113. The Synthesis of 4,11,18,25-Tetrachloro [1$_4$]metacyclophane-7,14,21,28-tetrol. Structural Analogues of Phloroglucides[1])

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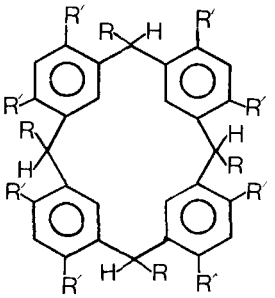
Summary

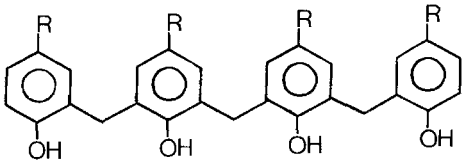
The synthesis of the title compounds is described. Some of the compounds prepared exhibited antimicrobial activity *in vitro*. Structure-activity relationship is briefly discussed.

Högberg et al. have found that the acid-catalyzed condensation of resorcinol with several aromatic aldehydes gave two stereoisomeric macrocycles of general structure **I** [1]. The configurations and conformations of the two isomers were investigated using molecular models and symmetry considerations combined with dynamic NMR. measurements [2].

In the previous paper [3] we described the synthesis of models and structural analogues of phloroglucides having the general structure **II**, possessing activity against a number of pathogenic microorganisms *in vitro*. The biological activity of these compounds might well be linked to the presence of functional groups suitably



I



II

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positioned to chelate with metal ions of enzymes and perhaps to the ease with which these molecules are transported across membranes. Since some of the reported compounds [3] [3a] exhibited biological activity, we prepared their analogues **1–17** and cyclic analogues **18–23** [3b]. Owing to the presence of various functional groups, these new compounds may exhibit a greater chelating ability and hence a more pronounced biological activity.

5,5′-Dihalo-2,2′-dihydroxydiphenylmethanes (**1a–c**) [3] were transformed to the acetates **2a–c** which by reaction with aluminium chloride [4] gave 3,3′-diacetyl-5,5′-dihalo-2,2′-dihydroxydiphenylmethanes (**3a–c**). Compounds **3a–c** were transformed to the corresponding acids **4a–c** by means of sodium hypoiodite [5].

Since the conversion of the CH_2-bridge to a carbonyl function may increase the chelating ability of these compounds, we oxidized **2a–c** with chromium trioxide in acetic anhydride to the corresponding benzophenones **5a–c**. Transformation of **5a** to **8a** was achieved by reaction with methylmagnesium iodide. *Fries* rearrangement of **5a–c** and **8a** gave the corresponding phenolic ketones **6a–c** and **10a**. Compounds **6a–c** were oxidized with sodium hypoiodite to the acids **7a–c**. Reaction of **10a** with sodium hypoiodite gave a mixture of the two acids **11a** and **12a** in about 80% yield (2:1). Compound **1c** was converted nearly quantitatively to **1d** using Zn/KOH. By *Fries* rearrangement, esters **2d** and **5d** gave mixtures of phenolic ketones, respectively **3d** and **1e** (3.5:1), and **6d** and **13e** (6.3:1). The mixtures were separated into their constituents by crystallization (see *Exper. Part*). Methyl ketones **3d**, **1e**, **6d** and **13e** were transformed respectively to the acids **4d**, **1f**, **7d** and **13f** as described above for **10a**. Reaction of **4c** with Zn/KOH gave **4d** identical to the oxidation product of **3d**.

Next, 5,5′-dichloro-2,2′-dihydroxydiphenylmethane (**1b**) was transformed to the phenolic alcohol **14b** by means of CH_2O/NaOH [6] in methanol. Acetylation of **14b** gave **15b** which was oxidized to **16b** with chromium trioxide. The ester groups in **16b** were hydrolyzed with sodium hydroxide to give 5,5′-dichloro-2,2′-dihydroxy-3,3′-dihydroxymethylbenzophenone (**17b**) (overall yield *ca.* 65% from **1b**).

Compound **28b** showed antibacterial activity [3], therefore the cyclo-analogue **18b** was prepared and its biological activity investigated. *Niederl & Vogel* have studied the reaction of resorcinol with a few aliphatic aldehydes in acidic medium [7]. In each case they obtained a single product to which they assigned the macrocyclic structure **I** [8]. *Högberg* has recently reinvestigated these condensations and reported the isolation in high yield of macrocycles **I** [9]. However, when we attempted to produce **18b** by a similar condensation (4-chlorophenol + CH_2O), a polymeric mixture was obtained.

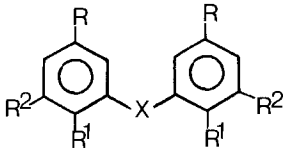
We now describe an alternative preparation giving the macrocycle **18b** in high yield. The reaction of **1b** with **14b** gave a mixture of **18b** and **23b** (7:1). The mixture was separated into its constituents by sublimation. The hydroxy functions in **18b** were acetylated to give 4,11,18,25-tetrachloro-7,14,21,28-tetraacetoxy-[1_4]-metacyclophane (**19b**) which was oxidized to **20b**. Subsequent hydrolysis of the ester groups gave the corresponding hydroxy ketone **21b** (92%). Having established a methode for the preparation of the macrocyclic compounds, the cyclization was repeated using **13b** and **17b** to give **22b** (60%).

Compounds **1–23** were tested *in vitro* against *S. aureus*, *E. coli*, *C. albicans* and *Ps. aeruginosa* up to 128 μg/ml. Results of biologically active compounds are summarized in *Table 1* along with some results from our earlier study (**24–29**) [3] for comparison. Compounds **18b**, **22b**, **24b**, **25b**, **28b** and **29b** showed noteworthy antimicrobial activity. Compounds **1a–b** and **4a–b** showed marginal activity which cannot be assessed. All the other analogues were inactive against the growth of bacteria.

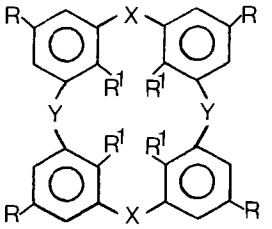
Table 1. *Minimal inhibitory concentration* (μg/ml) *against microorganisms*

Compound	*S. aureus*	*E. coli*	*C. albicans*	*Ps. aeruginosa*
4a	11–15	–	–	–
24b	0.30	15	15	–
25b	0.9	–	100	–
28b	0.6	11	15	–
29b	0.65	> 128	100	–
18b	3	–	–	> 128
22b	0.6	> 128	0.6	–

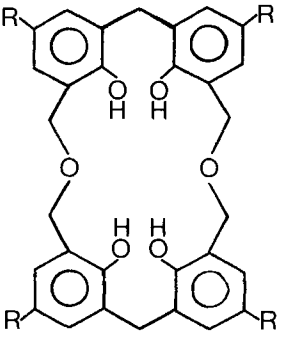
It has been previously shown that a direct relationship exists between the chelating abilities of some antibiotics and their bacteriostatic action [10]. The biological tests of our compounds suggest that other factors must also be considered. Therefore, it is difficult to tabulate any list of significant values as an index of antibacterial activity, although some observations on structure and activity relationships can be made.



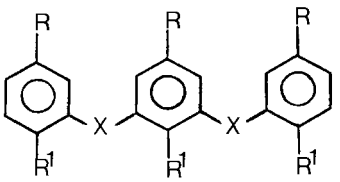
	R^1	R^2	X
1	OH	H	CH_2
2	OAc	H	CH_2
3	OH	$COCH_3$	CH_2
4	OH	COOH	CH_2
5	OAc	H	CO
6	OH	$COCH_3$	CO
7	OH	COOH	CO
8	OAc	H	$C(OH)CH_3$
9	OH	H	$C(OH)CH_3$
10	OH	$COCH_3$	$C(OH)CH_3$
11	OH	COOH	$C(OH)CH_3$
12	OH	COOH	$C{=}CH_2$
13	OH	H	CO
14	OH	CH_2OH	CH_2
15	OAc	CH_2OAc	CH_2
16	OAc	CH_2OAc	CO
17	OH	CH_2OH	CO



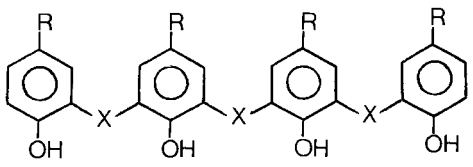
	R^1	X	Y
18	OH	$X{=}Y{=}CH_2$	
19	OAc	$X{=}Y{=}CH_2$	
20	OAc	$X{=}Y{=}CO$	
21	OH	$X{=}Y{=}CO$	
22	OH	$X{=}CH_2$	$Y{=}CO$



23



	X	R^1
24	CH_2	OH
25	CO	OH
26	CH_2	OAc
27	CO	OAc



28 X=CH_2
29 X=CO

a R=F; **b** R=Cl; **c** R=Br; **d** R=H; **e** R=$COCH_3$; **f** R=COOH

Thus, the three active compounds **18b**, **24b** and **28b** have the same substituents which are at the same position relatively to the hydroxy groups. Furthermore, **18b**, **24b** and **28b** show a strong tendency for chelation with divalent cations (*e.g.* Fe^{++}). Esterification of the hydroxy functions results in a loss of both chelating and biological activity as observed with **19b** and **26b**.

When the hydroxy groups are kept, and the methylene bridges are converted to carbonyl functions as in **25b** and **29b**, biological activity decreases. Model studies indicated that the phenolic ketones **25b** and **29b** are essentially planar. This should enable them to chelate more effectively with metal ions since the chelate ring is an unsaturated six-membered ring with considerable resonance character [11]. Indeed, when the copper chelate of **25b** was examined by IR. spectroscopy, a noticeable shift of the carbonyl stretching frequency (from 1643 to 1617 cm^{-1}) was observed. This shift has already been observed [12] and was shown to be directly related to the stability of the chelate. Similarly, oxidation of the CH_2-bridges in **18b** to carbonyl functions (**21b**) results in loss of activity, although the four-ring system in **21b** is nearly planar and exhibits a strong tendency for chelation with cations. On the other hand, when only two CH_2-bridges in **18b** are replaced with carbonyl functions (**22b**) the antimicrobial activity as well as the chelating ability are increased. Replacement of the carbonyl functions in **22b** with ether groups, as in **23b**, results in a loss of biological activity and a significant decrease in chelating ability. Finally, dechlorination of **18b**, **24b** and **28b** to the corresponding **18d**, **24d** and **28d** does not affect the chelating ability, although biological activity is lost.

Table 2. *^{13}C-NMR. spectral data of compounds* **3a** *and* **4a** (20 MHz, D_6-DMSO)

3a			**4a**		
C-Atom	δ (ppm)	Hz	C-Atom	δ (ppm)	Hz
5	153.9*d*	$^1J(C,F)=236$	5	153.9*d*	$^1J(C,F)=236$
4	124.0*d*	$^2J(C,F)=24$	4	124.0*d*	$^2J(C,F)=23.6$
3	129.7*d*	$^3J(C,F)=7$	3	129.3*d*	$^3J(C,F)=6.6$
2	155.8*s*		2	155.7*s*	
1	118.9*d*	$^3J(C,F)=7$	1	112.9*d*	$^3J(C,F)=6.6$
6	114.8*d*	$^2J(C,F)=23$	6	113.2*d*	$^2J(C,F)=23.6$
a	28.4*s*		*a*	28.4*s*	
7	205.2*d*	$^4J(C,F)(CO)=2.2$	7	171.3*d*	$^4J(C,F)(CO)=1.9$
8	27.2*s*				

We conclude that the structural features of macrocycle **I** and phloroglucide **II** necessary for antimicrobial activity are at least two CH_2-bridges and three or four chlorophenolic units. These findings suggest that metal chelation as well as the spatial disposition of the phenyl rings and the conformation of the molecule in solution affect bacteriostatic action. However, further studies are required to establish a definite structure-activity relationship. Studies in this area are already underway.

We are grateful to Dr. *M.J. Nemer* for helpful discussions. We are indebted to Mrs. *N.C. Behforouz* who carried out the biological tests at the School of Medicine, Shiraz University, Iran.

Experimental Part

General procedures: see [13].

Acetylation of hydroxy groups. Phenolic compounds **1a–d**, **14b** and **18b** were acetylated to **2a–d**, **15b** and **19b** according to Chapter 3 in [3]. The properties and the purification conditions are collected in *Table 3*, and elemental analyses in *Table 4*.

Oxidation of methylene groups with chromium trioxide. Esters **2a–d**, **15b** and **19b** were converted to the corresponding keto esters **5a–d**, **16b** and **20b** according to Chapter 11 in [3]. Melting points, yields, elemental analyses, spectroscopic data and purification methods of these compounds are presented in *Tables 3* and *4*.

Preparation of 1,1-bis(2-acetoxy-5-fluorophenyl)ethanol (**8a**) *and 1,1-bis(5-fluoro-2-hydroxyphenyl)-ethanol* (**9a**). To a 500 ml two-necked flask fitted with a dropping funnel and a condenser, containing 2 g magnesium turnings and 100 ml dry ether, was added, dropwise, a solution of 6 ml methyl iodide ($d = 2.28$) in 20 ml dry ether over a period of 1 h. A solution of compound **5a** (4.2 g, 0.013 mol) in ether (80 ml) was then added and the reaction mixture was stirred at reflux temperature for 4 h. After cooling, it was added to a mixture of 500 g crushed ice and 200 ml of concentrated hydrochloric acid. The aqueous solution was extracted with 100 ml of ether (3 times). The ethereal layer was washed with 10% aqueous $NaHSO_3$-solution (60 ml) and water (50 ml). The organic layer was then dried and evaporated to give 4 g crude product. Chromatography on silica gel with petroleum ether gave 0.79 g (16%) of **8a**. Crystallization with petroleum ether gave 0.75 g (15%) of **8a**; m.p. 114–115°. The column was then eluted with a mixture of benzene/petroleum ether 4:1 to give 0.35 g (8%) pure **9a**; m.p. 158–159°. This compound was treated with acetic anhydride to give **8a**.

Preparation of the phenolic ketones ***3a–d, 1e, 6a–d, 13e and 10a.*** – Compounds **2a–d**, 5a–**d** and **8a** were submitted to identical conditions which will be detailed for **2d** only. The purification conditions and the properties of the products are presented in *Tables 3* and *4* and the ^{13}C-NMR. data for compound **3a** in *Table 2*.

Preparation of 3,3'-diacetyl-2,2'-dihydroxydiphenylmethane (**3d**) *and 5,5'-diacetyl-2,2'-dihydroxy-diphenylmethane* (**1e**). Anhydrous aluminium chloride (15.0 g, 0.112 mol) in a 250 ml flask was heated in an oil bath at 140° for 5 min and stirred with a glass rod. Compound **2d** (5 g, 0.02 mol) was added. The temperature was allowed to rise to 160–180° where it maintained for 20 min. After cooling, the mixture was added to 200 ml of 2N HCl. After 12 h the precipitate was filtered off, washed with water and dried to give 4.4 g (88%) of the crude mixture **3d** and **1e**. This was suspended in 100 ml of CH_2Cl_2/acetone 1:1 to dissolve **3d**. Compound **1e** was filtered off and dried; m.p. 271–274°. The filtrate was evaporated and **3d** was chromatographed on silica gel with CH_2Cl_2 giving pure **3d**; m.p. 183–184°.

Oxidation of acetyl groups with sodium hypoiodite. Ketones **3a–d**, **1e**, **6a–d** and **13e** were transformed to the corresponding acids **4a–d**, **1f**, **7a–d** and **13f** respectively according to Chapter 7 in [3].

When **10a** was submitted to identical conditions, 70% of the expected product **11a** and 25% of **12a** were obtained. Purification conditions, properties and elemental analyses of the products are listed in *Tables 3* and *4*. The ^{13}C-NMR. data for compound **4a** are given in *Table 2*.

Table 3

Compound*	M.p. [°C]	Yield [%]	Purification method
1d	115–116	80	Crystallization (H_2O)
1e	271–274	20	Sublimation (180–190°/0.03 Torr)
2a	101–102	64	Crystallization (C_2H_5OH/H_2O 1:1)
2b	120–122	70	Crystallization (pet. ether)
2c	128–129	77	Crystallization (C_2H_4OH/H_2O 1:1)
3a	155–156	64	Crystallization (C_2H_5OH)
3b	202–203	70	Sublimation (155–160°/0.01 Torr)
3c	232–235	60	Sublimation (210°/0.01 Torr)
3d	183–184	70	Sublimation (220°/0.03 Torr)
4a	255 (dec.)	60	Sublimation (158°/0.03 Torr)
4b	280–284	60	Sublimation (230–235°/0.01 Torr)
4c	275 (dec.)	51	Sublimation (211–215°/0.02 Torr)
4d	276–279	74	Sublimation (215–220°/0.02 Torr)
5a	92–93	60	Crystallization (C_2H_5OH/H_2O 1:1)
5b	97–98	90	Crystallization (pet. ether)
5c	109–110	80	Crystallization (CH_3OH)
5d	118–120	80	Chromatography (SiO_2/CH_2Cl_2)
6a	149–150	72	Crystallization (C_2H_5OH)
6b	222–224	80	Sublimation (180–190°/0.01 Torr)
6c	230–231	50	Sublimation (170–180°/0.01 Torr)
6d	170–171	63	Sublimation (150–155°/0.02 Torr)
7a	280 (dec.)	55	Crystallization (CCl_4/acetone 3:1)
7b	295–297	90	Sublimation (260–265°/0.01 Torr)
7c	> 350	75	Sublimation (210–215°/0.02 Torr)
7d	207–208	70	Sublimation (190–200°/0.02 Torr)
8a	114–115	15	Crystallization (pet. ether)
9a	158–159	8	Crystallization (H_2O)
10a	156–157	50	Crystallization (C_2H_5OH)
11a	268–270	62	Sublimation (190–200°/0.02 Torr)
12a	205–207	25	Sublimation (160–165°/0.02 Torr)
13b	152–155	90	Crystallization (pet. ether)
13c	129–130	80	Crystallization (C_2H_5OH/H_2O 1:1)
13e	> 300	10	Crystallization (ether)
13f	> 300	73	Sublimation (220°/0.02 Torr)
14b	147–149	70	Crystallization (benzene)
15b	90–93	90	Crystallization (ether/pet. ether 1:1)
16b	83–86	97	Crystallization (C_2H_5OH/H_2O 1:1)
17b	139–141	57	Crystallization (H_2O)
18b	239–242	70	Sublimation (200–210°/0.01 Torr)
19b	180–183	80	Chromatography (silica gel/CH_2Cl_2)
20b	160–163	70	Chromatography (silica gel/CH_2Cl_2)
21b	> 250	54	Crystallization (ethanol)
22b	202–205	60	Sublimation (175–180°/0.01 Torr)
23b	218–222	50	Sublimation (175–180°/0.01 Torr)

* The IR. and NMR. spectra of all compounds agreed with the reported structures.

Hydrolysis of ester groups with sodium hydroxide. Ester hydrolysis of **16b** was done at RT., according to the standard hydrolysis procedure [3 (Chapter 11)] to give **17b** (57%). However, ester groups in **20b** could not be hydrolyzed by the standard procedure. The hydrolysis of **20b** was achieved as follows.

Keto ester **20b** (0.7 g, 0.8 mol) was suspended in 20 ml of 2N NaOH. The reaction mixture was stirred at reflux temperature for 2 h, then filtered and the filtrate was acidified with 2N HCl to give

Table 4. *Elemental analyses of the prepared compounds*

Compound	Mol-wt.	MS. (M^+)	Calc. % C	H	Halogen	Found % C	H	Halogen
1e	284.01	284	71.83	5.63	–	71.93	5.73	–
2a	320.08	320	63.76	4.37	11.08 (F)	63.69	4.22	10.98 (F)
3a	320.08	320	63.76	4.37	11.08 (F)	63.60	4.13	11.10 (F)
3b	353.10	–	58.09	3.99	–	57.88	3.78	–
3c	442.11	–	46.15	3.17	36.19 (Br)	46.01	3.20	36.11 (Br)
3d	284.03	284	71.83	5.63	–	71.72	5.52	–
4a	324.01	324	55.57	3.08	11.72 (F)	55.82	3.28	11.65 (F)
4b	357.13	–	50.44	2.82	–	50.43	3.06	–
4c	446.13	–	40.36	2.24	35.87 (Br)	40.30	2.31	35.84 (Br)
4d	288.00	288	62.50	4.17	–	62.47	4.21	–
5a	334.11	–	61.09	3.59	11.39 (F)	61.26	3.66	11.23 (F)
5d	298.03	298	68.40	4.60	–	68.31	4.55	–
6a	334.11	334	61.09	3.59	11.39 (F)	61.28	3.46	11.28 (F)
6b	367.18	–	55.61	3.29	–	55.38	3.41	–
6c	456.08	–	44.73	2.63	–	44.68	2.62	–
6d	298.00	298	68.40	4.60	–	68.54	4.73	–
7a	338.02	338	53.25	2.36	11.24 (F)	53.44	2.60	11.32 (F)
7b	371.12	370 (Cl-clusters)	48.58	2.17	–	48.46	1.97	–
7c	460.14	–	39.13	1.73	34.78 (Br)	39.17	1.87	34.87 (Br)
7d	302.01	302	59.60	3.31	–	60.01	3.52	–
9a	266.12	266	63.15	4.51	–	62.86	4.34	–
10a	350.02	350	61.71	4.57	–	61.94	4.47	–
11a	336.00	336	54.23	3.36	–	54.48	3.47	–
12a	318.00	318	57.14	3.00	–	57.34	3.30	–
13c	372.21	–	41.90	2.10	–	42.03	2.21	–
13e	298.01	298	68.40	4.60	–	68.43	4.51	–
13f	302.00	–	59.60	3.31	–	58.95	3.20	–
18b	562.32	560 (Cl-clusters)	59.38	3.50	25.22 (Cl)	59.68	3.68	25.25 (Cl)
19b	730.27	–	59.22	3.83	19.42 (Cl)	58.96	3.93	19.26 (Cl)
20b	786.27	784 (Cl-clusters)	54.98	2.26	18.03 (Cl)	55.05	2.26	18.00 (Cl)
22b	590.17	588 (Cl-clusters)	56.99	2.71	24.29 (Cl)	56.89	2.90	24.22 (Cl)
23b	622.18	620 (Cl-clusters)	58.12	4.06	24.06 (Cl)	58.42	3.98	24.18 (Cl)

yellow crystals. The crystals were filtered off, washed with water and dried to give the phenolic ketone **21b** (78%); m.p. > 250°.

Preparation of 5,5'-dichloro-2,2'-dihydroxy-3,3'-bis(hydroxymethyl)diphenylmethane (**14b**). To 5,5'-dichloro-2,2'-dihydroxydiphenylmethane (**1b**, 5 g, 0.018 mol) in methanol (5 ml), was added an aqueous solution of 25% NaOH (10 ml). Formaldehyde (38%, 20 ml) was added at RT. The reaction mixture was stirred at 80–90° for 1 h and then allowed to stand at RT. for 24 h. Acetic acid/water 1:1 was added for neutralization. The resulting white precipitate was filtered off, washed with water and dried to give 5.5 g (90%) crude product; m.p. 125–130°. Crystallization from benzene gave white needles of compound **14b** (70%); m.p. 147–149°.

Preparation of macrocyclic compounds *18b*, *22b* and *23b*. – The preparation of **22b** followed (with **17b** and **13b**) the procedure illustrated in the synthesis of **18b**, compound **23b** being a by-product from the preparation of **18b**. The IR. and NMR. spectra of **18b** and **22b** were similar except for the variations due to aromatic substituents. The MS. of the three compounds showed M^+. The yields, physical properties, elemental analyses and mass spectral data are collected in *Tables 3* and *4*.

Preparation of 4,11,18,25-tetrachloro[1$_4$]metacyclophane-7,14,21,28-tetrol (**18b**) *and compound* **23b**. A mixture of 5,5'-dichloro-2.2'-dihydroxydiphenylmethane (**1b**, 1.8 g, 6 mmol) and 5,5'-dichloro-2,2'-dihydroxy-3,3'-dihydroxymethyldiphenylmethane (**14b**, 2.0 g, 6 mmol) was dissolved in 10 ml of

methanol at 50°. Conc. hydrochloric acid (9 ml) was added and the reaction mixture was stirred at 50° for 30 min then allowed to stand at 25° for 24 h. The solvent was evaporated and the residue was suspended in boiling water (100 ml) to dissolve unreacted starting materials. The crude product (3 g) was collected by filtration, and dissolved in 2N NaOH (30 ml) at 40°. The solution was decolorized with charcoal (0.2 g) and filtered. The filtrate was acidified with 2N HCl (45 ml) to give a white precipitate which was filtered off, washed with water and dried. Crystallization from benzene gave a mixture of **18b** and **23b** (2.6 g). Sublimation at 175–180°/0.01 Torr gave 10% of **23b**; m.p. 219–220°, and further sublimation at 200–210°/0.01 Torr gave **18b** in 65% yield; m.p. 239–241°.

Preparation of macrocyclic compound **23b**. Compound **23b** was obtained from **1b** (0.01 mol) and formaldehyde (38%, 9 ml) in 50% yield according to the procedure which was described for the preparation of **14b** except that the reaction was carried out at RT. for 24 h.

REFERENCES

[1] *H. Erdtman, S. Högberg, S. Abrahamsson & B. Nilsson*, Tetrahedron Lett. *1968*, 1679.
[2] *A. G. S. Högberg*, J. Am. Chem. Soc. *102*, 6046 (1980).
[3] *G. H. Hakimelahi & A. A. Moshfegh*, Helv. Chim. Acta *64*, 599 (1981); a) Swiss patent No. 003848 (1977); b) Swiss patent No. 003849 (1977).
[4] *V. S. N. Dhar*, J. Chem. Soc. *117*, 1069 (1920).
[5] *A. A. Moshfegh, S. Fallab & H. Erlenmeyer*, Helv. Chim. Acta *40*, 1157 (1957).
[6] *A. Zinke & E. Ziegler*, Ber. Deutsch. Chem. Ges. *77*, 264 (1944).
[7] *J. B. Niederl & H. L. Vogel*, J. Am. Chem. Soc. *62*, 2512 (1940).
[8] *A. Zinke, R. Ott & F. H. Garrana*, Monatsh. Chem. *89*, 135 (1958); *J. Hyatt*, J. Org. Chem. *43*, 1808 (1978).
[9] *A. G. S. Högberg*, J. Org. Chem. *45*, 4498 (1980).
[10] *E. Sorkin, W. Roth & H. Erlenmeyer*, Helv. Chim. Acta *35*, 1736 (1952); *S. Fallab*, Helv. Chim. Acta *36*, 6 (1953).
[11] *B. L. Van Duuren, A. Segal, S. S. Tseng, G. M. Rusch, G. Loewengart, U. Mate, D. Roth, A. Smith, S. Melchionne & I. Seidman*, J. Med. Chem. *21*, 27 (1978).
[12] *L. J. Bellamy & R. F. Branch*, J. Chem. Soc. *1954*, 4491.
[13] *G. H. Hakimelahi, C. B. Boyce & H. S. Kasmai*, Helv. Chim. Acta *60*, 342 (1977).