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SYNTHESIS OF SUBSTITUTED AND CONDENSED TETRAHYDROSPIRO[BENZO-2-AZEPINECYCLOHEXANES] FROM 1-CYANO- AND 1-CARBAMOYL-5-METHYL-4,5-DIHYDRO-3H-SPIRO[BENZO-2-AZEPINE-3,1'-CYCLOHEXANES]

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Substitution of the nitrile group by hydroxylamine and hydrazine has been effected in 1-cyanodihydrospiro[benzo-2-azepine-3,1'-cyclohexane]. From the 1-cyano and 1-hydrazino derivatives tetrahydrospiro{1,2,3- and 1,2,4-triazolo[5,1-a]benzoazepine-5,1'-cyclohexanes} have been obtained. It was established that 1-carbamoyldihydrospiro[benzo-2-azepine-3,1'-cyclohexanes] are converted under the conditions of the Hoffmann reaction into spiro{diaziridino[3,1-a]benzo-2-azepine-3,1'-cyclohexane}, and is reduced by sodium borohydride to the tetrahydro derivative.

Keywords: diaziridinobenzo-2-azepinecyclohexane, spirobenzo-2-azepinecyclohexanes, triazolobenzo-2-azepinecyclohexanes.

Previously 1-cyano-5-methyl-4,5-dihydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] (**1**) was obtained in 30% yield [1] by the interaction of potassium cyanide with 5-methyl-4,5-dihydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] N-oxide. This compound is of interest as a synthon for design of new derivatives of spiro[benzo-2-azepinecyclohexane], interesting in the biological area, consequently we optimized the process of making it. It was established that if acetone cyanohydrin is used as the source of cyanide ion in the reaction with a nitrone of the benzoazepine series in absolute alcohol, then the yield of nitrile **1** may be increased to 84%. On using 95% ethanol as solvent the main reaction product is the corresponding 1-carbamoyl derivative **2** (90% yield).

Study of the conversions of 1-substituted dihydrospirobenzo-2-azepinecyclohexanes **1** and **2** is the subject of the present report.

On interacting compound **1** with sodium azide spiro{1,2,3-triazolo[5,1-*a*]benzo-2-azepine-5,1'-cyclohexane} **3** is obtained in 55% yield, in place of the expected 1-tetrazolyl-substituted spiro[benzo-2-azepine-3,1'-cyclohexane] [2].

On boiling nitrile **1** with hydroxylamine or hydrazine in absolute ethanol a nucleophilic substitution of the CN group by hydroxylamine or hydrazine respectively occurs with the formation of 1-substituted derivatives **4** and **5**. Such a regiodirection of the reaction is determined by the large deficiency of electrons at position $C_{(1)}$, which is caused by the effect of two electron-withdrawing groups, and by the ease of fission of the nitrile group. It should be mentioned that compound **1** does not react with sodium amide in boiling absolute benzene. The 1-hydrazino derivative **5** is converted by the action of ethyl orthoformate or acetic anhydride in boiling toluene

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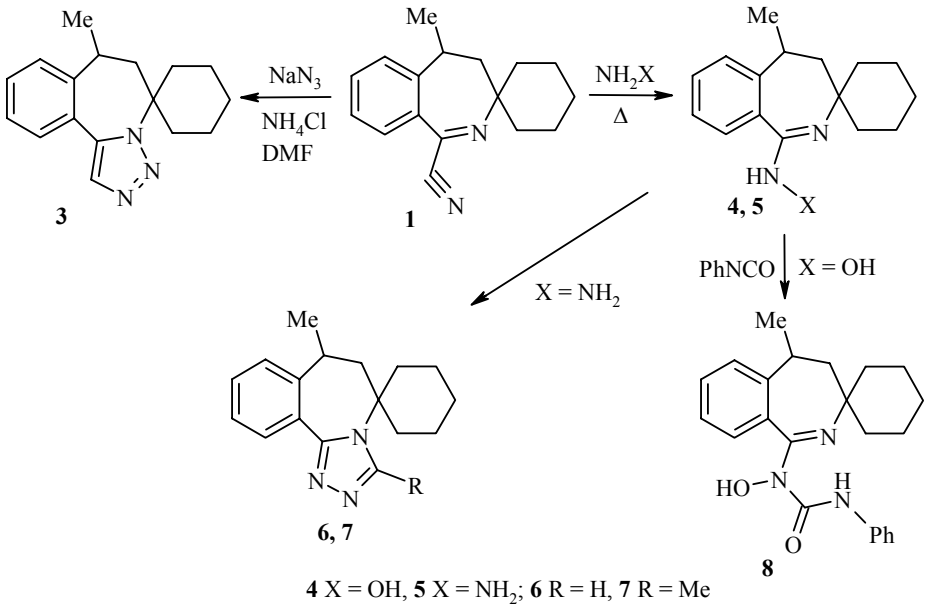
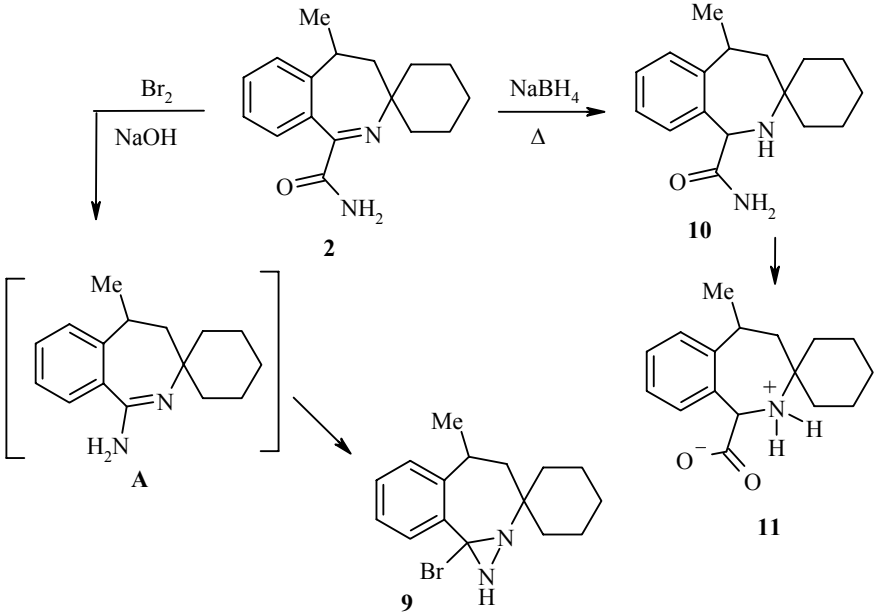
into spiro{1,3,4-triazolo[5,1-*a*]benzo-2-azepine-5,1'-cyclohexanes} **6** and **7** respectively. Interaction of compound **4** with phenyl isocyanate takes place at the more nucleophilic nitrogen atom of the hydroxylamine group with the formation of the N-hydroxyurea **8**.



4 X = OH, **5** X = NH_2; **6** R = H, **7** R = Me

The 1-carbamoyl spirobenzo-2-azepinecyclohexane **2** is converted under the conditions of the Hoffmann reaction into 9b-bromo-5-methyl-4,5-dihydro-3H-spiro{diaziridino[3,1-*a*]benzo-2-azepine-3,1'-cyclohexane} (**9**). By analogy with the conversion of amidines under Hoffmann reaction conditions [3] it is possible to confirm that the formation of compound **9** occurs through the 1-amino-substituted derivative **A**. Sodium borohydride in the presence of $CoCl_2$ selectively reduces the imine bond in compound **2**, giving 1-carbamoyltetrahydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] (**10**), acid hydrolysis of which leads to amino acid **11**.



In the mass spectra of compounds **2-11** there were peaks of various intensity for the molecular ions corresponding to their empirical formulae. The decomposition of $[M]^+$ ions of these compounds is linked with the elimination of a radical from $C_{(1)}$, and by decomposition of the cyclohexane and benzoazepine fragments [1, 4]. The IR spectra of amines **2**, **4**, **5**, **8** are characterized by the presence of bands for the stretching vibrations of the C=N bond at 1614-1648 cm^{-1}. Bands for the stretching vibrations linked with the hydrogen bond of OH, NH_2, and NH groups in compounds **2**, **4**, **5**, **8**, and **9** were observed at 3121-3428 cm^{-1}. The appearance in the IR spectrum of amino acid **11** of a group of bands at 2380-2650 cm^{-1} indicates unequivocally its existence in the zwitterion form. The band for the stretching vibrations of the CO group in ureide **8** are observed at 1728, and in the amino acid **11** at 1654 cm^{-1}. In the IR spectrum of carbamoyl derivative **2** one band was observed for the stretching vibrations of CO at 1691 cm^{-1}, and in the spectrum of its hydrogenated derivative **10** there were two bands at 1694 and 1654 cm^{-1}.

In the ^1H NMR spectra of compounds **2-10** signals were observed for all the protons of the benzo-2-azepine fragment with coupling constants and chemical shifts corresponding to their position in the molecule. The signals of protons in the ^1H NMR spectra of acid **11** were substantially broadened. The doublet of the protons of the 5-CH_3 group at 1.37, the broadened multiplet of the H-5 proton at 3.22, and the broadened singlet of the H-1 proton at 4.97 ppm may be regarded as reference signals. The ^1H NMR spectra of triazolobenzo-2-azepines **3** and **6** are characterized by the presence in the low field portion of singlet signals from the H-1 and H-3 protons at 7.76 and 8.38 ppm respectively. In the spectrum of triazole **7** a singlet is observed at 2.47 ppm for the protons of the 3-CH_3 group.

There was a signal at 4.79 ppm in the ^1H NMR spectrum of compound **10** for the H-1 proton. In the spectra of carbamoyl derivatives **2** and **10** two broadened signals are observed for the NH_2CO group protons at 5.34, 7.67, and 5.70, 7.85 ppm respectively, which is caused by hindrance to rotation around the amide bond.

We have therefore synthesized for the first time triazoles condensed with a spirobenzo-2-azepinecyclohexane fragment.

EXPERIMENTAL

The IR spectra were recorded on a Specord UR-75 and UR-20 spectrometers in KBr disks, nujol, or CCl_4. The mass spectra were obtained on a Finnigan MAT Incos 50 instrument with direct insertion of samples into the ion source at an ionizing radiation of 70 eV. The ^1H NMR spectra were recorded on a Bruker WP-200 (200 MHz) instrument in $CDCl_3$, internal standard was TMS. For TLC Silufol UV-254 plates were used (visualization in iodine vapor), for column chromatography silica gel L 100/250 and Woelm 32/63, and also aluminum oxide of Brockmann activity grade 1. Melting points were determined in glass capillaries and are not corrected.

7-Methyl-6,7-dihydro-5H-spiro{1H-1,2,3-triazolo[5,1-*a*]benzo-2-azepine-5,1'-cyclohexane} (3). A solution of cyanoimine **1** (0.5 g, 2 mmol), NaN_3 (0.39 g, 6 mmol), and NH_4Cl (0.32 g, 6 mmol) in dry DMF (20 ml) was boiled for 11 h (check by TLC). At the end of the reaction DMF was distilled off in vacuum. Water (50 ml) was added to the residue, the mixture was extracted with CH_2Cl_2 (3 × 30 ml), and the extract dried with magnesium sulfate. After distilling off the dichloromethane, the residue was chromatographed on aluminum oxide. The following were isolated sequentially: 1) a light-yellow oil (0.1 g), which was a complex mixture of unidentified compounds (eluent was hexane); 2) compound **3** (0.29 g, 55%) as a light-yellow oil (eluent ethyl acetate–hexane, 1:10), R_f 0.56 (ethyl acetate–hexane, 1:1). IR spectrum (nujol), ν, cm^{-1}: 3401 (=C–H), 1561 (C=CH–N=N–N, skeletal), 1114 (=C–H, in-plane def.), 848 and 828 (=C–H, out-of-plane def.). Mass spectrum, *m/z* (I_{rel}, %): 267 (39) $[M]^+$, 252 (2), 239 (4), 238 (13), 226 (6), 225 (13), 224 (19), 210 (10), 198 (7), 197 (15), 196 (30), 185 (17), 184 (46), 183 (7), 182 (14), 173 (19), 172 (72), 170 (11), 168 (15), 156 (9), 155 (12),

144 (26), 143 (52), 142 (17), 141 (27), 131 (10), 130 (23), 123 (38), 128 (68), 127 (27), 117 (31), 116 (89), 115 (100), 103 (13), 102 (14), 95 (16), 91 (27), 89 (13), 83 (11), 81 (11), 79 (13), 77 (27), 67 (19), 65 (14), 63 (12), 57 (17), 55 (33), 54 (13), 53 (24), 51 (17), 43 (11), 42 (14), 41 (77), 39 (50). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.76 (1H, s, H-1); 7.25-7.45 (4H, m, arom.); 2.85 (1H, qdd, $J_{7,Me}$ = 7.0, $J_{6e,7}$ = 4.9, $J_{6a,7}$ = 11.0, H-7); 2.41 (1H, dd, $J_{6a,6e}$ = 14.0, $J_{6e,7}$ = 4.9, H-6e); 2.03 (1H, dd, $J_{6a,6e}$ = 14.0, $J_{6a,7}$ = 11.0, H-6a); 1.33 (3H, d, $J_{7,Me}$ = 7.0, 7-CH_3); 2.6-2.7, 1.05-2.10 (10H, m, cyclohex.). Found, %: C 76.73; H 7.98; N 15.61. $C_{17}H_{21}N_3$. Calculated, %: C 76.40; H 7.87; N 15.73.

1-(N-Hydroxylamino)-5-methyl-4,5-dihydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] (4). A solution of cyanoimine **1** (0.45 g, 1.8 mmol), hydroxylamine hydrochloride (0.13 g, 1.8 mmol), and potassium carbonate (0.25 g, 1.8 mmol) in absolute ethanol (25 ml) was boiled for 1 h (check by TLC). At the end of the reaction the hot solution was filtered through a Schott funnel, and the solid was washed with absolute ethanol (10 ml). After distilling the alcohol, the residue was chromatographed on silica gel, using ethyl acetate–hexane, 1:1 as eluent. Compound **4** (0.23 g, 50%) was isolated as white crystals; mp 169-171.5°C, R_f 0.46 (ethyl acetate–hexane, 1:1). IR spectrum (KBr), ν, cm^{-1}: 3428 (OH), 3134 (NH), 1621 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 258 (100) $[M]^+$, 243 (14), 241 (31), 229 (3), 226 (7), 216 (10), 215 (61), 202 (12), 199 (8), 197 (17), 183 (10), 182 (11), 175 (9), 162 (6), 161 (19), 159 (12), 146 (29), 145 (42), 144 (46), 143 (13), 130 (37), 129 (14), 117 (12), 116 (14), 115 (13), 104 (8), 103 (16), 98 (93), 91 (9), 77 (20), 57 (11), 55 (14), 43 (15), 42 (12), 41 (33), 40 (16), 39 (16). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.08 (1H, br. s, NH); 7.5-7.6, 7.3-7.4, 7.15-7.25 (4H, m, arom.); 5.56 (1H, br. s, NOH); 3.38 (1H, qdd, $J_{5,Me}$ = 7.0, $J_{4e,5}$ = 5.5, $J_{4a,5}$ = 11.6, H-5); 1.94 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4e,5}$ = 5.5, H-4e); 1.56 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4a,5}$ = 11.6, H-4a); 1.32 (3H, d, $J_{5,Me}$ = 7.0, 5-CH_3); 0.75-1.7 (10H, m, cyclohex.). Found, %: C 74.57; H 8.74; N 10.49. $C_{16}H_{22}N_2O$. Calculated, %: C 74.42; H 8.53; N 10.85.

1-(N-Hydrazino)-5-methyl-4,5-dihydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] (5). A solution of cyanoimine **1** (1.00 g, 4 mmol), hydrazine hydrochloride (0.42 g, 4 mmol), and potassium carbonate (1.10 g, 8 mmol) in absolute ethanol (20 ml) was boiled for 2 h (check by TLC). At the end of the reaction the alcohol was distilled off, water (50 ml) was added to the residue, and the mixture was extracted with chloroform (3 × 30 ml). The extract was dried over magnesium sulfate. After distilling off the solvent, the residue was crystallized from hexane. Compound **5** (0.56 g, 55%) was obtained as light-yellow crystals; mp 67-69°C, R_f 0.79 (ethanol). IR spectrum (nujol), ν, cm^{-1}: 3374, 3294, 3161 (NH + NH_2), 1648 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 257 (89) $[M]^+$, 242 (9), 241 (18), 228 (5), 226 (29), 214 (45), 201 (8), 200 (6), 185 (5), 171 (6), 170 (7), 161 (6), 160 (30), 159 (9), 146 (18), 145 (35), 144 (25), 143 (12), 131 (15), 130 (49), 129 (15), 128 (24), 117 (13), 116 (19), 115 (19), 104 (9), 103 (20), 98 (100), 91 (11), 86 (10), 81 (9), 77 (26), 67 (8), 57 (31), 56 (22), 55 (18), 43 (28), 42 (20), 41 (59), 39 (22). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.50, 7.15-7.40 (4H, m, arom.); 5.10 (1H, br. s, NH); 4.19 (2H, br. s, NH_2); 3.32 (1H, qdd, $J_{5,Me}$ = 7.0, $J_{4e,5}$ = 5.5, $J_{4a,5}$ = 11.9, H-5); 1.93 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4e,5}$ = 5.5, H-4e); 1.58 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4a,5}$ = 11.9, H-4a); 1.31 (3H, d, $J_{5,Me}$ = 7.0, 5-CH_3); 0.9-1.8 (10H, m, cyclohex.). Found, %: C 74.55; H 8.79; N 10.59. $C_{16}H_{23}N_3$. Calculated, %: C 74.71; H 8.95; N 10.34.

7-Methyl-6,7-dihydro-5H-spiro{1,2,4-triazolo[3,4-*a*]benzo-2-azepine-5,1'-cyclohexane} (6). A solution of hydrazine **5** (0.23 g, 0.9 mmol) and ethyl orthoformate (0.42 ml, 2.7 mmol) in absolute toluene (15 ml) was boiled for 4 h (check by TLC). At the end of the reaction the toluene was distilled off, and the residue was purified on a column of aluminum oxide (eluent ethyl acetate). Compound **6** (0.14 g, 61%) was obtained as white crystals; mp 123-124°C, R_f 0.12 (ethyl acetate). IR spectrum (nujol), ν, cm^{-1}: 3121 (=C–H), 1521 (C=N–N=C–N, skeletal), 1194 (=C–H, in-plane def.), 861 and 848 (=C–H, out-of-plane def.). Mass spectrum, *m/z* (I_{rel}, %): 267 (38) $[M]^+$, 252 (5), 239 (2), 238 (9), 226 (1), 225 (10), 224 (24), 210 (6), 196 (24), 184 (40), 173 (31), 172 (40), 171 (11), 170 (24), 156 (11), 143 (10), 131 (18), 130 (17), 129 (30), 128 (30), 117 (12), 116 (23), 115 (66), 103 (22), 102 (13), 91 (14), 89 (14), 81 (11), 77 (31), 67 (24), 65 (12), 56 (9), 55 (38), 54 (12), 53 (23), 51 (17), 44 (36), 43 (33), 42 (19), 41 (100), 40 (53), 39 (54). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.38 (1H, s, H-3); 7.85, 7.25-7.50 (4H, m, arom.); 2.91 (1H, ddq, $J_{6e,7}$ = 5.5, $J_{6a,7}$ = 11.2, $J_{7,Me}$ = 7.0,

H-7); 2.26 (1H, dd, $J_{6a,6e}$ = 13.8, $J_{6a,7}$ = 11.2, H-6e); 2.07 (1H, dd, $J_{6a,6e}$ = 13.8, $J_{6e,7}$ = 5.5, H-6a); 1.34 (3H, d, $J_{7,Me}$ = 6.7, 7-CH_3); 1.15-2.15 (10H, m, cyclohex.). Found, %: C 76.11; H 7.60; N 16.10. $C_{17}H_{21}N_3$. Calculated, %: C 76.40; H 7.87; N 15.73.

3,7-Dimethyl-6,7-dihydro-5H-spiro{1,2,4-triazolo[3,4-*a*]benzo-2-azepine-5,1'-cyclohexane} (7). A solution of compound **5** (0.5 g, 1.9 mmol) in acetic anhydride (2 ml) was boiled for 2 h (check by TLC). The excess of anhydride was distilled off in vacuum, water (10 ml) was added, and the mixture extracted with ether. The extract was dried over magnesium sulfate. After distilling off the ether the residue (0.45 g) was purified on aluminum oxide, using ethyl acetate as eluent. Compound **7** (0.21 g, 38%) was obtained as white crystals; mp 134-135°C (heptane–ethyl acetate), R_f 0.10 (ethyl acetate). Mass spectrum, *m/z* (I_{rel}, %): 281 (9) $[M]^+$, 266 (6), 252 (5), 239 (35), 238 (18), 224 (4), 211 (6), 210 (17), 200 (6), 198 (25), 187 (62), 186 (100), 185 (9), 184 (17), 172 (6), 171 (7), 145 (7), 144 (6), 131 (22), 130 (11), 129 (19), 116 (14), 115 (18), 104 (9), 103 (22), 91 (13), 90 (6), 78 (10), 77 (22), 67 (13), 65 (7), 57 (14), 54 (11), 42 (18), 41 (24), 40 (18), 39 (14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.20-7.55 (4H, m, H-8-11); 3.57 (1H, qdd, $J_{7,Me}$ = 6.7, $J_{6a,7}$ = 8.2, $J_{6e,7}$ = 5.8, H-7); 2.47 (3H, s, 3-CH_3); 2.26 (1H, dd, $J_{6a,6e}$ = 13.4, $J_{6e,7}$ = 5.8, H-6e); 2.07 (1H, dd, $J_{6a,6e}$ = 13.4, $J_{6a,7}$ = 8.2, H-6a); 1.40-1.93 (10H, m, cyclohex.); 1.19 (3H, d, $J_{7,Me}$ = 6.7, 7-CH_3). Found, %: C 76.96; H 8.07; N 14.72. $C_{18}H_{23}N_3$. Calculated, %: C 76.87; H 8.20; N 14.93.

1-(N-Phenylcarbamoylhydroxylamino)-5-methyl-4,5-dihydro-3H-spiro[benzo-2-azepine-3,1'-cyclohexane] (8). Hydroxylamine **4** (0.33 g, 1.3 mmol) was dissolved in absolute benzene (10 ml) by heating. Phenyl isocyanate (0.17 ml, 1.6 mmol) was added to the warm solution (40-50°C). The reaction mixture was maintained at room temperature for 6 h. The benzene was distilled off, and the residue crystallized from hexane. Compound **8** (0.48 g, 98%) was obtained as white crystals; mp 173-179°C (decomp.), R_f 0.68 (ethyl acetate–hexane, 1:1). IR spectrum (nujol), ν, cm^{-1}: 3374 (OH), 3254, 3188, 3121 (NH), 1728 (C=O), 1614 (C=N), 1021 (N–O). Mass spectrum, *m/z* (I_{rel}, %): 259 (20), 258 (100) [M-PhNCO], 243 (10), 242 (8), 241 (28), 227 (5), 226 (17), 216 (7), 215 (41), 202 (8), 200 (8), 199 (16), 198 (5), 197 (15), 185 (7), 183 (10), 182 (8), 175 (6), 172 (8), 164 (8), 161 (14), 159 (11), 146 (32), 145 (39), 144 (38), 132 (8), 131 (17), 130 (45), 129 (18), 128 (38), 120 (12), 119 (98) [PhNCO], 117 (13), 116 (14), 115 (15), 103 (17), 98 (50), 93 (24), 91 (57), 77 (23), 64 (28), 55 (12), 51 (14), 41 (28), 39 (24). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.77 (1H, br. s, NH); 7.4-7.6, 7.2-7.4, 7.00-7.15 (9H, m, arom.); 5.78 (1H, br. s, NOH); 3.33 (1H, qdd, $J_{5,Me}$ = 7.0, $J_{4e,5}$ = 5.5, $J_{4a,5}$ = 11.9, H-5); 2.01 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4e,5}$ = 5.5, H-4e); 1.60 (1H, dd, $J_{4a,4e}$ = 13.4, $J_{4a,5}$ = 11.9, H-4a); 1.36 (3H, d, $J_{5,Me}$ = 7.0, 5-CH_3); 0.70-1.65 (10H, m, cyclohex.). Found, %: C 73.50; H 7.49; N 11.12. $C_{23}H_{27}N_3O_2$. Calculated, %: C 73.21; H 7.16; N 11.14.

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