Triterpenoids. Part XXXV. The Reactions of* 12-*Oxo*isoursa-9(11) : 14-*dien*-3β-*yl Acetate.*

By J. Douglas Easton and F. S. Spring.

[Reprint Order No. 6083.]

The major product obtained by oxidation of 12-oxours-9(11)-en-3β-yl acetate (I) with selenium dioxide is shown to be correctly represented as 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (II).

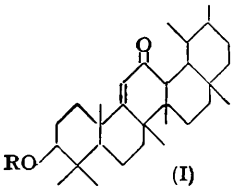
The present paper describes an investigation of the reactions of 12-oxo*iso*-α-amyradien-3β-yl acetate, including its reduction. The investigation leads to the view that this compound is correctly represented as (II) and it will in future be named 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate, in conformity with practice in the oleanane series.

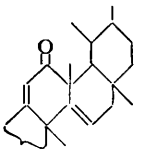
12-Oxours-9(11)-en-3β-yl acetate, represented as (I) † by Meisels, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 700), is oxidised by selenium dioxide to the diene (II) (Ruzicka, Rüegg, Volli, and Jeger, *ibid.*, 1947, **30**, 140; Meisels, Jeger, and Ruzicka, *loc. cit.*; Rüegg, Dreiding, Jeger, and Ruzicka, *ibid.*, 1950, **33**, 890). Ruzicka *et al.* (*loc. cit.*) reported that catalytic reduction of (II) under relatively mild conditions (room temperature, atmospheric pressure) regenerated 12-oxours-9(11)-en-3β-yl acetate (I) in high yield, together with a smaller quantity of ursa-9(11) : 12-dien-3β-yl acetate (III). This report led McLean, Ruff, and Spring (*J.*, 1951, 1093) to the view that (I) and (II) do not adequately express the relationship of 12-oxours-9(11)-en-3β-yl acetate and its oxidation product. In the meantime, an investigation of the analogous product obtained by oxidation of 12-oxo-olean-9(11)-en-3β-yl acetate has shown that it is (IV) [12-oxo*iso*oleana-9(11) : 14-dien-3β-yl acetate] (Allan, Johnston, and Spring, *J.*, 1954, 1546; Johnston and Spring, *J.*, 1954, 1556), a formula first advanced for it by Jeger and Ruzicka (*Helv. Chim. Acta*, 1945, **28**, 209). Similar treatment of 12-oxo*iso*oleana- and 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate gives the same degradation product (V) (Meisels, Jeger, and Ruzicka, *loc. cit.*), a behaviour which, with their parallel derivations, supports the structural relation implied by (II) and (IV). Two major differences in the behaviour of the oxo*iso*-dienyl acetates derived from α- and β-amyrin are to be noted. First, in contrast to the behaviour of the ursane analogue

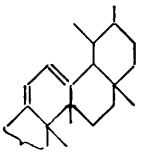
* Part XXXIV, *J.*, 1955, 1607.

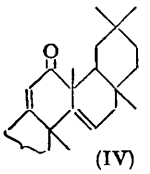
† Configurations are not implied in the formulæ used in this paper; unless otherwise specified R = Ac.

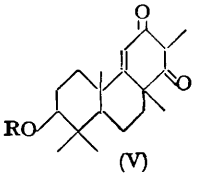
(II) described above, catalytic hydrogenation (hydrogenolysis) of 12-oxo*iso*oleana-9(11) : 14-dien-3β-yl acetate (IV) leads to *neo*-β-amyrin which, as expected, has a different carbocyclic structure from that of β-amyrin and has been formulated as (VI; R = H) (Allan, Johnston, and Spring, *loc. cit.*). Secondly, the diene (IV) is stable to prolonged treatment with mineral acid (Budziarek, Johnston, Manson, and Spring, *J.*, 1951, 3019) whereas this treatment converts the analogue (II) into an isomer "12-oxo*iso*-α-amyradien-3β-yl-II acetate" (Ruzicka *et al.*, *loc. cit.*). The latter difference will be discussed in a later paper.

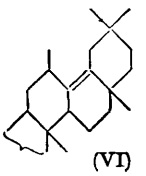

(I)


(II)

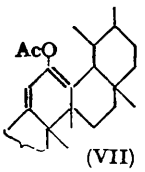

(III)

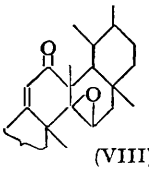

(IV)

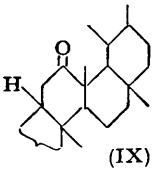

(V)


(VI)

The product obtained by oxidation of the monoenyl acetate (I) with selenium dioxide is not homogeneous. Careful chromatography gave pure 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate, $[\alpha]_D$ +7°, characterised by hydrolysis to the corresponding alcohol, $[\alpha]_D$ −6°. Later fractions from the chromatogram are mixtures which could not be resolved into their components; they are almost certainly mixtures of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate and "12-oxo*iso*-α-amyradien-3β-yl-II acetate," in varying proportions, since they are converted in high yield into pure "oxo-dienyl-II acetate" by treatment with hydrochloric acid.


(VII)

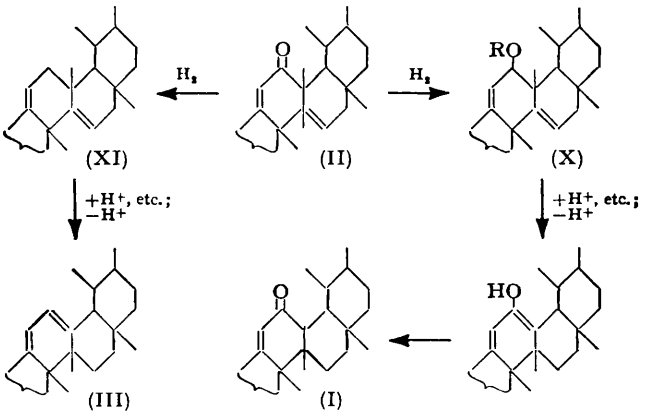

(VIII)


(IX)

12-Oxours-9(11)-en-3β-yl acetate (I) readily forms an enol acetate (VII) which shows the ultraviolet absorption spectrum and large dextrorotation associated with a 9(11) : 12-diene and is hydrolysed to 12-oxours-9(11)-en-3β-ol (I; R = H). As expected, 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (II) is recovered unchanged after attempted enol-acetylation. Oxidation of the enol acetate (VII) with selenium dioxide gives a low yield of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (II) which with potassium permanganate gives, in high yield, a compound, $C_{32}H_{48}O_4$, which shows the ultraviolet absorption of an αβ-unsaturated ketone but, in contrast to (II), does not give a colour with tetranitromethane; it is provisionally represented as the 14 : 15-epoxide (VIII). The reactions of the α-amyrin derivatives described in this paragraph are exactly analogous to those of the corresponding β-amyrin derivatives (Budziarek *et al.*; Johnston and Spring, *locc. cit.*).

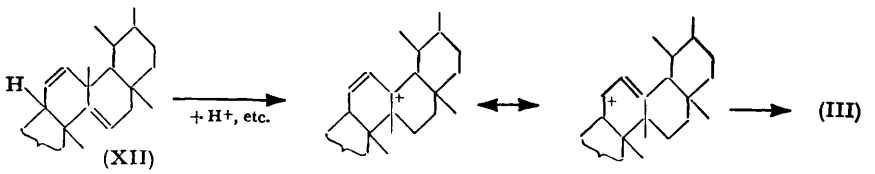
Hydrogenation of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (II), in our hands, gave products which were difficult to separate and varied considerably in nature with slight differences in the solvent. Two representative experiments are described in the Experimental section. In the first, with purified acetic acid as solvent, a mixture was obtained, chromatography of which gave 12-oxours-9(11)-en-3β-yl acetate (I) in maximum (crude) yield of 10%, the only other homogeneous product isolated being a saturated ketone (maximum crude yield, 27%), considered to be 12-oxo*iso*ursan-3β-yl acetate (IX). The

second experiment differed in that reduction was made in the presence of a trace of hydrochloric acid: 12-oxours-9(11)-en-3β-yl acetate was then isolated in considerably greater yield (maximum, crude, 36%) and, in addition, impure ursa-9(11) : 12-dien-3β-yl acetate



(III) in high yield. We attribute the formation of (I) and (III) from (II) to the great facility with which rearrangement of a reduced intermediate occurs; it is pertinent to our argument that (II) is recovered unchanged after being shaken in ethyl acetate with hydrogen and platinum. The formation of (I) and (III) from (II) is represented as annexed. Supporting evidence is presented below. Reduction of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate with lithium aluminium hydride, or with sodium and pentyl alcohol, followed by acetylation of the products, gave *iso*ursa-9(11) : 14-diene-3β : 12-diol diacetate (X) in good yield and this with hydrochloric acid in acetic acid or with hydrogen chloride in chloroform gave, in low yield, 12-oxours-9(11)-en-3β-yl acetate (I).

Reduction of 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate (II) by the Wolff–Kishner method gives, in good yield, a non-conjugated dienyl acetate. This does not show selective absorption above 2200 Å but shows strong ethylenic absorption between 2000 and 2230 Å and may be represented as *iso*ursa-9(11) : 14-dien-3β-yl acetate (XI). Alternatively it is possible that the formation of the non-conjugated dienyl acetate from (II) includes double-bond movement in which case it is *iso*ursa-11 : 14-dien-3β-yl acetate (XII). Treatment of this non-conjugated dienyl acetate with hydrochloric acid gives ursa-9(11) : 12-dien-3β-yl acetate (III) in high yield.



The fact that the non-conjugated dienyl acetate cannot be hydrogenated does not exclude formulation (XII). Wolff–Kishner reduction of 12-oxo*iso*oleana-9(11) : 14-dien-3β-yl acetate gives two isomeric non-conjugated dienyl acetates, one of which has a constitution corresponding to (XI), the other being the *iso*oleanane analogue of (XII) (Allan, Johnston, and Spring, *loc. cit.*). Neither of these is changed when shaken in acetic acid with platinum and hydrogen. Whereas the isomer corresponding to (XI) readily isomerises to oleana-9(11) : 12-dien-3β-yl acetate when treated with mineral acid, similar treatment of the 11 : 14-dienyl acetate gives the 11 : 13(18)-diene acetate. This behaviour appears to support formula (XI) for the *iso*oursane non-conjugated dienyl acetate. In our view, this argument by analogy is not valid, because of the extreme difficulty encountered in the formation of ursa-11 : 13(18)-dien-3β-yl acetate from α-amyrin acetate by methods which lead to the formation, in high yield, of oleana-11 : 13(18)-dien-3β-yl acetate from β-amyrin

acetate (Easton, Manson, and Spring, *J.*, 1953, 943); the conversion of (XII) into ursa-9(11) : 12-dien-3β-yl acetate may be represented as above.

Experimental

Specific rotations were measured in $CHCl_3$ solution at room temperature, and ultraviolet absorption spectra in EtOH. Grade II alumina and light petroleum, b. p. 60—80°, were used for chromatography.

Enol Acetate of 12-Oxours-9(11)-en-3β-yl Acetate.—12-Oxours-9(11)-en-3β-yl acetate (790 mg.) was refluxed for 60 hr. with acetic anhydride (60 c.c.) containing freshly fused sodium acetate (1·2 g.). The product was isolated in the usual manner and crystallised from methanol–benzene to give the *enol acetate* (500 mg.) as needles, m. p. 257—258°, $[\alpha]_D$ +231° (*c*, 0·5), $\lambda_{max.}$ 2780 Å (ε 9000) (Found: C, 77·9; H, 9·9. $C_{34}H_{52}O_4$ requires C, 77·8; H, 9·9%). The enol acetate gives a red-brown colour with tetranitromethane. Similar treatment of 12-oxours-9(11)-en-3β-ol gave the enol acetate, m. p. and mixed m. p. 257—258°. The enol acetate was refluxed for 2 hr. with 3% ethanolic potassium hydroxide to yield 12-oxours-9(11)-en-3β-ol as needles (from aqueous methanol), m. p. and mixed m. p. 238—240°, $[\alpha]_D$ +77° (*c*, 0·6).

12-*Oxo*iso*ursa*-9(11) : 14-*dien*-3β-*yl Acetate* (cf. Ruzicka, Rüegg, Volli, and Jeger, *loc. cit.*).—(*a*) A solution of 12-oxours-9(11)-en-3β-yl acetate (2·0 g.) in glacial acetic acid (65 c.c.) was refluxed for 24 hr. with selenium dioxide (3·0 g.). The crude product, isolated in the usual manner, crystallised from methanol to give a solid (600 mg.), m. p. 226—229°, $[\alpha]_D$ +26° (*c*, 2·0). A solution of the solid in benzene–light petroleum (1 : 4; 100 c.c.) was chromatographed on a column (8 × 2 cm.) of alumina, and the fraction eluted with the same solvent mixture (1 : 4, 500 c.c.; 1 : 2, 200 c.c.) was repeatedly crystallised from chloroform–methanol to yield 12-oxo-*iso*ursa-9(11) : 14-dien-3β-yl acetate as needles, m. p. 221—222°, $[\alpha]_D$ +7°, +8°, (*c*, 0·5; 1·1), $\lambda_{max.}$ 2100 and 2370 Å (ε 6100, 11,000) (Found: C, 79·8; H, 10·3. Calc. for $C_{32}H_{48}O_3$: C, 79·95; H, 10·1%). The second fraction {150 mg.; m. p. 228—230°, $[\alpha]_D$ +19° (*c*, 0·9)} and the third fraction {70 mg.; m. p. 250—253°, $[\alpha]_D$ +99° (*c*, 2·9)} from the column could not be purified by crystallisation and on treatment with hydrogen chloride in acetic acid [as described by Ruzicka, Rüegg, Volli, and Jeger, *loc. cit.*, for 12-oxo*iso*ursa-9(11)-14-dien-3β-yl acetate] gave the " oxo*iso*-dienyl-II acetate," m. p. 269—271°, $[\alpha]_D$ +157° (*c*, 2·0), in high yield.

(*b*) A solution of the enol acetate from 12-oxours-9(11)-en-3β-yl acetate (500 mg.) in glacial acetic acid (60 c.c.) was heated under reflux for 24 hr. with selenium dioxide (1·5 g.). The product was isolated in the usual way and fractionally crystallised from chloroform–methanol. The first three fractions were combined and recrystallised to give starting material (250 mg.; m. p. and mixed m. p.). The fourth and fifth crops differed from the first three in giving a yellow colour with tetranitromethane. They were combined and crystallised four times from chloroform–methanol to yield 12-oxo*iso*ursa-9(11) : 14-dien-3β-yl acetate as needles, m. p. and mixed m. p. 219—220°.

12-*Oxo*iso*ursa*-9(11) : 14-*dien*-3β-*ol* was obtained from the acetate by using 3% ethanolic potassium hydroxide. It separates from *n*-hexane–acetone as needles, m. p. 116—119°, $[\alpha]_D$ −6°, −6° (*c*, 1·6, 1·8) (Found: C, 81·9; H, 10·7. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). Treatment of the alcohol with pyridine and acetic anhydride regenerated the acetate, m. p. 220—221°, $[\alpha]_D$ +7° (*c*, 1·4).

Oxidation of 12-*Oxo*iso*ursa*-9(11) : 14-*dien*-3β-*yl Acetate with Potassium Permanganate.*—A stirred solution of the oxo-dienyl acetate (0·5 g.) in stabilised glacial acetic acid (200 c.c.) was treated during 30 min. with a solution of potassium permanganate (132 mg.) in water (20 c.c.). Stirring was continued for 30 min. and the product isolated in the usual manner. Crystallisation from chloroform–methanol gave 14 : 15-*epoxy*-12-*oxo*iso*urs*-9(11)-*en*-3β-*yl acetate* as needles (300 mg.), m. p. 280—283°, $[\alpha]_D$ +56°, +55° (*c*, 1·2, 0·9), $\lambda_{max.}$ 2400 Å (ε 8100) (Found: C, 77·5; H, 9·8. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·7%). It does not give a colour with tetranitromethane.

Catalytic Hydrogenation of 12-*Oxo*iso*ursa*-9(11) : 14-*dien*-3β-*yl Acetate.*—(*a*) The oxo-dienyl acetate (1·0 g.) in glacial acetic acid was shaken with platinum (from 300 mg. of PtO_2) and hydrogen for 20 hr. The product, isolated in the usual way, was chromatographed in benzene–light petroleum (1 : 2; 225 c.c.) on alumina (12 × 1·5 cm.). The fraction (750 mg.) eluted with the same solvent mixture (800 c.c.) had m. p. 207—240°. Washing with benzene–light petroleum (2 : 1; 200 c.c.) and benzene (200 c.c.) gave a fraction (100 mg.), repeated crystallisation of which from chloroform–methanol gave 12-oxours-9(11)-en-3β-yl acetate (59 mg.) as plates, m. p. and mixed m. p. 285—288°, $[\alpha]_D$ +82° (*c*, 1·3), $\lambda_{max.}$ 2520 Å (ε 10,300). A third

fraction (80 mg.), obtained by washing with benzene–ether (19 : 1; 400 c.c.), separated from chloroform–methanol as plates, m. p. 212—251°, and was not further examined.

The first fraction, from the chromatogram described above, in benzene–light petroleum (1 : 5; 220 c.c.) was re-chromatographed on alumina (10 × 2 cm.), and the column washed with benzene–light petroleum (1 : 5, 800 c.c.; 1 : 2, 400 c.c.) to yield a fraction (120 mg.), m. p. 176—190°. A fraction B (270 mg.) obtained by washing with benzene–light petroleum (2 : 1; 800 c.c.), benzene (400 c.c.), and ether–benzene (1 : 19; 200 c.c.) separated from chloroform–methanol as plates, m. p. 207—210°. Later fractions had spread m. p.s and were not examined. Fraction B, in light petroleum (170 c.c.), was again chromatographed on alumina (11 × 1 cm.), and the column washed with the same solvent giving a fraction (36 mg.). Washing with benzene–light petroleum (1 : 19; 300 c.c.) gave a second fraction (70 mg.) which was crystallised from chloroform–methanol to yield 12-*oxo*iso*oursan*-3β-*yl acetate* as plates, m. p. 222—223°, $[\alpha]_D$ +93°, +91° (*c*, 0·9, 1·1), $\lambda_{max.}$ 2890 Å (ε 63) (Found: C, 79·3; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). The ketone does not give a colour with tetranitromethane.

(*b*) A solution of 12-oxo*iso*oursa-9(11) : 14-dien-3β-yl acetate (1 g.) in glacial acetic acid was hydrogenated as described above with the difference that 1 drop of concentrated hydrochloric acid was added to th olution. The dried product in benzene–light petroleum (1 : 4; 100 c.c.) was chromatographed on alumina (12 × 2 cm.). Washing with benzene–light petroleum mixtures (1 : 4, 600 c.c.; 1 : 1, 450 c.c.) and benzene (300 c.c.) gave a fraction (420 mg.) crystallisation of which from chloroform–methanol gave needles, m. p. 178—179°, $[\alpha]_D$ +262° (*c*, 0·8), $\lambda_{max.}$ 2800 Å (ε 6900). This fraction, which gives a red-brown colour with tetranitromethane, is impure ursa-9(11) : 12-dien-3β-yl acetate; a mixture with the pure dienyl acetate had an intermediate m. p. The column was next washed with ether–benzene (1 : 19, 450 c.c.; 1 : 2, 300 c.c.; 2 : 1, 150 c.c.) to yield a fraction (360 mg.) crystallisation of which from chloroform–methanol yielded 12-oxours-9(11)-en-3β-yl acetate (156 mg.), m. p. and mixed m. p. 280—283°, $[\alpha]_D$ +89° (*c*, 1·0), $\lambda_{max.}$ 2480 Å (ε 9600).

Reduction of 12-*Oxo*iso*oursa*-9(11) : 14-*dien*-3β-*yl Acetate with Lithium Aluminium Hydride.*—A solution of the oxo-dienyl acetate (0·5 g.) in dry ether (150 c.c.) was refluxed for 4 hr. with lithium aluminium hydride (0·5 g.). The product was isolated in the usual manner (avoiding the use of acid) and acetylated by heating it with pyridine and acetic anhydride. The acetylated product was repeatedly crystallised from methanol to yield iso*ursa*-9(11) : 14-*diene*-3β : 12-*diol diacetate* as plates, m. p. 194—195°, $[\alpha]_D$ +59°, +60° (*c*, 1·9, 1·5) (Found C, 78·2; H, 10·1. $C_{34}H_{52}O_4$ requires C, 77·8; H, 10·0%). Light absorption: $\varepsilon_{2100} = 7000$, $\varepsilon_{2150} = 5200$, $\varepsilon_{2200} = 2400$. The diacetate gives a yellow colour with tetranitromethane.

Reduction of 12-*Oxo*iso*oursa*-9(11) : 14-*dien*-3β-*yl Acetate with Sodium and Pentyl Alcohol.*—A solution of the oxo-dienyl acetate (500 mg.) in boiling pentyl alcohol (20 c.c.) was treated with sodium (1·2 g.), and the mixture refluxed for 30 min. Pentyl alcohol (3·3 c.c.) was added and refluxing continued for 40 min. The product was isolated in the usual manner and boiled for 2 hr. with acetic anhydride (20 c.c.). The acetylated product was chromatographed on alumina to yield an easily eluted fraction (290 mg.) which crystallised from methanol and was purified by recrystallisation from chloroform–methanol to yield *iso*ursa-9(11) : 14-diene-3β : 12-diol diacetate (192 mg.) as plates, m. p. and mixed m. p. 193—194, $[\alpha]_D$ +58° (*c*, 2·0) (Found: 78·1; H, 10·0%).

Treatment of iso*Ursa*-9(11) : 14-*diene*-3β : 12-*diol Diacetate with Hydrochloric Acid.*—A solution of the diacetate (300 mg.) in acetic acid (30 c.c.) was treated with concentrated hydrochloric acid (1·5 c.c.), and the mixture kept at 90° for 15 min. and then at room temperature overnight. The product was isolated in the usual manner and acetylated by pyridine–acetic anhydride. The acetylated product was chromatographed on alumina to give readily eluted fractions (180 mg.) which could not be crystallised. Thereafter, ether–benzene (1 : 19) eluted a fraction (20 mg.) which on crystallisation from chloroform–methanol yielded 12-oxours-9(11)-en-3β-yl acetate as plates, m. p. and mixed m. p. 286—289°, $[\alpha]_D$ +83° (*c*, 0·7), $\lambda_{max.}$ 2480 Å (ε 10,700). The same product was obtained in approximately the same yield by treatment of the diacetate (260 mg.) in chloroform (30 c.c.) with dry hydrogen chloride for 1 hr., the mixture being kept at room temperature for 4 days.

Wolff–Kishner Reduction of 12-*Oxo*iso*oursa*-9(11) : 14-*dien*-3β-*yl Acetate.*—A mixture of the oxo-dienyl acetate (2·0 g.), 100% hydrazine hydrate (10 c.c.), sodium methoxide (from 2·0 g. of sodium), and methanol (25 c.c.) was kept at 200° for 13 hr. in an autoclave. The product was acetylated by pyridine and acetic anhydride and crystallised from methanol and then repeatedly from methanol–chloroform to yield iso*ursa*-x : 14-*dien*-3β-*yl acetate* as needles, m. p. 171—172°, $[\alpha]_D$ +43°, +42° (*c*, 1·3, 1·0) (Found: C, 8·26; H, 11·0. $C_{32}H_{50}O_2$ requires C, 82·3; H, 10·8%).

Light absorption : $\varepsilon_{2100} = 6900$, $\varepsilon_{2150} = 4100$, $\varepsilon_{2200} = 1500$, $\varepsilon_{2230} = 700$. The dienyl acetate gives a strong yellow colour with tetranitromethane. The dienyl acetate (150 mg.) was recovered unchanged after shaking of its solution in ethyl acetate–glacial acetic acid with hydrogen and platinum for 17 hr.

Conversion of iso*Ursa*-x : 14-*dien*-3β-*yl Acetate into Ursa*-9(11) : 12-*dien*-3β-*yl Acetate*.—A solution of *iso*ursa-*x* : 14-dien-3β-yl acetate (100 mg.) in dry chloroform (20 c.c.) was treated with a stream of dry hydrogen chloride for 45 min. and then kept at room temperature for 5 days. The mixture was evaporated and the residue crystallised from chloroform–methanol to yield ursa-9(11) : 12-dien-3β-yl acetate as needles, m. p. and mixed m. p. 168—169°, $[\alpha]_D$ +320° (c, 1·0), $\lambda_{max.}$ 2820 Å (ε 9200) (Found : C, 82·2; H, 11·2. Calc for $C_{32}H_{50}O_2$: C, 82·3; H, 10·8%).

We thank the Department of Scientific and Industrial Research for a Maintenance Award (to J. D. E.).

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, January 28th*, 1955.]