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HETEROADAMANTANES AND THEIR DERIVATIVES 26.* SYNTHESIS OF DERIVATIVES OF HYDROXY-BENZYLDIAZAHOMOADAMANTANE

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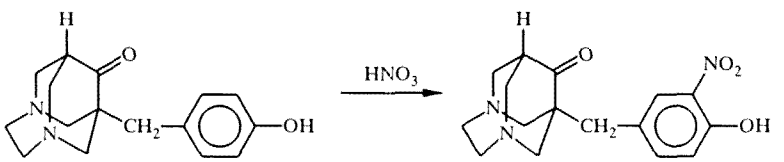
1-(4-Hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one was obtained by the nitration of hydroxybenzyldiazahomoadamantanone. The behavior of the carbonyl group of this ketone and of its nitro derivative has been studied. The structures of the functional derivatives obtained were confirmed by data of IR, PMR, and mass spectra.

Derivatives of 3,6-diazahomoadamantane containing substituents with functional groups in the angular positions have been studied little up to the present time. 1-(4-hydroxybenzyl)-3,6-diazahomoadamantane-9-one (Ia) has been used in the present work as the starting material for obtaining phenol-containing derivatives of diazahomoadamantane. Compound (Ia) was obtained in 56% yield by the condensation of 1,3,6,8-tetraazatricyclo[4.4.1.$1^{3,8}$]dodecane with 4-(3-hydroxyphenyl)butan-2-one (raspberry ketone) [2]. 1-(4-Hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantane-9-one (Ib) was obtained in 84% yield by the nitration of (Ia) with dilute nitric acid.



Ia Ib

Absorption bands were observed near 1350 and 1520 in the IR spectrum of (Ib) for the stretching vibrations of the nitro group, at 1700 for the keto group, and at 3200 cm^{-1} for the hydroxyl group.

Sodium borohydride in alcohol readily reduced ketones (Ia, b) to the corresponding diazahomoadamantanols (IIa, b). Reaction of ketones (Ia, b) with excess hydrazine hydrate led to the hydrazones (IIIa, b). When obtaining hydrazone (IIIb) the reaction temperature must not exceed 60°C since the nitro group may be reduced to an amino group by hydrazine at higher temperatures [3]. By fusing hydrazone (IIIa) with potassium hydroxide according to Wolff–Kishner the hydroxybenzyldiazahomoadamantane (IVa) was obtained. Nitration of the latter gave 1-(4-hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantane (IVb). Oximes (Va, b) of the diazahomoadamantanes were formed by the reaction of the corresponding ketones (Ia, b) with hydroxylamine. On reducing the oxime (Va) with Ni–Al alloy 9-amino-1-(4-hydroxybenzyl)-3,6-diazahomoadamantane (VIa) was formed, nitration of which led to 9-amino-1-(4-hydroxyl-3-nitrobenzyl)-3,6-diazahomoadamantane (VIb).

*For part 25 see [1].

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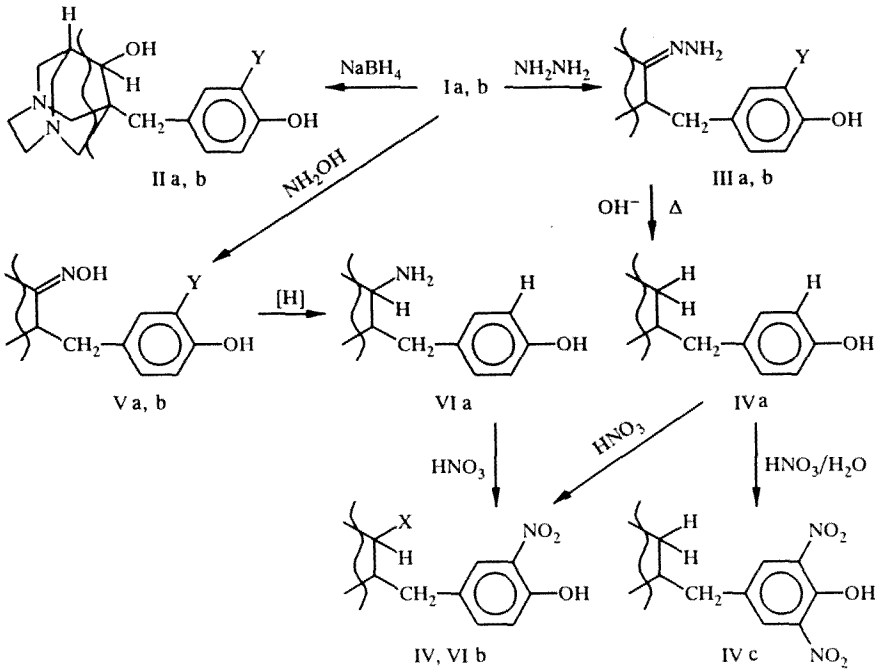

I, II, III, V a Y = H, b Y = NO_2; IVb X = H; VIb X = NH_2

Nitration of hydroxybenzyldiazahomoadamantane (IVa) in an excess of dilute nitric acid for 7 h gave 1-(4-hydroxy-3,5-dinitrobenzyl)-3,6-diazahomoadamantane (IVc).

The structures of the compounds (I)-(VI) synthesized were confirmed by data of IR, PMR, and mass spectra (Tables 1 and 2).

EXPERIMENTAL

The IR spectra of the compounds being investigated were recorded on a Bruker IFS 113v spectrometer in KBr disks, and PMR spectra on a Bruker WM 250 instrument (in $CDCl_3$) with TMS as internal standard. The mass spectra were obtained on a Finnigan MRT 90 instrument with direct insertion of samples into the ion source, the ionizing energy of electrons was 70 eV, temperature of the ionization chamber 200°C, and perfluorokerosene was used as standard. Resolution M/ΔM = 10000. The characteristics of compounds are given in Table 1.

Data of elemental analysis for C, H, and N agreed with calculated values.

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantan-9-one(Ia), 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-oneoxime (Va), and 9-amino-1-(4-hydroxybenzyl)-3,6-diazahomoadamantane (VIa) were obtained as described in [2].

1-(4-Hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one (Ib) $C_{16}H_{18}N_3O_4$. Concentrated nitric acid (32 ml) was added dropwise with stirring to a solution of 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (Ia) (2.0 g: 7.35 mmole) in water (40 ml). The reaction mixture was maintained at room temperature for 4 h, neutralized with sodium acetate to pH 6-7, and extracted with chloroform (3 × 20 ml). The solvent was distilled off, and the residue crystallized from heptane. Compound (Ib) (1.95 g. 83.7%) was obtained. PMR spectrum [$(CD_3)_2SO$, CF_3COOD]: 7.60 (d); 7.08 (d); 6.74 (4H, d, C_6H_4); 3.94 (4H, m, NCH_2CH_2N); 3.36 (d); 3.60 (d); 3.06 (d); 2.98 (8H, d, NCH_2C, J = 14.0 Hz); 2.72 (1H, s, CH); 2.32 (2H, s, CH_2); 3.60 ppm (1H, br s, COH).

Compounds (IVb) and (VIb) were obtained similarly.

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantan-9-ol (IIa) $C_{16}H_{22}N_2O_2$. Sodium borohydride (0.13 g) was added in portions with stirring to a solution of 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (Ia) (0.5 g. 1.85 mmole) in isopropyl alcohol (5 ml), and the mixture was stirred for 5 h. After removal of the solvent, water (1 ml) was added, the solution acidified to pH 1-2 with 7% HCl, and then saturated sodium carbonate solution was added to pH 9. The solvent was evaporated, and the solid residue extracted with hot toluene (4 × 15 ml). The solvent was distilled off. Compound (IIa) (0.40 g. 79.4%) was

TABLE 1. Characteristics of Compounds (Ib), (IIa, b), (IIIa, b), (IVa-c), (Vc), (VIc)

Compound	mp, °C	IR spectrum, ν, cm^{-1}	Yield, %
Ib	124...126	3200 (OH), 1700 (CO), 1520, 1350 (NO_2)	84
IIa	257...259	3200 (OH), 1600 (arom.)	79
IIb	184...186	3270 (OH), 1535, 1354 (NO_2)	95
IIIa	235...237	3337, 3315, 3205 (NH, OH), 1635 (C=N)	90
IIIb	123...125	3345, 3305, 3220 (NH, OH), 1626 (C=N), 1537, 1353 (NO_2)	86
IVa	221...223	3235, 3107 (OH), 1603 (arom.)	72
IVb	220...222	3430 (OH), 1542, 1346 (NO_2)	54
IVc	269...261	3188 (OH), 1548, 1345 (NO_2)	59
Vb	263...265	3190, 3070 (OH), 1662 (C=N), 1533, 1327 (NO_2)	88
VIb	210...212	3250, 3190 (NH, OH), 1576, 1348 (NO_2)	69

*Compounds (IIa, b), (IVb), and (Vb) were recrystallized from toluene, (IIIa) from isopropyl alcohol, and the remainder from heptane.

TABLE 2. Mass Spectra of Compounds (Ib), (IIa), (IIIb), (IVb), (IVc), and (VIb)*

Compound	Values of m/z (relative intensity, %)
Ib	317(75), 316(12), 152(7), 84(13), 77(8), 72(30), 58(100), 57(24), 55(19), 42(23), 41(13)
IIa	247(100), 200(22), 167(32), 111(24), 107(45), 72(40), 58(70), 57(24), 43(36), 42(26)
IIIb	331(23), 315(12), 165(5), 151(8), 83(17), 76(9), 72(35), 58(100), 57(10), 43(23), 42(12)
IVb	303(14), 273(35), 245(7), 151(38), 109(12), 86(20), 72(34), 58(100), 55(16), 44(13), 42(15)
VIb	318(15), 271(9), 259(5), 245(39), 152(53), 106(5), 94(16), 85(12), 72(84), 72(84), 58(88), 43(100)
IVc	348(100), 318(34), 304(14), 290(14), 151(31), 108(14), 95(19), 72(34), 58(45), 57(16), 42(14)

*Peaks of $[M^+]$ and of the 10 most intense ions are given.

obtained after recrystallization of the residue from toluene. PMR spectrum ($CDCl_3$): 7.10-7.32 (4H, m, C_6H_4); 3.16 (4H, m, NCH_2CH_2N); 3.68 (d); 3.56 (d); 3.35 (d); 3.20 (d); 3.05 (d); 2.95 (8H, d, NCH_2C, J = 14.0 Hz); 1.93 (1H, s, CH); 2.75 (2H, s, CH_2-$C_{(6)}$); 2.96 (1H, s, CHO); 4.19 ppm (1H, br.s, COH).

Compound (IIb) $C_{16}H_{21}N_3O_4$ was obtained similarly.

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantan-9-one Hydrazone (IIIa) $C_{16}H_{22}N_4O$. A mixture of 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (Ia) (2.0 g. 7.34 mmole) and 80% hydrazine hydrate (12 ml) was heated for 2 h. The crystals which precipitated after cooling were filtered off and recrystallized from isopropyl alcohol. Compound (IIIa) (1.90 g. 90.3%) was obtained.

1-(4-Hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one Hydrazone (IIIb) $C_{16}H_{21}N_5O_3$. A mixture of 1-(4-hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one (Ib) (0.2 g. 0.63 mmole) and 80% hydrazine hydrate (2 ml) was heated for 3 h at 50-60°C. The crystals which precipitated after cooling were filtered off and recrystallized from heptane. Compound (IIIb) (0.18 g. 86.2%) was obtained.

1-(4-Hydroxybenzyl)-3,6-diazahomoadamantane (IVa) $C_{16}H_{22}N_2O$. A mixture of 1-(4-hydroxybenzyl)-3,6-diazahomoadamantan-9-one hydrazone (IIIa) (0.39 g. 1.60 mmole) and powdered potassium hydroxide (0.60 g) was heated at 210-220°C for 3 h. The cooled melt was dissolved in 25% hydrochloric acid (20 ml) and the solution neutralized to pH 7-8 with

potassium carbonate. The water was distilled off. The dry residue was then extracted with toluene (3 × 10 ml). After removal of the solvent the residue was recrystallized from heptane. Compound (IVa) (0.30 g. 72.3%) was obtained. PMR spectrum ($CDCl_3$): 6.55-6.90 (4H, m, C_6H_4); 3.12 (4H, m, NCH_2CH_2N); 3.14 (d); 2.93 (d); 2.76 (d); 2.60 (8H, d, NCH_2C, J = 13.2 Hz); 2.30 (2H, s, CH_2-$C_{(6)}$), 1.90 (1H, br.s, CH); 1.58 (2H, br.s, CH_2); 1.30 ppm (1H, s, COH).

1-(4-Hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one Oxime (Vb) $C_{16}H_{20}N_4O_4$. A solution of hydroxylamine hydrochloride (0.10 g. 1.35 mmole) in water (5 ml) was added to a solution of 1-(4-hydroxy-3-nitrobenzyl)-3,6-diazahomoadamantan-9-one (Ib) in a mixture of water (5 ml) and isopropyl alcohol (2.5 ml). The mixture was heated to 60-70°C and a solution of sodium carbonate (0.13 g. 1.35 mmole) in water (10 ml) was added in portions with stirring. The mixture was heated at 60-70°C for 1.5 h. The solid which precipitated after cooling was filtered off and recrystallized from toluene. Compound (Vb) (0.11 g. 87.5%) was obtained.

1-(4-Hydroxy-3,5-dinitrobenzyl)-3,6-diazahomoadamantane (IVc) $C_{16}H_{20}N_3O_3$. Concentrated nitric acid (9 ml) was added with vigorous stirring to a solution of 1-(4-hydroxybenzyl)-3,6-diazahomoadamantane (IVa) in water (10 ml). The reaction mixture was maintained at room temperature for 7 h, water (10 ml) was added, and the solution neutralized to pH 7-8 with sodium acetate. The precipitated solid was filtered off, and the solution extracted with chloroform (3 × 20 ml). The chloroform was distilled off. The residue was combined with the solid and recrystallized from heptane. Compound (IVc) (0.16 g. 53.3%) was obtained. PMR spectrum (DMSO-D_6, CF_3COOD): 8.05 (2H, s, C_6H_2); 3.98 (4H, m, NCH_2CH_2N); 3.44 (d); 3.16 (d); 3.15 (d); 3.7-4.10 (8H, m, NCH_2C, J = 14.0 Hz); 2.82 (1H, s, CH); 3.55 (1H, br.s, $C_{(6)}$–OH); 1.98 (2H, br.s, $C_{(9)}$); 2.41 ppm (2H, d, CH_2–C, J = 10.0 Hz).

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