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SYNTHESIS OF MACROHETEROCYCLIC ANALOGS OF DIBENZOCROWN ETHERS.

5.* 16- AND 17-MEMBERED OXAAZACROWN ETHERS

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Macrocyclic diamides are synthesized by condensation of 1,5-bis(2-aminophenyl)-1,5-dioxapentane and 1,6-bis(2-aminophenyl)-1,6-dioxahexane with the dichlorides of glutaric, diglycolic, thiodiglycolic, and N-tosyliminodiacetic acids under high dilution conditions. Reduction with diborane gives the 16- and 17-membered dibenzodiazacrown ethers. The structure of the compounds synthesized is confirmed by IR, NMR (^1H and ^{13}C), and mass spectral data.

16- and 17-Membered crown ethers are very rare among known macroheterocyclic compounds [2]. 16- and 17-Membered macrocyclic compounds containing a variety of donor atoms (O, N, S, or a combination of these) are practically unknown. The synthesis of 16-membered crown lactams containing two nitrogens and four oxygens in various arrangements has been described [3].

16- and 17-Membered crown lactones containing two sulfurs and two oxygens were described in [4, 5]. Macrocyclic crown lactams with three different donors (S, O, and N) in the ring are known [5].

The number of azacrown ethers is even smaller. Only in [6, 7] is the synthesis of 16- and17-memberedoxaazacrown ethers with varying content of oxygens and nitrogens in the ring (2N–3O, 3N–3O, 4N–O) reported.

In an attempt to fill this gap and to continue the systematic search for highly selective macrocyclic compounds suitable for extraction of heavy and transition metals, we synthesized a series of 16- and 17-membered oxathiazacrown ethers in the 6,7;15,16-dibenzo-1,5-dioxa-8,14-diazacyclohexadecane and 7,8;16,17-dibenzo-1,6-dioxa-9,15-diazacycloheptadecane systems. These contained O, N, or S donor atoms in the 11 (n = 3) or 12 (n = 4) positions of the macroheterocycle (compounds IVa–h).

*For Communication 4, see [1].

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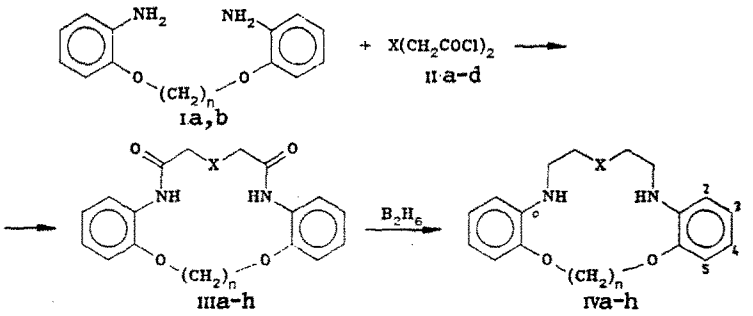
TABLE 1. Properties of Macrocyclic Amides IIIa–h

Compound	Empirical formula	M	mp, °C	R_f ($CHCl_3$)	Yield, %
III a	$C_{20}H_{22}N_2O_4$	354	195 ... 196	0,22	68
III b	$C_{21}H_{24}N_2O_4$	368	219 ... 220	0,36	84
III c	$C_{19}H_{20}N_2O_5$	356	200 ... 201	0,47	89
III d	$C_{20}H_{22}N_2O_5$	370	143 ... 144	0,42	81
III e	$C_{19}H_{20}N_2O_4S$	372	163 ... 164*	0,36	76
III f	$C_{20}H_{22}N_2O_4S$	386	233 ... 235	0,33	57
III g	$C_{28}H_{27}N_3O_6S$	519	242 ... 244	0,28	20
III h	$C_{27}H_{29}N_3O_6S$	533	213 ... 215	0,17	25

*According to [8], mp = 190–193°C.

TABLE 2. IR and PMR Spectra of Macrocyclic Amides IIIa–h

Compound	Chemical shifts ($CDCl_3$, TMS), δ, ppm						IR spectrum, cm^{-1}
	CH_2—O	CH_2, m	CH_2—X, s	X	NH, br.s	Ar, m	
IIIa	4,25 (4H, t J=5 Hz)	1,75 ... 2,92 (8H, m)			7,75 (2H)	8,05 ... 8,35 (2H); 6,62 ... 7,13 (6H)	3370
IIIb	3,96 ... 4,20 (4H, m)	1,67 ... 2,67 (10H, m)			7,90 (2H)	8,05 ... 8,40 (2H); 6,68 ... 7,25 (6H)	3360
IIIc	4,16 (4H, t J=5Hz)	2,30, (2H)	4,16 (4H)	—	8,70 (2H)	8,15 ... 8,40 (2H); 6,60 ... 6,95 (6H)	3340
IIId	3,94 ... 4,20 (4H, m)	1,87 ... 2,22 (4H)	4,24 (4H)	—	8,70 (2H)	8,20 ... 8,40 (2H); 6,58 ... 7,10 (6H)	3330
IIIe	4,20 (4H, t J=5 Hz)	2,40 ... 2,57 (2H)	3,50 (4H)	—	9,08 ... 9,22 (2H)	8,20 ... 8,45 (2H); 6,82 ... 6,97 (6H)	3180
IIIf	3,62 ... 4,16 (4H, m)	1,98 ... 2,12 (4H)	3,53 (4H)	—	8,72 ... 8,85 (2H)	8,10 ... 8,30 (2H); 6,20 ... 6,97 (6H)	3220
IIIg	4,15 (4H, t J=5 Hz)	2,23 (2H)	3,70 (4H)	2,40 (3H, s) 7,28 ... 7,55 m	9,05 (2H)	8,12 ... 8,32 (2H); 6,62 ... 6,88 (6H)	3360
IIIh	3,97 ... 4,18 (4H, m)	1,98 ... 2,17 (4H)	3,76 (4H)	2,40 (3H, s) 7,30 ... 7,65 s)	8,83 (2H)	7,95 ... 8,17 (2H); 6,78 ... 6,92 (6H)	3350



Ia, IIIa, c, e, g, IVa, c, e, g n = 3; Ib, IIIb, d, f, h, IVb, d, f, h n = 4; IIa, IIIa, b, IVa, b X = CH_2; IIb, IIIc, d, IVc, d X = O; IIc, IIIe, f, IVe, f X = S; IId, IIIg, h, IVg, h X = NTs.

Compounds IIIa-h were synthesized by acylating the bridging aromatic diamines Ia or Ib with the dichlorides of the dicarboxylic acids IIa–d under high dilution conditions. The macrocyclic crown lactams IIIa–h were reduced with diborane to the desired macrocyclic diamines IVa–h.

TABLE 3. Properties of Macrocyclic Amines IVa–h

Compound	Empirical formula	M	M^+	mp, °C	R_f ($CHCl_3$)	Yield, %
IVa	$C_{20}H_{26}N_2O_2$	326	326	105...107	0,78	53
IVb	$C_{21}H_{28}N_2O_2$	340	340	137...138	0,75	50
IVc	$C_{19}H_{24}N_2O_3$	328	328	173...174	0,71	54
IVd	$C_{20}H_{26}N_2O_3$	342	342	184...185	0,77	72
IVe	$C_{19}H_{24}N_2O_2S$	344	344	142...143	0,75	51
IVf	$C_{20}H_{26}N_2O_2S$	358	358	120...122	0,70	70
IVg	$C_{26}H_{31}N_3O_4S$	481	481	149...151	0,62	28
IVh	$C_{27}H_{33}N_3O_4S$	495	495	162...164	0,72	78

The starting aromatic diamines, 1,5-bis(2-aminophenyl)-1,5-dioxapentane (Ia) and 1,6-bis(2-aminophenyl)-1,6-dioxahexane (Ib), were synthesized by reducing the corresponding 2-nitrophenyl derivatives using $NaBH_4$ in the presence of 10% Pd/C.

The macrocyclic lactams IIIa–h were prepared by acylation of diamines Ia and Ib using the dichlorides of glutaric (IIa), diglycolic (IIb), thiodiglycolic (IIc), and N-tosyliminodiacetic (IId) acids in benzene with added pyridine. The concentration was 10^{-2} M in order to ensure high dilution conditions.

The structure and purity of the crown lactams IIIa–h were confirmed by TLC (Table 1), IR, and PMR (Table 2) data.

In [8], an attempt was made to prepare compound IIIe. The authors considered it sufficient to characterize the compound by giving only its melting point and molecular weight without describing the method used. The melting point of IIIe synthesized by us was lower than that in [8] by 20°C (Table 1). The complete characterization of IIIe (Tables 1 and 2) suggests to us that IIIe is here described for the first time.

The N–H stretching vibrations in the IR spectra of IIIa–h lie in the range 3370–3180 cm^{-1}. Two bands occur in the carbonyl region for IIIa–h. The first of these (amide I) lies between 1680-1650 cm^{-1} and is caused by combination vibrations of the carbonyl group. The second band (amide II) is found at 1590-1580 cm^{-1} and is apparently related to N–H deformations. Of the remaining IR bands, the medium intensity band (amide III) near 1280 cm^{-1} and the strong bands at 1110–1100 cm^{-1} and 1240–1200 cm^{-1} due to the simple ether bonds should be mentioned.

In the PMR spectra of IIIa–h, the weak-field signal near 9–8 ppm (Table 2) is assigned to the amide proton. The large shift (~4 ppm) to weak field of the signals for protons bonded to the N atom in the diamides IIIa–h compared to those for NH protons in the diamines IVa–h is explained by the influence of the neighboring carbonyl group. The carbonyl group has an analogous effect on the ortho-proton of the benzene rings, shifting these signals by 1.5–2.0 ppm to weak field relative to the remaining proton signals of the same ring. The proton signals of all methylene groups in the PMR spectra of IIIa and IIIb (except for the CH_2–O fragments) are poorly resolved multiplets of 8 and 10 protons, respectively, with centers near 2.34 ppm and 2.17 ppm (Table 2).

The macrocyclic amines IVa–h were prepared by reducing the corresponding amides with $NaBH_4$ in dry THF or dimethoxyethane. The structure and purity of the amines IVa–h obtained were confirmed by TLC, mass spectral (determination of the mass of the molecular ions) (Table 3), IR, PMR (Table 4), and ^{13}C NMR (Table 5) data. The strong bands between 3280–3200 cm^{-1} in the IR spectra are due to N–H stretching vibrations. These bands shift by 100–170 cm^{-1} to lower wavelength in comparison to the position of the analogous bands in IIIa-h (Tables 2 and 4). The shifting of these bands is due to lack of electron acceptors from the carbonyl groups.

In PMR spectra signals from aromatic protons from macrocyclic amines IVa-h shift 0.2–0.4 ppm in strong fields in comparison to signals of aromatic protons conforming to characteristics of compounds IIIa-h (Tables 2 and 4). Apparently in this case, also, the lack of carbonyl groups in the amines IV has an effect.

Protons of the $-CH_2-X-CH_2-$ groups in IVa and b (X = CH_2) give weakly resolved multiplets in the PMR spectra with centers near 1.53 and 1.56 ppm, respectively. Signals for the methylene protons in the $-NH-CH_2-$ and $-CH_2-N(Ts)-CH_2-$ fragments coincide in the PMR spectra of IVg and h (X = NTs). The shift to weak field for the signals of the $-CH_2-X-CH_2-$ protons is proportional to the electronegativity value of the X substituent.

The ^{13}C NMR spectra (Table 5) are consistent with the structure of the synthesized compounds IVa–h. The signals between 67.6–69.6 ppm are assigned to methylene groups next to the O atoms in the 1 and 5 or 1 and 6 positions. The signals at 41.5–43.0 ppm are assigned to the methylene groups next to the N atoms in the 8 and 14 or 9 and 15 positions, re-

TABLE 4. IR and PMR Spectra of Macrocyclic Amines IVa–h

Compound	Chemical shifts ($CDCl_3$, TMS), δ, ppm							IR spectrum, cm^{-1}
	CH_2—O	CH_2	CH_2—N	CH_2—X	X	NH, br.s	Ar	
IVa	4,03 (4H, t, J=5 Hz)	2,18 (2H)	2,96 ... 3,15 (4H)	1,46 ... 1,60 (6H)		4,22 (2H)	6,37 ... 6,83 (8H)	3200
IVb	3,85 ... 3,98 (4H)	1,80 ... 1,93 (4H)	3,08 ... 3,18 (4H)	1,50 ... 1,62 (6H)		4,23 (2H)	6,38 ... 6,83 (8H)	3280
IVc	4,08 (4H, t, J=5 Hz)	2,25 (2H)	3,10 ... 3,33 (4H)	3,53 ... 3,65 (4H)	—	4,48 (2H)	6,48 ... 6,73 (8H)	3200
IVd	3,87 ... 4,02 (4H)	1,90 ... 2,05 (4H)	3,36 (4H)	3,67 (4H, t, J=5 Hz)	—	4,75 (2H)	6,43 ... 6,83 (8H)	3220
IVe	4,15 (4H, t, J=5 Hz)	2,30 (2H)	3,10 ... 3,30 (4H)	2,26 ... 2,90 (4H)	—	4,90 (2H)	6,48 ... 6,73 (8H)	3200
IVf	3,88 ... 4,05 (4H)	1,97 (4H)	3,11 ... 3,38 (4H)	2,70 ... 2,93 (4H)	—	4,91 (2H)	6,50 ... 6,83 (8H)	3260
IVg	4,07 (4H, t, J=5 Hz)	2,27 (2H)	3,18 (8H)		2,25 (3H, s); 7,05 ... 7,50 (4H)	4,83 (2H)	6,27 ... 6,78 (8H)	3280
IVh	3,39 ... 4,25 (4H)	1,90 ... 2,07 (4H)	3,18 (8H)		2,30 (3H s); 7,08 ... 7,48 (4H)	4,83 (2H)	6,37 ... 6,78 (8H)	3270

*All signals, except for the cases indicated, are weakly resolved multiplets.

TABLE 5. ^{13}C NMR Spectra of Compounds IVa–h

Compound	Chemical shifts ($CDCl_3$, TMS, δ, ppm)										
	CH_2—O	CH_2	CH_2—N	CH_2—X	X	$C_{(1)}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$
IVa	67,3	26,7; 29,4	41,5	26,4	22,0	138,6	109,8	121,8	115,9	112,1	146,1
IVb	68,4	26,7	42,3	28,3	23,8	139,0	109,8	121,5	115,9	111,8	146,2
IVc	68,3	30,0; 29,5	43,0	67,8	—	138,9	110,1	121,7	116,6	111,8	146,7
IVd	69,6	26,7	42,9	67,3	—	138,1	109,5	120,8	116,1	110,4	146,3
IVe	67,4	29,8; 29,6	41,3	31,4	—	138,4	110,2	121,9	116,6	112,6	146,6
IVf	68,0	26,8	40,9	32,2	—	138,0	109,9	121,1	116,3	111,1	146,4
IVg	67,3	29,1	41,7	48,6	21,1; 129,3; 127,2; 135,9; 142,9	138,4	110,2	121,9	116,6	112,6	146,6
IVh	68,4	26,5	42,6	49,2	21,2; 127,2; 129,4; 135,8; 143,0	138,2	109,8	121,2	116,6	111,8	146,6

spectively. The remaining high-field signals were assigned on the basis of the chemical shifts in ^{13}C NMR spectra of related systems [9, 10], the relative signal intensities, and their multiplicity in proton decoupled spectra.

An interesting feature is seen in the ^{13}C NMR spectra of the 16-membered macroheterocycles IVa, c, e (X = CH_2, O, S) in chloroform. The central C atom in the trimethylene chain between the O atoms gives two signals that differ in chemical shift (by 0.3–0.5 ppm) and in intensity. For IVa (X = CH_2), the relative signal intensities are 1:1; for IVc (X = O), 2:1; and for IVe (X = NTs), 3.5:1. Each of these signals in partially proton-decoupled spectra splits into a triplet. Thus, they belong to the methylene group.

Such behavior for IVa, c, e is apparently due to the two conformations that are stabilized by intramolecular hydrogen bonds. Molecular models of IVg (X = NTs) show that only one conformation is possible for it due to the bulky substituent. One methylene group signal is seen for this compound near 29 ppm in the ^{13}C NMR spectrum. The fact that only one signal is seen between 29–30 ppm for IVa, c, e in DMSO, which effectively destroys hydrogen bonds, is further evidence for such frozen conformations.

Signals for the aromatic C atoms are assigned considering the effects of alkoxy- and alkylamino groups [10]. Signals with similar chemical shifts in the range 109.5–112.6 ppm are difficult to assign to atoms $C_{(2)}$ and $C_{(5)}$ (the C atom numbering in the aromatic ring is given in the figure) due to the inaccuracies of the additive scheme used.

EXPERIMENTAL

IR spectra were taken on a Specord IR-71 as $CHCl_3$ solutions in NaCl cells. PMR spectra were recorded on a Tesla BS-467 spectrometer (60 MHz) in $CDCl_3$ with TMS internal standard. ^{13}C NMR spectra were recorded on a Bruker AC-250 (250 MHz) in $CDCl_3$. Mass spectra were obtained on an MX-1303 spectrometer at an ionizing potential of 12–50 eV. TLC was carried out using $CHCl_3$ eluent on neutral aluminum oxide with visualization by iodine vapors.

1,5-Bis(2-aminophenyl)-1,5-dioxapentane (Ia). With cooling in a water bath, 7.6 g (200 mmoles) $NaBH_4$ was added in small portions to a vigorously stirred mixture of 15.9 g (50 mmoles) 1,5-bis(2-nitrophenyl)-1,5-dioxapentane and 0.25 g 10% Pd/C in 250 ml dry methanol. The mixture was stirred for 20 min after the addition was complete and then was filtered. The filtrate was evaporated to half its volume. Cold water (400 ml) was added. The mixture was extracted with $CHCl_3$ (4 × 50 ml). The extract was dried with Na_2SO_4 and evaporated. The residue was recrystallized from a mixture of water and ethanol in a 2:1 ratio. Yield 11.9 g (92%) Ia, mp 57°C, R_f 0.37. IR spectrum: 3290, 3210, 2880, 2830, 2770, 1595, 1490, 1455, 1440, 1370, 1320, 1260, 1230–1180, 1145, 1060, 1045, 990, 950 cm^{-1}. PMR spectrum: 2.18 (2H, q, J = 6 Hz), 3.67 (4H, br.s), 4.03 (4H, t, J = 6 Hz), 6.6 ppm (8H, br.s).

1,6-Bis(2-aminophenyl)-1,6-dioxahexane (Ib) was obtained as described above. Yield 86%, mp 106°C (from ethanol), R_f 0.47. IR spectrum: 3310, 3230, 2900, 2840, 1600, 1490, 1460, 1445, 1370, 1330, 1270, 1230–1185, 1140, 1070, 1040, 1010, 970, 900 cm^{-1}. PMR spectrum: 1.95 (4H, m), 3.65 (4H, br.s), 3.98 (4H, m), 6.65 ppm (8H, m).

The general method for preparing the macrocyclic amides IIIa-h was described in [10].Theproperties of compounds IIIa-h are given in Tables 1 and 2.

The general method for reducing amides IIIa–h to the amines IVa–h was described in [9, 10]. Compounds IVg, h were reduced using $NaBH_4$ in dimethoxyethane. The remaining amides were reduced in THF. Properties of compounds IVa–h are given in Tables 3–5. Elemental analyses (C, H, N, S) for IIIa–h and IVa–h correspond to those calculated.

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