2-(Piperidin-1-yl)-3-[α-cyano-α-benzimidazol-2-yl)methylene]3,4-dihydroquinoxalines (III, IV) and 1-R^1-2-Amino-3-(benzimidazol-2-yl)pyrrolo[2,3-b]quinoxalines (V, VI).* C. A 5 ml portion of the corresponding amine is added to 10 mmoles of compound I or II. The solution over the precipitate immediately becomes deep pink-red colored. The reaction mixture is boiled, and on completion of the reaction, the color of the solution brightens, turns red (in thin layer, into yellow), while the precipitate becomes transformed. The reaction mixture is cooled, 100 ml of water and 5 ml of acetic acid are added. The separated precipitate is filtered, washed with water, and dried.

D. A mixture of 3 mmoles of compound I or II, 3 ml of DMFA was heated for 4 h at 130°C in a sealed ampul (length 150 ml, external diameter 17 mm, internal diameter 14 mm). The ampul is then cooled, opened, and the reaction product is isolated as described in method C.

E. A mixture of 3 mmoles of compound I or II, 3 ml of the corresponding amine and 15 ml of DMFA is boiled, and at the end of the reaction, treated in the same way in methods C and D.

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SYNTHESIS AND PROPERTIES OF N-SUBSTITUTED AMINOFUROXANS IN THE ADAMANTANE SERIES

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3-N,N-Disubstituted aminofuroxans in the adamantane series have been obtained by the oxidation of anti[1,(3-R-adamantyl)]-amphi-glyoximes with excess $K_3Fe(CN)_6$ in the presence of the corresponding amines. Preparation of 3-amino and 3-methylamino-4-(1-adamantyl)furoxans requires initial synthesis of 2-(1-adamantyl)-2-hydroximinoacetonitrile oxide followed by addition of the corresponding amines and oxidation of the resulting glyoximes. Substituent positions in the furoxan ring were determined by PMR spectroscopy.

Aminofuroxans attract the attention of investigators because of their known depressive effect on the central nervous system and their anti-spasmodic activity [1]. A single stage preparation of arylaminofuroxans from amphi-glyoximes in the presence of potassium ferricyanide and the amine has been reported [2]. It was therefore of interest to study the use of [2] for synthesis of N-substituted aminofuroxans of the adamantane series.

We have shown that anti-[1-(3-R-adamantyl)]-amphi-clyoximes [3] (Ia-e, aR = H, bR = CH_3, cR = p-$CH_3C_6H_4$, d R = Cl, e R = OH) form the N,N-dimethylaminofuroxans IIa-e in 50-65% yield when treated with a 30 fold excess of dimethylamine in the presence of an 8 fold excess of $K_3Fe(CN)_6$ for 2-3 h at room temperature. Decrease in the amount of oxidant to a 4-5 fold excess leads to a decreased yield of the furoxans IIa-e. The N,N-substituted furoxans IIf-h are formed by treatment of glyoxime Ia with diethylamine, morpholine, and piperidine under the conditions above.

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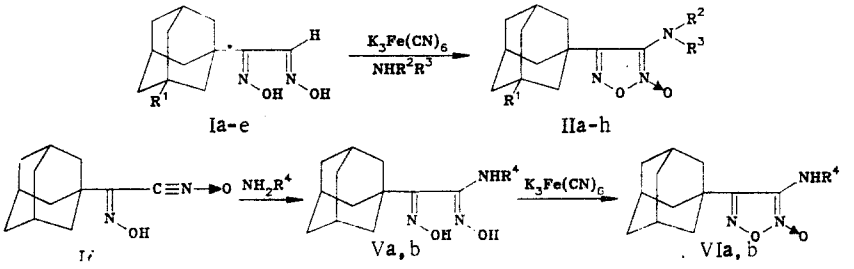


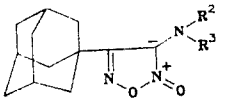
I, II $R^2=R^3=CH_3$, a $R^1=H$, b $R^1=CH_3$, c $R^1=p$-$CH_3C_6H_4$, d $R^1=Cl$, e $R^1=OH$; II $R^1=H$, f, $R^2=R^3=C_2H_5$, g $R^2+R^3=(CH_2-CH_2)_2O$, h $R^2+R^3=(CH_2)_5$; V, VI a $R^4=H$, b $R^4=CH_3$

Preparation of the furoxans VIa, b could not be achieved in one stage. At room temperature the reaction did not go to the stage of addition of ammonia to 2-(1-adamantyl)-2-hydroximinoacetonitrile oxide (IV, obtained by oxidation of Ia with an alkaline solution of $K_3Fe(CN)_6$). It has been shown that the best conditions for addition of ammonia and methylamine to IV are two hours refluxing in a mixture of excess amine and chloroform. The aminoglyoximes formed Va, b need much milder oxidation conditions (2-5 mole $K_3Fe(CN)_6$ in 2% ammonia at 0-5°C) than the 3-N,N-disubstituted aminofuroxans IIa-h.

Data in [2, 4, 5] shows that the position of the exocyclic oxygen in N-substituted aminofuroxans (obtained by oxidation of 1-R-2-N-substituted aminoglyoximes with R = Ar, CH_3) depends on the nature of the R substituent and the amino residue. Introduction of the bulky adamantyl substituent must significantly affect the formation and isomeric composition of the furoxans and raises the question of the position of the exocyclic oxygen in N-substituted aminofuroxans in the adamantane series.

It is known [2] that the amino gorup protons in 3-amino substituted arylaminofuroxans have PMR chemical shifts of 5.9-6.1 ppm whereas those for 4-amino furoxans are at 6.2 and 6.5 ppm. A significant difference in chemical shifts (0.15 ppm) has also been reported for the dimethylamino group singlets in the PMR spectrum of bis(dimethylamino)furoxan [6]. Hence PMR spectroscopy can be used to assign the isomers of the non-symmetrical N-substituted aminofuroxans of the adamantane series.

For identification of the position of the exocyclic oxygen in N,N-dimethylaminofuroxan (IIa) itwas isomerized to a mixture of the two isomers by refluxing in m-xylene. Two singlets were observed at 2.67 and 2.75 ppm in the PMR spectrum in the ratio 2:1. Comparison with the PMR spectrum of 3-(1-adamantyl)-4,N,N-dimethylaminofurazan (III) (2.82 ppm, s, 6H, $N(CH_3)_2$) proves that the dimethylamino group is adjacent to the exocyclic oxygen in compound IIA (Table 1). Furazan III was obtained by treating furoxan IIa with excess $SnCl_2 \cdot 2H_2O$ in a mixture of acetic and hydrochloric acids. Other furoxan isomers resulting from the oxidation reaction of glyoximes Ia-e were not observed. The sensitivity of the methyl protons of the dimethylamino group to the location with respect to the exocyclic oxygen can be explained by a significant contribution of structure (A). Charge separation in (A) results in a significant shielding of the protons of the N-substituted amino group.



(A)

EXPERIMENTAL

IR Spectra were recorded on an IRS-29 instrument for KBr tablets and PMR spectra on a Bruker WP-80DS (80 MHz) using HMDS as internal standard. Chemapol L (100-250) silica gel was used as sorbent for preparative chromatography.

Synthesis of anti-[1-(3-R-adamantyl)]-amphi-glyoximes (Ia-e) has been reported in [3]. The yields and physical parameters are given in Table 2.

4-(1-Adamantyl)-2-dimethylaminofurzan (IIa). A solution of $K_3Fe(CN)_6$ (11.8 g, 35.9 mmole) in water (40 ml) was added dropwise with stirring and at 25-28°C to a solution of anti-(-adamantyl)-amphi-glyoxime (Ia, 1.0 g, 4.5 mmole) in a solution of dimethylamine (33%, 20 ml) and ether (50 ml). After stirring for 2 h the reaction product was extracted with

TABLE 1. IR and PMR Spectra of Compounds IIa-h, III, and VIa,b

Compound	IR spectrum, cm^{-1}	PMR spectrum,*1 δ, ppm	
		3-R—Ad	NR^1R^2
IIa	1583	1,73—2,07 m (15H)	2,67 s [(6H, $N(CH_3)_2$]
IIb	1572	0,84 s (3H, CH_3); 1,48—2,08 m (14H)	2,67 s [(6H, $N(CH_3)_2$]
IIc	1581	1,85—2,49 m (14H, Ad, 3H, CH_3); 7,05—7,33 m (4H, Ar)	2,67 s [(6H, $N(CH_3)_2$]
IId	1571	1,67—2,37 m (14H)	2,67 s [(6H, $N(CH_3)_2$]
IIe	1565	1,61—1,87 m (14H); 5,54 s (1H, OH)	2,67 s [(6H, $N(CH_3)_2$]
IIf	1565	1,73—2,03 m (15H)	0,99 t (6H, CH_3)*2; 3,07 q (4H, CH_2)*2;
IIg	1588	1,79—2,05 m (15H)	3,03—3,05 (4H, NCH_2); 3,73—3,85 (4H, OCH_2);
IIh	1581	1,79—2,04 m (15H)	1,61 s (6H piperidine ring); 3,65 (4H, NCH_2)
III	1545	1,73—2,05 m (15H)	2,82 s [(6H, $N(CH_3)_2$]
VIa	1650	1,73—1,97 m (15H)	5,91 s (2H, NH_2)
VIb	1643	1,75—2,15 m (15H)	2,98 s (3H, CH_3)

*1The spectra of IIg, h and VIb were recorded in $CDCl_3$, the remainder in DMSO-D_6.
*2Ethyl groups.

TABLE 2. Parameters for Compounds IIa-h, III, VIa, b

Compound	mp,*1 °C	R_f*2	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIa	170—172 (decomp.)	0,48	64,0	8,1	16,0	$C_{14}H_{21}N_3O_2$	63,9	8,0	16,0	64
IIb	99—101	0,47	65,1	8,5	15,3	$C_{15}H_{23}N_3O_2$	65,0	8,4	15,2	50
IIc	146—148	0,39	71,5	7,8	12,0	$C_{21}H_{27}N_3O_2$	71,4	7,7	11,9	50
IId	116—118	0,34	56,6	6,9	14,3	$C_{14}H_{20}N_3O_2Cl$	56,4	6,8	14,1	52
IIe	159—161 (decomp.)	0,54	60,5	7,6	15,1	$C_{14}H_{21}N_3O_3$	60,2	7,6	15,0	62
IIf	102—104	0,57	66,1	8,8	14,5	$C_{16}H_{25}N_3O_2$	66,0	8,7	14,4	60
IIg	166—167,5	0,49	63,2	7,8	13,8	$C_{16}H_{23}N_3O_3$	62,9	7,7	13,7	37
IIh	184—186 (decomp.)	0,51	67,5	8,5	13,9	$C_{17}H_{25}N_3O_2$	67,3	8,3	13,8	33
III	73—74	0,60	68,1	8,7	17,1	$C_{14}H_{21}N_3O$	68,0	8,6	17,0	66
VIa	145—147 (decomp.)	0,18	61,3	7,4	18,0	$C_{12}H_{17}N_3O_2$	61,3	7,3	17,9	37
VIb	125—126 (decomp.)	0,33	62,9	7,8	16,9	$C_{13}H_{19}N_3O_2$	62,6	7,7	16,8	30

*1Compounds crystallized: IIa, f, g, h from hexane, IIe, VIa, b from heptane, III from pentane; IIb, c, d were purified chromatographically.
*2In the solvent system CCl_4-acetone (60:1) for IIa-d, IIf, h, III, (6:2) for IIe, (6:0.5) for IIg, and (6:1) for VIa, b.

ether and the ether layer washed with water and dried. After removal of ether the residue was chromatographed on a silica gel column using CCl_4-acetone (60:1) to give IIa (0.72 g).

4-[1-(3-methyladamantyl)]-3-N,N-dimethylaminofuroxan (IIb), 4-[1-(3-p-tolyladamantyl)]-3-N,N-dimethylaminofuroxan (IIc), 4-[1-(3-chloroadamantyl)]-3-N,N-dimethylaminofuroxan (IId), 4-[1-(3-hydroxyadamantyl)]-3-N,N-dimethylaminofuroxan (IIe), 4-(1-adamantyl)-3-morpholinofuroxan (IIg), and 4-(1-adamantyl)-3-piperidinofuroxan (IIh) were prepared similarly. Compounds IIe-h were separated on a column using CCl_4-acetone (6:1).

3-(1-Adamantyl)-4-dimethylaminofurazan (III). Glacial acetic acid (35 ml), HCl (37%, 7 ml) and $SnCl_2 \cdot 2H_2O$ (13.4 g, 59.2 mmole) were added to furoxan IIa (1.3 g, 4.9 mmole) and heated for 1.5 h at 100°C. The reaction mixture was diluted with water and the precipitated solid filtered off and recrystallized from pentane to give furazan III (0.8 g).

Isomerization of 4-(1-adamantyl)-3-dimethylaminofuroxan (IIa). m-Xylene (30 ml) was added to furoxan IIa (0.6 g) and refluxed for 2 h. The solvent was removed in vacuo to give a product which was a 2:1 mixture of isomers according to PMR spectral data.

2-(1-Adamantyl)-2-hydroximinoacetonitrile Oxide (IV). A solution of $K_3Fe(CN)_6$ (7.4 g, 22.5 mmole) and KOH (1.26 g, 22.5 mmole) in water (67 ml) was added dropwise with stirring to a solution of glyoxime Ia (2 g, 9 mmole) in ether (60 ml). The reaction mixture was stirred for 2 h at 25°C, the ether layer separated, wahsed with water, and dried. After removal of ether the residue was washed with pentane to give IV (1.4 g) which was chromatographed using CCl_4-acetone (6:1) [7].

4-(1-Adamantyl)-3-aminofuroxan (VIa). A 25% solution of ammonia (200 ml) and chloroform (100 ml) was added to IV (1 g, 4.5 mmole) and refluxed with stirring for 2 h and cooled to 0°C. The precipitated solid (0.6 g) was filtered off, transferred to a three necked flask, ether (50 ml) added, and a solution of $K_3Fe(CN)_6$ (1.66 g, 5 mmole) in ammonia solution (2%, 50 ml) added dropwise with stirring at 0°C over 15 min. Stirring was continued for 2 h at 0°C and a further 1 h at 20°C. The ether layer was separated, washed with water and dried. After removal of ether the residue was chromatographed on a silica gel column using CCl_4-acetone (6:1).

4-(1-Adamantyl)-3-methylaminofuroxan (VIb) was obtained similarly using a methylamine solution (33%, 60 ml) and compound IV (1 g).

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SYNTHESIS OF MACROHETEROCYCLES — ANALOGS OF DIBENZO-CROWN COMPOUNDS.

2.* 18-MEMBERED DIOXADIAZA-CROWN COMPOUNDS

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Macrocyclic diamides were synthesized by condensation of bridged 1,7-bis(2-aminophenyl)-1,7-dioxaheptanes that contain an additional donor oxygen or nitrogen atom in the bridge with glutaric, diglycolic, and N-tosyliminodiacetic acid dichlorides under high-dilution conditions. Subsequent reduction with boron hydride leads to 18-membered dibenzodiaza-crown-4-6 compounds. The structural assigments were made using the IR, ^1H and ^{13}C NMR, and mass spectra.

The replacement of some of the oxygen atoms in the crown ether molecule by other donor atoms, particularly by nitrogen atoms, leads to a significant change in the character of the complexing of such aza-crown ethers [2]. Aliphatic aza analogs of crown ethers have been studied in relatively great detail; however, aza-crown compounds with aromatic rings condensed with the macroheteroring have been studied to a much smaller extent [3, 4]. The presence of aromatic rings imparts a number of useful properties to aza-crown compounds: it increases their lyophilicity, it permits the possibility of diverse chemical modifications

*See [1] for Communication 1.

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