ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 7, pp. 932–938. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © V.A. Vasin, D.Yu. Korovin, V.V. Razin, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 7, pp. 940–946.

Conjugate Halo- and Mercuroazidation of 1-Phenyltricyclo-[4.1.0.0$^{2.7}$]heptane. Synthesis of a Conformationally Rigid α-Amino Acid with a Bicyclo[3.1.1]heptane Skeleton

V. A. Vasin[a],* D. Yu. Korovin[a], and V. V. Razin[b]

[a] *Ogarev Mordovian State University, ul. Bol'shevistskaya 68, Saransk, 430005 Russia*
**e-mail: vasin@mrsu.ru*

[b] *St. Petersburg State University, Universitetskii pr. 26, St. Petersburg, 198504 Russia*

Received March 28, 2016

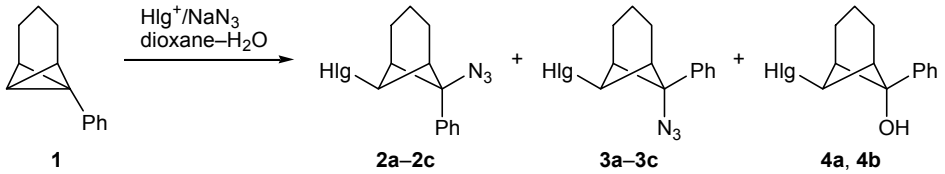
Abstract—1-Phenyltricyclo[4.1.0.0$^{2.7}$]heptane reacted with *N*-bromo-, *N*-chloro-, and *N*-iodosuccinimides and with mercury(II) acetate in the presence of sodium azide as external nucleophile to give conjugate addition products to the central C^1–C^7 bicyclobutane bond with a norpinane structure, where the azido group and the phenyl were attached to the same carbon atom (C^6). The bromo- and chloroazidation showed *anti*-stereoselectivity, and the iodoazidation, moderate *syn*-stereoselectivity; the mercuroazidation afforded exclusively the corresponding *syn*-addition product. Hydro-, bromo- and chlorodemercuration of the mercury adduct with sodium tetrahydridoborate and elemental bromine and chlorine, respectively, did not involve the azido group, and the original configuration was retained. The reduction of the hydrodemercuration product with $LiAlH_4$ gave 6-*exo*-phenylbicyclo[3.1.1]heptan-6-amine which was transformed in three steps into conformationally rigid 6-*endo*-(acetamido)bicyclo[3.1.1]heptane-6-carboxylic acid.

DOI: 10.1134/S1070428016070022

In continuation of our studies of ionic additions to 1-phenyltricyclo[4.1.0.0^{2,7}]heptane (**1**) [1–5], in the present work compound **1** was reacted with electrophilic halogenating agents and mercury(II) acetate in the presence of sodium azide as external nucleophile. We expected that the conjugate addition to **1** would be directed, as in analogous reactions studied previously, at the C^1–C^7 central bicyclobutane bond to give azides of the norpinane series, which in turn would open the way to 6-aminonorpinanes. In particular, it seemed promising to accomplish selective synthesis of conformationally rigid α-amino acids containing a cyclobutane fragment, which are likely to exhibit high biological activity [6–9].

The reactions of **1** with *N*-halosuccinimides (Hlg = Br, Cl, I) as a source of electrophilic halogen were carried out in aqueous 1,4-dioxane (1:1) at 20°C for 8–10 h in the presence of a slight excess of NaN_3. In the reactions with *N*-chloro- and *N*-bromosuccinimides we obtained mixtures containing three products. According to the ^{1}H NMR data, the products were diastereoisomeric 6-azido-6-phenylnorpinanes **2a**, **2b** and **3a**, **3b** and norpinan-6-ols **4a**, **4b** at ratios of 1:3.5:2.5 and 1:2.7:0.7, respectively. Analogous reaction with *N*-iodosuccinimide (NIS) gave a mixture of compounds **2c** and **3c** at a ratio of 1.8:1 (Scheme 1). For comparison, bicycloheptane derivative **1** was brought into reaction with iodine azide (IN_3) generated *in situ* from iodine(I) chloride and sodium azide in anhydrous acetonitrile [10]. The reaction was carried out at 20°C under argon, and the products were norpinane adducts **2c** and **3c** at a ratio of 2.8:1. In the reaction of **1** with

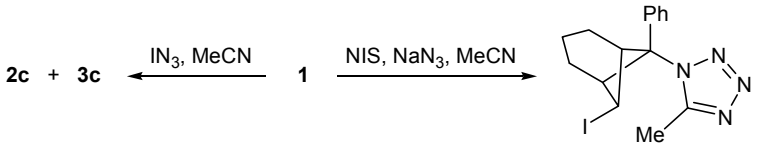
Scheme 1.



1 **2a–2c** **3a–3c** **4a**, **4b**

Hlg = Br (**a**), Cl (**b**), I (**c**).

Scheme 2.



5

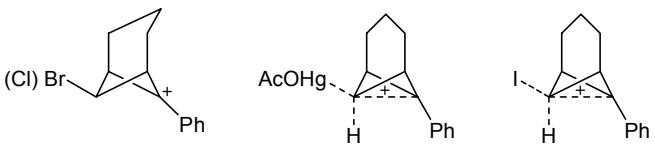
NIS in the presence of excess NaN_3 in anhydrous acetonitrile, inclusion of solvent molecule into the adduct was observed (cf. [11]), and the only product was tetrazole **5** resulting from *anti*-addition across the C^1–C^7 bond (Scheme 2).

Tricycloheptane **1** was then reacted with an equimolar amount of mercury(II) acetate in aqueous THF (1:1) in the presence of 3 equiv of sodium azide. We thus isolated mercury azide **6** which was converted into chloromercuro derivative **7** by treatment with a saturated solution of sodium chloride. Organomercury compound **7** reacted with elemental bromine and chlorine in anhydrous pyridine to give norpinanes **2a** and **2b**, respectively, with retention of the configuration of C^7 (cf. [1, 2]; Scheme 3).

Compounds **2a**–**2c**, **3a**, and **3b** were isolated in the pure state by flash chromatography on silica gel. Norpinane **3c** was characterized by spectral data in a mixture with diastereoisomer **2c**. Previously described norpinan-6-ols **4a** [1] and **4b** [3] were identified in the product mixtures by ^{1}H NMR spectra. Norpinanes **5**–**7** were purified by crystallization. The structure of the newly synthesized compounds was confirmed by IR, ^{1}H and ^{13}C NMR, and (in some cases) mass spectra. In particular, the azido group was identified by a medium-intensity IR band at ~2095 cm^{-1} [12]. The norpinane skeleton gave rise to five characteristic upfield signals in the ^{13}C NMR spectra.

The *syn* orientation of the substituent on C^7 was assigned on the basis of the ^{1}H NMR spectra which contained a triplet signal of 7-*anti*-H with a coupling constant *J* of ~5.8 Hz [13, 14]. The configuration of substituents on C^6 in **3a**–**3c** and **5** was determined by the position of the 3-H signal in the ^{1}H NMR spectra. In the case of *endo* orientation of the phenyl substituent, the 3-H proton is shielded by the aromatic ring, and it resonates as a one-proton multiplet at δ ~0.5 ppm; otherwise (*exo* orientation of the phenyl substituent), the 3-H signal is observed in a weaker field, δ >1.0 ppm (cf. the data for **2a**–**2c**, **6**, and **7** [5, 15]).

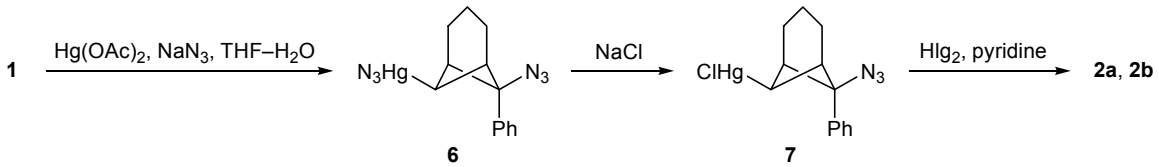
We can state that the bromo- and chloroazidation of **1** are characterized by *anti*-stereoselectivity, though not so high as in bromomethoxy(hydroxy)lation [1] or chloromethoxylation [3]. The iodoazidation shows moderate *syn*-stereoselectivity. By contrast, complete *syn*-stereoselectivity of the addition is observed in the mercuroazidation of **1**, as reported previously for the mercuromethoxy(hydroxy)lation of the same compound [1]. These findings may be rationalized in terms of our assumptions made in [2, 16]: the bromination and chlorination reactions are mediated by benzylic cation **A** to which *syn* approach of azide ion is hindered for steric reasons. Mercuroazidation and (partially) iodoazidation were presumed to involve intermediate nonclassical ions **B** and **C**, respectively. We also assume some contribution of a radical mechanism (involving formation of iodine azide) of the conjugate iodoazidation of **1**, which is likely to be responsible for the increased fraction of *anti* adduct **3c**.



A **B** **C**

Using norpinane **6** as starting compound, in this work we also accomplished directed synthesis of a conformationally hindered amine and a conforma-

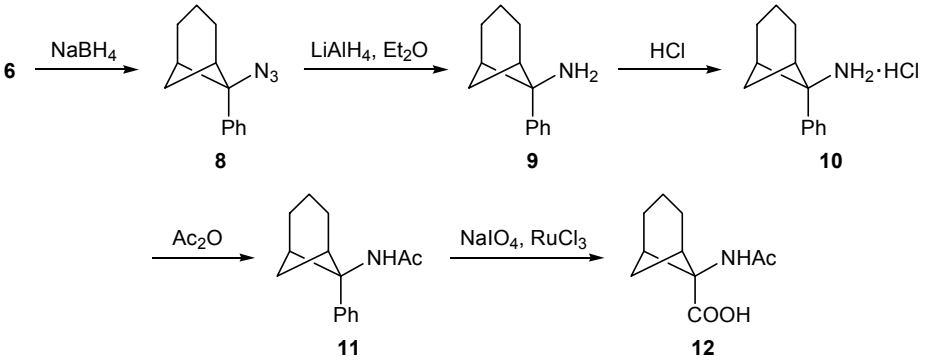
Scheme 3.



6 **7**

Hlg = Cl, Br.

Scheme 4.



tionally rigid α-amino acid with a norpinane skeleton. For this purpose, mercury azide **6** was subjected to hydrodemercuration by treatment with sodium tetrahydridoborate. Norpinane **8** thus formed was reduced to amine **9** with lithium tetrahydridoaluminate in diethyl ether, amine **9** was converted to hydrochloride **10** which was acylated to *N*-acetyl derivative **11**, and the latter was oxidized to carboxylic acid **12** with $RuCl_3$–$NaIO_4$ [17] (Scheme 4).

6,6-Disubstituted norpinanes **8**–**12** were isolated in the pure state, and their structure was confirmed by IR and ^{1}H and ^{13}C NMR spectra. Compounds **10**–**12** characteristically showed in the ^{1}H NMR spectra an upfield doublet due to 7-*syn*-H with a geminal coupling constant ^2J of 9.5–9.9 Hz. In the ^{1}H NMR spectra of **8** and **9**, signals from nonequivalent protons on C^7 overlapped each other. In the syntheses of **9**–**12**, the configuration of C^6 was retained, and diastereoisomers with *exo* orientation of the amino group were obtained.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol ECX-400 spectrometer at 400 and 100 MHz, respectively. The IR spectra were measured in KBr on an InfraLYuM FT-02 spectrometer with Fourier transform. The elemental analyses were obtained on a Vario MICRO CHNS analyzer. The mass spectra were recorded on an Konixbert HI-TECH SA RBK-HRGC5000B-MSQ12 instrument (Spain) (KAP5 column, 15 m × 0.25 mm, film thickness 0.25 μm; carrier gas helium, flow rate 1 mL/min; oven temperature programming from 50 to 250°C; electron impact, 70 eV). Sorbfil plates were used for analytical TLC (eluent light petroleum ether–ethyl acetate; development by treatment with iodine vapor or under UV light). Column chromatography was performed on aluminum oxide (Brockmann activity grade II) and Silica gel 60 (0.040–0.063 mm; Merck); silica gel L (5–40 μm) was used for dry-column flash chromatography (eluent light petroleum ether–ethyl acetate). Tricycloheptane **1** [1], *N*-chlorosuccinimide [18], and *N*-iodosuccinimide [19] were synthesized according to known procedures.

Reaction of tricycloheptane (1) with *N*-halosuccinimides and sodium azide in aqueous dioxane (*general procedure*). Sodium azide, 10 g (154 mmol), was added to a solution of 1.7 g (10 mmol) of compound **1** in 15 mL of aqueous dioxane (1:1), the mixture was cooled to 0°C, and 12 mmol of the corresponding *N*-halosuccinimide was added in portions over a period of 30 min. The mixture was stirred for 8–10 h at 20°C and extracted with diethyl ether (5×20 mL), the combined extracts were washed with water, dried over $MgSO_4$, and evaporated on a rotary evaporator, and the residue was analyzed by ^{1}H NMR. The reaction with NBS gave norpinanes **2a**, **3a**, and **4a** at a ratio of 1:3.5:2.5; in the reaction with NCS norpinanes **2b**, **3b**, and **4b** were formed at a ratio of 1:2.7:0.7; in the reaction with NIS the products were norpinanes **2c** and **3c** at a ratio of 1.8:1. The major product was isolated by flash chromatography on silica gel.

6-*endo*-Azido-7-*syn*-iodo-6-*exo*-phenylbicyclo[3.1.1]heptane (2c). Yield 37%, mp 97–98°C (from hexane). IR spectrum, ν, cm^{-1}: 2863 m, 2095 v.s, 1447 m, 1254 s, 768 m, 718 s, 698 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.73–1.91 m (2H, 3-H), 2.07–2.17 m (2H, 2-*endo*-H, 4-*endo*-H), 2.39–2.46 m (2H, 2-*exo*-H, 4-*exo*-H), 3.15 br.d (2H, 1-H, 5-H, J = 5.5 Hz), 4.28 t (1H, 7-*anti*-H, J = 5.7 Hz), 7.37–7.44 m (1H, H_{arom}), 7.46–7.50 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.1 (C^3), 26.9 (C^2, C^4), 27.6 (C^7), 48.8 (C^1, C^5), 66.3 (C^6), 126.8 (2C, C_{arom}), 128.6

(C_{arom}), 129.1 (2C, C_{arom}), 138.6 (C_{arom}). Found, %: C 46.22; H 4.05; N 12.32. $C_{13}H_{14}IN_3$. Calculated, %: C 46.04; H 4.16; N 12.39.

6-*exo*-Azido-7-*syn*-bromo-6-*endo*-phenylbicyclo-[3.1.1]heptane (3a). Yield 45%, colorless oil. IR spectrum, ν, cm^{-1}: 2107 v.s, 1256 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.53–0.69 m (1H, 3-*endo*-H), 1.13–1.27 m (1H, 3-*exo*-H), 1.97–2.04 m (2H, 2-*endo*-H, 4-*endo*-H), 2.11–2.19 m (2H, 2-*exo*-H, 4-*exo*-H), 2.95 br.s (2H, 1-H, 5-H), 5.38 t (1H, 7-*anti*-H, J = 5.8 Hz), 7.25–7.29 m (2H, H_{arom}), 7.31–7.35 m (1H, H_{arom}), 7.37–7.41 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.1 (C^3), 25.2 (C^2, C^4), 49.6 (C^1, C^5), 56.0 (C^7), 79.9 (C^6), 125.5 (2C, C_{arom}), 128.1 (C_{arom}), 129.0 (2C, C_{arom}), 142.4 (C_{arom}). Found, %: C 53.36; H 4.75; N 14.45. $C_{13}H_{14}BrN_3$. Calculated, %: C 53.44; H 4.83; N 14.38.

6-*exo*-Azido-7-*syn*-chloro-6-*endo*-phenylbicyclo-[3.1.1]heptane (3b). Yield 40%, colorless oil. IR spectrum, ν, cm^{-1}: 2917 w, 2098 v.s, 1262 m, 772 m, 710 m, 698 m. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.55–0.75 m (1H, 3-*endo*-H), 1.21–1.32 m (1H, 3-*exo*-H), 1.90–2.08 m (2H, 2-*endo*-H, 4-*endo*-H), 2.14–2.27 m (2H, 2-*exo*-H, 4-*exo*-H), 3.05 br.s (2H, 1-H, 5-H), 5.07 t (1H, 7-*anti*-H, J = 5.8 Hz), 7.24–7.31 m (1H, H_{arom}), 7.40–7.49 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.3 (C^3), 22.7 (C^2, C^4), 47.6 (C^1, C^5), 58.3 (C^7), 70.8 (C^6), 126.0 (2C, C_{arom}), 128.4 (C_{arom}), 129.0 (2C, C_{arom}), 137.2 (C_{arom}). Found, %: C 63.12; H 5.75; N 16.82. $C_{13}H_{14}ClN_3$. Calculated, %: C 63.03; H 5.70; N 16.96.

6-*exo*-Azido-7-*syn*-iodo-6-*endo*-phenylbicyclo-[3.1.1]heptane (3c). ^1H NMR spectrum ($CDCl_3$), δ, ppm (some signals are given): 0.53–0.69 m (1H, 3-*endo*-H), 1.16–1.29 m (3H, 2-*endo*-H, 4-*endo*-H, 3-*exo*-H), 2.97 br.s (2H, 1-H, 5-H), 5.38 t (1H, 7-*anti*-H, J = 5.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.8 (C^3), 27.8 (C^2, C^4), 36.5 (C^7), 47.5 (C^1, C^5), 76.5 (C^6), 125.5 (2C, C_{arom}), 127.2 (C_{arom}), 127.3 (2C, C_{arom}), 138.1 (C_{arom}).

Reaction of tricycloheptane 1 with iodine azide. A mixture of 10 g (154 mmol) of sodium azide and 20 mL of anhydrous acetonitrile was cooled to 0°C, 1.8 g (11 mmol) of ICl was added with stirring, and a solution of 1.7 g (10 mmol) of compound **1** in 7 mL of acetonitrile was then added dropwise over a period of 15 min. The mixture was stirred for 9 h at 20°C and concentrated under reduced pressure (water-jet pump). The residue was dissolved in 100 mL of diethyl ether, and the solution was washed with 20 mL of a 5% solution of Na_2SO_3 and with brine, dried over $MgSO_4$, and evaporated on a rotary evaporator. According to the ^1H NMR data, the residue contained norpinanes **2c** and **3c** at a ratio of 3:1. By flash chromatography on silica gel we isolated 2.2 g (65%) of **2c**.

1-(6-*syn*-Iodo-7-*endo*-phenylbicyclo[3.1.1]heptan-7-yl)-5-methyl-1*H*-tetrazole (5). A solution of 1.7 g (10 mmol) of **1** in 20 mL of anhydrous acetonitrile was mixed with 10 g (154 mmol) of sodium azide. The mixture was cooled to 0°C, 2.7 g (12 mmol) of *N*-iodosuccinimide was added in portions over a period of 30 min, and the mixture was stirred for 8 h at 20°C. The solvent was removed on a rotary evaporator, the residue was extracted with 100 mL of diethyl ether, and the extract was washed with a 5% solution of Na_2SO_3 and brine, dried over $MgSO_4$, and evaporated. The residue was subjected to flash chromatography on silica gel to isolate 1.7 g (46%) of tetrazole **5** with mp 135–136°C (from hexane–CH_2Cl_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.46–0.64 m (1H, 3-*endo*-H), 1.41–1.55 m (1H, 3-*exo*-H), 2.14–2.30 m (2H, 2-*endo*-H, 4-*endo*-H), 2.36 s (3H, CH_3), 2.46–2.54 m (2H, 2-*exo*-H, 4-*exo*-H), 3.54 br.s (2H, 1-H, 5-H), 4.72 t (1H, 7-*anti*-H, J = 5.6 Hz), 7.28–7.39 (3H, H_{arom}), 7.46–7.48 (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 9.9 (CH_3), 11.8 (C^3), 27.7 (C^2, C^4), 30.3 (C^7), 48.4 (C^1, C^5), 62.7 (C^6), 126.3 (2C, C_{arom}), 128.9 (C_{arom}), 129.5 (2C, C_{arom}), 138.7 (C_{arom}), Found, %: C 47.29; H 4.55; N 14.65. $C_{15}H_{17}IN_4$. Calculated, %: C 47.38; H 4.51; N 14.73.

6-*endo*-Azido-7-*syn*-(azidomercuro)-6-*exo*-phenylbicyclo[3.1.1]heptan (6). A solution of 1.95 g (30 mmol) of sodium azide in 60 mL of aqueous THF (1:1) was cooled to 0°C, 3.19 g (10 mmol) of mercury(II) acetate was added, and the mixture was stirred for 0.5 h. Tricycloheptane **1**, 1.7 g (10 mmol), was then added over a period of 10 min, and the mixture was stirred for 32 h at 20°C. The mixture was evaporated under reduced pressure, the residue was dissolved in 50 mL of methylene chloride, and the solution was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure (water-jet pump), and the oily residue was crystallized by grinding with diethyl ether. Yield 3.18 g (70%), mp 125–126°C (decomp.). IR spectrum, ν, cm^{-1}: 2936 m, 2855 w, 2095 v.s (N_3, asym.), 1447 w, 1242 m (N_3, sym.), 694 m. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.76–1.89 m (1H, 3-*endo*-H), 1.94–2.18 m (5H, 2-H, 4-H, 3-*exo*-H), 2.30 t (1H, 7-*anti*-H, J = 5.7 Hz), 3.14 br.d (2H, 1-H, 5-H), 7.40 t

(1H, H_{arom}, J = 7.3 Hz), 7.48 t (2H, H_{arom}, J = 7.3 Hz), 7.57 d (2H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.5 (C^3), 26.6 (C^2, C^4), 43.7 (C^7), 48.4 (C^1, C^5), 70.9 (C^6), 126.6 (2C, C_{arom}), 128.1 (C_{arom}), 128.7 (2C, C_{arom}), 140.0 (C_{arom}). Found, %: C 34.26; H 3.05; N 18.52. $C_{13}H_{14}HgN_6$. Calculated, %: C 34.33; H 3.10; N 18.48.

6-*endo*-Azido-7-*syn*-chloromercuro-6-*exo*-phenylbicyclo[3.1.1]heptane (7). Compound **6** prepared as described above was dissolved in aqueous dioxane, 5 mL of a saturated solution of sodium chloride acidified with several drops of concentrated aqueous HCl was added, and the mixture was stirred for 3 h at 20°C. The resulting suspension was diluted with 50 mL of water and evaporated by half under reduced pressure (water-jet pump). The precipitate was filtered off, washed with water, dried in air, and purified by recrystallization. Yield 2.7 g (67%), mp 155–156°C (from CCl_4). IR spectrum, ν, cm^{-1}: 2095 v.s, 1242 m, 764 w, 718 w, 695 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.89–1.98 m (2H, 3-H), 2.01–2.10 m (2H, 2-*endo*-H, 4-*endo*-H), 2.25–2.32 m (2H, 2-*exo*-H, 4-*exo*-H), 2.68 t (1H, 7-*anti*-H, J = 5.6 Hz), 3.22 br.s (2H, 1-H, 5-H), 7.36–7.40 m (1H, H_{arom}), 7.42–7.49 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.0 (C^3), 27.5 (C^2, C^4), 49.5 (C^1, C^5), 50.5 (C^7), 70.9 (C^6), 126.7 (2C, C_{arom}), 128.5 (C_{arom}), 129.0 (2C, C_{arom}), 139.4 (C_{arom}). Found, %: C 34.76; H 3.05; N 9.22. $C_{13}H_{14}ClHgN_3$. Calculated, %: C 34.83; H 3.15; N 9.37.

6-*endo*-Azido-7-*syn*-bromo-6-*exo*-phenylbicyclo[3.1.1]heptane (2a). A solution of 0.6 g (3.75 mmol) of bromine in 5 mL of pyridine was slowly added at 0°C in a stream of argon to a solution of 1 g (2.2 mmol) of bicycloheptane **7** in 15 mL of anhydrous pyridine. The mixture was stirred for 10 h at 20°C, diluted with 50 mL of water, and extracted with diethyl ether (3×15 mL). The combined extracts were washed with 30 mL of 5% aqueous H_2SO_4, 30 mL of a 5% solution of $NaHCO_3$, and water, dried over $MgSO_4$, and evaporated on a rotary evaporator. Crystallization of the residue gave 0.5 g (77%) of **2a** with mp 75–76°C (from petroleum ether). IR spectrum, ν, cm^{-1}: 2095 v.s, 1447 m, 1254 m, 768 m, 714 m, 698 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.80 q (2H, 3-H, J = 7.7 Hz), 2.16–2.24 m (2H, 2-*endo*-H, 4-*endo*-H), 2.27–2.35 m (2H, 2-*exo*-H, 4-*exo*-H), 3.18–3.20 m (2H, 1-H, 5-H), 4.20 t (1H, 7-*anti*-H, J = 5.8 Hz), 7.35–7.40 m (1H, H_{arom}), 7.42–7.46 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.7 (C^3), 24.4 (C^2, C^4), 48.7 (C^7), 48.8 (C^1, C^5), 67.3 (C^6), 126.8 (2C, C_{arom}), 128.7 (C_{arom}), 129.1 (2C, C_{arom}), 138.7 (C_{arom}). Found, %: C 53.46; H 4.80; N 14.33. $C_{13}H_{14}BrN_3$. Calculated, %: C 53.44; H 4.83; N 14.38.

6-*endo*-Azido-7-*syn*-chloro-6-*exo*-phenylbicyclo[3.1.1]heptane (2b). Gaseous chlorine was passed through a solution of 1 g (2.2 mmol) of bicycloheptane **7** in 20 mL of anhydrous pyridine cooled to 0°C. The mixture was diluted with 50 mL of water and extracted with diethyl ether (3×15 mL), and the extract was treated as described above in the synthesis of **2a**. By flash chromatography on silica gel we isolated 0.4 g (73%) of **2b** as a colorless viscous oil. IR spectrum, ν, cm^{-1}: 2095 v.s, 1254 s. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.91 m (2H, 3-H), 2.20–2.32 m (4H, 2-H, 4-H), 3.19–3.21 m (2H, 1-H, 5-H), 4.10 t (1H, 7-*anti*-H, J = 5.8 Hz), 7.37–7.42 m (1H, H_{arom}), 7.44–7.47 m (4H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.0 (C^3), 22.8 (C^2, C^4), 48.7 (C^1, C^5), 55.1 (C^7), 66.9 (C^6), 126.8 (2C, C_{arom}), 128.6 (C_{arom}), 129.1 (2C, C_{arom}), 138.8 (C_{arom}). Found, %: C 63.12; H 5.80; N 17.02. $C_{13}H_{14}ClN_3$. Calculated, %: C 63.03; H 5.70; N 16.96.

6-*endo*-Azido-6-*exo*-phenylbicyclo[3.1.1]heptane (8). A solution of 3.18 g (7 mmol) of **6** in 50 mL of methylene chloride was cooled to 0°C, 8 mL of a 15% aqueous solution of potassium hydroxide was added with stirring, and a solution of 0.2 g (5.3 mmol) of sodium tetrahydridoborate in 8 mL of 15% aqueous potassium hydroxide was then added. The mixture was stirred for 5 h at 20°C and left overnight. The precipitate of mercury metal was separated by decantation, the organic phase was separated, and the aqueous phase was extracted with methylene chloride (3×10 mL). The extracts were combined with the organic phase, washed with water, and dried over $MgSO_4$, the solvent was removed under reduced pressure, and the residue was purified by dry-column flash chromatography using petroleum ether as eluent. Yield 1.4 g (94%), colorless oil. IR spectrum, ν, cm^{-1}: 3059 w, 3029 w, 2951 m, 2867 w, 2095 v.s (N_3, asym.), 1493 w, 1447 w, 1254 w (N_3, sym.), 1088 w, 1030 w, 983 w, 718 m, 698 m. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.49–1.57 m (2H, 7-H), 1.66–1.86 m (2H, 3-H), 1.91–1.99 m (2H, 2-*endo*-H, 4-*endo*-H), 2.15–2.24 m (2H, 2-*exo*-H, 4-*exo*-H), 2.88–2.92 m (2H, 1-H, 5-H), 7.34–7.38 m (1H, H_{arom}), 7.42–7.46 m (2H, H_{arom}), 7.49–7.52 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.2 (C^3), 23.1 (C^7), 24.9 (C^2, C^4), 41.8 (C^1, C^5), 70.1 (C^6), 126.8 (2C, C_{arom}), 128.0 (C_{arom}), 128.7 (2C,

C_{arom}), 140.6 (C_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 185 (8.0) [$M - N_2$], 170 (12), 150 (25), 150 (32), 142 (16), 130 (35), 117 (18), 104 (100), 91 (72). Found, %: C 73.18; H 7.14; N 19.68. $C_{13}H_{15}N_3$. Calculated, %: C 73.21; H 7.09; N 19.70. *M* 213.28.

6-*exo*-Phenylbicyclo[3.1.1]heptan-6-*endo*-amine (9). A solution of 1.4 g (6.58 mmol) of **8** in 5 mL of anhydrous diethyl ether was added under with stirring under argon to a suspension of 0.38 g (10 mmol) of $LiAlH_4$ in 25 mL of anhydrous diethyl ether on cooling to –10°C. The mixture was stirred for 2 h at –10°C and for 15 h at 20°C, carefully treated with 15 mL of water, and stirred for 30 min more, and 20 mL of diethyl ether was added. The organic phase was separated and dried over $MgSO_4$, the solvent was removed under reduced pressure (water-jet pump), and the residue was purified by column chromatography on aluminum oxide. Yield 1.06 g (86%), yellowish viscous oil. IR spectrum (film), ν, cm^{-1}: 3391 br.m, 2936 s, 2867 m, 1605 m, 764 m, 702 s. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31–1.39 m (2H, 7-H), 1.50–1.59 m and 1.67–1.74 m (1H each, 3-H), 1.81–1.90 m and 2.02–2.11 m (2H each, 2-H, 4-H), 2.57–2.59 m (2H, 1-H, 5-H), 7.20–7.24 m (1H, H_{arom}), 7.31–7.36 m (2H, H_{arom}), 7.48–7.51 m (2H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δC, ppm: 13.3 (C^3), 22.8 (C^7), 23.3 (C^2, C^4), 41.9 (C^1, C^5), 60.5 (C^6), 126.4 (2C, C_{arom}), 126.5 (C_{arom}), 128.2 (2C, C_{arom}), 147.4 (1C, C_{arom}). Found, %: C 83.43; H 9.13; N 7.44. $C_{13}H_{17}N$. Calculated, %: C 83.37; H 9.15; N 7.48.

6-*exo*-Phenylbicyclo[3.1.1]heptan-6-*endo*-amine hydrochloride (10). Dry hydrogen chloride was passed over a period of 2 h through a solution of 1.06 g (5.66 mmol) of amine **9** in 40 mL of anhydrous diethyl ether. The precipitate was filtered off and recrystallized from ethanol–ethyl acetate. Yield 1.08 g (85%), mp 225–226°C. IR spectrum, ν, cm^{-1}: 3426 w, 2959 v.s, 2936 v.s, 2874 v.s, 1605 m, 1559 m, 1505 s, 1478 m, 1447 m, 764 m, 698 s. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.43 d.t (1H, 7-*anti*-H, *J* = 5.7, 9.9 Hz), 1.59 d (1H, 7-*syn*-H, *J* = 9.9 Hz), 1.64–1.86 m (2H, 3-H), 1.95–2.14 m (4H, 2-H, 4-H), 2.89 br.s (2H, 1-H, 5-H), 7.39 t (1H, H_{arom}, *J* = 6.2 Hz), 7.45 t (2H, H_{arom}, *J* = 7.0 Hz), 7.73 d (2H, H_{arom}, *J* = 7.1 Hz), 8.44 br.s (3H, NH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.6 (C^3), 22.8 (C^7), 23.2 (C^2, C^4), 39.9 (C^1, C^5), 60.4 (C^6), 127.5 (2C, C_{arom}), 128.2 (C_{arom}), 128.5 (2C, C_{arom}), 139.7 (C_{arom}). Found, %: C 69.87; H 8.19; N 6.32. $C_{13}H_{18}ClN$. Calculated, %: C 69.79; H 8.11; N 6.26.

***N*-(6-*exo*-Phenylbicyclo[3.1.1]heptan-6-*endo*-yl)-acetamide (11).** Hydrochloride **10**, 1.08 g (4.8 mmol), was dissolved in 25 mL of water, 1.6 mL of 6 M aqueous HCl was added (pH ~1.5), the solution was cooled on an ice bath, and 0.73 g (7.2 mmol) of acetic anhydride was added. The mixture was adjusted to pH ~5.5 by adding in portions crystalline sodium hydrogen carbonate, and the precipitate was filtered off, washed with water, and dried under reduced pressure. An additional amount of the product was isolated by extraction of the mother liquor with 3×10 mL of ethyl acetate, and the extract was dried over anhydrous Na_2SO_4 and evaporated. Overall yield 0.86 g (78%), mp 176–177°C (from EtOH). IR spectrum, ν, cm^{-1}: 3260 m, 3044 w, 2967 m, 2936 m, 2870 w, 1644 v.s (C=O), 1543 s, 1536 s, 1373 w, 1289 m, 772 m, 737 w, 698 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.43 d (1H, 7-*syn*-H, *J* = 9.6 Hz), 1.49–1.61 m (2H, 3-H, 7-*anti*-H), 1.65–1.74 m (1H, 3-H), 1.70 s (3H, CH_3), 1.74–1.86 m (2H, 2-*endo*-H, 4-*endo*-H), 2.00–2.08 m (2H, 2-*exo*-H, 4-*exo*-H), 2.79 br.s (2H, 1-H, 5-H), 7.17 t (1H, H_{arom}, *J* = 7.3 Hz), 7.29 t (2H, H_{arom}, *J* = 7.4 Hz), 7.51 d (2H, H_{arom}, *J* = 7.1 Hz), 8.23 br.s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.7 (C^3), 22.7 (CH_3), 24.0 (C^2, C^4), 24.4 (C^7), 39.8 (C^1, C^5), 60.2 (C^6), 125.9 (C_{arom}), 126.8 (2C, C_{arom}), 127.6 (2C, C_{arom}), 146.2 (C_{arom}), 167.9 (C=O). Found, %: C 78.58; H 8.32; N 6.07. $C_{15}H_{19}NO$. Calculated, %: C 78.56; H 8.35; N 6.11.

6-*endo*-(Acetamido)bicyclo[3.1.1]heptane-6-*exo*-carboxylic acid (12). Compound **11**, 0.86 g (3.8 mmol), was dissolved in 115 mL of a mixture of ethyl acetate, acetonitrile, and water at a volume ratio of 1:1:8, 23.6 g (110 mmol) of $NaIO_4$ and 0.05 g (0.19 mmol) of $RuCl_3 \cdot 3H_2O$ were added, and the mixture was stirred for 24 h at 20°C. The mixture was then treated with 100 mL of water and 170 mL of ethyl acetate and acidified with concentrated aqueous HCl to pH 3. The organic phase layer was separated, dried over Na_2SO_4, and filtered through a 1-cm layer of silica gel, and the filtrate was evaporated under reduced pressure. Yield 0.45 g (60%), mp 235–236°C (from EtOAc). IR spectrum, ν, cm^{-1}: 3357 m, 2955 m, 2867 w, 1709 v.s (C=O), 1620 v.s (C=O), 1536 s, 1308 m, 1254 m, 1235 m, 1196 m, 787 w, 694 w. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 d (1H, 7-*syn*-H, *J* = 9.5 Hz), 1.39–1.49 m and 1.57–1.63 m (1H each, 3-H), 1.65–1.77 m (2H, 2-*endo*-H, 4-*exo*-H), 1.78–1.91 m (2H, 2-*exo*-H, 4-*exo*-H), 1.84 s (3H, CH_3), 2.08 d.t (1H, 7-*anti*-H, *J* = 6.1, 9.5 Hz), 2.61 br.s (2H, 1-H, 5-H), 8.09 s (1H, NH), 12.12 br.s (1H,

COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.9 (C^3), 22.1 (CH_3), 23.8 (C^2, C^4), 24.8 (C^7), 38.2 (C^1, C^5), 61.5 (C^6), 169.5 (NHC=O), 174.8 (COOH). Found, %: C 60.83; H 7.61; N 7.17. $C_{10}H_{15}NO_3$. Calculated, %: C 60.90; H 7.67; N 7.10.

REFERENCES

1. Razin, V.V., Zadonskaya, N.Yu., and Shamurzaev, Kh.T., *Zh. Org. Khim*., 1991, vol. 27, p. 1253.
2. Vasin, V.A., Semenov, A.V., and Razin, V.V., *Russ. J. Org. Chem*., 2004, vol. 40, p. 1599.
3. Vasin, V.A., Semenov, A.V., and Razin, V.V., *Russ. Chem. Bull., Int. Ed*., 2005, vol. 54, p. 466.
4. Zolotarev, R.N., Yakovlev, M.E., and Razin, V.V., *Russ. J. Org. Chem*., 2006, vol. 42, p. 1636.
5. Razin, V.V., Makarychev, Yu.A., Zolotarev, R.N., Vasin, V.A., Hennig, L., and Baldamus, J., *Russ. J. Org. Chem*., 2007, vol. 43, p. 817.
6. Komarov, I.V., Grigorenko, A.O., Turov, V.A., and Khilya, V.P., *Russ. Chem. Rev*., 2004, vol. 73, p. 785.
7. Bell, E.A., Qureshi, M.Y., Pryce, R.J., Janzen, D.H., Lemke, P., and Clardy, J., *J. Am. Chem. Soc*., 1980, vol. 102, p. 1409.
8. Gaoni, Y., *Org. Prep. Proced. Int*., 1995, vol. 27, p. 185.
9. Austin, G.N., Baird, P.D., Chow, H.F., Fellows, L.E., Fleet, G.W.J., Nash, R.J., Peach, J.M., Pryce, R.J., and Stirton, C.H., *Tetrahedron*, 1987, vol. 43, p. 1857.
10. Smith-Palmer, T., *Chem. N. Z*., 1975, vol. 39, p. 116.
11. Boerwimkle, F. and Hassner, A., *Tetrahedron Lett*., 1968, vol. 9, p. 3921.
12. Silverstein, R.M., Webster, F.X., and Kiemle, D.J., *Spectrometric Identification of Organic Compounds*, Hoboken, NJ: Wiley, 2005, 7th ed.
13. Wiberg, K.B. and Hess, B.A., *J. Org. Chem*., 1966, vol. 31, p. 2250.
14. Razin, V.V., Vasin, V.A., and Blinkov, I.E., *Zh. Org. Khim*., 1993, vol. 29, p. 916.
15. Vasin, V.A., Kostryukov, S.G., and Razin, V.V., *Russ. J. Org. Chem*., 1996, vol. 32, p. 49.
16. Razin, V.V., *Sovremennye problemy organicheskoi khimii. Mezhvuzovskii sbornik* (Modern Problems of Organic Chemistry. Interinstitution Collection), St. Petersburg: Sankt-Peterb. Gos. Univ., 1996, p. 54.
17. Moutevelis-Minakakis, P., Sinanoglou, C., Loukas, V., and Kokotos, G., *Synthesis*, 2005, p. 933.
18. Hirst, E.L. and Macbeth, A.K., *J. Chem. Soc*., 1922, vol. 121, p. 2169.
19. Chaikovskii, V.K., Skorokhodov, V.I., and Filimonov, V.D., *Russ. J. Org. Chem*., 2001, vol. 37, p. 1503.