Asymmetric nitrogen

77.[*] Molecular structure of 3-methyl-1-((*S*)-1′-tosylprolyl)-1,2-diazacyclohex-2-ene

S. V. Konovalikhin,[a*] A. B. Zolotoi,[a] L. O. Atovmyan,[a] G. V. Shustov,[b]
S. N. Denisenko,[b] and R. G. Kostyanovsky[b]

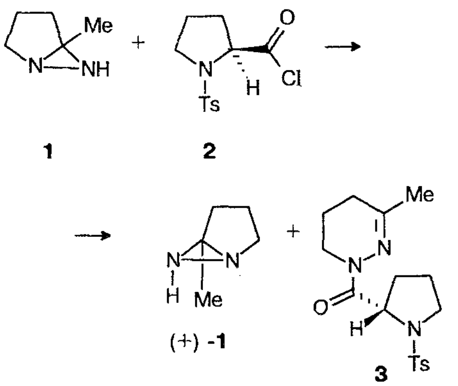
[a]*Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences,*
142432 Chernogolovka, Moscow Region, Russian Federation.
Fax: +7 (095) 265 5714
[b]*N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences,*
4 ul. Kosygina, 117977 Moscow, Russian Federation.
Fax: +7 (095) 938 2156

The molecular structure of 3-methyl-1-((*S*)-1′-tosylprolyl)1,2-diazacyclohex-2-ene, the product of the reaction of 5-methyl-1,6-diazabicyclo[3.1.0]hexane with (*S*)-*N*-tosylproline chloride, has been established by X-ray structural analysis. The pyrrolidine cycle has a half-chair conformation with the pyramidal nitrogen atom; the tosyl and pseudo axial carbamoyl groups have *trans* orientations. The diazacyclohexene cycle has an envelope conformation with folding along the C(7)...C(9) line. The stereochemistry of the transition state of the above-mentioned reaction is discussed.

Key words: molecular structure, conformation, proline, hydrazone, diaziridine.

Previously, a simple and efficient method for optical activation of 1,3,3-trialkyldiaziridines was found.[2,3] For example, the optical yield of the reaction of the racemate of 5-methyl-1,6-diazabicyclo[3.1.0]hexane (**1**) with a half-molar amount of (*S*)-*N*-tosylproline chloride (**2**) runs as high as 75%.[3]

Scheme 1



When performing kinetic enrichment, attention has been generally focused on optically active diaziridines, whereas the product of the reaction of acid chloride **2** with diaziridine has not been obtained in the pure state, and, correspondingly, direct evidence of the structure of this product is unavailable. Nevertheless, a knowledge of the structure of this compound is of fundamental importance for constructing a stereochemical model for the transition state of acylation of 1,3,3-trialkyldiaziridines, in which two nitrogen atoms are the competing nucleophile centers.[3] The attack of acid chloride **2** at the nonsubstituted nitrogen atom should give *N*-acyldiaziridine, whereas the attack at the alkylated nitrogen atom should afford the corresponding *N*-acylhydrazone.

In this work, we isolated the product of the reaction of diaziridine **1** with acid chloride **2** in the pure state; the structure of this product was studied by X-ray structural analysis and ^{13}C NMR spectroscopy.

Experimental

The ^{13}C NMR spectrum (20.15 MHz) was obtained on a Bruker WP 80 SY spectrometer in $CDCl_3$; the IR spectrum was recorded on a UR-20 spectrophotometer using KBr pellets; optical rotation was measured on a Polamat A polarimeter.

3-Methyl-1-((*S*)-1′-tosylprolyl)-1,2-diazacyclohex-2-ene (**3**). A solution of (*S*)-*N*-tosylproline chloride **2** (1.44 g, 5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise with cooling and stirring to a solution of diaziridine **1** (0.98 g, 10 mmol) in anhydrous CH_2Cl_2 (15 mL), and then a solution of triethylamine (0.71 g, 7 mmol) in anhydrous CH_2Cl_2 (5 mL) was added. The solution was kept at −70°C for 5 days, then the temperature was slowly raised to 20°C, the precipitate was

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[*] For the previous communication, see Ref. 1.

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Table 1. Coordinates for nonhydrogen atoms (×10^4) in the structure of **3**

Atom	*x*	*y*	*z*
S	851(1)	2125(1)	63(1)
O(1)	−182(3)	2081(2)	990(4)
O(2)	1861(3)	1854(2)	788(5)
O(3)	983(3)	462(2)	−2661(5)
N(1)	655(3)	1753(2)	−1787(5)
N(2)	2809(3)	59(2)	−3183(5)
N(3)	3664(3)	1049(2)	−3551(5)
C(1)	−359(4)	1912(3)	−2839(7)
C(2)	2(5)	1739(3)	−4689(7)
C(3)	1262(5)	1833(3)	−4692(7)
C(4)	1627(4)	1589(2)	−2892(6)
C(5)	1771(4)	838(2)	−2890(6)
C(6)	4632(4)	839(2)	−3802(7)
C(7)	5007(4)	125(3)	−3672(9)
C(8)	4170(5)	−286(2)	−2671(8)
C(9)	2992(4)	−127(2)	−3315(7)
C(10)	5540(5)	1355(3)	−4207(9)
C(11)	1084(3)	2972(2)	−391(5)
C(12)	2172(3)	3193(2)	−71(5)
C(13)	2351(4)	3852(2)	−1092(9)
C(14)	1476(4)	4303(2)	−1172(6)
C(15)	388(4)	4074(2)	−883(7)
C(16)	195(3)	341(2)	−471(7)
C(17)	166(5)	5035(2)	−1595(11)

Table 2. Bond lengths (*d*/Å) and bond angles (ω/deg) in molecule **3**

Bond	*d*	Bond	*d*
S—N(1)	1.622(3)	S—O(1)	1.426(1)
S—O(2)	1.433(3)	S—C(11)	1.763(3)
O(3)—C(5)	1.218(5)	N(1)—C(1)	1.489(6)
N(1)—C(4)	1.474(5)	N(2)—N(3)	1.404(4)
N(2)—C(5)	1.353(5)	N(2)—C(9)	1.463(4)
N(3)—C(6)	1.243(5)	C(1)—C(2)	1.523(7)
C(2)—C(3)	1.514(5)	C(3)—C(4)	1.529(7)
C(4)—C(5)	1.523(5)	C(6)—C(7)	1.510(6)
C(6)—C(10)	1.532(7)	C(7)—C(8)	1.506(7)
C(8)—C(9)	1.522(7)	C(11)—C(12)	1.393(5)
C(11)—C(16)	1.379(5)	C(12)—C(13)	1.375(6)
C(13)—C(14)	1.385(6)	C(14)—C(15)	1.394(6)
C(14)—C(17)	1.525(6)	C(15)—C(16)	1.393(6)
Angle	ω	Angle	ω
O(1)SO(2)	120.5(2)	O(1)SN(1)	106.4(2)
O(1)SC(11)	107.2(2)	O(2)SN(1)	106.5(2)
O(2)SC(11)	108.3(2)	N(1)SC(11)	107.3(2)
SN(1)C(1)	119.5(3)	SN(1)C(4)	119.6(3)
C(1)N(1)C(4)	112.0(4)	N(3)N(2)C(5)	117.0(3)
N(3)N(2)C(9)	121.8(3)	C(5)N(2)C(9)	120.8(3)
N(2)N(3)C(6)	118.7(3)	N(1)C(1)C(2)	103.1(4)
C(1)C(2)C(3)	104.7(4)	C(2)C(3)C(4)	104.0(4)
N(1)C(4)C(3)	102.9(4)	N(1)C(4)C(5)	108.1(3)
C(3)C(4)C(5)	110.6(4)	O(3)C(5)C(4)	122.1(4)
O(3)C(5)C(6)	119.9(3)	C(4)C(5)C(6)	118.0(3)
N(3)C(6)C(7)	126.0(4)	N(3)C(6)C(10)	117.2(4)
C(7)C(6)C(10)	116.7(4)	C(6)C(7)C(8)	111.2(4)
C(7)C(8)C(9)	109.2(4)	N(2)C(9)C(8)	108.8(3)
SC(11)C(12)	119.3(3)	SC(11)C(16)	120.4(3)
C(12)C(11)C(16)	120.2(4)	C(11)C(12)C(13)	119.3(4)
C(12)C(13)C(14)	121.7(4)	C(13)C(14)C(15)	118.4(4)
C(13)C(14)C(17)	122.4(4)	C(15)C(14)C(17)	119.2(4)
C(14)C(15)C(16)	120.5(4)	C(11)C(16)C(15)	119.8(4)

filtered off, the filtrate was evaporated *in vacuo*, and the products were extracted from the residue with absolute ether. After the removal of ether and excess diaziridine **1** *in vacuo*,[3] the residue was washed with water, dried *in vacuo*, and recrystallized from *i*-PrOH. The yield of *N*-acylhydrazone **3** was 1.47 g (84%), m. p. 116—117 °C, $[\alpha]^{20}{}_D$ −177.3° (*c* 1, MeOH). Found (%): C, 58.42; H, 6.71; N, 11.94. $C_{17}H_{23}N_3O_3S$. Calculated (%): C, 58.43; H, 6.63; N, 12.02. IR (ν/cm^{-1}): 1675, 1645. ^{13}C NMR (partial ^1H decoupling, δ) 17.63 (t, C(5)), 21.48 (t, C(4)), 24.25 (q, MeAr), 24.68 (t, C(4′)), 26.58 (q, MeC=N), 31.29 (t, C(3′)), 38.3 (t, C(6)), 48.9 (t, C(5′)), 58.24 (d, C(2′)), 127.7, 129.4, 136.44, 143.0 (C_6H_4), 150.14 (C=N), 171.66 (C=O).

X-ray structural study. The principal crystallographic data for crystals of **3**: $C_{17}H_{23}N_3O_3S$, M = 348.4, a = 11.919(2), b = 20.144(6), c = 7.672(3) Å, the space group is $P2_12_12_1$, V = 1842.0(7) Å^3, d_{calc}= 1.26 g/cm^3. Intensities of 1800 reflections with $I > 3\sigma(I)$ were measured on a three-circle automated DAR-UM diffractometer using Cu K_α radiation (absorption was ignored, μ(CuKα) = 16.9 cm^{-1}). The structure was solved by the direct method and from a series of subsequent Fourier syntheses. The anisotropic least-squares refinement for all nonhydrogen atoms converged to R = 0.075. All calculations were performed using the Rentgen-75 program. Atomic coordinates are given in Table 1; the bond lengths and bond angles are listed in Table 2.

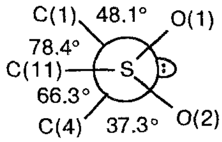
Results and Discussion

The ^{13}C NMR spectrum of the compound obtained shows the ^{13}C signal of the C=N double bond at 150 ppm, whereas the characteristic ^{13}C signal of the diaziridine cycle in the 73—80 ppm region[5] is absent, which supports *N*-acylhydrazone **3**. X-Ray structural analysis demonstrated that this compound has the structure of 3-methyl-1-((*S*)-1′-tosylprolyl)-1,2-diazacyclohex-2-ene **3** and is a new derivative of (*S*)-proline. The principal structural parameters of the tosylproline fragment of molecule **3** are close to those found previously for other derivatives of *N*-tosylproline.[6]

The conformation of the toluenesulfonylamide fragment of molecule **3** along the *S*—N(1) bond is shown in Scheme 2. The C(Ar)SNC torsion angles are in the range 65—80 °, which is typical of molecules containing the $ArSO_2NR_2$ fragment.[7] This conformation leads to a decrease in the OSN(1)C torsion angles (Scheme 2) and, correspondingly, to the appearance of shortened O(1)...C(1) and O(2)...C(4) contacts (2.965 and 2.887 Å, respectively).

The bond lengths and bond angles in the toluenesulfonyl fragment of molecule **3** are close to normal values. The S—C(11) bond (1.763 Å) is slightly shortened compared to those in phenyl sulfides,[8,9] which is indicative

Scheme 2

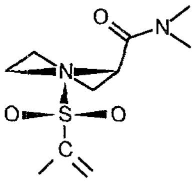


of the presence of weak orbital interactions between the aryl ring and the sulfonyl group resulting in strengthening of the S—C(Ar) bond.

According to the Cambridge Structural Database, the S—N bond length in arenesulfonamides varies from 1.596[10] to 1.653 Å[11] and is substantially shorter than that in sulfenamides (1.688 Å).[8] According to the data of Refs. 7 and 11, no correlation between the S—N bond length and the torsion angles in arenesulfonamides is observed, which may provide partial proof of the existence of n(N)—d(S) interactions in these fragments. Other types of interactions (Coulomb, steric, *etc.*) affecting the geometry of the fragment under consideration are also possible. Hence, the wide range of S—N bond lengths in arenesulfonamides is attributable to the combined effect of a number of factors.

The pyrrolidine cycle has a half-chair conformation with a right-twisted skew about the C_2 local symmetry axis passing through the N(1) atom and the middle of the C(2)—C(3) bond (Scheme 3). The C(2) and C(3) atoms deviate from the mean plane of the cycle by −0.222 and 0.210 Å, respectively.

Scheme 3



According to the results of gas phase electron diffraction analysis and *ab initio* quantum-chemical calculations,[12] the most favorable conformation of *N*-methylpyrrolidine is an envelope with the nitrogen atom deviating from the mean plane of the cycle. However, when a π or d acceptor substituent is introduced, the most favorable conformation is a half-chair,[5] similar to that observed for compound **3**.

Unlike the planar nitrogen atom in *N*-acyl derivatives of proline,[6] the N atom in *N*-tosylprolines and, specifically, in molecule **3** is slightly pyramidalized because n(N)—d(S) conjugation in *N*-tosylprolines is less efficient than n(N)—π^*(C=O) conjugation in *N*-acylprolines. Minimization of steric interactions between the tosyl and carbamoyl groups leads to their mutual *trans* arrangement with the pseudoaxial orientation of the latter.

The angle between the mean plane of the pyrrolidine cycle and the plane of the C(4)C(5)O(3)N(2) amide group is 89.5°; the N(1)C(4)C(5)O(3) torsion angle is 27.7°. Realization of this conformation along the C(4)—C(5) bond causes the two electronegative N(1) and O(3) atoms to approach each other to 2.714 Å. As a result, the C(4)C(5)O(3) angle increases to 122.1° compared to the remaining bond angles at the C(5) atom, and the C(4)—C(5) bond lengthens to 1.523 Å (the average $C(sp^3)$—C=O bond lengths is 1.511 Å).[13] According to the results of the PM3 quantum-chemical calculations of molecule **3**, the barrier of rotation about the C(4)—C(5) bond is 25 kcal/mol. Hence, the final product of the reaction (Scheme 1) should retain the conformation of the initial *N*-tosylproline chloride. The latter suggests that in solution molecule **2** has a conformation with the *gauche* orientation of the C=O and C—N bonds. This is supported by the results of the PM3 quantum-chemical calculations of molecule **2**, according to which the conformer with the N—C—C=O torsion angle of 36.7° is the most energetically favorable for this molecule.

The diazacyclohexene ring is characterized by an envelope conformation folded along the C(7)...C(9) line with the folding angle 45.9° (Fig. 1). All atoms of the ring, except C(8), are in a single plane. This conformation is stabilized by the conjugation effects in the *N*-acylhydrazone fragment. The characteristic features of the structure of the diazacyclohexene ring are the shortened

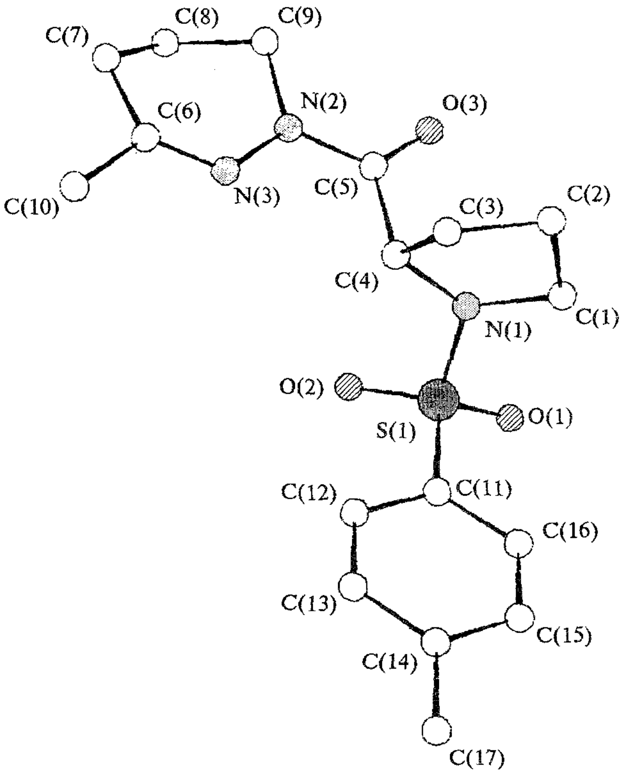
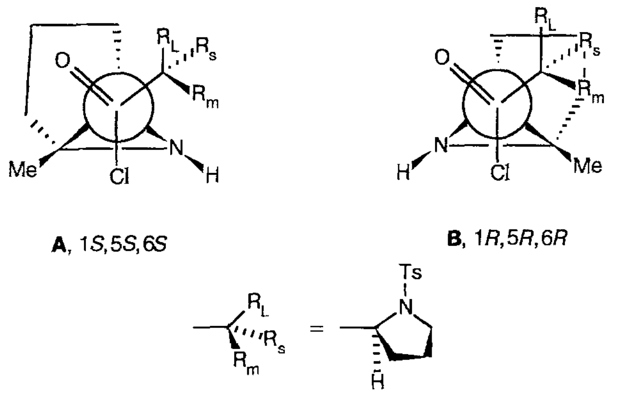


Fig. 1. The structure of molecule **3**.

Scheme 4



C(6)=N(3) bond (1.243 Å) compared to the normal C=N bond in hydrazones (1.286 Å)[14] and the increased endocyclic N(2)N(3)C(7) angle (126.0°). *N*-Acylhydrazone **3** is the only product of the reaction of diaziridine **1** with (*S*)-*N*-tosylproline chloride **2**, and, hence, the electrophilic attack of the latter occurs only at the nitrogen atom, which is a bridgehead atom of the bicyclic system of **1**. Based on this fact and on the principles that we have proposed previously,[3] two diastereomeric transition states (**A** and **B**) in this reaction can be assumed (Scheme 4).

Apparently, state **A** is sterically less hindered, and hence the (1*S*,5*S*,6*S*) enantiomer of diaziridine **1** should react faster than (1*R*,5*R*,6*R*)-**1**. Actually, in the kinetic enrichment (Scheme 1), unreacted (+)-enantiomer **1** has the 1*R*,5*R*,6*R* absolute configuration.[3]

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