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Cage-Like Amines in the Synthesis and Oxidation of Camphor-10-sulfonic Acid Amides

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Abstract—Reactions of bicyclo[2.2.1]hept-5-en-*exo*- and -*endo*-2-ylmethanamines, *exo*-5,6-epoxybicyclo-[2.2.1]hept-*exo*-2-ylmethanamine, 1-(bicyclo[2.2.1]hept-2-yl)ethanamine, and 1-(1-adamantyl)ethanamine with camphor-10-sulfonyl chloride in chloroform in the presence of triethylamine gave the corresponding sulfonamides having two cage-like fragments. Stereoisomeric *N*-(bicyclo[2.2.1]hept-5-en-2-ylmethyl)camphor-10-sulfonamides were oxidized with peroxyphthalic acid generated *in situ* from phthalic anhydride and 50% hydrogen peroxide. The *exo* stereoisomer was thus converted into the corresponding 5,6-epoxy derivative, while the *endo* isomer gave rise to 4-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylmethyl)-4-azatricyclo[4.2.1.$0^{3,7}$]-nonan-*exo*-2-ol (substituted azabrendane). The structure of the synthesized camphor-10-sulfonamides was confirmed by IR and ^{1}H and ^{13}C NMR spectra with the use of homo- (COSY) and heteronuclear ^{1}H–^{13}C correlation techniques (HMQC, HMBC). Heterocyclization of sulfonamides of the norbornene series was also simulated by quantum-chemical calculations at the PM3 and BHandHLYP/6-31G(*d*) levels of theory.

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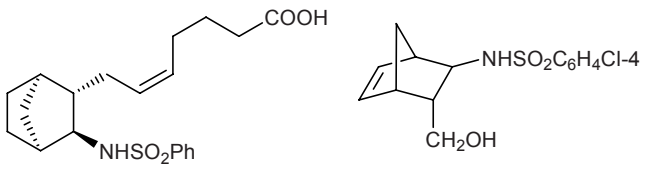
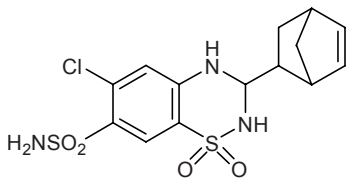
The chemistry of sulfonamides vigorously developed during the last century [1]; however, some its aspects have been extensively studied only in the recent years. Some new studies have been concerned with sulfonamides having norbornene, norbornane, or other cage-like structure and possessing two or more pharmacophoric fragments. Although the spectrum of biological activity of sulfonamides is very broad, there is no doubt that the activity of this group of compounds is largely determined by the contribution of rigid bicyclic skeleton which is structurally related to natural terpenoids. Amines of the norbornene and norbornane series were used to obtain sulfonamides acting as thromboxane receptor antagonists and exhibiting vasodilator and other kinds of biological activity [2]. For example, effective thromboxane receptor antagonists are compound **Ia** (S-145) and its three stereoisomers [3].



Ia

Ib

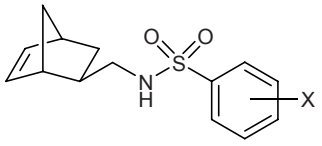


Ic

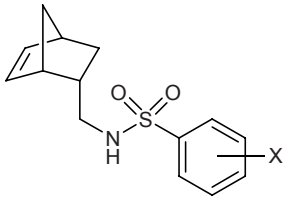
Hamanaka et al. [4] examined how the distance of sulfonamide group from the cage-like fragment and substituents in the aromatic fragment affect the biological activity of compounds like **Ia**. It was presumed that conformational rigidity of the bicyclic skeleton is the main factor responsible for biological activity. Numerous examples of biologically active sulfonamides with a simpler structure are known. Transformation of compound **Ib** at the hydroxymethyl group gave sulfonamides possessing antithrombotic, antisclerotic, and antiischemic activity [5]. Compound **Ic** [6] and its analogs are effective diuretics.

The results of a number of studies have shown that introduction of a pharmacophoric cage-like fragment into molecules of aromatic sulfonamides endows them with new valuable neurotropic properties [7]. In partic-

ular, *exo*- and *endo*-stereoisomeric sulfonamides **Id** and **Ie** exhibit analgesic, anticonvulsant, antihypoxic, tranquilizing, and (in some cases) antiphlogistic activity.



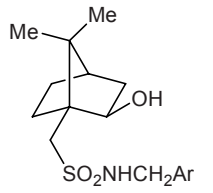
Id



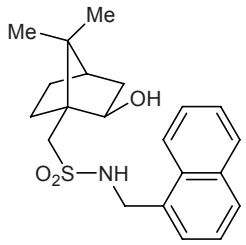
Ie

The goal of the present work to synthesize new potential biologically active compounds via introduction into molecules of neurotropic cage-like sulfonamides of the second cage-like fragment using camphor-10-sulfonyl chloride. The latter is an accessible derivative of natural or synthetic camphor. Both natural and synthetic camphor is widely used for the isolation of optically active compounds from their racemic mixtures [8] in the preparation of pharmaceutical agents [9] that are often salts derived from biologically active bases. Some of these compounds were found to exhibit antitumor effect [10] and control breath. Syntheses of chiral precursors, chiral catalysts, and chiral reagents on the basis of camphor are extensively studied [11, 12]. Syntheses of camphor-10-sulfonyl halides [13], reactions of the latter with ammonia, and transformations of optically active (+)- and (–)-sulfonamides into camphorsulfonyloxaziridines [14] were reported. Sulfonamides **IIa**–**IIe** are effective as ligands in enantioselective catalytic addition of diethylzinc to aldehydes and ketones [15]. Apart from traditional sulfonamides, Oppoltzer's sultam (**IIIa**) and its N-substituted derivatives **IIIb** and **IIIc** were synthesized [16].

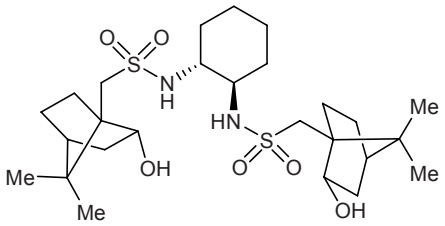
In the present work we examined reactions of camphor-10-sulfonyl chloride [17] with cage-like bicyclic amines **IVa**–**IVc** which were synthesized according to Scheme 1. The key stage in the synthesis of stereochemically pure *exo*- and *endo*-isomeric amines **IVa** and **IVb** was separation of the corresponding nitriles **Va** and **Vb** by fractional distillation. Compounds **Va**



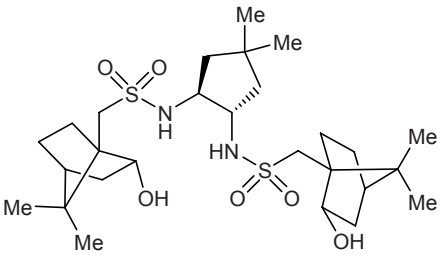
IIa



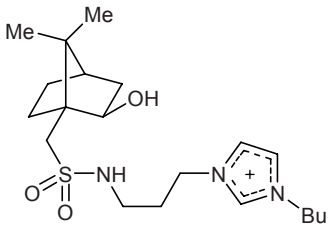
IIb



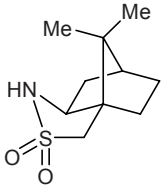
IIc



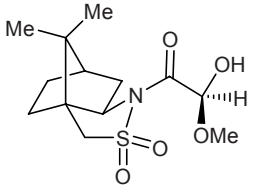
IId



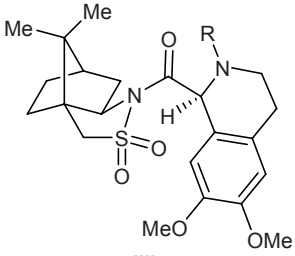
IIe



IIIa

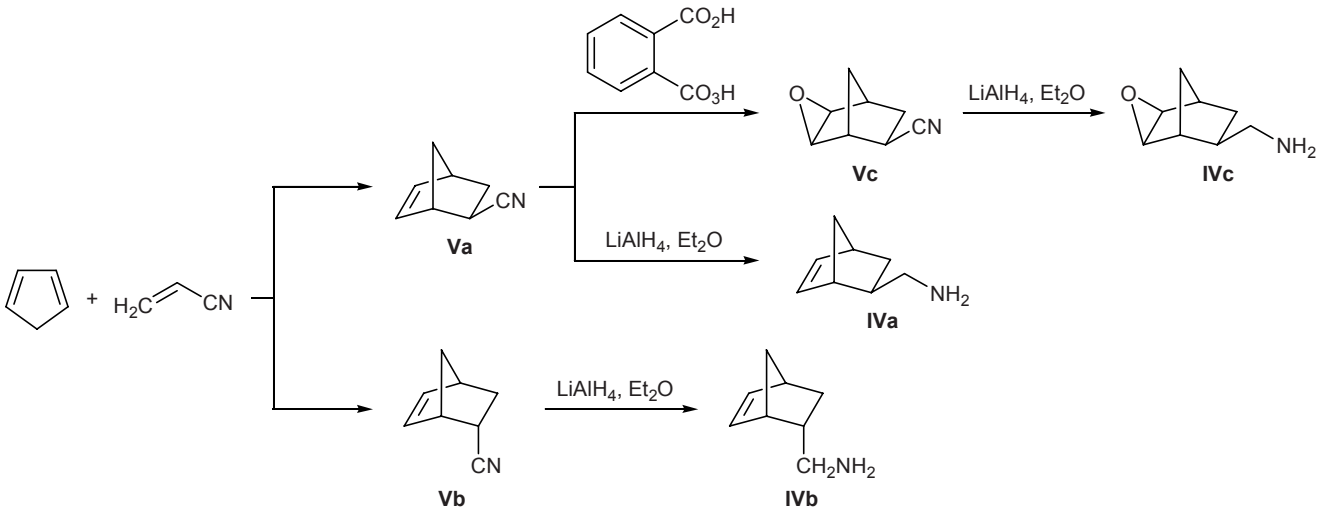


IIIb

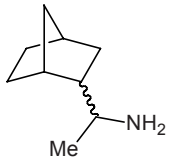


IIIb

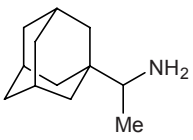
Scheme 1.



and **Vb** were obtained in turn by the Diels–Alder reaction of cyclopentadiene with acrylonitrile [18]. Nitriles **Va** and **Vb** were then converted into amines **IVa** and **IVb** by reduction with lithium tetrahydridoaluminate in boiling diethyl ether. Oxidation of *exo*-nitrile **Va** with peroxyphthalic acid generated *in situ* from phthalic anhydride and 30% aqueous hydrogen peroxide gave tricyclic compound **Vc** which was then reduced to amine **IVc** [19]. The reduction of **Vc** was chemoselective: only the cyano group was involved, while the oxirane ring remained unchanged. Here, the selectivity is determined by steric factors which hamper rear attack by $LiAlH_4$ on the electrophilic centers of the oxirane fragment [20]. In addition, amines with saturated hydrocarbon skeletons were included, namely 1-(bicyclo[2.2.1]hept-2-yl)ethanamine (**IVd**) [21] and 1-(1-adamantyl)ethanamine (**IVe**) [22]; the corresponding hydrochlorides are known as antiviral drugs Deitiforin and Rimantadine [6].



IVd



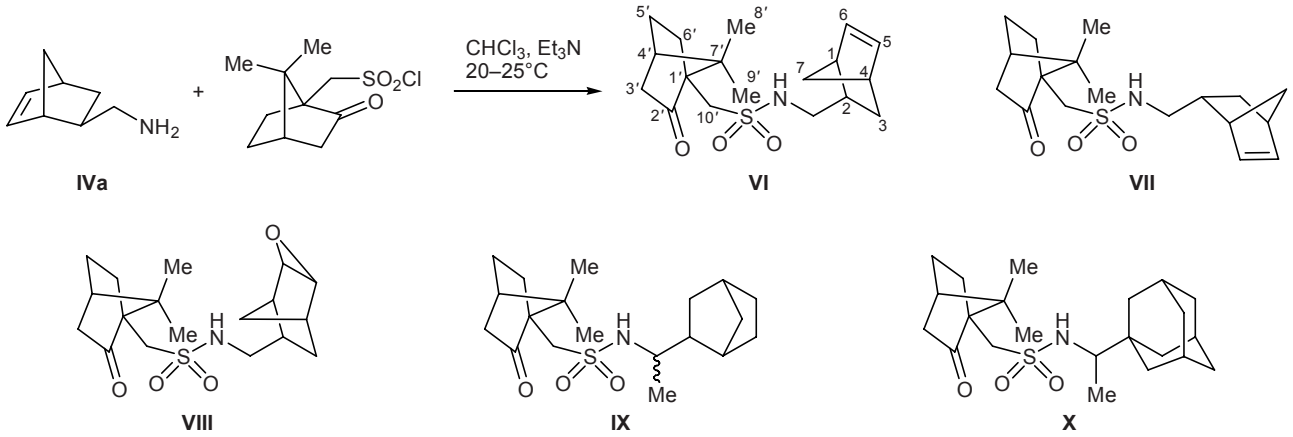
IVe

By reacting amines **IVa**–**IVe** with camphor-10-sulfonyl chloride in chloroform in the presence of triethylamine we obtained compounds **VI**–**X** (Scheme 2). The structure of crystalline sulfonamides **VI**–**X** having two cage-like fragments was confirmed by IR and NMR (^1H and ^{13}C) spectra. Their IR spectra contained absorption bands due to stretching vibrations of the sulfonamide group in the regions 1400–1335, 1180–1154 (SO_2), and 3315–3300 cm^{-1} (NH) and carbonyl group in the camphor fragment at 1752–1741 cm^{-1} [23]. Vibrations of the strained double C=C bond in molecule **VII** gave rise to absorption bands at 3072 [ν(=C–H)] and 730 cm^{-1} [δ(=C–H)] [24], and absorption at 855 cm^{-1} in the spectrum of **VIII** was assigned to the epoxynorbornane fragment [19, 20].

Compounds **VI**–**VIII** and **X** displayed complex patterns in the ^1H NMR spectra which were analyzed using the known spectrum of camphor-10-sulfonic acid. The latter contains doublet signals at δ 3.01 and 2.55 ppm (^2J = 15.0 Hz) due to protons in the exocyclic methylene group neighboring to the $C^{1'}$ chiral center. Signals from the methyl groups appeared at δ 1.04 and 0.76 ppm; the difference in the chemical shifts results from anisotropic properties of the carbonyl group which is closer to one of the methyl groups. Analogous signals are observed in the spectra of **VI**–**VIII** and **X**, but the spectral patterns were complicated by the presence of multiplet signals from seven nonequivalent protons on $C^{3'}$, $C^{4'}$, $C^{5'}$, and $C^{6'}$ in the camphor fragment, so that assignment of signals to particular protons was fairly difficult. For this purpose, we used homonuclear (COSY) and ^1H–^{13}C heteronuclear correlation techniques (HMQC, HMBC) [25, 26]; the complete list of correlations found for compound **VII** is given in Table 1.

Taking into account that signals from some protons in both bicyclic fragments of sulfonamide **VII** may be assigned unambiguously without resorting to special NMR techniques, the observed correlations allowed us to reliably assign all other signals in the spectrum of **VII** and, by analogy, in the spectra of **VI**, **VIII**, and **X**. The problem was facilitated by the fact that most

Scheme 2.



carbon atoms in the molecules of these compounds are linked to hydrogens, so that correlations through one bond could be used for signal assignment [25].

The ^{1}H NMR parameters of compounds **VI** and **VII** and ^{13}C NMR parameters of **VII** confirmed the validity of criteria proposed by us previously [27–29] for the assignment of *exo* or *endo* configuration to sulfonamides of the norbornane series. The ^{1}H NMR spectrum of *endo*-stereoisomer **VII** showed a considerable nonequivalence of the 5-H and 6-H protons in the norbornene fragment (δ 5.97 and 6.16 ppm), large difference in the chemical shifts of *exo*-3-H and *endo*-3-H

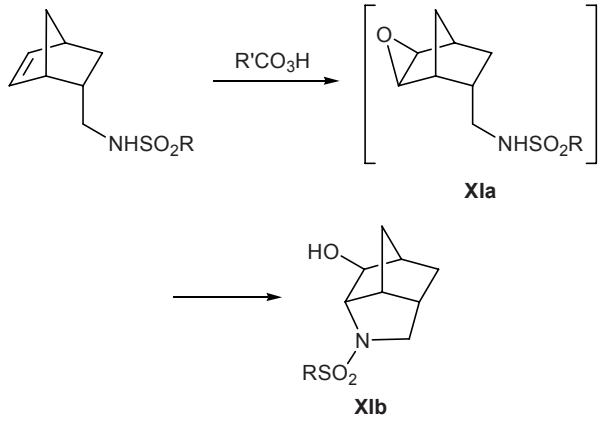
Table 1. Correlations in the two-dimensional NMR spectra of compound **VII**

δ_H, ppm	HMQC, δ_C, ppm	HMBC, δ_C, ppm	COSY, δ_H, ppm
7.03	–	–	2.61, 2.72
6.16	137.8	49.6, 44.3, 42.7	5.97, 2.76
5.97	133.0	49.6, 44.3, 42.7	6.16, 2.86
3.26	48.2	215.4, 58.6, 48.2, 25.2	2.86
2.86	44.3	137.8	3.26, 5.97
2.84	48.2	215.4, 58.6, 48.2, 25.2	1.33, 1.22
2.76	–	–	1.79, 1.33, 1.22, 6.16
2.72	47.4	39.6, 44.3, 30.5	2.61, 2.18, 7.03
2.61	47.4	39.6, 44.3, 30.5	2.72, 2.18, 7.03
2.36	25.2	58.6	1.51
2.33	42.7	215.4, 58.6, 42.7, 27.0	1.91, 2.04, 1.39
2.18	39.6	42.7	2.72, 2.61, 1.79, 0.49
2.04	42.7	215.4, 58.5, 25.2, 20.0	2.33, 1.91
1.94	27.0	–	1.51, 1.39
1.91	42.7	215.4, 58.5, 48.2, 42.8, 27.0, 20.0	2.33, 2.04
1.79	30.5	137.8, 47.4, 42.8	2.76, 2.18, 0.49
1.51	25.2	215.4, 58.5, 48.2, 27.0	2.36, 1.94, 1.39
1.39	27.0	42.8, 48.2, 58.5, 25.2	2.36, 1.94, 1.51
1.33	49.6	39.6, 30.5	1.22, 2.76, 2.86
1.22	49.6	137.8, 133.0, 44.3, 42.8, 39.6, 30.5, 27.0	2.86, 2.76, 1.33
1.01	20.2	48.2, 42.8, 20.0, 58.5	–
0.79	20.0	48.3, 42.8, 20.2, 58.5	–
0.49	30.5	137.8, 49.6, 47.4, 42.6, 39.6	1.79, 2.18

(δ 1.79 and 0.49 ppm), and unusually upfield position of the *endo*-3-H signal due to anisotropy of magnetic susceptibility of the exocyclic C^2–C^8 bond. *exo*-Sulfonamide **VI** is characterized by different parameters and quite different degree of nonequivalence of the 5-H/6-H and *exo*-3-H/*endo*-3-H protons (δ 6.11, 6.07; 1.14–1.19 ppm). Protons in the adamantane fragment of compound **X** resonated in the ^{1}H NMR spectrum in the regions δ 1.60–1.73 and 2.00–2.10 ppm.

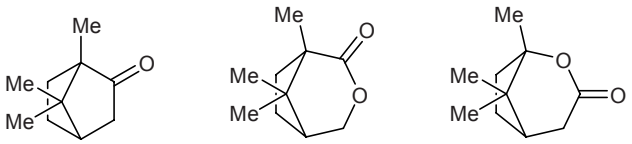
In the recent years, a number of studies were performed on stereochemical aspects of epoxidation of sulfonamides **Id** and **Ie** and their analogs having alkyl and cycloalkyl groups on the sulfonamide group. Treatment with peroxyphthalic acid of substituted norbornenes with *exo*-orientation of substituent in the cage-like fragment resulted in the formation of the corresponding epoxy derivatives, whereas the oxidation of *endo* stereoisomers was not selective, and both epoxy derivatives like **XIa** and heterocyclization products, substituted 4-azatricyclo[4.2.1.$0^{3,7}$]nonanes (azabrendanes) like **XIb** were obtained [20, 27, 30] (Scheme 3).

Scheme 3.



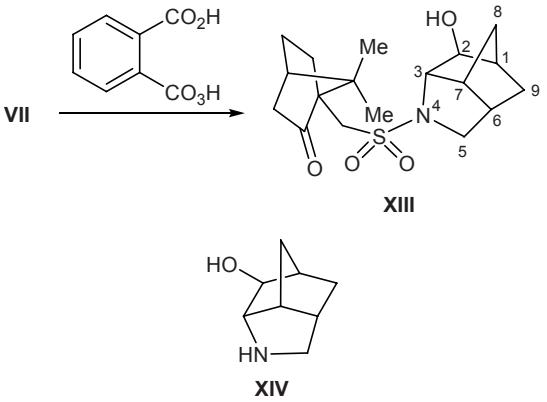
Heterocyclization accompanied epoxidation of all mono- and some disubstituted benzenesulfonamides of the *endo* series, as well as of *N*-alkyl- and *N*-benzylsulfonamides, but it did not occur in the oxidation of *endo*-isomeric arenesulfonamides having electron-withdrawing substituents (primarily in the *ortho* position of the benzene ring) and *N*-perfluoroalkyl sulfonamides [28]. No heterocyclization was observed in the epoxidation of *N*-(bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)cyclohexanesulfonamide [27], which suggests that the formation of azabrendane systems is hindered for steric reasons (the presence of a bulky substituent at the sulfonyl group).

Increased interest in compounds having camphor fragments arises from the possibility for their oxidation according to Baeyer–Villiger. It is known that oxidation of camphor (**XIIa**) with Caro's acid (H_2SO_5, peroxomonosulfuric acid) or 40% peroxyacetic acid gives campholide (**XIIb**) [31]. The formation of isomeric lactone **XIIc** in the oxidation of **XIIa** with peroxyacetic acid in the presence of sodium acetate was also reported.



We examined oxidation of unsaturated sulfonamides **VI** and **VII** with monoperoxyphthalic acid generated *in situ* from phthalic anhydride and 50% aqueous hydrogen peroxide in ethyl acetate. The oxidation of *exo*-sulfonamide **VI** was chemoselective: it occurred at the strained double C=C bond, the camphor fragment remaining intact, and afforded epoxynorbornane **VIII** which was also synthesized by independent method. The IR spectrum of **VIII** contained a carbonyl absorption band at 1752 cm^{-1}, and its ^{1}H NMR spectrum indicated the presence of an epoxynorbornane fragment: one-proton doublets were observed at δ 3.12 and 3.08 ppm ($^3J_{5,6}$ = 3.8 Hz). In addition, the *anti*-7-H signal was displaced upfield (δ 0.79 ppm), for that proton appears directly above the plane of the *exo*-oriented oxirane ring [32]. The oxidation of *endo*-sulfonamide **VII** gave compound **XIII** containing no epoxide ring [33] (Scheme 4).

Scheme 4.



Assignment of signals in the ^{1}H NMR spectrum of the oxidation product required increased attention, for the spectrum changed toward simpler pattern in several

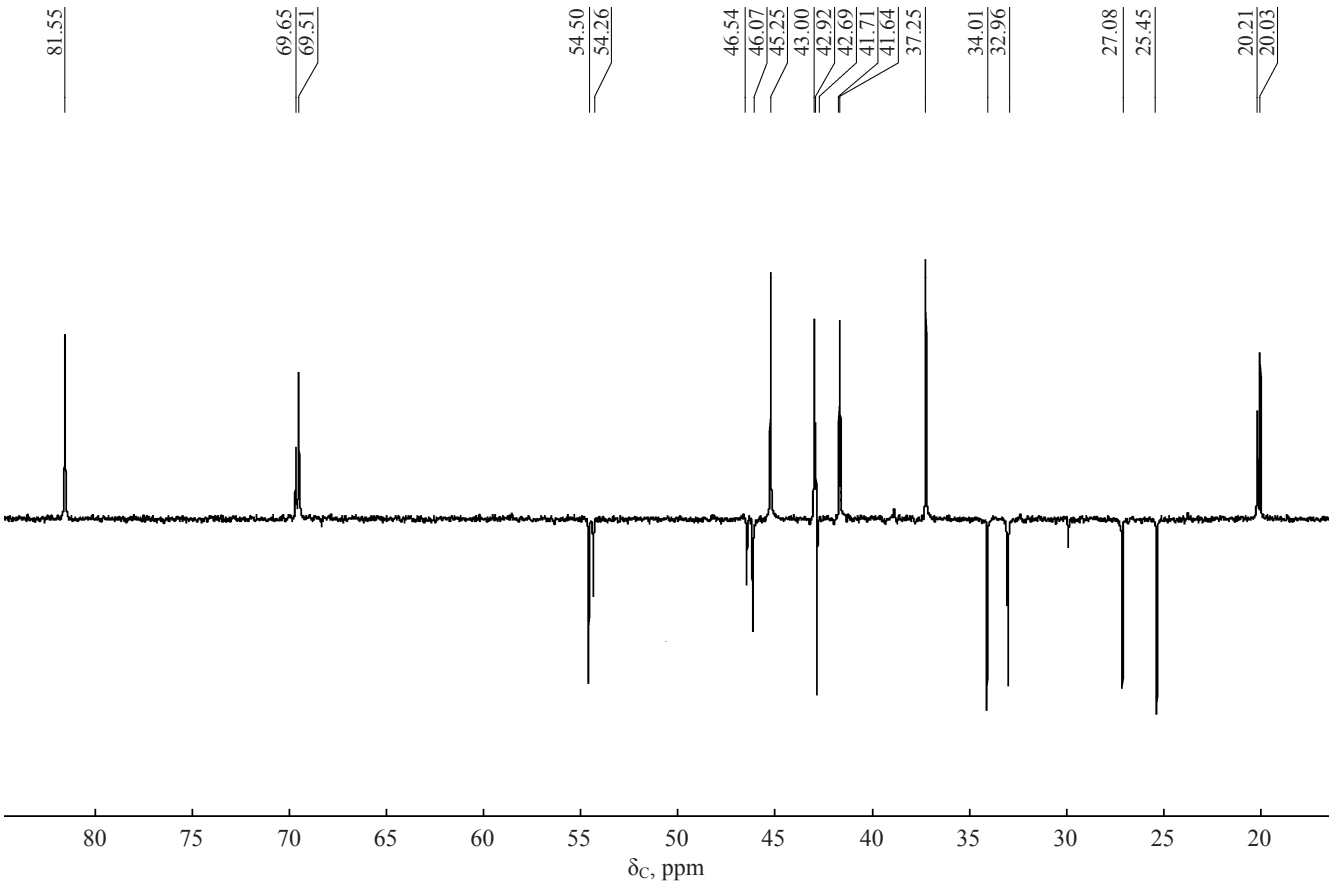


Fig. 1. ^{13}C NMR spectrum (DEPT) of compound **XIII** ($CDCl_3$, 100.7 MHz).

hours after dissolution. These findings, as well as doubling of some signals in the NMR spectra, are likely to indicate the presence of conformers or diastereoisomers. From the spectrum recorded using DEPT pulse sequence (Fig. 1) we determined the number of CH_2 and CH groups, which corresponded to structure **XIII**. Both ^{13}C and ^{1}H signals were assigned using homonuclear (COSY) and heteronuclear correlation experiments [through one (HMQC) and 2–3 chemical bonds (HMBC)]. The results are collected in Table 2 [25] and illustrated by Fig. 2.

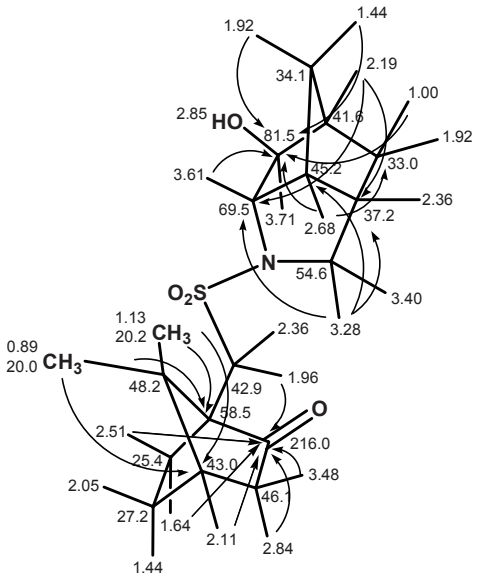


Fig. 2. Principal correlations in the NMR spectra of compound **XIII**.

The structure of **XIII** as substituted azabrendane is confirmed by the presence of one-proton signals at δ 3.71 and 3.61 ppm (a singlet and a doublet with $^{3}J_{3,7}$ = 5.1 Hz), which belong to 2-H and 3-H in the norbornane fragment, as well as of multiplet signals at δ 3.28 and 3.40 ppm (5-H). The ^{13}C NMR spectrum of **XIII** contained signals from C^2 and C^3 at δ_C 81.5 and 69.5 ppm, respectively, and other signals whose positions were similar to those in the spectrum of azabrendane (**XIV**) (δ_C 83.3, 69.7 ppm [34]). The presence of a signal at δ_C 216.0 ppm indicated that the carbonyl group remained unchanged. Presumably, participation of the carbonyl group in the Baeyer–Villiger oxidation is determined by the nature of oxidant (peroxyphthalic acid) or steric effect of the neighboring cage-like frag-

ment. It should be emphasized that the rigid bulky substituent in the epoxynorbornane intermediate creates no steric hindrances to heterocyclization.

The formation of compound **XIII** was studied by quantum-chemical simulation of heterocyclization of probable epoxy intermediate **XVa** in comparison to its analogs **XVb**–**XVd** having different substituents at the sulfonamide group [27]. Transition states were localized using theoretical models which ensured detailed determination of the heterocyclization conditions. Heterocyclization in the gas phase was described by model **A**; the effect of electrophilic activation of the oxygen atom in the epoxide ring by formic acid molecule was taken into account using structure **B**; and experimental conditions were reflected most completely by model **C** due to consideration of specific solvation with ethyl acetate (supermolecular approximation) [27, 35]. The calculations of models **A**–**C** were performed in terms of PM3 semiempirical quantum-chemical approximation [36], while solvent effect in model **C** was described with the aid of the Onsager solvation model [ε = 6.02, BHandHLYP hybrid potential, standard 6-31G(*d*) basis set] [37, 38]. The activation barriers were calculated relative to epoxides assumed to be the corresponding prereaction complexes. The results of calculations are collected in Table 3.

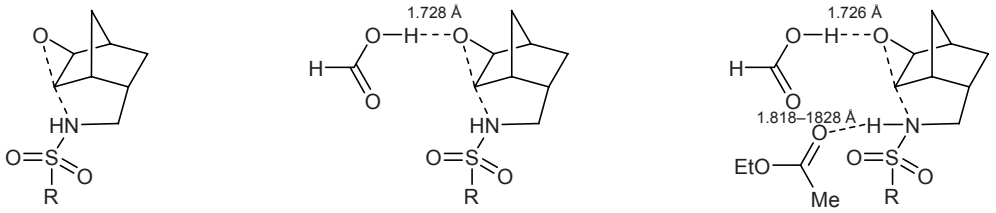
The calculated geometric parameters of the transition states correspond to the classical mechanism of epoxide ring opening [39]. As might be expected, the ΔE_a values calculated for model **C** were most consistent with the experimental data. In fact, the data in Table 3 show that structures **XVa**–**XVc** are equally prone to form tricyclic azabrendane systems, but the activation barrier for cyclohexanesulfonamide **XVd** hampers heterocyclization. The calculation results are very consistent with the experimental data [27, 30], demonstrating that the possibility for intramolecular cyclization is determined by not only size but also other parameters of substituents in the epoxide molecules, in particular by their conformational mobility which increases due to the presence of a methylene bridging group in structure **XVa**.

Table 2. Heteronuclear correlations in the two-dimensional NMR spectra of compound **XIII**

δ_H, ppm	HMQC, δ_C, ppm	HMBC, δ_C, ppm
3.71	81.5	45.2, 34.1
3.61	69.5	81.5, 54.6
3.48	46.1	58.5, 48.3, 25.4, 33.0, 215.9
3.40	54.6	
3.28	54.0	69.5, 45.2, 37.2, 33.0
2.84	46.1	58.5, 48.3, 25.4, 215.9
2.68	45.2	81.5, 41.6, 33.0
2.51	25.4	58.5, 27.2, 215.9
2.36	42.9, 37.3	41.6, 27.2
2.19	41.6	81.5, 69.6, 45.2, 37.2
2.11	43.0	58.5, 25.4, 215.9, 42.9
2.05	27.2	–
1.96	42.9	81.5, 54.4, 48.3, 42.9, 41.6, 37.3, 33.0, 27.2, 215.9
1.92	33.0, 34.1	
1.64	25.4	58.5, 48.3, 27.2, 215.9
1.44	27.2, 34.1	81.5, 69.6, 48.3, 46.1, 42.9, 41.6, 37.2, 33.0, 25.4
1.13	33.0	58.5, 48.2, 43.0, 20.0
1.00	20.0	81.5, 54.4, 42.9, 34.1
0.89	–	58.5, 48.2, 43.0, 20.2

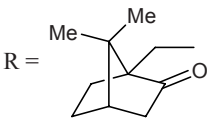
EXPERIMENTAL

The IR spectra were measured in the range from 4000 to 400 cm^{-1} on a UR-20 spectrometer from samples prepared as KBr pellets. The ^1H NMR spectra



A (gas phase) **B** (gas phase) **C** (solution)

XIVa–XIVd



R = (**a**), Ph (**b**), $PhCH_2$ (**c**), cyclo-C_6H_{11} (**d**).

Table 3. Principal geometric parameters of transition states in the formation of azabrendane systems and the corresponding activation barriers

Compound no.	Bond length, Å		Angle, deg			Activation barrier, kJ/mol
	$O–C^3$	$C^3–N$	OC^3N	OC^2C^3	OC^2C^3N	
Model **A** (PM3)						ΔH_a
XVa	2.097	1.979	144.73	93.25	146.43	242.80
XVb	2.087	1.985	144.89	92.75	146.93	235.59
XVc	2.095	1.981	144.79	93.15	146.40	244.17
XVd	2.099	1.977	144.75	93.36	146.63	241.01
Model **B** (PM3)						ΔH_a
XVa	2.069	2.026	145.71	91.65	148.73	216.56
XVb	2.059	2.031	145.95	91.10	148.91	209.65
XVc	2.069	2.028	145.79	91.63	148.59	218.07
XVd	2.075	2.030	145.71	91.96	148.29	222.45
Model **C** [BHandHLYP/6-31G(*d*)//PM3]						ΔE_a
XVa	2.045	2.033	145.72	90.40	149.32	114.69
XVb	2.038	2.036	146.08	89.97	149.62	115.73
XVc	2.043	2.032	145.97	90.24	149.42	118.27
XVd	2.047	2.031	145.60	90.49	149.51	139.38

were recorded on Mercury-400 and Varian-VXR spectrometers using tetramethylsilane as internal reference. The ^{13}C NMR spectra and two-dimensional spectra were measured on a Mercury-400 spectrometer. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using diethyl ether as eluent (development with iodine vapor).

Camphor-10-sulfonamides VI–X (*general procedure***).** A solution of 0.40 g (1.6 mmol) of camphor-10-sulfonyl chloride [17] in 8 ml of chloroform was added dropwise under stirring to a mixture of 1.6 mmol of amine **IVa**–**IVe** and 0.16 g (0.225 ml, 1.6 mmol) of triethylamine in 5 ml of chloroform, and the mixture was stirred at room temperature until the initial compound disappeared according to the TLC data. The solvent was distilled off, the residue was washed with 10 ml of 5% hydrochloric acid, and the product was purified by recrystallization from diethyl ether or propan-2-ol.

***N*-(Bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonamide (VI).** Yield 65%, mp 89–91°C, R_f 0.92 (diethyl ether). IR spectrum, ν, cm^{-1}: 3300, 3072, 1741, 1335, 1154, 730. ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 0.80 s (3H, *syn*-CH_3), 1.03 s (3H, *anti*-CH_3), 1.19–1.14 m (2H, 3-H), 1.23 d (1H, *anti*-7-H, ^2J = 8.4 Hz), 1.30 d (1H, *syn*-7-H), 1.39 d.d.d (1H, *endo*-5′-H), 1.48 m (1H, *endo*-2-H), 1.54 m (1H, *endo*-6′-H), 1.88 m (1H, *endo*-3′-H), 1.94 m (1H, *exo*-5′-H), 2.05 t (1H, 4′-H), 2.31 d.d (1H, *exo*-3′-H), 2.37 m (1H, *exo*-6′-H), 2.71 br.s (1H, 1-H), 2.79 br.s (1H, 4-H), 2.89 d (1H, 10′-H_B, ^2J = 14.9 Hz), 2.94–3.13 m (2H, 8-H), 3.30 d (1H, 10′-H_A), 6.07 d.d (1H, 6-H), 6.11 d.d (1H, 5-H), 7.09 t (1H, NH). Found, %: C 64.16; H 8.12; N 4.09. $C_{18}H_{27}NO_3S$. Calculated, %: C 64.06; H 8.06; N 4.15.

N-(Bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-methanesulfonamide (VII) [33]**.** Yield 75%, mp 94–95°C, R_f 0.91 (diethyl ether). IR spectrum, ν, cm^{-1}: 3300, 3072, 1741, 1335, 1154, 730. ^1H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 0.49 d (1H, *endo*-3-H), 0.79 s (3H, *syn*-CH_3), 1.01 s (3H, *anti*-CH_3), 1.22 d (1H, *anti*-7-H), 1.33 d (1H, *syn*-7-H), 1.39 d.d (1H, *endo*-5′-H), 1.51 m (1H, *endo*-6′-H), 1.79 d.d.d (1H, *exo*-3-H), 1.91 m (1H, *endo*-3′-H), 1.94 m (1H, *exo*-5′-H), 2.04 t (1H, 4′-H), 2.18 m (1H, 2-H), 2.33 d.d (1H, *exo*-3′-H), 2.36 m (1H, *exo*-6′-H), 2.61 m (1H, 8-H_A), 2.72 m (1H, 8-H_B), 2.76 m (1H, 4-H), 2.84 br.s (1H, 10′-H_A), 2.86 s (1H, 1-H), 3.26 m (1H, 10′-H_B), 5.97 d.d (1H, 6-H), 6.16 d.d (1H, 5-H), 7.03 t (1H, NH). ^{13}C NMR spectrum (100.7 MHz, DMSO-d_6), δ_C, ppm: 20.0, 20.2 ($C^{8'}$, $C^{9'}$), 25.2 ($C^{6'}$), 27.0 ($C^{5'}$), 30.5

(C^3), 39.6 (C^2), 42.7 ($C^{3'}$, $C^{4'}$), 42.8 (C^4), 44.3 (C^1), 47.4 (C^8), 48.1 ($C^{10'}$), 48.2 ($C^{7'}$), 49.6 (C^7), 58.5 ($C^{1'}$), 133.0 (C^6), 137.8 (C^5), 215.4 ($C^{2'}$). Found, %: C 64.00; H 8.14; N 4.25. $C_{18}H_{27}NO_3S$. Calculated, %: C 64.06; H 8.06; N 4.15.

(7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-(*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-methanesulfonamide (VIII). *a*. Yield 61%, mp 96–97°C, R_f 0.79 (diethyl ether). IR spectrum, ν, cm^{-1}: 3315, 2980, 1752, 1340, 1157, 855. ^1H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 0.79 d (1H, *anti*-7-H, ^2J = 10.6 Hz), 0.80 s (3H, *syn*-CH_3), 1.02 s (3H, *anti*-CH_3), 1.05 d (1H, *syn*-7-H), 1.17 m (1H, *endo*-3-H), 1.38 m (1H, *exo*-3-H), 1.43 m (1H, *endo*-5′-H), 1.52 m (1H, *endo*-6′-H), 1.63 m (1H, *endo*-2-H), 1.88 m (1H, *endo*-3′-H), 1.94 m (1H, *exo*-5′-H), 2.03 t (1H, 4′-H), 2.30 m (1H, *exo*-3′-H), 2.35 m (1H, *exo*-6′-H), 2.37 br.s (1H, 4-H), 2.49 br.s (1H, 1-H), 2.88 d (1H, 10′-H_B, ^2J = 15.0 Hz), 2.85–2.91 m (2H, 8-H), 3.08 d (1H, 6-H), 3.12 d (1H, 5-H, $^3J_{5,6}$ = 3.8), 3.29 d (1H, 10′-H_A), 7.07 t (1H, NH). Found, %: C 61.08; H 7.79; N 4.05. $C_{18}H_{27}NO_4S$. Calculated, %: C 61.16; H 7.70; N 3.96.

b. Sulfonamide **VI**, 0.75 g (2.2 mmol), urea, 0.06 g (1.1 mmol), and phthalic anhydride, 0.66 g (4.4 mmol), were dispersed in 10 ml of ethyl acetate, and 0.44 g (6.7 mmol) of 50% hydrogen peroxide was added under stirring. The mixture was stirred until the reaction was complete (TLC) and treated with a saturated solution of sodium carbonate. The organic phase was separated, the aqueous phase was extracted with three portions of chloroform, the extracts were combined with the organic phase and dried over calcined magnesium sulfate, and the solvent was removed under reduced pressure. Yield 69%.

***N*-[1-(Bicyclo[2.2.1]hept-2-yl)ethyl](7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide (IX).** Yield 72%, mp 121–123°C, R_f 0.21 (diethyl ether). IR spectrum, ν, cm^{-1}: 3300, 2970, 1745, 1400, 1180. Found, %: C 64.61; H 8.76; N 4.03. $C_{19}H_{31}NO_3S$. Calculated, %: C 64.55; H 8.84; N 3.96.

***N*-[1-(1-Adamantyl)ethyl](7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide (X).** Yield 77%, mp 156–158°C, R_f 0.11 (diethyl ether). IR spectrum, ν, cm^{-1}: 3300, 1745, 1400, 1175. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.83 s (3H, *syn*-CH_3), 1.08 s (3H, *anti*-CH_3), 1.31 d (3H, CH_3), 1.39 m (1H, *endo*-5-H), 1.60 m (1H, *endo*-6-H), 1.60–1.73 m (12H, Ad), 1.73 m (1H, *endo*-3-H), 1.86 m (1H, *exo*-5-H), 1.92 m (1H, 4-H), 2.00–2.10 (3H, Ad), 2.33 m (1H, *exo*-3-H), 2.62 m (1H, *exo*-6-H), 2.77 d (1H, 8-H_B, ^2J = 14.7 Hz), 2.93 m (1H, CH), 3.33 d (1H, 8-H_A), 7.81 br.s (1H, NH). Found, %: C 67.21; H 8.88; N 3.64. $C_{22}H_{35}NO_3S$. Calculated, %: C 67.14; H 8.96; N 3.56.

***N*-[(7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methylsulfonyl]-4-azatricyclo[4.2.1.0^{3,7}]nonan-*exo*-2-ol (XIII)** was synthesized by oxidation of compound **VII** according to the procedure described in [33]. Yield 67%, oily substance, R_f 0.74 (diethyl ether). IR spectrum, ν, cm^{-1}: 3500, 1755, 1341, 1164, 855. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm: 0.89 s (3H, *syn*-CH_3), 1.00 m (1H, *endo*-9-H), 1.13 s (3H, *anti*-CH_3), 1.44 m (2H, *anti*-8-H, *endo*-5′-H), 1.64 m (1H, *endo*-6′-H), 1.92 m (2H, *syn*-8-H, *exo*-9-H), 1.96 d (1H, *endo*-3′-H), 2.05 m (1H, *exo*-5′-H), 2.11 m (1H, 4′-H), 2.19 br.s (1H, 1-H), 2.36 br.s (2H, 6-H, *exo*-3-H), 2.51 m (1H, *exo*-6′-H), 2.68 m (1H, 7-H), 2.84 d.d (1H, 10′-H_A), 3.28 m (1H, 5-H_A), 3.40 m (1H, 5-H_B), 3.48 m (1H, 10′-H_B), 3.61 d (1H, 3-H), 3.71 br.s (1H, 2-H). ^{13}C NMR spectrum (100.7 MHz, $CDCl_3$), δ_C, ppm: 20.0, 20.2 ($C^{8'}$, $C^{9'}$), 25.4 ($C^{6'}$), 27.2 ($C^{5'}$), 33.0 (C^9), 34.1 (C^8), 37.2 (C^6), 41.6 (C^1), 42.9 ($C^{10'}$), 43.0 ($C^{4'}$), 45.2 (C^7), 46.1 ($C^{3'}$), 48.2 ($C^{7'}$), 54.6 (C^5), 58.5 ($C^{1'}$), 69.5 (C^3), 81.5 (C^2), 216.0 (C=O). Found, %: C 61.25; H 7.61; N 4.09. $C_{18}H_{27}NO_4S$. Calculated, %: C 61.16; H 7.70; N 3.96.

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