was filtered off and recrystallized from DMSO to give IVa (0.14 g, 67%, mp 269-270°C) and IVb (0.16 g, 69%, mp 260-262°C).

3-(β-Hydroxyethylamino)-1,2,5-thiadiazole-4-carboxylic Acid (V, $C_5H_7N_3SO_3$). Compound I (0.2 g, 1 mmole) was refluxed in NaOH solution (2N, 5 ml) for 1 h, cooled, and acidified with HCl until precipitation began. This was filtered and recrystallized from water to give 0.18 g (96%) with mp 149-151°C.

Guanines IVa, b were hydrolyzed under analogous conditions to give V.

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SYNTHESIS OF MACROHETEROCYCLIC ANALOGS OF DIBENZO-CROWN COMPOUNDS.

6.* HYDROXYLATED 16-MEMBERED OXAAZA-CROWN COMPOUNDS

A. A. Formanovskii and I. V. Mikhura

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High-dilution cycloacylation of 2-acetoxy-1,3-bis-(2-aminophenoxy)propane with the diacid chlorides of glutaric, diglycollic, thiodiglycollic, and N-tosyliminodiacetic acids gives the macrocyclic diamides. Subsequent reduction with boron hydride affords 16-membered dibenzodiaza-crown compounds.

Crown compounds bearing functional groups are of considerable interest, since their complexing properties differ from those of their unsubstituted analogs [2], and the presence of functional groups at the periphery of these macrocycles enables them to be modified in various ways [3, 4].

Two methods are used to obtain substituted crown compounds, namely introduction of substituents into the ready-formed macrocycle, and the cyclization of compounds already bearing the required substituents. The first method is that normally used to introduce substituents into the aromatic nucleus in benzo-crown compounds. The range of substituents which can be introduced is quite large (alkyl, acyl, halo, nitro, and sulfo), but the type of macrocycle is restricted to oxygen-containing benzo-crown compounds only [5].

In order to obtain benzo-crown compounds with substituents in the macrocyclic moiety, pyrocatechol or related compounds have been cycloannelated with glycol derivatives, often in the presence of template ions [3, 6-9].

In heterocyclic systems containing nitrogen, compounds with functional groups are relatively easy to obtain, albeit only by substitution at nitrogen [10, 11]. Compounds with functional groups attached to carbon atoms ofthe macrocycle appear to be unknown.

Sixteen-membered dioxadiaza-crown compounds have been reported previously [1]. Continuing a systematic search for highly selective macrocyclic compounds suitable for the extraction of heavy and transition metals, we have synthesized a range of hydroxy-crown compounds based on 6,7;15,16-dibenzo-3-hydroxy-1,5-dioxa-8,14-diazacyclohexadecane, containing additional donor atoms (oxygen, sulfur, or nitrogen) in the 11-position of the macroheterocycle (IVa-d).

*See [1] for communication 5.

V. I. Bernadskii Institute of Geochemistry and Analytical Chemistry, Academy of Sciences of the USSR, Moscow.

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TABLE 1. Properties of Macrocyclic Amides (IIIa-d)

Compound	Mp, °C	R_f*	Chemical shifts of protons, δ, ppm (J, Hz)							IR spectrum, cm^{-1}			Yield, %
			CH_2—O (4H)	CH (1H)	NH (2H)	CH_2—X (S 4H)	X	CH_2CO (S 3H)	Ar, m	ν_{NH}	$\nu_{C=O}$ (amide I)	δ_{NH} (amide II)	
IIIa	190...192	0,76	4,02...4,18 m	5,30 m	9,55	1,87	(6H,m)	2,17	6,70...6,92 (8H)	3200	1645	1545	95
IIIb	155...157	0,80	4,32 d (J=3)	5,33 KB (J=3)	8,77	4,13	—	2,12	6,95...7,06 (6H); 8,27...8,42 (2H)	3120	1640	1550	85
IIIc	79...81	0,71	4,30 d (J=4)	5,38 KB (J=4)	9,02	3,47	—	2,17	6,85...6,95 (6H); 8,18...8,28 (2H)	3100	1630	1550	31
IIId	248...250	0,15	4,31 m	5,45 m	9,02	3,82	2,40 (3H, s); 7,28 (2H, d); 7,72 (2H, d)	2,22	6,82...6,93 (6H); 8,13...8,23 (2H)	3100	1640	1560	18

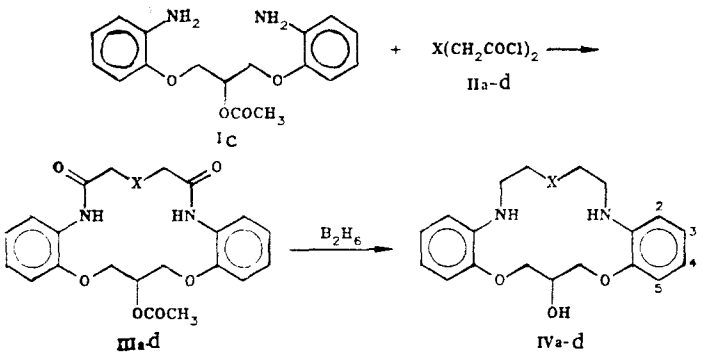
*Eluent chloroform—ethanol (99:1).

TABLE 2. Properties of Macrocyclic Amines (IVa-d)

Compound	Empirical formula	Mp, °C	R_f*	M	M*	PMR spectrum,** δ, ppm					IR spectrum, ν, cm^{-1}	Yield, %
						CH_2—O + CH (5H)	CH_2—N (4H)	CH_2—X	X	Ar (8H)		
IVa	$C_{20}H_{26}N_2O_3$	83...84	0,50	342	342	4,35	3,20	1,65 (6H)		6,65...7,00	3160	54
IVb	$C_{19}H_{24}N_2O_4$	149...150	0,48	344	344	4,20	3,30	3,72 (4H)	—	6,52...7,02	3120	95
IVc	$C_{19}H_{24}N_2O_3S$	158...160	0,39	360	360	4,25	3,25	2,77...3,00 (4H)	—	6,50...6,90	3100	62
IVd	$C_{26}H_{31}N_3O_5S$	101...102	0,40	497	497	4,22	3,18...3,32 (8H)		2,33 (3H, s); 7,12 (2H, d J=8 Hz); 7,55 (2H, d, J=8 Hz)	6,38...6,78	3100	41

*Eluent chloroform—ethanol (97.5:2.5).

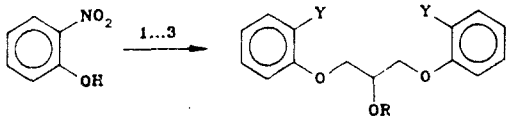
**All signals, except where otherwise indicated, were multiplets.



II—IV a X=CH_2, b X=O, c X=S, d X=NTs

Compounds (IIIa-d) were obtained by acylating the acetoxy-substituted bridged aromatic diamine (Ic) with the diacid chlorides (IIa-d) at high dilution (the overall concentration of the reactants was 10^{-2} mole/liter) in benzene in the presence of pyridine at 75°C. The resulting acetoxylated crown lactams (IIIa-d) were reduced with boron hydride to the macrocyclic diamines (IVa-d), with removal of the acetyl group.

The starting aromatic diamine (Ic) was obtained in three steps, as follows:



1. $(ClCH_2)_2CHOH$, K_2CO_3, DMF; Ia Y=NO_2, R=H; 2. Ac_2O, Py; Ib Y=NO_2, R=$COCH_3$; 3. Al/Hg, EtOH, H_2O; Ic Y=NH_2, R=$COCH_3$

Attempts to reduce the nitro-group in (Ib) to amino using sodium borohydride in methanol in the presence of 10% palladium on charcoal as catalyst, as described previously for other bridged aromatic diamines [12, 13], were unsuccessful, near-quantitative yields of a compound which, according to its IR and PMR spectra, was 1,3-bis-(2-aminophenoxy)propan-2-ol, being obtained, i.e., in addition to reduction of the nitro-group, the acetyl protecting group had been removed. This deacetylation appears to be due to base-catalyzed transesterification of the ester (Ib) or (Ic) in the excess of methanol. Conditions were therefore chosen for obtaining the required compound whch did not involve acids or bases, namely aluminum amalgam in aqueous ethanol. Under these conditions, 2-acetoxy-1,3-bis-(2-aminophenoxy)propane was obtained in 85% yield.

The structures and purity of the crown lactams (IIIa-d) obtained were confirmed by TLC and their IR and PMR spectra (Table 1).

In the PMR spectra of the crown lactams (IIIa-d), the signal at lowest field (around 9 ppm) was assigned to the amide group protons. In addition to these protons, the screening cone of the amide groups also covered the ortho-protons of the aromatic nuclei, the signals for which were shifted to lower field by 1.5-2.0 ppm relative to the remaining aromatic protons.

It appears that in these macrocyclic amides (IIIa-d), there is a strong intramolecular hydrogen bond between the amide protons and the carbonyl group of the acetoxy-substituent, the absorption for NH in the IR spectra of the amides (IIIa-d) being shifted by 160-260 cm^{-1} as compared with ν_{NH} in the spectra of analogous amides which do not contain an acetoxy-group [1], and the $\nu_{C=O}$ value for the acetoxy-group being low, at 1680-1700 cm^{-1}, in comparison with, for example, its value in (Ib) (1720 cm^{-1}), in which such a hydrogen bond is not possible.

It is worthy of mention that the conformation of (IIIa) is probably somewhat different from those of (IIIb-d) and other macrocyclic amides. The PMR spectrum of (IIIa) shows an anomalous low-field shift of the amide proton (9.55 ppm) and the absence of a low-field shift of the ortho-protons ($C_{(2)}$) in the aromatic nucleus, together with a somewhat higher (by 80-100 cm^{-1}) value of ν_{NH} in the IR spectrum as compared with (IIIb-d).

The macrocyclic amines (IVa-d) were obtained by reducing the appropriate amides (IIIa-d) with boron hydride in dimethoxyethane. Attempts to carry out the reduction in THF afforded only extremely stable complexes of the macrocyclic amines (IVa-d) with the solvent and, possibly, boron hydride.

The structures and purity of the products (IVa-d) were confirmed by TLC, mass spectroscopy (measurement of the masses of the molecular ions), and the IR, PMR (Table 2), and ^{13}C NMR spectra (Table 3).*

In the PMR spectra, the protons in positions 2-4 of the macroheterocycle give rise to multiplets centered around 4.25 ppm. Assignment of the signals in the ^{13}C NMR spectra was based on the spectra of related systems [1], and

on the relative intensities of the signals. It is interesting that in (IVa-d) there is only one signal for $C_{(3)}$ at 68.2-69.0 ppm, whereas in compounds without a hydroxyl group the carbon atom in the 3-position gives two signals in its region (26.7-29.8 ppm) [1], indicating, in our view, the presence of two conformations. The absence of doubling of the signal for the central carbon suggests that (IVa-d) exist in a single conformation. It appears that the hydroxy group is oriented in the center of the macrocycle in such a way that it can form weak donor–acceptor bonds with the oxygen and nitrogen atoms of the macroheterocycle.

EXPERIMENTAL

IR spectra were obtained on a Specord IR-71 in chloroform, in NaCl cells, ^{13}C NMR spectra on a Bruker HX-270 in $CDCl_3$, and PMR spectra on a Tesla BS-467 (60 MHz) in $CDCl_3$, internal standard TMS. Mass spectra were obtained on a Varian MAT-112.

TLC was carried out on neutral alumina, visualized with iodine vapor. The composition of the eluents is given in Tables 1 and 2.

1,3-Bis-(2-nitrophenoxy)propan-2-ol (Ia). To a solution of 20.0 g (144 mmoles) of o-nitrophenol in 50 ml of dry DMF was added 20.0 g of powdered anhydrous potassium carbonate, and the mixture heated to the boil. After 40 min, there was added dropwise with stirring 8.4 ml (88 mmoles) of 1,3-dichloropropan-2-ol, and the mixture boiled for 3 h. After cooling, the mixture was poured into 400 ml of water, and the solid which separated was filtered off and washed with 0.1 N sodium hydroxide solution until the washings were colorless, then with water until neutral, and dried in vacuo over KOH to give 16.8 g (70%) of (Ia), mp 114°C (from ethanol), R_f 0.7 (chloroform). PMR spectrum: 7.87 (d, 2H, J = 11 Hz), 7.56 (d.d, 2H, J = 9 Hz, J = 11 Hz), 7.15 (d, 2H, J = 9 Hz), 7.06 (d.d, 2H, J = 11 Hz, J = 9 Hz), 4.28-4.47 (m, 5H), 1.60 ppm (br.s, 1H). IR spectrum: 3420, 1500, 1330 cm^{-1}.

2-Acetoxy-1,3-bis-(2-nitrophenoxy)propane (Ib). To a solution of 25.8 g (77 mmoles) of (Ia) in 100 ml of dry pyridine was added at 20°C 25 ml (265 mmoles) of acetic anhydride, and the mixture kept for 50 h at room temperature. It was then poured into 600 ml of water, and acidified wth concentrated HCl to pH 3. The crystalline solid which separated was filtered off, washed with water, and dried in vacuo over KOH to give 27.5 g (92%) of (Ib), mp 106-107°C (from CCl_4), R_f 0.70 (chloroform). PMR spectrum: 8.26-7.18 (m, 8H), 5.83 (q, 1H, J = 5 Hz), 4.80 (d, 4H, J = 5 Hz), 2.47 ppm (s, 3H). IR spectrum: 1720, 1500, 1330 cm^{-1}.

2-Acetoxy-1,3-bis-(2-aminophenoxy)propane (Ic). To a stirred suspension of 15.0 g (500 mmoles) of aluminum powder in 70 ml of water was added 0.2 g of mercuric chloride, followed after 5 min by a suspension of 2.5 g (6.65 mmoles) of (Ib) in 50 ml of ethanol. The mixture was boiled with stirring for a further 3 h, cooled, 100 ml of water added, and extracted with chloroform (3 × 70 ml). The extract was dried over sodium sulfate, and the solvent removed to give 1.8 g (85%) of (Ic), mp 100°C, R_f 0.27 (chloroform). PMR spectrum: 6.78 (br.s, 8H), 5.61 (t, 1H, J = 6 Hz), 4.20 (d, 4H, J = 6 Hz), 3.93 (br.s, 4H), 2.13 ppm (s, 3H). IR spectrum: 3340, 3250, 1715 cm^{-1}.

The general method of preparation of the macrocyclic amides (IIIa-d) has been described [13]. The properties of (IIIa-d) are given in Table 1. The general method of reduction of the amides (IIIa-d) to the amines (IVa-d) has also been reported [12, 13], the solvent used for reduction being dimethoxyethane. The properties of compounds (IVa-d) are given in Tables 2 and 3.

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TABLE 3. ^{13}C NMR Spectra of (IVa-d)

Compound	Chemical shifts, δ, ppm										
	CH_2—O	CH(OH)	CH_2—N	CH_2—X	K	$C_{(1)}$*	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
IVa	71,9	69,0	41,9	26,8	23,1	139,4	110,8	123,2	116,5	115,1	145,9
IVb	71,7	68,8	42,9	68,4	—	139,0	110,6	123,0	117,0	114,1	146,2
IVc	71,2	68,7	41,0	31,0	—	138,6	110,6	122,8	117,0	114,2	145,9
IVd	70,7	68,2	42,0	48,6	21,3; 127,1; 129,5; 135,8; 143,3	137,6	109,1	121,9	116,5	111,5	145,8

*The numbering of the carbons of the aromatic nuclei is shown in the scheme.

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