Diastereoselective synthesis of substituted 1,3,6-triazabicyclo[3.1.0]hexanes

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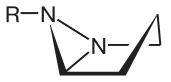
A general method was developed for the synthesis of substituted 1,3,6-triazabicyclo[3.1.0]hexanes *via* intramolecular aminomethylation of the NH group of the diaziridine ring by the reactions of 3-aminomethyl-1,3-dimethyldiaziridine with aliphatic, aromatic, and heteroaromatic carbonyl compounds. These reactions with aldehydes proceeded diastereoselectively to form mixtures of two racemates, *viz.*, 1*R**,2*R**,5*R**,6*R** and 1*R**,2*S**,5*R**,6*R**, in a ratio of (3—20) : 1, the predominant diastereomer being isolated in all cases. The reactions with symmetrical ketones gave rise exclusively to the (1*R**,5*R**,6*R**) racemate. The predominant diastereomer 1*R**,2*R**,5*R**,6*R**-2-(2-bromothien-5-yl)-1,3,6-triazabicyclo[3.1.0]hexane crystallized as a conglomerate. The structure of one of its enantiomers was established by X-ray diffraction analysis.

Key words: 1,3,6-triazabicyclo[3.1.0]hexanes, diastereomers, enantiomers, conglomerates, diastereoselective synthesis, X-ray diffraction analysis.

Among fused diaziridine derivatives, 1,6-diazabicyclo[3.1.0]hexanes **1** [1—3] and 1,3,5-triazabicyclo[3.1.0]hexanes **2** [4—6] have received the most study. These compounds along with monocyclic diaziridines[7,8] exhibit biological activities as potential neurotropic compounds.[9] Procedures were developed for the synthesis of structurally similar compounds containing two nitrogen atoms in bicycles, *viz.*, 1,5-diazabicyclo[3.1.0]hexanes **3** [10,11] and 1,3-diazabicyclo[3.1.0]hexanes **4**.[12—14]



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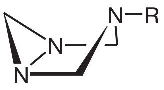

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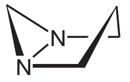

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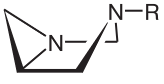

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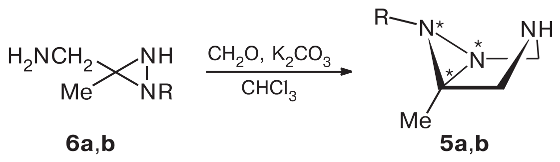
However, the synthesis of 1,3,6-triazabicyclo[3.1.0]hexanes **5** isomeric to structures **2** was described only for two compounds (**5a**,**b**). These compounds were prepared *via* intramolecular aminomethylation of the NH group in the diaziridine ring of 3-aminomethyl-1,3-dimethyldiaziridine or 3-aminomethyl-3-methyldiaziridines **6a**,**b** under the actions of formaldehyde[15] (Scheme 1).

Scheme 1



R = Me (**a**), H (**b**)

It can be assumed with high probability (by analogy with the data for heterocyclic systems **1**—**4** [1,11,14]) that compounds **5a**,**b** have the 1*R**,5*R**,6*R** configuration. However, this assumption calls for additional verification. Besides, it is worthwhile to extend the spectrum of compounds of this type by the involvement of other carbonyl compounds in the reactions with diaziridines **6**.

The aim of the present study was to examine the possibility of the synthesis of substituted 1,3,6-triazabicyclo[3.1.0]hexanes **5** by the reactions of 3-aminomethyldiaziridines with aliphatic, aromatic, and heteroaromatic carbonyl compounds followed by isolation of individual diastereomers in the case of reactions with aldehydes. It was also of interest to search for conglomerates in this series of compounds and explore the possibility of isolation of individual enantiomers.

We used 3-aminomethyl-1,3-dimethyldiaziridine (**6a**) as the starting 3-aminomethyldiaziridine. Compound **6a**

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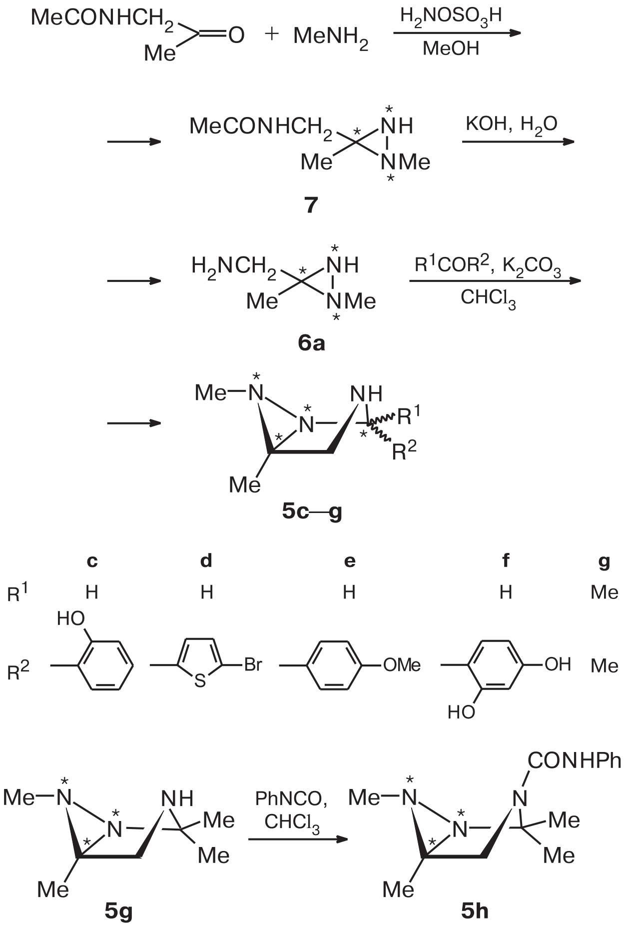
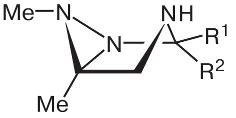
was synthesized according to a known procedure[15] by the reaction of *N*-acetamidoacetone, methylamine, and hydroxylamino-*O*-sulfonic acid followed by the removal of the acetyl protection in the resulting diaziridine **7** upon heating in aqueous alkali.* We examined such carbonyl compounds as 2-hydroxy-, 4-methoxy-, and 2,4-dihydroxybenzaldehydes, 5-bromothiophene-2-carboxaldehyde, and acetone. The reactions were carried out in $CHCl_3$ upon refluxing (reaction time was varied from 24 to 100 h) with the use of K_2CO_3 as a drying agent. The course of the reactions was monitored by TLC. In all cases, the reactions afforded the expected substituted 1,3,6-triazabicyclo[3.1.0]hexanes **5**, which were isolated by column chromatography on SiO_2 followed by recrystallization from hexane (for compounds **5c—f**) or as 3-phenylisocyanate derivative **5h** in the case of compound **5g** (Scheme 2).

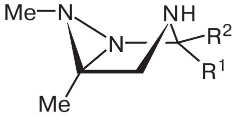
Scheme 2



Based on the *trans* rule[16] for the lone electron pairs and substituents at the N atoms of diaziridines and also taking into account the rule of the *cis*-[0]-bridge in bicyclo[3.1.0]hexanes,[17,18] compounds **5c—f** can produce only two diastereomers (racemates **5´** and **5″**), whereas the only racemate, *viz.*, *R**,5*R**,6*R**, is possible for compounds **5g**,**h**. Actually, bicyclic compounds **5c—e** were obtained (according to the NMR data) as mixtures of two diastereomers **5c´—e´** and **5c″—e″** in a ratio of (3—5) : 1, whereas bicyclic compound **5f** was obtained predominantly as the only diastereomer **5f´** (ratio was ≥20 : 1). The assignment of the signals of the second diastereomer **5f″** in the ^{1}H NMR spectrum presents difficulties because of an insignificant amount of this compound in the mixture. As expected, phenylcarbamoyl derivative **5h** was obtained as an individual compound, *viz.*, the 1*R**,5*R**,6*R** racemate. The predominant diastereomers **5c´—e´** were isolated by fractional crystallization from hexane. Compound **5f´** was isolated by single crystallization. Predominant diastereomer **5d´** proved to be a conglomerate. Crystallization of **5d´** from hexane made it possible to obtain crystals of one of its enantiomers whose structure was confirmed by X-ray diffraction analysis.



1*R**,2*R**,5*R**,6*R**
Racemate **5´**



1*R**,2*S**,5*R**,6*R**
Racemate **5″**

The reaction times, yields, diastereomer ratios, and selected physicochemical characteristics of bicyclic compounds **5** are given in Table 1. The spectroscopic characteristics of the diastereomers are listed in Table 2.

As can be seen from Table 1, the yields of all compounds **5** are rather high (in spite of the fact that the yields are given with respect to the isolated and recrystallized products) notwithstanding the fact that only one diastereomer (**6a´**) of the starting diaziridine **6a**, which occurs as a mixture of two diastereomers (**6a´** and **6a″** in a ratio of 3 : 1), can be involved in intramolecular aminomethylation. With the aim of establishing the configurations of the substituents in the starting diaziridine **6a**, we measured nuclear Overhauser effects (NOE). It was found that compound **6a** occurred predominantly as diastereomer **6a´** in which the aminomethyl group and the H atom bound to the N atom of the diaziridine ring are in *cis* positions. Compound **7** was also obtained as a mixture of diastereomers analogous to the diastereomers of **6a**, *viz.*, as **7´** and **7″** in a ratio of 5 : 1. An analogous situation was observed in the NOE experiments for structurally similar compounds, *viz.*, 3-aminomethyl-1-ethyl-3-methyldiaziridine and its *N*-acetyl derivative.[19] Ap-

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* Since the details of the synthesis as well as physicochemical and spectroscopic characteristics of compounds **6a** and **7** have not been reported in the cited study,[15] these data are presented in this paper.

Table 1. Yields, reaction times (*t*), diastereomer ratios, and selected physicochemical characteristics of 1,3,6-triazabicyclo[3.1.0]hexanes **5**

Compound	Yield (%) (diastereomer ratio)	M.p./°C	*t*/h	R_f [a]	Found / Calculated (%)			Molecular formula
					C	H	N	
5c′ + **5c″**	90 (5 : 1)	70—110	24	0.35	65.03	7.21	20.15	$C_{11}H_{15}N_3O$
5c′	60	108—110			64.37	7.37	20.47	
5d′ + **5d″**	87 (3 : 1)	50—70	100	0.37	40.19	5.02	15.02	$C_9H_{12}BrN_3S$
5d′ [b]	45	68—70			39.43	4.41	15.33	
5e′ + **5e″**	82 (3 : 1)	43—79	48	0.41	66.37	8 .02	18.56	$C_{12}H_{17}N_3O$
5e′	51	78—79			65.73	7.81	19.16	
5f′ + **5f″**	67 (≥20 : 1)	176—177	24	0.31	60.13	6.25	17.96	$C_{11}H_{15}N_3O_2$
					59.71	6.83	18.99	
5h	78	110—111	5	0.30	65.23	7.87	20.64	$C_{14}H_{20}N_4O$
					64.59	7.74	21.52	

[a] The following eluents were used: $CHCl_3$—MeOH, 9 : 1 (**5c—f**); $CHCl_3$—MeOH, 15 : 1 (**5h**).

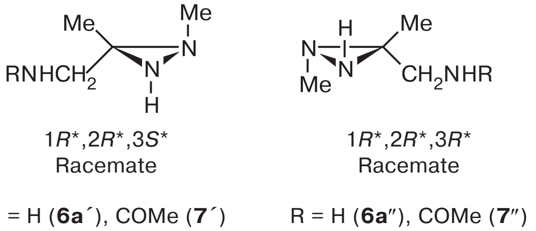
[b] Found (%): S, 11.71; Br, 29.90. Calculated (%): S, 11.69; Br, 29.14.

Table 2. Data from IR spectroscopy and ^{1}H and ^{13}C NMR spectroscopy for 1,3,6-triazabicyclo[3.1.0]hexanes **5**

Compound	IR, ν/cm^{-1} *	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)	^{13}C NMR ($CDCl_3$), δ (*J*/Hz)
5c	3256, 2968, 2912, 2856, 1588, 1488, 1480, 1468, 1400, 1344, 1296, 1248, 1064, 1032, 1032, 1024, 1016, 944, 936, 920, 880, 824, 752, 720, 676, 648	**5c′**: 1.62 (s, 3 H, CMe); 2.58 (s, 3 H, NMe); 2.92, 3.44 (AB system, 2 H, CCH_2N, ^2J = –12.0); 4.77 (s, 1 H, CH); 6.90—7.04 (m, 4 H, Ar). **5c″**: 1.49 (s, 3 H, CMe); 2.60 (s, 3 H, NMe); 3.17, 3.58 (AB system, 2 H, CCH_2N, ^2J = –12.0); 5.22 (s, 1 H, CH); 6.94—7.10 (m, 4 H, Ph)	**5c′**: 11.3 (C$\underline{Me}$); 38.1 (NMe); 52.9 (N$\underline{C}$H$_2$C); 68.4 (C); 82.1 (CH); 117.6, 119.6, 121.9, 129.9, 155.6 (Ar). **5c″**: 10.9 (C$\underline{Me}$); 38.9 (NMe); 50.4 (N$\underline{C}$H$_2$C); 67.8 (C); 80.3 (CH); 116.7, 118.9, 121.2, 130.9, 156.8 (Ar)
5d	3432, 3280, 2960, 2904, 2864, 2856, 1468, 1440, 1232, 1184, 1072, 984, 968, 872, 856, 840, 792, 736, 688	**5d′**: 1.54 (s, 3 H, CMe); 2.53 (s, 4 H, NH + NMe); 2.77, 3.28 (AB system, 2 H, CCH_2N, ^2J = –12.0); 4.82 (s, 1 H, CH); 6.87, 6.92 (both m, 1 H each, Het). **5d″**: 1.50 (s, 3 H, CMe); 2.54 (s, 4 H, NH + NMe); 2.51, 3.29 (AB system, 2 H, CCH_2N, ^2J = –12.0); 5.58 (s, 1 H, CH); 6.91, 6.96 (both m, 1 H each, Het)	**5d′**: 11.2 (C$\underline{Me}$); 38.6 (NMe); 53.4 (N$\underline{C}$H$_2$C); 68.6 (C); 79.5 (CH); 126.6, 128.6, 129.0, 142.1 (Het). **5d″**: 10.0 (C$\underline{Me}$); 38.8 (NMe); 51.4 (N$\underline{C}$H$_2$C); 69.7 (C); 79.3 (CH); 125.0, 128.2, 129.9, 142.3 (Het)
5e	3264, 2928, 2912, 2904, 2848, 1612, 1512, 1476, 1460, 1448, 1336, 1296, 1280, 1248, 1168, 1080, 1032, 1000, 888, 816, 800, 748	**5e′**: 1.51 (s, 3 H, CMe); 2.48 (br.s, 1 H, NH); 2.52 (s, 3 H, NMe); 2.73, 3.27 (AB system, 2 H, CCH_2N, ^2J = –12.0); 3.85 (s, 3 H, OMe); 4.60 (s, 1 H, CH); 6.90, 7.50 (both m, 2 H each, Ar). **5e″**: 1.50 (s, 3 H, CMe); 2.48 (br.s, 1 H, NH); 2.54 (s, 3 H, NMe); 2.62, 3.12 (AB system, 2 H, CCH_2N, ^2J = –12.0); 3.84 (s, 3 H, OMe); 5.10 (s, 1 H, CH); 6.85, 7.48 (both m, 2 H each, Ar)	**5e′**: 11.1 (C$\underline{Me}$); 38.9 (NMe); 53.0 (N$\underline{C}$H$_2$C); 55.3 (OMe); 67.0 (C); 82.1 (CH); 113.8, 128.3, 129.7, 159.5 (Ar). **5e″**: 11.2 (C$\underline{Me}$); 39.0 (NMe); 51.3 (N$\underline{C}$H$_2$C); 55.3 (OMe); 68.3 (C); 81.9 (CH); 113.6, 128.1, 129.7, 158.9 (Ar)
5f′	3312, 2992, 2960, 2936, 2704, 1692, 1628, 1612, 1600, 1516, 1480, 1456, 1432, 1396, 1384, 1304, 1208, 1192, 1180, 1152, 1120, 1096, 1032, 984, 780	1.62 (s, 3 H, CMe); 2.58 (s, 3 H, NMe); 3.50, 4.15 (AB system, 2 H, CCH_2N, ^2J = –12.0); 3.95 (t, 2 H, *o*-OH + NH); 5.39 (s, 1 H, CH); 6.25, 7.03 (both m, 1 H each, Ar); 6.35 (s, 1 H, Ar); 10.5 (br.s, 1 H, *p*-OH)	11.1 (C$\underline{Me}$); 39.4 (NMe); 56.0 (N$\underline{C}$H$_2$C); 66.5 (C); 81.5 (CH); 133.8, 144.0, 128.3, 154.7, 159.5, 125.6 (Ar)
5h	3304, 2968, 2936, 1648, 1620, 1596, 1544, 1512, 1500, 1464, 1456, 1444, 1368, 1320, 1232, 1168, 760, 728, 696	1.62 (s, 3 H, CMe); 2.13 (s, 3 H, NMe); 3.48, 4.15 (AB system, 2 H, CCH_2N, ^2J = 12.0); 1.51, 1.57 (both s, 3 H each, Me); 7.54—7.90 (m, 5 H, Ph)	12.3 (C(5)$\underline{Me}$); 24.6, 28.0 (both C(2)$\underline{Me}$); 38.1 (NMe); 52.9 (N$\underline{C}$H$_2$C); 68.4 (C); 82.1 (CH); 117.6, 119.6, 121.9, 129.9, 155.6 (Ph)

* For compounds **5c—e**, absorption bands for mixtures of diastereomers are given.

parently, inverse epimerization of the diastereomers took place under the reaction conditions as one of the diastereomers was involved in the reaction (**6a″** → **6a′**). This assumption does not contradict the published data on the inversion barriers of alkyl-substituted diaziridines.[19—21]



The predominant diastereomers **5c′**,**d′** of compounds **5c**,**d** were studied by X-ray diffraction analysis (Figs. 1 and 2). The principal geometric parameters of the compounds are close to the expected values (Table 3). The five-membered rings adopt an envelope conformation with the N(3) atom deviating from the planes through the remaining four atoms of the rings by 0.18 and 0.38 Å. The dihedral angle between the diaziridine ring and the N(1)C(2)C(4)C(5) plane is 96 and 102° in **5c′** and **5d′**, respectively. Hence, the overall conformation of the bicyclic core in diastereomers **5c′** and **5d′** can be described as a boat.

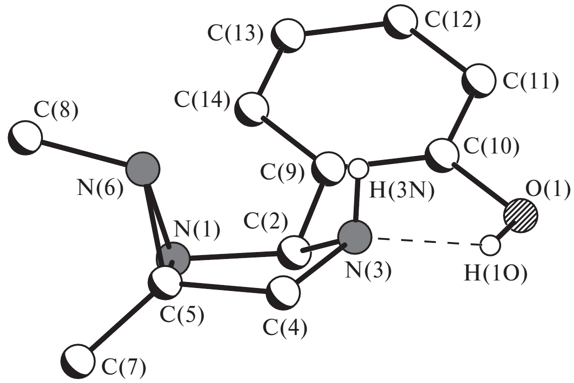


Fig. 1. Overall molecular view of diastereomer **5c′** (H atoms, which are not involved in hydrogen bonding, are omitted).

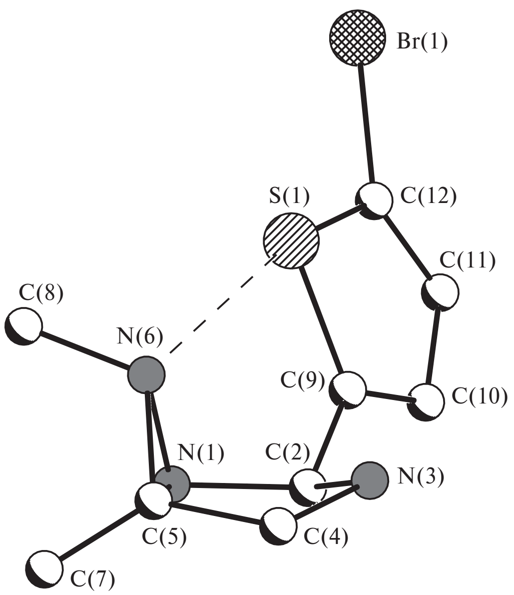


Fig. 2. Overall molecular view of diastereomer **5d′**.

Table 3. Bond lengths (*d*) and bond angles (ω) in the bicyclic fragments of diastereomers **5c′** and **5d′**

Parameter	**5c′**	**5d′**
Bond	*d*/Å	
N(1)—C(2)	1.475(3)	1.493(5)
N(1)—C(5)	1.464(3)	1.455(5)
N(1)—N(6)	1.512(2)	1.522(5)
N(3)—C(2)	1.466(3)	1.453(5)
N(3)—C(4)	1.466(3)	1.473(5)
N(6)—C(5)	1.452(3)	1.462(5)
N(6)—C(8)	1.464(3)	1.451(5)
C(4)—C(5)	1.520(3)	1.515(6)
Angle	ω/deg	
C(5)—N(1)—C(2)	104.3(1)	105.1(3)
C(5)—N(1)—N(6)	58.4(1)	58.8(2)
C(2)—N(1)—N(6)	108.4(1)	106.0(3)
C(2)—N(3)—C(4)	103.4(2)	104.7(3)
C(5)—N(6)—N(1)	59.2(1)	58.3(2)
C(8)—N(6)—N(1)	109.7(2)	110.2(3)
N(3)—C(4)—C(5)	105.2(2)	105.5(3)
N(1)—C(5)—N(6)	62.5(1)	62.9(3)
N(1)—C(5)—C(4)	108.0(2)	108.0(3)
N(6)—C(5)—C(4)	110.9(2)	111.5(3)
N(3)—C(2)—N(1)	109.9(2)	109.8(3)

The N(1)—N(6) bond length in **5c′** and **5d′** is virtually equal to the corresponding bond length in bidiaziridine (1.512 Å).[22] A slight elongation of this bond in **5d′** as well as the differences in the C(2)—N(1) and C(2)—N(3) bond lengths in **5c′** and **5d′** are, apparently, attributed to the electron-withdrawing effect of the bromothiophene substituent.

In addition to variations in the geometry of the bicycle, the nature of the substituent at the C(2) atom also has a substantial effect on the supramolecular structures of these compounds. Thus, diastereomer **5c′** crystallizes as a racemic compound (space group $P\bar{1}$), whereas diastereomer **5d′** provides a rather rare example of crystallization as a conglomerate (space group $P2_12_12_1$). The crystal under study is one of the enantiomers. This is the first instance of a compound of the diaziridine series, which crystallizes as a conglomerate.

In diastereomer **5c′**, the OH group of the substituent is involved in the intramolecular N(3)...H(1O)—O(1) hydrogen bond (N(3)...O(1), 2.751(3) Å; H(1O)...N(3), 2.01 Å; the N(3)H(1O)O(1) angle is 143°) with the closure of the six-membered H-bonded ring (see Fig. 1), which is, apparently, responsible for the observed flattening of the five-membered ring. In addition to the intramolecular hydrogen bond, the N(3) atom is involved in the weak intermolecular N(3)—H(3)...N(6′) hydrogen bond (N(3)...N(6′), 3.200(3) Å; H(3N)...N(6′), 2.43 Å; the N(3)H(3N)N(6′) angle is 150°) through which the molecules are linked in centrosymmetrical dimers. These dimers, in turn, are linked in heterochiral chains along the crystallographic axis *b* (Fig. 3, *a*) through the C(2)—H(2)...N(1″) contacts (H(2)...N(1″), 2.38 Å; C(2)...N(1″), 3.304(3) Å; the C(2)H(3)N(1″) angle is 144°).

In the crystal structure of **5d′**, the bromothiophene substituent, in spite of the absence of protons susceptible to hydrogen bonding, is also involved in an intramolecular contact, which, apparently, plays an important role in the formation of a homochiral packing. In diastereomer **5d′**, the S(1) atom forms a shortened directed contact with the N(6) atom (S(1)...N(6), 2.928(5) Å, the N(6)S(1)C(12) angle is 164°) thus hindering the formation of the above-described dimers. As a result, the H(3N) atom of the NH group forms an intermolecular hydrogen bond with the N(1) atom (H(3N)...N(1′), 2.33 Å; N(3)...N(1″), 3.215(5) Å, the N(3)H(3N)N(1″) angle is 162°), which is similar in strength to that present in **5c′**. These bonds link the molecules in helices along the crystallographic axis *a* (see Fig. 3, *b*).

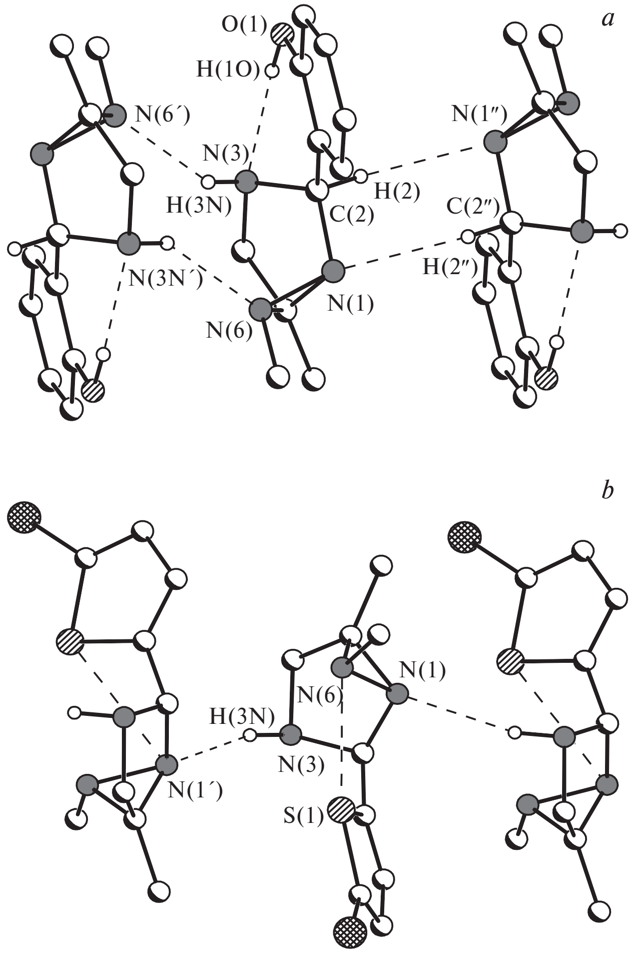


Fig. 3. Formation of hydrogen-bonded heterochiral chains in the crystal structure of diastereomer **5c′** (*a*) and homochiral helices in the crystal structure of diastereomer **5d′** (*b*) (H atoms, which are not involved in hydrogen bonding, are omitted).

It should be noted that the homo- and heterochiral H-bonded motifs in the structures of **5c′** and **5d′** are quasi-isomorphous (see Fig. 3), which is manifested, in particular, in the similarity of the corresponding unit cell parameters, *viz.*, *b* (8.272(5) Å) in **5c′** and *a* (8.6019(8) Å) in **5d′**. This fact enables one to use this series of compounds for the preparation of other conglomerates based on self-assembly of homochiral molecules in the crystals through N—H...N hydrogen bonds.

In spite of the fact that only compounds **5c′**,**d′** were studied by X-ray diffraction analysis, it can be stated with assurance that the predominant diastereomers of compounds **5e**,**f** are also the 1*R**,2*R**,5*R**,6*R** racemates (**5e′**,**f′**), whereas those of compounds **5a**,**b**,**h** are the 1*R**,5*R**,6*R** racemates. This assumption is based on the facts that these compounds adopt similar conformations (the *cis* arrangement of the Me groups at the C(5) and N(6) atoms and the axial position of the substituent at the C(2) atom) in the crystals, on the one hand, and that the corresponding NMR spectra have virtually identical chemical shifts of the H and C atoms of the Me groups and the bicyclic core, on the other hand. Hence, these reactions with aldehydes proceed diastereoselectively.

Experimental

The IR spectra were recorded on a UR-20 instrument in KBr pellets. The ^1H and ^{13}C NMR spectra were measured on Bruker WM-250 (250 MHz) and Bruker AM-300 (75.5 MHz) spectrometers, respectively. The TLC analysis was carried out on Silufol UV-254 plates (spots were visualized with iodine vapor, UV light, and a solution of diphenylamine in acetone followed by heating of the plates). The melting points were determined on a Boetius PHMK 05 stage. X-ray diffraction studies were carried out on a Smart 1000 CCD diffractometer.

(1*R,2*R**,3*S** + 1*R**,2*R**,3*R**)-3-(Acetamidomethyl)-1,3-dimethyldiaziridine (7′ + 7″).** *N*-Acetamidoacetone (8 g, 0.07 mol) was added to a solution of methylamine (11 g, 0.35 mol) in MeOH (80 mL) at the temperature from –60 to –50 °C and then 96% hydroxylamino-*O*-sulfonic acid (8.4 g, 0.07 mol) was added portionwise for 20 min. The reaction mixture was kept at this temperature for 2 h, then at 0—5 °C for 6 h, and finally at 18—20 °C for 12 h. The precipitate was filtered off and washed with MeOH. The solvent was evaporated *in vacuo*. The residue was dissolved in water, saturated with K_2CO_3, and extracted with $CHCl_3$ (3×50 mL). The extract was dried over K_2CO_3, the solvent was distilled off, and the residue was distilled *in vacuo*. A mixture of diastereomers **7´** + **7″** was obtained in a yield of 6.0 g (60%) in a ratio of 5 : 1, b.p. 123—124 °C (3 Torr), R_f 0.41 (MeOH), n_D^{20} 1.4528. IR, ν/cm^{-1}: 1010, 1050, 1080, 1110, 1130, 1160, 1290, 1380, 1410, 1450, 1560, 1580, 1650, 1670, 2950, 2980, 3100, 3300. ^{1}H NMR (CDCl$_3$), δ: **7´** 1.35 (s, 3 H, CCMe); 1.93 (s, 3 H, COMe); 2.20 (br.s, 1 H, HNN); 2.41 (s, 3 H, NMe); 3.15 and 3.71 (AB system, 2 H, NCH$_2$C, ^2J = 14.5 Hz); 6.12 (br.s, 1 H, NHCO); **7″** 1.39 (s, 3 H, CCMe); 2.00 (s, 3 H, COMe); 2.20 (br.s, 1 H, HNN); 2.51 (s, 3 H, NMe); 3.45 and 3.91 (AB system, 2 H, NCH$_2$C, ^2J = 14.5 Hz); 6.53 (br.s, 1 H, NHCO).

(1*R,2*R**,3*S** + 1*R**,2*R**,3*R**)-3-(Aminomethyl)-1,3-dimethyldiaziridine (6a´ + 6a″).** 3-(Acetamidomethyl)-1,3-dimethyldiaziridine **7** (6 g, 0.042 mol) was added to a 20% aqueous solution of KOH (30 mL). The reaction mixture was heated to 60 °C and stirred at this temperature for 24 h. The course of the reaction was monitored by TLC (MeOH as the eluent). The resulting solution was saturated with K$_2$CO$_3$, the upper layer was separated, and the aqueous layer was extracted with Et$_2$O (3×50 mL). The combined extracts were concentrated *in vacuo*, the residue was distilled off over solid alkali (KOH), and the fraction with the b.p. 60—63 °C (15 Torr) was collected. A mixture of diastereomers **6a´** + **6a″** was obtained in a yield of 0.85 g (20%) in a ratio of 3 : 1, R_f 0.43 (MeOH—NH$_3$ (20%), 5 : 1), n_D^{20} 1.3770. IR, ν/cm^{-1}: 1040, 1100, 1130, 1160, 1260, 1310, 1400, 1450, 1560, 2800, 2880, 2950, 3300. ^{1}H NMR (CDCl$_3$), δ: **6a´** 1.33 (s, 3 H, CMe); 1.52 (br.s, 2 H, NH$_2$); 2.47 (s, 3 H, NMe); 2.70 and 3.02 (AB system, 2 H, NCH$_2$C, ^2J = 12 Hz); 2.75 (br.s, 1 H, NH); **6a″** 1.32 (s, 3 H, CMe); 1.52 (br.s, 2 H, NH$_2$); 2.46 (s, 3 H, NMe); 2.65 and 2.97 (AB system, 2 H, NCH$_2$C, ^2J = 12 Hz); 2.75 (br.s, 1 H, NH).

Substituted 1,3,6-triazabicyclo[3.1.0]hexanes 5c—g (general procedure). The corresponding carbonyl compound (2.97 mmol) and K$_2$CO$_3$ (1 g, 5.84 mmol) were added to a solution of compound **6a** (0.3 g, 2.97 mmol) in dry CHCl$_3$ (20 mL). The reaction mixture was refluxed for 24—100 h, the course of the reaction being monitored by TLC. After completion of the reaction, the precipitate was filtered off and washed with dry CHCl$_3$. The solvent was removed *in vacuo*. Compounds **5c—g** were isolated by column chromatography (silica gel 40/100 μm, a 9 : 1 CHCl$_3$—MeOH mixture as the eluent) followed by recrystallization from hexane. Mixtures of the diastereomers (1*R**,2*R**,5*R**,6*R** + 1*R**,2*S**,5*R**,6*R**)-2-(2-hydroxyphenyl)-5,6-dimethyl-1,3,6-triazabicyclo[3.1.0]hexane (**5c´** + **5c″**, 0.55 g), (1*R**,2*R**,5*R**,6*R** + 1*R**,2*S**,5*R**,6*R**)-2-(2-bromothien-5-yl)-5,6-dimethyl-1,3,6-triazabicyclo[3.1.0]hexane (**5d´** + **5d″**, 0.68 g), and (1*R**,2*R**,5*R**,6*R** + 1*R**,2*S**,5*R**,6*R**)-2-(4-methoxyphenyl)-5,6-dimethyl-1,3,6-triazabicyclo[3.1.0]hexane (**5e´** + **5e″**, 0.53 g) were obtained. The diastereomer 1*R**,2*R**,5*R**,6*R**-2-(2,4-dihydroxyphenyl)-5,6-dimethyl-1,3,6-triazabicyclo[3.1.0]hexane (**5f´**, 0.44 g) and the diastereomer 1*R**,5*R**,6*R**-2,2,5,6-tetramethyl-1,3,6-triazabicyclo[3.1.0]hexane (**5g**) (0.31 g (75%)) were prepared.

Fractional crystallization of mixtures of the diastereomers of **5c—e** from hexane afforded racemates **5´**: **5c´** (0.37 g), **5d´** (0.36 g), and **5e´** (0.33 g).

(1*R,5*R**,6*R**)-2,2,5,6-Tetramethyl-3-(*N*-phenylcarboxamido)-1,3,6-triazabicyclo[3.1.0]hexane (5h).** Phenyl isocyanate (0.26 g, 2.25 mmol) was added dropwise to a solution of compound **5g** (0.31 g, 2.20 mmol) in dry CHCl$_3$ (30 mL). The reaction mixture was refluxed for 5 h and the solvent was concentrated *in vacuo*. The residue was washed with dry Et$_2$O and dried in air. Triazabicyclohexane **5h** was obtained in a yield of 0.45 g.

X-ray diffraction study of diastereomers 5c´ and 5d´. All X-ray data were collected on a Bruker SMART 1000K CCD diffractometer with the use of the SMART control program.[23] Three sets of frames corresponding to a hemisphere of reciprocal space were processed with the use of the SAINT Plus program[23] and merged using the SADABS program.[24] The structures were solved by direct methods and refined by the full-matrix least-squares method in the anisotropic-isotropic approximation based on F^2. The positions of the H atoms, except for the atoms of the NH and OH groups, were calculated geometrically and refined using the riding model. The refinement of the Flack parameter[25] demonstrated that diastereomer **5d´** is characterized by partial racemic twinning caused, apparently, by lamellar epitaxy, which did not allow us to unambiguously determine the absolute configurations of the asymmetric

Table 4. Principal details of X-ray study and crystallographic parameters of diastereomers **5c´** and **5d´**

Parameter	5c´	5d´
Diffractometer	«SMART 1000K CCD»	
Molecular formula	$C_{11}H_{15}N_3O$	$C_9H_{12}BrN_3S$
M	205.26	274.19
T/K	110	
Radiation	λ(Mo-Kα) = 0.71072 Å	
Space group	$P\bar{1}$	$P2_12_12_1$
a/Å	7.009(4)	8.6019(8)
b/Å	8.272(5)	10.591(1)
c/Å	10.080(6)	11.752(1)
α/deg	73.19(1)	—
β/deg	80.02(1)	—
γ/deg	75.11(1)	—
V/Å^3	537.5(6)	1070.6(2)
Z	2	4
d_{calc}/g cm^{-3}	1.268	1.701
μ/cm^{-1}	0.85	39.98
F(000)	220	552
Scan mode	ω, scan step was 0.3°, exposition time of each frame was 10 s	
$2\theta_{max}$/deg	54	58
Number of measured reflections	3510	8006
Number of independent reflections (R_{int})	2271 (0.0339)	2606 (0.0195)
Number of observed reflections with $I > 2\sigma(I)$	1393	2097
Flack parameter	—	0.35(2)
R_1 (based on F for reflections with $I > 2\sigma(I)$)	0.0605	0.0423
wR_2 (based on F^2 for all reflections)	0.1524	0.1088
GOF	1.004	1.011

centers. All calculations were carried out with the use of the SHELXTL PLUS program package[26] (version 5.10).

The principal details of X-ray diffraction analysis are given in Table 4.

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