

## Functionalisation of Saturated Hydrocarbons. Part 3. The Oxidation of 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -Triacetoxysteroids using the Gif System

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The minor products from the oxidation of 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triacetoxysteroids using the Gif System [iron cluster-metallic zinc-pyridine-(aqueous) acetic acid-triplet oxygen] have been identified. The nature of the side-chain fragmentation to give 20-ketones has been clarified. Some mechanistic explanation has been offered for this unusual process.

We have recently reported on the oxidation of several cholesterol derivatives using the Gif system.<sup>1</sup> In each case, the respective side-chain fission products (the 20-ketones) were obtained as the major products, together with some other steroidal ketones (usually the 15- and 16-keto derivatives) which were formed in lesser amounts. In the oxidation of 3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triacetoxysteroid (1) with the Gif system the three major products were the 20-ketone (2) (12%), the 15-ketone (8) (7%), and the 16-ketone (9) (6%). We now report on the minor products formed in this reaction and present some evidence bearing on the cleavage of the side chain.

After an initial chromatographic separation of the crude reaction mixture into three fractions, *i.e.* the unchanged starting material [the triacetate (1)], a *non-polar fraction* and a *polar fraction*, the compounds described here were obtained by separation of the non-polar fraction by h.p.l.c. (see Figure 1). Since the polar fraction was a minor proportion of the oxidised material, it was only studied as a mixture in lesser detail.

Apart from the major oxidation product, the 20-ketone (2), the Gif system appears to oxidise exclusively the secondary positions into ketones. We were able to isolate from the non-polar fraction all possible ring ketones with the exception of the 4-ketone, although some were only found in very minor amounts. The 4-position is apparently either too sterically hindered or electronically deactivated by the acetate groups to undergo reaction. The most abundant ring ketone was found to be the 15-ketone (8) followed by the 16-ketone (9) and the least abundant, as expected, the 11-ketone (6), the 11-position being the most hindered ring position. The three secondary positions of the side chain also underwent oxidation giving the corresponding ketones. Amongst these the yield of the 24-ketone (12) was large and comparable with the yields of the 15- and the 16-ketones [(8) and (9) respectively] (see Figure 2).

The formation of the 26-aldehyde (13) which is the first example of oxidation of a steroid at a primary centre by the Gif system is especially interesting. The 26-aldehyde (13) was obtained as a diastereoisomeric mixture which with time underwent further oxidation to the corresponding acids. These were separated into pure diastereoisomers [(14) and (15)].

We have also observed that the carbon-carbon bond cleavage occurs not only at the 20-22 linkage leading to the 20-ketone (2), the major product, but also at the 24-25 linkage as evident from the formation of small amounts of the 25-aldehyde (16). Furthermore, we obtained mass spectral evidence for the fragmentations of the 20-21 and/or 25-27 bonds giving 21-nor-20-ketone and/or 27-nor-25-ketone, respectively (a and b fission modes in Figure 3). There was also evidence for the formation of the 17-hydroxyandrostane derivative (23) by the fission of the C(17)-C(20) bond (c fission mode in Figure 3). We made, however, no attempt to isolate the latter compounds since they were

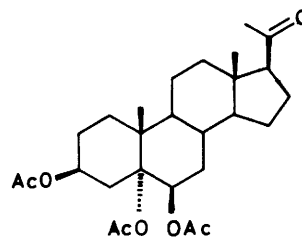
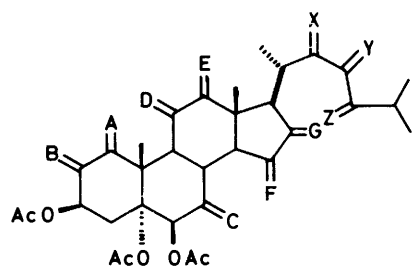
present in trace amounts. It is noteworthy that cleavages of carbon-carbon bonds always occur  $\alpha$  to a secondary centre and in the side chain rather than in the rigid steroid ring. No nucleus based seco-steroids were found in the oxidation.

*Structural Assignments.*—The oxidation products were characterised primarily by 400 MHz n.m.r. spectroscopy. The chemical shift values of the characteristic C-18 and C-19 angular methyl groups are diagnostic of the substitution pattern in the steroid nucleus and are, therefore, fundamental to structure elucidation.<sup>2,3</sup> The calculated and observed chemical shift values of the C-18 and C-19 singlets for the steroidal ring ketones were found to be in excellent agreement (see Table 1). Certain other characteristic signals such as those of the C-21 and C-26, -27 methyl groups, of the 3 $\alpha$ -, 4 $\alpha$ -, 6 $\alpha$ -protons and those of the protons  $\alpha$  to oxidised centres facilitated structure elucidation. However, in the side chain oxidised products, as expected, the C-18 and C-19 methyl signals show only very minor shifts compared with those of the parent triacetate (1); whereas shift differences of C-21 and C-26, -27 methyl groups are much more pronounced (see Table 2).

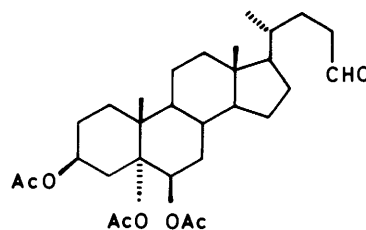
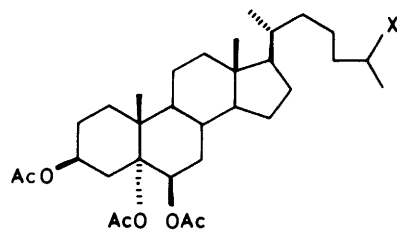
All assigned structures were further justified by molecular rotation difference studies.<sup>4,5</sup> Molecular rotation difference values ( $\Delta$ ) of both the steroidal ring ketones (see Table 3) and of the side-chain oxidised products (see Table 4) were, in general, in good agreement with  $\Delta$  values calculated from relevant literature data.

Electron-impact (e.i.) mass spectroscopy proved to be of limited use in determining the product structures. Generally, owing to simultaneous or successive loss of the acetate groups and by loss of a ketone fragment these types of compounds do not give rise to molecular peaks and additionally give poor and uncharacteristic fragmentation patterns. In certain structurally very similar cases, however, useful additional information was gained; *e.g.* the 22-ketone (10), the 23-ketone (11), and the 24-ketone (12) were easily differentiated by e.i. mass spectroscopy. All three compounds suffer cleavages  $\alpha$  to their ketonic functions. In the case of the 22-ketone (10) C(20)-C(22) bond fission results in a large peak at  $m/z$  99 (C<sub>6</sub>H<sub>11</sub>O<sup>+</sup>); in the case of the 23-ketone (11) the large peak at  $m/z$  85 (C<sub>5</sub>H<sub>9</sub>O<sup>+</sup>) arises from scission of the 22-23 bond. In the 24-ketone (12) the cleavage is observed at the C(23)-C(24) linkage giving a large peak at  $m/z$  71 (C<sub>4</sub>H<sub>7</sub>O<sup>+</sup>). The e.i. spectra of two compounds are atypical. The base peak of the 12-ketone (7) is the molecular ion at  $m/z$  560; the spectrum of the 7-ketone (5) consists effectively of a single peak at  $m/z$  398 which is apparently due to the loss of two acetic acid molecules and a ketene unit from the molecular ion, forming a highly conjugated stable ion.

Chemical ionisation (c.i./NH<sub>3</sub>) mass spectroscopy,<sup>6</sup> on the other hand, proved to be a more useful technique in the



- (1) A = B = C = D = E = F = G = X = Y = Z = H<sub>2</sub>  
 (3) A = O, B = C = D = E = F = G = X = Y = Z = H<sub>2</sub>  
 (4) B = O, A = C = D = E = F = G = X = Y = Z = H<sub>2</sub>  
 (5) C = O, A = B = D = E = F = G = X = Y = Z = H<sub>2</sub>  
 (6) D = O, A = B = C = E = F = G = X = Y = Z = H<sub>2</sub>  
 (7) E = O, A = B = C = D = F = G = X = Y = Z = H<sub>2</sub>  
 (8) F = O, A = B = C = D = E = G = X = Y = Z = H<sub>2</sub>  
 (9) G = O, A = B = C = D = E = F = X = Y = Z = H<sub>2</sub>  
 (10) X = O, A = B = C = D = E = F = G = Y = Z = H<sub>2</sub>  
 (11) Y = O, A = B = C = D = E = F = G = X = Z = H<sub>2</sub>  
 (12) Z = O, A = B = C = D = E = F = G = X = Y = H<sub>2</sub>



- (13) X = CHO (25*R,S*)  
 (14) X = CO<sub>2</sub>H (25*R*)  
 (15) X = CO<sub>2</sub>H (25*S*)

(16)

investigation of the oxidation products, especially in rapid determination of the molecular weights and, therefore, of the oxidation states of the products. For all compounds very large  $MNH_4^+$  peaks were obtained almost always as the base peaks. The simple fragmentation patterns usually related to the loss of one, two, and three acetic acid molecules. The *c.i./NH<sub>3</sub>* spectrum of the 11-ketone (6) is as follows: the  $MNH_4^+$  peak at  $m/z$  578 is the base peak which loses 28 mass units to give a peak at  $m/z$  550 (probably the C-1 and C-2 carbons as ethylene). The base peak also loses three acetic acid molecules ( $-180$ ) giving a peak at  $m/z$  398. The peak at  $m/z$  440 can be rationalised by the loss of two acetic acid molecules ( $-120$ ) from the molecular ion. Since the peak at  $m/z$  398 is formed from  $m/z$  440 by loss of 42 mass units (ketene), it is reasonable to assume that the C-11, C-12 units are lost as ketene, and that, furthermore, the  $NH_4^+$  group is attached to the C-11 carbonyl. Another interesting example of these chemical ionisation spectra is that of the diastereoisomeric 26-acids [(14) and (15)]. Both compounds display, beside a large  $MNH_4^+$  peak at  $m/z$  594, an exceptionally large peak at  $m/z$  102 which is the base peak in

both cases. Ions of mass 102 could possibly be formed by fragmentation of the C(22)–C(23) linkage as shown in Scheme 1.

The structure of the 26-aldehyde (13) was determined unambiguously by common spectroscopic techniques. The *c.i./NH<sub>3</sub>* mass spectrum was indicative of a compound with molecular weight 560 and the i.r. spectrum contained the typical aldehyde C–H stretch at  $2700\text{ cm}^{-1}$ . The aldehyde nature of the product was further confirmed by the presence of a one proton doublet at 9.61 p.p.m. in the n.m.r. spectrum, and, furthermore, the characteristic six proton doublet of the starting material at 0.86 p.p.m. had been transformed into a three-proton doublet at lower field at 1.09 p.p.m. Facile oxidation of this compound yielded a mixture of two very polar compounds in equimolar amounts which were separated by h.p.l.c. and shown to be the two diastereoisomeric 26-acids [(14) and (15)]. Spectroscopically these two compounds were virtually indistinguishable (i.e., mass spec., n.m.r.), however, the use of molecular rotation differences enabled us to differentiate between them. The (25*R*)-26-acids are known to have a molecular rotation difference of  $-9$  (ref. 7) whereas there only exists one precedent

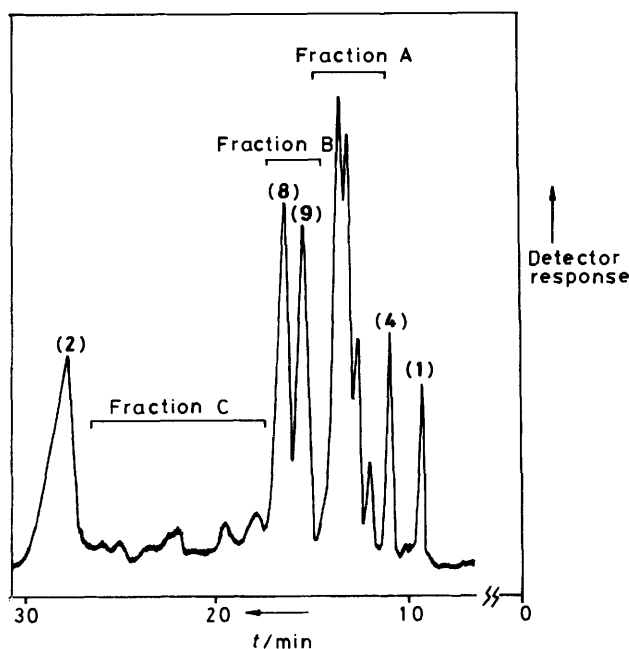


Figure 1. H.p.l.c.-separation of the non-polar fraction (Column: preparative normal phase; solvent: hexane-20% ethyl acetate; flow rate: 3.0 ml/min; detector: refractive index).

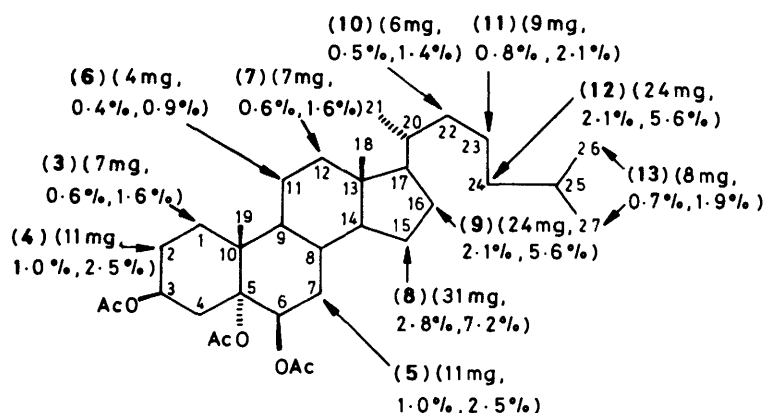


Figure 2. Oxidation of the triacetate (1) using the Gif system—primary oxidation products. Yields: (i) in mg, (ii) in mole % absolute, and (iii) in mole % based upon starting material consumed (in parentheses).

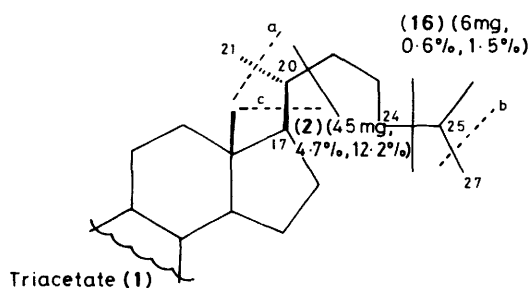
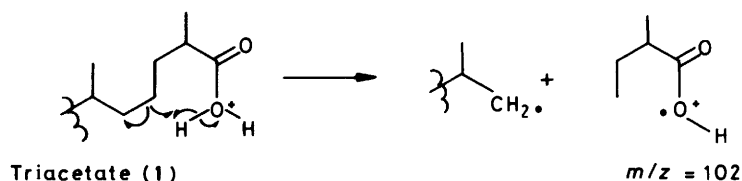


Figure 3. Oxidation of the triacetate (1) using the Gif system—side-chain fragmentation products (for compounds formed by the a, b, and c fission modes see text).

in the (25*S*) series: for a (25*S*)-26-acid of low (23%) optical purity a molecular rotation difference of +51 was calculated (the rotation of the acid being measured in methanol).<sup>7</sup> We

found for the (25*R*)-26-acid (14) the value -9 and for the (25*S*)-26-acid (15) +78.

*Desorption Chemical Ionisation Analysis of Mixtures.*—The compounds described so far constitute more than 60% of the total non-polar fraction. It was, however, surprising that no secondary or tertiary alcohols were detected, in view of the well known formation in the Gif system of such alcohols as minor products and the fact that the secondary alcohols do not suffer further oxidation to ketones.<sup>8</sup> Both fraction C obtained from the non-polar fraction (57 mg) (see Figure 1), which showed a very weak OH absorption in the i.r. region, and the polar fraction (120 mg), with a stronger absorption in the 3 000—3 600  $\text{cm}^{-1}$  region, were analysed for such products by desorption chemical ionisation (d.c.i./ $\text{NH}_3$ ) technique. Thus the major peaks in the higher mass region of the d.c.i. spectra were suggestive of the trace constituents in the mixtures when compared with the  $\text{MNH}_4^+$  peak of the triacetate (1) at  $m/z$  564. Surprisingly, small amounts of mono-alcohols of the



Scheme 1.

**Table 1.** Chemical shifts of C-18 and C-19 methyl protons in the steroidal ring ketones

Compd. Triacetate	Ketone position	C-18 Calc. (Found)	C-19 Calc. (Found)
(1)	—	—	—
(3)	1-	0.70 (0.71)	1.57 (1.42)
(4)	2-	0.69 (0.69)	1.16 (1.12)
(5)	7-	0.69 (0.69)	1.47 (1.41)
(6)	11-	0.65 (0.67)	1.41 (1.41)
(7)	12-	1.06 (1.07)	1.29 (1.30)
(8)	15-	0.76 (0.78)	1.20 (1.20)
(9)	16-	0.85 (0.85)	1.23 (1.24)

**Table 2.** Chemical shifts of C-18, C-19, C-21, and C-26, -27 methyl protons in the side chain oxidised products

Compd.	Position	C-18	C-19	C-21	C-26, -27
Triacetate					
(1)		0.68	1.19	0.90	0.86
(10)	22-Ketone	0.72	1.21	1.10	0.90
(11)	23-Ketone	0.74	1.20	0.90	0.92
(12)	24-Ketone	0.68	1.19	0.90	1.09
(13)	26-Aldehyde (25 <i>R,S</i> )	0.69	1.20	0.91	1.09*
(14)	26-Acid (25 <i>R</i> )	0.69	1.20	0.91	1.19*
(15)	26-Acid (25 <i>S</i> )	0.69	1.20	0.91	1.19*
(2)	20-Ketone	0.63	1.19	ca. 2.00	—
(16)	24-Aldehyde	0.70	1.20	0.93	—

\* C-27 methyl group only.

triacetate (1) ( $m/z$  580) were detected in the fraction C and none were found in the polar fraction. The main constituents of these mixtures were poly-functionalised, *i.e.* further oxidised forms of the 20-ketone (2) and of the triacetate (1). The following structures were tentatively assigned as derivatives of the 20-ketone (2): (i) with an extra unsaturation ( $m/z$  492), (ii) with an extra carbonyl group ( $m/z$  508), (iii) containing an additional hydroxy group ( $m/z$  510), (iv) with both extra hydroxy and carbonyl groups ( $m/z$  524). Derivatives of the triacetate (1) were found: (i) with both an additional carbonyl group and a double bond ( $m/z$  576), (ii) with an additional hydroxy group plus unsaturation ( $m/z$  578), (iii) as a mono-alcohol ( $m/z$  580), (iv) with two carbonyl groups ( $m/z$  592), (v) with a carbonyl in addition to a hydroxy group ( $m/z$  594). It is, however, feasible that the unsaturations found in the above structures may have arisen by elimination of water from the corresponding alcohols in the mass spectrometer. In these fractions, all the side-chain fragmentation products shown in Figure 3 were also detected.

**Table 3.** Molecular rotation relationships of the steroidal ring ketones

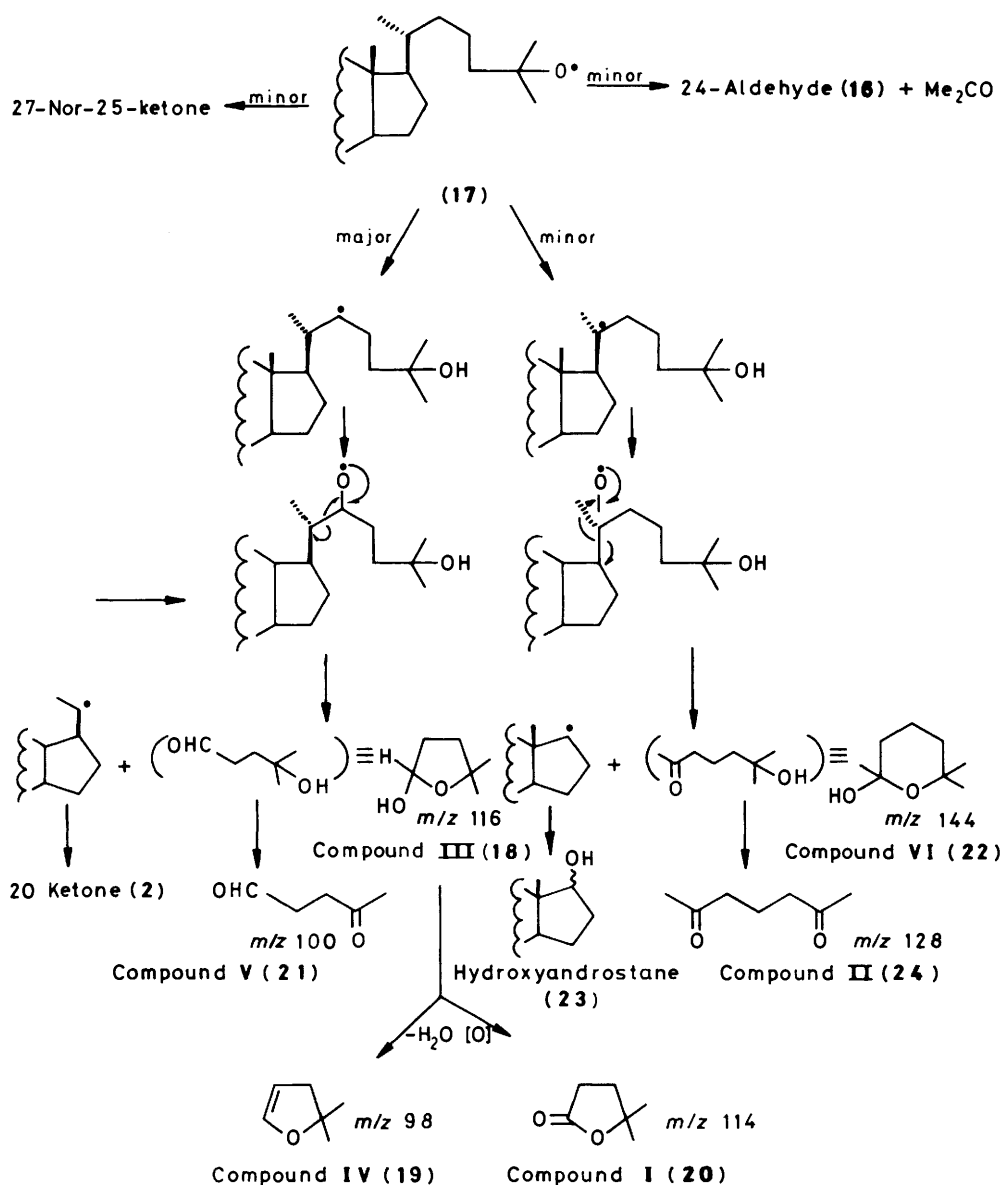
Compd. Triacetate	Ketone position	$[\alpha]_D^{25}$ (c)	$M_D^{25}$	$\Delta^*$ Calc. (Found)
(1)		-33.0 (1.0)	-180	
(3)	1-	+15.3 (0.6)	+86	+339 <sup>a</sup> (+266)
(4)	2-	+6.6 (1.1)	+37	+278 <sup>b</sup> (+217)
(5)	7-	-67.0 (1.2)	-376	-318 <sup>c</sup> (-196)
(6)	11-	-19.8 (0.5)	-111	+79 <sup>a</sup> (+69)
(7)	12-	+9.6 (1.4)	+54	+270 <sup>a</sup> (+234)
(8)	15-	-10.0 (2.9)	-56	+106 <sup>a</sup> (+124)
(9)	16-	-90.2 (1.3)	-506	-507 <sup>d</sup> (-326)

\* Molecular rotation differences ( $\Delta$ ) as defined (D. H. R. Barton and W. Klyne, *Chem. Ind.*, 1948, 755) were calculated using the following model structures: (a) respective 5 $\alpha$ -cholestanones and 5 $\alpha$ -cholestane;<sup>5</sup> (b) 2-oxo-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate (K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, 1961, 26, 4563) and 5 $\alpha$ -cholestan-3 $\beta$ -yl acetate; (c) 7-oxo-5 $\alpha$ -cholestan-6 $\beta$ -yl acetate (C. W. Dawey, E. L. McGinnis, J. M. McKeown, G. D. Meakins, M. W. Pemberton, and R. N. Young, *J. Chem. Soc. C*, 1968, 2674) and 5 $\alpha$ -cholestan-6 $\beta$ -yl acetate (C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1952, 3361); (d) kurchiphylline and dihydrodesoxokurchiphylline (M. M. Janot, P. Longevialle, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1966, 1212).

In addition to the 20-ketone (2) ( $m/z$  494), the 24-aldehyde (16) ( $m/z$  536) and the corresponding acid derivative ( $m/z$  552 which could also be interpreted as an hydroxy-24-aldehyde), the peaks at  $m/z$  564 were indicative of the 21-nor-20-ketone and/or the 27-nor-25 ketone derivatives of the triacetate (1). Furthermore, the peaks at  $m/z$  468 were tentatively assigned to the hydroxy-androstane (23) formed by C(17)–C(20) bond fission in the parent compound (fission mode c in Figure 3). It is noteworthy that fission here results in an alcohol rather than in a ketone ( $m/z$  466 was absent).

The low mass end of the d.c.i. spectra of fraction C contained two principal peaks, the base peak at  $m/z$  132 and a further peak at  $m/z$  146. It was shown by various techniques that these peaks were not fragment ions but the molecular peaks ( $MNH_4^+$ ) of two relatively volatile compounds with molecular weights of 114 [compound I, (20)] and of 128 [compound II, (24)], respectively. These compounds undoubtedly arise from various cleavages of the steroidal side chain in the oxidation reaction (see below).

*Mode of Side-chain Cleavage.*—The formation of the 20-ketone (2) as the major product in the Gif system oxidation of the triacetate (1) implies that the cleaved side chain is found as a C-6 or other low molecular weight fragment. A volatile fraction, obtained from the crude reaction mixture by distillation, as well as the pentane or ether extracts of the solid residue left after



Scheme 2. Mechanism for side-chain cleavage of triacetate (1).

distillation were examined for such products by g.c.—mass spec. and d.c.i. Apart from the usual reagents (pyridine,  $m/z$  79; acetic acid,  $m/z$  60), solvents (ether,  $m/z$  74) and the common oxidation by-products (bipyridines,  $m/z$  156),<sup>9</sup> the above mixtures contained several products. Every mixture contained acetone ( $m/z$  58) as proven by e.i. and c.i./NH<sub>3</sub> and CH<sub>4</sub> ionisation and further confirmed by mass chromatography performed on the molecular ions and the main fragments of the compound. Undoubtedly, acetone is derived from the C-25, -26, -27 carbons in the formation of the 24-aldehyde (16). A possible C<sub>6</sub> unit involved in the formation of the 20-ketone (2), 4-methylpentanal (molecular weight 100) was not present in these mixtures. The major components detected were a compound with molecular weight 116 (compound III), a compound with that of 114 (compound I) and a compound with molecular weight 98 (compound IV). It is evident that all three compounds are (formally) further oxidised forms of the expected 4-methylpentanal. The e.i. mass spectrum of compound III

showed a very weak  $M^+$  but an intense  $M - Me^{7+}$  and a somewhat less intense  $M - OH^{7+}$  and  $M - H_2O^{7+}$  ions. The c.i./NH<sub>3</sub> spectrum was characterised by the  $MNH_4^+$  peak at  $m/z$  134, the base peak, fragmentation of which gave an intense peak at  $m/z$  117 due to loss of an hydroxyl radical. The c.i./CH<sub>4</sub> spectrum displayed a weak  $MH^+$  peak at  $m/z$  117 but a strong peak at  $m/z$  99. Consequently we have assigned the 5-hydroxy-2,2-dimethyltetrahydrofuran (18) structure to this compound. Comparison with an authentic specimen<sup>10</sup> verified this assignment. The e.i. and c.i./NH<sub>3</sub> mass spectra of compound IV compared favourably with those of authentic 2,2-dimethyl-2,3-dihydrofuran (19)<sup>10</sup> (the e.i. mass spectrum contained a large  $M^+$  peak at  $m/z$  98 and the c.i./NH<sub>3</sub> spectrum possessed the  $MNH_4^+$  peak as the base peak at  $m/z$  116 and an intense peak at  $m/z$  99). The mass spectra of compound I were consistent with the lactone structure (20) which we did not further investigate.

The volatile fraction as well as the organic extracts contained

**Table 4.** Molecular rotation relationships of the side-chain oxidised products

Compd.	Position	$[\alpha]_D^{25}$ <sup>CHCl<sub>3</sub>/c</sup>	$M_D^{10}$	$\Delta^*$ Calc. (Found)
(1)		-33.0 (1.0)	-180	
(10)	22-Ketone	-42.8 (0.4)	-240	-100 <sup>a</sup> (-60)
(11)	23-Ketone	-30.9 (0.9)	-173	-19 <sup>b</sup> (+7)
(12)	24-Ketone	-28.0 (0.8)	-157	-10 <sup>c</sup> (+23)
(13)	26-Aldehyde (25 <i>R,S</i> )	-30.5 (0.6)	-171	-
(14)	26-Acid (25 <i>R</i> )	-32.8 (0.4)	-189	+9 -9 <sup>d</sup>
(15)	26-Acid (25 <i>S</i> )	-18.8 (0.2)	-108	-9 +51 <sup>e</sup>
(2)	20-Ketone	-8.9 (3.0)	-42	+78 197 <sup>f</sup>
(16)	24-Aldehyde	-36.5 (0.4)	-189	+138 -9 <sup>g</sup> (-9)

\* Molecular rotation differences ( $\Delta$ ) were calculated using the following model systems: (a) 22-oxo-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate (L. F. Fieser and W.-Y. Huang, *J. Am. Chem. Soc.*, 1953, **75**, 5356) and 5 $\alpha$ -cholestan-3 $\beta$ -yl acetate; (b) 23-oxocholest-5-en-3 $\beta$ -ol [M. Tanabe and K. Hayashi, *J. Am. Chem. Soc.*, 1980, **102**(2), 862] and cholesterol; (c) 24-oxo-5 $\alpha$ -cholestan-3 $\beta$ -yl acetate [W. Sucrow and W. Littmann, *Chem. Ber.*, 1976, **109**(8), 2884] and 5 $\alpha$ -cholestan-3 $\beta$ -yl acetate; (d) (25*R*)-26-carboxycholest-5- $\beta$ -yl acetate<sup>7</sup> and cholesteryl acetate; (e) (25*S*)-3 $\beta$ -hydroxycholest-5-en-26-oic acid (23% optical purity, in methanol)<sup>7</sup> and cholesterol (in chloroform); (f) 3 $\beta$ -hydroxy-5 $\alpha$ -pregnan-20-one (ref. 5, p. 541) and 5 $\alpha$ -cholestan-3 $\beta$ -ol; (g) allocholanic acid (ref. 5, pp. 28, 54) and 5 $\alpha$ -cholestane (ref. 5, pp. 28, 54).

a further compound with molecular weight of 100 (compound V). The molecular formula of this compound was shown to be C<sub>5</sub>H<sub>8</sub>O<sub>2</sub> (not C<sub>6</sub>H<sub>12</sub>O  $\equiv$  4-methylpentanal) by high resolution mass spectroscopy. The e.i. spectrum of compound V was consistent with it being 4-oxopentanal (21). With time, this compound oxidised to a more polar compound of molecular weight 116 which differed from compound III (18) in both retention time (g.c.) and in fragmentation pattern (mass spec.).

We have also found side chain fragments formed by fission of the steroidal C(17)-C(20) bond. A minor compound with molecular weight of 144 (compound VI) was tentatively assigned the 2-hydroxy-2,6,6-trimethyltetrahydropyran (22) structure, formed in a similar way to the compound III (18). Another compound detected by g.c.-mass spec. had a molecular weight of 128 (compound II). Interestingly, this compound was not 6-methylheptan-2-one (C<sub>8</sub>H<sub>16</sub>O), but had molecular formula of C<sub>7</sub>H<sub>12</sub>O<sub>2</sub> (high resolution mass spec.). We have assigned to this compound the heptane-2,6-dione (24) structure, the mass spectrum being in excellent agreement with this structure. This compound may arise, analogous to the formation of the compound V (21), by a further fragmentation of the C(25)-C(27) bond.

Some of the compounds described above were sufficiently stable and non-volatile to enable them to be detected in the h.p.l.c. separation of the steroids; i.e. the compound III (18) co-migrated in fraction A and was found as a major impurity of the 1-ketone (3); compound I (20) and compound II (24) were also detected in fraction C as mentioned above.

All the side-chain fragmentation products described above appear to have an oxygen function (or a potential oxygen function; e.g. unsaturation) at C-25 as a common feature. We are, therefore, inclined to suggest that they all originate from a

common precursor, i.e. from the 25-hydroxyl radical (17). Consideration of these observations leads us to propose the mechanism for side-chain cleavage shown in Scheme 2. The 25-hydroxyl radical (17), probably formed *via* a hydroperoxide undergoes fragmentation to give the minor products 27-nor-25-ketone and the 24-aldehyde (16). Hydrogen abstraction from the 22-position *via* a six-membered transition state by the same 25-hydroxyl radical (17) leads eventually to the major observed products, the 20-ketone (2) and the compound III (18). Hydrogen abstraction from the 20-position by a less favourable seven-membered transition state leads to the more stable tertiary radical and subsequently to the other minor products, i.e. hydroxyandrostane (23), compound VI (22), etc.

This detailed study of the oxidation of a steroid shows that the Gif system, at least as it is now constituted, is unlikely to compete with the excellent template procedure of Breslow.<sup>11</sup> However, if it could be modified to act in the template manner the results should be interesting.

### Experimental

The general experimental detail is as described in our earlier paper.<sup>1</sup> All rotations were measured in chloroform unless otherwise specified. <sup>1</sup>H N.m.r. spectra were obtained for solutions in deuteriochloroform on a 400 MHz Bruker WM 400 instrument. Mass spectroscopic experiments were performed using a Riber R-1010 quadrupole mass spectrometer (NERMAG, France), in the positive ionisation mode. Spectra were recorded and calculated on a PDP 8/M computer coupled to the spectrometer. Typical analytical conditions for c.i. were: source temperature 200–220 °C, the 5 mm filament (tungsten wire 60  $\mu$ m, 9 turns) was heated from 300–1 000 °C in 40s (current programmed from 200–600 mA, 10 mA s<sup>-1</sup>). The source was indirectly heated by a filament (variation of 10 °C)—for this reason the direct probe was removed at the end of the programme. The pressure of reagent gases (CH<sub>4</sub> or NH<sub>3</sub>), measured at the secondary vacuum gauge, was 10<sup>-4</sup> Torr. A constant alimation of buffer gas (He) was maintained. For reagent gases the initial pressure was ca. 3 Torr and the mean electron energy was maintained at 80 eV. The reagent gases ammonia and methane were obtained from Air Liquide (Alpha Gaz, France). E.i. spectra were recorded at 70 eV, direct probe temperature 70–200 °C, g.c.—mass spectrometry was performed on the above system using an OV-17 capillary column (25 m). Exact mass measurements were carried out with a VG 70-35E spectrometer in the dynamic mode.

*Oxidation of 5 $\alpha$ -Cholestane-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triyl Triacetate (1).*—The ether extracts of the crude reaction mixture obtained, as previously described<sup>1</sup> by oxidation of the triacetate (1) (1.092 g, 2 mmol), were washed with 5% sodium hydrogen carbonate,\* saturated aqueous sodium chloride, and water, dried (MgSO<sub>4</sub>), and evaporated to yield the crude oxidation mixture. This was then applied to a column of silica gel and eluted with hexane-ether (30%) giving first the unchanged starting material (670 mg, 61.3%). Further elution with the same solvent (ca. 600 ml) afforded the non-polar fraction (310 mg). Then by gradual increase of solvent polarity to hexane-ether (80%) the column was thoroughly washed (ca. 1 l), which gave the polar fraction (120 mg).

In order to investigate the volatile by-products, these were distilled from the crude oxidation mixture under reduced pressure at room temperature and condensed in a liquid

\* The basic extracts were acidified and extracted further with ether in order to isolate the steroidal acids. This acidic fraction (23 mg) which constituted only a very minor part of the total oxidation, was not further examined.

nitrogen trap. The residue was then further extracted with small amounts of ether or pentane.

*H.P.L.C. Separation of the Non-polar Fraction.*—The non-polar fraction obtained by column chromatography was first separated on a normal phase preparative h.p.l.c. column (hexane–20% ethyl acetate, 3 ml/min) to afford the following fractions: starting material triacetate (1) (trace,  $R_f$  9 min); the 2-ketone (4) (11 mg,  $R_f$  11 min); fraction A (71.5 mg,  $R_f$  11.5–14.6 min; a complex mixture); fraction B (62.7 mg,  $R_f$  14.6–17.3 min; consisting mainly of the 16-ketone (9),  $R_f$  15.3 min and the 15-ketone (8),  $R_f$  16.3 min); fraction C (57.5 mg,  $R_f$  17.3–27 min; a complex mixture of minor compounds) and the 20-ketone (2) (45 mg,  $R_f$  27.8 min). Fractions collected after the 20-ketone (2) ( $R_f$  > 30.6 min) were subsequently added to the polar fraction.

*H.P.L.C. Separation of Fraction A.*—This fraction was purified on a reverse-phase preparative h.p.l.c. column (acetonitrile–4.5% water–0.5% acetic acid, 4 ml/min) to give the following fractions: fraction D (40 mg,  $R_f$  10.3–12 min, a mixture of the 22-, 23-, and 24-ketones [(10), (11), and (12)]); the 26-aldehyde (13) (8 mg,  $R_f$  13.3 min); the 11-ketone (6) (4 mg,  $R_f$  15.8 min); compound III (18) [trace, a shoulder on the 1-ketone (3)]; the 1-ketone (3) (7 mg,  $R_f$  22.5 min), and the 7-ketone (5) (11 mg,  $R_f$  25 min).

Fraction D was resolved into two peaks by increasing the water content of the eluant (acetonitrile–10% water–0.5% acetic acid, 4 ml/min). This afforded the 23-ketone (11) (9 mg,  $R_f$  23 min) and the 22- and 24-ketones [(10) and (12)] (30.5 mg,  $R_f$  24 min). The 22- and 24-ketones [(10) and (12)] were then further separated on a normal phase preparative h.p.l.c. column (hexane–9% ethyl acetate–0.5% acetic acid, 3 ml/min) which gave the 22-ketone (10) (6 mg,  $R_f$  37 min) and the 24-ketone (12) (24 mg,  $R_f$  38.5 mg).

With time, the pure 26-aldehyde (13) and mixtures containing the 26-aldehyde (13) underwent further oxidation giving two polar compounds in equimolar amounts only traces of which were present in the original fraction A. These were separated on a reverse-phase preparative h.p.l.c. column (acetonitrile–10% water–0.5% acetic acid, 4 ml/min) affording the (25*S*)-26-acid (15) ( $R_f$  15 min) and the (25*R*)-26-acid (14) ( $R_f$  15.8 min).

*H.P.L.C. Separation of Fraction B.*—This fraction was purified on a reverse-phase preparative h.p.l.c. column (acetonitrile–4.5% water–0.5% acetic acid, 4 ml/min) giving the 12-ketone (7) (7 mg,  $R_f$  13 min); the 16-ketone (9) (24 mg,  $R_f$  14.6 min), and the 15-ketone (8) (31 mg,  $R_f$  15.5 min) (Note: the 16-ketone (9) has a shorter  $R_f$  than the 15-ketone (8) on both normal and reverse phase columns.)

*Investigation of Fraction C.*—We did not attempt to resolve this complex mixture completely, but only isolated the least polar major compound. Application of the mixture on a reverse-phase h.p.l.c. column (acetonitrile–4.5% water–0.5% acetic acid, 4 ml/min) allowed the isolation of the 24-aldehyde (16) (6 mg,  $R_f$  7.4 min) which decomposed with time to a still more polar compound. Fraction C [after removal of (16)];  $\nu_{\max}(\text{CCl}_4)$  3 000–3 600  $\text{cm}^{-1}$  (weak OH);  $m/z$  (d.c.i./ $\text{NH}_3$ ) 132 (100%) [compound I (20)], 146 [compound II (24)], 468 [probably the hydroxyandrostane (23)], 475 (an unidentified ion), 492 [the 20-ketone (2) with an extra unsaturation], 508 [the 20-ketone (2) with an extra carbonyl group], 510 [the 20-ketone (2) with an extra hydroxy group], 564 [21-nor-20-ketone or 27-nor-25-ketone derivative of the triacetate (1)], 576 [the triacetate (1) containing an ene-one group], 578 [the triacetate (1) nor-20-ketone or 27-nor-25-ketone derivative of the triacetate (1)], 576

[the triacetate (1) containing an ene-one group], 578 [the triacetate (1) containing an ene-ol group], 580 [the triacetate (1) plus an hydroxy group], 592 [the triacetate (1) with two carbonyl groups], and 594 [the triacetate (1) with one carbonyl and one hydroxy group].

*Investigation of the Polar Fraction.*—No separation of this complex mixture was attempted;  $\nu_{\max}(\text{CHCl}_3)$  3 000–3 600 (strong OH) and 1 640–1 780 (acetate and ketone CO); d.c.i./ $\text{NH}_3$ ,  $m/z$  168 (100%) (an unidentified ion), 468 [probably the hydroxyandrostane (23)], 482 [the hydroxyandrostane (23) with an extra carbonyl group], 492 [the 20-ketone (2) containing an extra unsaturation], 508 [the 20-ketone (2) with an extra carbonyl group], 510 [the 20-ketone (2) with an additional hydroxy group], 524 [the 20-ketone (2) containing one hydroxy and one carbonyl group], 528 [ $3\beta,5\alpha,6\beta$ -triacetoxyallopregnane with three hydroxy groups], 542 [the 20-ketone (2) with three extra hydroxy groups], 564 [21-nor-20-ketone or 27-nor-25-ketone derivative of the triacetate (1)], and 578 [the triacetate (1) containing an ene-ol group].

*Oxidation Products.*—The spectroscopic and analytical data of the triacetate (1), the 15-ketone (8), the 16-ketone (9) and those of the 20-ketone (2) were given in our previous publication.<sup>1</sup>

The 1-ketone (3) (7 mg, 0.6%, 1.6%),\* m.p. 129–131 °C (methanol);  $[\alpha]_D + 15.3^\circ$  ( $c$  0.6);  $\nu_{\max}(\text{CCl}_4)$  1 695–1 760  $\text{cm}^{-1}$  (acetate and ketone CO);  $\delta_{\text{H}}$  0.71 (3 H, s, 18-Me), 0.88 (6 H, d,  $J$  7.5 Hz, 26,27-Me),  $\ddagger$  0.93 (3 H, d,  $J$  7.5 Hz, 21-Me), 1.42 (3 H, s, 19-Me), 2.02, 2.05, and 2.14 (9 H, 3 s,  $3 \times \text{MeCO}_2$ ), 2.34 and 2.77 (2 H, 2 m, 2 $\alpha$ -H and 2 $\beta$ -H), 3.01 (1 H, m, 4 $\alpha$ -H), 4.88 (1 H, m, 3 $\alpha$ -H), and 5.98 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./ $\text{NH}_3$ ) 578 ( $\text{MNH}_4^+$ , 100%);  $m/z$  560 ( $M^+$  not present), 440, 398, 380 (100%), 370, 352, and 267 [Found:  $m/z$  (e.i.), 440.3318.  $\text{C}_{29}\text{H}_{44}\text{O}_3$  ( $M^+ - 2 \times \text{MeCO}_2\text{H}$ ) requires 440.3289], [Found:  $m/z$ , 398.3241.  $\text{C}_{27}\text{H}_{42}\text{O}_2$  ( $\text{C}_{29}\text{H}_{44}\text{O}_3 - \text{CH}_2\text{CO}$ ) requires 398.3182], [Found:  $m/z$ , 380.3052.  $\text{C}_{27}\text{H}_{40}\text{O}$  ( $\text{C}_{27}\text{H}_{42}\text{O}_2 - \text{H}_2\text{O}$ ) requires 380.3077], and [Found:  $m/z$ , 370.3208.  $\text{C}_{26}\text{H}_{42}\text{O}$  ( $\text{C}_{27}\text{H}_{42}\text{O}_2 - \text{CO}$ ) requires 370.3234].

The 2-ketone (4) (11 mg, 1.0%, 2.5%), m.p. 84–87 °C (acetone–water);  $[\alpha]_D + 6.6^\circ$  ( $c$  1.1);  $\nu_{\max}(\text{CCl}_4)$  1 690–1 760  $\text{cm}^{-1}$  (acetate and ketone CO);  $\delta_{\text{H}}$  0.69 (3 H, s, 18-Me), 0.87 (6 H, dd,  $J$  6.5 Hz, 26,27-Me), 0.92 (3 H, d,  $J$  6.5 Hz, 21-Me), 1.12 (3 H, s, 19-Me), 2.08, 2.15 and 2.17 (9 H, 3 s,  $3 \times \text{MeCO}_2$ ), 2.31 and 2.69 (2 H, 2 d,  $J$  13.5 Hz, 1 $\alpha$ -H and 1 $\beta$ -H), 3.28 (1 H, m, 4 $\alpha$ -H), 5.12 (1 H, m, 3 $\alpha$ -H), and 6.01 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./ $\text{NH}_3$ ) 578 ( $\text{MNH}_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$  not present), 543, 458, 440, 398 (100%), and 383 [Found:  $m/z$ , 458.3398.  $\text{C}_{29}\text{H}_{46}\text{O}_4$  ( $M^+ - \text{MeCO}_2\text{H} - \text{CH}_2\text{CO}$ ) requires 458.3394], [Found:  $m/z$ , 440.3261.  $\text{C}_{29}\text{H}_{44}\text{O}_3$  ( $M^+ - 2 \times \text{MeCO}_2\text{H}$ ) requires 440.3289], [Found:  $m/z$ , 398.3167.  $\text{C}_{27}\text{H}_{42}\text{O}_2$  ( $\text{C}_{29}\text{H}_{44}\text{O}_3 - \text{CH}_2\text{CO}$ ) requires 398.3182], and [Found:  $m/z$ , 383.2933.  $\text{C}_{26}\text{H}_{39}\text{O}_2$  ( $\text{C}_{27}\text{H}_{42}\text{O}_2 - \text{Me}$ ) requires 383.2949].

The 7-ketone (5) (11 mg, 1.0%, 2.5%), m.p. 153–156 °C (methanol);  $[\alpha]_D - 67.0^\circ$  ( $c$  1.2);  $\nu_{\max}(\text{CCl}_4)$  1 710–1 760  $\text{cm}^{-1}$  (acetate and ketone CO);  $\delta_{\text{H}}$  0.69 (3 H, s, 18-Me), 0.87 (6 H, dd,  $J$  7.5 Hz, 26,27-Me), 0.92 (3 H, d,  $J$  7.5 Hz, 21-Me), 1.41 (3 H, s, 19-Me), 2.00, 2.02, and 2.13 (9 H, 3 s,  $3 \times \text{MeCO}_2$ ), 2.71 (1 H, t,  $J$  10.7 Hz, 8 $\beta$ -H), 2.98 (1 H, m, 4 $\alpha$ -H), 4.76 (1 H, m, 3 $\alpha$ -H), and 5.56 (1 H, s, 6 $\alpha$ -H);  $m/z$  (c.i./ $\text{NH}_3$ ) 578 ( $\text{MNH}_4^+$ , 100%);  $m/z$

\* Yields in mole % are absolute (first number) and calculated upon recovered starting material (second number).

† Frequently in the i.r. spectra the ketone, aldehyde and acid CO absorptions are obscured by the three acetate groups.

‡ Owing to magnetic non-equivalence of the 26- and 27-methyl groups in certain products two superimposed doublets are produced. In these cases the mid points of these double doublets are given with one coupling constant.

(e.i.) 560 ( $M^+$  not observed), 440, 398 (100%), 382, and 369 [Found:  $m/z$ , 398.3087.  $C_{27}H_{42}O_2$  ( $M^+ - 2 \times MeCO_2H - CH_2CO$ ) requires 398.3152].

The 11-ketone (6) (4 mg, 0.4%, 0.9%);  $[\alpha]_D -19.8^\circ$  ( $c$  0.5);  $v_{max}$  (CCl<sub>4</sub>) 1705 (ketone CO), and 1720—1760  $cm^{-1}$  (acetates);  $\delta_H$  0.67 (3 H, s, 18-Me), 0.87 (6 H, dd,  $J$  7.5 Hz, 26,27-Me), 0.88 (3 H, d,  $J$  7.5 Hz, 21-Me), 1.41 (3 H, s, 19-Me), 2.01, 2.08, and 2.10 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.35 (2 H, m, 12 $\alpha$ -H and 12 $\beta$ -H), 2.60 (1 H, d,  $J$  13 Hz, 9 $\alpha$ -H), 2.80 (1 H, m, 4 $\alpha$ ), 4.70 (1 H, m, 3 $\alpha$ -H), and 5.86 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$  not present), 440, 398 (100%), 380, and 365 [Found:  $m/z$ , 440.3250.  $C_{29}H_{44}O_3$  ( $M^+ - 2 \times MeCO_2H$ ) requires 440.3289], [Found:  $m/z$ , 398.3224.  $C_{27}H_{42}O_2$  ( $C_{29}H_{44}O_3 - CH_2CO$ ) requires 398.3182], [Found:  $m/z$ , 380.3061.  $C_{27}H_{40}O$  ( $C_{27}H_{42}O_2 - H_2O$ ) requires 380.3077], and [Found:  $m/z$ , 365.2795.  $C_{26}H_{37}O$  ( $C_{27}H_{40}O - CH_3$ ) requires 365.2843].

The 12-ketone (7) (7 mg, 0.6%, 1.6%);  $[\alpha]_D +9.6^\circ$  ( $c$  1.4);  $v_{max}$  (CCl<sub>4</sub>) 1715 (ketone CO), and 1720—1760  $cm^{-1}$  (acetates);  $\delta_H$  0.86 (3 H, d,  $J$  7 Hz, 21-Me), 0.87 (6 H, dd,  $J$  7 Hz, 26,27-Me), 1.07 (3 H, s, 18-Me), 1.30 (3 H, s, 19-Me), 2.01, 2.06, and 2.11 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.59 (2 H, m, 11 $\alpha$ -H and 11 $\beta$ -H), 2.86 (1 H, m, 4 $\alpha$ -H), 4.72 (1 H, m, 3 $\alpha$ -H), and 5.91 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$ , 100%), 500, 440, 398 (95%), 380, and 227 [Found:  $m/z$ , 560.3690.  $C_{33}H_{52}O_7$  ( $M^+$ ) requires 560.3710], [Found:  $m/z$ , 500.3515.  $C_{31}H_{48}O_5$  ( $M^+ - MeCO_2H$ ) requires 500.3499], [Found:  $m/z$ , 440.3295.  $C_{29}H_{44}O_3$  ( $C_{31}H_{48}O_5 - MeCO_2H$ ) requires 440.3289], [Found:  $m/z$ , 398.3221.  $C_{27}H_{42}O_2$  ( $C_{29}H_{44}O_3 - CH_2CO$ ) requires 398.3182], and [Found:  $m/z$ , 380.3052.  $C_{27}H_{40}O$  ( $C_{27}H_{42}O_2 - H_2O$ ) requires 380.3077].

The 22-ketone (10) (6 mg, 0.5%, 1.4%);  $[\alpha]_D -42.8^\circ$  ( $c$  0.4);  $v_{max}$  (CCl<sub>4</sub>) 1715 (ketone CO), and 1720—1760  $cm^{-1}$  (acetates);  $\delta_H$  0.72 (3 H, s, 18-Me), 0.90 (6 H, d,  $J$  7 Hz, 26,27-Me), 1.10 (3 H, d,  $J$  7 Hz, 21-Me), 1.21 (3 H, s, 19-Me), 2.01, 2.07, and 2.09 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.37 and 2.43 (2 H, 2 m, 23R- and 23S-H), 2.52 (1 H, m, 20-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.73 (1 H, m, 3 $\alpha$ -H), and 5.85 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$  not observed), 440, 398 (100%), 383, 342, 281, and 99 [Found:  $m/z$ , 440.3330.  $C_{29}H_{44}O_3$  ( $M^+ - 2 \times MeCO_2H$ ) requires 440.3289], and [Found:  $m/z$ , 398.3187.  $C_{27}H_{42}O_2$  ( $C_{29}H_{44}O_3 - CH_2CO$ ) requires 398.3182].

The 23-ketone (11) (9 mg, 0.8%, 2.1%);  $[\alpha]_D -30.9^\circ$  ( $c$  0.9);  $v_{max}$  (CCl<sub>4</sub>) 1715 (ketone CO) and 1720—1760  $cm^{-1}$  (acetates);  $\delta_H$  0.74 (3 H, s, 18-Me), 0.90 (3 H, d,  $J$  7 Hz, 21-Me), 0.92 (6 H, d,  $J$  7 Hz, 26,27-Me), 1.20 (3 H, s, 19-Me), 2.01, 2.08, and 2.09 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.14 (1 H, m, 22R- or 22S-H), 2.25 (2 H, d,  $J$  7 Hz, 24R- and 24S-H), 2.41 (1 H, m, 22R- or 22S-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.73 (1 H, m, 3 $\alpha$ -H), and 5.86 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$  not present), 440, 398 (100%), 380, 384, 340, and 85 [Found:  $m/z$ , 440.3261.  $C_{29}H_{44}O_3$  ( $M^+ - 2 \times MeCO_2H$ ) requires 440.3289], [Found:  $m/z$ , 398.3224.  $C_{27}H_{42}O_2$  ( $C_{29}H_{44}O_3 - CH_2CO$ ) requires 398.3182], and [Found:  $m/z$ , 340.2355.  $C_{23}H_{32}O_2$  ( $C_{27}H_{42}O_2 - C_4H_{10}$ ) requires 340.2401].

The 24-ketone (12) (24 mg, 2.1%, 5.6%), m.p. 156—157 °C (hexane-ether);  $[\alpha]_D -28.0^\circ$  ( $c$  0.8);  $v_{max}$  (CHCl<sub>3</sub>) 1685—1760  $cm^{-1}$  (acetate and ketone CO);  $\delta_H$  0.68 (3 H, s, 18-Me), 0.90 (3 H, d,  $J$  7 Hz, 21-Me), 1.09 (6 H, d,  $J$  7 Hz, 26,27-Me), 1.19 (3 H, s, 19-Me), 2.00, 2.06, and 2.07 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.39 and 2.45 (2 H, 2 m, 23R- and 23S-H), 2.61 (1 H, m, 25-H), 2.81 (1 H, m, 4 $\alpha$ -H), 4.72 (1 H, m, 3 $\alpha$ -H), and 5.85 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%);  $m/z$  (e.i.) 560 ( $M^+$  not observed), 440, 398 (100%), 383, 380, and 71; [Found:  $m/z$ , 440.3223.  $C_{29}H_{44}O_3$  ( $M^+ - 2 \times MeCO_2H$ ) requires 440.3289], [Found:  $m/z$ , 398.3219.  $C_{27}H_{42}O_2$  ( $C_{29}H_{44}O_3 -$

$CH_2CO$ ) requires 398.3182], [Found:  $m/z$ , 383.2940.  $C_{26}H_{39}O_2$  ( $C_{27}H_{42}O_2 - CH_3$ ) requires 383.2949], and [Found:  $m/z$ , 380.3085.  $C_{27}H_{40}O$  ( $C_{27}H_{42}O_2 - H_2O$ ) requires 380.3077] (Found: C, 70.69; H, 9.40.  $C_{33}H_{52}O_7$  requires C, 70.68; H, 9.35%).

The 26-aldehyde (13) (8 mg, 0.7%, 1.9%), oil;  $[\alpha]_D -30.5^\circ$  ( $c$  0.6);  $v_{max}$  (CCl<sub>4</sub>) 1700—1760 (acetate and aldehyde CO), and 2700  $cm^{-1}$  (aldehyde CH);  $\delta_H$  0.69 (3 H, s, 18-Me), 0.91 (3 H, d,  $J$  7 Hz, 21-Me), 1.09 (3 H, d,  $J$  7 Hz, 27-Me), 1.20 (3 H, s, 19-Me), 2.00, 2.07, and 2.08 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.35 (1 H, m, 25-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.73 (1 H, m, 3 $\alpha$ -H), 5.86 (1 H, br s, 6 $\alpha$ -H), and 9.61 (1 H, d,  $J$  1.5 Hz, CHO);  $m/z$  (c.i./NH<sub>3</sub>) 578 ( $MNH_4^+$ , 100%), with time an additional peak at  $m/z$  594 ( $MNH_4^+$  of the corresponding acids).

The (25R)-26-acid (14), m.p. ca. 95 °C (crude);  $[\alpha]_D -32.8^\circ$  ( $c$  0.4);  $v_{max}$  (CCl<sub>4</sub>) 1705 (acid CO), 1720—1760 (acetates), and 3000—3600  $cm^{-1}$  (OH);  $\delta_H$  0.69 (3 H, s, 18-Me), 0.91 (3 H, d,  $J$  7 Hz, 21-Me), 1.19 (3 H, d,  $J$  7 Hz, 27-Me), 1.20 (3 H, s, 19-Me), 2.01, 2.08, and 2.09 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.48 (1 H, m, 25-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.74 (1 H, m, 3 $\alpha$ -H), and 5.86 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 594 ( $MNH_4^+$ , 80%), and 102 (100%);  $m/z$  (e.i.) 576 ( $M^+$  not present), 575, 519, 456, 428, 414 (100%), 398, and 386; [Found:  $m/z$ , 428.3298.  $C_{28}H_{44}O_3$  ( $M^+ - 2 \times MeCO_2H - CO$ ) requires 428.3288], [Found:  $m/z$ , 414.3174.  $C_{27}H_{42}O_3$  ( $M^+ - 2 \times MeCO_2H - CH_2CO$ ) requires 414.3133], [Found:  $m/z$ , 398.3170.  $C_{27}H_{42}O_2$  ( $C_{27}H_{42}O_3 - O$ ) requires 398.3182], and [Found:  $m/z$ , 386.3207.  $C_{26}H_{42}O_2$  ( $C_{27}H_{42}O_3 - CO$ ) requires 386.3183].

The (25S)-26-acid (15), m.p. ca. 60 °C (crude);  $[\alpha]_D -18.8^\circ$  ( $c$  0.2);  $v_{max}$  (CCl<sub>4</sub>) 1705 (acid CO), 1720—1760 (acetates), and 3000—3600  $cm^{-1}$  (OH);  $\delta_H$  0.69 (3 H, s, 18-Me), 0.91 (3 H, d,  $J$  7 Hz, 21-Me), 1.19 (3 H, d,  $J$  7 Hz, 27-Me), 1.20 (3 H, s, 19-Me), 2.01, 2.08, and 2.09 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.48 (1 H, m, 25-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.74 (1 H, m, 3 $\alpha$ -H), and 5.86 (1 H, br s, 6 $\alpha$ -H);  $m/z$  (c.i./NH<sub>3</sub>) 594 ( $MNH_4^+$ , 60%), and 102 (100%);  $m/z$  (e.i.) 576 ( $M^+$  not present), 536, 525, 469, 456, 440, 428, 414 (100%), 398, and 380; [Found:  $m/z$ , 456.3126.  $C_{29}H_{44}O_4$  ( $M^+ - 2 \times MeCO_2H$ ) requires 456.3237], [Found:  $m/z$ , 428.3274.  $C_{28}H_{44}O_3$  ( $C_{29}H_{44}O_4 - CO$ ) requires 428.3288], [Found:  $m/z$ , 414.3063.  $C_{27}H_{42}O_3$  ( $C_{29}H_{44}O_4 - CH_2CO$ ) requires 414.3133], [Found:  $m/z$ , 398.3146.  $C_{27}H_{42}O_2$  ( $C_{27}H_{42}O_3 - O$ ) requires 398.3182], and [Found:  $m/z$ , 380.3054.  $C_{27}H_{40}O$  ( $C_{27}H_{42}O_2 - H_2O$ ) requires 380.3077].

The 24-aldehyde (16) (6 mg, 0.6%, 1.5%), oil;  $[\alpha]_D -36.5^\circ$  ( $c$  0.4);  $v_{max}$  (CCl<sub>4</sub>) 1715—1760 (acetate and aldehyde CO), and 2725  $cm^{-1}$  (aldehyde CH);  $\delta_H$  0.70 (3 H, s, 18-Me), 0.93 (3 H, d,  $J$  6.5 Hz, 21-Me), 1.20 (3 H, s, 19-Me), 2.01, 2.08, and 2.09 (9 H, 3 s, 3  $\times$  MeCO<sub>2</sub>), 2.38 and 2.45 (2 H, 2 m, 23R- and 23S-H), 2.82 (1 H, m, 4 $\alpha$ -H), 4.73 (1 H, m, 3 $\alpha$ -H), 5.86 (1 H, br s, 6 $\alpha$ -H), and 9.78 (1 H, br s, CHO);  $m/z$  (c.i./NH<sub>3</sub>) 536 ( $MNH_4^+$ , 100%), with time an additional peak at  $m/z$  552 ( $MNH_4^+$  of the corresponding acid);  $m/z$  (e.i.) 518 ( $M^+$  not observed), 398, 356 (100%), 341, and 328 [Found:  $m/z$ , 398.2895.  $C_{26}H_{38}O_3$  ( $M^+ - MeCO_2H$ ) requires 398.2819], [Found:  $m/z$ , 356.2697.  $C_{24}H_{36}O_2$  ( $C_{26}H_{38}O_3 - CH_2CO$ ) requires 356.2713], and [Found:  $m/z$ , 341.2512.  $C_{23}H_{33}O_2$  ( $C_{24}H_{36}O_2 - Me$ ) requires 341.2479].

2,2-Dimethyl-2,3-dihydrofuran (19).—This compound was prepared from allyl bromide and acetone *via* 3-bromo-5,5-dimethyl-tetrahydrofuran according to a literature procedure.<sup>10</sup> Repeated distillation of the latter compound from potassium hydroxide pellets ( $\times$  3) yielded a clear liquid, b.p. 77—85 °C (lit.,<sup>10</sup> 77—82 °C) which was shown by g.c. (OV-17, 4m, column: 60 °C) to consist of two compounds in a ratio of 1.5:1, the less polar being the major product; 2,2-dimethyl-2,3-dihydrofuran (19) (the less polar product),  $\delta_H$  1.29 (6 H, s, 2  $\times$  Me), 2.39 (2 H, m, CH<sub>2</sub>), 4.74 (1 H, m, CH=CHO), and 6.17



(1 H, m, CH=CHO);  $m/z$  [g.c.—mass spec. (e.i.)] 98 ( $M^+$ , 100%), 83, 69, 55, and 41;  $m/z$  (c.i./NH<sub>3</sub>) 116 ( $MNH_4^+$ ), 99 (100%), and 81; and 2,2-dimethyl-2,5-dihydrofuran (the more polar product),  $\delta_H$  1.32 (6 H, s, 2 × Me), 4.64 (2 H, m, CH<sub>2</sub>), and 5.75 (2 H, m, CH=CH);  $m/z$  [g.c.—mass spec. (e.i.)] 98 ( $M^+$  not present), 83 (100%), 55, 43, and 39;  $m/z$  (c.i./NH<sub>3</sub>) 116 ( $MNH_4^+$ ), 83 (100%), and 81.

**5-Hydroxy-2,2-dimethyltetrahydrofuran (18).**—The isomeric mixture of dihydrofurans obtained as described above was treated with glacial acetic acid for 1 h at 60–70 °C, and the unchanged dihydrofuran isomer, *i.e.* 2,2-dimethyl-2,5-dihydrofuran was subsequently removed by distillation (77–80 °C). Fractional distillation of the residue gave 5-acetoxy-2,2-dimethyltetrahydrofuran, b.p. 80–83 °C/17 mmHg. After refluxing of the above compound with aqueous potassium carbonate for 1.5 h followed by neutralisation, the reaction mixture was extracted with ether to yield 5-hydroxy-2,2-dimethyltetrahydrofuran (**18**),<sup>12</sup> b.p. 75 °C/12 mmHg,  $\nu_{max}$  (CDCl<sub>3</sub>) 3 200—3 550 and 3 600 cm<sup>-1</sup> (OH);  $\delta_H$  1.19, 1.40 (6 H, 2 s, 2 × Me), 1.74 (1 H, m, Me<sub>2</sub>C—CH), 1.97 (2 H, m, Me<sub>2</sub>C—CH—CH), 2.10 (1 H, m, Me<sub>2</sub>C—CH—CH), 3.44 (1 H, br s, OH), and 5.49 (1 H, br s, CHOH);  $m/z$  (e.i.) 116 ( $M^+$  very weak), 101, 99, 98, 83, 70, 59 (100%), 55, and 43;  $m/z$  (c.i./CH<sub>4</sub>) 101, 99 (100%), and 81; h.p.l.c. (normal phase preparative column, hexane–20% ethyl acetate, 3 ml/min),  $R_f$  13.5 min.

**Side-chain Fragments.**—Compound **III (18)**, present in the ether and pentane extracts and in fraction A,  $m/z$  (c.i./NH<sub>3</sub>) 134 ( $MNH_4^+$ , 100%), 118, 117, and 99; similar e.i., c.i./CH<sub>4</sub> mass spectra and  $R_f$  (h.p.l.c.) to those of the authentic sample; compound **IV (19)**, present in the volatile fraction, similar e.i. c.i./NH<sub>3</sub> mass spectra and  $R_f$  (g.c.) to those of the authentic sample; compound **I (20)**, present in the ether and pentane extracts and in fraction C,  $m/z$  (e.i.) 114 ( $M^+$ ), 99 (100%), 84, 71, 70, 56, and 43;  $m/z$  (c.i./NH<sub>3</sub>) 132 ( $MNH_4^+$ );  $m/z$  (c.i./CH<sub>4</sub>) 115 ( $MH^+$ ) and 97 (100%); compound **V (21)**, present in the volatile fraction,  $m/z$  (e.i.) 100 ( $M^+$ ), 85, 58, 57, and 43 (100%) [Found:  $m/z$ , 100.0511. C<sub>5</sub>H<sub>8</sub>O<sub>2</sub> ( $M^+$ ) requires 100.0524]; compound **VI**

(**22**), present in fraction C,  $m/z$  (c.i./CH<sub>4</sub>) 145 ( $MH^+$ ), 127, 117, and 71 (100%); compound **II (24)**, present in the volatile fraction, in the ether extracts and in fraction C,  $m/z$  (e.i.) 128 ( $M^+$ ), 113, 110, 95, 85, 71, 70, 58, and 43 (100%);  $m/z$  (c.i./NH<sub>3</sub>) 146 ( $MNH_4^+$ );  $m/z$  (c.i./CH<sub>4</sub>) 129 ( $MH^+$ ), 111, and 69 (100%) [Found:  $m/z$ , 129.0893. C<sub>7</sub>H<sub>13</sub>O<sub>2</sub> ( $MH^+$ ) requires 129.0915].

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