Triterpenoids. Part XXXIX. The Constitution and Stereochemistry of the Ursane Group of Triterpenoids.*

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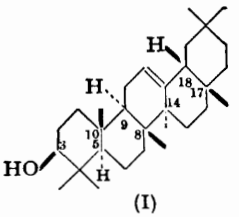
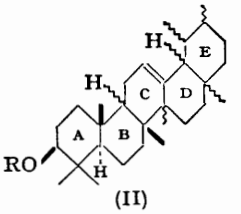
The dienyl acetate obtained by oxidation of α-amyrin acetate with selenium dioxide has been identified as ursa-11 : 13(18)-dien-3β-yl acetate. Its dihydro-derivative, urs-13(18)-en-3β-yl acetate, is isomerised by sulphuric acid to α-amyrin acetate. Ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) is isomerised by mineral acid to oleana-11 : 13(18)-dien-3β-yl acetate (VII). This is the first instance of the conversion of a simple ursane derivative into an isomer belonging to another triterpenoid group. The isomerisation proceeds *via* ursa-11 : 13(18)-dien-3β-yl acetate which is also isomerised by mineral acid to oleana-11 : 13(18)-dien-3β-yl acetate (VII), as is ursa-9(11) : 12-dien-3β-yl acetate. The rearrangements prove that α-amyrin and β-amyrin have the same configurations at positions 3, 5, 8, 9, 10, 14, and 17. These rearrangements and other reactions of members of the ursane group lead to the view that the constitution and stereochemistry of α-amyrin are represented by the expression (XV).

The constitution and stereochemistry of β-amyrin (olean-12-en-3β-ol) shown in (I) are supported by a wealth of experimental evidence (for literature see Jeger, " Fortschritte der Chemie der organischer Naturstoffe," Springer-Verlag, 1950, Vol. VII, p. 1; Barton and Holness, *J.*, 1952, 78; Barton, *J.*, 1953, 1027); they are as secure as is possible without the added support of total synthesis. Very different is the state of knowledge concerning the chemistry of α-amyrin (urs-12-en-3β-ol) and its relatives. In particular, the stereochemistry of the ursane group lacks clear definition, a circumstance well illustrated by the fact that, during the last two years, each of the four theoretically possible arrangements for the locking of rings D and E have been included in representations of the stereochemistry of α-amyrin (Ruzicka, *Experientia*, 1953, **9**, 357; Corey and Ursprung, *Chem. and Ind.*, 1954, 1387; Beton and Halsall, *ibid.*, p. 1560; Zürcher, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2149).

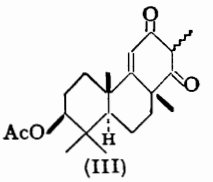
When the work described in this paper commenced, the constitution of α-amyrin was considered to be adequately expressed by (II; R = H).† The configurations at $C_{(3)}$, $C_{(5)}$, $C_{(8)}$, and $C_{(10)}$ in α-amyrin were established by its conversion into two enol ethers, derived from the diketone (III), which were also obtained by a series of parallel reactions from β-amyrin (I) (for literature see Jeger, *loc. cit.*). In addition, comparative studies on



(I)



(II)



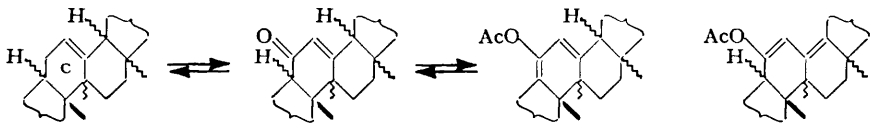
(III)

oleanane and ursane derivatives suggested that configuration at $C_{(9)}$ in both groups is identical (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075) although these did not constitute an absolute proof.

Our first approach to a clearer definition of the stereochemistry of α-amyrin was directed towards $C_{(9)}$. A cogent reason for the view that this centre has the more stable configuration is that 11-oxours-12-en-3β-yl acetate (IV), which is obtained by oxidation of

* Part XXXVIII, preceding paper.
† In the formulæ (II)—(XVII), R = Ac unless otherwise specified.

α-amyrin acetate with chromic acid (Spring and Vickerstaff, *J.*, 1937, 249) and is reduced catalytically to α-amyrin acetate (II) (Ruzicka, Leuenberger, and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1271), is recovered unchanged after prolonged heating with strong alkali followed by reacetylation. A similar observation has been made with the related methyl 11-oxours-12-en-3β-olate acetate (Barton and Holness, *loc. cit.*). Another proof that $C_{(9)}$ in α-amyrin has the more stable configuration is now presented. 11-Oxours-12-en-3β-yl acetate (IV) gives an enol acetate which is strongly dextrorotatory ($[\alpha]_D$ +275°) and shows an absorption maximum at 2760 Å (ε 8000). 9(11) : 12-Dienes in the oleanane and ursane series show a similarly strong dextrorotation and an absorption maximum at approximately 2800 Å (ε *ca.* 9000). In contrast, 11 : 13(18)-dienes in the oleanane series are lævorotatory and are characterised by an intense triplet absorption curve, the major peak of which is at approximately 2500 Å (ε *ca.* 30,000). These facts show that the enol acetate from 11-oxours-12-en-3β-yl acetate is 3β : 11-diacetoxyursa-9(11) : 12-diene (V) and not the heteroannular isomer (VI). Hydrolysis of the enol acetate (V), by either acid or alkali, followed by acetylation of the product, gives 11-oxours-12-en-3β-yl acetate (IV) in excellent yield.

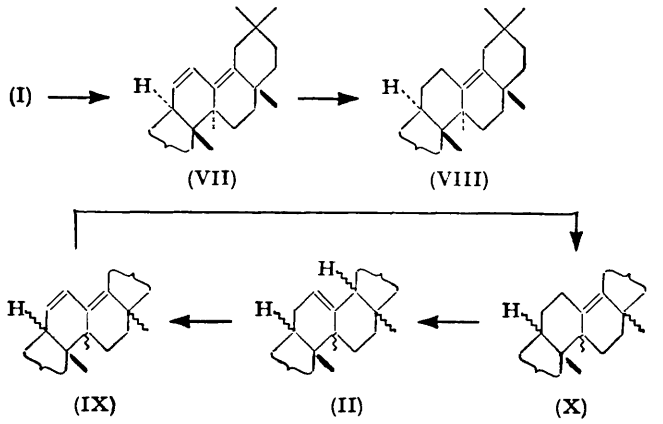


(II) (IV) (V) (VI)

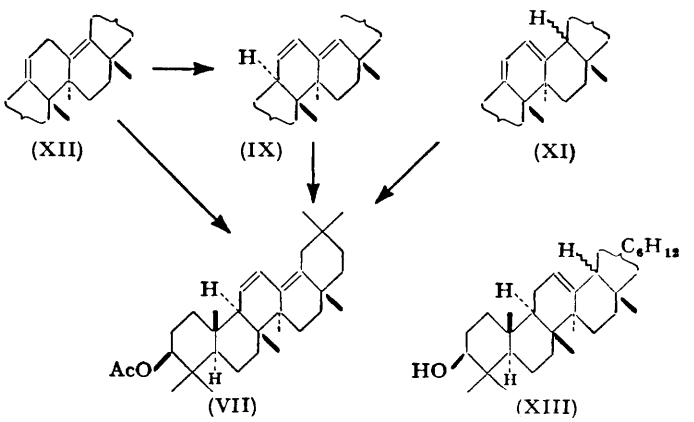
We next turned to a consideration of configuration at $C_{(18)}$ in α-amyrin. Whereas 11-oxo-olean-12-en-3β-yl benzoate is easily isomerised (and hydrolysed), by treatment with concentrated alkali, to give 11-oxo-18α-olean-12-en-3β-ol (Budziarek, Manson, and Spring, *J.*, 1951, 3336), similar treatment of 11-oxours-12-en-3β-yl acetate does not change the configuration at $C_{(18)}$. The related observation that reaction of methyl 11-oxours-12-en-3β-olate acetate with strong alkali does not cause inversion at $C_{(18)}$ has led to the conclusion that either the configuration at this centre is the more stable arrangement or there is no hydrogen attached to $C_{(18)}$ (Barton and Holness, *loc. cit.*). An alternative explanation of the failure of these αβ-unsaturated ketones to invert at $C_{(18)}$ with alkali, is that enolisation is directed towards $C_{(9)}$ exclusively. A proof of the stability of the configuration at $C_{(18)}$ in α-amyrin was found in the following way. Oxidation of α-amyrin acetate with selenium dioxide under forcing conditions gives, in low yield, a dienyl acetate (Easton, Manson, and Spring, *J.*, 1953, 943) very similar to oleana-11 : 13(18)-dien-3β-yl acetate (VII) (Barton and Brooks, *J.*, 1951, 257). The two dienyl acetates have very similar absorption spectra and they are both lævorotatory. Each is reduced to a dihydro-derivative and these also have very similar properties. The dihydro-derivative from oleana-11 : 13(18)-dien-3β-yl acetate has been identified as olean-13(18)-en-3β-yl acetate (VIII) (Ruzicka, Jeger, and Norymberski, *Helv. Chim. Acta*, 1942, **25**, 457). If a hydrogen atom is attached to $C_{(18)}$ in α-amyrin, the derived dienyl acetate is ursa-11 : 13(18)-dien-3β-yl acetate and its dihydro-derivative is urs-13(18)-en-3β-yl acetate. Since, at that time, no direct proof of the presence of a hydrogen attached to $C_{(18)}$ was available, Easton, Manson, and Spring (*loc. cit.*) emphasised that the forcing conditions used in the preparation of the dienyl acetate may eliminate a methyl group from $C_{(18)}$, in which case the dienyl acetate is norursa-11 : 13(18)-dien-3β-yl acetate. We now find that treatment of the dihydro-derivative of the dienyl acetate with sulphuric acid gives α-amyrin acetate (II). This experiment proves that the dienyl acetate is ursa-11 : 13(18)-dien-3β-yl acetate (IX) and that its dihydro-derivative is urs-13(18)-en-3β-yl acetate (X). Again, it proves that α-amyrin has the more stable configuration at $C_{(18)}$ and that, in contrast with the relative stabilities of the corresponding oleanane derivatives (Ames, Halsall, and Jones, *J.*, 1951, 450), urs-12-en-3β-yl acetate is thermodynamically more stable than urs-13(18)-en-3β-yl acetate. Finally it proves that ursa-11 : 13(18)-dien-3β-yl acetate and α-amyrin have the same configuration at $C_{(9)}$.

Three ursadien-3β-yl acetates have been prepared and characterised. These are the

homoannular ursa-9(11) : 12-dien-3β-yl acetate (XI) (Ewen, Spring, and Vickerstaff, *J.*, 1939, 1303), the heteroannular ursa-11 : 13(18)-dien-3β-yl acetate (IX), discussed above, and the non-conjugated ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) described in the preceding paper. The three corresponding oleanadien-3β-yl acetates are known and, of these, the 11 : 13(18)-dienyl acetate is thermodynamically the most stable since it is obtained from



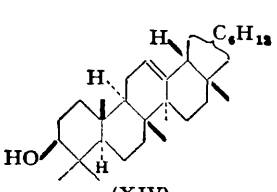
the isomeric 9(11) : 13(18)- and 9(11) : 12-dienyl acetates by treatment with mineral acid (Beaton, Johnston, McKean, and Spring, *J.*, 1953, 3660; Allan, Johnston, and Spring, *J.*, 1954, 1546). A study of the stabilities of the three ursadien-3β-yl acetates has now been made. Treatment of ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) with hydrochloric–acetic acid gives oleana-11 : 13(18)-dien-3β-yl acetate (VII) in 30% (crude) and 10% (pure) yield. The conversion of ursa-9(11) : 13(18)-dien-3β-yl acetate (XII) into oleana-11 : 13(18)-dien-3β-yl acetate proceeds through ursa-11 : 13(18)-dien-3β-yl acetate (IX) since the latter compound is obtained from (XII) under milder acid conditions, and treatment of (IX) with hydrochloric–acetic acid also gives oleana-11 : 13(18)-dienyl acetate (VII) in 10% (pure) yield. Again, the same treatment of the homoannular ursa-9(11) : 12-dien-3β-yl acetate (XI) gives oleana-11 : 13(18)-dien-3β-yl acetate (VII) in similar yield. The conversion of the three ursadien-3β-yl acetates into (VII) proves that the stereochemistry of α-amyrin is represented by the cipher (XIII); the configurations shown in (IX), (XI), and (XII) are consequential.



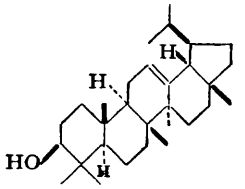
The ultraviolet absorption spectra of oleana- and ursa-11 : 13(18)-dien-3β-yl acetate show small differences which were of value in following the isomerisations described above There is a slight difference in the location of two of the three maxima [2440, 2510, and

2600 Å for ursa-11 : 13(18)-dien-3β-yl acetate and 2420, 2500, and 2600 Å for oleana-11 : 13(18)-dien-3β-yl acetate] but a more pronounced difference exists in the definition of one of the secondary maxima. Whereas in the spectrum of oleana-11 : 13(18)-dien-3β-yl acetate there is a well-defined minimum at 2560 Å, in that of ursa-11 : 13(18)-dien-3β-yl acetate, there is a shoulder and not a minimum at this wavelength.

In an earlier paper (Allan and Spring, *J.*, 1955, 2125) reasons have been given in support of the thesis that the hydrogen attached to $C_{(18)}$ in α-amyrin is β orientated and that, as in β-amyrin, rings D/E are *cis*-β fused. A comparison of the lactones derived from ursolic and oleanolic acid (and other reasons) led Corey and Ursprung (*loc. cit.*) to the same view. The proof, supplied above, that the $C_{(17)}$ attachment in the ursane group is β-orientated make these different reasons overwhelmingly compulsive. The stereochemistry of β-amyrin is therefore represented by (XIV).

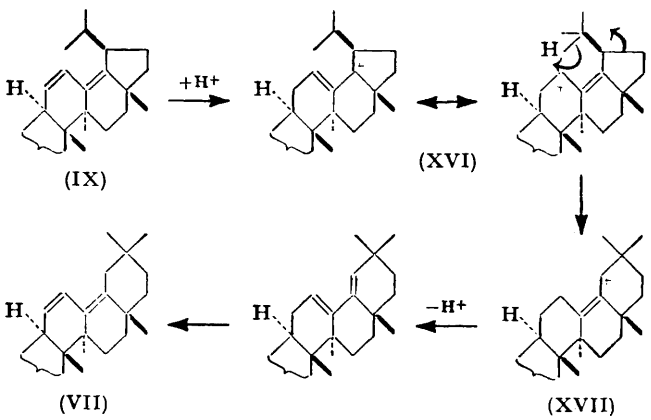


(XIV)



(XV)

We next turned to a consideration of the nature of ring E in α-amyrin. In ring E must repose the conformational and structural factors responsible for the stability of the *cis*-fusion of this ring with ring D. These factors must be responsible for the greater stability of urs-12-en-3β-yl acetate than that of urs-13(18)-en-3β-yl acetate, and also for a substantial hindering effect upon the double bond in α-amyrin and upon the ketone group in 12-oxoursan-3β-yl acetate. Again, ring E of the ursane group, although different from ring E of the oleanane group, must be so constituted that it can rearrange, under suitable conditions, to the latter. These factors and considerations are best reflected and explained, in our opinion, if ring E in α-amyrin is 5-membered with an *iso*propyl group attached to $C_{(19)}$. We therefore represent the constitution and stereochemistry of α-amyrin by (XV). The *iso*propyl group is given the β-configuration for two reasons. First, an α-*iso*propyl group gives a molecular structure in which there is severe interaction between this group and the $C_{(14)}$-methyl group. Secondly, the chosen configuration leads to a conformation in which the *iso*propyl



(IX) (XVI) (VII) (XVII)

group protects the double bond in α-amyrin and the carbonyl group in 12-oxoursan-3β-yl acetate, thus affording a satisfying explanation for the inert character of these two functional groups.

Ring E in α-amyrin has hitherto been represented as 6-membered with methyl groups attached to $C_{(19)}$ and $C_{(20)}$ (II). This representation depends upon reactions which include a

dehydrogenation. According to the formula (XV) for α-amyrin, these reactions involve rearrangement of ring E.

The acid-catalysed rearrangement of the ursadienyl acetates (XII) and (XI) probably includes, as a first phase, isomerisation to ursa-11 : 13(18)-dien-3β-yl acetate (IX), protonation of which gives the ion (XVI). The proximity of the $C_{(20)}$-hydrogen and C_{12}^{+} permits a transannular hydride exchange with synchronous ring enlargement, thus leading to the ion (XVII), the subsequent fate of which is depicted above.

Experimental

For general instructions see the preceding paper.

Attempted Isomerisation of 11-*Oxours*-12-*en*-3β-*yl Acetate* (IV).*—11-Oxours-12-en-3β-yl acetate (5 g.) in 15% ethanolic potassium hydroxide (400 c.c.) was heated under reflux for 50 hr. The product was isolated and acetylated in the usual way, and crystallised from chloroform–methanol, to refurnish 11-oxours-12-en-3β-yl acetate (4·5 g.) as plates, m. p. and mixed m. p. 283—286°, $[\alpha]_D$ +98° (*c*, 1·6).

3β : 11-*Diacetoxyursa*-9(11) : 12-*diene* (V).—A mixture of 11-oxours-12-en-3β-yl acetate (IX) (1·0 g.), acetic anhydride (140 c.c.), toluene-*p*-sulphonic acid (0·5 g.), and concentrated sulphuric acid (1 drop) was heated under reflux for 100 hr. The black solution was concentrated under reduced pressure on the steam-bath and diluted with water, and the product, a gum, isolated by means of ether. A solution of this in light petroleum was filtered through a short column of alumina. The filtrate was evaporated and the residue crystallised from chloroform–methanol, to give a first crop of plates, m. p. 275—283°, recrystallisation of which gave unchanged 11-oxours-12-en-3β-yl acetate (200 mg.), m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +100° (*c*, 1·1). Concentration of the mother-liquors yielded prismatic rods, m. p. 203—206°, which after four recrystallisations from methanol gave 3β : 11-*diacetoxyursa*-9(11) : 12-*diene* as prisms (260 mg.), m. p. 213—214°, $[\alpha]_D$ +275° (*c*, 0·7), $\lambda_{max.}$ 2760 Å (ε 8000) (Found : C, 77·9; H, 9·9. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%).

Hydrolysis of 3β : 11-*Diacetoxyursa*-9(11) : 12-*diene* (V).—(*a*) A mixture of the enol acetate (50 mg.), methanol (50 c.c.), and concentrated hydrochloric acid (3 c.c.) was heated under reflux for 2 hr. Isolation of the product using ether, followed by acetylation by acetic anhydride and pyridine at 100°, gave 11-oxours-12-en-3β-yl acetate (36 mg.) as plates, m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +98° (*c*, 1·9). (*b*) The enol acetate (100 mg.) in 3% aqueous-methanolic potassium hydroxide (50 c.c.) was heated under reflux for 1 hr. The product, isolated in the usual way, was acetylated by pyridine and acetic anhydride at 100°. Dilution of the mixture with water gave crystals, which were recrystallised from chloroform–methanol to yield 11-oxours-12-en-3β-yl acetate as plates, m. p. and mixed m. p. 287—288°, $[\alpha]_D$ +99° (*c*, 1·7).

Ursa-11 : 13(18)-dien-3β-yl acetate (IX) was prepared by refluxing a solution of α-amyrin acetate in benzyl acetate with selenium dioxide (Easton, Manson, and Spring, *loc. cit.*). It separated from chloroform–methanol as prismatic needles, m. p. 204—206°, $[\alpha]_D$ −76° (*c*, 1·0), $\lambda_{max.}$ 2440, 2510, and 2600 Å (ε 26,000, 29,000, and 18,400).

Urs-13(18)-*en*-3β-*yl Acetate* (X).—A solution of ursa-11 : 13(18)-dien-3β-yl acetate (400 mg.) in ethyl acetate (80 c.c.) and acetic acid (90 c.c.) was shaken with hydrogen and platinum (from 200 mg. of PtO_2) for 21 hr. The product crystallised from chloroform–methanol, to give urs-13(18)-en-3β-yl acetate as needles, m. p. 213—215°, $[\alpha]_D$ −22° (*c*, 1·1), ε 5500 at 2110 Å. Easton, Manson, and Spring (*loc. cit.*) give m. p. 214—216°, $[\alpha]_D$ −22° and ε 5100 at 2150 Å.

Hydrolysis of the acetate with 3% ethanolic potassium hydroxide and crystallisation of the product from methanol yielded urs-13(18)-en-3β-ol as blades, m. p. 201—202°, $[\alpha]_D$ −37°, −36° (*c*, 0·6, 1·1). Easton, Manson, and Spring (*loc. cit.*) give m. p. 204—205°, $[\alpha]_D$ −35°, −36·5°. Acetylation in the usual way gave the acetate, which after one crystallisation from methanol–chloroform had m. p. 210—212°, $[\alpha]_D$ −22° (*c*, 0·6).

Isomerisation of Urs-13(18)-*en*-3β-*yl Acetate to α-Amyrin Acetate.*—A solution of urs-13(18)-en-3β-yl acetate (150 mg.) in benzene (3 c.c.) and acetic acid (300 c.c.) was treated with concentrated sulphuric acid (5·7 c.c.), and the mixture heated at 80° for 5 min. and kept for 14 days at room temperature. The crystalline solid A (30 mg.) which had separated was collected. The filtrate was diluted with water, the mixture extracted with ether, and the extract washed in the

* This experiment was made by Dr. J. D. Easton, to whom we express our thanks.

usual way. Evaporation of the dried extract gave a gum, a solution of which in light petroleum–benzene (4 : 1) was chromatographed on alumina. Elution with the same solvent gave a crystalline fraction (53 mg.), which was combined with solid A, dissolved in light petroleum, and again chromatographed on alumina. Elution with light petroleum (150 c.c.) gave a crystalline fraction (35 mg.), which after two recrystallisations from chloroform–methanol yielded α-amyrin acetate as plates, m. p. 224—225°, $[\alpha]_D$ +78°. A mixture of this with an authentic sample, m. p. 226—227°, $[\alpha]_D$ +76° (*c*, 1·9), was undepressed in m. p.

Isomerisation of Ursa-9(11) : 13(18)-*dien*-3β-*yl Acetate* (XII) *to Ursa*-11 : 13(18)-*dien*-3β-*yl Acetate* (IX).—A solution of ursa-9(11) : 13(18)-dien-3β-yl acetate (105 mg.) in acetic acid (25 c.c.) and concentrated hydrochloric acid (1·0 c.c.) was heated on the steam-bath for 17 hr. Evaporation under reduced pressure gave a gum. A solution of this in chloroform–methanol deposited crystals, recrystallisation of which from the same solvent gave needles (35 mg.), m. p. 193—194°, ε 6900 at 2120 Å, $\lambda_{max.}$ 2440, 2500, and 2600 Å (ε 15,300, 16,300, and 10,800). This mixture in light petroleum (25 c.c.) was chromatographed on alumina (5 g.). Elution with light petroleum (100 c.c.) yielded mixtures. Continued elution with light petroleum (50 c.c.) furnished a fraction which crystallised from chloroform–methanol to give ursa-11 : 13(18)-dien-3β-yl acetate as needles (8 mg.), m. p. and mixed m. p. 203—204°, $[\alpha]_D$ −81° (*c*, 0·3), $\lambda_{max.}$ 2440, 2510, and 2600 Å (ε 26,800, 29,800, and 19,800).

Rearrangement of Ursa-9(11) : 13(18)-*dien*-3β-*yl Acetate* (XII) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of the 9(11) : 13(18)-dienyl acetate (500 mg.) in acetic acid (90 c.c.) and concentrated hydrochloric acid (7·5 c.c.) was heated on the steam-bath. After 4 hr. concentrated hydrochloric acid (2·5 c.c.) was added, and heating continued for 13 hr. The mixture was evaporated under reduced pressure, and the residue dissolved in light petroleum (100 c.c.) and chromatographed on alumina (25 g.). Elution with light petroleum (200 c.c.) gave a brown gum (269 mg.). Continued elution with light petroleum (600 c.c.) gave six fractions (145 mg.) which crystallised from chloroform–methanol as plates. These fractions ranged from m. p. 205—211°, $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 21,800, 25,000, 16,400), to m. p. 221—224°, $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 25,600, 29,000, and 18,500). They were combined and recrystallised from the same solvent to give oleana-11 : 13(18)-dien-3β-yl acetate (49 mg.) as hexagonal plates, m. p. and mixed m. p. 226—228°, $[\alpha]_D$ −63° (*c*, 1·0), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 26,100, 28,700, and 19,100).

Rearrangement of Ursa-11 : 13(18)-*dien*-3β-*yl Acetate* (IX) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of ursa-11 : 13(18)-dien-3β-yl acetate (200 mg.) in acetic acid (70 c.c.) and concentrated hydrochloric acid (5 c.c.) was heated on the steam-bath for 17 hr. The mixture was evaporated under reduced pressure, and the residue dissolved in light petroleum (40 c.c.) and chromatographed on alumina (12 g.). Elution with light petroleum (300 c.c.) gave a gum (50 mg.). Further elution with light petroleum (400 c.c.) and light petroleum–benzene (20 : 1, 400 c.c.; 10 : 1, 250 c.c.) gave fractions (48 mg.) which crystallised from chloroform–methanol as plates, m. p. 219—222°. Recrystallisation of the combined fractions from the same solvent gave oleana-11 : 13(18)-dien-3β-yl acetate as plates (20 mg.), m. p. and mixed m. p. 225—226°, $[\alpha]_D$ −61° (*c*, 1·0), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 23,500, 26,500, and 16,800).

Rearrangement of Ursa-9(11) : 12-*dien*-3β-*yl Acetate* (XI) *to Oleana*-11 : 13(18)-*dien*-3β-*yl Acetate* (VII).—A solution of the 9(11) : 12-dienyl acetate (1·0 g.) in acetic acid (180 c.c.) and concentrated hydrochloric acid (15 c.c.) was heated on the steam-bath for 2 hr. Concentrated hydrochloric acid (5 c.c.) was added, and heating continued for 17 hr. After evaporation under reduced pressure, the brown gum was dissolved in light petroleum (50 c.c.) and chromatographed on alumina (50 g.). Elution with light petroleum (600 c.c.) gave a gum (583 mg.). Further elution with light petroleum (1050 c.c.) gave fractions which crystallised from chloroform–methanol. These combined fractions recrystallised from chloroform–methanol, to give oleana-11 : 13(18)-dien-3β-yl acetate as hexagonal plates (82 mg.), m. p. and mixed m. p. 225—227°, $[\alpha]_D$ −64° (*c*, 0·9), $\lambda_{max.}$ 2420, 2500, and 2600 Å (ε 26,600, 30,000, and 19,300).

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