114. The Synthesis of Hetero-Halogenated Derivatives of Phloroglucide Analogues [1]

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Summary

A short synthesis of the title compounds is reported. Most of the compounds prepared were found to be active against a number of pathogenic microorganisms *in vitro*.

Previously [2] [2a], we described the synthesis of homo-halogenated derivatives of phloroglucide analogues possessing activity against a number of pathogenic microorganisms. Our study on the structure-activity relationship of these compounds [2b] suggested that the presence of halogen atoms is essential for biological activity. We now report the synthesis and antimicrobial properties of several hetero-halogenated derivatives of phloroglucide analogues.

As a model, *p*-chlorophenol (**1a**) was converted to 4-chloro-2,6-bis(hydroxymethyl)phenol (**2a**) by means of CH_2O/NaOH [3]. Acid-catalyzed condensation of

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

Compound	*S. aureus*	*E. coli*	*C. albicans*	*Ps. aeruginosa*
3a	0.3	15	15	–
3ab	0.9	–	20	–
3ba	0.3	–	30	–
4a	0.9	–	15	–
4b	3	–	6	–
4c	1.5	–	10	0.3
4d	100	–	–	–
5a	0.9	–	100	–
5b	100	–	–	–
7a	0.6	11	15	–
7b	–	–	30	3
7d	0.2	60	15	–
8a	0.65	> 128	100	–
8b	30	15	3	1

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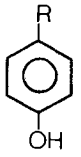
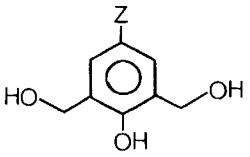
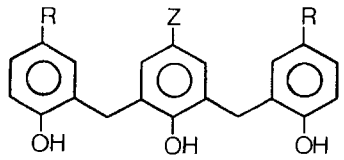


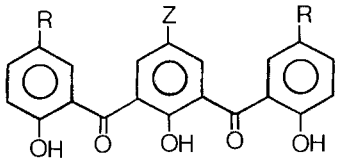
1a R = Cl
1b R = F
1c R = Br



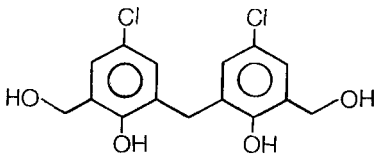
2a Z = Cl
2b Z = F
2c Z = Br



	R	Z		R	Z
3a	Cl	Cl	**3cb**	Br	F
3ab	Cl	F			
3ac	Cl	Br	**4a**	Cl	H
3ba	F	Cl	**4b**	F	H
3bc	F	Br	**4c**	H	Cl
3ca	Br	Cl	**4d**	H	F



5a R = Cl, Z = Cl
5b R = F, Z = H



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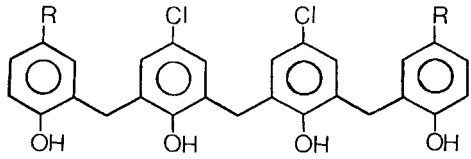
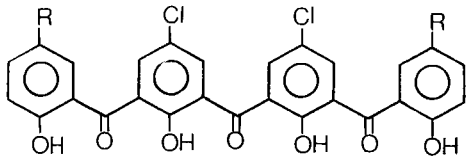


7a R = Cl
7b R = F
7c R = Br
7d R = H



8a R = Cl **8b** R = H

2a with **1a** gave 4-chloro-2,6-bis(5-chloro-2-hydroxy-α-tolyl)phenol (**3a**), identical to the compound characterized previously [2]. Since compound **3a** exhibited an interesting antimicrobial activity, it was decided to prepare its hetero-halogenated analogues **3ab–cb**. The results are summarized in *Tables 2* and *3*.

p-Chlorophenol (**1a**), *p*-fluorophenol (**1b**) and *p*-bromophenol (**1c**) were transformed to the corresponding 4-halo-2,6-bis(5-halo-2-hydroxy-α-tolyl)phenols **3ab–cb** by means of 4-halo-2,6-bis(hydroxymethyl)phenol **2a–c**/HCl by the method used for the preparation of **3a**. Hetero-halogenated derivatives **3ab** and **3ba** of phloroglucide analogues, possessing F- and Cl-atoms, exhibited interesting antibacterial activity, but the Br-derivatives **3ac**, **3bc**, **3ca** and **3cb** were inactive. However, their debrominated (Zn/KOH [2]) derivatives **4a–d** were bioactive.

Table 2. *Data of the prepared compounds*

Compound	Mol-wt.	M.p. [°C]	Yield [%]	MS. (M^+)
2a	$C_8H_9ClO_3$ (188.15)	166–168	80	188 (Cl-clusters)
2b	$C_8H_9FO_3$ (172.00)	137–139	50	172
2c	$C_8H_9BrO_3$ (233.06)	163–164	50	232 (Br-clusters)
3a	$C_{20}H_{15}Cl_3O_3$ (409.50)	232–234	78	408 (Cl-clusters)
3ab	$C_{20}H_{15}Cl_2FO_3$ (393.35)	205–207	40	393 (Cl-clusters)
3ac	$C_{20}H_{15}BrCl_2O_3$ (454.31)	234–238 (dec.)	77	453 (Cl, Br-clusters)
3ba	$C_{20}H_{15}ClF_2O_3$ (376.78)	223–226	90	376 (Cl-clusters)
3bc	$C_{20}H_{15}BrF_2O_3$ (421.32)	234–236	82	420 (Br-clusters)
3ca	$C_{20}H_{15}Br_2ClO_3$ (498.81)	> 250	68	–
3cb	$C_{20}H_{15}Br_2FO_3$ (482.31)	> 250	80	–
4a	$C_{20}H_{16}Cl_2O_3$ (375.24)	194–197	89	374 (Cl-clusters)
4b	$C_{20}H_{16}F_2O_3$ (342.33)	190–192	80	342
4c	$C_{20}H_{17}ClO_3$ (340.79)	188–190	85	340 (Cl-clusters)
4d	$C_{20}H_{17}FO_3$ (324.34)	177–178	90	324
5a	$C_{20}H_{11}Cl_3O_5$ (436.51)	196–198	85	435 (Cl-clusters)
5b	$C_{20}H_{12}F_2O_5$ (370.28)	140–143	80	370
7a	$C_{27}H_{20}Cl_4O_4$ (550.43)	242–244	70	548 (Cl-clusters)
7b	$C_{27}H_{20}Cl_2F_2O_4$ (517.40)	205–208	75	517 (Cl-clusters)
7c	$C_{27}H_{20}Br_2Cl_2O_4$ (639.39)	> 250 (dec.)	71	637 (Cl, Br-clusters)
7d	$C_{27}H_{22}Cl_2O_4$ (481.39)	189–191	80	480 (Cl-clusters)
8a	$C_{27}H_{14}Cl_4O_7$ (592.34)	224	90	590 (Cl-clusters)
8b	$C_{27}H_{16}Cl_2O_7$ (523.34)	183–185	83	522 (Cl-clusters)

Table 3. *Elemental analyses of the prepared compounds*

Com-pound	Purification method	Calc. %			Found %		
		C	H	Halogen	C	H	Halogen
2a	Sublimation (153°/0.01 Torr)	50.74	4.66	18.79 (Cl)	50.92	4.77	18.83 (Cl)
2b	Crystallization (ether)	–	–	–	–	–	–
2c	Sublimation (158°/0.01 Torr)	41.22	3.88	34.28 (Br)	41.06	3.82	34.13 (Br)
3a	Sublimation (210°/0.02 Torr)	58.61	3.66	26.01 (Cl)	58.75	3.77	26.07 (Cl)
3ab	Sublimation (192°/0.01 Torr)	60.92	3.90	4.76 (F) 18.20 (Cl)	61.06	3.81	4.83 (F) 18.60 (Cl)
3ac	Sublimation (205°/0.01 Torr)	–	–	–	–	–	–
3ba	Sublimation (195°/0.01 Torr)	63.75	4.00	10.08 (F) 9.40 (Cl)	63.67	4.03	9.96 (F) 9.19 (Cl)
3bc	Sublimation (203°/0.01 Torr)	–	–	–	–	–	–
3ca	Crystallization (benzene)	–	–	–	–	–	–
3cb	Crystallization (benzene)	–	–	–	–	–	–
4a	Sublimation (185°/0.01 Torr)	64.01	4.29	18.89 (Cl)	64.12	4.27	18.76 (Cl)
4b	Sublimation (167°/0.01 Torr)	70.17	4.70	11.10 (F)	70.10	4.74	11.06 (F)
4c	Sublimation (177°/0.01 Torr)	70.48	5.02	10.40 (Cl)	70.34	5.06	10.60 (Cl)
4d	Sublimation (175°/0.01 Torr)	74.06	5.27	5.85 (F)	74.00	5.16	5.71 (F)
5a	Sublimation (190°/0.01 Torr)	–	–	–	–	–	–
5b	Chromatography (silica gel, $CHCl_3$/MeOH 7:3)	–	–	–	–	–	–
7a	Sublimation (213°/0.02 Torr)	58.90	3.63	25.81 (Cl)	58.92	3.61	25.70 (Cl)
7b	Sublimation (190°/0.01 Torr)	–	–	–	–	–	–
7c	Chromatography (silica gel, EtOAc)	–	–	–	–	–	–
7d	Crystallization (ether)	67.36	4.57	14.76 (Cl)	67.30	4.53	14.67 (Cl)
8a	Sublimation (217°/0.02 Torr)	54.91	2.37	23.72 (Cl)	55.04	2.30	23.69 (Cl)
8b	Chromatography (silica gel, $CHCl_3$/MeOH 7:3)	–	–	–	–	–	–

Since the conversion of the CH_2-bridges to carbonyl functions increases the chelating ability of compounds **3a** and **4b** [2b], we prepared **5a** and **5b** by oxidation of **3a** and **4b** (CrO_3/Ac_2O), followed by hydrolysis of the ester groups [2].

The aforementioned compounds *(Table 1)* with three phenolic units showed biological activity. It therefore became of interest to prepare 5,5′-dihalo-3,3′-bis-(5-halo-2-hydroxy-α-tolyl)-2,2′-dihydroxydiphenylmethanes **7a–d** and their derivatives **8a–b**.

5,5′-Dichloro-2,2′-dihydroxy-3,3′-dihydroxymethyldiphenylmethane (**6**) [4] derived from 5,5′-dichloro-2,2′-dihydroxydiphenylmethane was condensed with *p*-halophenols **1a–c**, by the procedure described for the preparation of **3a**, to give the expected phenolic compounds **7a–c**. Conversion of **7c** to **7d** was achieved by means of Zn/KOH in excellent yield. Compounds **7a** and **7d** were oxidized (CrO_3/Ac_2O) to the corresponding keto esters which were hydrolyzed with sodium hydroxide to the hydroxy ketones **8a–b**.

All compounds prepared **3–8** were tested *in vitro* against *S. aureus, E. coli, C. albicans* and *Ps. aeruginosa* up to 128 μg/ml. Most of them showed notable activity against the above pathogenic microorganism *(Table 1)*.

The results in *Table 1* suggest that in addition to chelating abilities, a variety of other factors, namely the nature and position of halogen atoms, influence antimicrobial activity of molecules. Studies are already underway to establish a definite structure-activity relationship.

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Experimental Part

The general procedures can be illustrated in the preparation of compounds **2a** and **3a**.

4-Chloro-2,6-bis(hydroxymethyl)phenol (**2a**). To an aqueous solution of NaOH (25%, 50 ml) containing *p*-chlorophenol (**1a**, 12.8 g, 0.1 mol) and methanol (25 ml) was added formaldehyde (38%, 90 ml). The reaction mixture was shaken at 60–80° for 1 h and then was allowed to stand at RT. for 24 h. A mixture of water (50 ml) and acetic acid (15 ml) was added. The reaction mixture was stirred for 4 h at 25° to give a yellow precipitate. Filtration gave 14 g (80%) of **2a**.

4-Chloro-2,6-bis(5-chloro-2-hydroxy-α-tolyl)phenol (**3a**). To a solution of compounds **2a** (14 g, 0.07 mol) and **1a** (56 g, 0.43 mol) in methanol (140 ml) was added conc. hydrochloric acid (28 ml). The reaction mixture was left at RT. for 12 h. The solution was evaporated and the residue was suspended in boiling water to dissolve unreacted *p*-chlorophenol. The precipitate was filtered off, washed with water and dried to give 22.7 g (78%) of **3a**.

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