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Synthesis of 3,6-Diazahomoadamantane

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Abstract—Condensation of 1-phenylsulfanylpropan-2-one with 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane gave 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one which was reduced to 1-phenylsulfanyl-3,6-diazahomoadamantane, and the latter was subjected to desulfurization over Raney nickel to obtain previously unknown 3,6-diazahomoadamantane. Heating of 9-phenyl-3,6-diazahomoadamantan-9-ols with Raney nickel resulted in reduction of the hydroxy group with formation of 9-phenyl-3,6-diazahomoadamantanes.

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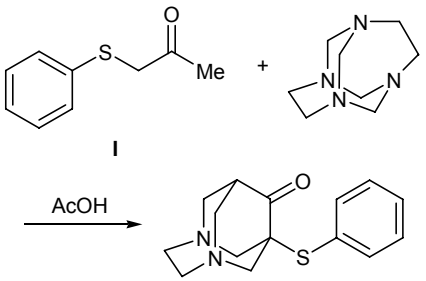
By condensation of methyl ketones with 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane [1] and subsequent Wolff–Kishner reduction of the resulting 3,6-diazahomoadamantan-9-ones we obtained a number of 3,6-diazahomoadamantane derivatives substituted at the bridgehead position [2–4]. In the present communication we report on the synthesis of 3,6-diazahomoadamantane in a similar way. For this purpose, as initial ketone we used 1-phenylsulfanylpropan-2-one (**I**); its condensation with 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane in propan-2-ol afforded more than 60% of 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one (**II**) (Scheme 1).

Scheme 1.

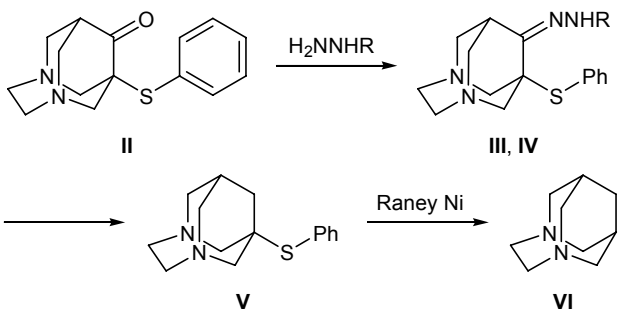


Ketone **II** displayed in the ^{13}C NMR spectrum a signal at δ_C 209.4 ppm from carbonyl carbon atom, two signals at δ_C 62.3 and 54.1 ppm from the bridgehead carbon atoms, a signal at δ_C 57.0 ppm from two carbon atoms in the ethylene bridge, and two signals at δ_C 65.63 and 59.45 ppm from four bridging methylene carbon atoms.

Ketone **II** was reduced to 1-phenylsulfanyl-3,6-diazahomoadamantane (**V**) in two ways: (1) through 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one hydrazone (**III**) according to Wolff–Kishner and (2) by reduction of 1-phenylsulfanyl-3,6-diazahomoadamantan-9-one *p*-tolylsulfonylhydrazone (**IV**) with sodium tetrahydridoborate in acetic acid [5] (Scheme 2). Desulfurization of 1-phenylsulfanyl-3,6-diazahomoadamantane (**V**) by heating over Raney nickel according to the procedure described in [6, 7] gave previously unknown unsubstituted 3,6-diazahomoadamantane (**VI**) [8] which was isolated as a readily sublimable white crystalline substance with mp 250–251°C.

In the ^{1}H NMR spectrum of diazahomoadamantane **VI**, the NCH_2CH_2N ethylene fragment gave rise to

Scheme 2.

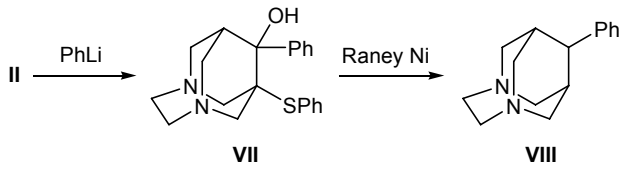


III, R = H; **IV**, R = 4-$MeC_6H_4SO_2$.

a multiplet at δ 3.12 ppm, protons in the four NCH_2C methylene groups resonated as two doublets at δ 3.42 and 2.80 ppm, the singlet at δ 1.30 ppm was assigned to the CH_2C methylene group, and two protons in the bridgehead positions gave a broadened singlet at δ 1.85 ppm. The ^{13}C NMR spectrum of compound **VI** contained four signals at δ_C 57.3 (NCH_2CH_2N), 62.4 ($N\mathbf{C}H_2C$), 34.1 ($C\mathbf{C}H_2C$), and 29.8 ppm (bridgehead carbon atoms).

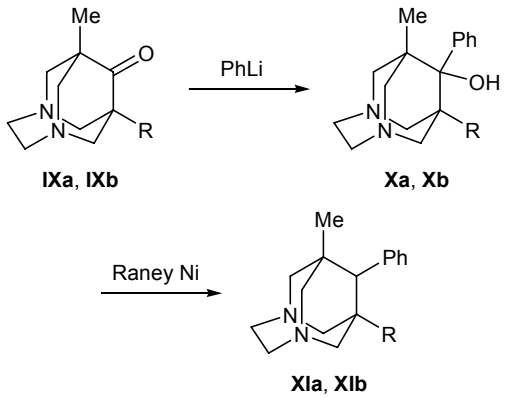
Desulfurization of other derivatives of phenylsulfanyldiazahomoadamantane provides a synthetic route to diazahomoadamantane derivatives which cannot be obtained by other methods. While studying products of desulfurization of 9-phenyl-1-phenylsulfanyl-3,6-diazahomoadamantan-9-ol (**VII**) we found that this reaction is accompanied by reduction of the hydroxy group with formation of 9-phenyl-3,6-diazahomoadamantane (**VIII**) [9] (Scheme 3).

Scheme 3.



The developed scheme of synthesis of phenyldiazahomoadamantane **VIII** is also applicable to the preparation of its derivatives. For instance, by heating 1-methyl- and 1,8-dimethyl-9-phenyl-3,6-diazahomoadamantan-9-ols **Xa** and **Xb** (obtained from 1-methyl- and 1,8-dimethyl-3,6-diazahomoadamantan-9-ones **IXa** and **IXb** [2]) over Raney nickel we synthesized 1-methyl- and 1,8-dimethyl-9-phenyl-3,6-diazahomoadamantanes **XIa** and **XIb**, respectively (Scheme 4).

Scheme 4.



R = H (**a**), Me (**b**).

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker IFS 66v/S spectrometer. The ^1H NMR spectra were measured from solutions in $CDCl_3$ on a Bruker WM-250 spectrometer at 250.13 MHz (for ^1H) using tetramethylsilane as internal reference. The mass spectra (were obtained on a Finnigan MAT 90 instrument with direct sample admission into the ion source (accelerating voltage 5.0 kV, cathode emission current 100 μA, electron impact, 70 eV, ion source temperature 200°C).

1-Phenylsulfanylpropan-2-one (I). A mixture of 13.80 g (125 mmol) of benzenethiol and 12.00 g (130 mmol) of chloroacetone was slowly heated to the boiling point and was kept boiling until hydrogen chloride no longer evolved. The mixture was cooled and diluted with double volume of petroleum ether, and the precipitate was filtered off. Yield 16.6 g (80%), white crystals, mp 31–32°C. The spectral parameters of the product were identical to those reported in [10].

1-Phenylsulfanyl-3,6-diazahomoadamantan-9-one (II). A mixture of 3.66 g (20 mmol) of 1,3,6,8-tetraazatricyclo[4.4.1.$1^{3,8}$]dodecane, 3.61 g (20 mmol) of ketone **I**, and 3.27 ml (55 mmol) of glacial acetic acid in 30 ml of isopropyl alcohol was stirred for 3 h at room temperature and was left to stand for 12 h. The precipitate was filtered off and recrystallized from heptane. Yield 3.7 g (61%), white crystals, mp 133–134°C. IR spectrum, ν, cm^{-1}: 1695 (C=O), 1600 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 2.78 s (1H, CH), 3.02 m (4H, NCH_2CH_2N), 2.90–3.12 m (4H, NCH_2C), 3.41 d (2H, NCH_2C, J = 14.0 Hz), 3.48 d (2H, NCH_2C, J = 14.0 Hz), 7.25–7.40 m (3H, Ph), 7.50 d (2H, Ph, J = 14.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 209.42 (C^9); 137.81, 129.11, 128.80, 128.78 (C_{arom}); 65.63 (C^2, C^{10}), 62.63 (C^1), 59.45 (C^7, C^{11}), 57.00 (C^4, C^5), 54.11 (C^8). Mass spectrum, m/z (I_{rel}, %): 274 (84) $[M]^+$, 241 (24), 232 (20), 136 (25), 122 (55), 91 (67), 81 (60), 68 (44), 55 (100), 42 (58). Found, %: C 65.64; H 6.81; N 10.31; S 11.50. $C_{15}H_{18}N_2OS$. Calculated, %: C 65.66; H 6.61; N 10.21; S 11.69. M 274.38.

1-Phenylsulfanyl-3,6-diazahomoadamantan-9-one hydrazone (III). A solution of 2.37 g (8.64 mmol) of ketone **II** in 40 ml of a 66% solution of hydrazine hydrate was heated for 3 h under reflux. The mixture was cooled to 0°C, and the precipitate was filtered off and recrystallized from isopropyl alcohol. Yield 2.0 g (80%), white crystals, mp 189–190°C. IR spectrum, ν, cm^{-1}: 3300, 1560 (NH_2); 1680 (C=N); 1600 ($C=C_{arom}$). ^1H NMR spectrum, δ, ppm: 2.88 m (4H, NCH_2CH_2N),

2.70–3.00 m (4H, NCH_2C), 3.21 d (2H, NCH_2C, J = 14.0 Hz), 3.40 d (2H, NCH_2C, J = 14.0 Hz), 3.16 s (1H, CH), 5.11 br.s (2H, NH_2), 7.15–7.45 m (3H, Ph), 7.46 d (2H, Ph, J = 14.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 155.21 (C^9); 137.98, 129.90, 128.85, 128.57 (C_{arom}); 64.92 (C^2, C^{10}), 57.20 (C^7, C^{11}), 57.16 (C^4, C^5), 53.78 (C^1), 36.46 (C^8). Mass spectrum, m/z (I_{rel}, %): 288 (100) $[M]^+$, 273 (11), 202 (9), 149 (11), 121 (23), 91 (24), 82 (16), 72 (87), 65 (28), 43 (67). Found, %: C 62.26; H 6.77; N 19.78; S 11.19. $C_{15}H_{20}N_4S$. Calculated, %: C 62.47; H 6.99; N 19.43; S 11.12. M 288.41.

1-Phenylsulfanyl-3,6-diazahomoadamantan-9-one 4-methylphenylsulfonylhydrazone (IV). 4-Methylbenzenesulfonohydrazide, 0.17 g (0.90 mmol), was added to a solution of 0.14 g (0.90 mmol) of ketone **II** in 10 ml of methanol, and the mixture was heated for 0.5 h under reflux. The solvent was distilled off, and the residue was recrystallized from heptane. Yield 0.21 g (72%), mp 150–151°C. IR spectrum, ν, cm^{-1}: 3300 (NH); 1640 (C=N), 1600 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.90 s (1H, CH), 2.30 s (3H, CH_3), 3.05 m (4H, NCH_2CH_2N), 2.70–3.30 m (8H, NCH_2C), 7.00–7.70 m (9H, H_{arom}), 8.30 br.s (1H, NH). Found, %: C 58.65; H 5.89; N 12.33; S 14.03. $C_{22}H_{26}N_4O_2S_2$. Calculated, %: C 58.70; H 5.92; N 12.66; S 14.49. M 442.60.

1-Phenylsulfanyl-3,6-diazahomoadamantane (V). *a*. A mixture of 1.90 g (6.59 mmol) of hydrazone **III** and 1.75 g (31 mmol) of potassium hydroxide was thoroughly stirred and heated for 2 h at 220–240°C. The mixture was cooled and extracted with diethyl ether (2×25 ml), the combined extracts were evaporated, and the reaidue was recrystallized from heptane. Yield 1.30 g (76%), white crystals, mp 87–89°C. IR spectrum: ν 1600 cm^{-1} (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 1.82 s (2H, CH_2), 1.88 s (1H, CH), 2.96 m (4H, NCH_2CH_2N), 2.66 d (2H, NCH_2C, J = 14.0 Hz), 2.71 d (2H, NCH_2C, J = 14.0 Hz), 3.15 d (2H, NCH_2C, J = 14.0 Hz), 3.25 d (2H, NCH_2C, J = 14.0 Hz), 7.25–7.40 m (3H, Ph), 7.47 d (2H, Ph, J = 14.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 137.62, 129.22, 128.90, 128.57 (C_{arom}); 62.78 (C^2, C^{10}), 57.38 (C^7, C^{11}), 56.73 (C^4, C^5), 45.17 (C^1), 40.43 (C^9), 33.17 (C^8). Mass spectrum, m/z (I_{rel}, %): 260 (25) $[M]^+$, 151 (100), 121 (44), 108 (51), 94 (50), 81 (32), 78 (50), 66 (70), 57 (61), 42 (69). Found, %: C 69.04; H 7.56; N 10.98; S 12.42. $C_{15}H_{20}N_2S$. Calculated, %: C 69.19; H 7.74; N 10.76; S 12.31. M 260.40.

b. A solution of 0.20 g (4.9 mmol) of sodium tetrahydridoborate in 5 ml of glacial acetic acid was added to a solution of 0.20 g (0.49 mmol) hydrazone **IV** in 5 ml of isopropyl alcohol. The mixture was heated for 7 h under reflux, the solvent was distilled off, the solid residue was treated with a small amount of water, water was distilled off, and the residue was recrystallized from heptane. Yield 0.07 g (68%).

3,6-Diazahomoadamantane (VI). Compound **V**, 0.40 g (2.33 mmol), was dissolved in 20 ml of isopropyl alcohol, 2 g of freshly prepared Raney nickel was added, and the mixture was heated for 20 h under reflux, additional 2-g portions of Raney nickel being added every 7 h. The catalyst was filtered off and washed with isopropyl alcohol, the solvent was distilled off from the filtrate, and the residue was recrystallized from heptane. Yield 0.18 g (76%), white crystals, mp 250–251°C. ^1H NMR spectrum, δ, ppm: 1.60 s (2H, CH_2), 1.88 s (2H, CH), 2.65 d (4H, NCH_2C, J = 14.0 Hz), 3.19 d (4H, NCH_2C, J = 14.0 Hz), 2.99 m (4H, NCH_2CH_2N). ^{13}C NMR spectrum, δ_C, ppm: 29.75 (C^1, C^8), 33.82 (C^9), 57.54 (C^2, C^7, C^{10}, C^{11}), 57.64 (C^4, C^5). Mass spectrum, m/z (I_{rel}, %): 152 (97) $[M]^+$, 108 (97), 95 (66), 85 (30), 72 (17), 60 (45), 55 (57), 57 (100), 42 (65). Found, %: C 71.57; H 10.72; N 17.71. $C_9H_{16}N_2$. Calculated, %: C 71.01; H 10.59; N 18.40. M 152.24.

9-Phenyl-1-phenylsulfanyl-3,6-diazahomoadamantan-9-ol (VII). A solution of 6.12 g (38.96 mmol) of bromobenzene in 15 ml of anhydrous diethyl ether was slowly added under vigorous stirring to 0.54 g (77.92 mmol) of metallic lithium (cut in small pieces) in 30 ml of anhydrous diethyl ether. The mixture was stirred for 40 min, 1.77 g (6.49 mmol) of ketone **II** was added over a period of 20 min, and the mixture was kept for 5.5 h at room temperature. The precipitate was dissolved in 24 ml of 18% hydrochloric acid. The aqueous layer was washed with diethyl ether (4×15 ml), neutralized with potassium carbonate, and extracted with chloroform (4×20 ml). The extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was recrystallized from ethanol. Yield 2.1 g (93%), white crystals, mp 182–183°C. IR spectrum, ν, cm^{-1}: 3432 (OH), 1636 (C=C_{arom}). ^1H NMR spectrum, δ, ppm: 2.50 br.s (1H, CH), 3.0 m (4H, NCH_2CH_2N), 2.05 d (2H, NCH_2C, J = 14.0 Hz), 2.85 d (2H, NCH_2C, J = 14.0 Hz), 3.10 d (2H, NCH_2C, J = 14.0 Hz), 3.40 d (2H, NCH_2C, J = 14.0 Hz), 4.40 br.s (1H, OH), 7.25–8.0 m (10H, H_{arom}). Mass spectrum, m/z (I_{rel}, %): 352 (77) $[M]^+$, 263 (27), 243 (51), 200 (38), 110 (69), 105 (100), 82 (42), 76 (70), 72 (41), 57 (37), 43 (49). Found, %: C 71.56; H 7.05; N 8.04; S 9.08. $C_{21}H_{24}N_2OS$. Calculated, %: C 71.55; H 6.86; N 7.95; S 9.10. M 352.49.

9-Phenyl-3,6-diazahomoadamantane (VIII). Alcohol **VII**, 0.51 g (1.46 mmol), was dissolved in 20 ml of isopropyl alcohol, 2.0 g of freshly prepared Raney nickel was added, and the mixture was heated for 20 h under reflux, additional 2-g portions of Raney nickel being added every 7 h. The catalyst was filtered off and washed with isopropyl alcohol, the solvent was distilled off from the filtrate, and the residue was recrystallized from heptane. Yield 0.25 g (76%), white crystals, mp 103–104°C. IR spectrum: ν 1535 cm^{-1} (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 2.30 br.s (2H, CH), 3.05 m (4H, NCH_2CH_2N), 2.50 d (2H, NCH_2C, J = 14.0 Hz), 3.00 d (2H, NCH_2C, J = 14.0 Hz), 3.15 d (2H, NCH_2C, J = 14.0 Hz), 3.40 d (2H, NCH_2C, J = 14.0 Hz), 3.50 s (1H, CH), 7.20–7.40 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 228 (100) $[M]^+$, 200 (39), 184 (45), 170 (70), 156 (46), 115 (66), 91 (57), 82 (98), 72 (53), 58 (100), 43 (75). Found, %: C 79.16; H 9.11; N 12.40. $C_{15}H_{20}N_2$. Calculated, %: C 78.90; H 8.83; N 12.27. M 228.33.

1-Methyl-9-phenyl-3,6-diazahomoadamantan-9-ol (Xa) was synthesized as described above for compound **VII** from 1.17 g (6.49 mmol) of ketone **IXa**. Yield 1.0 g (60%), white crystals, mp 141–142°C. IR spectrum, ν, cm^{-1}: 3100 (OH), 1535 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, CH_3), 2.05 br.s (1H, CH), 2.40–3.45 m (8H, NCH_2C), 3.05 m (4H, NCH_2CH_2N), 4.0 m (1H, OH), 7.25–7.75 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 258 (95) $[M]^+$, 184 (46), 176 (41), 110 (32), 105 (76), 98 (41), 91 (32), 82 (96), 72 (100), 55 (94), 43 (28). Found, %: C 74.05; H 8.72; N 10.92. $C_{16}H_{22}N_2O$. Calculated, %: C 74.38; H 8.58; N 10.84. M 258.36.

1,8-Dimethyl-9-phenyl-3,6-diazahomoadamantan-9-ol (Xb) was synthesized as described above for compound **VII** from 1.26 g (6.49 mmol) of ketone **IXb**. Yield 1.2 g (68%), white crystals, mp 217–218°C. IR spectrum, ν, cm^{-1}: 3320 (OH), 1535 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 0.5 s (6H, CH_3), 2.05 s (1H, OH), 2.30 d (2H, NCH_2C, J = 14.0 Hz), 2.50 d (2H, NCH_2C, J = 14.0 Hz), 3.70 d (2H, NCH_2C, J = 14.0 Hz), 3.80 d (2H, NCH_2C, J = 14.0 Hz), 3.15 m (4H, NCH_2CH_2N), 7.20–7.90 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 272 (48) $[M]^+$, 105 (43), 98 (100), 97 (15), 96 (64), 91 (33), 82 (30), 72 (68), 68 (52), 57 (48), 43 (62). Found, %: C 75.06; H 8.95; N 10.53. $C_{17}H_{24}N_2O$. Calculated, %: C 74.96; H 8.88; N 10.28. M 272.39.

1-Methyl-9-phenyl-3,6-diazahomoadamantane (XIa) was synthesized as described above for compound **VIII** from 0.7 g (2.9 mmol) of alcohol **Xa**. Yield 0.35 g (54%), white crystals, mp 94–95°C. IR spectrum: ν 1600 cm^{-1} (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 0.60 s (3H, CH_3), 1.85 br.s (1H, CH), 2.40–3.75 m (8H, NCH_2C), 3.15 m (4H, NCH_2CH_2N), 3.45 m (1H, CH), 7.20–7.50 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 242 (100) $[M]^+$, 184 (66), 171 (39), 129 (44), 115 (51), 91 (78), 82 (41), 72 (18), 68 (34), 56 (56), 43 (67). Found, %: C 79.15; H 8.89; N 11.67. $C_{16}H_{22}N_2$. Calculated, %: C 79.29; H 9.14; N 11.55. M 242.36.

1,8-Dimethyl-9-phenyl-3,6-diazahomoadamantane (XIb) was synthesized as described above for compound **VIII** from 0.78 g (2.9 mmol) of alcohol **Xb**. Yield 0.43 g (59%), white crystals, mp 184–185°C. IR spectrum: ν 1535 cm^{-1} (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 0.5 s (6H, CH_3), 3.10 m (4H, NCH_2CH_2N), 2.30 d (2H, NCH_2C, J = 14.0 Hz), 2.55 d (2H, NCH_2C, J = 14.0 Hz), 3.75 d (2H, NCH_2C, J = 14.0 Hz), 3.82 d (2H, NCH_2C, J = 14.0 Hz), 3.40 s (1H, CH), 7.20–7.85 m (5H, Ph). Mass spectrum, m/z (I_{rel}, %): 256 (90) $[M]^+$, 198 (22), 184 (46), 176 (41), 110 (32), 105 (76), 91 (32), 82 (96), 72 (100), 55 (94), 43 (28). Found, %: C 79.06; H 9.10; N 12.25. $C_{17}H_{24}N_2$. Calculated, %: C 78.95; H 8.90; N 12.10. M 256.39.

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