SYNTHESIS OF MACROHETEROCYCLES, ANALOGS OF DIBENZO-CROWN COMPOUNDS.

1. 15-MEMBERED OXATHIADIAMINES

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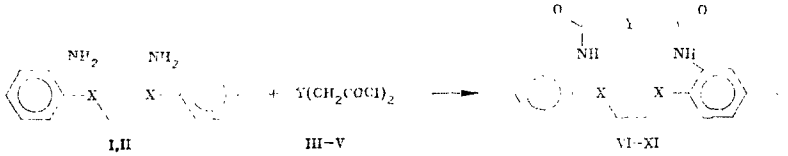
Macrocyclic diamides have been synthesized by the condensation of 1,4-bis(2-aminophenyl)-1,4-dioxa(dithia)butanes with the diacid chlorides of glutaric, diglycolic, and thiodiglycolic acids under conditions of high dilution. Subsequent reduction with diborane led to the corresponding macrocyclic diamine containing atoms of oxygen and (or) sulfur. Structural assignments were made using data of mass spectrometry and IR, PMR, and ^{13}C NMR spectra.

The name "coronand" was proposed in [1] for macrocyclic systems consisting of one ring including several heteroatoms as was the term "crown ether" for coronands containing only oxygen atoms. It should be noted that the term "coronand" has still not been widely accepted, and analogs of crown ethers containing heteroatoms other than oxygen are frequently called crown compounds. We will use this term from now on.

Crown ethers and their analogs, crown compounds, are widely used as selective complex-forming agents and extractants [2]. The choice of donor atoms in the structure of the macroheterocycle is determined in the most general case by the nature of the metal which it is proposed to extract proceeding from the concept of hard and soft acids and bases. Since the extraction of heavy and transition metals is of the greatest interest, this determines the choice of heteroatoms, first of all nitrogen, then oxygen, and sulfur. The presence in the molecule of the macroheterocycle of condensed aromatic nuclei gives the extracting agent several favorable properties. It increases the molecular weight, it raises the distribution coefficient of the extracting agent in systems of organic solvent—water, and opens wide possibilities for various modifications of the extracting agent by the introduction of substituents into the aromatic nucleus.

The system dibenzo-15-crown-5 has been studied mainly for those cases when the donor atoms are oxygen [3]. Nitrogen-containing analogs of such systems are practically unknown [4].

While studying different approaches to the synthesis of nitrogen-containing analogs of dibenzo-15-crown-5 compounds we decided on the reaction of acylation of aromatic diamines, viz., 1,4-bis(2-aminophenyl)-1,4-dioxabutane (I) and 1,4-bis(2-aminophenyl)-1,4-dithiabutane (II), with the diacid chlorides of the appropriate dicarboxylic acids, viz., glutaric (III), diglycolic (IV), and thiodiglycolic (V) acids.



I,II III–V VI–XI

I, VI–VIII X=O; II, IX–XI X=S; III, VI, IX Y=CH_2; IV, VII, X Y=O; V, VIII, XI Y=S

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TABLE 1. Characteristics of Macrocyclic Amides (VI)-(XI)

Compound*	mp, deg C	R_f ($CHCl_3$)	Found, %				Empirical formula	Calculated, %				Yield, %
			C	H	N	S		C	H	N	S	
VI	274	0,76	66,9	5,9	8,2		$C_{19}H_{20}N_2O_4$	67,0	5,9	8,2		50
VII	212	0,71	63,2	5,3	8,1		$C_{18}H_{18}N_2O_5$	63,1	5,3	8,2		87
VIII	231	0,72	60,4	5,1	7,8	8,9	$C_{18}H_{18}N_2O_4S$	60,3	5,1	7,8	8,9	64
IX	278	0,70	60,9	5,4	7,6	17,3	$C_{19}H_{20}N_2O_2S_2$	61,3	5,4	7,5	17,2	70
X	221	0,79	57,5	4,8	7,5	17,2	$C_{18}H_{18}N_2O_3S_2$	57,7	4,8	7,5	17,1	84
XI	271	0,70	55,2	4,7	7,2	25,0	$C_{18}H_{18}N_2O_2S_3$	55,4	4,6	7,2	24,6	90

*5,6;14,15-Dibenzo-1,4-dioxa-7,13- (VI), 5,6; 14,15-dibenzo-1,4,10-trioxa-7,13- (VII), 5,6;14,15-dibenzo-1,4-dioxa-10-thia-7,13- (VIII), 5,6;14,15-dibenzo-1,4-dithia-7,13- (IX), 5,6;14,15-dibenzo-1-oxa-7,10-dithia-4,13-diazacyclopentadeca-3,14-dione (X), 5,6; 14,15-dibenzo-1,4,10-trithia-7,13-diazacyclopentadeca-8,12-dione (XI).
†Eluent was $CHCl_3$ + 5% ethanol.

TABLE 2. IR Spectra of Compounds (VI)-(XI)

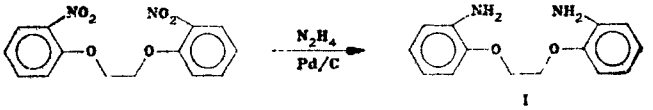
Compound	Absorption bands, cm^{-1}							
	N–H	C–H	amide I	amide II	aryl	CH_2	C–O–C	amide III
VI	3240	2920	1660	1580	1490	1465	1060, 1140, 1200	1280
VII	3270	2910, 2830	1670	1585	1520	1440	1040, 1115, 1200	1240
VIII	3140	2790	1660	1570	1500	1425	1030, 1105, 1200	1270
IX	3210	2890, 2830	1665	1560	1490	1425	—	1285
X	3116	2840, 2760	1660	1555	1505	1420	1030, 1130	1290
XI	3020	2820, 2740	1650	1555	1480	1410	—	1285

TABLE 3. Characteristics of Macrocyclic Amines (XII)-(XVII)

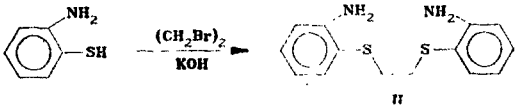
Compound*	mp, deg C	R_f (benzene)	Found					Empirical formula	Calculated					Yield, %
			C, %	H, %	N, %	S, %	M†		C, %	H, %	N, %	S, %	M	
XII	59	0,58	72,9	7,7	9,0		312	$C_{19}H_{24}N_2O_2$	73,0	7,7	9,0		312	80
XIII	135	0,41	69,0	7,0	9,0		314	$C_{18}H_{22}N_2O_3$	68,8	7,0	9,0		314	84
XIV	157	0,55	65,3	6,7	8,5	10,0	(320) 330	$C_{18}H_{22}N_2O_2S$	65,4	6,7	8,5	9,7	330	75
XV	140‡ (oil)	0,73	55,0‡	6,3	6,8	15,4	344 (352)	$C_{19}H_{24}N_2S_2\times$ $\times 2HCl$	54,7‡	6,3	6,7	15,4	344	78
XVI	136	0,66	62,4	6,5	8,1	18,2	346	$C_{18}H_{22}N_2OS_2$	62,4	6,4	8,1	18,5	346	95
XVII	134	0,77	60,0	6,1	7,8	26,4	(375)	$C_{18}H_{22}N_2S_3$	59,6	6,1	7,7	26,5	362	89

*5,6;14,15-Dibenzo-1,4-dioxa-7,13- (XII), 5,6;14,15-dibenzo-1,4,10-trioxa-7,13- (XIII), 5,6;14,15-dibenzo-1,4-dioxa-10-thia-7,13- (XIV), 5,6;14,15-dibenzo-1,4-dithia-7,13- (XV), 5,6;11,12-dibenzo-1-oxa-7,10-dithia-4,13- (XVI), 5,6;14,15-dibenzo-1,4,10-trithia-7,13-diazacyclopentadecane (XVII).
†From mass spectra, values in parentheses were obtained cryoscopically.
‡For dihydroxychloride.

The initial diamines (I) and (II) were obtained by the following scheme:



I



II

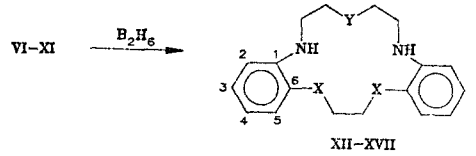
Carrying out the acylation under conditions of high dilution in benzene at 75°C made it possible to obtain macrocyclic amides (VI)-(XI) in preparative yields. Pyridine was used as acceptor of hydrogen chloride in spite of the availability of the initial amines. This did not significantly lower the yield of amides (VI)-(XI).

The macrocyclic amides (VI)-(XI) synthesized in this way were characterized by data of TLC, elemental analysis, IR spectra, and in certain cases also by PMR spectra.

Absorption bands were present in the IR spectra of amides (VI)-(XI) (Table 2) in the 3020-3270 cm^{-1} region characteristic of N—H vibrations in amides. In addition, intense absorption bands were observed in the 1650-1670 (amide I band), 1555-1585 (amide II band), and 1240-1295 cm^{-1} (amide III band) regions. Bands were present in the spectra of compounds (VI)-(VIII) and (X) in the 1030-1060, 1105-1130, and 1200 cm^{-1} regions characteristic of ethers.

Lithium aluminum hydride [5] or hydroboranes [6] are usually used for the reduction of substituted amides, including macrocyclic amides, to secondary amines. Attempts to reduce amides (VI)-(XI) with lithium aluminum hydride proved to be successful only in the case of compound (VI) (yield of amine XII was 77%). In the remaining cases the conversion of amide was low even after boiling with an excess of lithium aluminum hydride in THF for 24 h. The use of diborane generated from sodium borohydride and boron fluoride etherate made it possible to obtain the macrocyclic amines (XII-XVII) in satisfactory yield (Table 3).

Scheme 1



XII-XVII

XII—XIV X=O; XV—XVII X=S; XII, XV Y=CH_2; XIII, XVI Y=O; XIV, XVII Y=S

The synthesized macrocyclic amines (XII)-(XVII) were colorless, solid, crystalline substances (with the exception of compound XV), they were readily soluble in the majority of organic solvents, and were characterized by data of TLC, elemental analysis, IR and PMR spectra, and also by data of ^{13}C NMR spectra. The molecular weight was determined by the Rast method (cryoscopically) in camphor. In certain cases these data were confirmed mass spectrometrically.

Absorption bands were present in the IR spectra of amines (XII)-(XVII) (Table 4) in the 3170-3260 cm^{-1} region which were characteristic of N—H in secondary macrocyclic amines [7]. There were also bands in the 1560-1590 and 1480-1500 cm^{-1} regions characteristic of the aromatic nucleus, and bands in the 1030-1230 cm^{-1} region characteristic of ν(C—N) [7].

Signals were observed in the PMR spectra of amines (XII)-(XVII) (Table 4) for the equivalent protons of the methylene groups of the fragment —X—CH_2CH_2—X— at 4.11-4.25 (X = O) and 2.70-2.87 ppm (X = S), multiplets for the methylene group of —CH_2—N— fragments at 3.10-3.30 ppm and —CH_2—Y— at 1.47-1.52 (Y = CH_2), 3.47-3.58 (Y = O), and 2.78-2.80 ppm (Y = S). The proton of the amino group appeared as a poorly resolved wide multiplet in the range 3.90-5.33 ppm. A signal for the methylene group (fragment Y) was observed in the PMR spectra of compounds (XII) and (XV) in the 1.47-1.52 ppm region.

The ^{13}C NMR spectra confirmed the structure of the synthesized compounds (XII)-(XVII). Chemical shifts are given in Table 4. Assignment of the signals of the aliphatic carbon atoms was made on the basis of the chemical shifts of related systems from [8], by the relative intensity of signals, and by their multiplicity in spectra without proton decoupling. The assignment of the signals of the aromatic carbon atoms was made allowing for the effects of the influence of amino and methoxy groups from [9], of thioethoxy groups from [10], and also by comparison with spectra of appropriate model compounds. The assignment of signals to carbons C^4 and C^5 with close chemical shifts in compounds (XII)-(XIV) was made on the assumption that the substituent at the nitrogen atom influences more strongly the shielding of the pure carbon C^4 than the shielding of the meta carbon C^5, which is apparent on comparison of the chemical shifts of C^4 in compounds (XII)-(XIV). The assignment of the signals of carbons C^1 and C^6 was made on the basis of an analysis of the spectra without proton decoupling.

TABLE 4. IR, PMR, and ^{13}C NMR Spectra of Macrocyclic Amines XII-XVII

Compound	IR spectra, cm^{-1}		PMR spectra, chemical shifts of protons δ, TMS, ppm						^{13}C NMR spectra, chemical shifts of carbon nuclei, δ, TMS, ppm								
	NH	other bands	CH_2—X	CH_2—N	CH_2—Y	NH	Ar	Y	CH_2—X	CH_2—Y	CH_2—NH	aromatic*						other
												C^1	C^2	C^3	C^4	C^5	C^6	
XII	3210	2880, 2720, 1580, 1485, 1440, 1330, 1230, 1125, 1060, 1040, 930	4,25	3,13	1,52	3,90	6,35—6,98	1,52	67,3	26,3	41,8	139,1	116,0	122,0	111,7	110,6	145,7	21,8 (CH_2)
XIII	3260	2900, 2825, 2780, 1590, 1500, 1445, 1335, 1260, 1210, 1140, 1125, 1080, 1065, 1045	4,11	3,17	3,47	4,75	6,33—6,98	—	66,9	68,4	43,1	138,9	116,3	121,8	111,6	110,2	145,8	—
XIV	3230	2910, 2880, 2745, 1580, 1495, 1445, 1435, 1330, 1245, 1200, 1150, 1125, 1060, 1045	4,18	3,17	2,80	4,50	6,33—6,97	—	67,5	31,6	40,9	139,0	116,6	122,9	112,8	110,8	145,8	—
XV	3245	2960, 2900, 2830, 2770, 1570, 1490, 1440, 1410, 1355, 1315, 1275, 1160, 1140, 1110	2,70	3,10	1,47	4,80	6,20—6,60 6,85—7,40	1,47	35,8	27,9	41,5	148,9	109,5	136,4	116,5	130,3	116,1	23,9 (CH_2)
XVI	3200	2900, 1580, 1470, 1425, 1355, 1305, 1200, 1150, 1110, 1030, 905	2,85	3,30	3,58	5,00	6,33—6,63 6,93—7,43	—	36,4	69,0	43,4	149,2	109,3	136,7	116,7	130,2	117,7	—
XVII	3170	2900, 2850, 2780, 2720, 1560, 1480, 1430, 1405, 1305, 1265, 1150, 1125, 1090, 1030	2,87	3,23	2,78	5,33	6,30—7,36	—	36,2	31,9	41,2	148,6	109,9	136,4	116,8	130,0	117,6	—

*Numbers of carbon atoms are given in the Scheme.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-467 spectrometer (60 MHz), solutions were in $CDCl_3$, internal standard was HMDS, shifts are given in the δ scale from TMS. ^{13}C and $^{13}C-\{^1H\}$ NMR spectra were obtained on a Bruker HX-270 spectrometer (67.89 MHz), solutions in $CDCl_3$ of concentration ≥ 0.3 mole/liter. Impulse time was 12 μsec, time between impulses 1 sec, and the number of accumulations varied from 10^2 to 10^3. IR spectra were drawn on a Specord IR-71 instrument, in $CHCl_3$ solution, in NaCl cuvettes of thickness 0.156 and 0.623 mm. Thin-layer and preparative chromatography were carried out on neutral alumina of Brockmann activity grade II, visualizing with iodine vapor. Mass spectra were obtained on a Varian MAT-111 instrument, and camphor of mp 177.5°C was used for the cryoscopic determination of molecular weight. 1,4-Bis(2-nitrophenyl)-1,4-dioxabutane, mp 167°C [11], 1,4-bis(2-aminophenyl)-1,4-dioxabutane (I), mp 130°C, 2-aminothiophenol, bp 116°C (10.5 GPa) [12], and 1,4-bis(2-aminophenyl)-1,4-dithiabutane (II), mp 78°C [11], were obtained by the indicated procedures and were characterized by the necessary constants. The diacid chlorides of diglycolic (IV) and thiodiglycolic (V) acids were obtained by the reaction of the corresponding acids with thionyl chloride in benzene in the presence of catalytic amounts of DMF by the procedure of [13] and were used without additional purification.

General Procedure for the Synthesis of Macrocyclic Amides (VI)-(XI). Solutions of diamine (I) or (II) (10 mmoles) and the appropriate diacid chlorides (III), (IV), or (V) (10 mmoles) each in dry benzene (300 ml) were added simultaneously during 6 h to a solution of pyridine (8 ml) in dry benzene (800 ml) heated to 75°C. At the end of the addition the mixture was stirred at this temperature a further 3 h, the solvent was evaporated in a vacuum, and the residue was washed with 1 N hydrochloric acid (100 ml), dried, and crystallized from acetic acid. The characteristics of compounds (VI)-(XI) are given in Tables 1 and 2.

General Procedure for the Reduction of Amides (VI)-(XI) to Amines (XII)-(XVII). Sodium borohydride (50 mmoles) was added to a suspension of amide (10 mmoles) in dry tetrahydrofuran (THF) (50 ml), and a solution of boron fluoride etherate (75 mmole) in dry THF (10 ml) was added dropwise during 2 h. The reaction mixture was stirred for 1 h at room temperature, then boiled for 4 h. On cooling, the mixture was poured into water (100 ml), brought to pH 7-8, and extracted with chloroform. The organic solution was dried with sodium sulfate and evaporated, and the residue was chromatographed in the required cases with benzene as eluent. The characteristics of compounds (XII)-(XVII) are given in Tables 3 and 4.

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