Quinol Epoxides from *p*-Cresol and Estrone by Photooxygenation and Titanium(IV)- or Vanadium(V)-Catalyzed Oxygen Transfer

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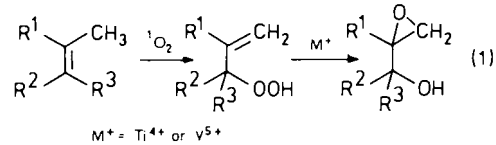
On treatment with $Ti(OiPr)_4$, 4-hydroperoxy-4-methyl-2,5-cyclohexadien-1-one (1) and 10β-hydroperoxy-1,4-estradiene-3,17-dione (3), readily available by photooxygenation of *p*-cresol and estrone, respectively, were converted to the corresponding epoxy quinols 5 and 6a,b. Also significant amounts of the respective quinols 2 and 4 were obtained, which could be transformed in high yields into 5 and 6a,b by Sharpless oxidation with *tert*-butyl hydroperoxide using $Ti(OiPr)_4$ or $VO(acac)_2$ as catalysts. Epoxidation of the quinol 4 with *m*-CPBA led preferentially to the lactone 7 by Bayer-Villiger rearrangement, showing the advantage of the present synthetic method.

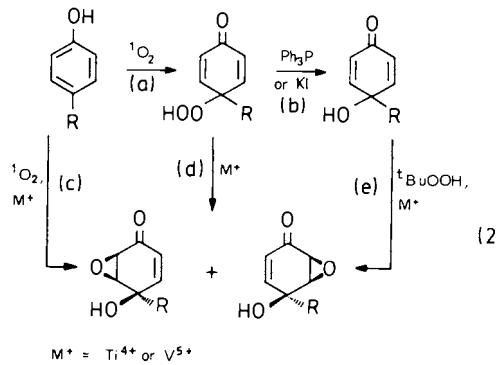
Die Chinolepoxide des *p*-Kresols und Östrons mittels Photooxygenierung und Titan(IV)- oder Vanadium(V)-katalysiertem Sauerstofftransfer

Wenn 4-Hydroperoxy-4-methyl-2,5-cyclohexadien-1-on (1) und 10β-Hydroperoxy-1,4-östradien-3,17-dion (3), die durch Photooxygenierung von *p*-Kresol bzw. Östron leicht zugänglich sind, mit $Ti(OiPr)_4$ behandelt werden, entstehen die Chinolepoxide 5 bzw. 6a,b. Es werden dabei auch signifikante Mengen der Chinole 2 bzw. 4 gebildet, welche durch Sharpless-Oxidation mit *tert*-Butylhydroperoxid und $Ti(OiPr)_4$ oder $VO(acac)_2$ als Katalysatoren in hohen Ausbeuten in 5 bzw. 6a,b übergeführt werden konnten. Epoxidierung des Chinols 4 mit *m*-CPBA ergab durch Bayer-Villiger-Umlagerung bevorzugt das Lacton 7, was den Vorzug der jetzigen synthetischen Methode unterstreicht.

The direct oxygen functionalization of alkenes by photosensitized oxygenation and titanium- or vanadium-catalyzed oxygen transfer sequence opened up a convenient entry to the synthetically valuable allylic epoxy alcohols (Eq. 1)[2)]. A particular advantage is the fact that this sequence can be performed as a "one-pot" synthesis by running the photooxygenation in the presence of the d^0 transition metal catalyst, without the necessity of isolating the potentially hazardous allylic hydroperoxides. Since alkyl-substituted phenols are readily converted to the 4-hydroperoxy-2,5-cyclohexadien-1-ones with singlet oxygen[3)], an attractive opportunity offered itself for the preparation of quinol epoxides by employing Ti(+4)- or V(+5)-catalyzed oxygen transfer, as illustrated in Eq. (2). Besides the options of the "one-pot" hydroxyepoxidation (step c, Eq. 2) and the stepwise functionalization (steps a and d, Eq. 2), also the Sharpless route (step e, Eq. 2) is feasible, for which the quinol would be made available via the steps a and b in Eq. (2).



(1)



(2)

Our interest[4)] centered on estrone since direct hydroxyepoxidation of its phenolic moiety by the above transformations (Eq. 2) would provide novel oxygen functionalized steroids with potentially interesting physiological activity[5)]. As model compound for these hydroxyepoxidations we chose *p*-cresol, for which the quinol epoxide is to date still unknown. We herewith report our experiences on the chemical transformations of *p*-cresol and estrone according to Eq. (2).

Results and Discussion

The photooxygenation of *p*-cresol was carried out in CCl_4 at 0°C using tetraphenylporphin (TPP) as sensitizer, affording crystalline 4-hydroperoxy-2,5-cyclohexadien-1-one (1) in ca. 95% yield. We found it unnecessary and, in fact, disadvantageous of using the recommended[3b)] tetra-*n*-butylammonium fluoride. Lower yields of impure hydroperoxide 1 were obtained. Reduction of the hydroperoxide 1 with triphenylphosphane in ethanol led essentially quantitatively to the quinol 2.

Similarly, the known[4)] steroidal hydroperoxide 3 was obtained in 54% yield free of quinol 4, employing TPP as sensitizer and methylene chloride as solvent. Reduction of 3 with potassium iodide in ethanol gave the quinol 4 in ca. 85% yield.

Since the quinol epoxide 5 derived from *p*-cresol was unknown, it was decided to employ first the Sharpless epoxidation[6)] on the quinol 2 (step e, Eq. 2), in order to make available authentic material. As expected, especially for electron poor substrates[6b,7)], $VO(acac)_2$ was the more effective catalyst for oxygen transfer to quinol 2 with *tert*-

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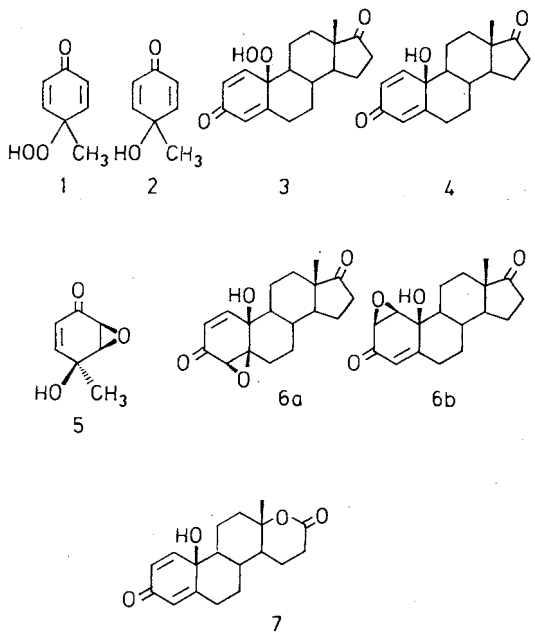

butyl hydroperoxide. Using two equiv. of *t*-BuOOH and 2.5% $VO(acac)_2$ in refluxing benzene, after 24 h 65% conversion of the quinol **2** was realized. With four equiv. of *t*-BuOOH and otherwise same conditions, 81% conversion was achieved. The pure quinol epoxide was isolated in ca. 70% yield (corrected for % conversion) after flash chromatography on silica gel. Its structure was established by analytical and spectral data (cf. Experimental). The *cis* stereochemistry of the hydroxy epoxide moiety in **5** is consistent with the Sharpless mechanism[6]. It is of interest to mention that attempts to produce the bisepoxide under these epoxidation conditions failed. Presumably steric hindrance prevents complexation of the substrate to the metal site for oxygen transfer.

The quinol **4** derived from estrone was more reactive towards Sharpless epoxidation than quinol **2**. With 2.0% $VO(acac)_2$ in refluxing benzene using two equiv. *t*-BuOOH, 100% conversion was obtained within 16 h, leading to a 50:50 mixture of the two epoxides **6a, b**. On the other hand, with 100% $Ti(OiPr)_4$ and otherwise same conditions, after 24 h 70% conversion into a 69:31 mixture of **6a** and **6b**, respectively, was achieved. The regioselectivity could only be slightly improved (73:27 mixture of **6a** and **6b**) when the oxygen transfer was performed in methylene chloride at 0°C (70% conversion after 48 h). The two quartets for the methyl group (δ = 13.57 and 13.72), the two singlets for C-10 (δ = 72.73 and 70.73), the two singlets for the cyclohexenone C=O (δ = 194.56 and 192.17) and the two singlets for the cyclopentanone C=O (δ = 220.33 and 220.07) in the ^{13}C-NMR spectrum clearly revealed that the regioisomers **6a, b** were on hand as mixture. Separation of **6a, b** could be accomplished by preparative HPLC. The structure assignment rests on analytical and spectral data (cf. Experimental).

For comparison, the epoxidation of quinol **4** was conducted with *m*-chloroperbenzoic acid (*m*-CPBA) in methylene chloride at room temperature (ca. 20°C), buffered with solid Na_2CO_3. Oxygen transfer was quite slow and after ca. 4 d about 55% of **4** was converted into a mixture of several products containing quinol lactone **7** as main one, with small amounts of epoxy quinol **6a** but no epoxy quinol **6b**. Lactone **7** was isolated by column chromatography in ca. 36% yield and was fully characterized on the basis of its analytical and spectral data (cf. Experimental). Clearly, the advantage of the Sharpless versus *m*-CPBA epoxidation of such ketonic quinols is demonstrated, since Bayer-Villiger rearrangement predominates in the latter for these substrates.

The stage was now set to perform the "one-pot" hydroxyepoxidation of *p*-cresol and estrone by conducting their photooxygenation directly in the presence of the Ti(+4) and V(+5) catalysts. $VO(acac)_2$ led with both phenols to a dark colored, illdefined product mixture. In the case of $Ti(OiPr)_4$, presumably the orange-red colored phenolate complexes[8] were obtained on mixing with the phenols, as evidenced by ligand exchange in the ^1H NMR. Photooxygenation did not afford the desired quinol epoxides **5** and **6a, b**. Consequently this methodology was abandoned.

Similar discouraging results were obtained in the attempted epoxidation of the hydroperoxides **1** and **3** with $VO(acac)_2$ as catalyst. Intractable and complex product mixtures resulted, presumably due to free radical chemistry that was initiated by $VO(acac)_2$. However, more encouraging turned out to be the $Ti(OiPr)_4$-catalyzed oxygen transfer, especially for the hydroperoxide **3** derived from estrone. Using one equiv. of $Ti(OiPr)_4$ in methylene chloride at 0°C, after ca. 15 h all hydroperoxide **1** was consumed, affording a 7:73:20 mixture (by ^1H NMR) of *p*-cresol, quinol **2**, and quinol epoxide **5**. Thus, the major process was reduction to the quinol **2** of the Meerwein-Ponndorf-Verley type[9].

Under the same conditions, the $Ti(OiPr)_4$ catalyst transformed the steroidal hydroperoxide **3** within 16 h completely into a 42:47:11 mixture of quinol **4** and its epoxides **6a** and **6b**, respectively. In this case, the epoxidation predominated over reduction. However, in principle, quinol **4** can be converted into the epoxides **6a, b** by exposing the crude reaction mixture to the Sharpless oxidation with *t*-BuOOH as external oxygen donor (path e in Eq. 2). Thus, a useful synthetic method is available for functionalizing estrone into its allylic epoxy alcohols **6a, b** by the photooxygenation and Ti(+4)-catalyzed oxygen transfer sequence.

We thank the *Deutsche Forschungsgemeinschaft* (SFB 172 "Molekulare Mechanismen Canzerogener Primärveränderungen"), the *Fonds der Chemischen Industrie*, the *Fritz Thyssen Stiftung* and the *CIRIT* for financial support. A sample of estrone was kindly provided by the *Schering A.G.* Berlin. For spectral services we are grateful to Dr. *G. Lange* (MS) and Dr. *D. Scheutzow* (NMR).

Experimental

Melting points: Reichert Thermovar Kofler apparatus (uncorrected). – Commercial solvents were purified according to standard procedures. – Unless otherwise specified, known compounds were either prepared according to literature procedures or purchased from standard suppliers and purified to match the reported physical and spectral data. – Rotary-evaporation of the solvent was carried out at 15–22°C/10–20 Torr. – Vacuum column chromatography[10] was run on silica gel (Merck, 60H) and flash

column chromatography on silica gel (0.032–0.063 mm, Woelm) using a ca. 1:50 substrate-adsorbant ratio. – Preparative HPLC: Prepacked LiChrospher-100, 5 μm (Merck), 20 × 250 mm column (Bischoff). – The usual workup of the titanium isopropoxide reactions entailed dilution of the reaction mixture with the double volume of ether and addition of 1 ml of water per mmol of titanium catalyst, followed by vigorous stirring for 1–2 h at room temp. (ca. 20°C). Subsequent filtration over Celite, drying with magnesium sulfate and rotary-evaporation of the solvent afforded the crude products, which were purified as described.

The photooxygenations were carried out at 0°C in a Pyrex vessel by purging with a gentle stream of dry oxygen. The solvent (CCl_4 or CH_2Cl_2) is specificied for each particular case. The light source was an external Phillips (G/28/2 SON) 150-W sodium high pressure lamp. Tetraphenylporphin (TPP) (ca. 3 mg per mmol substrate) was used as sensitizer. The reaction progress was monitored by TLC and peroxide test (potassium iodide in acetic acid).

IR spectra: Perkin-Elmer Ratio Recording Infrared Spectrophotometer 1420. – UV spectra: Perkin-Elmer 330 UV-VIS Spectrophotometer. – ^{1}H-NMR spectra: Bruker AC 200 (200 MHz) and Bruker WM 400 (400 MHz) spectrometers. – ^{13}C-NMR spectra: Bruker AC 200 (50 MHz) and Bruker WM 400 (100 MHz) Spectrometers. – MS: Varian MAT CH-7. – Elemental analyses: in-house.

4-Hydroperoxy-4-methyl-2,5-cyclohexadien-1-one (**1**): Analogous to the reported procedure[3b], except with a different choice of solvent and sensitizer, *p*-cresol (1.08 g, 10.00 mmol) in 80 ml of tetrachloromethane was photooxygenated during ca. 24 h. The crystalline product, that separated during the photooxygenation was collected by filtration, affording 1.32 g (94%). Further purification by column chromatography on silica gel at 0°C with methylene chloride/ethyl acetate (19:1) as eluent yielded 1.21 g (87%) of white plates, m.p. 94–98°C (methylene chloride). Iodometric titration indicated more than 98% of peroxidic product. – IR (KBr): 3240–3220 cm^{-1} (OH), 2995, 1670 (C=O), 1620 (C=C), 1610 (sh), 1400, 1315, 1190, 1095, 1065, 865. – UV (MeOH): λ_{max} (lg ε) = 226 nm (4.15). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 3H, CH_3), AB signal (δ_A = 7.02, δ_B = 6.30, J_{AB} = 9.9 Hz, 4H, CH=CH), 10.48 (br. s, 1H, OOH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.38 (q, CH_3), 78.43 (s, C-4), 129.55 (d, C-2,6), 151.76 (d, C-3,5), 186.71 (s, C-1). – MS (70 eV): *m/z* (%) = 140 (0.34, M^+), 125 (2), 124 (6), 122 (3), 109 (15), 108 (24), 107 (100), 79 (33), 77 (48), 54 (13), 53 (14), 52 (11), 51 (12), 43 (16), 39 (14).

4-Hydroxy-4-methyl-2,5-cyclohexadien-1-one (**2**): Reduction of **1** (1.40 g, 10.00 mmol) with triphenylphosphane (2.62 g, 10.00 mmol) in 25 ml of ethanol, followed by vacuum column chromatography[10] on silica gel using in sequence 7:3, 6:4 and 1:1 mixtures of petroleum ether (30–50) and ethyl acetate as eluants, gave 1.19 g (96%) of **2** as a pale yellow solid. Recrystallization from petroleum ether (30–50°C)/methylene chloride yielded white needles, m.p. 77.5–79°C (ref.[11] 74–75°C, ligroin). – IR (KBr): 3465–3450 cm^{-1} (OH), 3000, 2950, 1670, 1645 (C=O), 1630 (C=C), 1400, 1190, 1100, 1050, 870. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 3H, CH_3), 3.16 (br. s, 1H, OH), 6.09 and 6.90 (d, *J* = 10.1 Hz, 4H, CH=CH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.71 (q, CH_3), 67.05 (s, C-4), 126.93 (d, C-2,6), 152.44 (d, C-3,5), 185.54 (s, C-1).

10β-Hydroxy-1,4-estradiene-3,17-dione (**4**): In analogy to the literature procedure[4] with slight modifications, the photooxygenation (cf. general aspects) of estrone (540 mg, 2.00 mmol) in methylene chloride (80 ml) was conducted for ca. 24 h. Rotary-evaporation of the solvent, subsequent dilution of the crude reaction mixture with ethanol (20 ml), and reduction with an aqueous solution of potassium iodide (4 ml, 1.0 M) yielded after workup 430 mg of crude product. Column chromatography on silica gel using in sequence 9:1 and 8:2 mixtures of methylene chloride and ethyl acetate as eluants gave 239 mg (42%) of **4**, m.p. 202–204°C, needles (acetone/petroleum ether 30–50°C) (ref.[4] 210–211.5°C).

5-Hydroxy-5-methyl-7-oxabicyclo[4.1.0]hept-3-en-2-one (**5**): To a solution of 621 mg (5.00 mmol) of the quinol **2** in 50 ml of dry benzene was added at 0°C under nitrogen a freshly prepared solution of $VO(acac)_2$ catalyst (33 mg, 0.125 mmol) in 10 ml of benzene, followed by dropwise addition of 3.3 ml of a 3.0 M solution of *tert*-butyl hydroperoxide (10.0 mmol) prepared according to the usual procedure[12]. After complete addition (ca. 5 min), the solution was allowed to warm up and was refluxed for ca. 24 h. The reaction mixture was allowed to cool to room temp. and the solvent was removed. The residue (654 mg) was chromatographed on silica gel using in sequence 98:2, 97:3, and 95:5 mixtures of methylene chloride and ethyl acetate as eluants. The first fraction afforded after rotary-evaporation of the solvent 325 mg (46%) of a pale yellow solid, which after two recrystallizations from methylene chloride/petroleum ether (30–50°C) gave 234 mg (33%) of epoxide **5** as white plates, m.p. 90–91.5°C. The second fraction (65 mg) consisted of a mixture of **5** and quinol **2**. – IR (KBr): 3500–3460 cm^{-1} (OH), 3350, 3060, 3040, 3000, 2950, 1710–1640 (C=O), 1620 (C=C), 1340, 1160, 1085, 1045, 915, 900, 845, 825. – UV (MeOH): λ_{max} (lg ε) = 221 nm (3.80). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 3H, CH_3), 2.98 (s, 1H, OH), 3.50 (dd, $J_{1,6}$ = 3.9, $J_{1,3}$ = 2.1 Hz, 1H, 1-H), 3.64 (dd, $J_{6,1}$ = 3.9, $J_{6,4}$ = 2.8 Hz, 1H, 6-H), 5.82 (dd, $J_{3,4}$ = 10.5, $J_{3,1}$ = 2.1 Hz, 1H, 3-H), 6.49 (dd, $J_{4,3}$ = 10.5, $J_{4,6}$ = 2.8 Hz, 1H, 4-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.23 (q, CH_3), 54.19 (d), 58.95 (d), 68.49 (s, C-5), 123.53 (d, C-3), 150.01 (d, C-4), 193.05 (s, C-2). – MS (70 eV): *m/z* (%) = 140 (10, M^+), 125 (15, $M^+ - 15$), 111 (45), 97 (100, $M^+ - 43$), 71 (25), 69 (33), 55 (54), 43 (90, CH_3CO), 41 (46), 39 (42), 18 (34).

$C_7H_8O_3$ (140.1) Calcd. C 60.00 H 5.75
Found C 60.18 H 5.59

Attempted epoxidation of **5**: A solution of epoxide **5** (701 mg, 5.0 mmol) in 40 ml of benzene after addition of $VO(acac)_2$ catalyst (33 mg, 0.125 mmol) and 3 ml of a 3.35 M solution of *tert*-butyl hydroperoxide (10 mmol) gave even after 48 h under the same conditions used for the quinol **2** no conversion to the desired bisepoxide.

4β,5β-Epoxy-10β-hydroxy-1-estrene-3,17-dione (**6a**) *and 1β,2β-Epoxy-10β-hydroxy-4-estrene-3,17-dione* (**6b**): To a solution of 960 mg (3.35 mmol) of **4** in 75 ml of dry benzene was added while stirring at 0°C under nitrogen 20 ml of a freshly prepared solution of $VO(acac)_2$ (22 mg, 0.067 mmol) in benzene, followed by dropwise addition of 2 ml of a 3.35 M solution of *tert*-butyl hydroperoxide (6.70 mmol) in methylene chloride, prepared according to the reported procedure[12]. On completc addition (ca. 5 min), the reaction mixture was allowed to warm up to 80°C and was refluxed for ca. 17 h. A control by TLC showed no unreacted starting material **4**. Evaporation of the solvent yielded 1.28 g of crude product that was chromatographed on silica gel with methylene chloride/ethyl acetate (9:1) as eluant. As main fraction was obtained 962 mg (95%) of a white powder, whose ^{1}H-NMR spectrum showed that it consisted of a 50:50 mixture of the two regioisomers **6a** and **6b**. The two components, **6a** (R_t = 19 min) and **6b** (R_t = 23 min), were separated by HPLC with ethyl acetate/petroleum ether (25:75) as eluant.

6a: M.p. 201.5–203°C (acetone/petroleum ether). – IR (KBr): 3480–3420 cm^{-1} (OH), 2960, 2930, 2870, 1740 (saturated C=O), 1695, 1675 (unsaturated C=O), 1630 (sh, C=C), 1385, 1085, 1050,

1005, 845. – UV (MeOH): λ_{max} (lg ε) = 235 nm (3.67). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.95 (s, 3H, CH_3), 1.00–2.20 (m, 13H), 2.37–2.60 (m, 2H), 2.66 (br. s, 1H, OH), 3.32 (d, $J_{4,2}$ = 2.1 Hz, 1H, 4-H), 5.85 (dd, $J_{2,1}$ = 10.7, $J_{2,4}$ = 2.1 Hz, 1H, 2-H), 6.65 (d, $J_{1,2}$ = 10.7 Hz, 1H, 1-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.57 (q, CH_3), 20.74, 21.72, 28.14, 28.52, 30.73 (t), 34.06 (d), 35.45 (t), 47.46 (s), 49.95 (d), 53.71 (d), 61.17 (d, C-4), 64.69 (s, C-5), 72.73 (s, C-10), 123.43 (d, C-2), 150.58 (d, C-1), 194.56 (s, C-3), 220.33 (s, C-17). – MS (70 eV): *m/z* (%) = 303 (20, $M^+ + 1$), 302 (M^+), 274 (36), 199 (31), 149 (29), 145 (25), 126 (37), 123 (36), 110 (41), 107 (38), 105 (32), 93 (41), 91 (49), 81 (35), 79 (49), 77 (34), 71 (49), 67 (50), 55 (67), 43 (30), 41 (67).

$C_{18}H_{22}O_4$ (302.4) Calcd. C 71.50 H 7.33
Found C 71.89 H 7.50
$C_{18}H_{22}O_4$ Calcd. 302.1518 Found 302.1515

6b: M.p. 194–195°C (acetone/petroleum ether). – IR (KBr): 3495–3485 cm^{-1}, 3435–3425 (OH), 2970, 2670, 1750 (saturated C=O), 1680 (unsaturated C=O), 1635 (C=C), 1085, 1050, 1005, 885. – UV (MeOH): λ_{max} (lg ε) = 247 nm (3.99). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (s, 3H, CH_3), 1.00–2.84 (m, 16H), 3.50 (dd, $J_{2,1}$ = 3.8, $J_{2,4}$ = 2.1 Hz, 1H, 2-H), 3.91 (d, $J_{1,2}$ = 3.8 Hz, 1H, 1-H), 5.72 (br. s, 1H, 4-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.72 (q, CH_3), 20.09, 21.77, 30.81, 32.03, 32.38, 34.58, 35.49, 47.41 (s), 50.20 (d), 51.28 (d), 55.92 (d), 57.44 (d), 70.73 (s, C-10), 119.36 (d, C-4), 164.60 (s, C-5), 192.17 (s, C-3), 220.07 (s, C-17). – MS (70 eV): *m/z* (%) = 303 (20, $M^+ + 1$), 302 (100, M^+), 256 (36), 199 (33), 145 (23), 121 (27), 107 (33), 105 (27), 95 (25), 93 (36), 91 (37), 81 (37), 79 (43), 67 (44), 55 (88), 41 (54).

$C_{18}H_{22}O_4$ Calcd. 302.1518 Found 302.1520

Attempted Epoxidation of the Regioisomers **6a** *and* **6b**: To a solution of epoxides **6a** and **6b** (253 mg, 0.84 mmol) in 20 ml of dry benzene was added $VO(acac)_2$ catalyst (6.0 mg, 0.018 mmol) and 0.5 ml of a 3.35 M solution of *tert*-butyl hydroperoxide (1.68 mmol). After ca. 24 h no conversion to the bisepoxide was observed under the same conditions used for preparation of quinols **6**.

10β-Hydroxy-17a-oxa-D-homo-1,4-estradiene-3,17-dione (**7**): To a solution of hydroxydienone **4** (286 mg, 1.00 mmol) in methylene chloride (15 ml) was added 110 mg (1.00 mmol) of solid sodium carbonate. The suspension was cooled to 0°C and under vigorous stirring was added dropwise a solution of *m*-chloroperbenzoic acid (173 mg, 1.00 mmol) in methylene chloride (10 ml), followed by stirring at room temp. for 4 d. Removal of the solids by filtration, washing of the filtrate with 5% aqueous sodium sulfite (1 × 30 ml), with 10% aqueous sodium carbonate (2 × 30 ml), and water (2 × 50 ml), drying with magnesium sulfate, and rotary-evaporation of the solvent yielded 278 mg of a pale yellow solid. Column chromatography on silica gel using in sequence 9:1, 8:2, and 3:1 mixtures of methylene chloride and ethyl acetate as eluants gave as first fraction 98 mg (34%) of starting material **4** and as second fraction 60 mg (20%) of a white powder of lactone **7**, which on recrystallization from methylene chloride afforded white plates, m.p. 250–254°C (dec.). – IR (KBr): 3290 cm^{-1} (OH), 2955, 2940, 1695 (C=O lactone), 1660 (unsaturated C=O), 1630,1610 (C=C), 1335, 1290, 1170, 1100. – ^{1}H NMR (400 MHz, $CDCl_3$/[D_6]DMSO 5:2): δ = 1.38 (s, 3H, CH_3), 0.85–2.83 (c, 15H), 3.44 (br. s, 1H, OH), 5.93 (br. s, 1H, 5-H), 6.09 (d, $J_{2,1}$ = 10.2 Hz, 1H, 2-H), 7.09 (d, $J_{1,2}$ = 10.2 Hz, 1H, 1-H). – ^{13}C NMR (100 MHz, $CDCl_3$/[D_6]DMSO 5:2): δ = 18.66, 18.75, 21.68, 27.16, 30.11, 30.69, 35.57, 37.48, 43.57 (d), 51.91 (d), 67.54 (s, C-16), 81.43 (s, C-10), 120.73 (d, C-2 or C-4), 125.98 (d, C-2 or C-4), 150.47 (d, C-1), 165.03 (s, C-17 or C-5), 169.48 (s, C-17 or C-5), 184.04 (s, C-3). – MS (70 eV): *m/z* (%) = 302 (20, M^+), 284 (24), 147 (38), 138 (32), 124 (39), 123 (78), 119 (62), 110 (25), 107 (27), 105 (26), 79 (28), 55 (68), 43 (100), 41 (36).

$C_{18}H_{22}O_4$ (302.4) Calcd. C 71.50 H 7.33
Found C 71.40 H 7.36

Treatment of Hydroperoxydienone **1** *with Titanium Tetraisopropoxide:* A solution of **1** (1.12 g, 8.00 mmol) and titanium isopropoxide (2.27 g, 8.00 mmol) in 50 ml of methylene chloride was allowed to stand at 0°C for ca. 15 h. TLC [methylene chloride/ethyl acetate (8:2) as eluant] showed that the starting material **1** was consumed and three new spots appeared with the same R_f values as *p*-cresol (R_f = 0.70), epoxide **5** (R_f = 0.40), and quinol **2** (R_f = 0.25). After the usual workup there was obtained 910 mg of an oil, whose ^{1}H-NMR spectrum showed that *p*-cresol and the products **5** and **2** were formed in a 7:20:73 ratio by comparison with the ^{1}H-NMR signals corresponding to authentic materials. Column chromatography on silica gel using in sequence 19:1, 9:1, and 8:2 mixtures of methylene chloride and ethyl acetate as eluants yielded 55 mg (6%) of *p*-cresol, 110 mg (10%) of epoxide **5**, 123 mg of a mixture of **5** and **2**, and 420 mg (42%) of *p*-quinol **2** in order of elution.

Treatment of Hydroperoxydienone **3** *with Titanium Tetraisopropoxide:* A solution of **3** (677 mg, 2.24 mmol) and titanium isopropoxide (636 mg, 2.24 mmol) in methylene chloride (20 ml) was allowed to stand at 0°C for ca. 16 h. TLC [methylene chloride/ethyl acetate (8:2) as eluant] showed that the starting material **3** was consumed and two new spots appeared with the same R_f values as epoxides **6a** and **6b** (R_f = 0.36) and quinol **4** (R_f = 0.18). After the usual workup, there was obtained 633 mg of crude material, whose ^{1}H-NMR spectrum showed that the products **6a**, **6b**, and **4** were formed in a 47:11:42 ratio by comparison with the ^{1}H-NMR signals corresponding to authentic materials. Column chromatography on silica gel with methylene chloride/ethyl actate (9:1) yielded 271 mg (40%) of a mixture of epoxides **6a** and **6b** as first fraction and 180 mg (28%) of *p*-quinol **4** as second fraction.

CAS Registry Numbers

1: 57749-82-3 / **2**: 23438-23-5 / **3**: 86846-54-0 / **4**: 549-03-1 / **5**: 109613-02-7 / **6a**: 109613-03-8 / **6b**: 109613-05-0 / **7**: 109613-04-9 / Me-*p*-C_6H_4OH: 106-44-5 / estrone: 53-16-7

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