Synthesis of New Macrocycles. Part 5.[1] Cyclization of 2,2′-Dithiodibenzoic Acid Derivatives

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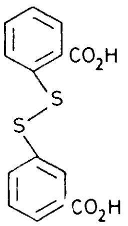
Condensation of 2,2′-dithiodibenzoyl chloride with a series of alkanediols, but-2-yne-1,4-diol, triethylene glycol, and tetraethylene glycol affords cyclic esters in yields ranging from 5 to 95%. On the basis of n.m.r. evidence, predictions are made regarding conformations of the macrocycles.

THE behaviour in selected cyclization reactions of derivatives of 2,2′-dithiodibenzoic acid (1), a difunctional acid possessing in its skeleton certain elements of rigidity, was investigated as an extension of our earlier studies on this theme.[2] Initial attempts at cyclization involved treatment of the dipotassium salt with dibromoalkanes, under conditions similar to those employed in synthesizing phthalic acid macrocycles.[3] Only 1,4-dibromobutane and 1,6-dibromohexane yielded cyclic products. Since the diacid chloride of (1) is readily prepared [4] and is also reasonably stable at room temperature, this derivative was employed in subsequent reactions with selected diols. Best results were achieved with benzene as solvent, and a low reaction temperature maintained over an extended period, with triethylamine as base. This technique yielded macrocyclic esters (2)—(9) in yields ranging from 5 to 95% and varying in ring size from 14 to 21 members, including both even and odd numbers of atoms (Table). Monomers only were isolated. With the lower diols (ethane-1,2-diol as well as propane-1,3-diol), solid material was obtained from the condensation but this proved insoluble in all organic solvents tried, making further investigation impossible. Similar insoluble products were obtained from reactions with hexa-2,4-diyne-1,6-diol and *o*-phenylenedimethanol. Smolinski and Jamrozik [5] report similar problems in the synthesis of macrocycles based on pentaerythritol.

In their recent review on the synthesis of macrocyclic sulphides, Bradshaw and Hui [6] draw attention to the lack of specific information regarding this type of macrocycle in comparison with oxygen and nitrogen macrocycles. However, Tanaka and his co-workers [7] report that 2,2′-thiodibenzyl bromide forms macrocycles on treatment with amines. Yields of the 8-membered monomers varied between 15 and 46% and of the corresponding 16-membered dimers between 3 and 27%. Yields of our cyclic ester disulphides (2)—(9) compare favourably with these dimer yields. Overall, they are also higher than our yields of macrocyclic phthalic acid esters.[1-3] Compound (7), which bears a rigid bridging group, was not obtained in higher yield than the corresponding 14-membereomd cpound (2) which contains a flexible bridge. Although our yields tended to be higher for the smaller rings, the



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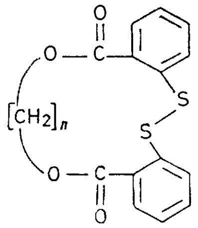
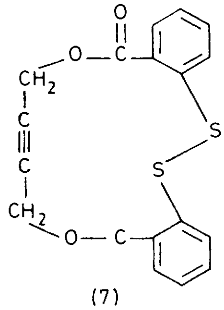


(2) $n = 4$ (5) $n = 7$
(3) $n = 5$ (6) $n = 8$
(4) $n = 6$



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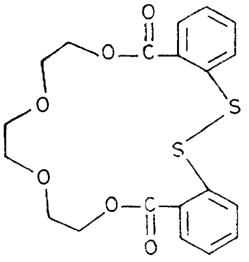

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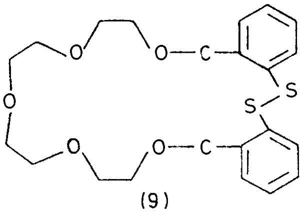

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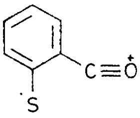

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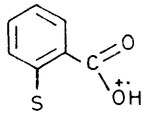

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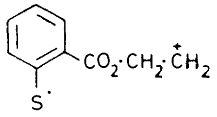

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opposite effect has been observed for a homologous series of dithia-heterocycles.[8]

All eight macrocycles were tested for complex formation with metal ions by using the picrate method.[9] No positive result was obtained. This was not surprising for the macrocycles (2)—(7) since Pedersen [9] has shown that complexing power for alkali and alkaline earth metals is largely destroyed by substituting –S– for –O– in the ring. Compounds (8) and (9), however, although they contain a poor complexing group in the form of a diester, still contain two sulphur atoms and at least two ether oxygen atoms in the rings. Nevertheless, both gave a negative result with sodium, potassium, and lithium cations. Even with silver nitrate, which usually forms strong complexes with macrocyclic polyether sulphides,[9] no success was achieved. It has to be assumed that these macrocycles are not capable of twisting in such a way that a favourable co-ordination geometry is achieved around the central ion.[10]

Stability of the Macrocycles.—The only way in which the macrocycles could be prepared satisfactorily involved a prolonged (3—5 days) reaction at room temperature. If the solvent (benzene) was refluxed, only 1,4-dibromobutane and 1,6-dibromohexane gave recognizable cyclic products, although in decreased yields. Recrystallization was performed from dioxan throughout, but even during this process considerable polymerization took place. This was particularly evident for the alkyne macrocycle (7). In the crystalline form all the macrocycles were stable for several months at room temperature.

N.m.r. and Mass Spectra.—All the macrocycles exhibited a molecular ion peak in the mass spectrum, and except for (2) and (7) this was of >35% relative abundance. The only other significant peaks were common to all the macrocycles, at *m/e* 136 (base peak), 153, and 180, probably due to the ions (10)—(12), respectively.

All eight macrocycles exhibited a complex eight-proton n.m.r. multiplet at δ 7—8.5 due to the aromatic protons. For (2)—(6) the terminal methylenes resonated as a triplet at about δ 4.4 and the central methylenes as a multiplet between δ 1.42 and 2.05. A similar pattern, differing only in chemical shifts was shown by (8) and (9). In (7) the signal for the two methylenes appeared as a sharp singlet at δ 5.07.

Possible Conformation of the Macrocycles.—The crystal structure of 2,2′-dithiodianiline [11] suggests that hydrogen bonds between the amino-groups tie the molecules in roughly parallel chains. The angle between the planes of the two rings is 29°. We suggest that the diacid (1) takes up a very similar conformation and further that the cyclic compounds (2)—(9) also possess a closely similar conformation. Accurate molecular models show that a bridging chain consisting of 4—8 methylene groups, in the staggered conformation, can be inserted between the two oxycarbonyl groups without disturbing the conformation. Such a conformation also satisfies the n.m.r. data since (i) it allows the two terminal methylenes in each macrocycle to exist in an identical magnetic environment and (ii) it can accommodate the observation that the complex but characteristic aromatic multiplet of (2) is identical in form with that exhibited by the other macrocycles (3)—(6).

EXPERIMENTAL

Mass spectra were obtained with a Varian CH7 spectrometer at 70 eV and n.m.r. spectra with a Varian T60 instrument.

2,2′-*Dithiodibenzoyl Chloride.*—Treatment of the acid (1) with thionyl chloride [4] gave the acid chloride, m.p. 153° (60%), which could be stored unchanged in a vacuum desiccator for extended periods.

7,8,9,10-*Tetrahydrodibenzo*[c,g][1,10,5,6]*dioxadithiacyclotetradecin*-5,12-*dione* (2).—The acid chloride (1.5 g, 4 mmol), butane-1,4-diol (0.39 g, 4 mmol), and triethylamine (1.23 ml, 8.8 mmol) in benzene (75 ml) were stirred for 72 h at 22 °C. Moisture was rigorously excluded. A precipitate of triethylamine hydrochloride formed during the reaction, and the reaction was terminated when precipitation was judged to be complete. After addition of water (100 ml) the benzene layer was separated, dried, and evaporated *in vacuo*. The solid product crystallized from dioxan as fine *needles* (1.5 g, 95%), m.p. 157° (Found: C, 60.2; H, 4.6. $C_{18}H_{16}O_4S_2$ requires C, 60.0; H, 4.5%).

8,9,10,11-*Tetrahydro*-7H-*dibenzo*[c,g][1,10,5,6]*dioxadithiacyclopentadecin*-5,13-*dione* (3).—This compound was prepared as above but was more difficult to obtain pure. Chromatography on an alumina column (chloroform as eluant) gave white *needles* (9.2%), m.p. 85—87° (from ethyl acetate) (Found: C, 60.7; H, 4.9. $C_{19}H_{18}O_4S_2$ requires C, 61.0; H, 4.85%).

Analytical and physical data for macrocycles (2)—(9)

Compd.	Ring size	Yield (%)	M.p. (°C)	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
(2)	14	95.0	157	60.2	4.6	$C_{18}H_{16}O_4S_2$	60.0	4.5
(3)	15	9.2	85—87	60.7	4.9	$C_{19}H_{18}O_4S_2$	61.0	4.85
(4)	16	53.1	147	61.5	5.3	$C_{20}H_{20}O_4S_2$	61.8	5.2
(5)	17	56.9	117	63.0	5.5	$C_{21}H_{22}O_4S_2$	62.7	5.5
(6)	18	5.5	186	63.4	6.25	$C_{22}H_{24}O_4S_2$	63.4	5.8
(7)	14	51.4	148—150	60.5	3.2	$C_{18}H_{12}O_4S_2$	60.7	3.4
(8)	18	5.4	193	57.3	4.75	$C_{20}H_{20}O_6S_2$	57.1	4.8
(9)	21	4.9	141—142	56.4	4.8	$C_{22}H_{24}O_7S_2$	56.9	5.2

The remaining macrocycles, 7,8,9,10,11,12-*hexahydrodibenzo*[c,g][1,10,5,6]*dioxadithiacyclohexadecin*-5,14-*dione* (4), 8,9,10,11,12,13-*hexahydro*-7H-*dibenzo*[c,g][1,10,5,6]*dioxadithiacycloheptadecin*-5,15-*dione* (5), 7,8,9,10,11,12,13,14-*octahydrodibenzo*[c,g][1,10,5,6]*dioxadithiacyclo-octadecin*-5,16-*dione* (6), 8,9-*didehydro*-7,10-*dihydrodibenzo*[c,g]-[1,10,5,6]*dioxadithiacyclotetradecin*-5,12-*dione* (7), 7,8,10,-11,13,14-*hexahydrodibenzo*[c,g][1,4,7,10,14,15]*tetraoxadithiacyclo-octadecin*-5,16-*dione* (8), and 7,8,10,11,13,14,16,17-*octahydrodibenzo*[c,g][1,4,7,10,13,17,18]*pentaoxadithiacycloheneicosin*-5,19-*dione* (9), were prepared by essentially the

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same procedure as for (2). Reaction times varied between 3 and 5 days at 22 °C. All the macrocycles were very soluble in chloroform, fairly soluble in benzene and dioxan, and insoluble in acetone. The alkanediols were purchased commercially as were but-2-yne-1,4-diol [for (7)], triethylene glycol [for (8)] and tetraethylene glycol [for (9)].

Analytical and physical data are summarized in the Table.

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