THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 17

AUGUST 27, 1971

Synthesis and Reactions of 5α,8-Epidioxyandrost-6-enes

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Received May 30, 1969

Photooxygenation of 3β-hydroxyandrosta-5,7-dien-17-one (1) yields the 5α,8-epidioxide **2a** accompanied by the 5,8-dien-7-one **6a** and the two unsaturated 5α,6-epoxides **5a** and **9a**. The epidioxide **2a** undergoes a palladium-catalyzed reaction to yield first the triolone **3a** and then androsta-4,6,8(14)-triene-3,17-dione (**4a**). The 3-keto epidioxide **7** rearranges at room temperature in pyridine to the 4α,5-epoxide **8**. This epoxide is transformed to the 3,4-seco acid **12** in acetic acid and to the 4-hydroxytriene **11** in base.

Reports of the physiological potency of the estra-4,9,11- and 4,9,8(14)-trienes[1] led to studies which culminated in the synthesis of several estra-4,6,8(14)-trienes.[2] Accompanying this research were investigations dealing with the preparation of the analogous androstatrienes. The discovery of a high yield transformation of ergosterol epidioxide to ergosta-4,6,8(14)-trien-3-one with a palladium catalyst[3] greatly simplified this undertaking. Although other routes to this conjugated system have been described,[4] none could match the efficacy of this direct approach.

A. Photooxygenation of the 5,7-Dienes.—Oxygenation of an illuminated solution of the 3β-acetoxyandrosta-5,7-diene (**1a** 3-acetate) in the classical manner[5] (eosin sensitized, in ethanol) gave by direct crystallization the expected 5α,8-epidioxide **2a** (3-acetate). As anticipated, the product contained two additional oxygen atoms, showed no new functionality in the infrared, and exhibited a pair of doublets for the 6 and 7 protons in the nmr spectrum. Configurational assignment is by analogy to the ergosterol and cholesterol work.[6] The observed deshielding of the 18-methyl group in the nmr can be rationalized by noting, in a molecular model, the nearly coplanar relationship of the 18-methyl and the 6,7 double bond caused by the ring B boat conformation. The 19-methyl signal is also shifted downfield, an effect ascribed to the 5α,8-epidioxide bridge.[7] Despite the strained appearance of the model, the compound was relatively stable to a variety of reagents (see below).

The nmr spectrum of the photooxygenation mother liquors contained clear signals for the angular methyl groups and characteristic C-6 protons of three new components. Chromatographic separation of the mixture afforded first an unsaturated ketone (λ_{max} 245 nm) in 15% yield. The unperturbed 3-proton signal and that of a single vinyl proton (368 Hz) suggested the 5,8-dien-7-one structure **6a** (3-acetate).[8,9] A chemical synthesis later supported this postulation.

The second major by-product of the eosin-sensitized photooxygenation (10% yield) was the hydroxy oxide **9a**. The gross structure, suggested by spectral data, was confirmed chemically by oxidation of its 3-monoacetate to the unsaturated ketone **10** and subsequent potassium iodide reduction[10] to the 5,8-dienone **6a**, described above. Since this photooxygenation product **9a** was identical with one of the pyrolysis products of the epidioxide **2a**, the stereochemistry at C-5, -6, and -7 is presumably the same as that assigned to an ergosterol epidioxide pyrolysis product.[10] The position of the double bond was decided by comparison of the cal-

(1) R. Joly, J. Warnant, J. Jolly, and J. Mathieu, *C. R. Acad. Sci.*, **258**, 5669 (1964) and references cited therein; T. B. Windholz, J. H. Fried, H. Schwam, and A. A. Patchett, *J. Amer. Chem. Soc.*, **85**, 1707 (1963).

(2) W. F. Johns, *J. Org. Chem.*, **31**, 3780 (1966).

(3) R. M. Dodson, G. D. Valiaveedan, H. Ogasawara, and H. M. Tsuchiya, the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 1966, p I-33; the author is indebted to Professor Dodson, University of Minnesota, for a private communication describing this reaction.

(4) See, *e.g.*, D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 2728 (1951); J. Elks, *ibid.*, 468 (1954); F. Bohlmann, U. Hinz, and B. Diedrich, *Chem. Ber.*, **96**, 1316 (1963); D. M. Sivanandaiah and W. R. Nes, *Steroids*, **5**, 539 (1965); J. D. White, and S. I. Taylor, *J. Amer. Chem. Soc.*, **92**, 5812 (1970); J. Lakeman, W. N. Speckamp, and H. O. Huisman, *Tetrahedron*, **24**, 5151 (1968); H. Morimoto, I. Imada, T. Murata, and N. Matsumoto, *Justus Liebigs Ann. Chem.*, **708**, 230 (1967); R. D. Daftary, Y. Pomeranz, R. G. Cooks, and N. L. Wolfe, *Experientia*, **26**, 1056 (1970).

(5) L. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 96.

(6) J. Suzuki and K. Tsuda, *Chem. Pharm. Bull.*, **11**, 1028 (1963); S. Iwasaki and K. Tsuda, *ibid.*, **11**, 1034 (1963); F. Dolton and G. D. Meakins, *J. Chem. Soc.*, 1880 (1961).

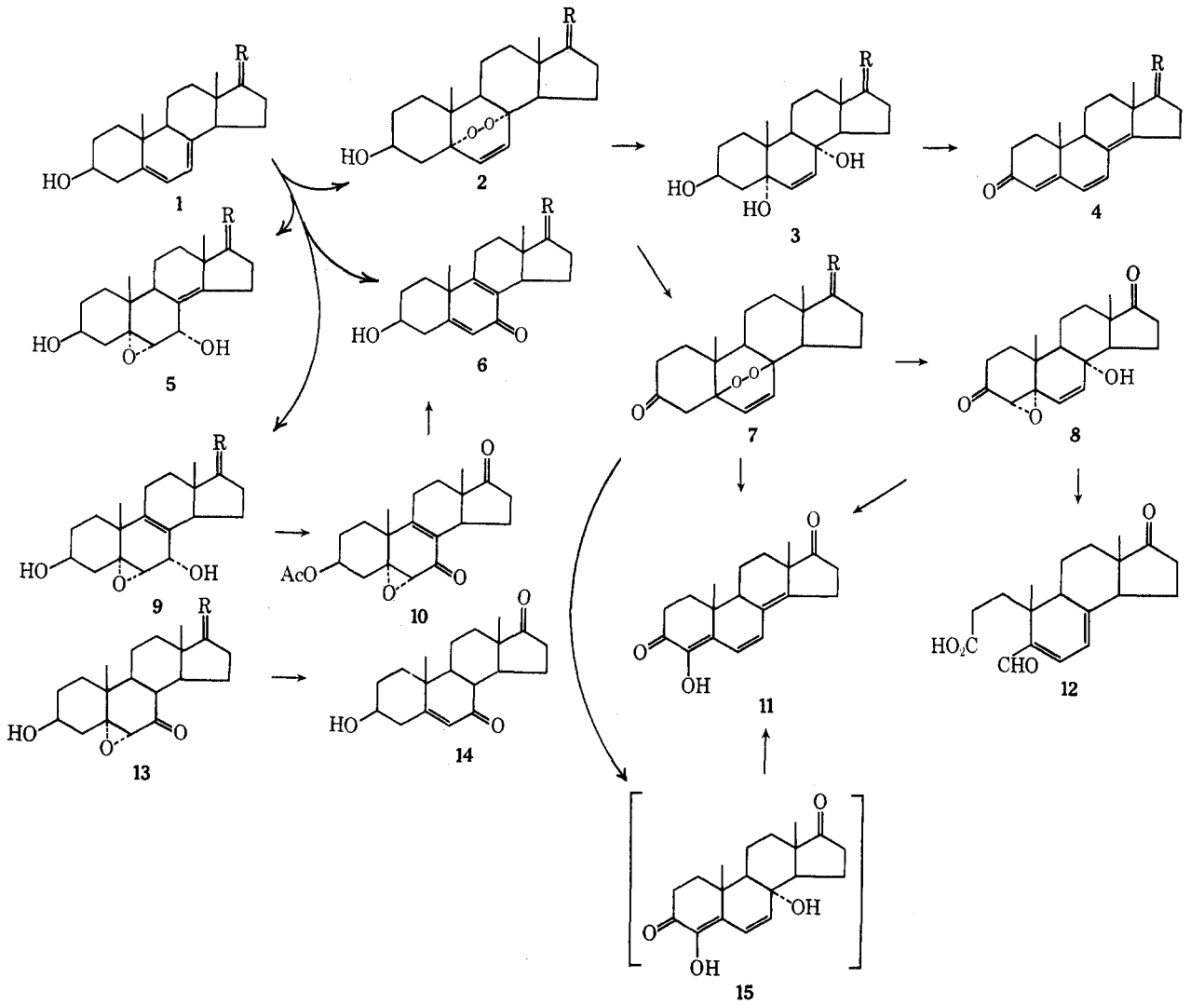
(7) This effect is similar to that recorded for the paramagnetic shift of the 5α,6-epoxides; see R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2071 (1963).

(8) The ergosterol analog of this compound has a similar absorption; see J. Elks, R. M. Evans, A. G. Long, and G. H. Thomas, *J. Chem. Soc.*, 451 (1954).

(9) K. Tsuda, J. Suzuki, and S. Iwasaki, *Chem. Pharm. Bull.*, **11**, 405 (1963).

(10) W. Bergmann and M. B. Meyers, *Justus Liebigs Ann. Chem.*, **620**, 46 (1959). An interesting microbiological preparation of analogous oxides from ergosterol peroxide has appeared: K. Petzoldt and K. Kieslich, *ibid.*, **724**, 194 (1969).

SCHEME I



a, R = O
b, R = β-OH, H
c, R = β-OH, CH_3

culated and observed angular methyl shifts for the 8 *vs.* the 8(14) olefins.[11]

The third by-product **5a** of the photooxygenation (8% yield) was also identical with a pyrolysis product of the epidioxide **2a**. It was separated in a pure state from the oxide **9a** by acetylation and careful rechromatography. Spectral characteristics quickly marked it as the double bond isomer of **9a**, the 8(14) olefin **5a**.[11] Evidence that **5a** was not the C-7 epimer of **9a** was obtained by oxidation of the 7-hydroxyl to a ketone different from ketone **10** (Scheme I).

Thermal isomerization of the epidioxide **2a**, effected by refluxing decane, yielded a ketone (**13**) isomeric to its companion hydroxy oxides **5a** and **9a**. The structure of the ketone **13** was demonstrated by potassium iodide reduction to the known unsaturated ketone **14**.[12] Thermal production of the photooxides implies that photochemical epimerization of C-13 has not occurred in spite of the 17-keto group. The formation of both epoxides (**5a**, **9a**) is analogous to the Δ^7 cholesterol work.[6]

The C-3 acetates of the three photooxygenation byproducts **5a**, **6a**, and **9a** underwent rapid basic hydrolysis to the corresponding hydroxy derivatives at room temperature. A sensitivity to base of these materials was shown by decreased yields with prolonged treatment.

The oxides **5a** and **9a** reasonably arise in the photooxygenation from the transformation of the epidioxide **2a** (as suggested by mechanistic considerations[6] and the thermal isomerization studies) rather than by a competing alternate oxidation of the diene **1a** itself. Conversion of the pure epidioxide **2a** to the oxide pair (**5a**, **9a**) with alcoholic acid or base failed. However, when the pure epidioxide itself was photooxygenated, the oxides **5a** and **9a** were produced slowly, demonstrating this to be a photochemically induced conversion.

The higher yield of oxide formation in the androstadienes as compared to the ergosterol derivatives[13] is

(11) Using the values in Zürcher's tables (see ref 7) the calculated signals for the 18- and 19-methyl signals are 47 and 72 Hz (found, 47 and 68) for the 8(9) olefin and 62 and 55 Hz (found, 64 and 52) for the 8(14) olefin.

(12) The comparison sample was kindly supplied by Dr. C. W. Marshall of these laboratories; *cf.* C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Amer. Chem. Soc.*, **79**, 6303 (1957).

(13) W. Furst, *Arch. Pharm. (Weinheim)*, **298**, 795 (1965); *Chem. Abstr.*, **64**, 4865*f* (1966).

reasonably ascribed to the longer reaction necessary in the former; the difference in reaction rate may be a result of the change in C-17 substituents. Methylene blue sensitized photooxygenation afforded a faster photooxygenation of the diene **1a** with a resultant higher yield of epidioxide **2a**; formation of the oxides **5a** and **9a** was not seen in this case.

Additional information about the mechanism of formation of the photooxygenation products, especially the dienone **6a**,[14] was sought by oxidizing the diene **1a** with singlet oxygen generated from hypochlorite and hydrogen peroxide.[15] The chief product of this reaction was the epidioxide **2a**. Careful investigation of the side products showed that the oxides **5a** and **9a** were absent, in agreement with the postulated photochemical nature of their formation. No dienone **6a** was found, suggesting that its origin may involve an activated oxygen species other than singlet oxygen, such as the $^1\Sigma^+_g$ state of oxygen[16] or the sensitizer-oxygen activated complex described by Schenk.[17]

Since the epidioxide group of **2a** reacted readily with methylmagnesium bromide, the 17-methyl derivatives were prepared starting from the 17-methyldiene **1c**. Photooxygenation of **1c** afforded an array of products (**2c**, **5c**, **6c**, **9c**) similar to those obtained in the 17-ketone series. In addition, the epoxy ketone **13c** was isolated and its structure shown by spectral comparison with the keto oxide **13a**.

B. Trienone Formation.—Despite the relative stability of the epidioxide **2a** to acid and base, when stirred with palladium catalysts in ethanol the epidioxide underwent a facile change to provide 70% of the highly polar triol **3a**. The same compound was obtained (in low yield) by reduction of the epidioxide with zinc in ethanolic hydroxide.[18] The nmr of the triol in deuterated dimethyl sulfoxide showed two vinyl protons coupled only with each other; in addition, each of the hydroxyl protons appeared, the secondary hydroxyl as a doublet and each of the two tertiary hydroxyls as a singlet. Acetylation of the triol provided the 3-monoacetate which again exhibited the tertiary hydroxyl protons as singlets; in addition, the vinyl proton pattern was unchanged from that seen in the starting triol. The same acetate was also prepared by palladium treatment of the epidioxide **2a** acetate in ethanol.

Use of lithium tri-*tert*-butoxyaluminohydride to effect the reduction of the epidioxide group gave only the diol **2b**. The product retained the vinyl hydrogen nmr pattern of starting material. Acetylation of this material gave a diacetate which lacked hydroxyl bands in the ir, in agreement with structure **2b** diacetate.

Prolonged treatment of the triolone **3a** (or the epidioxide **2a**) with palladium black in ethanol promoted the slow formation of the trienone **4a** (λ_{max} 340 nm), an optimum concentration (60%) of this material being reached after 10 days. The structure of the trienone **4a** is clearly defined by the characteristic uv absorption[4] and corroborated by ir, nmr, and elemental analysis. Similar palladium treatment of 17-hydroxy or 17-methyl epidioxides (**2b**, **2c**) led to the respective trienones **4b**, **4c**.

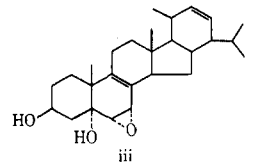
The reaction pathway from epidioxide to trienone would reasonably involve a discrete reductive cleavage of the epidioxide **2** to triolone **3**, involving a palladium-catalyzed transfer of hydrogen from the solvent. A subsequent hydrogen transfer would result in oxidation of the 3-hydroxyl group and loss of water to afford the trienone **4**. Attempts to follow the reaction path through the oxidation step were frustrated by the complexity and instability of the products obtained from the triolone **3a** with several mild oxidants.

One other intermediate, the 3-keto epidioxide **7**, might be envisioned in the conversion of the epidioxide **2** to the trienone **4**. That this was not so was shown by preparation of **7** (see below) and the demonstration of its stability to prolonged treatment with palladium black in ethanol.

C. Reactions of 3-Keto Epidioxide 7.—Oxidation of the epidioxide **2a** (or **2c**) with chromic acid proceeded smoothly to give the corresponding ketone **7a** (or **7c**). Evidence that the epidioxide group was intact was obtained from the unchanged nmr pattern of the C-6 and C-7 protons. Initial attempts to prepare **7a** by chromium trioxide–pyridine oxidation of the alcohol **2a** gave only minor amounts of the desired product. The major component, also obtained when **7a** was dissolved in pyridine or in dilute methanolic base, was shown to be the isomeric 4α,5-epoxide **8**.[19] The 3- and 17-carbonyl groups as well as a new hydroxyl group showed in the infrared. The nmr signals of the vinylic 6 and 7 protons were shifted from those of the starting ketone **7a**. In addition, a sharp singlet (218 Hz) appeared and was attributed to the proton on the oxirane ring. Formation of the epoxide from the ketone **7a** was followed directly in the nmr by use of deuteriopyridine as solvent; at room temperature the signals of starting material were completely replaced by those of the product within 2 hr with the intervention of no evident intermediate. With either reagent grade or anhydrous pyridine, the reaction was much slower, requiring 4 days at room temperature or 30 min at 90° for completion. The peculiar accelerative properties of the deuteriopyridine were not investigated further.

The epoxide **8** was labile in base, affording a mixture which possessed an ultraviolet maximum (298 nm), in accord with the 4,8-dihydroxydienone structure **15**. With more vigorous base treatment the 4-hydroxytrienone **11** was obtained; the uv spectrum (λ_{max} 361 nm) and the hydroxyl band in the infrared allowed

(14) Furst (ref 13) surprisingly isolated no dienone from the photooxygenation of ergosterol. He did find as a major component the epoxide iii



iii

which may represent an intermediate in an alternate, mechanistically more complex route to the dienone. No trace of an analog of iii was seen in the present studies, presumably because of its lability.

(15) C. S. Foote, S. Wexler, W. Ando and R. Higgins, *J. Amer. Chem. Soc.*, **90**, 975 (1968); C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968).

(16) D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Amer. Chem. Soc.*, **89**, 5455 (1967). The author wishes to thank a referee for pointing out this possibility.

(17) R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 604.

(18) A. Windaus and O. Linsert, *Justus Liebigs Ann. Chem.*, **465**, 148 (1928).

(19) Blandon has postulated, but not isolated, an analogous intermediate in the ergosterol series: P. Bladon and T. Sleigh, *J. Chem. Soc.*, 6991 (1965).

ready assignment of structure[20] to this compound. Since a by-product of the base treatment contained methoxyl groups, tetrahydrofuran was substituted as solvent; the trienone **11** was then accompanied by the seco acid **12** (see below).

Use of acid catalysts to effect conversion of the 3-keto epidioxide **7** to the trienone system **4** afforded instead an acidic product **12**. A 50% yield of this compound was obtained by use of acetic acid at room temperature either from the epidioxide **7** in 5 days or from the oxide **8** in 2 hr. The acid was isomeric with starting material and showed carboxyl and conjugated aldehyde functions as well as the undisturbed ring D ketone (ir and nmr analysis). The nmr also showed two adjacent vinylic protons (C-6, -7) coupled only with each other. The uv spectrum (λ_{max} 320 nm) was consistent with a homoannular diene conjugated with the aldehyde.[21] The seco acid structure **12** is in full accord with this data.

Formation of the acid **12** from the epidioxide **7a** probably proceeds by an initial conversion to the epoxide **8**; subsequent attack by hydroxide (in the base-catalyzed reaction) at the C-3 carbonyl group may occur, followed by C_3–C_4 bond rupture, shift of electrons, and expulsion of the 8-hydroxyl to give **12**. The acid-catalyzed transformation would proceed by an analogous route.

Chemical support for this seco acid structure was afforded by reactions of its functional groups: the carboxyl group formed a methyl ester with diazomethane, a change having no effect on the spectral properties of the dienic aldehyde system; the diene system readily added 2 mol equiv of hydrogen to provide an aldehydic acid lacking ultraviolet absorption; the aldehyde group gave a complex acetal mixture with methanolic acid.

Experimental Section[22]

3β-Acetoxy-5α,8-epidioxyandrost-6-en-17-one (2a Acetate). A. Eosin-Sensitized Photooxygenation. Procedure A.—A stream of oxygen was bubbled through a solution of 53 g of 3β-acetoxyandrosta-5,7-dien-17-one[23] and 0.5 g of eosin yellow in 4 l. of 2B ethanol illuminated with a 500-W tungsten lamp for 12 hr. The solvent volume was reduced to 0.5 l. and the resulting crystal mass was filtered and recrystallized from methylene chloride–methanol to give 20.1 g of the acetate **2a**: mp 253–260°; 5.72 μ; 56 (18-CH_3), 60 (19-CH_3), 381 (d, J = 8 Hz, C=CH) 393 Hz (d, J = 8 Hz, C=CH); $[\alpha]_D$ 51°.[24]

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.81; H, 7.65.

The stability of the diene acetate **1a** was tested by passing oxygen through a boiling ethanol solution. A slow decomposition resulted, affording a mixture of products; none of the photooxygenation products (**2a**, **5a**, **6a**, **9a**) could be discerned in this mixture (tlc and nmr analysis).

B. Methylene Blue Sensitized Photooxygenation.—The acetate of **1a** (10.2 g) in 0.8 l. of *n*-propyl alcohol containing 25 mg of methylene blue was photooxygenated as above for 1 hr. The cooled solution gave by direct crystallization 4.7 g of the pure acetate **2a**. Chromatography[25] gave another 0.7 g of **2a**.

3β-Hydroxy-5α,8-epidioxyandrost-6-en-17-one (2a). A. Photooxygenation.—3β-Hydroxyandrosta-5,7-diene (2.0 g, **1a**)[23] by use of procedure A for 7 hr was converted to 0.85 g of the alcohol **2a**, mp 184–190°. Recrystallization from acetone–hexane gave a pure sample: mp 200–202°; 2.72, 5.72 μ; $[\alpha]_D$ 32°. The nmr signals of vinyl protons and methyl groups were the same as for the acetate of **2a**.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.54; H, 8.13.

B. Nonphotochemical Oxygenation.—To a solution of 10 g of the diene **1a** in 1 l. of methanol at −5° was added 35 ml of 30% aqueous hydrogen peroxide. Sodium hypochlorite solution (5.25%, 350 ml) was added over a 35-min period. After an additional 10 min, the solution was poured into ice water and the product extracted with methylene chloride. The extract was washed with water and then aqueous potassium bicarbonate, dried over anhydrous magnesium sulfate, and concentrated.[26] The product was chromatographed and afforded fractions containing 4.2 g of the epidioxide **2a**, identical with the above sample. Later eluents provided 4.0 g of a more polar mixture which was acetylated and rechromatographed; neither nmr nor tlc analysis showed evidence of the presence of the dienone **6a** or the oxides **5a**, **9a**.

C. Saponification.—A solution of 12.6 g of **2a** acetate in 400 ml of 3A ethanol and 40 ml of 10% aqueous potassium hydroxide after 20 hr at room temperature was diluted with water to afford 8.9 g of the epidioxide **2a**. Distillation of the ethanol from the filtrate followed by filtration afforded an additional 3.0 g of the same compound.

By-products of the Photooxygenation.—Chromatography of the mother liquors (31 g) of the first experiment (procedure A) gave by elution with 15% ethyl acetate–benzene first additional epidioxide **2a** followed closely by fractions containing 6.3 g of semicrystalline material. Trituration of this material with ether and recrystallization of the insoluble portion from aqueous methanol yielded 2.25 g of **3β-acetoxyandrost-5,8-diene-7,17-dione (6a)**: mp 172–174°; 5.72, 6.01 μ; 245 nm (15,200); 50 (18-CH_3), 84 (19-CH_3), 367 Hz (7-H).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.62; H, 7.64.

Elution with 50% ethyl acetate–benzene gave material which was recrystallized from acetone to yield 1.46 g of **3β-acetoxy-7α-hydroxy-5α,6-epoxyandrost-8-en-17-one (9a)**: mp 185–191°; 2.78, 5.72 μ; 47 (18-CH_3), 72 (19-CH_3), 201 and 203 (6-H), 262 Hz (7β-H, $W_{1/2}$ = 7 Hz); $[\alpha]_D$ 24°.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.58; H, 8.00.

To assist in purification of the components eluted at 50% ethyl acetate–benzene, the noncrystalline eluates and mother liquors were acetylated with acetic anhydride–pyridine at room temperature and the product was rechromatographed. The material eluted at 25% ethyl acetate–benzene was further purified by preparative tlc. The first component obtained was recrystallized from acetone–hexane to yield **3β,7α-diacetoxy-5α,6-epoxyandrost-8-en-17-one (9a)**: mp 206–211°; 5.75 μ; 47 (18-CH_3), 73 (19-CH_3), 121 (OAc), 123 (OAc), 203 and 205 (6-H), 329 Hz (7-H, $W_{1/2}$ = 6 Hz).

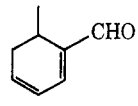
Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.56; H, 7.62.

This compound was also prepared in high yield by acetylation of the 3-monoacetate of **9a**.

A second component from the preparative tlc was crystallized from acetone–hexane to yield **3β,7α-diacetoxy-5α,6-epoxyandrost-8(14)-en-17-one (5a)**: mp 166–172°; 5.75 μ; 57 (18-CH_3), 62

(20) See ref 19 for a hydroxytriene analogous to **11**.

(21) C. Grundmann, *Chem. Ber.*, **81**, 513 (1948), has recorded max 303 mμ (7900) for



An additional increment of 18 mμ can be added to this value for the additional δ substituent (see ref 5, p 19). D. N. Kirk and J. M. Wiles [*Chem. Commun.*, 1015 (1970)] have described a similar type of cleavage.

(22) We wish to thank Dr. R. T. Dillon and staff for elemental and spectral analyses reported. Infrared spectra (μ) were determined in chloroform (5%), ultraviolet (nm) in methanol, and nmr (Hz) in deuteriochloroform (on a Varian A-60 spectrometer with tetramethylsilane as an internal standard, $\Delta\nu$ = 0). Rotations were run in chloroform (1%).

(23) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).

(24) This compound was first prepared in these laboratories by Dr. R. H. Bible. The author also acknowledges valuable discussions with Dr. Bible pertaining to the interpretation of several nmr spectra.

(25) The chromatographies described throughout this paper were run by the Chromatography Department under the direction of Mr. R. T. Nicholson. These were routinely run on a weight of silica gel (Davison) 60 times that of the compound, unless specified otherwise.

(26) This represents a standard method of isolating the products and was used routinely throughout the bulk of this work. The temperatures used in removal of solvents were normally kept below 50°, vacuum being used where necessary.

(19-CH_3), 121 (OAc), 127 (OAc), 195 and 198 (6-H), and multiplets centered at 343 and 346 Hz (7-H).

Anal. Found: C, 68.55; H, 7.42.

The remainder of the materials from these chromatograms were intractable mixtures which displayed no clear methyl signals in the nmr.

The methylene blue sensitized photooxygenation mother liquors (5.1 g) were also chromatographed and yielded, besides additional epidioxide acetate **2a**, fractions (1.2 g) consisting largely of the dienone acetate **6a** (nmr and tlc analysis). Later eluents were acetylated and rechromatographed but contained no discernible amount of the oxides **5a** or **9a** nor were any other discrete products seen (nmr, tlc).

3β-Hydroxyandrosta-5,8-diene-7,17-dione (6a).—Aqueous potassium hydroxide (10%, 0.5 ml) was added to a solution of 0.70 g of **6a** acetate in 5 ml of methanol. After 1 hr, a precipitate formed and was separated yielding 0.57 g of the crude alcohol **6a**. Recrystallization from methylene chloride–methanol yielded the pure material: mp 252–254°; 2.75, 5.72, 6.01 μ; 248 nm (14,200); 49 (18-CH_3), 83 (19-CH_3), 364 Hz (7-H); $[\alpha]_D$ 42°.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.81; H, 8.05. Found: C, 75.97; H, 7.90.

3β,7α-Dihydroxy-5α,6-epoxyandrost-8-en-17-one (9a). Procedure B.—A slurry of 0.10 g of **9a** 3-monoacetate in 2 ml of methanol was treated with 0.2 ml of 10% aqueous potassium hydroxide. The compound dissolved immediately and after 3 min was isolated by methylene chloride extraction. The product was crystallized from ether and from acetone–hexane to yield 50 mg of the diol **9a**: mp 196–203°; 2.75, 5.75 μ; 47 (18-CH_3), 68 Hz (19-CH_3).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.72; H, 8.33.

Longer base treatment decreased the yield of isolable diol **5a**. Treatment of the 3-monoacetate of **5a** with acidic ethanol led to an intractable mixture.

3β,7α-Dihydroxy-5α,6-epoxyandrost-8(14)-en-17-one (5a).—The diacetate of **5a** (120 mg) was treated according to procedure B. The crude product was recrystallized from ethyl acetate to yield 40 mg of the diol **9a**: mp 178–183°; 2.75, 5.72 μ; 54 (18-CH_3) and 66 Hz (19-CH_3).

Anal. Found: C, 71.12; H, 7.96.

Structure Proof of Epoxide 9a. A. Oxidation of the Epoxide 9a.—A solution of 0.38 g of the 3-monoacetate of **9a** in 5 ml of pyridine was added to the Sarett reagent[27] prepared from 0.5 g of chromium trioxide. After 3 hr at room temperature the solution was diluted with water and extracted with ether. The crystalline product was recrystallized from acetone–hexane and then from ether (Darco) to yield **3β-acetoxy-5α,6-epoxyandrost-8-ene-7,17-dione (10)**: mp 189–194°; 5.75, 5.98 μ; 259 nm (6800); 47 (18-CH_3), 78 (19-CH_3), 201 Hz (6-H).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.37; H, 7.31. Found: C, 70.10; H, 7.27.

A similar oxidation of the 8(14) olefin **5a** 3-acetate gave a different product (methyl signals 57, 72 Hz), but insufficient material was available to complete its purification and obtain a satisfactory elemental analysis.

B. Reduction of the Oxido Ketone 10a. Procedure C.—A solution of 60 mg of the unsaturated keto oxide **10a** in 2 ml of acetic acid saturated with potassium iodide was heated at 95° for 15 min resulting in the fast liberation of iodine. The solution was cooled and diluted with aqueous sodium thiosulfate. The product (45 mg of crystals) was isolated by methylene chloride extraction and was identical spectrally with the known 5,8-dienone **6a**.

Rearrangement of the Epoxide 2a.—A solution of the 0.38 g of the epidioxide **2a** (3-acetate) was treated as in procedure A for 7.5 hr. The crude product was chromatographed and yielded 0.18 g of starting material. A mixture (0.12 g) of compounds which eluted next consisted predominantly of the oxide 3-monoacetates (**5a**, **9a**) in a 6:4 ratio; the identification was made clear by nmr analysis of the characteristic methyl and C-6 proton signals and by tlc.

The stability of the epidioxide group was shown in separate experiments in which the compound was boiled in neat triethylamine[10] (20 hr), in aqueous ethanol containing either potassium hydroxide (22 hr) or hydrochloric acid (6 hr) with essentially no effect (nmr and tlc analysis). Prolonged contact at room temperature with alumina or silica gel also caused no appreciable change.

Thermal Isomerization of the Hydroxy Epidioxide 2a.—The epidioxide **2a** (0.75 g) in 60 ml of redistilled decane[10] was boiled under nitrogen for 36 hr. The solvent was distilled and the residue chromatographed. Fractions eluted at 20% ethyl acetate–benzene were recrystallized from aqueous acetone to give 65 mg of **3β-hydroxy-5α,6-epoxyandrostane-7,17-dione (13a)** solvated with 0.25 mol equiv of water: mp 168–173°; 2.75, 5.73, 5.88 μ; 54 (18-CH_3), 65 (19-CH_3), 185 Hz (6β-H).

Anal. Calcd for $C_{19}H_{26}O_4 \cdot 0.25H_2O$: C, 70.67; H, 8.28. Found: C, 70.62; H, 8.09.

Treatment of the oxido ketone **13a** according to procedure C at room temperature for 4 hr gave a product identical spectrally with an authentic sample of the unsaturated ketone **14a**.[12]

Further elution of the chromatographic column with 30% ethyl acetate–benzene gave 0.35 g of a 6:4 mixture of the epoxides **5a** and **9a** (nmr analysis).

5α,8-Epidioxyandrost-6-ene-3β,17β-diol (2b).—Lithium tri-*tert*-butoxyaluminohydride (3.56 g) was added to a solution of 1.78 g of the ketone **2a** in 30 ml of tetrahydrofuran at 5°. After 10 min the solution was removed from the cooling bath and allowed to stand at room temperature or 2 hr. The solution was poured into ice water containing 10 ml of acetic acid, the organic solvent was evaporated in a stream of nitrogen, and the product (1.62 g) was isolated by ethyl acetate extraction. The pure compound, obtained by crystallization from acetone, had mp 125–135° and 195–210°; 2.73 μ; 53 (18 and 19-CH_3), 376 (d, J = 9 Hz, C=CH), 390 Hz (d, J = 9 Hz, C=CH) (DMSO-d_5).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.90; H, 9.20.

Nmr analysis of the mother liquors showed no sign of the tetrol **3b**.

Acetylation of the diol **2b** afforded 5α,8-epidioxyandrost-6-ene-3β,17β-diol diacetate (**2b**): mp 200–202°; 5.79 μ (no hydroxyl absorption); 55 (18,19-CH_3), 121 (OAc), 123 (OAc), 377 (d, J = 8 Hz, C=CH), 393 Hz (d, J = 8 Hz, C=CH).

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.56; H, 8.18.

17α-Methylandrosta-5,7-diene-3β,17-diol (1c).—A solution of 9.5 g of the 17-ketone **1a** in 200 ml of tetrahydrofuran was added to a solution of 300 ml of ether containing 0.16 mol of methylmagnesium bromide. After 18 hr the reaction mixture was diluted with water and then dilute hydrochloric acid. The ether was distilled and the crystal mass obtained, after separation by filtration, was recrystallized from aqueous methanol to yield 8.7 g of crude adduct. Recrystallization from methanol–ethyl acetate gave pure **1c**: mp 211–213°; 2.75 μ; 270 (10,300), 280 (10,900), 287 nm (6180); 49 (18-CH_3), 58 (19-CH_3), 74 (17-CH_3), 220–240 Hz (broad multiplet, 6,7 H's).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.50; H, 9.88.

3β-Acetoxy-17α-methylandrosta-5,7-dien-17-ol was prepared by acetylation of the alcohol **1c** with pyridine–acetic anhydride; crystallization from methylene chloride–methanol gave a hemimethanolate: mp 134–139°; 2.75, 5.78 μ; 270 (10,400), 281 (10,750), 293 nm (6250); 48 (18-CH_3), 58 (19-CH_3), and 74 Hz (17-CH_3).

Anal. Calcd for $C_{22}H_{32}O_3 \cdot 0.5CH_3OH$: C, 74.96; H, 9.38. Found: C, 75.27; H, 9.51.

5α,8-Epidioxy-17a-methylandrost-6-ene-3β,17-diol (2c).—The diene **1c** (15 g) was treated according to procedure A and afforded by direct crystallization 3.3 g of the crude epidioxide **2c**. Recrystallization from acetone gave the pure material: mp 196–201°; 2.74 μ; 54 (19-CH_3), 58 (18-CH_3), 75 (17-CH_3), 372 (d, J = 8 Hz, C=CH), 393 Hz (d, J = 8 Hz, C=CH).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.55; H, 8.83.

The epidioxide **2c** was stable to reduction with lithium aluminum tri-*tert*-butoxyhydride at room temperature for 24 hr.

Running the photooxygenation with eosin blue in dimethylformamide or in methanol–benzene[9] slowed the reaction and decreased the yield of epidioxide; no increased proportion of the dienone was found as compared to the eosin yellow photooxygenation.

3β-Acetoxy-5α,8-epidioxy-17α-methylandrost-6-en-17-ol (2c) was prepared by procedure A from **1c** (3-acetate) and had mp 197–203°; 2.71, 572 μ; 55 (19-CH_3), 58 (18-CH_3), 75 (17-CH_3), 375 (d, J = 8 Hz, C=CH), 397 Hz (d, J = 8 Hz, C=CH); $[\alpha]_D$ −12°.

(27) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.50; H, 8.55.

Alkaline hydrolysis of this material gave the alcohol **2c** in good yield.

3β,17β-Dihydroxy-5α,6-epoxy-17α-methylandrostan-7-one (13c).—Photooxygenation of mother liquors upon acetylation and rechromatography afforded impure oxide **13c** 3-acetate. Room temperature hydrolysis of this material (procedure B) and rechromatography afforded pure oxide **13c**: mp 190–192° from methylene chloride–hexane; 2.75, 5.89 μ; 52 (18-CH_3), 65 (19-CH_3), 183 Hz (6-H).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.86; H, 9.19.

In the same manner, **3β,17β-dihydroxy-17-methylandrosta-5,8-dien-7-one (6c)** was obtained. Recrystallization from aqueous acetone afforded a monohydrate: mp 119–122°; 2.75, 6.10 μ; 247 nm (7700); 50 (18-CH_3), 75 (17-CH_3), 82 (19-CH_3), 364 Hz (6-H).

Anal. Calcd for $C_{20}H_{28}O_3 \cdot H_2O$: C, 71.82; H, 9.04. Found: C, 71.68; H, 8.99.

No pure samples of the oxides **5c** or **9c** were obtained.

3β,5α,8α-Trihydroxyandrost-6-en-17-one (3a).—A solution of 3.1 g of the epidioxide **2a** in 100 ml of 2B ethanol was stirred with 5 g of palladium black (Fischer) at room temperature. After 18 hr the mixture was filtered and the filtrate concentrated. Crystallization of the residue from acetone afforded 2.02 g of the triolone **3a**; mp 222–226°; 3.02, 5.72 μ; 47 (19-CH_3), 53 (18-CH_3), 259 (d, 3-OH), 306 (OH), 331 Hz (OH) (DMSO-d_5).

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.47; H, 8.60.

Chromatography of the mother liquors afforded 0.20 g of the starting material **2a** but very little of the trienone **4a** was found.

This reaction could also be effected at a comparable rate with 10% palladium on charcoal. Zinc–potassium hydroxide in ethanol reduced the epidioxide but the triolone **3c** was at best a minor component of the product (nmr and tlc analysis). Attempts to oxidize the triolone **3c** with Jones reagent,[28] the Sarett reagent,[27] pyridine chromate in methylene chloride,[29] or aluminum isopropoxide–cyclohexanone led to mixtures from which no pure products were isolated.

3β,5α,8α-Trihydroxyandrost-6-en-17-one 3-acetate was prepared from the triolone **3a** with acetic anhydride–pyridine and had mp 198–201°; 2.89, 5.70 and 5.83 μ (KBr); 52 (18-CH_3), 58 (19-CH_3), 122 Hz (OAc) (DMSO-d_5).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.58; H, 8.28. Found: C, 69.48; H, 8.34.

The same acetate (of **3a**) was obtained by treatment of the epidioxide acetate **2a** with palladium black in ethanol for 42 hr; the yield was lower than for the alcohol **3a** due to formation of unidentified side products.

Androsta-4,6,8(14)-triene-3,17-dione (4a). A. From the Epidioxide 2a.—The epidioxide **2a** (2.14 g) in 200 ml of 2B ethanol was stirred with 10 g of palladium black (Englehard) for 10 days. The mixture was filtered and the solvent evaporated. Uv analysis implied 60% of the material was the trienone **4a**. The product was crystallized from ether and then from acetone–hexane to yield 0.93 g of the trienone **4a**: mp 143–153°; $E_{340\ nm}$ 19,500. Further recrystallization from acetone–hexane gave material, mp 163–166°, solvated with 0.5 mol equiv of acetone: 5.72, 605 μ; 340 nm (26,400); 63 (18-CH_3), 73 (19-CH_3), 347 (4-H), 370 (d, J = 9 Hz, C=CH), 404 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{19}H_{22}O_2 \cdot 0.5C_3H_6O$: C, 79.06; H, 8.09. Found: C, 79.04; H, 8.00.

The polar by-products contained the triolone **3a** and ethoxyl-containing compounds (ethoxyl determination, 3.76%). Retreatment of this material with palladium black did not increase the amount of trienone present (uv analysis).

Use of freshly prepared sponge palladium black gave a mixture of compounds containing neither triolone **3a** or trienone **4a** (tlc and nmr analysis).

B. From the Triolone 3a.—A solution of 0.20 g of the triolone **3a** in 10 ml of 2B ethanol was stirred with 0.50 g of palladium black at room temperature for 3 days. The mixture was filtered and the filtrate concentrated to give a mixture containing 50% of the trienone **4a** (uv, nmr, and ir analysis).

17β-Hydroxyandrosta-4,6,8(14)-trien-3-one (4b).—A solution of 1.6 g of the diol **2b** in 50 ml of 2 B ethanol was stirred with 3 g of palladium black for 6 days. The product (1.52 g, $E_{346\ nm}$ 8700) was isolated and chromatographed. Fractions eluted with 20% ethyl acetate–benzene were recrystallized from acetone–hexane to afford 0.21 g of the triene **4b** as a hemiacetonate: mp 159–165°; 2.75, 6.08 μ; 346 nm (18,600); 61 (18, 19-CH_3's), 345 (4-H), 363, 372, 392, 401 Hz (6,7 H's).

Anal. Calcd for $C_{19}H_{24}O \cdot 0.5C_3H_6O$: C, 78.55; H, 8.68. Found: C, 78.16; H, 8.54.

The bulk of the remaining material from the chromatogram was more polar, indicating incomplete reaction. Very little saturated ketone was visible in the ir spectra of this material.

17β-Hydroxy-17-methylandrosta-4,6,8(14)-trien-3-one (4c).—The epidioxide **2c** (0.58 g) and 2 g of palladium black were stirred in 30 ml of 2B ethanol for 6 days. The mixture was filtered, the filtrate concentrated, and the resulting residue chromatographed. The product was eluted at 20% ethyl acetate–benzene and was recrystallized from acetone–hexane to give 50 mg of the trienone **4c**, as a hemietherate: mp 181–186°; 2.76 6.05 μ; 349 nm (25,400); 62 (18-CH_3), 69 Hz (19-CH_3).

Anal. Calcd for $C_{20}H_{26}O_2 \cdot 0.5C_4H_{10}O$: C, 78.76; H, 9.31. Found: C, 79.14; H, 9.22.

5α,8-Epidioxyandrost-6-ene-3,17-dione (7a). Procedure D.—Jones reagent[28] (10 ml) was added over a 5-min period to a solution of 8.6 g of the alcohol **2a** in 400 ml of acetone at −10°. After 30 min the solution was diluted with 10 ml of 2-propanol and then with water. The resulting precipitate was collected, air-dried, and recrystallized from methylene chloride–acetone to yield 7.19 g of the diketone **7a**, mp 173–177°. A second recrystallization raised the melting point to 185–189°; 5.72, 5.79 μ; 61 (18-CH_3), 65 (19-CH_3), 383 (d, J = 9 Hz, C=CH), 396 Hz (d, J = 9 Hz, C=CH); $[\alpha]_D$ +77°.

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.07; H, 7.46.

Treatment of the epidioxide **7a** with palladium black in ethanol at room temperature for 6 days gave no evidence of reaction.

17β-Hydroxy-5α,8-epidioxy-17-methylandrost-6-en-3-one (7c).—Oxidation of 190 mg of the alcohol **2c** according to procedure D gave after recrystallization from acetone–hexane 70 mg of the ketone **7c**: mp 175–180°; 2.75, 5.82 μ; 60 (18-CH_3), 65 (19-CH_3), 77 (17-CH_3), 380 (d, J = 9 Hz, C=CH), 399 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.16; H, 8.67.

8α-Hydroxy-4α,5-epoxyandrost-6-ene-3,17-dione (8).—The epidioxide **7a** (2 g) was dissolved in 50 ml of pyridine (Reilly). After 5 days pentane was added, precipitating an oil which then crystallized. Recrystallization of this material from acetone gave 1.77 g of the oxide **8**: mp 162–166°; 2.78, 5.74, 5.82 μ; 53 (18-CH_3), 61 (19-CH_3), 218 (4-H), 358 (d, J = 6 Hz, C=CH), 406 (d, J 6 Hz, C=CH), 530 (CO_2H), 567 Hz (CHO).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.68. Found: C, 72.40; H, 7.65.

Although use of anhydrous pyridine had no effect on the rate of this reaction, use of deuteriopyridine (in an nmr cell) caused the reaction to be complete in less than 2 hr. The reaction was also run in pyridine at 90° for 30 min or with aqueous potassium hydroxide in tetrahydrofuran at 5° for 10 min, but these procedures gave lower yields of **8**. The oxide **8** was also the principal product of oxidation of the epidioxide **2a** with the Sarett reagent.[27]

4-Hydroxyandrosta-4,6,8(14)-triene-3,17-dione (11).—A solution of 0.30 g of the epidioxide **7a** in 20 ml of ethanol and 2 ml of 10% aqueous potassium hydroxide was heated at reflux in a nitrogen atmosphere for 15 min. The solution was cooled and diluted with aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water, air-dried, and recrystallized from methylene chloride–acetone to yield 0.16 g of the triene **11**: mp 210–212°; 2.89, 6.01 μ; 361 nm (25,200), 403 nm (20,600) (in 0.1 N KOH–MeOH); 62 (18-CH_3), 73 (19-CH_3), 402 Hz (6,7-H's).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.46; H, 7.43. Found: C, 76.27; H, 7.52.

A similar treatment of the oxide **8** afforded the triene **11** in 30% yield.

In tetrahydrofuran–aqueous potassium hydroxide after 2 hr the neutral portion of the product (60% of the total) consisted largely of the triene **11**. The acidic portion was essentially pure seco acid **12** (see below). Room temperature treatment of the epidioxide **7a** in ethanol with aqueous potassium hydroxide for

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(29) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

18 hr gave an amorphous mixture displaying the ultraviolet maximum of the 4,8-dihydroxydiene **15**, 295 nm (9900); isolation of the pure compound failed.

4,17-Dioxo-3,4-secoandrosta-5,7-dien-3-oic Acid (12). A. From the Epidioxide 7a.—The epidioxide **7a** (0.85 g) in 10 ml of acetic acid was heated at 95° for 1.5 hr and the solvent was distilled. The crystalline residue resulting after ether trituration was washed with cold ethyl acetate and recrystallized from methylene chloride–ethyl acetate to yield 0.15 g of the seco acid **12**: mp 169–170°; 3.0–3.2 (shoulder), 5.72, 5.81, 5.92 μ; 320 nm (13,600); no change in the uv maximum was seen in the presence of either acid or base; 47 (18-CH_3), 74 (19-CH_3), 361 (d, J = 9 Hz, C=CH), 405 Hz (d, J = 9 Hz, C=CH).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 72.11; H, 7.55.

The same reaction required 5 days at room temperature to go to completion. Uv analysis of the total product in either case implied *ca.* 50% was the seco acid **12**.

B. From the Oxide 8.—A solution of 0.10 g of the oxide **8** in 5 ml of acetic acid was allowed to stand at room temperature for 2 hr and was then diluted with water. Methylene chloride extraction afforded 60 mg of crude product [λ_{max} 316 mμ (6600)] having the characteristic nmr and ir absorption spectra of the seco acid **12**. When the reaction was run in deuterioacetic acid and followed directly in an nmr cell, the reaction required a longer period of time for completion (*ca.* 18 hr); no intermediate was visible and no other discernible product was formed.

Treatment of 75 mg of pure **12** in tetrahydrofuran with an excess of ethereal diazomethane afforded an amorphous methyl ester: 3.64, 5.72, 5.93 μ; 318 nm (11,550). The major nmr signals were the same as those of the acid **12** with the addition of the 218-Hz signal (OCH_3). Treatment of this ester (or the oxide **8**) with methanolic acid gave a complex acetal mixture lacking the diene chromophore.

Hydrogenation of the seco acid **12** in ethanol with a palladium/charcoal catalyst effected uptake of 2 mol equiv of hydrogen. The product was an amorphous aldehydro acid lacking uv absorption.

Registry No.—**1c**, 23971-00-8; **1c** 3-acetate, 29851-14-7; **2a**, 23970-97-0; **2a** acetate, 23970-96-9; **2b**, 23970-98-1; **2b** diacetate, 29851-17-0; **2c**, 23971-02-0; **2c** 3-acetate, 29851-19-2; **3a**, 29851-20-5; **3a** 3-acetate, 29851-21-6; **4a**, 23970-99-2; **4b**, 23971-01-9; **4c**, 29851-24-9; **5a**, 29851-25-0; **5a** diacetate, 29851-26-1; **6a**, 29851-41-0; **6a** acetate, 29851-40-9; **6c**, 29851-27-2; **7a**, 29851-28-3; **7c**, 29851-29-4; **8**, 29851-30-7; **9a**, 29851-31-8; **9a** 3-acetate, 29851-32-9; **9a** diacetate, 29851-33-0; **10**, 29851-34-1; **11**, 29851-35-2; **12**, 29936-63-8; **13a**, 29851-36-3; **13c**, 29851-37-4.

Acknowledgment.—The competent technical assistance rendered by Mrs. Barbara Tucker is gratefully acknowledged by the author.

Steroidal Adducts. IV.[1] Variable Selectivity in Hydride Reductions of a Steroidal Cyclic Anhydride

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Received January 20, 1971

Variable selectivity has been observed in different hydride reductions of a steroidal cyclic anhydride to γ-lactones. There is strong selectivity with lithium aluminum hydride, less with sodium aluminum hydride, and none with sodium borohydride. Lactol formation *via* reduction of the anhydride with lithium aluminum tri-*tert*-butoxyhydride is also highly selective. These results support a proposed mechanism involving 1,4 attack by hydride on a complex involving an anhydride group, another carbonyl group, and a metal cation.

Steroids bearing appropriate functional groups are unsurpassed in their ability to reveal the stereochemical aspects of a wide variety of important reactions. In a previous paper in this series,[3] a study was made of the reduction of cyclic anhydrides by metal hydrides to γ-lactones, a reaction of considerable potential synthetic utility. In particular, the Inhoffen adduct **1**[4,5] of ergosteryl acetate and maleic anhydride was shown to be reduced selectively by sodium borohydride or lithium aluminum hydride to the lactone **2**. None of the isomeric **3** was obtained. Bloomfield and Lee[6] proposed for reductions of simple succinic anhydrides that differences in the steric environment of anhydride carbonyl groups induce preferential participation of these carbonyls in an intermolecular complex also involving a reagent cation. The complex is then selectively attacked by the hydride reagent. The 3′- and 4′-carbonyls of **1** are approximately equivalent in steric environment[3] (C-3′ is only slightly more hindered), and hence the high degree of selectivity observed in the reduction of **1** to **2** could not be ascribed to intermolecular complex formation alone. It can, however, be interpreted[3] in terms of a mechanism in which intramolecular complex **4** is formed, and the bulky solvated **4** is then attacked by hydride at the other anhydride carbonyl. This mechanism was also invoked[3] to explain the selective reduction of **1** by lithium aluminum tri-*tert*-butoxyhydride to the lactol **5**. (A related reduction in the aromatic series, of a dimethoxyphthalic anhydride to a hydroxyphthalide, has also been reported.)[7]

To test the validity of this mechanism, we have investigated the hydride reduction of the methoxy anhydride **6**. This compound, lacking the acetoxycarbonyl group to participate in an intramolecular complex, might be expected to give both possible lactones **7** and **8** on hydride reductions provided that intermolecular complex formation is absent or itself unselective.

The methoxy anhydride **6** was prepared from the Inhoffen adduct **1**. The known hydroxydicarboxylic diester **9**[5,8] with diazomethane and aluminum chloride[9]

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