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Azabrendanes. II. Chemo-, Regio- and Stereoselective Transformation of 3-Oxatricyclo[3.2.1.$0^{2,4}$]octane-endo-6-carbonitrile in Reaction with Lithium Aluminum Hydride

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ABSTRACT

The reduction of 3-oxatricyclo[3.2.1.$0^{2,4}$]octane-endo-6-carbonitrile by lithium aluminum hydride is completed by the formation of exo-2-hydroxy-4-azatricyclo[4.2.1.$0^{3,7}$]nonane with the structure confirmed (1) by the analysis of ^{1}H, ^{13}C, ^{14}N, and ^{17}O NMR spectra and the two-dimensional spectra (COSY-experiment); (2) by comparison with ^{1}H and ^{13}C NMR spectra of the corresponding oxygen analog of heterobrendane; (3) by the calculation of the vicinal constants for the spin–spin interaction in the molecules of both analogs by the MMX program; and (4) by transformation into N-(p-bromophenylsulfonyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.$0^{3,7}$]nonane prepared by an alternative synthesis, viz., epoxidation of N-(p-bromophenylsulfonyl)bicyclo[2.2.1]hept-2-en-endo-5-methylamine. The reduction of 3-oxatricyclo [3.2.1.$0^{2,4}$]octane-exo-6-carbonitrile affords the epoxide, 3-oxatricyclo[3.2.1.$0^{2,4}$]octane-exo-6-methylamine. Different behaviors of stereoisomers are discussed; analysis of the coefficients of the atomic orbitals in the MO LCAO equation (AM1 method) has been made, and the strengths of the C–O bonds in the epoxy ring has been analyzed. © 1997 John Wiley & Sons, Inc.

INTRODUCTION

Discovery of adamantane and the high biological activity of some of its derivatives encouraged researchers to synthesize new structures of the "cage" type. Brendanes and their unsaturated analogs of types analogous to substituted epoxynorbornanes [1] were prepared. Oxabrendanes are widely known [2], whereas sulfur [3] and nitrogen-containing analogs [4] are much less known.

Successful attempts to construct azabrendanes (**Ia–f**) of the type of endoamines of the norbornene series were made using iodine cyclization [5], chloromercuration [6], and solvolysis of *N*-chloroderivatives [7,4b]. Neuroleptic activity was studied for amides of type **1d** containing a piperidine fragment in the rigid tricyclic structure [8].

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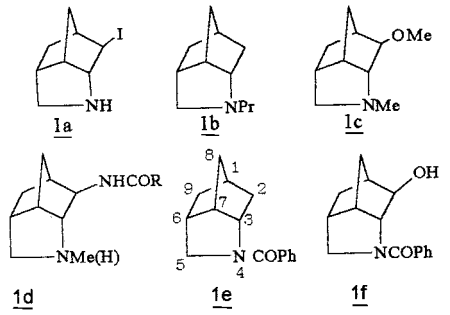
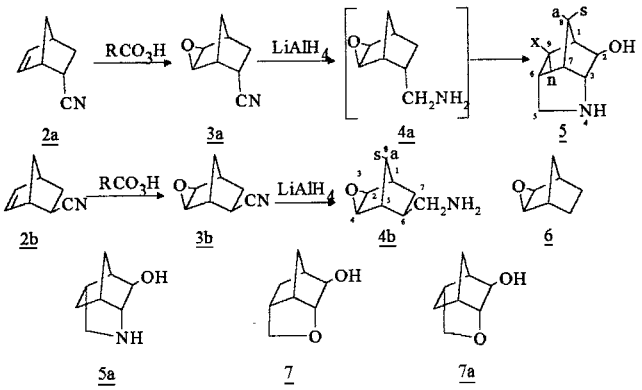


Methods for regio- and stereoselective hydroxylation to yield *N*-substituted exo-2-hydroxy-4-azatricyclo[4.2.1.$0^{3,7}$]nonanes have been developed in the functionalization study of amide **1e** and its analogs [8a].

RESULTS AND DISCUSSION

Chemical and Spectral Investigations

We have proposed a method for the synthesis of a precursor of the hydroxyazabrendane series, exo-2-hydroxy-4-azatricyclo[4.2.1.$0^{3,7}$]nonane on the basis of a practically available stereochemically homogeneous epoxy derivative, viz. bicyclo[2.2.1]hept-2-en-endo-5-carbonitrile (**2a**). Transformations of the stereoisomeric epoxides (**3b**) have been studied for comparison.



Stereochemically homogeneous nitriles (**2a**) and (**2b**) were obtained by methods described in the literature [9,10]. Epoxides (**3a**) and (**3b**) had been prepared at an earlier date by peroxyacetic and peroxybenzoic acids [11]. Epoxidation of the nitriles **2a** and **2b** was effected by use of peroxyphthalic acid in situ [10]. The use of phthalic anhydride and 30% hydrogen peroxide does not impede preparation of the epoxides in quantitative yield. Both epoxides have been reduced by lithium aluminum hydride. The presence of an exo-oriented epoxy ring in the series of epoxynorbornanes (**4b**) and in the original epoxynitriles (**3a** and **3b**) is indicated by the H^2 and H^4 proton signals in the region δ = 3.0 to 3.2, nonequivalence of the signals at C^8 and the effective shift of the proton signal of the H^{8a} bridge located directly over the plane of the epoxy ring to the strong field δ = 0.75 in its ^{1}H NMR spectra [12]. ^{13}C NMR spectra of the epoxides contain the signals of the epoxy ring carbon nuclei in the region δ = 49 to 51 which is in agreement with the literature [13]. Table 1 lists the parameters of carbon spectra and those of ^{14}N and ^{17}O NMR spectra for epoxides **3a**, **3b**, and **4b**. The data for the key compound, viz., exo-epoxynorbornane **6**, are also given. It can be seen from the Table 1 that orientation (exo or endo) of the substituent remarkably affects the parameters of the oxygen spectra, although it exerts no effect upon resonance of the nitrogen nuclei due to their remote position with respect to the skeleton fragment.

The reduction product of compound (**3a**) is not an epoxide. There is no band at 850–845 cm^{-1} characteristic of epoxynorbornane in its IR spectrum [11–13], and there is an absorption peak in the region 3304 cm^{-1}. The signals in the NMR spectrum have been assigned using a two-dimensional spectrum (COSY-experiment) and by comparison with the spectrum of exo-2-hydroxy-4-oxatricyclo[4.2.1.$0^{3,7}$]nonane (**7**) recorded earlier [2d]. There is no resonance for the epoxy fragment protons in the region δ = 3 in the spectrum (Table 2). This section of the field contains the signals of the protons of the methylene group N–CH_2 that display distinct anisochronisity due to their diastereotopy. The singlet and the doublet (δ = 3.34 and 3.13) prove the assignment of compounds (**5**) to cyclization products; splitting of the exo-proton H^3 is caused by its interaction with the proton H^7 with the constant 5.1 Hz. In contrast to epoxide (**4a**), hydroxyamine (**5**) has an H^{9n} proton multiplet in the strong field (δ = 0.86) undergoing splitting with respect to the H^{9x} proton, the constant being 12.9 Hz, as well as for the protons H^6 and H^{8s} with the equal constants 2.1 Hz. Table 3 lists the results of the ^{13}C NMR spectrum of the tricyclic amine (**5**). The signals were assigned by comparison with the spectrum for the ether (**7**) for

TABLE 1 The Values for the Chemical Shifts of ^{13}C, ^{17}O, and ^{14}N Nuclei of Compounds **3a**, **3b**, **4b**, and **6** in NMR spectra

Epoxide	**3a**	**3b**	**4b**	**6**
C_2, C_4	50.2, 48.4	49.9, 49.2	51.7, 51.4	51.2
C_1, C_5	39.9, 37.0	42.5, 36.7	39.2, 36.8	36.8
^{17}O	−18.5	−13.5	−14.0	−15.0
^{14}N	−127.5	−129.6	−352.5	

TABLE 2 ^{1}H NMR Spectral Data ($CDCl_3$) of Compounds **5**, **7**, **9–11** (δ/*J* Hz)

Compound	*H*^{1}	*H*^{2}	*H*^{3}	*H*^{5A}	*H*^{5B}	*H*^{6}	*H*^{7}	*H*^{8s}	*H*^{8a}	*H*^{9x}	*H*^{9n}	*NH*
5	2.06	3.34	3.13 $^{3}J_{3,7}$5.1	3.07 $^{2}J_{5A,5B}$10.5 $^{3}J_{5A,6}$5.4	2.81	2.23	2.44	1.98 $^{2}J_{8s,8a}$10.4	1.49	1.85 $^{2}J_{9x,9n}$12.9 $^{3}J_{9x,6}$9.3 $^{3}J_{9x,14.5}$	0.86 $^{3}J_{9n,6}$2.1 $^{4}J_{9n,8s}$2.1	
7	1.98	3.31	3.82 $^{3}J_{3,7}$5.9	3.70 $^{2}J_{5A,5B}$7.7 $^{3}J_{5A,6}$4.6	3.54	2.38	2.52	1.95 $^{2}J_{8s,8a}$9.6	1.45	1.84 $^{2}J_{9x,9n}$12.8 $^{3}J_{9x,6}$10.5 $^{3}J_{9x,1}$4.8	0.92 $^{3}J_{9n,6}$2.9 $^{4}J_{9n,8s}$2.9	
9	2.11	3.66	3.51 $^{3}J_{3,7}$5.2	3.23 $^{2}J_{5A,5B}$9.4	3.04 $^{3}J_{5B,6}$4.4	2.02	2.18	1.85 $^{2}J_{8s,8a}$11.0	1.34	1.82 $^{2}J_{9x,9n}$12.8	0.92 $^{3}J_{9n,6}$2.0 $^{4}J_{9n,8s}$2.0	
10	2.00	3.32	3.71 $^{3}J_{3,7}$5.5	3.36 $^{2}J_{5A,5B}$8.2	3.27	2.27	2.45	1.86 $^{2}J_{8s,8a}$10.2	1.35	1.83 $^{2}J_{9x,9n}$12.3 $^{3}J_{9x,6}$9.8 $^{3}J_{9x,1}$4.8	0.81	4.89
11	2.05	3.76	3.66	3.47 $^{2}J_{5A,5B}$8.0	3.24	2.23	2.42	1.89 $^{2}J_{8s,8a}$10.2	1.40	1.86 $^{2}J_{9x,9n}$12.8 $^{3}J_{9x,1}$4.6	0.85	4.78

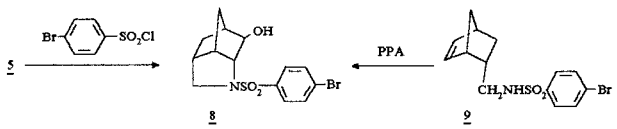
TABLE 3 ^{13}C NMR Spectral Data ($CDCl_3$) of Compounds **5**, **7**, **10**, **14**, **15**

Compound	*C*^{1}	*C*^{2}	*C*^{3}	*C*^{5}	*C*^{6}	*C*^{7}	*C*^{8}	*C*^{9}
5	42.31	83.84	69.68	53.96	37.54	45.94	35.01	35.12
7	41.01	80.73	87.68	75.07	37.37	44.59	33.66	33.86
10	41.73	79.51	65.93	52.57	35.72	43.64	32.81	33.57
14	41.17	81.17	69.34	54.20	36.66	44.06	32.23	33.54
15	41.32	81.28	69.49	54.39	36.62	44.47	32.27	33.48

which an experiment on ^{13}C(H) selective double resonance had been made.

In the spectra for compound (**5**), with respect to ^{14}N and ^{17}O nuclei, there are signals, i.e., δ = 333.0 and −0.25, respectively, differentiating it from epoxynorbornane (**4b**). The problem of the choice between structures containing five- and six-membered nitrogen-containing (**5** and **5a**) and oxygen-containing systems must apparently be discussed. The results of calculations using MMX display a considerable energetic advantage of structures (**5**) and (**7**), as compared to the alternative ones that are distinguished by a substantial growth in the angle stress and in Van der Waals interactions. Thus, the values for the heats of formation for structures **5**, **5a**, **7**, and **7a** are −33.06, −21.88, −80.43, and −66.56 kcal/mol, respectively, and those for the energy of stress are 27.51, 38.68, 19.28, and 33.15 kcal/mol, respectively. Calculation of the values for the vicinal Carplus spin–spin interaction constants made on the basis of the geometry obtained in the framework of the MMX method, and comparison of the calculated values with those experimentally found (Table 4) permit a conclusion about the reduction product having the skeleton structure (**5**).

From azabrendane (**5**), a number of new compounds have been obtained using both reaction sites, with their spectral characteristics being given in Tables 2 and 3. The sulfonamide (**8**) prepared from the amine (**5**) is identical to the product of epoxidation of the sulfonamide (**9**) by peroxyphthalic acid [14].



Amine (**5**) reacts in the cold with *m*-chlorophenyl isocyanate and with phenyl isothiocyanate to give the compounds (**10**, **11**) and with excess acetyl chloride to yield the diacetate (**12**). Reaction of amine (**5**) with *p*-nitrophenyloxirane has been carried out to afford the hydroxylamine (**13**).

TABLE 4 Calculated and Experimental Values for the Vicinal Constants of Spin–Spin Interaction of Structures **5**, **5a**, **7**, **7a** (Hz)

		Calculated			*Calculated*	
Bond	*Experimental*	**5**	**5a**	*Experimental*	**7**	**7a**
3–7	5.1	6.41	3.47	5.9	6.95	3.82
$6–5_B$	5.4	7.20	1.93	4.6	5.42	1.28
6–7	6.1	6.61	9.71	6.8	6.67	9.94
$6–9_x$	9.3	9.85	7.37	10.5	9.89	7.24
$6–9_n$	2.1	2.46	0.99	2.9	2.53	0.98
$1–9_x$	4.5	4.69	2.42	4.8	4.83	2.36

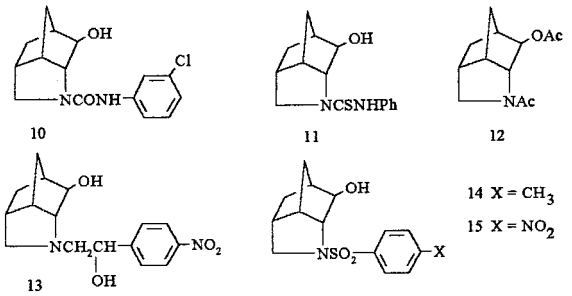


Table 3 contains the results of analysis of ^{13}C NMR spectra for the urea (**10**) and the sulfonamides (**14**, **15**) whose syntheses were described in Ref. [14]. The data of Table 3 show the structural similarity of these compounds. The structures of other amine (**5**) derivatives, i.e., compounds **11**–**13**, are supported by IR spectra.

The IR spectrum for compound **12** reveals absorption of two carbonyl groups included in the ester and amide fragments (1712 and 1620 cm^{-1}).

QUANTUM-CHEMICAL CALCULATIONS

The epoxynitrile (**3a**) conversion into azabrendane (**5**) can be described as two successive processes, i.e., chemoselective transformation of the nitrile group into the aminomethyl one with the epoxy fragment retained, with epoxyamine (**4a**) formation, and subsequent regio- and stereoselective intramolecular nucleophilic attack of the amino group from the rear of the norbornene skeleton at the C^4 atom of the epoxy ring. Similar processes were observed earlier in the reduction of epoxyesters [2d] and epoxyimides [15] of the norbornene series.

Table 5 depicts the values for the energies of borderline orbitals. Analysis of coefficients of the atomic orbitals in the MO LCAO equation (AM1 method [16]) proves that all of the orbitals of the epoxy ring make approximately equal principal contribution of each epoxyamine (**4a**, **4b**) to the HOMO is made by the lone nitrogen electron pair. The LUMO in each of the compounds (**4a**, **4b**, **6**) is centered on the atoms of the epoxy fragment, whereas, in the case of each epoxide (**3a**,, **3b**), both the LUMO and the UMO II are connected with the nitrile group (64 and 80% for epoxide **3a**). It is the latter data that account for the chemoselective course of the reaction by one of the centers (i.e., the nitrile group). The direction of the process seems to govern both the UMO nature and the steric factor that impedes intramolecular nucleophilic attack from the rear side of the skeleton.

Table 5 lists the values for the atomic charges and those for the bond order in the epoxides indicating the possibility of regioselective attack by the C^2 atom in epoxyamine (**4a**) due to a considerable decrease in the order of the C^4–O bond. For epoxides (**3a** and **4b**), selective reactions of epoxides are hardly probable. The given values for the charges of heteroatoms of stereoisomers (**3a** and **3b**) indicate some distinctions for the values of the oxygens and the proximity of the nitrogens. These data qualitatively correspond to the parameters of the ^{14}N and ^{17}O NMR spectra (Table 1).

EXPERIMENTAL

The structures of the organic compounds that have been obtained are confirmed by a number of physical methods. The IR spectra were measured on "Specord-80 M" and "Specord-75-IR" spectrometers (thin film, KBr pellets). ^1H NMR spectra were recorded on a "Varian-VXR-200" radiospectrometer, with a generator operating frequency of 200 MHz for deuterochloroform solutions of the compounds and using the internal standard HMDS. The "COSY" technique was also applied. ^{13}C NMR spectra were measured on a "Varian-VXR-200" radiospectrometer at the operating frequency 50.30 MHz; ^{14}N and ^{17}O NMR spectra were recorded on a "Bruker-CXP" spectrometer at the operating frequencies 14.45 and 27.13 MHz, respectively. The course of the reactions and the purity of the compounds that have been obtained was monitored by TLC on "Silufol-UV-254" plates in the system ether-hexane (2:1) with iodine vapor as a developer.

Bicyclo[2.2.1]hept-2-en-5-carbonitriles (**2a**, **2b**) were prepared according to the literature procedure [10] in 98% yield.

Exo-3-oxatricyclo[3.2.1.$0^{2,4}$]octane-6-carbonitriles (**3a** *and* **3b**). Into a 500 mL flask were placed nitrile **2** (11.9 g, 0.1 mol), urea (3 g, 0.05 mol) and

TABLE 5 The Values for the Energies of Borderline Orbitals, Atomic Charges, and Bond Order in the Molecules **3a**, **3b**, **4a**, **4b**, **6**

					Bond Order				Atomic Charges			
Compound	$E_{OMO\,11}$	E_{MOMO}	E_{LUMO}	E_{UMO11}	C^2–O	C^4–O	H^2	H^4	C^2	C^4	O	N
3a	−11.6368	−10.8947	1.4847	1.5687	0.9661	0.9664	0.154	0.159	−0.060	−0.063	−0.241	
3b	−11.6514	−10.9695	1.4813	1.5790	0.9660	0.9674	0.152	0.152	−0.061	−0.067	−0.239	−0.048
4a	−10.4308	−9.8503	2.6608	3.0670	0.9650	0.9618	0.145	0.158	−0.069	−0.050	−0.252	−0.046
4b	−10.6348	−9.8110	2.4787	2.8880	0.9646	0.9648	0.148	0.150	−0.061	−0.062	−0.248	−0.349
6	−10.9693	−9.6465	1.3382	3.6228	0.9650	0.9650	0.148	0.148	−0.071	−0.071	−0.228	−0.349

30% hydrogen peroxide (18 mL, 0.2 mol) in ethyl acetate (100 mL). Finely ground phthalic anhydride (29.6 g, 0.2 mol) was gradually added with stirring. Termination of the reaction was determined by TLC monitoring. Phthalic acid that had formed was neutralized by addition of saturated sodium carbonate solution (up to pH 7–8). The organic layer was separated, and the aqueous layer was extracted with chloroform three times. The united organic layer was dried with calcinated magnesium sulfate, and the solvent was removed. The epoxynitrile (**3a**) yield was 13.2 g (98%), mp 114–115°C. According to Ref. [2d], the mp was 114.5–115°C. IR spectrum, cm^{-1}: 2240, 855. Exo-isomer (**3b**) yield was 12.9 g (95%), mp 66–67°C. According to Ref. [2d], the mp was 62.5–64°C. IR spectrum, cm^{-1}: 2245, 857. The parameters of ^{13}C, ^{17}O, and ^{14}N NMR spectra of the stereoisomeric epoxynitriles are shown in Table 1.

Exo-3-oxatricyclo[3.2.1.0^{2,4}]octane-exo-6-methylamine (**4b**). To a suspension of lithium aluminum hydride (1.15 g, 0.03 mol) in absolute ether (15 mL), a solution of exo-3-oxatricyclo[3.2.1.0^{2,4}]octane-exo-6-carbonitrile (**3b**) (2.7 g, 0.02 mol) in absolute ether (20 mL) was added dropwise under stirring. Completion of the reaction was determined by the TLC monitoring method. The excess of the aluminum hydride was decomposed by ice water. The organic layer was isolated, dried with calcinated magnesium sulfate, the solvent removed, and the product distilled in vacuum. The epoxyamine (**4b**) yield was 2.08 g (76%), bp 110.5°C (11 mm Hg), $n_{D^{20}}$ 1.5051; IR spectrum, cm^{-1}: 3360, 3288, 3018, 848. The parameters of ^{13}C, ^{17}O, and ^{14}N NMR spectra are given in Table 1.

Exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonane (**5**) was prepared in a similar manner to epoxyamine (**4b**) via reduction of the epoxynitrile (**3a**) (13.5 g, 0.1 mol). The yield of oxyamine was 9.2 g (68%), mp 241.5–242°C. Found, %: C, 68.87; H, 9.45; N, 10.01. $C_8H_{13}NO$. Calculated, %: C, 69.03; H, 9.41; N, 10.06. IR spectrum, cm^{-1}: 3304, 1634, 1690, 1340. The parameters of the ^1H NMR-spectrum of compound **5** are given in Table 2; those of the ^{13}C NMR spectrum are given in Table 3.

N-(p-Bromophenylsulfonyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]-nonane (**8**). To an emulsion of the amine (**5**) (1.39 g, 0.01 mol) in chloroform (10 mL) and 20% aqueous sodium hydroxide solution (2 mL), a *p*-bromobenzenesulfonyl chloride solution (2.55 g, 0.01 mol) in chloroform (10 mL) was added dropwise. Termination of the reaction was determined by TLC monitoring. The organic layer was collected, washed with water, dried with calcinated magnesium sulfate, and the solvent removed by distillation. The yield of sulfonamide was 3.47 g (97%), mp 138–139°C. Found, %: C, 47.01; H, 4.55; N, 3.94. $C_{14}H_{16}BrNO_3S$. Calculated, %: C, 46.93; H, 4.50; N, 3.91. IR spectrum, cm^{-1}: 3488, 1584, 1545, 1328, 1168, 815. ^1H NMR-spectrum parameters are provided in Table 2.

N-(m-Chlorophenylcarbomoyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]-nonane (**10**). To a solution of the oxyamine (**5**) (1.39 g, 0.01 mol) in chloroform (10 mL), a solution of *m*-chlorophenyl isocyanate (1.53 g, 0.01 mol) in chloroform (10 mL) was added. Termination of the reaction was determined by TLC monitoring. The precipitate that had formed was filtered off, washed with benzene and chloroform, and dried. The yield of the urea (**10**) was 2.63 g (90%), mp 234–235°C. Found, %: C, 61.58; H, 5.74, N, 9.52. $C_{15}H_{17}ClN_2O_2$. Calculated, %: C, 61.54; H, 5.81; N, 9.57. IR spectrum, cm^{-1}: 3348, 3230, 1610, 1564, 1490, 1388, 1340, 1244, 1060. The parameters of NMR spectrum of the compound are provided in Table 2; those of ^{13}C NMR spectrum are given in Table 3.

N-(phenylthiocarbamoyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.0^{3,7}]nonane (**11**) was prepared in a similar manner to that of the urea (**10**) from oxyamine (**5**) (1.39 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol). The yield of the thiourea was

2.1 g (76%), mp 211–212°C. Found, %: C, 62.11; H, 6.18; N, 9.59. $C_{15}H_{18}N_2OS$. Calculated, %: C, 62.06; H, 6.20; N, 9.65. IR spectrum, cm^{-1}: 3298, 3276, 1578, 1506, 1440, 1382, 1334, 1312, 1046. The parameters of ^1H NMR spectrum of the compound are given in Table 2.

N-Acetyl-exo-2-acetoxy-4-azatricyclo[4.2.1.0^{3,7}]nonane (**12**). A mixture of the oxyamine (**5**) (1.39 g, 0.01 mol), acetic anhydride, (1.8 mL, 0.02 mol), and pyridine (4 mL, 0.05 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, dried with calcinated magnesium sulfate, the solvent removed by distillation, and the product distilled in vacuum. The yield of diacetate (**12**) was 1.67 g (75%), bp 146–147°C (3 mm Hg), $n_{D^{20}}$ 1.5040. Found, %: C, 64.51; H, 7.72; N, 6.21. $C_{12}H_{17}NO_3$. Calculated, %: C, 64.45; H, 7.68; N, 6.27. IR spectrum, cm^{-1}: 1712, 1620, 1020.

N-(2-Hydroxy-2-p-nitrophenylethyl)-exo-2-hydroxy-4-azatricyclo[4.2.1.10^{3,7}]nonane (**13**). The oxyamine (**5**) (1.39 g, 0.01 mol) and *p*-nitrostyrene oxide (1.65 g, 0.01 mol) were dissolved in isopropyl alcohol (15 ml). The completion of the reaction was determined by TLC monitoring. The precipitate that had formed was filtered off, washed with isopropyl alcohol, and dried. The yield of the product was 1.83 g (60%), mp 247–248°C. Found, %: C, 63.21; H, 6.64; N, 9.12. $C_{16}H_{20}N_2O_4$. Calculated, %: C, 63.14; H, 6.62; N, 9.21. IR spectrum, cm^{-1}: 3386, 3330, 1664, 1616, 1456, 1378, 1132, 1100.

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