Syntheses of 2α- and 2β-Deuterio-testosterones and -androst-4-ene-3,17-diones

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Testosterone and androst-4-ene-3,17-dione with a deuterium label in the 2α- or 2β-position have been synthesized from a common intermediate, 5α-androst-2-ene-5α,17β-diol. An improved preparation of the latter is described, together with its conversion *via* epoxidation, reductive epoxide opening, and subsequent oxidation and dehydration to 2β-labelled Δ⁴-3-oxo steroids. Treatment of the same precursor with labelled diborane leads, by a similar synthetic sequence, to both 2α- and 2β-labelled Δ⁴-3-oxo steroids. The stereochemical integrity of the products has been determined by high-field deuterium n.m.r.

The availability of steroids specifically labelled with deuterium or tritium is of prime importance in both medicinal investigations and studies of enzyme mechanism. Recently synthesized examples include Δ⁴-3-oxo steroids labelled with deuterium at the 6α-,[1] 6β-,[1,2] 15α-,[3] 15β-,[3] 16-,[4] and 19-[5] positions, and other steroidal skeletons with deuterium at the 2-,[6] 4-,[7] and 6- and 7-positions.[8,9]

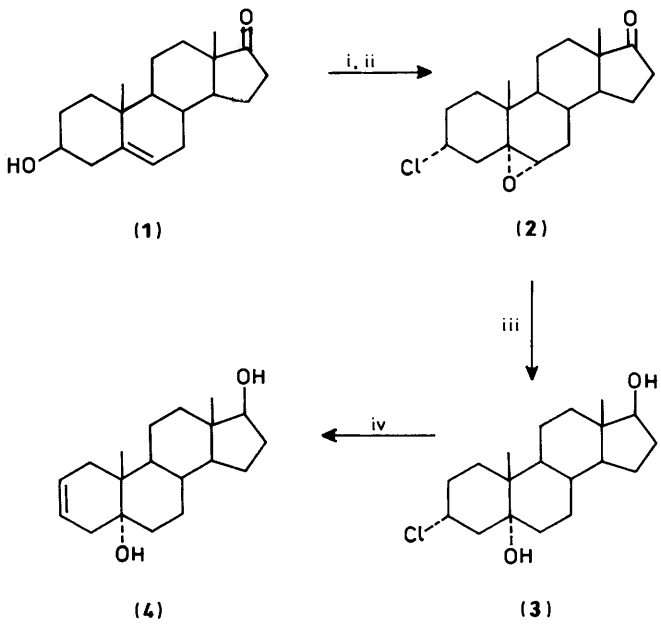
In connection with our studies on fungal hydroxylation of steroids we required the testosterones (**9**) and (**15**), with deuterium label specifically at the 2β- and 2α-positions, respectively. Such substrates are also of potential value for clarifying the stereochemistry of hydrogen loss from ring *A* of testosterone during its conversion into estradiol by the human placental aromatase enzyme. This process has been thought for many years to involve loss of the 1β- and 2β-hydrogen atoms,[10] but recent findings[11] have raised some doubts about the stereochemical conclusions of the earlier workers, particularly with respect to loss from C-1.

Earlier preparations of 2β-deuterio Δ⁴-3-oxo steroids by dehalogenation (with zinc–deuterioacetic acid) of 2α-iodoandrost-4-ene-3,17-dione[12] or deuteriation of the 2,4-dienolate of testosterone[13,14] produced material of low deuterium content or uncertain stereochemical integrity, and 2α-deuterio Δ⁴-3-oxo steroids have not been described. The preparation of both stereoisomers of a C-2 labelled steroid has been reported only for dehydroisoandrosterone (**1**).[6] In the latter case, although deuterium incorporation was reported to be high, the stereochemical integrity of label in the final products was not determined directly, but was assumed on the basis of the nature of the synthetic transformations involved.

The key intermediate in our syntheses was the Δ²-5α,17β-diol (**4**), the preparation of which is outlined in Scheme 1. The chloro epoxide (**2**), prepared by the published procedure,[15] was converted by lithium triethylborohydride into the diol (**3**) in high yield. In our hands, the published procedure[15] for the conversion of (**2**) into (**3**) by lithium aluminium hydride afforded mainly the dehalogenated 5α,17β-diol.

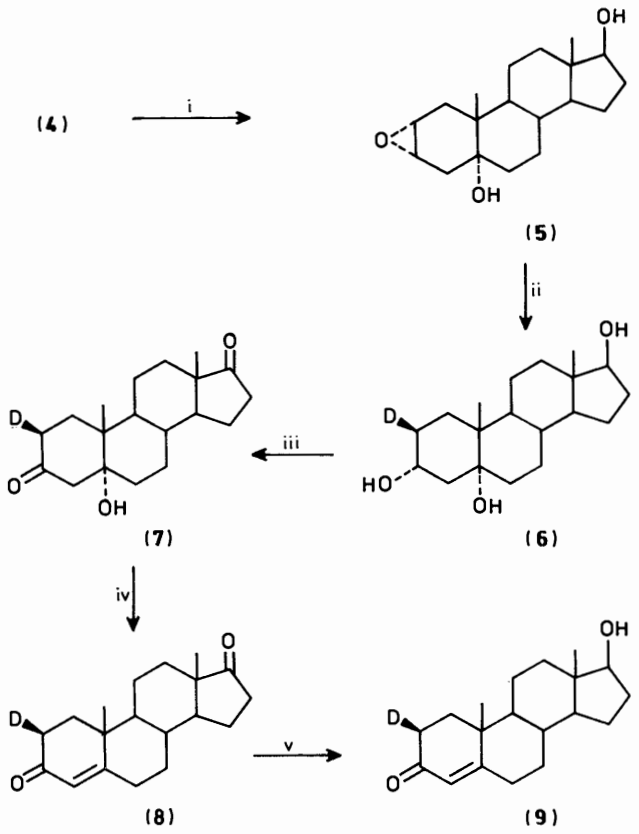
The Δ²-5α,17β-diol (**4**) was converted into 2β-deuterioandrost-4-ene-3,17-dione (**8**) and 2β-deuteriotestosterone (**9**) as outlined in Scheme 2. Epoxidation of (**4**) resulted in the stereoselective formation of the α-epoxide (**5**), the stereochemistry of which was indicated by ^{1}H n.m.r. [lack of downfield shift of the 10-methyl resonance as compared with those of (**3** and **4**)]; ^{13}C n.m.r. (upfield shift of C-1 and C-4 signals relative to (**4**), characteristic of α-epoxide stereochemistry[16]); and subsequent *trans* diaxial opening by lithium aluminium deuteride to give the labelled triol (**6**) in high yield.[17]

Jones' oxidation of (**6**) then gave the 3,17-dione (**7**) without loss of label. However, dehydration of the latter by any of the routine procedures (thionyl chloride–pyridine,[1] toluene-*p*-sulphonic acid,[18] or calcium chloride), gave androst-4-ene-3,17-dione in high yield, but devoid of deuterium! The use of some mild dehydrating reagents (5 Å molecular sieves[19] or iodine[20]) gave a similar result; others (hexamethylphosphoric triamide[21] or boron trifluoride–ether[22]) gave complex mixtures of products or [dicyclohexylcarbodi-imide–copper(I) chloride[23]] only recovered starting material. Dehydration of the dioxo alcohol (**7**) with minimal deuterium loss was achieved by using 1 equiv. of thionyl chloride and 2 equiv. of collidine in tetrahydrofuran (THF), although the product (**8**) did show some loss of label with respect to (**7**) (83 *vs.* 96%).



Scheme 1. *Reagents and conditions:* i, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C; ii, PPh_3, CCl_4, reflux; iii, $LiEt_3BH$, THF, 0 °C; iv, LiBr, Li_2CO_3, DMF, reflux

We were unable to establish directly the stereochemical integrity of the deuterium label in (**7**) by ^{2}H n.m.r., the signals from both 2β- and 2α-isomers, (**7**) and (**13**) respectively, being superimposable at the highest field available to us (76.8 MHz for ^{2}H), but on the basis of stereospecific and regiospecific epoxide opening by lithium aluminium hydride, and the lack of any subsequent transformations involving labelled species,[24] we assume that the label of (**7**) is located cleanly at C-2β. However, high resolution deuterium n.m.r. analysis of the dehydration product (**8**) showed two signals at δ 2.34 and 2.40 in the ratio

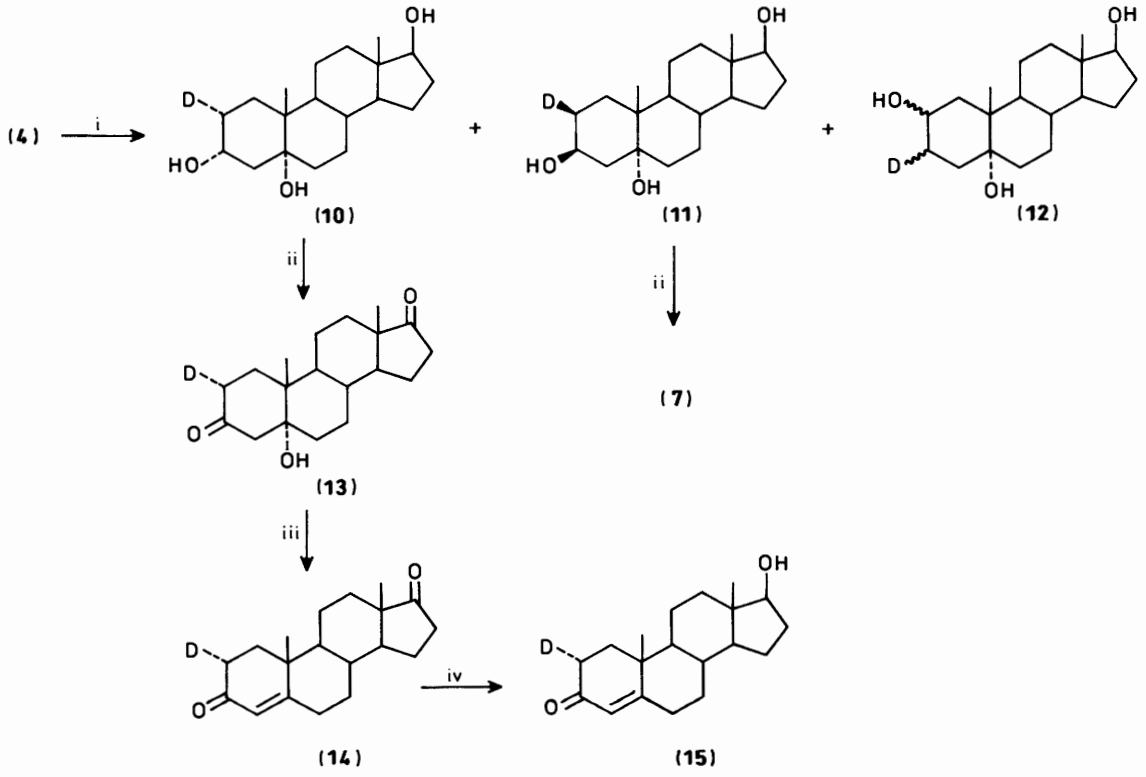


Scheme 2. *Reagents and conditions:* i, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 °C; ii, $LiAlD_4$, THF, 0 °C; iii, Jones reagent, 0 °C; iv, $SOCl_2$, collidine, THF, 0 °C; v, DIBAL-H, 0 °C; Me_2CO, Pr^iOH, 20 °C

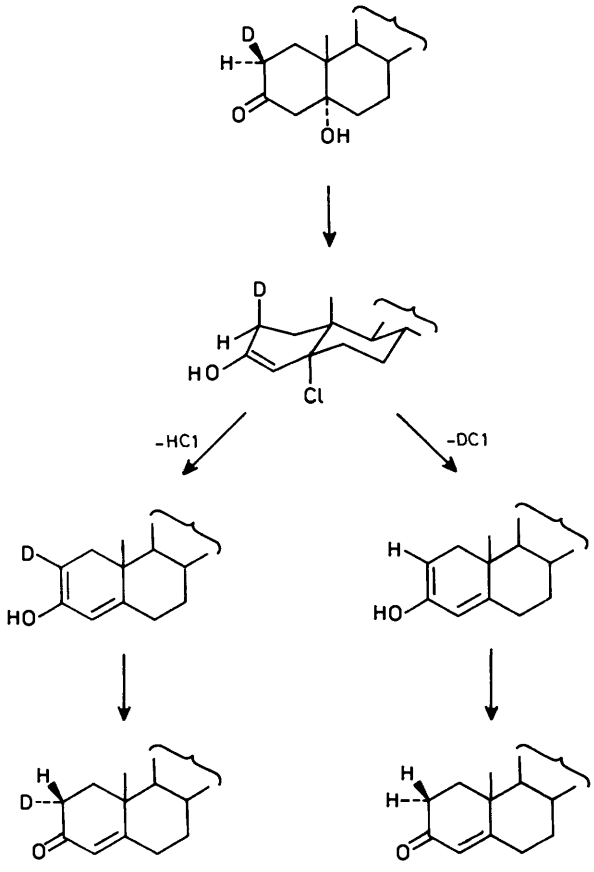
8:92. The latter is assigned to the β-deuterium, and the former to the α-labelled isomer, by analogy with the assignments for ^3H-labelled steroids[25] and by comparison with the spectrum of the α-labelled isomer (**15**) (see later). Both the loss of label and the extent of epimerization at C-2 were increased when the reaction was performed at a higher temperature (see Experimental section). Control experiments (see Experimental section) confirmed that the deuterium label of (**7**) is not lost or epimerized on exposure to collidine or collidine hydrochloride in THF (in the absence of thionyl chloride), and that both β- and α-labelled androstenediones neither lose nor epimerize label upon resubjection to the conditions used for dehydration.

The reason for this partial loss of label under our dehydration conditions is not clear, but we suggest that, by analogy with the well known dehydrohalogenation of 2-halogeno-3-oxo steroids to give Δ^4-3-ketones, which proceeds by conjugate elimination from the Δ^3-enolate,[26,27] a minor pathway for the dehydration of (**7**) may involve conjugate loss of HCl from the intermediate 5α-choro-Δ^3-enol in the conformation shown in Scheme 4. *anti*-Conjugate elimination would be preferred on stereoelectronic grounds in this case as it involves an all axial transition state,[28] as shown in Scheme 4. Such elimination would involve loss of the 2β-deuterium label, whereas the epimerization of label observed during this step may be attributable to *syn*-conjugate elimination involving loss of the 2α-hydrogen, with subsequent reprotonation of the intermediate 2,4-dienol from the preferred β-(axial) direction.[14,28] In support of this it should be noted that base-catalysed elimination of simple β-hydroxy ketones involves rate-determining enolate formation,[29,30] and that allylic rearrangements during solvolysis[31] and elimination[32] of steroidal halides are well known, in some cases[26,27,32,33] involving enolic intermediates.

Conversion of labelled androst-4-enedione into testosterone was then accomplished in high yield and without loss or epimerization of label, using the one-step procedure of Eder.[34]



Scheme 3. *Regents and conditions:* i, $LiAlD_4$, BF_3, THF, 0 °C; ii, Jones reagent, 0 °C; iii, $SOCl_2$, collidine, THF, 0 °C; iv, DIBAL-H (di-isobutylaluminium hydride), 0 °C; Me_2CO, Pr^iOH, 20 °C



Scheme 4.

The 2α-labelled compounds (**14**) and (**15**) were also prepared from the Δ^2-5α,17β-diol (**4**) the key step being hydroboration–oxidation of (**4**) with labelled diborane, prepared *in situ* from lithium aluminium deuteride and boron trifluoride–ether (Scheme 3). *cis*-Addition of the reagent from the α-face gave the 3α-alcohol (**10**) with label at C-2α.[35] This is the preferred mode of hydroboration of 5-unsubstituted Δ^2-steroids,[6,36] but in the present case was accompanied by some addition from the β-side leading to the 2β-labelled triol (**11**), and a mixture of 2α,5α,17β- and 2β,5α,17β-triols (**12**). The latter was not investigated further, but the 2β-labelled triol (**11**) was converted by oxidation into the labelled hydroxy dione (**7**), thus forming an alternative source of material for the later steps of Scheme 2.

Conversion of the 2α-labelled triol (**10**) into the labelled Δ^4-3-oxo steroids (**14**) and (**15**) proceeded as already outlined. The final products were of high deuterium content (80%), and by ^{2}H n.m.r. were composed of 85—87% α-labelled material, the balance of the label being at the 2β-position. In view of the known stereospecificity of the hydroboration–oxidation process,[35] it is assumed that this epimerization occurs during dehydration of (**13**) by a minor pathway involving *anti*-1,4-elimination followed by reprotonation from the α-face; although the latter is not the preferred direction of proton addition, the conformational mobility of ring *A* of Δ^4-3-oxo steroids is such that the stereoelectronic preference for β-addition at C-2 of a 2,4-dienol is not insurmountable.[37] In any event, β-protonation would lead to retention of the stereochemistry of label at C-2α. Loss of label during dehydration of (**13**) is not observed, involving as it would both an unfavourable equatorial/axial transition state, plus a counterproductive kinetic isotope effect. For the β-labelled isomer (**7**), the kinetic isotope effect is counteracted by the stereoelectronic preference for axial deuterium loss; in the case of the α-isomer, these effects are co-operative in suppression of deuterium loss.

The readily available 5α-androst-2-ene-5,17β-diol (**4**) can therefore be used as a common intermediate in the preparation of both 2α- and 2β-labelled 3-oxoandrost-4-enes with high regio- and stereo-specificity of label. In principle, the synthetic transformations described here are also applicable to steroids of the pregnane and cholestane series.

Experimental

M.p.s were determined with a Gallenkamp apparatus. I.r. spectra were recorded with an Analect 6260 FX FTIR instrument. ^{1}H N.m.r. spectra were recorded at 200 MHz and ^{13}C n.m.r. spectra at 50.3 MHz, with a Bruker AC200 spectrometer ($CDCl_3$ as solvent and Me_4Si as internal standard). ^{2}H N.m.r. spectra were recorded at 76.8 MHz with a Bruker AM500 instrument at McMaster University, Hamilton, Ontario ($CHCl_3$ as solvent, and referenced internally to natural abundance $CDCl_3$). Mass spectra were obtained with an A.E.I. MS30/Kratos DS55 system. Isotopic abundances were calculated from accumulated data for the molecular ion or $M - H_2O$ region following the appropriate corrections for natural abundances of ^{13}C. Values are accurate to ±2.5%. T.l.c. was performed on Merck silica gel 60F-254 and flash column chromatography on Merck 9385 silica gel (230–400 mesh). Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium and benzophenone. Dimethylformamide (DMF) was distilled from calcium hydride prior to use, and CCl_4 was distilled from phosphorus pentaoxide.

3α-*Chloro*-5α-*androstane*-5,17β-*diol* (**3**).—A solution of the epoxide (**2**)[15] (20 g) in THF (200 ml) was added dropwise to a solution of lithium triethylborohydride (150 ml; 1M) in THF at 0 °C, and the mixture was stirred at 0 °C for 2 h. The excess of reagent was then decomposed by careful addition of water (15 ml), followed by sequential addition of aqueous NaOH (90 ml; 3M) and hydrogen peroxide (30%; 90 ml—**CAUTION**!), while the mixture was maintained at 0 °C. The resulting solution was stirred for 1 h at room temperature, then evaporated under reduced pressure. The residue was dissolved in ethyl acetate (500 ml) and the solution washed with dilute aqueous sulphuric acid (25%; 2 × 250 ml), water (250 ml), aqueous sodium hydrogen carbonate (10%; 250 ml), and finally water (250 ml). The solution was dried and evaporated, and the residue crystallized from acetone–light petroleum (b.p. 40—60 °C) to give 3α-chloro-5α-androstane-5,17β-diol (18.1 g, 89%), m.p. 161—163 °C (lit.,[15] 162—164 °C); ^{1}H n.m.r. data identical with those reported;[15] δ(^{13}C) 11.2 (C-18), 16.2 (C-19), 20.5 (C-11), 23.3 (C-15), 24.8 (C-1), 26.2 (C-7), 29.9 (C-2), 30.5 (C-16), 33.8 (C-6), 34.9 (C-8), 36.8 (C-12), 39.4 (C-10), 40.0 (C-4), 43.1 (C-13), 45.2 (C-9), 50.7 (C-14), 59.0 (C-3), 73.5 (C-5), and 81.8 (C-17).

5α-*Androst*-2-*ene*-5,17β-*diol* (**4**).—A solution of 3α-chloro-5α-androstane-5,17β-diol (18 g) in dry DMF was refluxed with lithium carbonate (36 g) and lithium bromide (36 g) under nitrogen for 30 min. The solution was then cooled, poured into water (500 ml), and extracted with ethyl acetate (500 ml). The extract was washed with water, dried, and evaporated to yield a residue which, on crystallization from acetone–light petroleum (b.p. 40—60 °C), afforded 5α-*androst*-2-*ene*-5,17β-*diol* (13.3 g, 82%), m.p. 172—174 °C (Found: C, 78.5; H, 10.5. $C_{19}H_{30}O_2$ requires C, 78.6; H, 10.4%); δ_H 0.74 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 3.64 (1 H, t, *J* 8 Hz, 17-H), and 5.5—5.7 (2 H, m, 2- and 3-H); δ(^{13}C) 11.1 (C-18), 16.4 (C-19), 20.6 (C-11), 23.4 (C-15), 26.3 (C-7), 30.6 (C-16), 33.3 (C-6), 35.2 (C-8), 35.4 (C-1), 36.8 (C-12), 38.0 (C-4), 38.6 (C-10), 43.0 (C-13), 46.2 (C-9), 50.8 (C-14),

72.1 (C-5), 81.9 (C-17), 123.2 (C-3), and 126.8 (C-2); *m/z* 290 ($M^{+\bullet}$, 0.7%), 272 (68), 257 (11), 236 (100), and 221 (25).

2α,3α-*Epoxy*-5α-*androstane*-5,17β-*diol* (**5**).—A solution of the olefin (**4**) (13 g) in dichloromethane (260 ml) was cooled to 0 °C, and a solution of *m*-chloroperoxybenzoic acid (13 g; 85%) in dichloromethane (260 ml) was added. The combined solutions were stirred at 0 °C for 3 h, and then washed (10% sodium hydrogen sulphite followed by 10% sodium hydrogen carbonate), dried, and evaporated. The residue was crystallized from acetone–light petroleum (b.p. 40—60 °C) to give 2α,3α-*epoxy*-5α-*androstane*-5,17β-*diol* (11.6 g, 85%), m.p. 208—211 °C (Found: C, 74.6; H, 9.8. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.9%); δ_H 0.70 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 3.2—3.4 (2 H, m, 2- and 3-H), and 3.60 (1 H, t, *J* 8 Hz, 17-H); δ(^{13}C) 11.0 (C-18), 17.4 (C-19), 20.3 (C-11), 23.3 (C-15), 25.4 (C-7), 30.4 (C-16), 33.8, 33.9, 33.9 (C-1, C-4, C-6), 35.5 (C-8), 36.6 (C-12), 38.3 (C-10), 42.8 (C-13), 46.1 (C-9), 50.5 (C-14), 52.1 (C-3), 54.0 (C-2), 72.3 (C-5), and 81.7 (C-17); *m/z* 306 ($M^{+\bullet}$, 6%), 288 (23), 273 (17), 236 (91), 235 (50), 229 (24), 218 (22), and 159 (29) [relative to 55 (100)].

2β-*Deuterio*-5α-*androstane*-3α,5,17β-*triol* (**6**).—A solution of 2α,3α-epoxy-5α-androstane-5,17β-diol (11 g) in THF (125 ml) was added dropwise to a suspension of lithium aluminium deuteride (2.5 g) in THF (125 ml) at 0 °C. The mixture was stirred at 20 °C for 6 h and then the excess of reagent was destroyed with ethyl acetate. The residue was removed by filtration and washed with ethyl acetate, and the combined organic solvents were evaporated off. The residue was redissolved in ethyl acetate, and the solution washed (water), dried, and evaporated. Crystallization from acetone–light petroleum (b.p. 40—60 °C) gave 2β-deuterio-5α-androstane-3α,5,17,β-triol (9.3 g, 84%), m.p. 195—197 °C (lit.,[38] m.p. 194.5—196 °C for unlabelled material); δ_H 0.74 (3 H, s, 18-H_3), 0.95 (3 H, s, 19-H_3), 3.64 (1 H, t, 17-H), and 4.07 (1 H, m, 3-H); δ(^{13}C) 11.3 (C-18), 15.9 (C-19), 20.6 (C-11), 23.4 (C-15), 25.2 (C-7), 26.6 (C-1), 28.8 (weak t, C-2), 30.6 (C-16), 34.0 (C-6), 35.0 (C-8), 36.9 (C-12), 39.5 (C-4), 39.8 (C-10), 43.2 (C-13), 45.9 (C-9), 50.9 (C-14), 67.7 (C-3), 75.0 (C-5), and 82.0 (C-17); *m/z* 291 ($M - H_2O$, 51%), 276 (39), 273 (89), 258 (58), 247 (13), 240 (47), 237 (75), and 232 (21) [relative to 55 (100)]; deuterium content, $^2H_1$ 96, $^2H_0$ 4%.

2β-*Deuterio*-5-*hydroxy*-5α-*androstane*-3,17-*dione* (**7**).—Jones reagent (18 ml) was added dropwise to a stirred solution of 2β-deuterio-5α-androstane-3α,5,17β-triol (9 g) in acetone (100 ml) at 0 °C over 15 min. Work-up afforded 2β-deuterio-5-hydroxy-5α-androstanedione (6.9 g, 78%), m.p. 210—216 °C (lit.,[39] 217—222 °C for unlabelled material); δ_H and i.r. data identical with those of authentic unlabelled material;[1] δ(^{13}C) 13.8 (C-18), 15.7 (C-19), 20.8 (C-11), 21.8 (C-15), 25.1 (C-7), 31.6 (C-12), 32.6 (C-6), 34.2 (C-1), 34.5 (C-8), 35.8 (C-16), 37.5 (weak t, C-2), 39.4 (C-10), 45.9 (C-4), 47.8 (C-13), 51.0 (C-14), 51.9 (C-9), 77.4 (C-5), 210.8 (C-3), and 220.8 (C-17); *m/z* 305 ($M^{+\bullet}$, 19), 287 (97), 272 (17), 244 (69), 234 (65), 216 (26), 201 (32), and 187 (24) [relative to 125 (100)]; deuterium content, $^2H_1$ 96, $^2H_0$ 4%. Compound (**7**) can also be prepared from the triol (**11**) by an identical procedure.

2β-*Deuterioandrost*-4-*ene*-3,17-*dione* (**8**).—A solution of 2β-deuterio-5-hydroxy-5α-androstane-3,17-dione (6 g) in THF (120 ml) and collidine (5.2 ml) was cooled to −5 to 0 °C, and thionyl chloride (1.7 ml) was added dropwise. The mixture was stirred at 0 °C for 10 min and then filtered through a short column of silica gel. The column was washed with ethyl acetate, and the combined organic solvents were evaporated off. The residue was chromatographed on silica gel [hexane–ethyl acetate (2:1) as eluant] to give-2β-deuterioandrost-4-ene-3,17-dione (4.3 g, 75%), identified by m.p., t.l.c., and spectral comparison with an authentic sample of unlabelled material; deuterium content, $^2H_1$ 83%, $^2H_0$ 17%; δ_D 2.34 and 2.40 (8:92). A second batch prepared using a 10 min reaction time at 5 °C had $^2H_1$ 65, $^2H_0$ 35%; δ_D 2.33 and 2.40 (15:85).

2β-*Deuterio*-17β-*hydroxyandrost*-4-*en*-3-*one* (**9**).—This was prepared from 2β-deuterioandrost-4-ene-3,17-dione (2 g) by a reported method,[34] in 76% yield. The resulting testosterone, from batch 2 of the androstenedione just described, had $^2H_1$ 62, $^2H_0$ 38%; δ_D 2.32 and 2.40 (14:86).

2α-*Deuterio*-5α-*androstane*-3α,5,17β-*triol* (**10**).—Boron trifluoride–ether complex (12 ml) was added dropwise over 20 min to a mixture of lithium aluminium deuteride (1.75 g) and 5α-androst-2-ene-5,17β-diol (7 g) in THF (140 ml) at 0 °C, and the mixture was stirred under argon at 20 °C for 1 h. The excess of reagent was decomposed with moist ether, and the solution was then evaporated. The residue was extracted with ethyl acetate, and the extract washed (5% sodium hydrogen carbonate followed by water), dried, and evaporated. The residue was redissolved in THF, cooled to 0 °C, and treated with hydrogen peroxide (30%; 45 ml) followed by sodium hydroxide solution (10%; 45 ml). The resulting mixture was stirred at 0 °C for 1 h and then evaporated. The residue was taken up in ethyl acetate and washed successively with aqueous sodium hydrogen sulphite (5%), aqueous sodium hydrogen carbonate (5%), and water, and finally dried and evaporated. Chromatography of the residue (4.2 g) gave, in order of elution, (i) 2α-deuterio-5α-androstane-3α,5,17β-triol (1.4 g, 20%), m.p. 188—190 °C, with spectral data identical with those reported here for the β-labelled isomer (**6**); deuterium content, $^2H_1$ 82, $^2H_0$ 18%; (ii) a mixture (1.1 g) of approximately equal amounts of materials tentatively identified by ^{13}C n.m.r. as the isomeric 2-alcohols (**12**), which could not be separated by routine chromatographic methods and which was therefore not investigated further: and (iii) 2β-deuterio-5α-androstane-3β,5,17-triol (1.7 g, 23%), m.p. 192—194 °C (lit.,[39] 193–196 °C for unlabelled material); δ_H identical with those reported for unlabelled material;[40] deuterium content, $^2H_1$ 65, $^2H_0$ 35%.

2α-*Deuterio*-5-*hydroxy*-5α-*androstane*-3,17-*dione* (**13**).—This was prepared from the triol (**10**) as described for the conversion of the triol (**6**) into the diketone (**7**). Compound (**13**) showed physical and ^{1}H and ^{13}C n.m.r. spectral properties identical with those described here for the β-labelled isomer (**7**); deuterium content, $^2H_1$ 80, $^2H_0$ 20%.

2α-*Deuterioandrost*-4-*ene*-3,17-*dione* (**14**).—Treatment of 2α-deuterio-5-hydroxy-5α-androstane-3,17-dione by the method described for the preparation of (**8**) afforded compound (**14**) in a yield of 78%; deuterium content, $^2H_1$ 81, $^2H_0$ 19%; δ_D 2.33 and 2.41 (85:15).

2α-*Deuterio*-17β-*hydroxyandrost*-4-*en*-3-*one* (**15**).—This was prepared from the dione (**14**) in 75% yield by the method described for the preparation of (**9**); deuterium content, $^2H_1$ 80, $^2H_0$ 20%; δ_D 2.32 and 2.39 (87:13).

Treatment of the Epoxide (**2**) *with Lithium Aluminium Hydride*.[15]—Reaction of 3α-chloro-5,6α-epoxy-5α-androstan-17-one (0.25 g) with lithium aluminium hydride by the reported method[15] resulted in the isolation of (**4**) (0.02 g), and 5α-androstane-5,17β-diol (**16**) (0.19 g, 84%), characterized both as the diol, m.p. 163—165 °C;[40] δ_H 0.73 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), and 3.6 (1 H, t, *J* 8 Hz, 17-H); δ(^{13}C) 11.2 (C-18), 15.8 (C-19), 20.5, 20.6, and 20.7 (C-2, -3, and -11), 23.3 (C-15), 25.1 (C-7),

30.6 (C-16), 31.7 (C-1), 34.3 and 34.7 (C-4 and -6), 34.8 (C-8), 36.0 (C-12), 37.4 (C-10), 43.1 (C-13), 46.3 (C-9), 50.7 (C-14), 73.2 (C-5), and 81.7 (C-17); *m/z* 292 ($M^{+\bullet}$, 2%), 274 (96), 259 (20), 256 (40), and 241 (53) [relative to 55 (100)]; and as the 17-acetate.[41]

The use of 2 equiv. of lithium aluminium hydride led to a complex mixture of products (t.l.c. analysis) which was not characterized further. Reaction with 3 equiv. of lithium triethylborohydride for 16 h resulted in the formation of (**16**) as the major product.

Treatment of 2β-*Deuterioandrost*-4-*ene*-3,17-*dione* (**8**) *and* 2α-*Deuterioandrost*-4-*ene*-3,17-*dione* (**14**) *with Thionyl Chloride–Collidine.*—When either of these compounds was resubjected to the procedure for dehydration of the 5α-alcohols (**7**) and (**13**), the starting materials were re-isolated in yields exceeding 80%. Analysis by mass spectrometry and ^2H n.m.r. indicated the following properties: (**8**), deuterium content, $^2H_1$ 64, $^2H_0$ 36% from $^2H_1$ 65, $^2H_0$ 35%; δ_D 2.33 and 2.40 (16:84); (**14**), deuterium content, $^2H_1$ 82, $^2H_0$ 18% from $^1H_1$ 81, $^2H_0$ 19%; δ_D 2.32 and 2.40 (83:17).

Treatment of 2β-*Deuterio*-5-*hydroxy*-5α-*androstane*-3,17-*dione* (**7**) *with Collidine–THF.*—Subjection of (**7**) to the procedure for conversion of the alcohols (**7**) and (**13**) into the corresponding Δ^4-3-ketones, but with omission of thionyl chloride, led to the recovery of unchanged (**7**) (88%); deuterium content, $^2H_1$ 98, $^2H_0$ 2% from $^2H_1$ 96, $^2H_0$ 4%.

Treatment of 2β-*Deuterio*-5-*hydroxy*-5α-*androstane*-3,17-*dione* (**7**) *with Collidine Hydrochloride–THF.*—Treatment of (**7**) in THF with 2 equiv. of collidine hydrochloride under the conditions used for the dehydration of (**7**) and (**13**), but omitting thionyl chloride, resulted in the recovery of (**7**) with $^2H_1$ 98, $^2H_0$ 2% from $^2H_1$ 96, $^2H_0$ 4%.

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