

576. *The Isomeric Eudesmols and their Association with Carissone in Eucalyptus macarthuri.*

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Eudesmol from *Eucalyptus macarthuri* has been separated into the known α - and β -isomers and a third, synthetic γ -isomer has been characterised. Carissone has been shown to accompany eudesmol in this material, and has been synthesised unambiguously from α -eudesmol.

THE bicyclic sesquiterpene alcohol, eudesmol, $C_{15}H_{26}O$, which has been isolated from a number of sources,^{1, 2, 3} although crystalline, shows rather wide variation in melting point and specific rotation. Some representative figures are given in Table 1. It was shown by Ruzicka and his co-workers⁴ that highly purified eudesmol consists of a mixture of α - and β -isomers (I and II), apparently in proportions varying with the source. The ring fusion in eudesmol has been shown to be *trans*,⁵ and the absolute configuration established by correlation with the steroids.⁶ Separation of the pure isomers has not, however, been reported.

TABLE 1.

Source	M. p.	$[\alpha]$	Ref.
<i>Eucalyptus macarthuri</i>	82—83°	+31°	4
<i>Machilus kusanoi</i>	82—83	+31.4	4
<i>Melaleuca uncinata</i>	81—82	+33.4	a
<i>Leptospermum flavescens</i>	81	+38.9	b
<i>Balsamorhiza sagittata</i>	79—80	+37.2	3

^a Penfold, *J. Proc. Roy. Soc. New South Wales*, 1925, **59**, 124. ^b *Idem, ibid.*, 1921, **55**, 178.

α - and β -Eudesmol may clearly be characterised by their different infrared absorption. We therefore examined the chromatography of material from *Eucalyptus macarthuri* by this means. On biogenetic grounds we were interested to examine also any ketonic constituents of the crude material since carissone, recently characterised by Mohr, Schindler,

¹ Simonsen and Barton, "The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 146.

² Beilstein, "Handbuch der organische Chemie," Vol. VI, 2nd suppl., 1944, p. 110.

³ Gardner and Horton, *J. Amer. Chem. Soc.*, 1955, **77**, 3646; cf. Yanovsky, *ibid.*, 1930, **52**, 3466.

⁴ Ruzicka, Wind, and Koolhaas, *Helv. Chim. Acta*, 1931, **14**, 1132.

⁵ Barton, *Chem. and Ind.*, 1953, 664; cf. Klyne, *J.*, 1953, 3080; Birch and Mostyn, *Austral. J. Chem.*, 1954, **7**, 301.

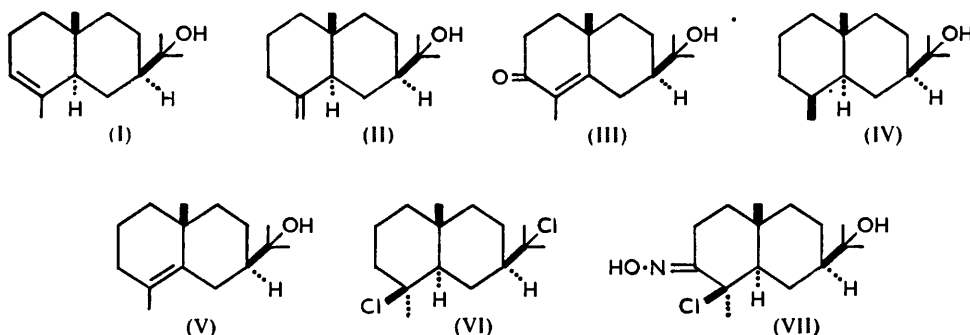
⁶ Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Amer. Chem. Soc.*, 1954, **76**, 313.

and Reichstein⁷ and shown by Barton and Tarleton⁸ to have the structure (III), may be regarded as an oxidation product of eudesmol.

Chromatography, on alumina, of eudesmol from *E. macarthuri* gave on elution, first, a liquid alcohol, C₁₅H₂₄O, in small amount, followed by crystalline material of $[\alpha]_D +33^\circ$ corresponding with samples of eudesmol previously described. This in turn was followed by material of gradually increasing optical rotation showing increasing absorption at 890 cm.⁻¹ (>C=CH_2) due to β -eudesmol. The most strongly absorbed material was found to be ketonic, and on rechromatography gave two ketonic fractions, one dextro- and one laevo-rotatory.

The first ketonic fraction, $[\alpha]_D +126^\circ$, gave analyses for C₁₅H₂₄O₂, showed ultraviolet absorption maxima at 250 m μ (ϵ 14,700) and 311 m μ (ϵ 95), and gave a 2:4-dinitrophenyl-hydrazone, m. p. 173—174°, $[\alpha]_D +540^\circ$, λ_{max} , 262 m μ (ϵ 15,500) and 393 m μ (ϵ 25,400). These characteristics correspond with those given for carissone,⁸ confirming our expectation that carissone might be a concomitant of crude eudesmol. The smaller, laevorotatory ketonic fraction was not obtained pure. It showed infrared frequencies at 3490 and 1168 cm.⁻¹ (OH) and at 1703 and 1681 cm.⁻¹ (>C=O and >C=C-CO-), with ultraviolet absorption at 254 m μ corresponding with the latter.

The eudesmol fraction, $[\alpha]_D +33^\circ$, chromatographed further, gave almost pure α -eudesmol, m. p. 81—82°, $[\alpha]_D +30.5^\circ$, showing strong infrared absorption at 3022 and 799 cm.⁻¹, with only small bands at 3080 and 885 cm.⁻¹. A very similar product, $[\alpha]_D +31.7^\circ$, was obtained directly by tenfold recrystallisation of crude eudesmol, but appreciable absorption at 885 cm.⁻¹ was still present. Removal of the last traces of β -eudesmol by crystallisation therefore appears to be difficult.



In the eudesmol crystal, hydrogen bonding will be a major force: in the infrared spectrum a broad associated-hydroxyl band is observed in the 3490 cm.⁻¹ region in carbon disulphide solution. Moreover, the minor difference between structures such as (I) and

TABLE 2. *Eudesmol isomers.*

Isomer	M. p.	$[\alpha]_D$	Infrared absorption *			3:5-Dinitrobenzoate		
			νCH	$\nu\text{C=C}$	δCH	M. p.	$[\alpha]_D$	$\Delta \dagger$
α	75°	+28.6°	3016	1645	802 (712)	102—103°	+31.4°	+67.1°
β	76	+63.8	3072	1642	889	136—137	+23.8	-42.6
γ	—	+62.5	—	(1640)	(818, 795, 763)	105—106	+73.0	+164.9

* Cf. Figure. † Molecular-rotational change on dinitrobenzoylation.

(II) will readily allow of mixed-crystal formation. Eudesmol esters were therefore examined as a means of separation of the isomers. The known acetate⁹ and benzoate⁴ are liquid. We have used the 3:5-dinitrobenzoate, and by crystallisation have isolated the different esters. Hydrolysis of these gave pure α - and β -eudesmol with the properties noted in Table 2. Both isomers absorbed hydrogen equivalent to one double bond, to give

⁷ Mohr, Schindler, and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 462.

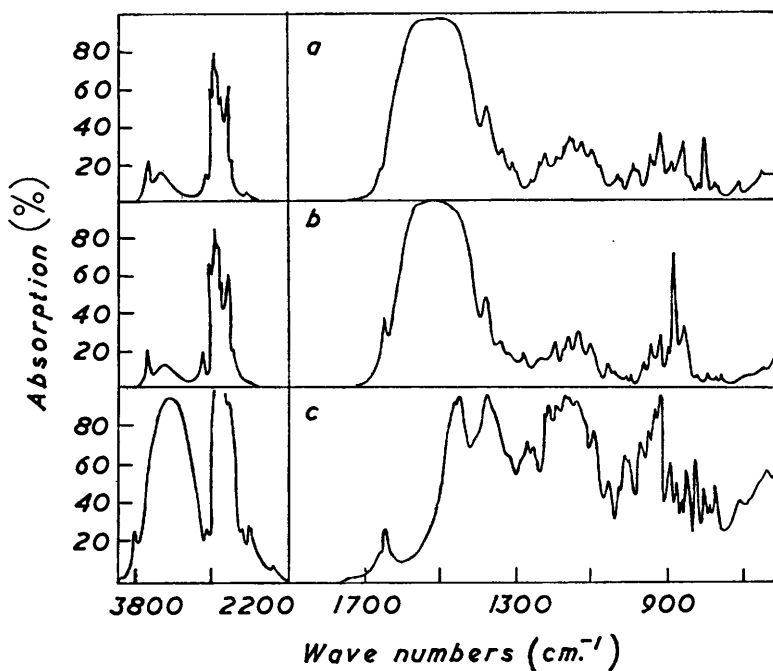
⁸ Barton and Tarleton, *J.*, 1954, 3492.

⁹ Semmler and Tobias, *Ber.*, 1913, **46**, 2026.

dihydro-derivatives identical in infrared spectra and corresponding with the known dihydro-eudesmol.⁹ Eudesmol is regarded as being hydrogenated from the α -face of the molecule,⁵ leading to a dihydro-derivative (IV).

It will be noted from the melting points that α - and β -eudesmol form a mixed crystal, or series of mixtures, of higher melting point than either of the pure isomers, emphasising the difficulty of purification by crystallisation.

By strong ultraviolet irradiation in benzene solution, the mixed eudesmol isomers are converted completely into the β -form (II). This is regarded as a less stable isomer (cf. discussion by Brown, Brewster, and Shechter,¹⁰ and the exo \rightarrow endo-cyclic isomerisation of di- and tri-terpenes containing the exocyclic methylene group¹¹). Formation of less stable isomers by strong illumination is known to occur.¹²



Infrared absorption spectra of (a) α -eudesmol and (b) β -eudesmol (both 35 mg./c.c.; 0.2 mm. cell) and (c) γ -eudesmol (liquid film; 0.05 mm.).

(These spectra have been made available to Butterworths Ltd. for the DMS publication.)

Semmler and Risse¹³ reported the preparation of a liquid isomer of eudesmol by careful hydrolysis of the selinene dihydrochloride,⁴ m. p. 74°. We have confirmed this, and by purification through the 3 : 5-dinitrobenzoate this third " γ "-isomer has been characterised. This isomer resisted hydrogenation in neutral solution, but in acetic acid gave the known dihydroeudesmol. The infrared absorption of γ -eudesmol is characteristic of substances containing a fully substituted double bond, with only weak bands in the 700—900 cm^{-1} region similar to those found in dihydroeudesmol. It is therefore regarded as having structure (V) formed from a dihydrochloride (VI) by the expected elimination and hydrolysis.

Ayer and Taylor¹⁴ report the isolation of carissone (III) in small yield as the 2 : 4-dinitrophenylhydrazone on successive action of nitrosyl chloride, sodium ethoxide, and

¹⁰ Brown, Brewster, and Shechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

¹¹ (a) Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1908; (b) Barton and Overton, *J.*, 1955, 2643.

¹² Cf. Crombie, *Quart. Rev.*, 1952, **6**, 101.

¹³ Semmler and Risse, *Ber.*, 1912, **45**, 3301; cf. ref. 4.

¹⁴ Ayer and Taylor, *J.*, 1955, 3027.

alcoholic hydrogen chloride on eudesmol. No intermediates were isolated. When their work was reported we had already examined these reactions and obtained chloronitroso- α -eudesmol and carissone oxime crystalline in satisfactory yield. Generation of nitrosyl chloride *in situ* for reaction with eudesmol leads to complex side reactions. Using ethyl nitrite with hydrochloric acid in ether or acetic acid we obtained, like Ayer and Taylor, only non-crystalline material from which in various experiments we were able to isolate as solid products a dichlorodinitrososelinane and a chlorodinitrososelinane in small yield, and the 2:4-dinitrophenylhydrazone of a dichloroselinane. With gaseous nitrosyl chloride in dry ether, however, the nitrosochloride may be obtained from α -eudesmol in good yield, and then dehydrochlorinated quantitatively by pyridine in acetone. From the ease of dehydrochlorination the nitrosochloride appears to have the structure (VII).

Carissone oxime has not previously been described. The molecular-rotation change, carissone \rightarrow oxime (+90.8°), is similar to the corresponding value for α -cyperone¹⁵ (+60.6°), in agreement with the corresponding configurations.⁸

EXPERIMENTAL

Optical rotations were measured in CHCl_3 and ultraviolet absorption spectra in EtOH, unless otherwise stated. Infrared absorption spectra were determined in CS_2 solution or as liquid films (0.05 mm.) as appropriate.

Purification of Eudesmol.—(i) Tenfold recrystallisation of crude eudesmol from the oil of *E. macarthurii* from aqueous acetone, followed by sublimation *in vacuo*, gave material, m. p. 83.5°, $[\alpha]_D + 31.7^\circ$ (*c* 2.42) (Found: C, 80.95; H, 11.7. Calc. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.1; H, 11.7%).

(ii) Crude eudesmol, m. p. 60–65° (20 g.), in light petroleum (b. p. 60–80°; 150 c.c.) was chromatographed on alumina (600 g.). Elution with light petroleum yielded: (a) an oil, b. p. 120–123°/1 mm. (90 mg.), n_D^{18} 1.5325, λ_{max} , 245 μ (ϵ 13,000) (Found: C, 81.45; H, 11.0. Calc. for $\text{C}_{15}\text{H}_{24}\text{O}$: C, 81.75; H, 11.0%); (b) crystals (2 g.), m. p. 79–81° after sublimation *in vacuo*, $[\alpha]_D + 33.0^\circ$ (*c* 2.69). Light petroleum–benzene gave (c) crystals (13 g.), m. p. 78–79°, after sublimation *in vacuo*, $[\alpha]_D + 48.5^\circ$ (*c* 2.01). Ethanol (400 c.c.) eluted (d) a ketonic oil (4 g.).

Fraction (b), rechromatographed on alumina (100 g.), with light petroleum (b. p. 60–80°) gave as main product a eudesmol, m. p. 81–82°, $[\alpha]_D + 30.5^\circ$ (*c* 1.95) (1.2 g.). This material absorbed strongly at 3022 and 799 cm^{-1} but only weakly at 3075 and 885 cm^{-1} , *i.e.*, it is regarded as essentially α -eudesmol.

The ethanol eluate (d) (4 g.), on alumina (100 g.), eluted with benzene gave: (i) eudesmol (1.6 g.); (ii) a colourless glass (0.3 g.), b. p. 123–125°/0.15 mm., $[\alpha]_D + 126^\circ$ (*c* 0.38), n_D^{18} 1.5274, λ_{max} , 250 μ (ϵ 14,700), 311 μ (ϵ 95) (Found: C, 76.1; H, 10.5. Calc. for $\text{C}_{15}\text{H}_{24}\text{O}_2$: C, 76.2; H, 10.25%). Mohr, Schindler, and Reichstein⁷ give for carissone $[\alpha]_D + 136.6^\circ$, λ_{max} , 250 μ (ϵ 15,000) and 308 μ (ϵ 91). The 2:4-dinitrophenylhydrazone formed needles (from chloroform–*isopropyl* ether), m. p. 173–174°, $[\alpha]_D + 540^\circ$ (*c* 0.17), λ_{max} , 262 μ (ϵ 15,500) and 393 μ (ϵ 25,400) in CHCl_3 (Found: C, 60.4; H, 6.8. Calc. for $\text{C}_{21}\text{H}_{28}\text{O}_5\text{N}_4$: C, 60.55; H, 6.9%). Barton and Tarleton⁸ give for carissone 2:4-dinitrophenylhydrazone, m. p. 174–175°, $[\alpha]_D + 538^\circ$, λ_{max} , 392 μ (ϵ 26,000) in CHCl_3 .

Elution with benzene containing 2–5% of chloroform gave an oil (0.2 g.), b. p. 107–110°/0.05 mm., $[\alpha]_D - 62.3^\circ$ (*c* 0.84), n_D^{18} 1.5272, λ_{max} , 254 μ (ϵ 14,600), inflexion at 310 μ (ϵ 398) (Found: C, 75.8; H, 10.8%), whose 2:4-dinitrophenylhydrazone had m. p. 142–145° (Kofler block) after chromatography on alumina (10 g.) and elution with benzene containing 5% of ether, λ_{max} , 262 μ (ϵ 18,300) and 398 μ (ϵ 25,500).

Elution with benzene containing 10% of chloroform gave a non-ketonic gum (0.4 g.), b. p. 130–135°/0.05 mm., n_D^{18} 1.5203, $[\alpha]_D + 28.4^\circ$ (*c* 2.70), insoluble in light petroleum and in alkali, unsaturated to tetranitromethane, and showing no strong ultraviolet absorption; this may be an unsaturated diol (Found: C, 75.8; H, 11.1. Calc. for $\text{C}_{15}\text{H}_{26}\text{O}_2$: C, 75.6; H, 11.0%).

Ultraviolet Irradiation of Eudesmol.—Material from fraction (c) above ($[\alpha]_D + 48.5^\circ$; 0.7 g.), in benzene (25 c.c.) was irradiated in a quartz tube by a mercury-vapour lamp. The optical rotation rose to a constant value, $[\alpha]_D + 62^\circ$, after 50 hr. The recovered material, in ether, was washed with sodium hydroxide solution and with water, and the residue chromatographed on alumina (20 g.), elution being with light petroleum to give: (a) colourless oil (20 mg.), b. p. 135–139°/14 mm., n_D^{18} 1.4975, unsaturated to tetranitromethane, but showing no ultraviolet

¹⁵ Howe and McQuillin, *J.*, 1955, 2423.

absorption (Found: C, 86.9; H, 13.0. Calc. for $C_{15}H_{26}$: C, 87.25; H, 12.75%). Ruzicka, Wind, and Koolhaas⁴ give b. p. 130—133°/10 mm., n_D^{20} 1.4972, for dihydroselinene; (b) β -eudesmol (0.6 g.), m. p. 75.5—76° after sublimation *in vacuo*, $[\alpha]_D + 65.1^\circ$ (*c* 2.84) (Found: C, 81.2; H, 11.55%). This material absorbed strongly at 3080 and 885 cm^{-1} , showing no absorption at 3020 or 799 cm^{-1} .

Separation of Eudesmol Isomers as their 3 : 5-Dinitrobenzoates.—(a) Eudesmol, m. p. 80—82°, $[\alpha]_D + 35^\circ$ (3.0 g.), in dry pyridine (15 c.c.) and dry benzene (15 c.c.) with 3 : 5-dinitrobenzoyl chloride (6.2 g.) was warmed on the water-bath for 3 hr. The product, triturated with light petroleum, afforded a solid (5.0 g.) which by crystallisation from light petroleum (b. p. 60—80°) and then from benzene-light petroleum (b. p. 60—80°), gave β -eudesmyl 3 : 5-dinitrobenzoate (0.8 g.), prisms, m. p. 136—137°, $[\alpha]_D + 23.8^\circ$ (*c* 2.06) (Found: C, 63.6; H, 6.95. $C_{22}H_{22}O_6N_2$ requires C, 63.5; H, 6.75%); further elution gave α -eudesmyl 3 : 5-dinitrobenzoate (1.1 g.), forming needles, m. p. 102—103°, $[\alpha]_D + 31.4^\circ$ (*c* 2.11), after repeated crystallisation from aqueous acetone or light petroleum (b. p. 60—80°) (Found: C, 63.55; H, 7.1%).

(b) β -Eudesmyl 3 : 5-dinitrobenzoate (0.2 g.) with 5% potassium hydroxide in 25% aqueous methanol (8 c.c.) was warmed on the water-bath for 5 hr. The product, when sublimed *in vacuo*, gave β -eudesmol (0.1 g.), m. p. and mixed m. p. with the material from ultraviolet isomerisation 75.5—76°, $[\alpha]_D + 63.8^\circ$ (*c* 1.90) (Found: C, 80.9; H, 11.55%).

α -Eudesmyl 3 : 5-dinitrobenzoate (0.13 g.), treated similarly, yielded α -eudesmol (60 mg.), m. p. 75°, $[\alpha]_D + 28.6^\circ$ (*c* 1.86) (Found: 80.85; H, 11.55%).

γ -Eudesmol.—Selinene dihydrochloride, m. p. 73—74° (needles from methanol), $[\alpha]_D + 18.7^\circ$ (*c* 0.70), was obtained in 70% yield from recrystallised eudesmol by the method of Ruzicka, Wind, and Koolhaas⁴ who give m. p. 74—75°, $[\alpha]_D + 20^\circ$.

The dihydrochloride (0.5 g.) was heated at 95° for 3 days with calcium oxide (0.4 g.) in water (15 c.c.) and ethanol (1 c.c.). The product, in ether, was washed with water, and distilled, having b. p. 80—84°/0.1 mm., n_D^{20} 1.5103, $[\alpha]_D + 55.6^\circ$ (*c* 2.33) (Found: C, 80.95; H, 12.1%). The infrared spectrum of the alcohol showed some terminal methylene absorption. γ -Eudesmyl 3 : 5-dinitrobenzoate, prepared as for the other isomers, formed needles, m. p. 105—106°, $[\alpha]_D + 73.0^\circ$ (*c* 1.05), from light petroleum (b. p. 60—80°) (Found: C, 63.6; H, 7.1%).

This 3 : 5-dinitrobenzoate (0.2 g.), when hydrolysed as above, gave γ -eudesmol, b. p. 83—86°/0.1 mm. (90 mg.), $[\alpha]_D + 62.5^\circ$ (*c* 0.73), n_D^{20} 1.5087 (Found: C, 80.75; H, 11.85%). The infrared spectrum (cf. Figure) showed no terminal methylene absorption.

Hydrogenation of Eudesmols.—Hydrogenated in the presence of Adams platinum oxide (5%), each eudesmol isomer smoothly absorbed 1 mol., giving a crystalline dihydro-derivative with the properties shown.

Isomer	Solvent	Dihydro-derivative			Found (%)	
		M. p.	$[\alpha]_D$		C	H
α	EtOH	82.5—83.5°	+15.6°	(<i>c</i> 1.76)	80.0	12.55
β	"	82.5—83.5	+15.0	(<i>c</i> 2.92)	80.15	12.6
γ	AcOH	82.5	+15.5	(<i>c</i> 2.17)	80.15	12.3
				Calc. for $C_{15}H_{28}O$:	80.3	12.55

Reaction of Eudesmol with Nitrosyl Chloride.—(a) *Ethyl nitrite and hydrochloric acid.* Recrystallised eudesmol and ethyl nitrite in ether were treated at -10° with ethereal hydrogen chloride (3 mols.). From the washed and dried solution only a viscous green mass was obtained, from which a small amount of solid material, m. p. 118—120° (decomp.), was isolated by means of ether-light petroleum (Found: C, 54.1; H, 7.0. $C_{15}H_{24}O_2N_2Cl_2$ requires C, 53.8; H, 7.1%), corresponding to a *dichlorodinitrososelinane*. In another experiment a small yield of a *chlorodinitrososelinene*, m. p. 98°, was isolated (Found: C, 60.1; H, 8.0. $C_{15}H_{23}O_2N_2Cl$ requires C, 60.2; H, 7.8%). The remaining non-crystalline material, by means of 2 : 4-dinitrophenylhydrazine, gave a *derivative*, m. p. 155° (from alcohol-ethyl acetate), corresponding to that of a dichloroselinanone, together with other products (Found: C, 53.4; H, 5.7. $C_{21}H_{28}O_4N_4Cl_2$ requires C, 53.4; H, 5.9%).

(b) *Nitrosyl chloride.* Freshly prepared nitrosyl chloride (2 g., 3 mols.) in dry ether (20 c.c.) was added rapidly to α -eudesmol (2 g.) in dry ether (20 c.c.) with cooling (ice-salt). The solution was kept overnight at 0°, solvent removed *in vacuo* at 20°, and the blue-green oil remaining dissolved in acetone (2.5 c.c.). Light petroleum, added dropwise with vigorous stirring, precipitated a colourless microcrystalline powder (0.8 g.), which afforded (+)-4 β -chloro-3-nitrosoeudesman-11-ol as needles, m. p. 85.5—86°, from benzene-light petroleum (b. p. 100—120°) (Found: C, 62.3; H, 9.3. $C_{15}H_{26}O_2NCl$ requires C, 62.6; H, 9.05%).

Carissone Oxime.—The nitrosochloride (250 mg.) in acetone (5 c.c.) was refluxed for 2 hr.

with dry pyridine (0.4 c.c.). Addition of water precipitated a solid (195 mg.) which afforded (+)-3-hydroxyiminoeudesm-4-en-11-ol as colourless needles, m. p. 148—149°, from light petroleum (b. p. 100—120°), $[\alpha]_D +165^\circ$ (*c* 0.73), λ_{\max} . 243 m μ (ϵ 16,700) (Found: C, 71.3; H, 10.05. C₁₅H₂₅O₂N requires C, 71.6; H, 10.05%).

Carisone 2:4-Dinitrophenylhydrazone.—The oxime, with 2:4-dinitrophenylhydrazine in alcoholic hydrogen chloride, yielded the 2:4-dinitrophenylhydrazone which was chromatographed on alumina (4 g.) and eluted with benzene; it had m. p. and mixed m. p. 174—175° (needles from chloroform-isopropyl ether), $[\alpha]_D +536^\circ$ (*c* 0.31), λ_{\max} . 394 m μ (ϵ 25,000), 262 m μ (ϵ 16,500) (Found: C, 60.3; H, 7.1. Calc. for C₂₁H₂₈O₅N₄: C, 60.55; H, 6.9%).

One of us (J. D. P.) is indebted to the Department of Scientific and Industrial Research for an award. We thank Miss S. Robinson and Mr. R. E. Dodd for the infrared determinations, and Professor G. R. Clemo, F.R.S., for a gift of eudesmol and for his interest in the early stages of this work.

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[Received, March 2nd, 1956.]
