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SYNTHESIS OF NORBORNANE SERIES TETRA- AND HEXAHYDROPYRIMIDINES

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Condensation of exo-2-amino-exo-3-aminomethylnorbornane with acetone, methyl cyclopropyl ketone, cyclohexanone, urea, and formic, acetic, and benzoic acids gave norbornane series tetra- and hexahydropyrimidines. It was found that 4-cyclopropyl-4-methyl-exo-3,5-diazatricyclo[6.2.1.0^{2,7}]undecane and 4-methyl-exo-3,5-diazatricyclo[6.2.1.0^{2,7}]undec-3-ene show analgesic activity.

Keywords: *exo*-2-amino-*exo*-3-aminomethylnorbornane, hexahydropyrimidines, *exo*-3,5-diazatricyclo-[6.2.1.0^{2,7}]undecanes, *exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undec-3-enes, carboxylic acids, ketones, urea, tetrahydropyrimidines, analgesic activity, condensation.

Pyrimidine derivatives attract the attention of synthetic chemists and of pharmacologists thanks to their unique properties of low toxicity and broad spectrum of physiological activity (analgesic, immunotropic, anti-inflammatory, antiviral, hepatoprotective, antioxidant, and antiradical) [1-7]. Many compounds used in medical practice are close analogs of pyrimidine nucleosides. Work on the synthesis of novel compounds amongst this class is very actively pursued [8-11]. It is known that pyrrolidinones containing a condensed norbornane fragment have antiarrhythmic properties and norbornane series amines and their acyl derivatives show neurotropic, anti-inflammatory, antiglycemic, and other types of activity [12-15]. There is, however, no information in the literature regarding the synthesis and properties of norbornanes containing condensed *exo*-orientated tetra- and hexahydropyrimidine structures at the 2, 3 position of the norbornane ring.

This report concerns the targeted synthesis of 3,5-diazatricyclo[6.2.1.0^{2,7}]undecanes containing tetra- and hexahydropyrimidine fragments in an *exo* position to a norbornane structure through study of the condensation reaction of *exo*-2-amino-*exo*-3-aminomethylnorbornane (**1**) with formaldehyde, acetaldehyde, benzaldehyde, salicylaldehyde, acetone, methylcyclopropyl ketone, cyclohexanone, and urea and with formic, acetic, and benzoic acids.

The reaction of diamine **1** with an equimolar amount of formaldehyde, acetaldehyde, benzaldehyde, or salicylaldehyde occurs at room temperature with heating of the reaction mass and gives a hard to separate mixture of condensation products.

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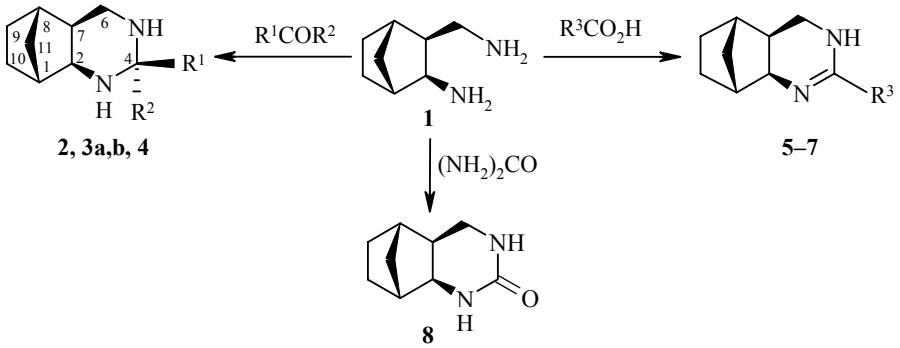
By contrast to the aldehydes, the ketones selectively react with *exo*-2-amino-*exo*-3-aminomethylnorbornane **1** in refluxing methanol to give hexahydropyrimidines. Hence reaction of diamine **1** with acetone (MeOH, 65ºC, 5 h) gives 4,4-dimethyl-*exo*-3,5-diazatricyclo[6.2.1.$0^{2,7}$]undecane (**2**) in 99% yield. Under the conditions used by us imines were not found in the condensation products, even when a 9-fold molar excess of acetone was used. The reaction of diamine **1** with methyl cyclopropyl ketone gives a hard to separate mixture (95%) of the stereoisomeric (4*S*)- (**3a**) and (4*R*)-4-cyclopropyl-4-methyl-*exo*-3,5-diazatricyclo-[6.2.1.$0^{2,7}$]undecanes (**3b)** in the ratio 3:1. The isomers were characterized using ^{1}H NMR spectroscopy and their composition was determined by the ratio of the area of the signals for the methine C-2 protons in the ^{1}H NMR spectrum. The use of cyclohexanone in this reaction gave a 95% yield of the hexahydropyrimidine **4** which contained a spirocyclic fragment. It should be noted that the nitrogen heterocycles obtained **2-4** in $CDCl_3$ solution did not show a tautomeric equilibrium with a noncyclic form [16-18].



2, 3a,b, 4 **1** **5–7** **8**

2 $R^1 = R^2$ = Me; **3 a** R^1 = Me, R^2 = cyclopropyl, **b** R^1 = cyclopropyl, R^2 = Me;
4 $R^1 + R^2 = (CH_2)_5$; **5** R^3 = H; **6** R^3 = Me; **7** R^3 = Ph

In view of their low reactivity the condensation with carboxylic acids was carried out without solvent at higher temperatures. Hence diamine **1** reacts with formic acid at 100ºC and acetic acid at 118ºC to give *exo*-3,5-diazatricyclo[6.2.1.$0^{2,7}$]undec-3-ene (**5**) and 4-methyl-*exo*-3,5-diazatricyclo[6.2.1.$0^{2,7}$]undec-3-ene (**6**). It should also be noted that the condensation of benzoic acid with diamine **1** occurs with difficulty and the substituted tetrahydropyrimidine **7** was obtained in 81% yield when carrying it out at 160ºC.

Study of the reaction of diamine **1** with urea showed that product formation was not seen when refluxing in methanol. Only use of the higher boiling ethanol and an increase in reaction time to 10 h gave the hexahydropyrimidine **8** in 42% yield.

The structure of the synthesized compounds was confirmed from their ^{1}H and ^{13}C NMR spectra with the use of HH COSY and CH CORR homo- and heteronuclear 2D spectra. The ^{13}C NMR spectra of the hexahydropyrimidines **2-4** showed signals for the C-4 NCN quaternary atoms at 64.56-65.97 ppm. Due to their nonequivalence the signals for the C-6 methylene protons in compounds **5-7** appear as a double doublet with a geminal spin-spin coupling of ^2J = 13.4-14.0 Hz. The ^{1}H and ^{13}C NMR spectra of the tetrahydropyrimidines **5-7** show only one set of signals and this can be due either to a rapid prototropic tautomeric process on the NMR time scale [19] or to a fixed position of the proton at the N-5 atom. A second set of proton signals for the C-2 and C-6 atoms in CD_3OD was not seen even at -60ºC and this suggests that only one of the possible isomers is formed.

At a dose of 2 mg/kg compounds **3a,b** and **6** show marked analgesic activity decreasing the amount of writhes by 39.6 and 46.3% respectively relatively to the *ketanov* control at 23.1%.

Hence a synthetic route has been proposed for the preparation of norbornane series tetra- and hexahydropyrimidines which show interest as physiologically active compounds.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were taken on a Bruker AM-300 instrument (300 and 75 MHz respectively) using $CDCl_3$ (compounds **2-7**) or CD_3OD (compound **8**) with TMS as internal standard. IR spectra were taken on UR-20 and Specord M-80 instruments as a thin layer (compounds **2, 4-6**) or in vaseline oil (compounds **3a,b, 7, 8**). Mass spectra were recorded on a Thermo Finnigan MAT 95 XP high resolution spectrometer with ionization intensity 70 eV (ionization chamber temperature 250ºC, direct introduction temperature 50-270ºC, heating rate 10ºC/min). Melting points were determined on a Boetius microstage. Elemental analysis of the compounds was carried out on an HEKAtech GmbH Analysen (Technik Euro-EA) CHN analyzer. TLC was performed on Silufol and Alufol chromatographic plates from the Kavalier company.

exo-2-Amino-*exo*-3-aminomethylnorbornane **1** was prepared by a known method [20].

Analgesic activity of compounds 3a,b and 6 was studied on 24 white, nonpedigree mice of weight 20-22 g using the acetic acid writhing test which was carried out by a single intraperitoneal introduction of a 0.75% solution of acetic acid based on a calculated 0.1 ml per 10 g of body weight. The compound studied and the *ketanov* standard were introduced *via* the stomach in single doses of 2 mg/kg one hour before injection of the acid. For 15 minutes following the introduction of acetic acid the degree of writhes was determined (including contraction of stomach muscles alternating with their relaxation, stretching of the tail extremity, and back flexion). The analgesic effect was calculated from the decrease in the amount of writhes when compared with the control.

4,4-Dimethyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undecane (2). Acetone (0.23 g, 4 mmol) was added dropwise with stirring to a solution of compound **1** (0.5 g, 3.6 mmol) in methanol (30 ml) and refluxed with a reflux condenser for 5 h under an argon atmosphere. The reaction product was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure to give the undecane **2** (0.64 g, 99%) as a colorless liquid (bp 73ºC, 2 mm Hg, n_D^{20} 1.5433) which rapidly became light-brown in color on exposure to air. IR spectrum, ν, cm^{-1}: 1160-1216, 1376, 1464, 1664, 2952-2872, 3288. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (1H, d, $^2J_{11anti,11syn}$ = 10.4, H$_{anti}$-11); 0.99 (3H, s, CH_3); 0.99-1.05 (2H, m, H$_{endo}$-9,10); 1.05 (3H, s, CH_3); 1.22-1.31 (3H, m, H-7, H$_{exo}$-9,10); 1.46 (1H, d, $^2J_{11anti,11syn}$ = 10.4, H$_{syn}$-11); 1.68 (1H, br. s, H-8); 1.87 (1H, br. s, H-1); 2.04 (1H, dd, $^2J_{6trans,6cis}$ = 13.3, $^3J_{6trans,7}$ = 12.0, H$_{trans}$-6); 2.52 (1H, dd, $^2J_{6trans,6cis}$ = 13.3, $^3J_{6cis,7}$ = 6.6, H$_{cis}$-6); 2.67 (1H, d, $^3J_{2,7}$ = 6.9, H-2). ^{13}C NMR spectrum, δ, ppm: 26.45 (C-10); 27.69 (CH_3); 28.99 (C-9); 30.21 (CH_3); 32.63 (C-11); 38.82 (C-8); 39.86 (C-6); 41.71 (C-1); 45.90 (C-7); 54.70 (C-2); 64.56 (C-4). Mass spectrum (EI), *m/z* (I_{rel}, %): 180 $[M]^+$ (100).

4-Cyclopropyl-4-methyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undecanes 3a,b. Methyl cyclopropyl ketone (0.6 g, 7 mmol) was added dropwise with stirring to a solution of compound **1** (1 g, 7 mmol) in methanol (30 ml) and refluxed using a reflux condenser for 5 h under an argon atmosphere. The reaction product was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give white crystals (1.39 g, 95%) of a mixture of the hexahydropyrimidines **3a** and **3b** in the ratio 3:1. Mp 35-36ºC (methanol), R_f 0.25 (Silufol, MeOH–H_2O–NH_3, 5:1:1). IR spectrum, ν, cm^{-1}: 1462, 2866-2998, 3280 (NH). The isomers were characterized in the mixture by NMR spectroscopy and their amounts were determined by the ratio of signal areas for the C-2 methine protons in the ^{1}H NMR spectrum. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.20-0.24 (4H, m, H cyclopropane ring **3a** and **3b**); 0.74-0.84 (1H, m, H cyclopropane ring **3a** and **3b**); 0.92-1.15 (6H, m, CH_3, H$_{anti}$-11, H$_{endo}$-9,10 **3a** and **3b**); 1.32-1.54 (3H, m, H-7, H$_{exo}$-9,10 **3a** and **3b**); 1.59 (1H, d, $^2J_{11anti,11syn}$ = 10.4, H$_{syn}$-11 **3a** and **3b**); 1.77-2.23 (3H, m, H-1, H$_{trans}$-6, H-8 **3a** and **3b**); 2.51-2.70 (1H, m, H$_{cis}$-6 **3a** and **3b**); 2.85 (1H, d, $^3J_{2,7}$ = 6.9, H-2 **3a**); 2.93 (1H, d, $^3J_{2,7}$ = 7.7, H-2 **3b**).

(4*S*)-4-Cyclopropyl-4-methyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undecane (3a). ^{13}C NMR spectrum, δ, ppm: -0.35 (CH_2 cyclopropane ring); 0.81 (4-C<u>H</u>C<u>H</u>$_2$); 21.26 (CH_3); 26.48 (CH cyclopropane ring); 26.92 (C-10); 28.91 (C-9); 32.72 (C-11); 39.08 (C-8); 41.24 (C-6); 41.82 (C-1); 45.84 (C-7); 54.77 (C-2); 65.22 (C-4).

(4*R*)-4-Cyclopropyl-4-methyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undecane (3b). ^{13}C NMR spectrum, δ, ppm: 5.98 (CH_2 cyclopropane ring); 10.43 (CH_2 cyclopropane ring); 20.18 (CH_3); 26.66 (C-10); 27.40 (CH cyclopropane ring); 29.00 (C-9); 32.18 (C-11); 39.63 (C-8); 39.92 (C-6); 42.11 (C-1); 45.58 (C-7); 55.43 (C-2); 65.97 (C-4). Found, %: C 75.64; H 10.78; N 13.60. $C_{13}H_{22}N_2$. Calculated, %: C 75.68; H 10.75; N 13.58.

Spiro[*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undecane-4,1'-cyclohexane] (4). Cyclohexanone (0.69 g, 7 mmol) was added dropwise with stirring to a solution of diamine **1** (1 g, 7 mmol) in methanol (30 ml) and refluxed using a reflux condenser for 5 h under an argon atmosphere. The reaction product was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give compound **4** as a light-yellow oil (1.49 g, 95%) with R_f 0.72 (Silufol, benzene–$CHCl_3$–MeOH–drop of aqueous ammonia solution, 2:2:1). IR spectrum, ν, cm^{-1}: 736, 1450, 2872-2938, 3292. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.71 (2H, br. s, NH); 0.99 (1H, d, $^2J_{11anti,11syn}$ = 10.3, H_{anti}-11); 1.06-1.11 (2H, m, H_{endo}-9,10); 1.28-1.49 (13H, m, –$(CH_2)_5$–, H-7, H_{exo}-9,10); 1.57 (1H, d, $^2J_{11anti,11syn}$ = 10.3, H_{syn}-11); 1.76 (1H, br. s, H-8); 1.95 (1H, br. s, H-1); 2.19 (1H, dd, $^2J_{6trans,6cis}$ = 13.0; $^3J_{6trans,7}$ = 12.3, H_{trans}-6); 2.60 (1H, dd, $^2J_{6trans,6cis}$ = 13.0, $^3J_{6cis,7}$ = 6.5, H_{cis}-6); 2.76 (1H, d, $^3J_{2,7}$ = 6.3, H-2). ^{13}C NMR spectrum, δ, ppm: 21.79 (C-4'); 25.20 (C-3',5'); 26.30 (C-10); 28.72 (C-9); 32.36 (C-11); 36.83, 38.60 (C-6',2'); 38.68 (C-8); 39.55 (C-6); 41.57 (C-1); 46.13 (C-7); 53.83 (C-2); 65.00 (C-4). Found, %: C 75.99; H 10.78; N 13.28. $C_{14}H_{24}N_2$. Calculated, %: C 76.31; H 10.98; N 13.01.

***exo*-3,5-Diazatricyclo[6.2.1.0^{2,7}]undec-3-ene (5)**. Formic acid (0.5 g, 11 mmol) was added dropwise with stirring to a solution of compound **1** (1 g, 7 mmol) and heated at 100ºC for 2 h under an argon atmosphere. The reaction product was treated with a 10% aqueous NaOH solution to pH ~8, extracted with diethyl ether, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give compound **5** as a yellowish oil (0.95 g, 86%) with R_f 0.53 (Alufol, MeOH–AcOEt–NH_3, 4:4:1). IR spectrum, ν, cm^{-1}: 1540, 1654, 2872-2944, 3196 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (1H, d, $^2J_{11anti,11syn}$ = 10.3, H_{anti}-11); 1.11-1.20 (2H, m, H_{endo}-9,10); 1.48-1.54 (2H, m, H_{exo}-9,10); 1.70 (1H, d, $^2J_{11anti,11syn}$ = 10.3, H_{syn}-11); 1.88-1.96 (2H, m, H-7,8); 2.10 (1H, br. s, H-1); 2.83 (1H, dd, $^2J_{6trans,6cis}$ = 14.0, $^3J_{6trans,7}$ = 6.1, H_{trans}-6); 3.10 (1H, d, $^3J_{2,7}$ = 7.9, H-2); 3.38 (1H, dd, $^2J_{6trans,6cis}$ = 14.0, $^3J_{6cis,7}$ = 7.8, H_{cis}-6); 7.28 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 26.16 (C-10); 29.20 (C-9); 33.06 (C-11), 39.19 (C-7); 42.11 (C-8); 43.64 (C-6); 44.59 (C-1); 55.86 (C-2); 149.98 (C-4). Found, %: C 71.94; H 9.68; N 18.38. $C_9H_{14}N_2$. Calculated, %: C 71.96; H 9.39; N 18.65.

4-Methyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undec-3-ene (6). Acetic acid (7.03 g, 122 mmol) was added dropwise with stirring to a solution of compound **1** (1 g, 7 mmol) and refluxed for 4 h under an argon atmosphere. The reaction product was treated with a 10% aqueous NaOH solution to pH ~8, extracted with diethyl ether, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give compound **6** (1 g, 85%) as a light-yellow oil with R_f 0.66 (Alufol, MeOH–H_2O–NH_3, 50:1:1). IR spectrum, ν, cm^{-1}: 1540 (C–N), 1654 (C=N), 2872-2908, 3160 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (1H, d, $^2J_{11anti,11syn}$ = 10.1, H_{anti}-11); 1.16-1.23 (2H, m, H_{endo}-9,10); 1.46-1.52 (2H, m, H_{exo}-9,10); 1.66 (1H, d, $^2J_{11anti,11syn}$ = 10.1, H_{syn}-11); 1.78-1.83 (1H, m, H-7); 1.86 (3H, s, CH_3); 1.95 (1H, br. s, H-8); 2.08 (1H, br. s, H-1); 2.79 (1H, dd, $^2J_{6trans,6cis}$ = 13.5, $^3J_{6trans,7}$ = 7.7, H_{trans}-6); 3.09 (1H, d, $^3J_{2,7}$ = 8.0, H-2); 3.39 (1H, dd, $^2J_{6trans,6cis}$ = 13.5, $^3J_{6cis,7}$ = 7.7, H_{cis}-6); 3.78 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 18.52 (CH_3); 25.53 (C-10); 28.74 (C-9); 32.72 (C-11); 39.42 (C-7); 41.65 (C-8); 42.50 (C-6); 43.84 (C-1); 55.89 (C-2); 158.81 (C-4). Found, %: C 73.24; H 9.78; N 16.88. $C_{10}H_{16}N_2$. Calculated, %: C 73.13; H 9.82; N 17.06.

4-Phenyl-*exo*-3,5-diazatricyclo[6.2.1.0^{2,7}]undec-3-ene (7). Benzoic acid (0.87 g, 7 mmol) was added dropwise with stirring to a solution of compound **1** (1 g, 7 mmol) and heated at 160ºC for 2 h under an argon atmosphere. The reaction product was treated with a 10% aqueous NaOH solution to pH ~8, extracted with diethyl ether, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure to give compound **7** (1.3 g, 81%) as a light-yellow powder with mp 69-70ºC (petroleum ether–benzene, 10:3) and R_f 0.65 (Alufol, MeOH–H_2O–NH_3, 50:1:1). IR spectrum, ν, cm^{-1}: 1462, 1642, 2854-2920, 3292 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (1H, d, $^2J_{11anti,11syn}$ = 10.4, H_{anti}-11); 1.22-1.27 (2H, m, H_{endo}-9,10); 1.53-1.59 (2H, m, H_{exo}-9,10); 1.81 (1H, d, $^2J_{11anti,11syn}$ = 10.4, H_{syn}-11); 1.99 (1H, ddd, $^3J_{6trans,7}$ = 7.1, $^3J_{6cis,7}$ = 7.2, $^3J_{2,7}$ = 8.0,

H-7); 2.06 (1H, br. s, H-8); 2.24 (1H, br. s, H-1); 3.08 (1H, dd, $^3J_{6trans,7}$ = 7.1, $^2J_{6trans,6cis}$ = 13.4, H_{trans}-6); 3.32 (1H, d, $^3J_{2,7}$ = 8.0; H-2); 3.65 (1H, dd, $^2J_{6trans,6cis}$ = 13.4, $^3J_{6cis,7}$ = 7.2, H_{cis}-6); 7.35-7.41 (4H, m, H_{Ar}); 7.65-7.68 (1H, m, H_{Ar}). ^{13}C NMR spectrum, δ, ppm: 26.31 (C-10); 29.40 (C-9); 33.27 (C-11); 41.73 (C-7); 42.40 (C-8); 45.11 (C-1); 46.34 (C-6); 58.05 (C-2); 125.88 (C_{Ar}); 128.35 (C_{Ar}); 129.74 (C_{Ar}); 136.99 (C_{Ar}); 157.75 (C-4). Found, %: C 79.21; H 8.38; N 12.61. $C_{15}H_{18}N_2$. Calculated, %: 79.61; H 8.02; N 12.38.

***exo*-3,5-Diazatricyclo[6.2.1.0^{2,7}]undecan-4-one (8)**. Urea (0.9 g, 15 mmol) was added to a solution of compound **1** (1.4 g, 10 mmol) in ethanol (15 ml) and refluxed for 10 h. The solvent was removed under reduced pressure. Recrystallization gave compound **8** (0.69 g, 42%) as white crystals with mp 108-109ºC (benzene-2-propanol–petroleum ether, 10:1:5). IR spectrum, ν, cm^{-1}: 1462 (C–N), 1600 (C=O), 2854-2920, 3340-3430 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (1H, d, $^2J_{11anti,11syn}$ = 10.3, H_{anti}-11); 1.13-1.17 (2H, m, H_{endo}-9,10); 1.51-1.53 (2H, m, H_{exo}-9,10); 1.62-1.77 (2H, m, H_{syn}-11, H-7); 2.02 (1H, br. s, H-8); 2.05 (1H, br. s, H-1); 2.92 (1H, d, $^3J_{2,7}$ = 6.9, H-2); 2.95-3.05 (1H, m, H_{trans}-6); 3.17 (1H, dd, $^3J_{6cis,7}$ = 6.7, $^3J_{6cis,6trans}$ = 13.8, H_{cis}-6). ^{13}C NMR spectrum, δ, ppm: 27.76 (C-10); 30.33 (C-9); 33.05 (C-11); 40.98 (C-7); 42.41 (C-6); 44.55 (C-8); 46.34 (C-1); 58.22 (C-2); 162.19 (C-4). Found, %: C 65.24; H 8.78; N 16.48. $C_9H_{14}N_2O$. Calculated, %: C 65.03; H 8.49; N 16.85.

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