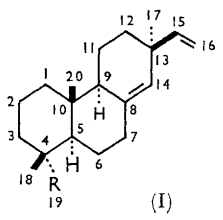
The Synthesis of (−)-Sandaracopimaradiene from Androstane Derivatives

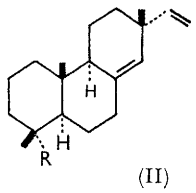
By P. Johnston, R. C. Sheppard, C. E. Stehr, and S. Turner

The conversion of testosterone and 3β-hydroxyandrost-5-en-17-one into the diterpene sandaracopimaradiene is described. 4,4-Dimethyl-5α-androst-14-ene and its 17β-hydroxy-derivative were prepared by acid-catalysed isomerisation of the 5,7-dienes, hydrogenation, and further isomerisation of the resulting 8(14)-olefins. Cleavage of ring D by reduction of the ozonide and selective oxidation of the seco-diol or triol with manganese dioxide yielded ring-D homo-lactones, which were converted by way of the β-keto-lactone into (−)-sandaracopimaradiene.

In recent years the stereochemistry of the isomeric pimaric acids has been the subject of much investigation.[1] By 1960 there was general agreement that pimaric acid was most probably represented by the stereoformula (I; R = CO_2H), and that sandaracopimaric acid was the 13-epimer (II; R = CO_2H).* Considerable support for these structures was subsequently provided by the synthetic studies of Ireland and Schiess,[2] who synthesised the racemates of pimaradiene (I; R = Me) and sandaracopimaradiene (II; R = Me) and established their structural identity (apart from the question of optical activity) with the hydrocarbons derived from the respective resin acids. Although this work proved conclusively the identical stereochemistry of pimaric and sandaracopimaric acids at C-5, C-9, and C-10, the vinyl substituent at C-13 was introduced in a non-stereospecific manner, and the evidence adduced for the assignment of relative configuration at this asymmetric centre in the two products was less compelling. The synthetic studies of Milne and Smith [3] in the dihydro series have been similarly criticised.[4]



(I)



(II)

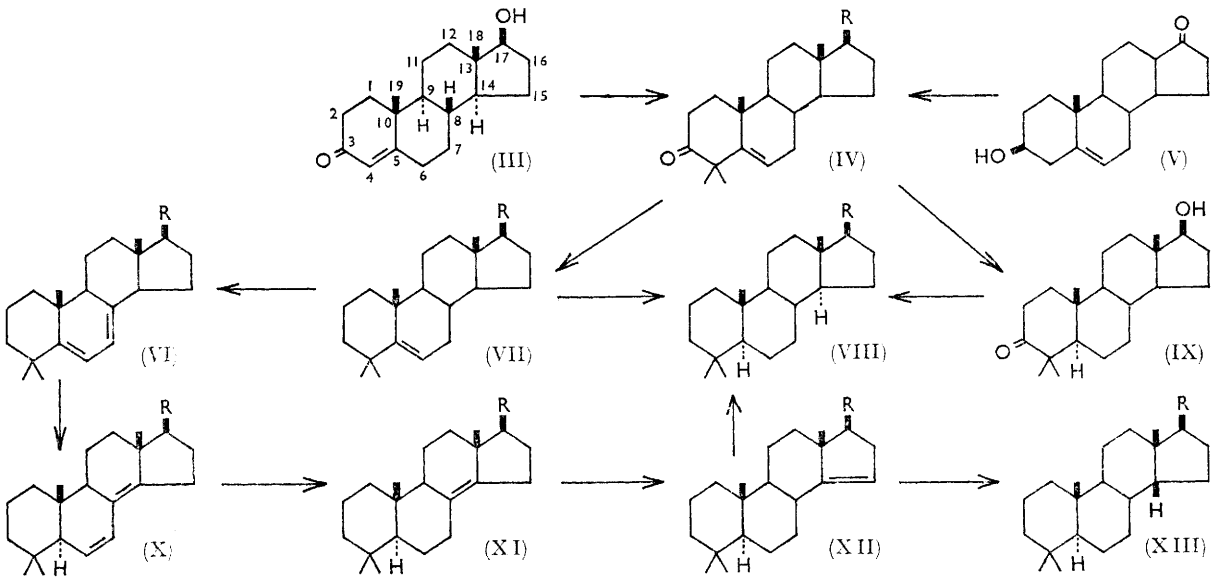
Our own interest in these compounds arose when the structure (II; R = Me) was suggested for the diterpene rimuene,[5,6] and for which a correlation with the tetracyclic diterpenes of the phyllocladene type had been claimed.[6] Although the structure of rimuene itself was subsequently modified,[7] structure (II; R = Me) was later established for the natural diterpene sandaracopimaradiene isolated from *Xylia dolabriformis*.[8] We and others [4,9] realised that sandaracopimaradiene and related compounds, having the same absolute stereochemistry throughout as steroids of the 5α series, should be accessible by synthesis from readily available steroid derivatives. Furthermore, the photochemical epimerisation of androsterone [10] into the 13-epimer, lumiandrosterone, opened also a possible route to compounds of the pimaradiene type. We describe here the conversion of testosterone and 3β-hydroxyandrost-5-en-17-one into sandaracopimaradiene by methods ensuring the stereochemical integrity of the product. This synthetic work confirms the assigned structure and absolute stereochemistry of the natural hydrocarbon, and hence provides further support for the structures of the related resin acids. While this work was in progress, Bose and Harrison [4] and Fetizon and Golfier [9] described briefly the realisation of the same objective but by different routes.

Testosterone (III) was converted by methyl iodide and potassium t-butoxide to the known 4,4-dimethyl derivative (IV; R = OH),[11] which in turn was reduced by the Wolff–Kishner or Barton's modification [12] of the Huang-Minlon procedures to the deoxo-compound (VII; R = OH). Catalytic hydrogenation of (VII; R = OH) then yielded the saturated alcohol (VIII; R = OH), the 5α stereochemistry of which is proved by its alternative synthesis from (IX) of established configuration.[13] Initially, we had hoped to utilise the 17-oxygen function of (VIII; R = OH) as the point of attack for the modification of ring D, and indeed Bose and Harrison [4] have since described briefly the preparation of impure sandaracopimaradiene from this compound. However, in our hands the yields obtained in several attempts to modify ring D directly were impracticably low, and work on this route was discontinued in favour of one involving migration of the ethylenic bond in the androst-5-ene derivative (VII; R = OH) from ring B to ring D. A similar route from the deoxy-compound (VII; R = H) was also adopted independently by Fetizon and Golfier,[9] although their subsequent steps leading to sandaracopimaradiene differed from those reported here.

* Tricyclic diterpene numbering as in ref. 1. Steroid numbering is retained for all tetracyclic (including D-homo) derivatives, and for tricyclic 14,15-seco-derivatives in which all the carbon atoms are retained.

[1] For a recent Review, see R. McCrindle and K. H. Overton, *Adv. Org. Chem.*, 1965, **5**, 47.
[2] R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, 1963, **28**, 6.
[3] G. W. A. Milne and H. Smith, *Chem. and Ind.*, 1961, 1307.
[4] A. K. Bose and S. Harrison, *Chem. and Ind.*, 1963, 254.
[5] L. H. Briggs, B. F. Cain, and J. K. Wilmshurst, *Chem. and Ind.*, 1958, 599.
[6] L. H. Briggs, B. F. Cain, B. R. Davis, and J. K. Wilmshurst, *Tetrahedron Letters*, 1959, No. 8, 13.
[7] J. D. Connolly, R. McGrindle, R. D. H. Murray, and K. H. Overton, *J. Chem. Soc.* (*C*), 1966, 273.
[8] R. A. Laidlaw and J. W. W. Morgan, *J. Chem. Soc.*, 1963, 644.
[9] M. Fetizon and M. Golfier, *Bull. Soc. chim. France*, 1963, 167.
[10] A. Butenandt and L. Poschmann, *Ber.*, 1944, **77**, 394.
[11] H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, 1957, **22**, 602.
[12] D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 1955, 2056.
[13] C. Djerassi, O. Halpern, V. Halpern, and B. Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

17β-Hydroxy-4,4-dimethylandrost-5-ene (VII; R = OH) was acetylated and converted by allylic bromination and dehydrobromination into the 5,7-diene (VI; R = OAc). It was advantageous to use a larger excess of *N*-bromosuccinimide and a longer irradiation time than originally described for the 4,4-dimethylcholesterol series,[14] since any unchanged olefin (VII; R = OAc) was difficult to separate from the diene (VI; R = OAc) or its subsequent transformation products by crystallisation. Treatment of the 5,7-diene (VI; R = OAc) under a variety of acidic conditions which have been reported to yield 7,14- or 8, 14-dienes in analogous cases [15] yielded only oily mixtures from which no pure diene could be isolated. However, when the course of the hydrogen chloride catalysed isomerisation of the diene (VI; R = OAc) was followed by u.v. spectroscopy, an almost instantaneous change to a new diene, $\lambda_{max.}$ 253 mμ, was observed, and this was followed by a slower change to a complex spectrum similar to that of the diene mixture previously obtained. Treatment of the 5,7-diene acetate with anhydrous hydrogen chloride at −50° for only 30 seconds then afforded a single crystalline isomerisation product in over 80% yield, the n.m.r. and u.v. spectra of which established its structure as the 6,8(14)-diene (X; R = OAc). The 5α stereochemistry of (X; R = OAc) rests on firm analogy,[14] and is proved in the sequel. The same product could also be obtained by isomerisation of the 5,7-diene with toluene-*p*-sulphonic acid for a longer reaction period, or, in lower yield, with sulphur dioxide in anhydrous pyridine. The latter reagent is reported to be specific for the formation of 6,8(14)-dienes in the ergosterol series.[16] Catalytic hydrogenation of (X; R = OAc) proceeded rapidly with the uptake of only 1 mol. of hydrogen, and the pure mono-ene (XI; R = OAc) was isolated without difficulty. The expected tetrasubstituted 8(14)-olefin structure was confirmed by molecular rotation and u.v. measurements, and by the n.m.r. spectrum. The latter provided a clear-cut distinction from the alternative Δ^8-olefin structure, 17β-acetoxy-4,4-dimethyl-5α-androst-8-ene, by consideration of the C–18 and C–19 methyl resonances in the light of the extensive data tabulated by Zürcher.[17]



The acid-catalysed isomerisation of 8(14)-olefins to their 14-isomers is well established in the cholesterol and ergosterol series,[18] but other steroidal 8(14)-olefins, *e.g.*, 3β,17β-diacetoxy-5α-androst-8(14)-ene [19] and 3β-acetoxy-5α-pregn-8(14)-en-20-one,[20] have been found to be stable under similar conditions. Both of the latter steroids contain oxygen functions adjacent to ring D, and their inertness to isomerisation by acids may probably be ascribed to this structural feature. Likewise, the 17β-acetoxy-8(14)-olefin (XI; R = OAc) proved to be completely resistant to isomerisation by acids under a variety of conditions, and it was therefore necessary to modify the substituent at C–17 prior to migration of the double bond into ring D.

Preliminary experiments showed that the 17β-acetoxy-androst-8(14)-ene derivative (XI; R = OAc) could be converted by saponification and chromic acid oxidation into the 17-ketone, and thence by Wolff–Kishner reduction to the hydrocarbon (XI; R = H). However, it was more efficient to enter the 17-deoxo series at an earlier stage by oxidation of 17β-hydroxy-4,4-dimethyl-androst-5-en-3-one (IV; R = OH) to the 3,17-dione,

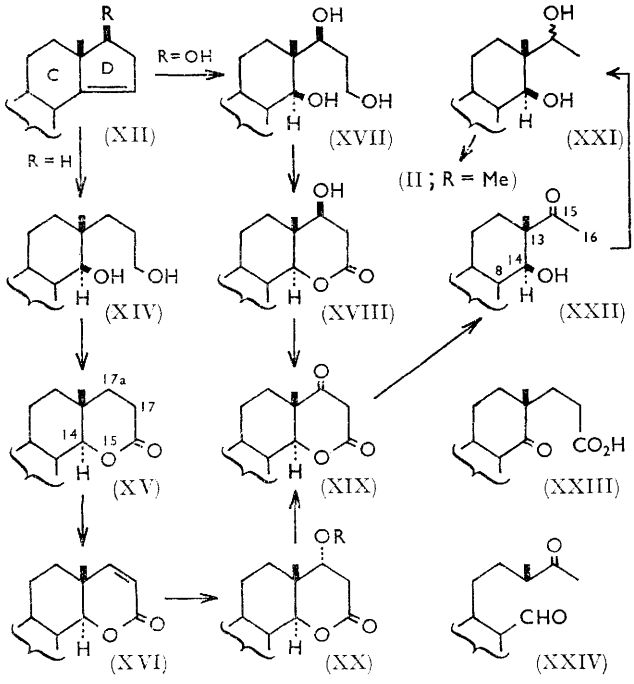
[14] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.
[15] L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, p. 115, and references there cited.
[16] G. D. Laubach, E. C. Schreiber, E. J. Agnello, and K. J. Brunnings, *J. Amer. Chem. Soc.*, 1956, **78**, 4743.
[17] R. F. Zürcher, *Helv. Chim. Acta*, 1963, **46**, 2054.
[18] Ref. 15, pp. 112 and 258, and references there cited.
[19] R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, 1951, **16**, 1891.
[20] O. Mancera, D. H. R. Barton, G. Rosenkranz, and C. Djerassi, *J. Chem. Soc.*, 1952, 1021.

and then to remove both oxygen functions simultaneously by Wolff–Kishner reduction. This series was also readily accessible from 3β-hydroxyandrost-5-en-17-one (V), by way of 3β-hydroxyandrost-5-ene, androst-4-en-3-one, and 4,4-dimethylandrost-5-en-3-one (IV; R = H). Conversion of 4,4-dimethylandrost-5-ene (VII; R = H) into the 5,7-diene (VI; R = H) was effected as in the acetate series, but isomerisation by hydrogen chloride to the 6,8(14)-diene (X; R = H) and further was too rapid for experimental convenience. This isomerisation was therefore effected with catalytic amounts of toluene-*p*-sulphonic acid. Hydrogenation of the diene (X; R = H) afforded the desired 8(14)-olefin (XI; R = H).

As expected by analogy with the cholestenol and ergostenol series,[18] 4,4-dimethyl-5α-androst-8(14)-ene (XI; R = H) was smoothly isomerised to the androst-14-ene derivative (XII; R = H) in 70—75% yield by treatment with hydrogen chloride in chloroform, followed by methanolic ammonia. An improved yield (90%) was obtained when the acid-catalysed isomerisation was carried out in the presence of 10% palladised charcoal catalyst. Although under these conditions the corresponding 17β-acetoxy-compound (XI; R = OAc) was recovered unchanged, the parent alcohol (XI; R = OH) was also isomerised, albeit more slowly, to (XII; R = OH) (75%). The differing behaviours of these three 8(14)-olefins and of the earlier examples cited above towards acidic reagents are interesting, and may be a consequence of a polar effect of the 17β substituent on the direction of protonation of the 8(14)-double bond.

Although the normal 5α,8β,9α stereochemistry of the androst-14-ene derivatives (XII; R = H and OH) was strongly indicated by analogy with other series, we considered it necessary at this stage to prove this stereochemistry conclusively. A simple way of achieving this would be by hydrogenation of (XII; R = H and OH) to the saturated derivatives (VIII; R = H and OH) of established configuration, with the important proviso that hydrogenation took place from the α-face of the molecule. This is the normal mode of hydrogenation of 17β-substituted steroidal 14-enes (lacking the 4,4-dimethyl group),[21] although 17-keto-14-enes are hydrogenated from the β-face.[22] In the event, both the hydrocarbon (XII; R = H) and the alcohol (XII; R = OH) were hydrogenated smoothly over a palladium–charcoal catalyst, affording pure saturated products in yields of 80—90%, but these were clearly different from the 5α,8β,9α,14α-derivatives (VIII; R = H and OH). Our supposition that hydrogenation had taken place from the β-face yielding almost exclusively the 14β-epimers (XIII; R = H and OH) was supported by their n.m.r. spectra and confirmed by oxidation of (XIII; R = OH) to the corresponding 17-ketone. The optical rotatory dispersion curve of this ketone showed a positive Cotton effect of reduced amplitude and at lower wavelength than did that of the 14α-17-ketone prepared from (VIII; R = OH), and similar differences have been found previously for similar pairs of 17-keto-steroids epimeric at C-14.[23] Huang-Minlon reduction of the 14β-17-ketone yielded (XIII; R = H), identical with the hydrogenation product of (XII; R = H), and confirming that β-hydrogenation had also taken place in the hydrocarbon series.

The residues from the crystallisation of the saturated alcohol (XIII; R = OH) contained a second component identical in chromatographic mobility with the 14α-isomer (VIII; R = OH). Attempts were made to improve the yield of this second component in the hydrogenation by increasing the bulk of the 17β-substituent in the 14-olefin, but benzoylation or conversion



into the tetrahydropyranyl ether served only to diminish the rate of hydrogenation. The steric course of hydrogenation reactions at ring junctions is known to be influenced by the acidity of the solvent;[24] when the hydrogenation of (XII; R = OH) was conducted in methanol containing one drop of hydrochloric acid, the rate of reaction was enormously accelerated (complete in less than 1 minute) and the yield of crystalline 14β-product (XIII; R = OH) was reduced to 54%. The residues from the crystallisation of (XIII; R = OH) were enriched in the second component, which was isolated after acetylation and shown to be identical with

[21] *Inter al.*, F. Schenck, K. Buchholz, and O. Wiese, *Ber.*, 1936, **69**, 2696; M. Steiger and T. Reichstein, *Helv. Chim. Acta*, 1938, **21**, 828; F. Hunziker and T. Reichstein, *ibid.*, 1945, **28**, 1472; A. Lardon and T. Reichstein, *Pharm. Acta Helv.*, 1952, **27**, 287.

[22] A. F. St. Andre, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Amer. Chem. Soc.*, 1952, **74**, 5506.

[23] C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, 1956, **78**, 6362; F. Sondheimer, S. Burstein, and R. Mechoulam, *ibid.*, 1960, **82**, 3209.

[24] *E.g.*, ref. 15, pp. 256 and 272.

the authentic 5α,8β,9α,14α-derivative (VIII; R = OAc). These transformations therefore provided experimental support for the expected 5α,8β,9α stereochemistry of the 14-olefins (XII; R = H and OH).

With the development of serviceable routes to the two Δ^{14}-olefins (XII; R = H and OH), each possessing the correct stereochemistry throughout, we turned our attention to the cleavage of ring D and the elimination of C-15 to yield the sandaracopimarane skeleton. In our hands the most satisfactory method for the cleavage of the hydrocarbon (XII; R = H) was by ozonolysis. The olefin formed a crystalline ozonide in quantitative yield, and this was decomposed by lithium aluminium hydride reduction, yielding a mixture of diols containing a preponderance of the isomer with the 14β-oriented hydroxyl group (XIV) (ratio 14β : 14α approximately 3 : 1 by t.l.c.). The β-isomer, which has the appropriate stereochemistry at C-14 for the envisaged introduction of the 8(14)-double bond of sandaracopimaradiene by a *cis* elimination process, was readily isolated from the mixture by direct trituration with methanol. Additional material could be isolated by preparative t.l.c. of the diol mixture, or by chromatography of the derived acetates, since it was observed that, whereas the 14β-diol (XIV) readily formed a diacetate, the 14α-epimer (axial hydroxyl group) formed largely a monoacetate under the same mild conditions. Some pure 14α-diol was isolated and characterised, but mixtures enriched in the α-diol could be more profitably oxidised to the keto-acid (XXIII) (see below). The relative stereochemistry of (XIV) and its 14-epimer was deduced from the coupling constants (J = 10 and <2 c./sec.) of the respective 14α and 14β protons in the diacetates.[25] These are in agreement with diaxial (14α,8β) and equatorial-axial (14β,8β) arrangements of the adjacent hydrogen atoms, and the expected chemical-shift differences between the axial 14α and equatorial 14β protons were also observed. These stereochemical assignments were subsequently confirmed by optical rotatory dispersion measurements (see below).

With the establishment of the desired stereochemistry of the secondary hydroxyl group in (XIV), it was desirable to retain this orientation while the primary hydroxyl group was suitably modified to allow elimination of its attached carbon atom. This was achieved by mild oxidation of the diol with the chromium trioxide–pyridine reagent, which yielded the δ-lactone (XV). Formation of this lactone presumably proceeds by selective oxidation of the primary hydroxyl group to an aldehyde, followed by rapid ring-closure to the hemiacetal and further oxidation. Other reagents tried at this time, *e.g.*, chromium trioxide in acetic acid and in sulphuric acid, were less specific and yielded non-crystalline neutral material, probably largely the keto-aldehyde, together with varying amounts of keto-acid (XXIII). The latter, on reduction with sodium borohydride, yielded further quantities of the lactone (XV), and all other over-oxidation products could be reduced with lithium aluminium hydride to the mixture of diols enriched in (XIV). The pure 14α-diol was also oxidised by chromium trioxide–pyridine, and yielded the epimeric 14α-lactone. Both lactones had n.m.r. spectra consistent with the assigned structures and stereochemistry, and both gave o.r.d. curves in full agreement with the recently proposed sector rule for steroidal lactones.[26]

At this stage the double bond which we hoped would form part of the vinyl side-chain of sandaracopimaradiene was introduced. Dehydrogenation of the lactone (XV) by dichlorodicyano-*p*-benzoquinone[27] was slow, but after 8 days in boiling dioxan containing acetic acid the dehydro-lactone (XVI) was produced in 80% yield. However, this double bond was short-lived in the synthetic scheme, for attempted alkaline hydrolysis of (XVI) and isomerisation of the double bond to the *trans* configuration yielded, after acidification, a saturated β-hydroxy-lactone (XX; R = H). Similarly, treatment of the dehydro-lactone with methanolic potassium hydroxide yielded the corresponding methoxy-derivative (XX; R = Me). These addition reactions appeared to be stereospecific, yielding only the 17aα-oriented products whose configurations were deduced from n.m.r. spectra, and from the independent synthesis of the 17aβ-hydroxy-lactone (XVIII) described below. Confirmation of structure was provided by oxidation of (XX; R = H) to the keto-lactone (XIX), which showed the bathochromic shift in ultraviolet spectrum on passing from neutral to alkaline solution expected for a β-dicarbonyl compound.

The keto-lactone (XIX) was accessible in fewer steps from the 17β-hydroxyandrost-14-ene derivative (XII; R = OH). Ozonolysis of the derived acetate and decomposition of the ozonide with lithium aluminium hydride yielded the 14β,15,17β-triol (XVII) (60%) together with the 14α-epimer (21%). The latter was readily separated by virtue of its extreme insolubility in organic solvents. The assignment of stereochemistry was made on the basis of the n.m.r. spectra of the triacetates (at 100 Mc./sec.) and was confirmed by correlation with the diol series already described. Chromium trioxide in pyridine was ineffective for the preferential oxidation of the primary hydroxyl group in the triol (XVII), and yielded a complex mixture of products from which no pure hydroxylactone could be obtained. We considered, however, that greater selectivity for attack at the relatively unhindered primary hydroxyl group might be achieved in a heterogeneous reaction using a solid oxidant, and therefore investigated the use of manganese dioxide for this purpose. In the past this reagent has generally been considered to be specific for the oxidation of allylic or benzylic hydroxyl groups, but oxidation of hydroxyl groups in saturated environ-

[25] N. S. Bhacca and D. H. Williams, "Applications of N.M.R. Spectroscopy in Organic Chemistry; Illustrations from the Steroid Field," Holden-Day, San Francisco, 1964, p. 80.

[26] J. P. Jennings, W. Klyne, and P. M. Scopes, *Proc. Chem. Soc.*, 1964, 412.

[27] B. Berkoz, L. Cuéllar, R. Grezemkovsky, N. V. Avila, and A. D. Cross, *Proc. Chem. Soc.*, 1964, 215.

ments has recently been shown to occur,[28] although much more slowly. In trial experiments using the diol (XIV), manganese dioxide proved in fact to be far superior to the chromium trioxide–pyridine reagent previously used for the selective oxidation of the primary hydroxyl group, and after treatment for 20 hours at room temperature the lactone (XV) was obtained in 90% yield. In the triol series, however, similar treatment of (XVII) gave only a low yield of impure 17aβ-hydroxylactone (XVIII), and most of the material was irreversibly adsorbed on the solid oxidant. This difficulty was overcome when the reaction period was shortened to $3\frac{1}{2}$ hours, but the major product was then the corresponding hemiacetal rather than the expected lactone (XVIII). Both the hemiacetal and the lactone (XVIII) could be isolated in individual experiments under appropriate conditions,* but for our purposes it was more efficient to oxidise further with chromic acid the crude product obtained from brief treatment of the triol (XVII) with manganese dioxide; in this way the keto-lactone (XIX) was obtained directly in 60% yield from (XVII).

When the keto-lactone (XIX) had been obtained it was a relatively simple matter to complete the synthesis of sandaracopimaradiene. Treatment of (XIX) with boiling ethanolic hydrogen chloride yielded 14β-hydroxy-15-oxosandaracopimarane (XXII). It might be argued that, insofar as (XXII) is a β-hydroxy-ketone, equilibration of stereochemistry at C-8, C-13, and C-14 through the reverse aldol product (XXIV) might have taken place during the treatment with ethanolic hydrogen chloride. However, it could easily be shown that the aldehyde (XXIV) was not present to any appreciable extent in the reaction mixture by carrying out the conversion of keto-lactone (XIX) into hydroxy-ketone (XXII) with deuterium chloride in deuteroethanolic solution. The product was shown by its mass spectrum to have incorporated only three atoms of deuterium in stable positions, and the fragmentation pattern showed clearly that all three of these were located in the acetyl substituent of (XXII). If the keto-aldehyde (XXIV) had been formed during the course of the reaction, some degree of incorporation of deuterium at C-8 by enolisation of the aldehyde group under the strongly acidic conditions would be expected. Reduction of the hydroxy-ketone (XXII) with sodium borohydride yielded the diol (XXI) as a mixture of epimers at C-15, which without separation were benzoylated, and the dibenzoate was pyrolysed at 420°. There was obtained a 50% yield of nearly pure (—)-sandaracopimaradiene, which after one crystallisation had m. p. 38—39°, mixed m. p. with natural (—)-sandaracopimaradiene [8] (m. p. 39·5—40°) 39—39·5°, $[\alpha]_D$ —13° (lit.,[8] —12·4°). The infrared spectra, mass spectra, retention times on vapour phase chromatography, and mobilities on thin-layer chromatography of the natural and synthetic diterpenes were also identical.

EXPERIMENTAL

Specific rotations were measured in chloroform solution at room temperature (21—25°). Ultraviolet spectra were determined for solutions in 95% ethanol, and n.m.r. spectra for solutions in deuterochloroform at 60 Mc./sec. unless stated otherwise. "Saponification in the usual manner" was by treatment of benzene solutions with an excess of M-methanolic potassium hydroxide for 18 hr. at room temperature.

4,4-Dimethylandrost-5-en-17β-ol (VII; R = OH).—Sodium (9·24 g.) was dissolved in warm diethylene glycol (450 ml.; redistilled), and 17β-hydroxy-4,4-dimethylandrost-5-en-3-one [11] (48 g.) and anhydrous hydrazine (90 ml.) were added. The solution was heated under reflux for 4 hr., the condenser removed, and the reaction mixture boiled vigorously until the temperature reached 210°. The solution was heated under reflux for a further 24 hr., poured into cold water (1 l.), and the precipitated product collected. Crystallisation from aqueous methanol gave *4,4-dimethylandrost-5-en-17β-ol* (41·4 g., 86%), m. p. 143—145°, $[\alpha]_D$ —90° (*c* 2·0) (Found: C, 83·3; H, 11·5. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%). The *acetate* crystallised from methanol, m. p. 165—166·5°, $[\alpha]_D$ —94° (*c* 2·0) (Found: C, 80·2; H, 10·7. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·5%).

4,4-Dimethyl-5α-androstan-17β-ol (VIII; R = OH).—(*a*) 4,4-Dimethylandrost-5-en-17β-ol (3·8 g.) in ethanol (50 ml.) was hydrogenated over 5% palladium–charcoal (300 mg.) at 100°/5 atm. for 2 days. After removal of the catalyst, concentration of the solution, and addition of water, 4,4-dimethyl-5α-androstan-17β-ol (3·6 g. 94%) separated. Crystallisation from aqueous methanol and sublimation at 110°/10^{-4} mm. gave m. p. 156—157·5°, $[\alpha]_D$ —6° (*c* 2·0) (Found: C, 82·75; H, 12·3. Calc. for $C_{21}H_{36}O$: C, 82·8; H, 11·9%) (lit.,[4] m. p. 143—146°). The *acetate* crystallised from methanol, m. p. 150·5—151·5°, $[\alpha]_D$ —6° (*c* 2·0) (Found: C, 79·8; H, 11·1. $C_{23}H_{38}O_2$ requires C, 79·7; H, 11·05%).

(*b*) 17β-Hydroxy-4,4-dimethyl-5α-androstan-3-one [13] (950 mg.) in diethylene glycol (30 ml.) was treated with potassium hydroxide (2 g.) and hydrazine hydrate (1 ml.) at 100° for 30 min. The solution was then heated under reflux for 30 min, the condenser removed, and heating continued until the temperature reached 200°. Heating under reflux was continued for 2 hr. further, and the solution then poured into water and extracted with ether. Isolation in the usual manner yielded 4,4-dimethyl-5α-androstan-17β-ol (650 mg., 70%) identical with that previously prepared.

4,4-Dimethylandrosta-5,7-dien-17β-yl Acetate (VI; R = OAc) *and* -17β-ol (VI; R = OH).—4,4-Dimethylandrost-5-en-17β-yl acetate (4·5 g.) in carbon tetrachloride (120 ml.; AnalaR) was treated with powdered N-bromosuccinimide (4·0 g.). The reaction vessel was half immersed in an oil-bath at 90—100° and illuminated from above with a 125-w Hanovia ultraviolet lamp. The lamp was switched off 30 sec. after the reaction started (appearance of succinimide), and $1\frac{1}{4}$ min. later the reaction mixture was cooled in ice for 5 min. with stirring. The solution was filtered into collidine (20 ml.), the carbon tetrachloride removed *in vacuo*, and the residue heated on a steam-bath for $1\frac{1}{2}$ hr. Dilution with light petroleum (b. p. 60—80°) (200 ml.) precipitated collidine hydrobromide which was filtered off, and the filtrate was washed with 2N-hydrochloric acid (3 × 60 ml.), N-sodium hydrogen carbonate solution (25 ml.), and water. After drying ($MgSO_4$), the solvent was removed *in vacuo* and the residual solid crystallised from ether–methanol to give

* These and related reactions are under further investigation and will be described in a future publication.

[28] I. T. Harrison, *Proc. Chem. Soc.*, 1964, 110.

the *diene acetate* (2·22 g., 50%), m. p. 159—160°, $[\alpha]_D$ −260° (*c* 0·3), $\lambda_{max.}$ 273 and 282 mμ (ε 10,200 and 10,000), with inflections at 262 and 292 mμ (Found: C, 80·6; H, 10·2. $C_{23}H_{34}O_2$ requires C, 80·65; H, 10·0%). Saponification in the usual manner yielded the corresponding *alcohol* (94%), m. p. 145—146°, $[\alpha]_D$ −265° (*c* 0·2) (Found: C, 83·9; H, 10·95. $C_{21}H_{32}O$ requires C, 83·9; H, 10·8%).

4,4-*Dimethyl*-5α-*androsta*-6,8(14)-*dien*-17β-*yl Acetate* (X; R = OAc) *and* −17β-*ol* (X; R = OH).—(*a*) Dry hydrogen chloride gas was passed through chloroform (5 ml.; AnalaR) for 45 sec., and this solution was added to a solution of 4,4-dimethylandrosta-5,7-dien-17β-yl acetate (500 mg.) in chloroform (15 ml.; AnalaR) maintained at −50°. The mixture was swirled for 30 sec., neutralised with methanolic ammonia (20 ml.), diluted with water (100 ml.), and extracted with ether. The ethereal solution was washed with water, dried ($MgSO_4$), and evaporated, and the residue crystallised from ether–methanol to give the 6,8(14)-*diene acetate* (410 mg., 82%), m. p. 143—145°, $[\alpha]_D$ −100° (*c* 0·3), $\lambda_{max.}$ 253 mμ (ε 22,100) with inflections at 245 and 261 mμ, τ 3·80 (quartet) and 4·32 (broad doublet) p.p.m. (C-6 and C-7 protons) (Found: C, 80·5; H, 10·3. $C_{23}H_{34}O_2$ requires C, 80·65; H 10·0%).

(*b*) 4,4-Dimethylandrosta-5,7-dien-17β-yl acetate (1·98 g.) was added to refluxing benzene (290 ml.) containing toluene-*p*-sulphonic acid (155 mg.). The mixture was heated under reflux for 40 min., washed with 1N-sodium hydrogen carbonate solution (100 ml.), water, and dried ($MgSO_4$). Removal of benzene and crystallisation of the product from ether–methanol gave 4,4-dimethyl-5α-androsta-6,8(14)-dien-17β-yl acetate (1·46 g., 74%) identical with that previously prepared.

(*c*) A mixture of 4,4-dimethylandrost-5,7-dien-17β-yl acetate (80 mg.), benzene (2 ml.), quinol (5 mg.), pyridine (0·1 ml.), and sulphur dioxide (1 ml.) was heated in a sealed tube at 100° for 18 hr. according to the procedure of Laubach *et al.*[16] Concentration of the reaction mixture and crystallisation of the residue from ether–methanol yielded 4,4-dimethyl-5α-androsta-6,8(14)-dien-17β-yl acetate (25 mg., 31%) identical with that previously prepared. Saponification in the usual manner yielded the corresponding *alcohol* (89%), m. p. 176—177°, $[\alpha]_D$ −98° (*c* 0·2) (Found: C, 84·1; H, 11·0. $C_{21}H_{32}O$ requires C, 83·9; H, 10·8%).

4,4-*Dimethyl*-5α-*androst*-8(14)-*en*-17β-*yl acetate* (XI; R = OAc) *and* -17β-*ol* (XI; R = OH).—4,4-Dimethyl-5α-androst-6,8(14)-dien-17β-yl acetate (1·0 g.) in ethyl acetate (70 ml.) was hydrogenated over 10% palladium–charcoal (100 mg.) at atmospheric pressure and room temperature for ½ hr. Removal of catalyst and solvent in the usual manner and crystallisation of the product from ether–methanol yielded 4,4-*dimethyl*-5α-*androst*-8(14)-*en*-17β-*yl acetate* (0·83 g., 83%), m. p. 131—132°, $[\alpha]_D$ −15° (*c* 0·2), ε_{210} 10,550, ε_{215} 8550, ε_{220} 6000; *C*-Me resonances [17] at 45, 50·5, 52·5, and 56 c./sec. from tetramethylsilane (Found: C, 80·05; H, 10·8%). Saponification in the usual manner yielded the corresponding *alcohol* (93%), m. p. 151—152°, $[\alpha]_D$ +10° (*c* 0·2). The analytical sample was prepared by sublimation at 130°/ 0·3 mm. (Found: C, 83·35; H, 11·1%).

4,4-*Dimethylandrost*-5-*ene*-3,17-*dione*.—17β-Hydroxy-4,4-dimethylandrost-5-en-3-one (5 g.) in acetone (400 ml.; AnalaR) was oxidised with 8N-chromic–sulphuric acid solution by the general procedure of Jones and his co-workers.[29] Dilution with water and extraction with ether yielded the crude product which crystallised from aqueous methanol giving the *diketone* (4·47 g., 89%), m. p. 163—164°, $[\alpha]_D$ +48° (*c* 0·1) (Found: C, 80·0; H, 9·6. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%). The dione (3 g.) and hydrazine hydrate (15 ml.) were heated under reflux in diethylene glycol (100 ml.) for 3½ hr. Addition of water (400 ml.) precipitated the crude *dihydrazone* (3·3 g., 100%) which crystallised from methanol, m. p. 265—280° (decomp.) (Found: C, 73·7; H, 9·9. $C_{21}H_{34}N_4$ requires C, 73·6; H, 10·0%).

4,4-*Dimethylandrost*-5-*en*-3-*one* (IV; R = H).—Androst-4-en-3-one (14·1 g.) was dissolved in a solution of potassium (6 g.) in t-butyl alcohol (300 ml.) under nitrogen. Methyl iodide (19·5 ml.) was added dropwise during 10 min., the flask stoppered, set aside for 4 hr., and finally the mixture was diluted with water (1 l.). The product (11·9 g., 76%), m. p. 174—178°, was collected by filtration; recrystallisation from ethanol yielded 4,4-dimethylandrost-5-en-3-one, m. p. 177—179°, $[\alpha]_D$ −20° (*c* 0·2) (Found: C, 84·1; H, 10·5. Calc. for $C_{21}H_{32}O$: C, 83·9; H, 10·7%) {lit.,[9] m. p. 175—176°, $[\alpha]_D$ −21° ± 2° (in dioxan)}.

4,4-*Dimethylandrost*-5-*ene* (VII; R = H).—(*a*) A mixture of 4,4-dimethylandrost-5-ene-3,17-dione dihydrazone (1·6 g.), hydrazine hydrate (2 ml.), and sodium ethoxide [from sodium (1·44 g.) and ethanol (20 ml.)] was heated in a sealed tube at 180° for 18 hr. Dilution with water and extraction with ether yielded the product which crystallised from ether–methanol to give 4,4-dimethylandrost-5-ene (1·06 g., 74%), m. p. 123—125°, $[\alpha]_D$ −94° (*c* 0·2) (Found: C, 88·0; H, 12·0. Calc. for $C_{21}H_{34}$: C, 88·0; H, 12·0%) {lit.,[9] m. p. 123·5—124°, $[\alpha]_D$ −98·5° (in dioxan)}.

(*b*) 4,4-Dimethylandrost-5-en-3-one (16·5 g.) and anhydrous hydrazine (50 ml.) were added to a solution of sodium (5·7 g.) in warm diethylene glycol (250 ml.). The mixture was heated under reflux for 4 hr., the condenser removed, and heating continued until the temperature reached 210°. The solution was then heated under reflux for a further 24 hr. Dilution with water and extraction with ether yielded the product which crystallised from ether–methanol to give 4,4-dimethylandrost-5-ene (14·2 g., 90%) identical with that previously prepared.

4,4-*Dimethylandrosta*-5,7-*diene* (VI; R = H).—A solution of 4,4-dimethylandrost-5-ene (4·5 g.) in carbon tetrachloride (120 ml.; AnalaR) was stirred, and powdered N-bromosuccinimide (4·5 g.) added. The reaction flask was half immersed in an oil-bath at 90—95° and irradiated from above with an ultraviolet lamp (Hanovia, 125 w). The irradiation was stopped 30 sec. after the reaction started, and 1½ min. later the mixture was cooled in ice for 5 min. Dehydrobromination with collidine and isolation of the product was then carried out as for the corresponding 17β-yl acetate, save that a solution of the end-product in light petroleum (b. p. 60—80°) was filtered through neutral alumina; removal of the solvent and crystallisation from ether–methanol then gave 4,4-*dimethylandrosta*-5,7-*diene* (2·7 g., 60%), m. p. 91—92°, $[\alpha]_D$ −257° (*c* 0·2), $\lambda_{max.}$ 273 and 282 mμ (ε 10,300 and 10,000) (Found: C, 88·4; H, 11·3. $C_{21}H_{32}$ requires C, 88·7; H, 11·3%).

4,4-*Dimethyl*-5α-*androsta*-6,8(14)-*diene* (X; R = H).—4,4-Dimethylandrosta-5,7-diene (3·0 g.) was added to boiling benzene (510 ml.) containing toluene-*p*-sulphonic acid (350 mg.). The solution was heated under reflux for 18½ min., washed with 1N-sodium hydrogen carbonate solution (50 ml.) and water, and dried ($MgSO_4$). The benzene was

[29] A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 1953, 2548.

removed *in vacuo* and the residue dissolved in light petroleum (b. p. 60—80°) and filtered through a column of neutral alumina. Evaporation of the eluate and crystallisation of the residue from ether–methanol with trituration gave 4,4-*dimethyl*-5α-*androsta*-6,8(14)-*diene* (2·5 g., 83%), m. p. 75—76°, $[\alpha]_D$ −20° (*c* 0·6), $\lambda_{max.}$ 253 mμ (ε 22,550) with inflections at 245 and 261 mμ (Found: C, 88·8; H, 11·2%.)

4,4-*Dimethyl*-5α-*androst*-8(14)-*ene* (XI; R = H).—4,4-Dimethyl-5α-androsta-6,8(14)-diene (1·0 g.) in ethyl acetate (100 ml.) was hydrogenated over 10% palladium–charcoal (100 mg.) at atmospheric pressure and room temperature for ½ hr. The solution was filtered through neutral alumina, the solvent removed *in vacuo*, and the residue crystallised from ether–methanol with trituration, to yield 4,4-dimethyl-5α-androst-8(14)-ene (0·8 g., 80%), m. p. 66·5—67°, $[\alpha]_D$ +30° (*c* 0·25), ε_{210} 9600, ε_{215} 8400, ε_{220} 6400 (Found: C, 88·3; H, 11·8. Calc. for $C_{21}H_{34}$: C, 88·0; H, 12·0%) {lit.,[9] m. p. 69—70°, $[\alpha]_D$ +30·5° (dioxan), ε_{215} 7000}.

4,4-*Dimethyl*-5α-*androst*-14-*ene* (XII; R = H).— 4,4-Dimethyl-5α-androst-8(14)-ene (1·0 g.) and 10% palladium–carbon [50 mg., from the preparation of the 8(14)-olefin] in chloroform (30 ml.) were treated with dry hydrogen chloride gas at −30° for 2 hr. Excess methanolic ammonia was added, followed by water, and the reaction mixture extracted with ether. The product was isolated in the usual manner and crystallised from ether–methanol with trituration, yielding 4,4-dimethyl-5α-androst-14-ene (0·89 g., 89%), m. p. 75—76°, $[\alpha]_D$ +24° (*c* 0·3) (Found: C, 88·3; H, 12·0%) {lit.,[9] m. p. 76·5—77°, $[\alpha]_D$ +25° (dioxan)}.

4,4-*Dimethyl*-5α-*androst*-14-*en*-17β-*ol* (XII; R = OH).—4,4-Dimethyl-5α-androst-8(14)-en-17β-ol (1·2 g.) and 10% palladium–charcoal (50 mg. from the preparation of the starting material) in chloroform (60 ml.; AnalaR) were treated with dry hydrogen chloride gas at −30° for 3 hr. The product was isolated in the same way as for the corresponding hydrocarbon and crystallised from aqueous methanol, to yield 4,4-*dimethyl*-5α-*androst*-14-*en*-17β-*ol* (0·9 g., 75%), m. p. 183—184°, $[\alpha]_D$ +30° (*c* 0·3) (Found: C, 83·5; H, 11·4. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%). The *acetate* had m. p. 106—108°, $[\alpha]_D$ +9° (*c* 0·3) (Found: C, 79·9; H, 10·8. $C_{23}H_{36}O_2$ requires C, 80·2; H, 10·5%). The *benzoate* had m. p. 184—186°, $[\alpha]_D$ +65° (*c* 0·2) (Found: C, 82·5; H, 9·2. $C_{28}H_{38}O_2$ requires C, 82·7; H, 9·4%).

4,4-*Dimethyl*-5α,14β-*androstane* (XIII; R = H).—4,4-Dimethyl-5α-androst-14-ene (126 mg.) in ethyl acetate (25 ml.) was hydrogenated over 10% palladium–charcoal (20 mg.) at room temperature and atmospheric pressure for 2½ hr. Removal of the catalyst, evaporation of the solvent, and crystallisation of the residue from ether–methanol yielded 4,4-*dimethyl*-5α,14β-*androstane* (107 mg., 84%), m. p. 107·5—108·5°, $[\alpha]_D$ +26° (*c* 0·6) (Found: C, 87·5; H, 12·4. $C_{21}H_{36}$ requires C, 87·5; H, 12·6%).

4,4-*Dimethyl*-5α,14β-*androstan*-17β-*ol* (XIII; R = OH).—4,4-Dimethyl-5α-androst-14-en-17β-ol (330 mg.) in ethyl acetate (60 ml.) was hydrogenated over 10% palladium–charcoal (30 mg.) for 3 hr. at atmospheric pressure and room temperature. Crystallisation of the product from aqueous methanol gave 4,4-*dimethyl*-5α,14β-*androstan*-17β-*ol* (290 mg., 88%), m. p. 156—157°, $[\alpha]_D$ +23° (*c* 0·7) (Found: C, 82·6; H, 11·85. $C_{21}H_{36}O$ requires C, 82·8; H, 11·9%).

4,4-*Dimethyl*-5α,14β-*androstan*-17-*one*.—4,4-Dimethyl-5α,14β-androstan-17β-ol (250 mg.) in acetone (40 ml.; AnalaR) was oxidised with 8N-chromic–sulphuric acid solution by the procedure of Jones and his co-workers.[29] Dilution with water and extraction with ether yielded the product, which crystallised from aqueous methanol to give 4,4-*dimethyl*-5α,14β-*androstan*-17-*one* (200 mg., 80%), m. p. 74—76°; o.r.d. (MeOH) $[\phi]_{308}$ +5880 (pk) and $[\phi]_{264}$ −3630 (tr) (Found: C, 83·7; H, 11·2. $C_{21}H_{34}O$ requires C, 83·4; H, 11·3%).

4,4-*Dimethyl*-5α,14α-*androstan*-17-*one*.—4,4-Dimethyl-5α-androstan-17β-ol (1·14 g.) was oxidised by the same procedure as for the 14β-isomer. The product crystallised from aqueous methanol to give 4,4-*dimethyl*-5α,14α-*androstan*-17-*one* (1·07 g., 93%), m. p. 152—153°, $[\alpha]_D$ +79° (*c* 2·0); o.r.d. (MeOH) $[\phi]_{313}$ +6450 (pk) and $[\phi]_{272}$ −6960 (tr) (Found: C, 83·4; H, 11·3%).

Huang-Minlon Reduction of 4,4-*Dimethyl*-5α,14β-*androstan*-17-*one*.—A solution of 4,4-dimethyl-5α,14β-androst-17-one (200 mg.) and potassium hydroxide (0·7 g.) in diethylene glycol (5 ml.) and hydrazine hydrate (1 ml.) was heated under reflux for 1½ hr. The condenser was removed and heating continued until the temperature reached 200°; the mixture was heated under reflux for a further 4 hr. Dilution with water and extraction with ether yielded the product, which crystallised ftom ether–methanol to give 4,4-dimethyl-5α,14β-androstane (101 mg., 54%) identical with that previously prepared.

4,4-*Dimethyl*-5α,14α-*androstane* (VIII; R = H).—(*a*) 4,4-Dimethyl-5α,14α-androstan-17-one (200 mg.) was reduced by the procedure described for the 14β-isomer. The product crystallised from ether–methanol to give 4,4-*dimethyl*-5α,14α-*androstane* (91 mg., 43%), m. p. 79·5—80·5°, $[\alpha]_D$ 11° (*c* 0·2) (Found: C, 87·7; H, 12·4%. $C_{21}H_{36}$ requires C, 87·5; H, 12·6%).

(*b*) 4,4-Dimethylandrost-5-ene (800 mg.) in acetic acid (120 ml.) was hydrogenated over 10% palladium–charcoal (100 mg.) at 150 atm. and 120° for 18 hr. The reaction mixture was diluted with ether (100 ml.) and filtered through Celite; evaporation of the solvent and crystallisation of the product from ether–methanol gave 4,4-dimethyl-5α,14α-androstane (600 mg., 75%) identical with that previously prepared.

Acidic Hydrogenation of 4,4-*Dimethyl*-5α-*androst*-14-*en*-17β-*ol*.—4,4-Dimethyl-5α-androst-14-en-17β-ol (110 mg.) was hydrogenated in methanol (50 ml.) containing one drop of concentrated hydrochloric acid, over 10% palladium–charcoal (10 mg.). 1 Mol. of hydrogen was absorbed in 1 min. The product crystallised from aqueous methanol to yield 4,4-dimethyl-5α,14β-androstan-17β-ol (60 mg., 54%) identical with that previously prepared. The residue from evaporation of the mother-liquors was acetylated and fractionated by preparative t.l.c. on silica with 14% petroleum–benzene as solvent; separation into two components was obtained. The faster moving component yielded, after crystallisation from ether–methanol, 4,4-dimethyl-5α,14α-androstan-17β-yl acetate (5 mg.) identical with that previously prepared.

Ozonolysis of 4,4-*Dimethyl*-5α-*androst*-14-*ene*.—4,4-Dimethyl-5α-androst-14-ene (400 mg.) in ethyl acetate (40 ml.) and n-hexane (10 ml.) was treated with ozonised oxygen for 3 hr. at −15°, followed by oxygen for 2 hr. The solvent was removed *in vacuo*, to yield the *ozonide* (456 mg., 97%); crystallisation from ether–methanol gave m. p. 160—164° (Found: C, 75·4; H, 10·2. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·25%).

4,4-*Dimethyl*-14,15-*seco*-5α-*androstane*-14β,15-*diol* (XIV) *and* -14α,15-*diol*.—A solution of the foregoing ozonide (0·452 g.) and lithium aluminium hydride (0·4 g.) in dry

ether (50 ml.) was heated under reflux for 2 hr. Excess hydride was decomposed with ethyl acetate, and ether (50 ml.), saturated aqueous ammonium chloride (50 ml.), and 2N-hydrochloric acid (10 ml.) were added. The aqueous layer was separated and extracted with ether (2 × 40 ml.). The combined ethereal solutions were worked up in the usual manner, to give a white solid (437 mg.). Trituration with methanol (1·4 ml.) yielded 4,4-*dimethyl*-14,15-*seco*-5α-*androstane*-14β,15-*diol* (231 mg., 51%), which crystallised from aqueous methanol with m. p. 171—173°, $[\alpha]_D$ −23° (*c* 0·4). The analytical sample was prepared by sublimation at 150°/0·2 mm. [Found: C, 78·1; H, 11·9%; *M* (mass spectrum), 322. $C_{21}H_{38}O_2$ requires C, 78·2; H, 11·9%; *M*, 322]. The *diacetate* crystallised from ether–methanol, m. p. 93—95°, $[\alpha]_D$ −1·5° (*c* 0·2), τ 5·5 p.p.m. (doublet, J = 9·5 c./sec.) (C-14 proton) (Found: C, 73·8; H, 10·3. $C_{25}H_{42}O_4$ requires C, 73·85; H, 10·4%).

The combined residues (2·3 g.) from several experiments were fractionated by preparative t.l.c. on silica with ether, yielding 4,4-*dimethyl*-14,15-*seco*-5α-*androstane*-14α,15-*diol* (0·54 g.), m. p. 132—133°, $[\alpha]_D$ −3° (*c* 0·2) (from aqueous methanol) [Found: C, 78·2; H, 11·6%; *M* (mass spectrum), 322·2866. $C_{21}H_{38}O_2$ requires *M*, 322·2872]. The diacetate (oil) had τ 5·30 p.p.m. (broad singlet) (C-14 proton). Saponification of the diacetate (145 mg.) in the usual manner and crystallisation of the product (123 mg., 96%) from aqueous methanol yielded 15-*hydroxy*-4,4-*dimethyl*-14,15-*seco*-5α-*androstan*-14α-*yl acetate* (87 mg.), m. p. 107—108·5°, $[\alpha]_D$ −34° (*c* 0·2) [Found: C, 75·6; H, 11·0%; *M* (mass spectrum), 364. $C_{23}H_{40}O_3$ requires C, 75·8; H, 11·1%; *M*, 364]. Saponification of this monoacetate in boiling benzene–M-methanolic potassium hydroxide for 48 hr. gave 14α,15-diol (100%) identical with that previously isolated.

Separation of the 14α,15- *and* 14β,15-*Diols by Chromatography of the Acetates*.—A mixture of the diols (850 mg.) was warmed with acetic anhydride (8 ml.) and pyridine (8 ml.) on a steam-bath for 5 min., and the acetylated products were isolated in the usual way, and chromatographed on silica with 7% ether–benzene as eluant. Separation into two fractions was obtained. The second fraction gave chromatographically pure 14-hydroxy-4,4-dimethyl-14,15-seco-5α-androstan-15-yl acetate (231 mg.) as an oil, τ 7·93 (singlet) (CH_3CO) and 6·80 p.p.m. (singlet, $J \leqslant 1·5$ c./sec.; C-14 proton) [Found: *M*, 364 (mass spectrum)]. Saponification of this acetate in the usual manner yielded only the 14α,15-diol (100%) identical with that previously prepared. Saponification of the first fraction (570 mg.) from the chromatography, by heating under reflux with benzene–M-methanolic potassium hydroxide for 40 hr., and isolation in the usual manner, gave a solid (410 mg.) shown by t.l.c. to be predominantly the 14β,15-diol with a little 14α,15-diol. Crystallisation from aqueous methanol gave 14β,15-diol (215 mg.) identical with that previously isolated.

4,4-*Dimethyl*-14-*oxo*-14,15-*seco*-5α-*androstane*-15-*carboxylic Acid* (XXIII).—4,4-Dimethyl-14,15-seco-5α-androstane-14β,15-diol (100 mg.) and chromium trioxide (200 mg.) in 90% acetic acid (23 ml.) were heated at 70° for 2 hr., before dilution with water and ether-extraction. The ethereal solution was extracted with 2N-sodium hydroxide, and the latter acidified and extracted with ether. The ether was washed with water, dried ($MgSO_4$), and evaporated, to yield the product, which crystallised from carbon tetrachloride–light petroleum (b. p. 60—80°) to give 4,4-dimethyl-14-oxo-14,15-seco-5α-androstane-15-carboxylic acid (56 mg., 54%), m. p. 163—164°, $[\alpha]_D$—50° (*c* 0·3). Similar treatment of a mixture of 14α,15- and 14β,15-diols gave the same keto-acid {lit.,[9] m. p. 164—165°, $[\alpha]_D$ −56·6° (in dioxan)}.

4,4-*Dimethyl*-15-*oxa*-D-*homo*-5α-*androstan*-16-*one* (XV).—(*a*) 4,4-Dimethyl-14,15-seco-5α-androstane-14β,15-diol (385 mg.) in pyridine (45 ml.) was treated with chromium trioxide (1·0 g.) at 20° for 18 hr. The solution was diluted with M-sodium hydrogen carbonate (250 ml.) and extracted with ether (4 × 125 ml.), and the combined extracts were washed with water, dried ($MgSO_4$), and evaporated. The product (441 mg.), dissolved in ether (100 ml.), was extracted with cold M-sodium hydroxide (20 ml.). Acidification of the alkaline extract and extraction with chloroform yielded 4,4-dimethyl-14-oxo-14,15-seco-5α-androstane-15-carboxylic acid (27 mg.).

Evaporation of the dried ethereal solution yielded a solid (389 mg.) which was dissolved in benzene (16 ml.) and treated with M-methanolic sodium hydroxide (13 ml.) at 20° for 18 hr. Most of the solvent was removed *in vacuo* and the mixture diluted with water; neutral products (117 mg.) were removed by washing with ether (3 × 20 ml.), and the aqueous solution was acidified and extracted with chloroform. The chloroform extract was washed with water and dried ($MgSO_4$) for 18 hr. at 20° before evaporation. Crystallisation of the product (275 mg.) from light petroleum (b. p. 60—80°) gave 4,4-*dimethyl*-15-*oxa*-D-*homo*-5α-*androstan*-16-*one* (224 mg., 55%, in two crops), m. p. 170—171°, $[\alpha]_D$ −92° (*c* 0·2), o.r.d. (MeOH) $[\alpha]_{223}$ −7650 (pk), τ 6·46 p.p.m. (doublet, J = 10·0 c./sec.) (C-14 proton) [Found: C, 79·1; H, 10·7%; *M* (mass spectrum), 318. $C_{21}H_{34}O_2$ requires C, 79·2; H, 10·8%; *M*, 318].

(*b*) 4,4-Dimethyl-14,15-seco-5α-androstane-14β,15-diol (50 mg.) in acetonitrile (10 ml.) was stirred at 20° for 20 hr. with active manganese dioxide[31] (1 g.). Filtration and removal of solvent and volatile material (acetamide) *in vacuo* yielded 4,4-dimethyl-15-oxa-D-homo-5α-androstan-16-one (46 mg., 90%) identical with the foregoing product.

4,4-*Dimethyl*-15-*oxa*-D-*homo*-5α,14β-*androstan*-16-*one*.—Chromium trioxide (0·7 g.) was added to a solution of 4,4-dimethyl-14,15-seco-5α-androstane-14α,15-diol (246 mg.) in pyridine (30 ml.) with swirling. The solution was left at 20° for 18 hr., and the product isolated in the same way as for the 5α,14α-lactone; the keto-acid (52 mg.) was isolated from the acidic fraction. The crude lactone (164 mg.) crystallised from light petroleum (b. p. 60—80°), yielding: 4,4-*dimethyl*-15-*oxa*-D-*homo*-5α,14β-*androstan*-16-*one* (123 mg., 50%, in two crops), m. p. 136—137°, $[\alpha]_D$ +48° (*c* 0·2), o.r.d. (hexane) $[\phi]_{222}$ +2750 (pk), τ 6·12 p.p.m. (broad singlet) (C-14 proton). The analytical sample was prepared by sublimation at 150°/0·1 mm. [Found: C, 79·45; H, 10·7%; *M* (mass spectrum), 318].

4,4-*Dimethyl*-15-*oxa*-D-*homo*-5α-*androst*-17(17a)-*en*-16-*one* (XVI).—A solution of 4,4-dimethyl-15-oxa-D-homo-5α-androstan-16-one (500 mg.) and 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (750 mg.) in dioxan (50 ml.) and acetic acid (7·5 ml.) was heated under reflux for 8 days. The solvents were removed *in vacuo* and the residue was dissolved in chloroform and filtered through neutral alumina. Removal of the solvent gave the crude dehydro-lactone (490 mg., 80% pure) which could be used in the next step without further purification. The analytical sample was prepared

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[31] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1952, 1094.

by extracting the crude product with ether (3 ml.) for 2 hr. at 20°. The residual solid crystallised from methanol, yielding 4,4-*dimethyl*-15-*oxa*-D-*homo*-5α-*androst*-17(17a)-*en*-16-*one* (177 mg., 36%), m. p. 222·5—223·5°, $[\alpha]_D$ +18° (*c* 0·2), $\lambda_{max.}$ (EtOH) 218·5 mμ (ε 6700) τ 3·32 and 4·16 (doublets, J = 10 c./sec.) (C-17, C-17a protons) and 6·38 p.p.m. (doublet, J = 10 c./sec.) (C-14 proton) [Found: C, 79·7; H, 10·35%; *M* (mass spectrum), 316. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%; *M*, 316].

17aα-*Hydroxy*-4,4-*dimethyl*-15-*oxa*-D-*homo*-5α-*androstan*-16-*one* (XX; R = H).—A solution of crude 4,4-dimethyl-15-oxa-D-homo-5α-androst-17(17a)-en-16-one (460 mg.) in dioxan (15 ml.) and M-sodium hydroxide (15 ml.) was heated under reflux for 70 hr. The solution was acidified with 2N-hydrochloric acid and extracted with chloroform. The chloroform solution was washed with water and boiled over anhydrous $MgSO_4$ for 20 hr. before evaporation. Crystallisation of the residue from acetone–light petroleum (b. p. 60—80°) gave 17aα-*hydroxy*-4,4-*dimethyl*-15-*oxa*-D-*homo*-5α-*androstan*-16-*one* (237 mg.), m. p. 235—236°, $[\alpha]_D$ −110° (*c* 0·2) [Found: C, 75·6; H, 10·2%; *M* (mass spectrum), 334. $C_{21}H_{34}O_3$ requires C, 75·4; H, 10·25%; *M*, 334]. Chromatography of the liquors on silica and elution with chloroform gave further product (35 mg., total yield 58%) and unchanged starting lactones (0·1 g.).

The *acetate* crystallised from acetone–light petroleum (b. p. 60—80°), m. p. 178—179°, $[\alpha]_D$ −105° (*c* 0·2), τ 6·00 (doublet, J = 10·0 c./sec.) (C-14 proton), and an ABX pattern at τ *ca.* 7·2 (multiplet) (C-17 protons) and 5·20 p.p.m. (quadruplet) (C-17a proton) ($J_{AX} + J_{BX}$ = 8 c./sec., J_{AB} = 19 c./sec.) [Found: C, 73·3; H, 9·4%; *M* (mass spectrum), 376. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%; *M*, 376]. Attempted saponification of the acetate (22 mg.) in dioxan (1 ml.) with M-sodium hydroxide (1 ml.) at 20° for 18 hr. yielded 4,4-dimethyl-15-oxa-D-homo-5α-androst-17(17a)-en-16-one (18 mg.) identical with that previously prepared.

4,4-*Dimethyl*-15-*oxa*-D-*homo*-5α-*androstane*-16,17a-*dione* (XIX).—(*a*) To 17aα-hydroxy-4,4-dimethyl-15-oxa-D-homo-5α-androstan-16-one (200 mg.) dissolved in acetone (18 ml., AnalaR) was added dropwise 8N-chromic–sulphuric acid solution.[29] Water was added and the solution cooled to 0° and filtered. The amorphous product was washed with water and dried, to give 4,4-*dimethyl*-15-*oxa*-D-*homo*-5α-*androstane*-16,17a-*dione* (0·184 g., 92%) which crystallised from methanol–chloroform–benzene with m. p. 264—265° (decomp.), $[\alpha]_D$ −29° (*c* 0·2), $\nu_{max.}$ (KBr disc or mull) 2600—3300, 1670, 1585, ($CHCl_3$) 1750, 1722 cm.$^{-1}$ (cf. ref. 30); $\lambda_{max.}$ (EtOH) 244 (ε 6000) with inflection at 270 mμ, $\lambda_{max.}$ (EtOH–NaOH) 269·5 mμ (ε 17,000). The analytical sample was prepared by sublimation at 200°/1·0 mm. [Found C, 76·0; H, 9·5%; *M* (mass spectrum), 332. $C_{21}H_{32}O_3$ requires C, 75·9; H, 9·7%; *M*, 332].

(b) A suspension of 4,4-dimethyl-14,15-seco-5α-androstane-14β,15,17β-triol (50 mg.) (see below) in acetonitrile (10 ml.) was stirred with active manganese dioxide[31] (1 g.) at 20° for 3½ hr. The reaction mixture was filtered through silica and eluted with chloroform until no more material was eluted. The white solid product (45 mg.) was dissolved in acetone (9 ml.; AnalaR) and oxidised by the procedure of Jones and his co-workers;[29] the acetone solution was diluted with excess water and filtered at 0°. The dried product (40 mg.) was extracted with light petroleum (b. p. 60—80°) (1 ml.) for ½ hr. at 20°. The residual keto-lactone (30 mg., 60%) had m. p. 258—263° (decomp.), mixed m. p. with sample prepared above (m. p. 264—265°) 260—265° (decomp.). The infrared spectrum and t.l.c. behaviour were identical with those of the sample previously prepared.

4,4-*Dimethyl*-14,15-*seco*-5α-*androstane*-14β,15,17β-*triol* (XVII) *and the* 14α-*Isomer*.—4,4-Dimethyl-5α-androst-14-en-17β-yl acetate (1·28 g.) in ethyl acetate (130 ml.) was treated with ozonised oxygen for 2 hr. at −15°, and then with oxygen for 2 hr. The solvent was removed *in vacuo* and the residue reduced with lithium aluminium hydride (2·6 g.) in boiling ether (200 ml.) for 2 hr. The reaction mixture was treated in a similar manner to that of the corresponding 17-deoxo-compound, and extraction with ether yielded 4,4-*dimethyl*-14,15-*seco*-5α-*androstane*-14β,15,17β-*triol* (780 mg., 60%). Crystallisation from acetone gave m. p. 153—155°, $[\alpha]_D$ −39° (*c* 0·3) (Found: C, 74·1; H, 11·1. $C_{21}H_{38}O_3$ requires C, 74·5; H, 11·3%). The *triacetate* crystallised from aqueous methanol, m.p.. 118—119°, $[\alpha]_D$ −24° (*c* 0·3), τ (100 Mc./sec.) 5·35 p.p.m. (doublet, J = 10·0 c./sec.) (C-14 proton) [Found: C, 69·6; H, 9·45%; *M* (mass spectrum), 464. $C_{27}H_{44}O_6$ requires C, 69·8; H, 9·55%; *M*, 464].

Filtration of the aqueous layer from the lithium aluminium hydride reduction above gave the very insoluble 4,4-dimethyl-14,15-seco-5α-androstane-14α,15,17β-triol (275 mg., 21%), m. p. 285—290° (sublimes and decomposes), whose *triacetate* crystallised from aqueous methanol, m. p. 88—89°, $[\alpha]_D$ −25° (*c* 0·3), τ (100 Mc./sec.) 5·24 p.p.m. (singlet)(C-14 proton) [Found: C, 69·6; H, 9·3%; *M* (mass spectrum), 464].

14β-*Hydroxysandaracopimaran*-15-*one* (XXII).—A solution of 4,4-dimethyl-15-oxa-D-homo-5α-androstane-16,17a-dione (169 mg.) in ethanol (25 ml.) and 2N-hydrochloric acid (14 ml.) was heated under reflux for 4 hr. M-Sodium hydrogen carbonate (40 ml.) was added, the solution extracted with chloroform, and the extract washed with water, dried ($MgSO_4$), and evaporated. The residue (165 mg.) was extracted with n-pentane; evaporation of the n-pentane gave 14β-*hydroxysandaracopimaran*-15-one (121 mg., 75%), which crystallised from aqueous methanol, m. p. 128—130°, $[\alpha]_D$ +8° (*c* 0·1), τ 7·83 (singlet) (CH_3CO) and 6·47 p.p.m. (doublet, J = 9·0 c./sec.) (C-14 proton). The analytical sample was prepared by sublimation at 130°/0·02 mm. [Found: C, 78·1; H, 11·2%; *M* (mass spectrum), 306. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%; *M*, 306].

Repetition of the experiment with the 16,17a-dione (11 mg.) in EtOD (2 ml.) and 2N-DCl–D_2O (1 ml.) gave keto-alcohol (9 mg.) [*M*, 309 (mass spectrum)]. Treatment of this product with M-methanolic potassium hydroxide (1 ml.) at 20° for 1 hr. gave keto-alcohol [*M*, 306 (mass spectrum)] These products were characterised by their i.r. and mass spectra, and by t.l.c.

(−)-*Sandaracopimaradiene* (II; R = Me).—14β-Hydroxysandaracopimaran-15-one (120 mg.) in methanol (5 ml.) made alkaline with methanolic potassium hydroxide was treated with sodium borohydride (20 mg.) at 20° for 18 hr. Isolation in the usual manner gave the diol (125 mg., 100%) which was benzoylated by heating with benzoyl chloride and pyridine at 140° for 18 hr. Isolation in the usual manner gave an oil (223 mg.) which was passed through neutral alumina in chloroform solution. The product was rechromatographed on silica and eluted with light petroleum (b. p. 60—80°) and benzene. Evaporation of the benzene eluate yielded the dibenzoate (148 mg., 75% from keto-alcohol) [Found: *M* (mass spectrum), 516. $C_{34}H_{44}O_4$ requires *M*, 516]. This dibenzoate (146 mg.) was distilled

at 180—220°/0·3 mm. into a 2-ft. column packed with glass wool and maintained at 420—440°. The condensate (130 mg.) was passed down neutral alumina in n-pentane solution, to give *ca.* 90% pure (by t.l.c.) (−)-sandaracopimaradiene (40 mg., 50%). Crystallisation from cold methanol gave m. p. 38—39°, mixed m. p. with natural (−)-sandaracopimaradiene [8] (m. p. 39·5—40°) 39—39·5°, $[\alpha]_D$ −13° (*c* 0·3) (lit.,[8] −12·4°); the infrared and mass spectra, and the t.l.c. and v.p.c. behaviour of the synthetic and natural sandaracopimaradiene were identical.

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Robert Robinson Laboratories,
Liverpool University, Oxford Street,
Liverpool 7. [6/601 *Received*, *May* 19*th*, 1966]