820. *The Chemistry of Gum Labdanum. Part II.*[1] *The Structure of Labdanolic Acid.*

By J. D. Cocker and T. G. Halsall.

The structure of labdanolic acid, a constituent of gum labdanum, has been shown to be (I).

In Part I [1] the isolation was described of labdanolic acid, a new bicyclic diterpene hydroxy-acid, $C_{20}H_{36}O_3$. It has now been shown to have structure (I).*

Labdanolic acid was obtained by relatively mild hydrolysis of its methyl ester, showing that its carboxyl group was unhindered and not situated in the sterically hindered 4-position as in the majority of diterpene acids. The hydroxyl group, on the other hand, was unreactive, being acetylated only under vigorous conditions. On attempted mild oxidation of methyl labdanolate with chromic acid the ester was recovered unchanged. Reduction of the ester with lithium aluminium hydride gave the diol (III) which on mild acetylation afforded a monoacetate. The hydroxyl group was accordingly tertiary.

Dehydration of methyl labdanolate with phosphoryl chloride in pyridine gave a homogeneous product (IV), the infrared spectrum of which indicated the presence of a vinylidene group (bands at 890 and 1645 cm.$^{-1}$). This was confirmed by ozonolysis, formaldehyde and a keto-ester (V) being obtained. Reduction of the dehydration product, which was also formed when methyl labdanolate was acetylated under vigorous conditions, gave the alcohol (VI). This was characterised by conversion with osmium tetroxide in pyridine into a triol which is provisionally formulated as (VII), addition being assumed on the less hindered (α) side of the molecule (see below, however).

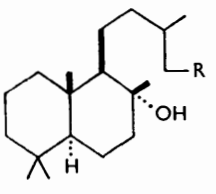
The keto-ester (V) formed an oxime but not a 2 : 4-dinitrophenylhydrazone. These observations together with the carbonyl bands in the infrared spectrum at 1735 cm.$^{-1}$ (ester band) and 1712 cm.$^{-1}$ (aliphatic or 6-membered ring ketone band) suggested that the keto-ester contained a somewhat hindered keto-group in a six-membered ring. The formation of a hindered keto-group in a side chain appeared unlikely as it could only be accounted for by a branched side chain unlike any found in bicyclic diterpenes. In turn, methyl labdanolate must have contained the grouping (VIII), with the hydroxyl group in the equatorial conformation to account for the formation of an exocyclic rather than an endocyclic double bond on dehydration.

Dehydrogenation of the unsaturated alcohol (VI) with a platinum–charcoal catalyst gave a trimethylnaphthalene. It was identified as the 1 : 2 : 5-trimethyl isomer by comparison of its ultraviolet absorption spectrum with the spectra of the trimethylnaphthalenes described by Heilbronner, Fröhlicher, and Plattner [2] and by formation of the 1 : 3 : 5-trinitrobenzene adduct. In addition 1 : 2 : 5 : 6-tetramethylnaphthalene was obtained and characterised as its 1 : 3 : 5-trinitrobenzene adduct.

* The nomenclature used in this paper is based on the parent hydrocarbon (II) which is provisionally called labdane and, on the advice of the Editor, is numbered on the principles used for steroids. This hydrocarbon was previously called agathane and numbered differently. It is to avoid confusion in numbering that a new name is suggested.

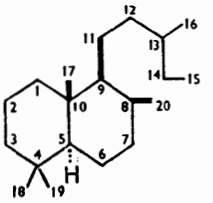
[1] Part I, Cocker, Halsall, and Bowers, preceding paper.
[2] Heilbronner, Fröhlicher, and Plattner, *Helv. Chim. Acta*, 1949, **32**, 2479.

The isolation of 1 : 2 : 5-trimethyl- and 1 : 2 : 5 : 6-tetramethyl-naphthalene suggested that labdanolic acid was related to the group of bicyclic diterpenes typified by sclareol (IX) * [3,4] and manoöl (X) * [3,4] and that its structure was either (I) (or a stereoisomer) or (XI). The former possibility led to structure (IV) (or a stereoisomer) for the dehydration product from methyl labdanolate. During the course of our work on labdanolic acid King



(I) R = CO_2H

(III) R = CH_2·OH



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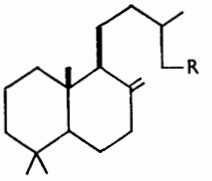
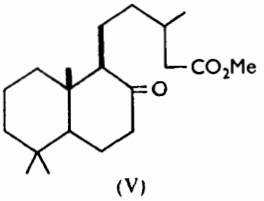


(IV) R = CO_2Me

(VI) R = CH_2·OH



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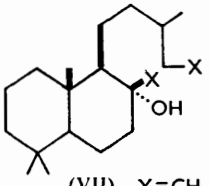
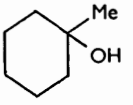


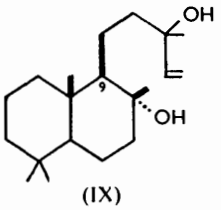
(VII) X = CH_2·OH



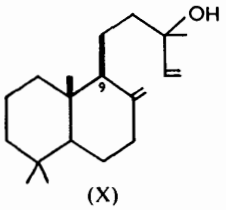
(VIII)

and Jones [5] showed that the methyl ester of eperuic acid, a new bicyclic diterpene from wallaba oleo-resin, was a stereoisomer of (IV). Comparison, however, of the rotation of methyl eperuate with that of the unsaturated ester (IV) from methyl labdanolate indicated that they were not identical (see below).

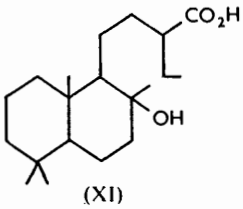
Treatment of the unsaturated ester (IV) with acid gave an isomer, the infrared spectrum



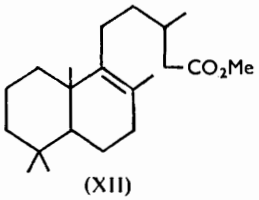
(IX)



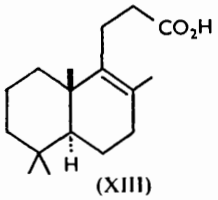
(X)



(XI)



(XII)



(XIII)

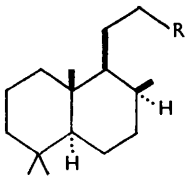
of which did not show any bands indicative of a trisubstituted double bond or a vinylidene group. The isomer had accordingly a tetrasubstituted double bond and it was formulated as (XII). Support for this conclusion was obtained on hydrogenating the isomer. Only one product was obtained and the change in molecular rotation (−112°) was very similar

* The configuration of $C_{(9)}$ in manoöl and sclareol has not been rigorously proved (cf. ref. 4).

[3] Barton, *Quart. Rev.*, 1949, **3**, 36.
[4] Klyne, *J.*, 1953, 3072.
[5] King and Jones, *J.*, 1955, 658.

to that (−136°) found when the acid (XIII) is hydrogenated.[6,7] The stereochemistry of the hydrogenation product is discussed below. Treatment of the isomer with osmium tetroxide in pyridine gave the glycol. The stereochemistry of the addition is uncertain. Addition from the less hindered (α) side would be expected, but Dietrich, Lederer, and Mercier [6] have described results which indicate that when the closely related compound (XIII) is similarly oxidised the product of β-addition is formed. When the original unsaturated ester (IV) was hydrogenated a mixture of two products, one liquid and one solid, was obtained which could only be separated by absorbing the liquid isomer on porous plates. The solid isomer was identical with that obtained by hydrogenation of the acid-isomerised ester (XII). This proved that no skeletal rearrangement had occurred during the acid-isomerisation.

That labdanolic acid had formula (I) rather than (XI) was proved by degradation of the solid hydrogenation product (XIV), formed from the esters (IV) or (XII), by the Barbier–Wieland technique to the acid (XV) and thence to the methyl ketone (XVI). Hypoiodite oxidation of this gave an acid, m. p. 141—143°, $[\alpha]_D$ +40°, which was shown to be identical (mixed m. p. and identical infrared spectra) with the acid (XVII) obtained by Burn and Rigby [7] starting from marrubiin and which was shown by these authors to be identical with material derived from ambrein. Our thanks are due to Dr. W. Rigby for supplying us with a sample of this acid.



(XIV) R = CHMe·CH_2·CO_2Me
(XV) R = CHMe·CO_2H
(XVI) R = COMe

(XVII) R = CO_2H
(XXV) R = CHMe·CH=CPh_2
(XXVI) R = CMe=CPh_2

The identity of the C_{17} acid from labdanolic acid with that from marrubiin and ambrein proved that the rings in labdanolic acid were *trans*-fused and that the absolute configuration at $C_{(10)}$ was the same as in ambrein and in the di- and tri-terpenes. In turn it followed that the 8-hydroxyl group, which had been shown to be equatorial, was in the α- and the 8-methyl group in the β-configuration. These configurations were confirmed by comparison of the molecular-rotation differences between sclareol (IX) and manoöl (X) (ΔM_D +98°) and between labdanolic acid (I) and its dehydration product [*i.e.*, the free acid corresponding to the ester (IV)] (ΔM_D = +99°).

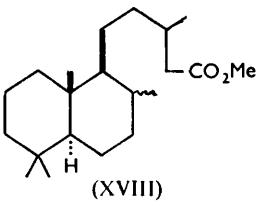
The configuration of the side chain at $C_{(9)}$ had to be β if one assumed that hydrogenation of the unsaturated ester (XII) occurred at the less hindered (α) face of the molecule. The saturated ester resulting would then be (XIV) with the side chain β-oriented. This ester was identical with one of the two isomers which were obtained by hydrogenation of the dehydration product (IV) from methyl labdanolate, and which must have had the same configuration at $C_{(9)}$ as labdanolic acid. However the results of Dietrich, Lederer, and Mercier [6] on the reaction of osmium tetroxide in pyridine with the acid (XIII) referred to above made the above assumption questionable.

If labdanolic acid had a β-side chain at $C_{(9)}$ then one of the two hydrogenation products mentioned in the previous paragraph had to be identical with methyl dihydrocativate. This had been shown by Grant and Zeiss [8] to have structure (XVIII) while our work on labdanolic acid was in progress. The β-configuration of the side chain at $C_{(9)}$ in the ester (XVIII) followed from the conversion of cativic acid and manoöl into a common degradation product, it being assumed, of course, that the side chain of manoöl is correctly represented as β-oriented. The configuration of the 8-methyl group of the ester (XVIII) was not elucidated. Methyl dihydrocativate was, in fact, identical (mixed m. p. and identical infrared spectra) with the hydrogenation product (XIV), m. p. 44—45°, $[\alpha]_D$ +28°, which had been obtained from both the unsaturated esters (IV) and (XII) derived from

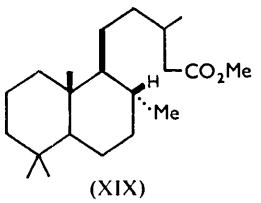
[6] Dietrich, Lederer, and Mercier, *Helv. Chim. Acta*, 1954, **37**, 705.
[7] Burn and Rigby, *Chem. and Ind.*, 1955, 386.
[8] Grant and Zeiss, *J. Amer. Chem. Soc.*, 1954, **76**, 5001.

methyl labdanolate. Labdanolic acid therefore had a side chain at $C_{(9)}$ with the same configuration (β) as that of manoöl, and hydrogenation of the ester (XII) had occurred at the α-face. The 8-methyl group in methyl dihydrocativate also had to have β-configuration (cf. XIV), while the second, liquid, hydrogenation product from (IV) could now be formulated as (XIX). We thank Dr. Harold H. Zeiss for kindly supplying us with a sample of methyl dihydrocativate. The only remaining stereochemical feature of labdanolic acid which has still to be elucidated is the configuration at position 13.

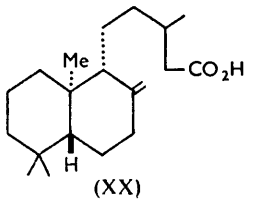
In the course of the degradation of the side chain of methyl dihydrocativate (XIV) derived from labdanolic acid we obtained the semicarbazone of the methyl ketone (XVI).



(XVIII)



(XIX)



(XX)

The melting point of our sample agreed with that quoted by Grant and Zeiss for the same compound but the rotation was only approximately half that reported. We have discussed this matter with Dr. H. Zeiss but so far have not been able to account for the difference.

When labdanolic acid had finally been shown to have structure (I) a comparison was made of the constants of its degradation products with those of the corresponding products of eperuic acid for which King and Jones [5] had proposed identical structures (excluding stereochemical differences). The comparison (cf. Table) showed that the corresponding

Structure (excluding stereochemical features) corresponding to	Constants of compound from eperuic acid		Constants of compound from labdanolic acid	
	$[\alpha]_D$ *		$[\alpha]_D$ *	
(IV)	−28·2°	n_D^{18} 1·4982	+27°	n_D^{15} 1·4980 n_D^{20} 1·4969
(XIV)	−26·3	n_D^{18} 1·4902	+28	n_D^{20} 1·4902 (M. p. 44—45°)
Oxime of the acid corresponding to (V)	−79·4 (in dioxan)	M. p. 223°	+74·5 (in dioxan)	M. p. 188—190°
(XXV)	—	n_D^{18} 1·5520	+116	n_D^{28} 1·5520
(XV)	—	n_D^{17} 1·5010	+49	M. p. 92—93·5°
(XXVI)	−24·4	M. p. 116°	+36	M. p. 118—120°
(XVII)	−29·9	M. p. 134—135°	+40·5	M. p. 141—143° †

* In $CHCl_3$. † Undepressed on admixture with an authentic sample supplied by Dr. Rigby.

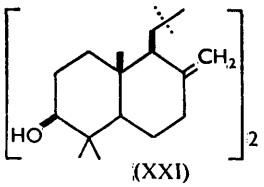
compounds had identical or similar constants except that the *sign* of the rotation was always opposite. This suggests the startling conclusion that eperuic acid is (XX) and has a carbon skeleton which is the mirror image of that of rings A and B of all the hitherto known natural di- and tri-terpenes and steroids.

[*Note added September 13th*, 1956.—Dr. F. E. King and Dr. G. Jones kindly provided us with a small sample of methyl eperuate freshly prepared from eperuic acid obtained from wallaba exudate. As noted by them, its rotation proved to be lower ($[\alpha]_D$ −47°) than that previously reported ($[\alpha]_D$ −28°).[5] Its infrared spectrum was identical with that of the dehydration product (IV) of methyl labdanolate except that the bands at 890 and 1645 $cm.^{-1}$ were less intense. This indicated that the methyl eperuate sample contained an isomer having a double bond and the most likely one appeared to be that corresponding to structure (XII). In the labdanolic acid series this has a rotation of $[\alpha]_D$ +64° and its mirror image would hence have $[\alpha]_D$ −64°, *i.e.*, more negative than that of methyl eperuate. Further, this isomer might well arise during the methylation of eperuic acid with methanolic sulphuric acid (0·6%) [5] as use of 6% methanolic sulphuric acid brings about isomerisation of the *exo*methylene ester (IV) to the ester (XII). To test these views a small amount of

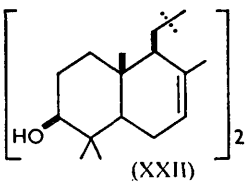
the methyl eperuate was refluxed for 6 hr. with methanolic sulphuric acid. The resulting product had $[\alpha]_D$ −63° and its infrared spectrum (liquid film) was identical with that of the ester (XII). These results support the conclusion suggested above.]

The double bond of the ester (IV) is very similarly situated to those of α-onocerin (XXI).[9] The acidic isomerisation of the exocyclic double bond of the ester (IV) to the tetrasubstituted position in the isomer (X) was in apparent contrast to the shift to the trisubstituted position which was proposed by Barton and Overton[9] to explain the acidic isomerisation of α-onocerin to β-onocerin (proposed structure XXII). Barton and Overton[9] themselves commented that the proposed course of the isomerisation was unexpected.

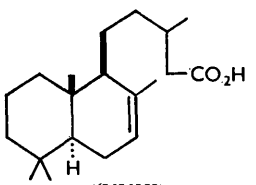
The molecular-rotation difference for the conversion of α-onocerin into β-onocerin is +205° for one double bond.[9] This is of the same sign as that found for the isomerisation of the ester (IV) to its isomer [(+)-XII] (119°) but not as that of the molecular-rotation difference (−97°) between the acid corresponding to (IV) and cativic acid (XXIII) [8] with a trisubstituted double bond. Again the molecular-rotation difference found on hydrogenating β-onocerin diacetate (−154° for one double bond [9]) is much closer to that found on hydrogenation of the ester (XII) (−112°) than to that occurring when cativic acid (XXIII) is hydrogenated (+ *ca.* 113°; in this calculation the rotation of dihydrocativic acid is assumed to be the same as that of methyl dihydrocativate). These results suggest that β-onocerin has in fact structure (XXIV), and Professor D. H. R. Barton and Dr. K. H. Overton have kindly informed us that they now have evidence (unpublished) which supports the new tetrasubstituted positions for the double bonds in β-onocerin.



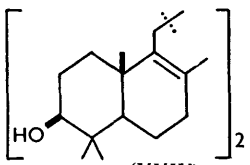
(XXI)



(XXII)



(XXIII)



(XXIV)

Experimental

Rotations refer to solutions in $CHCl_3$ (unless otherwise stated) at room temperature. M. p.s were determined on a Kofler block and are corrected. The alumina used for chromatography had an activity I—II unless otherwise stated. Light petroleum refers to the fraction with b. p. 60—80°. Unless stated otherwise ultraviolet spectra were determined on ethanol and infrared data on carbon disulphide solutions.

Methyl Labdanolate Acetate (*Methyl 8α-Acetoxylabdan-15-oate*).—Methyl labdanolate (960 mg.) in chloroform (15 c.c.) was heated under reflux for 17 hr. with dimethylaniline (18 c.c.) and acetyl chloride (4 c.c.). After the resultant deep blue solution had been diluted with water and acidified with dilute hydrochloric acid, ether-extraction afforded a product which was adsorbed from pentane on alumina (60 g.; activity II). Elution with pentane–benzene (9 : 1) yielded a liquid fraction (170 mg.) which was identified as methyl labd-8(20)-en-15-oate, $[\alpha]_D$ +27° (*c*, 1·03), n_D^{15} 1·4980, identical infrared spectrum (see below). Elution with benzene gave *methyl 8α-acetoxylabdan-15-oate* as needles (300 mg.) (from slightly aqueous methanol), m. p. 84—84·5°, $[\alpha]_D$ −29° (*c*, 1·15) (Found: C, 72·6; H, 10·35. $C_{23}H_{40}O_4$ requires C, 72·6; H, 10·6%).

Attempted Oxidation of Methyl Labdanolate.—Methyl labdanolate (100 mg.) in acetone

[9] Barton and Overton, *J.*, 1955, 2639.

(15 c.c.) was treated with chromic acid (8N) according to the method of Bowers *et al.*[10] After dilution with water, ether-extraction afforded unchanged starting material as needles (from pentane), m. p. and mixed m. p. 73—74°.

Reduction of Methyl Labdanolate.—Methyl labdanolate (580 mg.) in ether (15 c.c.) was slowly added to a slurry of lithium aluminium hydride (300 mg.) in ether (15 c.c.). The mixture was heated under reflux for 1 hr. and then kept at 20° overnight. After decomposition of an excess of the reagent with ethyl acetate and acidification ether-extraction afforded a solid which was recrystallised from pentane, to give *labdane*-8α : 15-*diol* (III) as cubes, m. p. 84—85°, $[\alpha]_D$ −7° (*c*, 1·7) (Found : C, 77·25; H, 12·3. $C_{20}H_{38}O_2$ requires C, 77·35; H, 12·35%). Acetylation with pyridine–acetic anhydride at 20° for 18 hr. gave *labdane*-8α : 15-*diol* 15-*monoacetate* which, after purification by chromatography on alumina deactivated with 5% of 10% aqueous acetic acid, was obtained as a gum, $[\alpha]_D$ −3·7° (*c*, 0·98), n_D^{19} 1·4944 (Found : C, 74·85; H, 11·25. $C_{22}H_{40}O_3$ requires C, 74·95; H, 11·45%). Infrared absorption bands at 1238, 1746, and 3615 cm.$^{-1}$.

Dehydration of Methyl Labdanolate.—Methyl labdanolate (26·8 g.) in pyridine (360 c.c.) was treated with phosphoryl chloride (70 c.c.). After 15 hr. at 20° it was added dropwise, with stirring, to ice and water (3 l.). Ether-extraction afforded a product which was adsorbed from light petroleum on alumina (120 g.). Elution with light petroleum–benzene (4 : 1; 400 c.c.) gave *methyl labd*-8(20)-*en*-15-*oate* (IV) (24·3 g., 96%) as a syrup, $[\alpha]_D$ +27° (*c*, 2·31), n_D^{15} 1·4980, n_D^{20} 1·4969 (Found : C, 78·85; H, 11·3. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%). Infrared absorption bands at 890, 1645, and 1745 cm.$^{-1}$. Hydrolysis of the ester with ethanolic sodium hydroxide gave *labd*-8(20)-*en*-15-*oic acid* as a gum, $[\alpha]_D$ +25° (*c*, 0·97) (Found : C, 78·35; H, 11·1. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%). The cyclo*hexylamine salt*, prepared as described above, was crystallised to constant rotation from ethyl acetate as needles, m. p. 123—136° (dependent upon rate of heating), $[\alpha]_D$ +22° (*c*, 0·78) (Found : C, 77·35; H, 11·8; N, 3·35. $C_{26}H_{47}O_2N$ requires C, 77·0; H, 11·7; N, 3·45%).

Ozonolysis of Methyl Labd-8(20)-*en*-15-*oate* (IV).—The ester (0·92 g.) in ethyl acetate (200 c.c.) was treated with ozonised oxygen at −70° until a faint blue colour persisted in the solution. The excess of ozone was removed by passing a stream of nitrogen through the solution for 10 min. The mixture was then stirred with acetic acid (18 c.c.) and zinc dust (4 g.) until it no longer gave a colour with a starch–iodide paper (approx. 45 min.). The zinc was removed and the filtrate washed with water. The aqueous washings, on treatment with a methanolic solution of 2 : 4-dinitrophenylhydrazine sulphate, gave formaldehyde 2 : 4-dinitrophenylhydrazone (40 mg., 30%), m. p. and mixed m. p. 166—167°. Evaporation of the organic phase gave methyl 20-nor-8-oxo-labdan-15-oate (V) as a gum, with infrared absorption bands at 1709 and 1736 cm.$^{-1}$. The ester was characterised by hydrolysis with methanolic 2N-potassium hydroxide under reflux for 1 hr., 20-*nor*-8-*oxolabdan*-15-*oic acid* being obtained as prismatic needles (from methanol–water), m. p. 110·5—111°, $[\alpha]_D^{14}$ −40° (*c*, 1·01) (Found : C, 74·1; H, 10·55. $C_{19}H_{32}O_3$ requires C, 74·0; H, 10·45%). Light absorption max. (in EtOH) at 2880 Å (ε 31). Infrared absorption band at 1703 cm.$^{-1}$. The keto-acid (76 mg.) in ethanol (0·5 c.c.) and hydroxylamine hydrochloride (0·163 g.) in water (1 c.c.) were treated with 2N-sodium hydroxide until just alkaline, then heated under reflux on the steam-bath for 30 min. After cooling, acidification with hydrochloric acid gave a precipitate, m. p. 184—188°, which crystallised from aqueous ethanol to give the *oxime* (62 mg.) as prisms, m. p. 188—190° after softening at 170°, $[\alpha]_D$ +74·5° (*c*, 1·14 in dioxan) (Found : C, 70·7; H, 10·25. $C_{19}H_{33}O_3N$ requires C, 70·55; H, 10·3%).

Reduction of Methyl Labd-8(20)-*en*-15-*oate* (IV).—The ester (2·0 g.) in ether (40 c.c.) was treated with a 0·76% solution of lithium aluminium hydride in ether (45 c.c.). After 1 hr. at 0°, water and then dilute acetic acid were added. Ether-extraction gave labd-8(20)-en-15-ol (VI) as a gum (1·75 g.), $[\alpha]_D$ +40° (*c*, 0·98). Infrared absorption bands at 890, 1645, 3090, and 3645 cm.$^{-1}$. The gum was not analysed but converted directly into the triol by reaction with osmium tetroxide.

Labd-8(20)-en-15-ol (1·60 g.) in pyridine–chloroform (1 : 1; 100 c.c.) was treated with osmium tetroxide (2 g.) and kept at 20° for 6 days. Removal of the solvents under reduced pressure gave a black residue which was heated under reflux for 3 hr. with benzene (35 c.c.), methanol (35 c.c.), potassium hydroxide (8 g.), and mannitol (8 g.) in ethanol (35 c.c.) and water (22 c.c.). After dilution with water, ether-extraction gave a gum (1·68 g.) which was adsorbed from benzene on alumina (100 g.) deactivated with 7·5% of 10% acetic acid. Elution with

[10] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2555.

ether gave *labdane*-8α : 15 : 20-*triol* (VII) as needles (0·343 g.) (twice crystallised from light petroleum–benzene), m. p. 124—125·5°, $[\alpha]_D$ −17° (*c*, 1·01) (Found: C, 73·45; H, 11·7. $C_{20}H_{38}O_3$ requires C, 73·55; H, 11·75%). Infrared absorption in carbon tetrachloride: broad band at 3400 cm.$^{-1}$.

Dehydrogenation of 15-*Hydroxylabd*-8(20)-*ene* (VI).—A mixture of 15-hydroxylabd-8(20)-ene (1·83 g.) and platinum-on-carbon (30%; 0·44 g.; prepared according to Vogel [11]) was heated at 315—330° for 48 hr. After cooling, the product was isolated by continuous ether-extraction. Removal of the ether gave a yellow oil (1·32 g.) which was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum gave two main oily fractions [(i) 650 and (ii) 144 mg.]. Elution with light petroleum–benzene (10 : 1) gave one main fraction [(iii) 54 mg.]. Further elution with light petroleum–benzene (4 : 1) and with benzene eluted only small amounts of material.

Fraction (i) consisted of non-aromatic hydrocarbons, b. p. 176° (bath-temp.)/10 mm., n_D^{17} 1·4868 (Found: C, 86·4; H, 13·1. Calc. for $C_{20}H_{36}$: C, 86·9; H, 13·1. Calc. for $C_{20}H_{38}$: C, 86·25; H, 13·75%). The infrared spectrum had no bands corresponding to an aromatic ring system; there were bands at 1368, 1388, and 1466 cm.$^{-1}$.

Fraction (ii) was 1 : 2 : 5-trimethylnaphthalene. Light absorption max. in hexane were at 2260, 2310, 2780, 2890, 3000 (infl.), 3100, and 3250 Å (log ε 4·8, 4·98, 3·78, 3·80, 3·65, 3·16, and 2·94). Heilbronner, Fröhlicher, and Plattner [2] give max. at 2260 (infl.), 2300, 2780, 2880, 3000 (infl.), and 3240 Å (log ε 4·73, 4·96, 3·78, 3·87, 3·68, and 2·96). Treatment of the trimethylnaphthalene with a saturated solution of 1 : 3 : 5-trinitrobenzene in alcohol gave the adduct as yellow needles, m. p. 150—158°, raised by several recrystallisations from alcohol to 153—158° (decomp.) (slow change of crystal shape from 120°). Ruzicka, Baumgartner, and Prelog [12] give m. p. 158—159° (sealed tube) (Found: C, 60·1; H, 4·45. Calc. for $C_{19}H_{17}O_6N_3$: C, 59·55; H, 4·45; N, 10·95%).

Fraction (iii) was 1 : 2 : 5 : 6-tetramethylnaphthalene. It was converted into the 1 : 3 : 5-trinitrobenzene adduct which was obtained as orange needles (from ethanol), m. p. 179—181°. Grant and Zeiss [8] give m. p. 180—181°. The pure adduct (27·4 mg.) was adsorbed from light petroleum–benzene on alumina (2 g.). Elution with the same solvent (8 c.c.) gave 1 : 2 : 5 : 6-tetramethylnaphthalene (12·5 mg.), m. p. 112·5—115°. Grant and Zeiss [8] give 114·5—115°. On the assumption that the two components of the adduct have a 1 : 1 molar ratio the weight of hydrocarbon recovered indicates a mol. wt. of 189 (Calc. for tetramethylnaphthalene: *M*, 184).

Isomerisation of Methyl Labd-8(20)-*en*-15-*oate* (IV).—Methyl labd-8(20)-en-15-oate (24·2 g.) in benzene (400 c.c.) was heated under reflux with methanolic sulphuric acid (6·7%; 1200 c.c.) for 3 hr. The mixture was then evaporated under reduced pressure below 30° to half its original volume. After dilution with water, extraction with benzene afforded *methyl labd*-8-*en*-15-*oate* (XII) as an oil (23·8 g.), $[\alpha]_D$ +64° (*c*, 1·07), n_D^{24} 1·4962 (Found: C, 78·5; H, 11·3. $C_{21}H_{36}O_2$ requires C, 78·7; H, 11·3%). Light absorption in EtOH: ε_{2100} 5340; ε_{2150} 3020; ε_{2200} 1650; ε_{2250} 850. Infrared absorption: no bands corresponding to a trisubstituted double bond or a vinylidene group; band at 1745 cm.$^{-1}$.

The ester (5 g.) was hydrolysed under reflux for 1 hr. with a solution from sodium (3·5 g.) in ethanol (100 c.c.) and water (2 c.c.). The resulting acidic fraction was crystallised several times from slightly aqueous methanol, to give *labd*-8-*en*-15-*oic acid* as needles, m. p. 110·5—112°, $[\alpha]_D$ +69° (*c*, 1·06) (Found: C, 78·15; H, 11·35. $C_{20}H_{34}O_2$ requires C, 78·4; H, 11·2%).

Action of Osmium Tetroxide on Labd-8-*en*-15-*oic Acid.*—Labd-8-en-15-oic acid (0·20 g.) in ether (15 c.c.) was treated with osmium tetroxide (0·217 g.; 20% excess) in ether (15 c.c.) and pyridine (0·3 c.c.) for 6 days at 20°. Removal of the solvents under reduced pressure gave a solid which was shaken for 15 min. with potassium hydroxide (2·8 g.) and mannitol (2·8 g.) in water (50 c.c.) and dioxan (30 c.c.). After dilution with water and acidification with 2N-hydrochloric acid, ether-extraction afforded crystals (0·18 g.), m. p. 122—126°, which, recrystallised several times from light petroleum, gave 8ξ : 9ξ-*dihydroxylabdan*-15-*oic acid* as cubes (0·185 g.), m. p. 125—126°, $[\alpha]_D$ −1·8° (*c*, 1·06) (Found: C, 70·85; H, 10·95. $C_{20}H_{36}O_4$ requires C, 70·55; H, 10·65%).

Hydrogenation of Methyl Labd-8(20)-*en*-15-*oate* (IV).—Methyl labd-8(20)-en-15-oate (10·32 g.) in acetic acid (90 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (0·51 g.). The uptake of hydrogen ceased after 15 min. After removal of the catalyst, evaporation under reduced pressure gave an oily solid, $[\alpha]_D$ +15° (*c*, 1·54). The oil was

[11] Vogel, " A Text Book of Practical Organic Chemistry," Longmans, Green and Co., London, 1948, p. 823.

[12] Ruzicka, Baumgartner, and Prelog, *Helv. Chim. Acta*, 1949, **32**, 2057.

removed by pressing the oily solid on porous tiles. The residual solid, m. p. 36—42°, $[\alpha]_D$ +23°, was recrystallised several times from methanol to give methyl labdan-15-oate (methyl dihydrocativate) (XIV) as flat spars (5 g.), m. p. 44—45°, undepressed on admixture with a sample of methyl dihydrocativate, m. p. 44—45°, kindly supplied by Dr. Harold H. Zeiss,[8] $[\alpha]_D$ +28° (*c*, 1·0), n_D^{20} 1·4902 (Found: C, 78·25; H, 11·85. Calc. for $C_{21}H_{38}O_2$: C, 78·2; H, 11·9%). Continuous extraction of the oil from the porous tiles with ether gave impure methyl 8β(H)-labdan-15-oate (XIX) as an oil (3·0 g.), $[\alpha]_D$ +14° (*c*, 1·09), n_D^{20} 1·4900. Hydrolysis of the ester with ethanolic sodium hydroxide gave 8β(H)-labdan-15-oic acid as a gum which was characterised as its cyclo*hexylamine salt*. This was crystallised from ethyl acetate to constant rotation to give needles, $[\alpha]_D$ +14° (*c*, 1·07) (Found: C, 76·9; H, 12·05; N, 3·25. $C_{26}H_{49}O_2N$ requires C, 76·6; H, 12·1; N, 3·45%).

Hydrogenation of Methyl Labd-8-en-15-oate (XII).—Methyl labd-8-en-15-oate (23·4 g.) in acetic acid (150 c.c.) was hydrogenated at atmospheric pressure in the presence of Adams catalyst (1 g.). The uptake of hydrogen ceased after 1 hr. After removal of the catalyst, evaporation under reduced pressure gave a solid, m. p. 40—42°, $[\alpha]_D$ +23·5° (*c*, 0·96). This was crystallised twice from methanol to give methyl labdan-15-oate (XIV) as flat spars, m. p. 44—45°, undepressed on admixture with a sample prepared by hydrogenation of methyl labd-8(20)-en-15-oate.

Hydrogenation of Labd-8-en-15-oic Acid.—Labd-8-en-15-oic acid (60 mg.) in acetic acid (20 c.c.) was hydrogenated at atmospheric pressure in the presence of pre-reduced Adams catalyst (100 mg.). After the uptake of hydrogen had ceased, filtration and evaporation gave the product as a gum. This was methylated with ethereal diazomethane, to give methyl labdan-15-oate as flat spars (from methanol), m. p. and mixed m. p. 44—44·5°.

Treatment of Methyl Labdan-15-oate (XIV) *with Phenylmagnesium Bromide.*—Methyl labdan-15-oate (4·4 g.) in ether (50 c.c.) was slowly added to the Grignard reagent from magnesium (2·8 g.) and bromobenzene (15 g.) in ether (120 c.c.). The mixture was then heated under reflux for 1½ hr. and kept overnight at 20°. After addition of ammonium chloride solution, ether-extraction gave a product which was adsorbed from light petroleum on alumina (250 g.). After elution with light petroleum to remove bromobenzene and diphenyl, elution with ether (1200 c.c.) gave a fraction (87% yield), m. p. 77—82°, which, crystallised from aqueous methanol, gave 15 : 15-*diphenyl-labdan-15-ol* as plates, m. p. 85—86°, $[\alpha]_D$ +10·5° (*c*, 0·94) (Found: C, 85·8; H, 10·65. $C_{32}H_{46}O$ requires C, 86·05; H, 10·4%).

The alcohol (5·3 g.) in acetic acid (60 c.c.) and acetic anhydride (10 c.c.) was heated under reflux for 2¼ hr. After removal of the solvents under reduced pressure the viscous product was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum (1600 c.c.) afforded 15 : 15-*diphenyl-labd-14-ene* (XXV) (4·8 g., 82%) as an oil, $[\alpha]_D$ +116° (*c*, 0·81), n_D^{28} 1·5520 (Found: C, 89·15; H, 10·7. $C_{32}H_{44}$ requires C, 89·65; H, 10·35%). Light absorption max. in *cyclo*hexane at 2515 Å (ε 14,100). In later preparations the crude alcohol was crystallised once and then dehydrated.

Oxidation of 15 : 15-*Diphenyl-labd-14-ene* (XXV).—(i) Chromic acid (0·64 g.) in acetic acid (7 c.c.) and water (2 c.c.) was added during 1 hr. to a stirred solution of 15 : 15-diphenyl-labd-14-ene (0·905 g.) in acetic acid (10 c.c.) and chloroform (8 c.c.) at 22°. Stirring was continued for a further hour and then the solvents were removed at 30° under reduced pressure. The residue was divided into acidic and neutral fractions (0·16 g. and 0·705 g.). The neutral fraction in acetic acid (10 c.c.) and chloroform (8 c.c.) was re-oxidised with chromic acid (0·40 g.) in acetic acid (7 c.c.) and water (1 c.c.) for 3 hr. at 60° and then overnight at 20°. Methanol (2 c.c.) was then added and the acidic product isolated. Several crystallisations of the total acidic material (0·295 g.) from aqueous methanol gave 15-*norlabdan-14-oic acid* (XV) as needles, m. p. 92—93·5°, $[\alpha]_D$ +49° (*c*, 1·0) (Found: C, 77·5; H, 11·5. $C_{19}H_{34}O_2$ requires C, 77·5; H, 11·65%).

(ii) 15 : 15-Diphenyl-labd-14-ene (6·91 g.) in chloroform (120 c.c.) was treated with a stream of ozonised oxygen at −50°, until the solution turned faintly blue. The excess of ozone was removed by passing a stream of nitrogen through the solution for 10 min., and then the ozonide was decomposed by zinc dust (8 g.) and acetic acid (40 c.c.). The mixture was allowed to warm to 20° and then stirred until it no longer gave a colour with starch–iodide paper. Filtration and evaporation under reduced pressure at 60° gave an oil which was oxidised in acetic acid (100 c.c.) with chromic acid (1·7 g.) in water (4 c.c.) for 20 hr. at 20°. The solvents were then removed under reduced pressure and the acidic product isolated, to give 15-norlabdan-14-oic acid (2·74 g.) as needles (from aqueous methanol), m. p. 92—93°.

Methylation of the acid (4·09 g.) with an excess of ethereal diazomethane gave a product which was adsorbed from light petroleum on neutral alumina (150 g.). Elution with light

petroleum–benzene (7 : 1; 1600 c.c.) gave a fraction (3·635 g.) which was crystallised from methanol to give *methyl* 15-*norlabdan*-14-*oate* as needles, m. p. 58·5—59·5°, $[\alpha]_D$ +50° (*c*, 1·08) (Found: C, 77·8; H, 11·75. $C_{20}H_{36}O_2$ requires C, 77·85; H, 11·75%).

Treatment of Methyl 15-*Norlabdan*-14-*oate with Phenylmagnesium Bromide.*—Methyl 15-norlabdan-14-oate (3·63 g.) in ether (100 c.c.) was added to the Grignard reagent from magnesium (2·4 g.), bromobenzene (16 g.), and ether (140 c.c.). The mixture was then heated under reflux for 1½ hr. and kept overnight at 20°. After addition of ammonium chloride solution, ether-extraction gave an oil which was adsorbed from light petroleum on neutral alumina (200 g.). After elution with light petroleum (1200 c.c.) to remove bromobenzene and diphenyl, elution with ether (900 c.c.) gave the crude alcohol which was heated under reflux in acetic acid (100 c.c.) and acetic anhydride (30 c.c.). After removal of the solvents under reduced pressure the product was adsorbed from light petroleum on alumina (200 g.). Elution with light petroleum (900 c.c.) afforded a fraction, m. p. 110—115°, which was crystallised from methanol–chloroform to give 14 : 14-*diphenyl*-15-*norlabd*-13-*ene* (XXVI) as plates (3·0 g.), m. p. 118—120°, $[\alpha]_D$ +36° (*c*, 1·07) (Found: C, 89·9; H, 10·2. $C_{31}H_{42}$ requires C, 89·8; H, 10·2%). Light absorption max. in *cyclo*hexane at 2450 Å (ε 13,800).

Ozonisation of 14 : 14-*Diphenyl*-15-*norlabd*-13-*ene* (XXVI).—The hydrocarbon (0·43 g.) in ethyl acetate (40 c.c.) was treated with a slow stream of ozonised oxygen at −60° until the solution became faintly blue. After the excess of ozone had been removed in nitrogen, acetic acid (10 c.c.) and zinc dust (3 g.) were added. The mixture was allowed to warm to 20° and was then stirred until it no longer gave a colour with a starch–iodide paper. Filtration and evaporation under reduced pressure gave a product which was taken up in ether, washed with potassium hydrogen carbonate solution, and dried. Evaporation gave an oily mixture (0·448 g.) of benzophenone and 15 : 16-bisnorlabdan-13-one (XVI), having infrared absorption bands at 1663 and 1712 cm.$^{-1}$.

The latter ketone was separated from the benzophenone as follows: (a) *Preferential formation of the* 2 : 4-*dinitrophenylhydrazone.* The mixture of ketones (208 mg.) in methanol (3 c.c.) was treated with methanolic 2 : 4-dinitrophenylhydrazine sulphate (2½%; 8 c.c.). After 5 min. at 20° the yellow precipitate which had formed was separated, dissolved in benzene (100 c.c.), and filtered through neutral alumina (15 g.), to give 15 : 16-*bisnorlabdan*-13-*one* 2 : 4-*dinitrophenylhydrazone* (126 mg.) as flat spars (from 95% ethanol), m. p. 148—149° with change in crystalline form to needles at 144° (Found: C, 65·0; H, 8·4; N, 12·7. $C_{24}H_{36}O_4N_4$ requires C, 64·85; H, 8·15; N, 12·6%).

(b) *Preferential formation of the semicarbazone.* The mixture of ketones (1 g.) in ethanol (2 c.c.) was treated with the filtrate from a mixture of semicarbazide hydrochloride (1 g.), sodium acetate (1·5 g.), water (2 c.c.), and ethanol (7 c.c.). After 10 min. at 20° the precipitated semicarbazone was separated. Repeated recrystallisation from ethanol gave 15 : 16-bisnorlabdan-13-one semicarbazone as needles, m. p. 199—201° with softening at 194°, $[\alpha]_D$ +36·5° (*c*, 1·0) (Found: C, 71·05; H, 11·0; N, 12·5. Calc. for $C_{19}H_{35}ON_3$: C, 71·0; H, 10·95; N, 13·05%). Grant and Zeiss [8] give m. p. 201·5—202°, $[\alpha]_D$ +66·6°.

Hydrolysis of 15 : 16-*Bisnorlabdan*-13-*one* 2 : 4-*Dinitrophenylhydrazone.*—The dinitrophenylhydrazone (95 mg.) in acetone (20 c.c.) was heated under reflux for 45 min. with hydrochloric acid (0·5 c.c.). Stannous chloride (500 mg.) in hydrochloric acid (2 c.c.) was added and the mixture heated under reflux for a further 45 min. under nitrogen. After removal of acetone at 20° under reduced pressure, the residue was extracted with benzene. The extract was washed with N-hydrochloric acid until no more coloured material was removed, and then evaporated to give 15 : 16-bisnorlabdan-13-one as an oil (50 mg.), having infrared absorption bands at 1711, 1408, and 1355 cm.$^{-1}$, due to a carbonyl group, a methylene group adjacent to a keto-group, and to a methyl group adjacent to a keto-group respectively.

Hydrolysis of 15 : 16-*Bisnorlabdan*-13-*one Semicarbazone.*—The semicarbazone (0·21 g.) was hydrolysed according to the method of Braude *et al.*[13] under reflux in light petroleum (40 c.c.) with 5% sulphuric acid (25 c.c.) for 18 hr. The light petroleum phase was then separated, washed, dried, and evaporated to give the ketone as an oil (0·165 g., 94%). Its infrared spectrum was identical with that of the oil from the dinitrophenylhydrazone.

Oxidation of 15 : 16-*Bisnorlabdan*-13-*one* (XVI).—The ketone (0·165 g.) in dioxan (10 c.c.) was treated with a solution of potassium iodide (1·0 g.) in water (1·5 c.c.) and 2N-potassium hydroxide solution (2 c.c.). Sodium hypochlorite solution (0·9 c.c.) was then added dropwise during 10 min. at 30°. The mixture was kept at 20° for 30 min. more and then diluted with

[13] Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890.

water and extracted with ether to remove non-acidic material. The aqueous phase was treated with a small quantity of sodium hydrogen sulphite, acidified with hydrochloric acid, and extracted with ether. Extraction of the ether solution with potassium hydroxide solution, followed by acidification of the alkaline phase and further extraction with ether gave the acidic product as a gummy solid. Several recrystallisations of this from aqueous methanol gave 14 : 15 : 16-trisnorlabdan-13-oic acid as needles (30 mg.), m. p. 141—143° (change of crystal form at 125°), undepressed on admixture with an authentic sample kindly supplied by Dr. W. Rigby, $[\alpha]_D$ +40·5° (*c*, 1·02) (Found : C, 76·7; H, 11·1. Calc. for $C_{17}H_{30}O_2$: C, 76·65; H, 11·35%). The infrared spectrum (" Nujol " paste) was identical with that of an authentic sample.

[*Added September 13th, 1956.—Isomerisation of methyl eperuate.* Methyl eperuate (200 mg.) {$[\alpha]_D$ −47° (*c*, 1·24)}, freshly prepared by Dr. F. E. King and Dr. G. Jones from eperuic acid obtained from wallaba exudate, was refluxed with methanolic sulphuric acid (6·7% ; 90 c.c.) for 6 hr. and then kept overnight. After dilution with water, the product was extracted with benzene. The extract was washed with water and dried (Na_2SO_4). Evaporation of the benzene gave a liquid, $[\alpha]_D$ −63·5° (*c*, 1·21). The infrared spectrum (liquid film) of the liquid was identical in every respect with that (liquid film) of methyl labd-8-en-15-oate (XII), $[\alpha]_D$ +64° (*c*, 1·07).]

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