

Steroids Derived from Fusidic Acid. Part 2.¹ Synthesis of an 8 α ,14 β -Dimethyl-18-norandrostane. A Revised Mechanism

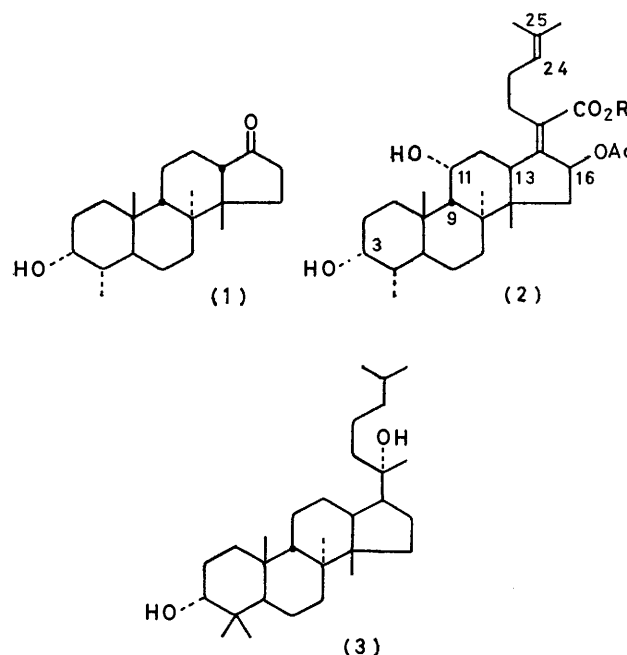
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An improved synthesis of 3 α -acetoxy-4 α ,8 α ,14 β -trimethyl-18-norandrostane-17-one (15) from fusidic acid is described. Ruthenium tetroxide is compared with ozone as a means of cleaving the side-chain. The thermal stability of the resulting androstanone (8) and its reactions with pyridine, acetic acid, and zinc in acetic acid is outlined. Evidence is presented for a *trans*- β -elimination of the 11 α -acetoxy-group from (8) and the formation of a transient $\Delta^{9,11}$ -androsterone (19). This mechanism contrasts with that previously suggested and questions the chemical basis for the stereochemistry previously assigned to C-9.

THE androstanone (1) has stereochemistry which has been observed in but a few natural products.² The 9 β -configuration forces the B-ring to adopt the strained boat conformation.³ Due to this strain and the stereochemistry of fusion of the B/C and C/D rings, it retains the latent ability to undergo backbone rearrangement when epimerised at C-13.⁴ Its synthesis was claimed³ in 1967 and its stereochemistry extrapolated from the parent fusidic acid (2; R = H).⁵ However, as will be shown, the basis³ for assigning a β -configuration to C-9 in (1) was inconclusive. The structure assigned to (1) was assumed by others,⁶ who used this androstanone as the starting point for a synthesis of protosterol (3), a suggested⁷ biosynthetic intermediate of lanosterol. That the protosterol (3) did not undergo rearrangement to lanosterol when incubated with rat liver homogenase⁶ could be due to 9 α -stereochemistry. We required androstanone (1) in quantity for further research. Our immediate objective then was to develop an improved synthesis of (1) and confirm the assigned stereochemistry. Our synthetic plan was to (a) protect the hydroxy-groups of methyl fusidate (2; R = Me) by acetylation, (b) oxidatively cleave the side-chain to an androstanone, and finally (c) eliminate the 11- and 16-acetoxy-groups.

Acetylation of Methyl Fusidate.—The diacetate of methyl fusidate (2; R = Me) had not been characterised previously. Acetylation was attempted initially by heating a solution of (2; R = Me) in dry pyridine⁸

with acetic anhydride. Acetylation of C-3 only occurred. Similar treatment of (2; R = Me) with anhydrous



zinc chloride in acetic anhydride⁹ gave a complex mixture which was seen as a continuous streak on t.l.c.

⁴ See for example: M. Jayme, P. C. Schaefer, and J. H. Richards, *J. Amer. Chem. Soc.*, 1970, **92**, 2059; E. J. Corey and H. Yamamoto, *Tetrahedron Letters*, 1970, 2385; D. H. R. Barton, G. Mellows, D. A. Widdowson, and J. J. Wright, *J. Chem. Soc. (C)*, 1971, 1142.

⁵ W. O. Godtfredsen, S. Jahnsen, H. Lorck, K. Roholt, and L. Tybring, *Nature*, 1962, **193**, 108.

⁶ V. H. Immer and K. Hüber, *Helv. Chim. Acta.*, 1971, **54**, 1346.

⁷ J. W. Cornforth, *Angew. Chem. Internat. Edn.*, 1968, **7**, 903.

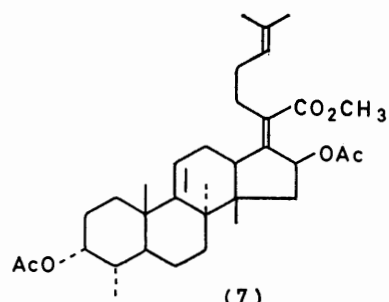
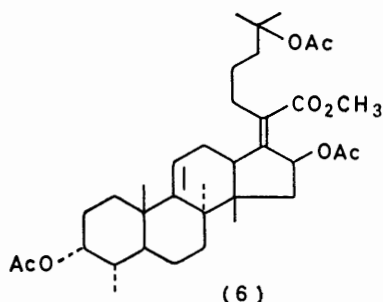
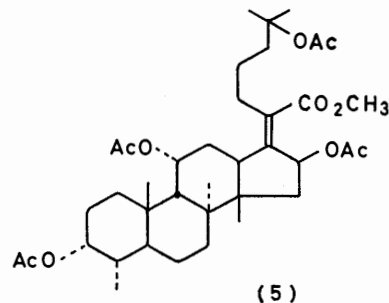
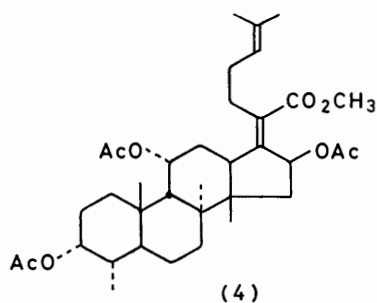
⁸ L. F. Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4400.

⁹ P. A. Diassi, I. Bacso, G. W. Krakower, and H. A. Van Dine, *Tetrahedron*, 1966, 3459.

¹ Part I. S. S. Welankiwar and W. S. Murphy, *J.C.S. Perkin I*, 1976, 710.

² (a) J. F. Biellmann, P. Crabbé, and G. Ourisson, *Tetrahedron*, 1958, **3**, 303; (b) S. Okuda, S. Isawaki, K. Tsuda, Y. Sano, T. Hata, S. Udagawa, Y. Nakayama, H. Yamaguchi, *Chem. Pharm. Bull.*, 1964, **12**, 121; (c) W. O. Godtfredsen, 'Fusidic Acid and Some Related Antibiotics,' Copenhagen, 1967; (d) F. G. Halsall, E. R. H. Jones, G. Lowe, and C. E. Newell, *Chem. Comm.*, 1966, 685; (e) W. J. Chin, R. E. Corbett, C. K. King, and A. L. Wilkins, *J.C.S. Perkin I*, 1973, 1437.

When catalysed by either toluene-*p*-sulphonic acid or perchloric acid,³ five products were formed of which four were characterised by n.m.r. spectroscopy: methyl fusidate 3,11-diacetate (4); methyl 24,25-dihydrofusidate 3,11,25-triacetate (5); methyl $\Delta^{9(11)}$ -24,25 dihydrofusidate-3,25-diacetate (6); and methyl $\Delta^{9(11)}$ -fusidate 3-acetate (7). This unexpectedly ready loss of the 11-hydroxy-group suggested that milder conditions might be effective while at the same time inhibiting attack at C-24. Methyl fusidate 3,11-diacetate (4)



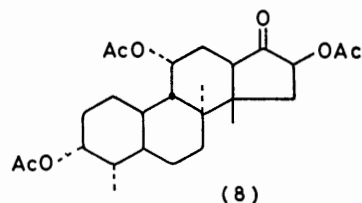
was prepared cleanly in high yield (98%) by heating (2; R = Me) in acetic anhydride with fused sodium acetate¹⁰ under reflux.

Side-chain Cleavage.—Following the procedure of Parikh and Jones,¹¹ catalytic ruthenium tetroxide oxidation was used initially. However, the co-oxidant sodium hypochlorite gave more reliable results than sodium metaperiodate. Methyl fusidate 3,11-diacetate (4) invariably gave a more complex mixture of products than methyl 24,25-dihydrofusidate 3,11-diacetate. High yields (88%) of triacetate (8) were at times obtained by this method, although isolation was complicated by the presence of methyl 6-methyl-2-oxoheptanoate and traces of the dienone (11). However, the method was not dependable. Both reaction times (up to 3 weeks) and yields were variable and seemed to depend on the batch of ruthenium dioxide. The low reactivity of the C(17)-C(21) double-bond in (2; R = Me) is not without precedent. The C(8)-C(9) conjugated double-bond in a grisene was found by Dean and Knight¹² to be resistant to ruthenium tetroxide. Also, the long reaction times

may have led to side-products resulting from attack by ruthenium tetroxide at saturated sites.¹³ It was noted that the precipitate was black and not readily oxidisable. It was probably a complex hydrate.¹⁴ The activity and violet appearance of ruthenium dioxide was restored by heating the black powder to red-heat and cooling in air.

Ozonolysis of the side-chain was alternatively investigated. Whereas cleavage of methyl 24,25-dihydrofusidate 3,11-diacetate occurred smoothly, separation

from the side-chain degradation product was tedious. It was reasoned that ozonolysis of methyl fusidate (2; R = Me) combined with neutral or oxidative work-up might yield an acidic side-chain degradation product which could be readily separated. We found that



dimethyl sulphide work-up¹⁵ of the ozonide at -78°C was effective. The triacetate (8) was obtained and isolated readily in 85% yield.

Removal of the 11- and 16-Acetoxy-groups, Synthesis of Androstanone (15).—An efficient route to (15) from the triacetate (8) was sought. Treatment of (8) with either pyridine, acetic and/or zinc in acetic acid readily

¹⁴ W. P. Griffith, 'The Chemistry of the Rarer Platinum Metals', Interscience, London, 1967, p. 156.

¹⁵ J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Letters*, 1966, 4273; P. S. Bailey, S. S. Bath, F. Dobinson, F. J. Garcia-Sharp, and C. D. Johnson, *J. Org. Chem.*, 1964, 29, 697.

¹⁰ E. Fischer, *Ber.*, 1961, 49, 584.

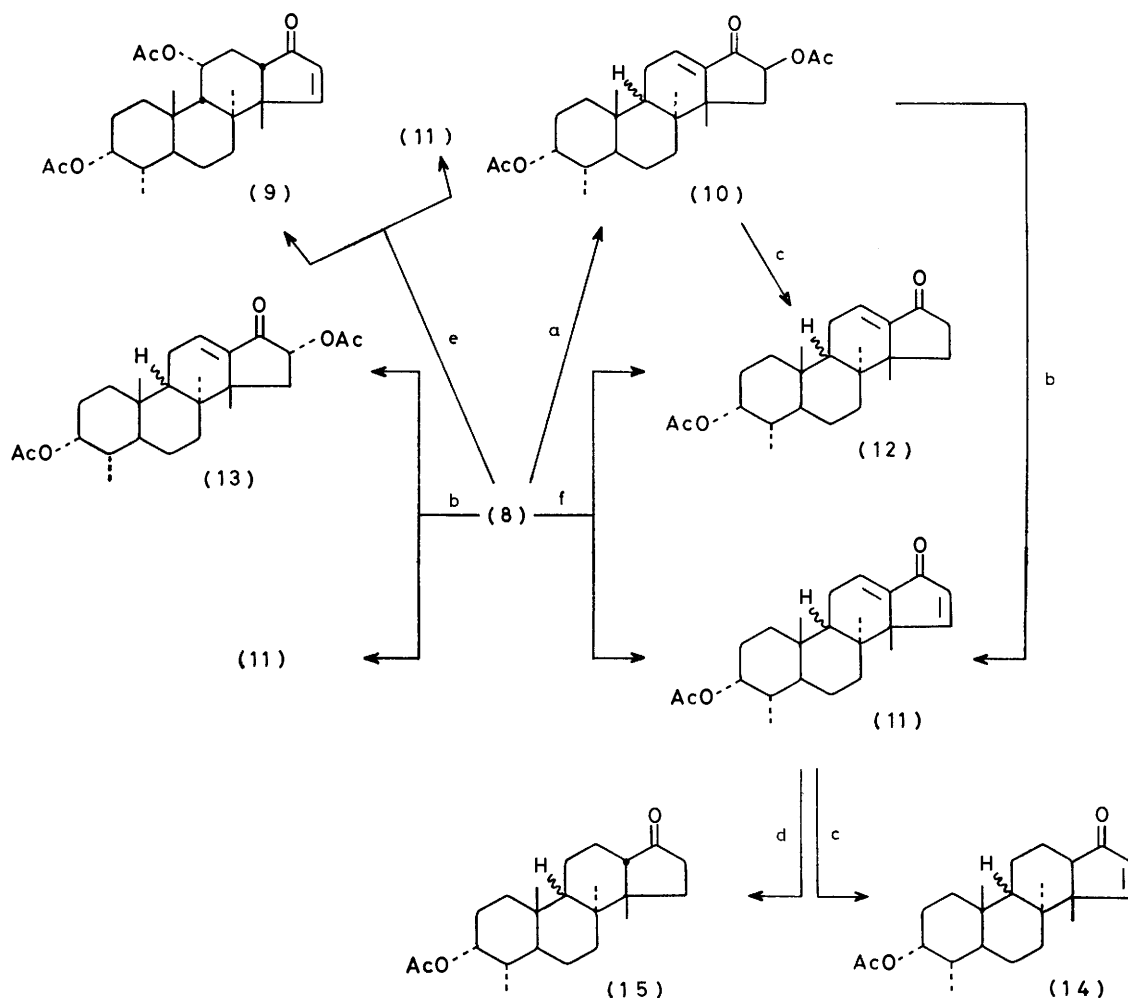
¹¹ V. M. Parikh and J. K. N. Jones, *Canad. J. Chem.*, 1965, 43, 3452.

¹² F. M. Dean and J. C. Knight, *J. Chem. Soc.*, 1962, 4745.

¹³ U. A. Spitzer and D. G. Lee, *J. Org. Chem.*, 1975, 40, 2539.

effected elimination of the 11-acetoxy-group (see Scheme). Elimination of the 16-acetoxy-group occurred only under acidic conditions. The isolation of acetate (13) from the acid treatment of (8) suggests that normally loss of the 16-acetoxy-group occurred faster than epimerisation at C-16 probably for stereoelectronic reasons.¹⁶ This we confirmed by deuteration experiments (see below). Formation of the enone (12) from both the reaction of (8) and (10) with zinc in acetic acid suggested two mechanisms for the loss of the 16-acetoxy-group: either reductive cleavage by electron transfer¹⁷

from the intermediate (10) and not from the dienone (11), during the zinc-acetic acid treatment of the diacetate (8). The reduction of the conjugated dienone (11) to the enone (14) by zinc in acetic acid is noteworthy. An analogous reduction has recently been observed.¹⁸ We noted also that triacetate (8) reacted with activated alumina. When stirred with a suspension of alumina (Grade 1) in methylene chloride, triacetate (8) was converted to a mixture of (9) and (11). This provided a route to the hitherto difficultly³ accessible enone (9). The most convenient and highest yielding route to



SCHEME a, py, reflux, 18 h. b, HOAc, reflux 18 h, unidentified product also formed. c, Zn-HOAc, reflux 4 h. d, H₂-Pd. e, Al₂O₃-CH₂Cl₂. f, Zn-HOAc reflux 4 h, unidentified product and (9) also formed

or elimination followed by reduction of the consequent C(15)-16 double-bond. The dienone (11) was therefore treated with zinc in acetic acid under the same conditions as were used in the reactions of (8) and (10). None of the enone (12) was formed. Two unidentified products were detected as well as enone (14) which was isolated (20%). Therefore the enone (12) is derived

(15) from (8) is: (8) → (10) → (11) → (15). The overall synthesis of (15) from (2; R = Me) is a marked improvement on the previous³ synthetic scheme which involved more frequent and difficult separations and much lower yields.

Mechanism of the Elimination of the 11 α -Acetoxy-group from the Triacetate (8).—Since the configuration of C-9 in (15) is dependent on the mechanism of the elimination

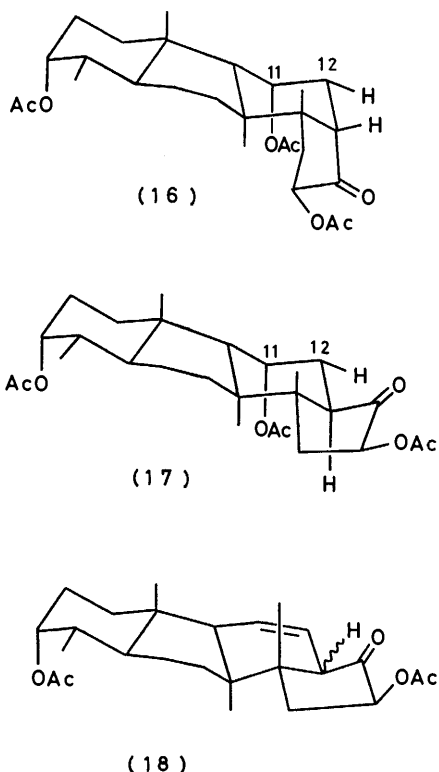
¹⁶ (a) H. E. Zimmerman and A. Mais, *J. Amer. Chem. Soc.*, 1959, **81**, 3644; (b) H. O. House, 'Modern Synthetic Reactions', Benjamin, California, 1972, p. 160.

¹⁷ Ref. 16b, p. 158.

¹⁸ F. Toda and K. Iida, *Chemistry Letters*, 1976, 695.

of the 11α -acetoxy-group, we decided to investigate it in detail. Krakower and his co-workers³ treated (8) with zinc in acetic acid.¹⁹ As well as (11) and (12) (see Scheme) they also isolated (9) (<1%). On the basis of detecting (9) they suggested³ that 'epimerisation at C-13 can be an important factor in the relative ease of elimination of the 11α -acetoxy-group due to the presence of three 1,3-interactions (8-CH₃, 11-OAc, and C-17) in the 13β -epimer (16). The pyrolytic *cis*-elimination of the acetoxy-group would then give a $\Delta^{11-\beta}$ -unsaturated ketone (18, 13β -epimer) which on conjugation would give the Δ^{12-17} -one (10). It would be attractive to suggest that (9) is the precursor to (11) and that refluxing (8) in acetic acid alone would be sufficient to produce these compounds. This hypothesis has as yet not been tested.'

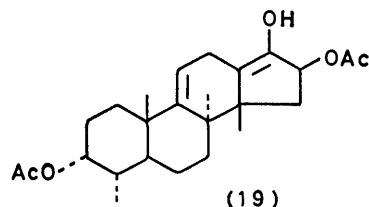
First, inspection of models indicates that in both the 13β -epimer (16) and 13α -epimer (17) of triacetate (8) the dihedral angle between the 11α -acetoxy-groups and the 12α -hydrogen is 60° . Pyrolytic *cis*-elimination of either (9) or (10) to (18), therefore seemed improbable.



The possibility, however, was tested by heating the triacetate (8) under reflux in both toluene and xylene for 24 h. No reaction occurred. Triacetate (8) was recovered. Thermal *cis*-elimination of the 11α -acetoxy-group in boiling acetic acid can, therefore, be ruled out. The enone (9) was not a precursor to (11) as suggested by Krakower.³ Heating the enone (9) with zinc in acetic acid under reflux for 4 h resulted in the recovery of (9).

¹⁹ R. S. Rosenfeld and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1955, **77**, 4367.

No dienone (11) was formed. A trace of an unidentified product was detected. Under the same conditions in acetic acid, (9) was recovered almost completely unchanged. Traces of both the dienone (11) and an unidentified product were observed. Elimination of the 11α -acetoxy-group is catalysed by both acetic acid and pyridine (see Scheme). Also we have noted in some reactions of (2; R = Me) (see above) and others²⁰ that elimination of the 11α -acetoxy-group from a 13α -system gave the corresponding $\Delta^{9(11)}$ -product. We, therefore, suggest that the reactions of (8) (see Scheme) involve the intermediate dienol (19), or the corresponding enolate, which then undergoes prototropic rearrangement to

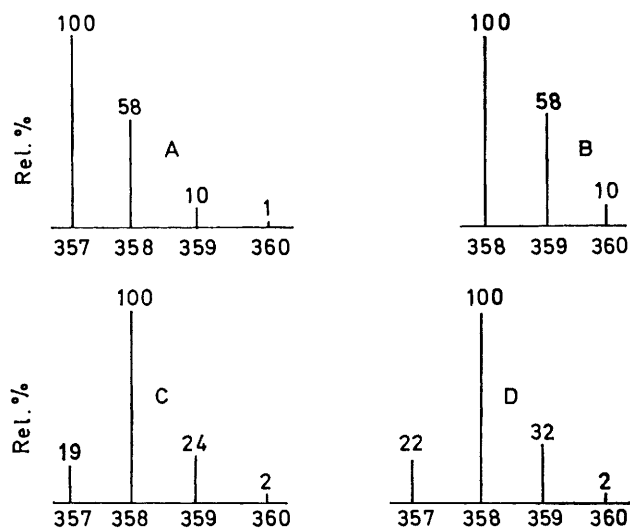


(10) *via* a conjugated dienol. In consequence, a 9β -configuration cannot be assumed in androstanone (15). As further evidence of C-9 involvement in the elimination of the 11α -acetoxy-group from (8) we undertook the reaction of (8) with zinc in deuterioacetic acid (DOAc). Involvement of C-9 should result in deuterium incorporation at that position. Deuteriated (11) was isolated and its ¹H FT n.m.r. and mass spectra were investigated.

Comparison between the ¹H n.m.r. spectra of the dienone (11) and deuteriated (11) shows that virtually complete monodeuteration has occurred at C-11 with a consequent collapse of the C-12 proton triplet at τ 3.47 to a doublet. Deuteration at C-16 is 25%, determined by integration of the H-16 doublet at τ 3.85. This partial deuteration of C-16 was confirmed by the appearance of the finely split singlet at τ 2.48 together with the finely split doublet centred at τ 2.48. The finely split doublet is 15-H and since it is coupled to 16-H ($J = 4.5$ Hz), it collapses to a finely split singlet on deuteration of C-16. We have been unable to determine the origin of the fine splitting of 15-H. The low incorporation of deuterium at C-16 is, no doubt, due to competition between elimination and enolisation. The ¹H n.m.r. was incapable of detecting deuteration at C-9. The mass spectrum of the deuteriated dienone (11) was therefore investigated. We shall confine this discussion to the groups of ions centred around m/e 358 (M'^+) {dideuteriated dienone (11)}, m/e 298 {(M')⁺ - CH₃CO₂H}, and m/e 283 {(M')⁺ - CH₃CO₂H - CH₃}. The relative abundance within the 358 group is 357 (22%), 358 (100%), 359 (32%), and 360 (2%) (see Figure). This group of

²⁰ (a) D. Arigoni, W. von Daehne, W. O. Godtfredsen, A. Melera, and S. Vangedal, *Experientia*, 1964, **20**, 344; (b) W. O. Godtfredsen, W. von Daehne, S. Vangedal, D. Arigoni, A. Marquet, and A. Melera, *Tetrahedron*, 1965, **21**, 3505; (c) D. Arigoni, W. von Daehne, W. O. Godtfredsen, A. Marquet, and A. Melera, *Experientia*, 1963, **19**, 521.

molecular ions must arise from either a composite of mono-deuteriated (C-11) dienone (11) and di-deuteriated (C-11 and -16) dienone (11) in the ratio of 1 : $\frac{1}{3}$ (from n.m.r.), or di-deuteriated (C-9 and -11) dienone (11) and tri-deuteriated (C-9, -11, and -16) dienone (11) in the ratio of 1 : $\frac{1}{3}$ (from n.m.r.). The expected spectrum for both extreme possibilities was calculated (see Figure) from natural abundance data²¹ and the n.m.r. spectrum. It is evident (see Figure) that tri-deuteriation has



A, Calculated mass spectrum of a composite of the mono- and di-deuteriated dienone (11) in the ratio 1 : $\frac{1}{3}$. B, Calculated mass spectrum of a composite of the di- and tri-deuteriated dienone (11) in the ratio 1 : $\frac{1}{3}$. C, Calculated mass spectrum of a composite of A (16%) and B (84%). D, observed mass spectrum.

occurred. The relative abundance of the ion m/e 357 (22%) indicates at least 84% incorporation of deuterium at C-9. A similar analysis of the groups of ions centred around the ions m/e 298 and 283 confirms this.

In conclusion then, we have shown that a β -configuration for (15) cannot be assigned unambiguously to C-9. However, the assignment of a 9β -configuration may be fortuitously correct. Some evidence for a 9β -configuration has been obtained³ from the position of the equilibrium between (15) and its 13α -epimer as determined by c.d.

EXPERIMENTAL

N.m.r. spectra were obtained for solutions in $CDCl_3$ at 60 MHz. I.r. spectra were recorded for KBr discs. Optical rotations were recorded for solutions in chloroform at ambient temperature with a Perkin-Elmer 141 polarimeter.

Methyl fusidate (2; R = Me) was synthesised from fusidic acid^{2c} according to the method of Godtfredsen and Vangedal.²² Methyl 24,25-dihydrofusidate 3,11-diacetate³ was synthesised from the corresponding diene by partial hydrogenation with a Brown hydrogenator.²³ T.l.c. plates were coated with silica gel G or GF254 and eluted with 40 or 50% ethyl acetate-light petroleum (b.p. 60–80 °C). Visualisation was most effective when plates

²¹ K. Biemann, 'Mass Spectroscopy', McGraw-Hill, New York, 1962, p. 63.

were sprayed with sulphuric acid–0.5% salicylaldehyde and heated. A wider range of colours was observed than with sulphuric acid alone. Where appropriate, u.v. visualisation was also used.

Synthesis of Methyl Fusidate 3,11-Diacetate (4).—(a) Methyl fusidate (2; R = Me) (250 mg) was dissolved in the acylating solution (1.25 ml). This solution was prepared by dissolving toluene-*p*-sulphonic acid (10 g) in a mixture of acetic acid (40 ml) and acetic anhydride (20 ml). The reaction was set aside for 40 min. An oil was isolated (200 mg) which contained no methyl fusidate. Repeated multiple elution preparative t.l.c. resulted in the isolation of four compounds, two of which could not be crystallised. Assignments are based on n.m.r. and i.r. (no OH stretch) spectroscopy: methyl fusidate 3,11-diacetate (4) identified by comparison with an authentic sample (see below); methyl 24,25-dihydrofusidate 3,11,25-triacetate (5) (40 mg); recrystallised from MeOH–H₂O to give a white solid, m.p. 163–165 °C $[\alpha]_D^{25} -24^\circ$ (*c* 0.6 $CHCl_3$) (Found: C, 68.0; H, 8.5. $C_{36}H_{58}O_{10}$ requires C, 67.7; H, 8.7%); τ 4.20 (1 H, d, 16-H), 4.77br (1 H, s, 11-H), 5.10br (1 H, s, 3-H), 6.40 (3 H, s, CO₂Me), 7.97, 8.01, 8.05, 8.08 (12 H, 4 \times s, 4 \times OAc), 8.62 (6 H, s, 26-H₃ + 27-H₃), 8.65 (3 H, s, 32-H₃), 9.03, 9.08 (6 H, 2 s, 18-H₃ + 19-H₃), and 9.20 (3 H, d, *J* = 6 Hz 30-H₃); methyl $\Delta^{9,11}$ -24,25-dihydrofusidate 3,25-diacetate (6) (20 mg), τ 4.14 (1 H, d, *J* = 8 Hz, 16-H), 4.60br (1 H, s, 11-H), 5.13 (1 H, s, 3-H), 6.37 (3 H, s, CO₂Me), 7.97, 8.03, 8.08 (9 H, 3 \times s, 3 \times OAc), 8.60 (6 H, s, 26-H₃ + 27-H₃), 8.78 (3 H, s, 32-H₃), 9.01, 9.11 (6 H, 2 s, 18-H₃ + 19-H₃) 9.20 (3 H, d, *J* = 6 Hz, 30-H₃); methyl $\Delta^{9,11}$ -fusidate 3-acetate (7) (20 mg), τ 4.20 (1 H, d, *J* = 8 Hz, 16-H), 4.66 (1 H, t, *J* = 8 Hz, 11-H), 4.86–5.25 (2 H, m, 24-H + 3-H), 6.43 (3 H, s, CO₂Me), 8.05, 8.10 (6 H, 2 s, 2 \times OAc), 8.40, 8.47 (6 H, s, 26-H₃ + 27-H₃), 8.85 (3 H, s, 32-H₃), 9.07, 9.23 (6 H, 2 s, 18-H₃ + 19-H₃), and 9.22 (3 H, d, *J* = 6 Hz 30-H₃).

(b) Methyl fusidate (2; R = Me) (18.8 g) and fused sodium acetate (12 g) were heated under reflux in acetic anhydride (150 ml) 2.5 h. The solution was poured into water (1 l) containing acetic acid (100 ml) and stirred 2 h. The oil slowly solidified. Recrystallisation from ethanol yielded white methyl fusidate 3,11-diacetate (4) (20.91 g, 97.5%), m.p. 109–110 °C, $[\alpha]_D^{25} -28^\circ$ (*c* 1 $CHCl_3$) (Found: C, 69.9; H, 8.8. $C_{36}H_{54}O_8$ requires C, 70.3; H, 8.9%); ν_{max} 1 730 cm^{-1} ; τ 4.25 (1 H, d, *J* = 8 Hz, 16-H), 4.7–5.3 (3 H, m, 3-H + 11-H + 24-H), 6.45 (3 H, s, CO₂Me), 8.04, 8.07, 8.17 (9 H, 3 \times s, 3 \times OAc), 8.40 (3 H, s, 27-H₃), 8.50 (3 H, s, 26-H₃), 8.70 (3 H, s, 32-H₃), 9.10 (3 H, s, 18-H₃), 9.15 (3 H, s, 19-H₃), and 9.25 (3 H, d, *J* = 6 Hz, 30-H₃).

Cleavage of the Side-chain.—(a) Ruthenium tetraoxide. A solution of methyl 24,25-dihydrofusidate 3,11-diacetate (7.0 g) in alcohol-free chloroform (70 ml) was added to a solution of sodium metaperiodate (17.5 g) in water (70 ml). Solid ruthenium dioxide (1.2 g) was added. The reaction was vigorously stirred. Further portions (9.0 g, each) of sodium metaperiodate were added over a 10-day period. Work-up gave, after treatment with charcoal and recrystallisation from methanol–water, the white solid androstanone (8) (4.77 g, 88%), m.p. 151–156 °C (lit.,³ 149–151 °C), $[\alpha]_D^{25} -107^\circ$ (*c* 1 $CHCl_3$) (lit.,³ -104°); ν_{max} 1 760sh (cyclopentanone), and 1 735 (OAc) cm^{-1} ; τ 4.72br (2 H, 11-H + 16-H), 5.10 br (1 H, s, 3-H), 7.90, 7.96, 8.01 (9 H, 3 \times s,

²² W. O. Godtfredsen and S. Vangedal, *Tetrahedron*, 1962, **18**, 1029.

²³ C. A. Brown and H. C. Brown, *J. Org. Chem.*, 1966, **31**, 3989.

3 × OAc), 8.53 (3 H, s, 32-H₃), 9.03 (6 H, s, 18-H₃ + 19-H₃), 9.18 (3 H, d, $J = 6$ Hz, 30-H₃). Purification of mother liquors by preparative t.l.c. afforded a small quantity (50 mg) of *androstenone* (10) (see below) and *methyl 6-methyl-2-oxoheptanoate* (500 mg) as an oil, b.p. 42 °C (10.1 mmHg), ν_{\max} 1 730 and 1 735 cm⁻¹; τ 6.20 (3 H, s, CO₂Me), 7.20 (2 H, t, $J = 7$ Hz, -COCH₂-), 7.6—8.9 (7 H, complex, alkyl), 9.1, 9.2 (6 H, 2 × d, $J = 7$ Hz, 2 × Me). *2,4-Dinitrophenylhydrazone derivative*; m.p. 94—96 °C (Found: C, 51.1; H, 5.7; N, 16.1. C₁₅H₂₀O₆H₄ requires C, 51.1; H, 5.7; N, 15.9%), τ 0.95 (d), 1.65 (q), 1.95 (aromatic H, d, J_{ortho} 10 Hz, J_{meta} 3 Hz), 6.15 (3 H, s, CO₂Me), 7.32 (2 H, t, $J = 8$ Hz, -CH₂C=N-), 8.2—8.9 (alkyl CH, complex), 9.1, 9.2 (6 H, 2 × d, $J = 7$ Hz, 2 × Me).

(b) *Ozone*. A solution of methyl fusidate 3,11-diacetate (4) (20.9 g) in redistilled dry methylene chloride (400 ml) and redistilled dry pyridine (4 ml) was cooled to -78 °C. Ozonised oxygen (0.45 mol O₃ l⁻¹) passed through the solution at 35 l h⁻¹ until the appearance of a deep blue colour (7½ h). Dimethyl sulphide (10 ml) was injected at -78 °C and the solution warmed to room temperature. Work-up yielded *androstanone* (8) (14.1 g, 88%) as an oil which t.l.c. indicated had only minute traces of impurities undetectable by n.m.r. Compound (8) was normally used as such without further purification. It is extremely difficult to crystallise.³

Reactions of Oxotriacetate (8).—(a) *Reflux in toluene*. A solution of the triacetate (8) (500 mg) in dry toluene (25 ml) was heated under reflux 18 h. The isolated product (470 mg) was seen by i.r. and n.m.r. spectroscopy to be unchanged (8). Inspection by multiple-elution t.l.c. confirmed this. Only minute traces of other materials were formed.

(b) *Reflux in xylene*. A solution of the triacetate (8) (200 mg) in xylene (20 ml) was heated under reflux 24 h. The recovered triacetate (180 mg) was unchanged.

(c) *Reflux in acetic acid with zinc dust*. A solution of the triacetate (8) (200 mg) in acetic acid (20 ml) was heated under reflux with zinc powder (400 mg) with stirring for 4 h. A clear gum was isolated which consisted of at least four components. These were separated by preparative t.l.c. The slowest moving band was dienone (11) (30 mg) (see below). The second band was Δ^{12} -en-17-one (12) (60 mg). Its structure was proved by comparison with an authentic sample (see below). The third band (20 mg) was a complex mixture according to its n.m.r. spectrum. The fastest moving band (5 mg) was probably the 11-acetate- Δ^{15} -17-androstanone (9). It had the same R_F value as authentic material (see below).

(d) *Reflux in acetic acid*. A solution of the triacetate (8) (1.0 g) was heated under reflux in redistilled acetic acid (50 ml) 24 h. T.l.c. indicated one major and two minor components. This crude product was separated by column chromatography on silica gel (30 g) in a gradient of ether-light petroleum. Fractions 17—22 yielded pure *androstenone* (13) (110 mg), m.p. 148—149 °C, $[\alpha]_D^{20} -132^\circ$ (c 2.3, MeOH) (Found: C, 72.1; H, 8.8. C₂₅H₃₆O₅ requires C, 72.1; H, 8.7%); τ 3.20 (1 H, t, $J = 8$ Hz, 16-H), 4.46br (1 H, s, 12-H), 5.10br (1 H, s, 3-H), 7.96 (6 H, s, 2 × OAc), 8.85 (1 H, s, 32-H₃), 9.09 (6 H, s, 18-H₃ + 19-H₃), and 9.11 (3 H, d, $J = 6$ Hz, 30-H₃). Fractions 24—28 afforded a yellow *compound* (140 mg), m.p. 159—169 °C, as yet unidentified (Found: C, 69.0; H, 8.1%), τ 3.27 (1 H, d, $J = 5$ Hz), 4.12 (1 H, d, $J = 5$ Hz), 5.06br (1 H, s, 3-H), 7.30—7.75 (m), 7.95 (6 H, s, 2 × OAc), 8.85 (9 H, s, 18-H₃ + 19-H₃ + 32-H₃) and 9.14 (3 H, d, $J = 6$ Hz, 30-H₃); M^+ 356. Fractions 30—45 afforded the dienone (11)

(360 mg), m.p. 170—171 °C (lit.,³ 173—175°) (Found: C, 76.9; H, 9.2. Calc. for C₂₅H₃₂O₃: C, 77.5; H, 9.1%); $[\alpha]_D^{20} -47^\circ$ (c 1) (lit.,³ -47°); ν_{\max} 1 730 (OAc), 1 690 ($\alpha\beta,\alpha\beta'$ unsat. ketone), 1 650 (C=C *s-cis* conj.), and 1 565 (C=C *s-trans* conj.) cm⁻¹; τ 2.53 (1H, d, $J = 7$ Hz, 15-H), 3.53 (1 H, t, $J = 3$ Hz, 12-H), 3.91 (1 H, d, $J = 7$ Hz, 16 H), 5.09br (1 H, s, 3-H), 7.95 (3 H, s, 3-OAc), 8.82, 8.94, 9.20 (9 H, s, 18-H₃ + 19-H₃ + 32-H₃), and 9.15 (3 H, d, $J = 5$ Hz, 30-H₃).

(e) *Reflux in pyridine*. A solution of the triacetate (8) (1.0 g) was heated under reflux 24 h in dry redistilled pyridine. T.l.c. indicated one product only which was the 16 β -acetate (10) (620 mg), m.p. 209—211 °C (decomp.) (methanol-water) (Found: C, 72.0; H, 8.7. C₂₅H₃₆O₅ requires C, 72.1; H, 8.7%); ν_{\max} 1 735 (OAc) and 1 655 (C=C, *s-cis* conj.) cm⁻¹; τ 3.46 (1 H, d, $J = 5$ Hz, 12-H), 4.58 (1 H, t, $J = 4$ Hz, 16 H), 5.08br (1 H, s, 3-H), 7.98 (6 H, s, 2 × OAc), 8.77 (3 H, s, 32-H₃), 8.86 (6 H, s, 18-H₃ + 19-H₃), and 9.15 (3 H, d, $J = 6$ Hz, 30-H₃). When piperidine was used extensive decomposition occurred. With triethylamine-chloroform, the reaction took the same course as pyridine but much more slowly.

Reaction of 16 β -Acetate (10) with Acetic Acid.—The acetate (10) (400 mg) was heated under reflux 18 h in redistilled acetic acid. The crude product (280 mg) was a gum and consisted of dienone (11) and a minor unidentified side-product previously observed from the reaction of (8) with acetic acid. The dienone (11) (215 mg), m.p. 172—174° (lit.,³ 173—175 °C) was isolated by treatment with charcoal and recrystallisation from methanol-water.

Reaction of the 16 β -Acetate (10) with Zinc in Acetic Acid.—A solution of the 16 β -acetate (10) (150 mg) in redistilled acetic acid (15 ml) was heated under reflux with zinc powder for 4 h. A pale yellow gum was isolated of which the enone (12) was the major product with traces of other products. The enone (12) (110 mg) was isolated by preparative t.l.c., m.p. 138—140 °C (lit.,³ 138—140 °C), $[\alpha]_D^{20} -260^\circ$ (c 1); τ 3.50 (1 H, d, $J = 4$ Hz, 12-H), 5.19br (1 H, s, 3-H), 7.96 (3 H, s, 3-OAc), 8.85, 8.98, 8.90 (9 H, 3 × s, 3 × Me), and 9.19 (3 H, d, $J = 6$ Hz, 30-H₃). A small quantity (5 mg) of the dienone (11) was also isolated.

Reaction of the Triacetate (8) with Alumina.—The oxotriacetate (8) (17 g) in methylene chloride (500 ml) was stirred with alumina (activity I, 500 g) for 1 h. The alumina was filtered off and surprisingly the methylene chloride did not contain either reactant (8) or products. The alumina was extracted (4 × 500 ml) with chloroform (containing 1% ethanol). The resulting gum was crystallised from acetone-hexane. The white solid (2 g) consisted of two components which were separated by preparative t.l.c. The minor component was the dienone (11) (240 mg). The major component (360 mg) was the 11 α -acetate (9), m.p. 210—213 °C (lit.,³ 215—217 °C) (Found: C, 72.1; H, 8.6. Calc. for C₂₅H₃₆O₅: C, 72.1; H, 8.7%); ν_{\max} 1 735 (acetate), 1 695 (cyclopentanone, conj. *s-trans*), and 1 585 (conj. C=C) cm⁻¹; $[\alpha]_{589}^{20} -76^\circ$, $[\alpha]_{578}^{20} -78^\circ$, $[\alpha]_{546}^{20} -86^\circ$, $[\alpha]_{436}^{20} -110^\circ$, $[\alpha]_{365}^{20} +72^\circ$ (c 1, CHCl₃) (lit.,³ $[\alpha] -82, -85, -94, -121, +35^\circ$); τ 2.61 (1 H, d, $J = 6$ Hz, 16-H), 3.96 (1 H, d, $J = 6$ Hz, 15-H), 4.83 br (1 H, m, 11-H), 5.05 br (1 H, s, 3-H), 8.01 (6 H, s, 11- + 3-OAc), 8.81, 8.91, 8.96 (3 H each, s, 3 × CH₃), and 9.18 (3 H, d, $J = 5$ Hz, 30-H₃).

Reaction of the 11 α -Acetate (9) with Zinc in Acetic Acid.—The solution of the 11 α -acetate (9) (100 mg) in acetic acid (8 ml) was heated under reflux with zinc dust (200 mg). A pale yellow solid (110 mg) was recovered which consisted

(t.l.c.) almost entirely of the 11 α -acetate (9) with a minor product which has an R_F value greater than that of the dienone (11). Recrystallisation of the crude product from ethanol-water afforded the 11 α -acetate (9) (80 mg).

Reaction of the 11 α -Acetate (9) with Acetic Acid.—A solution of the 11 α -acetate (9) in acetic acid (8 ml) was heated under reflux for 24 h. The recovered gum (100 mg) consisted (t.l.c.) mainly of 11 α -acetate (9) and two minor components, one of which corresponded with the dienone (11) and the other with that observed with zinc present.

Reaction of the Dienone (11) with Zinc in Acetic Acid.—A solution of the dienone (11) (100 mg) in redistilled acetic acid (10 ml) was heated under reflux and stirred with zinc powder (200 mg) 4 h. T.l.c. indicated the presence of three products. Whilst the two minor ones were not identified, the slowest-moving component was isolated by preparative t.l.c. and identified as the *enone* (14) (20 mg), m.p. 150—152 °C (Found: C, 76.8; H, 9.5. $C_{23}H_{34}O_3$ requires C, 77.1; H, 9.6%); τ 2.6 (1 H, d, $J = 6$ Hz, 15-H), 3.88 (1 H, d, $J = 6$ Hz, 16-H), 5.12 br (1 H, s, 3-H), 7.96 (3 H, s, OAc), 8.75, 8.95, 9.21 (9 H, 3 \times s, 18-H₃ + 19-H₃ + 32-

H₃), and 9.19 (3 H, d, $J = 8$ Hz, 30-H₃). Unchanged starting material (30 mg) was also recovered.

Hydrogenation of the Dienone (11).—A solution of the dienone (11) (520 mg) in acetic acid was injected into a pre-equilibrated Brown hydrogenator.²⁰ The catalyst was 10% Pd on BaSO₄ (250 mg) in acetic acid (10 ml). Sodium borohydride (0.1M) was used. Consumption of borohydride had ceased after 55 min. The androstanone (15) (470 mg, 90%) was isolated, m.p. 143—145° (lit.,³ 143—145°) (Found: C, 76.3; H, 10.0. Calc. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1%), $[\alpha]_D^{25} + 18^\circ$ (c 1, CHCl₃) (lit.,³ +18°); ν_{max} 1 730 cm⁻¹ (OAc + C=O); τ 5.10br (1 H, s, 3-H), 7.5—7.9 (3 H, complex, 13-H + 16-H₂), 7.97 (3 H, s, 3-OAc), 8.72, 9.08, 9.10 (9 H, 3 \times s, 3 \times Me), and 9.20 (3 H, d, $J = 6$ Hz, 30-H₃).

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