HETEROADAMANTANES AND THEIR DERIVATIVES.
14.* SYNTHESIS OF 3,6-DIAZAHOMOADAMANTAN-9-OLS AND THEIR ACETATES

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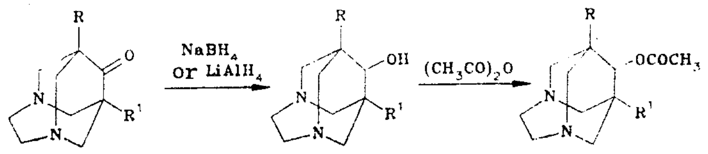
The reduction of 3,6-diazahomoadamantan-9-ones with metal hydrides gave 3,6-diazahomoadamantan-9-ols, which were converted to acetates by the action of acetic anhydride. The effect of the substituents in the nodal positions on the rates of reduction and acylation is demonstrated.

The simple and convenient method that we recently developed for obtaining 3,6-diazahomoadamantan-9-ones I by the condensation of tetramethylenediethylenetetramine with ketones has made them accessible intermediates for obtaining other 3,6-diazahomoadamantane derivatives [2, 3]. In the present communication we describe the synthesis of 3,6-diazahomoadamantan-9-ols II from ketones I and the conversion of II to 9-acetyloxy-3,6-diazahomoadamantanes III.



I a-k   II a-k   III a-k

Compound	R	R'	Compound	R	R'	Compound	R	R'	Compound	R	R'
a	H	H	d	H	C_3H_7	g	C_3H_7	C_3H_7	j	CH_3	C_6H_5
b	H	CH_3	e	CH_3	CH_3	h	C_6H_5	C_6H_5	k	CH_3	C_3H_7
c	H	C_6H_5	f	C_2H_5	C_2H_5	i	$C_6H_5CH_2$	$C_6H_5CH_2$			

Diazahomoadamantanones I are reduced to diazahomoadamantanols II by sodium borohydride; the rate of reduction decreases with an increase in the volume of the substituents in the nodal positions. Compounds I with two such substituents in the nodal positions, viz., phenyl (Ih) and benzyl (Ii) groups, are reduced to IIh and IIi only by lithium aluminum hydride in refluxing tetrahydrofuran; moreover, whereas 4 h are required for the reduction of diphenyldiazahomoadamantanone (in the case of IIh) [4], 7 h are required for the reduction of dibenzyldiazahomoadamantanone (in the case of IIi).

The addition of a hydride ion to the carbonyl carbon atom is the rate-determining step in the conversion of ketones to alcohols; this makes it possible to evaluate the relative reactivity of the carbonyl group [5]. For a qualitative evaluation of the effect of the substituents in the nodal positions on the reactivity of the carbonyl group in diazahomoadamantanones I we carried out their reduction with sodium borohydride in isopropyl alcohol at room temperature, since virtually no reaction between sodium borohydride and the alcohol occurs under these conditions [6]. The progress of the reaction was monitored by TLC.

A comparison of the times required to reduce unsubstituted diazahomoadamantanone Ia and its monomethyl (Ib) and dimethyl (Ie) analogs shows that Ia is reduced most slowly (in 4.5 h), Ib is reduced in 2 h, while Ie is reduced most rapidly (in 1.25 h). The difference in the rates of reduction of Ia, b, e probably constitutes evidence that the methyl group is an electron acceptor with respect to the diazahomoadamantane ring, i.e., it has a −I effect [7].

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*See [1] for Communication 13.

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TABLE 1. 3,6-Diazahomoadamantan-9-ols and 9-Acetyloxy-3,6-diazahomoadamantanes

Compound	Empirical formula	mp, °C*	IR spectrum, cm^{-1}	Yield, %
IIa	$C_9H_{16}N_2O$	127...128	3430, 3480 (OH)	70,3
IIb	$C_{10}H_{18}N_2O$	121...122	3460, 3510 (OH), 3600 (OH)**	98,9
IIc	$C_{15}H_{20}N_2O$	196...197	3100 (OH), 1620 (arom), 3570 (OH)**	99,1
IId	$C_{12}H_{22}N_2O$	104,5...106,5	3470, 3515 (OH)	86,5
IIe	$C_{11}H_{20}N_2O$	175...176	3050 (OH), 3620 (OH)**	92,8
IIf	$C_{13}H_{24}N_2O$	220...221	3050 (OH)	90,1
IIg	$C_{15}H_{28}N_2O$	211...212	3050 (OH)	89,4
IIi	$C_{23}H_{28}N_2O$	215...216	3110 (OH), 1605 (arom.)	86,8
IIj	$C_{16}H_{22}N_2O$	188...190	3080 (OH), 1600 (arom.)	84,6
IIk	$C_{15}H_{28}N_2O$	161...162	3050 (OH)	81,1
IIIa	$C_{11}H_{18}N_2O_2$	187...188***	1730 (CO)	99,0
IIIb	$C_{12}H_{20}N_2O_2$	64...65	1730 (CO)	80,6
IIIc	$C_{17}H_{22}N_2O_2$	207...208***	1730 (CO), 1600 (arom.)	85,7
IIId	$C_{17}H_{30}N_2O_2$	204...205***	1730 (CO)	87,3
IIIe	$C_{13}H_{22}N_2O_2$	69...70	1730 (CO)	84,7
IIIf	$C_{15}H_{26}N_2O_2$	256...257***	1730 (CO)	92,3
IIIg	$C_{17}H_{30}N_2O_2$	65...66	1730 (CO)	88,4
IIIk	$C_{15}H_{26}N_2O_2$	75...76	1730 (CO)	82,7

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*The melting points of the sublimed compounds are indicated for IIa-g, k and IIIb, e, g, k; IIi and IIIa, c, d, f were crystallized from toluene, while IIj was crystallized from heptane.

**The absorption band of a solution in chloroform ($c = 1.8 \cdot 10^{-2}$ mole/liter).

***These are the melting points of the methiodides of the corresponding compounds.

TABLE 2. PMR Spectra of IIb-g, i, k and IIIb, e

Compound	Chemical shifts, δ, ppm (SSCC, ^2J, Hz)				
	$N-CH_2-CH_2-N$	$N-CH_2-C$, d	R	R'	other protons
IIb	3,06 m*	3,34; 3,16; 2,92; 2,74; 2,64; 2,42 ($^2J = 14,0$)	1,96 m*	0,84 s	3,62 m*
IIc	3,05 m*	3,73; 3,56; 3,30; 2,87; 2,67; 2,47 ($^2J = 14,0$)	1,93 m*	7,35...7,16 m	2,96 m*, 4,19 m*
IId	3,04 m*	3,59; 3,26; 3,23; 2,88; 2,83; 2,63; 2,48; 2,36 ($^2J = 14,0$)	1,79 m*	0,91 m*; 1,35...1,1 m	3,55 m*, 3,62 m*
IIe	3,06 s	3,20; 2,90; 2,62; 2,39 ($^2J = 14,0$)	0,78 s		3,30 m*
IIf	3,05 s	3,19; 2,89; 2,61; 2,38 ($^2J = 14,0$)	0,84 m*; 1,40...1,17 m		3,38 m*
IIg	3,05 s	3,21; 2,91; 2,63; 2,38 ($^2J = 14,0$)	0,90 m*; 1,38...1,05 m		3,37 m*
IIi	2,54 m*	3,27; 2,52; 2,35; 2,12 ($^2J = 14,0$)	7,24...7,09 m; 2,70 s		3,11 m*
IIj	3,15 m*	3,79; 3,40; 3,24; 3,03; 2,70; 2,38 ($^2J = 14,0$)	0,90 s	7,43...7,22 m	3,98 s
IIk	3,05 s	3,27; 3,19; 2,95; 2,64; 2,66; 2,59; 2,37; 2,28 ($^2J = 14,0$)	0,77 s	0,91 m*; 1,37...1,08 m	3,29 m*
IIIb	3,08 m*	3,46; 3,36; 3,30; 2,96; 2,85; 2,63; 2,56; 2,36 ($^2J = 14,0$)	1,96 m*	0,78 s	4,77 d; 2,15 s
IIIe	3,08 m*	3,18; 2,96; 2,62; 2,35 ($^2J = 14,0$)	1,98 m*	0,65 s	4,73 d, 2,12 s

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*The centers of the multiplets are indicated.

In the series of investigated monosubstituted diazahomoadamantanones Ib-d phenyldiazahomoadamantanone Ic is reduced most rapidly (in 1.25 h). Monomethyl- and monopropyldiazahomoadamantanones Ib and Id are reduced in virtually the same amount of time, and thus lengthening of the carbon chain of a substituent in one of the nodal positions from one to three carbon atoms does not have a substantial effect on the reactivity of the carbonyl group of diazahomoadamantanones. At the same time, in the series of symmetrically disubstituted dialkyldiazahomoadamantanones Ie-g the rate of reduction decreases rapidly with lengthening of the carbon chain: dimethyldiazahomoadamant

TABLE 3. Mass Spectra of II and III

Compound	m/z values (I_{rel}, %)*
IIa	168 (100), 94 (34), 84 (40), 82 (41), 72 (39), 68 (38), 58 (81), 57 (46), 44 (34), 42 (84), 41 (60)
IIb	182 (100), 124 (34), 111 (30), 108 (41), 82 (37), 72 (33), 58 (71), 57 (35), 55 (33), 42 (74), 41 (48)
IIc	244 (79), 172 (12), 170 (19), 115 (12), 91 (23), 72 (28), 58 (100), 57 (15), 44 (15), 42 (38), 41 (16)
IId	210 (100), 181 (26), 136 (26), 72 (28), 58 (90), 57 (26), 55 (28), 44 (27), 43 (44), 42 (81), 41 (36)
IIe	196 (100), 138 (35), 124 (36), 122 (37), 98 (37), 96 (62), 72 (58), 58 (62), 55 (39), 42 (71), 41 (47)
IIf	224 (64), 152 (68), 150 (56), 112 (45), 110 (73), 72 (100), 58 (75), 57 (56), 56 (52), 55 (75), 42 (47)
IIg	252 (83), 223 (39), 180 (72), 126 (31), 124 (49), 72 (100), 50 (70), 57 (31), 55 (36), 42 (41), 41 (40)
IIi	348 (71), 276 (26), 257 (28), 91 (100), 72 (73), 58 (49), 45 (23), 44 (30), 43 (30), 42 (60), 41 (30)
IIj	258 (100), 200 (20), 186 (24), 184 (22), 98 (20). 96 (17), 91 (18), 72 (49), 58 (38), 42 (44), 41 (19)
IIk	224 (67), 166 (50), 152 (71), 150 (58), 124 (73), 96 (71), 82 (56), 72 (100), 58 (81), 57 (63), 55 (82)
IIIb	224 (64), 165 (31), 122 (24), 121 (43), 108 (60), 93 (31), 72 (100), 58 (27), 43 (60), 42 (53), 41 (30)
IIIc	286 (100), 227 (47), 183 (45), 170 (47), 156 (40), 155 (57), 115 (37), 91 (42), 72 (66), 71 (36), 42 (34)
IIId	252 (60), 193 (42), 149 (52), 136 (51), 121 (53), 83 (46), 82 (40), 72 (100), 58 (37), 55 (40), 42 (48)
IIIe	238 (46), 179 (21), 135 (28), 122 (37), 107 (36), 96 (17), 72 (100), 55 (20), 43 (48), 42 (36), 41 (19)
IIIf	266 (30), 207 (20), 163 (26), 150 (31), 136 (29), 135 (36), 72 (100), 58 (34), 55 (31), 43 (27), 42 (42)
IIIg	294 (78), 235 (41), 191 (35), 180 (22), 178 (29), 163 (50), 124 (24), 112 (23), 72 (100), 70 (23), 58 (28)
IIIk	266 (28), 207 (17), 150 (28), 136 (28), 135 (29), 72 (100), 55 (30), 44 (25), 43 (67), 42 (51), 41 (37)

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*The M^+ peaks and the 10 most intense ion peaks are presented.

TABLE 4. Intensities of the Peaks of the Characteristic Fragment Ions

Compound	I, % of the total ion current											
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	$[F_7-H]^+$	F_8	F_9	$(F_9-H]^+$	W_M
IIa	6,0	2,1	2,9	1,8	6,2	0,7	1,9	0,5	2,5	0,8	0,6	8,1
IIb	6,0	2,9	2,8	2,0	6,3	1,0	1,5	0,5	3,5	1,1	0,7	9,6
IIc	12,0	1,3	3,3	1,4	4,5	0,7	1,1	0,4	2,3	0,9	0,9	11,3
IId	4,4	1,1	1,4	1,5	4,0	1,1	1,0	1,0	1,3	1,0	1,0	5,8
IIe	4,8	2,7	4,5	2,8	5,5	0,9	0,8	0,2	2,9	1,2	0,7	8,8
IIf	2,7	1,4	3,6	2,5	1,7	0,7	0,7	0,5	2,0	1,6	1,0	3,3
IIg	4,2	1,5	6,1	4,4	2,5	1,3	0,3	0,3	1,4	1,2	0,6	6,4
IIi	3,9	0,5	5,8	2,1	4,8	0,6	—	—	0,7	0,4	0,3	7,4
IIj	3,9	2,0	5,0	2,4	4,5	1,0	0,6	0,2	2,2	1,2	1,0	2,2
IIk	2,8	1,7	3,4	2,4	1,4	0,6	0,5	0,4	2,0	1,4	0,9	3,1
IIIb	2,6	0,6	9,8	0,3	5,2	3,0	2,4	4,2	5,9	1,8	3,0	7,2
IIIc	1,7	0,5	3,8	0,2	2,0	2,6	1,9	2,6	2,7	2,3	3,2	6,5
IIId	2,3	0,4	6,2	0,5	3,0	2,6	1,7	3,2	3,2	1,6	3,3	4,0
IIIe	2,2	0,5	12,1	0,5	4,3	2,5	1,4	3,4	4,5	0,9	4,3	6,5
IIIf	2,8	0,3	8,2	0,7	3,5	1,6	0,5	2,2	2,5	2,4	3,0	2,8
IIIg	1,3	0,4	4,6	0,8	0,7	1,9	0,5	1,6	1,3	0,7	2,3	4,3
IIIk	1,4	0,6	7,8	0,7	4,0	1,3	1,0	1,4	2,2	2,2	2,3	2,9

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*The ion peak with m/z 91 (8.0% of the total ion current) has the maximum intensity in the spectrum.

anone Ib is reduced in 1.25 h, diethyldiazahomoadamantanone If is reduced in 2.5 h, and dipropyldiazahomoadamantanone Ig is reduced in 10 h.

Let us note that the time required to reduce methylpropyldiazahomoadamantanone Ik (1.75 h) is substantially shorter than the time required to reduce its isomer If (2.5 h); consequently, the reactivity of the carbonyl group in the case of two different substituents is determined by the least bulky substituent.

Diazahomoadamantanols II are converted to esters III by heating with acetic anhydride. Monosubstituted diazahomoadamantanols IIb-d are acetylated in 1 h under these conditions, while disubstituted IIe-g, i are acetylated in 3 h.

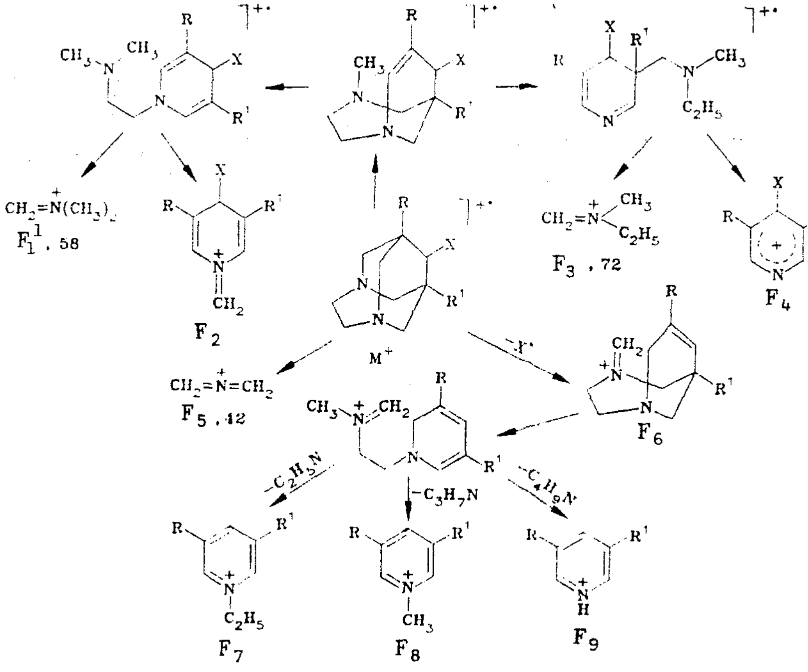
The structures of the compounds obtained were confirmed by spectral data (see Tables 1-4). Bands of stretching vibrations of the carbonyl group of starting ketones I vanish in the IR spectra of II, and bands of stretching vibrations of a hydroxy group are observed; in the case of suspensions of IIe-g in mineral oil a band appears at 3050 cm^{-1}, while in the case of unsubstituted diazahomoadamantanol IIa and its monoalkyl derivatives IIb, d it is split and shows up in the higher-frequency region at 3430-3515 cm^{-1}. The hydroxy group of phenyldiazahomoadamantanol absorbs at 3100 cm^{-1}. In the IR spectra of dilute solutions of IIb, c, e in chloroform the absorption of the hydroxy group shows up in the form of a narrow band at 3570-3620 cm^{-1}. The IR spectra of esters III contain bands of stretching vibrations of an ester carbonyl group at 1730 cm^{-1} (see Table 1).

Intense (and often maximum) molecular-ion peaks (M^+) are present in the mass spectra of diazahomoadamantanols II. The stabilities of the molecular ions with respect to fragmentation (the W_M values; see Table 4) for the functional diazahomoadamantane derivatives I, II, and III, taking into account the data in [3], decrease in the order $-OH > =O > -OCOCH_3$.

An analysis of the mass spectra of alcohols II and esters III (see Tables 3 and 4) shows that the fragmentation of their M^+ proceeds via the pathways that are characteristic for I [3]. A common pathway of the mass-spectral fragmentation is the formation of the nitrogen-containing F_1 fragment (see the scheme).

For ketones I 30.5% of the total ion current is due to the production of F_1 ions [3], while for alcohols and esters II and III the intensity of the F_1 ion peak is considerably lower (see Table 4). At the same time, the intensity of the peak of the homologous F_3 ion (see the scheme), which is maximal for esters III, increases in the spectra of II and III. Rather intense peaks of alternative F_2 and F_4 ions and F_5 peaks of amine fragments are present in the spectra of some alcohols II (see Table 4).

Scheme



One of the most important pathways in the fragmentation of the M^+ ions is the detachment of functional substituent X and the formation of an F_6 ion. The subsequent fragmentation of this ion, which occurs with the elimination of C_nH_{2n+1} molecules (n = 1-3), leads to the appearance of F_7-F_9 ion peaks in the spectra of II and III. The fragmentation of the F_6 ions proceeds primarily with the elimination of a C_3H_7N molecule. The increased intensities of the peaks of the $[F_7 - H]^+$ and $[F_9 - H]^+$ ions as compared with the intensities of the peaks of the F_7

and F_9 ions in the spectra of esters III (Table 4) are probably associated with the possibility of the formation for these compounds of a low-intensity peak of an $[M - HX]^+$ ion, the fragmentation of which then proceeds with the elimination of C_2H_5N and C_4H_9N molecules.

The elementary compositions of the principal ions were confirmed by the high-resolution mass spectra for IIb and IIIb.

EXPERIMENTAL

The IR spectra of suspensions in mineral oil and solutions in chloroform were recorded with a Specord IR-71 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Bruker WM-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The low- and high-resolution mass spectra were obtained with a Kratos MS-80 spectrometer with direct introduction of the samples into the ion source; the ionizing-electron energy was 70 eV, the temperature of the ionization chamber was 150°C, the standard was perfluorinated kerosene, and the resolution $M/\Delta M$ was 7500.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

3,6-Diazahomoadamantan-9-ol (IIa). A 0.04-g (1 mmole) sample of sodium borohydride was added at room temperature to a solution of 0.2 g (1.2 mmole) of 3,6-diazahomoadamantan-9-one (Ia) in 10 ml of isopropyl alcohol, and the mixture was stirred for 4.5 h. The solvent was then removed by distillation, and a few drops of water were added until the dry residue had dissolved completely. The water was removed by distillation, and the residue was extracted with toluene (2 × 10 ml). The solvent was removed by distillation, and the residue was purified by sublimation in the vacuum created by a water aspirator to give 0.15 g of IIa.

1-Methyl-3,6-diazahomoadamantan-9-ol (IIb), 1-phenyl-3,6-diazahomoadamantan-9-ol (IIc), 1-propyl-3,6-diazahomoadamantan-9-ol(IId),1,8-dimethyl-3,6-diazahomoadamantan-9-ol(IIe),1,8-diethyl-3,6-diazahomoadamantan-9-ol (IIf), 1,8-dipropyl-3,6-diazahomoadamantan-9-ol (IIg), 1-methyl-8-phenyl-3,6-diazahomoadamantan-9-ol (IIj), and 1-methyl-8-propyl-3,6-diazahomoadamantan-9-ol (IIk) were similarly obtained.

1,8-Dibenzyl-3,6-diazahomoadamantan-9-ol (IIi). A solution of 3.12 g (9 mmole) of Ii in 10 ml of tetrahydrofuran was added dropwise with stirring to a solution of 0.57 g (15 mmole) of lithium aluminum hydride in 5 ml of tetrahydrofuran, and the mixture was stirred for 1 h. The mixture was then treated successively with 0.6 ml of water, 1.8 ml of 15% aqueous NaOH solution, and 1.8 ml of water, and the precipitate was removed by filtration. The mother liquor was evaporated to dryness, and the dry residue was extracted with hot toluene (5 × 20 ml). The toluene was removed by distillation, and the residue was recrystallized from toluene to give 2.72 g of IIi.

1-Methyl-9-acetyloxy-3,6-diazahomoadamantane (IIIb). A solution of 0.3 g (1.6 mmole) of IIb in 5 ml of acetic anhydride was refluxed for 1 h, after which it was neutralized with aqueous alkali solution and evaporated to dryness. The residue was extracted with toluene (3 × 5 ml), and the extractant was removed by distillation to give 0.29 g of IIIb.

1-Phenyl-9-acetyloxy-3,6-diazahomoadamantane (IIIc), 1-propyl-9-acetyloxy-3,6-diazahomoadamantane (IIId), 1,8-dimethyl-9-acetyloxy-3,6-diazahomoadamantane (IIIe), 1,8-diethyl-9-acetyloxy-3,6-diazahomoadamantane (IIIf), and 1,8-dipropyl-9-acetyloxy-3,6-diazahomoadamantane (IIIg) were similarly obtained.

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