Anal. Calcd for $C_{30}H_{44}O_7$: C, 69.74; H, 8.58. Found: C, 69.81; H, 8.29.

3β-Acetoxy-16,22-dioxo-5α-cholestan-26-oic Acid (18c).—Acid **18c** was formed by the oxidation of tigogenin acetate (**17b**). Recrystallization of the material from ethyl acetate–pentane gave crystals: mp 145–147°; ν_{max} 3230, 1740, 1705 cm^{-1}.

Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.21; H, 8.97.

Methyl 3β-Acetoxy-16,22-dioxo-5α-cholestan-26-oate (18d).—By methylation with ethereal diazomethane acid **18c** was converted into ester **18d**: mp 103–105° (from ethyl acetate–pentane); ν_{max} 1730, 1710 cm^{-1}.

Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.31; H, 8.82.

Registry No.—**2**, 17955-23-6; **4**, 17955-24-7; **6**, 17955-25-8; **8**, 17955-26-9; **11a**, 17955-27-0; **11b**, 17955-28-1; **11c**, 15266-99-6; **11d**, 15267-00-2; **13**, 17955-31-6; **11e**, 17955-33-8; **11f**, 17955-32-7; **12c**, 17955-34-9; **15a**, 17955-35-0; **11i**, 17955-36-1; **15b**, 17955-37-2; **18a**, 17955-38-3; **18b**, 17955-39-4; **18c**, 17955-40-7; **18d**, 17955-41-8; RuO_4, 12036-58-7.

Steroids Containing Ring A Aromatic. XIV. The Ruthenium Tetroxide Oxidation of Aromatic Steroids[1,2]

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The use of ruthenium tetroxide for degrading aromatic steroids has been explored. An interesting double allylic oxidation of ring A phenols has been observed with this reagent.

We have been interested in the degradation of aromatic steroids as a means for elucidating the mechanistic pathway of the dienone–phenol and dienol–benzene rearrangements[5] and as a possible route for the preparation of intermediates required for the synthesis of heterocyclic steroids. Several oxidative methods for the selective degradation of ring A were investigated.[5c,6]

In continuing the search for better oxidative methods we turned our attention to ruthenium tetroxide, a powerful oxidant, which has attracted limited attention.[7] The reports that the reagent reacts vigorously with aromatic solvents led us to try ruthenium tetroxide for the cleavage and degradation of aromatic steroids. The reagent was found to be superior to ozonization but, in one instance, gave unexpected and interesting results.

The procedure finally adopted was easy to control and involved the use of acetone–water mixtures. The ruthenium tetroxide was generated *in situ* from ruthenium dioxide and sodium periodate. Rather than to generate large amounts of tetroxide initially, it was found practical to reoxidize the dioxide formed during the reaction with additional sodium periodate. Since the dioxide was black and the tetroxide yellow, the progress of the reaction could be followed visually.

When estrone was oxidized, a good yield of the diacid **1** was obtained. The product was identified by comparison with an authentic specimen.[6] The same acid **1** was also formed by the oxidation of the 1-hydroxy-4-methyl-1,3,5(10)-triene **2a**, obtained from the dienone–phenol rearrangement of 1-dehydrotestosterone. In this instance the 17-hydroxyl was also oxidized. Oxidation of the 4-methyl-1,3,5(10)-triene **2b** similarly gave acid **1** (Chart I).

In the above cases the degradation of ring A terminated at carbons 5 and 10, as expected. It was anticipated that oxidation of a 6-keto analog would yield diacid **4**. Indeed, when the 6-keto-4-methyl-1,3,5-(10)-triene **3** was treated with ruthenium tetroxide keto diacid **4** was produced. The product was identical with a previously prepared sample.[5c]

With estradiol diacetate the reaction took an unexpected, and totally different course. In this instance diacid **6a** was formed in a small amount, and a large neutral fraction was recovered. From this neutral fraction 9α-hydroxy-6-ketotriene **5a** was isolated in about 40% yield, with the remainder being unchanged estradiol diacetate. Product **5a** was identified on the basis of its elemental analysis, spectroscopic properties, and its structure was confirmed by chemical transformations. Ketotriene **5a** was analyzed for $C_{22}H_{26}O_6$ indicating the introduction of two additional oxygen atoms into estradiol diacetate. A sharp peak at 3490 cm^{-1} in the infrared spectrum suggested that one of these oxygens may be a tertiary hydroxyl, while a band at 1680 cm^{-1} indicated that the other oyygen was probably a ketone

(1) Part XIII: B. Pelc, J. Holubek, T. Wittstruck, and E. Caspi, *Collect. Czech. Chem. Commun.*, **33**, 1131 (1968).

(2) This work was supported by Public Health Service Grants A-5326 and CA-07137. To simplify discussion the steroid numbering is employed.

(3) (a) Department of Chemistry, Northern Illinois University, De Kalb, Ill.; (b) Merck, A.G., Darmstadt, W. Germany; (c) Department of Chemistry, Warsaw University, Warsaw, Poland.

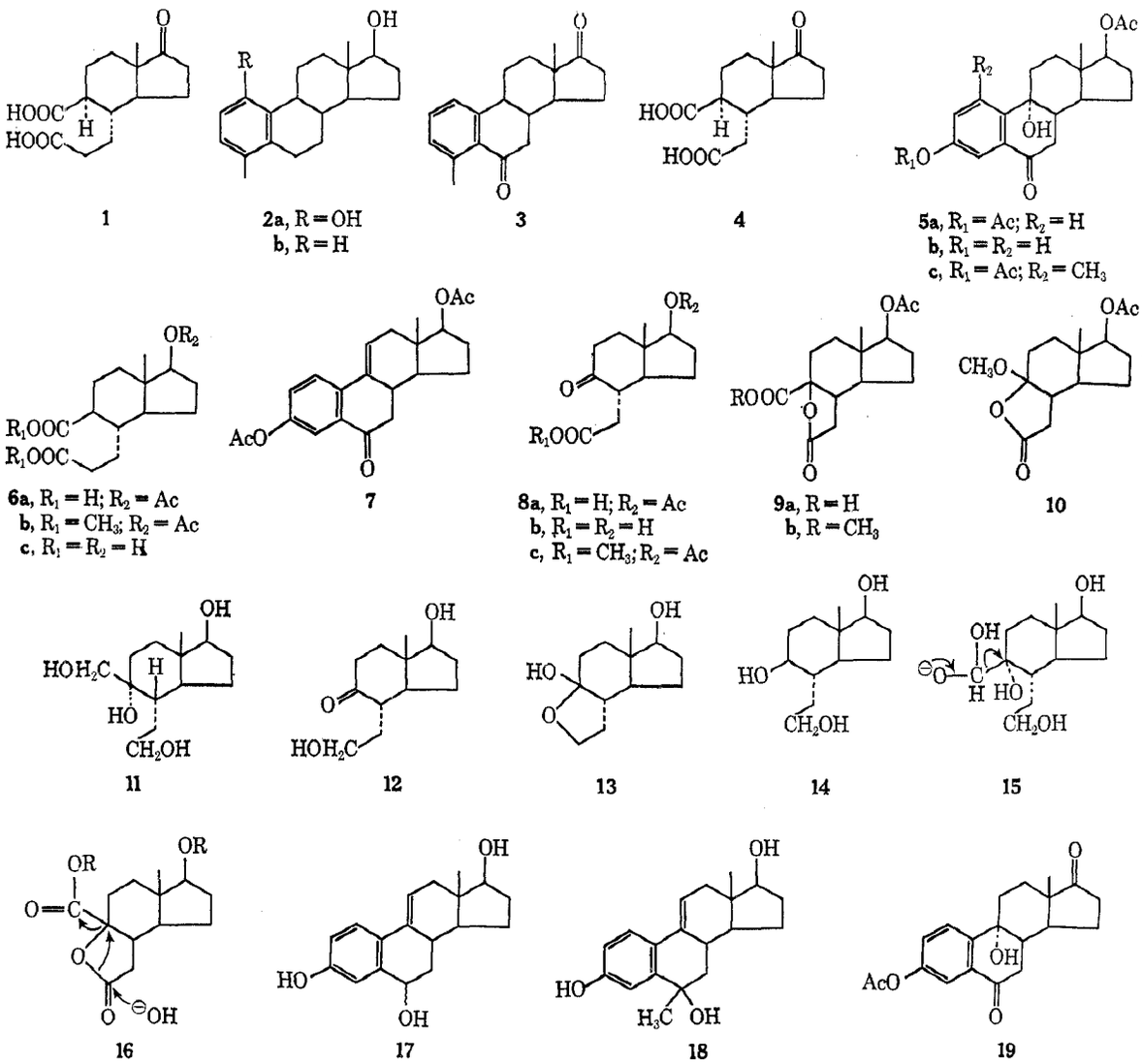
(4) Recipient of Public Health Service Research Career Program Award CA-K3-16614 from the National Cancer Institute.

(5) (a) E. Caspi, P. K. Grover, and Y. Shimizu, *J. Amer. Chem. Soc.*, **86**, 2463 (1963); (b) E. Caspi and P. K. Grover, *Tetrahedron Lett.*, 591 (1963); (c) E. Caspi, D. M. Piatak, and P. K. Grover, *J. Chem. Soc., C*, **10**, 34 (1966).

(6) (a) E. Caspi, P. K. Grover, D. M. Piatak, and Y. Shimizu, *J. Chem. Soc.*, 3052 (1965); (b) E. Caspi, P. K. Grover, and D. M. Piatak, *Chem. Ind.* (London), 1495 (1963).

(7) This reagent has been used throughout the literature for a variety of purposes, *e.g.*, oxidation of hydroxyl groups to ketones, formation of lactones from ethers, the cleavage of highly hindered double bonds, and, more recently, the oxidation of sugars: (a) C. Djerassi and R. R. Engle, *J. Amer. Chem. Soc.*, **75**, 3838 (1953); (b) P. D. Bartlett and M. Stiles, *ibid.*, **77**, 2806 (1955); (c) L. M. Berkowitz and D. N. Rylander, *ibid.*, **80**, 6682 (1958); (d) F. G. Oberender and J. A. Dixon, *J. Org. Chem.*, **24**, 1226 (1959); (e) S. Sarel and Y. Yonuka, *ibid.*, **24**, 2018 (1959); (f) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron Lett.*, **22**, 38 (1960); (g) J. Weinstock and M. E. Wolff, U. S. Patent 2,960,503 (Nov. 15, 1960); (h) F. M. Dean and J. C. Knight, *J. Chem. Soc.*, 4745 (1962); (i) H. Nakata, *Tetrahedron*, **19**, 1959 (1963); (j) E. Caspi and D. M. Piatak, *Experientia*, **19**, 465 (1963); (k) G. Snatzke, A. Nisar, and H. W. Fehlhaber, *Angew. Chem. Intern. Ed., Engl.*, **2**, 558 (1963); (l) D. M. Piatak and E. Caspi, *Steroids*, **3**, 631 (1964); (m) P. J. Beynon, P. M. Collins, and W. G. Overend, *Proc. Chem. Soc.*, 342 (1964); (n) P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc.*, 1131 (1966); (o) J. A. Caputo and R. Fuchs, *Tetrahedron Lett.*, 4729 (1967); (p) D. M. Piatak, H. Bhat, and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969). Reference 7o described the utilization of ruthenium tetroxide for the oxidation of aromatic rings and appeared after the completion (in 1965) of the present work.

CHART I



α to the aromatic ring.[8] The presence of a ketone α to the aromatic ring was verified by the ultraviolet maximum at 243 mμ. The structure assignment was substantiated by an nmr spectrum which exhibited, among others, signals at 121.5 and 137.5 cps for the 17 and 3 acetates, respectively. The aromatic proton pattern integrated for three hydrogens as expected, and the tertiary nature of the hydroxyl group was verified by the absence of a signal for an additional proton on a carbon bearing an oxygen. The assignment of the 9α configuration to the alcohol is based on the known greater susceptibility of the back side of the molecule to chemical attack.

Further proof that the hydroxyl was at C-9 ensued when triene **5a** was dehydrated to tetraene **7**. An infrared spectrum of **7** was devoid of the hydroxyl band, while a double bond peak appeared at 1650 cm^{-1}. An ultraviolet spectrum had maxima at 240 and 264 mμ, as might be expected for this system, and an nmr spectrum had a triplet at 386 cps (J = 4.0 cps) for the 11-vinylic proton.

The structure of acid **6a** obtained from the oxidation of estradiol diacetate was based on its analysis and its conversion to the dimethyl ester **6b** which was identical with an authentic sample. The authentic sample of **6b** was synthesized from the known[6] 17-hydroxy diacid **6c** by methylation and acetylation.

To test the applicability of this double allylic oxidation to similar compounds, 1-methylestradiol diacetate was subjected to the same reaction conditions. In this instance the major product was diacid **6a**. From the neutral fraction a minor amount of hydroxyketotriene **5c** was isolated. The structure of **5c** was established by its elemental analysis, infrared spectrum [bands at 3500 (9α-OH), and 1685 cm^{-1} (6-ketone)], and ultraviolet maximum at 252 mμ. Apparently, the 1-methyl substituent decreases the stability of the aromatic ring A to the reagent.

The results indicated that the diacetate **5a** is stable to the reagent, and resistant to further oxidation. On the other hand, we anticipated that oxidation of the 3-hydroxy analog **5b** would yield the keto acid **8a**. The required 3-hydroxy-17β-acetate **5b** was obtained by treating the 3,17β-diacetate **5a** with aqueous methanolic potassium hydrogen carbonate. Oxidation of **5b** gave a mixture of acids in nearly quantitative yield, which were methylated with diazomethane. At this point, instead of the expected product **8c** (or **10**) the

(8) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 472.

lactone ester **9b** was obtained in 30% yield. Compound **9b** analyzed for $C_{16}H_{22}O_6$ and the infrared spectrum had bands at 1795 cm^{-1} (strained five-membered lactone) and 1735 cm^{-1} (acetate and ester). In an nmr spectrum signals were observed at 54.5 cps for the 18 methyl, at 122.5 cps for the 17β-acetate, and at 228 cps for a carbomethoxyl. The mass spectrum of **9b** was devoid of the molecular ion (M^+ 310) and had peaks at *m/e* 267 (minute, M − 43; CH_3CO), 251 (base peak, M − 59, $COOCH_3$), 209 (251 − 42, C_2H_2O), 191 (251 − 60, CH_3OOH or 209 − H_2O). The presented evidence fully supports structure **9b**.

Additional evidence for structure **9b** was obtained by its reduction with lithium aluminum hydride to tetrol **11**. The tetrol had the anticipated $C_{13}H_{24}O_4$ elemental composition, and its infrared spectrum showed bands for hydroxyls and was devoid of carboxyl absorption. In order to determine the number and nature of the hydroxylic functions an nmr spectrum was recorded in dimethyl sulfoxide (DMSO). The spectrum revealed the presence of two triplets at 277 (J = 4.5 cps, 1 H), 267 (J = 5.5 cps, 1 H), one doublet at 261 (J = 4.5 cps, 1 H), and one singlet at 239.5 cps. Thus the expected four hydroxyls (two primary, one secondary and one tertiary) as required by structure **11** were fully accounted for. The mass spectrum of the tetrol showed peaks at *m/e* 213 (M − 31, CH_3O), 195 (213 − 18), 177 (195 − 18), and 159 (195 − 18) as expected for **11**. Tetrol **11** undergoes an interesting reaction when exposed to periodic acid. The spectroscopic data, and elemental analysis of the obtained product, were not consistent with the anticipated ($C_{12}H_{20}O_3$) structure **12** (no carbonyl in the ir spectrum) nor with the hemiketal **13**. A mass spectrum of the product had a peak for the molecular ion M^+ (214, $C_{12}H_{22}O_3$), and fragments at *m/e* 196 (M − 18), 178 (196 − 18), and 168 (M − 46, C_2H_5OH). This evidence can only be reconciled with structure **14**.

What actually happened during the exposure of tetrol **11** to periodic acid may be rationalized in two ways. It is possible that the initially formed **12** underwent an Oppenauer-type disproportionation, *e.g.*, with the methanol of the medium. Alternatively, the C-10 primary alcohol could have been oxidized by periodic acid to aldehyde **15** which underwent a reverse aldol reaction as indicated. Certain vicinal glycols, for example, those having one or two tertiary hydroxyls, are known to be somewhat resistant to C–C bond cleavage with periodic acid.[9] This is ascribed to difficulties in the formation of the cyclic transition state encompassing the two hydroxyls and the periodic acid. The same may be applicable to **11**, in which the primary and tertiary hydroxyls at C-9 have rigid orientations. Consequently instead of the C-9–10 bond being broken a C–H bond may have been cleaved, to give an aldehyde (**15**).

On treatment with base, **9b** undergoes an apparent reverse aldol reaction to yield **8b**, which after esterification with diazomethane and acetylation gives **8c**. The structure of **8c** follows from its elemental analysis and infrared spectrum which showed bands at 1735 (ester and acetate) and 1700 cm^{-1} (six-membered ketone) as expected. The nmr spectrum revealed a large (15 cps) downfield shift on the signal for the 18 methyl from that observed in **9b**, while the acetate and carbomethoxy signals were shifted by 2 and −6.0 cps, respectively.[10] The mass spectrum of **8c** had peaks at *m/e* 282 (M^+), 251 (M − 31), 240 (M − 42), 222 (240 − 18, or M − 60), and 209 (251 − 42), all of which are consistent for the proposed structure.

Formation of **9a** and its conversion to **8** require comment. Probably oxidation of **5b** first gave a C-6 carboxylic acid which lactonized with the 9α-hydroxyl. Subsequently, the remaining fragment of ring A was degraded to the C-9 carboxyl, and the resulting **9a** resisted further oxidation. The base-catalyzed conversion of **9b** into **8** can be viewed as proceeding as indicated in **16**.

In exploring other reactions of triene **5a** we had occasion to treat it with lithium aluminum hydride, but the resulting product proved to be **17**. Evidence for **17** was derived from elemental analysis, and infrared bands observed at 3420 cm^{-1} for the hydroxyls, and at 1625 cm^{-1} for a double bond. An ultraviolet maximum at 264 mμ, characteristic for a substituted styrene moiety of this type, and an nmr signal at 363 cps (W_H = 18 cps, 1 H) verified the location of the double bond. The same product **17** was obtained when **5a** was treated with sodium borohydride and base. Apparently, dehydration of the 9α-hydroxyl occurs readily under the reaction conditions employed.

The nmr spectrum of **17** showed, among others, a broad multiplet for the C-6 hydrogen at 273 cps (W_H ~21 cps), characteristic for an axial hydrogen.[10] If it is assumed that ring B retained the usual chairlike conformation, the hydroxyl would have the equatorial 6α configuration. On the other hand if ring B is in the boatlike conformation, the hydroxyl will have the 6β configuration. Though the former is more probable (chair, 6α-OH), no definitive assignment can be made on the basis of the nmr evidence alone. Finally, treatment of **5a** with methyllithium gave **18** in poor yield. In addition, from another fraction, after oxidation and acetylation, **19** was obtained. It is noteworthy that **5a** has considerable hypocholesteremic activity, and that its estrogenicity is of very low magnitude.

Experimental Section[11]

3-(1-Oxo-8β-methyl-5β-carboxy-*trans*-perhydroindanyl-4α)propionic Acid (1). A.—Estrone (1.00 g) in acetone (100 ml) was added to a stirred, yellow ruthenium tetroxide mixture obtained by combining ruthenium dioxide[12] (400 mg) in acetone (50 ml) with sodium periodate (3.00 g) in water (15 ml). The reaction was kept yellow by adding portionwise a solution[13] of sodium periodate (11.5 g) in acetone–water (1:1, 115 ml) to the stirring

(9) R. Stewart, "Oxidation Mechanism," W. A. Benjamin, Inc., New York, N. Y., 1964, p 97; *Cf.* L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, pp 816, 818.

(10) E. Caspi and T. Wittstruck in "Steroid Hormone Analysis," H. Carstensen, Ed., M. Dekker, Inc., New York, N. Y., 1967, p 93.

(11) Melting points were taken on a micro hot stage and are corrected. Infrared spectra were recorded on solids incorporated in a KBr wafer. Ultraviolet spectra were taken on methanol solutions. Unless otherwise stated, deuteriochloroform was used for nmr spectra which were recorded at 60 Mc on a Varian HA 60 instrument. Silica gel HF_{254} (Merck A.G. Darmstadt, Germany) was used for thin layer chromatograms (tlc) with the developing solution as stated. The mass spectra were taken on a Varian M66 instrument. The pertinent mass spectroscopic peaks were quoted in the general part of the paper and will not be repeated in this section. Analyses were performed by I. Beetz, Kronach, Germany.

(12) Ruthenium dioxide was purchased from Engelhard Industries, Newark, N. J. Analytical reagent grade acetone was used.

(13) This solution was best prepared fresh. The salt was first dissolved in the water and the acetone then added.

mixture. At the end of 4.5 hr a few milliliters of isopropyl alcohol was added to terminate the reaction, and the mixture was diluted with an equal amount of acetone. After collection of the precipitated solids on Celite, most of the acetone was removed *in vacuo* and solid sodium chloride added. The steroids were taken up in ethyl acetate–ether (1:1), and the acid fraction was isolated as usual with sodium bicarbonate.

An acid fraction (670 mg) crystallized on trituration with ethyl acetate. Product **1** was identical with a sample prepared as previously described.[6]

B.—To a stirred solution of ruthenium tetroxide from 400 mg of ruthenium dioxide, 100 ml of acetone, 3.0 g of sodium periodate and 18 ml of water was added 1.00 g of 1,17β-dihydroxy-4-methylestra-1,3,5(10)-triene (**2a**). A solution of 10.0 g of sodium periodate in 50 ml of water and 50 ml of acetone was used to maintain the reaction yellow. After 4 hr of stirring at room temperature, the reaction was terminated and 880 mg of acid **1** was obtained as described above.

C.—Aromatic **2b** (250 mg) was oxidized as described in **B** to yield 120 mg of acid **1**.

2-(1-Oxo-8β-methyl-5β-carboxy-*trans*-perhydroindanyl-4α)acetic Acid (4).—To the yellow-green ruthenium tetroxide prepared by stirring ruthenium dioxide (100 mg) in acetone (10 ml) with sodium periodate (750 mg) in water (3.5 ml) was added 6-keto steroid[5c] **3** (200 mg) in acetone (10 ml). Sodium periodate (2.50 g) in water (10 ml) and acetone (10 ml) was added at intervals to keep the reaction light yellow whenever darkening occurred. After stirring for 4.5 hr the reaction was terminated with a few milliliters of isopropyl alcohol, then diluted with acetone and processed as described above to yield **4**. The solid (90 mg) was crystallized from acetone–pentane to mp 183–186° and found to be identical with a previously prepared sample.[5c]

3,17β-Diacetoxy-9α-hydroxy-6-oxoestra-1,3,5(10)-triene (5a).—Estradiol diacetate (4.00 g) in acetone (200 ml) was added to the ruthenium tetroxide from ruthenium dioxide (1.60 g) in acetone (200 ml) and sodium periodate (12.0 g) in water (55 ml). A solution of sodium periodate (18.4 g) in water (80 ml) and acetone (80 ml) was added as needed. The reaction was carried out for 4.5 hr as described above. After termination of the reaction with isopropyl alcohol, it was processed as above into neutral and acidic fractions. The neutral fraction yielded 2.4 g of crude material which was recrystallized from ethyl acetate–pentane to give 1.5 g of 6-keto steroid **5a**. The acid fraction (1.27 g) crystallized to give diacid **6a** (see below).

Repeated recrystallization of **5a** from ethyl acetate–pentane gave a sample: mp 155–159°; ν_{max} 3490, 1765, 1735, 1680, 1620, 1585 cm^{-1}; λ_{max} 210 mμ (ε 18,700), 243 mμ (ε 7800); nmr (DMSO) 47.5 (18 methyl), 121.5 (17 acetate), 137.5 (3-acetate), 445.0–475.5 cps (aromatic proton signals).

Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.16; H, 6.87.

3,17β-Diacetoxy-6-oxoestra-1,3,5(10),9(11)-tetraene (7).—Hydroxyestratriene **5a** (38 mg) and freshly fused sodium bisulfate (20 mg) in acetic anhydride (1.0 ml) was refluxed for 1 hr. The reaction was decomposed with ice, and the steroids were dissolved in ether. The organic layer was washed with sodium bicarbonate and water, then evaporated to give 37 mg of tetraene **7**. Repeated recrystallization of the product from methanol gave an analytical sample: mp 162–165°; ν_{max} 1765, 1730, 1680, 1650, 1610 cm^{-1}; λ_{max} 240 mμ (ε 23,800), 264 (14,900); nmr 49.5 (18 methyl), 124 (17-acetate), 137 (3-acetate), 386 cps (triplet, J = 4.0 cps, C-11 proton).

Anal. Calcd for $C_{22}H_{24}O_5$: C, 71.72; H, 6.57. Found: C, 71.56; H, 6.68.

17-Acetoxy Diacid 6a.—The crystalline acid fraction from the preparation of **5a** was recrystallized from ethyl acetate to mp 176–178°, ν_{max} 1735, 1700 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.75; H, 7.82.

Dimethyl Acetate 6b. A.—Diacid **6a** was methylated as usual with diazomethane to yield diester **6b**, which recrystallized from ethyl acetate as colorless crystals, mp 68–70°, ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.35; H, 7.95.

B.—Hydroxy diacid **6c** described previously[6] was methylated and acetylated to diester **6b**, identical with the above sample.

3,17β-Diacetoxy-9α-hydroxy-1-methyl-6-oxoestra-1,3,5(10)-triene (5c).—3,17β-Diacetoxy-1-methylestra-1,3,5(10)-triene (500 mg) in acetone (25 ml) was added dropwise to a solution of ruthenium tetroxide from ruthenium dioxide (200 mg) in acetone (25 ml) and sodium periodate (1.5 g) in water (7.0 ml) The yellow color of the reaction was maintained by the addition of sodium periodate (4.8 g) in water (15 ml) and acetone (15 ml) during 4.5 hr, whenever needed. The reaction was terminated and worked up as described before. An acid fraction of 310 mg was obtained and identified as diacid **6a**. The neutral fraction (110 mg) was chromatographed on a silica plate (20 × 20 cm, 7:3 benzene–ethyl acetate) to yield 25 mg of product **5c**. Repeated recrystallization from ethyl acetate–pentane gave a sample melting at 193–196°; ν_{max} 3500, 1765, 1710, 1685, 1595 cm^{-1}; λ_{max} 252 mμ (ε 7500).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05. Found: C, 68.91; H, 7.21.

17β-Acetoxy-3,9α-dihydroxy-6-oxoestra-1,3,5(10)-triene (5b).—To a solution of hydroxyestratriene **5a** (100 mg) in methanol (15 ml) was added a solution of potassium bicarbonate (300 mg) in water (5 ml). After the reaction had been stored for 16 hr at room temperature, it was diluted with water and the steroids were recovered with ether. Removal of the solvent gave 86 mg of 3-hydroxytriene **5b**, which was recrystallized from chloroform–ethanol to mp 213–223°; ν_{max} 3465, 3310, 1730, 1675, and 1610 cm^{-1}; λ_{max} 256 mμ (ε 18,000); nmr (in DMSO) 46.5 (18 methyl), 121.5 cps (17-acetate).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.74; H, 7.09.

Lactone 9b.—Monoaceate **5b** (300 mg) was oxidized as above by adding it in acetone (20 ml) to a yellow solution of ruthenium tetroxide from ruthenium dioxide (50 mg) in 15 ml of acetone and sodium periodate (1.2 g) in water (5.4 ml). The reaction was kept yellow with sodium periodate (3.0 g) in water (18 ml) and acetone (18 ml). Work-up gave 15 mg of neutral material and 205 mg of acid, which was treated with an excess of ethereal diazomethane. Crystallization from methanol yielded 85 mg of **9b**, which was recrystallized to mp 165–167° (from methanol); ν_{max} 1795, 1735 cm^{-1}; nmr 54.5 (18 methyl), 122.5 (acetate methyl), 228 cps (carbomethoxyl).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.10, 61.96; H, 7.11, 6.96.

Keto Ester 8c.—Lactone **9b** (100 mg) was dissolved in methanol (5 ml) and 2 *N* sodium hydroxide (1 ml) added. The mixture was refluxed for 2 hr, the methanol was then removed *in vacuo*, and the reaction was acidified with 2 *N* hydrochloric acid. The products were isolated by extraction with ether, and the acids were methylated with ethereal diazomethane. The ester resisted crystallization and was acetylated to yield **8c**, which crystallized from ethyl acetate–pentane as colorless crystals (50 mg): mp 124 and 133°; ν_{max} 1735, 1700 cm^{-1}; nmr 69.5 (18 methyl), 124.5 (acetate methyl), 222 cps (carbomethoxyl).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.54; H, 7.79.

Tetrol 11.—To a solution of lactone **9b** (638 mg) in dry ether (50 ml) was added a slurry of lithium aluminum hydride (3.0 g) in ether (75 ml). The mixture was then stirred for 16 hr at ambient temperature followed by a refluxing period of 2 hr. The cooled reaction mixture (ice bath) was decomposed with ethyl acetate and water. After a conventional work-up, the residue (378 mg) was crystallized from methanol–methylene chloride. A portion of the material was recrystallized from the same solvent to mp 166–168°; ν_{max} 3300, 1260, 1045 cm^{-1}; nmr (in DMSO) 277 (triplet, J = 4.5 cps; primary OH), 267 (triplet, J = 5.5 cps, primary OH), 261 (doublet, J = 5.0 cps, secondary OH), 239.5 (singet, tertiary OH), and 37.5 cps (18 methyl).

Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.95; H, 9.78.

Triol 14.—A mixture of tetrol **11** (123 mg), methanol (5 ml), and periodic acid (100 mg) was stored for 3 hr at room temperature. The reaction was terminated with ethylene glyol, diluted with water, and the product was recovered with ethyl acetate. The extraction residue gave crystalline **14** (25 mg). Repeated recrystallization of the product gave a sample which exhibited mp 141–143°; ν_{max} 3300, 1345, 1025 cm^{-1}; nmr (in DMSO) 275 (triplet, J = 5.0 cps, primary OH), 265 (doublet, J = 6.0 cps secondary OH), 263.5 (doublet, J = 5.00 cps, secondary OH), 205 (multiplet, W_H = 25 cps, CH–OH) and 40 cps (18 methyl).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 66.91, 67.60; H, 10.13, 10.34.

3,6ξ-17β-Trihydroxyestra-1,3,5(10),9(11)-tetraene (17). A.—

To triene **5a** (500 mg) in anhydrous ether (100 ml) lithium aluminum hydride (500 mg) was added. The mixture was stirred for 2 hr, then decomposed with water. The aluminum hydroxide was dissolved with 2 *N* hydrochloric acid and the mixture was extracted with ether, washed, and dried. Removal of ether gave trihydroxytetraene **17**, which was recrystallized from ethyl acetate to mp 237–242° dec; ν_{max} 3420, 1625, 1610, 1575 cm^{-1}; λ_{max} 266 mμ (ϵ 15,400); nmr (DMSO) 449–389 (aromatic H), 363 (multiplet, W_H = 18 cps, 11-H), 312 (doublet, J = 7 cps, OH, disappeared on exchange with D_2O), 273 (multiplet, W_H = 21 cps, 6β-H), 211 (multiplet, W_H = 20 cps, 17-H), and 50 cps (18-CH_3).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.24; H, 7.43.

B.—A solution of **5a** (1.1 g) in methanol (100 ml) was made basic to phenolphthalein with 2 *N* sodium hydroxide, then sodium borohydride (6 g) was added, and the mixture was stored for 16 hr at room temperature. Most of the methanol was removed in a stream of nitrogen, water was added, and the steroids were recovered with ethyl acetate. The extract was washed with water, dried, and reduced to a residue to yield 549 mg of a syrup. Trituration with methanol gave **17** (237 mg) identical with the above sample.

3,6ξ,17β-Trihydroxy-6ξ-methylestra-1,3,5(10),9(11)-tetraene (18).—An ethereal solution of methyllithium (1.62 *M*, 50 ml) was added dropwise with cooing to a solution of **5a** (1000 mg) in ether–tetrahydrofuran (1:1, 50 ml). The mixture was stored for 16 hr, refluxed for 1 hr, and then terminated with a saturated aqueous solution of ammonium chloride. After a conventional work-up 1.1 g of a crude syrup was obtained and chromatographed on a silica gel column. The column was eluted with mixtures of ethyl acetate–acetone, and the various fractions were combined into four main groups according to their infrared spectra: fraction 1, starting material (78 mg); fraction 2, mainly **5b** (160 mg); fraction 3, a syrup (350 mg) which yielded **18** (78 mg) from acetone crystallization; and fraction 4, a syrup (415 mg).

Repeated recrystallizations of **18** obtained from fraction 3 gave a sample with mp 220–224°; λ_{max} 265.5 mμ (ϵ 14,200); ν_{max} 3575, 3360, 1620, 1610, 1570 cm^{-1}; nmr (in DMSO) 447–390 (aromatic H), 360 (multiplet, W_H = 13 cps, C-11 proton), 285 (singlet, C-6 OH, verified by D_2O exchange), 272 (doublet, J = 5.0 cps, C-17 OH, exchangeable with D_2O), 215 (multiplet, W_H = 20 cps, 17α-H), 84 (C-6 methyl), and 41 cps (18 methyl).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.05, 75.64; H, 8.28, 7.88.

3-Acetoxy-9α-hydroxyestra-1,3,5(10)-triene-6,17-dione (19).—Fraction 4 (415 mg) from the above experiment on rechromatography on tlc (silica gel, ethyl acetate) gave a residue (237 mg) which resisted crystallization: λ_{max} 258 mμ; λ_{max} (film) 3480, 1670, 1615 and 1580 cm^{-1}; nmr [$(CD_3)_2CO$] 525 (1 H, exchanges with D_2O), 452–414 (aromatic H), 224 and 173 (1 H each, exchange with D_2O), 224 (triplet, J = 8 cps, 17α-H), 49 (18-CH_3). The product (230 mg), presumably 3,9α,17β-trihydroxyestra-1,3,5(10)-trien-6-one, was treated first with Sarett's reagents [chromium trioxide (215 mg) in a total of 4.3 ml of pyridine] and then acetylated. After the recovery of the acetylated-oxidized material, it was purified by tlc to yield 90 mg of a crude solid. The solid was crystallized from ethyl acetate: mp 210–215°; λ_{max} 251 mμ (ϵ 10,000); ν_{max}^{KBr} 3530, 1760, 1735, 1665, 1600 cm^{-1}; nmr (CD_3OD) 421–478 (aromatic H), 138 (acetate) and 55 (18 CH_3), mass spectrum *m/e* 342 (M^+), 324 (M − 18), 300 (M − 42), 282 (M − 60 or 300 − 18), 267 (282 − 15).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 70.15; H, 6.69. Found: C, 69.68; H, 6.69.

Registry No.—**5a**, 18181-55-0; **5b**, 18181-56-1; **5c**, 18239-03-7; **6a**, 18239-04-8; **6b**, 18181-57-2; **7**, 10006-41-4; **8c**, 18181-59-4; **9b**, 18239-05-9; **11**, 18181-60-7; **14**, 18181-61-8; **17**, 18181-62-9; **18**, 18181-63-0; **19**, 18181-64-1; ruthenium tetroxide, 14103-93-6.

Naphthoquinones. On the Oxidative Cyclization of Isolapachol to Dehydro-α-lapachone and Prototypal Studies Related to the Synthesis of Lapachol and Its Derivatives[1]

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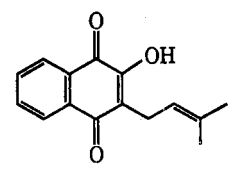
The reaction of isolapachol (**2**) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gives a mixture of dehydro-α-lapachone and dehydro-β-lapachone (*e.g.*, **3** and **4**). Treatment of the mixture with dilute acid–ethanol causes an "*ortho–para*" rearrangement of the latter compound (*e.g.*, **4**), and **3** is then isolated in an over-all 60% yield. Birch reduction (in the absence of ethanol) of **3** gives an acidic fraction (66%) comprised of a 7:3 mixture of isolapachol (**2**) and lapachol (**1**). In the presence of ethanol, Birch reduction gives an acidic fraction (33%) comprised of lapachol (**1**) and hydrolapachol (**5**) in the ratio 3:2, respectively.

Lapachol (**1**), the subject of a series of researches[2] culminating in the discovery of a new class of antimalarial agents,[3] has gained renewed interest as a consequence of its activity against the Walker carcinosarcoma 256 (intramuscular) and a favorable preclinical toxicological evaluation.[4] In view of the difficulties encountered in attempts to introduce directly



1

the Δ^2-isopentenyl side chain[5] and because we had at hand a novel oxidative ring closure (note below, Scheme I, **2** → **3**), it was of interest to test the feasibility of the two-step sequence in eq 1 as a means for deconjugation

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(2) S. C. Hooker, *J. Amer. Chem. Soc.*, **58**, 1163 (1936); see editor's note and references within.

(3) (a) L. F. Fieser, M. T. Leffler, *et al.*, *ibid.*, **70**, 3151 (1948); (b) L. F. Fieser, S. Archer, *et al.*, *J. Med. Chem.*, **10**, 513, 517 (1967).

(4) (a) Data were kindly provided by Dr. Harry B. Wood, Jr. (Cancer Chemotherapy National Service Center, National Institutes of Health). (b) A preliminary report on the pharmacology of lapachol has recently appeared: P. K. Nayak, D. Molins, F. J. Carelton, and R. K. Morrison, *Federation Proc.*, **27**, 532 (1968).

(5) (a) L. F. Fieser, *J. Amer. Chem. Soc.*, **49**, 857 (1927); (b) M. Gates and D. L. Moesta, *ibid.*, **70**, 614 (1948). (c) An unrelated synthesis of lapachol has been reported by S. C. Hooker, *ibid.*, **58**, 1181 (1936).