

## A General Method for Removal of a 4-Methyl Group from Triterpenoids. Synthesis of 4 $\beta$ -Demethylglycyrrhetic Acid<sup>1</sup>

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Using 4,4-dimethyl-5 $\alpha$ -cholestan-3-one (1) as a model compound, a short high-yielding sequence has been developed for removing a 4-methyl group from triterpenoids. The method makes use of the 'abnormal' Beckmann reaction which 3-hydroxyimino-4,4-dimethylsteroids undergo to yield 3,4-seco-nitriles. Epoxidation of the 4-methylene group, followed by treatment of the 3,4-seco-epoxy-nitrile with boron trifluoride in refluxing toluene affords the 4 $\beta$ -demethyl-3-ketone in an overall yield of 40–50%. The general nature of the method has been demonstrated in the conversion of dihydrolanosterol into 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17) and 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholestane-3,11-dione (3), and in the synthesis of 3 $\beta$ -hydroxy-11-oxo-24-nor-18 $\beta$ -olean-12-en-30-oic acid (4 $\beta$ -demethylglycyrrhetic acid) (27) and 3,11-dioxo-24-nor-18 $\beta$ -olean-12-en-30,22 $\beta$ -olactone (31).

THE removal of two C-4 methyl groups from tetracyclic triterpenoids has been the subject of a considerable number of reports.<sup>2-6</sup> There have been various objectives in this work, but the aim in the majority of cases has been the conversion of lanosterol into steroid hormones. Although 4-methylsteroids show interesting biological activity,<sup>7</sup> only recently have ap-

proaches to the synthesis of 4-demethyltriterpenoids been reported.<sup>1,4-6</sup> Our interest in the development of a general method for carrying out this conversion stems partly from this consideration but also from our interest in the synthesis of fusidane derivatives from lanostane type triterpenoids.<sup>8</sup> We now describe a

<sup>1</sup> Preliminary communication, K. F. Cohen, R. Kazlauskas, and J. T. Pinhey, *Chem. Comm.*, 1971, 1419.

<sup>2</sup> W. Voser, D. E. White, H. Heusser, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 830; W. Voser, H. Heusser, O. Jeger, and L. Ruzicka, *ibid.*, 1953, **36**, 299; D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 1954, 903; P. Crabbé, G. Ourisson, and T. Takahashi, *Tetrahedron*, 1958, **3**, 279; G. R. Pettit and P. Hofer, *Helv. Chim. Acta*, 1963, **46**, 2142; G. R. Pettit and J. R. Diaz, *Canad. J. Chem.*, 1969, **47**, 1091.

<sup>3</sup> C. W. Shoppee, N. W. Hughes, R. E. Lack, and J. T. Pinhey, *J. Chem. Soc. (C)*, 1970, 1443.

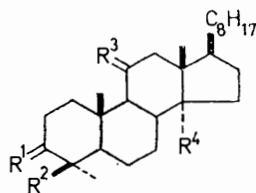
<sup>4</sup> D. H. R. Barton and D. Kumari, *Annalen*, 1970, **737**, 108.

<sup>5</sup> R. Kazlauskas, J. T. Pinhey, J. J. H. Simes, and T. G. Watson, *Chem. Comm.*, 1969, 945.

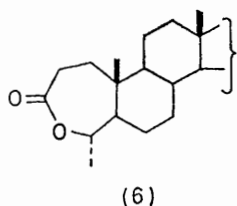
<sup>6</sup> G. R. Pettit and J. R. Diaz, *J. Org. Chem.*, 1972, **37**, 973.

<sup>7</sup> D. Burn, G. Cooley, B. Ellis, A. R. Heal, and V. Petrow, *Tetrahedron*, 1963, **19**, 1757.

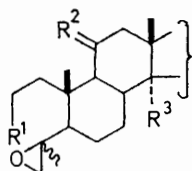
<sup>8</sup> R. Kazlauskas, J. T. Pinhey, and J. J. H. Simes, *J.C.S. Perkin I*, 1972, 1243.



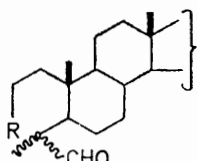
- (1)  $R^1 = O, R^2 = Me, R^3 = H_2, R^4 = H$   
 (2)  $R^1 = O, R^2 = H, R^3 = H_2, R^4 = H$   
 (3)  $R^1 = O, R^2 = H, R^3 = O, R^4 = Me$   
 (4)  $R^1 = O, R^2 = Me, R^3 = O, R^4 = Me$   
 (5)  $R^1 = NOH, R^2 = Me, R^3 = O, R^4 = Me$



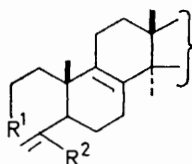
(6)



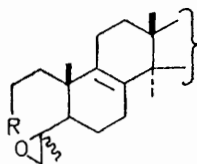
- (7)  $R^1 = CO_2H, R^2 = H_2, R^3 = H$   
 (8)  $R^1 = CN, R^2 = H_2, R^3 = H$   
 (9)  $R^1 = CN, R^2 = O_2, R^3 = Me$



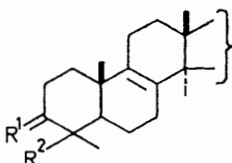
- (10)  $R = CO_2H$   
 (11)  $R = CN$



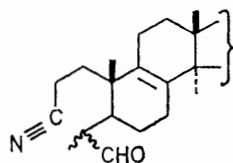
- (14)  $R^1 = CO_2H, R^2 = Me$   
 (15)  $R^1 = CN, R^2 = Me$   
 (16)  $R^1 = CN, R^2 = CH_2OH$



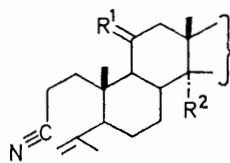
- (12)  $R = CO_2H$   
 (13)  $R = CN$



- (17)  $R^1 = O, R^2 = \beta-H$   
 (18)  $R^1 = O, R^2 = Me$   
 (19)  $R^1 = NH, R^2 = CHO$



(20)



- (21)  $R^1 = H_2, R^2 = H$   
 (22)  $R^1 = O, R^2 = Me$

method for effecting this monodemethylation in high overall yield.

During the course of their investigation of the sul-

phuric acid catalysed Baeyer-Villiger oxidation of 4,4-dimethyl-5 $\alpha$ -cholestan-3-one (1) to the lactone (6), Holker *et al.*<sup>9</sup> found that treatment of the epoxy-acid (7) with 10% sulphuric acid in acetic acid in the absence of oxygen afforded 4 $\alpha$ -methyl-5 $\alpha$ -cholestan-3-one (2) in *ca.* 35% yield, and the mixture of epimeric aldehyde-acids (10) in considerably lower yield. These workers suggested that (2) arose by an acid-catalysed Claisen condensation of (10) followed by the loss of formic acid.

Our initial aim in the present work was to examine the possibility of using the reaction of Holker *et al.*<sup>9</sup> to convert the epoxy-acid (12) into 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17).<sup>5</sup> The required selective epoxidation of the known<sup>10</sup> seco-acid (14), obtained by hydrolysis of the seco-nitrile (15),<sup>3,10</sup> was readily achieved in high yield with *m*-chloroperbenzoic acid at 0°. The structure (12) for the product followed from the analytical data and the <sup>1</sup>H n.m.r. spectrum, which showed a two-proton multiplet at  $\delta$  2.75 (28-H<sub>2</sub>), a three-proton singlet at 1.33 (29-H<sub>3</sub>), and an exchangeable (D<sub>2</sub>O) signal at 10.4. Although the epoxide (12) behaved like a single compound, the presence of a multiplet at  $\delta$  2.45 in the n.m.r. spectrum indicated that *ca.* 10% of the C-4 epimer was present.

Treatment of the epoxide (12) with 10% sulphuric acid in acetic acid under the conditions of Holker *et al.*<sup>9</sup> gave an intractable mixture of polar compounds which did not contain (t.l.c.) the 3-ketone (17). In a search for conditions for effecting this ring closure, we turned our attention to the cholestane derivative (7). We confirmed that the ketone (2) was produced on treatment of (7) with 10% sulphuric acid in acetic acid, the yield being consistently *ca.* 20%. A marginally higher yield (25%) of (2) was obtained by heating (7) at reflux in an inert atmosphere in dry benzene containing toluene-*p*-sulphonic acid; however, a marked improvement (*ca.* 50% yield) resulted when the benzene was replaced by toluene or xylene. The best conditions found for the conversion were an excess of boron trifluoride-ether in dry toluene at reflux under nitrogen, which gave the ketone (2) in 55% yield. When these improved conditions were applied to the lanostane seco-epoxide (12), ring closure occurred to give 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17), the yield being 41% for the boron trifluoride-ether-toluene reaction and 30% with toluene-*p*-sulphonic acid in toluene.

In a further attempt to improve the overall yield of the 4-demethyl compound (17) and shorten the sequence, we examined the possibility of using the epoxy-nitrile (13) in the ring closure step. We reasoned that the aldehyde (20), expected from treatment of (13) with acid, might also undergo an acid-catalysed internal Claisen-type reaction to give an aldehyde-imine (19), which should yield the ketone (17) in aqueous acid. In order to test this possibility, the seco-nitrile (21) from the

<sup>9</sup> J. S. E. Holker, W. R. Jones, and P. J. Ramm, *Chem. Comm.*, 1965, 435; *J. Chem. Soc. (C)*, 1969, 357.

<sup>10</sup> G. Quinkert and H. G. Heine, *Tetrahedron Letters*, 1963, 1659.

'abnormal' Beckmann rearrangement<sup>3,11</sup> of the oxime of 4,4-dimethyl-5 $\alpha$ -cholestan-3-one with toluene-*p*-sulphonyl chloride in pyridine was converted with *m*-chloroperbenzoic acid into the epoxy-nitrile (8). Unlike the 4-epoxymethylene compounds produced in the lanostane series, evidence for (8) being a mixture of C-4 epimers could not be found in the n.m.r. spectrum. The epoxide ring protons appeared as a singlet at  $\delta$  2.67, while the signal due to the C-4 methyl group was a singlet at 1.28. When the epoxy-nitrile (8) was treated with boron trifluoride-ether in toluene in the same way as the epoxy-acid (7), followed by aqueous acid work-up, the ketone (2) and the nitrile-aldehyde (11) were obtained in yields of 70 and 12% respectively. The structure of the more polar compound (11), which could not be obtained crystalline, followed from spectral data and elemental analysis of the DNP derivative. The n.m.r. data indicated that this material was not a mixture of C-4 epimers.

The scope of this potentially useful reaction, the mechanism of which would appear to be that foreshadowed above, was thus investigated with a number of triterpenoid derivatives. As in the case of the seco-acid (14), the 4,28 double bond of the seco-nitrile (15) was readily selectively epoxidised at 0° with *m*-chloroperbenzoic acid to give the epoxy-nitrile (13) in approximately quantitative yield. This reaction also yielded a mixture of C-4 epimers which, from the integrals for the epoxide ring proton resonances in the n.m.r. spectrum, were present in a ratio of *ca.* 9 : 1. The two epoxides, which were readily separated by p.l.c., gave analytical and spectral data in accord with the proposed structure (13).

Reaction of the mixture of epoxy-nitriles (13) with boron trifluoride-ether in toluene under the conditions described above gave 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17) in 66% yield, which again was considerably better than that produced (52%) using toluene-*p*-sulphonic acid. In addition, the Lewis acid catalysed reaction was somewhat faster than that conducted with toluene-*p*-sulphonic acid. In the case of the toluene-*p*-sulphonic acid catalysed reaction, the ketone (17) was accompanied by a small amount of the aldehyde-nitrile (20). The n.m.r. spectrum of this material (20) indicated that it was a *ca.* 1 : 1 mixture of C-4 epimers.

It should be noted that for optimum yields in these ring closure reactions, it is necessary to use at least 2 equivalents of the acid. The use of a catalytic amount of either toluene-*p*-sulphonic acid or boron trifluoride with (13) led to mixtures which contained a considerable amount of the mixture of aldehyde-nitriles (20). In the former case the mixture of aldehydes (20) was accom-

panied by a major amount of a more polar compound, which was shown to be the allylic alcohol (16), a not unexpected product of acid catalysed isomerisation of (13).<sup>12</sup> The mixture of aldehydes (20) was readily converted into the 3-ketone (17) on further treatment with excess of boron trifluoride in toluene, indicating that it is an intermediate in the ring closure reaction.

Since 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholestane-3,11-dione (3) was required in our study<sup>8</sup> of the lanostane  $\rightarrow$  fusi-dane conversion, the application of the above 4-demethylation procedure to 5 $\alpha$ -lanostane-3,11-dione (4)<sup>13</sup> was investigated. Reaction of the diketone (4) with hydroxylamine in the usual way led to a mono-oxime, assumed to have structure (5) on the grounds of the known steric hindrance to attack at the 11-position. This was verified by its subsequent 'abnormal' Beckmann rearrangement with toluene-*p*-sulphonyl chloride in pyridine to afford the seco-nitrile (22) in good yield. Epoxidation of the seco-nitrile (22) with *m*-chloroperbenzoic acid led in high yield to a mixture of C-4 epimeric epoxides (9), which were calculated from the n.m.r. spectrum to be present in a ratio of *ca.* 9 : 1. Separation by p.l.c. yielded the two epoxides, which gave the expected analytical and spectral data. Finally, treatment of the mixture (9) in toluene with boron trifluoride-ether, as in the case of (13), led to the formation of the 3,11-diketone (3) in 75% yield. In accord with this structure, there were two carbonyl absorptions (1705 and 1698 cm<sup>-1</sup>) in the i.r. spectrum, while in the n.m.r. spectrum there was a three-proton singlet at  $\delta$  1.25, which is the calculated chemical shift<sup>14</sup> for a 10-methyl group in a 3,11-dioxo-steroid.

Since the seco-nitrile (23) from the medicinally important<sup>15</sup> pentacyclic triterpenoid, 18 $\beta$ -glycyrrhetic acid (24) is readily prepared,<sup>16</sup> we selected this compound for a further test of the generality of the demethylation sequence. When the seco-nitrile (23) was prepared from commercial \* glycyrrhetic acid without rigorous purification of intermediates, we found that, in addition to (23), obtained in 64% yield, there was present a second seco-nitrile, separable from (23) by chromatography on silica gel. This compound, which was formed in *ca.* 3% overall yield, is shown below to have structure (29), and thus arose from glabrolide (30), one of a number of triterpenoids shown by Russo<sup>17</sup> to occur with glycyrrhetic acid in *Glycyrrhiza glabra*. The i.r. spectrum of (29) showed, in addition to bands due to  $\alpha\beta$ -unsaturated ketone, nitrile, and terminal methylene groups, absorption at 1764 cm<sup>-1</sup>, which may be assigned to the  $\gamma$ -lactone ring. In the n.m.r. spectrum, 22-H appeared as a sharp doublet (*J* 2.5 Hz) at  $\delta$  4.24, the coupling being between 22-H and 21 $\beta$ -H since measurement on a Dreiding model showed the dihedral angle between 21 $\alpha$ -H and 22-H to be *ca.* 80°,

\* Obtained from E. Merck AG, Darmstadt, Germany.

<sup>11</sup> G. P. Moss and S. A. Nicolaidis, *Chem. Comm.*, 1969, 1077.

<sup>12</sup> A. D. Cross, *Quart. Rev.*, 1960, **14**, 317.

<sup>13</sup> W. Voser, M. Montavon, Hs. H. Günthard, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893.

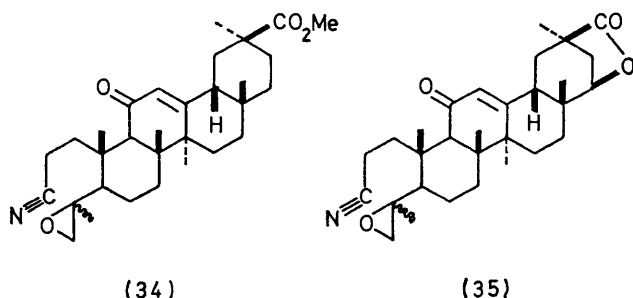
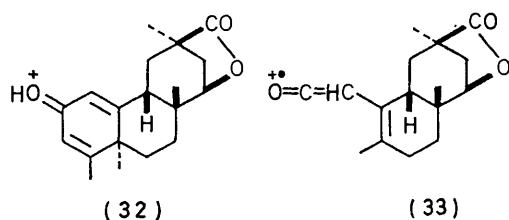
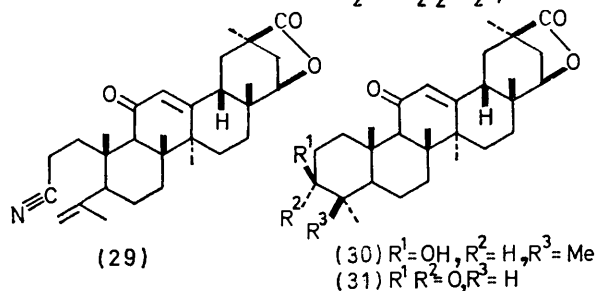
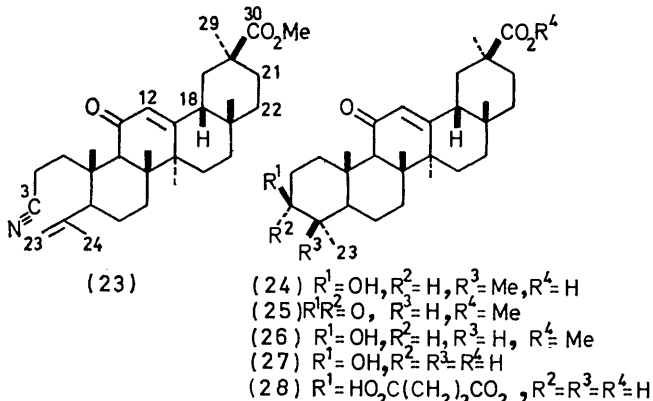
<sup>14</sup> N. S. Bhacca and D. H. Williams, 'Applications of N.M.R. Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 19.

<sup>15</sup> 'A Symposium on Carbenoxolone Sodium,' eds. J. M. Robson and F. M. Sullivan, Butterworth, London, 1968.

<sup>16</sup> V. Askam and D. M. Bradley, *J. Chem. Soc. (C)*, 1971, 1895 and references therein.

<sup>17</sup> G. Russo, *Corsi. Semin. Chim.*, 1968, **11**, 20 (*Chem. Abs.*, 1970, **72**, 21,799u).

and thus coupling between them would be expected to be negligible. The signal for the vinylic proton 12-H



was a singlet ( $W_{\frac{1}{2}}$  2.0 Hz) at  $\delta$  5.66, indicating that epimerisation to the 18 $\alpha$ -configuration had not occurred. In 18 $\alpha$ -glycyrrhetic acid derivatives the dihedral angle between 12-H and 18-H is *ca.* 100° and there is readily observable coupling between them.<sup>16,18,19</sup> The signal due to the 24-H<sub>3</sub> group was a broad singlet at

<sup>18</sup> D. J. Collins, J. J. Hobbs, and S. Sternhell, *Austral. J. Chem.*, 1963, **16**, 1030.

$\delta$  1.78, while the protons of the terminal methylene gave rise to broad signals at 4.73 and 4.93. The mass spectrum of (29) was also in keeping with the proposed structure. The molecular ion was at *m/e* 463, the base peak was at 301, and another significant ion occurred at 260. The last two ions may be assigned structures (32) and (33) respectively, in view of the known fragmentations of derivatives of glycyrrhetic acid.<sup>16</sup>

The seco-nitriles (23) and (29) were readily converted in high yield into the corresponding epoxides (34) and (35) with *m*-chloroperbenzoic acid. These structures were supported by elemental analyses and spectral data and, unlike the 24-epoxymethylene compounds (13) and (9), there was no n.m.r. spectroscopic evidence that they were mixtures of C-4 epimers. Treatment of the two epoxides (34) and (35) with boron trifluoride-ether in toluene, as previously described, gave the 3-ketones (25) and (31) in yields of 83 and 74% respectively. Both compounds retained the 18 $\beta$ -configuration, since the signals due to the vinylic protons (12-H) were relatively sharp singlets with  $W_{\frac{1}{2}}$  of *ca.* 2 Hz (see earlier).

Reduction of the ketone (25) with lithium tri-*t*-butoxy-aluminium hydride produced the 3 $\beta$ -hydroxy-ester (26), the assignment of configuration at C-3 being based on the signal due to 3-H in the n.m.r. spectrum. This appeared as a doublet of triplets, the triplet spacing of 10 Hz being due to equal couplings between 2 $\beta$ -H and 3 $\alpha$ -H, and 3 $\alpha$ -H and 4 $\beta$ -H, and the doublet spacing of 5.5 Hz being due to coupling between 2 $\alpha$ -H and 3 $\alpha$ -H. Alkaline hydrolysis of (26) gave 4 $\beta$ -demethylglycyrrhetic acid (27), which was readily converted into the 3 $\beta$ -succinate (28), the disodium salt of which was required for pharmacological testing.

#### EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. Unless otherwise stated, u.v. spectra were determined for solutions in dioxan using a Perkin-Elmer 402 spectrometer, i.r. spectra were obtained for Nujol mulls with a Perkin-Elmer 221 spectrometer, and rotations were measured for solutions in chloroform. N.m.r. spectra were recorded on either Varian A60 or HA100 instruments using *ca.* 10% solutions in deuteriochloroform with tetramethylsilane as internal reference. Mass spectra were obtained with an A.E.I. MS902 instrument operated at 70 eV and 150° inlet temperature. Silica gel used for column chromatography was Davison's grade 923, while alumina refers to Peter Spence type H. Preparative layer chromatography (p.l.c.) was performed on glass plates spread with a 0.5 mm layer of Merck silica gel G. Boron trifluoride-ether was freshly distilled from calcium hydride. Light petroleum refers to the fraction of b.p. 60–70°. Organic extracts were dried over anhydrous magnesium sulphate. Analyses were performed by the Australian Microanalytical Service, Melbourne.

4 $\xi$ ,28-Epoxy-3,4-seco-5 $\alpha$ -lanost-8-en-3-oic Acid (12).—*m*-Chloroperbenzoic acid (300 mg) was added to a solution of 3,4-seco-5 $\alpha$ -lanosta-4(28),8-dien-3-oic acid<sup>10</sup> (14) (500 mg) in dichloromethane (120 ml), and the mixture kept

<sup>19</sup> M. Mousseron-Canet, F. Crouzet, and J.-P. Chabaud, *Bull. Soc. chim. France*, 1967, 4668.

at 0° for 4 days. The mixture was then washed in turn with cold potassium iodide solution (5%; 3 × 50 ml), cold sodium hydrogen sulphite solution (5%; 50 ml), sodium hydrogen carbonate solution (3N; 2 × 50 ml), dried, and the solvent removed to yield 4ξ,28-epoxy-3,4-seco-5α-lanost-8-en-3-oic acid (12) (460 mg), m.p. 163—164° (plates from light petroleum),  $[\alpha]_D +78^\circ$  (c 0.73),  $\nu_{\max}$  (CHCl<sub>3</sub>) 3510, 3050 (w, epoxide), 1710, 905 (epoxide), and 875 (epoxide) cm<sup>-1</sup>,  $\delta$  10.4br (1H, s, exch. with D<sub>2</sub>O, CO<sub>2</sub>H), 2.75 (1.8H, m, 28-H<sub>2</sub>), 2.45 (0.2H, m, 28-H<sub>2</sub>), 1.33 (3H, s, 29-H<sub>3</sub>), and 1.08 (3H, s, 19-H<sub>3</sub>), *m/e* 458 (18%), 443 (24), 440 (10), 425 (18), 385 (100), 375 (8), 374 (8), 367 (40), and 261 (8) (Found: C, 78.7; H, 10.9. C<sub>30</sub>H<sub>50</sub>O<sub>3</sub> requires C, 78.6; H, 11.0%).

*Reaction of 4ξ-Methyl-4,4-methyleneoxy-3,4-seco-5α-cholestan-3-oic Acid (7) with Acids.*—(a) The epoxy-acid (7) (150 mg) was dissolved in dichloromethane containing sulphuric acid (10%) in acetic acid (1.5 ml) and the mixture kept at room temperature for 24 h. The product, obtained on dilution with water and extraction with ether, was separated by p.l.c. on silica gel using light petroleum-ether (9:1). The least polar material crystallised from aqueous methanol to give 4α-methyl-5α-cholestan-3-one (24 mg), m.p. 119—120°, undepressed on admixture with authentic material (i.r. spectrum identical).

(b) The epoxy-acid (7) (500 mg) was heated at reflux under nitrogen for 48 h in dry benzene (200 ml) containing toluene-*p*-sulphonic acid (200 mg), and the product separated by p.l.c. as in (a) to give 4α-methyl-5α-cholestan-3-one (117 mg).

(c) When the above experiment was repeated with the epoxide (7) (253 mg) in dry toluene (100 ml) containing toluene-*p*-sulphonic acid (100 mg) and a reaction time of 18 h, the only isolated product was 4α-methyl-5α-cholestan-3-one (115 mg).

(d) Repetition of the above experiment with the epoxide (7) (113 mg) in dry toluene (50 ml) containing boron trifluoride-ether (0.2 ml) and a reaction time of 18 h gave 4α-methyl-5α-cholestan-3-one (57 mg).

*Reaction of 4ξ,28-Epoxy-3,4-seco-5α-lanost-8-en-3-oic Acid (12) with Acids.*—(a) The epoxy-acid (12) (400 mg) was heated at reflux under nitrogen for 18 h in dry toluene (100 ml) containing boron trifluoride-ether (1.0 ml). The reaction mixture was then washed with sodium hydrogen carbonate solution (3N; 2 × 50 ml), followed by the usual work-up to yield a noncrystalline residue, which was chromatographed on a column of silica gel (24 g). Elution with light petroleum-ether (4:1) afforded 4α,14α-dimethyl-5α-cholest-8-en-3-one (154 mg), m.p. 109—111°, identical with authentic<sup>5</sup> material.

(b) When the above experiment was repeated with the epoxide (12) (200 mg) in dry toluene (100 ml) containing toluene-*p*-sulphonic acid (200 mg) and a reaction time of 18 h, 4α,14α-dimethyl-5α-cholest-8-en-3-one (57 mg) was the only product to be isolated.

*4-Methyl-4-methylene-3,4-seco-5α-cholestan-3-onitrile (21).*—3-Hydroxyimino-4,4-dimethyl-5α-cholestane (800 mg) was added to a solution of toluene-*p*-sulphonyl chloride (1 g) in anhydrous pyridine and the solution heated at reflux for 3 h. The mixture was diluted with water, treated with dilute sulphuric acid, and the product isolated by extraction into light petroleum. The residue (450 mg) was added to a column of alumina (30 g) in light petroleum and elution with benzene gave 4-methyl-4-methylene-5α-cholestan-3-onitrile (21) (380 mg), m.p. 70.5—71.5° (from methanol),

$[\alpha]_D +17^\circ$  (c 1.3),  $\nu_{\max}$  2270, 1630, and 895 cm<sup>-1</sup>;  $\delta$  4.88 (1H, m, methylene proton), 4.68 (1H, m, methylene proton), and 1.73br (3H, s, 4-Me), *m/e* 411 (100%), 396 (14), 331 (10), 330 (41), 329 (22), 328 (10), 299 (12), and 298 (40) (Found: C, 84.5; H, 11.7. C<sub>29</sub>H<sub>49</sub>N requires C, 84.6; H, 12.0%).

*4ξ-Methyl-4,4-methyleneoxy-3,4-seco-5α-cholestan-3-onitrile (8).*—*m*-Chloroperbenzoic acid (100 mg) was added to a solution of the seco-nitrile (21) (94 mg) in dichloromethane (10 ml), and the mixture kept at room temperature for 2 h. Work-up in the usual way afforded 4ξ-methyl-4,4-methyleneoxy-3,4-seco-5α-cholestan-3-onitrile (8) (56 mg), m.p. 90—91° (from methanol),  $[\alpha]_D +15^\circ$  (c 0.3),  $\nu_{\max}$  (CHCl<sub>3</sub>) 2260 cm<sup>-1</sup>, *m/e* 427 (100%), 412 (13), 409 (14), 399 (15), 385 (7), 384 (26), 373 (17), 328 (20), and 163 (26) (Found: C, 81.3; H, 11.9; N, 3.2. C<sub>29</sub>H<sub>49</sub>NO requires C, 81.4; H, 11.6; N, 3.3%).

*Reaction of 4ξ-Methyl-4,4-methyleneoxy-3,4-seco-5α-cholestan-3-onitrile (8) with Boron Trifluoride.*—The epoxy-nitrile (8) (500 mg) was heated at reflux under nitrogen for 2 h in dry toluene (180 ml) containing freshly distilled boron trifluoride-ether (0.5 ml). Hydrochloric acid (3N, 30 ml) was then added and the mixture heated under reflux for a further 0.5 h. The organic phase was separated, washed with saturated sodium hydrogen carbonate solution and water, dried, and the solvent removed. Separation of the residue by p.l.c. developed in light petroleum-ether (9:1) gave two main bands. The less polar material crystallised from methanol to yield 4α-methyl-5α-cholestan-3-one (2) (346 mg), m.p. 118—120°,  $[\alpha]_D +25^\circ$  (c 1.3) (lit.<sup>20</sup> m.p. 121—123°,  $[\alpha]_D +26^\circ$ ) identical with an authentic sample.<sup>20</sup>

The more polar fraction (60 mg), which could not be induced to crystallise, was 4ξ-formyl-4ξ-methyl-5α-cholestan-3-onitrile (11),  $\nu_{\max}$  (CHCl<sub>3</sub>) 2270 and 1710 cm<sup>-1</sup>,  $\delta$  9.53 (1H, s, CHO) and 1.13 (3H, d, *J* 7.5 Hz, 4-Me). The 2,4-dinitrophenylhydrazone derivative of the aldehyde had m.p. 209—212° (Found: C, 69.4; H, 9.2; N, 11.2. C<sub>35</sub>H<sub>53</sub>N<sub>5</sub>O<sub>4</sub> requires C, 69.1; H, 8.8; N, 11.5%).

*The C-4 Epimers of 4,28-Epoxy-3,4-seco-5α-lanost-8-en-3-onitrile (13).*—*m*-Chloroperbenzoic acid (2.2 g) was added to a solution of 3,4-seco-5α-lanosta-4(28),8-dien-3-onitrile (15) (3.0 g) in dichloromethane (500 ml) and the mixture kept at 0° for 2 days. The reaction was worked-up as for the preparation of the epoxy-acid (12) to give a mixture of C-4 epimers of 4,28-epoxy-3,4-seco-5α-lanost-8-en-3-onitrile (13) (2.38 g), m.p. 97—98° (needles from methanol). Analysis by t.l.c. showed that the material was a mixture of two compounds of very similar polarity, and the n.m.r. spectrum indicated that they were C-4 epimers in a 9:1 ratio. Separation of the two compounds was effected by p.l.c. with chloroform as the developing solvent. The less polar epimer, which was the minor component, crystallised from methanol as needles, m.p. 140—141°,  $[\alpha]_D +44^\circ$  (c 0.09);  $\nu_{\max}$  3045, 2248, 875, and 821 cm<sup>-1</sup>,  $\delta$  2.45 (2H, s, 28-H<sub>2</sub>), 1.31 (3H, s, 29-H<sub>3</sub>), and 1.17 (3H, s, 19-H<sub>3</sub>), *m/e* 439 (30%), 424 (100), 406 (20), 396 (19), 385 (56), 367 (24), 356 (17), and 270 (14) (Found: C, 82.3; H, 11.4; N, 2.9. Calc. for C<sub>30</sub>H<sub>49</sub>NO: C, 81.9; H, 11.2; N, 3.2%).

The major and more polar epimer crystallised from methanol as needles, m.p. 89—90°,  $[\alpha]_D +54^\circ$  (c 0.99),  $\nu_{\max}$  3055, 2251, 885, and 829 cm<sup>-1</sup>,  $\delta$  2.70 (2H, s, 28-H<sub>2</sub>), 1.32 (3H, s, 29-H<sub>3</sub>), and 1.08 (3H, s, 19-H<sub>3</sub>), *m/e* 439 (23%),

<sup>20</sup> F. Sondheimer and Y. Mazur, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

424 (100), 411 (5), 406 (11), 396 (20), 385 (53), 367 (11), and 270 (3) (Found: C, 82.1; H, 11.1; N, 3.1%).

*Reaction of the Mixture of Epoxy-nitriles (13) with Acids.*—(a) Toluene-*p*-sulphonic acid (400 mg) was added to a solution of the mixture of epoxy-nitriles (13) (300 mg) in anhydrous toluene (100 ml) and the mixture heated at reflux under nitrogen for 4 h. The usual work-up afforded a non-crystalline residue (280 mg) which was shown by t.l.c. to be a mixture of two compounds. A separation was effected by p.l.c. with light petroleum-ether (4:1) as the developing solvent. The less polar fraction crystallised from methanol to give 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17) (148 mg), m.p. 108–109°, identical with material obtained above.

The more polar fraction crystallised from methanol to yield a ca. 1:1 mixture (from the n.m.r. spectrum) of C-4 epimers of 4-formyl-4,14 $\alpha$ -dimethyl-3,4-*seco*-5 $\alpha$ -cholest-8-en-3-onitrile (20) (30 mg), m.p. 95–96°,  $[\alpha]_D +62^\circ$  (*c* 0.62),  $\nu_{\max}$  2730, 2250, and 1722 cm<sup>-1</sup>,  $\delta$  9.70br (0.5H, d, *J* 3 Hz, CHO), 9.61 (0.5H, s, CHO), 1.21 (3H, s, 19-H<sub>3</sub>), *m/e* 439 (11%), 424 (100), 406 (14), 396 (23), 385 (57), 367 (15), 327 (7), 284 (9), 270 (24), and 258 (16) (Found: C, 81.6; H, 11.1; N, 3.3. Calc. for C<sub>30</sub>H<sub>49</sub>NO: C, 81.9; H, 11.2; N, 3.2%).

(b) Boron trifluoride-ether (1.5 ml) was added to a solution of the epoxy-nitriles (13) (1.0 g) in anhydrous toluene (300 ml), and the mixture heated at reflux under nitrogen for 3.5 h. Work-up, as in the case of the reaction of (8) with boron trifluoride, afforded a crystalline residue (1.02 g) which was added in light petroleum to a column of silica gel (60 g). Elution with light petroleum-ether (4:1) yielded 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (620 mg), identical with the material obtained earlier.

(c) Toluene-*p*-sulphonic acid (1 mg) was added to a solution of the mixture of epoxides (13) (50 mg) in anhydrous benzene (50 ml) and the mixture heated at reflux under nitrogen for 24 h. Work-up in the usual way afforded a residue (49 mg), which was a mixture of two compounds by t.l.c. Separation was effected by p.l.c. using light petroleum-ether (7:3) as the developing solvent. The less polar material crystallised from methanol to give the mixture of aldehyde-nitriles (20) (14 mg), m.p. 95–96°, identical with the material obtained above.

The more polar material crystallised from methanol to yield 29-hydroxy-3,4-*seco*-5 $\alpha$ -lanosta-4(28),8-dien-3-onitrile (16) (35 mg), m.p. 126–127° (from methanol),  $[\alpha]_D +73^\circ$  (*c* 0.1),  $\nu_{\max}$  3498, 2257, 1648, and 900 cm<sup>-1</sup>,  $\delta$  5.30 (1H, m, 28-H), 4.96 (1H, m, 28-H), 4.10br (2H, s, 29-H<sub>2</sub>), 1.75br (1H, s, exch. with D<sub>2</sub>O, OH), *m/e* 439 (38%), 424 (100), 406 (28), 396 (18), 385 (97), 367 (22), 355 (12), 342 (7), 340 (9), 336 (7), 270 (14), and 242 (24) (Found: C, 82.1; H, 11.3; N, 3.2. C<sub>30</sub>H<sub>49</sub>NO requires C, 81.9; H, 11.2; N, 3.2%).

When the foregoing reaction was repeated with a reflux time of 2 h, the ratio of (20) to (16) was the same as above.

(d) When the reaction (b) was repeated using a catalytic amount (0.1 ml) of boron trifluoride-ether, the mixture of aldehyde-nitriles (20) (90 mg) was obtained.

*Reaction of the Mixture of Aldehyde-nitriles (20) with Boron Trifluoride.*—Boron trifluoride-ether (0.3 ml) was added to a solution of the aldehydes (20) (100 mg) in anhydrous toluene (30 ml) and the mixture heated at reflux under nitrogen for 4 h. The usual work-up afforded 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholest-8-en-3-one (17) (55 mg), identical with authentic material.

3-Hydroxyimino-5 $\alpha$ -lanostan-11-one (5).—5 $\alpha$ -Lanostane-3,11-dione (4) (442 mg) in ethanol (50 ml) was heated at reflux with anhydrous sodium acetate (160 mg) and hydroxylamine hydrochloride (100 mg) for 24 h. Dilution with water and extraction with chloroform yielded 3-hydroxyimino-5 $\alpha$ -lanostan-11-one (5) (355 mg), m.p. 202–203° (from ethanol),  $[\alpha]_D +44^\circ$  (*c* 0.89),  $\nu_{\max}$  (CHCl<sub>3</sub>) 3595, 1697, 1648, and 905 cm<sup>-1</sup>;  $\delta$  8.90 (1H, s, exch. with D<sub>2</sub>O, OH); *m/e* 457 (70%), 424 (8), 399 (7), 358 (12), 303 (15), 290 (8), 234 (9), and 140 (100) (Found: C, 79.0; H, 11.0; N, 3.3. C<sub>30</sub>H<sub>51</sub>NO<sub>2</sub> requires C, 78.7; H, 11.2; N, 3.1%).

11-Oxo-3,4-*seco*-5 $\alpha$ -lanost-4(28)-en-3-onitrile (22).—Toluene-*p*-sulphonyl chloride (10 g) was added to a solution of the oxime (5) (3.0 g) in anhydrous pyridine (200 ml) and the mixture heated at reflux under nitrogen for 14 h, with t.l.c. control to optimise the yield of the least polar material. The mixture was diluted with hydrochloric acid (3N; 500 ml) and extracted with ether to yield a dark residue (2.74 g), which was chromatographed on a column of silica gel (210 g). Elution with light petroleum-ether (7:3) gave 11-oxo-3,4-*seco*-5 $\alpha$ -lanost-4(28)-en-3-onitrile (22) (2.24 g), an oil which could not be induced to crystallise,  $\nu_{\max}$  (CHCl<sub>3</sub>) 3070, 2252, 1700, 1638, and 898 cm<sup>-1</sup>,  $\delta$  4.89 (1H, m, 28-H), 4.69 (1H, m, 28-H), 2.42 (3H, m, 9-H and 12-H<sub>2</sub>), 1.75br (3H, s, 29-H<sub>3</sub>), and 1.09 (3H, s, 19-H<sub>3</sub>) [Found: *M* (mass spectrum), 439.3812. C<sub>30</sub>H<sub>49</sub>NO requires *M*, 439.3813].

The C-4 Epimers of 4,28-Epoxy-11-oxo-3,4-*seco*-5 $\alpha$ -lanost-8-en-3-onitrile (9).—*m*-Chloroperbenzoic acid (2.0 g) was added to a solution of the *seco*-nitrile (22) (2.0 g) in dichloromethane (280 ml) and the mixture kept at 0° for 2 days. The reaction was worked up as for the preparation of the epoxy-acid (12) to give a mixture (t.l.c.) of C-4 epimers of 4,28-epoxy-11-oxo-3,4-*seco*-5 $\alpha$ -lanost-8-en-3-onitrile (9) (1.8 g), m.p. 118–120° (from methanol). The mixture was separated by p.l.c. with light petroleum-ether (3:2) as the developing solvent. The less polar epimer, which was the minor component, crystallised from methanol as needles, m.p. 181–182°,  $[\alpha]_D +63^\circ$  (*c* 0.07),  $\nu_{\max}$  3050, 2252, 1698, 874, and 815 cm<sup>-1</sup>,  $\delta$  2.40 (2H, m, 28-H<sub>2</sub>) and 1.24 (3H, s, 29-H<sub>3</sub>), *m/e* 455 (38%), 440 (11), 437 (8), 427 (10), 412 (13), 370 (20), 358 (13), 303 (45), 290 (12), 277 (15), 250 (17), 221 (18), 207 (25), 162 (37), 109 (56), and 95 (100) [Found: *M* (mass spectrum), 455.3762. Calc. for C<sub>30</sub>H<sub>49</sub>NO<sub>2</sub>: *M*, 455.3762].

The more polar epimer, which was the major component, crystallised from methanol as needles, m.p. 91–93°,  $[\alpha]_D +84^\circ$  (*c* 0.08),  $\nu_{\max}$  3052, 2251, 1697, 903, and 825 cm<sup>-1</sup>,  $\delta$  2.69 (2H, m, 28-H<sub>2</sub>), 1.27 (3H, s, 29-H<sub>3</sub>), and 1.14 (3H, s, 19-H<sub>3</sub>), *m/e* 455 (100%), 440 (15), 437 (17), 427 (28), 412 (34), 370 (31), 358 (25), 303 (97), 290 (26), 277 (29), 250 (49), 221 (33), 207 (31), 162 (44), 109 (57), and 95 (100) (Found: C, 78.8; H, 10.9; N, 2.9. C<sub>30</sub>H<sub>49</sub>NO<sub>2</sub> requires C, 79.1; H, 10.8; N, 3.1%).

4 $\alpha$ ,14 $\alpha$ -Dimethyl-5 $\alpha$ -cholestane-3,11-dione (3).—Boron trifluoride-ether (0.75 ml) was added to a solution of the mixture of epoxides (9) (500 mg) in anhydrous toluene (150 ml) and the mixture heated at reflux under nitrogen for 3.5 h. Work-up, as in the case of the reaction of (8) with boron trifluoride, gave a residue (450 mg) which was chromatographed on a column of silica gel (30 g). Elution with light petroleum-ether (4:1) yielded 4 $\alpha$ ,14 $\alpha$ -dimethyl-5 $\alpha$ -cholestane-3,11-dione (3) (368 mg), m.p. 121–123° (from methanol),  $[\alpha]_D +75^\circ$  (*c* 0.30),  $\nu_{\max}$  1705 and 1698

$\text{cm}^{-1}$ ,  $\delta$  1.25 (3H, s, 19- $\text{H}_3$ ) and 1.08 (3H, s, 4-Me) (Found: C, 81.6; H, 11.5.  $\text{C}_{29}\text{H}_{48}\text{O}_2$  requires C, 81.9; H, 11.2%).

*Methyl 3-Nitrilo-11-oxo-3,4-seco-18 $\beta$ -oleana-4(23),12-dien-30-oate (23) and 3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -oleana-4(23),12-dien-30,22 $\beta$ -olactone (29)*.—Crude methyl 3-hydroxyimino-11-oxo-18 $\beta$ -olean-12-en-30-oate<sup>16</sup> (17.9 g), prepared from commercial (Merck) glycyrrhetic acid without rigorous purification of intermediates, was dissolved in anhydrous pyridine (400 ml) containing toluene-*p*-sulphonyl chloride (30 g), and the mixture heated at reflux in an atmosphere of nitrogen for 3.5 h. Work-up in the usual way gave a brown crystalline residue (14.6 g) which was chromatographed on a column of silica gel (500 g). Elution with benzene-ether (7:3) afforded methyl 3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -oleana-4(23),12-dien-30-oate (23) (12.0 g), m.p. 188–190° (from dichloromethane-methanol),  $[\alpha]_{\text{D}} +154^\circ$  (*c* 0.75) (lit.,<sup>16</sup> m.p. 190–191°,  $[\alpha]_{\text{D}} +158^\circ$ ).

Elution of the column with ether-benzene (4:1) yielded material (600 mg) which crystallised from dichloromethane-ethyl acetate to give 3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -oleana-4(23),12-dien-30,22 $\beta$ -olactone (29), m.p. 321–322°,  $[\alpha]_{\text{D}} +102^\circ$  (*c* 0.54),  $\lambda_{\text{max}}$  246 nm ( $\epsilon$  12,100),  $\nu_{\text{max}}$  3090, 2249, 1764, 1653, 1626, and 890  $\text{cm}^{-1}$ ,  $\delta$  5.66 (1H, s,  $W_{\frac{1}{2}}$  2.0 Hz, 12-H), 4.93 and 4.73 (each 1H, both m, 23- $\text{H}_2$ ), 4.24 (1H, d, *J* 2.5 Hz, 22 $\alpha$ -H), and 1.78 (2H, s, 24- $\text{H}_3$ ), *m/e* 463 (22%), 448 (15), 423 (26), 382 (18), 381 (18), 380 (38), 334 (9), 301 (100), 299 (18), 260 (33), 214 (22), and 135 (42) (Found: C, 77.4; H, 9.0; N, 3.0.  $\text{C}_{30}\text{H}_{41}\text{NO}_3$  requires C, 77.7; H, 8.9; N, 3.0%).

*Methyl 4 $\xi$ ,23-Epoxy-3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -olean-12-en-30-oate (34) and 4 $\xi$ ,23-Epoxy-3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -olean-12-en-30,22 $\beta$ -olactone (35)*.—The seco-nitriles (23) and (29) were treated overnight with *m*-chloroperbenzoic acid (80% excess) in dichloromethane at room temperature, and the reactions were worked up in the same way as the previous epoxidation.

The product from (23) crystallised from methanol to give methyl 4 $\xi$ ,23-epoxy-3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -olean-12-en-30-oate (34), m.p. 217–218°,  $[\alpha] +158^\circ$  (*c* 0.75),  $\lambda_{\text{max}}$  247 nm ( $\epsilon$  13,130),  $\nu_{\text{max}}$  2250, 1721, 1645, 1614, and 880  $\text{cm}^{-1}$ ,  $\delta$  5.72 (1H, s, 12-H), 3.69 (3H, s,  $\text{CO}_2\text{Me}$ ), and 2.74 (2H, m, 23- $\text{H}_2$ ), *m/e* 495 (4%), 317 (23), and 136 (100) (Found: C, 74.9; H, 9.4; N, 3.0.  $\text{C}_{31}\text{H}_{45}\text{NO}_4$  requires C, 75.1; H, 9.2; N, 2.8%).

The material from epoxidation of (29) crystallised from dichloromethane-methanol to yield 4 $\xi$ ,23-epoxy-3-nitrilo-11-oxo-3,4-seco-18 $\beta$ -olean-12-en-30,22 $\beta$ -olactone (35), m.p. 254–255°,  $[\alpha]_{\text{D}} +93^\circ$  (*c* 0.82),  $\lambda_{\text{max}}$  246 nm ( $\epsilon$  11,500),  $\nu_{\text{max}}$  2254, 1780, 1655, 1610, 950, and 880  $\text{cm}^{-1}$ ;  $\delta$  5.66 (1H, s,  $W_{\frac{1}{2}}$  2.1 Hz, 12-H), 4.27 (1H, d, *J* 5 Hz, 22 $\alpha$ -H), and 2.77 (2H, m, 23- $\text{H}_2$ ), *m/e* 479 (17%), 464 (10), 308 (8), 301 (100), and 260 (17) (Found: C, 74.8; H, 8.6; N, 2.8.  $\text{C}_{30}\text{H}_{41}\text{NO}_4$  requires C, 75.1; H, 8.6; N, 2.9%).

*Methyl 3,11-Dioxo-24-nor-18 $\beta$ -olean-12-en-30-oate (25) and 3,11-Dioxo-24-nor-18 $\beta$ -olean-12-en-30,22 $\beta$ -olactone (31)*.—The epoxy-nitriles (34) and (35) were treated with boron trifluoride-ether in toluene under the conditions used for the conversion of the epoxides (9) into the diketone (3), and the reactions were worked-up as described.

The product from the reaction of (34) was chromatog-

raphed on silica gel (60:1 ratio) to give, on elution with light petroleum-ether (1:1), methyl 3,11-dioxo-24-nor-18 $\beta$ -olean-12-en-30-oate (25) (83%), m.p. 241–242° (from methanol),  $[\alpha]_{\text{D}} +190^\circ$  (*c* 1.07),  $\lambda_{\text{max}}$  246 nm ( $\epsilon$  13,000),  $\nu_{\text{max}}$  1724, 1702, 1649, and 1614  $\text{cm}^{-1}$ ,  $\delta$  5.72 (1H, s,  $W_{\frac{1}{2}}$  2.1 Hz, 12-H) and 3.69 (3H, s,  $\text{CO}_2\text{Me}$ ), *m/e* 468 (64%), 453 (13), 440 (17), 408 (11), 393 (7), 317 (38), 276 (100), 216 (22), and 135 (36) (Found: C, 77.2; H, 9.6.  $\text{C}_{30}\text{H}_{44}\text{O}_4$  requires C, 76.9; H, 9.5%).

The epoxy-nitrile (35) yielded a crystalline product which was chromatographed on silica gel (60:1 ratio). Elution with benzene-ether (1:1) afforded 3,11-dioxo-24-nor-18 $\beta$ -olean-12-en-30,22 $\beta$ -olactone (31) (74%), m.p. 329–330° (decomp.) (from dichloromethane-methanol),  $[\alpha]_{\text{D}} +101^\circ$  (*c* 0.04),  $\lambda_{\text{max}}$  245 nm ( $\epsilon$  10,700),  $\nu_{\text{max}}$  1773, 1710, 1670, and 1623  $\text{cm}^{-1}$ ,  $\delta$  5.67 (1H, s,  $W_{\frac{1}{2}}$  2.0 Hz, 12-H) and 4.22 (1H, d, *J* 5 Hz, 22 $\alpha$ -H), *m/e* 452 (12%), 437 (7), 424 (7), 260 (100), and 245 (6) (Found: C, 76.6; H, 9.0.  $\text{C}_{29}\text{H}_{40}\text{O}_4$  requires C, 76.9; H, 8.9%).

*3 $\beta$ -Hydroxy-11-oxo-24-nor-18 $\beta$ -olean-12-en-30-oic Acid (27) and Derivatives*.—Lithium tri-*t*-butoxyaluminium hydride (2.0 g) was added to a solution of methyl 3,11-dioxo-24-nor-18 $\beta$ -olean-12-en-30-oate (25) (1.0 g) in tetrahydrofuran (50 ml) at 0°, and the mixture stirred at room temperature for 20 min. Acetic acid (3*N*; 300 ml) was then added and the organic material extracted with chloroform. The usual work-up afforded methyl 3 $\beta$ -hydroxy-11-oxo-24-nor-18 $\beta$ -olean-12-en-30-oate (26) (0.74 g), m.p. 180–181° (from benzene),  $[\alpha]_{\text{D}} +189^\circ$  (*c* 0.53),  $\lambda_{\text{max}}$  245 nm ( $\epsilon$  11,200),  $\nu_{\text{max}}$  3620, 1727, 1658, and 1620  $\text{cm}^{-1}$ ,  $\delta$  5.70 (1H, s,  $W_{\frac{1}{2}}$  2.0 Hz, 12-H), 3.70 (3H, s,  $\text{CO}_2\text{Me}$ ), 3.10 (1H, dt, *J*<sub>d</sub> 5.5, *J*<sub>t</sub> 10.0 Hz, 3 $\alpha$ -H), and 1.69 (1H, s, exch. with  $\text{D}_2\text{O}$ , OH), *m/e* 470 (6%), 317 (12), 276 (100), 216 (19), and 136 (82) (Found: C, 76.7; H, 10.2.  $\text{C}_{30}\text{H}_{46}\text{O}_4$  requires C, 76.6; H, 9.9%).

The methyl ester (26) (0.74 g) was dissolved in ethanol (100 ml) containing potassium hydroxide (5 g), and the solution heated at reflux under nitrogen for 20 h. Acidification with dilute hydrochloric acid and extraction with chloroform afforded 3 $\beta$ -hydroxy-11-oxo-24-nor-18 $\beta$ -olean-12-en-30-oic acid (27) (610 mg), m.p. 283–284° (from acetone),  $[\alpha]_{\text{D}} +385^\circ$  (*c* 0.36),  $\lambda_{\text{max}}$  245 ( $\epsilon$  11,500),  $\nu_{\text{max}}$  3430, 1723, 1648, and 1612  $\text{cm}^{-1}$ ,  $\delta$  6.02br (2H, s, exch. with  $\text{D}_2\text{O}$ ,  $\text{CO}_2\text{H}$  and 3 $\beta$ -OH), 5.69 (1H, s,  $W_{\frac{1}{2}}$  2.0 Hz), and 3.25 (1H, m, 3 $\alpha$ -H), *m/e* 456 (16%), 410 (5), 303 (11), 262 (100), and 216 (11) (Found: C, 76.2; H, 9.5.  $\text{C}_{29}\text{H}_{44}\text{O}_4$  requires C, 76.3; H, 9.7%).

Succinic anhydride (360 mg) was added to a solution of 4 $\beta$ -demethylglycyrrhetic acid (27) (300 mg) in pyridine (10 ml) and the solution heated at reflux for 3 h. The usual work-up gave the 3 $\beta$ -succinate (28) (240 mg), m.p. 296–297° (from aqueous acetic acid),  $[\alpha]_{\text{D}} +180^\circ$  (*c* 0.55),  $\lambda_{\text{max}}$  247 nm ( $\epsilon$  17,600),  $\nu_{\text{max}}$  1730, 1705, 1667, and 1621  $\text{cm}^{-1}$ , *m/e* 556 (5%), 302 (19), 263 (19), 262 (100), 216 (21), and 135 (27) (Found: C, 71.0; H, 8.8.  $\text{C}_{38}\text{H}_{48}\text{O}_7$  requires C, 71.2; H, 8.7%).

K. F. C. and R. K. gratefully acknowledge receipt of Commonwealth Postgraduate Awards.

[3/625 Received, 26th March, 1973]