The Preparation and Dienone–Phenol Rearrangement of Androsta-2,5-diene-4,17-dione

By **James R. Hanson,* David Raines,** and **Steve G. Knights,** School of Molecular Sciences, University of Sussex, Brighton, Sussex BN1 9QJ

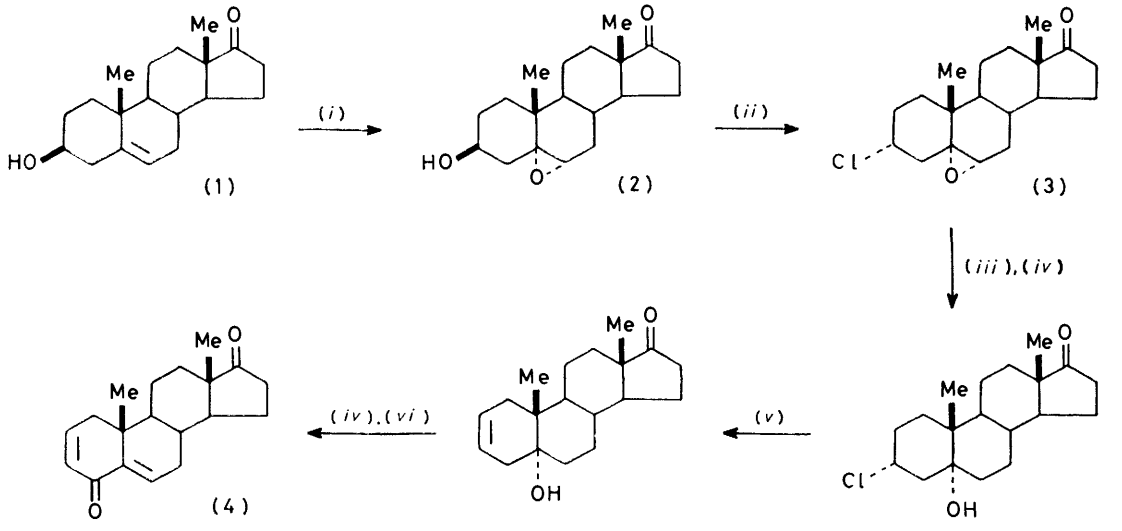
The preparation of androsta-2,5-diene-4,17-dione from dehydroisoandrosterone is described. Its dienone–phenol rearrangement, in the presence of hydrobromic acid and glacial acetic acid, affords 1-methyl-4-hydroxyestra-1,3,5(10)-trien-17-one.

THERE have been extensive studies on the dienone–phenol rearrangement of steroidal 1,4-dien-3-ones.[1,2] Two different reaction pathways are known leading either to a 1-hydroxy-4-methylphenol or to a 3-hydroxy-1-methylphenol. Whilst the former involves migration of the C-9–C-10 bond to C-4 *via* a spiran intermediate, the latter involves migration of C-10-Me to C-1. The preferred pathway depends upon the reaction conditions and on the nature of substituents in the substrate. In contrast there is a dearth of data on the rearrangements of other steroidal dienones such as the 2,5-dien-4-ones. In this paper we describe a better route for the preparation of androsta-2,5-diene-4,17-dione (4) [3] and report on its dienone–phenol rearrangement.

RESULTS AND DISCUSSION

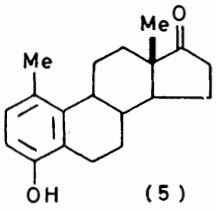
Activation to allylic oxidation of the 4-position of a steroidal 2-ene by a 5α-hydroxy-group provides a route to 5α-hydroxyandrost-2-en-4-ones [4] and thence the 2,5-dien-4-ones given that the corresponding 2-ene can be reliably prepared. In this context the elimination of a 3α-axial substituent is preferred to that of an equatorial 3β-substituent. Thus treatment of 3β-hydroxy-5α,6α-epoxyandrostan-17-one (2) with triphenylphosphine and carbon tetrachloride containing pyridine (to remove any hydrogen chloride) proceeds cleanly with inversion [5] to afford the 3α-chloro-5α,6α-epoxide (3). The axial nature of the 3α-chlorine atom was revealed by the relatively narrow half-width ($W_{\frac{1}{2}}$ 9 Hz) of the 3β-proton signal in the ^{1}H n.m.r. This provided the basis for the synthetic sequence starting from dehydroisoandrosterone (1) and shown in the Scheme.

Treatment of androsta-2,5-diene-4,17-dione (4) with hydrobromic acid in glacial acetic acid under reflux afforded a phenolic product in 45% yield which was easily purified chromatographically. Apart from absorption at 3 305 (OH), 1 745 (5 ring C=O), and 1 590 (Ar–C=C), the i.r. spectrum contained a band at 806 cm^{-1} characteristic [6] of a 1,2,3,4-tetrasubstituted benzene ring. The n.m.r. spectrum contained an aromatic C-Me resonance (δ 2.29) and a pair of single proton doublets (J 8.5 Hz) at δ 6.56 and 6.88. The product differed (i.r. and n.m.r.) from 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (6). It was assigned the structure 4-hydroxy-1-methylestra-1,3,5(10)-trien-17-one (5) on the basis of its ^{13}C n.m.r. spectrum (see Table). 1-Hydroxy-4-methyl- and 3-hydroxy-1-methyl-estratrien-17-one, (6) and (7), were prepared [7] from androsta-1,4-diene-3,17-dione. The spectra of the phenols (5), (6), and (7) were assigned by comparison with 3-hydroxyestra-1,3,5(10)-trien-17-one [8] and 17β-acetoxy-4-methyl- and 17β-acetoxy-1-methyl-estra-1,3,5(10)-triene.[9] In particular, the assignments for the aromatic signals were consistent with the phenolic substituent effects (*ortho*-C shielded by *ca.* 13, *meta*-C

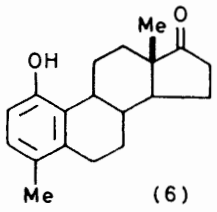


SCHEME (*i*), *m*-$ClC_6H_4CO_3H$; (*ii*), $(C_6H_5)_3P,CCl_4$,pyridine; (*iii*), $LiAlH_4$; (*iv*), 8N CrO_3; (*v*), Li_2CO_3,LiBr,DMF; (*vi*), $SOCl_2$

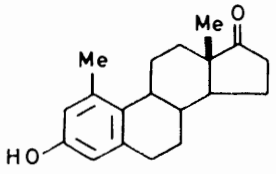
deshielded by 1.5 and *para*-C shielded by *ca.* 7 p.p.m.) observed between toluene and the *o*-, *m*-, and *p*-cresols.[10] Thus in (5) the signals assigned to C-1, C-3, and C-5 were



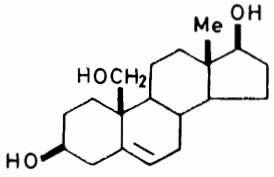
(5)



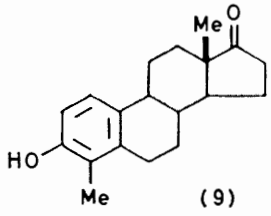
(6)



(7)



(8)



(9)

shielded compared to the corresponding dehydroxy-compound.

The assignment of structure (5) to the dienone–phenol rearrangement product was confirmed by reduction with sodium borohydride in methanol to give the known [11] 1-methylestra-1,3,5(10)-triene-4,17β-diol. The latter had been prepared from 17β-acetoxy-1-methylestra-1,3,5(10)-triene by nitration, reduction, diazotization, and hydrolysis.

The structure (5) has previously been assigned [12] to a minor phenol obtained by the Oppenauer oxidation of 3β,19-dihydroxyandrost-5-en-17-one. However the products were clearly different (i.r., n.m.r., and m.p.). Repetition of the work of Tanabe with 3β,17β,19-trihydroxyandrost-5-ene (8) gave a small amount of a phenol with the same aromatic proton resonances (δ 6.64 and 7.09, *J* 8 Hz; δ 2.14, Ar-Me) although it retained the 17β-hydroxy-group. An attempt to oxidize this compound to the same phenol as described by Tanabe was not successful. The presence of an AB aromatic doublet with a large coupling constant is indicative of an *ortho*-relationship between the protons. A plausible structure is that of a 3-hydroxy-4-methylestratriene (9) which might arise by a C-4 anion trapping for formaldehyde which is lost in a retro-Aldol reaction from C-19 under the basic conditions of the Oppenauer oxidation.

The aromatisation of the 2,5-dien-4-one may proceed by acid-catalysed enolization of the C-4 carbonyl group followed by attack of a proton at C-6. Rearrangement of the resulting carbocation then occurs with migration of the C-10 methyl group leading to an aromatic product. A dienone–phenol rearrangement *via* a spiran intermediate is unlikely in the case of a C-4 ketone since the formation of a C-5 carbocation, prior to the migration of the C-9–C-10 bond, is destabilized by the adjacent carbonyl group. The presence of a C-4 oxygen function also precludes subsequent steps in the formation of a 4-methylestratriene.

^{13}C N.m.r. spectra of some hydroxymethylestra-1,3,5(10)-trienes (in p.p.m. from $SiMe_4$, determined in [$^2H_5$]-pyridine at 25.15 MHz)

Carbon atom	Compound (5)	Compound (6)	Compound (7)
1	129.7	156.0	139.7
2	127.1	113.4	114.5
3	112.4	128.0	156.2
4	154.5	127.2	117.4
5	126.2	138.1	138.4
6	27.4	29.3	32.7
7	26.6	25.9	27.8
8	41.1	40.1	41.7
9	47.4	45.9	46.9
10	139.9	126.7	129.4
11	24.9	25.5	25.3
12	32.8	32.9	32.7
13	48.7	48.6	48.7
14	50.6	50.5	50.5
15	21.7	21.8	21.7
16	35.9	35.8	35.9
17	219.2	219.5	219.1
18	14.6	14.4	14.6
19	21.7	19.4	22.4

EXPERIMENTAL

General experimental details have been described previously.[13]

3α-*Chloro*-5α,6α-*epoxyandrostan*-17-*one*.—A solution of 5α,6α-epoxy-3β-hydroxyandrostan-17-one (30 g) (prepared from dehydroisoandrosterone and *m*-chloroperbenzoic acid) [14] in carbon tetrachloride (600 ml) and pyridine (30 ml) was heated under reflux with triphenylphosphine (60 g) for 3 h. The solution was filtered, washed with water, dried, and the solvent evaporated to give a gum which was chromatographed on silica. Elution with 7% ethyl acetate–light petroluem gave 5α,6α-epoxyandrost-2-en-17-one (1.2 g) which crystallized from acetone–light petroleum as plates, m.p. 171—173 °C, $[\alpha]_D$ +35° (*c* 0.2) (lit.,[15] 172—174 °C, $[\alpha]_D$ +49°), identified by its n.m.r. spectrum. Further elution with 10% ethyl acetate–light petroleum gave 3α-*chloro*-5α,6α-*epoxyandrostan*-17-*one* (15.45 g) which crystallized from acetone as prisms, m.p. 198—200 °C, $[\alpha]_D$ −28° (*c* 0.2) (Found: C, 70.9; H, 8.4. $C_{19}H_{27}O_2Cl$ requires C, 70.7; H, 8.4%); $\nu_{max.}$ 1 740 cm^{-1}; δ 0.84 (3 H, s, 18-Me), 1.09 (3 H, s, 19-Me), 2.81 (1 H, d, *J* 4 Hz, 6-H), and 4.51 (1 H m, $W_{\frac{1}{2}}$ 9 Hz, 3-H).

3α-*Chloro*-5α,17β-*Dihydroxyandrostane*.—The above chloro-epoxide (13.5 g) in dry tetrahydrofuran (675 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (6.75 g) in dry tetrahydrofuran (675 ml) at room temperature. The mixture was then heated under reflux for 30 min. Ethyl acetate, followed by brine, was carefully added to the solution. The upper organic layer was separated and the solvent evaporated. The residue was taken up in ethyl acetate, washed with brine and water, and dried. The solvent was evaporated to afford 3α-*chloro*-5α,-17β-*dihydroxyandrostane* (12.13 g). The analytical sample

was recrystallized from acetone–light petroleum as needles, m.p. 162—164 °C, $[\alpha]_D$ −2° (*c* 0.2) (Found: C, 70.3; H, 9.6. $C_{19}H_{31}O_2Cl$ requires C, 70.4; H, 9.6%); $\nu_{max.}$ 3 565, 3 480, and 3 320 cm^{-1}; δ 0.69 (3 H, s, 18-Me), 0.90 (3 H, s, 19-Me), 3.02 (1 H, s, exchangeable with D_2O, 5-OH), 3.56 (1 H, t, *J* 8 Hz, 17-H), and 4.50 (1 H, m, 3-H).

3α-Chloro-5α-hydroxyandrostan-17-one.—The above alcohol (12 g) was dissolved in acetone (300 ml) and treated with an excess of 8N chromium trioxide reagent for 1 h. Methanol was added, the solution was poured into water, and the product recovered in ethyl acetate. The extract was washed with aqueous sodium hydrogencarbonate and water, and dried. The solvent was evaporated to afford *3α-chloro-5α-hydroxyandrostan-17-one* (9.8 g) which crystallized from acetone–light petroleum as needles, m.p. 154—156 °C, $[\alpha]_D$ +71.2° (*c* 0.3) (Found: C, 70.5; H, 8.9. $C_{19}H_{29}O_2Cl$ requires C, 70.3; H, 8.9%); $\nu_{max.}$ 3 580 and 1 740 cm^{-1}; δ 0.82 (3 H, s, 18-Me), 0.92 (3 H, s, 19-Me), 3.08 (1 H, s, exchangeable with D_2O, 5α-OH), and 4.54 (1 H, m, 3-H).

5α-Hydroxyandrost-2-en-17-one.—A solution of 3α-chloro-5α-hydroxyandrostan-17-one (5.6 g) in dry dimethylformamide (224 ml) was refluxed with lithium carbonate (5.6 g) and lithium bromide (5.6 g) under nitrogen for 30 min. The solution was poured into water and extracted with ethyl acetate. The extract was washed with water, dried, the solvent evaporated, and the residue chromatographed on silica. Elution with 7% ethyl acetate–light petroleum gave 5α-hydroxyandrost-2-en-17-one (3.23 g) which crystallized from light petroleum as needles, m.p. 140—142 °C, $[\alpha]_D$ +98° (*c* 0.2) (lit.,[16] 126—130 °C) (Found: C, 79.0; H, 9.7. Calc. for $C_{19}H_{28}O_2$: C, 79.2; H, 9.7%); $\nu_{max.}$ 3 470, 3 020, 1 725, and 1 650 cm^{-1}; δ 0.84 (3 H, s, 18-Me), 0.87 (3 H, s, 19-Me), and 5.60 (2 H, m, 2- and 3-H). This material was oxidized as described previously.[3,4]

4-Hydroxy-1-methylestra-1,3,5(10)-trien-17-one (4).—Androsta-2,5-diene-4,17-dione[3] (200 mg) was dissolved in a mixture of 48% hydrobromic acid (1 ml) and glacial acetic acid (4 ml) and heated under reflux for 15 min. The deep red solution was cooled and then poured, with vigorous stirring, into aqueous sodium hydrogencarbonate. The pale yellow solid was recovered in ethyl acetate and chromatographed on alumina. Elution with 15% ethyl acetate–light petroleum gave *4-hydroxy-1-methylestra-1,3,5(10)-trien-17-one* (5) (88 mg) which crystallized from methanol as needles, m.p. 267—268 °C, $[\alpha]_D$ +235° (*c* 0.2) (Found: C, 79.9; H, 8.5. $C_{19}H_{24}O_2$ requires C, 80.2; H, 8.5%); $\nu_{max.}$ 3 305, 1 745, 1 590, and 806 cm^{-1}; δ 0.96 (3 H, s, 18-Me), 2.29 (3 H, s, 1-Me), 4.92 (1 H, m, exchangeable with D_2O, 4-OH), and 6.56 and 6.88 (each 1 H, d, *J* 8.5 Hz, 2- and 3-H).

1-Methylestra-1,3,5(10)-triene-4,17β-diol.— 4-Hydroxy-1-methylestra-1,3,5(10)-trien-17-one (100 mg) in methanol (25 ml) was treated with sodium borohydride (30 mg) at 0—5 °C for 1 h. Water (25 ml) was added and the reaction mixture was neutralized with acetic acid. The solution was concentrated and the product recovered in ethyl acetate. The extract was washed thoroughly with dilute hydrochloric acid, aqueous sodium hydrogencarbonate, water, and then dried. The solvent was evaporated to give 1-methylestra-1,3,5(10)-triene-4,17β-diol (96 mg) which was recrystallized from aqueous methanol (decolourizing charcoal) as needles, m.p. 105—107 °C, $[\alpha]_D$ +134° (*c* 0.2) (lit.,[11] 106—108 °C) (Found: C, 79.6; H, 9.2. Calc. for $C_{19}H_{26}O_2$: C, 79.7; H, 9.2%); $\nu_{max.}$ 3 300, 1 590, and 807 cm^{-1}; δ 0.83 (3 H, s, 18-Me) 2.21 (3 H, s, 1-Me), 3.76 (1 H, m, 17-H), and 6.56 and 6.85 (each 1 H, d, *J* 8 Hz, 2- and 3-H).

Oppenauer Oxidation of Androst-5-ene-3β,17β,19-triol.—The triol[12] (prepared from 3β,17β-diacetoxyandrost-5-ene *via* 3β,17β-diacetoxy-5α-bromoandrostan-6β-ol) (1.0 g) was dissolved in toluene (165 ml) and cyclohexanone (10 ml). The solution was refluxed and 25 ml of distillate was removed. A solution of aluminium isopropoxide (2.5 g) in toluene (16 ml) was added over 5 min and a further 25 ml of distillate was removed. The reaction mixture was heated under reflux for 3 h. The solution was cooled in ice, treated with dilute sulphuric acid, and extracted with ether. The extract was washed with aqueous sodium hydrogencarbonate and water, and dried. The solvent was evaporated and the residue chromatographed on silica. The aromatic products were further purified by repeated preparative layer chromatography on silica in 15% ethyl acetate–light petroleum. This gave a *phenol* (85 mg) (3,17β-dihydroxy-4-methylestratriene?) which crystallized from aqueous methanol as needles, m.p. 195—198 °C, $[\alpha]_D$ +135° (*c* 0.2) (Found: C, 80.1; H, 9.5. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.2%); $\nu_{max.}$ 3 440, 1 595, and 805 cm^{-1}; δ 0.72 (3 H, s, 18-Me), 2.14 (3 H, s, Ar-Me), 3.80 (1 H, m, 17-H), and 6.64 and 7.09 (each 1 H, d, *J* 8 Hz, Ar-H). Attempts at oxidation of the compound with pyridinium chlorochromate, to afford the corresponding 17-ketone,[12] gave an inseparable mixture.

[9/1306 *Received*, 16*th August*, 1979]

REFERENCES

[1] For a review see D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, London, 1968, p. 277.

[2] See B. A. Marples in 'Terpenoids and Steroids,' Specialist Periodical Reports, The Chemical Society, London, 1978, vol. 8, p. 247, and D. N. Kirk in the preceding volumes.

[3] J. R. Hanson, D. Raines, and H. Wadsworth, *J.C.S. Perkin I*, 1977, 499.

[4] J. R. Hanson and A. G. Ogilvie, *J.C.S. Perkin I*, 1972, 590.

[5] R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 1971, **36**, 403.

[6] L. J. Bellamy, 'Infrared Spectra of Complex Molecules,' Methuen, London, 1958, p. 78.

[7] C. Djerassi and C. R. Scholz, *J. Org. Chem.*, 1948, **13**, 697; A. S. Dreiding, W. L. Pummer, and A. J. Tomasewski, *J. Amer. Chem. Soc.*, 1953, **75**, 3159.

[8] T. A. Wittstruck and K. I. H. Williams, *J. Org. Chem.*, 1973, **38**, 1542.

[9] J. R. Hanson and M. Siverns, *J.C.S. Perkin I*, 1975, 1110.

[10] P. C. Lauterbur, *J. Amer. Chem. Soc.*, 1961, **83**, 1838; 1846.

[11] H. Dannenberg and H. J. Gross, *Annalen*, 1966, **692**, 180.

[12] K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, Y. Morisawa, and T. Hashimoto *Chem. Pharm. Bull.* (*Japan*), 1967, **15**, 15.

[13] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 513.

[14] K. Miescher and W. H. Fischer, *Helv. Chim. Acta*, 1938, **21**, 336.

[15] J. R. Hanson and T. D. Organ, *J. Chem. Soc.* (*C*), 1970, 2473.

[16] P. D. Klimstra, U.S.P. 3,271,425/1966 (*Chem. Abs.*, 1967, **66**, 11122).