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NEW APPROACH TO THE SYNTHESIS OF DIBENZODITHIA- AND BENZOTHIAAZACROWN ETHERS VIA THE AROMATIZATION OF 2-ALKYLTHIO(ARYLTHIO)-CYCLOHEXANES DURING BROMINATION

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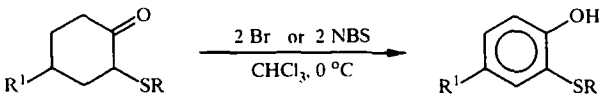
A new scheme for the synthesis of dibenzodithiacrown ethers is proposed based on the use of substituted phenol derivatives as intermediates, prepared by aromatization of 2-alkylthio(arylthio)cyclohexanes during bromination. 1,7-Dithia-8,9,17,18-dibenzo-18-crown-6 and 1,10-dithia-11,12,20,21-dibenzo-21-crown-7 without isomers relative to position of the sulfur atoms have been synthesized, and also new thiadiazamacroheterocycles — 1,4,7-trioxa-10,19-dithia-13,16-diaza-12,17-dioxo-8,9,14,15,20,21-tribenzoheneicosane and 1,4,7,10-tetraoxa-13,22-dithia-16,19-diaza-15,20-dioxo-11,12,17,18,23,24-tribenzotetracosane.

Sulfur containing macroheterocycles have found wide use as selective complexing agents and extractants for ions of the heavy metals and transition metals [1-3]. A series of useful properties associated with macrocyclic extractants are present in the molecules with aromatic rings: a high distribution coefficient between an organic solvent and water for the extractant, considerable possibility of modification by introducing substituents into the aromatic ring. However, the choice of a method for the synthesis of benzothiomacrocycles is rather limited and there is a real need for the development of new methods for their synthesis. The synthesis of crown ethers containing both sulfur and nitrogen atoms, which give outstanding properties to these complexing agents, is also of interest [4, 5]. In particular, the complexes of thiaazacrown compounds with copper(II) ions have spectroscopic and redox properties similar to those of copper containing "blue" proteins, including electron exchange, metabolism, and catalysis of the redox functions of respiratory tissues [6, 7]. The present work is concerned with the synthesis of such macrocycles using a new method — aromatization of 2-alkylthio(arylthio)cyclohexanones via bromination.

We have previously shown [8, 9] that bromination of 2-alkylthio(arylthio) derivatives of cyclohexanone I-V under mild conditions led to ready aromatization of the cyclohexane ring to give the *o*-alkylthio(arylthio)phenols VI-X:



I-V VI-X

70...92%

I, VI R = *n*-Bu, R^1 = H; II, VII R = *c*-C_6H_{11}, R^1 = H; III, VIII R = Ph, R^1 = H; IV, IX R = *o*-$O_2NC_6H_4$, R^1 = H; V, X R = *n*-Bu, R^1 = *t*-Bu

Using this reaction for the aromatization of 2-alkylthio(arylthio)cyclohexanones, we have developed and carried out a new scheme for the synthesis of dibenzodithiacrown ethers. It consists of the following stages: alkylation of dithiols of 2-chlorocyclohexanone or its derivatives; aromatization of the bisketones with bromine; and cyclization of the bisphenols. This scheme was carried out with the dithiol analogs of di- and triethylene glycols (XI, XII) which were converted into bisphenols (XV, XVI) via the bisketones (XIII, XIV). The 18- and 21- membered dibenzodithiacrown ethers (XVII, XVIII) were obtained

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TABLE 1. Physical Constants, Elemental Analyses, and Mass Spectra of the Compounds Synthesized

Compound	mp (bp), °C	(Found, %) (Calculated, %) C	H	N (S)	Molecular Formula	m/z, (relative intensity, %)	Yield, %
XIII	Oil	58.42 58,14	7.62 7,93	19.29 19,40 (S)	$C_{16}H_{26}O_3S_2$		65
XIV	Oil	57.36 57,72	7.95 8,07	17.35 17,12 (S)	$C_{18}H_{30}O_4S_2$		70
XV	Oil						62
XVI	Oil						71
XVII	137...138*1	61.35 61,20	6.24 6,16		$C_{20}H_{24}O_4S_2$	392 (M^+, 100), 267 (8), 240 (6), 223 (24), 197 (17), 196 (19), 179 (19), 170 (12), 165 (7), 152 (82), 137 (94), 125 (50), 109 (15), 96 (41)	30
XVIII	101...103*2	60.23 60,52	6.25 6,46		$C_{22}H_{28}O_5S_2$	436 (M^+, 55), 392 (1), 366 (2), 348 (2), 320 (5), 312 (3), 268 (8), 240 (5), 223 (21), 197 (15), 196 (15), 179 (17), 152 (100), 137 (85), 125 (45), 109 (17), 96 (38)	25
XIX	Oil						65
XXI	94...95 (2 mm)*3						60
XXII	145...146*4	59.95 59,98	4.71 4,58	5.95 6,36	$C_{22}H_{20}N_2O_4S_2$	440 (M^+, 4), 284 (5), 274 (24), 262 (10), 256 (18), 223 (17), 166 (39), 148 (19), 137 (45), 126 (28), 108 (100)	80
XXIII	203...204*5	61.13 61,15	5.05 5,13	5.31 5,49	$C_{26}H_{26}N_2O_5S_2$	510 (M^+, 95), 376 (5), 345 (5), 334 (17), 328 (12), 320 (7), 300 (8), 223 (8), 210 (15), 167 (25), 152 (41), 137 (100), 134 (39), 119 (40), 108 (82)	50
XXIV	166...167*5	60.79 60,63	5.21 5,45	5.38 5,05	$C_{28}H_{30}N_2O_6S_2$	555 ($M^+ + 1$, 11), 554 (M^+, 28), 389 (13), 301 (8), 300 (21), 254 (10), 241 (12), 237 (7), 223 (14), 211 (8), 210 (23), 193 (10), 184 (14), 175 (8), 168 (12), 167 (40), 166 (40), 165 (15), 163 (11), 161 (15), 152 (13), 151 (34), 150 (27), 149 (17), 148 (10), 147 (38), 141 (13), 140 (47), 139 (42), 138 (27), 137 (100), 135 (94), 134 (46), 133 (15), 132 (27), 131 (20), 125 (35), 123 (9), 121 (19), 120 (17), 119 (42), 118 (10), 108 (94), 107 (26), 106 (13)	35

*1From CCl_4. Lit. data [10]: m.p. 143-144°C

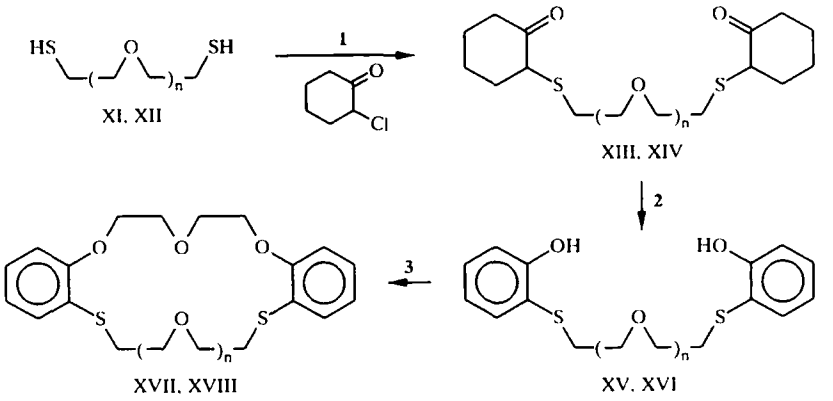
*2From CCl_4.

*3Lit. data [12]: b.p. 128°C (5 mm).

*4From methanol.

*5From acetone.

in 30% and 25% yields respectively by cyclization of compounds XV and XVI with 1,5-dibromo-3-oxapentane in aqueous ethanol:

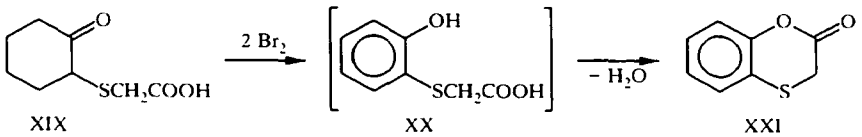


XI, XII, XV, XVII $n = 1$; XII, XIV, XVI, XVIII $n = 2$; 1, 2, 3 — see Experimental

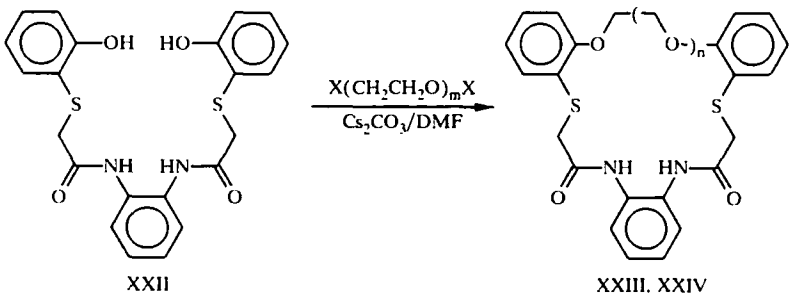
Dibenzo-1,7-dithia-18-crown-6 (XVII) has been synthesized previously [10], but in only 15% yield, and the isomer dibenzo-1,10-dithia-18-crown-6 was formed simultaneously. We have synthesized dibenzo-1,10-dithia-21-crown-7 (XVIII) for the first time.

The advantages of this scheme for the synthesis of dibenzodithiacrown ethers over the traditional method, which uses 2-mercaptophenol and its derivatives as intermediates [10], include the following points: formation of a single isomer — not possible when less suitable aromatic thiols are used — , the possibility of introducing substituents in the initial stage of the synthesis which retain their strict orientation in the benzene rings of the macrocycles produced. For example, when 2-halogeno-4-*t*-Bu-cyclohexanone or 2-halogeno-1-tetralone [9] are used as the cyclohexanone components, the thiacrown ethers produced have increased lipophilicity.

2-(Carboxymethylthio)cyclohexanone (XIX) should give the hydroxyacid (XIX) on aromatization, by analogy with 2-alkylthiocyclohexanone [8, 9]. However, dehydration occurs under the reaction conditions to give 2,3-benzo-5,6-dihydro-1,4-oxathiinone (XXI).



Lactone XXI is an excellent acylating agent for aromatic and aliphatic amines and is a suitable synthon for the synthesis of thiaazamacroheterocyclic ligands. Reaction of *o*-phenylenediamine with compound XXI gave the bisphenol XXII, the terminal hydroxy groups of which are suitable for further synthesis of macroheterocycles. Cyclization of bisphenol XXII with 2,2'-dibromoethyl ether or triethyleneglycol ditosylate in the presence of cesium carbonate under high dilution conditions gave the macroheterocycles XXIII and XXIV respectively, containing O, N and S atoms in a sequence not previously encountered.



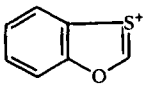
XXIII n = 2, 50%; XXIV n = 3, 35%

The mass spectra of compounds XXIII and XXIV contain intense peaks for the molecular ions M^+ 510 for XXIII (95%) and M^+ 554 for XXIV (28%). The most intense peaks in the mass spectra for compounds XXIII and XXIV have *m/z* 137 (100%), presumably corresponding to formula XXV:

TABLE 2. ^{1}H NMR Spectroscopic Parameters of the Compounds Synthesized

Compound	Aliphatic protons	CH_2S, CHS	CH_2O	Aromatic and other weak field protons
XIII	2,89 (2H, m); 1,55...2,2 (14H, m)	3,37 (2H, t, J = 5); 2,60 (4H, m)	3,52 (4H, t, J = 6,6)	
XIV	2,95 (2H, m); 1,6...2,3 (14H, m)	3,40 (2H, t, J = 5); 2,68 (4H, m)	3,61 (4H, t, J = 7,4); 3,58 (4H, s)	
XV		2,89 (4H, t, J = 6)	3,48 (4H, t, J = 6)	7,45 (2H, d, J = 7,8); 7,22 (2H, t, J = 7,8); 6,95 (2H, d, J = 7,8); 6,80 (2H, t, J = 7,8); 6,70 (2H, s)
XVI		2,80 (4H, t, J = 6)	3,57 (4H, s); 3,47 (4H, t, J = 6)	7,40 (2H, d, J = 7,9); 7,18 (2H, t, J = 7,9); 6,89 (2H, d, J = 7,9); 6,74 (2H, t, J = 7,9); 6,50 (2H, s)
XVII		3,06 (4H, t, J = 6,6)	4,22 (4H, t, J = 4,7); 4,07 (4H, t, J = 4,7); 3,64 (4H, t, J = 6,6)	7,26 (2H, d. d, J = 7,6, 1,4); 7,18 (2H, t. d, J = 7,8, 1,4); 6,88 (2H, t. d, J = 7,5, 1,0); 6,84 (2H, d, J = 8)
XVIII		3,12 (4H, t, J = 6,4)	4,19 (4H, t, J = 4,8); 4,07 (4H, t, J = 4,8); 3,69 (4H, t, J = 6,4); 3,54 (4H, s)	7,30 (2H, d. d, J = 7,6, 1,0); 7,16 (2H, t. d, J = 7,6, 1,0); 6,90 (2H, t, J = 7,5); 6,84 (2H, d, J = 8)
XIX	2,80 (1H, m); 2,26 (2H, m); 1,60...2,00 (5H, m)	3,57 (1H, t, J = 5,7); 3,24 (2H, q, J = 9,5, 15,5)		10,0 (1H, s)
XXI		3,47 (2H, s)		7,34 (1H, d. d, J = 8,3, 1,2); 7,27 (1H, d. t, J = 7,9, 1,2); 7,12 (2H, m)
XXII*		3,55 (4H, s)		9,90 (2H, s, OH); 9,57 (2H, s, NH); 7,24 (2H, t, J = 4,7); 7,18 (2H, d, J = 7,8); 7,14 (2H, t, J = 4,7); 7,05 (2H, t, J = 7,8); 6,80 (2H, d, J = 8); 6,75 (2H, t, J = 7,5)
XXIII		3,70 (4H, s)	4,30 (4H, m); 3,90 (4H, m)	8,85 (2H, s, NH); 7,44 (2H, dd, J = 7,5, 1,8); 7,43 (2H, d, J = 9,5); 7,31 (2H, t. d, J = 7,8, 1,7); 7,20 (2H, q, J = 3,5, 2,5); 6,98 (2H, t. d, J = 7,5, 1,3); 6,94 (2H, d. d, J = 8, 1,2)
XXIV		3,71 (4H, s)	4,19 (4H, m); 3,88 (4H, m); 3,74 (4H, s)	8,80 (2H, s, NH); 7,42 (2H, dd, J = 7,5, 1,8); 7,22 (2H, t. d, J = 7,8, 1,7); 7,18 (2H, m); 7,05 (m 2H); 6,90 (2H, t. d, J = 7,5, 1,1); 6,83 (2H, d. d, J = 8, 0,8)

*DMSO-D6.



XXV

Note that the amido groups in these compounds can be reduced, which opens the way to more nucleophilic ligands.

EXPERIMENTAL

^{1}H NMR spectra of 0.1-0.4 mol/dm^3 solutions in deuterochloroform were recorded with Bruker WH-360, WM-250, AC-200P and AM-300 spectrometers. Mass spectra were recorded with a Kratos MS-30 (direct inlet, ionizing voltage 70 eV).

1,5-Bis(2-cyclohexanonylthio)-3-oxapentane (XIII) and 1,8-bis(2-cyclohexanonylthio)-3,6-dioxaoctane (XIV) were obtained by the reaction of the disodium salts of compounds XI and XII with 2 moles of 2-chlorocyclohexanone in absolute ethanol [11].

General Method for the Synthesis of 1,2-Bis(*o*-hydroxyphenylthio)-3-oxapentane (XV) and 1,2-Bis(*o*-hydroxyphenylthio)-3,6-dioxaoctane (XVI). A solution of bromine (20 mmol) in dry chloroform (10 cm^3) was added dropwise with stirring to a solution of compound XV or XVI (5 mmol) in dry chloroform (30 cm^3) cooled in ice. The mixture was allowed to warm to room temperature and was kept at that temperature for several hours. It was washed with 10% sodium hydrogen carbonate solution until neutral, then with 10% sodium thiosulfate solution and water. The organic layer was separated, dried over $MgSO_4$, and the solvent evaporated. The residue was purified by chromatography (silica gel; eluents $CHCl_3$, and 10:1 $CHCl_3$–MeOH).

General Method for the Synthesis of 1,7-Dithia-8,9,17,18-dibenzo-18-crown-6 (XVII) and 1,10-Dithia-11,12,20,21-dibenzo-21-crown-7 (XVIII). A mixture of bisphenol XV or XVI (1 mmol) and 1,5-dibromo-3-oxapentane (0.23 g, 1 mmol) in ethanol (10 cm^3) was added with stirring over 2 h in an atmosphere of argon to a boiling solution of potassium carbonate (0.21 g, 1.5 mmol) in 50% ethanol (50 cm^3). The mixture was boiled for 40 h, extracted with chloroform (3 × 20 cm^3), the organic extract was evaporated, and the residue was purified by chromatography on silica gel (chloroform eluent) and recrystallized from CCl_4.

2-(Carboxymethylthio)cyclohexanone (XIX). An aqueous solution of thioglycolic acid (13.7 cm^3, 0.15 mol, 80%) was added with cooling and stirring to a 15% solution of NaOH (70 cm^3, 0.32 mol) at such a rate that the temperature of the solution did not exceed +5°C. A solution of 2-chlorohexanone (20 g) in methanol (10 cm^3) was then added with stirring and cooling at such a rate that the temperature of the reaction mixture did not exceed +5°C. After all the 2-chlorohexanone had been added, the reaction mixture was kept at room temperature for 6 h. The homogeneous solution was extracted with ether (30 cm^3), the aqueous layer was separated, cooled in ice, and salt and 39% H_2SO_4 (12 cm^3) added dropwise at such a rate that the temperature did not exceed 0°C. The precipitated oil was separated and the aqueous phase was extracted with ether (3 × 90 cm^3). The ether extracts and the oil were combined, dried over $MgSO_4$, and the solvent evaporated. Cyclohexanone XIX may be used in subsequent syntheses without further purification.

2,3-Dihydro-1,4-benzoxathion-2-one (XXI). A solution of bromine (10 mmol) in dry chloroform (10 cm^3) was added dropwise with stirring to an ice cooled solution of 2-(carboxymethylthio)cyclohexanone (XIX) (5 mmol) in dry chloroform (30 cm^3). It was allowed to warm to room temperature and was kept for several hours. The solution was washed until neutral with 10% sodium hydrogen carbonate solution, then with 10% sodium thiosulfate and water. The organic layer was separated and dried over $MgSO_4$. The residue was distilled in vacuum.

N,N′-Bis(*o*-hydroxyphenylthioacetyl)-*o*-phenylenediamine (XXII). A solution of *o*-phenylenediamine (9 mmol) in chloroform (30 cm^3) was added dropwise with stirring under argon at 50°C to a solution of 2,3-dihydro-1,4-benzoxathiin-2-one (2.88 g, 18 mmol) in $CHCl_3$ (50 cm^3) and the mixture was stirred for a further 6 h. The precipitate was filtered off and recrystallized from methanol.

1,4,7-Trioxa-10-19-dithia-13,16-diaza-12,17-dioxo-8,9,14,15,20,21-tribenzoheneicosane (XXIII). A solution of N,N′-bis-(*o*-hydroxyphenylthioacetyl)-*o*-phenylenediamine (1.5 g, 3.4 mmol) in DMF (100 cm^3) and a solution of 2,2′-dibromodiethyl ether (0.79 g, 3.4 mmol) in DMF (100 cm^3) were added dropwise from synchronized dropping funnels over 2.5 h to a suspension of cesium carbonate (2.2 g) in DMF (650 cm^3) with vigorous stirring under argon at a temperature of 60-70°C and stirring was continued for 33 h at 60-65°C. The mixture was filtered and the solvent removed in vacuum. Chloroform (120 cm^3) and water (50 cm^3) were added to the residue, the organic layer was separated, dried over $MgSO_4$, evaporated, and the

TABLE 3. ^{13}C NMR Spectroscopic Parameters of the Compounds Synthesized

Compound	Aliphatic carbon atoms	$\underline{C}H_2S$, $\underline{C}HS$	$\underline{C}H_2O$	Aromatic and carbonyl carbon atoms.
XIII	32,92, 30,90, 26,75, 21,60	52,05, 37,53	69,84	208,05 (C=O)
XIV	33,09, 31,08, 26,91, 21,70	52,18, 37,82	70,28, 70,27	208,23 (C=O)
XV		36,82	71,23	158,15, 137,00, 130,45, 120,83, 117,96, 114,87
XVI		36,61	70,17, 68,83	157,99, 136,59, 131,39, 120,67, 118,36, 115,30
XVII		32,85	70,06, 69,28, 68,33	157,62, 131,99, 127,90, 124,12, 121,11, 111,73
XVIII		32,32	70,64, 70,13, 69,80, 68,68	157,31, 130,95, 127,55, 124,53, 121,20, 111,99
XIX	32,61, 31,51, 26,63, 22,23	52,15, 38,28		208,31 (C=O), 174,86 (C=O)
XXI		28,07		162,48 (C=O), 150,22, 127,57, 127,52, 124,37, 119,22, 117,90
XXII*		36,58		167,65 (C=O), 155,59, 130,41, 130,22, 127,77, 125,16, 124,78, 120,95, 119,50, 115,08
XXIII		37,69	69,67, 68,11	167,86 (C=O), 157,51, 132,56, 130,26, 129,24, 126,33, 124,75, 122,18, 121,65, 112,00
XXIV		37,32	70,61, 69,50, 68,15	167,85 (C=O), 157,56, 132,73, 130,08, 129,23, 126,02, 124,87, 121,61, 121,09

*DMSO-D6.

residue was purified by chromatography on silica gel with 30:1 $CHCl_3$ – MeOH as eluent to give 0.86 g of a white solid which was recrystallized from acetone.

1,4,7,10-Tetraoxa-13,22-dithia-16,19-diaza-15,20-dioxo-11,12,17,18,23,24-tribenzotetracosane (XXIV) was obtained analogously from triethylene glycol.

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