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SYNTHESIS OF MACROHETEROCYCLIC ANALOGS OF DIBENZOCROWN-COMPOUNDS. 3.* 18-MEMBERED OXATHIAZACROWN-COMPOUNDS

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UDC 547.898:543.422

Condensation of 1,7-bis(2-aminophenyl)-4-thia-1,7-dioxaheptane with dichloroanhydrides of glutaric, diglycolic, thiodiglycolic, and N-tosyliminodiacetic acids under high dilution conditions with subsequent reduction of the macrocyclic diamides by borohydride leads to formation of 18-membered macrocylic diamines which contain a sulfur atom in the 4 position. An analogous series of reactions using 1,7-bis(2-aminophenyl)-4-(carba, oxa, aza)-1,7-dioxaheptanes and the dichloroanhydride of thiodiglycolic acid allows the sulfur atom to be introduced in the 13 position. The structure of the synthesized compounds was confirmed by IR, NMR, and mass spectral data.

Introduction of nitrogen, sulfur, and other heteroatoms into a crown-ether molecule along with oxygen atoms leads to a significant change in the complexing character of such macroheterocycles. The values of the stability constants of the complexes which are prepared from aza-, thia-, or azathiacrown-ethers with alkali or alkaline earth metals decrease significantly by comparison with those for corresponding crown-ethers upon a change in 18-crown-6- or dibenzo-18-crown-6-ethers of a part of the oxygen atoms by sulfur or nitrogen [2]. Relative to ions of transition or heavy metals, the complexing ability of azathiacrown-ethers increases markedly. Thus, exchange of two oxygen atoms by two sulfur atoms in the crown-ether molecule was shown to increase the extraction of Ag(I) from 6 to 92% [3]. An analogous effect was observed for Hg(II) [4], Cu (I), and Pd(III) [5-7].

Replacement of oxygen atoms by sulfur atoms in a series of diazadibenzo-15-crown-5-compounds described earlier by us [8] leads to a significant improvement of Hg(II) and Ag(I) extraction [9, 10].

*For communication 2, see [1].

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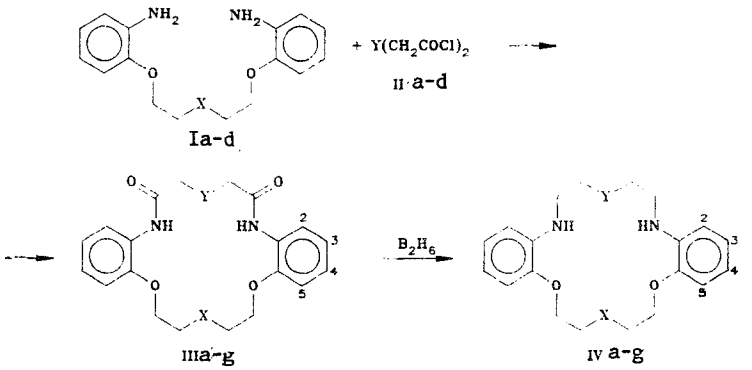
 0009-3122/89/2506-0704$12.50

Continuing the systematic search for new highly selective macrocyclic compounds which are suitable for extraction of transition and heavy metals, we have synthesized a series of



Ia, IIIa, IVa X=CH_2; Ib, IIIb, IVb X=O; Ic, IIIc, IIIe–g, IVc, IVe–g X=S; Id, IIId, IVd X=NTs; IIa, IIIa, IVe Y=CH_2; IIb, IIIf, IVf Y=O; IIc, IIIa–d, IVa–d Y=S; IId, IIIg, IVg Y=NTs

18-membered dioxadiazacrown-compounds IVa-g, which contain additionally in the macrocyclic ring one or two sulfur donor atoms.

The scheme which includes acylation of the bridging aromatic diamines Ia-d by the dichloroanhydride of thiodiglycolic acid (IIc) as well as acylation of 1,7-bis(2-aminophenyl)-4-thia-1,7-dioxaheptane (Ic) by the dichloroanhydrides of dicarboxylic acids IIa, b, and d under high dilution conditions was used for synthesis of compounds IVa-g.

Synthesis of the diamines Ia, b, and d was described earlier [1]. Diamine Ic was synthesized by alkylation of 2-nitrophenol by 1,5-dibromo-3-thiapentane (V) with subsequent reduction of 1,7-bis(2-nitrophenyl)-4-thia-1,7-dioxaheptane (VI) by sodium borohydride in the presence of 10% Pd/C.

The macrocyclic diamides IIIa-g were prepared by acylation of diamides Ia-d by dichloroanhydrides of glutaric (IIa), diglycolic (IIb), thiodiglycolic (IIc), and N-tosyliminodiacetic (IId) acids under high dilution conditions in benzene in the presence of pyridine. The structure and purity of the diamides IIIa-g prepared were confirmed by TLC data and elemental analysis and if the solubility of the compounds allowed, by IR and NMR spectra (Table 1).

Strong absorption bands in the 3410-3250 cm^{-1} region occur in the IR of compounds IIIa-g. These belong to stretching vibrations of free and bound NH groups in the secondary amides. The strong bands related to the stretching vibrations of the double bond of the carbonyl groups were observed in the 1690-1660 cm^{-1} region. Strong absorption bands which appear in the 1580-1610 cm^{-1} region are due to deformations of the N-H bond and vibrations of the C-N bond. The amide III band with medium intensity appears in the 1275-1290 cm^{-1} region. Bands of the antisymmetric (1340 cm^{-1}) and symmetric stretching vibrations (1150 cm^{-1}) of the sulfonyl group are observed in the spectrum of IIId which contains a tosyl group. Strong broad bands of symmetric stretching vibrations of the ether bond of the C=C–O–C group in the 1150-1120 cm^{-1} region and the asymmetric stretching vibrations of the C–C–O–C group (1260-1200 cm^{-1}) are observed in the spectra of all synthesized amides IIIa-g.

The signal at weakest field in the ^1H NMR spectra (9.01-8.03 ppm) of amides IIIa-g belongs to the amide proton (Table 1). A substantial shift of the NH proton signal to weak field by comparison with the NH proton signal in the corresponding macrocyclic amine is observed (Table 2), Besides this, the carbonyl group deshields the protons in the 2 position of the arimatic rings. This leads to a substantial (by 1.1-0.9 ppm) shift of the signal to weak field by comparison with the signals of protons 3-5 of the aromatic ring (numbering of aromatic ring atoms is given in the scheme). The sulfur atom in the alphatic chain causes a shift of the signals of the neighboring methylene protons by 1.4-1.1 ppm to weak field (this is smaller than the effect of an O or N atom). All protons of the $-CH_2-X-CH_2-$ (X = CH_2) fragment in the spectrum of IIIa give a poorly resolved six-proton multiplet with a center near 1.87 ppm (Table 1) while in the spectrum of IIId, an analogous effect is observed with X = NTs (the multiplet center is at 3.87 ppm, 8H).

TABLE 1. Characteristics and IR and ^{1}H NMR Spectral Data of Macrocyclic Amides IIIa-g

Compound	Empirical formula	mp, °C	R_f ($CHCl_3$)	^{1}H NMR spectrum, δ, ppm							IR spectrum ν, cm^{-1}	Yield, %
				CH_2—Y (m)	CH_2—O (m)	CH_2—X (m)	X (m)	Ar (m)	NH (br. s)	Y		
IIIa	$C_{21}H_{24}N_2O_4S$	274...275	0,85	3,52* (4H)	4,03 (4H)	1,87 (6H)		7,10...6,60 (6H); 8,22 d (2H)	8,63 (2H)	—	3350	80
IIIb	$C_{20}H_{22}N_2O_5S$	250...251	0,40	3,55 (4H)	4,12 (4H)	3,83 (4H)	—	7,10...6,70 (6H); 8,13 d (2H)	8,86 (2H)	—	3250	88
IIIc	$C_{20}H_{22}N_2O_4S_2$	262...264	0,08	—	—	—	—	—	—	—	—	30
IIId	$C_{27}H_{29}N_3O_6S_2$	271...272	0,26	3,75* (4H)	3,23...	4,40 (8H)	7,10...6,60 (10H) 8,18 d (2H)		8,70 (2H)	—	3360	96
IIIe	$C_{21}H_{24}N_2O_4S$	250...252	0,15	—	—	—	—	—	—	—	—	51
IIIf	$C_{20}H_{22}N_2O_5S$	175...177	0,26	4,36...4,20 (8H)		2,98** (4H)	—	7,26...6,94 (6H); 8,38 d (2H)	9,01 (2H)	—	3400	35
IIIg	$C_{27}H_{29}N_3O_6S_2$	160...162	0,19	4,02* (4H)	4,17** (4H)	3,13** (4H)	—	6,97...6,72 (6H)	8,99 (2H)	2,47 s (3H); 7,80 d (2H); 7,40 d (2H)	3410	27,5

*Singlet.
**Doublet of doublets.

TABLE 2. Characteristics and IR, ^{1}H NMR, and Mass Spectral Data of Macrocyclic Amines IVa-g

Compound	Empirical formula	mp, °C	R_f ($CHCl_3$)	^{1}H NMR spectrum δ, ppm								IR spectrum ν, cm^{-1}	M		Yield, %
				CH_2—O	CH_2—X	X	CH_2—N	CH_2—Y	Y	NH	Ar		found	calculated	
IVa	$C_{21}H_{28}N_2O_2S$	216...217	0,65**	3,97 (4H)	1,82 (6H)		3,28 (4H)	2,92 (4H)	—	4,67 (2H)	6,97...6,38 (8H)	3410	372	372,53	64
IVb	$C_{20}H_{26}N_2O_3S$	170...172	0,75	4,08 (4H)	3,91 (4H)	—	3,30 (4H)	2,88 (4H)	—	4,88 (2H)	7,03...6,43 (8H)	3410	374	374,50	77
IVc	$C_{20}H_{26}N_2O_2S_2$	170...171	0,46	4,25 (4H)	3,11 (4H)	—	3,37 (4H)	2,49 (4H)	—	4,80 (2H)	6,92...6,58 (8H)	3400	527	390,56	54
IVd	$C_{27}H_{33}N_3O_4S_2$	165...166	0,77	4,15 (4H)	3,78 (4H)	2,38 s (3H) 7,87...7,17 (4H)	3,27 (4H)	2,83 (4H)	—	4,67 (2H)	7,00...6,35 (8H)	3400	527	527,70	38
IVe	$C_{21}H_{28}N_2O_2S$	190...192	0,64	4,22 (4H)	3,06 (4H)	—	3,18 (4H)	1,73 (6H)		4,37 (2H)	6,92...6,58 (8H)	3440	372	372,53	70
IVf	$C_{20}H_{26}N_2O_3S$	200...201	0,50	4,22 (4H)	3,05 (4H)	—	3,32 (4H)	3,75 (4H)	—	4,63 (2H)	6,90...6,50 (8H)	3440	374	374,50	65
IVg	$C_{27}H_{33}N_3O_4S_2$	146...147	0,20	4,22 (4H)	3,10 (4H)	—	3,35 (8H)		2,39 s (3H) 7,65...7,41 (4H)	4,70 (2H)	6,83...6,30 (8H)	3310	527	527,70	57

*All signals, with the exception of the cases noted, are poorly resolved multiplets.
**C_6H_6 eluent.

TABLE 3. ^{13}C NMR Spectra of Compounds IVa-g

Compound	Chemical shifts, δ, ppm									
	CH_2—O	CH_2—N	CH_2—X	CH_2—Y	C^1	C^3	C^4	C^2, C^5	C^6	others
IVa	67,6	43,6	29,7	33,0	138,3	121,1	117,2	109,9; 109,8	147,1	23,9 (CH_2)
IVb	68,3	42,3	70,0	32,3	138,3	121,9	116,6	110,3; 111,8	146,3	—
IVc	68,2	42,5	32,4	32,4	138,9	121,8	116,7	110,2; 111,0	145,9	—
IVd	68,1	42,2	49,0	32,2	137,8	121,9	117,1	110,5; 111,5	145,8	21,1; 143,4; 135,9; 129,7; 127,0
IVe	67,3	43,1	33,1	28,7	138,8	121,8	115,9	109,8; 110,8	145,5	24,9
IVf	68,2	43,7	32,5	68,9	138,7	121,8	116,6	110,2; 111,4	145,9	—
IVg	69,4	43,4	31,7	49,7	137,8	121,8	116,6	110,2; 111,4	145,8	21,4; 143,4; 136,1; 129,6; 127,1

Macrocyclic amines IVa-g were prepared by reduction of the corresponding amides by borohydride in thoroughly dried tetrahydrofuran or dimethoxyethane. The structure and purity of the IVa-g amines prepared were confirmed by TLC data, elemental analysis, mass spectra, IR spectra, ^1H NMR spectra (Table 2), and ^{13}C NMR (Table 3).

A strong absorption band in the 3310-3410 cm^{-1} region in the IR spectra of these compounds is related to the stretching vibrations of the NH group of the amines. A shift by 100 cm^{-1} of this band for IVg is probably caused by formation of a hydrogen bond between the proton of the NH group and the substituent in the 4 position.

Signals of the aromatic protons of the macrocyclic amines IVa-g in the ^1H NMR spectra (Table 2) are shifted by 0.2-0.3 ppm to strong field by comparison with the aromatic protons of the corresponding amides IIIa-g. Apparently, this is related to elimination of the carbonyl groups which have strong electron-acceptor properties. Protons of the three methylene groups of the $-CH_2-X-CH_2-$ (X = CH_2) in IVa give a poorly resolved multiplet with a center near 1.8 ppm in the ^1H NMR spectrum. Analogously, protons of the $-CH_2-X-CH_2$ (X = CH_2) fragment of IVe give a broad six-proton multiplet with a center near 1.7 ppm in the ^1H NMR spectrum. The shift of the signal in the latter case by 0.1 ppm to weak field is explained by exchange of the oxygen donor atom by the less electronegative nitrogen atom.

The ^{13}C NMR spectra (Table 3) confirm the structure of the synthesized compounds IVa-g. Signals in the 67.6-69.4 ppm region are assigned to the methylene groups next to the oxygen atoms at postitions 1 and 7. Signals in the 42.2-43.7 ppm region are assigned to signals of the methylene groups next to nitrogen atoms 10 and 16, and signals in the 33.1-31.7 ppm region, to methylene groups bonded to the sulfur atoms.

Assignment of the remaining strong field signals is made based on analysis of chemical shifts of ^{13}C NMR of related systems [1, 8], the relative intensity of signals, and their multiplicity without proton decoupling.

Assignment of aromatic carbon signals with similar chemical shifts in the 111.8-109.8 ppm region to carbon atoms C^2 and C^5 (numbering of carbon atoms in the aromatic rings are given in the scheme) is hindered as a result of insufficient accuracy of the additive scheme used.

The molecular weight of the synthesized macrocyclic amines is determined by mass spectrometry. A significant part of the total ion current appears in the fragments with m/z 120, 122, 134, 136, and 148, the structure of which is discussed by us earlier [1]. The largest contribution to the total ion current (11-34%) belongs to the $[M - HS]^+$ ion. It is interesting to note the complete absence of the $[M - Ts]^+$ ion in the mass spectrum of IVd, although in the spectrum of its isomer (IVg) 6.8% of the total ion current appears in this fraction.

EXPERIMENTAL

IR spectra were taken on a Specord IR-71 instrument for solutions in chloroform in NaCl cuvettes. ^1H NMR spectra were recorded on Tesla BS-467 (60 MHz) and Bruker AC-250 (250 MHz) instruments in $CDCl_3$ with TMS internal standard; ^{13}C NMR spectra, on a Bruker AC-250 in $CDCl_3$. TLC were developed on neutral aluminum oxide II according to Brockman and visualized with iodine. Eluents are shown in Tables 1 and 2. Elemental analyses for III and IV compounds for C, H, N, and S corresponded to those calculated.

1,7-Bis(2-aminophenyl)-1,7-dioxaheptane (Ia), 1,7-bis(2-aminophenyl)-1,4,7-trioxaheptane (Ib), and 1,7-bis(2-aminophenyl-4-tosyl-1,7-dioxaheptane (Id) were prepared according to [1].

1,5-Dibromo-3-thiaheptane (V) was prepared according to [11] with 89% yield, mp 32°C. According to [11], mp 31-34°C.

1,7-Bis(2-nitrophenyl)-4-thia-1,7-dioxaheptane (VI). A solution of 19.6 g (0.079 mole) of V in 50 ml DMF was added over 20 min to a stirred suspension of 15.0 g (0.108 mole) potash and 27.8 g (0.200 mole) 2-nitrophenol in 50 ml dry DMF. The mixture was boiled for 6 h, cooled, and poured into 500 ml water. The oil which formed was mixed with 300 ml 5% KOH solution until solidification, filtered off, and recrystallized from 50% aqueous acetone.

Yield 27.4 g (95%) VI, mp 73°C, Rf 0.74 ($CHCl_3$). IR spectrum: 3060. 3000, 2950, 2890, 1615 1590, 1525, 1500, 1460, 1360, 1280, 1240, 1170, 1177, 1095, 1010, and 915 cm^{-1}. ^1H NMR spectrum: 7.92-7.75 m (2H), 7.62-7.44 m (2H), 7.21-6.94 m (4H), 4.32 m (4H), and 3.10 m (4H).

1,7-Bis(2-aminophenyl)-4-thia-1,7-dioxaheptane (Ic). Over 2 h by portions, 24.1 g (0.634 mole) $NaBH_4$ was added to a boiling suspension of 31.5 g (0.086 mole) VI and 2.5 g 10% Pd/C in 950 ml methanol. After addition was complete, the mixture was boiled for 3 more hours, filtered while hot, and cooled. Two ℓ water were added to the filtrate. The precipitate which formed was separated and dried in vacuum. Yield 18.4 g (70%) Ic. mp 87°C, Rf 0.35 ($CHCl_3$). IR spectrum: 3480, 3400, 2930, 1610, 1480, 1335, 1270, 1200, 1170, 1135, and 1070 cm^{-1}. ^1H NMR spectrum: 6.83-6.65 m (8H), 4.18 t, J = 6 Hz (4H), 3.60 m (4H), and 3.10 t, J = 6 Hz (4H).

A general method for preparation of macrocyclic amides IIIa-g was described by us earlier [8]. Solutions of bridging aromatic diamines Ia and Ib for acylation were prepared in dioxane, diamines Ic and Id, in pyridine. Data for IIIa-g are given in Table 1.

A general method for reduction of amides IIIa-g into amines IVa-g was described in [8]. Compounds IIIc and IIIg were reduced with $NaBH_4$ in dimethoxyethane, the remaining amides, in tetrahydrofuran. Data for IVa-g are given in Tables 2 and 3.

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