction of nucleophilic attack, showing that



*intramolecular* approach of the nucleophilic O-atom towards the electrophilic C-atom is accompanied by a displacement of the C-atom out of the plane defined by its three bonded atoms towards the nucleophilic centre when the O...C=O-distance is shorter than 3 Å [7].

This principle could not be applied in our case since the adopted conformation of **2a** in the crystal was not appropriate to describe the tetrahedral intermediate involved (distances between O...C=O of 3.90 and 3.97 Å) (*Fig. 1*). Examination of displacement from planarity (*Table 5*) and differences in bond lengths and angles (*Tables 3, 4 and 6*) of the two CO-functions in **2a** indicated considerable similarities.

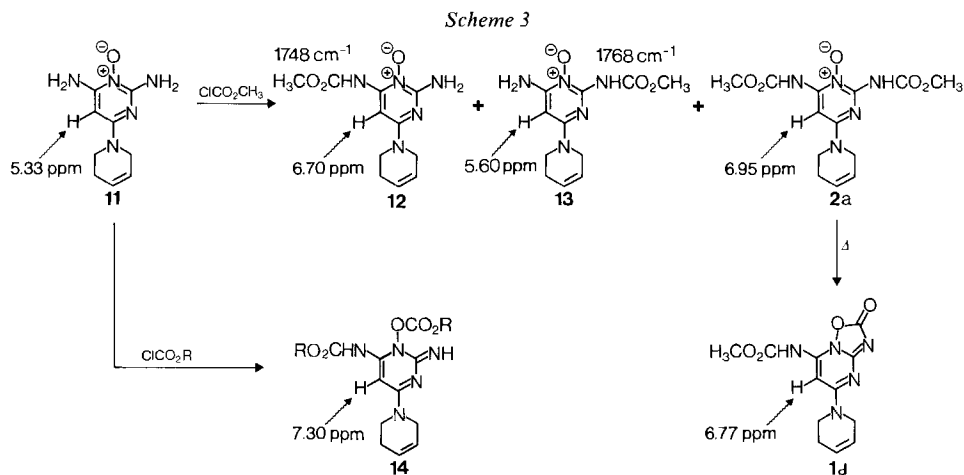
The two different carbamate moieties of **2** can be depicted as CO-functions attached to a guanidino and an amidino group. The assignment of each of the IR. CO-bands of **1a** and **2** to one of these moieties was based on comparison with data from model compounds. Compounds **3** and **4**, prepared according to the method of *Katritzky* [2] [3], possess a CO-group attached to an amidine moiety, whereas **5** and **6** [8] are representatives of acylated guanidines. The CO-absorption bands of **3** and of **4** at 1740 and 1744 cm<sup>-1</sup> are close to the lowest absorption band of **2** (1735–1745 cm<sup>-1</sup>). The CO-groups of **5** and **6** showed absorption bands at 1759 and 1775 cm<sup>-1</sup>, again in good concordance with the highest absorption band of **2** (1758–1768 cm<sup>-1</sup>). The positions of these CO-bands suggests that the absorption of the amidino CO-group occurs at 1735–1745 cm<sup>-1</sup>, that of the guanidino group being at 1758–1768 cm<sup>-1</sup>.

The CO-group involved in the cyclization of **2–6** undergoes a strong IR. shift from 1740–1775 cm<sup>-1</sup> to 1770–1797 cm<sup>-1</sup> (*Scheme 2*).

Cyclization of symmetrical substances such as **4** and **6** gave the 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo[2,3-*a*]pyridinecarbamate **8** and the 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo[2,3-*a*]-*s*-triazinecarbamate **10**, each retaining one unchanged carbamate group. In this reaction, the absorption band of the remaining CO-group is almost unaffected: 1744 to 1746 cm<sup>-1</sup> in the conversion of **4** into **8** and 1775 to 1780 cm<sup>-1</sup> in the formation of **10** from **6**. Only the CO-group involved in the cyclization had its absorption band shifted to a higher frequency. When this set of correlations is applied to the structural elucidation of **1**, it can be reasonably assumed that the CO-group flanking the guanidine moiety is involved in the heterocyclization process (**2** → **1**). This leads to the structure **1a** for the oxadiazolopyrimidine.

Treatment of **11** with one equivalent of methyl chloroformate leads to a mixture of monocarbamates **12** and **13**, dicarbamate **2a** and starting material. The aforementioned IR.-correlation was the basis of structure assignment for monocarbamates **12** and **13** (*Scheme 3*). The chemical shift of H-C(5) of various derivatives of the 2,4,6-triaminopyrimidine 1-oxide series was also indicative of structure. The singlet for H-C(5) in compounds **11**, **2a** and **14** appears respectively at 5.33, 6.95 and 6.77 ppm (*Scheme 3*). The relatively important shielding of H-C(5) due to a neighbouring CO-moiety was used to assign the chemical shift of 5.60 to **12** and 6.70 ppm to **13**.

When R is isobutyl, an unstable intermediate evolving to **2** could be trapped. The absence of the *N*-oxide function, monitored by the disappearance of a colour reaction with ferric ions, and the H-C(5) downfield shift at 7.30 ppm were indica-


*X-Ray analysis of dicarbamate 2a and salt 1c<sup>a)</sup>b)*

	Dicarbamate 2a	Salt 1c
Formula	$\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_5$	$\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}_4 + \text{C}_8\text{H}_{15}\text{N}$
Molecular weight	323.31	416.48
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Z	2	2
Cell constants		
<i>a</i> (Å)	8.019 (3)	12.269 (5)
<i>b</i> (Å)	7.537 (3)	9.817 (4)
<i>c</i> (Å)	13.285 (6)	9.688 (4)
$\alpha$ (deg)	84.48 (2)	63.07 (2)
$\beta$ (deg)	73.99 (2)	95.45 (2)
$\gamma$ (deg)	71.36 (2)	93.99 (2)
Volume of the unit cell (Å <sup>3</sup> )	731.23	1035.19
Calculated density (g · cm <sup>-3</sup> )	1.47	1.35
Radiation used	$\text{MoK}_\alpha$	$\text{MoK}_\alpha$ ( $\lambda = 0.71069$ Å)
Filter	Zr	Zr
Scan		
Voltage (kV)	48	48
Current (mA)	32	32
Number of planes measured	3518	4771
Number of planes in the refinement	2088	3324
Structure solved with		SHELX [11]
Refinement		anisotropic [11]
	the positions of the H-atoms have been calculated after each cycle of refinement	
Final <i>R</i> -value	7.6%	5.4%

<sup>a)</sup> *Crystal data, structure determination and refinement.* Intensities were measured on a four circle diffractometer Hilger and Watts Y290/PDP8. <sup>b)</sup> *Atomic coordinates, final parameters, bond lengths, bond angles, least square planes and some torsion angles [12] are set out in the Tables 1 to 10. The Figures 1 to 4 show projections with the labeling and PLUTO stereoprojections [13] of 2a and 1c.*

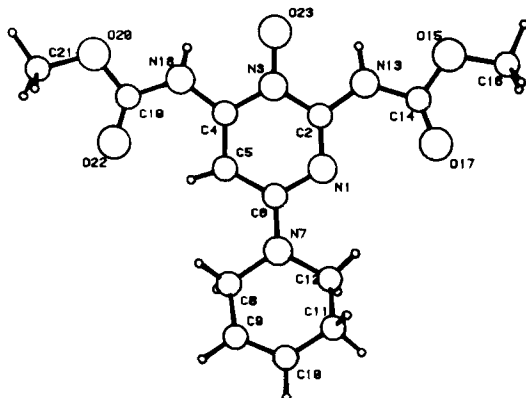


Fig. 1. Projection with labeling of 2a

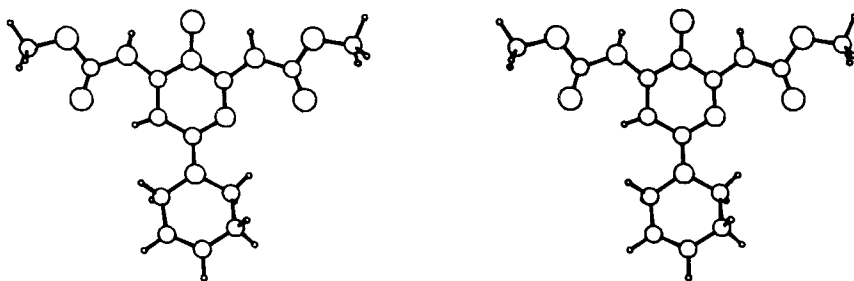


Fig. 2. PLUTO stereoprojection of 2a

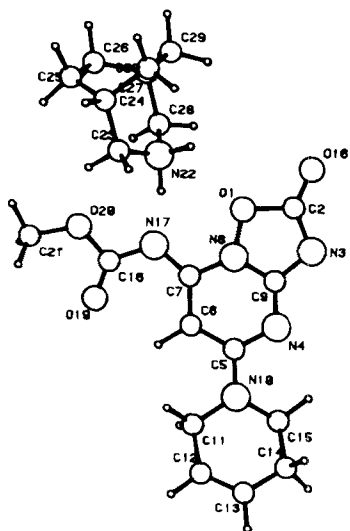


Fig. 3. Projection with labeling of 1c

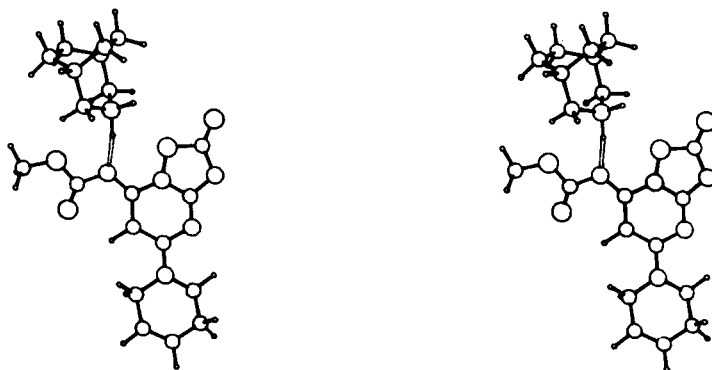


Fig. 4. PLUTO stereoprojection of **1c** with the hydrogen bond N(17)–N(22) of 2.87 Å length

Table 1. Atomic coordinates (standard deviations) for **2a**

Atoms	<i>x</i>	<i>y</i>	<i>z</i>
N(1)	0.6414 (4)	0.0851 (5)	0.7579 (3)
C(2)	0.7872 (5)	–0.0014 (5)	0.7901 (3)
N(3)	0.8032 (4)	0.0112 (5)	0.8881 (3)
C(4)	0.6619 (5)	0.1325 (5)	0.9566 (3)
C(5)	0.5059 (5)	0.2260 (6)	0.9273 (3)
C(6)	0.4962 (5)	0.1955 (5)	0.8272 (3)
N(7)	0.3401 (4)	0.2711 (5)	0.7957 (3)
C(8)	0.1798 (6)	0.3991 (7)	0.8633 (4)
C(9)	0.0087 (6)	0.4122 (9)	0.8398 (5)
C(10)	0.0044 (6)	0.3414 (8)	0.7498 (4)
C(11)	0.1647 (7)	0.2432 (9)	0.6777 (4)
C(12)	0.3403 (6)	0.2588 (7)	0.6870 (4)
N(13)	0.9428 (4)	–0.1180 (5)	0.7282 (3)
C(14)	0.9700 (5)	–0.1719 (6)	0.6271 (3)
O(15)	1.1447 (4)	–0.2754 (5)	0.5936 (2)
C(16)	1.1989 (7)	–0.3434 (8)	0.4880 (4)
O(17)	0.8612 (4)	–0.1348 (6)	0.5771 (3)
N(18)	0.6973 (4)	0.1408 (5)	1.0513 (3)
C(19)	0.5674 (6)	0.2325 (7)	1.1365 (4)
O(20)	0.6395 (4)	0.2089 (5)	1.2183 (2)
C(21)	0.5096 (6)	0.2919 (8)	1.3139 (4)
O(22)	0.4130 (4)	0.3170 (5)	1.1397 (3)
O(23)	0.9552 (3)	–0.0907 (4)	0.9154 (2)
H(1)–C(5)	0.4293	0.2977	0.9793
H(1)–C(8)	0.1721	0.3546	0.9387
H(2)–C(8)	0.1941	0.5274	0.8573
H(1)–C(9)	–0.1119	0.4734	0.8915
H(1)–C(10)	–0.1211	0.3768	0.7339
H(1)–C(11)	0.1546	0.2864	0.6048
H(2)–C(11)	0.1756	0.1052	0.6836
H(1)–C(12)	0.4465	0.1732	0.6574
H(2)–C(12)	0.3638	0.3730	0.6420
H(1)–N(13)	1.0404	–0.1669	0.7569

Table 1 (continued)

Atoms	x	y	z
H(1)–C(16)	1.3415	– 0.4249	0.4758
H(2)–C(16)	1.1859	– 0.2292	0.4330
H(3)–C(16)	1.1232	– 0.4327	0.4778
H(1)–N(18)	0.7950	0.0764	1.0564
H(1)–C(21)	0.5759	0.2656	1.3772
H(2)–C(21)	0.4025	0.2254	1.3334
H(3)–C(21)	0.4507	0.4400	1.3046

Table 2. Anisotropic thermal parameters for 2a

$$T = \exp(-B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{23}kl + B_{13}hl + B_{12}hk)$$

Atoms	B <sub>11</sub>	B <sub>22</sub>	B <sub>33</sub>	B <sub>23</sub>	B <sub>13</sub>	B <sub>12</sub>
N(1)	0.0116	0.0201	0.0045	– 0.0038	– 0.0058	– 0.0045
C(2)	0.0106	0.0160	0.0045	– 0.0033	– 0.0044	– 0.0067
N(3)	0.0098	0.0178	0.0048	– 0.0041	– 0.0058	– 0.0062
C(4)	0.0107	0.0154	0.0042	– 0.0026	– 0.0049	– 0.0074
C(5)	0.0107	0.0182	0.0050	– 0.0036	– 0.0057	– 0.0028
C(6)	0.0108	0.0168	0.0052	– 0.0021	– 0.0058	– 0.0085
N(7)	0.0119	0.0218	0.0052	– 0.0045	– 0.0078	– 0.0032
C(8)	0.0117	0.0289	0.0085	– 0.0106	– 0.0100	0.0022
C(9)	0.0111	0.0356	0.0116	– 0.0107	– 0.0068	– 0.0048
C(10)	0.0155	0.0323	0.0083	0.0008	– 0.0113	– 0.0169
C(11)	0.0220	0.0407	0.0076	– 0.0011	– 0.0149	– 0.0266
C(12)	0.0149	0.0303	0.0054	– 0.0049	– 0.0092	– 0.0068
N(13)	0.0112	0.0218	0.0049	– 0.0067	– 0.0056	– 0.0041
C(14)	0.0109	0.0183	0.0047	– 0.0029	– 0.0047	– 0.0079
O(15)	0.0133	0.0272	0.0052	– 0.0087	– 0.0058	– 0.0008
C(16)	0.0206	0.0313	0.0042	– 0.0090	– 0.0033	– 0.0032
O(17)	0.0136	0.0398	0.0059	– 0.0105	– 0.0074	– 0.0041
N(18)	0.0090	0.0193	0.0051	– 0.0055	– 0.0053	– 0.0021
C(19)	0.0105	0.0179	0.0050	– 0.0048	– 0.0047	– 0.0065
O(20)	0.0113	0.0288	0.0050	– 0.0102	– 0.0039	– 0.0082
C(21)	0.0161	0.0368	0.0052	– 0.0140	– 0.0021	– 0.0153
O(22)	0.0111	0.0330	0.0063	– 0.0098	– 0.0051	0.0034
O(23)	0.0094	0.0216	0.0057	– 0.0062	– 0.0084	0.0018

Table 3. Bond lengths (standard deviations) in Å for 2a

Bond	Lengths	Bond	Lengths
C(2)–N(1)	1.307 (0.005)	C(9)–C(8)	1.460 (0.008)
C(6)–N(1)	1.353 (0.005)	C(10)–C(9)	1.369 (0.008)
N(3)–C(2)	1.358 (0.005)	C(11)–C(10)	1.402 (0.008)
N(13)–C(2)	1.370 (0.005)	C(12)–C(11)	1.489 (0.008)
C(4)–N(3)	1.370 (0.005)	C(14)–N(13)	1.379 (0.005)
O(23)–N(3)	1.342 (0.005)	O(15)–C(14)	1.340 (0.005)
C(5)–C(4)	1.366 (0.006)	O(17)–C(14)	1.187 (0.005)
N(18)–C(4)	1.376 (0.005)	C(16)–O(15)	1.442 (0.006)
C(6)–C(5)	1.398 (0.006)	C(19)–N(18)	1.372 (0.006)
N(7)–C(6)	1.362 (0.006)	O(20)–C(19)	1.338 (0.006)
C(8)–N(7)	1.459 (0.006)	O(22)–C(19)	1.188 (0.006)
C(12)–N(7)	1.454 (0.006)	C(21)–O(20)	1.448 (0.006)

Table 4. *Bond angles (standard deviations) for 2a*

Angles	Degrees	Angles	Degrees
C(6)–N(1)–C(2)	117.6 (0.4)	C(12)–N(7)–C(8)	117.5 (0.4)
N(3)–C(2)–N(1)	124.7 (0.4)	C(9)–C(8)–N(7)	114.0 (0.4)
N(13)–C(2)–N(1)	123.6 (0.4)	C(10)–C(9)–C(8)	122.0 (0.5)
N(13)–C(2)–N(3)	111.7 (0.3)	C(11)–C(10)–C(9)	121.6 (0.5)
C(4)–N(3)–C(2)	118.1 (0.3)	C(12)–C(11)–C(10)	117.7 (0.5)
O(23)–N(3)–C(2)	120.3 (0.3)	C(11)–C(12)–N(7)	111.9 (0.4)
O(23)–N(3)–C(4)	121.5 (0.3)	C(14)–N(13)–C(2)	127.2 (0.4)
C(5)–C(4)–N(3)	119.5 (0.4)	O(15)–C(14)–N(13)	107.5 (0.3)
N(18)–C(4)–N(3)	113.0 (0.3)	O(17)–C(14)–N(13)	127.4 (0.4)
N(18)–C(4)–C(5)	127.5 (0.4)	O(17)–C(14)–O(15)	125.1 (0.4)
C(6)–C(5)–C(4)	118.5 (0.4)	C(16)–O(15)–C(14)	115.3 (0.4)
C(5)–C(6)–N(1)	121.2 (0.4)	C(19)–N(18)–C(4)	123.1 (0.4)
N(7)–C(6)–N(1)	116.9 (0.4)	O(20)–C(19)–N(18)	109.5 (0.4)
N(7)–C(6)–C(5)	121.9 (0.4)	O(22)–C(19)–N(18)	126.4 (0.5)
C(8)–N(7)–C(6)	120.6 (0.4)	O(22)–C(19)–O(20)	124.2 (0.5)
C(12)–N(7)–C(6)	120.6 (0.4)	C(21)–O(20)–C(19)	113.6 (0.4)

 Table 5. *Atomic distances from best planes in A for 2a*

Plane through O(23), N(3), C(2), N(13), O(17), O(15)					
O(23)	– 0.103	N(3)	0.033	C(2)	0.080
N(13)	0.039	O(17)	– 0.104	O(15)	0.056
C(14)	– 0.015				
RMS-Distance of the atoms from the plane = 0.0750					
Plane through O(23), N(3), C(4), N(18), O(22), O(20)					
O(23)	– 0.088	N(3)	– 0.007	C(4)	0.074
N(18)	0.110	O(22)	– 0.100	O(20)	0.011
C(19)	0.007				
RMS-Distance of the atoms from the plane = 0.0767					

 Table 6. *Torsion angles for 2a*

Angles	Degrees
C(21), (O(20)–C(19)), N(18)	– 176.7
O(20), (C(19)–N(18)), C(4)	177.1
C(19), (N(18)–C(4)), N(3)	– 170.8
N(18), (C(4)–N(3)), C(2)	– 176.7
C(4), (N(3)–C(2)), N(13)	175.9
N(3), (C(2)–N(13)), C(14)	175.6
C(2), (N(13)–C(14)), O(15)	175.7
N(13), (C(14)–O(15)), C(16)	– 179.5

 Table 7. *Atomic coordinates (standard deviations) for 1c*

Atoms	x	y	z
O(1)	0.5741 (1)	0.1615 (2)	– 0.1493 (2)
C(2)	0.4629 (2)	0.1646 (3)	– 0.1147 (3)
N(3)	0.4604 (2)	0.2161 (3)	– 0.0083 (3)
N(4)	0.5999 (2)	0.3030 (3)	0.1241 (3)
C(5)	0.7104 (2)	0.3215 (3)	0.1415 (3)



Table 7 (continued)

Atoms	x	y	z
C(6)	0.7846 (2)	0.2812 (3)	0.0652 (3)
C(7)	0.7459 (2)	0.2209 (3)	–0.0377 (3)
N(8)	0.6338 (2)	0.2168 (3)	–0.0553 (2)
C(9)	0.5651 (2)	0.2480 (3)	0.0269 (3)
N(10)	0.7459 (2)	0.3787 (3)	0.2421 (3)
C(11)	0.8627 (2)	0.4059 (4)	0.2687 (4)
C(12)	0.8873 (3)	0.4135 (4)	0.4178 (4)
C(13)	0.8109 (3)	0.4406 (4)	0.4913 (4)
C(14)	0.6972 (3)	0.4537 (4)	0.4381 (4)
C(15)	0.6728 (3)	0.4679 (4)	0.2787 (4)
O(16)	0.3919 (2)	0.1222 (3)	–0.1823 (3)
N(17)	0.7971 (2)	0.1673 (3)	–0.1176 (3)
C(18)	0.9067 (2)	0.1963 (3)	–0.1302 (3)
O(19)	0.9673 (2)	0.2800 (3)	–0.0948 (3)
O(20)	0.9442 (2)	0.1146 (2)	–0.1948 (2)
C(21)	1.0590 (2)	0.1327 (4)	–0.2204 (4)
N(22)	0.7139 (2)	–0.0706 (3)	–0.1967 (3)
C(23)	0.7996 (3)	–0.1855 (4)	–0.1503 (4)
C(24)	0.7885 (3)	–0.2875 (4)	–0.2325 (4)
C(25)	0.8403 (3)	–0.2142 (4)	–0.3889 (4)
C(26)	0.7750 (3)	–0.0866 (4)	–0.5162 (4)
C(27)	0.6696 (2)	–0.0602 (4)	–0.4645 (3)
C(28)	0.6856 (3)	0.0245 (4)	–0.3655 (4)
C(29)	0.6038 (3)	–0.2102 (4)	–0.3873 (4)
C(30)	0.6692 (3)	–0.3364 (4)	–0.2543 (4)
H(1)–C(6)	0.8711	0.2958	0.0857
H(1)–C(11)	0.8891	0.5122	0.1761
H(2)–C(11)	0.9067	0.3130	0.2721
H(1)–C(12)	0.9703	0.3979	0.4702
H(1)–C(13)	0.8339	0.4495	0.5978
H(1)–C(14)	0.6534	0.3505	0.5147
H(2)–C(14)	0.6654	0.5508	0.4428
H(1)–C(15)	0.6837	0.5888	0.1969
H(2)–C(15)	0.5889	0.4329	0.2633
H(1)–C(21)	1.0701	0.0543	–0.2694
H(2)–C(21)	1.1087	0.0974	–0.1131
H(3)–C(21)	1.0810	0.2463	–0.3012
H(1)–N(22)	0.7390	0.0060	–0.1472
H(2)–N(22)	0.6394	–0.1324	–0.1475
H(1)–C(23)	0.7963	–0.2574	–0.0292
H(2)–C(23)	0.8775	–0.1234	–0.1744
H(1)–C(24)	0.8342	–0.3896	–0.1584
H(1)–C(25)	0.9200	–0.1667	–0.3727
H(2)–C(25)	0.8488	–0.3000	–0.4260
H(1)–C(26)	0.7545	–0.1166	–0.6098
H(2)–C(26)	0.8234	0.0160	–0.5534
H(1)–C(27)	0.6205	0.0136	–0.5645
H(1)–C(28)	0.6106	0.0836	–0.3800
H(2)–C(28)	0.7513	0.1079	–0.4119
H(1)–C(29)	0.5790	–0.2464	–0.4761
H(2)–C(29)	0.5324	–0.1883	–0.3449
H(1)–C(30)	0.6309	–0.3672	–0.1486
H(2)–C(30)	0.6685	–0.4350	–0.2771

Table 8. *Anisotropic thermal parameters for 1c*  
 $T = \exp - (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{23}kl + B_{13}hl + B_{12}hk)$

Atoms	B <sub>11</sub>	B <sub>22</sub>	B <sub>33</sub>	B <sub>23</sub>	B <sub>13</sub>	B <sub>12</sub>
O(1)	0.0053	0.0167	0.0138	-0.0197	0.0000	-0.0007
C(2)	0.0053	0.0137	0.0136	-0.0130	-0.0009	0.0007
N(3)	0.0045	0.0145	0.0142	-0.0150	0.0008	0.0001
N(4)	0.0050	0.0142	0.0133	-0.0163	0.0015	0.0001
C(5)	0.0053	0.0118	0.0121	-0.0128	0.0001	-0.0000
C(6)	0.0047	0.0128	0.0133	-0.0149	0.0016	-0.0008
C(7)	0.0046	0.0117	0.0111	-0.0111	0.0021	-0.0009
N(8)	0.0046	0.0148	0.0131	-0.0177	0.0005	-0.0008
C(9)	0.0047	0.0116	0.0113	-0.0105	0.0019	0.0005
N(10)	0.0059	0.0166	0.0169	-0.0230	-0.0002	0.0004
C(11)	0.0064	0.0217	0.0218	-0.0306	-0.0011	-0.0013
C(12)	0.0100	0.0203	0.0182	-0.0211	-0.0058	-0.0021
C(13)	0.0120	0.0168	0.0158	-0.0196	-0.0033	0.0022
C(14)	0.0142	0.0181	0.0183	-0.0238	0.0008	0.0052
C(15)	0.0082	0.0216	0.0192	-0.0287	-0.0011	0.0053
O(16)	0.0062	0.0211	0.0182	-0.0232	-0.0040	-0.0007
N(17)	0.0050	0.0150	0.0132	-0.0166	0.0032	-0.0010
C(18)	0.0053	0.0148	0.0130	-0.0143	0.0033	-0.0013
O(19)	0.0061	0.0251	0.0281	-0.0371	0.0092	-0.0075
O(20)	0.0059	0.0196	0.0184	-0.0232	0.0066	-0.0013
C(21)	0.0061	0.0223	0.0193	-0.0187	0.0081	0.0018
N(22)	0.0060	0.0151	0.0132	-0.0179	0.0022	-0.0005
C(23)	0.0078	0.0182	0.0183	-0.0198	-0.0049	0.0055
C(24)	0.0080	0.0144	0.0173	-0.0153	0.0002	0.0052
C(25)	0.0093	0.0225	0.0235	-0.0218	0.0095	0.0059
C(26)	0.0083	0.0258	0.0154	-0.0199	0.0052	0.0005
C(27)	0.0072	0.0175	0.0117	-0.0144	0.0003	0.0026
C(28)	0.0107	0.0152	0.0149	-0.0149	-0.0015	0.0050
C(29)	0.0069	0.0206	0.0193	-0.0244	0.0018	-0.0016
C(30)	0.0096	0.0154	0.0194	-0.0177	0.0024	-0.0029

Table 9. *Bond lengths (standard deviations) in Å for 1c*

Bond	Lengths	Bond	Lengths
C(2)–O(1)	1.441 (0.003)	C(14)–C(13)	1.434 (0.006)
N(8)–O(1)	1.387 (0.003)	C(15)–C(14)	1.489 (0.005)
N(3)–C(2)	1.341 (0.004)	C(18)–N(17)	1.360 (0.003)
O(16)–C(2)	1.204 (0.004)	O(19)–C(18)	1.211 (0.004)
C(9)–N(3)	1.349 (0.003)	O(20)–C(18)	1.345 (0.004)
C(5)–N(4)	1.360 (0.003)	C(21)–O(20)	1.438 (0.004)
C(9)–N(4)	1.309 (0.004)	C(23)–N(22)	1.482 (0.004)
C(6)–C(5)	1.405 (0.004)	C(28)–N(22)	1.491 (0.004)
N(10)–C(5)	1.355 (0.004)	C(24)–C(23)	1.529 (0.005)
C(7)–C(6)	1.405 (0.004)	C(25)–C(24)	1.533 (0.005)
N(8)–C(7)	1.370 (0.003)	C(30)–C(24)	1.533 (0.005)
N(17)–C(7)	1.333 (0.004)	C(26)–C(25)	1.512 (0.005)
C(9)–N(8)	1.350 (0.003)	C(27)–C(26)	1.509 (0.005)
C(11)–N(10)	1.460 (0.004)	C(28)–C(27)	1.521 (0.005)
C(15)–N(10)	1.465 (0.005)	C(29)–C(27)	1.526 (0.005)
C(12)–C(11)	1.481 (0.005)	C(30)–C(29)	1.529 (0.005)
C(13)–C(12)	1.339 (0.005)		

Table 10. Bond angles (standard deviations) for **1c**

Angles	Degrees	Angles	Degrees
N(8)–O(1)–C(2)	102.6 (0.2)	C(13)–C(12)–C(11)	122.7 (0.4)
N(3)–C(2)–O(1)	110.5 (0.2)	C(14)–C(13)–C(12)	122.7 (0.4)
O(16)–C(2)–O(1)	117.0 (0.3)	C(15)–C(14)–C(13)	115.1 (0.3)
O(16)–C(2)–N(3)	132.5 (0.3)	C(14)–C(15)–N(10)	112.8 (0.3)
C(9)–N(3)–C(2)	106.9 (0.2)	C(18)–N(17)–C(7)	118.4 (0.2)
C(9)–N(4)–C(5)	115.6 (0.2)	O(19)–C(18)–N(17)	130.2 (0.3)
C(6)–C(5)–N(4)	123.5 (0.2)	O(20)–C(18)–N(17)	108.6 (0.2)
N(10)–C(5)–N(4)	115.3 (0.2)	O(20)–C(18)–O(19)	121.2 (0.3)
N(10)–C(5)–C(6)	121.2 (0.3)	C(21)–O(20)–C(18)	116.8 (0.2)
C(7)–C(6)–C(5)	120.2 (0.2)	C(28)–N(22)–C(23)	118.2 (0.3)
N(8)–C(7)–C(6)	111.8 (0.2)	C(24)–C(23)–N(22)	115.6 (0.3)
N(17)–C(7)–C(6)	132.3 (0.2)	C(25)–C(24)–C(23)	112.8 (0.3)
N(17)–C(7)–N(8)	115.8 (0.2)	C(30)–C(24)–C(23)	112.5 (0.3)
C(7)–N(8)–O(1)	123.8 (0.2)	C(30)–C(24)–C(25)	109.9 (0.3)
C(9)–N(8)–O(1)	109.7 (0.2)	C(26)–C(25)–C(24)	114.0 (0.3)
C(9)–N(8)–C(7)	126.1 (0.2)	C(27)–C(26)–C(25)	113.1 (0.3)
N(4)–C(9)–N(3)	127.3 (0.2)	C(28)–C(27)–C(26)	113.7 (0.3)
N(8)–C(9)–N(3)	110.3 (0.2)	C(29)–C(27)–C(26)	110.4 (0.3)
N(8)–C(9)–N(4)	122.4 (0.2)	C(29)–C(27)–C(28)	112.7 (0.3)
C(11)–N(10)–C(5)	120.4 (0.3)	C(27)–C(28)–N(22)	116.2 (0.3)
C(15)–N(10)–C(5)	120.3 (0.3)	C(30)–C(29)–C(27)	113.1 (0.3)
C(15)–N(10)–C(11)	115.2 (0.3)	C(29)–C(30)–C(24)	113.1 (0.3)
C(12)–C(11)–N(10)	111.5 (0.3)		

Table 11. Atom distances from best planes in Å for **1c**

Plane through O(1), N(8), C(7), N(17), O(19), O(20)					
O(1)	0.205	N(8)	– 0.048	C(7)	– 0.203
N(17)	– 0.098	O(19)	0.220	O(20)	– 0.075
C(18)	0.029				
RMS-Distance of the atoms from the plane = 0.1576					
Plane through O(1), C(2), N(3), C(9), N(8)					
O(1)	– 0.003	C(2)	0.003	N(3)	– 0.002
C(9)	0.0	N(8)	0.002		
RMS-Distance of the atoms from the plane = 0.0021					

Table 12. Torsion angles for **1c**

Angles	Degrees
C(21), (O(20)–C(18)), N(17)	178.8
O(20), (C(18)–N(17)), C(7)	171.2
C(18), (N(17)–C(7)), N(8)	166.9
N(17), (C(7)–N(8)), O(1)	– 0.1

tive of structure **14** (Scheme 3). The preferential formation of **12** and the isolation of **14** indicated a higher reactivity of the 4-amino group towards acylating agents [1]. Similar results have been reported [9].

2-Oxo-2, 8-dihydro-[1, 2, 4]-oxadiazolo[2, 3-*a*]pyrimidine-7-carbamates are weak acids. Treatment of **1d** with 3-azabicyclo[3, 2, 2]nonane gave the crystalline stable

salt **1c**. The unequivocal proof of the structure of **1** was obtained by X-ray crystallographic analysis of **1c** (see *Fig. 2* and *Tables 7–11*) which corroborated the structural assignments based on IR. and NMR. data.

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### Experimental Part

*General remarks.* See [1].

*Preparation of 2,6-bis(ethoxycarbonylamino)pyridine oxide (4).* A solution of 8.8 g (0.081 mol) of 2,6-diaminopyridine in 50 ml of pyridine was treated at 5° with 20 ml (0.259 mol) ClOOCCH<sub>3</sub>. The mixture was stirred during 72 h, and the solvent evaporated to dryness under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and acidified with 2N HCl. The organic phase was washed with H<sub>2</sub>O, brine, and dried (MgSO<sub>4</sub>). The solvent was evaporated and the solid residue was recrystallized from ethanol to give 4.5 g (23%) of ethyl 2,6-pyridinedicarbamate, m.p. 133–134°. – IR. (KBr): 3350, 3222, 1730, 1601, 1589, 1534, 1244, 1224, 1209. – <sup>1</sup>H-NMR. (CDCl<sub>3</sub>): 1.35 (*t*, *J* = 7, 3 H); 4.30 (*qa*, *J* = 7, 2 H); 7.70 (*m*, 3 H); 7.99 (*br. s*, 2 H). – MS.: 229 (*M*<sup>+</sup>).

C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub> (253.26) Calc. C 52.17 H 5.97 N 16.59% Found C 52.12 H 5.87 N 16.61%

A solution of 1.3 g (5.3 mmol) of ethyl 2,6-pyridinecarbamate in 20 ml of C<sub>2</sub>H<sub>5</sub>OH/CH<sub>2</sub>Cl<sub>2</sub> 1:1 was treated at 0° with 3 ml of 40% solution of peracetic acid. The mixture was stirred at r.t. overnight, cooled to 0° and the oxidizing agent in excess reduced with a sat. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>-solution. The mixture was extracted 3 times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried (MgSO<sub>4</sub>) and partially evaporated. Addition of hexane to the solution induced crystallization of 1.15 g of **4** (83%), m.p. 115°. – IR. (KBr): 3278, 3178, 1744, 1548, 1524, 1499, 1254, 1200. – <sup>1</sup>H-NMR. (CDCl<sub>3</sub>): 1.35 (*t*, *J* = 7, 3 H); 4.30 (*qa*, *J* = 7, 2 H); 7.80 (*m*, 3 H); 9.67 (*br. s*, 2 H). – MS.: 269 (*M*<sup>+</sup>).

C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>5</sub> (269.26) Calc. C 49.07 H 5.62 N 15.61% Found C 49.06 H 5.61 N 15.49%

*Preparation of ethyl 2-oxo-2H-[1,2,4]oxadiazolo[2,3-a]pyridine-7-carbamate (8).* A suspension of 750 mg (2.88 mmol) of **4** in 25 ml of DMF was heated at 125° during 90 min. The solvent was evaporated under reduced pressure and the residue recrystallized from ethanol to afford 250 mg (40%) of **8**, m.p. 165°. – IR. (KBr): 3436, 3240, 1783, 1746, 1632, 1612, 1557, 1522, 1260. – <sup>1</sup>H-NMR. (CDCl<sub>3</sub> + D<sub>6</sub>-DMSO): 1.38 (*t*, *J* = 7, 3 H); 4.33 (*qa*, *J* = 7, 2 H); 6.92 (*d* × *d*, *J* = 2 and 8, 1 H); 7.51 (*d* × *d*, *J* = 2 and 11, 1 H); 7.69 (*d* × *d*, *J* = 8 and 11, 1 H); 9.05 (*br.*, 1 H). – MS.: 215 (*M*<sup>+</sup>).

C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>4</sub> (223.19) Calc. C 48.43 H 4.06 N 18.83% Found C 48.47 H 4.17 N 18.83%

*Preparation of 2-(ethoxycarbonylamino)pyrimidine 1-oxide (5).* A solution of 2.22 g (20 mmol) of 2-aminopyrimidine 1-oxide [10] in 12 ml of water and 25 ml (25 mmol) of 1N NaOH was treated at 5° with 2.4 ml (25 mmol) of ClCOOC<sub>2</sub>H<sub>5</sub>. The mixture was stirred at 5° during 2 h and at r.t. overnight and then acidified with 2N HCl. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 200 ml). The organic phase was dried (MgSO<sub>4</sub>) and the solvent evaporated under reduced pressure. The crude residue was chromatographed over silica gel and eluted with CHCl<sub>3</sub> containing up to 7.5% of ethanol: 1.3 g (35%) of **5**, m.p. 130–132°. – IR. (KBr): 3292, 1759, 1574, 1532, 1524, 1477, 1244. – <sup>1</sup>H-NMR. (CDCl<sub>3</sub>): 1.35 (*t*, *J* = 7, 3 H); 4.37 (*qa*, *J* = 7, 2 H); 7.08 (*d* × *d*, *J* = 5 and 7, 1 H); 8.28 (*d* × *d*, *J* = 2 and 5, 1 H); 8.42 (*d* × *d*, *J* = 2 and 7, 1 H); 9.15 (*br.*, 1 H). – MS.: 183 (*M*<sup>+</sup>).

C<sub>7</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub> (183.17) Calc. C 45.90 H 4.95 N 22.94% Found C 45.78 H 4.51 N 22.86%

*Preparation of 2H-[1,2,4]Oxadiazolo[2,3-a]pyrimidine (9).* A suspension of 630 mg (3.4 mmol) of **5** in 20 ml of DMF was heated for 90 min at 120°. The solvent was evaporated under reduced pressure and the crystalline residue was washed several times with CH<sub>2</sub>Cl<sub>2</sub> to give 230 mg (49%) of a pure sample of **9**, m.p. 147–149°. – IR. (KBr): 1780, 1609, 1555, 1507. – <sup>1</sup>H-NMR. (D<sub>6</sub>-DMSO): 7.38

( $d \times d$ ,  $J = 4.5$  and  $6.5$ , 1 H); 8.78 ( $d \times d$ ,  $J = 2$  and  $4.5$ , 1 H); 9.37 ( $d \times d$ ,  $J = 2$  and  $6.5$ , 1 H). – MS.: 137 ( $M^+$ ).

$C_5H_3N_3O_2$  (137.098) Calc. C 43.80 H 2.21 N 30.65% Found C 43.66 H 2.18 N 30.50%

*Preparation of 2,6-bis(ethoxycarbonylamino)-4-[1,2,3,6-tetrahydro-1-pyridyl]-s-triazine 1-oxide (6).* A suspension of 5.0 g (24 mmol) of 2,6-diamino-4-[1,2,3,6-tetrahydro-1-pyridyl]-s-triazine 1-oxide [8] in 170 ml  $CH_2Cl_2$  and 20 ml of triethylamine was treated dropwise at  $0^\circ$  with a solution of 65 ml (64.7 mmol) of  $ClCOOCH_3$ . The mixture was stirred at  $0^\circ$  for 1 h at r.t. for an additional hour, and subsequently washed with water. The organic phase was dried ( $MgSO_4$ ) and evaporated to dryness. The solid residue was recrystallized from  $CH_2Cl_2$ /ether to give 4.8 g (79%) of **6**, m.p. 143–148°. – IR. (KBr): 3244, 3166, 1775, 1631, 1555, 1545, 1520, 1286, 1243, 1156. –  $^1H$ -NMR. ( $CDCl_3$ ): 1.38 (*t*,  $J = 7$ , 6 H); 2.28 (*m*, 2 H); 4.05 (*t*,  $J = 6$ , 2 H); 4.35 (*qa*,  $J = 7$ , 4 H); 4.41 (*m*, 2 H); 5.85 (*m*, 2 H, olefinic); 9.83 (*br. s*, 2 H, NH). – MS.: 352 ( $M^+$ ).

$C_{14}H_{20}N_6O_5$  (352.35) Calc. C 47.72 H 5.72 N 23.85% Found C 47.96 H 5.80 N 23.57%

*Preparation of ethyl 5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1,2,4]-oxadiazolo[2,3-a]-s-triazine-7-carbamate (10).* A mixture of 4.8 g (13.6 mmol) of **6** in 100 ml of DMF was heated for 30 min at  $140^\circ$ . The solvent was evaporated to dryness and the residue was chromatographed over silica gel and eluted with  $CH_2Cl_2/C_2H_5OH$  98:2. The isolated product was crystallized from ethanol to afford 1.5 g (36%) of pure **10**, m.p. 220–225°. – IR. (KBr): 3284, 3180, 1797, 1780, 1653, 1619, 1564, 1536, 1282, 1234. –  $^1H$ -NMR. ( $D_6$ -DMSO): 1.28 (*t*,  $J = 7$ , 3 H); 2.25 (*m*, 2 H); 3.95 (*m*, 2 H); 4.27 (*qa*,  $J = 7$ , 2 H); 4.31 (*m*, 2 H); 5.87 (*m*, 2 H, olefinic); 10.05 (*br. s*, 1 H, NH). – MS.: 306 ( $M^+$ ).

$C_{12}H_{14}N_6O_4$  (306.28) Calc. C 47.06 H 4.61 N 27.44% Found C 46.85 H 4.59 N 27.29%

*Preparation of 3-azabicyclo[3,2,2]nonane salt of methyl 5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1,2,4]oxadiazolo[2,3-a]pyrimidine-7-carbamate (1c).* A suspension of 4.0 g (13.6 mmol) of methyl 5-[3,6-dihydro-1(2H)-pyridyl]-2-oxo-2H-[1,2,4]oxadiazolo[2,3-a]pyrimidine-7-carbamate (**1d**) in 25 ml of  $CH_3CN$  was treated with a solution of 1.7 g (13.6 mmol) of 3-azabicyclo[3.2.2]nonane in 20 ml of  $CH_3CN$ . The crystalline precipitate of **1c** was filtered off and recrystallized from  $CH_3CN$  to afford pure **1c**, m.p. 164–168°.

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