Synthesis of fragrant 3,6-diazahomoadamantan-9-ones

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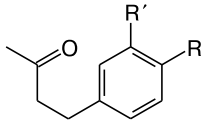
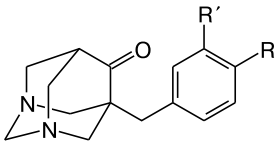
A condensation of tetramethylenediethylenetetramine with 4-phenylbutan-2-one and its derivatives such as 4-(4-hydroxyphenyl)butan-2-one, 4-(4-methoxyphenyl)butan-2-one, and 4-(4-hydroxy-3-methoxyphenyl)butan-2-one led to fragrant compounds: 1-benzyl-3,6-diazahomoadamantan-9-one and its derivatives at the benzene ring.

Key words: tetramethylenediethylenetetramine, 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane, 3,6-diazahomoadamantan-9-one, 4-phenylbutan-2-one, benzylacetone, 4-(4-hydroxyphenyl)butan-2-one, 4-(4-methoxyphenyl)butan-2-one, 4-(4-hydroxy-3-methoxyphenyl)-butan-2-one.

Earlier, we have shown[1] that the incorporation of the fragrant ketone molecules, such as 4-phenylbutan-2-one and its derivatives at the benzene ring (4-(4-hydroxyphenyl)-, 4-(4-methoxyphenyl)-, and 4-(4-hydroxy-3-methoxyphenyl)butan-2-ones (**1a—d**)), in the structure of 1,3-diazaadamantane by their condensation with hexamethylenetetramine resulted in 1,3-diazaadamantan-6-ones **2a—d**, in which the fragrance characteristic of the starting ketones was retained.



1a—d

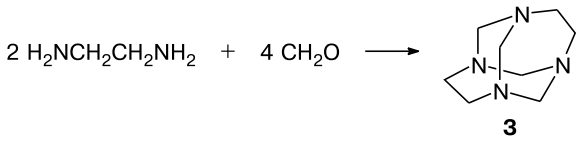


2a—d

In continuation of these studies, in the present work we synthesize 3,6-diazahomoadamantan-9-ones **4a—d** by the condensation of fragrant ketones **1a—d** with 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (tetramethylenediethylenetetramine,[2] **3**), the product of the condensation of ethylenediamine and formaldehyde (Scheme 1). The molecules of the same fragrant ketones **1a—d** were incorporated in the structure of 3,6-diazahomoadamantane, and their odor was retained in the formed 3,6-diazahomoadamantan-9-ones **4a—d**.

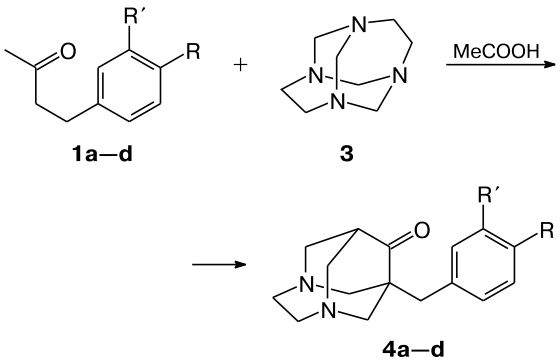
The reaction of tetramethylenediethylenetetramine **3** with ketones **1a—d** (Scheme 2) were carried out in isopropyl alcohol at ambient temperature (method ***A***). The condensation gave 1-benzyl-3,6-diazahomoadamantan-9-one (**4a**),[3] 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (**4b**),[4] 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-one (**4c**), and 1-(4-hydroxy-3-methoxybenzyl)-3,6-diazahomoadamantan-9-one (**4d**) in about 30% yield.

Scheme 1



3

Scheme 2



1a—d **3** **4a—d**

R = R′ = H (**a**), R = OH, R′ = H (**b**), R = OMe, R′ = H (**c**), R = OH, R′ = OMe (**d**)

An alternative one-pot synthesis of diazahomoadamantanone derivatives **4a—d** was also developed, in which

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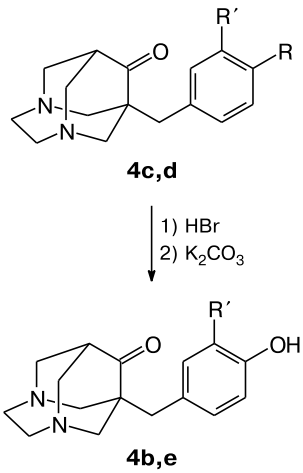
the synthesis of tetramethylenediethylenetetramine **3** and its condensation with ketones **1a—d** were carried out in one vessel without isolation (method ***B***). The yields of the target products **4a—d** obtained by either methods were virtually the same and averaged about 30%.

The fragrant diazahomoadamantanones **4a—d** can be used not only in perfumery, but also as pheromones in agriculture. Besides, they can serve as the intermediate products in the synthesis of other diazahomoadamantanones.

It is known that ordinary phenol ethers undergo cleavage under drastic conditions upon heating to 120—150 °C with concentrated solutions of hydrobromic or hydroiodic acid. It was found that the reflux of 1-(4-methoxybenzyl)- (**4c**) and 1-(4-hydroxy-3-methoxybenzyl)-3,6-diazahomoadamantan-9-one (**4d**) with concentrated hydrobromic acid over 3 h resulted in their cleavage with the formation of alcohols, 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (**4b**) and 1-(3,4-dihydroxybenzyl)-3,6-diazahomoadamantan-9-one (**4e**), respectively (Scheme 3).

Scheme 3



R = OMe, R′ = H (**c**);
R = OH, R′ = OMe (**d**), H (**b**), OH (**e**)

The structure of newly obtained compounds **4a—e** was confirmed by elemental analysis, NMR spectroscopy, and mass spectrometry.

The synthesized fragrant 3,6-diazahomoadamantan-9-ones **4a—e** are high-melting crystalline compounds, soluble in water. Together with 1,3-diazaadamantan-6-ones **2a—d**, they belong to a new class of fragrant ketones, fragrant diazaadamantanones. It can be suggested that they inherited from the parent ketones **1a—d** not only the odor, but also therapeutic and other properties.[5—10]

Experimental

4-Phenylbutan-2-one, 4-(4-hydroxyphenyl)butan-2-one, 4-(4-methoxyphenyl)butan-2-one, and 4-(4-hydroxy-3-methoxyphenyl)butan-2-one were purchased from Sigma-Aldrich, other reactants (reagent grade) and solvents used in the work were made in Russia. IR spectra of compounds were recorded on a Bruker IFSv spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra of solutions of compounds in $CDCl_3$ were recorded on a Bruker AM-300 spectrometer (300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C), using $SiMe_4$ as an internal standard. Electron impact mass spectra were recorded on a MS-30 Kratos instrument with direct injection of the sample into the source of ions at 70 eV energy of ionizing electrons and 200 °C temperature of the source of ions. Melting points were determined on a PTP-M appliance.

1-Substituted 3,6-diazahomoadamantan-9-ones 4a—d (general procedure). ***A.*** A mixture of tetramethylenediethylenetetramine **3** (8.50 g, 50 mmol), ketone **1a—d** (55 mmol), and AcOH (9.00 g, 150 mmol) in Pr^{i}OH (50 mL) was stirred for 72 h at room temperature. The reaction mixture was concentrated *in vacuo*, a dense residue was extracted with hot *n*-heptane (4×40 mL). A warm extract was purified, passing through a layer of anhydrous aluminum oxide (10 g, Brockmann activity II) placed on a Shott filter. The solvent was evaporated, the residue was recrystallized from *n*-heptane.

B. Paraform aldehyde (6.00 g, 200 mmol) was added to a solution of ethylenediamine (6.00 g, 100 mmol) in Pr^{i}OH (50 mL), and the mixture was stirred until complete dissolution. Then, ketone **1a—d** (55 mmol) and AcOH (9.00 g, 150 mmol) were added to this solution. The reaction mixture was stirred for 72 h at room temperature and concentrated *in vacuo*. A dense residue was extracted with hot *n*-heptane (4×40 mL). A warm extract was purified, passing through a layer of anhydrous aluminum oxide (10 g, Brockmann activity II) placed on a Shott filter. The extractant was evaporated *in vacuo*, the residue was recrystallized from *n*-heptane.

1-Benzyl-3,6-diazahomoadamantan-9-one (4a). The yield was 4.10 g (32%) (***A***), 4.00 g (31%) (***B***), white crystals, m.p. 102—104 °C (from *n*-heptane) (*cf.* Ref. 3: m.p. 102—104 °C). ^{13}C NMR ($CDCl_3$), δ: 213.54 CO(9); 136.50, 130.34, 127.86, 127.82 (Ph); 60.41 (C(2), C(10)); 58.23 (C(4), C(5)); 57.10 (C(7), C(11)); 49.77 C(8); 45.52 C(1); 41.62 ($\underline{C}H_2Ar$).

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantan-9-one (4b). The yield was 2.54 g (33%) (***A***), 4.40 g (32%) (***B***), white crystals, m.p. 209—210 °C (from *n*-heptane) (*cf.* Ref. 4: m.p. 209—210 °C).

1-(4-Methoxybenzyl)-3,6-diazahomoadamantan-9-one (4c). The yield was 5.57 g (39%) (***A***), 4.88 g (34%) (***B***), white crystals, m.p. 106—107 °C (from *n*-heptane). Found (%): C, 71.43; H, 7.60; N, 9.85. $C_{17}H_{22}N_2O_2$. Calculated (%): C, 71.30; H, 7.74; N, 9.78. IR, ν/cm^{-1}: 1711 (C=O); 1609 (Ar); 1251, 1041 (OCH_3). ^{1}H NMR ($CDCl_3$), δ: 2.67 (br.s, 1 H, CH); 2.79 (s, 2 H, CH_2Ar); 2.97, 3.48 (both d, 4 H, 2 NCH_2C, J = 3.9 Hz); 3.15 (m, 4 H, NCH_2CH_2N); 3.07—3.20 (m, 4 H, 2 $NC\underline{H}_2CH$); 3.80 (s, 3 H, OCH_3); 6.82, 7.00 (both d, 4 H, Ar, J = 8.8 Hz). MS, m/z (I_{rel} (%)): 286 $[M]^+$ (76), 213 (73), 165 (14), 137 (19), 131 (21), 122 (20), 101 (50), 91 (72), 72 (99), 58 (100), 43 (41).

1-(4-Hydroxy-3-methoxybenzyl)-3,6-diazahomoadamantan-9-one (4d). The yield was 5.30 g (35%) (***A***), 4.85 g, 32%) (***B***), white crystals, m.p. 180—182 °C (from *n*-heptane). Found (%): C, 67.44; H, 7.40; N, 9.32. $C_{17}H_{22}N_2O_3$. Calculated (%): C, 67.53; H, 7.33; N, 9.26. IR, ν/cm^{-1}: 1711 (C=O); 1609 (Ar); 1245, 1032 (OCH_3), 3322 (OH). ^{1}H NMR ($CDCl_3$), δ: 2.71 (br.s, 1 H, CH); 2.78 (s, 2 H, CH_2Ar); 3.03 (d, 2 H, NCH_2C, J = 13.9 Hz); 3.22 (m, 4 H, NCH_2CH_2N); 3.17—3.24 (m, 4 H, 2 $NC\underline{H}_2CH$); 3.53 (d, 2 H, NCH_2C, J = 13.2 Hz); 3.88 (s, 3 H,

OCH_3); 5.58 (br.s, 1 H, OH); 6.56 (d, 1 H, Ar, J = 8.0 Hz); 6.62 (s, 1 H, Ar); 6.83 (d, 1 H, Ar, J = 8.0 Hz). MS, m/z (I_{rel} (%)): 302 $[M]^+$ (76), 213 (73), 165 (14), 137 (19), 131 (21), 122 (20), 101 (50), 91 (72), 72 (99), 58 (100), 43 (41).

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantan-9-one (4b). Concentrated hydrobromic acid (5 mL) was added to a solution of 1-(4-methoxybenzyl)diazahomoadamantan-9-one (**4c**) in Pr^iOH (10 mL). The reaction mixture was refluxed for 3 h, neutralized with K_2CO_3 to pH 7, filtered, and extracted with toluene (3×20 mL). The solvent was evaporated, the residue was recrystallized from *n*-heptane. The yield was 0.24 g (47%), white crystals, m.p. 209—210 °C (from *n*-heptane) (*cf.* Ref. 4: m.p. 209—210 °C).

1-(3,4-Dihydroxybenzyl)-3,6-diazahomoadamantan-9-one (4e). Concentrated hydrobromic acid (5 mL) was added to a solution of 1-(4-hydroxy-3-methoxybenzyl)-3,6-diazahomoadamantan-9-one (**4d**) (0.60 g, 2 mmol) in Pr^iOH (10 mL). The reaction mixture was refluxed for 3 h, neutralized with K_2CO_3 to pH 7, filtered, and extracted with toluene (3×20 mL). The solvent was evaporated, the residue was recrystallized from toluene. The yield was 0.25 g (43%), white crystals, m.p. 245—243 °C (from toluene). Found (%): C, 66.56; H, 7.12; N, 9.60. $C_{16}H_{20}N_2O_3$. Calculated (%): C, 66.65; H, 6.99; N, 9.72. IR, ν/cm^{-1}: 1705 (C=O); 1603 (Ar); 3345 (OH). ^1H NMR ($CDCl_3$), δ: 2.37 (s, 2 H, CH_2Ar); 2.74 (br.s, 1 H, CH); 3.19—3.24 (m, 2 H, $NC\underline{H}_2CH$); 3.26—3.29 (m, 4 H, NCH_2CH_2N); 3.32—3.37 (m, 2 H, $NC\underline{H}_2CH$); 3.61 (t, 4 H, 2 NCH_2C, J = 13.9 Hz); 5.73 (br.s, 2 H, 2 OH); 7.08—7.27 (m, 3 H, Ar). MS, m/z (I_{rel} (%)): 288 $[M]^+$ (100), 244 (11), 230 (21), 214 (29), 200 (11), 167 (20), 149 (08), 121 (59), 91 (09), 58 (17), 42 (20).

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