Structural features of diastereomeric oxazolidin-2-ones

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Model diastereomeric oxazolidinones containing various substituents at positions 3 and 5 were synthesized. Several individual diastereomers bearing methyl groups at positions 4 and 5 in *cis*- and *trans* orientations were isolated. The TLC and ^{1}H NMR spectroscopic data suggest that diastereomers, particularly those containing the aryl substituent at position 5, are substantially different in the physical and spectral properties. The configurations of some diastereomers were established by X-ray diffraction and NOESY spectroscopy. For these compounds, the reliable assignment of the characteristic ^{1}H NMR signals of individual groups was made, which provided evidence for the *cis* or *trans* orientation of the methyl groups at positions 4 and 5. The scope of the method as applied to the determination of the *cis* and *trans* isomers from their ^{1}H NMR spectra is discussed.

Key words: dioxolanones, oxazolidinones, tetrahydrooxazoloisoquinolinones.

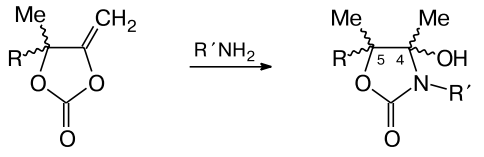
Oxazolidinones substituted in a certain fashion have found use as auxiliaries in asymmetric synthesis (see the reviews[1,2]). One of the well-developed procedures for the synthesis of oxazolidinones is based on the reaction of dioxolanones **1** (cyclic carbonates) with various primary amines.[3—9] In the general case, due to the presence of two asymmetric centers in oxazolidinones **2—5**, the reactions produce four isomers, *viz.*, a pair of enantiomers containing *cis*-methyl groups at positions 4 and 5 and a pair of enantiomers containing methyl groups in *trans* orientations relative to the mean plane of the oxazolidinone ring. In other words, the reaction affords two diastereomers, one of which is composed of molecules adopting the 4*S*,5*R* and 4*R*,5*S* configurations, which corresponds to the *cis* orientation of the 4,5-methyl groups, whereas another diastereomer is composed of 4*S*,5*S* and 4*R*,5*R* molecules, which corresponds to the *trans* orientation of these methyl groups. As a result, the ^{1}H NMR spectra clearly show two sets of signals for all protons. In some cases, the properties of these diastereomers are strongly different, which is manifested in different solubility and different chromatographic behavior.

It seemed worthwhile to find simple ways to establish the mutual *cis* or *trans* arrangement of the methyl groups at positions 4 and 5 of the oxazolidinone ring and to examine the possibility of separating diastereomers, which would open prospects for using readily accessible oxazolidinones of types **2—5** in asymmetric synthesis followed by separation of their enantiomers.

Results and Discussion

We synthesized the starting dioxolanones according to a known procedure from the corresponding acetylenic alcohols.[8,10] The reactions of these compounds with various primary amines produced oxazolidinones **2** and **3** (Scheme 1). The characteristics of the resulting com-

Scheme 1



1 **2—5**

Compound	R	R´
1a	Ph	—
2a	Ph	H
2b	Ph	Me
2c	Ph	Et
1b	3-C_5H_4N	—
3a	3-C_5H_4N	H
3b	3-C_5H_4N	Me
3c	3-C_5H_4N	Et
3d	3-C_5H_4N	CH_2Ph
3e	3-C_5H_4N	$(CH_2)_2Ph$
3f	3-C_5H_4N	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$

Compound	R	R´
1c	$PhCH_2$	—
4a	$PhCH_2$	Me
4b	$PhCH_2$	CH_2Ph
1d	$Ph(CH_2)_2$	—
5a	$Ph(CH_2)_2$	H
5b	$Ph(CH_2)_2$	Et

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Table 1. Constants and yields of compounds **2a—c**, **3a—f**, and **6a,b**

Compound	R_f[a], *trans*/*cis*	M.p.[b] /°C	Yield (%)	Found / Calculated (%)			Molecular formula
				C	H	N	
2a	0.57/0.62	215[c]	89	63.74 63.76	6.35 6.32	6.75 6.76	$C_{11}H_{13}NO_3$
2b	0.60/0.74	128—134	78	65.26 65.14	6.78 6.83	6.27 6.33	$C_{12}H_{15}NO_3$
2c	0.72/0.78	159[d]	79	66.42 66.36	7.26 7.28	5.92 5.95	$C_{13}H_{17}NO_3$
3a	0.15/0.25	160—161[c]	94	57.86 57.69	5.81 5.81	13.28 13.45	$C_{10}H_{12}N_2O_3$
3b	0.16/0.25	170—172	99	59.55 59.45	6.33 6.35	12.52 12.60	$C_{11}H_{14}N_2O_3$
3c	0.20/0.31	112—115	93	61.12 61.00	6.79 6.83	11.78 11.86	$C_{12}H_{16}N_2O_3$
3d	0.40/0.49	158—161	88	68.50 68.44	6.08 6.08	9.33 9.39	$C_{17}H_{18}N_2O_3$
3e	0.48/0.51	184—190	63	69.25 69.21	6.49 6.45	8.90 8.97	$C_{18}H_{20}N_2O_3$
3f	0.18/0.30	118—120	70	64.37 64.50	6.55 6.50	7.60 7.52	$C_{20}H_{24}N_2O_5$
6a	0.42/0.49	137[d]	86	73.50 73.45	6.18 6.16	9.46 9.52	$C_{18}H_{18}N_2O_2$
6b	0.30/0.41	151—162	95	67.73 67.78	6.29 6.26	7.92 7.90	$C_{20}H_{22}N_2O_4$

[a] Ethyl acetate (EA) was used as the solvent.
[b] All compounds listed in the table were purified by recrystallization: **2**, from a methyl *tert*-butyl ether (MTBE)—petroleum ether (PE) mixture; **3** and **6**, from an EA—MTBE mixture. The table gives the melting points of mixtures of diastereomers, which accounts for a wide melting range.
[c] The melting point of the individual *cis* isomer.
[d] The melting point of the individual *trans* isomer.

pounds are given in Tables 1 and 2. The synthesis of oxazolidinones **4** and **5** has been described earlier.[8]

In all reactions, oxazolidinones were formed initially as ~1 : 1 mixtures of diastereomers. However, almost in all cases, one of diastereomers was isolated as the major product after crystallization due to the difference in solubility. In the case of oxazolidinones **2** and **3** containing an aromatic substituent at position 5, the differences in the properties of diastereomers are particularly considerable. In the TLC analysis, their R_f differ, on the average, by 0.09. After partial evaporation, one of diastereomers generally crystallizes first.

For compounds **2c** and **3a**, we succeeded in isolating one diastereomer in pure form. The two-dimensional homonuclear NOESY experiments demonstrated that the methyl groups in **2c** are in *trans* orientations (cross-peaks between the methyl groups at positions 4 and 5 are absent), whereas the methyl groups in **3a** are in *cis* orientations (the spectrum shows strong cross-peaks).

In the ^{1}H NMR spectra of compounds **2** and **3**, each diastereomer is characterized by its own set of signals, which differ in the chemical shifts of all protons of the molecules, the most substantial differences being observed for the chemical shifts of the methyl groups at positions 4 and 5 and the hydroxy group at position 4 of the oxazolidinone ring. For example, the ^{1}H NMR spectrum for isomers of compound **3a**, *cis*/*trans*, has signals at δ 1.49/0.89 (s, 3 H, 4-Me); 1.61/1.71 (s, 3 H, 5-Me); 5.70/6.33 (s, 1 H, 4-OH). Apparently, the aromatic ring at position 5 is arranged so that it shields the substituent at position 4, which is in a *cis* orientation with respect to this ring. This fact accounts for a large upfield shift (~0.6 ppm) of the signal of 4-Me in the *trans* isomer compared to the *cis* isomer. The singlet of 4-OH in the spectrum of the *cis* isomer is observed at higher field (by *ca*. 0.6 ppm). A similar spectral pattern is observed for compound **2c** (δ), *cis*/*trans*: 1.51/0.88 (s, 3 H, 4-Me); 1.56/1.67 (s, 3 H, 5-Me); 5.60/6.32 (s, 1 H, 4-OH). It can be seen that the aromatic ring in this compound has an analogous effect on the chemical shifts.

Based on the above fact, the assignment of signals belonging to *cis* and *trans* diastereomers can be made for

Table 2. Mass spectra of compounds **2a—c**, **3a—f**, and **6a,b**

Compound	M	m/z (I_{rel} (%))
2a	207	207 (9), 145 (28), 121 (95), 104 (100), 77 (65), 59 (42), 51 (49), 43 (30)
2b	221	221 (3), 121 (66), 104 (37), 77 (26), 73 (39), 56 (28), 51 (14), 43 (100)
2c	235	235 (18), 217 (35), 172 (33), 158 (22), 121 (100), 104 (69), 86 (59), 72 (63), 51 (23)
3a	208	208 (1), 145 (10), 122 (87), 104 (42), 78 (44), 59 (14), 51 (46), 43 (100)
3b	222	222 (3), 145 (5), 122 (100), 104 (21), 78 (23), 73 (32), 56 (37), 51 (25), 43 (77)
3c	236	236 (2), 122 (100), 106 (15), 104 (17), 87 (15), 78 (23), 72 (54), 51 (26), 43 (97)
3d	298	298 (4), 149 (18), 122 (98), 106 (28), 91 (86), 78 (22), 65 (29), 51 (27), 43 (100)
3e	312	312 (7), 148 (58), 130 (12), 122 (66), 104 (73), 91 (61), 77 (29), 65 (30), 43 (100)
3f	372	372 (3), 164 (100), 151 (47), 122 (14), 106 (12), 91 (10), 78 (18), 51 (12), 43 (62)
6a	294	294 (4), 173 (10), 145 (100), 115 (17), 106 (15), 103 (13), 78 (27)
6b	354	354 (10), 205 (100), 147 (4), 190 (20), 106 (15), 78 (19)

all oxazolidinones **2** or **3** using a spectrum of a mixture of diastereomers or a spectrum of one of diastereomers. The assignment was made for all compounds **2** and **3** (Table 3).

We made an attempt to reveal such features for oxazolidinones **4** derived from dioxolanone **1c** (earlier, we have characterized a number of compounds of this oxazolidinone series[8,9]). For this purpose, we recorded the NOESY spectra of compounds **4a** and **4b** (mixtures of both diastereomers), which allowed the assignment of the signals of the hydroxy and methyl groups to the *cis* and *trans* diastereomers. The chemical shifts of the protons of the methyl groups of different diastereomers differ insignificantly from each other, but these parameters strongly depend on the nature of the substituent at the nitrogen atom (spectroscopic data for **4a** and **4b** are given in Table 3; the spectra of other compounds of this series were described in the studies[8,9]). Therefore, the positions of these signals in the spectra are not exactly characteristic. A change in the nature of the substituent at the nitrogen atom from H to CH_2CH_2Ph leads to a change in the relative arrangement of the singlets of the Me groups of different diastereomers. However, the mutual arrangement of the chemical shifts for the hydroxy groups remains unchanged. Thus, the signal for the proton of the hydroxy group of the *cis* isomer appears as a singlet, which is shifted downfield by approximately 0.2 ppm compared to the analogous signal of the *trans* isomer. Therefore, if the spectra of both individual diastereomers of compounds **4** are available, the configurations of two diastereomers can be determined by comparing the chemical shifts of the signals of the OH groups at position 4.

We also isolated one of diastereomers of oxazolidinones **5a** and **5b** by crystallization after their synthesis from carbonate **1d**. The crystals of both compounds were studied by X-ray diffraction (Fig. 1).

The diastereomers containing the methyl groups in *trans* and *cis* orientations were isolated in the case of **5a** and **5b**, respectively. In both molecules, the oxazolidine ring is nonplanar and adopts a C(1)-envelop conformation. The geometric parameters of the molecules are identical and have standard values (Table 4). The fragments of the structures of compounds **5a** and **5b** are shown in Fig. 2. The configurations of the C(2) atoms are identical, whereas the configurations of the C(1) atoms are different.

The crystal structures of both compounds are centrosymmetric. The crystals of **5a** and **5b** consist of mixtures of enantiomeric molecules, (*R*)-C(2),(*R*)-C(1) + + (*S*)-C(2),(*S*)-C(1) and (*R*)-C(2),(*S*)-C(1) + + (*S*)-C(2),(*R*)-C(1), respectively. In both crystal structures, the molecules are linked to each other to form

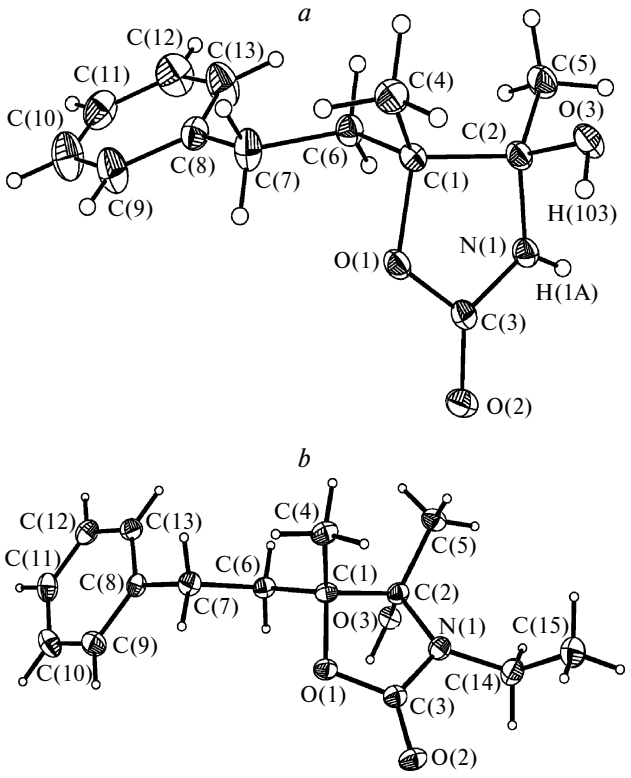


Fig. 1. Molecular structures of oxazolidinones **5a** (*a*) and **5b** (*b*). The methyl groups at the oxazolidinone ring in **5a** are in *trans* positions; in **5b**, in *cis* positions. The C(4)—C(1)—C(2)—C(5) torsion angle is 95.5(2)° and 33.5(2)° in **5a** and **5b**, respectively.

Table 3. ^{1}H NMR spectra of oxazolidinones **2—5**

Compound	δ (*J*/Hz)				
	4-Me[a] (s, 3 H)	5-Me[a] (s, 3 H)	4-OH[a] (s, 1 H)	Ar	Other signals
2a	1.49 0.87	1.58 1.68	5.54 6.20	7.24—7.51 (m, 5 H)	8.25, 8.29 (both s, 1 H, NH)
2b	1.50 0.86	1.57 1.69	5.65 6.36	7.27—7.45 (m, 5 H)	2.65, 2.31 (both s, 3 H, NMe)
2c[b]	1.51 0.88	1.56 1.67	5.60 6.32	7.25—7.43 (m, 5 H)	1.06, 1.15 (both t, 3 H, *J* = 7.0), 3.01, 3.14 (both q, 2 H, *J* = 7.0), NEt
3a[b]	1.49 0.89	1.61 1.71	5.70 6.33	7.35—7.45 (m, 1 H); 7.69, 7.81 (both d, 1 H, *J* = 8.5); 8.49— 8.53 (m, 1 H); 8.63, 8.64 (both s, 1 H)	8.38, 8.41 (both s, 1 H, NH)
3b	1.50 0.90	1.61 1.72	5.85 6.48	7.34—7.45 (m, 1 H); 7.67, 7.82 (both d, 1 H, *J* = 8.5); 8.49—8.52 (m, 1 H); 8.54, 8.65 (both s, 1 H)	2.66, 2.72 (both s, 3 H, NMe)
3c	1.53 0.92	1.61 1.72	5.80 6.45	7.37—7.46 (m, 1 H); 7.68, 7.83 (both d, 1 H, *J* = 8.3); 8.50, 8.56 (both d, 1 H, *J* = 4.3); 8.53, 8.66 (both s, 1 H)	1.06, 1.14 (both t, 3 H, *J* = 7.5), 3.12—3.24 (m, 2 H), NEt
3d	1.39 0.78	1.66 1.77	6.06 6.68	7.17—7.45 (m, 6 H); 7.73, 7.85 (both d, 1 H, *J* = 8.4); 8.53, 8.57 (both d, 1 H, *J* = 4.4); 8.52, 8.67 (both s, 1 H)	4.19—4.27, 4.45—4.56 (both m, 1 H each, $NC\underline{H}_2Ph$)
3e	1.23 0.66	1.50 1.68	5.82 6.44	7.09—7.42 (m, 6 H); 7.60, 7.79 (both d, 1 H, *J* = 8.4); 8.48, 8.50 (both s, 1 H); 8.54, 8.62 (both d, 1 H, *J* = 4.6)	2.75—2.95 (m, 2 H), 3.18—3.27, 3.33—3.45 (both m, 1 H each), $NC\underline{H}_2C\underline{H}_2Ph$
3f	1.25 0.70	1.51 1.68	5.82 6.45	6.56—6.90 (m, 3 H); 7.34—7.40 (m, 1 H); 7.57, 7.80 (both d, 1 H, *J* = 8.6); 8.49 (s, 1 H); 8.53, 8.63 (both d, 1 H, *J* = 4.7)	2.67—2.86 (m, 2 H), 3.17—3.26, 3.31—3.42 (both m, 1 H each), $NC\underline{H}_2C\underline{H}_2Ar$; 3.66, 3.68, 3.72, 3.74 (all s, 6 H, $ArO\underline{Me}$)
4a[b]	1.15 1.05	1.42 1.28	5.96 5.78	7.16—7.31 (m, 5 H)	2.63, 2.87, 2.88, 3.14 (all d, 2 H, $PhC\underline{H}_2$, *J* = 17.3); 2.71, 2.74 (both s, 3 H, NMe)
4b[b]	1.14 1.25	1.03 1.17	6.42 6.27	7.20—7.36 (m, 10 H)	2.77, 2.86, 2.88, 3.19 (all d, 2 H, $PhC\underline{H}_2C$, *J* = 17.4); 4.27 (d, 1 H, *J* = 19.3), 4.48, 4.49 (both d, 1 H, *J* = 10.4), $NC\underline{H}_2Ph$
5a[c]	1.34 1.35	1.31 1.29	5.91 5.88	7.17—7.32 (m, 5 H)	1.75—2.02, 2.53—2.77 (both m, 2 H each, $PhC\underline{H}_2C\underline{H}_2$); 8.11 (s, 1 H, NH)
5b[c]	1.37 1.40	1.29 1.26	5.98 5.95	7.16—7.31 (m, 5 H)	1.08, 1.11 (both t, 3 H, *J* = 7.3), 3.10—3.18 (m, 2 H), NEt; 1.86—2.02, 2.57—2.77 (both m, 2 H each, $PhC\underline{H}_2C\underline{H}_2$)

[a] The characteristic signals, which were assigned to *cis* (upper row) and *trans* diastereomers (low row), are given.
[b] The NOESY spectrum was recorded.
[c] The crystal structure was studied by X-ray diffraction.

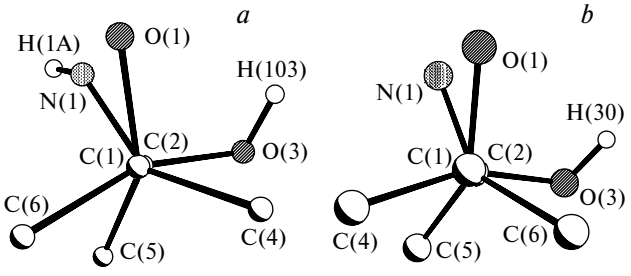


Fig. 2. Fragments of the structures of **5a** (*a*) and **5b** (*b*) projected along the C(1)—C(2) bond.

centrosymmetric hydrogen-bonded dimers through the strong intermolecular O(3)—H(3O)...O(2) hydrogen bonds (see Table 4). In the crystal structure of **5a**, the hydrogen-bonded dimers are linked to each other by the N(1)—H(1A)...O(3) hydrogen bonds to form layers parallel to the *bc* plane.

An analysis of the ^{1}H NMR spectra of these compounds and other compounds of series **5**, which differ in the nature of the substituent at the nitrogen atom,[8] did not allow us to find a reliable criterion for assigning all compounds of this series to *cis* or *trans* isomers based on

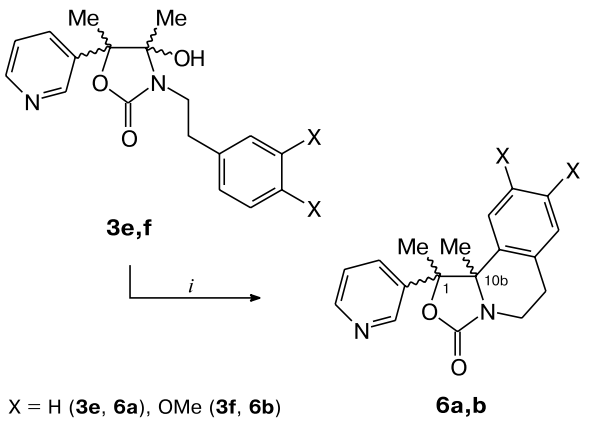
Table 4. Selected bond lengths and distances (*d*), bond angles (ω), and torsion angles (φ) in the structures of **5a** and **5b**

Parameter	**5a**	**5b**
Bond	*d*/Å	
C(1)—C(6)	1.534(3)	1.514(2)
C(1)—C(2)	1.568(3)	1.567(2)
C(1)—C(4)	1.515(3)	1.517(2)
C(2)—C(5)	1.507(3)	1.513(2)
C(2)—O(3)	1.430(3)	1.413(2)
C(1)—O(1)	1.473(2)	1.482(2)
C(2)—N(1)	1.445(3)	1.469(2)
N(1)—C(3)	1.344(3)	1.344(2)
C(3)—O(1)	1.350(2)	1.344(2)
C(3)—O(2)	1.217(2)	1.225(2)
Bond angle	ω/deg	
C(2)—N(1)—C(3)	112.1(2)	111.1(1)
C(4)—C(1)—C(6)	113.0(2)	113.4(1)
C(4)—C(1)—C(2)	113.3(2)	113.1(1)
C(6)—C(1)—C(2)	112.3(2)	112.6(1)
C(5)—C(2)—C(1)	116.2(2)	114.7(1)
C(5)—C(2)—O(3)	105.8(2)	105.0(1)
Torsion angle	φ/deg	
C(4)—C(1)—C(2)—C(5)	95.5(2)	33.5(2)
C(4)—C(1)—C(2)—O(3)	26.6(2)	154.5(1)
C(5)—C(2)—C(1)—C(6)	34.1(3)	96.5(2)
O(3)—H(3O)...O(2) Fragment		
Distance	*d*/Å	
O...O	2.768(2)	2.730(2)
H...O	1.88(3)	1.84(3)
	ω/deg	
O—H...O Angle	175(3)	176(2)
N(1)—H(1A)...O(3) Fragment		
Distance	*d*/Å	
N...O	2.927(2)	—
H...O	2.16(3)	—
	ω/deg	
N—H...O Angle	149(3)	—
Deviation of the C(1) atom from the plane through the C(2)N(1)C(3)O(1) atoms	*l*/Å 0.404	0.407

one-dimensional ^{1}H NMR spectra. The difference in the chemical shifts of the singlets of the hydroxy groups is small (about 0.03 ppm), whereas the positions of these signals in the spectrum vary in a wider range (~0.1 ppm). The same tendencies are true for the methyl groups. In the spectra of many compounds of series **5**, the singlets of the methyl groups overlap with each other or are arranged in different sequences.

As expected, the treatment of compounds **3e,f** containing the phenylethyl substituent at the nitrogen atom with polyphosphoric acid (PPA) afforded oxazolotetrahydroisoquinolines **6** (Scheme 2). These compounds, like the starting oxazolidinones, contain two asymmetric centers (positions 1 and 10b). The ^{1}H NMR spectra of these compounds (Table 5) also have a double set of all signals. For compounds **6**, the assignment of the chemical shifts of diastereomers containing *cis*- or *trans*-methyl groups at positions 1 and 10b was also made. For this purpose, we recorded the two-dimensional NOESY spectrum of a sample of compound **6b** containing both diastereomers. For one set of signals (*cis*), we observed cross-peaks between the methyl groups. In another case (*trans*), the nuclear Overhauser effect for the methyl groups was absent. By analogy, the assignment of the signals in the ^{1}H NMR spectrum for compound **6a** was made taking into account the similarity of the spatial structures.

Scheme 2



i. Polyphosphoric acid.

Earlier, a number of oxazolidinones containing two asymmetric centers at positions 4 and 5 (analogously to compounds **2—5**) have already been documented.[8—12] Many oxazolidinones containing Me and Et groups at position 5 were described, but the influence of these groups on the oxazolidinone ring is virtually the same and does not lead to a clear doubling of signals in the ^{1}H NMR spectra. Hence, it can be assumed that the asymmetric center at position 5 in these oxazolidinones has only a slight effect on the properties of different oxazolidinones. Considerable differences in the influence of substituents at position 5 on the oxazolidinone ring are observed if these substituents are substantially different in the size and nature.

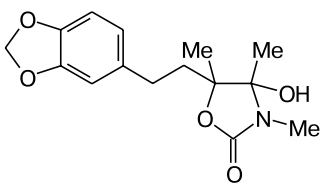
For example, 5-[2-(1,3-benzodioxol-5-yl)ethyl]-4-hydroxy-3,4,5-trimethyl-1,3-oxazolidin-2-one (**7**) was described in the study,[11] where this compound was used in the subsequent synthesis without isolation. This compound was not characterized by ^{1}H NMR spectroscopy.

Table 5. ^{1}H NMR spectra of oxazolotetrahydroisoquinolines **6**[a]

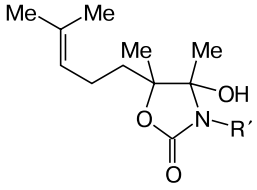
Compound	δ (*J*/Hz)				
	C(10b)Me (s, 3 H)	C(1)Me (s, 3 H)	CH_2CH_2Ar	Ar	Other signals
6a	1.67 1.12	2.05 1.25	2.77—2.85 (m 1 H); 2.97—3.21 (m, 2 H); 3.84—3.99 (m, 1 H)	6.85, 7.00 (both d, 1 H, *J* = 8.2); 7.25—7.34 (m, 3 H), 7.51—7.56 (m, 1 H); 8.04, 8.20 (both d, 1 H, *J* = 8.9); 8.66 (d, 1 H, *J* = 4.8); 8.82 (s, 1 H)	—
6b[b]	1.67 1.11	2.05 1.27	2.15—2.24, 2.87—2.96 (both m, 1 H); 2.46, 2.74 (both d, 1 H, *J* = 16); 3.00—3.16 (m, 1 H); 3.82—3.96 (m, 1 H)	6.37, 6.43 (both s, 1 H); 6.67, 6.84 (both s, 1 H); 7.11—7.16, 7.51—7.55 (both m, 1 H); 7.40, 8.08 (both d, 1 H, *J* = 8.5); 8.26, 8.65 (both d, 1 H, *J* = 4.7); 8.24, 8.87 (both s, 1 H)	3.58, 3.72, 3.76, 3.77 (all s, 6 H, ArOMe)

[a] The characteristic signals were assigned to *cis* (upper row) and *trans* diastereomers (low row).
[b] For compound **6b**, the NOESY spectrum was recorded.

4-Hydroxy-4,5-dimethyl-5-(4-methylpent-3-enyl)-1,3-oxazolidin-2-ones (**8**) containing different substituents at the nitrogen atom were also documented.[12]



7



8

In the study,[12] the formation of two diastereomers of these compounds characterized by different R_f in TLC was documented. The ^{1}H NMR spectra of these compounds having double sets of signals were reported, with mention that it was not always possible to make the assignment. Nevertheless, diastereomers of this oxazolidinone containing the benzyl group at the N atom were separated by chromatography, and these individual diastereomers were characterized, but it was not determined which diastereomer adopts a *cis* orientation and which diastereomer contains *trans*-substituents. In our studies,[8,9] oxazolidinones, which are analogous to compounds **2—5** and contain different substituents at position 5 (2-phenylethyl, 2-(2-furyl)ethyl, 2-methyl-2-phenylpropyl, or benzyl), were described. In these studies, we also synthesized tetrahydrooxazoloisoquinolines analogous to compounds **6a,b** (bearing the benzyl or 2-phenylethyl substituent at position 1 instead of the pyridyl substituent). These compounds were not separated into *cis* and *trans* diastereomers. The ^{1}H NMR spectra showed double sets of signals.

From the description of the ^{1}H NMR spectra of compounds **2** and **3** containing an aromatic substituent at position 5, it follows that there is a clear criterion allowing the reliable assignment of the signals of methyl groups and the signal of the hydroxy group to *cis* and *trans* diastereomers. The singlets of *cis* isomers are observed rather close to each other between the singlets of the methyl groups of the *trans* isomers. The signal of the hydroxy group of *cis* isomers is shifted upfield by approximately 0.6—0.7 ppm. For compounds **4** containing the benzyl substituent at position 5 of the oxazolidinone ring, an analogous criterion, which is manifested only in the mutual arrangement of the singlets of the hydroxy groups, is less reliable. For compounds **5** and also for other compounds (see Refs 8 and 10—12), in which the oxazolidinone ring is separated from the aromatic ring or the double bond by two carbon units, the arrangement of the chemical shifts of the methyl and hydroxy groups cannot be used for the assignment. For the reliable assignment of the signals of the *cis* and *trans* isomers in these compounds, it is necessary to record the NOESY spectrum or, if crystals are available, to perform X-ray diffraction study.

Experimental

The NMR spectra were recorded on a Bruker DRX500 instrument (500.13 MHz) in DMSO-d_6. The mass spectra were obtained on a Kratos MS-30 instrument using a direct inlet system; the electron impact energy was 70 eV; the temperature of the ionization chamber was 250 °C. The course of the reactions was monitored by TLC on Baker-flex plates (Silica gel IB-F). The following commercial solvents were used: petroleum ether (PE), ethyl acetate (EA), and methyl *tert*-butyl ether (MTBE).

All solvents, except for MTBE, were purified according to standard procedures;[13] MTBE was purified by distillation over CaH_2, after which no impurities were found by GLC.

Crystals of **5a** and **5b** suitable for X-ray diffraction were grown by crystallization from an aqueous acetonitrile solution. The X-ray diffraction data sets were collected on Syntex P21 and Bruker SMART CCD area detector diffractometers

(λMo-Kα radiation) at low temperatures. The structures were solved by direct methods. All nonhydrogen atoms were located in difference electron density maps and refined anisotropically against F^2_{hkl}. All hydrogen atoms (except for the hydrogen atoms of the OH and NH groups) were placed in geometrically calculated positions and refined using a riding model with $U(H) = 1.2U(C)$, where $U(C)$ are the equivalent thermal parameters of the carbon atoms to which the corresponding H atoms are bound. The hydrogen atoms of the OH and NH groups were located in difference Fourier maps and refined isotropically. All calculations were carried out using the SHELXTL PLUS 5 program package.

The crystallographic characteristics, including the unit cell parameters, and the X-ray data collection and refinement statistics are given in Table 6. The atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database. Selected geometric parameters of the molecules are listed in Table 4.

Table 6. Crystallographic data and the refinement statistics for compounds **5a** and **5b**

Compound	**5a**	**5b**
Molecular formula	$C_{13}H_{17}NO_3$	$C_{15}H_{21}NO_3$
Molecular weight	235.28	263.33
Space group	$P2_1/c$	$P2_1/c$
T/K	110(2)	120(2)
a/Å	12.884(3)	10.940(4)
b/Å	7.382(2)	8.847(3)
c/Å	12.932(3)	14.759(5)
β/deg	96.67(2)	97.873(6)
V/Å^3	1221.7(5)	1415.0(8)
Z	4	4
d_{calc}/g cm^{-3}	1.279	1.236
Crystal color and shape	Colorless needle	Colorless plate
Crystal dimensions/mm	0.40×0.25×0.15	0.25×0.52×0.60
Diffractometer	«Syntex P21»	«SMART Bruker»
μ/cm^{-1}	0.91	0.86
Scanning mode	θ-2θ	φ/ω
$2\theta_{max}$/deg	52	56
Total number of reflections	2394	13993
Number of independent reflections (R_{int})	2287 (0.0390)	3383 (0.0407)
Number of reflections with $I > 2\sigma(I)$)	1608	2212
R_1 (based on F for reflections with $I > 2\sigma(I)$)	0.0519	0.0619
wR_2 (based on F^2 for all reflections)	0.1214	0.1457
Number of parameters in refinement	158	176
Weighed scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (1/3)(F_o^2 + 2F_c^2)$	
a	0.0623	0.0910
b	0.5216	0.00
GOOF	0.998	1.042
F(000)	504	568

Compounds **4a,b** and **5a,b** have been characterized earlier.[8] Their diastereomers are hardly distinguishable in R_f.

Synthesis of oxazolidinones 2 and 3 (general procedure). Amine (10 mmol) was added (ammonia, methylamine, and ethylamine were used as aqueous solutions) to a solution of the corresponding dioxolanone **1** (10 mmol) in acetonitrile (7 mL). The reaction mixture was kept at 45 °C for 3—10 h until the starting reagents were consumed (TLC). The solvent was evaporated, most of oxazolidinones being obtained as yellow oils. In all cases, the oils were crystallized from MTBE. The yields were 80—100%.

The following new compounds were synthesized: **4-hydroxy-4,5-dimethyl-5-phenyloxazolidin-2-one (2a), 4-hydroxy-3,4,5-trimethyl-5-phenyloxazolidin-2-one (2b), 3-ethyl-4-hydroxy-4,5-dimethyl-5-phenyloxazolidin-2-one (2c), 4-hydroxy-4,5-dimethyl-5-(pyridin-3-yl)oxazolidin-2-one (3a), 4-hydroxy-3,4,5-trimethyl-5-(pyridin-3-yl)oxazolidin-2-one (3b), 3-ethyl-4-hydroxy-4,5-dimethyl-5-(pyridin-3-yl)oxazolidin-2-one (3c), 3-benzyl-4-hydroxy-4,5-dimethyl-5-(pyridin-3-yl)oxazolidin-2-one (3d), 4-hydroxy-4,5-dimethyl-5-(pyridin-3-yl)-3-(2-phenylethyl)oxazolidin-2-one (3e), and 4-hydroxy-4,5-dimethyl-3-[2-(3,4-dimethoxyphenyl)ethyl]-5-(pyridin-3-yl)oxazolidin-2-one (3f)**.

Synthesis of tetrahydrooxazoloisoquinolinones 6 (general procedure). A 20-fold excess (by weight) of PPA was added to oxazolidinones **3e,f**. The reaction mixture was stirred at 90 °C for 2 h, poured onto ice, and neutralized with a 40% NaOH solution, the temperature being maintained no higher than 30 °C. The precipitate that formed was filtered off and washed with water. The product was additionally purified by recrystallization from MTBE.

The following new compounds were synthesized: **1,10b-dimethyl-1-(pyridin-3-yl)-1,5,6,10b-tetrahydrooxazolo[4,3-*a*]isoquinolin-3-one (6a) and 8,9-dimethoxy-1,10b-dimethyl-1-(pyridin-3-yl)-1,5,6,10b-tetrahydrooxazolo[4,3-*a*]isoquinolin-3-one (6b)**.

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