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Studies on Catechol Esters

Part I. Synthesis of Cyclic Succinoylcatechols and o-Hydroxyphenyl Acid Succinates

LEIF-ÅKE SVENSSON

AB Draco, Fack, S-221 01 Lund, Sweden, and Division of Organic Chemistry, University of Lund, Chemical Center, P.O. Box 740, S-220 07 Lund 7, Sweden

Some synthetic routes to cyclic succinoylcatechols, 3,4-dihydro-1,6-benzodioxocin-2,5-diones, (*1*), are described together with the synthesis of a series of *o*-hydroxyphenyl acid succinates, (*2*). Compounds *1* are best prepared by Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalene-diones, (*6*), or of ε-lactones of β-(*o*-hydroxybenzoyl)-propionic acids, (*15*), with peroxy-trifluoroacetic acid. Also, the direct condensation of catechol with an appropriate succinoyl chloride in the presence of base is, in certain cases, applicable for the synthesis of *1*. Compounds, *2* are prepared by reaction of catechol monoanion with the appropriate succinic anhydride.

It is well established that catecholamines, when administered *per os*, metabolize *via* conjugation to form ethereal sulphates and are *O*-methylated by the enzyme catechol-*O*-methyl transferase (COMT).[1] These metabolic pathways cause inactivation of the pharmacological effects of the catecholamines, and consequently drugs containing catecholamines are not suitable for peroral administration.

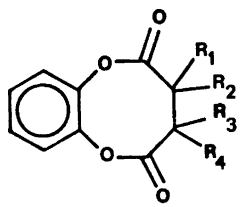
The most sensitive part of the catecholamine is the catechol moiety, which already in the small intestine is attacked by conjugating enzymes. Intact resorbed molecules are rapidly inactivated in the liver by COMT. One way to make the catecholamines resistant to enzymatic conjugation is to block the phenolic hydroxyl groups with some suitable function. This blocking group must fulfil at least three requirements: (1) it must be stable enough to acid to permit passage through the stomach; (2) it must be relatively easy to split off by means of enzymatic action in the blood plasma; and (3) if there are two blocking groups, both should be split off simultaneously, in order to avoid undesired effects from or excretion of the monosubstituted derivative.

It is known that catechol diacetate hydrolyzes *via* a two step mechanism, in which the first step is about 150 times slower than the second one.[2] The second step was supposed to hydrolyze *via* intramolecular general acid catal-

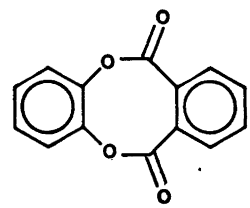
ysis, but it has recently been shown that the rate enhancement in the second step is better explained in terms of intramolecular general base catalysis.[3] Catechol diacetate also has the feature of being relatively stable to acid solutions.

Since the ester function is readily hydrolyzed by enzymes and the two ester groups in catechol diacetate are split off at different rates, the ester function would seem to be well suited as a blocking group. Moreover, phenyl acid succinates are known to hydrolyze *via* intramolecular carboxylate ion catalysis with much higher rates than in the case of general base catalyzed hydrolysis of catechol monoacetate.[4] It has also been shown that increased alkyl substitution in the succinic acid moiety, the *gem*-dialkyl effect, highly increases the rate of the intramolecularly catalyzed step.[5] Since the first step in the hydrolysis of catechol diacetate is effected *via* the $B_{AC}2$-mechanism, increased alkyl substitution in the acid moiety will make the attack at the carbonyl carbon atom more difficult and hence the rate of hydrolysis slower.[6]

With this in mind, we decided to synthesize the hitherto not described cyclic succinoylcatechols *1 a–e* as model compounds for the more complicated cate-



1. *a*. R_{1-4}=H. *c*. $R_{1,3}$=H. $R_{2,4}$=Me.
b. R_1=Me. R_{2-4}=H. *d*. R_{1-4}=Me.



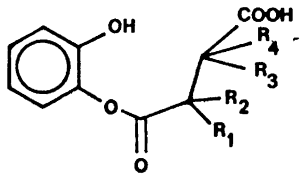
1 e.

cholamine structures, in order to study the kinetics of the two steps involved in the hydrolysis of these compounds. Thus, it was expected that in *1 a–e*, the rate of hydrolysis of the first step would be slowed down by increased alkyl substitution in the succinic acid moiety, which at the same time would highly increase the rate of the second step.

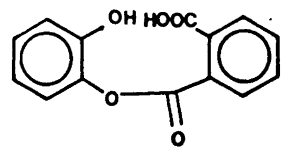
The following methods have been tried for the synthesis of compounds *1 a–e*:

1. Reaction between catechol and the appropriate succinoyl chloride in the presence of pyridine. 2. Condensation of catechol and the appropriate succinic acid in the presence of dicyclohexylcarbodiimide (DCC). 3. Intramolecular condensation of *o*-hydroxyphenyl acid succinates in the presence of DCC. 4. Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalenediones and ε-lactones of β-(*o*-hydroxybenzoyl)-propionic acids. 5. Trichloroisocyanuric acid (TCC)-oxidation of 2,3,4,5-tetrahydro-1,6-benzodioxocin in the presence of water.

This paper also describes the synthesis of the corresponding *o*-hydroxyphenyl acid succinates *2 a–g*.



2. *a*. R_{1-4}=H. *d*. $R_{1,3}$=H. $R_{2,4}$=Me *meso* and DL
b. R_1=Me. R_{2-4}=H.
c. $R_{1,2}$=Me. $R_{3,4}$=H.
e. R_{1-3}=Me. R_4=H.
f. R_{1-4}=Me



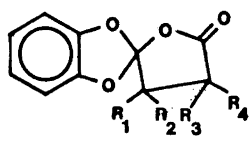
2 g.

The following papers of this series describe the kinetic and mass spectrometric behaviour of these compounds.

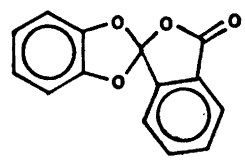
RESULTS AND DISCUSSION

A. Cyclic succinoylcatechols

1. *Reaction between catechol and the appropriate succinoyl chloride in the presence of pyridine*. The first report of the synthesis of cyclic catechol esters was given in 1902 by Bischoff and von Hedenström,[7] who heated succinoyl chloride with catechol in order to prepare cyclic catechol succinate. They were, however, not successful and only a polymeric material could be isolated. This approach has also been considered by us, but in order to achieve cyclization to a higher extent, we have instead used tetramethylsuccinoyl chloride and *sym*-phthaloyl chloride, which were allowed to react with catechol in pyridine solution at low temperature to give *1d* and *1e* in very low yield (3–5 %). The formation of compounds *1d* and *1e* was accompanied by the isomeric pseudo esters *3a* and *3b*, which rendered the isolation of pure *1d* and *1e* more difficult. When other methyl substituted succinoyl chlorides were used, polymer formation and increased amounts of pseudo ester *3* made this method inapplica-



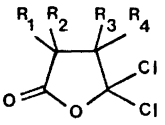
3. *a*. R_{1-4}=Me.
c. $R_{1,3}$=H. $R_{2,4}$=Me.



3. b.

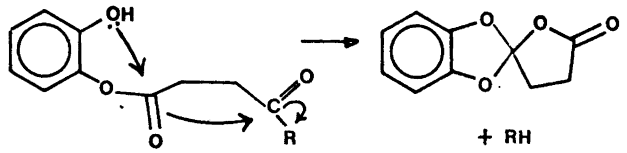
ble for the synthesis of the other compounds in this series. The preparation of *3a* can be performed with moderate yield by reacting catechol or sodium catecholate with tetramethylsuccinoyl chloride in a suitable solvent.

The formation of pseudo esters like *3a* and *3b* can be interpreted in two ways: (*i*) either reaction of the ring form *4b* of the acid chloride with catechol; or



4. *a*. R_{1-4} = H.
b. R_{1-4} = Me.

(ii) according to the mechanism described in eqn. 1. A recent investigation on the ring-chain tautomerism of succinoyl chloride has given no evidence for existence of the ring form *4a*.[8] The ring-chain forms in this system may, how-



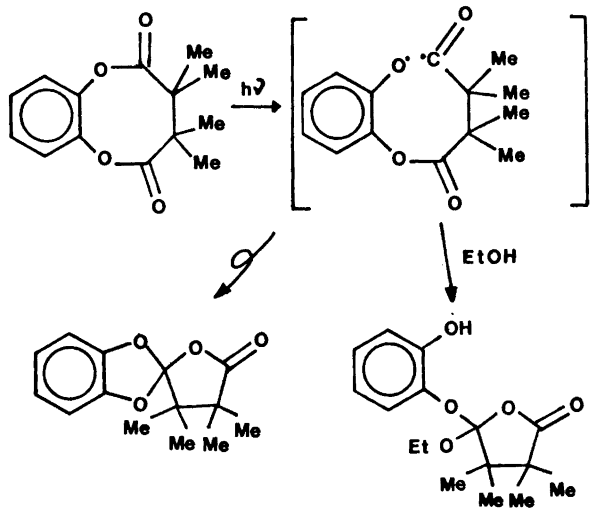
(1)

R = Cl or $C_6H_{11}N{=}C(O)-NHC_6H_{11}$

ever, be in a rapid equilibrium with a very low concentration of the ring form, undetectable by the usual spectroscopic methods. α,α-Dimethylsuccinaldehydic acid has recently been reported to exhibit ring-chain tautomerism.[9] It is reasonable to assume that the *gem*-dimethyl effect may be operating also in the succinoyl chloride series, thus making the tetramethyl derivative *4b* more stable. NMR-spectroscopy of neat tetramethylsuccinoyl chloride reveals a small doublet located between the two peaks from the methyl groups in the *sym*-acid chloride and the anhydride, which is present as an impurity. This doublet may derive from the two pairs of non-equivalent methyl groups in the ring from *4b*. Phthaloyl chloride, which is known to exhibit ring-chain tautomerism,[10] gives both *1e* and *3b* when the pure *sym*-form is utilized as starting material. Thus, it seems most probable that both mechanisms are working simultaneously.

Formation of pseudo ester *3a* also takes place in the photolysis of *1d* in ethanol solution, (eqn. 2). The main product here is *ortho* ester *5*, which also may derive from ethanolysis of *1d*. However, when an ethanol solution of *1d* is kept in the dark for the same period of time, only traces of *ortho* ester *5* can be detected by GLPC-analysis.

2. *Condensation of catechol and the appropriate succinic acid in the presence of DCC*. Condensation of catechol with α-methyl succinic acid in the presence

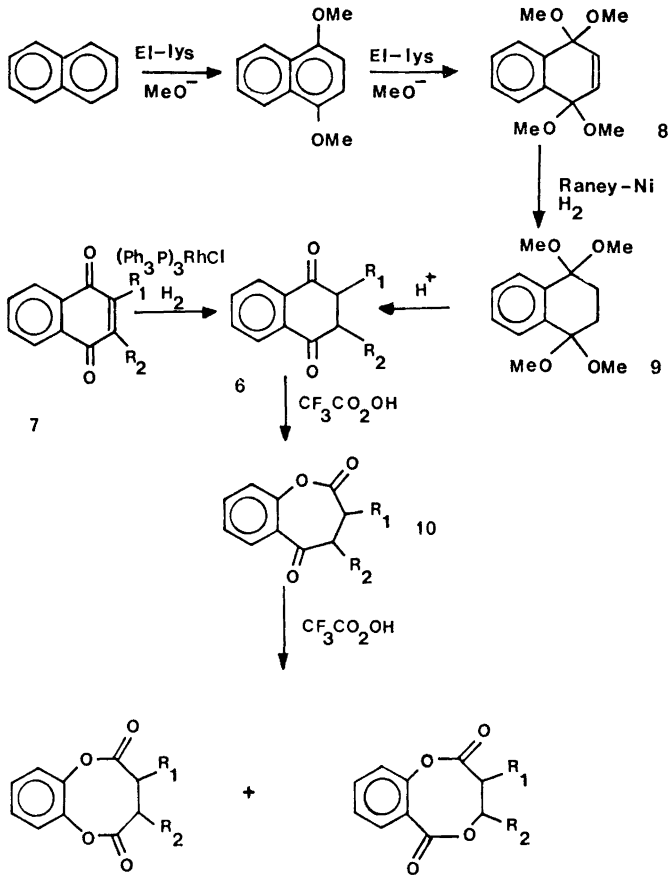


3 a 5 (2)

of DCC gave a very small amount of *1b*, as analyzed by GC/MS, but no pseudo ester formation was observed.

3. *Intramolecular condensation of o-hydroxyphenyl acid succinates in the presence of DCC.* Attempts to cyclize *o*-hydroxyphenyl acid succinates by use of DCC in ethyl acetate at high dilution resulted in moderate yields of *3c* and only traces (GC/MS) of the desired cyclic ester *1c*, again demonstrating the preference for formation of pseudo esters like *3a*, *b* and *c* in this system.

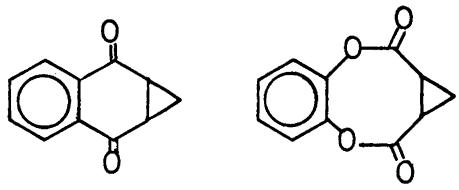
4. *Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalenediones and of ε-lactones.* Synthesis of compounds like *1* may, in certain cases, be effected *via* Baeyer-Villiger oxidation of 1,2,3,4-tetrahydro-1,4-naphthalene diones, *6*, with peroxytrifluoroacetic acid.[11] Compounds *6* are available *via* catalytic hydrogenation of the corresponding 1,4-naphthoquinones, *7*, in the presence of Wilkinsons catalyst, $(Ph_3P)_3RhCl$[12] (Scheme 1). In accordance with the proposed mechanism of action of this catalyst,[13] the reduction is very sensitive to steric hindrance, so that in the case of 2,3-dimethyl-1,4-naphthoquinone, only traces of *6*, $R_{1,2}$=Me, are formed (TLC). An alternative pathway for synthesis of *6*, $R_{1,2}$=H, is shown in Scheme 1. Here naphthalene, or better 1,4-dimethoxynaphthalene, is electrochemically oxidized between two platinum electrodes in the presence of methoxide[14] to yield 1,1,4,4-tetra-methoxy-naphthalene, *8*, which then undergoes catalytic hydrogenation in the presence of Raney-Ni to 1,2,3,4-tetrahydro-1,1,4,4-tetramethoxy-naphthalene, *9*. Acid hydrolysis of *9* gives a mixture of *6* and *7*. Baeyer-Villiger oxidation of *6* was found to proceed *via* the ε-lactone *10* which is rapidly oxidized to *1* (Scheme 1). Since the reaction products are very sensitive to moisture, the peroxyacid solution has to be carefully dried over molecular sieves, which also have to be present in the reaction mixture. It is also necessary to buffer the reaction mixture with NaH_2PO_4 to prevent transesterification of the ester formed with CF_3COOH.



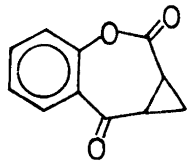
Scheme 1.

Complications were encountered for *6* $R_{1,2}$=Me. Baeyer-Villiger oxidation of this compound gave predominantly the isomeric salicylate *11* which made the isolation of *1c* unsuccessful. The formation of the salicylate is in agreement with earlier results concerning migratory aptitudes of different groups in the Baeyer-Villiger oxidation of phenyl alkyl ketones.[15]

Attempts have also been made to oxidize compound *12*, which in analogy



12. *13.*

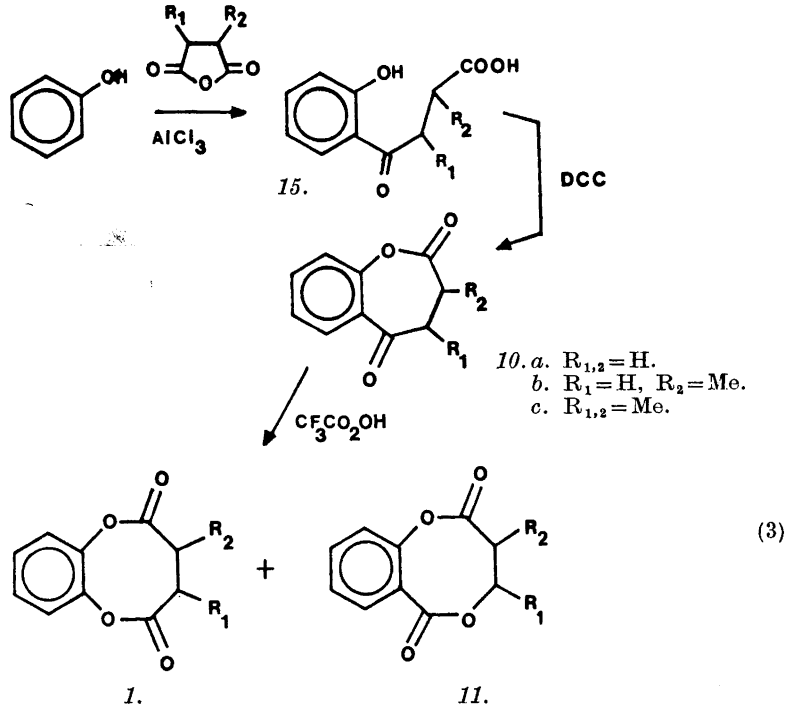


14.

with phenyl cyclopropyl ketone [16] should give the desired ester *13*. However, *12* was found to resist peroxytrifluoroacetic acid oxidation. Inspection of molecular models shows that the intermediate compound *14* has a very strained and rigid seven-membered ring, and since migration has been shown to be the rate determining step in the reaction,[17] the energy of activation must be too high to allow its formation. Anthraquinone also reacts very slowly with peroxytrifluoroacetic acid to give *1e* in low yield. This behaviour may be rationalized in the same way as for *14*.

As described above, ε-lactones with the structure *10* (Scheme 1) are first formed in the Baeyer-Villiger oxidation of *6* to *1*. Due to complications (formation of salicylate) in the oxidation of alkyl substituted derivatives of *6*, compounds *10b* and *10c* seemed more suitable as precursors to *1b* and *1c*.

Cyclization of β-(*o*-hydroxybenzoyl)-propionic acids *15* with Ac_2O according to Lammchen [18] gave low yields of the desired ε-lactone. However, DCC in

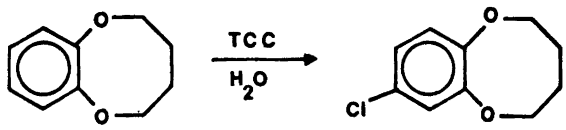


(3)

1. *11.*

diethyl ether was found to be an excellent condensing agent for the rapid and quantitative conversion of *15* to *10* (eqn. 3). The synthesis of *1b*, without concomitant formation of the isomeric salicylate, was thus effected by Baeyer-Villiger oxidation of ε-lactone *10b*, $R_1 = H, R_2 = Me$. Oxidation of *10c*, $R_{1,2} = Me$, resulted predominantly in formation of the salicylate *11* and no catechol succinate could be isolated. Again, methyl substitution α to the carbonyl group makes this carbon atom a better migrating group than phenyl, in accordance with what is found in the peroxytrifluoroacetic acid oxidation of phenyl alkyl ketones.[15]

5. *TCC-oxidation of 2,3,4,5-tetrahydro-1,6-benzodioxocin, 16.* Juenge *et al.*[19] have reported that TCC oxidizes ethers to esters. This approach was tried on phenetole and compound *16*,[20] which both reacted rapidly with TCC in acetonitrile-water. GC/MS-analysis of the reaction mixtures did not reveal any esters. Instead, it was found that quantitative conversion of the ethers to their monochlorinated derivatives had taken place (eqn. 4). When the reaction was allowed to proceed for a longer period of time (3 h), polychlorinated derivatives were formed. Reaction of TCC with activated benzene compounds thus seems to be a convenient route to the corresponding chlorinated derivatives, a method which has recently been reported by Juenge *et al.*[21]



(4)

16. *17.*

B. *o*-Hydroxyphenyl acid succinates

Since difficulties were to be expected in analyzing the kinetics of the two consecutive steps in the hydrolysis of compounds *1*, the corresponding *o*-hydroxyphenyl acid succinates *2 a – g* were also prepared in order to investigate their hydrolytic behaviour. Only one compound, *2a*, in this series has been described in the literature.[4a] The synthesis of this compound was performed by reaction of catechol monoanion with succinic anhydride in water solution followed by acidification of the reaction mixture. A modification of this method has been used by us for the preparation of the other compounds in this series.

Due to the hydrolytic sensitivity of compounds like *2*, together with the rapid rise in the rate of hydrolysis by increased alkyl substitution in the succinic acid moiety, the synthesis of compounds *2b – g* at first seemed difficult to achieve. However, the pH-rate profile for the hydrolysis of compound *2a* revealed competing intramolecular nucleophilic and general base catalysis, as recently reported by us.[22] This phenomenon made it possible to prepare compounds *2 b – g* by reacting catechol and the appropriate methyl substituted succinic anhydride at $pH \geq 10$, where the general base catalyzed hydrolysis of the ester formed was relatively slow due to steric hindrance from the methyl substituent(s). After drowning the reaction mixture in dilute hydrochloric

acid and immediate extraction with chloroform, the crude product was recrystallized from a suitable solvent. It is interesting to notice that even the tetramethyl derivative *2f*, with $t_{\frac{1}{2}} = 3.3$ sec at pH 7 and 25°C, was successfully synthesized in this manner.

In the case of unsymmetrically substituted anhydrides, where two isomeric esters are formed,[23] this method is supposed to give the structures formulated (*2 b, c* and *e*), with the most substituted carbon atom closest to the ester group, because of the more rapid hydrolysis of the other isomer during the work up procedure. Both NMR and mass spectrometry fail to give an answer about the correct substitution pattern. However, kinetic data fit well with the proposed structures.[24]

EXPERIMENTAL

Melting points were determined with the Kofler apparatus. Several of the described compounds decompose and/or sublime when heated, which makes their melting points less well defined. IR spectra (in KBr) were recorded on a Perkin-Elmer 257 and on a Unicam SP 200 G spectrophotometer. NMR spectra were recorded on a Varian A 60 NMR spectrometer. Mass spectra were recorded on an LKB A-9000 mass spectrometer at 70 eV. GLC analysis was performed on a Varian Aerograph Series 200 and on a Perkin-Elmer 880 instrument, on a 2 m × 0.3 cm 5 % NPGS on Chromosorb W column, and on a 5 % SE-30 on Chromosorb W column. TLC analyses were performed on Merck Fertigplatten F_{254}. Hydrogen peroxide (85 %) was obtained from the Research Institute of National Defence. Methyl substituted succinic anhydrides were prepared from their acids, which were available at the Division of Organic Chemistry, by refluxing with acetyl chloride. TMS-derivatives of *o*-hydroxyphenyl acid succinates, *2*, were prepared by reaction of *N,O*-bis(trimethylsilyl)-acetamide (BSA), (Pierce Chemical Co.), with a suspension of *2* in tetrahydrofuran.

3,4-Dihydro-1,6-benzodioxocin-2,5-dione, 1a. To a mixture of *3*, $R_{1,2} = H$ [25] (0.25 g, 1.6 mmol), NaH_2PO_4 (3.0 g dried at 110°C for 1 h) and molecular sieves (1 g, 3 Å) in dry CH_2Cl_2 (20 ml) was added dropwise with stirring a dried (mol. sieves 3 Å, 15 min) solution of CF_3CO_3OH (5 mmol, prepared from 1.0 ml $(CF_3CO)_2O$ and 0.18 ml 85 % H_2O_2 in 20 ml CH_2Cl_2). The mixture was stirred for 1 h at room temperature and then refluxed for 3 h, whereafter another portion (3 mmol) peroxyacid solution was added. After refluxing the mixture for another 3 h, it was left at room temperature overnight. The mixture was freed from inorganic salts by filtration and the filtrate evaporated to dryness to give a brown-yellow residue, which was extracted with dry ethyl ether. When the ether extracts were concentrated *in vacuo*, *1a* crystallized out of the solution. Yield 40 mg: m.p. 133°C. IR: 1785, 1770, 1500, 1460, 1290, 1260, 1150, 780 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 2.73$ ppm (s, 4 H), 7.37 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 192 (19), 110 (17) 55 (100).

Benzo-1,6-benzodioxocin-2,5-dione, 1e, was prepared from anthraquinone in the same manner as described for *1a*; m.p. ~ 184°C (subl.). IR: 1770, 1500, 1270, 1100, 1040, 770, 720 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 7.20$ ppm (m, 4 H), 7.55 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 240 (38), 196 (30), 132 (14), 104 (100), 76 (50).

3,4-Dihydro-3-methyl-1,6-benzodioxocin-2,6-dione, 1b, was prepared from *10b*, $R_1 = H$, $R_2 = Me$ (0.7 g), according to the method described for *1a*, using one portion of peroxyacid solution (prepared from 2.5 ml $(CF_3CO)_2O$ and 0.5 ml 85 % H_2O_2). Yield: 150 mg (ether): m.p. 95°C. IR: 1785, 1770, 1490, 1300, 1250, 1160, 1130, 780 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 1.32$ ppm (d, $J = 5.7$ cps, 3 H), 2.65 ppm (m, 3 H) 7.30 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 206 (10), 110 (5), 69 (100), 52 (13), 42 (12), 41 (21).

Attempted preparation of 3,4-dihydro-3,4-dimethyl-1,6-benzodioxocin-2,5-dione, 1c. ε-Lactone *10c*, $R_{1,2} = Me$, (0.2 g) was oxidized according to the method described for *1a*. Although TLC (silica gel, benzene) indicated that minor amounts of *1c* had been formed, isolation of this product was unsuccessful. Instead, the isomeric salicylate *11* was isolated

in low yield (10 mg) from diethyl ether – hexane; m.p. 70°C (decomp.). IR: 1775, 1715, 1450, 1290, 1210, 1150, 760 cm^{-1}. Mass spectrum *m/e* [rel. int. (%)]: 220 (4), 120 (100), 92 (42), 83 (45), 64 (15).

3,3,4,4-Tetramethyl-1,6-benzodioxocin-2,5-dione, 1d. To a solution of catechol (2.2 g, 0.02 mol) in dry pyridine (100 ml). cooled in an icebath, was added a solution of tetramethylsuccinoyl chloride [26] (4.3 g, 0.02 mol) in $CHCl_3$ (20 ml), The red solution was left in the refrigerator for 3 days, whereafter the mixture was poured into ice-water (1 l). A brown oil separated and was isolated from the water phase in a separating funnel. The water phase was extracted with $CHCl_3$ and the combined extracts were dried over anhydrous $MgSO_4$. After filtration, the filtrate was evaporated to dryness to yield a brown sirup which was dissolved in ethanol. After addition of water, a precipitate (2.0 g) was formed. GLPC analysis of this material revealed two close-lying peaks in the ratio 4 : 1. After recrystallization from petroleum ether (b.p. 40 – 60°C), 1.5 g rods, m.p. 147°C, could be isolated. GLPC analysis of this material showed only one peak with the same retention time as the predominant peak from the mixture above. The compound was found to be pseudo ester *3a*. IR: 1800, 1480, 1275, 1230, 1150, 1105, 950, 930, 840, 740 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 1.18$ ppm (s, 6 H), 1.33 ppm (s, 6 H), 6.95 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 248 (38), 189 (46), 121 (15), 110 (25), 83 (100), 69 (14), 55 (12), 41 (17). The mother-liquor from above was evaporated to dryness and the residue recrystallized from petroleum ether (b.p. 80 – 110°C) yielding 150 mg *1d*, m.p. 156 – 158°C, gas chromatographically pure. IR: 1770, 1490, 1250, 1170, 1090, 760 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 1.34$ ppm (s, 12 H), 7.15 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 248 (14), 110 (25), 83 (100), 69 (17), 55 (12), 41 (15).

Benzo-1,6-benzodioxocin-2,5-dione, 1e, was also prepared according to the method described for *1d*, yielding a mixture of *1e* and *3b*. The following data were measured for *3b:* m.p. ~ 240°C (subl.). IR: 1785, 1480, 1310, 1290, 1230, 1110, 930, 910, 840, 750 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 7.05$ ppm (m, 4 H), 7.75 ppm (m, 4 H). Mass spectrum *m/e* [rel. int. (%)]: 240 (45), 196 (41), 132 (13), 110 (13), 104 (100), 76 (57), 50 (85).

o-*Hydroxyphenyl acid* meso-α,α′-*dimethylsuccinate, 2d.* A solution of *meso*-α,α′-dimethylsuccinic anhydride (1.3 g, 0.01 mol) in dioxane (10 ml) was added in small portions to a stirred and chilled (+10°) water solution of catechol (1.1 g, 0.01 mol) and KOH (0.6 g). The reaction was allowed to proceed for 5 min at 10°C, whereafter the mixture was poured into 5 M HCl (20 ml). The acid solution was immediately extracted with $CHCl_3$ and the combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. After addition of hexane, a crystalline precipitate of *2d* formed. Yield: 1.3 g, m.p. 108 – 109°C. IR: 3410, 1740, 1710, 1510, 1460, 1220, 1160, 760 cm^{-1}. NMR spectrum ($CDCl_3$) $\delta = 1.34$ ppm (d, $J = 6.9$ cps, 6 H), 3.08 ppm (m, 2 H), 6.97 ppm (m, 4 H), 8.55 ppm (broad, 1 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 367 (M – 15) (0.9), 254 (13), 201 (34), 75 (13), 73 (100).

Compounds *2 a, b, c, rac-2d* and *e – g* were prepared in the same manner as described above for *meso-2d*.

o-*Hydroxyphenyl acid succinate, 2a*, m.p. 132 – 133°C (lit.[4a] m.p. 122 – 123°C). IR: 3370, 1730, 1710, 1500, 1250, 1210, 930, 765 cm^{-1}. NMR spectrum ($(CD_3)_2CO$): $\delta = 2.83$ ppm (m, 4 H), 7.03 ppm (m, 4 H), 8.71 (broad, 1 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 339 (M – 15) (1.2), 254 (13), 173 (48), 75 (17), 73 (100).

o-*Hydroxyphenyl acid* α-*methylsuccinate, 2b*, m.p. = 124°C. IR: 3420, 1740, 1710, 1510, 1460, 1220, 1180, 940, 745 cm^{-1}. NMR spectrum ($CDCl_3$): $\delta = 1.31$ ppm (d, $J = 6.8$ cps, 3 H), 2.87 ppm (m, 3 H), 6.83 ppm and 6.97 ppm (m, 4 H), 7.91 ppm (broad, 1 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 353 (M – 15) (1.2), 254 (15), 187 (40), 75 (13), 73 (100).

o-*Hydroxyphenyl acid* α,α-*dimethylsuccinate, 2c*, m.p. 100°C. IR: 3420, 1755, 1685, 1500, 1260, 1220, 1110, 930, 755 cm^{-1}. NMR spectrum ($(CD_3)_2CO$): $\delta = 1.40$ ppm (s, 6 H), 2.85 ppm (s, 2 H), 6.95 ppm (m, 4 H), 8.33 ppm (broad, 1 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 367 (M – 15) (0.3), 254 (15), 201 (18), 117 (9), 75 (13), 73 (100).

o-*Hydroxyphenyl acid* DL-α-α′-*dimethylsuccinate, 2d*, m.p. 108°C. IR: 3420, 1740, 1710, 1510, 1460, 1215, 1150, 750 cm^{-1}. NMR spectrum ($CDCl_3$): $\delta = 1.34$ ppm (d, $J = 6.9$ cps, 6 H), 3.08 ppm (m, 2 H), 6.97 ppm (m, 4 H), 8.00 ppm (broad, 1 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 367 (M – 15) (0.1), 254 (13), 201 (30), 75 (13), 73 (100).

o-Hydroxyphenyl acid phthalate, 2g, m.p. 130°C. IR: 3300, 1760, 1720, 1500, 1265, 1100, 1050, 745 cm^{-1}. NMR spectrum ($(CD_3)_2CO$): $\delta = 7.1$ ppm (m, 4 H), 7.8 ppm (m, 4 H). Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 254 (6), 221 (20), 100 (15), 74 (10), 73 (100).

In the case of compounds *2e* and *2f*, no pure crystalline material could be obtained. IR spectra of the crude products showed contamination with catechol and anhydride. However, GC/MS analysis of the silylated crude material showed that *2e* and *2f* were present. IR spectrum of the crude material obtained from the synthesis of *2f* showed the following absorption bands: 3440, 1725, 1700, 1510, 1460, 1220, 1160, 750 cm^{-1}. Mass spectrum of di-TMS derivative, *m/e* [rel. int. (%)]: 395 (M − 15) (traces), 254 (100), 229 (40), 73 (30) at 7.5 eV. Mass spectrum of di-TMS derivative of *2e*, *m/e* [rel. int. (%)]: 381 (M − 15) (0.4), 254 (100), 215 (48) at 9.0 eV.

Pseudo ester, 3a. To a solution of catechol (1.1 g, 0.01 mol) and Na_2CO_3 (1.1 g) in dry benzene (250 ml) was added a solution of tetramethylsuccinoyl chloride (2.1 g, 0.01 mol) in benzene (25 ml). The mixture was refluxed with stirring for 2 days. GLPC analysis of the reaction mixture showed that only *3a* had been formed; no *1d* could be detected. *3a* was isolated after recrystallization from ethyl ether. Yield 2.0 g.

Photolysis of compound, 1d. A solution of *1d* (5 mg) in ethanol (2 ml) in a Pyrex glass tube was allowed to stand in the daylight for 11 days, when GLPC analysis revealed two new peaks in the ratio 1 : 3. The mixture was analyzed by GC/MS and the two products formed were found to be pseudo ester *3a* and ortho ester *5*. The latter compound showed no molecular ion in the mass spectrum which showed the following fragment ions, *m/e* [rel. int. (%)]: 249 (5), 221 (5), 185 (45), 157 (37), 151 (11), 110 (28), 87 (80), 85 (10), 84 (40), 83 (100), 69 (57).

1,1,4,4-Tetramethoxynaphthalene, 8. 1,4-Dimethoxynaphthalene [27] (1.8 g) was dissolved in 1 % KOH/MeOH and the solution electrolyzed between two Pt-electrodes. 1.3 A passed through the solution, which was chilled in an ice-bath during the electrolysis. The reaction was stopped after 2 h when the current had dropped to 1.0 A. The solvent was evaporated *in vacuo* (30°C, water-bath) and the residue was taken up in diethyl ether and washed with water. The ether solution was dried over anhydrous $MgSO_4$and filtered, and the filtrate was evaporated to yield an oily residue to which hexane was added. After one night in the refrigerator an oil had separated. The *supernatant* was decanted and evaporated to give 1.5 g of a yellow oil which crystallized after standing for several months in the refrigerator; m.p. 35 − 38°C (decomp.). IR: 2940, 2830, 1460, 1390, 1310, 1070, 975, 950, 770 cm^{-1}. NMR spectrum ($CDCl_3$): $\delta = 3.32$ ppm (s, 12 H), 6.50 ppm (s, 2 H), 7.70 ppm (m, 4 H).

Compound *8* can also be obtained by electrolysis of naphthalene in the same manner as described above. The formation of *8* is accompanied by 1-methoxynaphthalene and 1,4-dimethoxynaphthalene, which on prolonged methoxylation give the desired ketal *8*. In a typical run, the composition of the reaction mixture after 4 h electrolysis was found to be 1-methoxynaphthalene, 1,4-dimethoxynaphthalene, and *8* in the ratio 2:4:1.

1,2,3,4-Tetrahydro-1,1,4,4-tetramethoxynaphthalene, 9. A solution of *8* (1.0 g) in methanol (50 ml) was hydrogenated at room temperature and athmospheric pressure in the presence of Raney-Ni. After 30 h the hydrogen uptake was 90 ml (calculated value). The catalyst was filtered off and the filtrate analyzed by TLC (silica gel, cyclohexane − diethyl ether 7 : 3) which revealed *9* (IR: 2950, 2830, 1460, 1390, 1265, 1185, 1140, 1070, 1050, 930, 765 cm^{-1}) as a spot with a lower R_F-value than the starting material. Two other spots were also seen, one of which was identified as 1,4-dimethoxynaphthalene (IR identical with an authentic sample) and the other tentatively as 4,4-dimethoxy-α-tetralone. IR: 2940, 2830, 1690, 1460, 1320, 1190, 1140, 1075, 1050, 930, 770 cm^{-1}. Acid hydrolysis of the crude product *9* gave *6* ($R_{1,2}$ = H) and *7* ($R_{1,2}$ = H) as analyzed by TLC (silica gel, benzene).

ε-Lactone of α-methyl-β-(o-hydroxybenzoyl)-propionic acid, 10b (R_1 = H, R_2 = Me). α-Methyl-β-(*o*-hydroxybenzoyl)-propionic acid [28] (0.2 g) was dissolved in dry ethyl ether (100 ml), whereafter a solution of DCC (0.2 g) in a small volume of diethyl ether was added. After a few minutes, *N,N*-dicyclohexylurea began to precipitate. The mixture was allowed to stand for 1 h at room temperature, whereafter the urea was filtered off. The filtrate was concentrated *in vacuo* and hexane added to cloudiness. The solution was left in the refrigerator for a couple of hours to deposit 150 mg of crystalline title compound; m.p. 95°C. IR: 1770, 1680, 1450, 1200, 1140, 1100, 770 cm^{-1}. NMR spectrum ($CDCl_3$): $\delta = 1.31$

ppm (d, $J=4.8$ cps, 3 H), 3.0 ppm (m, 3 H), 7.35 ppm (m, 4 H). Mass spectrum, *m/e* [rel. int. (%)]: 190 (40), 162 (20), 147 (78), 121 (100), 120 (40), 93 (10), 92 (40), 65 (10), 64 (20), 63 (18). In the same manner were prepared ε-lactone *10a* ($R_{1,2}=H$) [IR: 1770, 1685 cm^{-1}; NMR spectrum ($CDCl_3$): $\delta=2.98$ ppm (s, 4 H), 7.45 (m, 4 H); mass spectrum *m/e* [rel. int. (%)]: 176 (20), 148 (20), 147 (17), 121 (100), 93 (14), 92 (10), 65 (10), 63 (10)] and ε-lactone *10c* ($R_{1,2}=Me$) [IR: 1760, 1680 cm^{-1}; mass spectrum *m/e* [rel. int. (%)]: 204 (50), 161 (87), 121 (100), 120 (52), 92 (74), 83 (46), 65 (22), 64 (35), 63 (30), 55 (41)].

TCC oxidation of 1,6-benzodioxocin, 16. Small portions of TCC (total 1.4 g) were added, with stirring, to a chilled (ice-bath) suspension of *16* (0.5 g) and H_2O (0.32 ml). After a short induction period, an exothermic reaction started. The reaction was followed by GLPC and after 1 h it was found that only traces of the starting material were left, and a new peak with longer retention time than the starting material was found. GC/MS analysis of this peak revealed 8-chloro-1,6-benzodioxocin, *17*. Mass spectrum, *m/e* [rel. int. (%)]: 200 (10), 198 (38), 157 (10), 156 (10), 155 (30), 146 (15), 144 (43), 79 (10), 63 (10), 55 (100).

When the same method was used for the attempted oxidation of phenetole to phenyl acetate, GLPC analysis after 5 min reaction time revealed quantitative conversion of phenetole to *p*-chlorophenetole, together with traces of the *o*-isomer. (Mass spectrum and retention time identical with authentic samples.) When the reaction mixture was allowed to stand for 3 h at room temperature, it became orange red, and GC/MS analysis revealed 2,4-dichlorophenetole. Mass spectrum, *m/e* [rel. int. (%)]: 192 (21), 190 (34), 166 (10), 164 (62), 162 (100), 131 (10), 99 (10), 98 (26), 73 (10), 63 (26). Also minor amounts of trichlorophenetole were formed: Mass spectrum, *m/e* [rel. int. (%)]: 228 (6), 226 (20), 224 (20), 200 (35), 198 (100), 196 (100), 164 (12), 162 (25), 160 (10), 134 (11), 132 (20), 99 (10), 97 (30), 62 (10).

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