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Amides Containing Two Norbornene Fragments. Synthesis and Chemical Transformations

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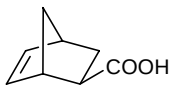
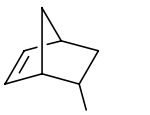
Abstract—Reactions of stereochemically pure bicyclo[2.2.1]hept-5-en-*exo*- and *endo*-2-ylmethylamines with bicyclo[2.2.1]hept-2-ene-5-carbonyl chlorides gave the corresponding carboxamides having two norbornene fragments. Their conformations and steric strains were studied by the MM2 molecular mechanics method, and electron density distribution in their molecules was determined by PM3 quantum-chemical calculations. The results of calculation of the energy of activation for epoxidation of the dienes in the gas phase and in solution (COSMO) showed that chemoselective oxidation of only one double bond therein is impossible. The corresponding diepoxy derivatives were synthesized by oxidation of the dienes with peroxyacetic acid; the oxidation of amides with *endo* orientation of the carbonyl group was accompanied by heterocyclization with formation of *exo*-2-hydroxy-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one. Reduction of the amides and their epoxy derivatives with lithium tetrahydridoaluminate afforded the corresponding secondary amines possessing two cage-like fragments; the reduction products were functionalized at the nitrogen atom by treatment with *p*-nitrobenzenesulfonyl chloride and *p*-toluenesulfonyl isocyanate. The structure of the prepared compounds was confirmed by the IR and ^{1}H and ^{13}C NMR spectra.

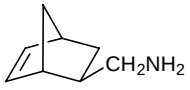
Among all bi- and polycyclic compounds, amides of the norbornene and norbornane series have been studied most thoroughly [1]. Despite vast experimental data accumulated in this field, a considerable part of them was obtained by studying mixtures of stereoisomeric compounds. Amides having cage-like fragments are synthesized from both norbornenecarboxylic acids, in particular compounds **Ia** and **Ib** and their saturated analogs, and cage-like amines, e.g., **IIa** and **IIb**.



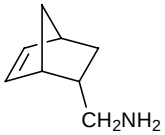
Ia



Ib



IIa



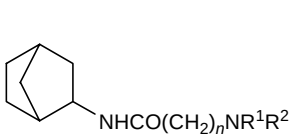
IIb

N-Aryl- and *N*-alkyl-substituted amides derived from bicyclic acids **Ia** and **Ib** were described previously [2], and their reduction [3], hydrolysis [4], and epoxidation with peroxy acids [5] were studied. *N*-Acyl derivatives of bicyclic amines **IIa** and **IIb** were synthesized by the action of acyl chlorides [6, 7] and anhydrides [8]; in addition, their stereochemical behavior [9], alkylation [10], reduction [6, 7], and epoxidation [9] were reported.

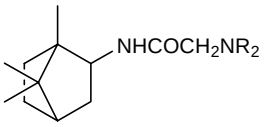
Various amides were tested for biological activity [1]; unsaturated amides in which the amino group is attached directly to the bicyclic skeleton were studied most extensively. Compounds **IIIa** (n = 1, 2; R^1, R^2 = H, lower alkyl groups; R^1R^2N = 1-pyrrolidinyl) and their analogs with a double bond in the bicyclic skeleton or substituents in positions *1* and *7* were found to exhibit antiarrhythmic activity [11]. Norbornane derivatives **IIIb** showed no antiarrhythmic acitivity but exhibited pronounced hypnotic properties [12]. Antiarrhythmic, hypoglycemic, and hypotensive activity was found for amide **IIIc** possessing two bicyclic fragments [13].

Unlike *N*-acyl derivatives of cage-like amines, norbornene- and norbornanecarboxamides exhibit anticon-

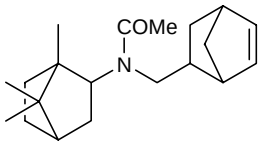
vulsant effect [1]. Comparison of biological activity of *exo* and *endo* isomers of amides by pentetrazole test revealed a persistent favorable therapeutic index for the *endo* stereoisomers which turned out to be less active [14]. Taking into account high biological activity of both groups of cage-like amides and indisputable importance of the stereochemical factor for biological activity, we have synthesized amides **Va**–**Vd** from stereochemically pure bicyclo[2.2.1]hept-5-ene-*exo*- and -*endo*-2-carboxylic acids **Ia** and **Ib** and bicyclo[2.2.1]hept-5-en-*exo*- and -*endo*-2-ylmethylamines **IIa** and **IIb**.



IIIa

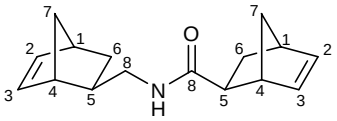


IIIb

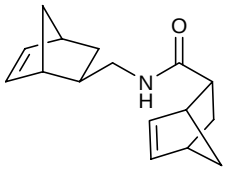


IIIc

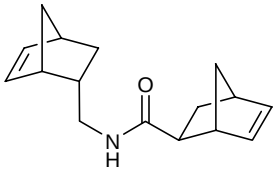
Initial acids **Ia** and **Ib** and amines **IIa** and **IIb** were prepared from the corresponding individual stereoisomers of bicyclo[2.2.1]hept-5-ene-2-carbonitrile which is a Diels–Alder adduct of cyclopentadiene and acrylonitrile. The stereoisomers were separated by fractional distillation [15]. Amines **IIa** and **IIb** were synthesized by reduction of bicyclic nitriles with lithium tetrahydridoaluminate [16], and mild hydrolysis of the same nitriles afforded acids **Ia** and **Ib**. For the synthesis of acyl chlorides **IVa** and **IVb** we selected conditions which prevented isomerization of the products



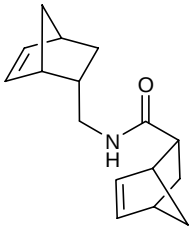
Va



Vb



Vc



Vd

[17]. Cross reactions of stereoisomeric carbonyl chlorides **IVa** and **IVb** with amines **IIa** and **IIb** were carried out in chloroform in the presence of triethylamine under standard conditions for preparation of amides [6, 7, 9].

The structure and conformational behavior of amides **Va**–**Vd** were studied by the MM2 molecular mechanics method [18]. Molecules **Va**–**Vd** contain conformationally labile groups which undergo steric effect of two bulky rigid bicyclic fragments. The optimal conformations of molecules **Va**–**Vd** were determined by analysis of the total steric energy upon variation of the torsion angle $C^4C^5C^8N$ (for atom numbering, see structure **Va**) via rotation of the aminomethyl fragment about the C^5–C^8 bond. In addition, rotation about the NH–CO and C(O)–C^5 bonds was examined. The results of MM2 calculations revealed *syn* orientation of the two methylene bridges in molecules **Vb** and **Vd** (with *endo*-carbonyl group) and *anti* orientation of the CH_2 bridges in isomers **Va** and **Vc**.

The calculated total steric energies of amides **Va**–**Vd** were 205.86, 199.00, 199.81, and 198.58 kJ/mol, respectively, and the corresponding strain energies were 191.3, 184.2, 185.1, and 183.8 kJ/mol. It is seen that the strain energy slightly decreases in the series **Va** > **Vc** ≈ **Vb** > **Vd**; this means insignificant energy preference of the amides with *endo* orientation of the carbonyl group, presumably due to smaller contribution of the torsion strain to the total strain energy of amides **Vb** and **Vd**. The main contribution is that originating from distortion of bond angles (143.59–148.56 kJ/mol).

The IR spectra of amides **Va**–**Vd** contain absorption bands in the regions 1661–1628 (νC=O, amide I) and 1570–1553 cm^{-1} (δN–H, amide II) [19]. Stretching vibrations of the N–H bond give rise to absorption at 3278–3267 cm^{-1}, and unsaturated bicyclic fragments are characterized by absorption bands at 3060–3030 (νC–H) and 720–705 cm^{-1} (δC–H). The band corresponding to stretching vibrations of the double C=C bond is overlapped by weak bands belonging to bending vibrations of the N–H bond; The νC=C frequency changes to 1575–1550 cm^{-1} due to steric strain in the norbornene fragment [20].

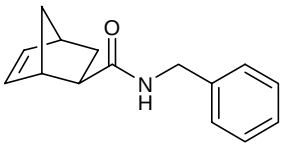
The different steric structures of amides **Va**–**Vd** are reflected in their ^1H NMR spectra (Table 1). For each compound, signals from protons in the acid and amine moieties are given. The spectral patterns are fairly complex, for the chemical shifts of the corresponding protons in the two norbornene fragments are very

Table 1. ^{1}H NMR spectra of compounds **IIa**, **IIb**, **Va**–**Vd**, **VIa**, and **VIb**

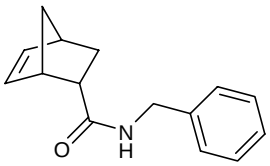
Comp. no.	Fragment	Chemical shifts δ, ppm, and coupling constants *J*, Hz							
		1-H, 4-H	2-H, 3-H	5-H	*exo*-6-H	*endo*-6-H	*syn*-7-H, *anti*-7-H	8-H$_A$, 8-H$_B$	NH$_2$ (NH)
IIa	Amine	2.73, 2.59	5.96, 6.03 $^3J_{2,3}$ = 6.0, $^3J_{2,1}$ = 2.8, $^3J_{3,4}$ = 2.8	1.35	1.14 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.3, $^3J_{exo\text{-}6,1}$ = 8.0	1.04 $^3J_{endo\text{-}6,5}$ = 3.6	1.14, 1.22	2.65	1.13
IIb	Amine	2.81, 2.72	5.86, 6.07 $^3J_{2,3}$ = 5.8, $^3J_{2,1}$ = 2.8, $^3J_{3,4}$ = 3.0	2.03	1.75 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.4, $^3J_{exo\text{-}6,5}$ = 9.2, $^3J_{exo\text{-}6,1}$ = 3.9	0.42 $^3J_{endo\text{-}6,5}$ = 4.1, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.6	1.37, 1.18 $^2J_{syn\text{-}7,anti\text{-}7}$ = 7.9	2.37, 2.29 $^2J_{8A,8B}$ = 12.2, $^3J_{8A,5}$ = 7.3, $^3J_{8B,5}$ = 8.2	1.21
Va	Amine	2.84, 2.61	6.07	1.93	1.36 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.0, $^3J_{exo\text{-}6,5}$ = 7.8	1.17	1.36	3.30	5.62
	Acid	2.92	6.15	2.00	1.55 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.0	1.27	1.36, 1.73 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.1	–	
Vb	Amine	2.92, 2.83	6.14	1.93	1.35 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.0	1.15	1.23, 1.44 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.5	3.25	5.56
	Acid	2.92, 2.58	6.24, 5.96	1.98	1.54 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.8, $^3J_{exo\text{-}6,5}$ = 8.6, $^3J_{exo\text{-}6,1}$ = 4.3	1.35	1.35, 1.74 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.9	–	
Vc	Amine	2.81	6.16, 5.96 $^3J_{2,3}$ = 3.0, $^3J_{2,1}$ = 2.4, $^3J_{3,4}$ = 2.7	2.20	1.84 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.6, $^3J_{exo\text{-}6,5}$ = 9.0, $^3J_{exo\text{-}6,1}$ = 3.9	0.54 $^3J_{endo\text{-}6,5}$ = 3.0, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.2	1.42, 1.27 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.1	2.95, 3.03 $^2J_{8A,8B}$ = 13.5, $^3J_{8A,5}$ = 7.2, $^3J_{8B,5}$ = 5.7	5.61
	Acid	2.88	6.14, 6.11	1.99	1.89	1.33	1.30, 1.69 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.3	–	
Vd	Amine	2.84, 2.74	6.09, 5.91	2.15	1.78 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.3	0.49	1.66, 1.24	3.17	5.55
	Acid	3.07, 2.85	6.17, 5.87	1.90	1.90 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.5, $^3J_{exo\text{-}6,5}$ = 3.9	1.08	1.28, 1.17 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.2	–	
VIa	Acid	2.88, 2.85	6.06, 6.01 $^3J_{2,3}$ = 5.5, $^3J_{2,1}$ = 3.0, $^3J_{3,4}$ = 3.0	1.95	1.27 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.1, $^3J_{exo\text{-}6,5}$ = 8.5, $^3J_{exo\text{-}6,1}$ = 2.5	1.88 $^3J_{endo\text{-}6,5}$ = 3.7, $^4J_{endo\text{-}6,syn\text{-}7}$ = 3.7	1.32, 1.68 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.4	4.39, 4.34[a]	5.79
VIb	Acid	2.92, 3.16	6.23, 5.98	2.91	1.93 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.8, $^3J_{exo\text{-}6,5}$ = 9.4, $^3J_{exo\text{-}6,1}$ = 3.8	1.41 $^3J_{endo\text{-}6,5}$ = 4.0, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.7	1.46, 1.29 $^2J_{syn\text{-}7,anti\text{-}7}$ = 7.9	4.43, 4.35[a]	6.02

[a] Benzyl CH_2 group.

similar. The signals were assigned using the ^{1}H NMR data for initial amines **IIa** and **IIb**. Two-dimensional ^{1}H–{^{1}H} NMR spectra were recorded for *endo* isomer **IIb** and related *N*-arylamides [6, 7]. As models of the carbonyl-containing fragments we used specially synthesized amides **VIa** and **VIb** for which two-dimensional ^{1}H–{^{1}H} and ^{13}C–{^{1}H} NMR spectra were recorded. As follows from the data in Table 1, the amides with *exo*-oriented substituents in both amine and acid fragment are characterized by more similar chemical shifts of protons at the double bonds (2-H and 3-H), while *endo* orientation of the substituents



VIa



VIb

differentiates these protons, the greater difference being observed for protons in the acid fragment. The isomers can be identified by the position of the 5-H signal: the *exo*-5-H protons (*endo* isomers) resonate in a weaker field ($\Delta\delta \approx 0.5$ ppm) than *endo*-5-H (*exo* isomers). This difference originates from magnetically anisotropic effect of the carbon–carbon bonds in the bicyclic moieties. *endo* Orientation of the amine fragment unambiguously follows from the position and multiplicity of the *endo*-6-H signal which appears in the spectrum of amide **Vc** as an octet at δ 0.54 ppm [$^2J_{endo\text{-}6,exo\text{-}6}$ = 12.6, $^3J_{endo\text{-}6,5}$ = 3.0, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.2 Hz (*W*-coupling)]; an analogous pattern is observed in the spectra of **IIb** and **Vd**. Undoubtedly, the upfield position of the above signal is determined by magnetically anisotropic effect on the C^5–C^8 bond in the *endo*-amine and its derivatives. No such effect is observed for the carbonyl-containing fragments of the amides (cf. ^{1}H NMR spectral data for compounds **Vb** and **Vd**).

Amides **Va**–**Vd** are polyfunctional compounds in which the double bonds are influenced by electron-acceptor carbonyl group and weakly electron-donor aminomethyl group. In order to elucidate the possibility for chemoselective epoxidation of only one of the double bonds we performed [21] quantum-chemical calculations of the energies of occupied molecular orbitals (OMO) of amides **Va**–**Vd** and contributions of atomic orbitals to the OMO using the PM3 semiempirical method. The results are summarized in Table 2. It is seen that in all cases the HOMO is localized mainly on the amide nitrogen and oxygen atoms. The olefinic C^2 and C^3 atoms contribute mainly to the II-OMO and III-OMO whose energies are very similar. The small contribution of these atoms in the acid fragment of **Vd** is explained by distribution of the corresponding atomic orbitals over IV-OMO–VII-OMO. According to the obtained results, the reactivities of the double bonds do not differ appreciably.

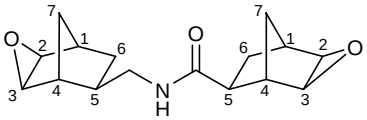
Table 2 also contains the calculated (COSMO [23]) energies of activation ($\Delta H^{\neq}$) for epoxidation of amides **Va**–**Vd** at both double bonds in the gas phase and in solution. The activation barriers were calculated relative to the sum of the enthalpies of formation of the initial reactants; vibration frequencies were calculated for each stationary point. Transition states were characterized by a single imaginary frequency, while frequencies for the initial reactants and products (minima on the potential energy surface) were positive. The structures of the transition states are similar to those determined previously for epoxidation of substituted norbornenes [24]. As follows from the data in Table 2, the energies of activation for reactions at both olefinic fragments are similar; therefore, their chemoselective transformation seems to be impossible. Taking into account these results, epoxidation of dienes **Va**–**Vd** was performed with excess oxidant to obtain compounds containing two epoxy rings. The reactions were carried out with peroxyacetic acid which was prepared *in situ* from acetic anhydride and 70% hydrogen peroxide; the amide–acetic anhydride–hydrogen per-

Table 2. Calculated energies of occupied molecular orbitals (E_{OMO}, eV), contributions of particular atomic orbitals to OMOs, and energies of activation ($\Delta H^{\neq}$, $\Delta H^{\neq}_{solv}$, eV) for epoxidation of amides **Va**–**Vd**

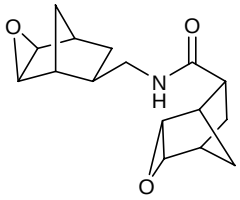
Comp. no.	Fragment	E_{HOMO}, eV	E_{OMO}, eV	Contributions to OMO, %	$\Delta H^{\neq}$	$\Delta H^{\neq}_{solv}$
Va	Amine	–9.53	III-OMO, –10.04	C^2, 39.73; C^3, 40.84	14.71	11.30
	Acid		II-OMO, –9.97	C^2, 41.15; C^3, 40.66	15.83	11.42
Vb	Amine	–9.55	II-OMO, –9.94	II, C^2, 32.27; C^3, 32.34 III, C^2, 7.03; C^3, 7.26	14.42	11.35
	Acid		III-OMO, –9.99	II: C^2, 8.21; S^3, 8.38 III: C^2, 33.13; S^3, 33.13	15.74	12.39
Vc	Amine	–9.54	II-OMO, –9.91	C^2, 39.82; C^3, 40.11	14.79	10.69
	Acid		III-OMO, –10.05	C^2, 43.37; C^3, 40.93	14.58	11.14
Vd	Amine	–9.41	III-OMO, –9.95	C^2, 40.11; C^3, 40.16	14.71	11.38
	Acid		II-OMO, –9.86	C^2, 3.93; C^3, 3.27	14.22	11.75

oxide molar ratio was 1:3:3, and chloroform was used as solvent.

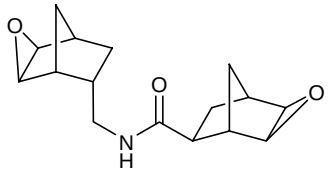
Unlike the data of [5], the only or major oxidation products were bis-epoxy derivatives **VIIa**–**VIId**. Compounds **VIIa** and **VIIc** were isolated as crystalline substances, and their isomers **VIIb** and **VIId** were oily liquids. The latter were subjected to chromatographic purification on silica gel; as a result, from amide **Vb** we obtained 60.5% of epoxide **VIIb** and 10% of lactone **VIII**, and from amide **Vd**, 57.4% of epoxide **VIId** and 7.3% of lactone **VIII**. The ^{1}H NMR spectra of the crude products obtained by oxidation of amides **Vb** and **Vd** also showed the presence of lactone **VIII**.



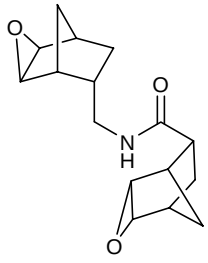
VIIa



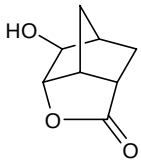
VIIb



VIIc

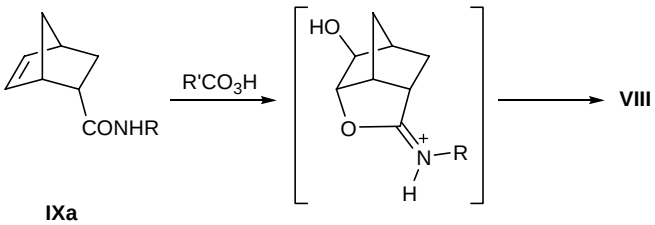


VIId

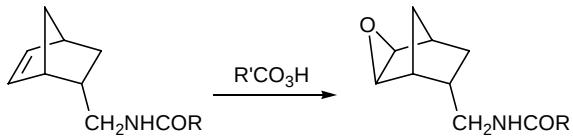


VIII

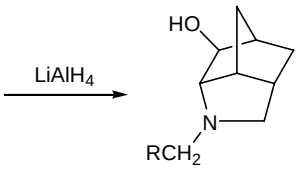
In the recent years, numerous examples of formation of heterocyclic systems from epoxy derivatives attract researchers' attention [22, 23]. It is known that orientation of substituents in the bicyclic skeleton is the main factor determining the possibility for heterocyclization in reactions of substituted norbornenes with peroxy acids. Compounds having *exo*-oriented substituents (such as carboxy, methoxycarbonyl, carbamoyl, acylamino, sulfonylamino, and other groups) react with peroxy acids to afford only the corresponding epoxy derivatives, while their *endo* isomers could give rise to heterocyclization, depending on the substituent nature. Epoxidation of carbamoyl-substituted norbornenes **IXa** (R = H, alkyl, benzyl, aryl) led to formation of lactone **VIII** as the only product [5], while acyl derivatives **IXb** (R = alkyl, aryl) of amine **IIb** were converted exclusively into epoxides **IXc** under the same conditions. Heterocyclization to azabrendane structures like **IXd** occurred only after subsequent reduction of epoxy derivatives **IXc** with lithium tetrahydridoaluminate [9].



IXa



IXb **IXc**



IXd

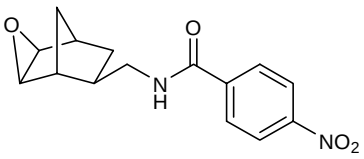
Amides **Va**–**Vd** are especially interesting from the viewpoint of their oxidation with peroxy acids, for their molecules include both carbamoyl and acylaminomethyl groups which are oriented differently with respect to the conformationally rigid bicyclic fragments. On the basis of published data, we expected formation of diepoxy derivatives from amides **Va** and **Vc** and of lactone **VIII** from amides **Vb** and **Vd**. The formation of bis-epoxides as major products in the oxidation of amides **Vb** and **Vd** indicates strong steric hindrances to location of one cage-like fragment at the rear (*endo*) area of the other; such arrangement is necessary for intramolecular attack by the nucleophilic carbonyl oxygen atom at the electrophilic carbon atom of the activated epoxy ring [25].

In the IR spectra of the oxidation products, the most characteristic are absorption bands in the region 850–840 cm^{-1}, which belong to stretching vibrations of the C–O bonds. The absorption typical of carboxamide groups is retained, whereas bands at 730–700 cm^{-1} (δC–H) due to olefinic fragments in substituted norbornenes disappear from the spectra.

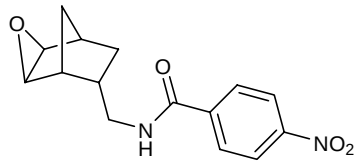
Table 3. ^{1}H NMR spectra of compounds **VIIa**, **VIIc**, **Xa**, and **Xb** obtained by epoxidation of the corresponding amides

Comp. no.	Fragment	Chemical shifts δ, ppm, and coupling constants *J*, Hz							
		1-H, 4-H	2-H, 3-H	5-H	*exo*-6-H	*endo*-6-H	*syn*-7-H, *anti*-7-H	8-H$_A$, 8-H$_B$	NH$_2$ (NH)
VIIa	Amine	2.57, 2.25	3.00–3.10	1.60	1.36 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.5, $^3J_{exo\text{-}6,5}$ = 8.4, $^3J_{exo\text{-}6,1}$ = 2.4	1.05	1.25, 0.81 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.2	3.00–3.10	5.72
	Acid	2.47, 2.41	3.00–3.10	2.08	1.64 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.4	1.20	1.39, 1.18 $^2J_{syn\text{-}7,anti\text{-}7}$ = 8.3	–	–
VIIc	Amine	2.51, 2.48	3.28, 3.09 $^3J_{2,3}$ = 3.0	1.50	1.73 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.7, $^3J_{exo\text{-}6,5}$ = 10.7, $^3J_{exo\text{-}6,1}$ = 4.3	0.81 $^3J_{endo\text{-}6,5}$ = 4.9, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.3	1.37, 0.76 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.0	3.20–3.32 $^2J_{8A,8B}$ = 13.6, $^3J_{8B,5}$ = 7.8	5.59
	Acid	2.60, 2.40	3.14, 3.11	2.11	1.94 $^2J_{exo\text{-}6,endo\text{-}6}$ = 8.6	1.24	1.26, 1.18 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.0	–	–
Xa	Amine	2.47, 2.36	3.09, 3.05 $^3J_{2,3}$ = 3.5	1.82	1.52 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.6, $^3J_{exo\text{-}6,5}$ = 8.4, $^3J_{exo\text{-}6,1}$ = 2.4	1.17 $^3J_{endo\text{-}6,5}$ = 4.1	1.28, 0.88 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.4	3.37, 3.31 $^2J_{8A,8B}$ = 13.4, $^3J_{8A,5}$ = 7.1, $^3J_{8B,5}$ = 8.3	6.48
Xb	Amine	2.55, 2.51	3.22, 3.27 $^3J_{2,3}$ = 3.8	2.27	1.83 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.5, $^3J_{exo\text{-}6,5}$ = 9.9, $^3J_{exo\text{-}6,1}$ = 4.3	0.93 $^3J_{endo\text{-}6,5}$ = 4.8, $^4J_{endo\text{-}6,syn\text{-}7}$ = 2.7	1.43, 0.82 $^2J_{syn\text{-}7,anti\text{-}7}$ = 9.9	3.57, 3.42 $^2J_{8A,8B}$ = 13.7, $^3J_{8A,5}$ = 9.0, $^3J_{8B,5}$ = 7.6	6.29

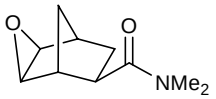
The ^{1}H NMR spectra of epoxy derivatives **VIIa** and **VIIc** contained signals at δ 3.10–3.30 ppm (Table 3), which are typical of epoxynorbornanes. The stereochemistry of epoxidation (Alder's *exo*-attack rule [26]) follows from the presence of a doublet signal in the region δ 0.80–1.20 ppm, which belongs to the *anti*-7-H proton. The latter is located directly above the oxirane ring plane in the molecules of *exo*-epoxynorbornanes, so that it appears in the area of anisotropic effect of the oxirane ring. Compounds **VIIa** and **VIIc** differing by the orientation of the amine fragments are characterized by different chemical shifts of protons in those fragments; the observed spectral patterns are consistent with our previous data for *N*-acyl derivatives of stereoisomeric amines **IIa** and **IIb** [9]. These differences include primarily resonances of protons in the oxirane ring (2-H, 3-H), protons in the bridgehead positions (1-H, 4-H), methylene protons in the substituent, and proton on C^6 [9, 27]. For comparison, Table 3 contains the ^{1}H NMR spectral parameters of stereoisomeric epoxides **Xa** and **Xb** for which two-dimensional spectra were also measured [7].



Xa

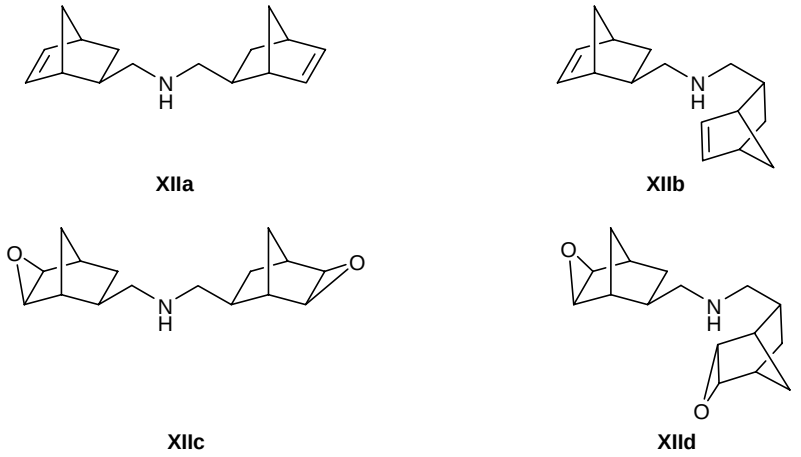


Xb



XI

The ^{13}C NMR spectra of compounds **VIIa**–**VIIc** are given in Table 4. In particular, the carbonyl carbon atoms resonate at δ_C 174–175 ppm, and signals from carbon atoms involved in the oxirane ring appear at δ_C 51–53 ppm. In most cases the chemical shifts of C^2 and C^3 are almost similar, and only the corresponding signals from the amine fragment of **VIIc** differ by 2.8 ppm. The ^{13}C signals were assigned on the basis of the two-dimensional spectra of compounds **Xa** and **Xb**,



XIIa **XIIb**

XIIc **XIId**

as well as of epoxy amide **XI** described in [28]; the ^{13}C NMR spectrum of the latter was solved using the selective double $^{13}C–\{H\}$ resonance technique.

The amide group in compounds **Va** and **Vc** can be reduced to obtain previously unknown and difficultly accessible amines **XIIa** and **XIIb** which possess two norbornene fragments. The reduction of epoxy derivatives **VIIa** and **VIIc** under analogous conditions was strictly chemoselective; as a result, we obtained epoxy amines **XIIc** and **XIId** in which the oxirane fragments remained intact. The observed reaction path is typical of epoxynorbornanes in neutral and alkaline media. It indicates the crucial role of steric factor which hinders intermolecular attack by bulky nucleophilic reagent on the electrophilic oxirane carbon atoms from the rear side of the bicyclic carbon skeleton (in keeping with the known relations holding in bimolecular nucleophilic substitution mechanism [29]).

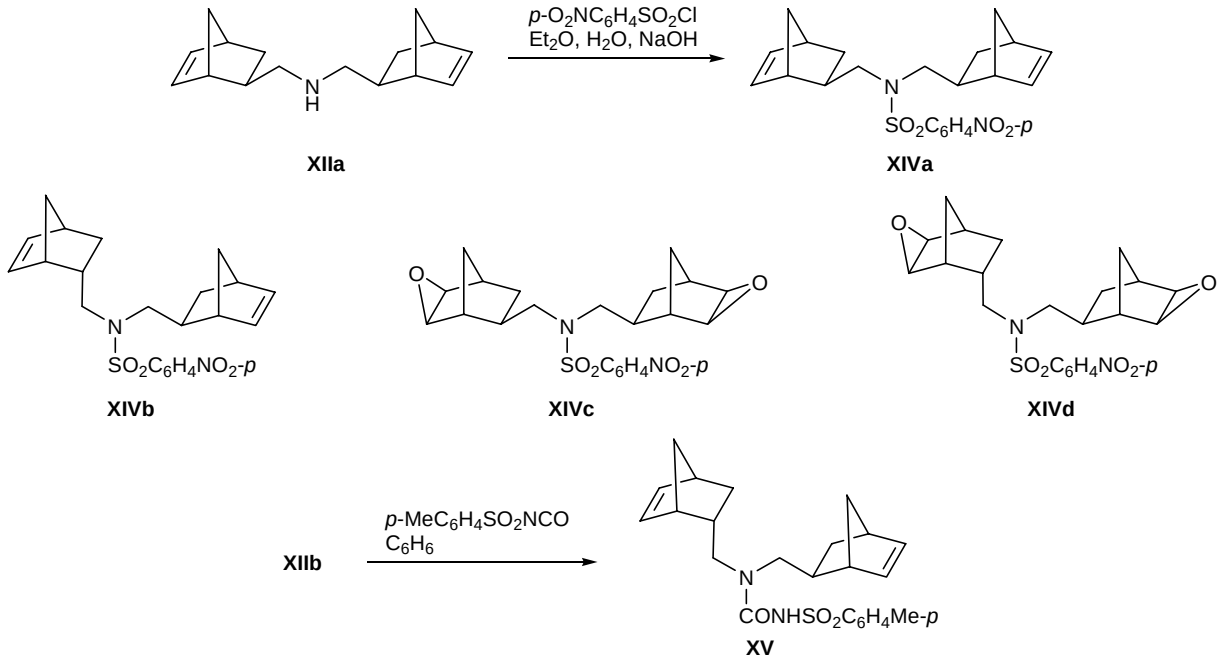
The IR spectra of oily amines **XIIa**–**XIId** lack absorption bands due to carboxamide fragment but νNH bands are present at 3360–3310 cm^{-1}. In addition, compounds **XIIa** and **XIIb** showed in the IR spectra absorption bands at 3066 and 3068 cm^{-1} due to stretching vibrations of the C–H bonds contiguous to the strained double C=C bond; epoxy amines **XIIc** and **XIId** were characterized by absorption at 855 and 860 cm^{-1} due to C–O stretching vibrations and at 3040 and 3035 cm^{-1} due to vibrations of the C–H bonds in the three-membered ring [19].

Amines **XIIa**–**XIId** were converted into the corresponding hydrochlorides **XIIIa**–**XIIId**. In the IR spectra of **XIIIa**–**XIIId** we observed ammonium bands in the region 2768–2740 cm^{-1} [$\nu_{as}(^{+}NH_2)$ and $\nu_{s}(^{+}NH_2)$], which were not overlapped by C–H stretching vibration bands [19]. The absorption patterns due to cyclic fragments were almost the same as in the spectra of the corresponding free bases.

We previously found that *p*-nitrobenzenesulfonamides derived from amines **IIa** and **IIb** exhibit a high and versatile neurotropic activity [30]. Taking these data into account, we synthesized sulfonamides **XIVa**–**XIVd** by treatment of amines **XIIa**–**XIId** with equi-

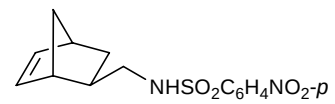
Table 4. ^{13}C NMR spectra of epoxy derivatives **VIIa**–**VIIc** and compounds **Xa**, **Xb**, and **XI**, δ, ppm

Compound no.	Fragment	C^1, C^4	C^2, C^3	C^5	C^6	C^7	C^8	C=O
VIIa	Amine	36.6, 42.2	51.2, 51.1	38.4	30.2	23.2	43.2	–
	Acid	36.9, 46.7	51.8, 51.7	39.6	31.1	23.9	–	174.1
VIIb	Amine	36.5, 43.4	51.7, 51.1	38.2	31.6	23.1	43.2	–
	Acid	36.9, 43.5	51.9, 51.3	39.5	33.7	23.9	–	174.3
VIIc	Amine	37.6, 44.7	52.8, 50.0	42.3	30.5	28.1	41.8	–
	Acid	28.2, 43.2	52.1, 52.1	39.3	31.1	24.9	–	175.1
Xa	Amine	36.9, 39.7	51.6, 51.1	38.3	31.2	23.2	43.9	–
Xb	Amine	38.2, 42.2	52.1, 49.9	39.4	30.7	28.2	42.7	–
XI	Acid	36.7, 40.1	51.5, 50.4	41.1	30.6	23.9	–	173.1

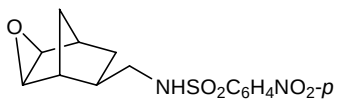


molar amounts of *p*-nitrobenzenesulfonyl chloride and sodium hydroxide in a two-phase system (water–diethyl ether). Amine **XIIb** was also brought into reaction with *p*-toluenesulfonyl isocyanate, which afforded sulfonylurea **XV**.

In the IR spectra of sulfonamides **XIVa**–**XIVd** we observed no N–H stretching vibration bands in the region 3300–3200 cm^{-1}, but absorption bands belonging to vibrations of the sulfonyl (1338–1310 and 1168–1165 cm^{-1}) and nitro groups (1540–1530 and 1355–1335 cm^{-1}) were present. The amide fragment in sulfonylurea **XV** gave rise to amide absorption at 1640 (ν C=O) and 1270 cm^{-1} (ν C–N) and N–H absorption at 3370 cm^{-1}. Table 5 contains the ^{1}H NMR spectral parameters of compounds **XIVa**, **XIVc**, and **XIVd**, as well as of previously described sulfonamides **XVIa** and **XVIb** [31].



XVIa



XVIb

Unlike symmetric structures **XIVa** and **XIVc**, the aminomethyl fragments in molecule **XIVd** differ by orientation with respect to the bicyclic fragments. The signals in the ^{1}H NMR spectrum of **XIVd** were assigned by comparing with the spectra of epoxy derivatives **XIVc** and **XVIb**. Quite demonstrative is the position of signal from 5-H in different fragments of **XIVd**: δ 1.65 and 2.15 ppm for the *exo*- and *endo*-amine, respectively; also, a considerable difference in the chemical shifts of *exo*-6-H is observed: δ 1.45 and 1.89 ppm, respectively. On the other hand, the presence in a single molecule of two bicyclic fragments with different orientations of the substituents levels the spectral differences which were proposed previously as criteria for determination of steric structure of sulfonamides of the norbornene series [27].

EXPERIMENTAL

The IR spectra were recorded on a Specord 75-IR spectrometer in the range from 4000 to 400 cm^{-1} from samples prepared as thin films or KBr pellets. The ^{1}H NMR spectra were obtained on Varian VXR (300 MHz) and Varian Gemini-BB (500 MHz) instruments from solutions in chloroform-*d* or DMSO-d_6 using TMS or HMDS as internal reference. The ^{13}C NMR spectra were measured on a Varian Gemini-BB spectrometer at 100.7 MHz using COSY and NOESY techniques. The progress of reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates using diethyl ether as eluent; spots were visualized by treatment with iodine vapor. The elemental compositions were determined on a Carlo Erba analyzer.

Table 5. ^{1}H NMR spectra of sulfonamides **XIVa**–**XIVd** and compounds **XVIa** and **XVIb**

Comp. no.	Isomer	Chemical shifts δ, ppm, and coupling constants *J*, Hz							
		1-H, 4-H	2-H, 3-H	5-H	*exo*-6-H	*endo*-6-H	*syn*-7-H, *anti*-7-H	8-H_A, 8-H_B	NH_2, H_{arom}
XIVa	*exo*	2.79, 2.68	6.01	1.62	1.09	0.88	1.23, 1.32 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.0	3.32, 3.12 $^2J_{8A,8B}$ = 12.9	8.38 (2H, H_{arom}), 8.04 (2H, H_{arom})
XIVb	*exo*	2.80, 2.61	5.97, 5.94	1.68	1.18	1.05	1.26, 1.36	3.10–3.21	8.40 (2H, H_{arom}), 8.05 (2H, H_{arom})
	endo	2.79, 2.73	6.17, 6.04 $^3J_{2,3}$ = 6.0, $^3J_{2,1}$ = 3.2, $^3J_{3,4}$ = 3.0	2.33	1.80 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.5	0.55	1.22, 1.42 $^2J_{syn\text{-}7,anti\text{-}7}$ = 11.0	2.82–2.90	
XIVc	*exo*	2.45, 2.31	3.06, 3.02 $^3J_{2,3}$ = 3.8	1.65	1.47 $^2J_{exo\text{-}6,endo\text{-}6}$ = 13.4	1.05	1.24, 0.71 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.4	2.88, 2.83 $^2J_{8A,8B}$ = 13.6	7.92 (2H, H_{arom}), 7.65 (2H, H_{arom})
XIVd	*exo*	2.45, 2.31	3.07, 3.01 $^3J_{2,3}$ = 3.8	1.65	1.45 $^2J_{exo\text{-}6,endo\text{-}6}$ = 13.0	1.08	1.20, 0.72 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.6	2.80–2.90	7.92 (2H, H_{arom}), 7.63 (2H, H_{arom})
	endo	2.57, 2.44	3.12, 3.00 $^3J_{2,3}$ = 3.1	2.15	1.89 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.6	1.08	1.44, 0.72 $^2J_{syn\text{-}7,anti\text{-}7}$ = 9.8	3.00–3.10	
XVIa	*exo*	2.74, 2.53	5.99, 5.94 $^3J_{2,3}$ = 5.6, $^3J_{2,1}$ = 3.3, $^3J_{3,4}$ = 3.7	1.45	1.16 $^2J_{exo\text{-}6,endo\text{-}6}$ = 11.7, $^3J_{exo\text{-}6,5}$ = 7.8	1.01 $^3J_{endo\text{-}6,5}$ = 3.7	1.14, 1.28 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.0	3.02, 2.90 $^2J_{8A,8B}$ = 12.6, $^3J_{8A,5}$ = 5.9, $^3J_{8B,5}$ = 6.3	4.85 (1H, NH), 8.31 (2H, H_{arom}), 8.00 (2H, H_{arom})
XVIb	*exo*	2.41, 2.27	3.04, 2.97 $^3J_{2,3}$ = 3.8	1.56	1.43 $^2J_{exo\text{-}6,endo\text{-}6}$ = 12.4, $^3J_{exo\text{-}6,5}$ = 8.2, $^3J_{exo\text{-}6,1}$ = 2.8	1.01 $^3J_{endo\text{-}6,5}$ = 4.1, $^3J_{endo\text{-}6,syn\text{-}7}$ = 3.8	1.22, 0.67 $^2J_{syn\text{-}7,anti\text{-}7}$ = 10.1	2.85, 2.82	4.76 (1H, NH) 8.31 (2H, H_{arom}), 8.00 (2H, H_{arom})

Stereoisomeric bicyclo[2.2.1]hept-5-en-2-ylmethylamines **IIa** and **IIb** were synthesized by the procedure reported in [6]. Stereoisomeric acid chlorides **IVa** and **IVb** were prepared from norbornenecarboxylic acids **Ia** and **Ib** as described in [17].

***N*-(Bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-*exo*-2-carboxamide (Va).** A solution of 1.38 g (10 mmol) of bicyclo[2.2.1]hept-5-ene-*exo*-2-carbonyl chloride (**IVa**) in chloroform was added dropwise under stirring to a mixture of 1.23 g (10 mmol) of amine **IIa** and 1.01 g (1.40 ml, 10 mmol) of triethylamine in 20 ml of chloroform. The mixture was stirred at room temperature until the reaction was complete (TLC) and treated in succession with water, 20% hydrochloric acid, and water again. The organic phase was separated, dried over calcined magnesium sulfate, and evaporated, and the residue was recrystallized from aqueous isopropyl alcohol. Yield 80%, mp 144–146°C, R_f 0.44. IR spectrum, ν, cm^{-1}: 3271, 3057, 1640, 1553, 1415, 1241, 709. Found, %: N 5.79. $C_{16}H_{21}NO$. Calculated, %: N 5.76.

Amides **Vb**–**Vd** were synthesized in a similar way.

***N*-(Bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (Vb).** Yield 3%, mp 146–148°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 3278, 3049, 1661, 1564, 1421, 1240, 705. Found, %: N 5.82. $C_{16}H_{21}NO$. Calculated, %: N 5.76.

***N*-(Bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-*exo*-2-carboxamide (Vc).** Yield 84%, mp 159–160°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 3278, 3038, 1628, 1557, 1529, 1436, 1245, 713. Found, %: N 5.67. $C_{16}H_{21}NO$. Calculated, %: N 5.76.

***N*-(Bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (Vd).** Yield 80%, mp 137–139°C, R_f 0.44. IR spectrum, ν,

cm^{-1}: 3267, 3031, 1632, 1520, 1427, 1240, 710. Found, %: N 5.84. $C_{16}H_{21}NO$. Calculated, %: N 5.76.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-*exo*-5,6-epoxybicyclo[2.2.1]heptane-*exo*-2-carboxamide (VIIa).** A 70% solution of hydrogen peroxide, 0.51 g (0.44 ml, 15 mmol), was added dropwise under stirring to a mixture of 1.21 g (5 mmol) of amide **Va**, 1.53 g (15 mmol) of acetic anhydride, and 0.15 g (2.5 mmol) of urea in 50 ml of chloroform. The mixture was stirred at room temperature until the reaction was complete (TLC) and neutralized with a saturated solution of sodium hydrogen carbonate, the organic phase was separated and dried over calcined magnesium sulfate, the solvent was removed, and the product was purified by recrystallization from aqueous isopropyl alcohol. Yield 71%, mp 110–112°C. IR spectrum, ν, cm^{-1}: 3282, 3020, 1645, 1550, 1373, 1310, 1082, 841. Found, %: N 5.12. $C_{16}H_{21}NO_3$. Calculated, %: N 5.09.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-*exo*-5,6-epoxybicyclo[2.2.1]heptane-*endo*-2-carboxamide (VIIb)** was synthesized in a similar way. The crude product was subjected to column chromatography on silica gel using diethyl ether as eluent. The first fraction contained compound **VIIb**; yield 61%, mp 123–124°C (from ethyl acetate–hexane), R_f 0.62. IR spectrum, ν, cm^{-1}: 3287, 3031, 1655, 1571, 1369, 1308, 1075, 852. Found, %: N 5.14. $C_{16}H_{21}NO_3$. Calculated, %: N 5.09. From the second fraction we isolated *exo*-2-hydroxy-4-oxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one (**VIII**), yield 10%, mp 157–158°C, R_f 0.10. IR spectrum, ν, cm^{-1}: 3300, 1760. Compound **VIII** was identical to an authentic sample described in [5].

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*endo*-2-ylmethyl)-*exo*-5,6-epoxybicyclo[2.2.1]heptane-*exo*-2-carboxamide (VIIc)** was synthesized as described above for **VIIa**. Yield 66%, mp 135–136°C (from aqueous isopropyl alcohol). IR spectrum, ν, cm^{-1}: 3306, 3032, 1641, 1546, 1284, 1120, 847. Found, %: N 5.02. $C_{16}H_{21}NO_3$. Calculated, %: N 5.09.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*endo*-2-ylmethyl)-*exo*-5,6-epoxybicyclo[2.2.1]heptane-*endo*-2-carboxamide (VIId)** was synthesized in a similar way. The crude product was subjected to column chromatography on silica gel using diethyl ether as eluent. The first fraction contained compound **VIId**; yield 57%, mp 169–171°C (from aqueous isopropyl alcohol), R_f 0.65. IR spectrum, ν, cm^{-1}: 3294, 3015, 1657, 1567, 840. Found, %: N 5.11. $C_{16}H_{21}NO_3$. Calculated, %: N 5.09. From the second fraction we isolated 7% of lactone **VIII**, mp 157–158°C [5].

Bis(bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)amine (XIIa). A solution of 0.58 g (2.4 mmol) of amide **Va** in 10 ml of anhydrous diethyl ether was added dropwise under stirring to a suspension of 0.20 g (5.2 mmol) of $LiAlH_4$ in 10 ml of anhydrous diethyl ether. The mixture was stirred for 6–8 h, maintaining it slightly boiling, until the reaction was complete (TLC). Excess $LiAlH_4$ was decomposed with moist diethyl ether and ice water, the precipitate was filtered off, the organic phase was dried over calcined magnesium sulfate, the solvent was removed, and the residue was distilled under reduced pressure. Yield 89%, bp 88–90°C (28 mm), R_f 0.06. IR spectrum, ν, cm^{-1}: 3340, 3066, 1550, 712. Found, %: N 6.37. $C_{16}H_{23}N$. Calculated, %: N 6.11. Hydrochloride **XIIIa**: yield 85%, mp 332–334°C. IR spectrum, ν, cm^{-1}: 3180, 3070, 2768, 1555, 1450, 720.

***N*-(Bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethylamine (XIIb)** was synthesized in a similar way. Yield 91%, bp 70–71°C (32 mm), R_f 0.07. IR spectrum, ν, cm^{-1}: 3310, 3068, 1552, 728, 708. Found, %: N 6.29. $C_{16}H_{23}N$. Calculated, %: N 6.11. Hydrochloride **XIIIb**: yield 88%, mp 268–270°C. IR spectrum, ν, cm^{-1}: 3170, 3060, 2740, 1450, 740, 710.

Bis(*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)amine (XIIc) was synthesized in a similar way. Yield 70%, bp 92–94°C (20 mm), R_f 0.01. IR spectrum, ν, cm^{-1}: 3300, 3041, 1580, 855. Found, %: N 5.53. $C_{16}H_{23}NO_2$. Calculated, %: N 5.36. Hydrochloride **XIIIc**: yield 56%, mp 316–317°C. IR spectrum, ν, cm^{-1}: 3170, 3038, 2750, 1550, 1450, 858.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*endo*-2-ylmethyl)-*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethylamine (XIId)** was synthesized in a similar way. Yield 87%, oily substance, R_f 0.01. IR spectrum, ν, cm^{-1}: 3360, 3035, 1581, 860. Found, %: N 5.51. $C_{16}H_{23}NO_2$. Calculated, %: N 5.36. Hydrochloride **XIIId**: yield 77%, mp 235–237°C. IR spectrum, ν, cm^{-1}: 3150, 3035, 2740, 1550, 1450, 855.

***N*,*N*-Bis(bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)-*p*-nitrobenzenesulfonamide (XIVa).** A solution of 0.17 g (0.9 mmol) of *p*-nitrobenzenesulfonyl chloride in 10 ml of diethyl ether was added dropwise under stirring to a mixture of 0.20 g (0.87 mmol) of amine **XIIa**, 0.035 g (0.03 ml, 0.87 mmol) of 20% aqueous sodium hydroxide, and 15 ml of diethyl ether. The

mixture was stirred at room temperature until the reaction was complete (TLC), the organic layer was separated and washed with calcined magnesium sulfate, the solvent was removed, and the product was recrystallized from aqueous ethyl alcohol. Yield 65%, mp 86–88°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 3060, 1605, 1536, 1352, 1318, 1168, 705. Found, %: N 6.70. $C_{22}H_{26}N_2O_4S$. Calculated, %: N 6.76.

***N*-(Bicyclo[2.2.1]hept-5-en-*endo*-2-ylmethyl)-*N*-(bicyclo[2.2.1]hept-5-en-*exo*-2-ylmethyl)-*p*-nitrobenzenesulfonamide (XIVb)** was synthesized in a similar way. Yield 56%, mp 122–123°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 3070, 1602, 1530, 1350, 1310, 1165, 750, 712. Found, %: N 6.81. $C_{22}H_{26}N_2O_4S$. Calculated, %: N 6.76.

***N*,*N*-Bis(*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-*p*-nitrobenzenesulfonamide (XIVc)** was synthesized in a similar way. Yield 51%, mp 72–73°C, R_f 0.56. Found, %: N 6.34. $C_{22}H_{26}N_2O_6S$. Calculated, %: N 6.28.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*endo*-2-ylmethyl)-*N*-(*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-*p*-nitrobenzenesulfonamide (XIVd)** was synthesized in a similar way. Yield 50%, mp 90–91°C, R_f 0.52. Found, %: N 6.44. $C_{22}H_{26}N_2O_6S$. Calculated, %: N 6.28.

***N*-(*exo*-5,6-Epoxybicyclo[2.2.1]hept-*endo*-2-ylmethyl)-*N*-(*exo*-5,6-epoxybicyclo[2.2.1]hept-*exo*-2-ylmethyl)-*N'*-*p*-tolylsulfonylurea (XV).** *p*-Toluenesulfonyl isocyanate, 0.15 g (0.76 mmol), was added at room temperature to a solution of 0.17 g (0.74 mmol) of amine **XIIb** in 3 ml of benzene. The precipitate was filtered off, washed with benzene on a filter, dried, and purified by recrystallization from isopropyl alcohol–benzene. Yield 71%, mp 186–187°C, R_f 0.74. IR spectrum, ν, cm^{-1}: 3370, 3071, 1640, 1550, 1378, 1338, 1270, 1168, 725, 710. Found, %: N 6.82. $C_{24}H_{30}N_2O_3S$. Calculated, %: N 6.57.

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