Synthetic Carboxyl-Containing Polyethers, Analogues of Natural Antibiotics[1]

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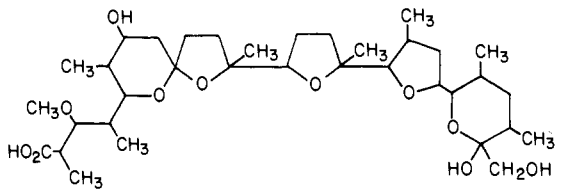
The design and synthesis of a number of carboxyl-containing polyethers as analogues of natural antibiotics are described. No anticoccidial activity was observed.

The monocarboxylic acid polyether antibiotics have recently been reviewed.[2] The antibiotics have the ability to form lipophilic complexes with a variety of organic and inorganic cations. The inner surface of these materials consists of an array of oxygen atoms present in ether, hydroxyl, or carbonyl groups while the outer surface is composed of hydrophobic alkyl groups. There is evidence that these complexes act as carriers, especially in the cases of Na^+ and K^+, and allow passive diffusion of ions across biological membranes, down a concentration gradient. It is probable that this type of ion-transport phenomenon is an important part of the mechanism of the biological activities of this class of compounds.

While various biological activities have been reported for the polyether antibiotics, the most widely studied and so far most useful of these is the prevention and treatment of poultry coccidiosis. Monensin (1) is a highly successful



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coccidiostat, and there are no reports of resistance to this drug.

We felt that it would be of interest to prepare a number of carboxyl-containing polyethers to see if a simple molecule could be synthesized which would exhibit properties analogous to the natural products. The present communication describes part of the results of this work.

Design of Target Molecules. An examination of published x-ray structures[2] of a number of polyether antibiotics revealed several features common to all or many of them. They are all acyclic molecules with a carboxyl group at one end and a hydroxyl at the other. Generally, six oxygen atoms are available for coordination with the complexed cation. Five atoms usually separate the carboxyl group from the carbon bearing the first oxygen atom available for coordination and this oxygen is frequently a secondary alcohol and is separated from the next coordinating oxygen by three atoms. The remaining coordinating oxygen atoms are frequently in a 1,2-glycol arrangement.

Compounds **6**, **10**, **13**, **16**, **17**, **24**, **26**, and **29** in Table I were designed to incorporate these features. The second phenyl ring in **13**, **16**, **17**, and **24** and *tert*-butyl groups in **16**, **17**, **24**, and **26** were included to increase lipophilicity. The tetrahydrofuran group is common in many polyether antibiotics and Cram has shown[3] that it dramatically increases the binding ability of certain crown ethers. These facts led us to prepare the tetrahydrofuran-containing compound **10**.

The recent report[4] of a lipophilic potassium acetate complex derived by oxidation of geraniol acetate suggested the synthesis of **29**. This simple four oxygen unit not only has the proven ability to form complexes of the type we desired but also lends a certain amount of rigidity to the molecule.

Table I

Compd	Formula[a]	R_m[b]	Dose[e] in coccidiosis assay[f]
6	$C_{21}H_{34}O_8$	0.58[d]	250
10	$C_{23}H_{36}O_8$	0.94[d]	250
13	$C_{25}H_{34}O_8$	1.90[d]	115
16	$C_{33}H_{50}O_8$	0.12[c]	150
17	$C_{34}H_{52}O_8$	0.33[c]	157
24	$C_{41}H_{66}O_8$	2.25[c]	150
26	$C_{29}H_{50}O_8$	0.12[c]	110
29	$C_{26}H_{42}O_8$	2.31[d]	210
1		2.00[c]	

[a] All target compounds were analyzed for C and H and gave results within 0.4% of the theoretical values. [b] The procedure for determining R_m values is described in detail in the Experimental Section. [c] Solvent system of 60% MeOH–40% 0.01 N NaOH. [d] Solvent system of 25% MeOH–75% 0.01 N NaOH. [e] Dosages are parts per million by weight in the feed. [f] The coccidiosis assay is described in detail in the Experimental Section.

Chemistry. The synthetic sequences used to prepare the target molecules are outlined in Schemes I and II. The monoprotected catechol **4**[5] was used as the starting material in several procedures. Typically, the alcohol terminal chain was first constructed, the protecting group removed, and the acid terminal chain attached. The phenol groups were easily alkylated in the presence of unprotected aliphatic hydroxyls.

3,5-Di-*tert*-butylcatechol was easily monoalkylated without protection. It is assumed that the least hindered phenol reacts first.

The interesting bisepoxide opening, which is the key step in the synthesis of **7**, is based on an analogous reaction reported by Wiggins and Wood[6] in which the same bisepoxide was reacted with methoxide to give 2-methoxymethyl-5-hydroxymethyltetrahydrofuran.

The permanganate oxidation of **27** is analogous to the reaction reported by Klein and Rojahn[7] for the oxidation of geranyl acetate. The THP-protecting group was exchanged for acetate to give **27** as neither the THP nor the free phenol were expected to survive the oxidation reaction.

In several instances the synthesis of hydroxyethyl ethers was required. Both direct alkylation with bromoethanol and reaction with ethylene oxide gave very poor yields. In some related work, alkylation with allyl bromide followed by ozonolysis and sodium borohydride workup gave good results, but the oxidation step was not compatible with many of the present substrates. The most satisfactory sequence proved to be alkylation with ethyl bromoacetate followed by lithium aluminum hydride reduction.

Biological Results and Discussion. When submitted to a standard challenge assay[8] against *E. tennela* and *E. necatrix* at the indicated dosages, none of the target molecules showed significant activity relative to infected nonmedicated controls. There was no indication of toxicity.

There are two general situations which may explain these disappointing results. Either the compounds failed to form the necessary lipophilic complexes or the complexes did form and failed to act in a manner analogous

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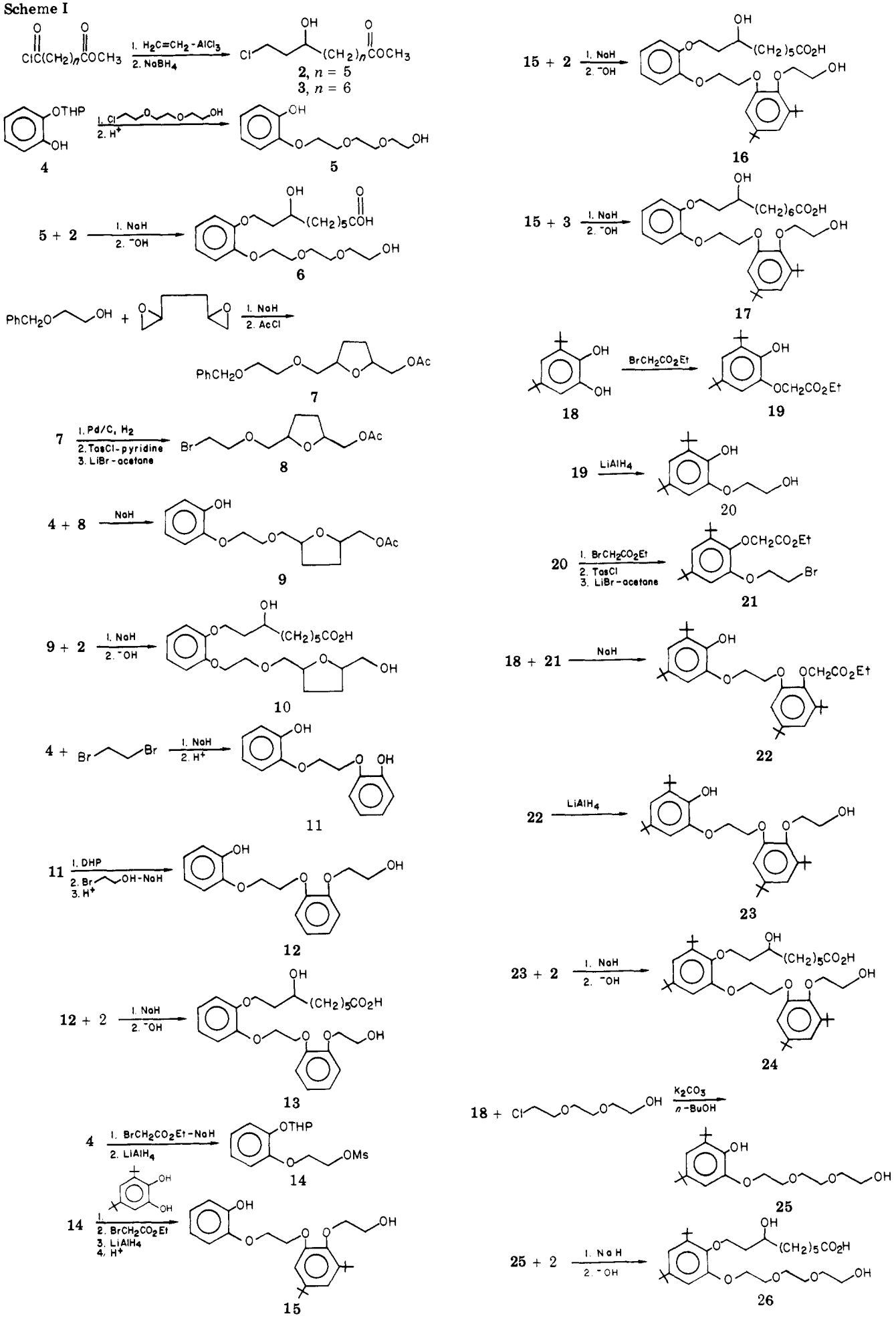
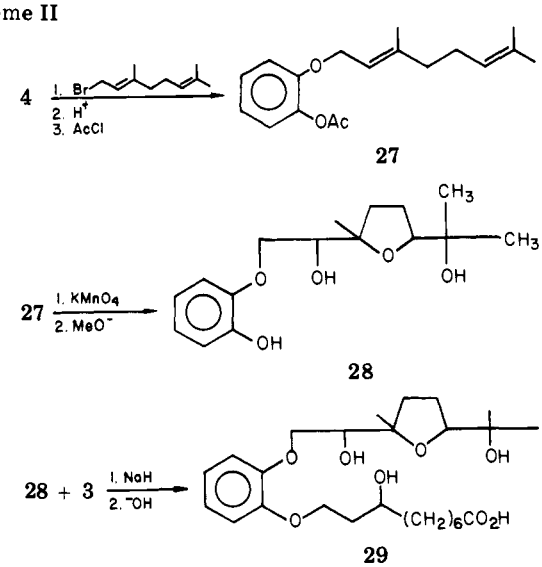
Scheme I


ClC(CH2)nCOCH3
1. H2C=CH2-AlCl3
2. NaBH4
2, n = 5
3, n = 6
4
5
5 + 2
1. NaH
2. -OH
6
PhCH2O
1. NaH
2. AcCl
7
1. Pd/C, H2
2. TosCl-pyridine
3. LiBr-acetone
8
4 + 8
NaH
9
9 + 2
10
4 + Br
1. NaH
2. H+
11
1. DHP
2. Br
3. H+
12
12 + 2
13
1. BrCH2CO2Et-NaH
2. LiAlH4
14
1. 2. BrCH2CO2Et 3. LiAlH4 4. H+
15
15 + 2
16
15 + 3
17
BrCH2CO2Et
18
19
LiAlH4
20
1. BrCH2CO2Et
2. TosCl
3. LiBr-acetone
21
18 + 21
22
LiAlH4
23
23 + 2
24
18 + Cl
K2CO3
n-BuOH
25
25 + 2
26

Scheme II



to the natural products. Although detailed physical-chemical and ion-transport studies have not been done on these compounds, the sodium salts of the acids exhibited solubility properties of ordinary carboxylate salts; while the sodium salt of monensin is essentially insoluble in water and easily soluble in common organic solvents. In addition, the apparent lipophilicities of the target compounds and of monensin have been measured by reverse phase thin-layer chromatography. These data are presented in Table I. It is obvious from these results that **24** approximates the lipophilicity of monensin. It is assumed that the unusual solubility properties of the sodium salt of monensin are due to the formation of a stable complex. Since at least some of the target compounds have R_m values comparable to monensin, yet fail to form organic soluble salts, it is likely that they do not complex sodium ions in the manner described for natural polyether antibiotics.

A convincing explanation of the failure of our synthetic materials to form a stable complex is not immediately obvious. It may be that the molecules lack sufficient hydrophobic groups to adequately "cover" all hydrophilic sites in a complexed conformation. Furthermore, many of the natural products have a quite rigid conformation due to the presence of many highly substituted and spiro centers. This rigidity may be necessary to hold the antibiotics in a conformation favorable to complex formation.

It is interesting to note that other workers have prepared neutral acyclic ligands by alkylation of catechol and other 1,2-diols. Although no biological properties of these materials are reported, extensive physical-chemical studies have been conducted to demonstrate selective binding with alkaline earth cations.[9]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$ with Varian A-60 and HA-100 instruments, and mass spectra were determined with a Varian-MAT CH4 spectrometer. Elemental analyses were performed by the analytical department of Syntex Research, Institute of Organic Chemistry. Chromatography was done on Merck silica gel 60. Eluting solvents are indicated in parentheses. Anhydrous magnesium sulfate was used to dry all organic solutions.

Methyl 9-Chloro-7-hydroxynonanoate (2). A suspension of 10 g (75 mmol) of $AlCl_3$ in 250 mL of CH_2Cl_2 was thoroughly flushed with N_2 and cooled to 10 °C. A solution of 9.6 g (50 mmol) of methylpimoyl chloride in 20 mL of CH_2Cl_2 was then added dropwise while maintaining a temperature of 10 °C to give a clear solution. Ethylene gas was passed sequentially through a column of KOH and then anhydrous $CaSO_4$ and bubbled into the reaction at room temperature for 24 h. The yellow solution was slowly added to a well-stirred mixture of 200 mL of CH_2Cl_2, 500 mL of H_2O, and 50 mL of concentrated HCl, while the temperature was maintained at 5 °C. The layers were separated and the aqueous phase was extracted with 2 × 100 mL of CH_2Cl_2. The combined organic layers were dried and evaporated to give 9.5 g of an unstable oil. This material was immediately dissolved in 150 mL of MeOH and cooled to −65 °C under N_2, and 4 g of $NaBH_4$ was added in one portion. After 20 min, the mixture was made acidic with Et_2O–HCl and evaporated. The residue was partitioned between Et_2O and H_2O, and the organic phase was dried and evaporated. The residue was chromatographed ($CHCl_3$) to afford 3.8 g (34%) of **2** as an oil sufficiently pure for further use: NMR δ 3.65 (s, 3 H, CO_2CH_3), 3.65 (t, 2 H, CH_2Cl), 2.3 (t, 2 H, $CH_2CO_2CH_3$); MS *m/e* 222 (M^+).

Methyl 10-Chloro-8-hydroxydecanoate (3). The procedure was the same as that used for **2** to give **3** as an oil in 51% yield: NMR δ 3.65 (s, 3 H, CO_2CH_3), 3.65 (t, 2 H, CH_2Cl), 2.3 (t, 2 H, $CH_2CO_2CH_3$); MS *m/e* 236 (M^+).

1-(3′-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2″-[2-(2-hydroxyethoxy)ethoxy]ethoxy]benzene (6). A mixture of 16.8 g (100 mmol) of 2-[2-(2-chloroethoxy)ethoxy]ethanol, 19.4 g (100 mmol) of **4**, and 13.6 g (100 mmol) of K_2CO_3 in 200 mL of *n*-BuOH was refluxed for 18 h, then cooled, and evaporated. The residue was partitioned between ether and water, and the organic phase was dried and evaporated. The residue was allowed to stand in 65% aqueous HOAc overnight, then evaporated, and chromatographed (5% MeOH–$CHCl_3$) to give 11.6 g (48%) of **5** as a viscous oil: MS *m/e* 242.

A solution of 1 g (4.1 mmol) of **5** in 20 mL of THF was flushed with N_2, and 100 mg (4.1 mmol) of 100% NaH was added. After 15 min, a solution of 1 g (4.5 mmol) of **2** in 10 mL of THF and 5 mL of HMPA was added, and the mixture was refluxed under N_2 for 24 h. The reaction mixture was evaporated, the residue was dissolved in 30 mL of MeOH, 3 mL of 1 N NaOH was added, and the mixture was refluxed for 1 h. After evaporation the residue was dissolved in water and extracted with 2 × 20 mL of ether. The aqueous layer was made acidic with 5 mL of 1 N HCl and extracted with 3 × 50 mL of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and evaporated. Chromatography of the residue (10% MeOH–$CHCl_3$) afforded 425 mg (25%) of **6** as a thick gum: NMR δ 6.88 (m, 4 H, aromatic), 3.5–4.3 (m, 15 H, CHO), 2.3 (t, 2 H, $-CH_2CO_2H$); MS *m/e* 414 (M^+).

1-(3-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2′-(2-hydroxymethyltetrahydrofuran-5-yl)methoxyethoxy]benzene (10). A flask containing 10.5 g of benzyloxyethanol (Eastman) was flushed with N_2 and 480 mg (20 mmol) of 100% NaH was added. After 30 min, 2.2 g (20 mmol) of 1,2,5,6-diepoxyhexane[6] was added and the temperature was raised to 80 °C for 4 h. The reaction mixture was diluted with 200 mL of $CHCl_3$, washed with 3 × 50 mL of H_2O, dried, and evaporated. The residue was chromatographed ($CHCl_3$) to elute unreacted benzyloxyethanol and (5% MeOH–$CHCl_3$) to elute 12 g of a viscous oil. This material was dissolved in 200 mL of anhydrous Et_2O and 11 mL of triethylamine; then 5 mL of acetyl chloride was added. The reaction was stirred overnight at room temperature and worked up under standard conditions to give a gum. The material was chromatographed ($CHCl_3$) to give 6.6 g (100%) of **7** as a gum: NMR δ 7.35 (s, 5 H, aromatic), 4.55 (s, 2 H, $PhCH_2O$), 4.1 (s, 2 H, CH_2OAc), 2.05 [s, 3 H, $OC(=O)CH_3$].

Hydrogenolysis of 6.5 g of **7** in 150 mL of EtOH with 2 g of 10% Pd/C on a Parr shaker at 40 psi afforded, after chromatography (5% MeOH–$CHCl_3$), 3.5 g of a thick oil. This material was cooled in 50 mL of pyridine and 5 g of tosyl chloride added. After 20 h at 10 °C, standard workup gave an oil which was dissolved in 50 mL of acetone and stirred with 10 g of LiBr at room temperature for 48 h. Standard workup gave 3.4 g (63% from **7**) of **8** as an oil: NMR δ 4.15 (s, 2 H, CH_2OAc), 3.3–4.0 (m, 6 H, $BrCH_2CH_2OCH_2$), 2.1 [s, 3 H, $OC(=O)CH_3$].

A solution of 2 g (10.3 mmol) of **4** in 30 mL of THF was flushed with N_2, and 250 mg (10.4 mmol) of 100% NaH was added. After 15 min, a solution of 3.4 g (12.6 mmol) of **8** in 10 mL of THF and 6 mL of HMPA was added, and the mixture was refluxed under N_2 for 4 h. After evaporation the residue was dissolved in 50 mL

of ether, 20 mL of pentane was added, and the organic phase was extracted with 3 × 50 mL of H_2O. Drying and evaporation gave a residue which was chromatographed ($CHCl_3$) to give 1.1 g (35% from **8**) of **9** as a gum: NMR δ 6.85 (m, 4 H, aromatic), 4.0–4.3 (m, 4 H, $PhOCH_2$, CH_2OAc), 3.7 (m, 2 H, CH_2O), 3.55 (d, 2 H, c-C_4H_7O-2-OCH_2), 2.05 [s, 3 H, $OC(=O)CH_3$]; MS *m/e* 310 (M^+).

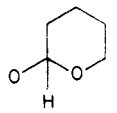
A solution of 1 g (3.2 mmol) of **9** in 50 mL of THF was flushed with N_2 and 80 mg (3.3 mmol) of 100% NaH was added. After 30 min, a solution of 1 g (4.5 mmol) of **2** in 5 mL of HMPA was added and the reaction refluxed under N_2 for 3 h. Workup as described for **6** and chromatography (5% MeOH–$CHCl_3$) gave a mixture of partially acetylated materials. The mixture was refluxed in 15 mL of MeOH with 5 mL of 1 N NaOH for 30 min and then worked up as described for **6**. Chromatography (12% MeOH–$CHCl_3$) gave 600 mg (43% from **9**) of **10** as a thick oil: NMR δ 6.8 (s, 4 H, aromatic), 3.3–4.3 (m, 11 H, $-CH_2O$), 2.35 (t, 2 H, CH_2CO_2H); MS *m/e* 440 (M^+).

1-(3-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2′-[*o*-(2-hydroxyethoxy)phenoxy]ethoxy]benzene (13). To a solution of 19.4 g (100 mmol) of **4** in 50 mL of DMF was added 2.5 g (104 mmol) of 100% NaH and, after 20 min, 60 g (350 mmol) of dibromoethane. Additional increments (total 5 g) of 100% NaH were necessary to drive the reaction to completion. The reaction was diluted with 500 mL of 1:1 ether–hexane and extracted with 3 × 100 mL of H_2O. Standard workup gave a residue which was chromatographed ($CHCl_3$) to give 13.5 g of a viscous oil. This material was dissolved in 60 mL of 65% HOAc for 48 h and then evaporated. Trituration with ether–hexane of the residue gave a solid. The liquors were chromatographed ($CHCl_3$) to give material which was combined with the first solid and crystallized from ether–hexane to afford 6 g (25% from **4**) of **11**: mp 118–119 °C; NMR δ 6.9 (s, 8 H, aromatic), 4.4 (s, 4 H, OCH_2CH_2O); MS *m/e* 246 (M^+).

A solution of 5 g (2.03 mmol) of **11** and 2 g (2.3 mmol) of dihydropyran in 200 mL of ether was treated with 2 drops of $POCl_3$ and kept at room temperature for 24 h. After quenching with 1 mL of triethylamine, standard workup gave a residue which was chromatographed ($CHCl_3$) to give 1.5 g of an oil. This oil was dissolved in 100 mL of 1-butanol and 6 g of K_2CO_3, and 5 mL of 2-bromoethanol was added. After 24 h of reflux, the reaction was evaporated and standard workup gave a residue which was chromatographed ($CHCl_3$) to give an oil which was dissolved in 65% HOAc for 24 h and then evaporated. The residue was chromatographed ($CHCl_3$) to give a gum which crystallized from ether to afford 220 mg (4% from **11**) of **12**: mp 95.5–96.5 °C; NMR δ 6.95 (m, 8 H, aromatic), 4.35 (s, 4 H, $PhOCH_2CH_2OPh$), 4 (m, 4 H, $PhOCH_2CH_2OH$); MS *m/e* 290 (M^+).

A solution of 220 mg (0.76 mmol) of **12** in 10 mL of THF and 2 mL of HMPA was flushed with N_2, and 60 mg (1.4 mmol) of 57% NaH–mineral oil was added. After 15 min, 300 mg (1.35 mmol) of **2** was added, and the reaction was refluxed under N_2 for 24 h. Workup as described for **6** gave a residue which was refluxed in 15 mL of MeOH with 2 mL of 1 N NaOH for 4 h. The reaction was evaporated and the residue dissolved in water and extracted with 2 × 20 mL of ether. The aqueous layer was treated with 2 mL of 1 N HCl and extracted with 4 × 25 mL of CH_2Cl_2. Drying and evaporation of the CH_2Cl_2 gave a residue which, on trituration with ether–hexane, afforded 65 mg of a solid. The liquors were chromatographed (2% MeOH–$CHCl_3$) to give 80 mg of material which was combined with the original solid and crystallized from ether–hexane to give 122 mg (33% from **12**) of **13**: mp 82–85 °C; NMR δ 6.8–7.1 (m, 8 H, aromatic), 2.25 (t, 2 H, $-CH_2CO_2H$); *m/e* 462 (M^+).

1-(3-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2′-[2″-(2-hydroxyethoxy)-3″,5″-di-*tert*-butylphenoxy]ethoxy]benzene (16). A solution of 10 g (56 mmol) of **4** in 200 mL of THF was treated with 2.5 g (60 mmol) of 57% NaH–mineral oil and, after 15 min, 6 mL (56 mmol) of ethyl bromoacetate was added. After refluxing for 2 h, standard workup gave an oil which was dissolved in 50 mL of THF and added to a suspension of 5 g (132 mmol) of lithium aluminum hydride in 300 mL of THF. After refluxing for 2 h, standard workup with saturated Na_2SO_4 gave a residue which was dissolved in 50 mL of dry pyridine and cooled in an ice bath, and 10 mL (121 mmol) of mesyl chloride was added. The reaction was kept at 10 °C for 24 h. Standard workup gave a solid residue which on trituration with ether afforded 8.75 g (40%) of **14** of sufficient purity for further use: mp 81–86 °C; NMR δ 6.9–7.2 (m, 4 H, aromatic), 5.4 (m, 1 H, see structure i), 4.1–4.7 (m, 4 H, $PhOCH_2CH_2OMs$), 3.1 (s, 3 H, OSO_2CH_3).



i

A solution of 6.5 g (29.3 mmol) of 3,5-di-*tert*-butylcatechol in 200 mL of THF under N_2 was treated with 1.3 g (30 mmol) of 57% NaH–mineral oil and, after 10 min, a solution of 8.7 g (28 mmol) of **14** in 100 mL of THF was added. After refluxing for 4 h, standard workup gave a residue which was chromatographed (15% hexane–$CHCl_3$) to give a dark gum (7 g). This material was dissolved in 100 mL of THF and 820 mg (19.7 mmol) of 57% NaH–mineral oil was added. After 10 min, 2 mL (19 mmol) of ethyl bromoacetate was added and the reaction was refluxed for 1 h. Standard workup gave a residue which was dissolved in 100 mL of THF and added to a suspension of 3 g (80 mmol) of lithium aluminum hydride in 300 mL of THF. One hour's reflux followed by standard saturated Na_2SO_4 workup afforded material which was dissolved in 65% HOAc and heated on the steam bath for 2 h. The mixture was evaporated and the residue chromatographed (5% MeOH–$CHCl_3$). Crystallization from ether–hexane gave 2.9 g (25% from **14**) of **15**: mp 116–120 °C; NMR δ 6.7–7.2 (m, 6 H, aromatic), 3.5–4.5 (m, 8 H, OCH_2CH_2O), 1.4 [s, 9 H, $C(CH_3)_3$], 1.2 [s, 9 H, $C(CH_3)_3$]; MS *m/e* 402 (M^+).

A solution of 510 mg (1.3 mmol) of **15** in 30 mL of THF was treated under N_2 with 85 mg (2 mmol) of 57% NaH–mineral oil. After 10 min, 300 mg (1.3 mmol) of **2** in 2 mL of THF and 3 mL of HMPA was added. The reaction was refluxed for 24 h and worked up as described for **6**. Chromatography (1% MeOH–$CHCl_3$) gave 200 mg of material which was dissolved in 10 mL of MeOH with 2 mL of 1 N NaOH and refluxed for 3 h. Workup as described for **6** gave 180 mg (24%) of **16** as an oil: NMR δ 6.9 (m, 6 H, aromatic), 2.25 (t, 2 H, CH_2CO_2H); MS *m/e* 574 (M^+).

1-(3-Hydroxy-9-carboxy-*n*-nonyloxy)-2-[2′-[2″-(2-hydroxyethoxy)-3″,5″-di-*tert*-butylphenoxy]ethoxy]benzene (17). In a manner analogous to **16**, **17** was prepared from 600 mg of **15** in a yield of 40%: MS *m/e* 588 (M^+).

1-(3-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2′-[2″-(2-hydroxyethoxy)-3″,5″-di-*tert*-butylphenoxy]ethoxy]-4,6-di-*tert*-butylbenzene (24). A solution of 11.1 g (50 mmol) of 3,5-di-*tert*-butylcatechol in 100 mL of THF was treated with 1.25 g (50 mmol) of 100% NaH and, after 30 min, 5.5 mL (50 mmol) of ethyl bromoacetate. The reaction was refluxed for 2 h and after standard workup gave a mixture which was chromatographically separated (1:1 hexane–$CHCl_3$) to isolate 5 g (32%) of **19** as an oil: NMR δ 6.8–7.1 (m, 2 H, aromatic), 4.7 (s, 2 H, $PhOCH_2$), 4.3 [q, 2 H, $C(=O)OCH_2CH_3$], 1.45 [s, 9 H, $C(CH_3)_3$], 1.3 [s, 9 H, $C(CH_3)_3$], 1.3 [t, 3 H, $C(=O)OCH_2CH_3$].

A solution of 5 g (16 mmol) of **19** in 100 mL of THF was added to a suspension of 3 g of $LiAlH_4$ in 200 mL of THF, and the mixture was refluxed under N_2 for 1.5 h. Standard workup gave a residue which crystallized from pentane to give 4 g (94%) of **20** of sufficient purity for further use: mp 145–145.5 °C; NMR δ 6.8–7 (m, 2 H, aromatic), 3.8–4.3 (m, 4 H, $PhOCH_2CH_2OH$), 1.4 [s, 9 H, $C(CH_3)_3$], 1.3 [s, 9 H, $C(CH_3)_3$].

A solution of 4 g (15 mmol) of **20** in 100 mL of THF was treated with 720 mg (17 mmol) of 57% NaH–mineral oil and, after 10 min, with a solution of 1.6 mL (15 mmol) of ethyl bromoacetate in 10 mL of HMPA. After refluxing for 3 h, standard workup gave a residue which was dissolved in 50 mL of pyridine and 5 g of tosyl chloride was added. After 24 h at 10 °C, standard workup gave a residue which was dissolved in 60 mL of acetone and stirred for 3 days with 15 g of LiBr. The solvent was removed under reduced pressure, and the residue was partitioned between ether and water. Standard workup gave a mixture which was separated by chromatography ($CHCl_3$) to give 2.5 g (40%) of **21** as an oil which crystallized from pentane to give material of sufficient purity for further use: mp 72–76 °C; NMR δ 7.05 (d, 1 H, aromatic), 6.85 (d, 1 H, aromatic), 4.75 [s, 2 H, $PhOCH_2C(=O)$], 4.1–4.6 (m, 4 H, $COCH_2CH_3$, CH_2Br), 3.7 (t, 2 H,

$PhOCH_2$), 1.2–1.5 [m, 21 H, $C(CH_3)_3$, $C(=O)OCH_2CH_3$].

A solution of 1.4 g (6.3 mmol) of 3,5-di-*tert*-butylcatechol in 50 mL of THF was treated with 290 mg (6.8 mmol) of 57% NaH–mineral oil and, after 10 min, 2.5 g (6.1 mmol) of **21** was added in 3 mL of HMPA. The reaction was refluxed for 18 h and then worked up as **6** to give a residue which was chromatographed (20% hexane–$CHCl_3$) to give 2.5 g (73%) of **22** as an oil which crystallized from hexane: mp 119–121 °C; NMR δ 6.8–7.1 (4 m, 4 H, aromatic), 4.65 [s, 2 H, $OCH_2C(=O)$], 4.0–4.5 (m, 6 H, OCH_2CH_2O, $COCH_2CH_3$), 1.1–1.6 [m, 39 H, $C(CH_3)_3$, $C(=O)OCH_2CH_3$].

A solution of 2.5 g (4.6 mmol) of **22** in 50 mL of THF was added to a suspension of 2 g of $LiAlH_4$ in 100 mL of THF, and the reaction was refluxed under N_2 for 1.5 h. Workup with saturated Na_2SO_4 as described for **15** gave a residue which crystallized from hexane to give 1.5 g of **23**: mp 133 °C; NMR δ 6.8–7.1 (m, 4 H, aromatic), 3.8–4.4 (m, 8 H, OCH_2CH_2O), 1.2–1.5 [m, 36 H, $C(CH_3)_3$]; MS *m/e* 514 (M^+).

A solution of 500 mg (0.97 mmol) of **23** in 25 mL of THF was treated with 50 mg (1.1 mmol) of 57% NaH–mineral oil and then 400 mg (1.8 mmol) of **2** in 5 mL of HMPA. The reaction was refluxed under N_2 for 24 h and then worked up as described for **6**. The residue was chromatographed ($CHCl_3$) to give material which was dissolved in 20 mL of MeOH and refluxed for 1 h with 3 mL of 1 N NaOH. After workup as described for **6**, the resulting material was crystallized from hexane to give 300 mg (45%) of **24**: mp 138–150 °C; NMR δ 6.8–7.1 (m, 4 H, aromatic), 2.25 (t, 2 H, CH_2CO_2H); MS *m/e* 686 (M^+).

1-(3-Hydroxy-8-carboxy-*n*-octyloxy)-2-[2′-[2-(2-hydroxyethoxy)ethoxy]ethoxy]-4,6-di-*tert*-butylbenzene (26). A mixture of 2.2 g (10 mmol) of 3,5-di-*tert*-butylcatechol, 5 mL (34 mmol) of 2-[2-(2-chloroethoxy)ethoxy]ethanol, and 4 g (30 mmol) of K_2CO_3 in 50 mL of *n*-BuOH was refluxed for 1.5 h. After evaporation, the residue was partitioned between ether and water, followed by standard workup, to give a mixture of mono- and dialkylated products. The mixture was separated by chromatography (2% MeOH–$CHCl_3$) to give **25** which crystallized from hexane to give 1.8 g (50%): mp 55–70 °C; NMR δ 6.75–7.1 (m, 2 H, aromatic), 3.5–4.2 (m, 6 H, OCH_2CH_2O), 1.4 [s, 9 H, $C(CH_3)_3$], 1.3 [s, 9 H, $C(CH_3)_3$]; MS *m/e* 354 (M^+).

A solution of 900 mg (2.5 mmol) of **25** in 50 mL of THF and 5 mL of HMPA was treated with 130 mg (3.1 mmol) of 57% NaH–mineral oil and then 750 mg (3.4 mmol) of **2**. The reaction was refluxed under N_2 for 18 h and then worked up and hydrolyzed as described for **6**. The material thus obtained was chromatographed (2% MeOH–$CHCl_3$) to give 180 mg (14%) of **26** as an oil: NMR δ 6.8 (d, 1 H, aromatic), 6.95 (d, 1 H, aromatic), 2.35 (t, 2 H, CH_2CO_2H); MS *m/e* 526 (M^+).

1-[2-Hydroxy-2-[2′-methyl-5′-(1″-hydroxy-1″-methylethyl)tetrahydrofuran-2′-yl]ethoxy]-2-(3-hydroxy-9-carboxy-*n*-nonyloxy)benzene (29). A solution of 17 g (87.6 mmol) of **4** in 150 mL of THF with 5 mL of HMPA was treated with 4.4 g (100 mmol) of 57% NaH–mineral oil and, after 10 min, 20 g (92 mmol) of geranyl bromide was added. The reaction was stirred for 1 h at room temperature, the solvent evaporated, and the residue worked up in a normal fashion with ether–water. The product was dissolved in ether (200 mL) and treated with 10 mL of concentrated HCl at room temperature for 4 h. Quenching with triethylamine and washing with water gave, after drying and evaporation, an oil which was chromatographed (1:1 hexane–$CHCl_3$) to give 15 g of material which was acetylated under standard conditions in ether with AcCl and triethylamine to give 15.4 g (61%) of **27** as an oil: NMR δ 6.85–7.3 (m, 4 H, aromatic), 5–5.6 (m, 2 H, vinyl), 4.6 (d, 2 H, $PhOCH_2$), 2.3 [s, 3 H, $OC(=O)CH_3$], 2–2.2 (m, 4 H, CH_2CH_2), 1.5–1.8 (m, 9 H, CH_3).

A solution of 15 g (52 mmol) of **27** in 50 mL of acetone and 5 mL of water was cooled to 0 °C and a stream of CO_2 passed through the mixture. A solution of 12 g (76 mmol) of $KMnO_4$ in 500 mL of acetone and 50 mL of H_2O was then added at such a rate that the reaction temperature did not exceed 6 °C. The stream of CO_2 was continually maintained. The addition took 45 min, after which time the reaction was stirred at 0 °C for an additonal 1.5 h. A 20% aqueous sodium metabisulfite solution was then added to discharge color of excess $KMnO_4$. After the addition of 50 g of Celite, the reaction was filtered through a Celite pad and the acetone removed under reduced pressure at 50 °C. The aqueous mixture was extracted with CH_2Cl_2 which afforded a thick oil that was estimated by TLC to be ca. 85% pure. This material was dissolved in 50 mL of MeOH, and 100 mg of 100% NaH was added. After 1 h at room temperature, 5 mL of 1 N HCl was added and the mixture was concentrated. Standard workup with ether–water gave a gum which was chromatographed (2% MeOH–$CHCl_3$) to give material which crystallized from ether to give 5 g (32%) of **28**: mp 144–145.5 °C; NMR δ 6.6–7 (m, 4 H, aromatic), 3.7–4.3 (m, 4 H, CHO), 1.5–2.3 (m, 4 H, $H_{3,3,4,4}$ of THF component), 1–1.4 (m, 9 H, CH_3); MS *m/e* 296 (M^+).

A solution of 1.5 g (5 mmol) of **28** in 50 mL of THF and 5 mL of HMPA was treated with 300 mg (7 mmol) of 57% NaH–mineral oil and then 2 g (8.5 mmol) of **3**. The reaction was refluxed for 24 h and worked up as described for **6** to give a product that was chromatographed (1% MeOH–$CHCl_3$) to give 2.1 g of material which was dissolved in 50 mL of MeOH and refluxed with 5 mL of 1 N NaOH for 3 h. Workup as described for **6** gave 1.7 g (70%) of **29** as an oil: NMR δ 6.7–7 (m, 4 H, aromatic), 2.27 (t, 2 H, CH_2CO_2H); MS *m/e* 482 (M^+).

Anticoccidial Assay.[8] White leghorn cockerels are raised in groups of five in test cages under standard conditions. At 13 days of age the birds are started on medicated diets, and on day 14 they are infected with *E. tennella* and *E. necatrix*. Control groups include nonmedicated noninfected, infected nonmedicated, and several standard anticoccidial drugs. The birds are sacrificed 7 days after infection. Efficacy is based on mortality, weight gain, and severity of lesions.

Reverse Phase Thin-Layer Chromatograph Procedure. In a manner based on the work of Biagi,[10] commercial Analtech 20 × 20 cm plates precoated with 250 μ of silica gel GF were immersed in a solution of 20% Dow Corning 200 fluid silicone oil in methylene chloride. After air bubbles ceased escaping from the surface of the plates, they were removed and air-dried. Samples were spotted in a normal manner and developed in chambers saturated with the solvents indicated in Table I. A molybdic acid spray was used for visualization. R_m values were calculated as described by Biagi.[10]

References and Notes

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