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INTRAMOLECULAR CYCLIZATION OF *gem*-BENZYLAMINOALLYLCYCLOHEXANE UNDER THE ACTION OF SULFURIC ACID

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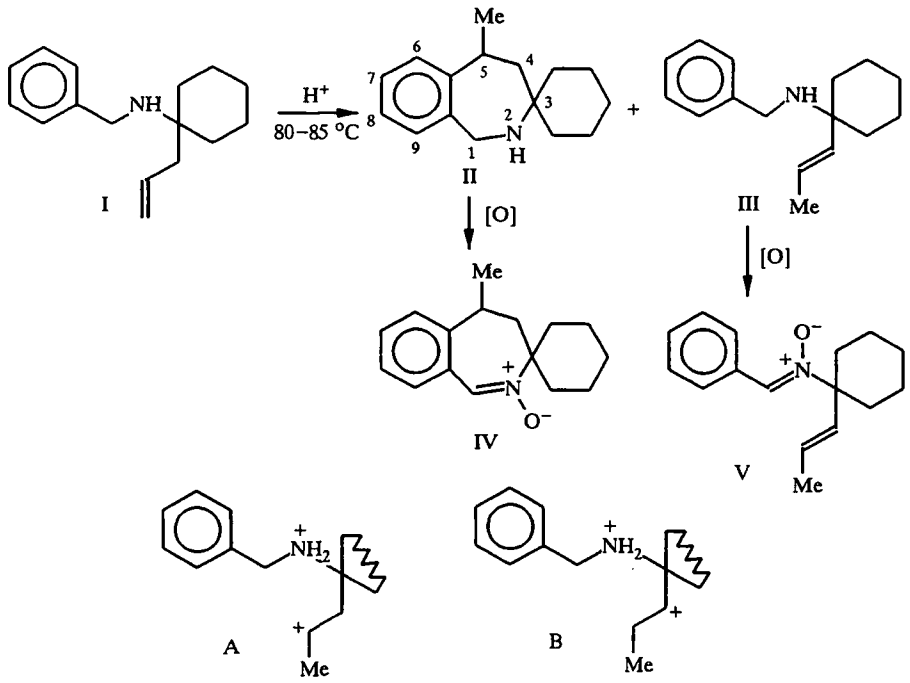
When treated with 85% sulfuric acid at 85°C, gem-benzylaminoallylcyclohexane is converted to spiro[tetrahydrobenz-2-azepine-3-cyclohexane], while at 20°C or in boiling chloroform 3,4,5,6-tetrahydro-3-benzyl-6-methylspiro[1,2,3-oxathiazine-2,2-dioxide-4-cyclohexane] is formed as the major product. The second compound is cleaved by alcohol solution of alkali to 1-benzyl-4-methylspiro[azetidine-2-cyclohexane].

By intramolecular cyclization of 1-allyl-1-benzylaminocyclohexane (I) in concentrated sulfuric acid at 70-80°C, 1,2,4,5-tetrahydro-5-methyl-3H-spiro[benz-2-azepine-3-cyclohexane] (II) has been obtained in 35% yield [1].



Beginning a systematic study of conversions of this novel heterocyclic system, with the objective of improving the yield we have studied the reaction of compound I with boron trifluoride etherate, aluminum chloride, phosphoric and polyphosphoric acids, and also with sulfuric acid of different concentrations. The reaction temperature ranged from 20°C ($BF_3 \times Et_2O$) to 110°C (polyphosphoric acids).

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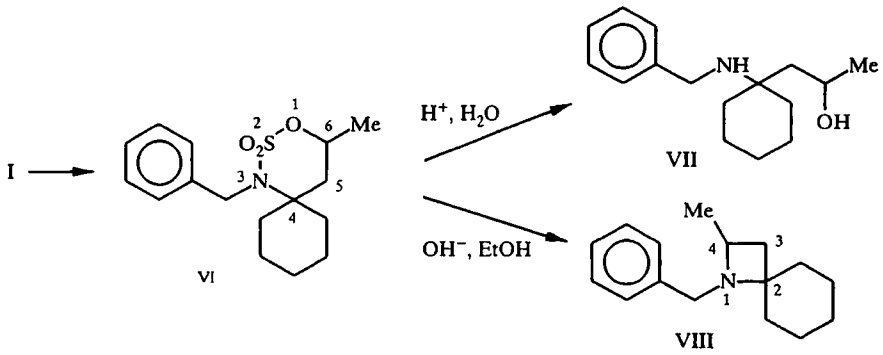
The most suitable reagent for intramolecular cyclization proved to be 85% sulfuric acid in 15-25-fold molar excess at temperature of 80-85°C. Under these conditions, the yield of compound II was 45-50%. The intramolecular cyclization of compound I did not occur in the presence of 70% sulfuric acid, boron trifluoride etherate, aluminum chloride, phosphoric acid. In polyphosphoric acid, the reaction was accompanied by significant tar formation and the yield of compound II was lower than in [1].

We have established that isomerization of the allyl radical to propenyl occurs in parallel with formation of 1-benzylamino-1-(*trans*-propen-1-yl)cyclohexane (III), the yield of which decreases as the reaction time increases: from 13% (40 min) to 3% (90 min). We established experimentally that compound III when treated with 85% sulfuric acid is converted to compound II, while the alternative cyclization product with participation of the $C_{(1)}$ atom of the propenyl radical, 1,2,3,4-tetrahydro-4-ethylspiro[isoquinoline-3-cyclohexane], was not found among the reaction products. Thus of the two possible cations A and B which may be formed upon protonation of the amino group and the double bond of compound III, the first is more stable, the fact being quite consistent with the data in [2,3].

Compounds II and III were oxidized by hydrogen peroxide in the presence of sodium tungstate to the corresponding nitrones IV and V.

Upon reaction of compound I with 4 to 5-fold molar excess of 92% sulfuric acid in boiling chloroform, for the first time we obtained 3,4,5,6-tetrahydro-3-benzyl-6-methylspiro[1,2,3-oxathiazine-2,2-dioxide-4-cyclohexane] (VI) as the major product in 40% yield: a white powder, difficultly soluble in most organic solvents, quite soluble in DMSO. The spiro compound II was isolated in this case in 20% yield. Upon reaction of compound I with 85% sulfuric acid at 20°C for 24 h, compound VI is formed in 55% yield; according to TLC data, the spiro compound II is not formed.



Probably the first stage of formation of compound VI is addition (in accordance with Markovnikov's rule) of sulfuric acid to the double bond of the allyl radical of compound I, with formation of intramolecular ammonium salt. The latter under the action of excess sulfuric acid loses a water molecule and is converted to oxathiazine VI. In its IR spectrum two strong absorption bands at 1215 and 1270 cm^{-1} due to vibrations of the SO_2 group are observed, and the absorption bands in the 1650 cm^{-1} region (C=C) and 2700-2250 cm^{-1} region (NH_2^+) are missing. In the mass spectrum, molecular ion peak with *m/z* 309 (1%) of low intensity occurs, corresponding to empirical formula of the compound. Fragmentation of the M^+ ion is characterized by elimination of sulfur(VI) oxide with formation of the fragmentary ion $[M-80]^+$ with *m/z* 229 (3%). The maximum intensity is observed for the ion peak with *m/z* 91, due to detachment of the benzyl radical from the nitrogen atom. Furthermore, in the mass spectrum ion peaks are observed due to cleavage of the cyclohexyl moiety in the ion $[M-SO_3]^+$ with *m/z* 214 (2%) and *m/z* 186 (12%).

In the PMR spectrum of compound VI, along with multiplets for protons of the benzyl and cyclohexane radicals, a signal from the 6-H proton at 4.59 ppm is detected. The presence of a large vicinal spin—spin coupling constant J_{56} = 8.4 Hz suggests a pseudoequatorial position for 6-H. Upfield in the spectrum at 1.30 ppm, a doublet signal from methyl protons is observed with constant $J_{Me,6}$ = 6.2 Hz. In the ^{13}C NMR spectrum in the 43-70 ppm region, three signals from carbon atoms bonded to electronegative atoms are detected: a doublet for the $C_{(6)}$ atom at 69.66 ppm ($^1J_{C,H}$ = 145.3 Hz), a singlet for the quaternary $C_{(4)}$ atom with chemical shift of 61.06 ppm, and a triplet signal for the CH_2N group at 43.91 ppm ($^1J_{C,H}$ = 145.3 Hz).

The structure of oxathiazine VI is confirmed by its hydrolysis in acidic medium to aminoalcohol VII. In the IR spectrum of aminoalcohol VII, broad absorption bands for the associated NH and OH groups are observed in the 3255 cm^{-1} region. In its mass spectrum, there is a low-intensity molecular ion peak with *m/z* 247 (3%), corresponding to empirical formula of VII. In the PMR spectrum, characteristic signals from the protons in the molecule are observed (see Experimental), which from the magnitudes of the chemical shifts and the spin-spin coupling constants correspond to structure VII.

When oxathiazine VI was treated with boiling alcoholic solution of base, we obtained 1-benzyl-4-methylspiro[azetidine-2-cyclohexane] (VIII) in 70% yield. In the mass spectrum of compound VIII, there is a molecular ion peak with *m/z* 229 (17%) corresponding to its empirical formula, and also fragmentary ions typical of azetidines with *m/z* 186 (55%) and 43 (2%) are observed due to the ring breaking in half. In the PMR spectrum of compound VIII, signals from 4-H protons at 3.25 ppm ($J_{4,Me}$ = 5.8, $J_{3A,4} = J_{3B,4}$ = 7.6 Hz) and 3A-H and $3B^+$-H protons at 2.02, 1.42 ppm ($J_{3A,3B}$ = 10.2 Hz, $J_{3A,4} = J_{3B,4}$ = 7.6 Hz) are present. In the ^{13}C NMR spectrum, signals from carbon atoms bonded to the electronegative nitrogen atom are located in the 53-64 ppm region: a singlet signal from the quaternary $C_{(2)}$ atom at 63.5 ppm, a doublet from the methine $C_{(4)}$ at 56.65 ppm ($^1J_{C,H}$ = 133.7 Hz), and a triplet from the methylene group at 54.41 ppm ($^1J_{C,H}$ = 129.3 Hz). These data also suggest the presence of azetidine cyclic system in compound VIII.

Thus we propose a novel preparative method for synthesis of N-substituted azetidines from readily available *gem*-allylamines.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in KBr pellets or in a film; the mass spectra were recorded on a Varian MAT-112 with direct injection of the sample into the ion source or on an HP MS 5988 chromatograph/mass spectrometer with ionizing potential 70 eV. The NMR spectra of 2% (^1H) and 10% (^{13}C) solutions of the synthesized compounds in $CDCl_3$ or DMSO-d_6 were recorded on Bruker WP-200 and WH-400 spectrometers with working frequencies 200 MHz, 400 MHz (^1H), and 100.61 MHz (^{13}C) at 30°C; internal standard TMS. For the TLC, we used Silufol UV-254 plates (visualized by iodine vapors); for the column chromatography, we used aluminum oxide (Brockmann activity 0).

1,2,4,5-Tetrahydro-5-methyl-3H-spiro[benz-2-azepine-3-cyclohexane] (II) and *trans*-1-Benzylamino-1-(propen-1-yl)cyclohexane (III). A. Compound I (3.0 g, 13.1 mmol) in 3 ml of chloroform was added dropwise to 10 ml of 85% sulfuric acid and the mixture was heated under stirring for 40 min at 80°C. The mixture was cooled down, poured on ice, and alkalized with a 25% aqueous solution of ammonia to pH 10 and then extracted with chloroform. The residue after driving off the solvent was chromatographed on column (1.5×80 cm) with aluminum oxide, eluent ethyl acetate—hexane, 1:20. Compound III (0.33 g, 13%) was isolated as yellow oil, R_f 0.50 (ethyl acetate—hexane, 1:3). IR spectrum: 3320 (NH), 1615 cm^{-1} (C=C). Mass spectrum, *m/z* (I_{rel}, %): 229 (52, M^+), 214 (21), 186 (75), 172 (8), 171 (7), 158 (15), 147 (5), 138 (11), 106 (15), 105 (15), 91 (100), 81 (12). PMR spectrum ($CDCl_3$, 200 MHz): 7.35-7.20 (5H, m, Ph); 5.56 (1H, dq, J = 15.6 and J = 6.4 Hz, C<u>H</u>Me); 5.35 (1H, dq, J = 15.6 and J = 1.5 Hz, C<u>H</u>=CHMe); 3.59 (2H, s, NCH_2); 1.78 (3H, dd, J = 6.4 and J = 1.5 Hz, Me); 1.59-1.35 ppm (10H, m, $(CH_2)_5$). Then 1.25 g (40%) of spiro compound II were eluted as yellow oil, R_f 0.2 (ethyl acetate—hexane, 1:3), n_D^{20} 1.5512. (Lit. data: n_D^{20} 1.5510, R_f 0.2 (Silufol, ethyl acetate—hexane, 1:3) [1]. IR spectrum: 3311 cm^{-1} (NH). Mass spectrum: M^+ 229 (17%). Compound II. Found, %: C 84.90; H 9.79; N 6.21. $C_{16}H_{23}N$. Calculated, %; C 83.84; H 10.04; N 6.11. Compound III. Found, %: C 83.54; H 10.24; N 5.93. $C_{16}H_{23}N$. Calculated, %: C 83.84; H 10.04; N 6.11.

B. Compound I (30 g, 0.131 mol) was dissolved in 100 ml of 85% H_2SO_4 and heated at 80-85°C for 1.5 h. Solution was cooled, poured on ice, and alkalized with 25% aqueous solution of ammonia to pH 10, then extracted with ether (3 × 70 ml) and dried with magnesium sulfate. The residue after driving off the ether was fractionated under vacuum. The fraction (25 g) with bp 110-150°C (2 mm) was collected, and by treatment with 11 ml of concentrated hydrochloric acid was converted to hydrochloride. The crystals of hydrochloride were filtered off and washed with ethyl acetate. In this case, the impurities of hydrochlorides of compounds I and III, easily soluble in ethyl acetate, were washed away. Hydrochloride of compound II (19.1 g, 55%) was obtained as colorless crystals,

mp 276-283°C (with decomposition). Hydrochloride of compound II was decomposed with aqueous solution of sodium carbonate, extracted with ether, and dried with magnesium sulfate. The residue after driving off the ether was fractionated under vacuum. Compound II (15 g, 50%) was obtained as yellow oil, bp 145-147°C (3 mm), n_D^{20} 1.5507, R_f 0.2 (ethyl acetate—hexane, 1:3) (Lit. data: n_D^{20} 1.5510, bp 143-145°C (3 mm) [1]. Compound II, hydrochloride. Found, %: H 13.01; N 5.19. $C_{16}H_{24}NCl$. Calculated, %: H 13.37; N 5.27.

N-Oxide of 4,5-dihydro-5-methyl-3H-spiro[benz-2-azepine-3-cyclohexane] (IV). $Na_2WO_4 \cdot 2H_2O$ (0.88 g, 2.6 mmol) was added to solution of 12.0 g (52.4 mmol) of compound II in 50 ml of acetone, and 21 ml (0.21 mol) of 30% hydrogen peroxide was added with stirring and water-cooling. On the next day, the precipitated crystals were filtered off, dried, and recrystallized from ethyl acetate. Compound IV (10.2 g, 80%) was obtained as white crystals, mp 136-139°C, R_f 0.48 (ethyl acetate). IR spectrum: 1647 (C=N), 1230 and 928 cm^{-1} (N→O). Mass spectrum, *m/z* (I_{rel}, %): 243 (M^+, 13), 226 (100), 211 (8), 184 (10), 148 (15), 132 (90), 131 (63), 130 (36), 115 (16), 104 (14), 103 (13), 91 (16). PMR spectrum ($CDCl_3$, 200 MHz): 7.95 (1H, s, 1-H); 7.1-7.3 (4H, m, Ph); 3.12 (1H, qdd, $J_{5,Me}$ = 7.0, $J_{4e,5}$ = 5.0, $J_{4a,5}$ = 10.0 Hz, 5-H); 2.38 (1H, dd, $J_{4a,4e}$ = 15.0, $J_{4e,5}$ = 5.0 Hz, 4e-H); 1.90 (1H, dd, $J_{4a,4e}$ = 15.0, $J_{4a,5}$ = 10.0 Hz, 4a-H); 1.43 (3H, d, $J_{5,Me}$ = 7.0 Hz, Me); 2.5-1.1 ppm (10H, m, $(CH_2)_5$). Compound IV. Found, %: C 79.45; H 8.81; N 5.92. $C_{16}H_{21}NO$. Calculated, %: C 79.01; H 8.64; N 5.76.

N-Oxide of N-benzylidene(1-*trans*-propen-1-yl-1-cyclohexyl)amine (V). $Na_2WO_4 \cdot 2H_2O$ (0.17 g, 0,5 mmol) was added to solution of 2,29 g (10 mmol) of compound III in 50 ml of acetone and then 3 ml (30 mmol) of 30% hydrogen peroxide were added with water cooling. After 3 days, the mixture was poured into 30 ml water, extracted with ether (3 × 20 ml), and dried with magnesium sulfate. After driving off the ether, the residue was chromatographed on aluminum oxide (3×3 cm), eluent hexane—ethyl acetate, 10:1. Nitrone V (1.6 g, 70%) was obtained as white crystals, mp 73.0-74.5°C (heptane—ethyl acetate), R_f 0.40 (ethyl acetate—hexane, 1:5). IR spectrum: 940 and 1125 (N→O), 1577 and 1562 (C=N), 1660 cm^{-1} (C=C). PMR spectrum ($CDCl_3$, 200 MHz): 8.3-8.2 (2H, m, *o*-Ph); 7.59 (1H, s, CH=N); 7.40-7.35 (3H, m, *m*-Ph and *p*-Ph); 5.87 (1H, dq, J = 15.8 and J = 6.4 Hz, CH=C<u>H</u>Me); 5.59 (1H, dq, J = 15.8 and J = 1.5 Hz, C<u>H</u>=CHMe); 2.5-1.4 (10H, m, $(CH_2)_5$); 1.83 ppm (3H, dd, J = 1.5 and J = 6.4 Hz, Me). Found, %: C 79.40; H 8.88; N 5.38. $C_{16}H_{21}NO$. Calculated, %: C 79.01; H 8.64; N 5.76.

3,4,5,6-Tetrahydro-6-methyl-3-benzylspiro[1,2,3-oxathiazine-2,2-dioxide-4-cyclohexane] (VI). A. A total of 5 ml (81 mmol) of 92% sulfuric acid were added to solution of 5 g (21.8 mmol) of compound I in 75 ml of chloroform. The mixture was boiled for 6 h, cooled, poured on ice, and alkalized with 20% solution of sodium hydroxide to pH 10. The chloroform layer was removed, the aqueous layer was extracted with chloroform (2 × 15 ml). The combined extract was dried with magnesium sulfate. Chloroform was driven off down to volume of ~10 ml. The precipitated crystals were filtered off, boiled with ethyl acetate, and filtered again. Oxathiazine VI (2.57 g, 41%) was obtained as white powder, mp 231-233°C (with decomposition). IR spectrum: 1272 and 1217 cm^{-1} (SO_2). Mass spectrum, *m/z* (I_{rel}, %): 309 (M^+, 1), 229 (3), 214 (2), 201 (1), 188 (44), 186 (12), 172 (1), 134 (31), 122 (20), 107 (65), 106 (65), 91 (100), 79 (68), 77 (23), 64 (30), 50 (14), 38 (33). PMR spectrum (DMSO-d_6, 200 MHz): 7.62-7.56 (2H, m, *o*-Ph); 7.42-7.37 (3H, m, *p*- and *m*-Ph); 4.59 (1H, ddq, $J_{6,Me}$ = 6.2, $J^*_{6a,5e}$ = 4.0, $J^*_{6a,5a}$ = 8.4 Hz, 6a-H); 4.28 and 4.05 (2H, AB, J_{AB} = 12.6 Hz, NCH_2); 2.2-1.8 (10H, m, $(CH_2)_5$); 1.30 ppm (3H, d, $J_{Me,6}$ = 6.2 Hz, Me). ^{13}C NMR spectrum (DMSO-d_6): 132.21 (s, *i*-Ph); 130.28 (d, *m*-Ph); 128.74 (d, *p*-Ph); 128.50 (d, *o*-Ph); 69.66 (d, $^1J_{C,H}$ = 145.3 Hz, $C_{(6)}$); 61.06 (s, $C_{(4)}$); 43.91 (t, $^1J_{C,H}$ = 145.3 Hz, CH_2N); 35.40 (t, 1 $J_{C,H}$ = 127.9 Hz, $C_{(5)}$); 22.70 (q, $^1J_{C,H}$ = 126.4 Hz, CH_3); 32.65, 31.15, 24.69, 21.16, 20.74 ppm (t, $(CH_2)_5$). Found, %: C 62.03; H 7.44; N 4.44. $C_{16}H_{23}NO_3S$. Calculated, %: C 62.13; H 7.44; N 4.53.

B. Compound I (10 g, 43.7 mmol) was added to 30 ml of 85% sulfuric acid at 0°C. The mixture was stirred at room temperature until complete homogenization and allowed to stand for 24 h at 20°C, then treated as described in A. Compound VI (7.04 g, 52%) was obtained as white powder, mp 230-232°C (with decomposition).

1-(2-Hydroxypropyl)-1-N-benzylaminocyclohexane (VII). Oxathiazine VI (0.2 g, 0.65 mmol) was boiled in 40 ml of 20% hydrochloric acid for 5 h. The mixture was cooled and alkalized with 25% aqueous solution of ammonia, then extracted with ether and dried with magnesium sulfate. After driving off the ether, the residue was purified on aluminum oxide (2×3 cm), with ether as the eluent. Aminoalcohol VII (80 mg, 50%) was obtained as yellow oil, R_f 0.30 (ethyl acetate—hexane, 1;4). IR spectrum: 3255 cm^{-1} (NH+OH). Mass spectrum, *m/z* (I_{rel}, %): 247 (M^+, 3), 204 (13), 188 (32), 156 (4), 91 (100), 65 (16). PMR spectrum ($CDCl_3$, 400 MHz): 7.35-7.20 (5H, m, Ph); 4.15 (1H, ddq, $J_{Me,2}$ = 6.4 Hz, 2-H); 3.77 and 3.61 (2H, AB, $J_{A,B}$ = 11.6 Hz, NCH_2); 1.80-1.15

(12H, m, 1-H and $(CH_2)_5$); 1.17 ppm (3H, d, $J_{Me,2}$ = 6.4 Hz, Me). Found, %: C 77.22; H 10.53; N 5.56. $C_{16}H_{25}NO$. Calculated, %: C 77.73; H 10.12; N 5.67.

4-Methyl-1-benzylspiro[azetidine-2-cyclohexane] (VIII). Oxathiazine VI (1.26 g, 4.07 mmol) was boiled in 20 ml of 15% KOH solution in ethanol for 20 h, then poured into water and extracted with ether. The extract was dried with magnesium sulfate. After driving off the solvent, the residue was purified on aluminum oxide (2×3 cm), with ether as the eluent. Azetidine VIII (0.64 g, 68%) was obtained as yellow oil, R_f 0.50 (ethyl acetate—hexane, 1:4). Mass spectrum, *m/z* (I_{rel}, %): 229 (M^+, 17), 187 (10), 186 (55), 158 (4), 91 (100), 82 (16), 67 (7), 55 (8), 54 (6), 53 (5), 42 (8), 41 (19). PMR spectrum ($CDCl_3$, 200 MHz): 7.3-7.1 (5H, m, Ph), 3.78 and 3.46 (2H, AB, J_{AB} = 13.1 Hz, CH_2N); 3.25 (1H, tq, $J_{Me,4}$ = 5.8, $J_{4,3A}$ = $J_{4,3B}$ = 7.6 Hz, 4-H); 2.02 (1H, dd, $J_{3A,4}$ = 7.6, $J_{3A,3B}$ = 10.2 Hz, 3A-H); 1.42 (1H, dd, $J_{4,3B}$ = 7.6, $J_{3A,3B}$ = 10.2 Hz, 3B-H); 0.93 (3H, d, $J_{Me,4}$ = 5.8 Hz, Me); 1.0-2.1 ppm (10H, m, $(CH_2)_5$). ^{13}C NMR spectrum ($CDCl_3$): 140.97 (s, *ipso*-Ph); 128.87 (d, *m*-Ph); 127.77 (d, *o*-Ph); 126.32 (d, *p*-Ph); 63.5 (s, $C_{(2)}$); 56.65 (d, $^1J_{C,H}$ = 133.7 Hz, $C_{(4)}$); 53.41 (t, $^1J_{C,H}$ = 129.3 Hz, CH_2N); 37.33 (t, $^1J_{C,H}$ = 136.6 Hz, $C_{(3)}$); 22.65 (q, $^1J_{C,H}$ = 126.4 Hz, Me); 40.88, 30.02, 25.91, 23.27, 23.21 ppm (t, $^1J_{C,H}$ = 125-129 Hz, $(CH_2)_5$). Found, %: C 83.60; H 9.91; N 6.46. $C_{16}H_{23}N$. Calculated, %: C 83.84; H 10.04; N 6.11.

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