Synthesis of 5-[bromo(aryl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-ones*

V. A. Mamedov,[a,b] V. L. Mamedova,[a,b] G. Z. Khikmatova,[a,b] D. B. Krivolapov,[a] and I. A. Litvinov[a]*

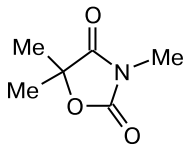
[a]*A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center of the Russian Academy of Sciences, 8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation. Fax: +7 (843) 275 532. E-mail: mamedov@iopc.ru*

[b]*Kazan National Research Technological University, 68 ul. K. Marksa, 420015 Kazan, Russian Federation*

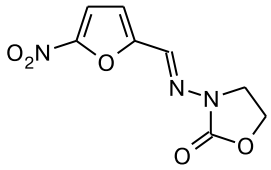
A Darzens condensation of α-chloroacetamide with aromatic aldehydes furnished a series of 3-aryl-2,3-epoxypropionamides, which were further converted to 5-[bromo(aryl)methyl]-2,2-dimethyl-1,3-oxazolidin-2-ones.

Key words: 3-aryl-2,3-epoxypropionamides, 3-bromo-2-hydroxy-3-arylpropionamides, 5-[bromo(aryl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-ones, 5-(arylidene)-2,2-dimethyl-1,3-oxazolidin-4-ones, diastereomers, X-ray diffraction analysis.

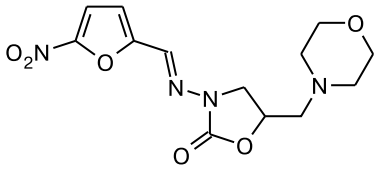
An oxazolidine ring is a part of such pharmaceutical drugs as trimethin[1] (anticonvulsant), furazolidone and furazoline[2] (antimicrobial agents), linezolid[3] (synthetic antibiotic). An oxazolidine ring in the composition of fused polycyclic systems is a part of ergotamine and bromocriptine, which are widely used in obstetric and gynecological practice,[2] as well as in quinocarcin suggested[4] for treatment of leukemia. *N*-(2-Chloroethyl)oxazolidin-2-one is a metabolite of antitumor agent cyclophosphane (Scheme 1), whereas benzoxazolidin-2-one



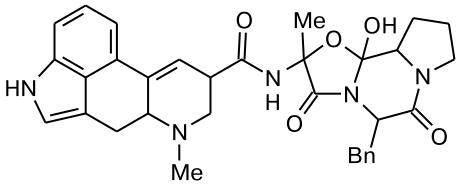
Trimethin



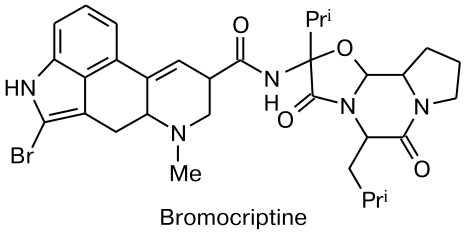
Furazolidone



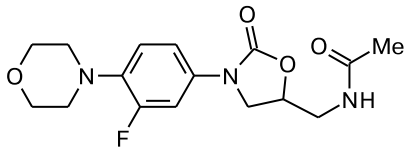
Furazoline



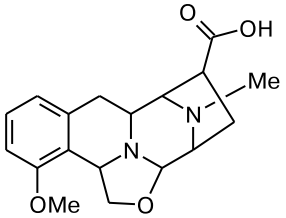
Ergotamine



Bromocriptine



Linezolid

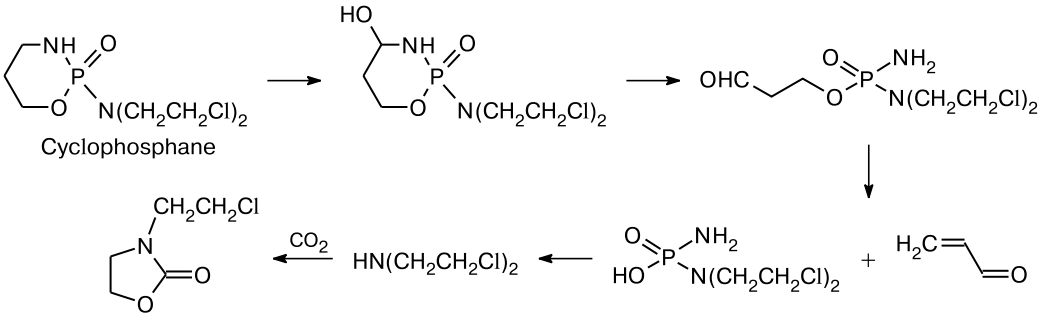


Quinocarcin

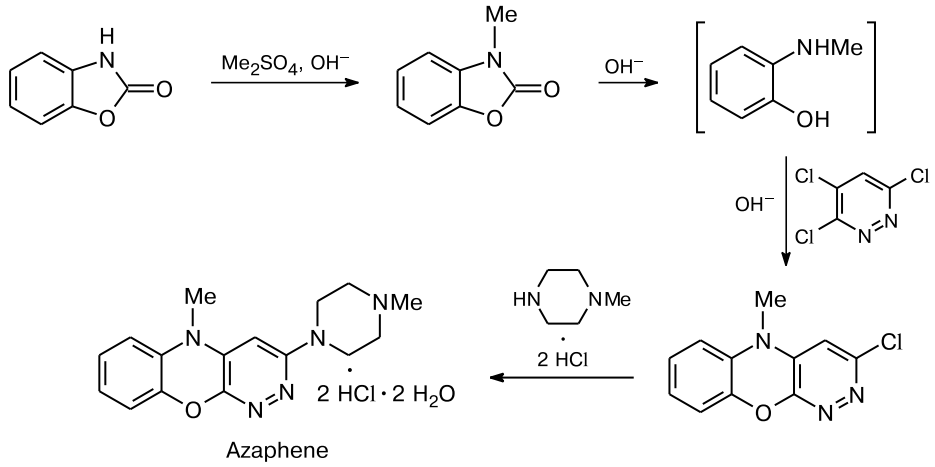
* Dedicated to Academician of the Russian Academy of Sciences O. G. Sinyashin on the occasion of his 60th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 5, pp. 1260—1267, May, 2016.

Scheme 1



Scheme 2

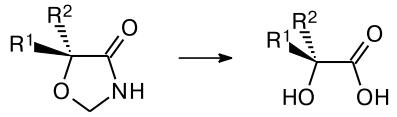


was used in the synthesis of antidepressant azaphene (Scheme 2).[1]

1,3-Oxazolidin-4-ones are of interest not only from the point of view of their biological activity, but also as the starting compounds for the preparation of α-hydroxy acids.[5—8] The last mentioned compounds are widely used in synthetic organic chemistry,[9] and there is no doubt in the importance of the development of simple methods for the preparation of their various representatives. Due to the development of asymmetric synthesis, the interest to oxazolidin-4-one derivatives with chiral C(5) atom has grown. It was shown[7,8] that hydrolysis of enantiopure oxazolidinone derivatives occurred with retention of configuration at atom C(5) and the formation of enantiopure forms of α-hydroxy acids (Scheme 3).

1,3-Oxazolidin-4-ones are commonly obtained upon treatment of α-hydroxy acid anilides with carbonyl compounds.[10—15] This method, which uses available and inexpensive starting material, gives oxazolidinones with a limited set of substituents at position 5. However, these are the substituents, which determine the variety of α-hydroxy acids obtained from oxazolidines, therefore, the development of simple approaches to the synthesis of new 5-substituted oxazolidine derivatives from available material is an actual problem. In the present work, we describe the synthesis (Scheme 4) of 5-[bromo(aryl)methyl]-2,2-dimethyloxazolidin-4-ones **3** from 3-aryl-2,3-epoxypropionamides **1**. The last mentioned compounds, in turn, are easily obtained by the reaction of chloroacetamide with aromatic aldehydes under mild conditions of Darzens reaction.

Scheme 3



Results and Discussion

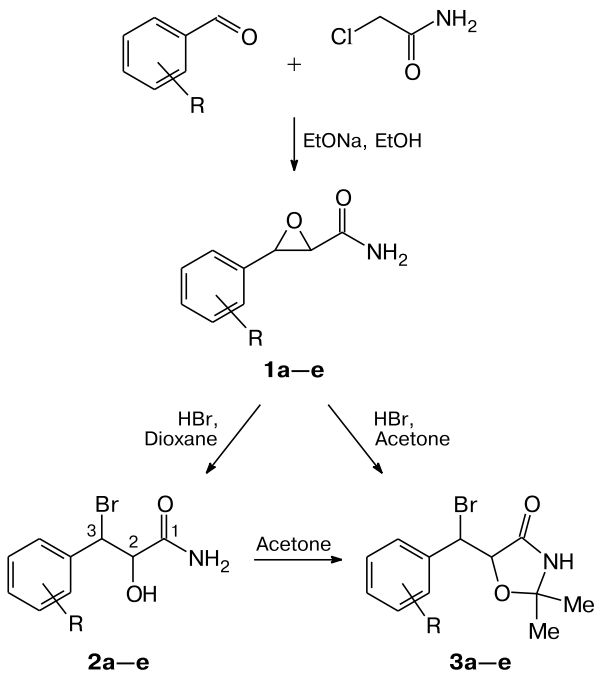
3-Aryl-2,3-epoxypropionamides **1a—e** (Scheme 4, Table 1) were synthesized under conditions of Darzens condensation (NaOEt, NaOH) at room temperature from the corresponding aromatic aldehydes and α-chloroacetamide. Under these conditions, epoxypropionamides are predominantly obtained as *E*-isomers.[16]

Table 1. Synthesis of 3-aryl-2,3-epoxypropionamides **1a—e**

Compound	Yield (%)	Ratio[a] *Z* : *E*	Yield of isomers[b] (%)	
			Z	*E*
1a[17,18]	92	1 : 2	20	58
1b	98	1 : 5	—[c]	79
1c	87	1 : 5	—[d]	69
1d	99	0 : 1	—	99
1e	100	0 : 1	—	100

[a] ^{1}H NMR spectroscopy data.
[b] Yields of isolated isomers.
[c] After isolation of *E*-isomer, a mixture of *Z*-**1b** : *E*-**1b** = 1 : 1 was obtained in 19% yield.
[d] After isolation of *E*-isomer, a mixture of *Z*-**1c** : *E*-**1c** = 1 : 1 was obtained in 18% yield.

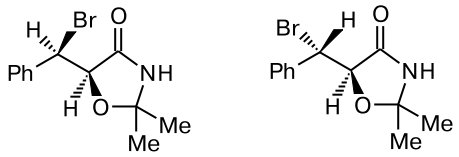
Scheme 4



1—3: R = H (**a**), 4-Br (**b**), 3-MeO (**c**), 4-F_3C (**d**), 2-O_2N (**e**)

In the preceding works,[16,19] we studied the behavior of 3-aryl-2,3-epoxypropionanilides under acidic conditions. These compounds treated with HBr in acetone at room temperature were quantitatively converted to anilides (depending on the substituent in the aryl fragment) of 3-bromo-2-hydroxy-3-phenylpropionic, 2-bromo-3-hydroxy-3-phenylpropionic, or 3-arylpyruvic acids.[17] 3-Bromo-2-hydroxy-3-phenylpropionanilide heated to 100 °C in dimethyl sulfate in the presence of sulfuric acid underwent intramolecular Friedel—Crafts reaction with the migration of the aryl group and aromatization of the bicyclic system with the formation of 3-arylquinolin-2-ones, which are analogs of natural alkaloid compounds. The same result was obtained when 3-aryl-2,3-epoxypropionanilides were treated with sulfuric acid upon heating in dimethyl sulfate or refluxed in benzene with azeptropic removal of water.[16] In the present work, replacing an anilide fragment in the starting compounds with the amide group, we exclude a possibility of the formation of the quinoline systems.

Amides of (*E*)-3-aryl-2,3-epoxypropionic acid *E*-**1**, like its anilides,[19] were treated with HBr in acetone at room temperature for 1 h (see Scheme 4). The reaction of *E*-**1a** with HBr in acetone for 24 h led to a mixture of *syn*- (δ 4.82, 5.41 (both d, J = 2.6 Hz)) and *anti*-diastereomers (δ 4.63, 5.44 (both d, J = 1.7 Hz)) of oxazolidinone **3a** in about 1 : 1 ratio. The diastereomer *anti*-**3a** crystallized from the reaction mixture within several minutes after addition of water, whereas diastereomer *syn*-**3a**, only after 24 h. Amides *E*-**1b** and *E*-**1c** under similar conditions gave mixtures of compounds containing both the hydrobrominated products and oxazolidinones. The reactions of *E*-**1d**,**e** with HBr and acetone for 24 h at room temperature proceeded diastereoselectively with the formation of only *syn*-diastereomers **3d**,**e**. The structure of *syn*-**3e** was established by X-ray diffraction analysis (Fig. 1).



syn-**3a** *anti*-**3a**

The conversion of arylepoxypropionamides **1** to oxazolidinones **3** proceeds through hydrobrominated deriva-

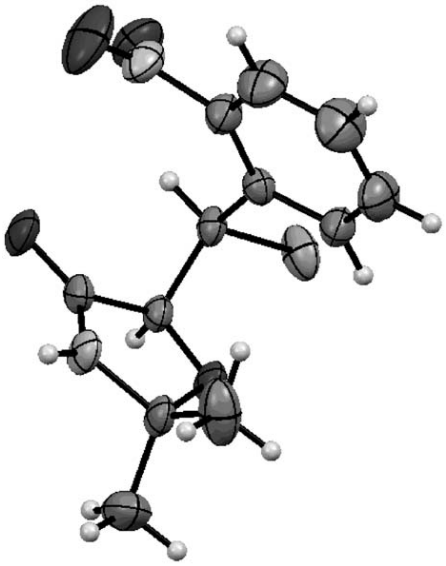


Fig. 1. Molecular geometry of *syn*-5-[bromo(2-nitrophenyl)-methyl]-2,2-dimethyloxazolidin-4-one (*syn*-**3e**) in crystal according to the X-ray diffraction data.

Table 2. Synthesis of 3-aryl-3-bromo-2-hydroxypropionamides **2a—e**

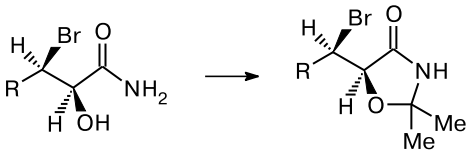
Compound	Yield (%)	Ratio[a] *syn* : *anti*	Yield of isomers[b] (%)	
			syn	*anti*
2a	98	1 : 1	35	42
2b	83	1 : 1	35	32
2c	85	4 : 1	65	16
2d	100	1 : 0	100	0
2e	92	1 : 0	92	0

[a] ^{1}H NMR spectroscopy data.
[b] Yields of isolated diastereomers.

tives **2** of starting epoxides (see Scheme 4). Compounds **2a—e** (Table 2) were obtained by the reaction of the corresponding epoxides with HBr in dioxane. These compounds have two chiral centers and can exist in two diastereomeric forms, easily distinguished by the signals for protons H(2) and H(3) in the NMR spectra. The assignment of the signals to *syn*- or *anti*-diastereomers was made as described earlier.[19] Each of the diastereomers **2a—c** was isolated in the individual state, whereas compounds **2d** and **2e** were obtained in the reactions only as *syn*-diastereomers (see Table 2).

The conditions for the cyclization of 3-bromo-2-hydroxypropionamides **2** to oxazolidinones **3** were optimized using *syn*-**2a** as a model. The reaction was carried out for 24 h in acetone either without acid or with the addition of HBr, H_2SO_4, or AcOH. In the absence of acid, the reaction diastereoselectively proceeded on 77% (^{1}H NMR spectral data), when an acid was added, the reactions proceeded quantitatively and also diastereoselectively. The cyclization of compounds **2b—e** was carried out in acetone with the addition of H_2SO_4. The reactions were diastereoselective: the oxazolidinones obtained from *syn*-**2** were assigned to *syn*-**3** (Scheme 5), whereas *anti*-**2** gave rise to *anti*-**3** (Table 3).

Scheme 5



syn-**2a—e** *syn*-**3a—e**

2, 3: R = Ph (**a**), 4-BrC_6H_4 (**b**), 3-$MeOC_6H_4$ (**c**), 4-$F_3CC_6H_4$ (**d**), 2-$O_2NC_6H_4$ (**e**)

Conditions: H_2SO_4, acetone, ~20 °C, 24 h.

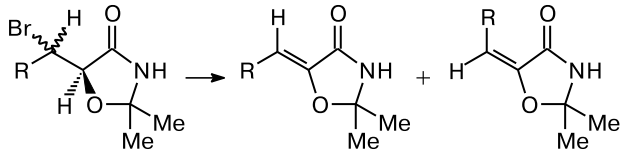
Figure 1 shows the geometry of compound *syn*-**3e** obtained directly from *E*-**1e** without isolation of the intermediate product **2e** (see Scheme 4). ^{1}H NMR and other characteristics of this product and the product obtained from the only isolated from the reaction with HBr in dioxane diastereomer **2e** are identical. This confirms the correctness of the assignment to diastereomer **2e** of *syn*-configuration (see Table 2).

Table 3. Yields of 5-(α-bromobenzyl)-2,2-dimethyl-1,3-oxazolidin-4-ones **3a—e**

Amide	Oxazolidinone	Yield (%)
syn-**2a**	*syn*-**3a**	98
anti-**2a**	*anti*-**3a**	90
syn-**2b**	*syn*-**3b**	96
anti-**2b**	*anti*-**3b**	92
syn-**2c**	*syn*-**3c**	88
anti-**2c**	*anti*-**3c**	92
syn-**2d**	*syn*-**3d**	89
syn-**2e**	*syn*-**3e**	92

Further, we made an attempt to transform the bromoarylmethyl substituent at position 5 of oxazolidine cycle. Stirring the solution of *anti*-**3a** in MeOH with K_2CO_3 for 3 h at room temperature led to the formation of (*Z*)-5-(benzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (*Z*-**4a**) (Scheme 6, Table 4), the structure of which was established by X-ray diffraction study (Fig. 2).

Scheme 6*



3a—e *Z*-**4a,c** *E*-**4a—e**

* Substituents R and configurations of starting compounds **3a—e** and products **4** are given in Table 4.

Similar conversions were carried out for *syn*-**3a—e** and *anti*-**3a**,**c** (see Table 4). The products were assigned to

Table 4. Synthesis of 5-(arylidene)-2,2-dimethyl-1,3-oxazolidin-4-ones **4a—e** and chemical shifts (δ_H) for the proton of the RCH=C group in the ^{1}H NMR spectra (DMSO-d_6)

Starting compound	Product	R	Yield (%)	δ_H (s)
syn-**3a**	*E*-**4a** + *Z*-**4a***	Ph	73	6.20, 6.04
anti-**3a**	*Z*-**4a**	Ph	89	6.04
syn-**3b**	*E*-**4b**	4-BrC_6H_4	83	6.18
syn-**3c**	*E*-**4c**	3-$MeOC_6H_4$	79	6.18
anti-**3c**	*Z*-**4c**	3-$MeOC_6H_4$	92	6.00
syn-**3d**	*E*-**4d**	4-$F_3CC_6H_4$	100	6.28
syn-**3e**	*E*-**4e**	2-$O_2NC_6H_4$	100	6.29

* The ratio of isomers *E*-**4a** : *Z*-**4a** = 4 : 1 (^{1}H NMR spectral data).

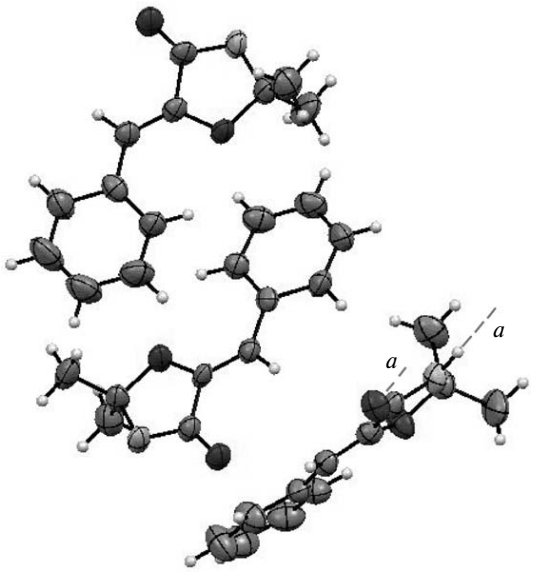


Fig. 2. Geometries of three independent molecules of (*Z*)-5-benzylidene-2,2-dimethyloxazolidin-4-one (*Z*-**4a**) in crystal according to the X-ray diffraction data.

Z- or *E*-isomers comparing their ^{1}H NMR spectra with the spectrum of *Z*-**4a**, whose structure was known (see Fig. 2). The spectra of the products contained mainly one signal corresponding to the proton at the double bond that indicates the stereoselective character of the processes. In the spectrum of the product obtained from *syn*-**3a**, the proton at the double bond is represented by two signals with different intensities that is apparently explained by the formation of both isomers *Z*-**4a** and *E*-**4a** (see Table 4).

In conclusion, in the presents the work we have developed an efficient method for diastereoselective synthesis of 5-[bromo(aryl)methyl}-2,2-dimethyl-1,3-oxazolidin-4-ones, the representatives of pharmaceutically important class of compounds.

Experimental

Melting points were determined using a Stuart SMP-10 appliance. IR spectra were obtained on a Bruker Vector-22 spectrometer in Nujol. ^{1}H NMR spectra were recorded on a Bruker Avance-600 spectrometer in DMSO-d_6.

X-ray diffraction studies of crystals of *syn*-**3e** and *Z*-**4a** grown in ethanolic solutions were carried out on a Bruker Kappa Apex II diffractometer (graphite monochromator, λMoKα = 0.71073 Å) at 20 °C. Semi-empirical correction for absorption was performed using the SADABS[20] program. The structures were solved by direct method using the SHELX[21] program. Nonhydrogen atoms were refined in isotropic and then in anisotropic approximation using the SHELX[21] program. Hydrogen atoms were placed in calculated positions and refined using a riding model. The position of the hydrogen atom at the nitrogen atom in compound *syn*-**3e** was found from the difference Fourier series and refined in isotropic approximation in both structures. All the calculations were carried out using the WinGX[22] and APEX2[23] programs. Crystals of *syn*-**3e**, $C_{12}H_{13}BrN_2O_4$, are monoclinic. At 20 °C a = 11.809(2), b = 13.814(3), c = 9.2415(18) Å, β = 110.38(3)°, V = 1413.2(6) Å^3, Z = 4, d_{calc} = 1.547 g cm^{-3}, space group $P2_1/n$, μMo = 29.20 cm^{-1}. There were measured intensities of 12037 reflections, 2263 of which were with $I \geq 2\sigma$. The final divergence factors were as follows: R = 0.0388, R_w = 0.0786. Crystals *Z*-**4a**, $C_{12}H_{13}NO_2$, are monoclinic. At 20 °C a = 19.966(18), b = 11.132(10), c = 15.339(14) Å, β = 97.743(15)°, V = 3378(5) Å^3, Z = 12 (there are three independent molecules in the asymmetric part), d_{calc} = 1.199 g cm^{-3}, space group $P2_1/c$, μMo = 0.82 cm^{-1}. There were measured intensities of 6628 reflections, 2220 of which were with $I \geq 2\sigma$. The final divergence factors were as follows: R = 0.1268, R_w = 0.2325. The X-ray diffraction data were deposited with the Cambridge Crystallographic Data Center (CCDC 1438779 (*syn*-**3e**) and CCDC 1438778 (*Z*-**4a**).

3-Aryl-2,3-epoxypropionamides (1a—e) were obtained similarly to the procedure described earlier[19] for the anilides of this acid. Equimolar amounts of α-chloroacetamide and the corresponding benzaldehyde were mixed in EtOH at room temperature, then an equimolar amount of NaOEt in EtOH was added, and the reaction mixture was stirred for 5 h. A precipitate formed was filtered, washed with water, and dried in air. An additional amount of the precipitate was collected from the water—ethanol filtrates after 15 h by filtration, washed with water, and dried. Both precipitates corresponded to the product and were combined. Compounds **1a—c** were obtained as mixtures of *Z*- and *E*-isomers. Isomers *E*-**1a—c** were isolated by washing these mixtures with diethyl ether on a Schott funnel. The filtrates obtained after washing the mixtures of isomers were concentrated, the residues were washed with Et_2O once more, and after evaporation of the solvent, the individual *Z*-**1a** and mixtures of *Z*- and *E*-isomers of compounds **1b**,**c** with the ratio of $Z : E$ = 1 : 1 were isolated. The yields of the products and the ratios of *Z*- and *E*-isomers (in the initial mixtures) are given in Table 1.

(*E*)-2,3-Epoxy-3-phenylpropionamide (*E*-1a). M.p. 142—144 °C (*cf.* Ref. 17: 148 °C; *cf.* Ref. 18: 149.5—150 °C). Found (%): C, 66.14; H, 5.52; N, 8.60. $C_9H_9NO_2$. Calculated (%): C, 66.25; H, 5.56; N, 8.58. IR, ν/cm^{-1}: 1670 (C=O), 3405 (NH_2). ^{1}H NMR, δ: 3.51, 4.03 (both d, 1 H each, H(2), H(3), J = 1.7 Hz); 7.28—7.42 (m, 5 H, Ph); 7.43, 7.61 (both br.s, 1 H each, NH_2).

(*Z*)-2,3-Epoxy-3-phenylpropionamide (*Z*-1a). M.p. 139—140 °C. Found (%): C, 66.32; H, 5.58; N, 8.57. $C_9H_9NO_2$. Calculated (%): C, 66.25; H, 5.56; N, 8.58. IR, ν/cm^{-1}: 1668 (C=O), 3408 (C(O)NH_2). ^{1}H NMR, δ: 3.74, 4.29 (both d, 1 H each, H(2), H(3), J = 4.5 Hz); 7.19 (br.s, 1 H, C(O)NH_2); 7.20—7.45 (m, 6 H, Ph and NH).

(*E*)-2,3-Epoxy-3-(4-bromophenyl)propionamide (*E*-1b). M.p. 178—179 °C. Found (%): C, 44.59; H, 3.32; Br, 33.08; N, 5.73. $C_9H_8BrNO_2$. Calculated (%): C, 44.66; H, 3.33; Br, 33.01; N, 5.79. IR, ν/cm^{-1}: 1661 (C=O), 3459 (C(O)NH_2). ^{1}H NMR, δ: 3.50, 4.01 (both d, 1 H each, H(2); H(3), J = 1.7 Hz); 7.27, 7.54 (both d, 2 H each, Ar, J = 8.4 Hz); 7.42, 7.68 (both br.s, 1 H each, NH_2). The signals for *Z*-**1b** in the ^{1}H NMR spectrum (a mixture of *Z*-**1b** : *E*-**1b** = 1 : 1), δ: 3.75, 4.28 (both d, 1 H each, H(2), H(3), J = 5.0 Hz); 7,19, 7.43 (both br.s, 1 H each, NH_2); 7.35, 7.51 (both d, 2 H each, Ar, J = 8.4 Hz).

(*E*)-2,3-Epoxy-3-(3-methoxyphenyl)propionamide (*E*-1c). M.p. 130—131 °C. $C_{10}H_{11}NO_3$. Found (%): C, 62.08; H, 5.71; N, 7.27. Calculated (%): C, 62.17; H, 5.74; N, 7.25. IR, ν/cm^{-1}: 1641 (C=O), 3392 (C(O)NH_2). ^{1}H NMR, δ: 3.50, 3.99 (both d,

1 H each, H(2), H(3), J = 1.9 Hz); 3.68 (s, 3 H, OMe); 6.87 (s, 1 H, H(2), Ar); 6.90 (br.d, 2 H, H(4) and H(6), Ar); 7.25 (dd, 1 H, H(5), Ar, J = 8.1 Hz, J = 7.9 Hz). The signals for *Z*-**1c** in the ^{1}H NMR spectrum (a mixture of *Z*-**1c** : *E*-**1c** = 1 : 1), δ: 3.73, 4.25 (both d, 1 H each, H(2), H(3), J = 4.9 Hz); 3.67 (s, 3 H, OMe); 6.89 (s, 1 H, H(2), Ar), 6.93 (br.d, 2 H, H(4) and H(6), Ar); 7.18, 7.50 (both br.s, 1 H each, NH_2); 7.19 (dd, 1 H, H(5), Ar, J = 7.9 Hz).

(*E*)-2,3-Epoxy-3-(4-trifluoromethylphenyl)propionamide (*E*-1d). M.p. 171—172 °C. Found (%): C, 51.90; H, 3.42; F, 24.87; N, 6.09. $C_{10}H_8F_3NO_2$. Calculated (%): C, 51.96; H, 3.49; F, 24.65; N, 6.06. IR, ν/cm^{-1}: 1672 (C=O), 3423 (C(O)NH_2). ^{1}H NMR, δ: 3.53, 4.17 (both d, 1 H each, H(2), H(3), J = 1.6 Hz); 7.47, 7.65 (both br.s, 1 H each, NH_2); 7.57, 7.74 (both d, 2 H each, Ar, J = 8.1 Hz).

(*E*)-2,3-Epoxy-3-(2-nitrophenyl)propionamide (*E*-1e). M.p. 209—210 °C. Found (%): C, 52.02; H, 3.85; N, 13.43. $C_9H_8N_2O_4$. Calculated (%): C, 51.93; H, 3.87; N, 13.46. IR, ν/cm^{-1}: 1665 (C=O), 3185, 3368 (C(O)NH_2). ^{1}H NMR, δ: 3.39, 4.52 (both d, 1 H each, H(2), H(3), J = 1.9 Hz); 7.48, 7.69 (both br.s, 1 H each, NH_2); 7.53 (d, 1 H, H(6), Ar, J = 7.7 Hz); 7.65 (ddd, 1 H, H(4), Ar, J = 8.1 Hz, J = 7.8 Hz, J = 1.2 Hz); 7.82 (ddd, 1 H, H(5), Ar, J = 7.8 Hz, J = 7.8 Hz, J = 1.0 Hz); 8.18 (dd, 1 H, H(3), Ar, J = 8.1 Hz, J = 1.0 Hz).

3-Aryl-3-bromo-2-hydroxypropionamides (2a—e) were obtained similarly to the procedure described earlier[19] for anilides of this acid in dioxane as a solvent. *syn*-Diastereomers crystallized in the reaction mixture within 1 h. The products were filtered, washed with water, and dried. Diastereomers *anti*-**2a—c** were isolated from the water—dioxane filtrates after 24 h.

***syn*-3-Bromo-2-hydroxy-3-phenylpropionamide (*syn*-2a).** M.p. 145—146 °C. Found (%): C, 44.38; H, 4.01; Br, 32.31; N, 5.35. $C_9H_{10}BrNO_2$. Calculated (%): C, 44.29; H, 4.13; Br, 32.74; N, 5.74. IR, ν/cm^{-1}: 1656 (C=O), 3186, 3381 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.42, 5.37 (both d, 1 H each, H(2), H(3), J = 5.7 Hz); 7.17, 7.37 (both br.s, 1 H each, NH_2); 7.23—7.50 (m, 5 H, Ph).

***anti*-3-Bromo-2-hydroxy-3-phenylpropionamide (*anti*-2a).** M.p. 146—147 °C. Found (%): C, 44.21; H, 4.02; Br, 32.70; N, 5.79. $C_9H_{10}BrNO_2$. Calculated (%): C, 44.29; H, 4.13; Br, 32.74; N, 5.74. IR, ν/cm^{-1}: 1682 (C=O), 3187, 3334, 3435 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.14, 5.49 (both d, 1 H each, H(2) and H(3), J = 2.8 Hz); 7.26—7.55 (m, 7 H, Ph, NH_2).

***syn*-3-Bromo-3-(4-bromophenyl)-2-hydroxypropionamide (*syn*-2b).** M.p. 150—151 °C. Found (%): C, 33.58; H, 2.78; Br, 49.35, N, 4.50. $C_9H_9Br_2NO_2$. Calculated (%): C, 33.47; H, 2.81; Br, 49.48; N, 4.34. IR, ν/cm^{-1}: 1673 (C=O), 3140, 3341, 3442 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.39, 5.37 (both d, 1 H each, H(2) and H(3), J = 5.2 Hz); 7.18, 7.35 (both br.s, 1 H each, NH_2); 7.41, 7.49 (both d, 2 H each, Ar, J = 8.1 Hz).

***anti*-3-Bromo-3-(4-bromophenyl)-2-hydroxypropionamide (*anti*-2b).** M.p. 149—150 °C. Found (%): C, 33.25; H, 2.58; Br, 49.29; N, 4.38. $C_9H_9Br_2NO_2$. Calculated (%): C, 33.47; H, 2.81; Br, 49.48; N, 4.34. IR, ν/cm^{-1}: 1689 (C=O), 3283, 3375 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.11, 5.48 (both d, 1 H each, H(2) and H(3), J = 2.9 Hz); 7.35, 7.41 (both br.s, 1 H each, NH_2); 7.49, 7.52 (both d, 2 H each, Ar, J = 8.1 Hz).

***syn*-3-Bromo-2-hydroxy-3-(3-methoxyphenyl)propionamide (*syn*-2c).** M.p. 123—124 °C. Found (%): C, 43.57; H, 4.38; Br, 28.95; N, 5.15. $C_{10}H_{12}BrNO_3$. Calculated (%): C, 43.82; H, 4.41; Br, 29.15; N, 5.11. IR, ν/cm^{-1}: 1662 (C=O), 3189, 3375 (OH, C(O)NH_2). ^{1}H NMR, δ: 3.74 (s, 3 H, OMe); 4.41, 5.33 (both d, 1 H each, H(2) and H(3), J = 5.7 Hz); 6.85 (dd, 1 H, H(4), Ar, J = 8.1 Hz, J = 1.7 Hz); 7.03 (d, 1 H, H(6), Ar, J = 7.9 Hz); 7.04 (s, 1 H, H(2), Ar); 7.19, 7.39 (both br.s, 1 H each, NH_2); 7.22 (dd, 1 H, H(5), Ar, J = 8.1 Hz, J = 7.9 Hz).

***anti*-3-Bromo-2-hydroxy-3-(3-methoxyphenyl)propionamide (*anti*-2c).** M.p. 129—130 °C. Found (%): C, 43.89; H, 4.32; Br, 29.28; N, 5.18. $C_{10}H_{12}BrNO_3$. Calculated (%): C, 43.82; H, 4.41; Br, 29.15; N, 5.11. IR, ν/cm^{-1}: 1651 (C=O), 3289, 3385 (OH, C(O)NH_2). ^{1}H NMR, δ: 3.55 (s, 3 H, OMe); 4.14, 5.46 (both d, 1 H each, H(2) and H(3), J = 2.9 Hz); 6.87 (dd, 1 H, H(4), Ar, J = 8.1 Hz, J = 1.9 Hz); 7.10 (d, 1 H, H(6), Ar, J = 8.1 Hz); 7.13 (s, 1 H, H(2), Ar); 7.25 (dd, 1 H, H(5), Ar, J = 8.1 Hz); 7.33, 7.41 (both br.s, 1 H each, NH_2).

***syn*-3-Bromo-2-hydroxy-3-(4-trifluoromethylphenyl)propionamide (*syn*-2d).** M.p. 144—145 °C. Found (%): C, 38.38; H, 2.89; Br, 25.66; F, 18.21; N, 4.52. $C_{10}H_9BrF_3NO_2$. Calculated (%): C, 38.49; H, 2.91; Br, 25.60; F, 18.26; N, 4.49. IR, ν/cm^{-1}: 1665 (C=O), 3189, 3396 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.43, 5.44 (both d, 1 H each, H(2) and H(3), J = 5.2 Hz); 7.19, 7.38 (both br.s, 1 H each, NH_2); 7.60—7.70 (m, Ar).

***syn*-3-Bromo-2-hydroxy-3-(2-nitrophenyl)propionamide (*syn*-2e).** M.p. 167—168 °C. Found (%): C, 37.56; H, 3.12; Br, 27.58; N, 9.72. $C_9H_9BrN_2O_4$. Calculated (%): C, 37.39; H, 3.14; Br, 27.64; N, 9.69. IR, ν/cm^{-1}: 1524 (NO_2), 1681 (C=O), 3317, 3441 (OH, C(O)NH_2). ^{1}H NMR, δ: 4.48, 5.79 (both d, 1 H each, H(2) and H(3), J = 6.6 Hz); 7.23, 7.50 (both br.s, 1 H each, NH_2); 7.54 (dd, 1 H, H(5), Ar, J = 8.2 Hz, J = 7.7 Hz); 7.71 (dd, 1 H, H(4), Ar, J = 7.2 Hz); 7.83 (d, 1 H, H(6), Ar, J = 8.2 Hz); 7.99 (d, 1 H, H(3), Ar, J = 7.7 Hz).

Synthesis of 5-[bromo(aryl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-ones (3a—e). ***A.*** A 47% aqueous HBr (10 mL) was added to a solution of *E*-3-aryl-2,3-epoxypropionamide **1** (1 mmol) in acetone (10 mL). The solution was allowed to stand at room temperature for 24 h and poured into water (20 mL). A precipitate formed within 1 h was filtered, washed with water, and dried in air. This procedure was used to obtain *syn*-**3d** (0.35 g, 99%) and *syn*-**3e** (0.32 g, 98%). The product *syn*-**3a** (0.04 g, 14%)) was isolated from the water—acetone mixture after 15 min. The next portion of the precipitate collected after 1 h was a 3 : 1 mixture of *syn*-**3a** and *anti*-**3a** (0.13 g, 46%). A precipitate formed after 24 h corresponded to *anti*-**3a** (0.10 g, 36%).

B. A solution of the corresponding amide **2a—e** (1 mmol) in acetone (10 mL) and concentrated H_2SO_4 (0.1 mL) was allowed to stand for 24 h at room temperature and poured into water (30 mL). A precipitate formed was filtered, washed with water, and dried in air. The yields of obtained products **3** are given in Table 3.

Characteristics of the same compounds obtained by alternative procedures were identical.

***syn*-5-[Bromo(phenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*syn*-3a).** M.p. 192—194 °C. Found (%): C, 50.53; H, 5.02; Br, 28.27; N, 4.91. $C_{12}H_{14}BrNO_2$. Calculated (%): C, 50.72; H, 4.97; Br, 28.12; N, 4.93. IR, ν/cm^{-1}: 1684, 1722 (C=O), 3437 (C(O)NH). ^{1}H NMR, δ: 1.12, 1.34 (both s, 3 H each, 2 Me); 4.83, 5.41 (both d, 1 H each, 2 CH, J = 3.0 Hz); 7.26—7.32 (m, 3 H, H(3), H(4) and H(5), Ph); 7.51 (d, 2 H, H(2) and H(6), Ph, J = 6.6 Hz); 8.95 (br.s, 1 H, NH).

***anti*-5-[Bromo(phenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*anti*-3a).** M.p. 148—149 °C. Found (%): C, 50.90; H, 4.98; Br, 28.18, N, 4.79. $C_{12}H_{14}BrNO_2$. Calculated (%): C, 50.72; H, 4.97; Br, 28.12; N, 4.93. IR, ν/cm^{-1}: 1710 (C=O), 3213,

3265 (C(O)NH). ^{1}H NMR, δ: 1.41, 1.55 (both s, 3 H each, 2 Me); 4.63, 5.44 (both d, 1 H each, 2 CH, J = 1.7 Hz); 7.28—7.33 (m, 3 H, H(3), H(4) and H(5), Ph); 7.57 (d, 2 H, H(2) and H(6), Ph, J = 7.2 Hz); 9.18 (br.s, 1 H, NH).

***syn*-5-[Bromo(4-bromophenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*syn*-3b).** M.p. 181—182 °C. Found (%): C, 39.67; H, 3.58; Br, 44.13; N, 3.92. $C_{12}H_{13}Br_2NO_2$. Calculated (%): C, 39.70; H, 3.61; Br, 44.02; N, 3.86. IR, ν/cm^{-1}: 1707 (C=O), 3189 (C(O)NH). ^{1}H NMR, δ: 1.16, 1.34 (both s, 3 H each, 2 Me); 4.81, 5.42 (both d, 1 H each, 2 CH, J = 2.8 Hz); 7.47, 7.52 (both d, 2 H each, Ar, J = 8.6 Hz); 8.99 (s, 1 H, NH).

***anti*-5-[Bromo(4-bromophenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*anti*-3b).** M.p. 147—149 °C. Found (%): C, 39.67; H, 3.65; Br, 44.24; N, 3.88. $C_{12}H_{13}Br_2NO_2$. Calculated (%): C, 39.70; H, 3.61; Br, 44.02; N, 3.86. IR, ν/cm^{-1}: 1711 (C=O), 3173 (C(O)NH). ^{1}H NMR, δ: 1.40, 1.54 (both s, 3 H each, 2 Me); 4.63, 5.46 (both d, 1 H each, 2 CH, J = 1.9 Hz); 7.53 (d, 4 H, Ar, J = 7.7 Hz); 9.20 (br.s, 1 H, NH).

***syn*-5-[Bromo(3-methoxyphenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*syn*-3c).** M.p. 135—136 °C. $C_{13}H_{16}BrNO_3$. Found (%): C, 49.79; H, 5.12; Br, 25.03; N, 4.48. $C_{13}H_{16}BrNO_3$. Calculated (%): C, 49.70; H, 5.13; Br, 25.43; N, 4.46. IR, ν/cm^{-1}: 1683, 1726 (C=O), 3218 (C(O)NH). ^{1}H NMR, δ: 1.16, 1.35 (both s, 3 H each, 2 Me); 3.73 (s, 3 H, OMe); 4.82, 5.38 (both d, 1 H each, 2 CH, J = 2.6 Hz); 6.87 (dd, 1 H, H(4), Ar, J = 8.1 Hz, J = 1.9 Hz); 7.08 (d, 1 H, H(6), Ar, J = 8.6 Hz); 7.13 (s, 1 H, H(2); Ar); 7.23 (dd, 1 H, H(5), Ar, J = 8.1 Hz, J = 8.6 Hz); 8.97 (s, 1 H, NH).

***anti*-5-[Bromo(3-methoxyphenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*anti*-3c).** M.p. 153—154 °C. Found (%): C, 49.58; H, 5.11; Br, 25.38; N, 4.49. $C_{13}H_{16}BrNO_3$. Calculated (%): C, 49.70; H, 5.13; Br, 25.43; N, 4.46. IR, ν/cm^{-1}: 1715 (C=O), 3164 (C(O)NH). ^{1}H NMR, δ: 1.39, 1.53 (both s, 3 H each, 2 Me); 4.59, 5.38 (both br.s, 1 H each, 2 CH); 6.87 (d, 1 H, H(4), Ar, J = 8.1 Hz); 7.11 (s, 1 H, H(2), Ar); 7.12 (d, 1 H, H(6), Ar, J = 7.6 Hz); 7.25 (dd, 1 H, H(5), Ar, J = 8.1 Hz, J = 7.6 Hz); 9.18 (br.s, 1 H, NH).

***syn*-5-[Bromo(2-trifluoromethylphenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*syn*-3d).** M.p. 158—159 °C. Found (%): C, 44.42; H, 3.73; Br, 22.58; F, 16.25; N, 4.01. $C_{13}H_{13}BrF_3NO_2$. Calculated (%): C, 44.34; H, 3.72; Br, 22.69; F, 16.19; N, 3.98. IR, ν/cm^{-1}: 1711 (C=O), 3079, 3175 (C(O)NH). ^{1}H NMR, δ: 1.14, 1.35 (both s, 3 H each, 2 Me); 4.87, 5.53 (both d, 1 H each, 2 CH, J = 2.4 Hz); 7.69, 7.74 (both d, 2 H each, Ar, J = 8.2 Hz); 9.02 (s, 1 H, NH).

***syn*-5-[Bromo(2-nitrophenyl)methyl]-2,2-dimethyl-1,3-oxazolidin-4-one (*syn*-3e).** M.p. 164—155 °C. Found (%): C, 43.57; H, 3.93; Br, 24.21; N, 8.58. $C_{12}H_{13}BrN_2O_4$. Calculated (%): C, 43.79; H, 3.98; Br, 24.28; N, 8.51. IR, ν/cm^{-1}: 1597 (NO_2), 1682, 1719 (C=O), 3170, 3426 (C(O)NH). ^{1}H NMR, δ: 1.28, 1.36 (both s, 3 H each, 2 Me); 4.93, 5.86 (both d, 1 H each, 2 CH, J = 3.0 Hz); 7.58 (dd, 1 H, H(4), Ar, J = 7.2 Hz); 7.75 (dd, 1 H, H(5), Ar, J = 7.2 Hz, J = 7.7 Hz); 7.87 (d, 1 H, H(6), Ar, J = 7.7 Hz); 8.13 (d, 1 H, H(3), Ar, J = 7.2 Hz); 9.08 (s, 1 H, NH).

Synthesis of 5-(arylmethylidene)-2,2-dimethyl-1,3-oxazolidin-4-ones (4a—e) (general procedure). The salt K_2CO_3 (0.41 g, 3 mmol) and MeOH (15 mL) were added to compound **3** (1 mmol). The mixture was stirred at room temperature for 3 h, poured into water (30 mL), and allowed to stand for 12 h. A precipitate formed was filtered, washed with water, and dried in air.

(*Z*)-5-Benzylidene-2,2-dimethyl-1,3-oxazolidin-4-one (*Z*-4a). M.p. 157—158 °C. Found (%): C, 70.81; H, 6.46; N, 6.82. $C_{12}H_{13}NO_2$. Calculated (%): C, 70.92; H, 6.45; N, 6.89. IR, ν/cm^{-1}: 1671 (C=C), 1703 (C=O), 3026, 3161 (C(O)NH). ^{1}H NMR, δ: 1.53 (s, 6 H, 2 Me); 6.04 (s, 1 H, =CH); 7.22 (dd, 1 H, H(4), Ph, J = 7.5 Hz); 7.34 (dd, 2 H, H(3) and H(5), Ph, J = 7.5 Hz); 7.64 (d, 2 H, H(2) and H(6), Ph, J = 7.5 Hz); 9.76 (br.s, 1 H, NH).

(*E*)-5-Benzylidene-2,2-dimethyl-1,3-oxazolidin-4-one (*E*-4a) was obtained in the mixture with *Z*-**4a** (the ratio *E*-**4a** : *Z*-**4a** = 4 : 1). ^{1}H NMR, δ: 1.46 (s, 6 H, 2 Me); 6.20 (s, 1 H, =CH); 7.17 (dd, 1 H, H(4), Ph, J = 7.6 Hz); 7.26 (dd, 2 H, H(3) and H(5); Ph, J = 7.6 Hz); 7.78 (d, 2 H, H(2) and H(6), Ph, J = 7.6 Hz); 9.64 (br.s, 1 H, NH).

(*E*)-5-(4-Bromobenzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (*E*-4b). M.p. 143—144 °C. Found (%): C, 49.92; H, 4.28; Br, 28.28; N, 5.02. $C_{12}H_{12}BrNO_2$. Calculated (%): C, 51.08, H, 4.30, N, 4.97, Br, 28.32. IR, ν/cm^{-1}: 1655 (C=C), 1705 (C=O), 3049, 3160 (C(O)NH). ^{1}H NMR, δ: 1.48 (s, 6 H, 2 Me); 6.18 (s, 1 H, =CH); 7.45, 7.77 (both d, 2 H each, Ar, J = 8.4 Hz).

(*Z*)-5-(3-Methoxybenzylidene)-2,2-dimethyl-1,3-oxazolidin-4-one (*Z*-4c). M.p. 145—146 °C. Found (%): C, 66.83; H, 6.51; N, 6.18. $C_{13}H_{15}NO_3$. Calculated (%): C, 66.94; H, 6.48; N, 6.00. IR, ν/cm^{-1}: 1682 (C=C), 1714 (C=O), 3017, 3160 (C(O)NH). ^{1}H NMR, δ: 1.54 (s, 6 H, 2 Me); 3.76 (s, 3 H, OMe); 6.00 (s, 1 H, =CH); 6.83 (dd, 1 H, H(4), Ar, J = 8.1 Hz, J = 1.8 Hz); 7.21 (s, 1 H, H(2), Ar); 7.22 (d, 1 H, H(6), Ar, J = 7.6 Hz); 7.27 (dd, 1 H, H(5), Ar, J = 8.1 Hz, J = 7.6 Hz); 9.66 (br.s, 1 H, NH).

(*E*)-2,2-Dimethyl-5-(3-methoxybenzylidene)-1,3-oxazolidin-4-one (*E*-4c). M.p. 151—152 °C. Found (%): C, 66.82; H, 6. 45; N, 6.15. $C_{13}H_{15}NO_3$. Calculated (%): C, 66.94; H, 6.48; N, 6.00. IR, ν/cm^{-1}: 1650 (C=C), 1707 (C=O), 3081, 3215 (C(O)NH). ^{1}H NMR, δ: 1.48 (s, 6 H, 2 Me); 6.18 (s, 1 H, =CH); 6.76 (dd, 1 H, H(4), Ar, J = 8.1 Hz, J = 2.5 Hz); 7.18 (dd, 1 H, H(5), Ar, J = 7.8 Hz, J = 8.1 Hz); 7.28 (d, 1 H, H(6), Ar, J = 7.8 Hz); 7.66 (s, 1 H, H(2), Ar); 9.63 (br.s, 1 H, NH).

(*E*)-2,2-Dimethyl-5-(4-trifluoromethylbenzylidene)-1,3-oxazolidin-4-one (*E*-4d). M.p. 179 °C. Found (%): C, 57.38; H, 4.42; F, 21.25; N, 5.18. $C_{13}H_{12}F_3NO_2$. Calculated (%): C, 57.57; H, 4.46; F, 21.01; N, 5.16. IR, ν/cm^{-1}: 1714 (C=O), 3057, 3171 (C(O)NH). ^{1}H NMR, δ: 1.49 (s, 6 H, 2 Me); 6.28 (s, 1 H, =CH); 7.61, 7.99 (both d, 2 H each, Ar, J = 8.1 Hz); 9.81 (br.s, 1 H, NH).

(*E*)-2,2-Dimethyl-5-(2-nitrobenzylidene)-1,3-oxazolidin-4-one (*E*-4e). M.p. 189—90 °C. Found (%): C, 57.91; H, 4.88; N, 11.32. $C_{12}H_{12}N_2O_4$. Calculated (%): C, 58.06; H, 4.87; N, 11.29. IR, ν/cm^{-1}: 1520 (NO_2), 1692 (C=C), 1706 (C=O), 3095, 3274 (C(O)NH). ^{1}H NMR, δ: 1.54 (s, 6 H, 2 Me); 6.27 (s, 1 H, =CH); 7.45, 7.69 (both dd, 1 H each, H(4) and H(5), Ar, J = 7.3 Hz); 7.91, 8.07 (both d, 1 H each, H(3) and H(6), Ar, J = 7.5 Hz); 9.95 (br.s, 1 H, NH).

This work was financially supported by the Russian Science Foundation (Priority Area of Studies "Fundamental Scientific Studies and Scientific Search by the Personal of Existing Research Laboratories (Departments)" (Project No. 14-23-00073)).

References

1. V. G. Granik, *Lekarctva* [*Medicines*], Vuzovskaya kniga, Moscow, 2001, 407 pp. (in Russian).
2. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicinal Drugs*], Novaya volna, Moscow, 2007, 1206 pp. (in Russian).

3. S. J. Brickner, D. R. Hutchinson, M. R. Barbachyn, P. R. Manninen, D. A. Ulanowicz, S. A. Garmon, K. C. Grega, S. K. Hendges, D. S. Toops, C. W. Ford, G. E. Zurenko, *J. Med. Chem.*, 1996, **39**, 673.
4. F. Tomita, K. Takahashi, T. Tamaoki, *J. Antibiot.*, 1984, **37**, 1268.
5. T. Ooi, K. Fukumoto, K. Maruoka, *Angew. Chem.*, *Int. Ed.*, 2006, **45**, 3839.
6. P.-L. Shao, X.-Y. Chen, S. Ye, *Angew. Chem.*, *Int. Ed.*, 2010, **49**, 8412.
7. G. Cardillo, M. A. Hashem, C. Tomasini, *J. Chem. Soc.*, *Perkin Trans. 1*, 1990, 1487.
8. Y. Numajiri, G. Jimenez-Oses, B. Wang, K. N. Houk, B. M. Stoltz, *Org. Lett.*, 2015, **17**, 1082.
9. G. M. Coppola, H. F. Schuster, α-*Hydroxy Acids in Enantioselective Synthesis*, VCH, Weinheim, 1997.
10. J. W. Cornforth, in *Heterocyclic Compounds,* Ed. R. C. Elderfield, Wiley, New York, 1957, Vol. **5**, pp. 298, 402.
11. J. B. Bicking, S. F. Kwong, M. H. Fleischer, W. H. Nicholson, *J. Med. Chem.*, 1965, **8**, 95.
12. I. I. Lapkin, N. A. Samoilovskikh, L. M. Mikryukova, *Zh. Org. Khim.* [*J. Org. Chem. USSR*], 1974, **10**, 1769 (in Russian).
13. T. Pokonski, *Tetrahedron*, 1983, **39**, 3139.
14. W. R. Roush, A. P. Essenfeld, J. S. Warmus, B. B. Brown, *Tetrahedron Lett.*, 1989, **30**, 7305.
15. S. Cesa, V. Mucciante, L. Rossi, *Tetrahedron*, 1999, **55**, 193.
16. V. A. Mamedov, V. L. Mamedova, S. F. Kadyrova, G. Z. Khikmatova, A. T. Gubaidullin, I. Kh. Rizvanov, Sh. K. Latypov, *Tetrahedron*, 2015, **71**, 2670.
17. E. Fourneau, J. R. Billeter, *Bull. Soc. Chim. Fr.*, 1940, **7**, 593.
18. J. Baldas, Q. N. Porter, *Aust. J. Chem.*, 1967, **20**, 2655.
19. V. A. Mamedov, V. L. Mamedova, G. Z. Khikmatova, A. I. Samigullina, A. T. Gubaidullin, O. B. Bazanova, I. Kh. Rizvanov, O. G. Sinyashin, *Russ. Chem. Bull.* (*Int. Ed.*), 2015, **64**, 2857 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2015, 2857].
20. G. M. Sheldrick, *SADABS, Program for Empirical X-ray Absorption Correction,* Bruker-Nonius, 1990—2004.
21. G. M. Sheldrick, *SHELXL-97, Program for Cristal Structure Refinement,* University of Goettingen, Goettingen, Germany, 1997.
22. L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
23. *APEX2* (*Version 2.1*), *SAINTPlus. Data Reduction and Correction Program* (Version 7.31A), Bruker Advansed X-ray Solutions, Inc., Madison (WI), 2006.

Received November 19, 2015;
in revised form March 29, 2016