Russian Journal of Organic Chemistry, Vol. 38, No. 2, 2002, pp. 165–175. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 2, 2002, pp. 185–195.
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Stereoisomeric *N*-(*p*-Nitrobenzoyl)-5-aminomethylbicyclo[2.2.1]hept-2-enes. Synthesis, Epoxidation, ^{1}H and ^{13}C NMR Spectra

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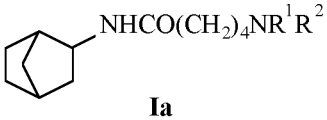
Received July 12, 2000

Abstract—Preparation is described of stereoisomeric (*p*-nitrobenzoyl)-5-aminomethylbicyclo[2.2.1]-hept-2-enes and their epoxidation by peracetic acid. A possibility of selective reduction of separated fragments in the polyfunctional compound using sulfur in alkaline medium, hydrazine hydrate in the presence of a nickel catalyst, and lithium aluminum hydride was demonstrated by an example of one of amides. By reaction with electrophilic reagents from the amines synthesized, (*p*-aminobenzoyl)-*endo*-5-aminomethylbicyclo[2.2.1]hept-2-ene and (*p*-aminobenzoyl)-*endo*-2-aminomethylbicyclo-[2.2.1]hept-2-ene, new bicyclic compounds containing alongside the amide group also sulfonamide, carboxamide, urea, and thiourea moieties were obtained. The structure of compounds obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy, by two-dimensional spectra measured along COSY and NOESY procedures.

Norbornene and norbornane derivatives are the most extensively studied among all bicyclic and polycyclic systems. Formerly the compounds of this group were prepared from natural substances, later from the products of diene synthesis with the available cyclopentadiene and various dienophiles [1, 2]. The fixed spatial orientation of substituents in the molecules of norbornene (norbornane) derivatives provided new opportunities for the study of relations between the structure and biological activity of *exo*- and *endo*-isomers from these series.

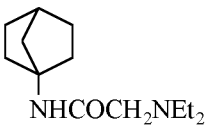
In the structure of the known bicyclic biologically active compounds a carboxamide group is often present. However individual *exo*- and *endo*-forms of amides with bicyclic skeleton hardly were investigated [1]. The majority of known data was obtained by the study of acyl derivatives originating from saturated amines with amino group adjacent to the skeleton **Ia–e**.

Compounds **Ia–e** possess antarrhythmic activity; similar in structure bornane derivatives lack it, but the *endo*-forms show pronounced hypnotic properties [3]. A number of bornanamine acyl derivatives **Id** and those of 7,7-dimethylbicyclo[2.2.1]heptane-1-amine possess antiviral, hypnosedative, and spasmolytic activity [5]. In compounds with the second bi-



Ia

Ib



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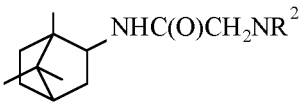
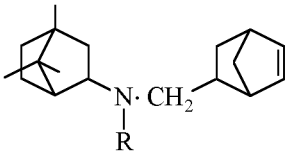
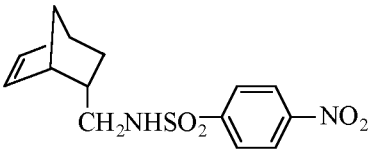


Id



Ie



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cyclic fragment (**Ie**, R = $COCH_3$, CONHAr) antarrhythmic activity is accompanied by hypoglycomic and hypotensive function [6]. The substituted aminonorbornanes were successfully used as analogs of sympathomimetic catecholamines [7].

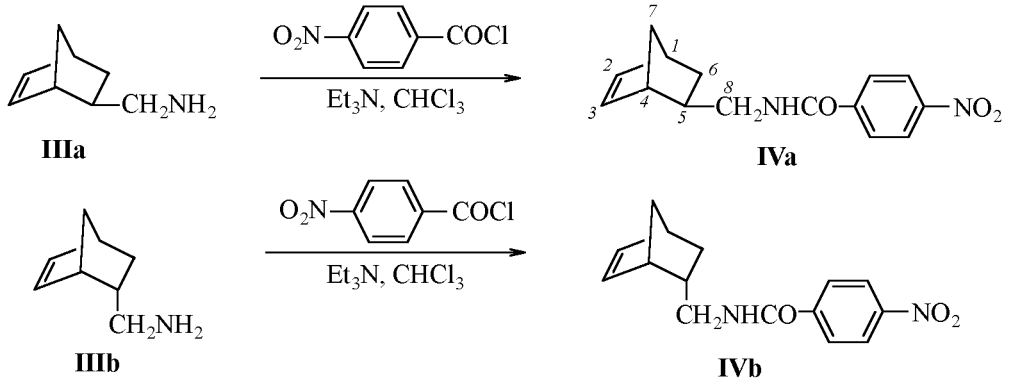
The derivatives of aminomethylnorbornanes were a lot less investigated. They were shown to act as antihystaminics and topical anesthetics [8] and spasmolytics of papaverine type [9].

Inasmuch as there were no data on biological activity of amides related to 5-aminomethylbicyclo-[2.2.1]hept-2-ene we carried out the synthesis and pharmacological trials of stereoisomeric *p*-nitrobenzoylamines and of the corresponding epoxides, studies of the spectra and certain reactions of amides.

We selected as objects of this study the *p*-nitrophenylamides since the substituent in the amide group possessed special pharmacological characteristics. We also planned to compare the biological activity of the amides with that of analogous sulfonamides, one among which, endo-isomer "nitrosulfane" (**II**), demonstrated a considerable analgetic, anticonvulsant, and tranquilizing activity [10]. The above pharmacological activity, also antihypoxic and antiphlogistic functions are characteristic of a large sulfonamide group from the norbornene and norbornane series [11]. The stereoisomeric *p*-nitrophenylamides were synthesized previously to characterize stereoisomeric *exo* and *endo*-5-aminomethylbicyclo[2.2.1]hept-2-enes (**IIIa, b**) [12], but no data was reported on the amides properties besides melting points and elemental analyses.

We applied to the synthesis of amines **IIIa, b** the repeatedly described method consisting in reduction by lithium aluminum hydride of individual carboxynitriles prepared by diene synthesis from cyclopentadiene and acrylonitrile and separated by fractional distillation [13]. During reduction about 5–9% of *endo*-isomer **IIIb** suffers epimerization whereas *exo*-isomer **IIIa** forms as an individual compound in agreement with the published data [14].

Stereoisomeric *N*-(*p*-nitrobenzoyl)-5-aminomethylbicyclo[2.2.1]hept-2-enes (**IVa, b)** were prepared in high yields from amines **IIIa, b** by treating them with *p*-nitrobenzoyl chloride in anhydrous chloroform in the presence of triethylamine at room temperature. In the IR spectra of the amides are present absorption bands, virtually indistinguishable for both isomers (3440–3430, 3290–3280, 1640, 1555–1550, 1525–1520, 1350–1345 cm^{-1}) and belonging respectively to vibrations of N–H bond, amide carbonyl, ad nitro group (Table 1) [15]. The unsaturated fragment has the bands in the region 3080–3070 and 720–710 cm^{-1}. The latter bands (δ =C–H) for the *exo*-amide are nearer to the lower part of the region, and for the *endo*-isomer to the higher part; this difference is also characteristic of the other stereoisomeric substituted norbornenes [16].



In Table 2 are presented the ^1H NMR spectra of amides **IVa, b** that are very similar to those of the corresponding sulfonamides of the norbornene series [17, 18]. The signals were assigned after comparing with the ^1H NMR spectrum of the initial amide **IIIb** whose two-dimensional spectrum COSY we had measured. The protons at the double bond (H^2, H^3) resonate in the region 6.00–6.20 ppm, then in succession appear the proton signals from the extrocyclic fragment (H^8), of bridgehead protons (H^1 and H^4), of protons H^5, H^{6x}, H^{7s} and H^{7a}, the proton H^{6n} gives the most downfield signal. The peaks of protons from NH groups are registered at 6.40 and 6.36 ppm, the protons of benzene ring give rise to doublet signals in the regions respectively 8.23 and 7.90 ppm (**IVa**), 8.24 and 7.89 ppm (**IVb**). The signals of dia-

Table 1. Yields, melting points, IR spectra, and elemental analyses of compounds **IVa, b, V–IX, XI–XIII, XIVa, b**

Compd. no.	Yield, %	mp, °C	IR spectrum, cm^{-1}	Found, %	Formula	Calculated, %
				N		N
IVa	81	164–165	3286, 1640, 1554, 1522, 1347, 1302, 712	10.21	$C_{15}H_{16}N_2O_3$	10.29
IVb	95	142–143	3292, 3079, 1640, 1522, 1521, 1346, 721	10.34	$C_{15}H_{16}N_2O_3$	10.29
V	75	115–117	3343, 1605, 1542, 1507, 1290, 1184, 727	11.62	$C_{15}H_{18}N_2O$	11.57
VI	71	204–205	3323, 1630, 1604, 1550, 1528, 1321, 1169, 1082	9.95	$C_{21}H_{21}N_3O_5S$	9.84
VII	75	189–190	3340, 1644, 1538, 1514, 1354, 1328, 1270, 720	10.71	$C_{22}H_{21}N_3O_4$	10.74
VIII	68	159–160	3286, 3043, 1620, 1589, 1523, 1324, 1249, 1174	11.05	$C_{22}H_{23}N_3OS$	11.14
IX	74	75–77	3300, 3200, 1636, 1596, 1286, 1174, 833	11.34	$C_{15}H_{20}N_2O$	11.47
XI	65	267–268	3336, 1657, 1626, 1526, 1510, 1344, 1325, 1264	10.79	$C_{22}H_{23}N_3O_4$	10.69
XII	70	247–248.5	3364, 3310, 1627, 1596, 1548, 1526, 1323, 1249	13.63	$C_{22}H_{24}N_4O_4$	13.72
XIII	72[a]		3320, 3040, 1568, 1445, 845, 724	12.30	$C_{30}H_{36}N_4$	12.39
XIVa	94	159.5–160.5	3431, 3268, 1643, 1558, 1522, 1346, 850	9.61	$C_{15}H_{16}N_2O_4$	9.72
XIVb	95	150–151	3344, 3072, 1661, 1544, 1514, 1342, 1320, 848	9.68	$C_{15}H_{16}N_2O_4$	9.72

[a] Oily substance.

stereotopic protons H^{8A} and H^{8B} located close to the chiral center at the C^5 atom are distinguished both by position and by the values of vicinal coupling constants with the proton attached to C^5 atom. Besides these signals are different in the spectra of stereoisomers **IVa, b**, namely, the protons at C^8 in the spectrum of the *endo*-amine **IVb** give signals upfield from those of the corresponding protons in the *exo*-amine **IVa** (3.23 and 3.16 ppm; 3.52 and 3.45 ppm respectively).

^{13}C NMR spectra of amides **IVa, b** are presented in Table 3. The spectra confirm the presence of the norbornene skeleton, carbonyl groups, and demonstrate the difference in the spectral pattern originating from the stereochemical distinctions of the amide molecules. The assignment of signals was performed basing on the spectra of the other substituted norbornenes where had been registered two-dimensional spectra $^{13}C\{H\}$ and $^{13}C\{^{13}C\}$ [19].

Polyfunctional unsaturated amides **IVa, b** containing several groups fit to be reduced are convenient models for investigation of chemoselective reactions. The possibility of selective reduction of separate groups by treating with various reductants (sulfur in alkaline medium, hydrazine hydrate in the presence of a nickel catalyst, and lithium aluminum hydride) was demonstrated by an example of amide **IVb**.

The reduction of amide **IVb** with sulfur in alkaline medium [20] occurred chemoselectively at the nitro group and resulted in its conversion into amino group. It is evidenced by the conservation in the IR spectrum of reduction product V of the absorption bands of amide moiety (1605, 1542, and 1290 cm^{-1}) and the lack of absorption bands belonging to nitro group (Table 1). In the ^1H NMR spectrum appears a signal at 3.97 ppm corresponding to the protons of the new amino group; the proton signal of the amide group NH at 6.07 ppm remains intact. A very informative upfield shift undergo the doublets of the benzene ring protons: due to electron-donor characteristics of the new substituent in the ring the signals appear at 7.60 and 6.60 ppm. As to the protons attached to the

Table 2. ^{1}H NMR spectra of substituted norbornenes **IVa, b, V, VI, XIII**, δ, ppm, coupling constants, Hz

Compd. no.	H^{1}	H^{2}, H^{3}	H^{4}	H^{5}	H^{6x}	H^{6n}	H^{7s}, H^{7a}	H^{8A}, H^{8B}	NH, H arom
IVa	2.85	6.07, 6.05, $^{3}J_{2,3}$ 5.7	2.65	1.68	1.38	1.21, $^{2}J_{6n,6x}$ 11.6, $^{3}J_{6n,5}$ 7.6, $^{4}J_{6n,7s}$ 3.9	1.30, 1.38, $^{2}J_{7s,7a}$ 8.6	3.52, 3.45, $^{2}J_{8A,8B}$ 13.5, $^{3}J_{8A,5}$ 7.0, $^{3}J_{8B,5}$ 8.5	6.40 (NH), 8.23 (H arom), 7.90 (H arom)
IVb	2.86	6.20, 5.99, $^{3}J_{2,3}$ 5.7, $^{3}J_{2,1}$ 3.1, $^{3}J_{3,4}$ 2.9	2.86	2.38	1.90, $^{2}J_{6n,6x}$ 11.5, $^{3}J_{6x,5}$ 8.7, $^{3}J_{6x,1}$ 3.7	0.63, $^{3}J_{6n,5}$ 4.3, $^{4}J_{6n,7s}$ 2.7	1.46, 1.26 $^{2}J_{7s,7a}$ 8.0	3.23, 3.16, $^{2}J_{8A,8B}$ 13.3, $^{3}J_{8A,5}$ 6.0, $^{3}J_{8B,5}$ 5.7	6.36 (NH), 8.25 (H arom), 7.89 (H arom)
V	2.86	6.18, 6.00, $^{3}J_{2,3}$ 5.7, $^{3}J_{2,1}$ 3.1, $^{3}J_{3,4}$ 2.9	2.81	2.34	1.87, $^{2}J_{6n,6x}$ 11.7, $^{3}J_{6x,5}$ 9.1, $^{3}J_{6x,1}$ 3.9	0.62, $^{3}J_{6n,5}$ 4.3, $^{4}J_{6n,7s}$ 2.6	1.44, 1.24 $^{2}J_{7s,7a}$ 8.2	3.18, 3.10, $^{2}J_{8A,8B}$ 13.3, $^{3}J_{8A,5}$ 7.0, $^{3}J_{8B,5}$ 8.1	6.07 (NH), 3.97 (NH_2), 7.57 (H arom), 6.64 (H arom)
VI	2.81	6.18, 6.03, $^{3}J_{2,3}$ 5.7, $^{3}J_{2,1}$ 2.9, $^{3}J_{3,4}$ 2.6	2.77	2.33	1.80, $^{2}J_{6n,6x}$ 11.3, $^{3}J_{6x,5}$ 9.1, $^{3}J_{6x,1}$ 3.8	0.53	1.37, 0.89 $^{2}J_{7s,7a}$ 9.0	3.03, 2.90, $^{2}J_{8A,8B}$ 13.4, $^{3}J_{8A,5}$ 6.9, $^{3}J_{8B,5}$ 8.6	8.51 (H arom), 8.11 (H arom), 7.91 (H arom), 7.24 (H arom)
XIII	2.88	6.20, 6.02, $^{3}J_{2,3}$ 5.6	2.83	2.39	1.89, $^{2}J_{6n,6x}$ 11.6	0.65	1.46, 1.27, $^{2}J_{7s,7a}$ 8.0	3.22, 3.12, $^{2}J_{8A,8B}$ 13.6	4.77 (NH), 7.89 (H arom), 7.49 (H arom), 7.24 (H arom), 3.58 ($\underline{C}\underline{H}_2$Ph)

Table 3. ^{13}C NMR spectra of compounds **IVa, b, V, XIVa, b**, δ, ppm

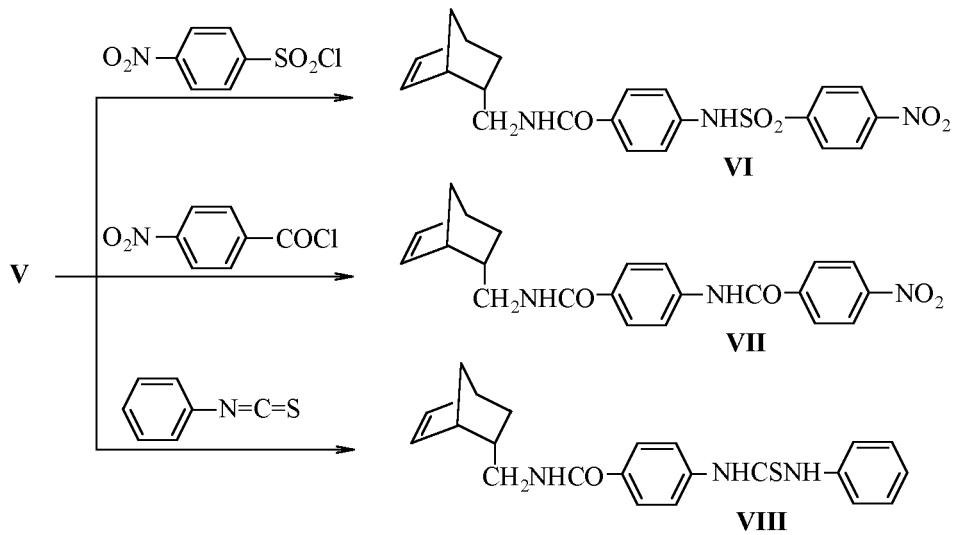
Compd. no.	C^{1}	C^{2}	C^{3}	C^{4}	C^{5}	C^{6}	C^{7}	C^{8}	C= O, C arom
IVa	39.2	137.0	136.1	44.4	41.8	30.9	45.1	45.6	165.2, 149.5, 140.4, 128.1, 123.8
IVb	38.8	138.1	131.9	44.4	42.4	30.1	45.1	49.6	165.4, 149.5, 140.5, 128.0, 123.8
V	39.9	138.8	133.2	45.3	43.4	44.9	31.0	50.5	168.3, 150.6, 129.7, 125.6, 115.2
XIVa	36.9	51.6	51.1	39.7	38.3	31.2	23.2	43.9	165.7, 149.7, 140.2, 128.2, 123.9
XIVb	38.2	49.9	52.1	42.2	39.4	30.7	28.2	42.7	165.6, 149.7, 140.2, 128.1, 123.9

bicyclic skeleton, they virtually conserve the same positions as in the initial amide **IVb** (Table 2).

As seen from Table 3, the position of signals in the ^{13}C NMR spectra of compounds **IVb** and **V** mostly remains unchanged after reduction of the nitro group, in particular, the signal from the carbonyl carbon is still at 168.3 ppm. The only difference observed is the notable upfield shift of the carbon atoms of the benzene ring due to the replacement of an electron-donor for electron-withdrawing substituent. The signal of the quaternary carbon atom linked to nitrogen shifts after reduction from 140.5 to 125.6 ppm (Table 3).

The conversion of nitro group into amino group was also proved by chemical reactions, namely, by transformation of amine **V** into sulfonamide **VI** and diamide **VII** on treating it respectively with *p*-nitrophenylsulfonyl chloride and *p*-nitrobenzoyl chloride, and also by reaction with phenyl isothiocyanate providing thioureide **VIII**.

In the IR spectra of compounds **VI–VIII** are present the absorption bands of the double bond from the norbornene fragment (3060–3040 and 720–710 cm^{-1}), of N–H bonds (3320–3280 cm^{-1}), and of carbonyl groups (1630–1620 cm^{-1}) in the amide moieties. In the spectrum of compound **VI** are also observed the absorption bands of sulfonyl and nitro



groups (1550, 1528, 1354, 1169 cm^{-1}), and in the spectrum of compound **VIII** a band in the region 1324 cm^{-1} belonging to vibrations of the thiocarbonyl group [15] (Table 1).

The analysis of the ^1H NMR spectrum of compound **VI** confirms the structure of the transformation product. The spectrum contains two pairs of doublet signals corresponding to two *p*-substitutes benzene rings. The new signals in a weak field (8.51 and 8.11 ppm), downfield shift of the signals corresponding to the benzene ring originating from amine **V** (7.91 and 7.24 ppm), and also the downfield shift of the protons attached to C^8 neighboring to the aromatic system (Table 2) are compelling evidence of formation of *p*-substituted nitrosulfonamide **VI**.

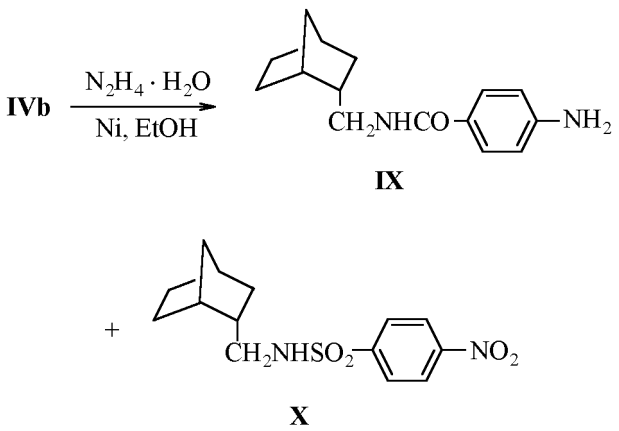
The reaction of amide **IVb** with excess hydrazine hydrate in the presence of nickel catalyst [21] results in reduction of both nitro group and double bond; the amide moiety remains intact. This course of the reaction is evidenced by the IR spectrum of product **IX** where are lacking the characteristic bands in the 720–710 cm^{-1} region, but are present the absorption band of amide moiety and amino group (3300, 3200, 1636, 1550, 1286 cm^{-1}) (Table 1).

The analysis of ^1H NMR spectrum confirms the structure of amine **IX** as also its comparison with the corresponding spectrum of sulfonamide **X** described in [22] (Table 4). In the ^1H NMR spectrum of compound **IX** are observed the signals from the protons of the amine **V** present as an impurity (up to 15%); the latter shows that the reductant interacts more efficiently with nitro group than with double bond. It should be noted that amine **IX** as amine **V** was isolated in a glassy state, and that we characterized its derivatives at the amino group.

From amine **IX** were prepared amide **XI** and ureide **XII**. Both polyfunctional compounds unlike

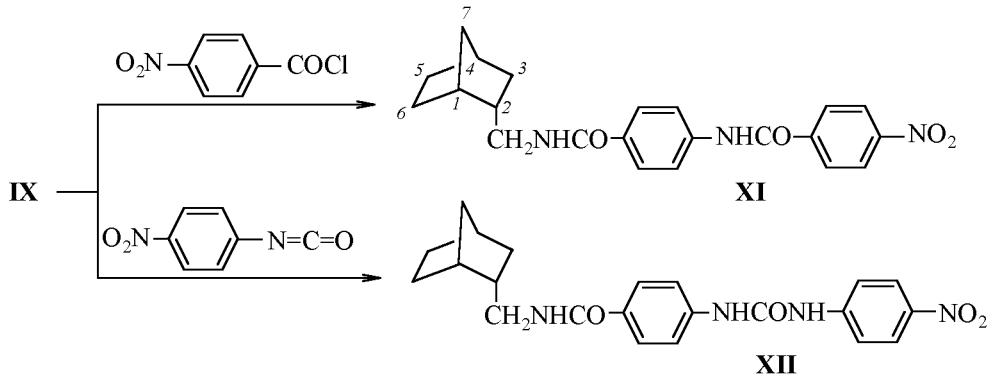
Table 4. ^1H NMR spectra of compounds **IX, X, XII,** δ, ppm, coupling constants, Hz

Compd. no.	H^1	H^2	H^{3x}	H^{3n}	H^4	H^{7s}, H^{7a}	H^{8A}, H^{8B}	NH, H arom
IX	2.16	2.05	1.71, $^2J_{3x,3n}$ 11.5, $^3J_{3x,2}$ 7.3, $^3J_{3x,1}$ 3.0	0.63, $^3J_{3n,2}$ 5.0, $^4J_{3n,7s}$ 2.0	2.16	1.31, 1.27	3.23, 3.08	6.23 (NH), 4.03 (NH_2), 7.54 (H arom), 6.58 (H arom)
X	2.15	1.94	1.61, $^2J_{3x,3n}$	0.57, $^3J_{3n,2}$ 4.7	2.18	1.30, 1.20	3.02, 2.90	7.57 (H arom), 6.64 H arom
XII	2.14	2.04	1.68	0.68	2.14	1.30, 1.24, $^2J_{7s,7a}$ 9.0	3.33, 3.23	8.19, 7.80 (H arom), 7.69, 7.52 (H arom), 9.52, 9.18 (NH), 3.36 (NH)



the initial amine contain amide groups, and in their IR spectra appear absorption bands in the region 3380–3370, 1630–1620, 1550, 1260–1250 cm^{-1} and also absorption bands of nitro group (1530–1520, 1340–1320 cm^{-1}) (Table 1). The structure of compound **XII** was also confirmed by ^1H NMR spectrum.

The ureide moiety does not significantly affect the signals of protons H^{3x}, H^{3n}, H^{7s}, H^{7a}, but effects a considerable downfield shift of protons close to the substituent H^1, H^2 and H^8. As expected, the signals of H^{3x} atoms appear in the strong field (0.67, 0.57, and 0.68 ppm in the spectra of compounds **IX, X**, and **XII** respectively; the signal at 1.11 ppm belongs apparently to the *endo*-protons at C^6; both these nuclei (H^{3n} and H^{6n}) are the most affected by the

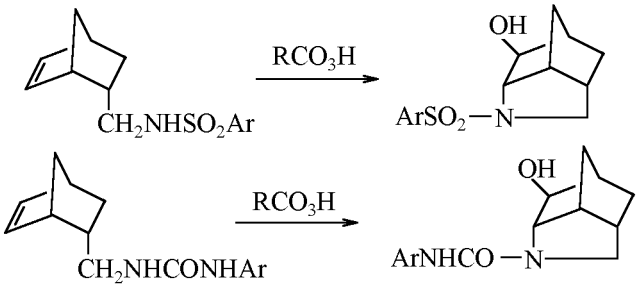


magnetically anisotropic influence of the exocyclic C^2–C^8 bond (Table 4).

The reduction of amide **IVb** with lithium aluminum hydride provides the only orange-colored product that was assigned azostructure **XIII** basing on the spectral data.

Although in the IR spectrum of compound **XIII** the absorption bands of carbonyl and nitro groups are lacking, this fact is not sufficient for establishing its structure (Table 1). Structure **XIII** is more reliably confirmed by the ^1H NMR spectrum where alongside the proton signals from the unsaturated skeleton and aromatic fragment appear signals of a secondary amino group (4.77 ppm) and of a new methylene group (3.58 ppm) (Table 2).

Besides the reduction we also studied the reaction of the stereoisomeric amides **IVa, b** with peracetic



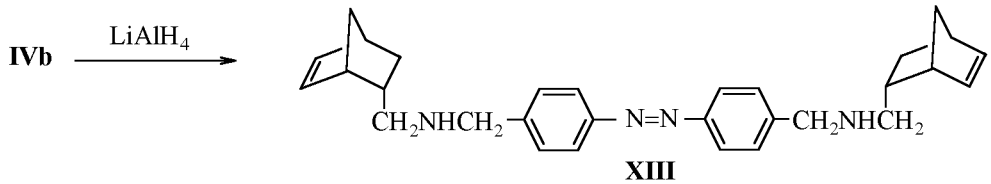


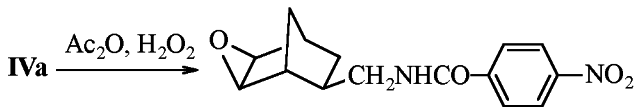
Table 5. ^{1}H NMR spectra of epoxides from norbornane series (**XIVa, b, XV**), δ, ppm, coupling constants, Hz

Compd. no.	H^1	H^2, H^3	H^4	H^5	H^{6x}	H^{6n}	H^{7s}, H^{7a}	H^{8A}, H^{8B}	NH, H arom
XIVa	2.47	3.09, 3.05, $^3J_{2,3}$ 3.5	2.36	1.82	1.52, $^2J_{6n,6x}$ 12.6, $^3J_{6x,5}$ 8.4, $^3J_{6x,1}$ 2.4	1.17, $^3J_{6n,5}$ 4.1	1.28, 0.88, $^2J_{7s,7a}$ 10.4	3.37, 3.31, $^2J_{8A,8B}$ 13.4, $^3J_{8A,5}$ 7.1, $^3J_{8A,5}$ 8.3	6.48 (NH), 8.24 (H arom), 7.91 (H arom)
XIVb	2.55	3.22, 3.37, $^3J_{2,3}$ 3.6	2.51	2.27	1.83, $^2J_{6n,6x}$ 12.5, $^3J_{6x,5}$ 9.9, $^3J_{6x,1}$ 4.3	0.93, $^3J_{6n,5}$ 4.8, $^4J_{6n,7s}$ 2.7	1.43, 0.82, $^2J_{7s,7a}$ 9.9	3.57, 3.42, $^2J_{8A,8B}$ 13.7, $^3J_{8A,5}$ 9.0, $^3J_{8A,5}$ 7.6	6.29 (NH), 8.26 (H arom), 7.90 (H arom)
XV	2.41	3.04, 2.97, $^3J_{2,3}$ 3.8	2.27	1.56	1.43, $^2J_{6n,6x}$ 12.4, $^3J_{6x,5}$ 8.2, $^3J_{6x,1}$ 2.8	1.01, $^3J_{6n,5}$ 4.1, $^4J_{6n,7s}$ 3.8	1.22, 0.67, $^2J_{7s,7a}$ 10.1	2.85, 2.82	

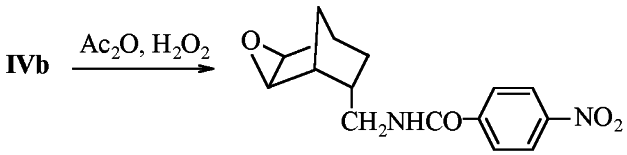
acid. The epoxidation of amides from the norbornene series attracted lately a special interest because of recently discovered intramolecular cyclizations of arylsulfonamides [18] and arylureas [23] treated with peroxyacids to furnish substituted azabrandanes.

In contrast to these data we showed that the epoxidation of *N*-benzoyl-*endo*-5-aminomethylbicyclo-[2.2.1]hept-2-ene with peroxyphthalic acid afforded epoxy derivative [24].

The epoxidation of amides **IVa, b** was carried out under the most favorable conditions for the epoxy ring opening, namely, with peracetic acid *in statu* nascendi from acetic anhydride and 50% hydrogen peroxide. However in both cases the only reaction products were epoxides obtained in a high yield. The epoxidation of the endo-amide under these conditions, as in [24], was not followed by heterocyclization.



XIVa



XIVb

The epoxides structure was proved by various spectral methods. Their IR spectra lack the characteristic absorption band of = C –H bond at 720–710 cm^{-1}, and contain absorption bands of C–O bonds (850 and 848 cm^{-1}) and C–H bonds (3072 cm^{-1}) belonging to the epoxy moieties. The latter bands are characteristic of the substituted epoxynorbornanes [25] (Table 1). In Table 5 are given the ^{1}H NMR spectra, and in Table 3 the ^{13}C NMR spectra of epoxides **XIVa, b**. For the sake of comparison in Table 5 is also presented the spectrum of previously investigated *N*-(*p*-nitrophenylsulfonyl)-*exo*-5-aminomethyl-ex-2,3-epoxybicyclo[2.2.1]heptane (**XV**) [25]. The signals were identified with the use of two-dimensional spectra (Figs. 1, 2).

The most characteristic in the ^{1}H NMR spectra of compounds **XIVa, b** and epoxide **XV** are the proton signals of the epoxy ring (H^2, H^3) in the region 3.05–3.37 ppm, and of protons of the bridge, among which one (H^{7a}) appears in the strong field (0.88 and 0.82 ppm) for it is strongly shielded by the oxirane ring. Under these conditions in agreement with the known published data [16, 18, 26] considerably increases the nonequivalence of the bridge protons (H^{7s}, H^{7a}) as compared to the spectra of the corresponding unsaturated compounds. The introduction of the epoxy ring is also reflected in the upfield shift of the resonances of bridgehead protons (H^1, H^4) compared to those in the spectra of olefins **IVa, b**.

The NMR spectra of epoxy derivatives of amines are especially interesting since they provide a possibility of criteria development for estimation of the isomeric composition in the series of epoxy derivatives of substituted norbornene amines; it cannot be done for the series of sulfonamides and ureides due to heterocyclization of the endo-isomer at epoxidation. The comparison of the ^{1}H NMR spectra of epoxides **XIVa, XIVb** confirms the general sense of the

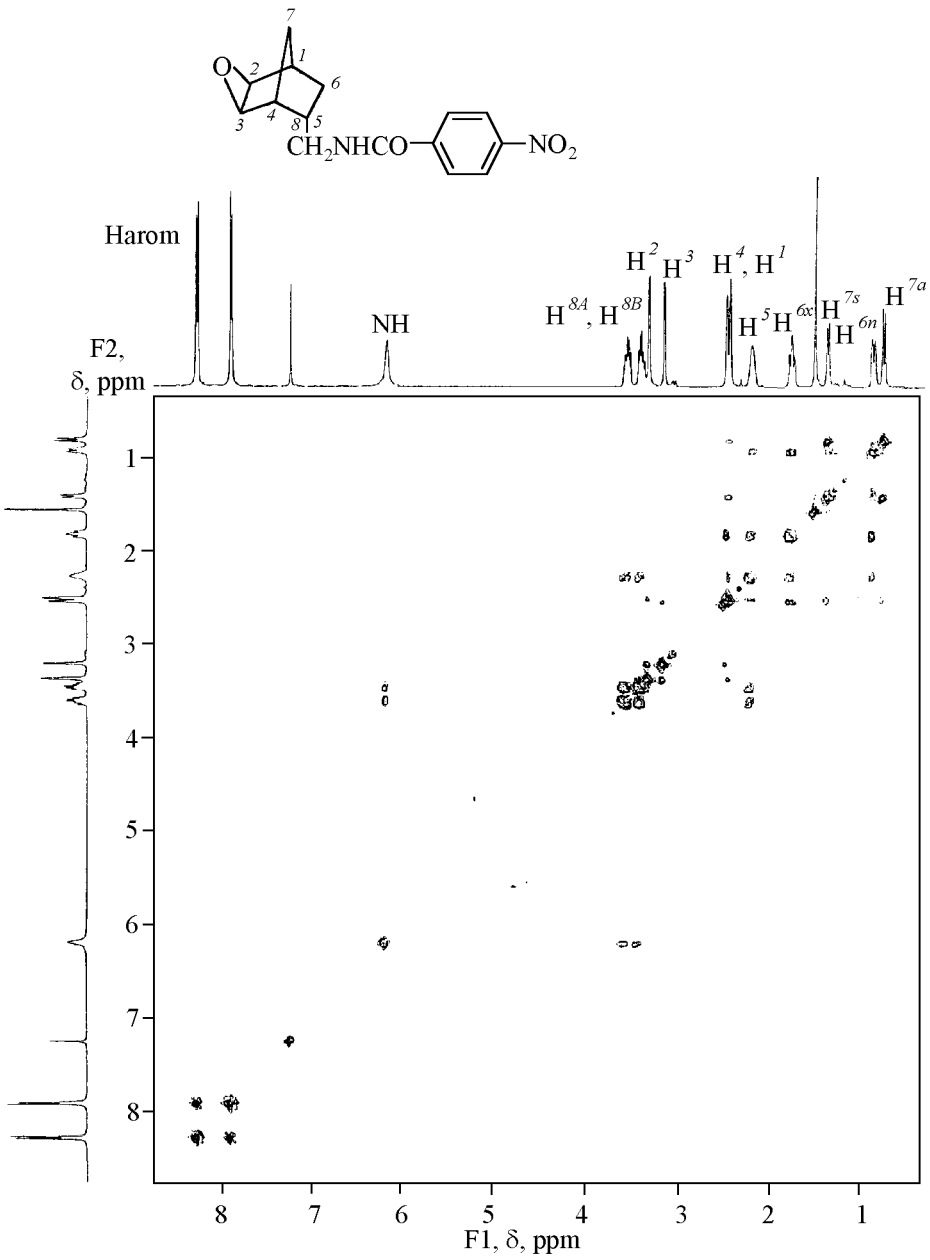


Fig. 1. HH-COSY spectrum of *N*-(4-nitrobenzoyl)-*endo*-5-aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane (**XIVb**).

criteria we have disclosed earlier in the studies of isomeric unsaturated sulfonamides [18], ureides [16], and in this work with isomeric amides: similar relations are observed also with the epoxy analogs.

Actually, in the *exo*-epoxide **XIVa** and *endo*-epoxide **XIVb** nonequivalent are proton signals from H^2 and H^3 (significantly more for the *endo*-isomer), from H^1 and H^4 (here more notably for the *exo*-isomer), and also from the protons H^{6x} and H^{6n} (in the spectra under consideration the difference is respectively 0.35 and 0.90 ppm). These differences originate from the reciprocal influence of the substituent and epoxy (olefin) fragment in the *exo*- and *endo*-isomers, and also by the properties of the exocyclic fragment C^5–C^8 that has a rigid spatial orientation. The magnetic anisotropy of the C^5–C^8 bond produces additional shielding of the protons linked to the skeleton by bonds parallel to the carbon–carbon bond of the above fragment (H^4 and H^{6x} in the *exo*-isomer and H^{6n} in the *endo*-isomer); this effect is less

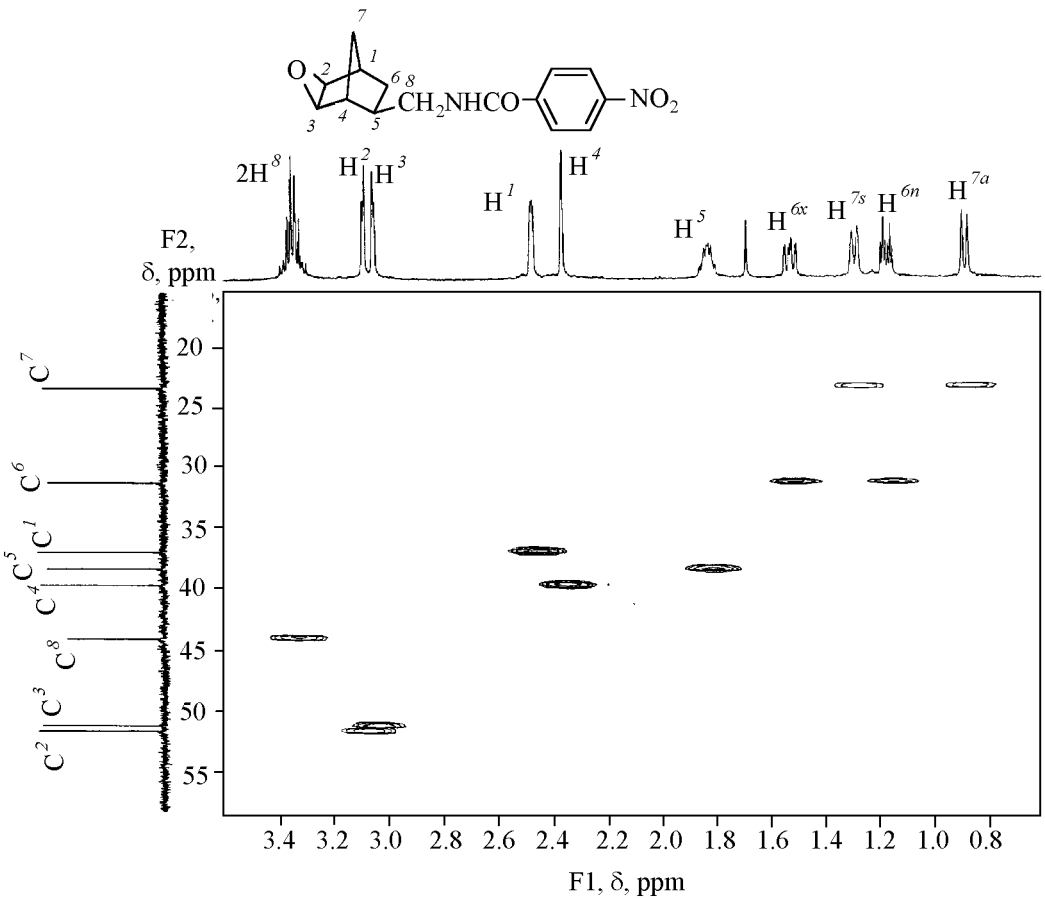


Fig. 2. CH-NOESY spectrum of *N*-(4-nitrobenzoyl)-*exo*-5-aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane (**XIVa**).

pronounced in the spectra of epoxides than in those of unsaturated amides.

The ^{13}C NMR spectra of epoxides (Table 2) are distinguished from the spectra of the initial amides by the shift of signals from atoms C^2 and C^3 to the region 50–52 ppm, and the signals of carbon atoms in the methylene bridge (C^7) to 23–28 ppm. The position of these signals reliably proves the exo-orientation of the epoxy ring. In the ^{13}C NMR spectra of epoxides were determined the differences depending on the orientation of the substituent with respect to the carbon skeleton; they are related to the mutual position of the carbons of the epoxy ring (C^2 and C^3), and also of C^7 and C^4.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Specord 75IR from samples as thin films or pellets with KBr. ^1H NMR spectra were registered on spectrometers Varian VXR-300 and GEMINI-BB (operating frequencies 300 and 500 MHz respectively) using solutions of compounds in $CDCl_3$ with HMDS as internal reference. ^{13}C NMR spectra were measured on spectrometer GEMINI-BB (operating frequencies 100.58 and 125.71 MHz). Some spectra were registered in COSY and NOESY mode. The reaction progress was monitored and products purity was controlled by TLC on Silufol UV-254 plates, eluent ether, development in iodine vapor. The physical characteristics of compounds synthesized are presented in Tables 1–5.

The preparation of stereoisomeric 5-aminomethylbicyclo[2.2.1]hept-2-enes (**IIIa, b**) was carried out along procedure described in [17]; the characteristics of amines obtained were consistent with the data of [17].

Stereoisomeric (*p*-nitrobenzoyl)-5-aminomethylbicyclo[2.2.1]hept-2-enes (IVa, b). To a stirred mixture of 0.01 mol of amine **IIIa** or **IIIb** and 0.003 mol of triethylamine in 30 ml of chloroform was added dropwise 0.013 mol of *p*-nitrobenzoyl chloride, and the stirring was continued till completion of reaction

(TLC monitoring). The product obtained was thrice washed with water, with 20% HCl solution and again with water. The organic layer was separated, dried with calcined magnesium sulfate, the solvent was removed, and the reaction product was subjected to further purification.

***N*-(*p*-Aminobenzoyl)-endo-5-aminomethylbicyclo[2.2.1]hept-2-ene (V).** A suspension obtained by mixing of 2.8 g (0.01 mol) of amide **IVb**, 1.25 g (0.031 mol) of sodium hydroxide, and 1 g (0.031 mol) of sulfur in 20 ml of water–ethanol mixture (1 : 2) was boiled till completion of reaction (TLC monitoring). On cooling the reaction mixture it was filtered from excess sulfur, the filtrate was diluted with water and thrice extracted with ether. The combined extracts were dried with calcined magnesium sulfate, the solvent was removed, and the reaction product was subjected to chromatography on silica gel, eluent ether.

***N*-[4-(4-Nitrobenzenesulfonylamido)benzoyl]-*endo*-5-aminomethylbicyclo[2.2.1]hept-2-ene (VI).** To a stirred mixture of 0.5 g (2.1 mmol) of amine **V** and 0.4 g (2.1 mmol) of 20% water solution of NaOH in 19 ml of ether was added dropwise a solution of 0.47 g (2.1 mmol) of *p*-nitrobenzenesulfonyl chloride in 5 ml of ether. The stirring at room temperature was continued till the end of the reaction (TLC monitoring). The solvent was removed, the solid residue was dissolved in 20 ml of chloroform–water mixture (1 : 1), the organic layer was separated, dried on calcined magnesium sulfate, the solvent was removed, and the reaction product recrystallized.

***N*-[4-(4-Nitrobenzamido)benzoyl]-endo-5-aminomethylbicyclo[2.2.1]hept-2-ene (VII).** To a stirred mixture of 0.15 g (0.62 mmol) of amine **V** and 0.2 ml of triethylamine in 10 ml of chloroform was added dropwise a solution of 0.15 g (0.81 mmol) of *p*-nitrobenzoyl chloride in 5 ml of chloroform, and the stirring was continued till the end of the reaction (TLC monitoring). After the usual workup the product was purified.

***N*-[4-(Phenylthioureido)benzoyl]-*endo*-5-aminomethylbicyclo[2.2.1]hept-2-ene (VIII).** To a solution of 0.3 g (1.24 mmol) of amine **V** in 3 ml of benzene was added 0.17 g (1.24 mmol) of phenyl isothiocyanate, and the mixture was left standing till crystals precipitated. The crystals were filtered off, washed with benzene on the filter, dried, and recrystallized.

***N*-(*p*-Aminobenzoyl)-*endo*-5-aminomethylbicyclo[2.2.1]heptane (IX)** was prepared by boiling a mixture of 1.2 g (4.4 mmol) of amide **IVb**, 0.55 g (11 mmol) of hydrazine hydrate, and 0.05 g (0.9 mmol) of a freshly prepared nickel catalyst in 20 ml of ethanol. The course of reaction was monitored by TLC. On cooling the reaction mixture the catalyst was filtered off, the solvent was removed, and the residue was subjected to chromatography on silica gel, eluent ether.

***NN*-[4-(4-Nitrobenzamido)benzoyl]-*endo*-5-aminomethylbicyclo[2.2.1]heptane (XI)** was prepared similarly to compound **VII** from 0.1 g (0.41 mmol) of amine **IX** and 0.1 g (0.54 mmol) of *p*-nitrobenzoyl chloride.

***N*-[4-(4-Nitrophenylureido)benzoyl]-*endo*-5-aminomethylbicyclo[2.2.1]heptane (XII)** was obtained similarly to compound **VIII** from 0.1 g (0.41 mmol) of amine **IX** and 0.07 g (0.41 mmol) of *p*-nitrophenyl isocyanate.

4,4'-Bis(bicyclo[2.2.1]hept-2-ene-5-(methylaminomethyl)azobenzene (XIII) was obtained by boiling a mixture of 1 g (3.7 mmol) of amide **IVb** and 0.63 g (16.6 mmol) of lithium aluminum hydride in 20 ml of anhydrous ether till completion of the reaction (TLC monitoring). The excess lithium aluminum hydride was decomposed with cold water, the solution was separated from the precipitate formed, dried with calcined magnesium sulfate, the solvent was removed, and the product was subjected to column chromatography on silica gel.

***N*-(4-Nitrobenzoyl)-*exo*- and *endo*-5-aminomethyl-*exo*-2,3-epoxybicyclo[2.2.1]heptanes (XIVa, b).** To a stirred mixture of 0.5 g (2.2 mmol) of amide **IVa** or **IVb**, 0.4 g (4.4 mmol) of sodium hydrogen carbonate, and 0.45 g (4.4 mmol) of acetic anhydride in 10 ml of chloroform was added dropwise 0.3 g (4.4 mmol) of 50% solution of hydrogen peroxide. On completion of the reaction (TLC) the reaction mixture was neutralized with a saturated solution of sodium hydrogen carbonate, the organic layer was separated, dried with calcined magnesium sulfate, the solvent was removed, and the reaction product was subjected to purification.

REFERENCES

1. Kriger, M., *Arzn.-Forsch.*, 1968, vol. 18, pp. 129–134.
2. Kriger, M., *Arzn.–Forsch.*, 1968, vol. 18, pp. 324–330.
3. US Patent 2926172, 1960. *Ref. Zh. Khim.*, 1961, 18 L 278; Australian Patent 220063, 1960. *Ref. Zh. Khim.*, 1961, 8L 347.
4. UK Patent 10894173, 1977. *Ref. Zh. Khim.*, 1977, 21 O 51.

5. Kriger, M., *Arzn.-Forsch.*, 1968, vol. 18, pp. 487–493.
6. Renise, A., Bondavalli, F., and Schenone, P., *Farmaco Ed. Sci.*, 1988, vol. 43, no. 1, pp. 79–89.
7. Balsamo, A., Breshi, M.C., and Lapucci, A., *J. Med. Chem.*, 1989, vol. 32, no. 4, pp. 856–859.
8. German Patent 1493078, 1974. *Ref. Zh. Khim.*, 1976, 5O14P.
9. Antoniu, D., Ganzina, F., Magi, M., and Serino, E., *Farmaco. Ed. Sci.*, 1970, vol. 25, no. 8, pp. 573–591.
10. Kas'yan, L.I., Zlenko, E.T., Mamchur, V.I., Kas'yan, A.O., and Tarabara, I.N., *Farm. Zh.*, 2001, no. 4, pp. 54–57.
11. Zlenko, H.T., Kas'yan, L.I., Mamchur, V.I., Kasy'an, A.O., Tarabara, I.N., and Budchenko, S.I., *Abstr. of Papers of the 8th Central European Neuropsychopharmacological Symposium*, Vienna, 1998, pp. 307–308; Kas'yan, L.I., Zlenko, H.T., Kas'yan, A.O., and Tarabara, I.N., Abstracts of Papers, 12th Camerino-Noordmiykerhout Symposium, Camerino, 1999, p. 168.
12. Sauers, R.R., Parent, R.A., and How, H.W., *Tetrahedron*, 1965, vol. 21, pp. 2907–2912.
13. Alder, K., Krieger, H., and Weib, H., *Chem. Ber.*, 1955, vol. 88, no. 1, pp. 144–145; Alder, K., Heimbach, K., and Reubke, R., *Chem. Ber.*, 1958, vol. 91, no. 7, pp. 1516–1524.
14. Wilder, P. and Knight, D.B., *J. Org. Chem.*, 1965, vol. 30, no. 9, pp. 3078–3081.
15. Nakanisi, K., *Infrakrasnye spektry organicheskikh soedinenii* (IT Spectra of Organic Compounds), Moscow: Mir, 1965.
16. Kas'yan, A.O., Krasnovskaya, O.Yu., Okovityi, S.I., and Kas'yan, L.I., *Zh. Org. Khim.*, 1995, vol. 31, no. 3, pp. 347–356.
17. Markov, V.I., Kas'yan, A.O., Tudvaseva, S.P., Okovityi, S.I., *Ukr. Khim. Zh.*, 1993, vol. 59, no. 6, pp. 650–654; Markov, V.I., Kas'yan, A.O., and Selyutin, O.B., *Ukr. Khim. Zh.*, 1994, vol. 60, no. 8, pp. 575–581.
18. Kas'yan, L.I., Sereda, S.V., Potekhin, K.A., and Kas'yan A.O., *Heteroatom Chem.*, 1997, vol. 8, no. 2, pp. 177–184.
19. Kas'yan, A.O., Tarabara, I.N., Zlenko, E.T., Okovityi, S.I., and Kas'yan, L.I., *Zh. Org. Khim.*, 1999, vol. 35, no. 7, pp. 1042–1055.
20. *Weygand—Hilgetag, Organisch-Chemische Experimentierkunst*, 3d ed., Leipzig: Verlag, 1964.
21. *Organikum. Organisch-Chemisches Grundpraktikum*, 15th ed., Berlin: VEB Deutscher Verlag der Wissenschaften, 1976.
22. Kas'yan, A.O., Krasnovskaya, O.Yu., Zlenko, E.T., Okovityi, S.I., and Kas'yan, L.I., *Zh. Org. Khim.*, 1996, vol. 32, no. 8, pp. 1156–1164.
23. Kas'yan, L.I., Krasnovskaya, O.Yu., and Kas'yan, A.O., *Zh. Org. Khim.*, 1996, vol. 32, no. 7, pp. 1106–1107.
24. Kas'yan, L.I., Tarabara, I.N., Savel'eva, O.A., Kas'yan A.O., *Zh. Org. Khim.*, 1997, vol. 33, no. 9, pp. 1429–1430.
25. Kas'yan, L.I., Kas'yan, A.O., Gorb, L.G., and Klebanov, B.M., *Zh. Org. Khim.*, 1995, vol. 31, no. 5, pp. 678–688.
26. Kas'yan, A.O., Maletina, I.I., Yagupol'skii, L.M., Markov V.I., and Kas'yan L.I., *Zh. Org. Khim.*, 1995, vol. 31, no. 3, pp. 357–364.