HETEROADAMANTANES AND THEIR DERIVATIVES. 15.* SYNTHESIS OF DERIVATIVES OF 9-AMINO-3,6-DIAZAHOMOADAMANTANES

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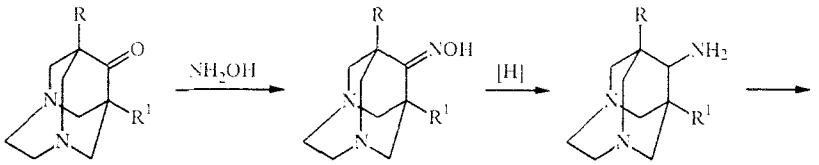
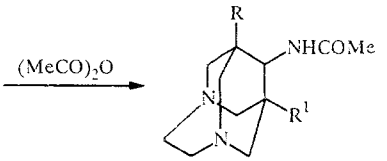
9-Amino-3,6-diazahomoadamantanes were prepared from 3,6-diazahomo-adamantan-9-ones through oximes and converted into 9-acetylamino-3,6-diaza-homoadamantanes with acetic anhydride. It was shown that oximes with one substituent in the nodal position are formed as one geometric isomer with the E-position of the hydroxyl group relative to the substituent.

The effect of substituents in nodal positions on the reactivity of their carbonyl group was demonstrated in a previous communication [1] in reduction of 3,6-diazahomoadamantan-9-ones I with sodium borohydride. The previously described [2, 3] diazahomoadamantanones Ia-d and 1-(*p*-hydroxybenzyl)-3,6-diazahomoadamantan-9-one (Ie), newly synthesized by condensation of 1,3,6,8-tetraazatricyclo[4.4.1.$1^{3,8}$]dodecane (tetramethylenediethylenetetramine) with 4-(*p*-hydroxyphenyl)-2-butanone (raspberry ketone), were converted into oximes 2a-e with hydroxylamine in aqueous medium in the present study.



I a-e IIa-e IIIa-e



IVb-d, f

I—IV a $R=R^1=H$; b $R=Me$, $R^1=H$; c $R=R^1=Me$; d $R=Ph$, $R^1=H$; e $R=4\text{-}HOC_6H_4CH_2$, $R^1=H$; f $R=4\text{-}MeCOOC_6H_4CH_2$, $R^1=H$

The effect of substituents in nodal positions on the reactivity of the carbonyl group in this reaction is more a function of the steric hindrances created by them than in the reaction of reduction with sodium borohydride. Dimethyldiazahomoadamantanone Ic thus reacts with hydroxylamine more slowly than monomethyldiazahomoadamantane Ib,

*See [1] for Communication 14.

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TABLE 1. Properties of Compounds I-IV

Compound	Empirical formula	Mp, °C (solvent for crystallization)	IR spectrum, ν, cm^{-1}	Yield, %
Ie	$C_{16}H_{20}N_2O_2$	209...210 (toluyl)	1700(CO), 1600 (arom)	56
IIa	$C_9H_{15}N_3O$	232...234 (toluyl)	3200, 3055(OH), 1657(C=N)	91
IIb	$C_{10}H_{17}N_3O$	139...140* (toluyl)	3200, 3070(OH), 1630(C=N)	99
IIc	$C_{11}H_{19}N_3O$	196...197* (toluyl)	3200, 3070(OH), 1650(C=N)	58
IId	$C_{15}H_{19}N_3O$	206...208 (toluyl)	3300, 3130(OH), 1655(C=N), 1605(arom)	99
IIe	$C_{16}H_{21}N_3O_2$	290...291 (ether)	3660(OH), 1650(C=N), 1600 (arom)	94
IIIb	$C_{10}H_{19}N_3$	104...105* (ether)	3350, 3150, 1600(NH)	71
IIIc	$C_{11}H_{21}N_3$	218...219** (ether)	3340, 3150, 1600(NH)	99
IIId	$C_{15}H_{21}N_3$	71...72 (ether)	3320, 3240, 1580(NH), 1605 (arom)	84
IIIe	$C_{16}H_{23}N_3O$	255...256 (toluyl)	3200, 3100(OH,NH), 1610 (arom)	35
IVb	$C_{12}H_{21}N_3O$	185...186 (heptane)	3300, 1630, 1530(CONH)	55
IVc	$C_{13}H_{23}N_3O$	179...181 (heptane)	3310, 1640, 1525(CONH)	82
IVd	$C_{17}H_{23}N_3O$	134...135 (toluyl)	3305, 1640, 1540(CONH), 1600(arom)	36
IVf	$C_{20}H_{27}N_3O_3$	224...225 (toluyl)	3294, 1633, 1543(CONH), 1612(arom)	54

*Sublimate.

**Mp of the corresponding iodomethylate.

TABLE 2. Parameters of the ESR Spectra of Compounds I-III

Compound	Chemical shifts of protons, δ, ppm		R, R^1
	NCH_2CH_2N	NCH_2C, d	
Ie	3,15 m^a	3,30, 3,02; 3,15, 2,90	2,54 br.s H, 2,76 s CH_2, 7,4...7,12m C_6H_4
IIa	3,15 m^a	3,28, 2,95; 3,21, 2,78	3,06 br.s H, 3,61 m^a
IIb	3,24 m^a	3,40, 3,02; 3,07, 2,88	3,70 s H, 0,98 s CH_3
IIc	3,14 m^a	3,22, 2,75; 3,02, 2,58	1,38 s, 0,90 s CH_3
IIe	3,16 m^a	3,32, 2,96; 3,18, 2,94	2,58 s H, 2,78 s CH_2, 7,30...7,08 m C_6H_4
IIIc	3,34 m^a	3,49, 2,88; 3,16, 2,56	1,02 s CH_3, 1,83 br.s NH_2, 2,72 sH with CNH_2
IIIe	3,15 m^a	3,80, 3,60; 3,42, 3,22; 3,00, 2,96; 2,61, 2,55	1,18 br.s NH_2, 3,48s H with CNH_2, 1,93s H, 2,78 s CH_2, 7,39...7,18 m C_6H_4

m^a: the center of the multiplet is indicated.

while the opposite is true for sodium borohydride [1]. Other monosubstituted diazahomoadamantanones also react with hydroxylamine more rapidly than dimethyldiazahomoadamantanone Ic. This suggests that the reactivity of diazahomoadamantanones with two different substituents in nodal positions with respect to hydroxylamine and with respect to sodium borohydride [1] is determined by the least bulky one. Unsubstituted diazahomoadamantanone Ia is less reactive with respect to both reagents than its monomethyl analog Ib.

The formation of oximes IIa-e from ketones Ia-e is confirmed by the presence of absorption bands of stretching vibrations of azomethine and hydroxyl groups in the 1655-1630 and 3700-3180 cm^{-1} region, respectively, in their IR spectra (Table 1).

The question of the orientation of the hydroxyl group relative to the substituent arises in the case of monosubstituted diazahomoadamantanone oximes. This can be judged by comparing the chemical shifts of the protons in nodal positions and methyl group protons in the ESR spectra (Table 2) of oximes IIa-c reported below.

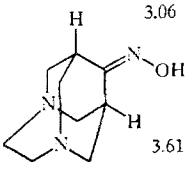
The proton in the nodal position and the methyl group protons of monomethyldiazahomoadamantanone oxime IIb form one singlet signal at 3.70 and 0.98 ppm, respectively, while the analogous protons in the oximes of unsubstituted and dimethyldiazahomoadamantanones IIa, c form two singlet signals. If we assume that the hydroxyl group of compounds IIb is

TABLE 3. Mass Spectra of Compounds I-IV

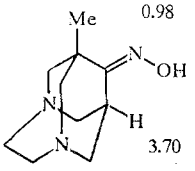
Compound	m/z (relative intensity, %)*
Ie	272(24), 107(13), 73(17), 72(39), 58(100), 57(11), 55(15), 44(10), 43(26), 42(26), 41(13)
IIa	181(100), 164(42), 136(19), 135(34), 123(22), 121(41), 94(20), 58(39), 55(23), 42(41), 41(22)
IIb	195(52), 178(58), 149(22), 135(33), 72(12), 58(100), 57(17), 55(20), 43(19), 42(36), 41(24)
IIc	209(41), 193(38), 192(37), 149(48), 122(23), 96(18), 72(26), 58(100), 55(23), 42(47), 41(29)
IIe	287(43), 271(30), 270(75), 227(24), 107(41), 72(97), 58(100), 44(74), 43(31), 42(64), 41(29)
IIIb	181(100), 108(32), 82(28), 72(29), 70(28), 58(34), 57(31), 56(65), 55(40), 44(30), 42(65)
IIIc	195(100), 122(42), 108(32), 98(72), 96(31), 82(30), 72(42), 70(43), 44(42), 43(28), 42(59)
IIId	243(100), 214(23), 170(37), 156(28), 91(21), 72(35), 58(38), 56(50), 44(45), 42(66), 41(21)
IIIe	273(100), 200(30), 186(27), 107(74), 94(25), 82(25), 72(88), 58(76), 56(42), 44(68), 42(71)
IVc	237(100), 165(43), 122(32), 108(28), 98(33), 96(34), 82(24), 72(39), 71(25), 70(28), 42(34)
IVb	223(100), 165(32), 151(47), 121(33), 108(36), 98(33), 96(31), 82(36), 72(31), 58(39), 56(34)
IVd	285(100), 227(21), 226(16), 213(33), 183(19), 170(23), 155(21), 85(16), 72(36), 58(20), 42(19)
IVf	357(33), 315(100), 314(32), 149(26), 107(40), 91(32), 84(30), 82(39), 72(45), 58(26), 42(27)

*The peaks of M^+ ions and the ten most intense ion peaks in the mass spectra are reported.

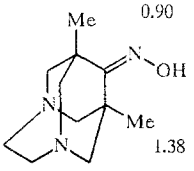
in the Z- or E-position with respect to the substituent, then we can hypothesize that the singlet at 3.61 ppm in the spectrum of compound IIa belongs to the proton in the Z-position and the singlet at 3.06 ppm belongs to the proton in the E-position in nodal positions. The singlet at 1.38 ppm in the spectrum of oxime IIc can be assigned to protons of Z-positioned and the one at 0.90 ppm can be assigned to protons of E-positioned methyl groups.



IIa



IIb



IIc

Oximes IIb-e were reduced by melting nickel with aluminum (50:50) in aqueous-alkaline medium in 9-amino-3,6-diazahomoadamantanes IIb-e, confirmed by the disappearance of the absorption bands of the azomethine group and appearance of absorption bands of the amino group in the 3350-3150 cm^{-1} region in the IR spectra.

9-Acetylamino-3,6-diazahomoadamantanes IVb-d were prepared from amines IIIb-d by heating with acetic anhydride. Aminophenol IIIe was also acetylated at the phenol hydroxyl in these conditions into 9-acetylamino-1-(*p*-acetylhydroxybenzyl)-3,6-diazahomoadamantane (IVf). The structure of amides IVb-d, f was confirmed by the IR spectra which exhibit the absorption bands of amide group stretching vibrations.

The mass spectra of the compounds obtained (Table 3) which exhibited intense and in many cases maximum peaks of the M^+ ion were also recorded. As for the previously investigated [1, 3] diazahomoadamantanones I and alcohols prepared from them, the formation of $[C_3H_8N]^+$ (*m/z* 58) and $[C_4H_{10}N]^+$ ions (*m/z* 72) is most characteristic of the mass spectral decomposition of compounds II-III. The other directions of decomposition of M^+ of these compounds are due to the nature

of the functional substituent in position 9 of the diazahomoadamantane backbone. Fragmentation of the ions of 9-amino- and 9-acetylamino derivatives III and IV takes place primarily with successive cleavage of the functional substituent and $C_nH_{2n+1}N$ molecules (n = 1-3). Splitting of an oxygen atom from the M^+ ion and loss of a hydroxyl group is most probable for oximes II. The $[M—OH]^+$ ion subsequently decomposes with splitting of the $C_nH_{2n+1}N$ molecule (n = 1-3), as the high-resolution spectrum of methyldiazahomoadamantanone oxime IIb shows.

EXPERIMENTAL

The IR spectra were recorded on Specord 71-1P and Bruker IRFTIES-113 spectrometers in petrolatum, the ESR spectra were recorded on a Bruker M-250 in $CDCl_3$, TMS internal standard, and the low- and high-resolution mass spectra were obtained on a Kratos MS-80 with direct introduction of the sample into the ion source, 70 eV ionizing electron energy, 150°C ionization chamber temperature, perfluorokerosene standard, and resolution of $M/\Delta M$ = 10,000. The properties of the compounds are reported in Tables 1-3.

The data from elemental analysis corresponded to the calculated data.

1-(p-Hydroxybenzyl)-3,6-diazahomoadamanatan-9-one (Ie). A solution of 2.46 g (15 mole) of 4-(*p*-hydroxyphenyl)-2-butanone, 2.52 g (15 mmole) of tetramethylenediethylenetetramine, and 2.57 ml (45 mmole) of acetic acid in 25 ml of isopropyl alcohol was stirred for 4 h at room temperature. The reaction mass was evaporated, extracted with hot heptane (6 × 30 ml), and the extract was purified through a layer of anhydrous Al_2O_3 placed on a Schott filter. The extracting agent was distilled off in a vacuum, and the solid residue was recrystallized from heptane. Then 2.28 g (56%) of diazahomoadamantanone Ie was obtained.

3,6-Diazahomoadamantan-9-one oxime (IIa). Here 0.1 g (0.6 mmole) of diazahomoadamantanone Ia and 0.06 g (0.84 mmole) of hydroxylamine hydrochloride were dissolved in 1 ml of water at 60-70°C, 0.07 g (1.6 mmole) of sodium hydroxide in 0.5 ml of water was added and heated for 3 h in a boiling water bath, evaporated dry, and the sediment was extracted with toluene. The sediment formed on cooling of the extract was filtered off, yielding 0.1 g (91%) of diazahomoadamantanone IIa.

1-Methyl-3,6-diazahomoadamantan-9-one oxime (IIb). A solution of 5.30 g (50 mmole) of NaOH in 20 ml of water was added by portions to a solution of 3.60 g (20 mmole) of diazahomoadamantanone Ib and 3.47 g (50 mmole) of hydroxylamine hydrochloride in 20 ml of water at 60-70°C while stirring for 15 min and stirring was continued at this temperature for another 10 min. The precipitated sediment was filtered off, dried, and recrystallized from toluene. Then 3.86 g (99%) of methyldiazahomoadamantanone oxime IIb was obtained.

1,8-Dimethyl-3,6-diazahomoadamantan-9-one oxime (IIc) was prepared similar to compound IIb from 3.89 g (20 mmole) of dimethyldiazahomoadamantanone Ic and the same amounts of the other reagents after heating for 7 h. After recrystallization from toluene, 2.42 g (58%) of dimethyldiazahomoadamantanone oxime IIc was obtained.

1-Phenyl-3,6-diazahomoadamantan-9-one oxime (IId) was obtained similar to compound IIb from 4.84 g (20 mmole) of phenyldiazahomoadamantanone Id and the same amounts of the other reagents. After recrystallization from toluene, 5.07 g (99%) of phenyldiazahomoadamantanone oxime IId was obtained.

1-(*p*-Hydroxybenzyl)-3,6-diazahomoadamantan-9-one oxime (IIe) was prepared similar to compound IIb from 2.59 g (9.5 mmole) of hydroxybenzyldiazahomoadamantanone Id, 1.66 g (23.9 mmole) of hydroxylamine hydrochloride, and 2.54 g (24 mmole) of sodium carbonate while boiling gently for 1.5 h. It was washed with water, dried, and 2.56 g (94%) of hydroxybenzyldiazahomoadamantanone oxime IIe was obtained.

9-Amino-1-methyl-3,6-diazahomoadamantane (IIIb). A solution of 7.8 g of sodium hydroxide in 10 ml of water was added dropwise over 1 h to a suspension of 1.52 g (7.8 mmole) of methyldiazahomoadamantanone oxime IIb in 15 ml of water and 7.8 group of Ni—Al alloy (50:50) in 15 ml of water while intensely stirring and not allowing the reaction mixture to heat above 50°C, stirred for another 2 h, cooled, and extracted with ether (6 × 15 ml). The ether solution was dried with sodium hydroxide and evaporated. Then 1.10 g (71%) of amine IIIb was obtained.

9-Amino-1,8-dimethyl-3,6-diazahomoadamantane (IIIc) was prepared similar to compound IIIb from 0.5 g (2.5 mmole) of dimethyldiazahomoadamantanone oxime IIc, 2.6 g of Ni—Al alloy (50:50), and 2.6 g of sodium hydroxide. After evaporation of the ether, 0.47 g (99%) of amine IIIc was obtained.

9-Amino-1-phenyl-3,6-diazahomoadamantane (IIId) was prepared similar to compound IIIb from 3.32 g (13 mmole) of phenyldiazahomoadamantanone oxime IId, 13 g of Ni—Al alloy (50:50), and 13 g of sodium hydroxide. After evaporation of the extracting agent, 2.63 g (84%) of amine IIId was obtained.

9-Amino-1-(*p*-hydroxybenzyl)-3,6-diazahomoadamantane (IIIe). A solution of 1.9 g of sodium hydroxide in 2 ml of water was added to a mixture of 0.6 g (2.1 mmole) of hydroxybenzyldiazahomoadamantanone oxime IIe and 1.9 g of Ni—Al alloy in 2 ml methanol while stirring for 2 h and stirring was continued for another 2 h. The precipitated sediment was filtered, washed with water, and the solution was acidified with dilute HCl to pH 4-5 and alkalized to pH 9 with a saturated solution of sodium carbonate, evaporated in a vacuum, and the solid residue was extracted with boiling isopropyl alcohol. The extract was filtered and passed through a layer of aluminum oxide, vacuum evaporated, and the residue was dried. This produced 0.20 g (35%) of amine IIIe.

9-Acetylamino-1-methyl-3,6-diazahomoadamantane (IVb). A solution of 0.45 g (2.5 mmole) of methylaminodiazahomoadamantane IIIb in 12.5 ml of acetic anhydride was heated for 2 h at boiling, cooled, poured in 20 ml of water, alkalized to pH 9 with concentrated soda solution, evaporated dry, and extracted with toluene. The precipitated sediment was filtered off and vacuum dried. Then 0.3 g (55%) of amide IVb was obtained.

9-Acetylamino-1,8-dimethyl-3,6-diazahomoadamantane (IVc) was prepared similar to compound IVb from 0.27 g (1.4 mmole) of aminodimethyldiazahomoadamantane IIIc and 7.5 ml of acetic anhydride. After recrystallization from *n*-heptane, 0.27 g (82%) of amide IVc was obtained.

9-Acetylamino-1-phenyl-3,6-diazahomoadamantane (IVd) was prepared similar to compound IVb from 0.48 g (2 mmole) of aminophenyldiazahomoadamantane IIId and 7.5 ml of acetic anhydride. After recrystallization of *n*-heptane, 0.2 g (36%) of amide IVd was obtained.

9-Acetylamino-9-(*p*-acetylhydroxybenzyl)-3,6-diazahomoadamantane (IVf) was prepared similar to compound IVb from 0.27 g (0.99 mmole) of aminohydroxybenzyldiazahomoadamantane IIIe and 7.5 ml of acetic anhydride. After recrystallization from toluene, 0.17 g (54%) of amide IVf was obtained.

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