PREPARATION OF CHLOROMETHYL DERIVATIVES OF DIBENZO-18-CROWN-6 AND SYNTHESES BASED ON THEM

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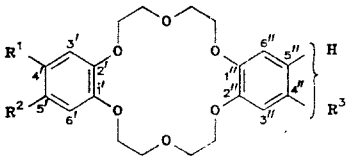
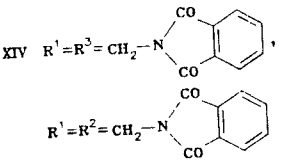
The reaction of chloromethylated dibenzo-18-crown-6 and some monosubstituted derivatives (4'-acetyl-, 4'-propionyl-, and 4'-tert-butyldibenzo-18-crown-6) was studied. Modification of the chloromethyl group resulted in the synthesis of various dibenzo-18-crown-6 derivatives.

This report details the preparation of new derivatives of dibenzo-18-crown-6 (DB18C6) by modification of its chloromethyl derivatives. The described chloromethyl derivatives of benzo-15-crown-5 and benzo-18-crown-6 were prepared by reduction of formyl groups of the benzo-crownethers to oxymethyls with subsequent exchange of the OH for Cl [1]. The method developed by us earlier [2] for chloromethylation of DB18C6 (I) and some 4-substituted derivatives (II-IV) is a direct method for introduction of the CH_2Cl group into the benzo-crown ethers.

New functionalized derivatives were obtained by modification of the chloromethyl group. Besides this, the chloromethyl group is a suitable anchor for immobilization of the crown ether onto a polymer [3].



I-XXIII



XIV

I $R^1=R^2=R^3=H$; II $R^1=COCH_3$, $R^2=R^3=H$; III $R^1=COC_2H_5$, $R^2=R^3=H$; IV $R^1=C(CH_3)_3$, $R^2=R^3=H$; V $R^1=H$, $R^3=CH_2Cl$, from hereon except IX, XIV and XV $R^2=H$; VI $R^1=COCH_3$, $R^3=CH_2Cl$; VII $R^1=COC_2H_5$, $R^3=CH_2Cl$; VIII $R^1=C(CH_3)_3$, $R^3=CH_2Cl$; IX — mixture of isomers $R^1=R^3=CH_2Cl$, $R^2=H$ and $R^1=R^2=CH_2Cl$, $R^3=H$; X $R^1=H$; $R^3=CHO$; XI $R^1=H$, $R^3=CH_2OH$; XII $R^1=R^3=CHO$; XIII $R^1=R^3=COOH$; XIV — mixture of isomers $R^2=H$ and $R^3=H$; XV — mixture of isomers $R^1=R^3=CH_2NO_2$, $R^2=H$ and $R^1=R^2=CH_2NO_2$, $R^3=H$; XVI $R^1=R^3=CH_2NH_2$; XVII—XX $R^1=R^3=CH_2OR$; XXI—XXIII $R^1=R^3=CH_2O(CH_2)_nOH$

Physicochemical constants of the prepared compounds are given in Table 1.

Chloromethylation of DB18C6 proceeds by more than one path and the reaction product is a mixture of derivatives of various degrees of substitution which cannot be separated by column chromatography and crystallization. Conditions were chosen under which mainly the monosubstituted product V is obtained upon chloromethylation of DB18C6. The protons of the CH_2Cl group appear as a singlet at 4.47 ppm in its PMR spectrum and the aromatic protons of the unsubstituted benzene ring as a singlet at 6.80 ppm (Table 1).

Product V was oxidized by the Sommle reaction [4] to the formyl derivative X for determination of the position of the substituent. The nature of the splitting of the aromatic protons in its PMR spectrum shows a 4'-substitution. Thus, compound V was proven to be 4'-chloromethyl-DB18C6, the CH_2Cl signals of which appear at 4.47 ppm. Its modification also produced 4'-oxymethyl-DB18C6 (XI). DB18C6 is difficultly soluble in benzene and use of this solvent is unsuitable, but the reaction goes poorly in chloroform. Therefore, chloromethylation of DB18C6 was done in a mixture of benzene:chloroform (3:2), but under these conditions,

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TABLE 1. Characteristics of the Prepared Compounds

Compound	Empirical formula	mp, °C	Molecular weight		PMR spectrum
			found	calculated	
II	$C_{22}H_{26}O_7$	166...168	402	402,4	7,48 (1H, d), 7,43 (1H, s), 6,76 (1H, d), 6,81 (4H, s) — ArH; 3,84...4,24 (16H, m, OCH_2); 2,47 (3H, s, $COCH_3$)
III	$C_{23}H_{28}O_7$	170...172	416	416,5	7,50 (1H, d), 7,44 (1H, s), 6,76 (1H, d), 6,81 (4H, s) — ArH; 3,88...4,28 (16H, m, OCH_2); 2,86 (2H, q $COCH_2$); 1,14 (3H, t, CH_3)
V	$C_{21}H_{25}O_6Cl$	140...143	408	408,9	6,80 (4H, s), 6,66...6,92 (3H, m) — ArH; 4,47 (2H, s, CH_2Cl); 3,86...4,26 (16H, m, OCH_2)
VI	$C_{23}H_{27}O_7Cl$	130...135	450	450,9	7,40...7,60 (2H, m), 6,70...6,90 (4H, m) — ArH; 4,48 (2H, s, CH_2Cl); 3,80...4,26 (16H, m, OCH_2); 2,48 (3H, s, CH_3)
VII	$C_{24}H_{29}O_7Cl$	154...157	464	464,9	7,40...7,60 (2H, m), 6,66...6,94 (4H m) — ArH; 4,47 (2H, s, CH_2Cl); 3,80...4,34 (16H, m, OCH_2); 2,88 (2H, q, $COCH_2$); 1,10 (3H, t, CH_3)
VIII	$C_{25}H_{33}O_6Cl$	110...112	464	464,9	6,50...6,82 (6H, m, ArH); 4,40 (2H, (4H, 2 s, CH_2Cl)*; 3,80...4,20 (16H, OCH_2); 1,20 (9H, s, CH_3)
IXa	$C_{22}H_{26}O_6Cl_2$	134...140	457	457,3	6,65...6,92 (6H, m, ArH); 4,60, 4,47 (4H, 2 s, CH_2Cl)*; 3,80...4,20 (16H, m OCH_2)
IXb	$C_{22}H_{26}O_6Cl_2$	152...168	457	457,3	The same
X	$C_{21}H_{24}O_7$	175...179	388	388,4	9,73 (1H, s, CHO); 7,36 (1H, d), 7,29 (1H, s), 6,84 (1H, d), 6,78 (4H, s) — ArH, 3,80...4,26 (16H, m, OCH_2)
XI	$C_{21}H_{26}O_7$	165...168	390	390,4	3,44...6,86 (7H, m, ArH); 4,50 (2H, s, CH_2OH); 3,82...4,18 (16H, m, OCH_2); 1,52 (1H, s, OH)
XIV	$C_{38}H_{34}N_2O_{10}$	189...195	—	—	7,48...7,88 (8H, m), 6,58...6,98 (6H, m) — ArH; 5,10, 4,66 (4H, 2 s, CH_2Phth); 3,70...4,24 (16H, m, OCH_2)
XV	$C_{22}H_{26}N_2O_{10}$	102...107	—	—	3,66...6,82 (6H, m, ArH); 4,52, 4,36 (4H, 2 s, CH_2NO_2); 3,78...4,26 (16H, m, OCH_2)
XVI	$C_{22}H_{30}N_2O_6$	110...120	—	—	6,60...6,92 (6H, m, ArH); 3,80...4,26 (16H, m, OCH_2); 3,70 (4H, s, CH_2NH_2); 1,96 (4H, s, NH_2)
XVII	$C_{25}H_{36}O_8$	84...86	—	—	6,70...6,90 (6H, m, ArH); 4,36 (4H, s, α-CH_2); 3,86...4,24 (16H, m, OCH_2); 3,48 (4H, q, β-CH_2); 1,15 (6H, t, CH_3)
XVIII	$C_{24}H_{32}O_8$	107...110	—	—	The same
XIX	$C_{28}H_{40}O_8$	78...81	—	—	„ „
XX	$C_{30}H_{44}O_8$	67...72	—	—	„ „
XXI	$C_{26}H_{36}O_{10}$	123...125	—	—	6,60...6,86 (6H, m, ArH); 4,40 (4H, s, α-CH_2); 3,80...4,20 (16H, m, OCH_2); 3,36...3,78 (8H, m, β- и γ-CH_2); 2,05 (2H, s, OH)
XXII	$C_{28}H_{40}O_{10}$	99...103	—	—	The same
XXIII	$C_{30}H_{44}O_{10}$	75...80	—	—	„ „

*In the spectrum of compound IXa, the ratio of signals at 4.47 and 4.60 ppm is equal to 4:1, for compound IXb, 3:2.

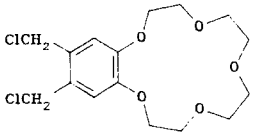
the reaction is complicated by the formation of disubstituted products and the single product V could not be prepared.

The monochloromethylated derivative of DB18C6 can be prepared by protecting one benzene ring with an acyl (VI, VII) or tert-butyl (VIII) group. As in compound V, the protons of the chloromethyl group in the PMR spectra of compounds VI-VIII appear as a singlet at 4.47 ppm. This indicates the introduction of the CH_2Cl group at position 4" or 5".

Conditions were chosen so that the main product was dichloromethyl-DB18C6 (IX). Analysis of the PMR spectrum of the product obtained showed that besides the two symmetric 4', 4"(5")-isomers, which have a singlet for the protons of the CH_2Cl group at 4.47 ppm, the asymmetric isomer is present, whose protons of the CH_2Cl group appear at 4.60 ppm. The quantity of this isomer increases upon running the reaction at milder conditions (see Experimental). Entry

of the second CH_2Cl group can be expected either in the 3'(3")-, 6'(6")-position or in the o-position to the first CH_3Cl group (the 5'-position).

In order to explore the possible introduction of two chloromethyl groups on one benzene ring, we carried out chloromethylation of benzene-15-crown-5 (B15C5) with a stoichiometric ratio of reagents and with a large excess of paraformaldehyde. In the first case, 4'-chloromethyl-B15C5 with a signal from the CH_2Cl protons at 4.47 ppm was formed. In the second case, dichloromethyl-B15C5 with a signal from the CH_2Cl protons at 4.60 ppm appeared. In this this case the two aromatic protons also gave a singlet at 6.78 ppm. This indicated the formation of 4',5'-dichloromethyl-B15C5:



Based on the data obtained, we believe that upon chloromethylation of DB18C6 product IX is formed which contains mainly two symmetric 4',4",(5")-isomers with an impurity of 4',5'-dichloromethyl-DB18C6, which could not be separated. Depending on their ratio, the melting points of the samples of IXa and IXb obtained are somewhat variable. Their quantitative ratio can be judged by the relative magnitude of the signals at 4.47 and 4.60 ppm.

Only the two symmetric 4',4"(5")-diformyl derivatives (XII) were prepared upon oxidation of product IX by potassium chromate in benzene under phase transfer catalysis.

The 4',4"(5")-dicarboxy-DB18C6 (XII) were synthesized under these same conditions by oxidation of IX by potassium permanganate. The possibility in principle of preparation of carboxyl derivatives by oxidation of the chloromethyl group was demonstrated, however, these compounds are prepared more conveniently by hypobromite oxidation of the acetyl group [5].

The diphthalimidomethyl (XIV) and dinitromethyl (XV) DB18C6 derivatives were prepared with phthalimide and potassium nitrite in reactions of compound IX. They are a mixture of symmetric 4',4"(5")-isomers with an impurity of the 4',5'-isomer according to PMR data. They could not be separated.

The diaminomethyl derivatives of DB18C6 (XVI) were prepared by two routes: hydrolysis of compound XIV and reduction of derivative XV. In both cases fractional crystallization from benzene gave a mixture of the two symmetric 4',4"(5")-isomers. The protons of the CH_2NH_2 groups appear as one singlet at 3.70 ppm.

Condensation of IX with ROH alcohols (where R = $CH_3C_4H_9$) produced a number of alkoxymethyl derivatives of DB18C6 (XVII-XX). These are a mixture of two main 4',4"(5")-isomers. The α-methylene protons appear as one singlet at 4.36 ppm.

The DB18C6 derivatives with an oxy group removed from the nucleus (XXI-XXIII) were prepared by reaction of IX with glycolates $HO(CH_2)_nOK$ (where n = 2...4). As in the previous case, a mixture of 4',4"(5")-isomers could be separated by column chromatography.

The reactions described above were done under phase transfer catalytic conditions, where the role of the catalyst is apparently fulfilled by the substrate itself. A similar case of self-catalysis is described for the reaction of potassium salts of dicarboxylic acids with chloromethyl-B15C5, in which the latter acts as the phase transfer catalyst [6].

The new derivatives of DB18C6 obtained are potential ionophores and extractants which have anchor groups capable of being immobilized on solid supports.

EXPERIMENTAL

IR spectra (KBR pellets) were taken on Specord IR-75 and UR-20 spectrophotometers. PMR spectra were obtained on a Varian XL-100 (100 MHz) spectrometer in $CDCl_3$, with HMDS internal standard. The molecular weights were determined mass spectrometrically on a Varian MAT-311 at 150°C and an ionizing electron energy of 70 eV. Neutral aluminum oxide and Silufol UV-254 were used for thin-layer and column chromatography.

Elemental analyses of the prepared compounds for C, H, N, and Cl corresponded to those calculated.

Dibenzo-18-crown-6 (DB18C6) (I) from NIOKh Sib. Otd. Akad. Nauk SSSR was used. 4'-acetyl-DB18C6 (II) and 4'-propionyl-DB18C6 (III) were prepared analogously to [7] at a mole ratio DB18C6:RCOH = 1:2 and DB18C6:PPA = 1:5 (by mass). 4'-tert-Butyl-DB18C6 (IV) was prepared according to [8].

4'-Chloromethyl-DB18C6 (V). A solution of 3.6 g I in 500 ml benzene was saturated with gaseous HCl at 20°C, 1.2 g paraformaldehyde were added, HCl was passed through for another 30 min, the HCl flow was stopped, and the mixture was stirred for 12 h at 40°C. The reaction mixture was decomposed with water. The precipitate which formed was separated. The filtrate was neutralized with saturated $NaHCO_3$. Yield 2.6 g (63%).

Analogously prepared: 4'-acetyl-4"(5")-chloromethyl-DB18C6 (VI), yield 54%; 4'-propionyl-4"(5")-chloromethyl-DB18C6 (VII), yield 64%; and 4'-tert-butyl-4"(5")-chloromethyl-DB18C6 (VIII), yield 82%.

4'-Formyl DB18C6 (X). A solution of 0.4 g V in dilute acetic acid, 0.42 g urotropine, and 2 ml dilute HCl (1:10) was boiled for 3 h and then purified by column chromatography with benzene-alcohol (10:1) eluent. Yield 0.03 g (~8%).

4-Oxymethyl-DB18C6 (XI). A solution of 0.4 g V and 0.8 g sodium acetate in 15 ml glacial acetic acid was boiled for 3 h, poured onto 50 g ice, and extracted with benzene. The extract was evaporated to 20 ml, added to a solution of 0.8 g KOH in 5 ml 50% ethanol, boiled for 1 h, and decomposed by ice. The benzene layer was separated and the aqueous solution was extracted with chloroform. It was purified by column chromatography using chloroform—alcohol, 50:1. Yield 0.1 g (26%) of XI.

4',4"(5")- and 4',5'-Dichloromethyl-DBI8C6 (IX). A sample of IXa was prepared analogously to V from 36 g I and 28 g paraformaldehyde in 1400 ml benzene:chloroform, 3:2. The stirring time at 40°C was 7 h. Yield 16 g (37%).

A sample of IXb was prepared from 0.36 g I and 0.27 g paraformaldehyde in 100 ml benzene at 8°C for 37 h. Yield 0.31 g (68%).

4',4"(5")Diformyl-DB18C6 (XII). A 0.9 g portion of IX was dissolved in 20 ml benzene, 2 g potassium chromate in 2 ml 10% H_2SO_4 were added, and the mixture was boiled for 9 h. The precipitate was filtered and washed with chloroform. The chloroform extracts were combined with the benzene solution, the solvents were removed, and the residue was purified by column chromatography with a chloroform-acetone (6:1) eluent. Yield 0.5 g (68%). The reaction product was identical to that prepared earlier [5].

4',4"(5")-Dicarboxy-DB18C6 (XIII). To 1.3 g IX in 150 ml benzene were added 3 ml 10% KOH and 1.58 g $KMnO_4$. As the solution faded, potassium permanganate (another 3 g) was added over 3 days. A solution of base was added until pH 10 and the precipitate was filtered. The filtrate was evaporated on a water bath and acidified with HCl. The precipitate was separated and washed with hot water. Yield 0.67 g (53%). The reaction product is identical to that prepared earlier [5].

4',4"(5")- and 4',5'-Diphthalimidomethyl-DB18C6 (XIV). A 7.33 g portion of IX was dissolved in 80 ml acetonitrile, 11.0 g potassium phthalimide were added, and the mixture was stirred for 1 h 30 min at 80°C. The precipitate was filtered and washed with water. Yield 9.14 g (84%).

4,4"(5")- and 4',5'-Dinitromethyl-DB18C6 (XV). A solution of 1.0 g IX and 0.6 g KNO_2 was boiled in 10 ml acetonitrile for 1 h 30 min. The solvent was removed and the residue was chromatographed on a column with chloroform-alcohol (50:1). Yield 0.21 g (20%).

4',4"(5")-Diaminomethyl-DB18C6 (XVI). A. A suspension of 9.14 g XIV and 1.2 ml hydrazine hydrate in 70 ml absolute alcohol was boiled for 1 h, 30 ml conc. HCl were added, and the mixture was boiled for another 1 h. The precipitate was filtered, the filtrate was evaporated, basicified with a NaOH solution, and extracted with chloroform. The solvent was removed and the residue was recrystallized from benzene. Yield 1.18 g (21%).

B. To a solution of 0.9 g XV in 15 ml absolute alcohol were added 2.4 ml hydrazine hydrate and Rainey nickel. The mixture was boiled for 2 h. The catalyst was filtered, the alcohol removed, the residue acidified with HCl, and the precipitate which formed was separated. The filtrate was basicified with a NaOH solution and extracted with chloroform. Yield 0.14 g (16%).

4',4"(5")-Diethoxymethyl-DB18C6 (XVII). A solution of 0.23 g IX in 5 ml absolute alcohol was boiled for 7 h, neutralized with a $NaHCO_3$ solution, and extracted with chloroform. The solvent was removed and the residue was chromatographed on a column using chloroform—alcohol (50:1). Yield 0.07 g (30%).

Analogously prepared: 4',4"(5")-dimethoxymethyl-DB18C6 (XVIII), yield 25%; 4',4"(5")-dipropoxymethyl-DB18C6 (XIX), yield 32%; and 4',4"(5")-dibutoxymethyl-DB18C6 (XX), yield 28%.

4',4"(5")-Dioxyethoxymethyl-DB18C6 (XXI). To 0.08 g potassium dispersed in 10 ml absolute benzene were added dropwise 5.5 ml absolute ethyleneglycol and a solution of 0.45 g IX in 10 ml benzene. The mixture was boiled for 1 h. The glycol layer was separated, diluted with water, and extracted with chloroform. After removal of solvent the residue was dissolved in acetone and precipitated with hexane. The wet product (0.25 g, 55%) was purified on a column with chloroform—alcohol (50:1). Yield 0.15 g (30%).

Analogously prepared: 4',4"(5")-dioxypropoxymethyl-DB18C6 (XXII), yield 35%; and 4',4"-(5")-dioxybutoxymethyl-DB18C6 (XXIII), yield 32%.

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REACTION OF CHLOROSULFONYLTHIOLENE- AND -THIOLANE-1,1-DIOXIDES WITH AMINES AND HYDROXYCOMPOUNDS

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Sulfonylamides and sulfonylesters of thiolene- and thiolane-1,1-dioxides are prepared by reaction of chlorosulfonylthiolene- and -thiolane-1,1-dioxides with amines and hydroxycompounds. The structure of the compounds is proved based on IR spectra and ^{13}C NMR spectroscopy.

Derivatives of thiolene-1,1-dioxides are known to be used successfully for synthesis of difficultly available functionally-substituted dienes [1-3]. Further use of such dienes in the Diels-Alder reaction leads to substituted cyclohexenes [4, 5]. The presence of a sulfur-containing substituent in the diene enables the regioselective course of the reaction. This allows the preparation of products which are unattainable or difficultly available by other routes [6, 7]. Earlier, the synthesis of chlorosulfonylthiolene- and -thiolane-1,1-dioxides I-IV was reported [8, 9]. Compound IV was synthesized from trans-3-hydroxy-4-isothioureido-

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