Synthesis of fused nonaromatic heterocyclic systems based on dioxolanones and hydrazine

Yu. B. Chudinov, S. B. Gashev, and V. V. Semenov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (495) 137 2966. E-mail: vs@zelinsky.ru

Transformations of *N*-aminooxazolidinones were studied. These transformations occur by different pathways depending on the reaction conditions and the structure of the starting compound. Heating of *N*-aminooxazolidinones in an acidic medium leads to the ring expansion to form 1,3,4-oxadiazin-2-ones. The treatment of *N*-benzoylamino- and *N*-benzylaminooxazolidinones with polyphosphoric acid (PPA) affords tricyclic structures, *viz.*, phthalazine derivatives. In the reactions with PPA, 5-(2-phenylethyl)-substituted *N*-aminooxazolidinones and 6-(2-phenylethyl)-substituted oxatetrahydropyridazin-2-ones undergo intramolecular amidoalkylation to form compounds containing the tetrahydronaphthalene fragment.

Key words: hydrazine, dioxolanones, oxazolidin-2-ones, oxapyridazinones, oxazolophthalazinone, naphthooxazolidinones, naphthooxadiazinones, amidoalkylation.

The reactions of acetylenic alcohols **1** with CO_2 (Scheme 1) produce dioxolanones **2** (cyclic carbonates), which are promising synthons for the preparation of oxadiazinones **4** [1,2] exhibiting anticonvulsant activity.[3] In addition, tetrahydrooxadiazinones of type **4** are used in the stereoselective synthesis of *cis*- and *trans*-alkenes prepared by thermal or photolytic decomposition.[4]

The reactions of carbonates with various primary amines and ammonia produce 4-hydroxyoxazolidin-2-ones. The electrophilic attack of the acyliminium species generated in an acidic medium on the activated aromatic ring is responsible for numerous amidoalkylation reactions, which were described in the literature and occur primarily in an intramolecular fashion.[5]

Unlike the reactions of amines, the reactions of dioxolanones **2** with hydrazines studied earlier[1,2] proceed ambiguously and require additional investigation to search for conditions for the synthesis of the target five- or six-membered heterocycles (see Scheme 1). The published data are not exactly correct. For example, the structure of 5-hydroxytetrahydro-1,3,4-oxadiazinone **A** (see Scheme 1) was assigned[1] to the product of the reaction of carbonate **2a** with hydrazine, which, in turn, undergoes dehydration to form 3,6-dihydro-1,3,4-oxadiazinone **4**. These authors stated[1] that the signals for the protons of two NH groups appear in the ^{1}H NMR spectrum as two singlets with the chemical shift difference as small as 0.02 ppm. This seems unexplainable because one of the N atoms is adjacent to the aliphatic C atom, whereas another N atom is adjacent to the carbonyl C atom and, consequently, the chemical shift difference should be substantially larger. In the more recent study,[2] six-membered structures of compound **A** and its analogs were also reported. Taking into account that the derivatives prepared by this reaction are of interest from the viewpoint of both their biological activity and the synthesis of new fused nonaromatic heterocyclic systems, we reproduced the published procedures and performed new investigation.

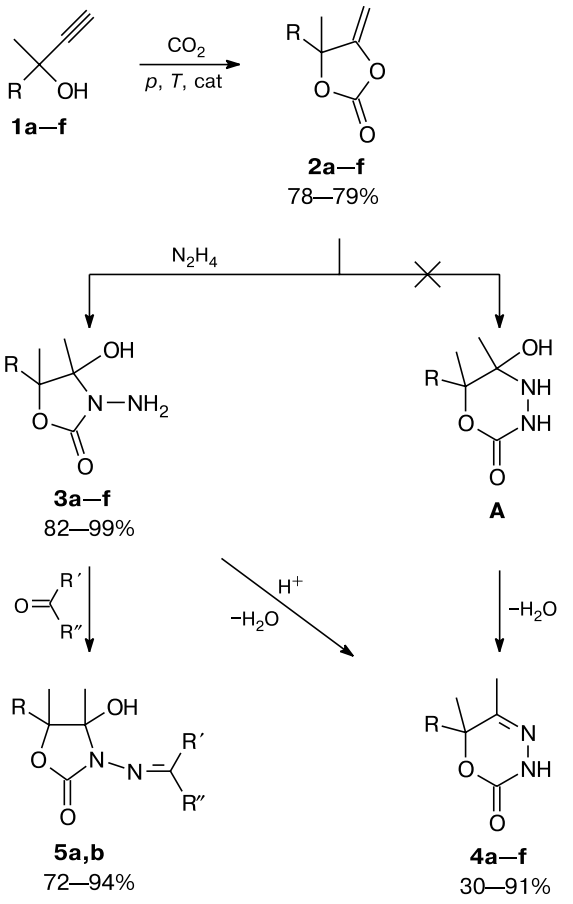
Results and Discussion

By repeating and improving the published[1,2] procedures and extending the range of compounds (both dioxolanones and nitrogen components), we confirmed that 4-methylenedioxolanones readily react with hydrazine and its derivatives. The melting point and the chemical shifts in the ^{1}H NMR spectrum of compound **3a** are identical to those described in the study;[1] however, we observed only one singlet at δ 4.12 with the integral intensity corresponding to two protons. The ^{1}H NMR spectroscopic data and the reactivity of compound **3a** (the formation of hydrazones **5**) provide evidence that this reaction produces 4-hydroxy-4,5,5-trimethyloxazolidin-2-one **3a**, which is a five-membered heterocycle containing the exocyclic *N*-amino group, rather that the previously mentioned 5-hydroxyoxadiazinone **A**. The same results were obtained in the synthesis of analogous *N*-aminooxazolidinones by the reaction of hydrazine with other 4-methylenedioxolanones.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2156—2163, December, 2006.

1066-5285/06/5512-2238

Scheme 1



Compound	R
1a, 2a, 3a, 4a, 5a	Me
1b, 2b, 3b, 4b, 5b	$PhCH_2$
1c, 2c, 3c, 4c	$Ph(CH_2)_2$
1d, 2d, 3d, 4d	$PhCMe_2CH_2$
1e, 2e, 3e, 4e	Ph
1f, 2f, 3f, 4f	3-Pyridyl

Compound	R′	R″
5a	H	Ph
5b	Me	Me

Oxazolidinones **3** were transformed into the corresponding oxadiazinones **4** in high yields by refluxing in a mixture of toluene and acetic acid (Schemes 1 and 2). The only exception is compound **3b**, for which more drastic reaction conditions are required. The multistep syntheses of oxadiazinones **4a**,**e** were documented.[3,4] The procedure developed in the present study is simpler and provides substantially higher yields. Oxazolidinones, which have been prepared earlier[2] from benzylhydrazine (for example, **6**, see Scheme 2) or phenylhydrazine, are not rearranged in this fashion into analogous substituted oxadiazinones; instead, they are dehydrated with elimination of the hydroxy group at position 4 of the oxazolidinone ring.

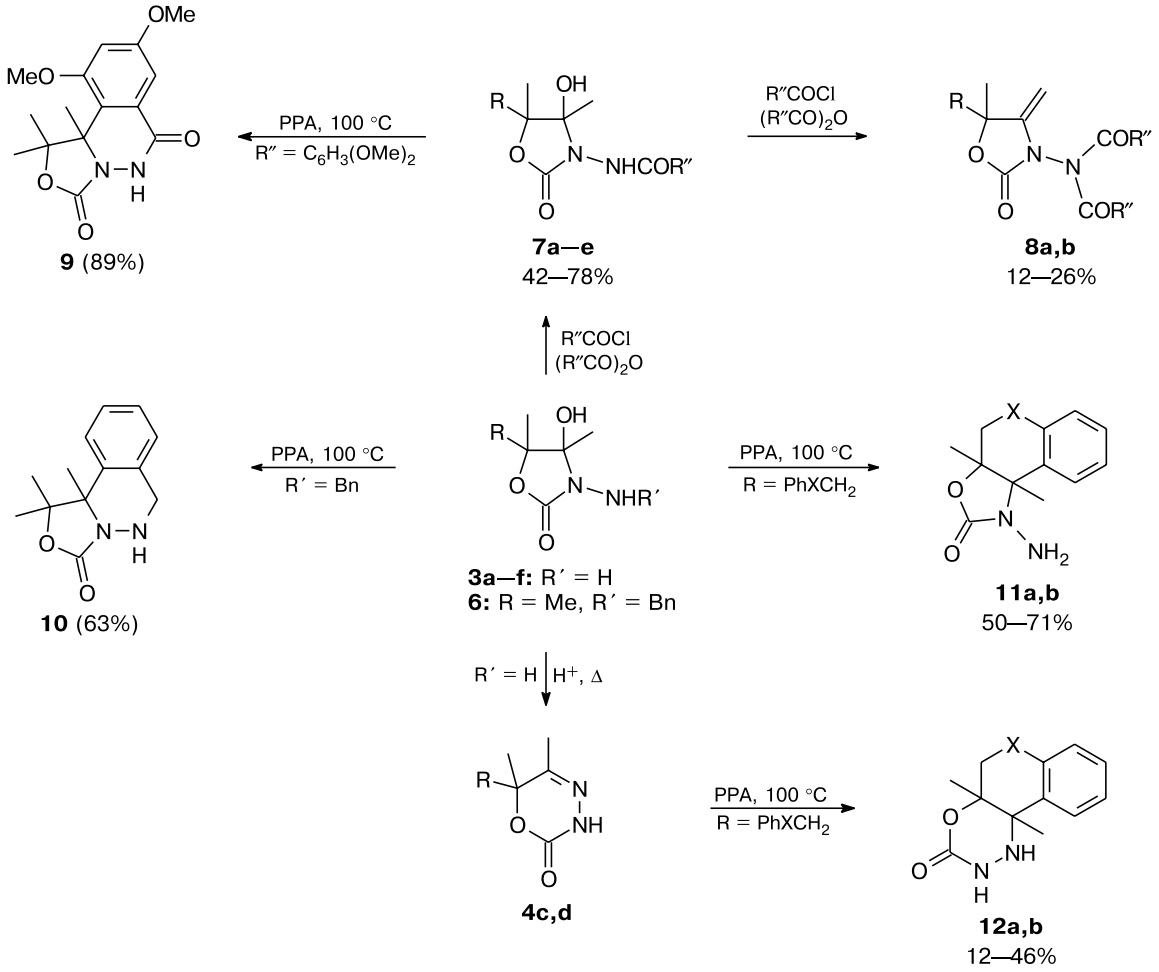
The reactions of acid chlorides with oxazolidinones **3** and **6** gave acylation products (see Scheme 2). Mono- (**7**) and disubstituted (**8**) products can be prepared by varying the reaction conditions (the solvent, the temperature, and the reagent ratio). Diacylation performed in the presence of an excess of an acylating agent is accompanied by dehydration to form 4-methylene-substituted compounds **8**. Refluxing in benzene in the presence of acetic anhydride affords monoacetyl derivatives (for example, **7e**). Attempts to alkylate the *N*-amino group with benzyl chloride in the presence of various bases failed. By contrast, *N*-aminooxazolidinones **3e** and **3f** are not acylated with anhydrides or acid chlorides; instead, these compounds are quantitatively transformed into oxadiazinones **4e** and **4f**, respectively.

The ^{1}H NMR spectra of monoacylation products **7** show a singlet of the amide proton at δ 9.90—10.46. The mass spectra of compounds **7** have molecular ion peaks. It should be noted that the hydroxy group at position 4 of the oxazolidinone ring, which is usually eliminated under the action of dehydrating agents,[5] remains intact in the course of acylation. The ^{1}H NMR spectra show the characteristic singlet of this hydroxy group at δ 6.03—6.59 (1 H).

Earlier, it has been demonstrated[6,7] that the hydroxy group at position 4 is eliminated under the action of polyphosphoric acid (PPA) to form an acyliminium species, due to which the electrophilic attack on the aromatic ring can occur. For example, the treatment of compound **7d** with PPA afforded the cyclization product, *viz.*, dihydrooxazolophthalazinedione **9** (see Scheme 2). Related compound **7a**, in which the benzene ring is not activated by the methoxy groups, proved to be incapable of being involved in this reaction due to the deactivating action of the adjacent carbonyl group. By contrast, the treatment of oxazolidinone **6** (see Ref. 2), which is generated in the reaction of carbonate **2a** with benzylhydrazine, with PPA affords the cyclization product, *viz.*, tetrahydrooxazolophthalazinone **10**. Cyclizations of various oxazolidinones bearing the phenylethyl substituent at position 5, which gave tetrahydronaphthalene structures, have been documented earlier.[7] *N*-Aminooxazolidinones **3c,d** also appeared to be able to react with PPA and give tetrahydronaphthooxazolidinones **11a,b**. Cyclization of oxadiazinones **4c** and **4d**, which proceeds through the formation of the less reactive iminium species, is of particular interest. For example, hexahydronaphthooxadiazinones **12a** and **12b**, respectively, were synthesized by the reactions with PPA. Compounds **9**, **10**, and **12** (see Scheme 2) are new, previously unknown, fused heterocyclic systems.

As mentioned above, oxadiazinones **4**, which were prepared by expansion of the *N*-aminooxazolidinone ring under the action of weakly acidic reagents (acetic acid in toluene), can undergo further transformations if their molecules contain particular functional groups. With the aim of finding the optimal conditions for cyclization, we treated compound **4c** with 100% orthophosphoric acid

Scheme 2



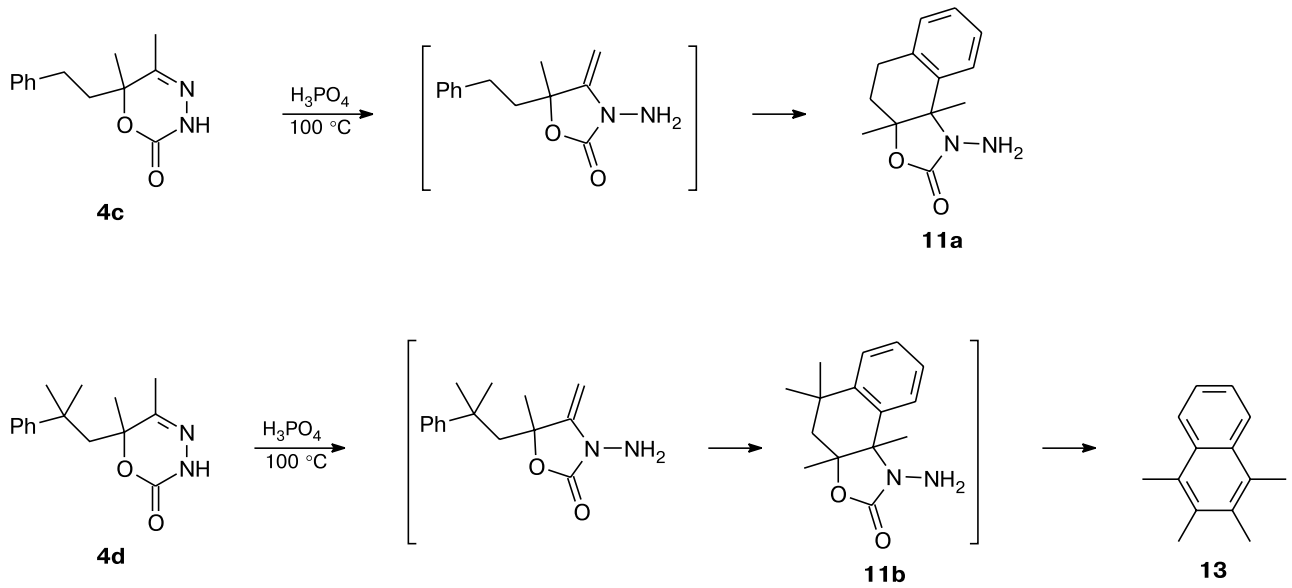
PPA is polyphosphoric acid

Compound	R	Compound	R″	Compound	X
7a, 7d, 7e, 8b	Me	**7a, 7b, 7c, 8a**	Ph	**11a, 12a**	CH_2
7b	$PhCH_2$	**7d, 8b**	$3,5\text{-}(MeO)_2C_6H_3$	**11b, 12b**	CMe_2
7c, 8a	$PhCMe_2CH_2$	**7e**	Me		

under heating (Scheme 3). Tetrahydronaphthooxazolidinone **11a** was obtained as the only reaction product. The analogous reaction of oxadiazinone **4d** containing two methyl groups in the side chain produced 1,2,3,4-tetramethylnaphthalene **13** (as evident from the melting point and the ^{1}H NMR spectrum), which we have synthesized earlier.[7] Apparently, compound **13** was generated as a result of acidolysis of intermediate tetrahydronaphthooxazolidinone **11b** followed by elimination of water and hydrazine, which is accompanied by migration of the methyl group (the Wagner—Meerwein rearrangement). This reaction pathway indicates that recyclization of compounds **3** to **4** is reversible. The first step of this transformation involves the contraction of six-membered oxadiazinone **4** to give five-membered *N*-aminooxazolidinone **3** followed by cyclization to compound **11** through the above-described pathway. The formation of compound **13** additionally confirms the above-mentioned hypothesis. We have studied the formation of this compound according to an analogous scheme when performing hydrolysis of related oxazolotetrahydronaphthalenes.[7] These experimental data suggest that there is an equilibrium between five-membered *N*-aminooxazolidinones **3** and the corresponding oxadiazinones **4** in acidic media.

Therefore, the reaction of *N*-aminooxazolidinones **3** with a weak acid (acetic or monochloroacetic) in an aprotic solvent leads to their transformation into thermodynamically more favorable oxadiazinones **4**, while compounds **3c** and **3d** virtually do not undergo cyclization to **11a** and **11b**, respectively. Under treatment with PPA, compounds **3c**, **3d** and **4c**, **4d** undergo rapid cyclization to compounds **11a**, **11b** and **12a**, **12b**, respectively (see

Scheme 3

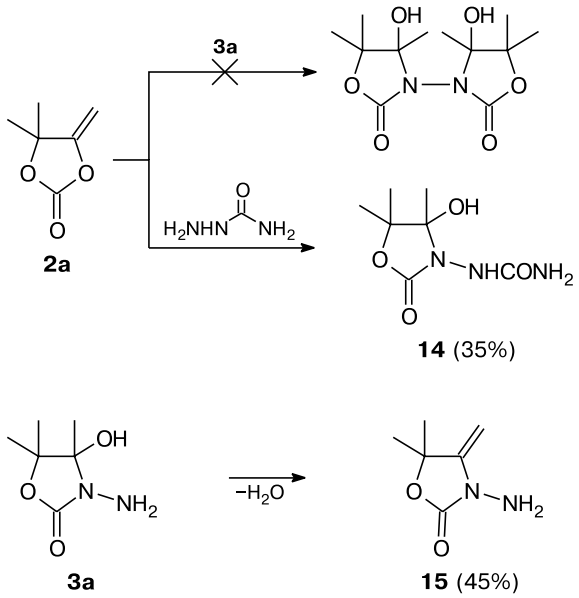


Scheme 2). Under treatment with 100% orthophosphoric acid (see Scheme 3), in which cyclization occurs more slowly than in PPA, the starting oxadiazinones **4c,d** are in an equilibrium with *N*-aminooxazolidinones **3c,d**. As mentioned above, in an acidic medium the latter can form the acyliminium species, which is more reactive than the iminium species generated from compounds **4c,d**. Hence, oxazolidinones **3c,d**, which are present in a small amount in the equilibrium mixture, can undergo intramolecular amidoalkylation under the action of 100% orthophosphoric acid (unlike **4c,d**). As a result, this reaction irreversibly produces compounds **11a** and **13** (see Scheme 3).

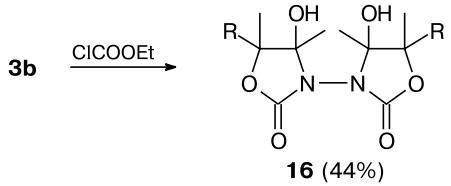
Many examples of the synthesis of oxazolidinones by the reactions of dioxolanones **2** with various primary amines were documented. Data on the formation of oxazolidinones in the reactions of dioxolanones with acid hydrazides are lacking in the literature. We performed this reaction with carbonate **2a**. Its reaction with semicarbazide produced oxazolidinone **14** (Scheme 4). By contrast, the reaction of equimolar amounts of carbonate **2a** and *N*-aminooxazolidinone **3a**, which can be considered as cyclic hydrazide of carbonic acid, did not afford the expected bis-oxazolidinone; instead, dehydration product of **3a**, *viz.*, 5,5-dimethyl-4-methyleneoxazolidin-2-one, was isolated. More recently, it was found that dehydration of **3a** occurs already under reflux in acetonitrile.

In attempting to acylate *N*-aminooxazolidinone **3b** with ethyl chloroformate (Scheme 5), we unexpectedly obtained bis-oxazolidinone **16**, whereas normal acylation products were not isolated from the reaction mixture. This fact requires further investigation and explanation.

Scheme 4



Scheme 5



The reaction of *N*-aminooxazolidinone **3b** with 3,4,5-trimethoxybenzoyl chloride in the presence of tri-

ethylamine also did not lead to acylation of the amino group. The starting compound remained intact, and 3,4,5-trimethoxybenzoic anhydride was isolated in quantitative yield. In other cases, the reactions with the use of 3,4,5-trimethoxybenzoyl chloride as the acylating agent also produced small amounts of 3,4,5-trimethoxybenzoic anhydride. The above-considered data are apparently indicative of nonobvious pathways of the well-known reactions with such substrates. Presumably, this is due to the presence of the hydroxy group at position 4 of the oxazolidinone ring, which is readily eliminated.

Experimental

The NMR spectra were recorded on a Bruker DRX-500 instrument (500.13 MHz). Unless otherwise indicated, DMSO-d_6 was used as the solvent. The mass spectra were obtained on a Kratos MS-30 instrument using a direct inlet system (the electron impact energy was 70 eV, the ionization chamber temperature was 250 °C). The course of the reactions was monitored by TLC on Baker-flex plates (silica gel IB-F).

The yields and physicochemical parameters of all compounds are listed in Table 1. The mass-spectrometric data are given in Table 2. All yields are given for the isolated and purified compounds. The following abbreviations were used: PE is petroleum ether, MTBE is methyl *tert*-butyl ether, EA is ethyl acetate, and Bzl is benzene.

The syntheses of acetylenic alcohols **1b,c,d** [7] and **1e** [8] were described earlier.

2-(Pyridin-3-yl)but-3-yn-2-ol (1f). Liquid ammonia (3.5 L), technical acetylene (780 g, 30 mol), and 3-acetylpyridine (910 g, 7.5 mol) were placed in a shaking stainless steel autoclave. Then, a solution of KOH (42 g) in anhydrous EtOH (150 mL) was added with stirring at −15 °C for 30 min. The temperature of the

Table 1. Physicochemical parameters and the yields of the compounds

Compound	M.p. /°C	R_f (eluent)*	Yield (%)	Found / Calculated (%) C	H	N	Molecular formula
1f	— (oil)	—	78	73.43 / 73.45	6.17 / 6.16	9.50 / 9.52	C_9H_9NO
2e	23—27	0.65 (Bzl)	78	69.45 / 69.46	5.32 / 5.30	— / 0	$C_{11}H_{10}O_3$
2f	26—27	0.64 (EA)	79	62.77 / 62.82	4.76 / 4.75	7.36 / 7.33	$C_{10}H_9NO_3$
3a	95	0.03 (*A*)	87	45.02 / 44.99	7.57 / 7.55	17.45 / 17.49	$C_6H_{12}N_2O_3$
3b	155—157	0.04 (*A*)	85	60.97 / 61.00	6.83 / 6.83	11.88 / 11.86	$C_{12}H_{16}N_2O_3$
3c	105—106	0.12 (*A*)	82	62.45 / 62.38	7.22 / 7.25	11.15 / 11.19	$C_{13}H_{18}N_2O_3$
3d	163	0.46 (EA)	99	64.70 / 64.72	7.97 / 7.97	10.09 / 10.06	$C_{15}H_{22}N_2O_3$
3e	146—147	0.17 (*A*)	92	59.36 / 59.45	6.35 / 6.35	12.69 / 12.61	$C_{11}H_{14}N_2O_3$
3f	193—194	0.14 (EA)	99	53.80 / 53.80	5.84 / 5.87	18.85 / 18.82	$C_{10}H_{13}N_3O_3$
4a	78—79	0.45 (*A*)	91	50.68 / 50.69	7.06 / 7.09	19.75 / 19.71	$C_6H_{10}N_2O_2$
4b	118—119	0.53 (*A*)	75	66.00 / 66.04	6.47 / 6.47	12.87 / 12.84	$C_{12}H_{14}N_2O_2$
4c	81—82	0.65 (*A*)	89	67.26 / 67.22	6.95 / 6.94	12.02 / 12.06	$C_{13}H_{16}N_2O_2$
4d	134—135	0.72 (*A*)	30	69.20 / 69.20	7.75 / 7.74	10.76 / 10.76	$C_{15}H_{20}N_2O_2$
4e	147—149	0.27 (*B*)	69	64.68 / 64.69	5.90 / 5.92	13.74 / 13.72	$C_{11}H_{12}N_2O_2$
4f	160—161	0.40 (EA)	82	58.58 / 58.53	5.40 / 5.40	20.43 / 20.48	$C_{10}H_{11}N_3O_2$
5a	150—151	0.73 (*A*)	72	62.86 / 62.89	6.53 / 6.50	11.28 / 11.28	$C_{13}H_{16}N_2O_3$
5b	148—149	0.24 (*A*)	94	65.26 / 65.20	7.29 / 7.30	10.07 / 10.14	$C_{15}H_{20}N_2O_3$
7a	185	0.24 (*A*)	64	59.16 / 59.08	6.10 / 6.10	10.52 / 10.60	$C_{13}H_{16}N_2O_4$
7b	157—158	0.47 (*A*)	78	67.00 / 67.04	5.93 / 5.92	8.27 / 8.23	$C_{19}H_{20}N_2O_4$
7c	179—180	0.38 (*A*)	60	69.10 / 69.09	6.86 / 6.85	7.31 / 7.33	$C_{22}H_{26}N_2O_4$
7d	176	0.58 (*A*)	42	55.56 / 55.55	6.22 / 6.22	8.62 / 8.64	$C_{15}H_{20}N_2O_6$
7e	182—183	0.09 (*A*)	74	47.54 / 47.52	6.99 / 6.98	13.83 / 13.85	$C_8H_{14}N_2O_4$
8a	163—164	0.90 (*A*)	12	74.30 / 74.34	6.03 / 6.02	6.01 / 5.98	$C_{29}H_{28}N_2O_4$
8b	151—152	0.86 (*A*)	26	61.28 / 61.27	5.58 / 5.57	5.94 / 5.95	$C_{24}H_{26}N_2O_8$
9	253	0.25 (*A*)	89	58.85 / 58.81	5.92 / 5.92	9.11 / 9.15	$C_{15}H_{18}N_2O_5$
10	198—200	0.21 (*A*)	63	67.20 / 67.22	6.95 / 6.94	12.07 / 12.06	$C_{13}H_{16}N_2O_2$
11a	141—142	0.44 (*A*)	71	67.25 / 67.22	6.94 / 6.94	12.04 / 12.06	$C_{13}H_{16}N_2O_2$
11b	149—150	0.45 (*A*)	50	69.22 / 69.20	7.73 / 7.74	10.76 / 10.76	$C_{15}H_{20}N_2O_2$
12a	208—210	0.11 (*A*)	46	67.23 / 67.22	6.97 / 6.94	12.03 / 12.06	$C_{13}H_{16}N_2O_2$
12b	211—213	0.15 (*A*)	12	69.22 / 69.20	7.71 / 7.74	10.77 / 10.76	$C_{15}H_{20}N_2O_2$
14	175—176	0.40 (EA)	35	41.38 / 41.37	6.45 / 6.45	20.67 / 20.68	$C_7H_{13}N_3O_4$
15	84	0.11 (Bzl)	45	50.71 / 50.69	7.13 / 7.09	19.65 / 19.71	$C_6H_{10}N_2O_2$
16	212—214	0.21 (*A*)	44	65.44 / 65.44	6.43 / 6.41	6.34 / 6.36	$C_{24}H_{28}N_2O_6$

* (*A*), Bzl—EA (2 : 1); (*B*), Bzl—EA (5 : 1).

Table 2. Mass spectra of the compounds

Compound	M /g mol^{-1}	m/z (I_{rel} (%)) for main lines
1f	147	147 (8); 132 (100); 106 (11); 78 (19); 53 (25); 51 (26); 40 (22)
2f	191	191 (1); 146 (19); 132 (26); 118 (100); 104 (57); 91 (27); 78 (29); 51 (79); 43 (40)
3a	160	160 (4); 85 (30); 73 (21); 71 (23); 59 (21); 57 (46); 43 (100)
3b	236	236 (5); 161 (12); 117 (7); 91 (25); 65 (8); 43 (100)
3c	250	250 (19); 175 (30); 174 (32); 128 (15); 91 (100); 43 (59)
3d	278	278 (2); 171 (28); 119 (100); 91 (57); 77 (19); 43 (64)
3e	222	222 (1); 147 (42); 135 (22); 119 (24); 105 (24); 91 (29); 77 (25); 51 (14); 43 (100)
3f	223	223 (1); 148 (68); 136 (26); 122 (22); 106 (22); 92 (14); 78 (23); 51 (28); 43 (100)
4a	142	142 (7); 98 (10); 69 (22); 57 (17); 43 (54); 41 (100)
4b	218	218 (5); 127 (18); 91 (86); 65 (26); 51 (13); 43 (100)
4c	232	232 (60); 172 (13); 127 (33); 105 (100); 91 (90); 77 (20); 65 (21); 43 (74)
4d	260	260 (4); 186 (7); 128 (49); 119 (85); 91 (100); 77 (13); 43 (70)
4e	204	204 (11); 159 (83); 145 (100); 115 (48); 105 (57); 91 (81); 77 (67); 51 (52); 43 (38)
4f	205	205 (2); 160 (30); 146 (78); 117 (80); 106 (30); 78 (49); 63 (30); 51 (100); 43 (71)
5a	248	248 (12); 161 (8); 147 (32); 104 (35); 90 (100); 71 (19); 59 (93)
5b	276	276 (14); 234 (16); 219 (28); 157 (22); 143 (61); 91 (34); 43 (100)
7a	264	264 (3); 178 (2); 163 (9); 136 (8); 105 (100); 77 (29); 43 (10)
7b	340	340 (1); 322 (1); 278 (3); 157 (18); 136 (10); 105 (100); 91 (16); 77 (29); 43 (44)
7c	382	382 (1); 364 (4); 119 (34); 105 (100); 91 (20); 77 (31); 43 (16)
7d	324	324 (2); 238 (4); 187 (37); 165 (100); 159 (58); 77 (28); 43 (24)
7e	202	202 (2); 160 (18); 101 (14); 85 (20); 74 (11); 57 (30); 43 (100)
8a	468	362 (1); 335 (6); 257 (8); 125 (100); 97 (21); 88 (34); 77 (11); 63 (14)
8b	470	360 (2); 346 (8); 165 (100); 137 (20); 122 (18); 107 (10); 77 (10); 63 (9)
9	306	306 (34), 291 (31); 247 (85), 220 (35); 204 (29); 206 (100), 164 (28)
10	232	232 (14); 173 (17); 145 (33); 132 (100); 128 (20); 117 (38); 115 (24); 91 (12); 43 (15)
11a	232	232 (5); 207 (15); 163 (19); 135 (22); 108 (20); 99 (29); 77 (34); 49 (32); 43 (100)
11b	260	260 (26); 186 (29); 171 (86); 159 (43); 156 (47); 141 (40); 128 (42); 91 (38); 57 (100); 43 (65)
12a	232	232 (23); 173 (9); 158 (100); 143 (96); 128 (60); 115 (38); 91 (16)
12b	260	260 (20); 186 (68); 171 (100); 156 (29); 141 (19); 115 (18); 91 (16)
14	203	203 (2); 160 (21); 102 (18); 85 (63); 57 (84); 43 (100)
15	142	142 (26); 99 (51); 82 (18); 69 (28); 56 (31); 41 (100)
16	440	440 (1); 317 (9); 219 (100); 175 (36); 158 (31); 117 (20); 91 (83)

reaction mixture was gradually raised to +18 °C for 8 h, and then the mixture was kept for 50 h. By this time, the percentage of the starting 3-acetylpyridine was 4% (GLC data); the percentage of **1f**, 79%. The acetylene—ammonia mixture was slowly removed at <10 °C. Ice (3 kg) was added to the residue. Then 30% H_2SO_4 (to pH = 5—6) and Na_2SO_4 (150 g) were added. The product was extracted with MTBE (1 L, then 2×200 mL). The ethereal solution was dried with Na_2SO_4 and concentrated. The residue was distilled *in vacuo* using a 15-cm dephlegmator. Compound **1f** was obtained in a yield of 856 g (78%) as a viscous semitransparent substance, b.p. 106—111 °C (0.5 Torr). ^{1}H NMR, δ: 1.66 (s, 3 H, Me); 3.51 (s, 1 H, —CCH); 6.19 (s, 1 H, OH); 7.37 (dd, 1 H, J = 7.7 Hz, J = 4.8 Hz); 7.90 (d, 1 H, Py, J = 7.7 Hz); 8.48 (d, 1 H, Py, J = 4.8 Hz); 8.77 (s, 1 H, Py).

Dioxolanones 2. Dioxolanones **2a** [9] and **2b,c,d** [7] were synthesized according to known procedures. Dioxolanones **2e,f** were synthesized according to a modified procedure. The corresponding acetylenic alcohol **1** (0.2 mol), triethylamine (0.5 mL), tetraethylammonium bromide (0.2 g), and CuBr (0.2 g) were placed in a heated 250-mL rotating autoclave. Carbon dioxide was pumped so that the initial pressure at 80 °C was 250 atm. The reaction time was 10—20 h, during which the pressure was maintained close to the initial value, the temperature being raised (but no higher than 100 °C). As a result, the degree of conversion was higher than 95% (GLC). The reaction mixture was diluted with acetonitrile to ~1/1, filtered through a 2-cm layer of silica gel, and concentrated. The product was purified by vacuum distillation. 4-Methyl-5-methylene-4-phenyl-1,3-dioxolan-2-one (**2e**) and 4-methyl-5-methylene-4-(pyridin-3-yl)-1,3-dioxolan-2-one (**2f**) were obtained. The boiling point and the ^{1}H NMR spectrum of compound **2e** are consistent with the published data.[10]

Compound **2f**. B.p. 124—130 °C (1 Torr). ^{1}H NMR, δ: 2.06 (s, 3 H, Me); 4.89 and 5.05 (both d, 1 H each, =CH_2, J = 3.0 Hz); 7.50 (dd, 1 H, Py, J = 6.4 Hz, J = 4.2 Hz); 7.98 (d, 1 H, Py, J = 6.4 Hz); 8.63 (d, 1 H, Py, J = 4.2 Hz); 8.81 (s, 1 H, Py).

Oxazolidinones 3a—f. A solution of the corresponding dioxolanone **2** (10 mmol) in acetonitrile (7 mL) was added with stirring to hydrazine hydrate (3 mL, 60 mmol) for 15 min. The reaction mixture was kept at 40 °C for 1 days. In the case of **3a,b,e,f**, the reaction mixture was concentrated to dryness, and the product was crystallized from MTBE. In the case of **3c,d**,

Table 3. ^{1}H NMR spectra of compounds **3**

Compound*	δ (*J*/Hz)				
	4-Me, 5-Me	N—NH_2	4-OH	Ar	Other signals
3a	1.22 (s, 3 H); 1.30 (s, 6 H)	4.12 (s, 2 H)	5.81 (s, 1 H)	—	—
3b (1 : 5)	1.02, 1.11, 1.27, 1.40 (all s, 6 H)	4.22, 4.24 (both s, 2 H)	6.00, 6.18 (both s, 1 H)	7.16—7.33 (m, 5 H)	2.72, 2.88, 2.85, 3.11 (all d, 2 H, CH_2, J = 13.7)
3c	1.31, 1.37 (both s, 3 H each)	4.16 (s, 2 H)	5.93 (s, 1 H)	7.16—7.31 (m, 5 H)	1.90—2.04, 2.58—2.77 (both m, 2 H each, CH_2—CH_2)
3d	0.58, 1.45 (both s, 3 H each)	4.12 (s, 2 H)	5.93 (s, 1 H)	7.16 (t, 1 H, J = 7.5); 7.30 (t, 2 H, J = 7.5); 7.43 (d, 2 H, J = 7.5)	1.15, 1.26 (both s, 3 H each, CMe_2); 2.15, 2.22 (both d, 1 H each, CH_2, J = 14.2)
3e (3 : 5)	0.88, 1.49, 1.59, 1.68 (all s, 6 H)	4.30 (s, 2 H)	5.70, 6.35 (both s, 1 H)	7.26—7.51 (m, 5 H)	—
3f (2 : 3)	0.81, 1.49, 1.62, 1.72 (all s, 6 H)	4.34 (s, 2 H)	5.90, 6.45 (both s, 1 H)	7.38—7.44 (m, 1 H); 7.69, 7.80 (both d, 1 H, J = 8.0); 8.49—8.62 (m, 2 H)	—

* For compounds **3b—f**, diastereomers with either *cis*- or *trans*-methyl groups at positions 4 and 5 of the oxazolidinone ring can form, which accounts for the presence of the double set of signals (for more details, see Ref. 11). For compounds **3c** and **3d**, the spectrum of one major isomer, which was isolated in pure form, is given.

the reaction mixture was diluted with water until a precipitate was obtained. The precipitate was filtered off, washed with water, and dried on a filter. 3-Amino-4-hydroxy-4,5,5-trimethyl-1,3-oxazolidin-2-one (**3a**), 3-amino-5-benzyl-4-hydroxy-4,5-dimethyloxazolidin-2-one (**3b**), 3-amino-4-hydroxy-4,5-dimethyl-5-(2-phenylethyl)oxazolidin-2-one (**3c**), 3-amino-4-hydroxy-4,5-dimethyl-5-(2-methyl-2-phenylpropyl)oxazolidin-2-one (**3d**), 3-amino-4-hydroxy-4,5-dimethyl-5-phenyloxazolidin-2-one (**3e**), and 3-amino-4-hydroxy-4,5-dimethyl-5-(pyridin-3-yl)oxazolidin-2-one (**3f**) were synthesized. Their ^{1}H NMR spectra are given in Table 3.

Oxadiazinones 4a—f. Toluene (15 mL) was added to a solution of the corresponding oxazolidinone **3** (3 mmol) in acetic acid (10 mL). The reaction mixture was refluxed using a Dean—Stark trap until all the water was removed. In the case of **4b**, *o*-xylene was used instead of toluene, and monochloroacetic acid (2.5 g), which was predissolved in *o*-xylene, was used instead of acetic acid. In the case of **4d**, benzene (30 mL) was used as the solvent, the amount of acetic acid was 1 mL, and azeotropic distillation of a mixture of benzene and water (12 mL) was slowly performed (~30 min). The reaction mixture was concentrated to dryness, toluene (10 mL) was added (in all cases), and the mixture was again concentrated to dryness. The products slowly crystallized from MTBE. 5,6,6-Trimethyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4a**), 6-benzyl-5,6-dimethyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4b**), 5,6-dimethyl-6-(2-phenylethyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4c**), 5,6-dimethyl-6-(2-methyl-2-phenylpropyl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4d**), 5,6-dimethyl-6-phenyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4e**), and 5,6-dimethyl-6-(pyridin-3-yl)-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one (**4f**) were synthesized. Their ^{1}H NMR spectra are given in Table 4.

4-Hydroxy-4,5,5-trimethyl-3-(phenylmethylidene)aminooxazolidin-2-one (5a). Benzaldehyde (0.51 g, 5 mmol) was added

Table 4. ^{1}H NMR spectra of compounds **4**

Compound	δ (*J*/Hz)			
	6-Me, 5-Me	Ar	NH	Other signals
4a	1.39 (s, 6 H); 1.91 (s, 3 H)	—	10.60 (s, 1 H)	—
4b	1.38, 1.91 (both s, 3 H each)	7.18—7.38 (m, 5 H)	10.41 (s, 1 H)	2.94, 3.07 (both d, 1 H each, CH_2, J = 14.5)
4c	1.42, 1.98 (both s, 3 H each)	7.15—7.32 (m, 5 H)	10.62 (s, 1 H)	1.90—2.04 (m, 2 H, CH_2—CH_2); 2.50—2.59, 2.61—2.71 (both m, 1 H each, CH_2—CH_2)
4d	1.29, 1.71 (both s, 3 H each)	7.18 (t, 1 H, J = 7.6); 7.29 (t, 2 H, J = 7.6); 7.43 (d, 2 H, J = 7.6)	10.49 (s, 1 H)	0.97, 1.44 (both s, 3 H each, CMe_2); 2.06, 2.19 (both d, 1 H each, CH_2, J = 12.8)
4e	1.75, 2.02 (both s, 3 H each)	7.34—7.45 (m, 5 H)	10.71 (s, 1 H)	—
4f	1.82, 2.04 (both s, 3 H each)	7.49 (dd, 1 H, J = 8.0, J = 4.6); 7.82 (d, 1 H, J = 8.0); 8.60 (d, 1 H, J = 4.6); 8.62 (s, 1 H)	10.84 (s, 1 H)	—

to a solution of oxazolidinone **3a** (0.8 g, 5 mmol) in benzene (10 mL). The reaction mixture was refluxed using a Dean—Stark trap until all the water was removed. The product with an impurity of **4a** crystallized on cooling. After recrystallization from MTBE, pure hydrazone **5a** was obtained. ^{1}H NMR, δ: 1.34, 1.39, and 1.50 (all s, 3 H each, Me); 6.61 (s, 1 H, OH); 7.44—7.49 (m, 3 H, Ph); 7.75—7.79 (m, 2 H, Ph); 9.10 (s, 1 H, NC<u>H</u>Ph).

5-Benzyl-4-hydroxy-4,5-dimethyl-3-[(1-methylethylidene)amino]oxazolidin-2-one (5b). A solution of oxazolidinone **3b** (0.71 g, 3 mmol) in acetone (10 mL) was refluxed for 30 min. Then the reaction mixture was concentrated, and the product was crystallized from an MTBE—PE mixture. ^{1}H NMR of hydrazone **5b** (mixture of isomers, 1 : 1) (δ): 1.14, 1.20, 1.25, and 1.40 (all s, 6 H, Me); 1.83 and 2.08 (both s, 3 H each, NC(C<u>H</u>$_3$)$_2$); 2.80, 2.94, 3.03, and 3.17 (all s, 2 H, PhC<u>H</u>$_2$); 6.45 and 6.66 (bot s, 1 H, OH); 7.17—7.34 (m, 5 H, Ph).

Monoacylhydrazines 7. Triethylamine (1.46 mL, 10 mmol) was added to a solution of the corresponding oxazolidinone **3** (5 mmol) in chloroform (15 mL). The corresponding acid chloride (10 mmol) was added under reflux for 30 min. Then the reaction mixture was heated for 2 h, concentrated, dissolved in toluene, and successively washed with water, a Na_2CO_3 solution, and twice with water. Toluene was partially evaporated, and the product crystallized on cooling. In the case of **7e**, benzene was used instead of chloroform; Ac_2O (10 mmol) was immediately dissolved in benzene (triethylamine was not added). Substrate **3a**, which was subjected to acylation, was added in one portion. The isolation was carried out as described above.

***N*-(4-Hydroxy-4,5,5-trimethyl-2-oxooxazolidin-3-yl)benzamide (7a).** ^{1}H NMR, δ: 1.32, 1.40, and 1.43 (all s, 3 H each, Me); 6.14 (s, 1 H, OH); 7.49—7.65 (m, 3 H, Ph); 7.93 (d, 2 H, Ph, J = 7.5 Hz); 10.46 (s, 1 H, NH).

***N*-(5-Benzyl-4-hydroxy-4,5-dimethyl-2-oxooxazolidin-3-yl)benzamide (7b) (mixture of isomers, 3 : 4).** ^{1}H NMR, δ: 1.10, 1.22, 1.30, and 1.42 (all s, 6 H, Me); 2.81—3.28 (m, 2 H, CH_2); 6.42 and 6.59 (both s, 1 H, OH); 7.21—7.37, 7.51—7.65, and 7.92—7.99 (all m, 10 H, Ar); 10.61 and 10.68 (both s, 1 H, NH).

***N*-[4-Hydroxy-4,5-dimethyl-5-(2-methyl-2-phenylpropyl)-2-oxooxazolidin-3-yl]benzamide (7c).** ^{1}H NMR, δ: 0.86, 1.20, 1.32, and 1.51 (all s, 3 H each, Me); 2.23—2.37 (m, 2 H, CH_2); 6.12 (s, 1 H, OH); 7.18 and 7.59 (both t, 1 H each, Ar, J = 7.5 Hz); 7.33 and 7.50 (both t, 2 H each, Ar, J = 7.5 Hz); 7.46 and 7.91 (both d, 2 H each, Ar, J = 7.5 Hz); 10.40 (s, 1 H, NH).

***N*-(4-Hydroxy-4,5,5-trimethyl-2-oxooxazolidin-3-yl)-3,5-dimethoxybenzamide (7d).** ^{1}H NMR, δ: 1.31, 1.39, and 1.43 (all s, 3 H each, Me); 3.80 (s, 6 H, OMe); 6.18 (s, 1 H, OH); 6.71 (s, 1 H, Ar); 7.12 (s, 2 H, Ar); 10.43 (s, 1 H, NH).

***N*-(4-Hydroxy-4,5,5-trimethyl-2-oxooxazolidin-3-yl)acetamide (7e).** ^{1}H NMR, δ: 1.11 (s, 3 H, 4-Me); 1.18 (s, 6 H, 5-Me); 1.97 (s, 3 H, COMe); 6.03 (s, 1 H, OH); 9.90 (s, 1 H, NH).

Diacylhydrazines 8. Triethylamine (1.46 mL, 15 mmol) and the corresponding acid chloride (15 mmol) were added to a solution of the corresponding oxazolidinone **3** (5 mmol) in toluene (25 mL). The reaction mixture was refluxed for 2 h and then cooled. Ethyl acetate (10 mL) was added to the reaction mixture, and the mixture was successively washed with water, a Na_2CO_3 solution, and twice with water. The solvent was evaporated, and the product was crystallized from benzene.

***N*-Benzoyl-*N*-[5-(2-methyl-2-phenylpropyl)-5-methyl-4-methylene-2-oxooxazolidin-3-yl]benzamide (8a).** ^{1}H NMR, δ: 1.01 (s, 3 H, 5-Me); 1.18 and 1.27 (both s, 3 H each, PhC<u>Me</u>$_2$); 1.94 and 2.36 (both d, 1 H each, CH_2, J = 19.0 Hz); 4.45 and 4.57 (both d, 1 H each, =CH_2, J = 2.1 Hz); 7.12—7.84 (m, 15 H, Ar).

***N*-(3,5-Dimethoxybenzoyl)-*N*-(5,5-dimethyl-4-methylene-2-oxooxazolidin-3-yl)-3,5-dimethoxybenzamide (8b).** ^{1}H NMR, δ: 1.31 (s, 3 H, 4-Me); 1.60 (s, 6 H, 5-Me); 3.78 (s, 12 H, OMe); 4.19 and 4.37 (both d, 1 H each, =CH_2, J = 1.9 Hz); 6.72—6.76 (m, 2 H, Ar); 7.06—7.12 (m, 4 H, Ar).

Tricyclic compounds 9, 10, 11a,b, and 12a,b. Oxazolidinone **3c**, **3d**, **6**, or **7d** or oxadiazinone **4c**,**d** (5 mmol) was dissolved with heating in chloroform (5 mL). Then PPA containing 84% of P_2O_5 (10 mL) was added, and chloroform was removed on a rotary evaporator. The reaction mixture was heated at 100 °C with stirring for 15 min, cooled, and poured onto ice, Then 12 *M* NaOH was added to pH ~9 (in the case of **9**, to pH ~7), and the mixture was extracted with ethyl acetate (2×10 mL). The combined extracts were dried with Na_2SO_4 and concentrated. The products were recrystallized from an appropriate solvent (**9** and **10**, from an EtOAc—MTBE mixture; **11a,b** and **12a,b**, from MTBE).

8,10-Dimethoxy-1,1,10b-trimethyl-1,10b-dihydrooxazolo[4,3-*a*]phthalazine-3,6(5*H*)-dione (9). ^{1}H NMR, δ: 1.12, 1.44, and 1.68 (all s, 3 H each, Me); 3.82 and 3.89 (both s, 3 H each, OMe); 6.84 and 7.11 (both s, 1 H each, Ar); 11.02 (s, 1 H, NH).

1,1,10b-Trimethyl-1,5,6,10b-tetrahydrooxazolo[4,3-*a*]-phthalazin-3-one (10). ^{1}H NMR, δ: 0.85, 1.51, and 1.61 (all s, 3 H each, Me); 3.87 (dd, 1 H, CH_2, J = 0.9 Hz, J = 18.0 Hz); 4.01 (dd, 1 H, CH_2, J = 14.8 Hz, J = 18.0 Hz); 5.43 (dd, 1 H, NH, J = 0.9 Hz, J = 14.8 Hz); 7.16—7.29 (m, 4 H, Ar).

1-Amino-3a,9b-dimethyl-3a,4,5,9b-tetrahydronaphtho-[1,2-*d*]oxazol-2(1*H*)-one (11a). ^{1}H NMR, δ: 1.40 and 1.50 (both s, 3 H each, Me); 1.86—1.94, 2.05—2.12, 2.64—2.72, and 2.79—2.87 (all m, 1 H each, CH_2—CH_2); 4.28 (s, 2 H, NH_2); 7.05—7.15 (m, 1 H, Ar); 7.20—7.24 (m, 2 H, Ar); 7.69—7.76 (m, 1 H, Ar).

1-Amino-3a,5,5,9b-tetramethyl-3a,4,5,9b-tetrahydronaphtho[1,2-*d*]oxazol-2(1*H*)-one (11b). ^{1}H NMR, δ: 1.29 and 1.32 (both s, 3 H each, CMe_2); 1.38 and 1.52 (both s, 3 H each, Me); 1.93 and 2.04 (both d, 1 H each, CH_2, J = 14.5 Hz); 4.41 (s, 2 H, NH_2); 7.10 and 7.27 (both t, 1 H each, Ar, J = 7.6 Hz); 7.41 and 7.82 (both d, 1 H each, Ar, J = 7.6 Hz).

4a,10b-Dimethyl-1,2,4a,5,6,10b-hexahydro-3*H*-naphtho-[1,2-*e*][1,3,4]oxadiazin-3-one (12a). ^{1}H NMR, δ: 1.20 and 1.48 (both s, 3 H each, Me); 1.89—2.13 and 2.59—2.97 (both m, 2 H each, CH_2—CH_2); 5.60 (s, 1 H, NH); 7.00—7.29 (m, 3 H, Ar); 7.68 (d, 1 H, Ar, J = 7.6 Hz); 8.19 (s, 1 H, NH).

4a,6,6,10b-Tetramethyl-1,2,4a,5,6,10b-hexahydro-3*H*-naphtho[1,2-*e*][1,3,4]oxadiazin-3-one (12b). ^{1}H NMR, δ: 1.16, 1.27, 1.35, and 1.44 (all s, 3 H each, Me); 1.96—1.98 (m, 2 H, CH_2); 5.60 (s, 1 H, NH); 7.17—7.25 (m, 2 H, Ar); 7.34 and 7.71 (both d, 1 H each, Ar, J = 7.5 Hz); 8.24 (s, 1 H, NH).

Compounds **11a** and **13** were synthesized from **4c** and **4d**, respectively, under the reaction conditions identical to those described in the previous procedure, with the exceptions that the starting compounds were not predissolved in chloroform, and 100% H_3PO_4 was used instead of PPA. The yields of compounds **11a** and **13** were 58 and 70%, respectively.

***N*-(4-Hydroxy-4,5,5-trimethyl-2-oxooxazolidin-3-yl)urea (14).** Triethylamine (1.46 mL, 10 mmol) was added to a solution of dioxolanone **2a** (0.64 g, 5 mmol) in acetonitrile (10 mL). Semicarbazide hydrochloride (0.56 g, 5 mmol) was dissolved in a minimum amount of water, and this solution was added to the

first solution. The reaction mixture was refluxed with stirring for 3 days. The white crystals that precipitated after cooling were filtered off, washed with petroleum ether, and dried. ^{1}H NMR, δ: 1.24 (s, 6 H, Me); 1.81 (s, 3 H, Me); 4.77 (s, 1 H, OH); 6.24 (s, 2 H, NH_2); 8.75 (s, 1 H, NH).

3-Amino-5,5-dimethyl-4-methyleneoxazolidin-2-one (15). Compound **3a** (1.60 g, 10 mmol) was added to a solution of dioxolanone **2a** (1.28 g, 10 mmol) in acetonitrile (10 mL). The reaction mixture was placed in an autoclave and heated at 150 °C (under a pressure of 60 atm) for 40 h. The product was isolated by column chromatography using benzene as the eluent. ^{1}H NMR, δ: 1.45 (s, 6 H, Me); 4.12 and 4.30 (both s, 1 H each, $=CH_2$); 4.86 (s, 2 H, NH_2).

5,5′-Dibenzyl-4,4′-dihydroxy-4,4′,5,5′-tetramethyl-3,3′-bioxazolidine-2,2′-dione (16). Ethyl chloroformate (10 mmol) was added to a solution of oxazolidinone **3b** (1.18 g, 5 mmol) in toluene (25 mL). The reaction mixture was refluxed for 1 h and then ethyl acetate (10 mL) was added. The mixture was successively washed with water, a Na_2CO_3 solution, and twice with water. The solvent was evaporated, and the product was recrystallized from MTBE. ^{1}H NMR of compound **16** (mixture of isomers), δ: 1.11, 1.29, 1.37, 1.48, and 1.53 (all s, 12 H, Me); 2.85—3.07 and 3.33—3.41 (both m, 4 H, CH_2); 5.98, 6.00, and 6.25 (all s, 2 H, OH); 7.20—7.42 (m, 10 H, Ph).

References

1. J. M. Joumier, R. Grainger, Ch. Bruneau, and P. H. Dixneuf, *Synlett*, 1993, **6**, 423.
2. N. B. Chernysheva, A. A. Bogolyubov, and V. V. Semenov, *Khim. Geterotsikl. Soedin.*, 2003, 1212 [*Chem. Heterocycl. Compd.*, 2003 (Engl. Transl.)].
3. Y. Gohee, A. Boucherle, and M. Robin, *Eur. J. Med. Chem. — Chim. Ther.*, 1986, **21**, 403.
4. B. Fuchs and M. Rosenblum, *J. Am. Chem. Soc.*, 1968, **90**, 1061.
5. N. B. Chernysheva, A. A. Bogolyubov, and V. V. Semenov, *Khim. Geterotsikl. Soedin.*, 1999, 241 [*Chem. Heterocycl. Compd.*, 1999, **35** (Engl. Transl.)].
6. I. Yu. Titov, N. B. Chernysheva, Yu. B. Chudinov, A. A. Bogolyubov, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 548 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 569].
7. Yu. B. Chudinov, S. B. Gashev, N. B. Chernysheva, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 2006, 119 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 123].
8. R. J. Tadeschi, A. W. Casey, G. S. Clark, R. W. Huckel, L. M. Kindley, and J. P. Russel, *J. Org. Chem.*, 1963, **28**, 1740.
9. Germ. Pat. 1.098.953; *Chem. Abstr.*, 1962, **56**, 2453b.
10. J. M. Joumier, J. Fournier, Ch. Bruneau, and P. H. Dixneuf, *J. Chem. Soc., Perkin Trans. 1*, 1991, 3271.
11. Yu. B. Chudinov, S. B. Gashev, Yu. A. Strelenko, Z. A. Starikova, M. Yu. Antipin, and V. V. Semenov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 133 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, No. 1].

Received September 25, 2006;
in revised form November 2, 2006