107. *The Structure of* cyclo*Eucalenol.*

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Further investigation of the triterpene *cyclo*eucalenol, already recognised as a near analogue of *cyclo*artanol, has now defined it as 4β-demethyl-24-methylene*cyclo*artanol. The crucial experiment was the methylation of 24-demethyl*cyclo*eucalanone which gave *cyclo*artanone by introducing a single methyl group at $C_{(4)}$.

*cyclo*EUCALENOL was discovered in tallow-wood (*Eucalyptus microcorys*) and shortly afterwards in *Erythrophloeum guineense*,[1] and our early investigations disclosed its general resemblance to the tetracyclic triterpenes. In particular it appeared to contain (i) a *cyclo*propane ring, which from the nature of oxidation products probably involved $C_{(9)}$; (ii) a methylene substituted grouping, $\cdot CH_2 \cdot C(:CH_2) \cdot CHMe_2$, believed to be part of a side-chain $\cdot CHMe \cdot CH_2 \cdot CH_2 \cdot C(:CH_2) \cdot CHMe_2$; and (iii) a 3β-hydroxyl group. However, removal of the side-chain methylene group did not give *cyclo*artanol (I), and the enedione formed by oxidation of the acid-isomerised 24-demethyl*cyclo*eucalanyl acetate was not identical with 7 : 11-dioxolanost-8-enyl acetate (II; R = Me, R′ = COMe).

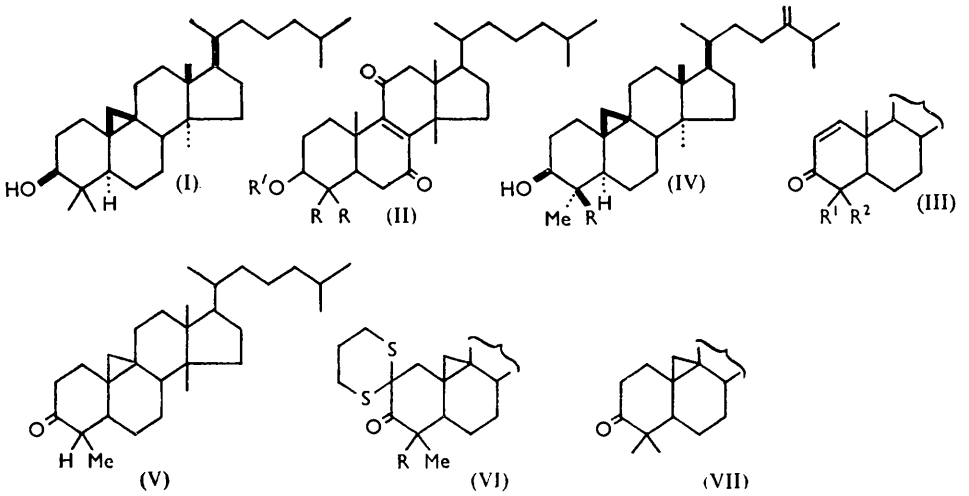
It was the underlying assumption of further work that *cyclo*eucalenol had the conventional perhydro*cyclo*pentanophenanthrene nucleus. On this hypothesis it is readily established that position 14 is substituted, otherwise, by analogy with sterols, opening of the *cyclo*propane ring and oxidation of the product (eucalenyl acetate) would afford a *cisoid* 8(14)-ene-7 : 15-dione readily distinguishable from the *transoid* enedione actually obtained.[1,2] A further indication of the lanostane rather than euphane configuration at $C_{(13)}$ and $C_{(14)}$ is the formation from the previously described epoxyeucalenyl acetate of a product with the characteristic ultraviolet absorption of a 7 : 9(11)-diene of the lanostane series.[3]

The first significant difference between *cyclo*eucalanol and the normal tetracyclic triterpenes was observed in its reaction with phosphorus pentachloride. Instead of the usual A-ring contraction leading to an *iso*propylidene compound, a stable chloride was obtained in high yield, comparable in the unreactivity of its halogen atom with cholesteryl chloride. A similar chloro-compound was likewise derived from eucalenol thus eliminating the possibility that the *cyclo*propane unit was the origin of the unusual reaction with phosphorus pentachloride. It seemed probable therefore that the anomaly derived from incomplete substitution of the $C_{(4)}$ position and a quantitative bromination of eucalanone, in which four molecules of bromine were consumed, appeared to confirm this explanation. The only isolable product, however, was an unstable tribromo-αβ-unsaturated ketone, and although superficially in agreement with presence of the unit $\cdot CH_2 \cdot CO \cdot CH_2 \cdot$, earlier work on cholestanone–bromine reactions does not support the view that a grouping of this type would necessarily react with four molecules of halogen.[4] The nature of the bromination product remains unproved but its formation obviously gives evidence of the abnormal structure of the A-ring. Very recently [5] Djerassi and Burstein have shown that a derivative of iresin having a 4-monomethylated 3-oxo ring A, and also 4-methyldihydrotestosterone, give 2 : 6-dibromo-3-oxo-Δ^4-derivatives. It is thus possibe that the brominated eucalanone is a 2 : 2 : 6-tribromo-3-oxo-Δ^4-compound. A monobromoeucalanone was also obtained, and was transformed with boiling collidine into a product having ultraviolet absorption compatible with the 1-en-3-one structure (III). This unsaturated carbonyl group can occur only in ring A of the normal *cyclo*pentanophenanthrene terpenoids, but its formation

[1] Cox, King, and King, *J.*, 1956, 1384.
[2] Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, 3rd Edn., 1949, pp. 243, 248.
[3] Dorée, McGhie, and Kurzer, *J.*, 1949, 570; Barbour, Bennett, and Warren, *J.*, 1951, 2540.
[4] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[5] Djerassi and Burstein, *J. Amer. Chem. Soc.*, 1958, **80**, 2593.

gives no indication of the $C_{(4)}$ substituents R^1 and R^2. The evidence of light-absorption measurements appears to support the possibility of incomplete alkylation at position 4 since the infrared spectrum of a *cyclo*eucalenyl acetate derivative with a degraded side-chain lacks the 1390 and 1365 cm.$^{-1}$ bands characteristic of the *gem*-dimethyl group. *cyclo*Eucalenol therefore appears to be either a 4-demethyl- or 4 : 4-bisdemethyl-24-methylene*cyclo*artanol (IV), but molecular-weight estimations by the usual methods were inadequate to differentiate between the alternative C_{29} and C_{30} formulæ. Nevertheless, *cyclo*eucalenol cannot be the 4 : 4-bisdemethyl-24-methylene*cyclo*artanol since the enedione from 24-demethyl*cyclo*eucalanyl benzoate would then be (II; R = H, R′ = COPh), *viz.* 3β-benzoyloxy-14-methylcholest-8-ene-7 : 11-dione, and a compound of this structure is known [6] and is clearly not identical with the analogous product from *cyclo*eucalenol. The crystallographic molecular-weight estimation was also unsuccessful in this case owing to imperfections in the crystals of *cyclo*eucalenol and of its derivatives, but volumetrically determined equivalents of *cyclo*eucalenyl hydrogen phthalate gave very consistent results favouring a C_{30} molecule, thus strongly supporting the structure (IV; R = H) monomethylated at position 4.

The constitution of *cyclo*eucalenol and its relation to *cyclo*artanol were finally established by methylation of the 24-demethyl*cyclo*eucalanone (V) by the method of Woodward, Patchett, Barton, Ives, and Kelly,[6] used by Beton, Halsall, Jones, and Phillips [7] for the



methylation of cholestanone. Formylation of the ketone readily gave a colourless hydroxymethylene derivative having the expected ultraviolet absorption, and by replacement of the formyl group the dithian (VI; R = H) was obtained, after chromatography, as a glassy resin. Methylation of the thio-compound afforded a product consisting of unchanged dithian (72%) and a more easily eluted crystalline material (23%). The recovered dithian was identified by reconversion into the crystalline demethyl*cyclo*eucalanone (V). The crystalline product, which exhibited the infrared carbonyl stretching frequency regarded as characteristic of a fully substituted ketone,[7] was readily converted into the corresponding ketone identical (m. p., mixed m. p., and infrared absorption) with *cyclo*artanone (VII). We are indebted to Professor F. S. Spring, F.R.S., for arranging these comparisons.

It is thus conclusively proved that 24-demethyl*cyclo*eucalanone is identical with 4-demethyl*cyclo*artanone and that one methyl group only is attached to position 4 in

[6] Barton, Ives, Kelly, Woodward, and Patchett, *Chem. and Ind.*, 1954, 605; Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131.
[7] Beton, Halsall, Jones, and Phillips, *J.*, 1957, 753.

*cyclo*eucalenol. It is possible to establish the orientation of this methyl group from the stability of the dithian (VI; R = H) to alkali, thus indicating its equatorial conformation. *cyclo*Eucalenol can therefore be unambigously described as 4β-demethyl-24-methylene-*cyclo*artanol (IV; R = H), as recorded in a recent preliminary communication.[8]

Professor Djerassi has measured the optical rotatory dispersion of *cyclo*eucalanone and finds it compatible with the structure now deduced, although in fact rotatory dispersion does not distinguish between cholestanone and either of its 4-monomethyl derivatives.

During the examination of specimens of the hydrocarbon (*cyclo*eucalane) obtained from *cyclo*eucalanyl chloride and from the corresponding ketone, certain discrepancies were observed which were finally attributed to the formation of mixed isomers during the reduction of the $C_{(24)}$ methylene group. Similar results have been noted in the reduction of polyporenic acid A.[9] Although this observation implies that the reported properties of *cyclo*eucalanol derivatives may refer to mixtures, the structural arguments are unaffected. Furthermore, no discrepancies were detected in the case of the *cyclo*eucalenyl chloride and *cyclo*eucalenone reduction products, which consisted of the identical homogeneous hydrocarbon, thus confirming that the formation of the chloride occurred without rearrangement of the nucleus.

Experimental

Optical rotations are recorded for chloroform solutions and sodium light at room temperature. Light petroleum refers to the fraction of b. p. 60—80°, and alumina for chromatography was P. Spence's Grade H.

Eucala-7 : 9(11)-*dienyl Acetate*.—Epoxyeucalanyl acetate [1] (610 mg.) in acetic acid (30 c.c.) with concentrated sulphuric acid (6 drops) was heated on a steam-bath for 1 hr., and then kept overnight at room temperature. Then the dark brown solution was diluted and the precipitate was collected with ether. The *diene acetate* was purified by chromatography on alumina, from which it was eluted by light petroleum–benzene (9 : 1), and then crystallised from chloroform–methanol as rhombs, m. p. 129—130°, [α] +93° (*c* 1·1) (Found: C, 81·8; H, 11·1. $C_{32}H_{52}O_2$ requires C, 82·0; H 11·2%), light absorption in ethanol: $\lambda_{max.}$ 236, 243, and 252 mμ (ε 14,800, 17,300, and 11,700, respectively).

Chlorination of cyclo*Eucalanol*.—(*a*) *cyclo*Eucalanol (1 g.) in light petroleum (350 c.c.) was shaken with excess of phosphorus pentachloride for 1 hr. at room temperature. The solution was then washed with aqueous sodium hydroxide and water and percolated through alumina from which benzene–light petroleum (1 : 4) eluted a chloro*cyclo*eucalone, crystallising as needles or prisms (from chloroform–methanol), m. p. 97—98°, [α] +37° (*c* 0·5) (Found: C, 80·6; H, 11·6; Cl, 8·1. Calc. for $C_{30}H_{51}Cl$: C, 80·6; H, 11·5; Cl, 7·9%). (*b*) *cyclo*Eucalanol (0·5 g.) in dry pyridine (5 c.c.) with phosphorus oxychloride (1·25 c.c.) was heated at 100° for 2 hr. The product was a chlorohydrocarbon, m. p. 97—98°, identical with that obtained by method (*a*).

The chloro-compounds obtained from different samples of *cyclo*eucalanol had slightly different properties, the m. p. varying from 92° to 104°. The chloro-compounds were unaffected by boiling collidine during 4 hr., or by boiling 20% methanolic potassium hydroxide during 3 hr.

A similar chloro-compound was obtained when the mixed isomers resulting from the action of acid on *cyclo*eucalanol were treated as in (*b*).

Eucalan-3-*one*.—Eucalanol [1] (also prepared by vigorous Huang-Minlon reduction of 7 : 11-dioxoeucalanyl acetate [1]) (500 mg.) was oxidised by chromic oxide (100 mg.) in acetic acid (20 c.c.) during 14 hr. at room temperature. The *ketone* (360 mg.) obtained from the reaction in the usual way separated from chloroform–methanol as plates, m. p. 132—134°, [α] +40° (*c* 2·7) (Found: C, 84·0; H, 12·3. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%). The *dinitrophenylhydrazone* separated from chloroform–methanol as orange plates, m. p. 252—254° (Found: C, 70·7; H, 8·9; N, 9·6. $C_{36}H_{56}O_4N_4$ requires C, 71·0; H, 9·3; N, 9·2%).

Bromination of Eucalanone.—Eucalanone (119·6 mg.) in acetic acid (10 c.c.) was mixed with a solution of bromine (200 mg.) in acetic acid (10 c.c.) with the addition of 2 drops of 50% hydrobromic acid–acetic acid, and kept at 35°. A blank solution identical with the above but for the absence of the ketone was simultaneously prepared. The uptake of bromine was

[8] Cox, King, and King, *Proc.*, 1957, 290.
[9] Jones and Woods, *J.*, 1953, 464.

measured volumetrically on aliquot portions of 1 c.c. by using thiosulphate. 4 mols. of bromine were absorbed after 72 hr.

The *product* obtained by diluting a similar bromination mixture after 72 hr. crystallised as colourless needles, turning yellow on exposure to light, m. p. 181—182° (decomp.), [α] −74° (*c* 1·8) (Found: C, 53·2; H, 6·9; Br, 37·0. $C_{30}H_{47}OBr_3$ requires C, 54·3; H, 7·1; Br, 36·1%), light absorption: $\lambda_{max.}$ 271 mμ (ε 12,000 in hexane).

2-*Bromoeucalan*-3-*one*.—Eucalanone (434 mg.) in acetic acid (30 c.c.) was mixed with a solution of bromine in acetic acid (1M; 1·1 c.c.) at room temperature. Next day the solution was diluted and the product was crystallised from chloroform–methanol giving 2-*bromoeucalan*-3-*one* (337 mg.) as plates, m. p. 191°, [α] +47° (*c* 1·9) (Found: Br, 16·3. $C_{30}H_{51}OBr$ requires Br, 15·8%).

Eucal-1-*en*-3-*one*.—2-Bromoeucalanone (750 mg.) in collidine (5 c.c.) was heated under reflux for 4 hr. The solution was then diluted and the product collected in light petroleum. Chromatography over alumina afforded, in the benzene–light petroleum (1 : 1) fraction, *eucal*-1-*en*-3-*one* which crystallised from methanol in plates, m. p. 147—148° (Found: C, 84·5; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%), light absorption: $\lambda_{max.}$ 229 mμ (ε, 9,400). The *dinitrophenylhydrazone* separated from chloroform–methanol as bright red plates, m. p. 255—257° (Found: C, 70·9; H, 8·8; N, 9·7. $C_{36}H_{54}O_4N_4$ requires C, 71·2; H, 9·0; N, 9·2%), light absorption: $\lambda_{max.}$ 260, 385 mμ (ε, 15,800, 28,300).

24-*Demethyl*cyclo*eucalanyl Benzoate*.—A mixture of demethyloxo*cyclo*eucalanyl acetate (4·9 g.) and anhydrous hydrazine (20 c.c.) in dry ethylene glycol (150 c.c.), containing sodium (3·2 g.), was heated under reflux for 14 hr. Worked up in the usual way, demethyl*cyclo*eucalanol was obtained in 87% yield. The *benzoate* crystallised from ethyl acetate–methanol as plates, m. p. 121—122°, [α] +91° (*c* 2·4) (Found: C, 83·2; H, 10·3. $C_{36}H_{54}O_2$ requires C, 83·3; H, 10·5%).

24-*Demethyleucal*-9(11)-*enyl Benzoate*.—A solution of the above benzoate (4·5 g.) in chloroform (350 c.c.) was treated with a stream of dry hydrogen chloride for 4 hr. The product crystallised from methanol as plates, m. p. 144—150°. This mixture (3·5 g.) in acetic acid (250 c.c.) was oxidised with chromic oxide (1·5 g. in 100 c.c. acetic acid) for 20 min. at 90°. The crude product, isolated in the usual way, was absorbed from light petroleum by alumina (200 g.). Elution of the column by light petroleum–benzene (9 : 1; 1 l. and 4 : 1; 2½ l.) afforded a fraction which crystallised from chloroform–methanol, giving 24-*demethyleucal*-9(11)-*enyl benzoate* (650 mg.) as needles, m. p. 186—187°, [α] +104° (*c* 0·9) (Found: C, 83·3; H, 10·5. $C_{36}H_{54}O_2$ requires C, 83·3; H, 10·5%). The acetate [1] had [α] +83° (*c* 0·6).

24-*Demethyl*-7 : 11-*dioxoeucal*-8-*enyl Benzoate*.—Further elution of the above chromatogram with light petroleum–benzene (7 : 3) afforded, after crystallisation from chloroform–methanol, 24-*demethyl*-7 : 11-*dioxoeucal*-8-*enyl benzoate* (370 mg.) as blades, m. p. 141—143°, [α] +125° (*c* 0·59) (Found: C, 79·2; H, 9·2. $C_{36}H_{50}O_4$ requires C, 79·1; H, 9·2%).

24-*Demethyl*-12-*oxoeucal*-9(11)-*enyl Benzoate*.—From the same column benzene eluted 24-*demethyl*-12-*oxoeucal*-9(11)-*enyl benzoate* (450 mg.), which crystallised from methanol as needles, m. p. 223—224°, [α] +128° (*c* 2·8) (Found: C, 80·9; H, 9·7. $C_{36}H_{52}O_3$ requires C, 81·1; H, 9·8%).

24-*Demethyleucalanol*.—24-Demethyleucal-9(11)-enyl benzoate (430 mg.) in acetic acid (70 c.c.) was shaken at 80° for 24 hr. with platinum (from 800 mg. of platinic oxide) in an atmosphere of hydrogen. The product crystallised from methanol and was then hydrolysed to give 24-*demethyleucalanol* (360 mg.) as plates (from chloroform–methanol), m. p. 154—155°, [α] +38° (*c* 0·6) (Found: C, 83·4; H, 12·2. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%).

cyclo*Eucalenyl Hydrogen Phthalate*.—*cyclo*Eucalenol and an equivalent amount of phthalic anhydride were heated at 100° in pyridine for 1 hr. The *product* crystallised from methanol in long, stout needles, m. p. 174°, [α] +80° (*c* 0·64) (Found: C, 79·1; H, 9·3. $C_{38}H_{54}O_4$ requires C, 79·4; H, 9·5%). The equivalent weight was determined by direct titration in aqueous alcoholic solution of the acid against approx. 0·1N-sodium hydroxide. About 500 mg. of acid were used in each titration and the values of five determinations were 572, 573, 576, 575, and 580, giving an average value of 575. The calculated equivalent is 574·8.

24-*Demethyl*cyclo*eucalan*-3-*one*.—24-Demethyl*cyclo*eucalanol [1] (2 g.) was oxidised overnight by a solution of chromic oxide (0·5 g.) in pyridine (20 c.c.). The mixture was worked up in the usual way and the *ketone* (1·8 g.) was obtained from methanol in plates, m. p. 109°, [α] +55° (*c* 2·3) (Found: C, 84·6; H, 11·9. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%). The *oxime* crystallised from aqueous ethanol as felted needles, m. p. 187° (Found: N, 3·2. $C_{29}H_{49}ON$ requires N, 3·3%).

2-*Hydroxymethylene*-24-*demethyl*cyclo*eucalan*-3-*one*.—24-Demethyl*cyclo*eucalan-3-one (2 g.) in ether (50 c.c.) was treated with sodium methoxide (from 1·5 g. of sodium) in methanol (15 c.c.) and ethyl formate (24 c.c.) for 4 days with occasional shaking. The mixture was neutralised with a buffered phosphate solution (pH = 8) and the product was collected in ether. The *hydroxymethylene derivative* (1·7 g.) crystallised in colourless prisms (from chloroform–methanol), m. p. 102°, [α] +94° (*c* 1·07) (Found: C, 81·5; H, 10·7. $C_{30}H_{48}O_2$ requires C, 81·8; H, 11·0%), light absorption: $\lambda_{max.}$, 289 mμ (ε, 7,500).

24-*Demethyl*-3-*oxo*cyclo*eucalane*-2-spiro-2′-(1′ : 3′-*dithian*).—2-Hydroxymethylene-24-demethyl*cyclo*eucalanone (1·3 g.) and trimethylene ditoluene-*p*-thiosulphonate (1·5 g.) in ethanol (40 c.c.) were treated with potassium acetate (4 g.) in ethanol (60 c.c.). The mixture was heated under reflux for 6 hr. and the solvent was then evaporated. The residue was extracted with light petroleum, and the resulting solution was filtered and passed down an alumina column (50 g.). The *dithian* (1·1 g.) was eluted from the column by benzene–light petroleum (1 : 4) and when the solvent was removed formed an amorphous, clear gum, [α] +160° (*c* 1·6) (Found: C, 74·2; H, 9·9. $C_{32}H_{52}OS_2$ requires C, 74·4; H, 10·1%), infrared absorption band at 1702 cm.$^{-1}$.

4-*Methyl*-24-*demethyl*-3-*oxo*cyclo*eucalane*-2-spiro-2′-(1′ : 3′-*dithian*).—The above dithian (1 g.) was heated under reflux in a mixture of benzene (15 c.c.) and a solution of potassium *tert.*-butoxide (from 0·3 g. of potassium) in *tert.*-butyl alcohol (15 c.c.). Excess of methyl iodide (2 c.c.) was added to the hot solution which was heated for a further 1 hr. Water was then added and the benzene layer was separated, and the aqueous layer extracted with ether. The combined extracts were evaporated and the residue was taken up in light petroleum. This solution was then passed down an alumina (50 g.) column from which, by elution with light petroleum–benzene (9 : 1), was obtained the *methylation product* (230 mg.) which crystallised from chloroform–methanol as needles, m. p. 168—170°, [α] +107° (*c* 1·2) (Found: C, 74·6; H, 10·3. $C_{33}H_{54}OS_2$ requires C, 74·7; H, 10·3%), infrared absorption band at 1689 cm.$^{-1}$.

Further elution of the column with light petroleum–benzene (4 : 1) afforded an amorphous fraction (720 mg.) which was identified as starting material by reconversion into demethyl*cyclo*eucalanone by the method used below. The identity was established by m. p., mixed m. p., and the identity of infrared absorption.

cyclo*Artanone*.—The above methylated dithian (120 mg.) in ethanol (10 c.c.) was heated under reflux with Raney nickel (1 g.) for 6 hr. The metal was removed, the solvent evaporated, and the residue treated overnight with a solution of chromic oxide (100 mg.) in pyridine (5 c.c.). The product (69 mg.), obtained in the usual way, crystallised from methanol in long, thin blades, m. p. 109°, [α] +25° (*c* 0·4) (Found: C, 84·2; H, 11·7. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%), the m. p. was not depressed by admixture with authentic *cyclo*artanone, and the infrared absorption of the product and of *cyclo*artanone were indistinguishable.

cyclo*Eucalenyl Chloride*.—*cyclo*Eucalenol (1 g.) in pyridine with phosphorus oxychloride (excess) at the boiling point for 2 hr. gave the *chloride* (0·8 g.) which was readily purified from chloroform–methanol as flattened needles, m. p. 106°, [α] +24° (*c* 0·95) (Found: C, 81·2; H, 11·1. $C_{30}H_{49}Cl$ requires C, 80·9; H, 11·1%).

cyclo*Eucalene*.—(*a*) The above chloride (0·5 g.) in *n*-butanol (50 c.c.) was treated, at the boiling point, with sodium (1 g.) until the metal had dissolved. Water was then added and the alcohol was removed by distillation in steam. The cyclo*eucalene* (0·4 g.) which remained crystallised from chloroform–methanol as needles, m. p. 71—72°, [α] +35° (*c* 0·76) (Found: C, 87·7; H, 12·1. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%). (*b*) A mixture of *cyclo*eucalenone (0·5 g.) and anhydrous hydrazine (2 c.c.) in ethylene glycol (15 c.c.) containing sodium (0·3 g.) was heated under reflux for 12 hr. The cooled solution was diluted and the product collected into ether. The ether was evaporated and the residual hydrocarbon crystallised from chloroform–methanol forming needles, m. p. 70—71° undepressed by the material prepared in (*a*).

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