

**700. Steroids. Part CCLII.<sup>1a</sup> Spectra and Stereochemistry. Part XII.<sup>1b</sup> Dienone-Phenol Rearrangement of 6,19-Epoxyandrosta-1,4-diene-3,17-dione.**

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The compound named in the title undergoes dienone-phenol rearrangement with formation of the 1,4-disubstituted products (IV) and (V). The rearrangement leaves the 6,19-epoxy-bridge intact. Structures were assigned largely on the basis of nuclear magnetic resonance spectral studies. The reaction mechanism is discussed.

ONE interesting facet of steroid chemistry which has attracted numerous investigators is the acid-catalysed rearrangement of steroidal 1,4-dien-3-ones to phenolic compounds or derivatives thereof.<sup>2</sup> Primarily as a result of the efforts of Inhoffen, Woodward, Dreiding, and their collaborators it has been found that a 1,4-dien-3-one usually rearranges to a 1,4-disubstituted ring A aromatic steroid with an oxygen substituent at C-1, whereas a steroidal 1,4,6-trien-3-one rearranges to a 1,3,5(10),6-tetraene with retention of the oxygen substituent at C-3.<sup>2</sup>

Recently, there have been described a number of methods for forming a functional group from a non-activated steroid angular methyl group.<sup>3</sup> One route involves lead tetra-acetate oxidation of a 6 $\beta$ -hydroxy-steroid to the corresponding 6,19-epoxide.<sup>4-6</sup> The resulting availability of 6,19-epoxyandrost-4-ene-3,17-dione<sup>6</sup> offered the opportunity to study the dienone-phenol rearrangement in a molecule where the 10 $\beta$ -substituent is also anchored to C-6. It was expected that, provided the 6,19-epoxy-bridge remained intact during the rearrangement, one or both of two possible mechanisms should operate, leading, respectively, to a 1,4-disubstituted (scheme A) or 3,4-disubstituted oestra-1,3,5(10)-triene (scheme B). Formation of the latter product (III) would constitute a novel form of the dienone-phenol rearrangement.

6,19-Epoxyandrost-4-ene-3,17-dione<sup>6</sup> was dehydrogenated by means of 2,3-dichloro-5,6-dicyanobenzoquinone<sup>7</sup> to obtain 6,19-epoxyandrosta-1,4-diene-3,17-dione (I). Treatment of the latter with toluene-*p*-sulphonic acid-acetic anhydride or with sulphuric acid-acetic anhydride gave ambiguous results with formation of water-soluble products, but no isolable homogeneous compounds. However, the dienone (I) on exposure to aqueous perchloric acid and acetic anhydride for 6 hours at room temperature gave two crystalline compounds, separable by chromatography. Product A showed a strong ultraviolet maximum at 266 m $\mu$  characteristic of the styryl chromophore, whilst product B displayed a less intense absorption ( $\lambda_{\text{max}}$  268—270 m $\mu$ ) typical of a non-conjugated benzenoid chromophore.

The possibility that the 6,19-epoxy-bridge had opened prior to rearrangement was excluded when it was found that 19-hydroxyandrosta-1,4-diene-3,17-dione acetate<sup>6</sup> when

<sup>1</sup> (a) Steroids, Part CCLI, Kaufmann, *J. Org. Chem.*, 1964, **29**, 1348; (b) Spectra and stereochemistry, Part XI, Cross, Santavý, and Trivedi, *Coll. Czech. Chem. Comm.*, 1963, **28**, 3402.

<sup>2</sup> Fieser and Fieser in "Steroids," Reinhold, New York, 1959, pp. 327—329, have summarised many of the investigations of this rearrangement.

<sup>3</sup> For a review see Schaffner, Arigoni, and Jeger, *Experientia*, 1960, **16**, 169.

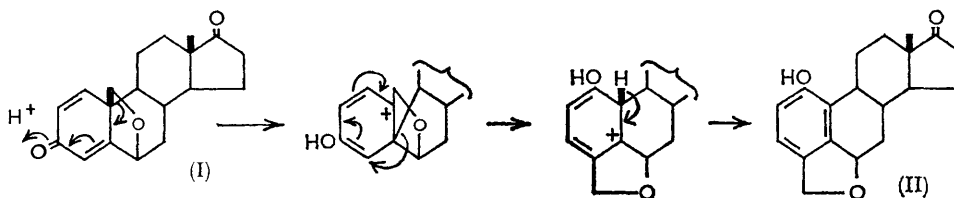
<sup>4</sup> Bowers, Ibáñez, Cabezas, and Ringold, *Chem. and Ind.*, 1960, 1299.

<sup>5</sup> Bowers, Denot, Ibáñez, Cabezas, and Ringold, *J. Org. Chem.*, 1962, **27**, 1862; Meystre, Heusler, Kalvoda, Wieland, Anner, and Wettstein, *Experientia*, 1961, **17**, 475; Bowers, Villotti, Edwards, Denot, and Halpern, *J. Amer. Chem. Soc.*, 1962, **84**, 3204; Tanabe, Takasaki, Sakai, Hayashi, and Morisawa, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 1126; Heller, Wehrli, Schaffner, and Jeger, *Helv. Chim. Acta*, 1962, **45**, 1261; Moriarty and D'Silva, *J. Org. Chem.*, 1963, **28**, 2445; Bagli, Morand, and Gaudry, *ibid.*, 1963, **28**, 1207.

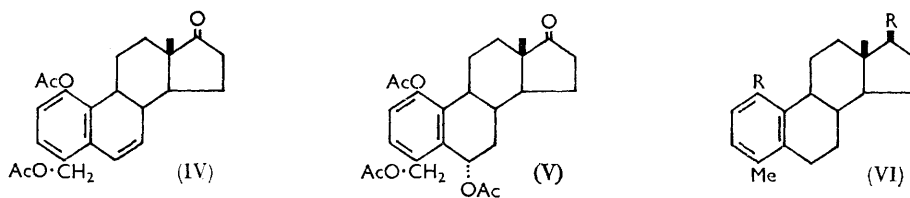
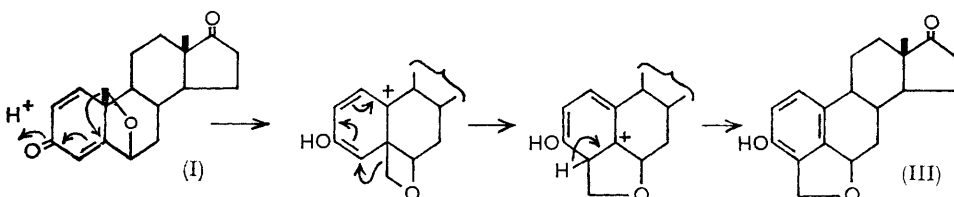
<sup>6</sup> Heusler, Kalvoda, Meystre, Ueberwasser, Wieland, Anner, and Wettstein, *Experientia*, 1962, **18**, 464; Berkoz, Denot, and Bowers, *Steroids*, 1963, **1**, 251.

<sup>7</sup> Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.

similarly treated with perchloric acid–acetic anhydride underwent reaction with loss of the 10 $\beta$ -substituent to afford oestrone acetate as the only product. Since both products A and B show only two aromatic protons in the nuclear magnetic resonance (n.m.r.) spectrum (see Table I), C-19 is retained in both products as a ring A substituent, and therefore no ring-opening occurred before rearrangement. (Opening of the 6,19-epoxy-ring by acetic anhydride is known<sup>4</sup> to furnish a 19-acetoxymethyl group.) Compounds A and B are assigned structures (IV) and (V), respectively, on the basis of the following evidence.



Scheme A.



Scheme B.

In the n.m.r. spectrum of product A (IV) there were observed 3-proton singlet resonances at 9.09 (H-18), 7.93 (acetate), and 7.71 $\tau$  (phenolic acetate). In addition to an AB quartet<sup>8a</sup> centred at 2.98 $\tau$  ( $J$  8.1 c./sec.), for *ortho* aromatic protons, resonance peaks were present for the two adjacent olefinic protons at C-6 and C-7 as the AB portion of an ABX pattern.<sup>8b</sup> For an olefinic double bond conjugated to ring A the observed pattern can only arise for a 6,7-double bond. A singlet resonance at 4.83  $\tau$  corresponds to two equivalent methylene protons in the environment Ar-CH<sub>2</sub>-O.

Product B, (V), gave an n.m.r. spectrum with 3-proton singlet resonances at 9.03 (H-18), 7.70 (phenolic acetate), 7.87, and 7.91 $\tau$  (two acetates). The AB quartet<sup>8a</sup> for *ortho* aromatic protons was visible at 2.82 $\tau$  ( $J_{H,H}$  ca. 9 c./sec.), but no other low-field resonance was apparent. A 2-proton singlet at 4.92 $\tau$  was again attributable to equivalent methylene protons in the environment Ar-CH<sub>2</sub>-O. An additional multiplet resonance at 4.83  $\tau$  was assigned to the benzylic C-6 proton. Thus, it appeared probable that A (IV) and B (V) were the two expected products from acetic anhydride–acid catalysed opening of the oxide bridge in the non-isolated intermediate (II). The mechanism of the oxide opening suggests that incoming acetate should lead to the 6 $\alpha$ -acetoxy-derivative B (V).

<sup>8</sup> Pople, Schneider, and Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959, (a) p. 119; (b) p. 132.

An attempt was made to convert both products (IV and V) into a common derivative by hydrogenation of the double bond in the styrene (IV), and hydrogenolytic removal of the benzylic acetates from both products. When the styrene (IV) was hydrogenated over 10% palladium-charcoal, a dihydro-derivative (IV; 6,7-dihydro) was obtained whose ultraviolet spectrum,  $\lambda_{\max}$  266—268  $\mu$  ( $\log \epsilon$  3.53), confirmed that the styryl double bond had been reduced. Surprisingly, no hydrogenolysis of the benzylic acetate resulted, as was shown by the n.m.r. spectrum (see Table). Under the same reduction conditions the

N.m.r. spectral data ( $\tau$  values) for four 1,4-disubstituted  $\alpha$ estra-1,3,5(10)-trien-17-ones.

Compound	H-18	Ar·CH <sub>2</sub> ·OAc	1-OAc	Other methyls	Ar·CH <sub>2</sub> ·O	Aromatic H-2 and H-3	H-6	H-7
(IV) * †	9.09	7.93	7.71	—	4.83	2.98 (403.6, 411.7, 430.9, and 439.1 c./sec.) $J_{2,3}$ 8.1	3.22 (401.0, 403.3, 409.7, and 412 c./sec.) $J_{6,7}$ ca. 9 $J_{6,8}$ ca. 2.3	3.82 (365.5 and 375.8 c./sec.) $J_{7,8}$ < 1 $J_{6,7}$ ca. 9
(V)	9.03	7.91	7.70	7.87 (6 $\alpha$ -OAc)	4.92	2.82 (416.1, 425, 436.7 and 445 c./sec.) $J_{2,3}$ ca. 9		
(IV; 6,7-dihydro)	9.06	7.89	7.72	—	4.90	2.97 (407, 414, 430, and 437 c./sec.) $J_{2,3}$ 7		
(VI; R = OAc) ‡	9.14 (9.15)		7.74 (7.73)	7.94 (7.95) (17 $\beta$ -OAc) 7.79 (7.81) (4-methyl)	—	3.14 (398.5, 406.5, 417.1 and 425.4 c./sec.) (3.15) $J_{2,3}$ ca. 8		

\* The olefinic and aromatic proton coupling constants were measured from a spectrum run on a Varian HR60 spectrometer through the courtesy of P. W. Landis, Eli Lilly and Co., Indianapolis, U.S.A. † Dreiding models of the tetraene (IV) reveal that the C<sub>3</sub>-proton bond is almost perpendicular to the 6,7-double bond. Accordingly  $J_{7,8}$  should be very small, but this stereochemical arrangement meets the requirements for allylic coupling of protons (cf. Wittstruck, Malhotra, and Ringold, *J. Amer. Chem. Soc.*, 1963, **85**, 1699; Collins, Hobbs, and Sternhell, *Tetrahedron Letters*, 1963, 197). Assignments of resonances to H-6 and H-7 agree with these predictions. ‡ Values in parentheses are those kindly furnished for comparative purposes by Dr. K. Schaffner.

triacetate (V) was recovered largely unchanged, but on prolonged hydrogenation a mixture of two compounds resulted. From the n.m.r. spectrum, this mixture consisted of unchanged triacetate (V) together with a compound lacking the 6 $\alpha$ -acetate and with proton resonance patterns identical with those of the 6,7-dihydro-compound obtained from (IV). The triacetate (V) was not converted into the styrene (IV) by prolonged reflux in boron trifluoride etherate.

Treatment of both rearrangement products with sodium in liquid ammonia removed the benzylic acetates and the double bond, and furnished the same diol (VI; R = OH) which was converted into the corresponding diacetate (VI; R = OAc). The n.m.r. spectrum of this diacetate showed 3-proton singlets at 9.14 (18-H), 7.94 (17 $\beta$ -acetate), 7.97 (aromatic methyl), and 7.74 $\tau$  (phenolic acetate). A mixed melting point and comparative infrared and n.m.r. spectra of this diacetate with authentic 4-methyl $\alpha$ estra-1,3,5(10)-triene-1,17-diol diacetate (VI; R = OAc)<sup>9</sup> established its identity. The diol precursor therefore has structure (VI; R = OH) and products A and B are thereby uniquely defined by the structures (IV) and (V), respectively. Analyses, and ultraviolet and infrared spectral data provided further strong evidence for the assigned structures (see Experimental section). It is apparent that the rearrangement of 1,4-diene-3-ones normally proceeds by one mechanism (scheme A) whether the 6,19-epoxy-bridge is present or not.

#### EXPERIMENTAL

Rotations were for chloroform solutions and ultraviolet spectra for ethanol solutions. Except where stated otherwise, infrared spectra were measured in potassium bromide discs.

<sup>9</sup> Dutler, Bosshard, and Jeger, *Helv. Chim. Acta*, 1957, **40**, 494; we thank Dr. Schaffner (E.T.H., Zürich) for an authentic sample for comparative purposes.

N.m.r. spectra were recorded at 60 Mc with solutions in deuteriochloroform containing tetramethylsilane as an internal reference. Chemical shifts are quoted on the  $\tau$  scale and are accurate to  $\pm 0.01$  p.p.m. Coupling constants are quoted in c./sec. and are accurate to  $\pm 0.5$  c.p.s.

**6,19-Epoxyandrosta-1,4-diene-3,17-dione (I).**—The dione (13.9 g.)<sup>6</sup> and 2,3-dichloro-5,6-dicyanobenzoquinone (27.8 g.)<sup>7</sup> were dissolved in dry dioxan (800 ml.) and the solution was maintained under reflux for 24 hr. The cooled mixture was diluted with methylene chloride and the resultant mixture filtered through Celite. Passage of the remaining solution through a column of activated alumina, then evaporation, afforded the *dienone* (I) (6.7 g., m. p. 164—166° (from acetone–hexane)  $[\alpha]_D +102^\circ$ ;  $\lambda_{\max}$ . 244 m $\mu$  (log  $\epsilon$  4.14),  $\nu_{\max}$ . 1745, 1680, 1665, and 1620 cm.<sup>-1</sup> (Found: C, 76.35; H, 7.4; O, 16.2. C<sub>19</sub>H<sub>22</sub>O<sub>3</sub> requires C, 76.5; H, 7.45; O, 16.1%).

**Dienone–Phenol Rearrangement of the Dienone (I).**—A solution of the dienone (6.7 g.) in acetic anhydride (185 ml.) was cooled to 0°, and perchloric acid (0.3 ml., 60% aqueous perchloric acid in 20 ml. acetic anhydride) was added. After being stirred at room temperature for 6 hr. the mixture was poured into saturated aqueous sodium hydrogen carbonate solution, extracted with ethyl acetate, washed with water, and dried (Na<sub>2</sub>SO<sub>4</sub>). The residue upon evaporation was taken up in hexane–benzene (1:1) and adsorbed on to a column of Florisil (600 g.). Elution with benzene afforded 1-acetoxy-4-acetoxymethylæstra-1,3,5(10),6-tetraen-17-one (IV), m. p. 111—113° (from benzene),  $[\alpha]_D -156^\circ$ ,  $\lambda_{\max}$ . 222 and 266 m $\mu$  (log  $\epsilon$  4.37 and 4.04),  $\nu_{\max}$ . 1760, 1745, 1730, 1630, 1580, 1480, 1250, and 1205 cm.<sup>-1</sup> (Found: C, 72.65; H, 6.95; O, 20.7. C<sub>23</sub>H<sub>26</sub>O<sub>5</sub> requires C, 72.25; H, 6.85; O, 20.9%).

Further elution of the column with methylene chloride gave 1,6 $\alpha$ -diacetoxy-4-acetoxymethylæstra-1,3,5(10)-trien-17-one (V) (810 mg.), m. p. 144—145° (from ethanol),  $[\alpha]_D +178^\circ$ ,  $\lambda_{\max}$ . 268—270 m $\mu$  (log  $\epsilon$  2.71),  $\nu_{\max}$ . 1765, 1735, 1600, 1500, 1240 and 1195 cm.<sup>-1</sup> (Found: C, 68.0; H, 6.9; O, 24.95. C<sub>25</sub>H<sub>30</sub>O<sub>7</sub> requires C, 67.85; H, 6.85; O, 25.3%).

**Dienone–Phenol Rearrangement of 19-Acetoxyandrosta-1,4-diene-3,17-dione.**—The dione<sup>6</sup> (250 mg.) in acetic anhydride (10.2 ml.) was treated at 0° with perchloric acid (0.3 ml. 60% aqueous perchloric acid in 20 ml. acetic anhydride) as outlined above. A single product was isolated upon evaporation of the ethyl acetate extracts. This was dissolved in hexane–benzene and passed through a column of Florisil to afford 3-acetoxyæstra-1,3,5(10)-trien-17-one m. p. 123—125° (from ethanol),  $\lambda_{\max}$ . 268 (log  $\epsilon$  2.89) and 276 m $\mu$  (log  $\epsilon$  2.86), identical (infrared spectrum in chloroform and mixed m. p.) with an authentic sample.

**1-Acetoxy-4-acetoxymethylæstra-1,3,5(10)-trien-17-one (IV; 6,7-dihydro).**—The tetraene (IV) (300 mg.) in ethyl acetate–ethanol (30 ml.; 1:1) was shaken with hydrogen over 10% palladium–charcoal until the uptake of hydrogen ceased. After removal of the catalyst by filtration the solution was evaporated to dryness to yield the *trienone* (230 mg.), m. p. 138—140° (from acetone–hexane),  $[\alpha]_D +215^\circ$ ,  $\lambda_{\max}$ . 266—268 m $\mu$  (log  $\epsilon$  3.53),  $\nu_{\max}$ . 1765, 1740, 1595, 1490, 1245, and 1200 cm.<sup>-1</sup> (Found: C, 72.65; H, 7.4; O, 20.8. C<sub>23</sub>H<sub>28</sub>O<sub>5</sub> requires C, 71.85; H, 7.35; O, 20.8%).

A similar, though prolonged, hydrogenation of the triacetate (V) furnished an inseparable mixture which was shown by n.m.r. spectroscopy to consist of unchanged starting material (V) and the above dihydro-derivative.

**4-Methylæstra-1,3,5(10)-triene-1,17 $\beta$ -diol (VI; R = OH).**—(a) A solution of the tetraene (IV) (500 mg.) in dry ether was added slowly to a stirred solution of lithium (2 g.) in ammonia (200 ml.). Stirring was continued for 2 hr. after which time ethanol was added dropwise to discharge the blue colour. The residue after evaporation of the ammonia was taken up in ethyl acetate, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and recovered by solvent distillation *in vacuo*. A solution of the product in hexane–benzene (1:1) was chromatographed on Florisil (15 g.). Fractions eluted with methylene chloride containing 2% of acetone were combined and recrystallised from acetone–hexane to furnish the *diol* (VI; R = OH) (160 mg.), m. p. 232—234°,  $[\alpha]_D +154^\circ$ ,  $\lambda_{\max}$ . 284 m $\mu$  (log  $\epsilon$  3.25),  $\nu_{\max}$ . 3530, 3220, 1585, and 1495 cm.<sup>-1</sup> (Found: C, 79.45; H, 9.65; O, 10.85. C<sub>18</sub>H<sub>26</sub>O<sub>2</sub> requires C, 79.7; H, 9.15; O, 11.15%).

(b) Substitution of the tetraene (IV) in the above metal–ammonia reduction by the triacetate (V) (200 mg.) and work-up as described led to 150 mg. of the same diol (VI; R = OH), identical (mixed m. p., infrared spectrum, and chromatographic behaviour) with the above sample.

**4-Methylæstra-1,3,5(10)-triene-1,17 $\beta$ -diol Diacetate (VI; R = Ac).**—The above diol (VI;

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R = OH) (200 mg.) in pyridine (4 ml.) was acetylated at room temperature for 24 hr. with acetic anhydride (2 ml.). After being poured on to ice the mixture was extracted in the normal manner to afford the diacetate (185 mg.), m. p. 135—136° (from acetone-hexane),  $[\alpha]_D^{25} +139^\circ$ ,  $\lambda_{\max}$  268 m $\mu$  (log  $\epsilon$  2.49),  $\nu_{\max}$  1765, 1735, 1600, 1495, 1250, and 1200 cm.<sup>-1</sup> (Found: C, 74.95; H, 8.35; O, 16.8. Calc. for C<sub>23</sub>H<sub>30</sub>O<sub>4</sub>: C, 74.55; H, 8.15; O, 17.3%) identical (mixed m. p., infrared spectrum, and chromatographic behaviour) with an authentic sample.<sup>9</sup>

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