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Steroid Series. XX.[1] Reaction of α,β-Epoxyketone with Dimethyl Sulfoxide[2]

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The oxidation of 17β-hydroxy-4β,5-epoxy-5α-androstan-3-one (I) and its 4α,5α-isomer (II) with dimethyl sulfoxide gave 4,17β-dihydroxyandrost-4-en-3-one (IV), 17β-hydroxyandrosta-1,4-dien-3-one (V), 2,17β-dihydroxyandrosta-1,4-dien-3-one (VI) and 2α,17β-dihydroxyandrost-4-en-3-one (VII). The same reaction of 17β-acetoxy-4β,5-epoxy-19-nor-5β-androstan-3-one (IIIa) afforded 4,17β-dihydroxy-19-norandrost-4-en-3-one 17-acetate (VIIIa), estra-1,3,5 (10)-triene-3,17β-diol 17-acetate (IX) and estra-1,3,5 (10)-triene-2,3,17β-triol 17-acetate (X). The corresponding 19-oxosteroid (IIIb) yielded the estrane derivatives (IX and X), while 19-hydroxymethyl steroid (IIIc) gave, in addition to the estrane derivatives (IX and X), 4,17β,19-trihydroxyandrost-4-en-3-one 17-acetate (VIIIc) and 17β-acetoxy-2β,19-oxidoandrost-4-en-3-one (XI).

An increasing number of reactions with dimethyl sulfoxide as an oxidizing agent have recently been reported.[4] One of them is an oxidative ring opening of an epoxide leading to an α-hydroxy ketone[5-7] or an aldehyde.[8] In this connection studies on the behavior of the α,β-epoxyketone with the reagent would be of interest. We describe here the results obtained by the reactions of dimethyl sulfoxide on the 4,5-epoxy-3-oxo system in 19-methyl, 19-nor and 19-oxygenated steroids.

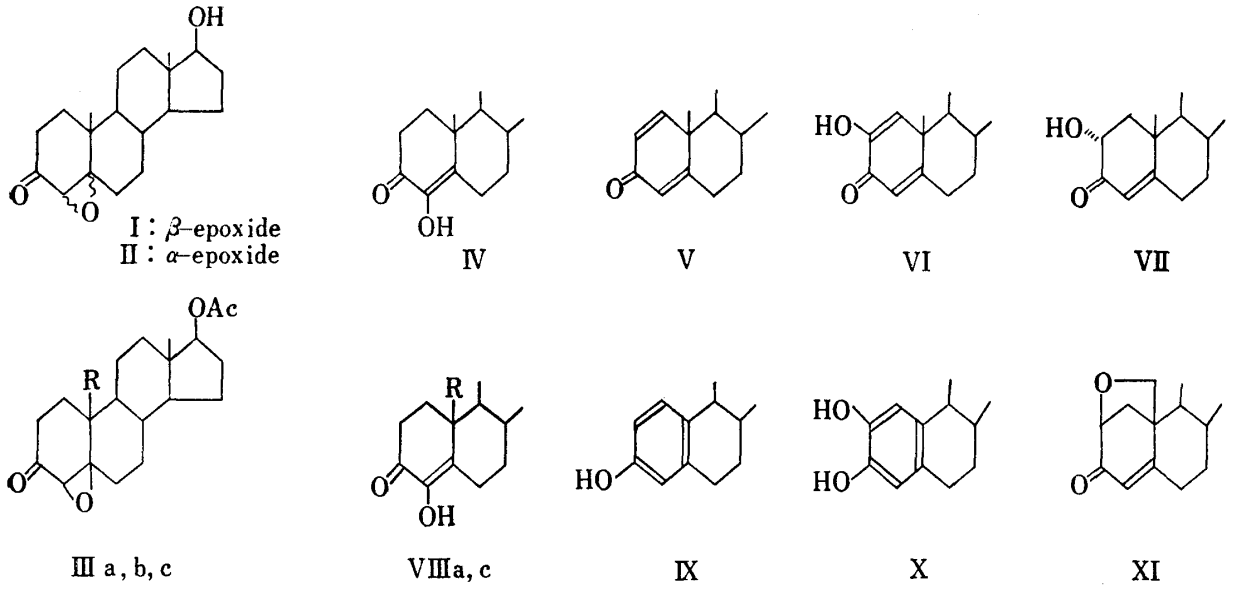
The epoxides (I, II, IIIa) were prepared from 17β-hydroxyandrost-4-en-3-one and 17β-acetoxy-19-norandrost-4-en-3-one according to the method of Camerino, *et al.*[9] 17β,19-Dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (IIIc) was analogously prepared from the corresponding Δ^4-3-oxosteroid using alkaline hydrogen peroxide in methanol, no α-epoxide being observed by thin-layer chromatography (TLC). The epoxidation of 17β-acetoxyandrost-4-ene-3,19-dione was carried out in dimethylformamide with hydrogen peroxide, since ready deformylation of the 19-oxo-group in the starting material is known under alkaline conditions.[10]

The configuration of the epoxide (IIIc) was deduced by optical rotatory dispersion, the curve showing a positive Cotton effect[11] and by the negative contribution in the molecular rotation value associated with the introduction of an epoxy function into the 3-oxo-4-ene.[12]

The Cotton effect of the epoxide (IIIb) was quite similar in the sign and amplitude to those of I, IIIa and IIIc, and the effect associated with 19-oxo function appears to be small

1) Part XIX: R. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **15**, 139 (1967).
2) This work was presented at the 24th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, Apr. 1967.
3) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
4) W.W. Epstein and F.W. Sweat, *Angew. Chem. (International Edition)*, **67**, 248 (1967).
5) E. Brousse and M.D. Lefort, *Compt. Rend.*, **261**, 1990 (1965).
6) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961).
7) T. Tsuji, *Tetrahedron Letters*, **1966**, 2413.
8) R. Oda, Y. Hayashi and T. Yoshida, *Nippon Kagaku Zasshi*, **87**, 975 (1966).
9) B. Camerino, B. Patelli and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3540 (1956).
10) H. Hagiwara, S. Noguchi and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **8**, 84 (1960).
11) C. Djerassi, W. Klyne, T. Norin, G. Ohloff and E. Klein, *Tetrahedron*, **21**, 163 (1965).
12) J. Jacques, H. Kagan, G. Ourisson and S. Alland, "Optical Rotatory Power" Ia, Steroids, Pergamon Press, 1965.

enough to be neglected.[13] However, the observed positive contribution to the molecular rotation value by the epoxy group makes it difficult to give a conclusive configuration from these data. The β-configuration of the epoxy group in IIIb was established definitely by oxidation of the epoxide (IIIc) to IIIb in good yield using the chromic acid–pyridine complex.



a : R=H, b : R=CHO, c : R=CH_2OH

Chart 1

When the epoxyketone (I) was heated in dimethyl sulfoxide with a catalytic amount of trifluoroacetic acid at 120° in nitrogen, a complex mixture of products was obtained. From this the following four substances were isolated chromatographically: 4,17β-dihydroxyandrost-4-en-3-one (IV; 4.5%), 2,17β-dihydroxyandrosta-1,4-dien-3-one (VI; 54.4%), 17β-hydroxyandrosta-1,4-dien-3-one (V; 11.8%) and 2α,17β-dihydroxyandrost-4-en-3-one (VII; 14.6%). These compounds were identified by direct comparisons with authentic samples prepared according to the descriptions of Camerino,[9] Rao[14] and Ringold.[15]

The 2α-hydroxyketone (VII) appears to be, at least partly, the precursor of the diosphenol (VI), because the ketone was converted into the latter (46% yield) on heating in dimethyl sulfoxide at 120°. An analogous oxidation reaction has been described by Nace,[16] *et al.*, who converted 2α-hydroxy-5α-cholestan-3-one to 3-hydroxy-5α-cholest-3-en-2-one in 30% yield by heating in the same solvent with sodium hydrogencarbonate.

The α-epoxide (II) was treated in the same manner as with I to afford IV and VI in 12.0 and 39.0% yields respectively after purification by silica gel chromatography. The TLC of the reaction mixture showed the presence of V and VII, together with three compounds or more, but they could not be isolated in crystalline form.

Under the same reaction conditions used with I, 17β-acetoxy-4β,5-epoxy-19-nor-5β-androstan-3-one (IIIa) afforded 4,17β-dihydroxy-19-norandrost-4-en-3-one 17-acetate (VIIIa), estra-1,3,5(10)-triene-3,17β-diol 17-acetate (IX) and estra-1,3,5(10)-triene-2,3,17β-triol 17-acetate (X) in 26.7, 14.0 and 36.0% yields respectively and the corresponding 19-oxo-derivative (IIIb) yielded IX (17.9%) and X (33.2%), accompanying, at least, with other five compounds, as shown by TLC of the reaction mixture.

13) C. Djerassi, O. Halpern, V. Halpern, O. Shindler and Ch. Tamm, *Helv. Chim. Acta*, **41**, 250 (1958).
14) P.N. Rao and L.R. Axelrod, *J. Am. Chem. Soc.*, **82**, 2830 (1960).
15) H.J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **21**. 239 (1956).
16) H.R. Nace and R.N. Iacona, *J. Org. Chem.*, **29**, 3498 (1964)

The same work-up of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (IIIc) gave IX and X, along with 4,17β,19-trihydroxyandrost-4-en-3-one 17-acetate (VIIIc), and 17β-acetoxy-2β,19-oxidoandrost-4-en-3-one (XI) in 17.9, 43.7, 8.6 and 13.6% yields, respectively. The estradiol (IX) and estriol (X) were identical with the authentic samples, prepared from 17β-acetoxy-19-norandrost-4-en-3-one by the method of Rao.[17] The authentic diosphenol (VIIIa) was prepared from the 19-norepoxide (IIIa) by the method of Camerino.[18] The structure of the compound (VIIIc) was based on its strong positive ferric chloride test, the elementary analysis, infrared absorption bands at 1672 and 1645 cm^{-1}, ultraviolet absorption maximum at 278 mμ (ε=13850) characteristic of 4-hydroxy-Δ^4-3-oxosteroids[9] and the nuclear magnetic resonance (NMR) spectrum signals at τ 3.6 (4-OH), 5.37 (17α-H), 5.90, 6.15 (a pair of doublets, J=12 cps, 19-CH_2-), 7.96 (OAc) and 9.18 (18-CH_3).

The compound (XI) analyzed correctly for $C_{21}H_{24}O_4$, had strong absorption bands at 1680 and 1605 cm^{-1} in the infrared spectrum with no hydroxy band around at 3500 cm^{-1}, and an absorption maximum at 242 mμ in the ultraviolet region, indicating the presence of an α,β-unsaturated ketone. The NMR spectrum in deuteriochloroform showed signals assignable to the 18-methyl (τ, 9.18), acetoxy (τ, 7.98), 19-methylene (a pair of doublets: τ 6.55; J=7 cps and τ 5.98; J=7 cps), 17α-hydrogen (a quartet centered at τ 5.40), and 4-hydrogen (a quartet-like centered at τ 4.24).

Other signals were assigned by utilizing the double resonance technique: Thus, a quartet centered at τ 5.77 having an area equivalent to one proton was assigned to 2α-hydrogen, which is split by 4-hydrogen (J=2 cps) and 1β-hydrogen (J=7 cps), and not by 1α-hydrogen due to a dihedral angle of approximately 90° between the two atoms. A quartet centered at τ 7.63 (J=7 and 12 cps) was found to degenerate to a doublet (J=12 cps) by an irradiation of 2α-hydrogen and thus assigned to 1β-hydrogen. Irradiation of the 4-hydrogen degenerated the 2α-hydrogen quartet to a doublet (J=7 cps).

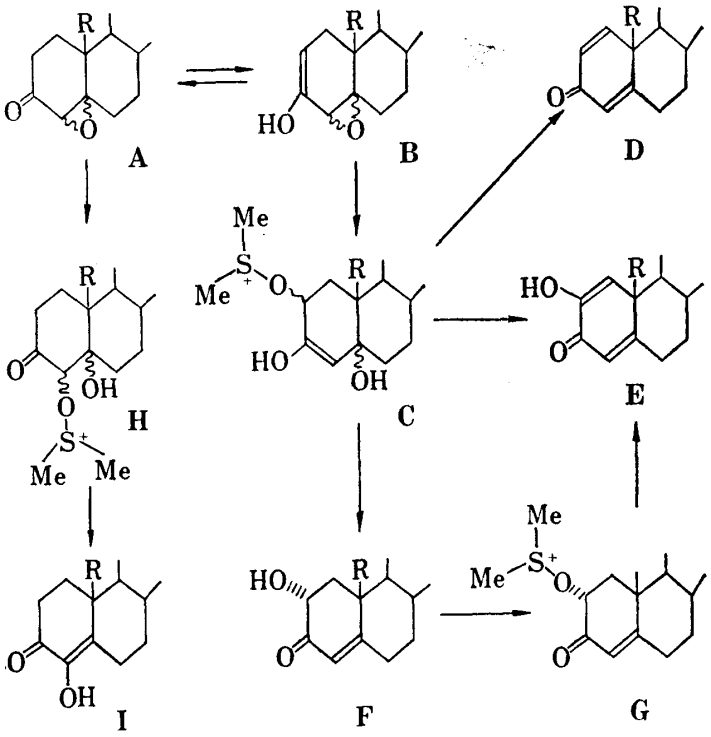


Chart 2

17) P.N. Rao and L.R. Axelrod, *Tetrahedron*, **10**, 144 (1960).
18) B. Camerino, U.S. Patent 3025310 (1962) [*C.A.*, **57**, 9926*a* (1962)].

These data and the fact that reduction of the compound (XI) with zinc powder in acetic acid affords 17β,19-dihydroxyandrost-4-en-3-one 17-acetate, are compatible with the structure proposed.

In the reactions of these 4,5-epoxides with dimethyl sulfoxide, the ratio of the products is very sensitive to the amount of the catalyst and reaction temperature.

One of the possible mechanism for the oxidation reactions described here are suggested as outlined in Chart 2.

The ring-opening of the epoxide (A) might be initiated by the formation of an enolate (B),[19] followed by a nucleophilic attack with dimethyl sulfoxide at C_2 affording a sulfoxonium salt (C). This, as suggested by Nace, *et al.*,[16] may give rise to i) a dienone (D) by fission of the C_2–O bond, proton abstraction from C_1, and elimination of water, ii) a diosphenol (E) by fission of the O–S bond, loss of proton from C_2 and elimination of water, and iii) a hydroxy ketone (F) by hydrolysis of the C_2–O bond. The oxidation of the hydroxyketone (F) to the diosphenol (E) might proceed *via* a sulfoxonium salt (G) in the manner described above. The formation of the 2β,19-oxido compound (XIII) may be rationalized by considering an intramolecular substitution of the 19-hydroxyl group at C_2-position of the salt (C). The diosphenol (I) can be formed through hydrolysis of a sulfoxonium salt (H) and elimination of water.

Experimental[20]

17β,19-Dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-Acetate (IIIc)——To a solution of 17β,19-dihydroxyandrost-4-en-3-one 17-acetate (15 g) in MeOH (900 ml) was consecutively added aq. 4N NaOH solution (30 ml) at 0° and 30% H_2O_2 (75 ml). The mixture was stirred at room temperature for 1 hr showing no starting material remained by TLC. After neutralization with AcOH, the mixture was concentrated under a reduced pressure, diluted with water, and then the product was taken up in AcOEt. The extract was washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was evaporated to give 15.28 g of a crystalline residue, which was recrystallized from a mixture of *n*-hexane and AcOEt to give 10.325 g of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (IIIc), mp 192—193°. *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.51; H, 8.32. IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1738 (OAc), 1710 (3-CO), 1255 (OAc). NMR τ: 9.20 (18-CH_3), 8.00 (OAc), 7.13 (4α-H), 6.84 (doublet) and 5.84 (doublet, J=10 cps, 19-CH_2-). ORD (c=0.257, dioxane) $[\alpha]_D^{25}$ (mμ): −2060° (286) (trough), +1950° (328) (peak), +1980° (340) (peak), +97° (589). The mother liquor was condensed to leave 4.77 g of a residue, which was chromatographed over 125 g of Al_2O_3 (neutral, Woelm Grade III). Elution with benzene–AcOEt (9:1 and 8:2) afforded 1.6 g of the epoxide (IIIc), which was recrystallized from a mixture of *n*-hexane and AcOEt to give 1.345 g of IIIc with mp 190—192°. Total yield is 11.77 g (74.4%). Elution with benzene–AcOEt (7:3) gave 1.45 g of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one which gave 1.35 g (9.6%) of an analytical sample, mp 150—153° after recrystallization from *n*-hexane–AcOEt. *Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.21; H, 8.77. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3450 (OH), 1705 (3-CO). NMR τ: 9.25 (18-CH_3), 7.08 (4α-H), 6.21 (doublet) and 5.75 (doublet, J=12 cps, 19-CH_2-).

17β-Acetoxy-4β,5-epoxy-5β-androstane-3,19-dione (IIIb)——a) To a solution of 17β-acetoxyandrost-4-ene-3,19-dione (3.8 g) in DMF (60 ml) was added 30% H_2O_2 (15 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, diluted with cold-water and extracted with AcOEt. The extract was washed with saturated NaCl solution until neutral and dried over Na_2SO_4. The solvent was evaporated to give a crystalline residue, which was recrystallized from *n*-hexane–AcOEt to give 2.75 g of 17β-acetoxy-4β,5-epoxy-5β-androstane-3,19-dione (IIIb), as plates of mp 142—143°. The mother liquor was concentrated to give 0.51 g of IIIb of mp 142°. *Anal.* Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.98; H, 7.84. IR ν_{max}^{Nujol} cm^{-1}: 1729 (OAc), 1713 (CHO), 1250 (OAc). NMR τ: 9.10 (18-CH_3), 7.95 (OAc), 6.98 (4α-H), 5.33 (triplet, J=8 cps, 17α-H), 0.05 (CHO). ORD (c=0.26, dioxane) $[\alpha]_D^{25}$ (mμ): −2280° (284) (trough), +2040° (328) (peak), +2080° (338) (peak), +104° (589).

19) M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka and T. Furuta, *Tetrahedron*, **21**, 733 (1965).

20) All melting points were uncorrected. The nuclear magnetic resonance (NMR) spectra were determined with Varian A-60 and HA-100 spectrometers in deuteriochloroform solution containing tetramethylsilane as internal standard. The optical rotatory dispersion curves and $[\alpha]_D$ values were taken with JASCO model ORD/UV-5, Japan Spectroscopic Co., Ltd.

b) To a solution of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (IIIc; 0.100 g) in pyridine (0.5 ml) was added CrO_3 (0.100 g)–pyridine (3 ml) complex. The mixture was left at room temperature for 1 hr, and diluted with AcOEt after the excess reagent was decomposed with EtOH. The precipitate was filtered off. The filtrate was washed successively with 3% aq. AcOH solution, 3% $NaHCO_3$ solution and H_2O. After dried over Na_2SO_4, the solvent was evaporated to give a crystalline product (92 mg), which was shown to be almost a pure compound by TLC. Recrystallization from AcOEt afforded 0.063 g of IIIb of mp 142—143°. The infrared (IR) spectrum was superimposable with that of the epoxide obtained above.

DMSO Reaction of 4β,5-Epoxy-17β-hydroxy-5β-androstan-3-one (I)——A solution of the epoxide (I; 4 g) in DMSO (200 ml) was heated at 120° with CF_3CO_2H (0.1 ml) under N_2 atmosphere for 12 hr. The solvent was evaporated to dryness *in vacuo* and the products were taken up in AcOEt. The extract was washed with 3% $NaHCO_3$ solution and saturated NaCl solution until neutral. After dried over Na_2SO_4, the solvent was evaporated to leave a syrup, which was chromatographed over 160 g of silica gel. Elution with benzene–AcOEt (7:3) afforded 0.179 g (4.5%) of 4,17β-dihydroxyandrost-4-en-3-one (IV). Repeated recrystallization from AcOEt gave an analytical sample as needles, mp 222° (lit.[9] mp 222—224°), the IR spectrum being superimposable with that of an authentic sample, prepared from I by the method of Camerino.[9] *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.74; H, 9.23. IR ν_{max}^{Nujol} cm^{-1}: 3550, 3470 (OH), 1665, 1650 (shoulder), 1623 (CO). UV λ_{max}^{EtOH} mμ (ε): 277 (13200). The second elution with the same mixture of solvents gave 2.178 g (54.4%) of 2,17β-dihydroxyandrosta-1,4-dien-3-one (VI), which was recrystallized from AcOEt to afford needles of mp 206—208° (lit.[14] mp 204—205°). *Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.21; H, 8.59. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3375 (OH), 1675 (shoulder), 1640, 1610 (shoulder) (C=O). UV λ_{max}^{EtOH} mμ (ε): 254 (14600). NMR τ: 9.18 (18-CH_3), 8.76 (19-CH_3), 6.35 (triplet, J=8 cps, 17α-H), 3.82 (2-OH), 3.64 and 3.53 (1-H, 4-H). The IR spectrum was identical with that of an authentic sample, prepated by the method of Rao.[14] Elution with benzene–AcOEt (6:4) yielded 0.445 g (11.8%) of 17β-hydroxyandrosta-1,4-dien-3-one (V). Recrystallization from *n*-hexane–AcOEt afforded sticks of mp 171° (lit.[15] mp 168—170°). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.49; H, 9.18. IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1663 (3-CO), 1620, 1600 ($\Delta^{1,4}$). UV λ_{max}^{EtOH} mμ (ε): 244 (15400). The compound eluted with benzene–AcOEt (5:5) was 0.585 g (14.6%) of 2α,17β-dihydroxyandrost-4-en-3-one (VII), which was recrystallized from AcOEt to give plates, mp 160°—161° (lit.[9] mp 160—162°). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.92; H, 9.24. The IR spectrum was superimposable with that of the authentic sample.[9] Further elution with more polar mixture of solvents gave a small amount of an oily substance which was not further investigated.

DMSO Oxidation of 2α,17β-Dihydroxyandrost-4-en-3-one (VII)——A solution of VI (0.15 g) in DMSO (10 ml) was heated at 120° with CF_3COOH (0.01 ml) under N_2 atmosphere for 7 hr. The residue (0.175 g), obtained after worked up as usual, was chromatographed over 10 g of silica gel. Fraction eluted with benzene–AcOEt (9:1) afforded 0.069 g (46%) of 2,17β-dihydroxyandrosta-1,4-dien-3-one (VI), which showed mp 204—206° after recrystallization from AcOEt. The IR spectrum was superimposable with that of the authentic sample.

DMSO Reaction of 4α,5-Epoxy-17β-hydroxy-5β-androstan-3-one (II)——A solution of the epoxide (II; 0.5 g) in DMSO (30 ml) was heated at 120° with CF_3CO_2H (0.1 ml) under N_2 atmosphere for 40 hr. The reaction mixture was concentrated into a small volume under a reduced pressure, diluted with H_2O and extracted with AcOEt. The extract was washed with aq. 2% $NaHCO_3$ solution and the solvent was evaporated to give 0.512 g of a syrupy residue. The crude product was chromatographed on 20 g of silica gel. Elution with benzene–AcOEt (9:1) gave 0.063 g (12%) of 4,17β-dihydroxyandrost-4-en-3-one (IV), which had mp 221—222° after recrystallization from AcOEt and the infrared spectrum was completely identical with that of the diosphenol (IV) obtained by the above experiment. Continued elution with the same mixture of solvents gave 0.194 g (39%) of 2,17β-dihydroxyandrosta-1,4-dien-3-one(VI), which melted at 206—207° after recrystallization from AcOEt. The mixed mp with the authentic sample showed no depression and their IR and UV spectra were identical. The thin-layer chromatography showed aparently the presence of 2α,17β-dihydroxyandrost-4-en-3-one (VII) and 17β-hydroxyandrosta-1,4-dien-3-one (V) in some fractions, but they could not be isolated.

DMSO Reaction of 17β-Acetoxy-4β,5-epoxy-19-nor-5β-androstan-3-one (IIIa)——A solution of the epoxide (IIIa; 1 g) in DMSO (70 ml) was stirred at 120° with CF_3CO_2H (0.025 ml) under N_2 atmosphere for 6.5 hr. The reaction mixture was concentrated into dryness under a reduced pressure to give an oily residue, which was dissolved in AcOEt. The solution was washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was evaporated to give 1.05 g of a syrup, which was chromatographed over silica gel (30 g). The first fraction eluted with benzene–AcOEt (95:5) gave a mixture of the two compounds. The second fraction with the same mixture of solvents gave 0.358 g (36%) of estra-1,3,5(10)-triene-2,3,17β-triol 17-acetate (X), which after recrystallization from *n*-hexane–benzene afforded granules of an analytically pure sample, mp 183—185° (lit.[17] mp 180—182°). *Anal.* Calcd. for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.53; H, 7.82. UV λ_{max}^{EtOH} mμ (ε): 253 (410), 288 (4250). The third fraction with benzene–AcOEt (85:15) gave 0.05 g of another product, which failed to be purified even after rechromatography over silica gel.

The mixture obtaind from the first fraction was rechromatographed over 30 g of Al_2O_3 (neutral, Woelm Grade III) to give 0.132 g (14%) of estra-1,3,5(10)-triene-3,17β-diol 17-acetate (IX) from the eluate with

benzene, which had mp 219—219.5° after recrystallization from AcOEt (lit.[17] mp 217—218°). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.10; H, 8.41. UV λ_{max}^{EtOH} mμ (ε): 281 (2000), 288 (1860). Another product eluted with benzene–ether (98:2) was 0.267 g (26.7%) of 4,17β-dihydroxy-19-norandrost-4-en-3-one 17-acetate (VIIIa) with mp 207—210° after recrystallization from *n*-hexane–AcOEt. (lit.[18] mp 210—212°). *Anal.* Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.27. UV λ_{max}^{EtOH} mμ (ε): 276 (13100). The IR spectra of these three compounds were superimposable with those of the authentic samples, prepared by the methods of Rao[17] and Camerino.[18]

DMSO Reaction of 17β-Acetoxy-4β,5-epoxy-5β-androstane-3,19-dione (IIIb)——A solution of the epoxide (IIIb; 1 g) in DMSO (50 ml) was stirred at 120° with CF_3CO_2H (0.025 ml) under N_2 atmosphere for 12 hr. The residue (1.04 g) obtained after distillation of the solvent under a reduced pressure, was chromatographed over 30 g of silica gel. Elution with benzene furnished 0.156 g (17.9%) of estra-1,3,5(10)-triene-3,17β-diol 17-acetate (IX), which was recrystallized from AcOEt to give an analytical sample as needles of mp 217—219°. The IR spectrum was identical with the sample obtained above. Elution with benzene–AcOEt (9:1) gave 0.305 g (33.2%) of estra-1,3,5(10)-triene-2,3,17β-triol 17-acetate (X) melting at 181—183° after recrystallization from *n*-hexane–benzene, which showed no depression of mp on admixture with the authentic sample.

DMSO Reaction of 17β,19-Dihydroxy-4β,5-epoxy-5β-androstan-3-one 17β-Acetate (IIIc)——A solution of the epoxide (IIIc: 4 g) in DMSO (280 ml) was stirred at 120° with conc. H_2SO_4 (0.01 ml) under N_2 atmosphere for 10 hr. The reaction mixture was worked up as usual to afford 3.9 g the residue, which was chromatoraphed over 100 g of silica gel. The first fraction eluted with benzene–AcOEt (9:1) gave 0.621 g (17.9%) of estra-1,3,5(10)-triene-3,17β-diol 17-acetate (IX), mp 216—217° (from AcOEt). The second fraction eluted with the same mixture of solvents, gave a mixture which showed two spots on TLC. The third fraction eluted with benzene–AcOEt (8:2) gave 0.344 g (8.6%) of 4,17β,19-trihydroxyandrost-4-en-3-one 17-acetate (VIIIc). Recrystallization from benzene afforded an analytical sample as needles of mp 176—177.5°. *Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.42; H, 8.25. IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 1725 (OAc), 1672, 1645 (3,4-diketone). UV λ_{max}^{EtOH} mμ (ε): 278 (13850). NMR τ: 9.18 (18-CH_3), 7.96 (OAc), 6.15 (doublet) and 5.90 (doublet, J=12 cps, 19-CH_2-), 5.37 (triplet, J=8 cps, 17α-H), 3.60 (4-OH).

The mixture (2.38 g) obtained from the second fraction described above was rechromatographed over 100 g of silica gel. Elution with benzene–AcOEt (9:1) gave 0.517 g (13.6%) of 17β-acetoxy-2β,19-oxidoandrost-4-en-3-one (XI) which gave needles of mp 190—191° after recrystallization from AcOEt. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.00; H, 8.25. IR ν_{max}^{Nujol} cm^{-1}: 1734 (OAc), 1675, 1603 (Δ^4-3-CO), 1240 (OAc). UV λ_{max}^{EtOH} mμ (ε): 242 (14600). ORD (c=0.47, dioxane) $[\alpha]_D^{25}$ (mμ): −9500° (320) (trough), +14560° (380) (peak), +154° (589). Continued elution with the same solvent and benzene–AcOEt (8:2) afforded 1.595 g (43.7%) of estra-1,3,5(10)-triene-2,3,17β-triol 17-acetate (X), which had mp 182—183° after recrystallization from *n*-hexane–benzene and showed no depression of mp on admixture with the authentic sample.

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