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Azabrendanes. III. Synthesis of Stereoisomeric Exo- and Endo-5-Acylaminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptanes and their Reduction by Lithium Aluminum Hydride

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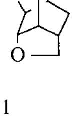
ABSTRACT: *A number of stereoisomeric N-[aryl (alkyl, cycloalkyl)carbonyl]-exo(endo)-5-aminomethylbicyclo[2.2.1]hept-2-enes have been synthesized from bicyclo[2.2.1]hept-2-en-exo(endo)-5-carbonitrile via reduction of the latter by lithium aluminum hydride and subsequent reactions of the resulting amines with aryl(alkyl, cycloalkyl)carbonyl chlorides and anhydrides. The direction of reaction of amides with peroxy acids does not depend on orientation of substituents in the bicyclic fragment: that is, for both exo- and endo-isomers the epoxidations are completed by the formation of N-[aryl(alkyl, cycloalkyl)carbonyl]-exo (endo)-5-aminomethyl-exo-2,3-epoxybicyclo[2.2.1] heptanes. The reduction of stereoisomeric epoxides by lithium aluminium hydride proceeds in different directions; that is, isomers with an exo-oriented amido group form the substituted exo-5-alkylaminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptanes and the reactions of epoxides of endo-amides are accompanied by intramolecular cyclization and completed by the formation of N-[aryl(alkyl, cycloalkyl)]-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonanes. The structures and stereochemical homogenity of the products have been confirmed by the analysis of ^{1}H and ^{13}C NMR spectra, correlation spectroscopy, and nuclear Overhauser enhancement spectroscopy experiments. We discuss the behavior of epoxides and provide an analysis of the coefficients of the atomic orbitals in the molecular orbital–linear combination of atomic orbitals equation (AM1 method).* © 2001 John Wiley & Sons, Inc. Heteroatom Chem12:119–130, 2001

INTRODUCTION

Fast development of the chemistry of cage-type structures [1–3] is determined primarily by the varied biological activity of these compounds. Syntheses of these polycyclic structures require the use of new selective transformations of these compounds.



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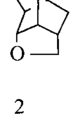

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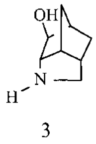

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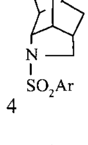

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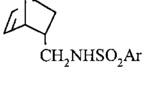

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Oxabrendanes (**1**, **2**) and their derivatives are widely

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known [1,2]. Azabrendanes have been much less known until recently. The precursor of the exo-2-hydroxy-4-azabrendane series (**3**) has been obtained by chemoselective, regioselective, and stereoselective reduction of endo-5-cyano-exo-2,3-epoxybicyclo[2.2.1]heptane with lithium aluminum hydride [3]. A number of derivatives (**4**) of tricyclic amine (**3**) were obtained in the reactions of arylsulfonamides (**5**) with peroxyphthalic acid. These reactions are accompanied by intramolecular cyclizations and are completed by the formation of *N*-(arylsulfonyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonanes [4]. The molecular structure of *N*-(*p*-methoxycarbonylaminophenylsulfonyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonane was determined by X-ray diffraction analysis. More than 20 exo- and endo-stereoisomeric arylsulfonamides, as well as azabrendane (**4**) (Ar = $C_6H_4NO_2$-*p*), have exhibited high pharmacological activity (analgesic, anticonvulsive, anti-inflammatory, etc.). Both rigid framework systems with fixed-in-space orientation of substituents are suitable objects to study the relationship between pharmacological activity and chemical structure.

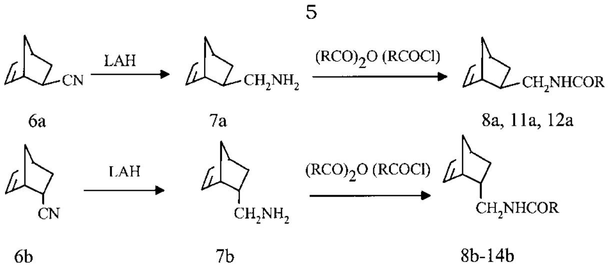
Epoxidation of other derivatives of amines of the norbornene series, as well as bicyclic amines, has not been given any special attention. The only attempt to oxidize endo-5-aminomethylbicyclo[2.2.1]hept-2-ene by the action of oxaziridine has terminated with isolation of the products of amino group transformation only [5]. Although epoxidation of acylated amines of the norbornene series was not studied previously, the compounds of this group are noted as compounds with antiarhythmic, antidiabetic, and hypotensive activity [6]. Saturated analogs of amides that exhibit spasmolytic and antiviral activity in addition to hypotensive activity have been studied much more often [7]. However, the study of the biological activity of mixtures of isomers, not separate, stereochemically homogeneous exo and endo forms, has been characteristic for most of the mentioned investigations.

RESULTS AND DISCUSSION: CHEMICAL AND SPECTRAL INVESTIGATIONS

Stereochemically homogeneous carboxamides have been obtained from carbonitriles (**6a, 6b**), isolable by fractional distillation from the mixture of products obtained by the diene synthesis of cyclopentadiene with acrylonitrile, and they have been converted into exo- and endo-5-aminomethylbicyclo[2.2.1]hept-2-enes (**7a, 7b**) by the action of lithium aluminum hydride [4,8]. Epimerization of 5–9% of the endo-isomer was observed in the reaction; the exo-amine (**7a**) was isolated in a pure state [9].

A number of acylamides (**8–14**) have been obtained from the amines (**7a, 7b**) by the action of various acyl chlorides or anhydrides of carboxylic acids; high product yields have been achieved when the reactions were carried out in dry chloroform in the presence of bases (pyridine, triethylamine) at room temperature (see Scheme 1).

Special attention has been paid to various endo-amines because they are the ones to be later transformed into substituted azabrendanes. Therefore, methyl, trifluoromethyl, as well as various aryl and 1-adamantyl groups have been used as substituents in the acyl group.



R = CH_3 (8), CF_3 (9), 1-Ad (10), C_6H_5 (11), $C_6H_4CH_3$-p (12), C_6H_4Cl-p (13), C_6H_4Cl-o (14)

SCHEME 1

Only poor structural information can be obtained from IR spectra in studies of amides. This is primarily due to the presence of two unsaturated fragments; namely, the double bond and the benzene ring (Table 1). The amide group is identified by the presence of intensive absorption in the regions 3400–3200, 1650–1620, 1560–1530 cm^{-1}.

Tables 2 and 3 list the parameters of ^1H NMR spectra for exo- and endo-amides, which are quite comparable to those of the corresponding sulfonamides of the norbornene series [4,10,11]. The signals were assigned by comparison with the ^1H NMR spectrum of the initial amine (**7a**), for which a two-dimensional spectrum was obtained using correlation spectroscopy (COSY). The resonance of the olefinic protons (H^2, H^3) is observed in the region $\delta = 5.90$–6.25, followed by the signals of the outer fragment protons (H^8), prebridge protons (H^1 and H^4), and the signals of the protons H^5, H^{6x}, H^{7s} and H^{7a}; the strongest field usually contains the signals of the proton H^{6n}. There are signals of the protons of the NH group, and also the signals assigned to substituents bonded to the carbonyl group, in the spectra of the amides. The signals of the protons at the atoms C^8 and C^6 are of special interest. In the spectra of exo- and endo-amides, the signals of diastereotopic pro-

TABLE 1 *N*-Acyl-5-Aminomethylbicyclo[2.2.1]hept-2-enes **8–14**

Compound	*Yield (%)*	*m.p./b.p. (°C)*	*Formula*	*Anal. % Calcd/Found* C	H	N	*IR Spectral Parameters*
8a	96[a]	126–127/4 mmHg	$C_{10}H_{15}NO$	72.73 73.01	9.09 9.20	8.48 8.51	3202, 3042, 1638, 1538, 1370, 900, 706
11a	71	133.5–134.5	$C_{15}H_{17}NO$	79.29 79.08	7.49 7.59	6.17 6.10	3290, 3042, 1621, 1528, 1254, 930, 708
12a	86	126.5–127.5	$C_{16}H_{19}NO$	79.67 79.60	7.88 7.74	5.81 5.85	3408, 3028, 1622, 1525, 1266, 900
8b	82[b]	146–147/8 mmHg	$C_{10}H_{15}NO$	72.73 72.59	9.09 9.21	8.48 8.31	3303, 3068, 1650, 1560, 1462, 1370, 714
9b	78[c]	110–111/6 mmHg	$C_{10}H_{12}F_3NO$	54.79 54.61	5.48 5.39	6.39 6.32	3245, 3077, 1667, 1532, 1332, 700
10b	82	179–181	$C_{19}H_{27}NO$	80.00 79.87	9.47 9.41	4.91 4.95	3430, 3026, 2882, 1622, 1526, 1243
11b	96	94.5–95.5	$C_{15}H_{17}NO$	79.29 79.46	7.49 7.56	6.17 6.07	3332, 3053, 1623, 1531, 1251, 931, 711
12b	91	105–106.5	$C_{16}H_{19}NO$	79.67 80.25	7.88 8.21	5.81 6.17	3408, 3280, 1625, 1526, 1309, 1270
13b	99	108–109	$C_{15}H_{16}ClNO$	68.83 68.55	6.12 6.30	5.35 5.24	3300, 3026, 1625, 1513, 1322, 1263, 1079
14b	88	119–120	$C_{15}H_{16}ClNO$	68.83 68.43	6.12 6.18	5.35 5.31	3310, 3029, 1628, 1520, 1470, 1265, 718

[a] n_D^{20} 1.5075.
[b] n_D^{20} 1.5074.
[c] n_D^{20} 1.4465

TABLE 2 ^1H NMR ($CDCl_3$) Spectra of Compounds **8a, 11a, 12a** (δ/J Hz)

Compound	H^1	H^2, H^3	H^4	H^5	H^{6x}	H^{6n}	H^{7s}	H^{7a}	H^{8A}	H^{8B}
8a	2.82	6.06	2.63	2.06	1.56 $^2J_{6x,6n}$ 12.0 $^3J_{6x,5}$ 7.8 $^3J_{6x,1}$ 4.2	1.14 $^3J_{6n,5}$ 4.7 $^4J_{6n,7s}$ 3.3	1.25 $^2J_{7s,7a}$ 8.4	1.34	3.31 $^2J_{8A,8B}$ 12.7 $^3J_{8A,5}$ 6.0	3.18 $^3J_{8B,5}$ 5.6
11a	2.87	6.09	2.76	2.05	1.69 $^2J_{6x,6n}$ 12.1 $^3J_{6x,5}$ 7.6 $^3J_{6x,1}$ 3.8	1.24 $^3J_{6n,5}$ 4.7 $^4J_{6n,7s}$ 3.3	1.34 $^2J_{7s,7a}$ 8.7	1.54	3.55 $^2J_{8A,8B}$ 13.8 $^3J_{8A,5}$ 7.3	3.46 $^3J_{8B,5}$ 7.1
12a	2.86	6.06	2.72	2.06	1.73 $^2J_{6x,6n}$ 12.5 $^3J_{6x,5}$ 6.8	1.26	1.30 $^2J_{7s,7a}$ 8.7	1.44	3.49 $^2J_{8A,8B}$ 13.6 $^3J_{8A,5}$ 6.8	3.34 $^3J_{8B,5}$ 6.4

tons H^{8A} and H^{8B} located near the chiral center at C^5 differ in position, as well as in the values for the vicinal constants of spin-spin splitting with respect to the proton at C^5. The positions of these signals are different in the spectra of stereoisomers; that is, the protons at C^8 in the molecules of endo-amides resonate in stronger field and are characterized by larger geminal spin-spin interaction constants (12.7–13.8 Hz for exo- and 13.5–14.9 Hz for endo-amides) (Tables 2 and 3). On the contrary, the geminal splitting constants for the protons at C^6 are 12.0–12.5 Hz for exo- and 11.0–11.7 Hz for endo-amides.

The parameters of ^{13}C NMR spectra for amides (**11a, 11b**) are listed in Table 4; they prove the structure of the norbornene fragment and the presence of a carbonyl group in the molecules of amides, and they demonstrate the difference in spectral characteristics caused by exo- and endo-orientation of substituents at the unsaturated skeleton. The signals were assigned by comparison with spectra of other substituted norbornenes for which an experiment on ^{13}C(H) selective double resonance had been made [12].

The epoxidation of amides of the norbornene series is of special interest because of recently found cases of intramolecular cyclization for endo-arylsulfonamides (**5**) of the norbornene series by the action of peroxyphthalic acid forming the substituted azabrendanes (**4**).

By way of contrast, the amides of the norbor-

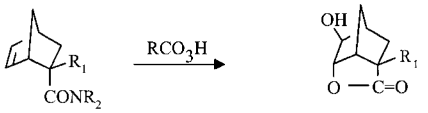
TABLE 3 ^{1}H NMR ($CDCl_3$) Spectra of Compounds **8b–13b**(δ/J Hz)

Compound	H^1	H^2, H^3	H^4	H^5	H^{6x}	H^{6n}	H^{7s}	H^{7a}	H^{8A}	H^{8B}
8b	2.51	6.17 5.95 $^3J_{2,3}$ 5.6 $^3J_{2,1}$ 3.3 $^3J_{3,4}$ 2.7	2.82	2.18	1.85 $^2J_{6x,6n}$ 11.7 $^3J_{6x,5}$ 8.6 $^3J_{6x,1}$ 3.8	0.54 $^3J_{6n,5}$ 4.3 $^4J_{6n,7s}$ 2.7	1.44 $^2J_{7s,7a}$ 8.1	1.24	3.01 $^2J_{8A,8B}$ 14.0 $^3J_{8A,5}$ 8.5	2.90 $^3J_{8B,5}$ 7.8
9b	2.79	6.13 5.91 $^3J_{2,3}$ 5.4 $^3J_{2,1}$ 3.3 $^3J_{3,4}$ 3.0	2.79	2.26	1.79 $^2J_{6x,6n}$ 10.9 $^3J_{6x,5}$ 7.6 $^3J_{6x,1}$ 3.4	0.65 $^3J_{6n,5}$ 4.3 $^4J_{6n,7s}$ 2.7	1.34 $^2J_{7s,7a}$ 7.9	1.18	3.22 $^2J_{8A,8B}$ 14.4 $^3J_{8A,5}$ 8.5	3.10 $^3J_{8B,5}$ 7.8
10b	2.74	6.11 6.06	2.78	2.30	1.86 $^2J_{6x,6n}$ 12.4	0.52	1.35 $^2J_{7s,7a}$ 8.1	1.22	2.93 $^2J_{8A,8B}$ 14.3 $^3J_{8A,5}$ 7.1	2.86 $^3J_{8B,5}$ 6.6
11b	2.84	6.21 6.02 $^3J_{2,3}$ 5.4 $^3J_{2,1}$ 3.3 $^3J_{3,4}$ 2.7	2.88	2.38	1.90 $^2J_{6x,6n}$ 11.7 $^3J_{6x,5}$ 8.9 $^3J_{6x,1}$ 3.9	0.65 $^3J_{6n,5}$ 4.2 $^4J_{6n,7s}$ 2.7	1.47 $^2J_{7s,7a}$ 7.8	1.28	3.25 $^2J_{8A,8B}$ 13.5 $^3J_{8A,5}$ 6.6	3.14 $^3J_{8B,5}$ 6.2
12b	2.83	6.19 6.00 $^3J_{2,3}$ 5.6 $^3J_{2,1}$ 3.0 $^3J_{3,4}$ 2.6	2.87	2.37	1.87 $^2J_{6x,6n}$ 11.6 $^3J_{6x,5}$ 9.6 $^3J_{6x,1}$ 4.0	0.64 $^3J_{6n,5}$ 4.1 $^4J_{6n,7s}$ 2.7	1.46 $^2J_{7s,7a}$ 8.4	1.26	3.20 $^2J_{8A,8B}$ 14.9 $^3J_{8A,5}$ 8.1	3.12 $^3J_{8B,5}$ 7.6
13b	2.84	6.20 6.01 $^3J_{2,3}$ 5.4 $^3J_{2,1}$ 3.2 $^3J_{3,4}$ 2.7	2.37	2.84	1.89 $^2J_{6x,6n}$ 11.3 $^3J_{6x,5}$ 9.6 $^3J_{6x,1}$ 3.7	0.63 $^3J_{6n,5}$ 4.3 $^4J_{6n,7s}$ 2.7	1.46 $^2J_{7s,7a}$ 8.4	1.26	3.22 $^2J_{8A,8B}$ 14.3 $^3J_{8A,5}$ 8.0	3.12 $^3J_{8B,5}$ 7.2

TABLE 4 ^{13}C NMR Spectra ($CDCl_3$) of Compounds **11a, 11b, 18a, 18b**

Compound	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C=O
11a	41.7	136.8	136.2	44.4	39.2	30.9	45.2	45.1	167.5
11b	42.4	137.8	132.0	44.4	38.9	30.1	49.5	44.1	167.4
18a	39.7	51.9	51.4	40.0	37.6	31.1	23.2	43.7	170.5
18b	38.6	51.2	49.1	41.7	37.5	29.8	27.4	41.5	167.6

nene series were transformed under the action of peroxy acids differently, that is, with participation of the carbonyl group of the amide and subsequent slow transformation into lactones [13] (Scheme 2).

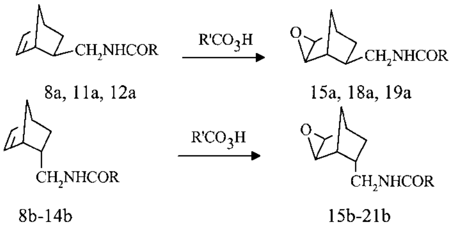


R_1 = H, Me; R_2 = H, Alk, Ar

SCHEME 2

Exo-isomers of sulfonamides and amides are easily oxidized under the same conditions to give epoxides [11,14].

Contrary to claims in the literature, we have shown that the epoxidation of exo-amides, as well as endo-amides (**8–14**), proceeds with the formation of the epoxide derivatives (**15–21**) and is not accompanied by heterocyclization for the endo-isomers (Scheme 3).



R = CH_3 (15), CF_3(16), 1-Ad (17), C_6H_5 (18), $C_6H_4CH_3$-p (19), C_6H_4Cl-p (20), C_6H_4Cl-o (21)

SCHEME 3

In the case of endo-amides, it is especially important to define the dependence of the direction of transformation on peroxy acid character and reaction conditions. The amide (**11b**) was oxidized by various means; namely, by the action of crystalline peroxyphthalic acid, the latter being obtained in situ from phthalic anhydride and 50% hydrogen peroxide; and by the action of peroxyacetic acid in the form of 40% aqueous solution and obtained in situ from acetic acid and 50% hydrogen peroxide [14]. In the capacity of epoxidizing agents, we also used peroxyimide acids obtained by the action of hydrogen peroxide on dicyclohexylcarbodiimide in the presence of acetic acid [15], and also by the reaction of hydrogen peroxide with trichloroacetonitrile in the presence of sodium hydrophosphate [16]. Both the analysis of the reaction medium by thin-layer chromatography and the study of the properties and spectral parameters of oxidation products prove the formation of only the epoxide (**18b**) in all cases. A minimal yield of the epoxide (**18b**) (40%) was achieved in the last trial; in the previous cases it exceeded 68%. Maximal yields of the epoxide (**18b**) (94 and 95%) have been achieved by use of peroxyacetic acid.

IR spectra of all products of oxidation (Table 5) contain the bands in the region 860–840 cm^{-1}, which are characteristic for epoxynorbornanes (ν C–O) and bonds in the region 3050–3030 cm^{-1} (ν C–H in three-membered rings); however, the latter is often shielded by the absorption of aromatic system bonds. IR spectra also provide proofs of the presence of an amido group and substituents in the amide fragment. Table 6 lists the results of analysis of ^1H NMR spectra for the epoxides. The most characteristic signals in the spectra of epoxides are those of the epoxide ring protons in the region δ = 3.10–3.40 and those of the bridge protons; one of them (H^{7a}) exhibits considerable shielding because of magnetic anisotropy of the oxirane ring, with a corresponding signal shift to the region δ = 0.8–0.9. At the same time, according to literature data, nonequivalence of the H^{7s} and H^{7a} signals increases considerably, achieving δ = 0.4–0.6 [17]. The introduction of the epoxide ring is also manifested in the strong-field shift of the protons H^1, H^4, H^5, and H^{6x} signals as compared with spectra of unsaturated amides. Weak-field shifts are observed only for the signals of some protons of endoamide epoxide derivatives (H^{6n}, H^{8A}, H^{8B}).

^1H NMR spectra of the epoxide derivatives of amides are of special interest because they make it possible, for the first time, to compare the spectra of stereoisomeric epoxides of the norbornene series, including the substituted amino group, and also to elaborate the criteria for the determination of the content of the stereoisomers. These criteria were elaborated earlier for the analyses of the mixtures of unsaturated analogs, for example, sulfonamides [4,10,18], ureas, and thioureas [19]. Determinations of the configuration of compounds were made by comparison of the nonequivalence ($\Delta\delta$) of signals for the protons H^2 and H^3, H^1 and H^4, H^{6x} and H^{6n}, which were different for exo- and endo-isomers. The data of Tables 2, 3, and 6 confirm that the criteria proposed earlier can be used in the analysis of the ^1H NMR spectra for carboxamides and epoxyamides having a bicyclic skeleton.

Indeed, the values of $\Delta\delta$ (H^1, H^4) for exo-amides and the values of $\Delta\delta$ (H^{6x}, H^{6n}) are on average 0.20 and 0.40–0.45 ppm, respectively, and the signals H^2 and H^3 have almost equivalent values of chemical shifts. For epoxide derivatives of the exo-amides (**15a, 18a**), the values of $\Delta\delta$ are 0.10–0.15, 0.35–0.40, and 0.03 ppm, respectively. On the contrary, the corresponding values of $\Delta\delta$ for endo-amides are close to 0.01–0.04, 1.20–1.30, and 0.10–0.20 ppm, and, for

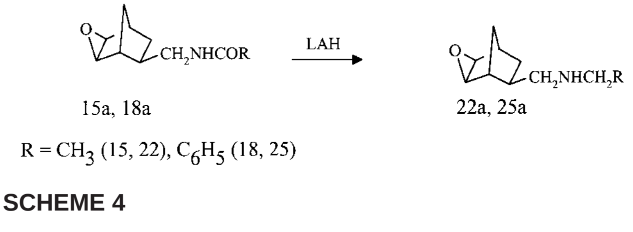
TABLE 5 N-Aryl(alkyl, cycloalkyl)carbonyl-5-aminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptanes **15-21**

				Anal. % Calcd/Found			
Compound	*Yield (%)*	*m.p./b.p. (°C)*	*Formula*	*C*	*H*	*N*	*IR Spectral Parameters*
15a	84[a]	179–180/5 mmHg	$C_{10}H_{15}NO_2$	66.30 66.41	8.29 8.32	7.73 7.53	3250, 3035, 1648, 1532, 846
18a	74	115–116	$C_{15}H_{17}NO_2$	74.07 73.95	6.99 6.90	5.76 5.62	3260, 3048, 1638, 1542, 1240, 910, 838
19a	87	112–113	$C_{16}H_{19}NO_2$	74.71 74.63	7.39 7.31	5.45 5.32	3280, 3049, 1634, 1530, 1246, 912, 836
15b	83[b]	192–193/5 mmHg	$C_{10}H_{15}NO_2$	66.30 66.41	8.29 8.32	7.73 7.58	3340, 3200, 3053, 1600, 1533, 1256, 839
16b	78[c]	163–164/7 mmHg	$C_{10}H_{12}F_3NO_2$	51.06 50.89	5.11 5.02	5.96 5.88	3315, 3267, 3053, 1665, 1533, 1248, 837
17b	77	198–200	$C_{19}H_{27}NO_2$	75.75 75.64	8.97 8.90	4.65 4.76	3310, 3052, 1642, 1531, 1243, 918, 840
18b	82	108–109	$C_{15}H_{17}NO_2$	74.07 74.14	6.99 7.04	5.76 5.79	3244, 3056, 1625, 1545, 1440, 1227, 924, 844
19b	87	120–121	$C_{16}H_{19}NO_2$	74.71 74.64	7.39 7.30	5.45 5.41	3288, 3050, 1656, 1542, 1261, 928, 838
20b	89	132–133	$C_{15}H_{16}ClNO_2$	64.86 64.77	5.77 5.71	5.05 5.18	3312, 3220, 1664, 1570, 1238, 930, 842
21b	94	131–132	$C_{15}H_{16}ClNO_2$	64.86 64.79	5.77 5.84	5.05 5.11	3387, 3206, 1680, 1573, 1460, 1233, 933, 840

[a] n_D^{20} 1.5128.
[b] n_D^{20} 1.5172.
[c] n_D^{20} 1.4588.

their epoxide derivatives, the values are 0.04–0.06, 0.92–0.98, and 0.12–0.20 ppm, respectively.

^{13}C NMR spectra (Table 4) of the epoxides (**18a, 18b**) differ from those of amides in the assigned shifts of the carbon atoms C^2 and C^3 to the region $d = 49–52$, and also of those of bridge carbons to the region $\delta = 23–27$. The latter convincingly testifies to the exo-orientation of the epoxide ring [17b]. The parameters of ^{13}C NMR spectra, as well as ^1H NMR spectra, differ considerably for both stereoisomeric epoxides and unsaturated compounds, depending on the orientation of substituents in the norbornene fragment. Thus, stereoisomers differ in the values of C^2 and C^3 nonequivalence signals ($\Delta\delta$ (C^2, C^3)), which are 0.6 and 0.5 ppm for the exo-isomers (**11a, 18a**), and 5.8 and 2.1 ppm for the endo-isomers (**11b, 18b**). The positions of the signals of bridge carbons are also different; besides, in both series, the endo-isomers are characterized by the presence of the weaker field signal (Table 4).



SCHEME 4

The reduction of epoxides of both series has been carried out by lithium aluminum hydride in boiling absolute ether. The chemoselective reduction of an amido group into an amino group with preservation of the epoxide ring occurs for the epoxides with the exo-orientation of the amido group, which is remote from the oxirane ring. High stability of epoxynorbornanes in the reactions with lithium aluminum hydride is known; in this process the groups that are being easily transformed in the molecules are nitrile [3], carbamoyl [20], and carbomethoxy-ones [2], and also outer epoxide fragments of the series of diepoxide compounds (diepoxides of vinylnorbornene, ethylidennorbornene, and cyclopentadiene dimer) [2]. High stability of exo-epoxynorbornanes in the reactions with lithium aluminum hydride were observed, and we connected this with the manifestation of steric hindrance appearing under intramolecular attack by an outside nucleophilic reagent at the rear (endo-) side of a rigid bicyclic skeleton.

The structures of the epoxides (**22a, 25a**) are confirmed by the presence of absorption bands in the region 850–840 and 3030–3020 cm^{-1} (ν C-O and ν C-H of epoxynorbornanes). Chemoselective reduction of the epoxyamide (**15a**) is also supported by the structure of the ^1H NMR spectrum of the reaction product. (See Scheme 4.) Indeed, the spectrum re-

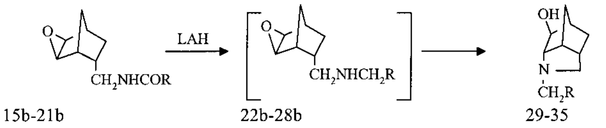
TABLE 6 ^{1}H NMR ($CDCl_3$) Spectra of Compounds **15a, 18a, 15b, 16b, 18b, 20b** (δ/J Hz)

Compound	H^1	H^2, H^3	H^4	H^5	H^{6x}	H^{6n}	H^{7s}	H^{7a}	H^{8A}	H^{8B}
15a	2.46	3.11 3.08	2.35	1.71	1.48 $^2J_{6x,6n}$ 12.6 $^3J_{6x,5}$ 8.0	1.11 $^3J_{6n,5}$ 4.1	1.25 $^2J_{7s,7a}$ 9.6	0.86	3.15	3.05
18a	2.48	3.10 3.08	2.36	1.85	1.53 $^2J_{6x,6n}$ 12.3 $^3J_{6x,5}$ 9.0 $^3J_{6x,1}$ 4.2	1.19 $^3J_{6n,5}$ 4.5	1.30 $^2J_{7s,7a}$ 10.2	0.92	3.37 $^2J_{8A,8B}$ 14.0 $^3J_{8A,5}$ 6.3	3.30 $^3J_{8B,5}$ 5.7
15b	2.46	3.29 3.17 $^3J_{2,3}$ 3.0	2.50	2.35	1.76 $^2J_{6x,6n}$ 12.3 $^3J_{6x,5}$ 10.2 $^3J_{6x,1}$ 5.7	0.84 $^3J_{6n,5}$ 4.2 $^4J_{6n,7s}$ 2.7	1.38 $^2J_{7s,7a}$ 10.2	0.78	3.34 $^2J_{8A,8B}$ 13.6 $^3J_{8A,5}$ 8.5	3.24 $^3J_{8B,5}$ 7.8
16b	2.47	3.35 3.21 $^3J_{2,3}$ 3.6	2.53	2.23	1.82 $^2J_{6x,6n}$ 12.7 $^3J_{6x,5}$ 11.1 $^3J_{6x,1}$ 4.4	0.88 $^3J_{6n,5}$ 4.3 $^4J_{6n,7s}$ 2.7	1.36 $^2J_{7s,7a}$ 9.9	0.81	3.47 $^2J_{8A,8B}$ 13.9 $^3J_{8A,5}$ 8.7	3.29 $^3J_{8B,5}$ 7.2
18b	2.53	3.39 3.21 $^3J_{2,3}$ 3.4	2.53	2.27	1.81 $^2J_{6x,6n}$ 12.2 $^3J_{6x,5}$ 10.2 $^3J_{6x,1}$ 5.7	0.93 $^3J_{6n,5}$ 4.3 $^4J_{6n,7s}$ 2.6	1.42 $^2J_{7s,7a}$ 9.9	0.81	3.57 $^2J_{8A,8B}$ 13.5 $^3J_{8A,5}$ 8.2	3.46 $^3J_{8B,5}$ 7.6
20b	2.48	3.39 3.19 $^3J_{2,3}$ 3.0	2.50	2.26	1.83 $^2J_{6x,6n}$ 12.7 $^3J_{6x,5}$ 10.3 $^3J_{6x,1}$ 4.4	0.89	1.34 $^2J_{7s,7a}$ 10.0	0.78	3.47 $^2J_{8A,8B}$ 13.4 $^3J_{8A,5}$ 6.3	3.31 $^3J_{8B,5}$ 5.9

tains the signals of the epoxy ring protons (unresolved multiplets in the region δ = 3.10) and the characteristic position of the doublet of the proton H^{7a} in the strong-field part of the spectrum (δ = 0.83). The amide fragment is being transformed into an ethylamine group having the resonances of the methylene and methyl groups in the regions δ = 2.65 and 1.12, respectively. As in the cases of other exo-series epoxides, a considerable difference in the resonances of the protons H^1 and H^4 (δ = 2.45 and 2.36) is characteristic for the epoxyamine (**22a**). As compared with the spectrum of the epoxyamide (**15a**), most signals are shifted to the strong field. In particular, protons H^{8A} and H^{8B} resonate in the region δ = 2.72 and 2.62, respectively.

Stereochemical peculiarities of the epoxides with the endoorientation of the substituent (**15b–21b**) predetermine other characteristics of the products of their reactions with lithium aluminium hydride. We described the reduction of one of the epoxides (**18b**) [21]. It can be assumed that the epoxyamides (**22b–28b**) being formed in the reaction as intermediates undergo intramolecular cyclization to give the substituted azabrendanes (exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonanes) (**29–35**) (Scheme 5). Chromatographic analysis has shown the absence of other possible products of the epoxides reduction. Probably, heterocyclization is promoted by the presence of a highly nucleophilic amino group at the rear of the epoxynorbornane skeleton and also by the activation of the oxygen atom of the epoxy ring by aluminum hydride, which is always contained as an impurity in lithium aluminum hydride. The comparison of the behavior of the intermediates (**22b–28b**) with that of epoxyamides, which do not undergo heterocyclization under the epoxidation conditions, suggests the decisive role of the character of the attacking nitrogen-containing nucleophilic moiety.

13



R = CH_3 (22, 29), CF_3 (23, 30), 1-Ad (24, 31), C_6H_5 (25, 32), $C_6H_4CH_3$-p (26, 33), C_6H_4Cl-p (27, 34), C_6H_4Cl-o (28, 35)

SCHEME 5

The properties of the substituted azabrendanes (**29–35**) are listed in Table 7. The IR spectra of the compounds do not contain the absorption peak in the region 860–840 cm^{-1} (ν C–O), but do contain the intensive absorption bands of a hydroxy group (3500–3300 cm^{-1}). Proof of the heterocyclization products structures have been obtained by the analysis of ^{1}H NMR spectra of the compounds (**29–33**) (Table 8) and by the comparison with the spectrum of the series precursor (**3**) for which a two-dimensional spectrum (COSY technique) had been made earlier [3]. The key signals of the spectra are two peaks in the region of weak field, namely, the doublet of the H^{3x} proton in the region δ = 2.9–3.1, and an unresolved multiplet of the H^{2n} proton in the region δ = 3.5–3.9. The resonance of a newly formed (at C^{10}) methylene group, and also those of analogous groups at C^5, C^8, and C^9, whose protons are anisochronic, are quite revealing.

The resonance of the methylene group at C^{10} depends on the character of the substituent, that is, a phenyl, trifluoromethyl, methyl, or adamantyl group (δ = 3.70–3.90, 3.22, 2.70, and 2.50, respectively). Protons at C^5 resonate as doublets, one of which is additionally split with respect to the H^6 proton with the coupling constant being 4.7–5.1 Hz. Prebridge protons (H^7 and H^1) have become considerably nonequivalent (δ = 2.4–2.7 and 2.1) because of inclusion of one of them (H^7) into a newly formed five-membered heterocycle.

Epoxide compounds with substituents at the nitrogen atom which are capable of undergoing changes in the reactions with reducing agents (epoxides **16, 20, 21**) are examined in the current work. Spectral data testify to the unreactivity of the trifluoromethyl, and *o*- and *p*-chlorophenyl groups in the reactions with lithium aluminum hydride.

The proximity of the bulky adamantane skeleton, the resonances of its protons being distinctly manifested in the spectrum of the azabrendane (**31**) in the region δ = 1.5–1.7, does not impede the reduction and cyclization. Probably, the steric effect of the bulky adamantyl group, as well as the polar effect of other groups in the intermediates (**22b–28b**), are moderated by the proximity of the methylene group at C^{10} appearing during reduction. The formation of a nitrogen-containing polycyclic system proceeds as easily as for the analogous oxabrendanes (**2**) under reduction of epoxynorbornanes with endo-orienta-

TABLE 7 *N*-Aryl(alkyl, cycloalkyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonanes **29–35**

Compound	*Yield (%)*	*m.p./b.p. (°C)*	n_D^{20}	*Formula*	*Anal. % Calcd/Found* C	H	N	*IR Spectral Parameters*
29	75	182–184/4 mmHg	1.5034	$C_{10}H_{17}NO$	71.86	10.18	8.38	3480, 3284, 1570, 1440, 1042
					71.80	10.02	8.31	
30	68	126–127/8 mmHg	—	$C_{10}H_{14}F_3NO$	54.30	6.33	6.33	3510, 3270, 1571, 1453, 1176, 1030
					54.23	6.39	6.29	
31	71	130–133	—	$C_{19}H_{29}NO$	79.44	10.10	4.88	3481, 3230, 3053, 1580, 1120, 1048
					79.31	9.96	4.80	
32	56	201–202/4 mmHg	—	$C_{15}H_{19}NO$	78.60	8.29	6.11	3400, 3277, 3064, 1584, 1440, 1042
					78.67	8.21	5.80	1440, 1042
33	82	178–179/4 mmHg	1.5454	$C_{16}H_{21}NO$	79.01	8.64	5.76	3492, 3060, 1542, 1436, 1051, 918
					79.18	8.47	5.70	
34	74	159–161/4 mmHg	1.5650	$C_{15}H_{18}ClNO$	68.31	6.83	5.31	3500, 3076, 1436, 1227, 1065, 943
					68.34	6.75	5.38	
35	88	147–148/4 mmHg	1.5676	$C_{15}H_{18}ClNO$	68.31	6.83	5.31	3510, 3286, 3070, 1447, 1190, 1050
					68.30	6.69	5.35	

TABLE 8 ^{1}H NMR ($CDCl_3$) of Compounds **29–33** (δ/J Hz)

Compound	H^1	H^2	H^3	$H^{5A,5B}$	H^6	H^7	$H^{8s,8a}$	H^{9x}	H^{9n}
3	2.06	3.34	3.73 $^3J_{3,7}$ 5.1	3.07 2.81 $^2J_{5A,5B}$ 10.5	2.23	2.44	1.98 1.49 $^2J_{8s,8a}$ 9.9	1.85 $^2J_{9x,9n}$ 12.9 $^3J_{9x,6}$ 9.3 $^3J_{9x,1}$ 4.5	0.86 $^3J_{9n,6}$ 2.1 $^4J_{9n,7s}$ 2.1
29	2.06	3.65	2.92	2.91 2.68	2.20	2.54	1.89 1.36 $^2J_{8s,8a}$ 10.6	1.78 $^2J_{9x,9n}$ 12.6 $^3J_{9x,6}$ 10.2 $^3J_{9x,1}$ 4.2	0.92
30	2.07	3.54	2.90 $^3J_{3,7}$ 4.9	3.06 2.71 $^2J_{5A,5B}$ 9.0 $^3J_{5A,6}$ 4.7	2.21	2.56	1.86 1.40 $^2J_{8s,8a}$ 11.1	1.83 $^2J_{9x,9n}$ 12.9 $^3J_{9x,6}$ 9.9 $^3J_{9x,1}$ 4.3	0.93
31	2.13	3.86	3.09	3.22 2.90 $^2J_{5A,5B}$ 9.9 $^3J_{5A,6}$ 5.0	2.26	2.63	1.88 1.40 $^2J_{8s,8a}$ 11.4	1.80 $^2J_{9x,9n}$ 12.0	0.85
32	2.11	3.86	3.02	2.96 2.74 $^2J_{5A,5B}$ 10.8	2.24	2.55	1.88 1.38 $^2J_{8s,8a}$ 10.5	1.81 $^2J_{9x,9n}$ 12.6	1.01
33	2.06	3.74	2.91 $^3J_{3,7}$ 5.0	2.91 2.60 $^2J_{5A,5B}$ 9.9 $^3J_{5A,6}$ 5.1	2.17	2.49	1.84 1.33 $^2J_{8s,8a}$ 10.2	1.77 $^2J_{9x,9n}$ 12.9 $^3J_{9x,6}$ 9.9 $^3J_{9x,1}$ 4.3	0.94

tion of the carbomethoxy group by lithium aluminum hydride [2].

QUANTUM-CHEMICAL CALCULATIONS

In the synthesis of the substituted exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonanes (**29–35**), reactions taking place with high selectivity were discovered, such as chemoselective transformation of the epoxyamides (**15–21**) into epoxyamines under the action of lithium aluminium hydride, as well as regiospecific heterocyclization of the intermediate epoxyamines (**22b–28b**) accompanied by the breaking of the C^3–O bond of the epoxide ring and resulting in azabrendane (**29–35**) formation. Taking into account the priority character of research of selective transformations of organic compounds, including epoxides, we have carried out a theoretical study of the stereoisomeric epoxides (**15a,b, 18a,b, 22a,b,** and **25a,b**) using the semiempirical AM1 method [22]. The major part of these compounds is described in this work, as well as those of compounds (**22b, 25b**) present as intermediates formed in the reactions of lithium aluminium hydride with epoxyamides (**15b, 18b**). In Table 9, energies of borderline orbitals, atomic charges, and bond orders of the epoxy compounds (**18a,b**) are given.

Analysis of the atomic orbital coefficients in the molecular orbital–linear combination of atomic orbitals (MO LCAO) equation was carried out for stereoisomeric epoxides (**15a, 15b**). Analysis showed that, in both cases, the LUMO basically consists of the atomic orbitals of carbonyl group carbon atom (43.6% and 56.7%, respectively) and also carbonyl group oxygen atom (24.7% for epoxide **15b**). It is the latter data that accounts for the chemoselective course of the reaction by one of the centers, namely, by the carbonyl group. For epoxyamines (**22a, 22b**) that are the products of reduction of the compounds (**15a, 15b**), the LUMO was localized on the epoxide ring atoms, mainly on the C^3 atom (39.1% and 38.7%) and oxygen atom (35.5% and 38.9%), whereas the HOMO was localized on the nitrogen atom of the amino group (42.4% and 28.2% for **22a** and **22b**, respectively). The described localization of the borderline orbitals predetermines intramolecular cyclization of endo-epoxyamine (**22b**) in that the steric convergence of borderline orbitals at the rear area of the norbornane carbon moiety promotes their primary overlap.

TABLE 9 The Values of the Energies of Borderline Orbitals, Atomic Charges, and Bond Order in Molecules **18a, 18b**

						Bond Order		*Atomic Charges*		
Compound	$E_{OMO\ II}$	E_{HOMO}	E_{LUMO}	$E_{UMO\ II}$	$E_{LMO(N)}$	C^2–O	C^3–O	C^2	C^3	N
18a	−10.029	−9.941	−0.166	0.202	−12.1122	0.9651	0.9652	−0.0632	−0.0604	−0.3804
18b	−10.420	−9.958	−0.221	0.197	−12.2567	0.9664	0.9629	−0.0687	−0.0588	−0.3762

Differences in the strength of the epoxide ring bonds in the epoxide molecules (**22b, 25b**) probably also assist in the regiospecific course of heterocyclization. Actually, the minor strength of the C^3–O bond, in comparison with other carbon–oxygen bonds of epoxides, follows from Table 9 data.

EXPERIMENTAL

IR spectra were recorded on a Specord-75-IR instrument in the region 4000–400 cm^{-1} using KBr pellets. NMR spectra were measured on a Varian Gemin 400 radiospectrometer (operating frequency for the ^1H nuclei, 400 MHz; ^{13}C nuclei, 100.58 MHz) in deuterochloroform or deuteroacetone solutions using the domestic standards HMDS or tetramethylsilane (TMS). Thin-layer chromatography (TLC) data were obtained using the Silufol UV-254 plates with ether as an eluent and iodine vapor as a developer. Elemental analyses were carried out on a Karlo Erba analyzer.

The syntheses of the unsaturated nitriles (**6a, 6b**) and the amines (**7a, 7b**) were performed by methods described in the literature [10].

*N-Acetyl-exo-5-aminomethylbicyclo[2.2.1]hept-2-ene (***8a***)*

A mixture of the amine (**7a**) (1.23 g, 0.01 mol), acetic anhydride (1.8 mL, 0.02 mol), and pyridine (2.4 mL, 0.03 mol) in dry chloroform (20 mL) was heated in a water bath (70°C). Completion of the reaction was determined by TLC monitoring. The product of acylation was washed with water three times; the organic layer was collected and washed with 20% hydrochloric acid until the pyridine had been removed. The organic layer was collected and dried with calcinated magnesium sulfate, the solvent was removed by distillation, and the product was distilled in vacuum. The yield of amide (**8a**) was 96%. The amides (**8b, 9b**) were synthesized by this method. The properties of the compounds are listed in Table 1, and the parameters of ^1H NMR spectra are given in Tables 2 and 3.

*N-Benzoyl-endo-5-aminomethylbicyclo[2.2.1]hept-2-ene (***11b***)*

To a stirred mixture of the amine (**7b**) (1.23 g, 0.01 mol) and pyridine (2.4 mL, 0.03 mol) in dry chloroform (30 mL), benzoyl chloride was added dropwise. The stirring was continued at room temperature. Termination of the reaction was determined by TLC monitoring. After the usual treatment, the amide (**11b**) was isolated with a 96% yield. The amides (**10b, 11a, 12a, 12b, 13b, 14b**) were synthesized by this method. The properties of these compounds are listed in Table 1; the parameters of ^1H NMR spectra are given in Tables 2 and 3.

*Epoxydation of acyl derivatives of the amines (***7a, 7b***)*

Method A. A mixture of the amide (**11b**) (0.50 g, 0.0022 mol), urea (0.07 g, 0.0011 mol) and 75% monoperoxyphthalic acid (1.10 g, 0.0044 mol) in ethyl acetate (20 mL) was stirred at room temperature. Termination of the reaction was determined by TLC monitoring. After neutralization of the reaction mixture by a saturated solution of sodium bicarbonate, the organic layer was collected and dried with calcinated magnesium sulfate, and the solvent was removed by distillation. The epoxyamide (**18b**) was recrystallized with an 81% yield. The epoxyamides (**15a, 15b, 16b, 17b, 18a, 19a, 19b**) were obtained in a similar manner. The properties of these compounds and IR spectral parameters are provided in Table 5; the parameters of ^1H NMR spectra are given in Table 6.

Method B. To a stirred mixture of the amide (**11b**) (0.50 g, 0.0022 mol), phthalic anhydride (0.65 g, 0.0044 mol) and urea (0.07 g, 0.0011 mol) in ethyl acetate (20 mL), a 50% hydrogen peroxide solution was added gradually. Termination of the reaction was determined by TLC monitoring. After the usual treatment, the organic layer was isolated and dried with calcinated magnesium sulfate, and the solvent was removed. The yield of the epoxyamide (**18b**) was 68%.

Method C. To a stirred mixture of the amide (**11b**) (0.50 g, 0.0022 mol) and sodium carbonate (0.47 g, 0.0044 mol) in chloroform (10 mL), a 40% solution of peroxyacetic acid (0.84 g, 0.0044 mol) was added dropwise. In 3 hours the reaction mixture was treated by the usual method, and the solvent was removed. The yield of the epoxyamide (**18b**) was 94%.

Method D. To a stirred mixture of the amide (**11b**) (0.50 g, 0.0022 mol), sodium hydrocarbonate (0.40 g, 0.0044 mol) and acetic anhydride (0.45 g, 0.0044 mol) in chloroform (10 mL), a 50% solution of hydrogen peroxide (0.30 g, 0.0044 mol) was added dropwise. Termination of the reaction was determined by TLC monitoring. After the usual treatment, the yield of the epoxyamide (**18b**) was 95%. The epoxyamide (**21b**) was also synthesized by this method with 94% yield. The properties are given in Table 5.

Method E. To a stirred mixture of the amide (**11b**) (0.50 g, 0.0022 mol), absolute acetic acid (0.26 g, 0.0044 mol), a 50% solution of hydrogen peroxide (0.60 g, 0.0088 mol) in ethyl acetate (10 mL), and a solution of dicyclohexylcarbodiimide (0.90 g, 0.0044 mol) in ethyl acetate (10 mL) was gradually added. Termination of the reaction was determined by TLC monitoring. The precipitate of dicyclohexyl urea was filtered off. After the usual treatment the yield of the epoxyamide (**18b**) was 90%.

Method F. To a stirred mixture of the amide (**11b**) (0.50 g, 0.0022 mol), trichloroacetonitrile (0.64 g, 0.0044 mol), and sodium hydrophosphate (0.26 g, 0.0022 mol) in chloroform (15 mL), a 50% solution of hydrogen peroxide (0.30 g, 0.0044 mol) was added dropwise. After 120 hours of stirring the ratio of the amide (**11b**) and epoxyamide (**18b**) in the reaction mixture was ca. 3:2 (TLC monitoring).

*N-Benzyl-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonane (**32**)*

To a suspension of lithium aluminum hydride (0.50 g, 0.013 mol) in absolute ether (15 mL), a solution of epoxyamide (**18b**) (1.22 g, 0.005 mol) in absolute tetrahydrofuran (10 mL) was added dropwise under stirring. Completion of the reaction was determined by TLC monitoring. The excess of the lithium aluminum hydride was decomposed by ice water. The precipitate was filtered off. The organic layer was dried with calcinated magnesium sulfate, and the solvent was removed. The yield of the azabrendane (**32**) was 56%. The azabrendanes (**29–31, 33–35**) were obtained in similar manner. The properties of the compounds are listed in Table 7; the parameters of ^{1}H NMR spectra are given in Table 8.

N-Ethyl-exo-5-aminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptane (**22a**) and N-benzyl-exo-5-aminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptane (**25a**) were prepared in a similar manner. The yield of the epoxyamine (**22a**) was 95%, b.p. 106.5–107°C (5 mmHg), n_D^{20} 1.4912. Found (%): C, 71.94; H, 10.27; N, 8.30. $C_{10}H_{17}NO$. Calculated (%): C, 71.86; H, 10.18; N, 8.38. IR spectrum (cm^{-1}) 3324, 3032, 1570, 1160, 843. ^{1}H NMR spectrum (ppm): 3.10 m (H^2, H^3), 2.72 m (H^{8A}), 2.62 m (H^{8B}), 2.45 m (H^1), 2.36 m (H^4), 1.68 m (H^5), 1.52 m (H^{6x}), 1.26 d (H^{7s}), 1.12 d.t (H^{6n}), 0.83 d (H^{7a}). The yield of the epoxyamine (**25a**) was 89%, b.p. 112–113.5°C (4 mmHg), n_D^{20} 1.5278. IR spectrum (cm^{-1}): 3330, 3280, 3028, 1564, 1480, 1158, 930, 848.

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