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CATALYTIC HYDROGENATION OF METHYL 3,4-DIAZATRICYCLO-[5.2.1.0^{2,6}]DEC-4-ENE-5-CARBOXYLATE

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The hydrogenation at Raney nickel of the pyrazoline ring in methyl exo-3,4-diazatricyclo-[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate takes place quantitatively with the preferential formation of the trans isomer of 5-amino-exo-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one. The 3-methoxycarbonylmethyl-, 3-acetyl-, and 3-nitroso-substituted esters are not hydrogenated under these conditions.

Keywords: 5-amino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decane, 5-amino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one, methyl 3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate, Raney nickel, catalytic hydrogenation.

The hydrogenation of pyrazolines is a convenient method for the production of 1,3-propylenediamines [1, 2], which are converted in the presence of an ester group or lactone ring into pyrrolidin-2-ones [3-7]. The latter find use in the synthesis of derivatives of pyrrolidine and analogs of γ-aminobutyric acid – the main neurotransmitter in the central nervous system of mammals [8, 9]. The presence of the pyrrolidine ring in the molecule of many natural and synthetic compounds gives rise to a wide range of biological activity [6-16].

Recently we showed that 3-aminopyrrolidin-2-one, coupled with a norbornane fragment, exhibits antiarrhythmic, analgesic, nootropic, and anti-inflammatory activity [7].

In a continuation of our investigations into the chemistry of pyrazolines [2, 5-7, 17, 18] in the present work we studied the reduction of methyl *exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate (**1**) and its 3-methoxycarbonylmethyl-, 3-acetyl-, and 3-nitroso-substituted analogs **2**-**4** respectively.

It should be noted that at the beginning of our researches there were no data in the literature on the synthesis of tricyclic γ-lactams based on derivatives of norbornene.

As a result of a search for the optimum reaction conditions for the case of the ester **1** it was established that the most effective of the methods that have widespread application for the reduction of C=N and N=N bonds (H_2–Raney nickel, H_2–Pdc, H_2–PtO_2, H_2–Rh/Al_2O_3, Na–*n*-BuOH, $RhCl(PPh_3)_3$–*i*-PrOH–KOH, $LiAlH_4$, $NaBH_4$, $NaBH_4$–Cu(acac)$_2$) is hydrogenation with hydrogen in the presence of Raney nickel in

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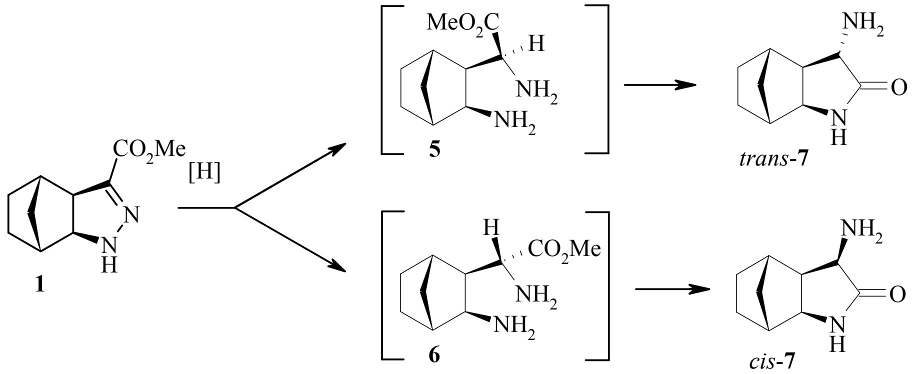
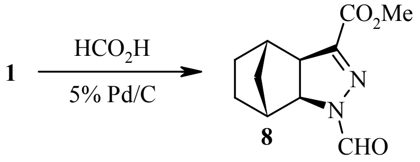
methanol (100°C, H_2 pressure 7.1 MPa, 5 h), leading probably through the intermediate diamines **5** and **6** to a mixture of the *trans* and *cis* isomers of 5-amino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decan-4-one (**7**) with an overall yield of 98%. The composition and structure of the obtained isomers of the lactam **7** are confirmed by the data from the ^{1}H and ^{13}C NMR spectra.



Under analogous conditions 5% Pd/C and Rh/Al_2O_3 did not exhibit catalytic activity, and with other reagents reduction either did not occur or a difficultly separated mixture of products was formed. In the presence of 5% Pd/C in boiling formic acid for 2 h formylation occurred at the N-3 atom, and N-formyl-pyrazoline **8** was formed with a yield of 98%.



In the ^{1}H NMR spectrum of compound **8** the signal for the proton of the CHO group is at 8.84 ppm while the signal of the H-2 proton is downfield from the signal for the analogous proton of the initial compound **1** ($\Delta\delta_H$ = 0.35 ppm). The presence of the N–CHO fragment is also confirmed by the presence of a band characteristic of the C=O group of amides in the IR spectrum.

The results obtained from the experiments on the hydrogenation of the ester **1** at Raney nickel at various temperatures (Table 1) and the data from quantum-chemical calculations show that the process takes place with cleavage of the N–N bond of the pyrazoline ring through the intermediate diastereomeric diamines **5** and **6** and their subsequent cyclocondensation with the formation of a mixture of the *trans* and *cis* isomers of the required product **7**. The predominance of the *trans* isomer in the mixtures (according to the ^{1}H NMR spectra of the mixtures) indicates that the addition of hydrogen to the C=N bond takes place preferentially from the less sterically hindered side – in the *trans* position to the norbornane fragment. The configuration of the carbon atom in the amino acid substituent of the intermediate diamines **5** and **6** predetermines the formation of the *trans* and *cis* isomers of **7** respectively.

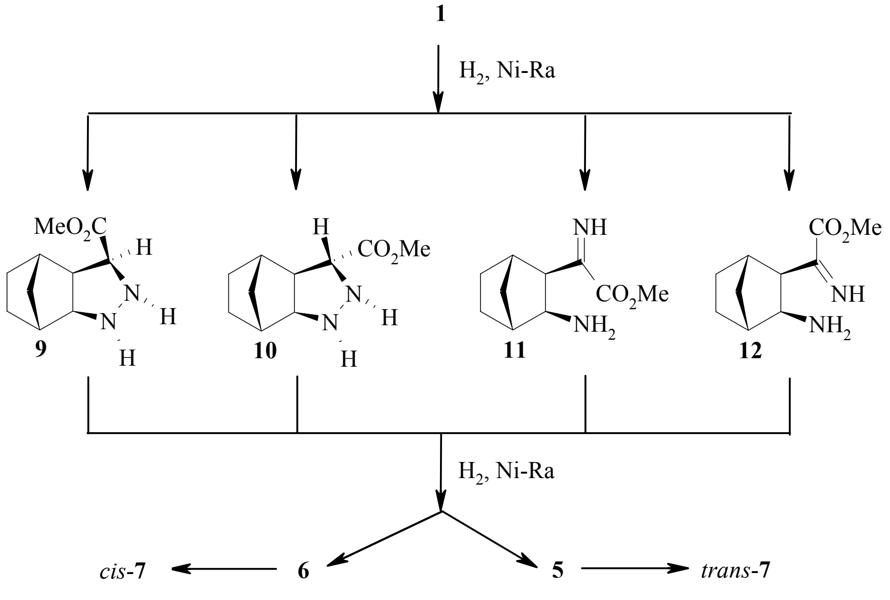
The total yield of the reaction products does not depend on the temperature, which does affect their ratio; the relative content of the *trans* isomer of **7** increases with decrease of temperature (expts. 1-3). It should be noted that we were unable to change the ratio of the isomers substantially during the hydrogenation of the pyrazoline **1** in the presence of a nickel catalyst modified with D(+)-tartaric acid according to the method described in [19] (expt. 4). Reduction of the pyrazoline **1** in methanol saturated with ammonia (expt. 5) was also tried in order to synthesize the supposed intermediate diamines **5** and **6**, but they were not found in the reaction mixture. Low selectivity was observed when PtO_2 was used as hydrogenation catalyst (expt. 6).

TABLE 1. The Effect of the Hydrogenation Conditions of the Ester **1** on the Yield and Ratio of the *trans*/*cis* Isomers of Product **7**

Experiment	Catalyst	Reaction, temperature, °C	Yield of **7**, %	*trans*-**7**:*cis*-**7**
1	Raney-Ni	20	93	2.8:1
2	Raney-Ni	100	98	2.6:1
3	Raney-Ni	150	98	2.4:1
4	Raney-Ni and D(+)–tartaric acid	100	98	2.2:1
5	Raney-Ni (NH_3–MeOH)	100	98	2:1
6	PtO_2	100	80	1.3:1

The quantitative composition of the obtained mixtures of isomers was determined by means of the ^1H NMR spectra from the ratio of the total area of the signals for the methine protons H-6 and H-7 of the main isomer to the area of the analogous signals of the second isomer. A characteristic feature of the spectra of the mixtures is the presence of a double set of signals for the H-5, H-6, and H-7 protons, where the stronger signals are upfield (at 3.04, 1.99, and 2.20 ppm respectively) from the weaker signals (at 3.53, 2.28, and 2.37 respectively). The spin-spin coupling constant of the main isomer is $^3J_{5,6}$ = 3.8 Hz, and that of the second isomer is $^3J_{5,6}$ = 10.5 ppm. The presented data confirm that the main isomer in the mixture is the *trans* isomer. The lactam ring in compound **7** is in the *exo* configuration to the norbornane fragment ($^3J_{1,2} = {}^3J_{6,7}$ = 0 Hz). The carbonyl groups in the *trans* and *cis* stereoisomers of **7** appear in the ^{13}C NMR spectrum at δ 180.06 and 179.82 ppm respectively. In the IR spectra there are absorption bands at 1688 and 3336 cm^{-1} characteristic of the lactam C=O and NH_2 groups respectively.

The Gaussian 98 software was used [20] (Table 2) to analyze the most probable routes to the formation of the *trans* and *cis* isomers of the product **7** and also for quantum-chemical calculation of the standard enthalpies and relative energies of the most stable conformers of compounds **1**, **5**-**7**, and **9**-**12**. Quantum-chemical modelling of the chain in the synthesis of the *cis* and *trans* isomers of compound **7** shows that the reduction of the ester **1** can take place in two directions: with retention of the pyrazoline ring or with cleavage of the N–N bond. Comparison of the standard enthalpies of the isomeric intermediates **9**-**12** showed that cleavage of the ring is energetically more favorable (a gain of 62.4 kJ/mol for compound **11** in the gas phase compared with the cyclic isomer **10**).



The fact that the CO_2Me group lies in the plane of the pyrazoline ring of compound **1** indicates that the formation of conformers **11** and **12** differing in the positioning of the C=NH group is possible during the hydrogenation. The first is thermodynamically more stable than the second, $\Delta H^\circ = 17.9$ kJ/mol. Calculation of the populations of the conformers at the hydrogenation temperatures of the ester **1** (20-150°C) shows that the conformer **11**, the fraction of which amounts to more than 99%, predominates. Allowance for the effect of the solvent (methanol) by the Cosmo polarization continuum method [21] hardly changes the relative energies of the conformers **11** and **12** at all.

During further reduction of the imines **11** and **12** the stereoisomeric diamines **5** and **6** are formed. To determine the thermodynamic probability of the formation of these compounds we calculated the structures produced directly after addition of the hydrogen atoms to the carbon and nitrogen atoms of the imine group. The structures **5** and **6** were obtained by changing the hybridization of the C and N atoms of the initial imines **11** and **12** from sp^2 to sp^3 and subsequent optimization of all the geometric parameters. We note that the nature of the chiral center of compound **5** or **6** will inevitably lead to the *trans*-**7** or *cis*-**7** irrespective of the subsequent conformational transformations of the diamine. The results of the calculations are presented in Table 2. The stereoisomer **5** is more stable than **6**; in the gas phase the difference in standard enthalpies amounts 3.1, and in methanol 3.3 kJ/mol.

The products from intramolecular cyclization of the diamines **5** and **6** are the compounds *trans*- and *cis*-**7**, in which the arrangement of the substituents at the asymmetric carbon atom is retained: the *trans* isomer **7** corresponds to the diamine **5**, and the *cis* isomer **7** to the diamine **6**. Consequently, the ratio of the experimentally obtained *trans* and *cis* isomers of **7** depends on the relative stability of the initial diamines. The ratio of the populations of the enantiomers **5** and **6** amounts to 3.88:1 at 20°C, 2.90:1 at 100°C, and 2.56:1 at 150°C respectively, which agrees satisfactorily with the experimentally obtained ratio of the *trans* and *cis* isomers of the product **7** in the reaction mixture.

Quantum-chemical calculations show that the *trans* and *cis* isomers of **7** have approximately the same standard enthalpy in the gas phase, while the relative stability of the *trans* isomer increases in the solution (Table 2).

We obtained different results during attempts at the hydrogenation of 3-substituted analogs of the ester **1** – compounds **2-4**. It is known that the hydrogenolysis of N-alkyl-substituted pyrazolines in the presence of a nickel catalyst takes place with the formation of monoalkylated 1,3-propylenediamines at 100-120°C and hydrogen pressure 100-140 atm [22].

TABLE 2. The Results of Calculations of the Standard Enthalpies of the Most Stable Conformers of Compounds **1**, **5-7**, and **9-12** in the B3LYP/6-31G(d,p) Approximation

Compound	H°, Hartree	ΔH°, kJ/mol	ΔH° Solv, kJ/mol
1	-649.183348	0	0
9	-650.354128	69.2	—
10	-650.356714	62.4	42.0 *
11	-650.380479	0	0
12	-650.373661	17.9	17.5 *
5	-651.575752	0	0
6	-651.574571	3.1	3.3 *
trans-**7**	-535.906416	0	0
cis-**7**	-535.905596	2.2	6.2 *

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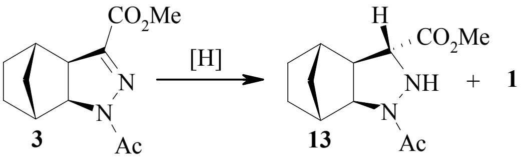
*Solvent, methanol.

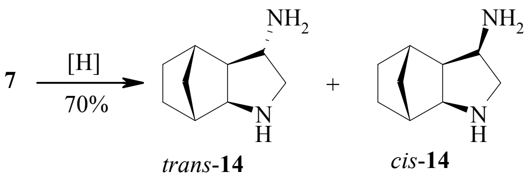
The hydrogenation of the 3-methoxycarbonylmethyl-substituted ester **2** does not occur under our selected conditions (Raney nickel, 150°C, 8.31 MPa, 5 h); the initial compound **2** was isolated from the reaction mixture.

N-Nitrosoamines are converted by catalytic hydrogenation into the corresponding hydrazines [23]. However, our attempts to convert the 3-nitroso ester **4** into the corresponding hydrazine in the presence of Raney nickel or 5% Pd/C (H_2 pressure 6.08 MPa, 80°C, 5 h) did not lead to the desired result. Hydrogenolysis of the N–NO bond, leading to the ester **1**, occurred during the reaction.

In the case of the N-acetylpyrazoline **3** both reductive cleavage of the Ac–N bond and reduction of the C=N bond of the pyrazoline ring occurred, leading to the ester **1** (yield 34%) and the 3-acetyl-substituted ester **13** (yield 5%), isolated from the reaction mixture by column chromatography, respectively. The structure of compound **13** is supported by the data from the ^{1}H and ^{13}C NMR and mass spectra. The H-5 proton appears in the ^{1}H NMR spectrum in the form of a doublet at 4.20 ppm, while its spin-spin coupling constant $^3J_{5,6} = 8.5$ Hz indicates the *trans* arrangement for the methoxycarbonyl group.



In order to synthesize 5-amino-*exo*-4-azatricyclo[5.2.1.0^{2,6}]decane (**14**), which according to calculated data [24] can exhibit antiviral and nootropic activity, the reductive deoxygenation of a mixture (2.6:1) of the *trans* and *cis* isomers of compound **7** with $LiAlH_4$ and $(i\text{-}Bu)_2AlH$ was undertaken. In boiling THF with an equimolar amount of $LiAlH_4$ for 8 h a mixture of the isomeric aminopyrrolidines **14** was obtained with a yield of 30%. With a fivefold molar excess of $LiAlH_4$ the yield amounted to 70%. A more effective reducing agent is $(i\text{-}Bu)_2AlH$, with a 7.5-fold excess of which at room temperature in ether the isomeric amines **14** were obtained with a total yield of 70%. The reduction of the carbonyl group is indicated by the absence of signals in the region of 170-180 ppm in the ^{13}C NMR spectrum and by the presence of signals for the C-4 atom of the *trans* and *cis* isomers of **14** at 56.00 and 57.06 ppm respectively. By means of the {C, H} correlation procedure it was possible to confirm unambiguously the structures of the isomers of **7**; the signals of the C-4 atoms correspond to the signals of two protons each in the form of a doublet of doublets at δ 2.35 and 3.09 ppm for the *trans* isomer and 2.92 and 2.58 ppm for the *cis* isomer of **14**.



Thus, it was shown that reduction of the nitrogen heterocycle in methyl *exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate with hydrogen in the presence of Raney nickel takes place quantitatively and leads to the preferential formation of the *trans*-substituted 3-aminopyrrolidin-2-one. The analogous reaction does not occur when there are substituents such as methoxycarbonylmethyl, acetyl, or nitroso at position 3 of the ester.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300 and 75 MHz respectively) in $CDCl_3$ with TMS as internal standard. The IR spectra were recorded on UR-20 and Specord M-80 instruments in thin layers or vaseline oil. The melting points were determined on a Boetius bench. Elemental analysis of the compounds was performed on the HEKAtech GmbH Analysen – Technik's Euro-EA – CHN analyzer. Thin-layer chromatography was performed on Kavalier Silufol plates, and preparative separation was realized on a column of Lancaster 70-230 mesh silica gel. The quantum-chemical calculations were performed with the GAUSSIAN 98 software (Version A.7) [20]. The structure of the compounds **1**, **5**-**7**, and **9**-**12** was optimized in the RB3LYP/6-31G(d,p) approximation. The search for all stable conformers was made with full optimization of all the geometric parameters, including the possibility of free rotation about the C–C and C–N bonds. The relative energies of the conformers were determined in the form of the difference in the standard enthalpies of the compared structures. The total energy of the compound was reduced to $H°_{298}$ by the addition of the energy of zero vibrations (ZPE), the work of expansion of one mol of the ideal gas (RT), and a thermal correction ($H°_{298}–H°_0$), calculated by the equations of statistical thermodynamics, to E_{total}. Allowance for nonspecific solvation (solvent methanol) was made in terms of the COSMO polarization continuum model [21]. The pyrazolines **1**-**4** were synthesized by the described methods [7, 18].

***trans*- and *cis*-5-Amino-*exo*-3-azatricyclo[5.2.1.9^{2,6}]decan-4-one (7).** A solution of the ester **1** (1.0 g, 5.15 mmol) in methanol (50 ml) and Raney nickel (0.30 g) were kept in a rotating 100 ml steel autoclave at 100°C and H_2 pressure 7.09 MPa for 5 h. The reaction mixture was then cooled and filtered. The filtrate was evaporated at reduced pressure, and 0.84 g (98%) of a mixture (2.6:1) of the *trans* and *cis* isomers of the product **7** was obtained in the form of white crystals; mp 97-98 °C (sublimation). IR spectrum, ν, cm^{-1}: 1460 (C–NH_2), 1584 (C–NH), 1688 (C=O), 2960-2856, 3336 (NH). Found, %: C 65.50; H 8.85; N 16.75. $C_9H_{14}N_2O$. Calculated, %: C 65.03; H 8.49; N 16.85.

***trans* Isomer 7**. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.10 (1H, m, H-9); 1.13 (1H, d, $^2J_{10anti,10syn}$ = 10.3, H_{anti}-10); 1.15 (1H, m, H_{endo}-8); 1.33 (1H, d, $^2J_{10anti,10syn}$ = 10.3, H_{syn}-10); 1.50 (2H, m, H_{exo}-8, H_{exo}-9); 1.66 (2H, br. s, NH_2); 1.99 (1H, dd, $^3J_{6,2}$ =7.2, $^3J_{6,5exo}$ = 3.8, H-6); 2.13 (1H, br. s, H-1); 2.20 (1H, br. s, H-7); 3.04 (1H, d, $^3J_{6,5exo}$ =3.8, H_{exo}-5); 3.45 (1H, d, $^3J_{6,2}$ =7.2, H-2); 7.45 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 25.15 (C-9); 27.78 (C-8); 31.72 (C-10); 40.84 (C-1); 40.96 (C-7); 50.63 (C-6); 57.33 (C-5); 59.84 (C-2); 180.06 (C=O).

***cis* Isomer 7**. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.10 (1H, m, H-9); 1.13 (1H, d, $^2J_{10anti,10syn}$ = 10.3, H_{anti}-10); 1.15 (1H, m, H_{endo}-8); 1.33 (1H, d, $^2J_{10anti,10syn}$ = 10.3, H_{syn}-10); 1.50 (2H, m, H_{exo}-8, H_{exo}-9); 1.66 (2H, br. s, NH_2); 2.13 (1H, br. s, H-1); 2.28 (1H, dd, $^3J_{6,2}$ = 7.0, $^3J_{6,5exo}$ = 10.5, H-6); 2.37 (1H, br. s, H-7); 3.49 (1H, d, $^3J_{6,2}$ = 7.0, H-2); 3.53 (1H, d, $^3J_{6,5endo}$ = 10.5, H_{endo}-5); 7.30 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 24.48 (C-9); 28.59 (C-8); 32.15 (C-10); 34.92 (C-7); 41.16 (C-1); 44.68 (C-6); 52.68 (C-5); 59.47 (C-2); 179.82 (C=O).

The ester **1** was hydrogenated by a similar procedure under the conditions indicated in Table 1 (expts. 1-6).

Methyl 3-Formyl-*exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]dec-4-ene-5-carboxylate (8). A solution of the pyrazoline **1** (0.8 g, 4.12 mmol) in HCOOH (15 ml) was boiled for 2 h in the presence of 0.08 g of 5% Pd/C with vigorous stirring. The cooled reaction mixture was filtered, and the filtrate was evaporated at reduced pressure. We obtained 0.98 g (98%) of compound **8** in the form of colorless crystals; mp 86-87°C (HCO_2H). IR spectrum, ν, cm^{-1}: 724, 952, 1114, 1318, 1372, 1456, 1690, 2848-2926. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.22 (2H, s, H-10); 1.27-1.37 (2H, m, H_{endo}-8 and H_{endo}-9); 1.56-1.60 (2H, m, H_{exo}-9 and H_{exo}-8); 2.63 (1H, br. s, H-7); 2.84 (1H, br. s, H-1); 3.31 (1H, d, $^3J_{6,2}$ = 8.8, H-6); 3.87 (3H, s, CH_3); 4.25 (1H, d, $^3J_{6,2}$ = 8.8, H-2); 8.84 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 24.32 (C-9); 27.35 (C-8); 32.55 (C-10); 40.12 (C-7); 40.95 (C-1); 52.73 (CH_3); 54.55 (C-6); 64.84 (C-2); 151.12 (C-5); 161.23 (CHO); 161.69 (CO_2). Found, %: C 59.31; H 6.40; N 12.60. $C_{11}H_{14}N_2O_3$. Calculated, %: C 59.45; H 6.35; N 12.61.

Methyl 3-Acetyl-*exo*-3,4-diazatricyclo[5.2.1.0^{2,6}]decane-*trans*-5-carboxylate (13). By the procedure for the hydrogenation of the ester **1** from of the ester **3** (0.6 g, 2.54 mmol) in the presence of Raney nickel, prepared from 0.3 g of nickel–aluminum alloy (50%), at 150°C and H_2 pressure 8.61 MPa for 5 h we obtained 0.5 g of an oily mixture of the esters **3** and **1** and the product **13** in ratios of 11.5:7.7:1 (determined from the ratio of the areas of the signals for the methine protons H-2 of compounds **1**, **3**, and **13** in the ^{1}H NMR spectrum of their mixture) respectively. From the mixture by column chromatography (6:1 hexane–*i*-PrOH) we isolated 0.03 g (5%) of compound **13** in the form of an oily product with R_f 0.15 (Silufol, 6:1 hexane–*i*-PrOH). IR spectrum, ν, cm^{-1}: 1100, 1265, 1350, 1372, 1456, 1650, 3100–3250. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11-1.16 (2H, m, H_{endo}-8 and H_{endo}-9); 1.24 (1H, d, $^2J_{10anti,10syn}$ = 10.7, H_{anti}-10); 1.37 (1H, d, $^2J_{10anti,10syn}$ = 10.7, H_{syn}-10); 1.46-1.52 (2H, m, H_{exo}-9 and H_{exo}-8); 1.98 (1H, br. s, H-7); 2.16 (3H, s, $COCH_3$); 2.56 (1H, br. s, H-1); 2.57 (1H, br. s, NH); 3.84 (3H, s, CO_2CH_3); 3.91 (1H, dd, $^3J_{6,2}$ = 12.5, $^3J_{6,5trans}$ = 8.5, H-6); 4.20 (1H, d, $^3J_{6,5trans}$ = 8.5, H_{trans}-5); 4.53 (1H, d, $^3J_{6,2}$ = 12.5, H-2). ^{13}C NMR spectrum, δ, ppm: 21.70 ($CO\underline{C}H_3$); 24.72 (C-9); 28.53 (C-8); 35.12 (C-10); 38.12 (C-7); 41.50 (C-1); 52.10 (OCH_3); 52.25 (C-6); 63.23 (C-5); 64.28 (C-2); 170.21 ($\underline{C}O_2CH_3$); 171.24 ($\underline{C}OCH_3$). Found, %: C 60.52; H 7.54; N 11.82. $C_{12}H_{18}N_2O_3$. Calculated, %: C 60.49; H 7.61; N 11.76.

5-Amino-*exo*-3-azatricyclo[5.2.1.0^{2,6}]decane (14). A. A mixture of compound **7** (0.50 g, 3 mmol) and $LiAlH_4$ (0.55 g, 14.49 mmol) in THF (30 ml) was boiled in an atmosphere of argon with stirring for 16 h. At room temperature 100 ml of a 30% aqueous solution of sodium hydroxide was added to the mixture, the mixture was extracted with 40 ml of ether, the extract was dried over Na_2SO_4, and the solvent was evaporated at reduced pressure. We obtained 0.32 g (70%) of a mixture of the *trans* and *cis* isomers of compound **14** in the form of an oily liquid. IR spectrum, ν, cm^{-1}: 1170, 1204, 1238, 1508, 1654, 1736, 1774, 1846, 2332, 2360. Found, %: C 70.97; H 10.57; N 18.37. $C_9H_{16}N_2$. Calculated, %: C 71.01; H 10.59; N 18.40.

B. To a suspension of compound **7** (0.50 g, 3 mmol) in ether (5 ml) in an atmosphere of argon at room temperature over 20 min we added $(i\text{-Bu})_2AlH$ (3.8 g) (a 73% solution in toluene) in ether (15 ml). The reaction mixture was stirred at room temperature for 3 h, and 100 ml of a 30% aqueous solution of sodium hydroxide was added. As a result of further treatment as described in method A we obtained 0.32 g (70%) of a mixture of the *trans* and *cis* isomers of compound **14** in the form of an oily liquid.

***trans* Isomer 14**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98–1.02 (1H, m, H_{endo}-9); 1.01 (1H, d, $^2J_{10anti,10syn}$ = 10.4, H_{anti}-10); 1.02-1.06 (1H, m, H_{endo}-8); 1.38 (1H, d, $^2J_{10anti,10syn}$ = 10.4, H_{syn}-10); 1.37–1.41 (1H, m, H_{exo}-9); 1.41-1.45 (1H, m, H_{exo}-8); 1.47 (1H, dd, $^3J_{6,2}$ = 7.7, $^3J_{5,6trans}$ = 6.5, H-6); 1.69 (2H, br. s, NH_2); 2.02 (1H, br. s, H-1); 2.19 (1H, br. s, H-7); 2.35 (1H, dd, $^2J_{4anti,4syn}$ = 9.6, $^3J_{4syn,5trans}$ = 9.2, H_{syn}-4); 2.88 (1H, ddd, $^3J_{5trans,6}$ = 6.5, $^3J_{4anti,5trans}$ = 6.3, $^3J_{4syn,5trans}$ = 9.2, H_{trans}-5); 3.09 (1H, dd, $^2J_{4anti,4syn}$ = 9.6, $^3J_{4anti,5trans}$ = 6.3, H_{anti}-4); 3.14 (1H, d, $^3J_{6,2}$ = 7.7, H-2). ^{13}C NMR spectrum, δ, ppm: 25.52 (C-9); 28.29 (C-8); 32.74 (C-10); 38.83 (C-7); 41.39 (C-1); 56.00 (C-4); 57.59 (C-6); 58.03 (C-5); 66.91 (C-2).

***cis* Isomer 14**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.98–1.02 (1H, m, H_{endo}-9); 1.02–1.06 (1H, m, H_{endo}-8); 1.07 (1H, d, $^2J_{10anti,10syn}$ = 10.4, H_{anti}-10); 1.37–1.41 (1H, m, H_{exo}-9); 1.41-1.45 (1H, m, H_{exo}-8); 1.44 (1H, d, $^2J_{10anti,10syn}$ = 10.4, H_{syn}-10); 1.69 (2H, br. s, NH_2); 1.89 (1H, dd, $^3J_{6,2}$ = 7.8, $^3J_{5cis,6}$ = 8.0, H-6); 2.17 (1H, br. s, H-1); 2.21 (1H, br. s, H-7); 2.58 (1H, dd, $^2J_{4anti,4syn}$ = 11.0, $^3J_{4anti,5cis}$ = 5.5, H_{anti}-4); 2.92 (1H, dd, $^2J_{4anti,4syn}$ = 11.0, $^3J_{4syn,5cis}$ = 6.4, H_{syn}-4); 3.11 (1H, d, $^3J_{6,2}$ = 7.8, H-2); 3.49 (1H, ddd, $^3J_{5cis,6}$ = 8.0, $^3J_{4anti,5cis}$ = 5.5, $^3J_{4syn,5cis}$ = 6.4, H_{cis}-5). ^{13}C NMR spectrum, δ, ppm: 25.68 (C-9); 29.07 (C-8); 35.12 (C-10); 35.35 (C-7); 42.10 (C-1); 51.36 (C-6); 54.74 (C-5); 57.06 (C-4); 68.23 (C-2).

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