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Steroid Series. XXI.[1] Reaction of 4-Halo-Δ^4-3-oxosteroides with Dimethyl Sulfoxide

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The reaction of 4-chloro-Δ^4-3-oxosteroids (Ia, c, e) with dimethyl sulfoxide were shown to yield $\Delta^{4,6}$-3-oxosteroids (IIg, h, i). These were accompanied by the 3,6-dione (III) and Δ^4-3,6-dione (IV) in the case of 19-methylsteroid, by estra-1,3,5(10)-triene-3, 17β-diol 17-acetate (VII) from 19-norsteroid, and by Δ^4-3-oxo-6β,19-oxide (VI) from 19-hydroxymethylsteroid. With dimethylsulfoxide 4-bromo-Δ^4-3-oxosteroids (Ib, d, f) gave the 4-bromo-$\Delta^{4,6}$-3-oxosteroids (IIb, d, V) under the same reaction conditions.

Bromination of 17β-acetoxyandrosta-4,6-dien-3-one (IIg) in dimethylsulfoxide afforded the bromotrienone (X), the 2α-bromo (VIII) and 2,2-dibromo (IX)-derivatives of IIg being intermediates in the conversion.

Oxidation of α-haloketone with dimethyl sulfoxide yielding α-diketone has been reported by several workers.[3-5] Recent publication by Iacona, *et al.*[6] described that both elimination and oxidation reactions can occur in steroid α-bromoketones, the situation being governed by stereochemical features. In continuing our work on the reaction of dimethyl sulfoxide with steroides,[1] the behavior of 4-halo-Δ^4-3-oxosteroid toward this reagent was investigated.

17β-Acetoxy-4-haloandrost-4-en-3-one (Ia, b) and its 19-nor analogue (Ic, d) were prepared from the corresponding 4β,5-epoxy-3-oxo-5β-steroids with hydrogen halide according to the method of Camerino.[7] 17β,19-Dihydroxy-4-haloandrost-4-en-3-one 17-acetate (Ie, f) were analogously synthesized from the corresponding 4β,5β-epoxy compounds.[1]

When 17β-acetoxy-4-chloroandrost-4-en-3-one (Ia) was heated at 120° in dimethyl sulfoxide in the presence of a catalytic amount of sulfuric acid, 17β-acetoxyandrosta-4,6-dien-3-one (IIg)[8] was obtained as a main product in 49% yield. This was accompanied by 17-hydroxyandrosta-4,6-dien-3-one, formed by saponification of IIg, and 17β-acetoxy-5α-androstane-3,6-dione (III)[9] in 12 and 2.9% yield, respectively. In the absence of acid the reaction proceeded in substantially the same way, except that 17β-acetoxyandrost-4-en-3,6-dione (IV)[10] was isolated (4.2% yield) as an additional product.

The reaction of the corresponding bromo compound (Ib) was completed much faster than that of the chloro derivative (Ia) and was found to differently proceed producing 17β-acetoxy-4-bromoandrosta-4,6-dien-3-one (IIb) in 65% yield. The structure of the bromodienone (IIb) was deduced from the elemental analysis and spectroscopic examination: The

1) Part XX: Y. Morisawa and K. Tanabe, *Chem. Pharm. Bull.* (Tokyo), **17**, 1206 (1969).
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo.*
3) N. Kornblum, J.W. Powers, G.J. Anderson, W.J. Jones, H.O. Larson, O. Levand and W.M. Weaver, *J. Am. Chem. Soc.*, **76**, 6562 (1957).
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5) I.M. Hunsberger and J.M. Tien, *Chem. Ind.* (London), **1959**, 88.
6) R.N. Iacona, A.T. Rowland and H.R. Nace, *J. Org. Chem.*, **29**, 3495 (1964); H.R. Nace and R.N. Iacona, *ibid.*, **29**, 3498 (1964).
7) B. Camerino, B. Pattelli and A. Vercellone, *J. Am. Chem. Soc.*, **78**, 3540 (1956).
8) L.H. Knof, E. Velarde, S. Berger, D. Cuadriello and A.D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).
9) R.L. Clark, *J. Am. Chem. Soc.*, **82**, 4629 (1960).
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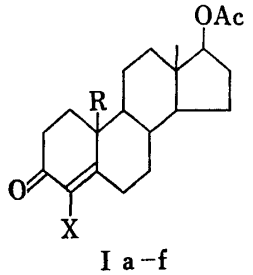
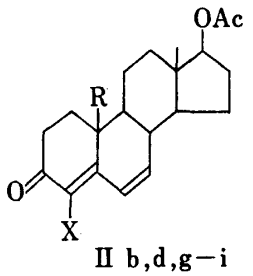
infrared spectrum exhibits maxima at 1676, 1612 and 1550 cm^{-1} and the ultraviolet spectrum shows absorption at 299.5 mμ (ε=22450), characteristic of 4-bromo-$\Delta^{4,6}$-3-oxo-steroid.[11] The nuclear magnetic resonance (NMR) spectrum shows a pair of quartets centered at τ 3.70 (J=10 and 2 cps) and 3.18 (J=10 and 3 cps), indicating the presence of the –CH=CH–CH= system.

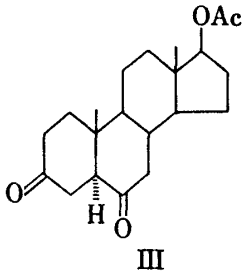
Treatment of 17β-acetoxy-4-chloro-19-norandrost-4-en-3-one (Ic)[12] under the same reaction conditions afforded 17β-acetoxy-19-norandrosta-4,6-dien-3-one (IIh)[13] and estra-1,3,5(10)-triene-3,17β-diol 17-acetate (VII)[14] in 30.7 and 21.3% yields, respectively, while the corresponding 4-bromo derivative (Id) led to 17β-acetoxy-4-bromo-19-norandrosta-4,6-dien-3-one (IId) in 59.4% yield as the only crystalline and isolatable product. The elemental analysis and the following spectroscopic data established the structure of IId. Absorption maxima at 1675, 1608 and 1547 cm^{-1} in the infrared region, and a maximum at 300 mμ (ε= 20500) in the ultraviolet spectrum indicate the presence of a 4-bromo-$\Delta^{4,6}$-3-oxo system,[11] which is also supported by NMR signals at τ 3,63 (quartet, J=10 and 2 cps) and 3.11 (quartet, J=10 and 3 cps) assignable to the 6- and 7-protons.



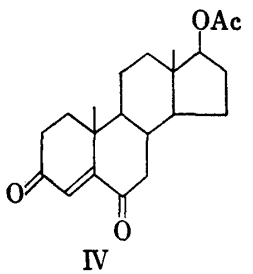
I a–f



II b,d,g–i

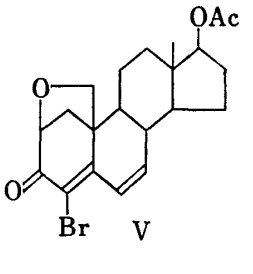


III

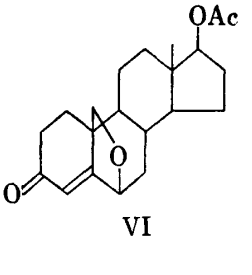


IV

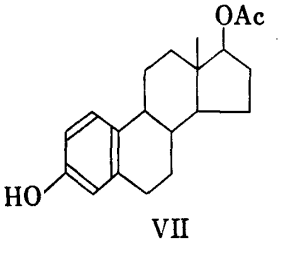
a : X=Cl, R=CH_3
b : X=Br, R=CH_3
c : X=Cl, R=H
d : X=Br, R=H
e : X=Cl, R=CH_2OH
f : X=Br, R=CH_2OH
g : X=H, R=CH_3
h : X=R=H
i : X=H, R=CH_2OH



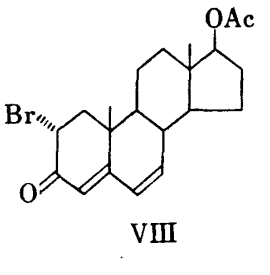
V



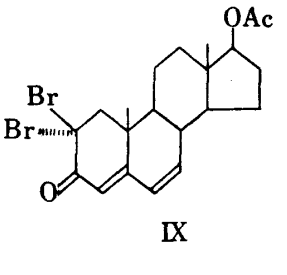
VI



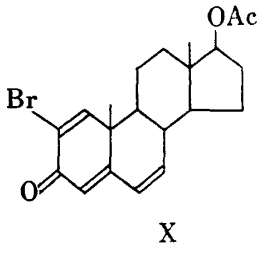
VII



VIII



IX



X

The next halovinyl ketones studied were 17β,19-dihydroxy-4-chloroandrost-4-en-3-one 17-acetate (Ie) and the corresponding bromo compound (If). When the chloro ketone (Ie) was heated with dimethyl sulfoxide at 150° under a nitrogen atmosphere for 30 hours, there were obtained 17β,19-dihydroxyandrosta-4,6-dien-3-one 17-acetate (IIi) and 17β-acetoxy-6,19-oxidoandrost-4-en-3-one (VI)[15] in 35.8 and 19.0% yields, respectively. When the bromo ketone (If) was treated under the same reaction conditions for 14 hours, the only

11) K. Brückner, H. Hampel and U. Johnsen, *Chem. Ber.*, **94**, 1225 (1961).
12) B. Camerino, U.S. Patent 3025310 (1962).
13) J.A. Zderic, A. Bowers, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 2596 (1958).
14) P.N. Rao and L.R. Axelrod, *Tetrahedron*, **10**, 144 (1960).
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product isolated was 17β-acetoxy-2β,19-oxido-4-bromoandrosta-4,6-dien-3-one (V) in 51.7% yield, which analyzed for $C_{21}H_{25}O_4Br$. The infrared spectrum exhibited bands at 1684, 1611 and 1539 cm^{-1}, but no hydroxyl band appeared around 3500 cm^{-1}. The ultraviolet absorption spectrum had maximum at 303 mμ (ε=20800). These indicate the presence of the 4-bromo-$\Delta^{4,6}$-3-oxo system.[11] The NMR spectrum showed two vinyl proton signals as a pair of quartets centered at τ 3.58 (J=10 and 2 cps) and 3.11 (J=10 and 2 cps), assignable to the 6- and 7-protons. An AB type quartet (τ 6.55; J=7.5 cps and τ 5.92; J=7.5 cps) and a doublet (τ 5.40; J=6 cps) were assigned to the 19-methylene and 2α-protons, respectively.

So far as the results obtained here are concerned, 4-chlorovinyl ketones were found always to give the 4,6-dien-3-ones, while the corresponding bromo compounds yielded the 4-bromo-4,6-dien-3-ones without exception. As a possible explanation for the difference of products in both series of compounds, it was first assumed that $\Delta^{4,6}$-3-oxosteroid, *e.g.* IIg, might be a common product initially formed in both cases: the hydrogen bromide then liberated would be oxidized by dimethylsulfoxide to molecular bromine,[16,17] which would yield the 6,7-dibromide of *e.g.* IIg by addition to the 6,7-double bond. The dibromide might then be rearranged into a 4-bromo-4,6-dien-3-one. Such a rearrangement under basic conditions has been described by Brückner, *et al.*[11]

In order to test this assumption, 17β-acetoxyandrosta-4,6-dien-3-one (IIg) was treated with one mole equivalent of bromine in dimethyl sulfoxide at 115° for one hour, but this unexpectedly gave 17β-acetoxy-2-bromoandrosta-1,4,6-trien-3-one (X) in 74.4% yield.
When this reaction was quenched before completion, 17β-acetoxy-2α-bromoandrosta-4,6-dien-3-one (VIII) and 17β-acetoxy-2,2-dibromoandrosta-4,6-dien-3-one (IX) could be isolated in addition to the 2-bromotrienone (X). The monobromodienone (VIII) was found to be smoothly converted into the bromotrienone (X) in 71.7% yield by heating in dimethyl sulfoxide with 0.5 mole equivalents of bromine, while the dibromodienone (IX) could also be transformed into X in 92.6% yield merely by heating in dimethyl sulfoxide. These results and stoichiometric features suggest that, contrary to our expectation, the dienone (IIg) is brominated first at the carbon 2 yielding the monobromide (VIII). The liberated hydrogen bromide is then oxidized by dimethyl sulfoxide to molecular bromine, and the monobromide (VIII) is further brominated at the carbon 2 forming the dibromide (IX), which dehydrobrominated to the bromotrienone (X).

The structures of the bromo derivatives (VIII, IX and X) were assigned by the elemental analysis and spectroscopic measurements. The ultraviolet spectrum of X had maxima at 224 (ε=15800), 270 (ε=12800) and 307 mμ (ε=10300), characteristic of a 2-bromo-1,4,6-trien-3-one system.[18] The NMR spectrum showed signals in the olefinic proton region centered at τ 3.95 (quartet, J=8 and 2 cps) and τ 3.70 (quartet, J=8 and 2 cps), which were assignable to two protons of the Δ^6-double bond. Two singlets at τ 3.87 and 2.48 were assigned to protons at positions 4 and 1, respectively.

The monobromo compound (VIII) showed in the NMR spectrum a quartet centered at τ 5.05 (J=13 and 6 cps) attributed to a hydrogen at the carbon 2, in addition to signals at τ 4.22 and 3.83 assignable to one proton at the carbon 4 and two protons of the Δ^6-double bond, respectively. The ultraviolet spectrum had maximum at 287 mμ (ε=21800). The 2α-configuration of the bromine atom was deduced from the observed bathochromic shift of 5 mμ in the ultraviolet[18] and a higher frequency shift of 10 cm^{-1} in the infrared spectra[19] for the 3-carbonyl stretching absorption in VIII, as compared with those of the non-substituted $\Delta^{4,6}$-3-oxosteroid.

16) N. Kharasch, ed., "Organic Sulfur Compounds," Pergamon Press, New York, N.Y., 1961, p. 170.
17) D. Lardini and F. Montanari, *Tetrahedron Letters*, **1964**, 2691
18) M. Fieser, M.A. Romero and L.F. Fieser, *J. Am. Chem. Soc.*, **77**, 3305 (1955).
19) R.N. Jones, D.A. Ramsay, F. Herling and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

The structural assignment of the dibromo compound (IX) was based on the maximum at 300 mμ (ε=23100) in the ultraviolet and absorptions at 1668, 1617 and 1558 cm^{-1} in the infrared spectra. The NMR spectrum showed AB type signals centered at τ 6.96 and 6.61 (J=15 cps) due to two hydrogens at the carbon 1, and signals at τ 4.22 and 3.80 assignable to one proton at the carbon 4 and two protons at the Δ^6-double bond.

Experimental[20]

17β,19-Dihydroxy-4-chloroandrost-4-en-3-one 17-Acetate (Ie)——A solution of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (2.02 g) in acetone (42 ml) was stirred with conc. HCl (2.1 ml) at room temperature for 3 hr. The reaction mixture was neutralized with aq. 5% $NaHCO_3$ solution, concentrated into a small volume under a reduced pressure, diluted with water and extracted with ether. The extract was washed with water, dried and condensed to dryness to yield 2.106 g of a crystalline residue, which was chromatographed over alumina (neutral, Woelm Grade III; 60 g). The eluate with benzene and benzene–ether (9:1) gave, after recrystallization from *n*-hexane–benzene, 0.886 g of Ie, mp 211°. *Anal.* Calcd. for $C_{21}H_{29}O_4Cl$: C, 66.21; H, 7.61; Cl, 9.30. Found: C, 66.21; H, 7.66; Cl, 9.10. IR ν_{max}^{Nujol} cm^{-1}: 3500 (OH), 1738 (OAc), 1680, 1582 (Δ^4-3CO). UV λ_{max}^{EtOH} mμ (ε): 256 (17100).

17β,19-Dihydroxy-4-bromoandrost-4-en-3-one 17-Acetate (If)——A solution of 17β,19-dihydroxy-4β,5-epoxy-5β-androstan-3-one 17-acetate (2 g) in acetone (40 ml) was stirred with 48% HBr (1.8 ml) at 10° for 40 minutes. The reaction mixture was diluted with ice–water and extracted with AcOEt. The extract was washed with 3% $NaHCO_3$ solution, saturated NaCl–solution and worked up as usual. The crystalline residue was recrystallized from *n*-hexane–AcOEt to give 17β,19-dihydroxy-4-bromoandrost-4-en-3-one 17-acetate (If: 1.88 g), mp 117—118°. *Anal.* Calcd. for $C_{21}H_{29}O_4Br$: C, 59.29; H, 6.87; Br, 18.79. Found: C, 59.19; H, 6.88; Br, 18.46. IR ν_{max}^{Nujol} cm^{-1}: 3520 (OH), 1732 (OAc), 1672, 1572 (Δ^4-3-CO), 1240, 1040 (OAc). UV λ_{max}^{EtOH} mμ (ε): 262 (11450).

DMSO Reaction of 17β-Acetoxy-4-chloroandrost-4-en-3-one (Ia)——a) A solution of Ia (2.7 g) in DMSO (135 ml) was heated at 120° with conc. H_2SO_4 (0.135 ml) under N_2 for 39 hr. The reaction mixture was concentrated *in vacuo* into a small volume under N_2 atmosphere, poured into ice–water and extracted with AcOEt. The extract was washed with 3% $NaHCO_3$ solution and saturated NaCl–solution, and dried over Na_2SO_4. Evaporation of the solvent gave 2.49 g of a sirupy residue, which was chromatographed over alumina (neutral, Woelm Grade III: 80 g). Elution with *n*-hexane–benzene (1:1 and 2:3) afforded crude 17β-acetoxyandrosta-4,6-dien-3-one (IIg, 1.2 g, 49.3%) which was recrystallized from *n*-hexane–benzene to give an analytical sample of mp 143—144°. (lit.[8] mp 145—147°). *Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.53; H, 8.70. IR ν_{max}^{Nujol} cm^{-1}: 1740 (OAc), 1665, 1624, 1587 ($\Delta^{4,6}$-3-CO), 1240, 1225 (OAc). UV λ_{max}^{EtOH} mμ (ε): 282 (26900). NMR τ: 9.13 (18-CH_3), 8.88 (19-CH_3), 7.96 (OAc), 5.32 (17α-H), 4.29 (4-H), 3.87 (singlet, 6- and 7-H). The second compound eluted with the same mixture of solvents and benzene, was further purified by rechromatography over alumina to give 17-β-acetoxy-5α-androstane-3,6-dione (III: 0.075 g, 2.9%), which showed mp 183—186° after recrystallization from *n*-hexane–benzene (lit.[9] mp 183—186°). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.55; H, 8.56. IR ν_{max}^{Nujol} cm^{-1}: 1730—1720 (CO), 1250 (OAc). The third compound obtained from the eluate with benzene–AcOEt (8:2) was 17β-hydroxyandrosta-4,6-dien-3-one (0.254 g, 12%) with mp 195—198° after recrystallization from AcOEt. IR ν_{max}^{Nujol} cm^{-1}: 3400 (OH), 1650, 1620, 1588 ($\Delta^{4,6}$-3CO). UV λ_{max}^{EtOH} mμ (ε): 283 (24400). NMR τ: 9.14 (18-CH_3), 8.86 (19-CH_3), 6.29 (17α-H), 4.31 (4-H), 3.88 (singlet, 6- and 7-H).

b) A solution of Ia (2 g) in DMSO (100 ml) was heated at 150° under N_2 atmosphere for 18 hr. The reaction mixture was worked up as described above. A sirupy residue (1.89 g) obtained was chromatographed over alumina (neutral; Woelm Grade III: 100 g). The eluate with *n*-hexane–benzene (4:5 and 3:7) and benzene gave the dienone (IIg: 0.998 g, 55.4%), which showed mp 137—140° after recrystallization from *n*-hexane–AcOEt. The IR spectrum was superimposable with the sample obtained above. Further elution with benzene gave 17β-acetoxyandrost-4-ene-3,6-dione (IV: 0.08 g, 4.2%), which had mp 201—204° after recrystallization from EtOH (lit.[10] mp 198—201°). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.35; H, 8.42. IR ν_{max}^{Nujol} cm^{-1}: 1740 (OAc), 1685, 1610 (Δ^4-3,6-dione), 1235, 1037 (OAc). UV λ_{max}^{EtOH} mμ (ε): 250 (10900) (lit.[9] λ_{max}^{EtOH} mμ: 252). NMR τ: 9.11 (18-CH_3), 8.79 (19-CH_3), 7.93 (OAc), 5.31 (17α-H), 3.82 (4-H). TLC showed apparently the presence of 17β-acetoxy-5α-androstan-3,6-dione (III) in some fractions, but it failed to be isolated.

DMSO Reaction of 17β-Acetoxy-4-bromoandrost-4-en-3-one (Ib)——A solution of Ib (2 g) in DMSO (100 ml) was stirred at 120° under N_2 atmosphere for 22 hr. The reaction mixture was worked up as usual

20) All melting points were uncorrected. The nuclear magnetic resonance spectra were determined with Varian A–60 spectrometer in deuteriochloroform solution containing tetramethylsilane as internal standard.

and the AcOEt extract was concentrated into dryness to give a crystalline brown residue (2.11 g), which was decolorized by passing through alumina (neutral, Woelm Grade III: 20 g) with benzene and ether to give a crystalline product (1.674 g). Recrystallization from AcOEt–hexane afforded 17β-acetoxy-4-bromoandrosta-4,6-dien-3-one (IIb: 1.113 g), mp 184.5—185° (decomp.). *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.92; H, 6.68; Br, 19.62. Found: C, 61.85; H, 6.80; Br, 19.41. IR ν_{max}^{Nujol} cm^{-1}: 1732 (OAc), 1676, 1614, 1553 ($\Delta^{4,6}$-3-CO), 1247, 1044, 1030 (OAc). UV λ_{max}^{EtOH} mμ (ε): 299.5 (22500). NMR τ: 9.10 (18-CH_3), 8.85 (19-CH_3), 7.95 (OAc), 5.32 (17α-H), 3.70 (quartet, $J=10$ and 2 cps) and 3.18 (quartet, $J=10$ and 3 cps, 6- and 7-H). The residue (0.53 g) obtained from the mother liquor was chromatographed over alumina (neutral, Woelm, Grade III: 19 g). The eluate with *n*-hexane–benzene (5:4) gave an additional 0.217 g of crude IIb, which after recrystallization from *n*-hexane–AcOEt gave 0.176 g of pure IIb melting at 182—184°. The total yield amounts to 64.8%. At an elevated temperature (150°) the same reaction was completed for 4 hr, affording the bromo dienone (IIb) in 63.3% yield.

DMSO Reaction of 17β-Acetoxy-4-chloro-19-norandrost-4-en-3-one (Ic)——A solution of Ic (1 g) in DMSO (50 ml) was stirred at 150° under N_2 atmosphere for 12 hr. The reaction mixture was diluted with ice–water and extracted with AcOEt. The extract was washed with saturated NaCl–solution and dried over Na_2SO_4. The residue (1.013 g) obtained after evaporation of the solvent was chromatographed over silica gel (30 g). The first eluate with benzene–ether (98:2) was estra-1,3,5 (10)-triene-3,17β-diol 17-acetate (VII: 0.191 g, 21.3%), which showed mp 216—218° after recrystallization from AcOEt (lit.[14] mp 217—218°). The infrared spectrum was identical with the authentic sample in all respects. The second eluate with benzene–ether (96:4) was 17β-acetoxy-19-norandrosta-4,6-dien-3-one (IIh: 0.275 g, 30.7%), which was recrystallized from isopropyl ether to give an analytical sample of mp 103—104° (lit.[13] mp 113—144°). *Anal.* Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.35; H, 8.31. IR ν_{max}^{Nujol} cm^{-1}: 1737 (OAc), 1668, 1620, 1586 ($\Delta^{4,6}$-3CO), 1255, 1035 (OAc). UV λ_{max}^{EtOH} mμ (ε): 282 (27100). NMR τ: 9.11 (18-CH_3), 7.94 (OAc), 5.29 (17α-H), 4.18 (4-H), 3.74 (singlet, 6- and 7-H).

DMSO Reaction of 17β-Acetoxy-4-bromo-19-norandrost-4-en-3-one (Id)——A solution of Id (1 g). DMSO (50 ml) was stirred at 150° under N_2 atmosphere for 1.5 hr. The reaction mixture was diluted with ice–water and extracted with ether. The extract was worked up as usual to give a browny residue. The residue (1.045 g) was dissolved in AcOEt and passed through alumina (neutral, Woelm, Grade III: 10 g). A crystalline eluate (0.61 g) was recrystallized from AcOEt to give 17β-acetoxy-4-bromo-19-norandrosta-4, 6-dien-3-one (IId: 0.395 g), mp 148° (decomp.). An additional crop of the bromo-dienone (IId: 0.196 g) of mp 147° was obtained from the concentrated mother liquor. The total yield amounts to 59.4%. *Anal.* Calcd. for $C_{20}H_{25}O_3Br$: C, 61.07; H, 6.41; Br, 20.32. Found: C, 61.44; H, 6.66; Br, 19.96. IR ν_{max}^{Nujol} cm^{-1}: 1738 (OAc), 1675, 1608, 1547 ($\Delta^{4,6}$-3CO). UV λ_{max}^{EtOH} mμ (ε): 300 (20500). NMR τ: 9.11 (18-CH_3), 7.95 (OAc), 5.30 (17α-H), 3.63 (quartet, $J=10$ and 2 cps) and 3.11 (quartet, $J=10$ and 3 cps, 6- and 7-H).

DMSO Reaction of 17β,19-Dihydroxy-4-chlorandrost-4-en-3-one 17-Acetate (Ie)——A solution of Ie (0.250 g) in DMSO (15 ml) was stirred at 150° under N_2 atmosphere for 30 hr. The reaction mixture was poured into ice–water and extracted with AcOEt. The extract was washed with aq. 3% $NaHCO_3$ solution, saturated NaCl–solution successively and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue (0.27 g), which was chromatographed over alumina (neutral, Woelm Grade III: 10 g). The first compound eluted with benzene–hexane (6:4) was 17β-acetoxy-6β,19-oxidoandrost-4-en-3-one (VI: 0.043 g, 19.0%), which was recrystallized from *n*-hexane–AcOEt to give an analytical sample of mp 151—152° (lit[15] mp 149—152°). *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22.; H, 8.19. Found: C, 73.40; H, 8.40. IR ν_{max}^{Nujol} cm^{-1}: 1740, (OAc), 1673, 1620 (Δ^4-3CO). UV λ_{max}^{EtOH} mμ: 237. NMR τ: 9.13 (18-CH_3), 7.96 (OAc), 6.49 (doublet, $J=8$ cps) and 5.77 (doublet, $J=8$ cps, 19-CH_2-), 5.35 (17α-H), 5.30 (6α-H), 4.18 (4-H). The second compound eluted with ether was 17β,19-dihydroxyandrosta-4,6-dien-3-one 17-acetate (IIi: 0.081g, 35.8%), which had mp 169—170° after recrystallization from *n*-hexane–AcOEt. *Anal.* Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.86; H, 8.27. IR ν_{max}^{Nujol} cm^{-1}: 3430 (OH), 1740 (OAc), 1670, 1619, 1583 ($\Delta^{4,6}$-3CO), 1266, 1252, 1054, 1028. UV λ_{max}^{EtOH} mμ (ε): 282 (25450). NMR τ: 9.10 (18-CH_3), 7.95 (OAc), 6.25 (doublet, $J=10.5$ cps) and 6.03 (doublet, $J=10.5$ cps, 19-CH_2-), 5.35 (17α-H), 4.20 (4-H), 3.86 (singlet, 6- and 7-H).

DMSO Reaction of 17β,19-Dihydroxy-4-bromoandrost-4-en-3-one 17-Acetate (If)——A solution of If (1 g) in DMSO (50 ml) was stirred at 150° under N_2 atmosphere for 14 hr. The reaction mixture was poured into ice–water and the product was taken up in ether. The extract was worked up as described above and the residue (1.0 g) was chromatographed over silica gel (30 g). The crystalline product, eluted with benzene–ether (98:2) was recrystallized from *n*-hexane–AcOEt to give 17β-acetoxy-4-bromo-2β,19-epoxyandrosta-4, 6-dien-3-one 17-acetate (V: 0.400 g), mp 194—196°. *Anal.* Calcd. for $C_{21}H_{25}O_4Br$: C, 59.86; H, 5.98; Br, 18.97. Found: C, 60.28; H, 5.69; Br, 18.99. IR ν_{max}^{Nujol} cm^{-1}: 1729 (OAc), 1684, 1611, 1539 ($\Delta^{4,6}$-3CO), 1255, 1242, 1047. UV λ_{max}^{EtOH} mμ (ε): 303 (20800). NMR τ: 9.14 (18-CH_3), 7.95 (OAc), 6.37 (doublet, $J=7.5$ cps) and 5.92 (doublet, $J=7.5$ cps, 19-CH_2-), 5.40 (doublet, $J=6$ cps, 2α-H), 5.28 (17α-H), 3.58 (quartet, $J=10$ and 2 cps, 6-H) and 3.11 (quartet, $J=10$ and 3 cps, 7-H). The residue (0.220 g) obtained from the mother liquor was purified by rechromatography over alumina (neutral, Woelm Grade III: 6.6 g). Elution from *n*-hexane–benzene (6:4) and benzene gave another crop of 4-bromodienone (V: 0.112 g), mp 194—196° after recrystallization from *n*-hexane–AcOEt. The total yield is 51.7%.

Bromination of 17β-Acetoxyandrosta-4,6-dien-3-one (IIg) in DMSO——a) A solution of IIg (1 g, 3.045 mmoles) in DMSO (50 ml) was stirred with bromine (0.487 g, 3.053 mmoles) at 115—117° under N_2 atmosphere for 1 hr. The reaction mixture was diluted with H_2O and extracted with ether. The extract was washed with aq. 3% $NaHCO_3$ solution, saturated NaCl-solution, dried and the solvent was evaporated to afford a crystalline brown residue, which was dissolved in AcOEt, and the solution was passed through alumina (neutral, Woelm, Grade III: 12 g) to afford 1.17 g of a crystalline substance. Recrystallization from *n*-hexane–AcOEt gave 17β-acetoxy-2-bromoandrosta-1,4,6-trien-3-one (X: 0.759 g) melting at 161—163°. An analytical sample of mp 167—168° was prepared by repeated recrystallization from the same solvent. *Anal.* Calcd. for $C_{21}H_{25}O_3Br$: C, 62.22; H, 6.22; Br, 19.72. Found: C, 62.04; H, 6.34; Br, 19.73. IR ν_{max}^{Nujol} cm^{-1}: 1737 (OAc), 1653, 1607, 1588 ($\Delta^{1,4,6}$-3-CO), 1245, 1040 (OAc). UV λ_{max}^{EtOH} mμ (ε): 306 (9950), 270 (13340), 222—224 (15010). NMR τ: 9.07 (18-CH_3), 8.75 (19-CH_3), 7.95 (OAc), 5.30 (17α-H), 3.95 (quartet, J=8 and 3 cps) and 3.70 (quartet, J=8 and 2 cps, 6- and 7-H), 3.87 (4-H), 2.50 (1-H). The residue (0.415 g) obtained from the mother liquor was chromatographed over alumina (neutral, Woelm Grade III: 20 g). Recrystallization of the product from the eluate with *n*-hexane–benzene (6:4) afforded another crop of the bromotrienone (X: 0.159 g) of mp 162°. The total yield of X is 74.4%.

b) A solution of dienone (IIg: 0.500 g, 1.523 mmoles) in DMSO (25 ml) was stirred with bromine (0.244 g, 1.527 mmoles) at 115° under N_2 atmosphere for 15 min. The reaction mixture was worked up as described above. The residue (0.700 g) thus obtained was chromatographed over silica gel (28 g). The first compound eluted with benzene was 17β-acetoxy-2,2-dibromoandrosta-4,6-dien-3-one (IX: 0.171 g, 23.1%), which gave an analytical sample of mp 167° (decomp.) after recrystallization from *n*-hexane–AcOEt. *Anal.* Calcd. for $C_{21}H_{26}O_3Br_2$: C, 51.87; H, 5.39; Br, 32.66. Found: C, 52.12; H, 5.57; Br, 32.85. IR ν_{max}^{Nujol} cm^{-1}: 1730 (OAc), 1668, 1617, 1588 ($\Delta^{4,6}$-3CO), 1253, 1247, 1046. UV λ_{max}^{EtOH} mμ (ε): 300 (23100). NMR τ: 9.08 (18-CH_3), 8.53 (19-CH_3), 6.96 (doublet, J=15 cps) and 6.61 (doublet, J=15 cps, 1α- and 1β-H), 5.33 (17α-H), 4.22 (4-H), 3.80 (singlet, 6- and 7-H). The second compound eluted with benzene–ether (99:1 and 98:2) was 17β-acetoxy-2α-bromoandrosta-4,6-dien-3-one (VIII: 0.274 g, 44.2%) which was recrystallized from *n*-hexane–AcOEt to give an analytical sample of mp 151—152° (decomp.). *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.92; H, 6.68; Br, 19.62. Found: C, 61.90; H, 6.67; Br, 19.90. IR ν_{max}^{Nujol} cm^{-1}: 1732 (OAc), 1674, 1618, 1585 ($\Delta^{4,6}$-3CO), 1246, 1045, 1028. UV λ_{max}^{EtOH} mμ (ε): 287 (21800). NMR τ: 9.10 (18-CH_3), 8.78 (19-CH_3), 7.94 (OAc), 5.33 (17α-H), 5.05 (quartet, J=13 and 6 cps, 2-H), 4.22 (4-H), 3.84 (singlet, 6- and 7-H). The third compound (0.200 g) eluted with benzene–ether (98:2) was purified by rechromatography over silica gel (8 g). Elution with benzene–ether (99:1) afforded 17β-acetoxy-2-bromoandrosta-1,4,6-trien-3-one (X: 0.089 g, 14.1%), which was recrystallized from *n*-hexane–AcOEt to give a pure sample of mp 165—167°. The infrared spectrum was superimposable with that of X obtained above.

Br_2-DMSO Reaction of 17β-Acetoxy-2α-bromoandrosta-4,6-dien-3-one (VIII)——A solution of the monobromodienone (VIII: 0.400 g, 0.9821 mmoles) in DMSO (20 ml) was stirred at 115° with Br_2 (0.079 g, 0.494 mmoles) for 5 hr. The reaction mixture was worked up as described above and the residue (0.455 g) was chromatographed over silica gel (19 g). The eluate with benzene–ether (99:1) afforded 2-bromotrienone (X: 0.279 g) which had mp 162—163.5° after recrystallization from *n*-hexane–AcOEt. The infrared spectrum was identical with that of X obtained above.

DMSO Reaction of 17β-Acetoxy-2,2-dibromoandrosta-4,6-dien-3-one (IX)——A solution of the dibromo compound (IX: 0.500 g) in DMSO (25 ml) was heated at 115° under stirring for 1 hr. The reaction mixture was diluted with ice–water and extracted with ether. The extract was washed with aq. 3% $NaHCO_3$ solution, saturated NaCl-solution and dried over Na_2SO_4. Evaporation of the solvent gave a crystalline residue (0.473 g), which was recrystallized from *n*-hexane–AcOEt to give 2-bromotrienone (X: 0.352 g), mp 165—167°. The residue (0.097 g) obtained from the mother liquor was chromatographed over silica gel. The eluate with benzene–ether (99:1) was recrystallized from *n*-hexane–AcOEt to afford another crop of X (0.037 g), mp 165°. The total yield of the bromotrienone (X) is 92.6%.

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