118. The Synthesis of 5,11,17-Trihalotetracyclo[13.3.1.1^{3,7}.1^{9,13}]henicosa-1(19),3,5,7(20),9,11,13(21),15,17-nonaene-19,20,21-triols and 5,11,17-Trihalo-19,20,21-trihydroxytetracyclo[13.3.1.1^{3,7}.1^{9,13}]henicosa-1(19),3,5,7(20),9,11,13(21),15,17-nonaene-8,14-dione [1]. Cyclo-derivatives of Phloroglucide Analogues

by **Ali A. Moshfegh, Effat Beladi, Lida Radnia, Afsaneh S. Hosseini, Soosan Tofigh** and **Gholam H. Hakimelahi**[1])

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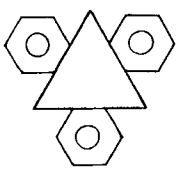
(4.I.82)

Summary

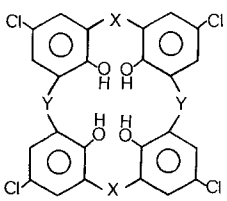
The synthesis of the title compounds (**1** and **3**) is described. Some of the compounds prepared were found to be active against a number of pathogenic microorganisms *in vitro*. Structure-activity relationship is briefly discussed.

Lindsey has found that the acid-catalyzed condensation of veratrole with formaldehyde gave cyclotriveratrylene (= 5,6,12,13,19,20-hexamethoxytetracyclo-[15.4.0.0^{3,8}.0^{10,15}]henicosa-1(17),3(8),4,6,10(15),11,13,18,20-nonaene) [2]. The parent ring system I was similarly named cyclotribenzylene (= tetracyclo-[15.4.0^{3,8}.0^{10,15}]henicosa-1(17),3(8),4,10(15),11,13,18,20-nonaene) [2]. The conformation of cyclotriveratrylene was investigated using molecular models combined with ^{1}H-NMR. measurements [3].

In the previous papers [4] [5] we described the synthesis of halogenated derivatives of phloroglucide analogues as well as of their cyclic analogues [6] containing four phenolic units and having the general structure II. The compounds



I



IIa X = Y = CH_2
IIb X = Y = CO
IIc X = CH_2, Y = CO

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II are active against a number of pathogenic microorganisms *in vitro*. In this paper we report the synthesis and antimicrobial properties of the cyclic analogues **1–3** containing three phenolic units and having functionality similar to that of phloroglucides [7][2]).

In a model reaction, 4-chloro-2,6-bis(hydroxymethyl)phenol (**4a**) [5] was reacted with 4,4′-dichloro-2,2′-methylenediphenol (**5a**) [4] and HCl to give 5,11,17-trichlorometacyclotribenzylene-19,20,21-triol (**1a**) in high yield. The ^{1}H-NMR., IR., UV., electron impact and chemical ionization mass spectra and the microanalysis of **1a** were consistent with the proposed structure.

Using the same procedure, 4-chloro-2,6-bis(hydroxymethyl)phenol (**4a**), 4-fluoro-2,6-bis(hydroxymethyl)phenol (**4b**) and 4-bromo-2,6-bis(hydroxymethyl)-phenol (**4c**) were transformed to the corresponding cyclic compounds **1b–i** by reaction with the 4,4′-dihalo-2,2′-methylenediphenol **5a–c** and HCl. Conversion of **1c**, **1f**, **1g**, **1h** and **1i** to **2a–e**, respectively, was achieved in good yield by treatment with Zn/KOH [4].

Since the oxidation of the CH_2-bridges to carbonyl functions may increase the chelating ability, the derivatives **3a–i** were prepared from **1a**, **1d**, **1g**, **1i** and **2a–e**

Table 1. *Properties of metacyclotribenzylenes* **1–3**

Compound[a])	(MW)	m.p. [°C]	Yield [%]	MS. (M^+)
1a	($C_{21}H_{15}Cl_3O_3$, 421.84)	225–227	71	420 (Cl-clusters)
1b	($C_{21}H_{15}ClF_2O_3$, 388.50)	189–190	90	388 (Cl-cluster)
1c	($C_{21}H_{15}Br_2ClO_3$, 430.41)	156–158	76	429 (Cl, Br-clusters)
1d	($C_{21}H_{15}Cl_2FO_3$, 405.11)	212–214	87	404 (Cl-clusters)
1e	($C_{21}H_{15}F_3O_3$, 372.00)	160–163	80	372
1f	($C_{21}H_{15}Br_2FO_3$, 413.91)	145–147	85	412 (Br-clusters)
1g	($C_{21}H_{15}BrCl_2O_3$, 466.34)	218–220	70	464 (Cl, Br-clusters)
1h	($C_{21}H_{15}BrF_2O_3$, 432.98)	205–208	70	431 (Br-cluster)
1i	($C_{21}H_{15}Br_3O_3$, 554.93)	210 (dec.)	69	552 (Br-clusters)
2a	($C_{21}H_{17}ClO_3$, 352.50)	160–162	24	352 (Cl-cluster)
2b	($C_{21}H_{17}FO_3$, 336.00)	155–157	35	336
2c	($C_{21}H_{16}Cl_2O_3$, 387.12)	193–196	95	386 (Cl-clusters)
2d	($C_{21}H_{16}F_2O_3$, 354.32)	170–172	90	354
2e	($C_{21}H_{18}O_3$, 318.00)	151–152	68	318
3a	($C_{21}H_{18}Cl_3O_5$, 450.62)	180–183	50	449 (Cl-clusters)
3b	($C_{21}H_{18}Cl_2FO_5$, 432.90)	176–177	60	431 (Cl-clusters)
3c	($C_{21}H_{11}BrCl_2O_5$, 493.98)	200–202	58	492 (Cl, Br-clusters)
3d	($C_{21}H_{11}Br_3O_5$, 583.00)	250 (dec.)	40	580 (Br-clusters)
3e	($C_{21}H_{13}ClO_5$, 380.50)	108–109	30	380 (Cl-clusters)
3f	($C_{21}H_{13}FO_5$, 364.00)	200 (dec.)	53	364
3g	($C_{21}H_{12}Cl_2O_5$, 415.32)	178–180	80	414 (Cl-clusters)
3h	($C_{21}H_{12}F_2O_5$, 382.15)	161–162	65	382
3i	($C_{21}H_{14}O_5$, 346.14)	140–142	75	346

[a]) The NMR. and IR. spectra of all compounds are compatible with the proposed structures.

[2]) The systematic name of *e.g.* **1a** is 5,11,17-trichlorotetracyclo[13.3.1.1^{3,7}.1^{9,13}]henicosa-1(19),3,5,7(20),9,11,13(21),15,17-nonaene-19,20,21-triol and of *e.g.* **3a** 5,11,17-trichloro-19,20,21-trihydroxy-tetracyclo[13.3.1.1^{3,7}.1^{9,13}]henicosa-1(19),3,5,7(20),9,11,13(21),15,17-nonaene-8,14-dione. For convenience we call the parent structure metacyclotribenzylene [8].

Table 2. *Purification conditions and elemental analyses of metacyclotribenzylenes* **1-3**

Compound	Purification Method	Calc. [%] C	H	Halogen	Found [%] C	H	Halogen
1a	Sublimation (190°/0.01 Torr)	60.00	3.57	25.00 (Cl)	59.91	3.61	25.04 (Cl)
1b	Sublimation (173°/0.01 Torr)	64.86	3.86	9.14 (Cl) 9.78 (F)	64.77	3.81	9.05 (Cl) 9.80 (F)
1c	Crystallization ($CHCl_3$)	–	–	–	–	–	–
1d	Sublimation (200°/0.01 Torr)	62.25	3.70	17.50 (Cl) 4.69 (F)	62.17	3.72	17.25 (Cl) 4.58 (F)
1e	Sublimation (160°/0.01 Torr)	67.74	4.03	15.32 (F)	67.71	4.01	15.29 (F)
1f	Crystallization (ether)	–	–	–	–	–	–
1g	Sublimation (180°/0.01 Torr)	54.07	3.21	17.16 (Br)	54.27	3.13	16.98 (Br)
1h	Chromatography (silica gel, EtOAc)	–	–	–	–	–	–
1i	Crystallization (ether)	45.51	2.70	43.24 (Br)	54.22	2.88	43.21 (Br)
2a	Sublimation (165°/0.01 Torr)	71.59	4.82	10.08 (Cl)	71.98	4.71	10.18 (Cl)
2b	Sublimation (185°/0.01 Torr)	75.00	5.06	5.65 (F)	74.99	5.15	5.61 (F)
2c	Sublimation (180°/0.01 Torr)	65.11	4.13	18.34 (Cl)	64.99	3.98	18.21 (Cl)
2d	Sublimation (168°/0.01 Torr)	71.19	4.52	10.73 (F)	71.21	4.62	10.64 (F)
2e	Sublimation (185°/0.01 Torr)	79.20	5.60	–	79.18	5.68	–
3a	Sublimation (175°/0.01 Torr)	56.25	2.45	23.43 (Cl)	56.15	2.36	23.36 (Cl)
3b	Sublimation (165°/0.01 Torr)	58.23	2.53	16.36 (Cl) 4.38 (F)	58.21	2.56	16.51 (Cl) 4.28 (F)
3c	Chromatography (silica gel, EtOAc)	–	–	–	–	–	–
3d	Crystallization (EtOAc)	–	–	–	–	–	–
3e	Crystallization (CH_2Cl_2)	66.23	3.42	9.33 (Cl)	66.21	3.48	9.09 (Cl)
3f	Sublimation (149°/0.01 Torr)	69.23	3.57	5.22 (F)	69.22	3.57	5.23 (F)
3g	Sublimation (170°/0.01 Torr)	60.72	2.89	17.11 (Cl)	60.59	2.99	17.18 (Cl)
3h	Sublimation (156°/0.01 Torr)	65.96	3.14	9.94 (F)	65.93	3.09	10.00 (F)
3i	Sublimation (159°/0.01 Torr)	72.83	4.04	–	72.81	4.07	–

by the action of CrO_3/Ac_2O [4] followed by hydrolysis of the ester groups. It should be noted that the oxidation of all three CH_2-bridges in compounds **1** and **2** were impossible due to the highly strained macrocyclic ring in **3**.

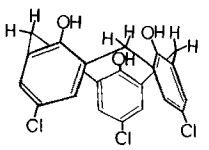
The purification conditions, the properties and elemental analyses of all products **1-3** are summarized in *Tables 1* and *2*. All compounds **1-3** were tested *in vitro* against *S. aureus*, *E. coli*, *C. albicans* and *Ps. aeruginosa* up to 128 µg/ml. Some of them showed notable activity against the above bacteria *(Table 3)*. When a (1:1)-mixture of compounds **1d** and **2c** was prepared and tested against the above microorganisms, an interesting antimicrobial activity was observed in the case of *Ps. aeruginosa* (experiment No. 5, *Table 3*). Owing to the fact that there is no explanation for the behavior of **1d/2c**, studies in this area are underway.

Table 3. *Minimal inhibitory concentrations [µg/ml]*

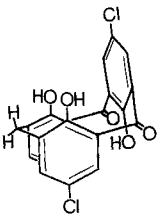
No.	Compound	*S. aureus*	*E. coli*	*C. albicans*	*Ps. aeruginosa*
1	**1a**	0.1	–	128	–
2	**1d**	30	1.5	3	1
3	**2c**	0.1	> 128	15	–
4	**3g**	30	100	> 128	–
5	**1d/2c** 1:1	1.5	3	6	0.1

It has been previously shown that the presence of heavy metal ions plays an important role in the effect and mechanism of action of certain antibiotics against the growth of some bacteria [9–11]. The biological tests on our compounds suggest that the structural features of macrocycles **1** and **2** necessary for antimicrobial activity are at least the two chlorophenolic units. Examples include **1a** and **1d** possessing fluorine and chlorine atoms, in contrast to the bromo-substituted derivative **1g**. However, when **1g** was debrominated, the bioactive compound **2c** was obtained. The reasons for the inactivity of bromo derivatives are not known, but this inactivity has been noticed previously [4–6]. When **2c** is replaced by **3g**, biological activity decreases. All the other analogues are inactive against the growth of bacteria. These results suggest that in addition to chelating abilities, a variety of other factors must be considered. Therefore, it is difficult to rank the order of biological activity accurately. However, some observations on structure and activity relationship can be made.

Model studies indicate that the steric requirements of the three active compounds **1a**, **1d** and **2c** favor the 'crown' conformation III. The H-bonded hydroxyl groups ($\tilde{\nu}_{max}$ 3200 cm^{-1}) lie close together at the apex. This is confirmed by ^{1}H-NMR. investigations which show that the methylene protons in **1a**, **1d** and **2c** are nonequivalent and appear as doublets at about 4.53 ($J = 12$ Hz) and 3.82 ($J = 12$ Hz) ppm. In such a rigid 'crown' conformation the hydroxy groups would be in a suitable spatial arrangement for chelate formation with metal ions of enzymes. Indeed, **1a**, **1d** and **2c** show a strong tendency for chelation with cations (*i.e.* $FeCl_3$). Esterification of the hydroxy functions results in loss of both chelating ability and biological activity.

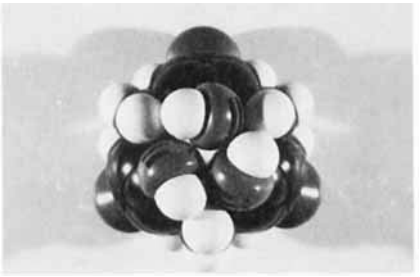


III

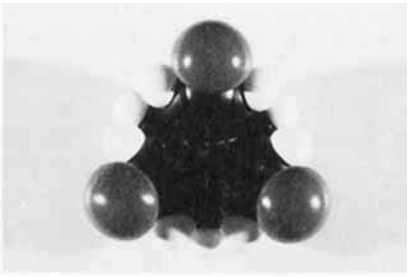


IV

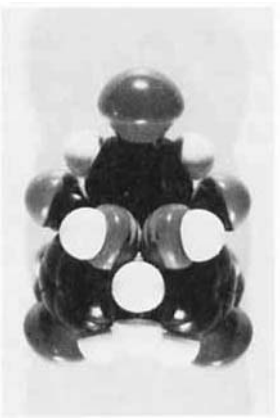
When two CH_2-bridges are oxidized to carbonyl functions as in **3a**, **3b** and **3g**, the biological activity is either drastically diminished or lost. ^{1}H-NMR. spectra of **3a**, **3b** and **3g** show the two nonequivalent methylene protons as doublets at about 4.87 ($J = 15$ Hz) and 4.01 ($J = 15$ Hz) ppm. IR. spectra exhibit two different types of carbonyl groups (1630, 1603 cm^{-1}), and the signal of free hydroxyl functions appear at 3500–3300 cm^{-1}. These spectroscopic results and model studies indicate that **3** must possess the rigid conformation IV. The space-filling models *(Figure)* of **3** indicate also that the conformation III is unlikely. As the conformational transformation III → IV is not feasible, conformation IV of **3** might be built up during the oxidation of **1** to **3** by the oxidation followed by the scission of the methylene-aryl C,C-bond, subsequent recombination [12–14]. Although the compounds **3** exhibit tendency for chelation with some cations (*i.e.* $FeCl_3$),



1a, conformation III
(top view)



1a, conformation III
(bottom view)



3a, conformation IV
(top view)

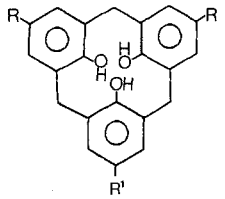
3a, conformation IV
(bottom view)

Figure. *Space-filling molecular models of compounds* **1a** *and* **3a**.

apparently, the functional groups are not in a suitable spatial arrangement (s. IV) for chelate formation with metal ions of enzymes, (loss of biological activity). It should be noted that when the hydroxy groups in **3** were acetylated, the carbonyl group absorbed in the IR. at 1676 cm^{-1} as a sharp singlet and the ester groups at 1771 cm^{-1}.

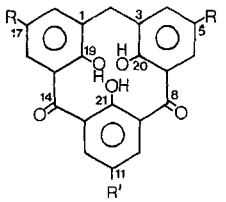
These findings suggest that metal chelation as well as the spatial disposition of the various groups and the structural conformations are important in fitting the molecule in an enzyme site. However, further studies are required to establish a definite structure-activity relationship.

We are grateful to Mrs. *N.C. Behforouz* who carried out the biological tests at the School of Medicine, Shiraz University, Iran.

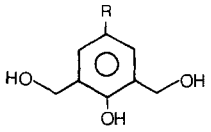


1a R = Cl, R′ = Cl
1b R = F R′ = Cl
1c R = Br, R′ = Cl
1d R = Cl, R′ = F
1e R = F, R′ = F
1f R = Br, R′ = F
1g R = Cl, R′ = Br
1h R = F, R′ = Br
1i R = Br, R′ = Br

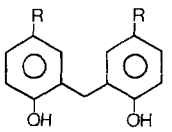
2a R = H, R′ = Cl
2b R = H, R′ = F
2c R = Cl, R′ = H
2d R = F, R′ = H
2e R = H, R′ = H



3a R = Cl, R′ = Cl
3b R = Cl, R′ = F
3c R = Cl, R′ = Br
3d R = Br, R′ = Br
3e R = H, R′ = Cl
3f R = H, R′ = F
3g R = Cl, R′ = H
3h R = F, R′ = H
3i R = H, R′ = H



4a R = Cl, **4b** R = F
4c R = Br



5a R = Cl, **5b** R = F
5c R = Br

Experimental Part

General Procedures. See [4].

Synthesis of the metacyclotribenzylenes **1a–i**. They were all prepared in the same manner we give as an example the preparation of *5,11,17-trichlorometacyclotribenzylene-19,20,21-triol* (**1a**). To a solution of **4a** (1.84 g, 0.01 mol) and **5a** (5.4 g, 0.02 mol) in methanol (20 ml) was added concentrated hydrochloric acid (5 ml). The mixture was shaken at 60–85° for 45 min and then allowed to stand at 25° for 24 h. The solution was evaporated and the residue suspended in boiling water to dissolve unreacted starting materials. The precipitate was filtered off, washed with water and dried to give 6.2 g (71%) of **1a**. – IR. (KBr): 3200 br., 1586*w*, 1485*s*, 1450*s*, 1390*m*, 1255*m*, 1230*s*, 1180*w*, 930*w* and 810*w*. – ^{1}H-NMR. ($CDCl_3$): 9.41 (br., 3 H, 3 HO, exchangeable with D_2O); 7.09 (*s*, 6 H, 6 arom. H); 4.53 (*d*, J = 12, 3 H, 3 *H*CH); 3.82 (*d*, J = 12, 3 H, 3 HC*H*).

Synthesis of the trihydroxydiones **3a–i**. They were all prepared in the same manner as given for the preparation of *5,11,17-trichloro-19,20,21-trihydroxy-metacyclotribenzylene-8,14-dione* (**3a**). Compound **1a** (2 g, 4 mmol) was dissolved in acetic anhydride (15 ml). One drop of concentrated sulfuric acid was added and the mixture heated under reflux for 2 h. A solution of CrO_3 (1.9 g) in Ac_2O/AcOH 3:1 (20 ml) was added dropwise within 2 h at 25° with continuous stirring. The mixture was kept at 45° for 4 h, and then heated under reflux for 2 h. After cooling, it was poured into cold water (200 ml) and allowed to stand for 15 h. The yellow precipitate was filtered off, washed with water and dried (2.2 g). The product was dissolved in 10% aq. NaOH-solution (50 ml) and heated at 45° for 1.5 h. The solution was filtered, and the filtrate acidified with 2N HCl to give a pale yellow precipitate which was filtered off, washed with water and dried to afford 1.28 g (50%, based on **1a**) of **3a**. – IR. (KBr): 3500–3300 br., 1630*s*, 1603*s*, 1490*m*, 1430*s*, 1345*m*, 1240*s*, 1170*w*, 1030*m*, 810*m*. – ^{1}H-NMR. ($CDCl_3$): 8.98 (br., 1 H, HO, exchangeable with D_2O); 8.60 (br., 2 H, 2 HO, exchangeable with D_2O); 7.11–7.48 (*m*, 6 H, 6 arom. H); 4.87 (*d*, J = 15, 1 H, *H*CH); 4.01 (*d*, J = 15, 1 H, HC*H*).

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