59. The Synthesis of Polyfunctional Aromatic Ring Systems. Structural Analogues of Phloroglucides, Aranciamycin, Cryptosporin and Terramycin[1])

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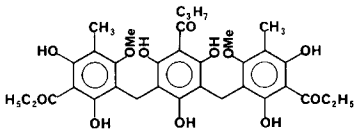
(23.X.80)

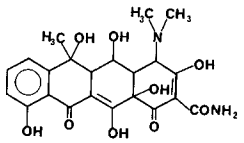
Summary

The synthesis of the title compounds is described. Some of the compounds prepared were found to be active against a number of pathogenic microorganisms *in vitro*.

A significant feature common to several classes of antibiotics is the presence of functional groups in a suitable spatial arrangement for chelate formation with metal ions of enzymes [1]. Examples include phloroglucides [2] (*i.e.* trisaspidinol), aranciamycin [3], cryptosporin [4] and terramycin [5]. These compounds show varying degrees of activity against gram-positive bacteria as well as other microorganisms.



Trisaspidinol



Terramycin

In this paper we describe the synthesis of models and structural analogues possessing functionality similarly capable of chelate formation.

As a model, *p*-chlorophenol (**1a**) was converted to a mixture of 5,5′-dichloro-2,2′-dihydroxy-diphenyl-methane (**2a**) and 4-chloro-2,6-bis(5′-chloro-2′-hydroxy-α-tolyl)phenol (**2′a**) using the *Baeyer* condensation method [6]. The mixture was separated into its constituents by crystallization (water). The hydroxy functions in **2a** were acylated with acetic anhydride to give 2,2′-diacetoxy-5,5′-dichloro-diphenyl-methane (**2a**$_1$). Reaction with aluminium chloride [7] gave 3,3′-diacetyl-5,5′-dichloro-2,2′-dihydroxy-diphenyl-methane (**2a**$_2$) in 85% yield. The structure of

[1]) Key Words. Tetracycline-like compounds. Benzophenone and diphenylmethane derivatives. Phloroglucide analogues.

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2a$_2$ and the spatial disposition of the two substituted phenyl rings were confirmed by X-ray analysis [8] (see *Fig.*).

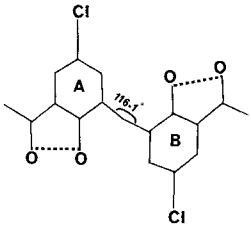


Figure. *The structure of* **2a**$_2$

Next, *p*-fluorophenol (**1b**), *p*-bromophenol (**1c**), hydroquinone (**1d**) and *N*-(*p*-hydroxyphenyl)acetamide (**1e**) were transformed to the corresponding diphenylmethanes **2b–e** and **2′b–e** by means of CH_2O/H_2SO_4 in methanol, or acetic acid in the case of **2d–e** and **2′d–e**. Separation of the two- and three-aromatic-ring systems was achieved by crystallization with appropriate solvents (see exper. part). Acylation of the hydroxy groups in **2e** and **2′b** with acetic anhydride gave esters **2e**$_1$ and **2′b**$_1$ in quantitative yield.

Since compounds **2′a** and **2′b** exhibited an interesting anti-bacterial activity, it was decided to prepare their analogues **2′d**$_1$ and **2′f**. Compound **2′d**$_1$ was obtained by mild hydrolysis of **2′d** with 6 mol-equiv. of NaOH in methanol as a 1% solution at room temperature. Conversion of **2′c** to **2′f** was achieved by means of Zn/KOH in an excellent yield. It should be noted that all attempts to convert *p*-iodophenol to the corresponding diphenyl methane failed.

Compounds **2d**, **2e**$_1$, **2′b**$_1$ and **2′d** were subjected to *Fries* rearrangement [9] to give the corresponding phenolic ketones **3d**, **3e**, **3′b** and **3′d** in good yield. Reaction with acetic anhydride gave the expected esters **3d**$_1$, **3e**$_1$, **3′b**$_3$ and **3′d**$_1$ in quantitative yield. 2,6-Bis(3-acetyl-5-fluoro-2-hydroxy-α-tolyl)-4-fluorophenol (**3′b**) was reduced with zinc dust in 40% KOH-solution at boiling temperature to give 2,6-bis[5′-fluoro-2′-hydroxy-3′-(1-hydroxy ethyl)-α-tolyl]-4-fluorophenol (**3′b**$_1$) in 92% yield. The acetyl groups in **3′b** were also oxidized with sodium hypoiodite to give **3′b**$_2$ in a good yield. The proposed structures of the fluoro derivatives were confirmed by ^{13}C-NMR. spectra of **3′b** and **3′b**$_2$, in which the chemical shifts were assigned to the various C-atoms, using the information supplied by the C,F-coupling constants as well as the extensive ^{13}C-NMR. literature for substituted benzenes [10]. We observed a C,F-coupling constant of 1.9–2.2 Hz from the above compounds. It is quite clear, from the C,F-coupling constants which have been previously determined for fluorobenzene $^4J(C,F) = 3.3$ Hz [11] and *m*-fluorobenzoic acid $^4J(C,F)(CO) = 2.2$ Hz [12], that the acetyl groups as well as the carboxyl functions are four bonds from the F-atoms. This puts them in *m*-position to the F-atoms. The observed carbonyl absorption at $\delta = 205.2$ ppm was very close to that observed for *o*-hydroxy-acetophenone, $\delta = 204.4$ ppm [13]. The absorption of the acid carbonyl groups at $\delta = 171.2$ ppm was also very close to those obtained for *o*-hydroxy-benzoic acid, $\delta = 171.8$ ppm and *m*-fluorobenzoic acid, $\delta = 171.3$ ppm [12].

It was, therefore, concluded that the acetyl groups as well as the carboxyl functions must be *ortho* to the hydroxy groups. Most importantly the ^{13}C-NMR.

spectra established the position of the CH_2-bridge as *ortho* to the hydroxy groups. If the CH_2 bridge was *ortho* to the fluorines, then we should observe a noticeable C,F-coupling constant of 7 Hz [11] [12]. This was not observed for the CH_2-resonance of either compounds. The ^{13}C-NMR. data for compounds **3'b** and **3'b$_2$** are given in *Table 1*.

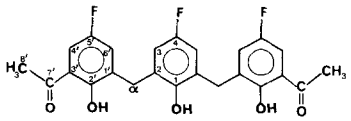
Previous experiments have verified that the presence of heavy metal ions play an important role in the effect and mechanism of action of certain antibiotics against the growth of some bacteria [14].

Based on the results of the previous experiments with chelating agents [15], the stronger the affinity of compounds for chelation with metal ions, the stronger will be their bacteriostatic action [16]. Therefore it was decided to prepare compounds with stronger tendency for chelation with cations.

The methylene groups in **2d**, **2e$_1$**, **2'b$_1$** and **2'd** were oxidized to carbonyl groups by means of chromium trioxide in acetic anhydride to give **4d**, **4e**, **4'b** and **4'd** in excellent yield. Hydrolysis of ester groups in **4'b** and **4'd** gave the corresponding hydroxy ketones **4'b$_1$** in 90% yield and **4'd$_1$** in 15% only. 2,2',5,5'-Tetraacetoxy-benzophenone (**4d**), 5,5'-diacetamido-2,2'-diacetoxy-benzophenone (**4e**) and 1-acetoxy-2,6-bis(2'-acetoxy-5'-fluorobenzoyl)-4-fluorobenzene (**4'b**) were subjected to *Fries* rearrangement [9], and the resulting phenolic ketones **5d**, **5e**, and **5'b** were obtained in good yield, and then were acylated to give **5d$_1$**, **5e$_1$** and **5'b$_1$** in nearly quantitative yield.

In the case of compounds **2d**, **2e$_1$** and **2'b$_1$** there were no *meta*-directing substituents on the rings to force the *Fries* rearrangement [12] to produce the desired compounds **3d**, **3e** and **3'b**; in order to confirm their structures, it was decided to

Table 1. *^{13}C-NMR. spectra* (20 MHz, DMSO-d$_6$)



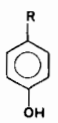
3'b			**3'b$_2$** (COCH$_3$ → COOH)		
C-Atom	δ (ppm)	Hz	C-Atom	δ (ppm)	Hz
C(5')	153.9*d*	^1J(C,F) = 236	C(5')	153.9*d*	^1J(C,F) = 236
C(4')	124.0*d*	^2J(C,F) = 24	C(4')	124.0*d*	^2J(C,F) = 23.6
C(3')	129.7*d*	^3J(C,F) = 7	C(3')	129.3*d*	^3J(C,F) = 6.6
C(2')	155.8*s*		C(2')	155.7*s*	
C(1')	118.3*d*	^3J(C,F) = 7	C(1')	112.9*d*	^3J(C,F) = 6.6
C(6')	114.8*d*	^2J(C,F) = 23	C(6')	113.2*d*	^2J(C,F) = 23.6
C(α)	28.4*s*		C(α)	28.8*s*	
C(7')	205.2*d*	^4J(C,F)(CO) = 2.2	C(7')	171.2*d*	^4J(C,F)(CO) = 1.9
C(8')	27.2*s*		C(4)	150.1*d*	^1J(C,F) = 239
C(4)	150.1*d*	^1J(C,F) = 239	C(3)	111.6*d*	^2J(C,F) = 22.7
C(3)	111.2*d*	^2J(C,F) = 22.7	C(2)	110.8*d*	^3J(C,F) = 7.3
C(2)	110.8*d*	^3J(C,F) = 7.3	C(1)	149.9*s*	
C(1)	149.9*s*				

oxidize their corresponding esters **3d**$_1$, **3e**$_1$ and **3′b**$_3$ with chromium trioxide in acetic anhydride at reflux temperature. Esters **3d**$_1$, **3e**$_1$ and **3′b**$_3$ were transformed to the corresponding acetoxy ketones **5d**$_1$, **5e**$_1$ and **5′b**$_1$, and were found to be identical to those obtained before. These results confirmed the position of the acetyl groups in compounds **3d**, **3e** and **3′b**.

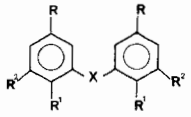
2,6-Bis(3′-acetyl-5′-fluoro-2′-hydroxybenzoyl)-4-fluorophenol (**5′b**) was transformed to the corresponding acid **5′b**$_2$ by means of sodium hypoiodite in a good yield.

The aforementioned compounds *(Table 1)* showed biological activity. It therefore became of interest to prepare 3,3′-bis(5″-halo-2″-hydroxy-α-tolyl)-2,2′-dihydroxy (or 2,2′-diacetoxy)-5,5′-dihalodiphenyl-methanes **6a**–**b**$_1$ and their derivatives, which would allow the synthesis of cyclized compounds **8a**–**d**$_1$ [19]. This will be described in another paper.

5,5′-Dihalo-2,2′-dihydroxy-diphenyl-methanes **2a** and **2b** derived from *p*-halophenols **1a**–**b** were condensed with formaldehyde in methanol at 0–5° to give the expected phenolic compounds **6a** and **6b** in good yield. In the case of **2b** a negligible quantity of polymeric compounds **6′** was isolated. Compounds **6a** and



1a R = Cl
1b R = F
1c R = Br
1d R = OH
1e R = NHAc

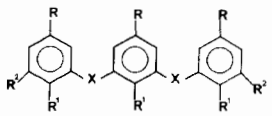


2a R = Cl, R^1 = OH, R^2 = H, X = CH_2
2a$_1$ R = Cl, R^1 = OAc, R^2 = H, X = CH_2
2a$_2$ R = Cl, R^1 = OH, R^2 = Ac, X = CH_2
2b R = F, R^1 = OH, R^2 = H, X = CH_2
2c R = Br, R^1 = OH, R^2 = H, X = CH_2
2d R = OAc, R^1 = OAc, R^2 = H, X = CH_2
2e R = NHAc, R^1 = OH, R^2 = H, X = CH_2
2e$_1$ R = NHAc, R^1 = OAc, R^2 = H, X = CH_2

3d R = OH, R^1 = OH, R^2 = Ac, X = CH_2
3d$_1$ R = OAc, R^1 = OAc, R^2 = Ac, X = CH_2
3e R = NH_2, R^1 = OH, R^2 = Ac, X = CH_2
3e$_1$ R = NHAc, R^1 = OAc, R^2 = Ac, X = CH_2

4d R = OAc, R^1 = OAc, R^2 = H, X = CO
4e R = NHAc, R^1 = OAc, R^2 = H, X = CO

5d R = OH, R^1 = OH, R^2 = Ac, X = CO
5d$_1$ R = OAc, R^1 = OAc, R^2 = Ac, X = CO
5e R = NH_2, R^1 = OH, R^2 = Ac, X = CO
5e$_1$ R = NHAc, R^1 = OAc, R^2 = Ac, X = CO

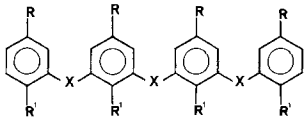


2′a R = Cl, R^1 = OH, R^2 = H, X = CH_2
2′b R = F, R^1 = OH, R^2 = H, X = CH_2
2′c R = Br, R^1 = OH, R = H, X = CH_2
2′d R = OAc, R^1 = OAc, R^2 = H, X = CH_2
2′e R = NHAc, R^1 = OH, R^2 = H, X = CH_2
2′b$_1$ R = F, R^1 = OAc, R^2 = H, X = CH_2
2′d$_1$ R = OH, R^1 = OH, R^2 = H, X = CH_2
2′f R = H, R^1 = OH, R^2 = H, X = CH_2

3′b R = F, R^1 = OH, R^2 = Ac, X = CH_2
3′b$_1$ R = F, R^1 = OH, R^2 = $CHOHCH_3$, X = CH_2
3′b$_2$ R = F, R^1 = OH, R^2 = COOH, X = CH_2
3′b$_3$ R = F, R^1 = OAc, R^2 = Ac, X = CH_2
3′d R = OH, R^1 = OH, R^2 = Ac, X = CH_2
3′d$_1$ R = OAc, R^1 = OAc, R^2 = Ac, X = CH_2

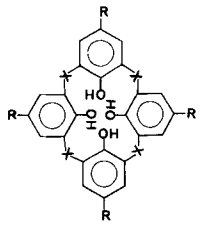
4′b R = F, R^1 = OAc, R^2 = H, X = CO
4′b$_1$ R = F, R^1 = OH, R^2 = H, X = CO
4′d R = OAc, R^1 = OAc, R^2 = H, X = CO
4′d$_1$ R = OH, R^1 = OH, R^2 = H, X = CO

5′b R = F, R^1 = OH, R^2 = Ac, X = CO
5′b$_1$ R = F, R^1 = OAc, R^2 = Ac, X = CO
5′b$_2$ R = F, R^1 = OH, R^2 = COOH, X = CO

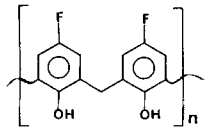


6a R = Cl, R^1 = OH, X = CH_2
6a$_1$ R = Cl, R^1 = OAc, X = CH_2
6b R = F, R^1 = OH, X = CH_2
6b$_1$ R = F, R^1 = OAc, X = CH_2

7a R = Cl, R^1 = OAc, X = CO
7a$_1$ R = Cl, R^1 = OH, X = CO
7b R = F, R^1 = OAc, X = CO
7b$_1$ R = F, R^1 = OH, X = CO



8a R = Cl, X = CH_2
8a$_1$ R = Cl, X = CO
8b R = F, X = CH_2
8b$_1$ R = F, X = CO
8c R = Br, X = CH_2
8c$_1$ R = Br, X = CO
8d R = H, X = CH_2
8d$_1$ R = H, X = CO



6′

6b were treated with acetic anhydride to give the corresponding esters **6a$_1$** and **6b$_1$** in nearly quantitative yield. Reaction with chromium trioxide in acetic anhydride gave 50 and 85% of keto esters **7a** and **7b**, respectively. The ester functions in **7a** and **7b** were hydrolyzed with sodium hydroxide to the corresponding hydroxy groups of **7a$_1$** and **7b$_1$** in an excellent yield.

It should be noted that most of these compounds have a strong tendency for chelation with metal ions (*i.e.* $FeCl_3$).

All compounds prepared **2a–7b$_1$** were tested *in vitro* against *S. aureus, E. coli, C. albicans* and *Ps. aeruginosa* up to levels as high as 128 μg/ml. Some of them showed notable activity against the above pathogenic microorganisms *(Table 2)*.

Table 2. *Minimal Inhibitory Concentration μg/ml*

No.	Compound	*S. aureus*	*E. coli*	*C. albicans*	*Ps. aeruginosa*
1	**2a**	100	–	–	–
2	**2b**	128	–	–	–
3	**2′a**	0.30	15	15	–
4	**2′b**	1–1.3	100	15–30	–
5	**2′b$_1$**	1.3–2.7	–	–	–
6	**2′d$_1$**	100	128	64	–
7	**2′f**	5.5	> 128	–	–
8	**3d**	22	–	–	–
9	**3′b$_1$**	30	–	> 128	–
10	**3′b$_2$**	11–15	30	64	–
11	**3′d**	5.5	100	33	–
12	**4′b**	15–30	–	–	–
13	**4′b$_1$**	15	–	–	–
14	**5′b$_2$**	64	> 128	100	64
15	**6a**	0.60	11	15	–
16	**6a$_1$**	100	–	–	–
17	**6b**	1.5	100	> 128	–
18	**6′**	3	–	–	–
19	**7a**	6	–	–	–
20	**7a$_1$**	0.65	> 128	100	–
21	**7b$_1$**	100	–	–	–

It should be noted that some of the cyclized compounds **8**, as well as their derivatives prepared, exhibited very interesting anti-microbial activity which will be reported in another paper.

Experimental Part

1. *General procedures.* See [17] [18]. Abbreviations: i.V. = in vacuum, RT. = room temperature.

2. *Preparation of 5,5'-dichloro-2,2'-dihydroxy-diphenyl-methane* (**2a**), *4-chloro-2,6-bis(5'-chloro-2'-hydroxy)phenol* (**2'a**) *and 2,2'-diacetoxy-5,5'-dichloro-diphenyl-methane* (**2a**$_1$). *p*-Chlorophenol (5 g, 0.01 mol) was dissolved in 12 ml of methanol. Distilled water was added (1 ml). The solution was cooled to $-5°$ and stirred. Concentrated sulfuric acid (40 ml) was added dropwise. Formalin (38%, 9 ml) was then added over a period of 10 min at -5 to 0°. The stirring was continued for 2 h at the same temperature. The solution was left overnight and then was poured into 500 ml of cold water. The crystals were filtered off, washed with water, dried, and washed with hot water, to dissolve **2a**. Then it was dried and washed with boiling CCl_4 to dissolve the remaining **2a** and **2'a** from the unidentified insoluble part. The mixture of **2a** and **2'a** was treated with cold $CHCl_3$ to dissolve **2a**. Filtration gave 3 g (20%) of **2'a**; m.p. 225–230° (after sublimation at 210°/0.02 Torr, m.p. 240–241°). – IR. (KBr): 3400*s*, 2940*m*, 1591*w*, 1492*s*, 1210*m* and 995*m*. – MS.: 408 (M^+, Cl clusters).

$C_{20}H_{15}Cl_3O_3$ (409.50) Calc. C 58.61 H 3.66 Cl 26.01% Found C 58.75 H 3.77 Cl 26.07%

The total yield collected of **2a** was 70%; m.p. 174–175° (Lit. [6] m.p. 176°). **2a** was treated with boiling acetic anhydride to give **2a**$_1$ quantitatively. This was characterized by its hydrolysis to **2a** in 90% yield.

3. *Preparation of 5,5'-difluoro-2,2'-dihydroxy-diphenyl-methane* (**2b**). *4-fluoro-2,6-bis(5'-fluoro-2'-hydroxy-α-tolyl)phenol* (**2'b**) *and his acetyl derivative* (**2'b**$_1$). Concentrated sulfuric acid (160 ml) was added dropwise to a solution of 4-fluorophenol (30 g, 0.26 mol) in 80 ml of methanol while stirring at $-10°$. A solution of 8 ml of 38% formalin in 10 ml of methanol was added dropwise over a period of 4 h. The stirring was continued for another 2 h at -10 to 5°. The solution was then poured in a beaker containing 800 ml of cold water. The white precipitate was filtered off, washed with water and dried. The filtrate was left overnight to give a crystalline white precipitate (4 g of **2b**); the filtrate was evaporated to give another 2 g of **2b**. The crude precipitate (m.p. 95–120°) was suspended in hot water and some of it became oily. This oil was shown to be **2'b**, which was crystallized from methanol/water, m.p. 190–194°. The water solution was evaporated to give 4.5 g of **2b**; m.p. 110–111°. The total yield of **2b** was 10.5 g (32%) of **2'b** was 15.5 g (47%).

Compound **2b**. After sublimation at 100–105°/0.02 Torr, m.p. 110–111°. – IR. (KBr): 3400*s*, 2940*m*, 1590*m*, 1490*s*, 1210*m* and 995*w*. – MS.: 236 (M^+).

$C_{13}H_{10}F_2O_2$ (236.19) Calc. C 66.10 H 4.19 F 16.10% Found C 66.20 H 4.24 F 15.98%

Compound **2'b**. After sublimation at 160–170° and 0.02 Torr, m.p. 193–194°. – IR. (KBr): 3400*s*, 2940*m*, 1590*m*, 1490*s*, 1210*m* and 995*m*. – MS.: 360 (M^+).

$C_{20}H_{15}F_3O_3$ (360.20) Calc. C 66.35 H 4.13 F 15.83% Found C 66.66 H 4.16 F 15.67%

Reaction of **2'b** (5 g, 0.014 mol) with acetic anhydride (60 ml) in the presence of one drop H_2SO_4 at reflux temp. after 1 h gave 6.2 g (92%) of **2b**$_1$, m.p. 110–112°. – IR. (KBr): 3100*w*, 2940*w*, 1750*s*, 1168*s*, 1590*w*, 1490*m*, 1210*m* and 995*w*. – MS.: 486 (M^+).

4. *Preparation of 5,5'-dibromo-2,2'-dihydroxy-diphenyl-methane* (**2c**) *and 4-bromo-2,6-bis(5'-bromo-2'-hydroxy-α-tolyl)phenol* (**2'c**). Analogously to Chapt. 3. Crystallization from methanol/water gave 80% of **2c** and 10% of **2'c**.

Compound **2c**. M.p. 183–185°. – IR. (KBr): 3400*m*, 1590*s* and 996*w*.

$C_{13}H_{10}Br_2O_2$ (358.21) Calc. C 43.75 H 2.80% Found C 43.70 H 2.96%

Compound **2'c**. M.p. 263–264°. – IR. (KBr): 3400*m*, 1590*s* and 996*m*.

$C_{20}H_{15}Br_3O_3$ (546.20) Calc. C 44.19 H 2.76 Br 44.19% Found C 44.10 H 2.81 Br 44.08%

5. *Preparation of 2,6-bis(2'-hydroxy-α-tolyl)phenol* (**2'f**). Compound **2'c** (2 g, 0.0036 mol) was dissolved in 40 ml of 40% aqueous KOH-solution at boiling temp. with stirring. Zinc dust (7 g) was added during 1 h. The stirring was continued for another 3 h at the same temperature. Then the mixture was cooled, filtered and acidified to give 1 g (88%) of **2'f**, m.p. 160–161°. – MS.: 306 (M^+).

$C_{20}H_{18}O_3$ (306.34) Calc. C 78.43 H 5.88% Found C 78.36 H 5.82%

6. *Preparation of 2,2',5,5'-tetraacetoxy-diphenyl-methane* (**2d**), *1,4-diacetoxy-2,6-bis(2',5'-diacetoxy-α-tolyl)benzene* (**2'd**) *and 1,4-dihydroxy-2,6-bis(2',5'-dihydroxy-α-tolyl)benzene* (**2'd$_1$**). Hydroquinone (11 g, 0.10 mol) was dissolved in 100 ml of hot glacial acetic acid at 45°. Formalin (38%, 2 g, 0.06 mol) was added dropwise at RT. A solution of 1 g conc. sulfuric acid in 10 ml of acetic acid was added during 15 min while stirring. After stirring for another 30 h, acetic anhydride (100 ml) was added. After 30 min the reaction mixture was filtered and the filtrate was poured into 800 ml of cold water and stirred. The resulting white precipitate was filtered, washed with water and dried to give 20 g of crude product, m.p. 110–120°. The crude product was suspended in 200 ml of methanol at 45–50°, while stirring with a glass rod for 5 min to dissolve 1,4-diacetoxybenzene. Then it was filtered and the precipitate was suspended in 150 ml of acetone at 50–60°. The polymeric compounds were separated by filtration and the filtrate was evaporated to give a precipitate. This was suspended in 50 ml of diethyl ether to dissolve the remainder of 1,4-diacetoxybenzene. After filtration, the product was shown to be a mixture of **2d** and **2'd**, which were separated by crystallization with boiling methanol.

Compound **2d**. Yield: 30%, m.p. 178–180°. – IR. (KBr): 3000*m*, 1750*s*. – MS.: 400 (M^+).

$C_{21}H_{20}O_8$ (400.37) Calc. C 63.00 H 5.00% Found C 62.82 H 4.93%

Compound **2'd**. Yield: 20%, m.p. 238–240°. – IR. (KBr): 3000*m*, 1750*s*. – MS.: 606 (M^+).

$C_{32}H_{30}O_{12}$ (606.56) Calc. C 63.36 H 4.95% Found C 63.24 H 5.02%

Separation of **2d** and **2'd** was also achieved by sublimation, in which **2d** was sublimed at 165–170°/0.05 Torr and **2'd** was sublimed at 231–233°/0.05 Torr. Hydrolysis of **2'd** with 6 mol-equiv. of NaOH in methanol gave **2'd$_1$** in 40% yield, which was characterized by reesterification.

7. *Preparation of 5,5'-diacetamido-2,2'-dihydroxy-diphenyl-methane* (**2e**), *4-acetamido-2,6-bis(5'-acetamido-2'-hydroxy-α-tolyl)phenol* (**2e** and **2e$_1$**). Analogously to chapt. 6 from *p*-hydroxy-phenylacetamide. Chromatography of the crude product with silica gel and elution with $CHCl_3$/MeOH 8:2 gave **2e** in 30% and **2'e** in 10% yield.

Compound **2e**. M.p. 213–215°. – IR. (KBr): 3400*s* and 1625*s*. – MS.: 314 (M^+).

$C_{17}H_{18}N_2O_4$ (314.33) Calc. C 64.90 H 5.75 N 8.80% Found C 64.83 H 5.98 N 8.61%

Compound **2'e**. M.p. 298–300°. – IR. (KBr): 3400*s* and 1625*s*. – MS.: 477 (M^+).

Compound **2e$_1$** was prepared in 80% yield by treatment of **2e** with boiling Ac_2O for 2 h. M.p. 170–173°. Chromatography with silica gel and elution with CH_2Cl_2/MeOH 9:1 gave **2e$_1$** in 70% yield, m.p. 172–174°. – IR. (KBr): 3350*s*, 1750*s* and 1651*s*. – MS.: 398 (M^+).

$C_{21}H_{22}N_2O_6$ (398.40) Calc. C 63.29 H 5.52 N 7.03% Found C 63.11 H 5.66 N 6.98%

8. *Preparation of* **2a$_2$**, **3d**, **3e**, **3'b** *and* **3'd**. Compounds **2a$_1$**, **2d**, **2e$_1$**, **2'b$_1$** and **2'd** were submitted to identical reaction conditions which will be described for **2'b$_1$** only.

2,6-Bis(3'-acetyl-5'-fluoro-2'-hydroxy-α-tolyl)-4-fluorophenol (**3'b**). Anhydrous aluminium chloride (15.0 g, 0.112 mol) in a 250 ml flask was heated in an oil bath at 115° for 15 min and stirred with a glass rod. Compound **2'b$_1$** (7 g, 0.014 mol) was added. The temp. was allowed to rise to 150–155°. The mixture was kept at this temp. for 20 min. After cooling, it was added to a mixture of 500 g crushed ice and 100 ml of conc. hydrochloric acid. After 6 h a yellow precipitate was obtained. This was filtered off, washed with water and dried to give 6.2 g (99%) of crude product. Crystallization with ethanol gave 5.2 g (83%) of **3'b**, m.p. 189–191°. It gave a violet color with $FeCl_3$. – IR. (KBr): 3400*m*, 1650*s*, 1168*s*, 1360*m*, 1200*s* and 780*w*. – MS.: 444 (M^+).

$C_{24}H_{19}F_3O_5$ (444.25) Calc. C 64.86 H 4.27 F 12.83% Found C 65.01 H 4.36 F 12.79%

Compound **3d** was purified by chromatography on silica gel using $CHCl_3$ as eluent to yield 50% of pure **3d**, m.p. 227–228°. – IR. (KBr): 3400*s* and 1610*s*. – MS.: 316 (M^+).

$C_{17}H_{16}O_6$ (316.30) Calc. C 64.55 H 5.06% Found C 64.46 H 5.24%

Compound **3'd** was obtained in 10% yield by the same purification method as **3d**. M.p. 301–302. – MS.: 438 (M^+).

Compound **3e** was purified by chromatography on alumina with $CHCl_3$: yield: 83%, m.p. 233–234°. – IR. (KBr): 3350*s* and 1650*s*. – MS.: 314 (M^+).

$C_{17}H_{18}N_2O_4$ (314.33) Calc. C 64.90 H 5.75 N 8.80% Found C 64.78 H 5.65 N 8.49%

Compound $\mathbf{2a}_2$ was obtained by the same method in 80% yield, m.p. 202–203°. Its structure was confirmed by X-ray analysis [8].

9. *Preparation of 2,6-Bis[5'-fluoro-2'-hydroxy-3'-(1-hydroxy-ethyl)-α-tolyl]-4-fluorophenol* ($\mathbf{3'b}_1$). Methyl ketone **3'b** (2 g, 0.004 mol) was dissolved in 80 ml of 40% aqueous KOH-solution at 100°. Zinc dust (15 g) was added gradually during 1 h. The mixture was kept at the same temperature for another 2 h. The solution was then cooled and filtered. The filtrate was acidified with hydrochloric acid to give a white precipitate, m.p. >350°. This compound was presumed to be an organometallic complex which was refluxed in 10% aqueous HCl-solution (30 ml) for 3 h. The resulting precipitate was filtered off, washed with water, dried. Chromatography with silica gel and CH_2Cl_2 gave compound $\mathbf{3'b}_1$ in 70% yield, m.p. 100–102°. It gave a violet color with $FeCl_3$. – IR. (KBr): 3400*m*, 2940*w*, 1168*s*, 1200*s* and 840*w*. – MS.: 448 (M^+).

$C_{24}H_{23}F_3O_5$ (448.42) Calc. C 64.28 H 4.71% Found C 64.13 H 5.01%

10. *Preparation of* $\mathbf{3d}_1$, $\mathbf{3e}_1$, $\mathbf{3'b}_3$ *and* $\mathbf{3'd}_1$. All compounds were obtained in an identical manner in nearly quantitative yield. Their spectra were similar except for the variations due to aromatic substituents. All their mass spectra showed M^+. The following is a representative procedure.

2,2',5,5'-Tetraacetoxy-3,3'-diacetyl-diphenyl-methane ($\mathbf{3d}_1$). Methyl ketone **3d** (2 g, 0.006 mol) was dissolved in 70 ml of acetic anhydride. The solution was refluxed for 2 h. Then it was cooled and poured into 500 ml of cold water. A dark oily precipitate was obtained. After 7 h the precipitate was dissolved in acetone; the solution was treated with charcoal, filtered and his volume reduced to 30 ml. By adding water a white precipitate ($\mathbf{3d}_1$) was obtained in 70% yield, m.p. 110–113°. – IR. (KBr): 1748*s* and 1659*s*. – MS.: 480 (M^+).

11. *Preparation of* **4d**, **4e**, **4'b**, **4'd**, $\mathbf{4'b}_1$ *and* $\mathbf{4'd}_1$. Compounds **2d**, $\mathbf{2e}_1$, $\mathbf{2'b}_1$ and **2'd** were submitted to identical reaction conditions which will be described for $\mathbf{2'b}_1$ only.

1-Acetoxy-2,6-bis(2'-acetoxy-5'-fluorobenzoyl)-4-fluorobenzene (**4'b**). Compound $\mathbf{2'b}_1$ (5 g, 0.01 mol) was dissolved in 100 ml of acetic anhydride at r.t. and stirred. Chromium trioxide (4 g) was added over a period of 1 h at the same temperature. The reaction mixture was stirred for 2 h at 30° and for another 2 h at reflux temperature. At this point, the brown color of the solution was turned to green. Then it was cooled and poured into 600 ml of cold water. The oily product was crystallized after 24 h. The crystals were filtered off, washed with water and dried to give the crude product **4'b**. Crystallization with ether gave 5 g (97%) of **4'b**, m.p. 88–90°. – IR. (KBr): 3100*w*, 1750*s*, 1650*s*, 1168*s*, 1590*m*, 1490*w*, and 995*w*. – MS.: 514 (M^+).

Treatment of **4'b** with 15% aqueous NaOH-solution, after neutralization with hydrochloric acid, gave $\mathbf{4'b}_1$ in 90% yield. Sublimation at 145–150°/0.02 Torr gave $\mathbf{4'b}_1$, m.p. 154–155°. Upon treatment with $FeCl_3$ a violet color was produced. – IR. (KBr): 3100*w*, 1610*s*, 1168*s*, 1590*m*, 1490*w*, 1210*m* and 995*w*. – MS.: 388 (M^+).

$C_{20}H_{11}F_3O_5$ (388.28) Calc. C 62.00 H 2.87 F 14.42% Found C 61.88 H 2.84 F 14.60%

Compound **4'd** was obtained by the same method. Chromatography on silica gel with $CHCl_3$ gave 80% of product, m.p. 290–292°. – IR. (KBr): 1750*s*, 1650*m*, 1169*m* and 655*s*. – MS.: 634 (M^+).

Hydrolysis of **4'd** to $\mathbf{4'd}_1$ was achieved with 6 mol-equiv. of NaOH in methanol as a 1% aqueous solution.

Compound $\mathbf{4'd}_1$, m.p. > 300°, was characterized by reesterification with acetic anhydride.

Compound **4d** was purified by the same purification method as **4'd**, m.p. 219–220°. – IR. (KBr): 1750*s* and 655*s*. – MS.: 414 (M^+).

$C_{21}H_{18}O_9$ (414.35) Calc. C 60.86 H 4.30% Found C 60.72 H 4.28%

Compound **4e** was chromatographed on silica gel with CH_2Cl_2/MeOH 9:1 and pure **4e** was obtained in 70% yield, m.p. 152–153°. – IR. (KBr): 3350*s*, 1755*s* and 1700*s*. – MS.: 412 (M^+).

$C_{21}H_{20}N_2O_7$ (412.39) Calc. C 59.37 H 4.71 N 6.79% Found C 59.28 H 4.71 N 7.06%

12. *Preparation of* **5d**, **5e** *and* **5'b**. Compounds **4d**, **4e** and **4'b** were submitted to identical reaction conditions which will be described for **4'b** only.

2,6-Bis(3-acetyl-5-fluoro-2-hydroxy-benzoyl)-4-fluorophenol (**5'b**). Anhydrous $AlCl_3$ (20 g) in a 500 ml cylindrical tube was heated in an oil bath at 140° for 20 min. Compound **4'b** (5 g, 9.7 mmol) was added. The temperature was raised to 175–178°, while the reaction mixture was stirred with a glass rod and kept at this temp. for 20 min. After cooling the mixture was poured on 500 g of crushed ice and 100 ml of conc. HCl-solution was added. The solution was left overnight to give precipitate. Filtration and chromatography on silica gel with $CHCl_3$ gave 2.5 g (50%) of **5'b**, m.p. 171–173°. – IR. (KBr): 3100*w*, 1615*s*, 1168*s*, 1599*m*, 1491*w*, 1210*m* and 993*w*. – MS.: 472 (M^+).

$C_{24}H_{15}F_3O_7$ (472.33) Calc. C 61.15 H 3.19 F 11.88% Found C 61.02 H 3.18 F 12.07%

Compound **5d** was obtained in 30% yield, m.p. > 300°, and was characterized by its corresponding ester **5d**$_1$, m.p. 254–256°. – IR. (KBr): 1749*s* and 1660*s*. – MS.: 498 (M^+).

$C_{25}H_{22}O_{11}$ (498.43) Calc. C 60.24 H 4.41% Found C 60.21 H 4.29%

Compound **5e** was prepared by the same method as **5'b**, except that HCl was not added. Chromatography on Al_2O_3 with $CHCl_3$/MeOH 9:1 gave **5e** in 80% yield, m.p. 254–255°. – IR. (KBr): 3350*s*, 1650*s* and 993*w*. – MS.: 328 (M^+).

$C_{17}H_{16}N_2O_5$ (328.31) Calc. C 58.12 H 4.56 N 7.98% Found C 57.86 H 4.81 N 8.21%

13. *Preparation of* **5d**$_1$, **5e**$_1$ *and* **5'b**$_1$. All these compounds were obtained in an identical manner in approximately 90–97% yield using method 1 and 80–85% using method 2. Their spectra were similar except for variations due to aromatic substituents. All their mass spectra showed M^+ and other appropriate fragments.

The following is a representative procedure.

5,5'-Diacetamido-2,2'-diacetoxy-3,3'-diacetyl-benzophenone (**5e**$_1$). *Method 1.* The solution of 0.5 g (0.0015 mol) **5e** in 30 ml of acetic anhydride was refluxed for 2 h, then cooled and poured in 100 ml of cold water to give an oily product which was solidified after 12 h. The precipitate was filtered off, washed with water and dried to give 0.6 g (93%) yellow crude, m.p. 180–184°. Chromatography on silica gel with $CHCl_3$ gave **5e**$_1$ in 90% yield, m.p. 184–185°. – IR. (KBr): 3350*s*, 1750*s*, 1660*s* and 1210*m*. – MS.: 496 (M^+).

$C_{25}H_{24}N_2O_9$ (496.46) Calc. C 30.12 H 2.40 N 2.81% Found C 30.02 H 2.43 N 2.72%

Method 2. Compound **3e**$_1$ (2.9 g, 0.006 mol) was dissolved in 80 ml of acetic anhydride. Chromium trioxide (4 g) was added gradually in 1 h at RT. The solution was stirred at the same temp. for 1 h and at reflux temp. for another 2 h. The solution was then cooled and poured in 400 ml of cold water. After 24 h a yellow precipitate was obtained. Filtration and chromatography on silica gel with $CHCl_3$ gave **5e**$_1$ in 80% yield (the product was identical to that obtained from acylation of **5e**).

Compound **5d**$_1$ was obtained from **5d**, in 97% yield, using *Method 1* and was purified by the same manner which was described for **5e**$_1$, m.p. 254–256°. – IR. (KBr): 1749*s* and 1660*s*. – MS.: 498 (M^+).

$C_{25}H_{22}O_{11}$ (498.43) Calc. C 60.24 H 4.41% Found C 60.21 H 4.29%

Compound **5d**$_1$ was also obtained from **3d**$_1$, in 85% yield, using *Method 2.* M.p. of **5d**$_1$ obtained from *Method 1*, m.p. of **5d**$_1$ obtained from *Method 2* and mixed m.p. are the same. – MS.: 498 (M^+).

$C_{25}H_{22}O_{11}$ (498.43) Calc. C 60.24 H 4.41% Found C 60.07 H 4.28%

Compound **5'b**$_1$ *was obtained from* **5'b**, in nearly quantitative yield, using *Method 1*, m.p. 110–111°, and it was characterized by its hydrolysis to **5'b.**

Compound **5b**$_1$ was also prepared from **3'b**$_3$, in 81% yield using *Method 2.*

14. *Preparation of compounds* **6a** *and* **6a**$_1$. 5,5'-Dichloro-2,2'-dihydroxy-diphenyl-methane (**2a**) (2 g, 0.007 mol) was dissolved in 55 ml of methanol. Distilled water (1 ml) was added. The stirred

solution was cooled to $-5°$ and 20 ml of sulfuric acid was added slowly. Five ml of 38% formalin was then added over a period of 1 h at the same temperature. After 3 h stirring at -5 to $0°$ the temp. of the mixture was allowed to raise to 25–30°. After 34 h the solution was poured on 300 g of crushed ice. The precipitate was filtered off and washed with hot water. Crystallization with chloroform gave 0.9 g (24%) of **6a**, m.p. 242–244°. Sublimation at 210–215°/0.02 Torr gave pure **6a**, m.p. 243–244°. – IR. (KBr): 3400*s*, 2941*m*, 1590*w*, 1490*s*, 1210*m* and 995*m*. – MS.: 548 (M^+, Cl-clusters).

$C_{27}H_{20}Cl_4O_4$ (550.43) Calc. C 58.90 H 3.63 Cl 25.81% Found C 58.92 H 3.61 Cl 25.70%

Compound $\mathbf{6a_1}$ was prepared by treatment of **6a** with acetic anhydride at reflux temp. for 2 h by the same way which was already described, in 80% yield, m.p. 128–130°. – IR. (KBr): 3020*m*, 1740*s* and 1290*s*. – MS.: 716 (M^+, Cl-clusters).

15. *Preparation of* **6b**, **6′** *and* $\mathbf{6b_1}$. Conc. sulfuric acid (40 ml) was added gradually to 40 ml of methanol containing **2b** (1.5 g, 0.006 mol) at 0–5° and stirred. A solution of 38% formalin (0.8 ml) in 6 ml of methanol was added dropwise over a period of 30 min. The solution was stirred for another 30 min at 15–25° to give a pale brown cloudy solution. After 3 h the solution was poured in 800 ml of cold water. The resulting precipitate was filtered off, washed with water and dried to give 1.7 g crude product. After rinsing with hot water chromatography on silica gel with benzene/chloroform 1:1 gave 0.75 g (25%) of **6b**, m.p. 172–174°. – IR. (KBr): 3400*s*, 2940*w*, 1590*w*, 1490*s*, 1210*m* and 875 *w*. – MS.: 484 (M^+).

$C_{27}H_{20}F_4O_4$ (484.43) Calc. C 66.94 H 4.13 F 15.70% Found C 67.01 H 4.11 F 15.63%

Compound **6′** was also formed in this reaction in 5% yield, m.p. > 350°. – IR. (KBr): 3400*s*, 3040*m*, 1590*s*, 1490*s*, 1210*m* and 665*s*.

Compound $\mathbf{6b_1}$ was prepared by treatment of **6b** with boiling acetic anhydride for 2 h, in 90% yield, m.p. 130–132°. – IR. (KBr): 3100*w*, 2940*w*, 1750*s*, 1590*m*, 1169*s*, 1490*m*, 1210*m* and 900*m*. – MS.: 652 (M^+).

16. *Preparation of* **7a**, **7b**, $\mathbf{7a_1}$ *and* $\mathbf{7b_1}$. *Compounds* $\mathbf{6a_1}$ *and* $\mathbf{6b_1}$ were submitted to the identical reaction conditions and purification procedures, which will be described for $\mathbf{6a_1}$ only.

Compound $\mathbf{6a_1}$ (0.3 g, 0.4 mmol) was dissolved in 15 ml of acetic anhydride and 2.5 g of chromium trioxide was added in a period of 2 h at 30°. The reaction mixture was refluxed for 2 h. Then it was cooled and poured on 50 g of crushed ice and was left overnight to give a precipitate. Filtration and crystallization with ethanol gave **7a** (0.15 g, 50%). This compound was deformed at 200°. M.p. > 300°. – IR. (KBr): 3020*m*, 1740*s*, 1650*s*, 1550*w*, 1180*m* and 995*w*. – MS.: 758 (M^+, Cl-clusters).

Compound $\mathbf{7a_1}$ was prepared, by treatment of **7a** with 15% NaOH-solution at 40° for 1 h, in 90% yield. Sublimation at 215–220°/0.02 Torr gave $\mathbf{7a_1}$ as yellow needles, m.p. 224°. – MS.: 590 (M^+, Cl-clusters).

$C_{27}H_{14}Cl_4O_7$ (592.34) Calc. C 54.91 H 2.37 Cl 23.72% Found C 55.04 H 2.30 Cl 23.69%

Compound **7b** was obtained in 85% yield, m.p. 112–115°. – IR.: (KBr): 3100*w*, 1750*s*, 1660*s*, 1168*m*, 1590*m*, 1490 and 1000*w*. – MS.: 694 (M^+).

$C_{35}H_{22}F_4O_{11}$ (694.52) Calc. C 60.51 H 3.17 F 10.95% Found C 60.41 H 3.18 F 11.02%

Compound $\mathbf{7b_1}$ was prepared in 95% yield, m.p. 165–167°. – UV. (EtOH): λ_{max} 360. – IR. (KBr): 3100*m*, 1600*s*, 1168*s*, 1590*m*, 1490*w*, 1210*m* and 670*w*. – MS.: 526 (M^+).

17. *Preparation of* $\mathbf{3'b_2}$ *and* $\mathbf{5'b_2}$. Both compounds were synthesized by the same method which will be described for $\mathbf{3'b_2}$ only.

2,6-Bis(3′-carboxy-5′-fluoro-2′-hydroxy-α-tolyl)-4-fluorophenol ($\mathbf{3'b_2}$). Compound **3′b** (0.98 g, 2.2 mmol) was dissolved in 50 ml of 2N aqueous NaOH. A solution of 4 g iodine and 10 g potassium iodide in 20 ml of water was added and stirred. The solution was warmed on a water bath for 30 min. Iodoform was removed by filtration. Then 15 g of $NaHSO_3$ was added to the filtrate. The yellow precipitate formed by adding conc. HCl-solution was filtered off, washed with water and dried. The crude product was dissolved in 10% aqueous $NaHCO_3$-solution and treated with charcoal. After filtration, the solution was acidified with hydrochloric acid. The product was sublimed at 175–185°/0.03 Torr, dec. > 300°. – IR. (KBr): 3400*s* br., 1620*s*, 1211*w* and 995*m*.

$C_{22}H_{15}F_3O_7$ (448.30) Calc. C 58.92 H 3.34 F 12.72% Found C 59.01 H 3.27 F 12.79%

Compound **5'b$_2$** was obtained from **5'b** in 30% yield. dec. > 300°. – IR. (KBr): 3350*s* br., 1660*s*, 1630*s* and 1210*w*.

$C_{22}H_{11}F_3O_9$ (476.22) Calc. C 55.46 H 2.31 F 11.97% Found C 55.41 H 2.29 F 12.01%

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