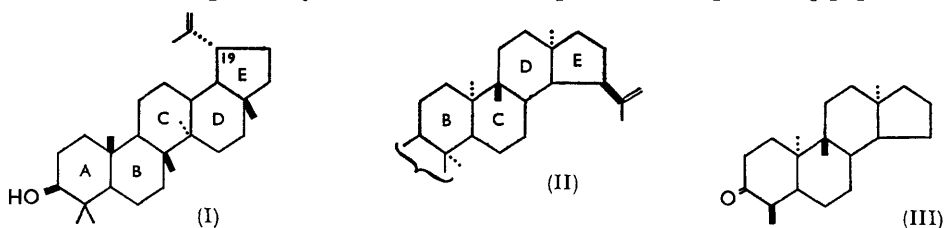


**223.** *The Chemistry of Triterpenes and Related Compounds. Part XLIV.\* The Conversion of Lupeol into enantio-4 $\alpha$ ,9 $\alpha$ -Dimethyl-5 $\alpha$ -androstan-3-one.*

By G. V. BADDELEY, T. G. HALSALL, and SIR EWART R. H. JONES.

By removal of a C<sub>6</sub> fragment from ring A and the C<sub>3</sub> side-chain from ring E, lupeol (I) has been converted into the tetracyclic C<sub>21</sub> ketone (III). This has been shown to be enantiomeric with 4 $\alpha$ ,9 $\alpha$ -dimethyl-5 $\alpha$ -androstan-3-one, the partial synthesis of which is described in the preceding paper.

So far, no direct transformations between the pentacyclic triterpenes and the steroids have been achieved. Examination of the structure of the triterpene lupeol (I) reveals that rings B—E (II) represent the mirror image of the steroid nucleus.<sup>1</sup> We now describe the excision of a C<sub>6</sub> fragment from ring A and the isopropenyl side-chain from the terminal ring of lupeol, leading to the production of the enantiomer (III) of 4 $\alpha$ ,9 $\alpha$ -dimethyl-5 $\alpha$ -androstan-3-one, the partial synthesis of which is reported in the preceding paper.



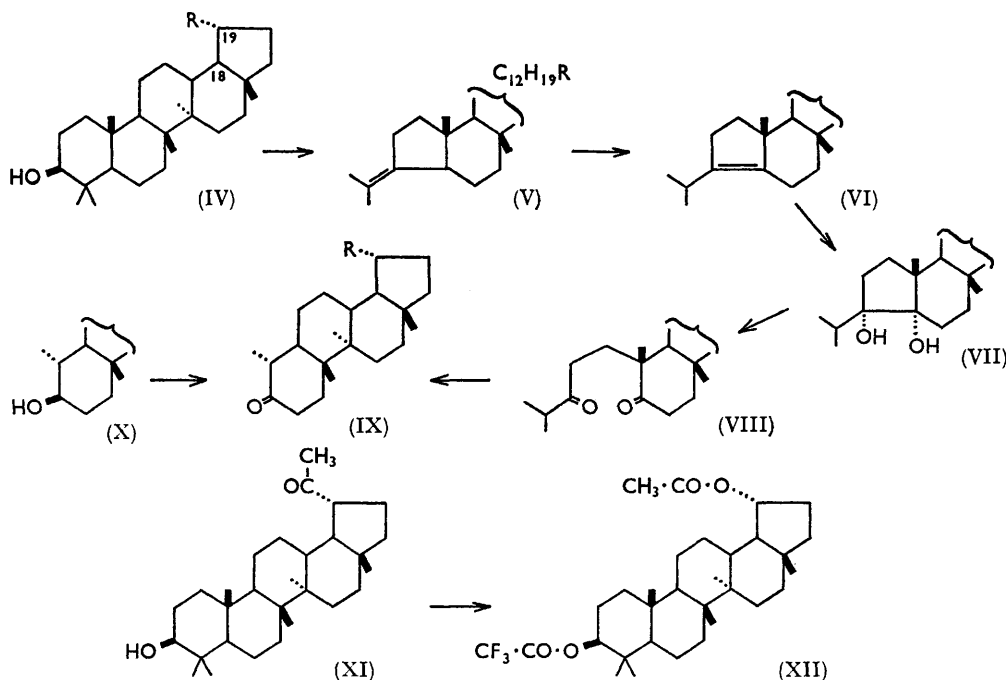
Methods of removing ring A from lupane derivatives, still containing the isopropyl side-chain, were first investigated. After detailed examination of a route (described later)

\* Part XLIII, *J.*, 1963, 3269.

<sup>1</sup> Jones, Meakins, and Stephenson, *J.*, 1958, 2156.

involving the scission of a  $\delta$ -keto-acid (XVII), attention was turned to the cleavage of the 1,5-diketone (VIII;  $R = \text{Me}_2\text{CH}$ ) by analogy with the work of Barton, de Mayo, and Orr<sup>2</sup> in the degradation of zeorin. Dehydration of lupanol (IV;  $R = \text{Me}_2\text{CH}$ ) proceeds with retropinacolinic rearrangement to  $\gamma$ -lupene (V;  $R = \text{Me}_2\text{CH}$ ), isomerised<sup>3</sup> with boiling acetic acid to iso- $\gamma$ -lupene (VI;  $R = \text{Me}_2\text{CH}$ ). Hydroxylation gave the glycol (VII;  $R = \text{Me}_2\text{CH}$ ), cleaved with lead tetra-acetate in benzene to the noncrystalline diketone (VIII;  $R = \text{Me}_2\text{CH}$ ), which gave a crystalline dioxime. The same diketone was obtained by oxonolysis of iso- $\gamma$ -lupene in hexane-chloroform at  $-70^\circ$ , after reduction of the ozonide with zinc and acetic acid.

An attempt to purify the diketone (VIII;  $R = \text{Me}_2\text{CH}$ ) by short-path distillation at  $315^\circ/0.15$  mm. produced a surprising but most satisfactory result. The distillation was accompanied by the production of a pungent odour, presumably of isopropyl vinyl ketone, and the yellow oily distillate crystallised (m. p.  $176^\circ$ ). This proved to be the monoketone (IX;  $R = \text{Me}_2\text{CH}$ ), identical with a specimen prepared by a more rational route (see below). Obviously the desired reversed Michael reaction had been brought about by the alkaline glass at  $300^\circ$ . An earlier attempt to employ standard conditions<sup>2</sup> for this cleavage resulted in the production only of the alcohol (X;  $R = \text{Me}_2\text{CH}$ ) (presumably with the hydroxyl group in the thermodynamically more stable equatorial configuration), giving the ketone (IX;  $R = \text{Me}_2\text{CH}$ ) on chromic acid oxidation. The comparatively high yield (55%) of the ketone by pyrolysis of the diketone (VIII;  $R = \text{Me}_2\text{CH}$ ) made this route much more promising than the alternative described below, for application in the case where the  $\text{C}_3$  side-chain had been removed.



The removal of this side-chain from C-19 in lupeol (I) required a method which did not permit isomerisation of the *trans* to the more stable *cis* D/E ring junction. Baeyer-Villiger oxidation of the known norketone (XI) with trifluoroacetic acid at  $20^\circ$  gave the 19-acetoxy-compound (XII), the free hydroxyl group having been trifluoroacetylated.

<sup>2</sup> Barton, de Mayo, and Orr, *J.*, 1958, 2239.

<sup>3</sup> Nowak, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 323.

Selective hydrolysis of the trifluoroacetate group was effected either with one equivalent of barium hydroxide in methanol or, and more easily, by delayed elution from alumina. The resulting diol monoacetate (IV; R = OAc) when treated under the standard retro-pinacolinic dehydration conditions gave the expected acetoxy-olefin (V; R = OAc). This with lithium aluminium hydride gave the alcohol (V; R = OH); acetylation regenerated the acetate showing that migration of the double bond had not occurred. To obtain trisnor- $\gamma$ -lupene (V; R = H) itself now only required removal of the hydroxyl group.

To avoid epimerisation at C-18 the method chosen involved conversion<sup>4</sup> of the alcohol (V; R = OH) into its toluene-*p*-sulphonate (V; R = OTs) and cleavage with lithium aluminium hydride to the hydrocarbon (V; R = H). The position of the double bond was demonstrated by the method of Castells and Meakins,<sup>5</sup> a cyclopentanone (cf. XIII) ( $\nu_{\max}$ , 1740  $\text{cm}^{-1}$ ) being obtained. Acid treatment gave a new ketone (cf. XIV); the  $\Delta[M]_D$  (+653°) for this isomerisation is close to those observed<sup>6</sup> in the base catalysed conversion of the analogous *trans*-oxotrisnorlupane (+752°) and *trans*-oxotrisnorhopane (+706°).

The olefin (V; R = H) was first isomerised to the analogue (VI; R = H) of iso- $\gamma$ -lupene (VI; R = Me<sub>2</sub>CH), indifferently in boiling acetic acid (cf. above and ref. 3) but in high yield with boron trifluoride etherate in benzene.<sup>7</sup> The  $\Delta[M]_D$  (+88°) for this conversion parallels that (+127°) for the  $\gamma$ -lupene  $\rightarrow$  iso- $\gamma$ -lupene isomerisation.

The glycol (VII; R = H) was prepared by the improved technique of heating it under reflux with osmium tetroxide and pyridine and ether, and cleaved by lead tetra-acetate to the noncrystalline diketone (VIII; R = H). It formed a crystalline dioxime which gave back the parent diketone on acid hydrolysis.

The diketone (VIII; R = H) distilled unchanged at 210–230°/0.05 mm. but at 300°/8 mm. afforded the required des-A-compound (IX; R = H) [*i.e.*, *enantio-4 $\alpha$ ,9 $\alpha$* -dimethyl-5 $\alpha$ -androstan-3-one (III)], characterised as the oxime. The ketone was unchanged under acidic conditions effective in isomerising 4 $\beta$ -methyl-3-oxo-steroids to the more stable 4 $\alpha$ -epimers, showing that the C-10 angular methyl group of the triterpene nucleus had adopted the more stable equatorial configuration during the reversed Michael reaction.

The  $\Delta[M]_D$  values between corresponding pairs of compounds in the two series of degradation products from iso- $\gamma$ -lupene (VI; R = Me<sub>2</sub>CH) and the trisnor-analogue (VI; R = H) to the respective des-A-ketones (IX; R = Me<sub>2</sub>CH) and (IX; R = H) are given in Table 1.

TABLE 1.

	$[M]_D$ Lupane series (R = Me <sub>2</sub> CH)	$[M]_D$ Trisnorlupane series (R = H)	$\Delta[M]_D$
(V) .....	-66°	+81°	+147°
(VI) .....	+61	+169	+108
(VII) .....	-102	+58	+160
(VIII) .....	-154	-31	+123
(IX) .....	-65	+63	+128

The optical rotatory dispersions of the des-A-ketones (IX; R = Me<sub>2</sub>CH and R = H) are compared in Table 2 with those of a number of steroidal ketones. Their curves were near-reflections of and had nearly the same amplitudes as those of dihydrotestosterone, 4 $\alpha$ -methylcholestan-3-one, and 5 $\alpha$ -androstan-3-one, all of whose A/B rings are enantiomeric with the B/C rings of the triterpene degradation products. The curves were comparable with those of 17 $\beta$ -hydroxydes-A-androstan-5-one and des-A-cholestan-5-one whose B/C rings are similar to those of the ketones (IX; R = H) and (IX; R = Me<sub>2</sub>CH), differing only in the presence of a hydrogen atom in place of a methyl group at C-9. The lack of the angular methyl group at C-10 in the principal steroidal series does not alter the general

<sup>4</sup> Plattner and Lang, *Helv. Chim. Acta*, 1944, 27, 1872.

<sup>5</sup> Castells and Meakins, *Chem. and Ind.*, 1956, 248.

<sup>6</sup> Baddeley, Halsall, and Jones, *J.*, 1960, 1715.

<sup>7</sup> Powell and Whiting, *Proc. Chem. Soc.*, 1960, 412.

TABLE 2.

Compound	Amplitude *	Ref.	Compound	Amplitude
Dihydrotestosterone .....	+55°	8	Des-A-(10 $\beta$ H)-lupan-5-one (IX; R = Me <sub>2</sub> CH) .....	-51°
5 $\alpha$ -Androstan-3-one .....	+52		<i>enantio</i> -4 $\alpha$ ,9 $\alpha$ -Dimethyl-5 $\alpha$ -androstan-3-one (IX; R = H) .....	-51
4 $\alpha$ -Methylcholestan-3-one .....	+53	9	17 $\beta$ -Hydroxydes-A-androstan-5-one .....	-50
9 $\alpha$ -Methyl-5 $\alpha$ -androstan-3-one .....	+50		Des-A-cholestan-5-one .....	-93
4 $\alpha$ ,9 $\alpha$ -Dimethyl-5 $\alpha$ -androstan-3-one .....	+55			
19-Nordihydrotestosterone ...	+90	9		
4 $\beta$ -Methylcholestan-3-one .....	+11	9		

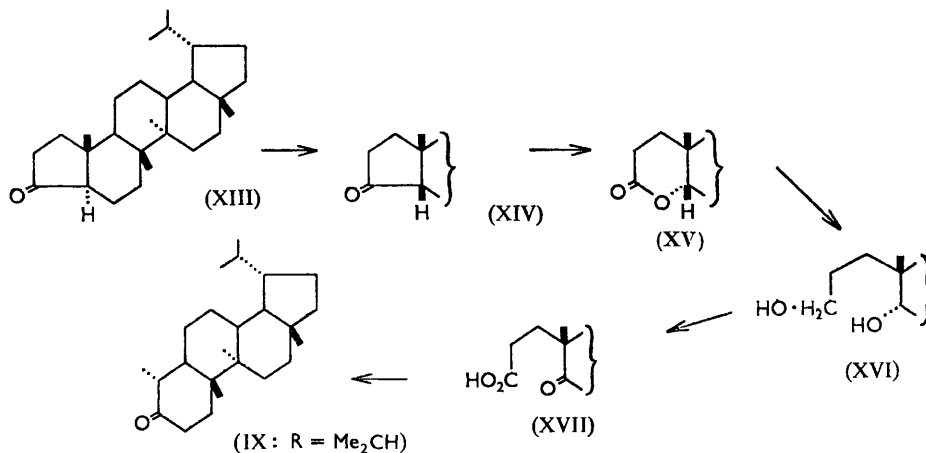
\* Amplitude is the difference between the  $[M]_D \times 10^{-2}$  at the peak and trough of the Cotton curve. The values were recorded for solutions in MeOH ( $c$  0.1).

shape of the dispersion curve, the curve for 19-nordihydrotestosterone closely resembling that of dihydrotestosterone, only the amplitude being appreciably different.

From the above and the comparisons made in the preceding paper it is clear that both the triterpene-derived des-A-ketones (IX) possess a nucleus which is enantiomeric with that of the 4,9-dimethyl-steroids. Additional evidence for assigning the 4 $\alpha$ (equatorial)-configuration to the methyl group in the  $\alpha$ -position to the keto-group in these ketones (IX) is provided by comparison of the dispersion curves with that of 4 $\beta$ -methylcholestan-3-one, the amplitude of which is much smaller due to the axial methyl group.

Before using the diketone-cleavage route described above, removal of ring A *via* the  $\delta$ -keto-acid (XVII) was explored, since the keto-acid scission has been successfully applied<sup>10,11</sup> following the development of an improved pyrolytic technique by Woodward and Wiesner.<sup>12</sup>

$\gamma$ -Lupene (V; R = Me<sub>2</sub>CH) was converted<sup>6</sup> *via* the easily isomerised *trans*-trisketone (XIII) into the *cis*-ketone (XIV) which, on Baeyer-Villiger oxidation with trifluoroacetic acid gave the  $\delta$ -lactone (XV) with the lactonic oxygen attached axially to ring B and the configuration of the C-5 hydrogen atom unchanged.



Reduction of the lactone (XV) with lithium aluminium hydride afforded a noncrystalline diol (XVI) which gave both a mono- and a di-acetate with acetic anhydride-pyridine at 100°. The slow rate of acetylation of one of the hydroxyl groups is consistent with its being axial. Oxidation of the monoacetate gave a keto-acetate. The  $\Delta[M]_D$  value

<sup>6</sup> Djerassi, Mitscher, and Mitscher, *J. Amer. Chem. Soc.*, 1959, **81**, 947.

<sup>9</sup> Djerassi, Halpern, Halpern, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 4001.

<sup>10</sup> Hartshorn and Jones, *J.*, 1962, 1312.

<sup>11</sup> Castells, Jones, Meakins, and Williams, *J.*, 1959, 1159.

<sup>12</sup> Woodward and Wiesner, personal communication.

(+27°) between the mono- and di-acetates is in good agreement with predictions based on the rule of Klyne and Stokes.<sup>13</sup> It is in accord with the values for the analogously sited 3 $\beta$ -hydroxyl group of the triterpenes ( $\Delta[M]_D$  +22° for the oleanene series)<sup>13</sup> and differs markedly from values obtained for the corresponding epimeric 3 $\alpha$ -hydroxyl group ( $\Delta[M]_D$  -137°).<sup>13</sup> This evidence shows that the 5-hydroxyl group in the diol (XVI) has the  $\alpha$ -configuration and is, indeed, axially disposed.

Alkaline hydrolysis of its crystalline diacetate regenerated the diol (XVI) which was oxidised with chromic acid in acetone<sup>14</sup> to the noncrystalline keto-acid (XVII). This was converted, after purification through the cyclohexylamine salt, into the crystalline methyl ester. This thorough characterisation of the keto-acid (XVII) completely eliminated the possibility that oxidative fission of the ketone (XIV) had occurred between C-2 and C-3.

Pyrolysis of the sodium salt of the keto-acid (XVII) with sodium phenylacetate gave the desired des-A-ketone (IX; R = Me<sub>2</sub>CH), identical with the compound arising from the diketone cleavage.

### EXPERIMENTAL

For general directions see preceding paper.

*Iso- $\gamma$ -lupene* (VI; R = Me<sub>2</sub>CH).—This was prepared as described by Nowak, Jeger, and Ruzicka<sup>3</sup> by heating  $\gamma$ -lupene under reflux in acetic acid. A single crystallisation from light petroleum-ethyl acetate gave iso- $\gamma$ -lupene as plates, m. p. 132–137°,  $[\alpha]_D$  +11° (c 1.84) (lit.,<sup>3</sup> m. p. 133–134°,  $[\alpha]_D$  +14°).

*Hydroxylation of Iso- $\gamma$ -lupene*.—Iso- $\gamma$ -lupene (740 mg.) in pyridine (12 c.c.) and ether (60 c.c.) was heated under reflux with osmium tetroxide (468 mg.; 1 mol.) for 48 hr.; cleavage of the resultant osmate gave iso- $\gamma$ -lupene glycol [5(4 $\rightarrow$ 3)-abeolupane-3 $\alpha$ ,5 $\alpha$ -diol] (VII; R = Me<sub>2</sub>CH) as prisms (from benzene-light petroleum), m. p. 191–194°,  $[\alpha]_D$  -23° (c 0.99) (lit.,<sup>3</sup> m. p. 189–190°,  $[\alpha]_D$  -23°) (Found: C, 81.15; H, 11.9. Calc. for C<sub>30</sub>H<sub>52</sub>O<sub>2</sub>: C, 81.0; H, 11.8%).

*Cleavage of Iso- $\gamma$ -lupene Glycol* (VI; R = Me<sub>2</sub>CH) *with Lead Tetra-acetate*.—Lead tetra-acetate (6.8 g.; 1.5 mol.) was added with stirring to a solution of the glycol (4.65 g.) in dry benzene (400 c.c.). Stirring was continued for 12 hr. at 20°, the crude product was adsorbed from light petroleum on alumina (200 g.), and elution with light petroleum-benzene (1:1) gave 3,5-dioxo-4,5-secolupane (VIII; R = Me<sub>2</sub>CH) as a gum<sup>cf. 3</sup> (4.5 g.),  $[\alpha]_D$  -35° (c 1.49) (Found: C, 81.45; H, 11.25. C<sub>30</sub>H<sub>50</sub>O<sub>2</sub> requires C, 81.4; H, 11.4%),  $\nu_{\max}$ . (in CCl<sub>4</sub>) 1710br cm<sup>-1</sup>. The *dioxime* (hydroxylamine hydrochloride-pyridine procedure) formed needles (from benzene-light petroleum), m. p. 118°,  $[\alpha]_D$  -28° (c 1.27) (Found: C, 76.05; H, 10.75; N, 6.15. C<sub>30</sub>H<sub>52</sub>N<sub>2</sub>O<sub>2</sub> requires C, 76.2; H, 11.1; N, 5.95%).

*Distillation of 3,5-Dioxo-4,5-secolupane* (VIII; R = Me<sub>2</sub>CH).—The diketone (352 mg.) was distilled from soft (alkaline) glass in a "bulb" apparatus at 350°/0.15 mm. to give a pale yellow oil (150 mg.) which solidified on cooling. Crystallisation from acetone afforded *des-A*-(10 $\beta$ H)-lupan-5-one (IX; R = Me<sub>2</sub>CH) as prisms, m. p. 176°,  $[\alpha]_D$  -19° (c 1.50) (Found: C, 83.3; H, 11.55. C<sub>24</sub>H<sub>40</sub>O requires C, 83.65; H, 11.7%),  $\nu_{\max}$ . (in CCl<sub>4</sub>) 1710sh cm<sup>-1</sup>. The *oxime* (hydroxylamine hydrochloride-pyridine procedure) formed fine needles (from aqueous methanol), m. p. 200–201°,  $[\alpha]_D$  +59° (c 0.83) (Found: C, 79.75; H, 11.2; N, 4.15. C<sub>24</sub>H<sub>41</sub>NO requires C, 80.15; H, 11.5; N, 3.9%).

*Reversed Michael Addition with 3,5-Dioxo-4,5-secolupane* (VIII; R = Me<sub>2</sub>CH).—The diketone (848 mg.) was heated under reflux in diethylene glycol (10 c.c.) with potassium hydroxide (0.5 g.) as described by Barton, de Mayo, and Orr<sup>2</sup> for 1 hr. in nitrogen. Isolation with ether afforded a gum (550 mg.), adsorbed from light petroleum-benzene (2:1) on to alumina (35 g.). Elution with the same solvent gave oils (250 mg.);  $\nu_{\max}$ . 3450, 1700, and 1660 cm<sup>-1</sup>. Elution with light petroleum-benzene (1:1) gave an alcohol (115 mg.), supposedly *des-A*-(10 $\beta$ H)-lupan-5 $\beta$ -ol (X), as needles (from acetone), m. p. 225–229°,  $[\alpha]_D$  -41° (c 0.74) (Found: C, 82.95; H, 12.05. C<sub>24</sub>H<sub>42</sub>O requires C, 83.15; H, 12.2%);  $\nu_{\max}$ . (in CCl<sub>4</sub>) 3600 and 1035 cm<sup>-1</sup>.

*Oxidation of Des-A*-(10 $\beta$ H)-lupan-5 $\beta$ -ol (X).—The alcohol (90 mg.) in acetone (20 c.c.) was

<sup>13</sup> Klyne and Stokes, *J.*, 1954, 1979.

<sup>14</sup> Bowers, Halsall, Jones, and Lemlin, *J.*, 1953, 2555.

treated with a solution of chromic oxide<sup>14</sup> (8N; 0.28 c.c.) at 0° for 1.5 min. Dilution with water followed by ethereal extraction gave des-A-(10 $\beta$ H)-lupan-5-one (80 mg.) as prisms (from acetone), m. p. and mixed m. p. 174°,  $[\alpha]_D -18^\circ$  (*c* 2.09).

*Ozonolysis of Iso- $\gamma$ -lupene* (VI; R = Me<sub>2</sub>CH).—Iso- $\gamma$ -lupene (600 mg.) in hexane-chloroform (1 : 1; 80 c.c.) was cooled to -70° and ozonised oxygen (6%) was bubbled through the solution until a persistent blue colour was observed. Excess of ozone was removed by a stream of nitrogen, and the solution was then evaporated to give a gum which was eluted from alumina (50 g.) with light petroleum to give a pale yellow glass which did not give either a coloration with tetranitromethane or a positive starch-iodide test for oxidising agents;  $\nu_{\max}$ . (nat. film) 1720w and 904 cm.<sup>-1</sup>. A stable ozonide was suspected. The material was heated under reflux in acetic acid (35 c.c.) with zinc dust (0.9 g.) for 0.5 hr. to give a gum [ $\nu_{\max}$ . (Nujol) 1710 cm.<sup>-1</sup>] which was adsorbed from light petroleum on alumina (25 g.). Elution with benzene gave a gum (325 mg.) [ $\nu_{\max}$ . (nat. film) 1705 cm.<sup>-1</sup>] which was 3,5-dioxo-4,5-secolupane (VIII; R = Me<sub>2</sub>CH) since it gave des-A-(10 $\beta$ H)-lupan-5-one by the distillation procedure described above.

*Ozonolysis of Lupenyl Acetate*.—Lupenyl acetate (1.80 g.) in methylene dichloride (90 c.c.) was cooled to -70° and ozone was passed through the solution until a faint blue colour persisted. Excess of ozone was removed by a stream of nitrogen, and acetic acid (30 c.c.) and zinc dust (5 g.) were immediately added. The mixture was kept at 20° for 1 hr. and then heated under reflux for 5 min. The product was isolated and adsorbed from light petroleum-benzene (5 : 1) on alumina (150 g.). Elution with light petroleum-benzene (1 : 1) gave norlupanonyl acetate (20-oxo-29-norlupan-3 $\beta$ -yl acetate) (1.46 g.) as needles (from acetone-methanol), m. p. 258—264°,  $[\alpha]_D$  0° (*c* 1.09) (lit.,<sup>15</sup> m. p. 260—262°,  $[\alpha]_D +3.7^\circ$ ) (Found: C, 78.75; H, 10.6. Calc. for C<sub>31</sub>H<sub>50</sub>O<sub>3</sub>: C, 79.1; H, 10.7%);  $\nu_{\max}$ . (in CS<sub>2</sub>) 1735, 1715, 1240, 1025, and 980 cm.<sup>-1</sup>.

*Lupane-3 $\beta$ ,20,29-triol*.—The triol, m. p. 266—272° (decomp.) was prepared as described by Jones and Meakins<sup>15</sup> by the action of osmium tetroxide on lupeol.

*20-Oxo-29-norlupan-3 $\beta$ -ol* (XI).—The ketol was prepared by the lead tetra-acetate cleavage of lupane-3 $\beta$ ,20,29-triol, as described.<sup>15</sup> It crystallised as plates (from acetone-methanol), m. p. 238—239°,  $[\alpha]_D -15^\circ$  (*c* 1.56) (lit., m. p. 234—236°,  $[\alpha]_D -15^\circ$ ). The alkaline hydrolysis of norlupanonyl acetate also afforded the ketol as plates (from acetone-methanol), m. p. 235—237°,  $[\alpha]_D -15^\circ$  (*c* 1.51). The benzoate was prepared by treatment of the alcohol (650 mg.) in pyridine (10 c.c.) with benzoyl chloride (3 c.c.) at 100° for 4 hr. It crystallised as plates (from acetone-methanol), m. p. 253—258°,  $[\alpha]_D +35^\circ$  (*c* 1.69) (lit.,<sup>15</sup> m. p. 260°).

*Oxidation of 20-Oxo-29-norlupan-3 $\beta$ -ol* (XI) with *Trifluoroacetic Acid*.—Trifluoroacetic anhydride (1.7 c.c.) was added slowly and with shaking to a suspension of aqueous hydrogen peroxide (90%; 0.30 c.c.) in methylene dichloride (7 c.c.) at 0°. The mixture was shaken for 15 min. and the resultant solution was added slowly to the ketol (450 mg.) in methylene dichloride (20 c.c.) at 0°. After being kept at 0° for 24 hr. the reaction mixture was worked up as usual. The solid [ $\nu_{\max}$ . (Nujol) 1770, 1720, 1210, 1170, and 1050 cm.<sup>-1</sup>] obtained was heated under reflux for 0.5 hr. in methanol (200 c.c.) with hydrated barium hydroxide (170 mg.) to give a gum [ $\nu_{\max}$ . (Nujol) 3400, 1725, 1250, and 1050 cm.<sup>-1</sup>] which was adsorbed from light petroleum-benzene (1 : 1) on alumina (25 g.). Elution with light petroleum-benzene (1 : 3) gave 19 $\alpha$ -acetoxy-20,29,30-trisnorlupan-3 $\beta$ -ol (IV; R = OAc) (234 mg.) as needles (from di-isopropyl ether-light petroleum), m. p. 170—171°,  $[\alpha]_D -20^\circ$  (*c* 0.77) (Found: C, 78.35; H, 10.7. C<sub>29</sub>H<sub>48</sub>O<sub>3</sub> requires C, 78.3; H, 10.9%);  $\nu_{\max}$ . (in CS<sub>2</sub>) 3500, 1730, 1245, and 1040 cm.<sup>-1</sup>.

*Oxidation of 20-Oxo-29-norlupan-3 $\beta$ -yl Benzoate with Trifluoroacetic acid*.—The oxidation was carried out, as for the alcohol, with the benzoate (450 mg.) and with a reaction time of 3 days. The gum which was obtained was heated under reflux for 0.5 hr. in methanol (150 c.c.) with hydrated barium hydroxide (150 mg.) to give a product which was adsorbed from light petroleum-benzene (3 : 1) on alumina (50 g.). Elution with light petroleum-benzene (1 : 1) gave 19 $\alpha$ -acetoxy-20,29,30-trisnorlupan-3 $\beta$ -yl benzoate (135 mg.) as plates (from acetone-methanol), m. p. 261—263°,  $[\alpha]_D +23^\circ$  (*c* 1.55) (Found: C, 78.55; H, 9.4. C<sub>36</sub>H<sub>52</sub>O<sub>4</sub> requires C, 78.8; H, 9.55%);  $\nu_{\max}$ . (in CCl<sub>4</sub>) 1730, 1715, 1270, 1250, 1110, 1030, and 706 cm.<sup>-1</sup>.

*Retropinacolic Dehydration of 19 $\alpha$ -Acetoxy-20,29,30-trisnorlupan-3 $\beta$ -ol* (IV; R = OAc).—The diol monoacetate (1.25 g.) was added during 2 min. to phosphorus pentachloride suspended in anhydrous petroleum (b. p. 40—60°; 800 c.c.). The mixture was swirled for 8 min., the solution was decanted from residual phosphorus pentachloride, washed thoroughly with sodium

<sup>15</sup> Jones and Meakins, *J.*, 1940, 456.

hydrogen carbonate solution, and dried. The ultraviolet spectrum of the product showed intense "end absorption;" crystallisation gave prisms (930 mg.), m. p. 157—162°, which on repeated recrystallisation from acetone-methanol gave 19 $\alpha$ -acetoxy-20,29,30-trisnor-5(4 $\rightarrow$ 3)-abeolup-3-ene (V; R = OAc), m. p. 168—172°,  $[\alpha]_D^{20}$  -22° (c 1.17) (Found: C, 81.45; H, 10.8. C<sub>29</sub>H<sub>44</sub>O<sub>2</sub> requires C, 81.65; H, 10.85%);  $\nu_{\max}$ . (in CS<sub>2</sub>) 1727, 1243, 1040, and 1028 cm.<sup>-1</sup>.

*Hydrolysis of 19 $\alpha$ -Acetoxy-20,29,30-trisnor-5(4 $\rightarrow$ 3)abeolup-3-ene* (V; R = OAc).—The acetate (930 mg.) in ether (150 c.c.) was heated under reflux for 2 hr. with powdered lithium aluminium hydride (4 g.). Cautious removal of the excess of hydride by the addition of ethyl acetate followed by extraction with ether afforded a solid (850 mg.) which gave 20,29,30-trisnor-5(4 $\rightarrow$ 3)abeolup-3-en-19 $\alpha$ -ol (V; R = OH) as cubes (from light petroleum), m. p. 180° ( $\rightarrow$  needles at 111—125°),  $[\alpha]_D^{20}$  -17° (c 1.50) (Found: C, 84.35; H, 11.55. C<sub>27</sub>H<sub>44</sub>O requires C, 84.35; H, 11.45%);  $\nu_{\max}$ . (in CS<sub>2</sub>) 3540 and 1055 cm.<sup>-1</sup>. Acetylation regenerated the acetate, m. p. 161—173°,  $[\alpha]_D^{20}$  -22°.

20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolup-3-en-19 $\alpha$ -yl Toluene-*p*-sulphonate (V; R = OTs).—20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolup-3-en-19 $\alpha$ -ol (300 mg.) in pyridine (4 c.c.) was treated with toluene-*p*-sulphonyl chloride (300 mg.) at 3° for 60 hr. The toluene-*p*-sulphonate formed prisms (280 mg.) (from light petroleum), m. p. 105—106° (decomp.),  $[\alpha]_D^{20}$  -13° (c 1.57) (Found: C, 75.7; H, 9.25. C<sub>34</sub>H<sub>50</sub>O<sub>3</sub>S requires C, 75.8; H, 9.35%);  $\nu_{\max}$ . (in CCl<sub>4</sub>) 1183, 1173, 1095, 945, and 900 cm.<sup>-1</sup>.

*Cleavage of the Toluene-*p*-sulphonate* (V; R = OTs) with Lithium Aluminium Hydride.—The toluene-*p*-sulphonate (250 mg.) in ether (40 c.c.) was heated under reflux for 6 hr. with lithium aluminium hydride (500 mg.); removal of the excess of hydride followed by isolation through petroleum (b. p. 40—60°) then gave 20,29,30-trisnor-5(4 $\rightarrow$ 3)abeolup-3-ene (V; R = H) (165 mg.) as prisms (from acetone), m. p. 184—186°,  $[\alpha]_D^{20}$  +22° (c 1.39) (Found: C, 88.05; H, 11.9. C<sub>27</sub>H<sub>44</sub> requires C, 87.95; H, 12.05%).

*Cleavage of 20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolup-3-ene* (V; R = H).—The olefin (56 mg.) in pyridine (2 c.c.) and ether (10 c.c.) was heated under reflux for 16 hr. with osmium tetroxide (85 mg.). After the solvent had been evaporated (100°/12 mm.) the residual osmate was cleaved by the mannitol-potassium hydroxide procedure to give the glycol (60 mg.) which was dissolved in benzene (10 c.c.) and treated with lead tetra-acetate (86 mg.) at 15° for 0.5 hr. Working up in the usual manner afforded needles (55 mg.) which were filtered through cellulose<sup>cf. 6</sup> in light petroleum to give 4,20,23,24,29,30-hexanor-5(4 $\rightarrow$ 3)abeolupan-3-one (cf. XIII) as needles (from di-isopropyl ether), m. p. 146—148°,  $[\alpha]_D^{20}$  -51° (c 0.72),  $\nu_{\max}$ . (in CHCl<sub>3</sub>) 1740 cm.<sup>-1</sup>.

*Isomerisation of 4,20,23,24,29,30-Hexanor-5(4 $\rightarrow$ 3)abeolupan-3-one* (cf. XIII).—The ketone (50 mg.) in ethanol (5 c.c.) was heated under reflux for 1 hr. with sulphuric acid (2N; 0.2 c.c.). Isolation *via* ether gave a product (48 mg.) which afforded 4,20,23,24,29,30-hexanor-5(5*H*)-5(4 $\rightarrow$ 3)abeolupan-3-one (XIV; R = H) as needles (from acetone-methanol), m. p. 164—168°,  $[\alpha]_D^{20}$  +140° (c 0.72).

*Isomerisation of 20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolup-3-ene* (V; R = H).—The olefin (140 mg.) in benzene (6 c.c.) was treated with boron trifluoride etherate in benzene (12%; 3 c.c.) for 3 hr. at 20°. Isolation *via* petroleum (b. p. 40—60°) gave a solid (135 mg.) which afforded 20,29,30-trisnor-5(4 $\rightarrow$ 3)abeolup-3(5)-ene (VI; R = H) as needles (from acetone-methanol), m. p. 135—137°,  $[\alpha]_D^{20}$  +46° (c 1.07) (Found: C, 87.9; H, 12.1. C<sub>27</sub>H<sub>44</sub> requires C, 87.95; H, 12.05%).

*Hydroxylation of 20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolup-3(5)-ene* (VI; R = H). The olefin (430 mg.) in ether (40 c.c.) and pyridine (6 c.c.) was heated under reflux for 3 days with osmium tetroxide (450 mg.). Cleavage of the resultant osmate by the mannitol-potassium hydroxide procedure afforded a yellow gum which was filtered through alumina (50 g.) in benzene to give 20,29,30-trisnor-5(4 $\rightarrow$ 3)abeolupane-3 $\alpha$ ,5 $\alpha$ -diol (VII; R = H) (330 mg.) as plates (from light petroleum), m. p. 219—220°,  $[\alpha]_D^{20}$  +15° (c 0.98) (Found: C, 80.35; H, 11.8. C<sub>27</sub>H<sub>46</sub>O<sub>2</sub> requires C, 80.55; H, 11.5%),  $\nu_{\max}$ . (Nujol) 3500 and 1070 cm.<sup>-1</sup>.

*Cleavage of 20,29,30-Trisnor-5(4 $\rightarrow$ 3)abeolupane-3 $\alpha$ ,5 $\alpha$ -diol* (VII; R = H).—The glycol (330 mg.) in benzene (30 c.c.) was treated with lead tetra-acetate (550 mg.) at 20° for 1 hr. The product was isolated by ether, and filtered on alumina (17 g.) in light petroleum-benzene (1 : 1) to give 20,29,30-trisnor-4,5-secolupane-3,5-dione (VIII; R = H) as a gum (300 mg.),  $[\alpha]_D^{20}$  -8° (c 1.96) (Found: C, 81.8; H, 11.3. C<sub>27</sub>H<sub>44</sub>O<sub>2</sub> requires C, 80.95; H, 11.05%),  $\nu_{\max}$ . (in CCl<sub>4</sub>) 1700br cm.<sup>-1</sup>.

The *dioxime* was prepared (hydroxylamine hydrochloride-pyridine method) as prisms (from benzene-light petroleum), m. p. 227—229°,  $[\alpha]_D^{20}$  -12° (c 0.90, in CHCl<sub>3</sub> containing 5% of

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pyridine) (Found: C, 75.45; H, 10.7; N, 6.6.  $C_{27}H_{46}N_2O_2$  requires C, 75.3; H, 10.75; N, 6.5%);  $\nu_{\max}$ . (Nujol) 3300, 1660, and 935  $cm^{-1}$ . The dioxime (200 mg.) in ethanol (80 c.c.) was heated under reflux for 3 hr. with 2N-hydrochloric acid (5 c.c.), the diketone being regenerated as a gum.

20,29,30-*Trisnor-des-A-(10 $\beta$ H)-lupan-5-one* (IX; R = H) (enantio-4 $\alpha$ ,9 $\alpha$ -dimethyl-5 $\alpha$ -androstan-3-one (III).—The diketone (VIII; R = H) (200 mg.) was distilled from soft (alkaline) glass in a "bulb" apparatus at 300°/8 mm. to give a yellow oil (120 mg.) which slowly solidified at 20°. The solid was adsorbed from light petroleum on alumina (10 g.). Elution with light petroleum–benzene (9 : 1) gave microcrystals (100 mg.) which afforded 20,29,30-*trisnor-des-A-(10 $\beta$ H)-lupan-5-one* (IX; R = H) as plates (from acetone), m. p. 162–164° (prisms at 130°)  $[\alpha]_D + 21^\circ$  (c 0.94) (Found: C, 83.3; H, 11.5.  $C_{21}H_{34}O$  requires C, 83.4; H, 11.35%);  $\nu_{\max}$ . (in  $CS_2$ ) 1723s  $cm^{-1}$ ; R.D.  $[M]$  (6000 Å) +250°, (5000) +200, (4000) 0°, (3500), –100°, (3200) –710°, (3100) –1530°, (3050) –1580°, (3025) –1680°, (3000) –1580°, (2900) 0°, (2800) +1840°, (2070) +3160°, (2675), +3370° (2650) +2760°; g.l.c. analysis, see under 4 $\alpha$ ,9 $\alpha$ -dimethyl-5 $\alpha$ -androstan-3-one (preceding paper).

The *oxime* was prepared (hydroxylamine hydrochloride–pyridine method) as fine needles (from light petroleum), m. p. 216–218°,  $[\alpha]_D + 6^\circ$  (c 0.305) (Found: C, 79.45; H, 11.2; N, 4.4.  $C_{21}H_{33}NO$  requires C, 79.45; H, 11.0; N, 4.4%);  $\nu_{\max}$ . 3546, 3226, 1653w, and 939s  $cm^{-1}$ ; R.D.  $[M]$  (6000 Å) –160°, (5000) +150°, (4000) +460°; (3500) +680°, (3300) +820°, (3200) +910°, (3100) +950°.

The ketone (40 mg.) was heated under reflux for 2 hr. in ethanol (5 c.c.) containing sulphuric acid (20%; 0.2 c.c.). Extraction with ether afforded a product (40 mg.) which gave the starting ketone as plates (from acetone), m. p. and mixed m. p. 167–168°,  $[\alpha]_D + 21^\circ$  (c 0.73).

*Oxidation of 4,23,24-Trisnor-(5 $\beta$ H)-5(4 $\rightarrow$ 3)abeolupan-3-one* (XIV) \* with *Trifluoroacetic Acid*.—Aqueous hydrogen peroxide (90%; 0.30 c.c.) was suspended in methylene dichloride (10 c.c.) and trifluoroacetic anhydride (1.7 c.c.) was added slowly and with continuous agitation, the temperature being kept below 10°. After 15 min. the resultant solution was added to an ice-cooled mixture of the trisnor-ketone (690 mg.), disodium hydrogen phosphate (1 g.), and methylene dichloride (20 c.c.). This was kept at 20° for 4 days and isolation in the normal way yielded 5 $\alpha$ -hydroxy-3,5-*seco*-4,23,24-*trisnorlupan-3-oic acid lactone* (XV) (410 mg.) as needles (from acetone–methanol), m. p. 235–237°,  $[\alpha]_D - 15^\circ$  (c 0.91) (Found: C, 81.1; H, 11.3.  $C_{27}H_{44}O_2$  requires C, 80.95; H, 11.0%);  $\nu_{\max}$ . ( $CS_2$ ) 1748, 1250, 1035, and 995  $cm^{-1}$ .

*Reduction of 5 $\alpha$ -Hydroxy-3,5-*seco*-4,23,24-*trisnorlupan-3-oic Acid Lactone* (XV).—The lactone (452 mg.) in ether (100 c.c.) was added slowly with stirring to a slurry of lithium aluminium hydride (1.1 g.) in ether (150 c.c.). The mixture was heated under reflux for 6 hr. when the excess of hydride was destroyed with ethyl acetate (3 c.c.). After acidification with hydrochloric acid (2N) ethereal extraction afforded a gelatinous product which was adsorbed from benzene on alumina (45 g.). Elution with benzene–ether (1 : 1) gave the diol (XVI) as a gum which failed to crystallise. It was characterised as its mono- and di-acetate as follows. The diol (450 mg.) in pyridine (15 c.c.) was treated at 100° with acetic anhydride (15 c.c.) for 1 hr. After dilution with water extraction with ether afforded a product which was adsorbed from light petroleum–benzene (1 : 1) on alumina (45 g.). Elution with the same solvent gave 3,5 $\alpha$ -diacetoxy-3,5-*seco*-4,23,24-*trisnorlupane* (300 mg.) as plates (from acetone–methanol), m. p. 181–182.5°,  $[\alpha]_D + 11^\circ$  (c 1.86) (Found: C, 76.4; H, 10.55.  $C_{31}H_{52}O_4$  requires C, 76.2; H, 10.7%);  $\nu_{\max}$ . (in  $CS_2$ ) 1729, 1237, 1050, and 1025  $cm^{-1}$ . Elution with benzene afforded 3-acetoxy-3,5-*seco*-4,23,24-*trisnorlupan-5 $\alpha$ -ol* as prisms (from acetone–methanol), m. p. 170–171°,  $[\alpha]_D + 6^\circ$  (c 1.13) (Found: C, 78.0; H, 11.4.  $C_{29}H_{50}O_3$  requires C, 77.95; H, 11.3%);  $\nu_{\max}$ . (in  $CS_2$ ) 3500, 1731, 1235, 1050, 1029, and 993  $cm^{-1}$ .*

Hydrolysis of the diacetate regenerated the diol (XVI) as a gum.

*Oxidation* <sup>14</sup> of 3,4-*Seco*-4,23,24-*trisnorlupane-3,5 $\alpha$ -diol* (XVI).—The diol (1.05 g.) was dissolved in acetone (60 c.c.) at 0°. Chromic acid solution [chromic oxide (4 g.) in water (20 c.c.) and sulphuric acid (1.8 c.c.)] was added slowly and with continuous shaking and the mixture was kept at 20° for 20 hr. Methanol (20 c.c.) was added and the dark residue obtained on evaporation was extracted with ether–chloroform (19 : 1). The extract was washed twice with water and then with sodium hydroxide solution (10%; 3  $\times$  100 c.c.). The alkaline extracts were acidified with concentrated hydrochloric acid. Extraction with ether–chloroform (19 : 1) afforded a gum (570 mg.);  $\nu_{\max}$ . (nat. film) 3390vbr and 1690  $cm^{-1}$ . The spectrum was that expected of a keto-acid. The acid was dissolved in ethyl acetate (10 c.c.) and treated with



cyclohexylamine (1 c.c.). The resultant cyclohexylamine salt of 5-oxo-3,5-seco-4,23,24-trisnorlupan-3-oic acid (XVII) (503 mg.) crystallised from light petroleum-benzene as needles, m. p. 149—155° (rapid heat),  $[\alpha]_D -23^\circ$  (*c* 2.20) (Found: C, 77.0; H, 11.05; N, 3.05.  $C_{33}H_{57}NO_3$  requires C, 76.85; H, 11.15; N, 2.7%);  $\nu_{max}$  (Nujol) 1700, 1625, and 1530  $cm^{-1}$ . Treatment of the salt (250 mg.) with 2N-hydrochloric acid regenerated the acid as a gum (200 mg.),  $[\alpha]_D -24^\circ$  (*c* 1.0), which failed to crystallise. The acid (543 mg.) in ether (35 c.c.) was treated with ethereal diazomethane to give methyl 5-oxo-3,5-seco-4,23,24-trisnorlupan-3-oate as needles (after purification by chromatography and crystallisation from acetone-methanol), m. p. 100—103°,  $[\alpha]_D -30^\circ$  (*c* 1.17) (Found: C, 78.2; H, 10.95.  $C_{28}H_{46}O_3$  requires C, 78.1; H, 10.75%);  $\nu_{max}$  (in  $CS_2$ ) 1750, 1710, 1170, and 1020  $cm^{-1}$ .

*Pyrolysis of Sodium 5-Oxo-3,5-seco-4,23,24-trisnorlupan-3-oate with Sodium Phenylacetate.*—The sodium salt of the keto-acid (XVII) was prepared by the titration to phenolphthalein of a solution of the acid (400 mg.) in carbon dioxide-free methanol (10 c.c.) with a methanolic solution of sodium hydroxide (0.31%; 15 c.c.). One drop of 0.1N-hydrochloric acid was added and the resultant solution was combined with a methanolic solution of sodium phenylacetate (from 2.3 g. of acid) similarly prepared. Evaporation to dryness gave an intimate mixture of salts which was heated at 300—320°/0.3 mm. in a large "bulb" apparatus. The distillate was adsorbed from light petroleum on alumina (30 g.). Elution with light petroleum-benzene (9 : 1) afforded des-A-(10 $\beta$ H)-lupan-5-one (IX; R = Me<sub>2</sub>CH) as prisms (200 mg.) (from acetone), m. p. and mixed m. p. 172—174°,  $[\alpha]_D -18^\circ$  (*c* 1.03).

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