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# THE ABSOLUTE STEREOSTRUCTURE OF COPAENE[1]

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**Abstract**—Authentic copaene has been isolated from two sources. The cadinane carbon skeleton and the position of the double bond has been confirmed. By a series of steps involving aromatisation of one ring, and by another sequence resulting in the isolation of a cyclobutanone, copaene has been shown to contain a cyclobutane ring. The structure deduced, together with the conversion of copaene to (−)-cadinene dihydrochloride permits the allocation of the absolute stereostructure (VI) to this sesquiterpene.

THE sesquiterpene copaene has been reported as present in a number of oils,[2] and its structure has been under investigation since the early work of Schimmel and Co.[3] However, in by no means all cases was the copaene identified as a crystalline derivative, and, in fact, the number of sources from which the derived copaene has been adequately characterised is severely limited.[4]

When these studies were initiated the following facts had been reported with regards to the structure of copaene. It was known that with hydrogen chloride cadinene dihydrochloride was obtained, but that on hydrogenation only one molecule of hydrogen was taken up to give the saturated (but not necessarily homogeneous) dihydrocopaene.[6] Dehydrogenation gave cadalene.[7] It was presumed, therefore, that copaene was a tricyclic substance in the cadalene series.

Later work,[8] by application of the method of Campbell and Soffer,[9] led to the conclusion that the ethylenic linkage was in the 3,4 position as indicated in the part structure (I). Since no intermediates were isolated, and rearrangements, both during reaction of oxides with Grignard reagents, and during selenium dehydrogenations,

[1] This paper is *Terpenoids*—VII (Part VI: J. J. Dugan, P. de Mayo and A. N. Starrett, *Tetrahedron Letters* 2567 (1964), in the London series, and *Terpenes*—XX (Part XIX: G. Büchi. W. D. MacLeod and J. Padilla O., *J. Amer. Chem. Soc.* in the press.

[2] For an historical background and a fuller description of early work, J. L. Simonsen and D. H. R. Barton, *The Terpenes* Vol III; p. 88 *et seq.* Cambridge Univ. Press (1952).

[3] *Schimmel's Report* April p. 48 (1914).

[4] The substance speculatively termed 'copaene,' isolated by Czech workers[5] (see J. Pliva, M. Horak, V. Herout and F. Sorm: *Die Terpene.* Teil 1: Sesquiterpene. Akademie-Verlag. Berlin. 1960) is, for instance, not this substance as may be judged from the reproduced IR spectrum.

[5] F. Vonasek, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **25**, 919 (1960).

[6] F. W. Semmler and H. Stenzel, *Ber. Dtsch. Chem. Ges.* **47**, 2555 (1914).

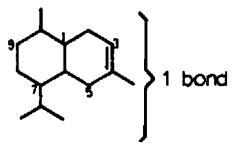
[7] G. G. Henderson, W. M'Nab and J. M. Robertson, *J. Chem. Soc.* 3077 (1926).

[8] L. H. Briggs and W. I. Taylor, *J. Chem. Soc.* 1338 (1947).

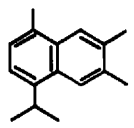
[9] W. P. Campbell and M. D. Soffer, *J. Amer. Chem. Soc.* **64**, 417 (1942).

are known to occur, the isolation[8] of the naphthalene (II) was persuasive rather than compelling evidence for I.

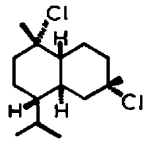
The problem at issue was, therefore, the nature and location of the acid-labile ring. It has been tacitly assumed that this ring was three membered, but in the structures currently accepted (e.g. IV and V)[2,5,8] non-Markownikoff cleavage of this ring in the formation of (—)-cadinene dihydrochloride (III) was implied: a requirement lacking extenuating circumstance.



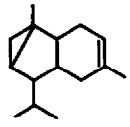

I



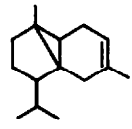
II




III



IV



V

The identification of authentic copaene presented some difficulty since no original specimen appeared available and recorded constants were variable. The only satisfactory method appeared to be the oxidative cleavage, with ozone or potassium permanganate, of the ethylenic linkage in I to give a liquid keto-acid[6,8] which had been characterised[6,8] as a semicarbazone, m.p. 222°, and a methyl ester semicarbazone, m.p. 194–196°. The only oil available to us in which the copaene had been so characterised was that from *Cedrela toona*, Roxb.[10,11]

After fractionation of the oil, to confirm identity of the hydrocarbon, oxidation to the keto-acid was attempted. Because of the comparatively small amounts of copaene available to us the ozonolytic cleavage[6] was attempted. However, although material having the properties of a keto-acid was obtained, the derived semicarbazone, m.p. 180–182° appeared not to be identical with that reported. Further, the NMR spectrum of the crude material indicated the presence of two (acetyl) methyl peaks, at $\tau$8·1 and 7·9, suggesting the presence of *two* ketones. The problem was resolved when it was found that treatment with alkali isomerised the keto-acid to a homogeneous substance showing only one (acetyl) methyl absorption. This substance and its methyl ester gave semicarbazones of the correct m.p.[6,8,10] Presumably under the alkaline conditions of potassium permanganate oxidation[8] or of hydrolysis[6] an epimerisation had occurred before isolation. Such an epimerisation would require an asymmetric centre at $C_2$ or $C_5$, and therefore indicates that one of these centres is a terminus of the missing bond in I. The mildness of the conditions of inversion render such a process adjacent to a carboxylate anion improbable, and so, by default, implicate $C_5$.

[10] P. P. Pillai and B. S. Rao, *J. Soc. Chem. Ind.* **50**, 220T (1931).

[11] We wish to thank Dr. G. B. Pickering (Tropical Products Institute, London, England) for a supply of the oil.

Investigation of the constituents of a chloranthus oil of Chinese origin (*Chloranthus spicatus*?) revealed the presence of humulene,[12] and of another hydrocarbon. The latter was contaminated by $\gamma$-elemene[13] which could be removed by selective oxidation. Comparison of this hydrocarbon with the copaene from *Cedrela toona*, Roxb. revealed their identity.

Since preliminary experiments had suggested a probable structure two approaches, designed to reveal the nature of the remaining structural feature were planned, one for each group. Both were successful, and a preliminary account of these researches has already been reported.[14] The results will now be discussed in terms of the structure elucidated (VI).

The NMR spectrum of copaene and closely related compounds confirmed those structural features represented in I and excluded, incidentally, the possibility of the presence of a cyclopropane ring having a methylene group. Further, whilst showing that the number of methyl groups in I was correct, the presence in these substances of a singlet methyl near $\tau$9·0 requires that $C_{10}$ be a quaternary carbon indicating that it was the remaining terminus of the missing bond in I.

That copaene indeed only contained one ethylenic linkage located in a six-membered ring was shown by its conversion to an optically transparent glycol (VII, R = OH)[15] with osmium tetroxide and then, oxidation of VII, R = OH with chromium trioxide in pyridine to give the ketol (VIII, R = OH). This showed absorption at 1718 and 1408 $cm^{-1}$, indicating the presence of a cyclohexanone, and revealing the presence of a methylene group flanking the carbonyl. In addition, hydroboration of copaene gave an alcohol (VII, R = H) oxidised to copaone (VIII, R = H). This was equilibrated under alkaline conditions to a mixture of copaone and its $C_4$ epimer. These substances showed maximal absorption at 1715 and 1710 $cm^{-1}$ respectively, and under equilibrating conditions incorporated the required three deuterium atoms.

Treatment of the ketol (VIII, R = OH) with refluxing formic acid gave the formate of an optically active phenol; the latter was obtained from it by alkaline hydrolysis. This phenol (IX), characterised as the crystalline 3,5-dinitrobenzoate, showed the appropriate absorption in the UV spectrum ($\lambda_{max}^{cyclohexane}$ 280 m$\mu$, $\varepsilon$ = 2,300). In the NMR spectrum two doublets for the isopropyl group, a further doublet for the methyl group at $C_{10}$ and one aromatic methyl group were evident. Two singlet aromatic protons (at $\tau$3·54 and 3·49) were visible, and their lack of mutual splitting indicated that they were not adjacent. Since aromatisation would involve removal of the hydroxyl group in the ketol (VIII, R = OH), position $C_3$ for this hydroxyl (and so 3,4 for the ethylenic linkage in copaene) is thus indicated.

Since the appearance of our preliminary communication the correctness of IX has been shown by synthesis of the racemate by Professor W. Cocker (Dublin), and we have confirmed identity by a comparison of solution IR spectra.[16]

Cleavage of the diol (VII, R = OH) with periodate gave a ketoaldehyde (X) oxidized with potassium permanganate to the keto-acid (XI, R = H). This keto-acid is that obtained by ozonolytic cleavage of the double bond, as described above.

[12] Private communication from Dr. K. Weinberg, M.I.T.

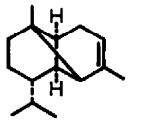
[13] Private communication from Mr. H. Wuest, M.I.T.

[14] G. Büchi, S. H. Feairheller, P. de Mayo and R. E. Williams, *Proc. Chem. Soc.* 214 (1963).

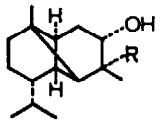
[15] The reagent is shown as having approached from the less hindered side of the molecule.

[16] We wish to thank Professor Cocker for permission to reveal this synthesis in advance of publication.

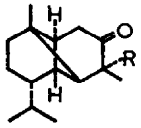
Methylation, followed by oxidation with peroxytrifluoroacetic acid gave the ester acetate (XII, R = OAc, R′ = COOMe). After hydrolysis the hydroxy-acid (XII, R = OH, R′ = COOH) which was not isolated, was directly oxidised with potassium permanganate to the keto-acid (XIII, R = H). These conditions were selected for oxidation to avoid possible lactone formation and because further oxidation of (XIII, R = H) was improbable, enolisation being sterically restricted. The ketone



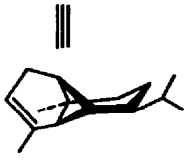
VI

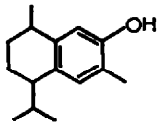


VII



VIII

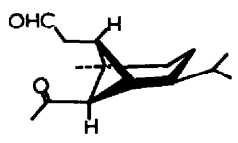




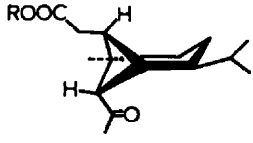
IX

carbonyl in this compound, and in the corresponding methyl ester (XIII, R = Me) absorbed at 1780 and 1775 $cm^{-1}$, as expected for a cyclobutanone, confirming the size of the acid labile ring.

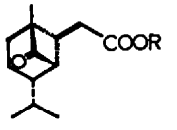
The conversion of copaene to (−)-cadinene dihydrochloride is a process which should not involve the centres at $C_6$ or $C_7$. Consequently the stereochemical relationship of these centres in the dihydrochloride (III) will be that in copaene. In copaene the



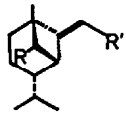
X



XI



XIII



XII

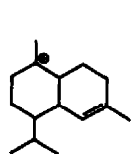
nature of the ring fusion requires that the protons at $C_1$ and $C_6$ be *cis*. Since the absolute stereochemistry of (−)-cadinene dihydrochloride is known[17] to be as in III that of copaene may be written as VI.[18]

[17] V. Sykora, V. Herout and F. Sorm, *Coll. Czech. Chem. Comm.* **23**, 2181 (1958).

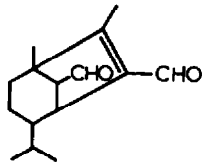
[18] Since the publication of our communication Dr. S. Dev (Poona) has independently arrived at identical conclusions[19] with regards the structure of copaene. We thank Dr. Dev for a copy of his MS prior to publication.

[19] V. H. Kapadia, B. A. Nagasampagi, V. G. Naik and S. Dev, *Tetrahedron Letters* 1933 (1963).

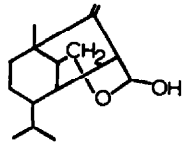
Biogenetic speculations with regards copaene suggest the ion (XIV) as its immediate precursor. This would involve Markownikoff attack on the ethylenic linkage. This ion has previously[20] been proposed as an intermediate in the genesis of helminthosporal[21] (XV)—following non-Markownikoff attack of the ethylenic linkage



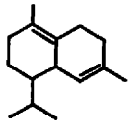
XIV



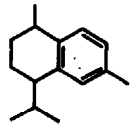

XV




XVI



XVII



XVIII

followed by rearrangement—a conception which has become more plausible with the isolation of prehelminthosporol (XVI),[22] the immediate precursor of helminthosporol.[22,23] The presence of δ-cadinene (XVII)—together with calamenene, XVIII—formed from XIV by simple proton loss, in the oil of *Cedrela toona* provides circumstantial support for this view.

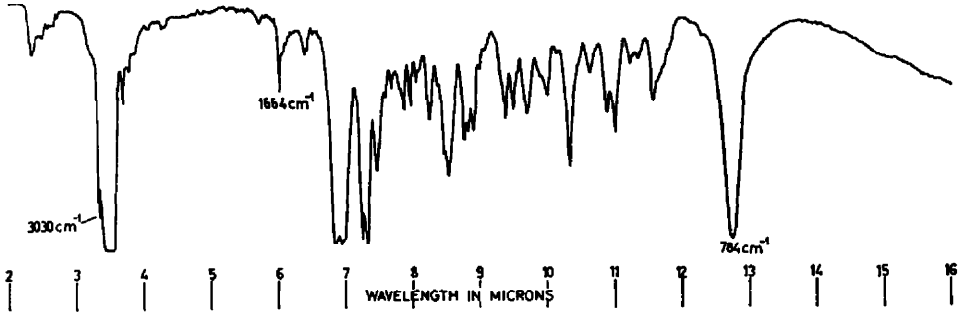



FIG. 1. Infrared spectrum of copaene as a liquid film (0·05 mm).

## EXPERIMENTAL

M.p. were determined on a Kofler block unless otherwise stated, and both m.ps. and b.ps. are uncorrected. Rotations were determined in $CHCl_3$ solution. NMR proton chemical shifts (60 mc) are reported in τ units. Vapour phase chromatographic separations were performed using columns ¾″ × 10′ for preparative work and ¼″ × 10′ for analytical work. Light petroleum refers to the fraction of b.p. 35–60°. Fractional distillations were carried out using spinning band columns.

[20] P. de Mayo, E. Y. Spencer and R. W. White, *Experientia* **18**, 359 (1962).
[21] P. de Mayo, E. Y. Spencer and R. W. White, *Canad. J. Chem.* **41**, 2996 (1963).
[22] R. E. Williams, University of Western Ontario, unpublished observations.
[23] S. Tamura, A. Sakurai, K. Kainuma and M. Takai, *Agr. Biol. Chem.* **27**, 938 (1963).

*Isolation of copaene* (VI), *calamenene* (XVIII) *and δ-cadinene* (XVII) *from* Cedrela toona, *Roxb*[*24]

The oil (54 g) obtained from the steam distillation of the wood was fractionally distilled (36″ column) (Table 1). Fractions 1–5 contained copaene, fractions 2 and 3 being >90% pure copaene. Further purification was effected by VPC on Carbowax 20 M (20% on Chromosorb P, 180°) to give pure copaene, $n_D^{26}$ 1·4884, $[\alpha]_D^{25}$ −6·3° (*c*, 1·20). IR spectrum: Fig. 1. NMR spectrum: 9·21 (3H, singlet); 9·17 (6H, broad doublet, J ~ 6 c/s); 4·85 (1H, broad multiplet). (Found: C, 88·29; H, 11·74. Calc. for $C_{15}H_{24}$: C, 88·16; 11·84%).

Table 1

| Fraction no. | Wt. (g) | Temp (°) | Press. (Torr) |
|---|---|---|---|
| 1 | 0·89 | 76 | 1·5 |
| 2,3 | 4·76 | 76 | 1·5 |
| 4 | 2·36 | 76 | 1·5 |
| 5 | 1·48 | 77–79 | 1·5 |
| 6,7 | 8·68 | 79–93 | 1·2 |
| 8 | 3·24 | 90–94 | 1·1 |
| 9,10,11 | 15·48 | 92–104 | 0·8 |
| Pot residue | 16·86 | | |

Fraction 8 contained two major components which were separated by redistillation (8″ column) and further purified by VPC on Carbowax 20 M (20% on Chromosorb P, 180°).

The first major fraction, $n_D^{25}$ 1·5080, $[\alpha]_D^{27}$ +4·5 (*c*, 1·30) was identified as *δ*-cadinene by its IR spectrum, by its conversion to (−)-cadinene dihydrochloride, m.p. 117–118° undepressed on admixture with an authentic specimen, $[\alpha]_D$ −38° (*c*, 1·27), and by its NMR spectrum. This included the following signals: 9·21 (3H, doublet, J ~ 6·0 c/s); 9·05 (3H, doublet, J ~ 6·0 c/s); 8·39 (6H, broad singlet); 8·08 (4H, multiplet); 4·67 (1H, broad multiplet).

The second major fraction, $[\alpha]_D^{26}$ −68° (*c*, 0·84), $\lambda_{max}^{MeOH}$ 270, 279 (*ε*, 765, 765), was identified as calamenene by comparison of its IR spectrum with that of an authentic spectrum.[25] The two specimens also had identical retention times on the column indicated. The NMR spectrum included the following signals: 9·29 (3H, doublet, J ~ 6·0 c/s); 9·02 (3H, doublet, J ~ 6·0 c/s); 8·77 (3H, doublet, J ~ 7·2 c/s); 7·76 (3H, singlet); 3·14 (3H, broad multiplet).

*Isolation of copaene* (VI) *and humulene from chloranthus oil.*† A solution of the chloranthus oil (100 g) in n-pentane was applied to a column of alumina (1·3 kg, Merck, acid-washed) and the column eluted with n-pentane until no more material emerged. After evaporation the residue (88 g) was dissolved in n-pentane to make a 30% solution. This was shaken for 48 hr. with an equal volume of a 30% $AgNO_3$aq. The mixture was filtered and the residue washed with n-pentane. The filtrate layers were separated and the aqueous layer washed with n-pentane. The combined pentane solutions were dried ($MgSO_4$) and evaporated (red. press.) to a residue weighing 46 g.

The residue from the filtration and the aqueous filtrate layer were combined and made strongly basic with conc. $NH_4OH$. The solution was then extracted with n-pentane. Removal of the solvent then gave humulene.

10% $KMnO_4$aq was added dropwise to a 10% solution of the humulene-free oil in acetone with stirring at room temp until the colour of the oxidant just persisted. Excess oxidant was removed with $NaHSO_3$aq and the mixture filtered. The residue was washed with n-pentane, and the washing and filtrate extract combined. A pentane solution of the product was filtered through alumina (300 g) and the pentane-eluted material evaporated to give an oil (25 g).

Chromatography of this oil on alumina (1·25 kg, Woelm, neutral, grade I) gave, on elution with n-pentane, an oil (13 g) containing about 75% copaene. Rechromatography gave an oil (10 g) containing about 90% copaene. Further purification was then effected by VPC. The material so obtained was identical in every respect with that obtained from *Cedrela toona*.

*The ozonolysis of copaene.** Copaene (517 mg) was ozonised in acetic acid solution (6 ml) for 45 min at room temp. After decomposition of the ozonide with alkaline peroxide, the product was

[24] Experiments by the London group are indicated by an asterisk.* Those by the Cambridge group are indicated by a dagger.†

[25] B. S. Tyagi, B. B. Ghatge and S. C. Bhattacharyya, *Tetrahedron* **19**, 1189 (1963). We wish to express our thanks to Dr. Bhattacharyya for providing us with an authentic sample.

allowed to stand at room temp for 1 hr in this solution. After extraction into ether the acidic material was isolated with $Na_2CO_3$aq. Acidification of the aqueous phase and isolation with ether gave the crude keto-acid (356 mg). This showed NMR signals at $\tau$8·1 and 7·9 indicating the presence of two acetyl groups.

Methylation (diazomethane) gave a methyl ester which, by TLC on silica gel, was shown to consist of two components. The main product copaene keto-ester (see below) had $[\alpha]_D$ +25° (*c*, 2·57).

The crude keto-acid (64 mg) with excess semicarbazide hydrochloride in pyridine at room temp overnight gave a semicarbazone which on crystallisation from MeOH had m.p. 180–182° (evacuated capillary). (Found: C, 62·26; H, 8·93; N, 13·31. Calc. for $C_{16}H_{27}O_3N_3$: C, 62·11; H, 8·80; N, 13·58%).

*Epimerisation of keto-acid* (XI, R = H). The crude keto-acid (79 mg) and KOH (30 mg) were dissolved in water (0·6 ml) and allowed to stand overnight at room temp. After acidification the product was isolated with ether. The material so obtained only showed the NMR signal at $\tau$8·07 indicating the presence of only one of the two acetyl groups present in the crude keto-acid.

The epimerised keto-acid (79 mg) with excess semicarbazide hydrochloride in pyridine at room temp overnight gave a semicarbazone which, on crystallisation from MeOH, had m.p. 220–221° (evacuated capillary) [reported m.p. 222°[8]]. (Found: N, 13·63, Calc. for $C_{16}H_{27}O_3N_3$: N, 13·58%).

Methylation of the isomerised acid (57 mg; diazomethane) and conversion to the semicarbazone gave, from MeOH, material of m.p. 195–196° (evacuated capillary) [reported m.p. 194–196°[8]]. (Found: N, 11·69, 12·07. Calc. for $C_{17}H_{29}O_3N_3 \cdot CH_3OH$: N, 11·82%).

*Conversion of copaene to (−)-cadinene dihydrochloride* (III).*† A solution of copaene (68 mg) in ether (3 ml) was saturated with dry HCl gas (Matheson, purified) for 45 min at 0°. The container was stoppered and let stand overnight at 4°. The ether was evaporated (red. press.) and the semi-crystalline residue was recrystallised from light petroleum to yield cadinene dihydrochloride (40 mg) m.p. and mixed m.p. 114–117°, $[\alpha]_D^{20}$ −37° (*c*, 1·0).

*Copaenediol* (VII, R = OH).*† Copaene (790 mg) was dissolved in a dioxane (10 ml)—pyridine (0·5 ml) solution. Osmium tetroxide (1 g, Engelhard) was added and the mixture was let stand at room temp for 22 days. After addition of 95% EtOH (5 ml), the solution was purged with $H_2S$ gas (Matheson) for 3½ hr. The osmium sulphide was filtered off and washed with ether. The combined filtrate and ether washings were evaporated to give an oily residue which was chromatographed on alumina (Woelm, neutral, Grade III). Elution with ether gave the diol (420 mg) m.p. 73–74°, $[\alpha]_D^{22}$ +0·58° (*c*, 2·08), +0·31° (*c*, 9·60). (Found: C, 75·80; H, 10·86. Calc. for $C_{15}H_{26}O_2$: C, 75·58; H, 11·00%). IR spectrum: $\nu_{max}^{CCl_4}$ 3610, 3540, 1080, 1057 cm$^{-1}$. The compound showed signals in the NMR spectrum at 9·11 (6H, doublet, J ~ 7·8 c/s), 9·05 (3H, singlet), 8·78 (3H, singlet).

*Copaene ketol* (VIII, R = OH).* Copaene diol (354 mg) was oxidised with $CrO_3$ (370 mg) in pyridine (5·5 ml) at 0° for 1 hr. It was then allowed to warm to room temp and poured into cold dil. $NaHSO_3$aq. After isolation with ether and washing, the crude product was chromatographed on alumina (8 g, Woelm, neutral, Grade III). Elution with benzene–ether (3:1) gave the ketol (121 mg), m.p. (from light petroleum) 71–72°, $[\alpha]_D^{21}$ +28° (*c*, 1·39). (Found: C, 76·57; H, 10·44. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24%). The compound showed $\nu_{max}^{CCl_4}$ 3575, 1718, 1408 cm$^{-1}$. NMR spectrum: 9·15 (3H, singlet); 9·11 (6H, doublet, J ~ 6·6 c/s); 8·75 (3H, singlet); 7·47 (2H, doublet, J ~ 3 c/s).

*The aromatisation of copaene ketol.** Copaene ketol (46 mg) was heated under reflux under $N_2$ for 16 hr in 97% formic acid (2 ml, Eastman). The formic acid was pumped off (red. press.). MeOH (2 ml) and 5% $Na_2CO_3$ aq (0·25 ml) were added and the solution refluxed under $N_2$ for ½ hr. After acidification with dilute HCl, the solution was extracted with ether. The combined ether extracts were washed with water until neutral and evaporated to give the crude phenol (37 mg). This was further purified by TLC on silica gel to give the phenol (IX), $[\alpha]_D^{24}$ −50° (*c*, 2·21), $\lambda_{max}^{cyclohexane}$ 280 m$\mu$ ($\varepsilon$, 2,300), $\nu_{max}^{CCl_4}$ 3610, 1765, 1625, 1500, 880 cm$^{-1}$. NMR spectrum: 9·29 (3H, doublet, J ~ 6·0 c/s); 9·01 (3H, doublet, J ~ 6·0 c/s); 8·80 (3H, doublet, J ~ 11·4 c/s); 7·84 (3H, singlet); 3.54 (1H, singlet); 3.19 (1H, singlet).

The compound was characterised as the crystalline 3,5-dinitrobenzoate, m.p. 124–125·5° (evacuated capillary), $[\alpha]_D^{25}$ −23° (*c*, 0·43). (Found: C, 63·90; H, 6·02; N, 7·00. Calc. for $C_{22}H_{24}O_6N_2$: C, 64·06; H, 5·87; N, 6·79%). This material had the same solution IR spectrum as a synthetic specimen prepared by Professor W. Cocker (Dublin).[16] NMR spectrum: 9·18 (3H, doublet, J ~ 6·6

c/s); 8·94 (3H, doublet, J ~ 6·6 c/s); 8·74 (3H, doublet, J ~ 5·4 c/s); 7·82 (3H, singlet); 3·05 (1H, singlet); 2·82 (1H, singlet); 0·68 (3H, apparent singlet).

*The cleavage of copaene diol.*† A solution of $NaIO_4 3H_2O$ (3·05 g) in water (125 ml) was added to a solution of copaene diol (2·35 g) in EtOH (150 ml). The resulting solution was stirred at room temp for 1 hr, water (250 ml) was added, and then extracted thoroughly with ether. The combined extracts were dried ($MgSO_4$) and evaporated (red. press.) to a colourless oil (2·05 g) which on distillation (short path, bath temp 80–85°, 1 Torr) yielded copaene keto-aldehyde (X; 1·95 g), $[\alpha]_D^{27}$ +4·2° (*c*, 4·5). IR spectrum: $\nu_{max}$ (liquid film) 2710, 1715, 1700, 1390, 1360 (shoulder), 1335 $cm^{-1}$.

A solution of $KMnO_4$ (0·95 g) in acetone (50 ml) was added dropwise to a stirred solution of copaene keto-aldehyde (X; 1·95 g) in acetone (125 ml) in which anhy. $MgSO_4$ (0·35 g) was suspended. The resulting mixture was filtered and the filtrate evaporated (red. press.) to a dark brown oil (2·00 g) which was dissolved in ether (50 ml), washed with a dil. $NaHSO_3$aq, dried ($MgSO_4$) and evaporated (red. press.) to give the crude copaene keto-acid (XI; R = H). IR spectrum: $\nu_{max}^{CCl_4}$ 3400–2400 (broad), 1705 (s), 1415, 1385, 1370, 1360 $cm^{-1}$.

The crude keto-acid (1·53 g) was methylated (diazomethane) to give, after chromatography on alumina (200 g, Woelm, neutral, grade III) and distillation (short path, bath temp 96–98°, 1 Torr) copaene keto-ester (XI; R = Me; 1·23 g), $[\alpha]_D$ +27° (*c*, 6·2) (lit. +27°[6]). This material is the keto-ester described above. (Found: C, 71·84; H, 9·59. Calc. for $C_{16}H_{26}O_3$: C, 72·14; H, 9·84%).

*Peroxyacid oxidation of the keto-ester* (XI, R = Me).† Copaene keto-ester (1·23 g) was treated with trifluoroperacetic acid, from trifluoroacetic anhydride (1·63 ml) and 90% $H_2O_2$ (0·27 ml), in dichloromethane (90 ml) in which $Na_2HPO_4$ (3·32 g) was suspended.[26] After refluxing 6 hr, the mixture was washed with a dil. $NaHCO_3$aq, dried ($MgSO_4$) and evaporated (red. press.) to a pale yellow oil (1·38 g). Chromatography on alumina (150 g, Woelm, neutral, Grade II) and distillation (short path, bath temp 90–95°, 1 Torr) yielded the pure diester (XII; R = OAc, R' = COOMl; 0·44 g), $[\alpha]_D^{26}$ +31° (*c*, 7·0). IR spectrum: $\nu_{max}$ (liquid film) 1740, 1370, 1240 $cm^{-1}$. NMR spectrum: 9·19 (3H, singlet); 9·12 (6H, doublet, J ~ 7·0 c/s); 8·24 (5H, many lines); 7·91 (3H, singlet); 7·20–8·05 (3H, many lines); 6·33 (3H, singlet); 5·72 (1H, doublet, J ~ 5 c/s). (Found: C, 67·72; H, 9·37. Calc. for $C_{16}H_{26}O_4$: C, 68·05; H, 9·28%).

*Preparation of the keto-ester* (XIII, R = Me).† The diester (XII, R = OAc, R' = COOMe; 0·32 g) was hydrolysed in methanolic NaOHaq at room temp for 24 hr. The MeOH was removed (red. press.) and the residue treated with $KMnO_4$ aq until the purple colour just persisted. The mixture was acidified with dil. $H_2SO_4$ and $NaHSO_3$ was added until a clear colourless solution was obtained. The solution was saturated with $Na_2SO_4$ and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated (red. press.) to yield the crude keto-acid (XIII, R = H; 0·23 g). IR spectrum: $\nu_{max}$ (liquid film) 3750–2450, 1780, 1720, 1395, 1380 $cm^{-1}$.

The crude keto-acid (0·23 g) was methylated (diazomethane) to yield, after chromatography on alumina (25 g, Woelm, neutral, grade II) and distillation (short path, bath temp 90–95°, 1 Torr), the pure keto-ester (XIII, R = Me; 0·17 g), $[\alpha]_D^{27}$ +41° (*c*, 4·9). IR spectrum: $\nu_{max}$ (liquid film) 1775, 1740, 1380 (shoulder), 1375, 1205, 1175 $cm^{-1}$. NMR spectrum: 9·10 (3H, singlet): 9·05 (6H, doublet, J ~ 6·0 c/s); 7·80–8·70 (6H, many lines); 7·69 (2H, doublet, J ~ 5·0 c/s); 7·44 (1H, triplet, J ~ 5·0 c/s); 7·24 (1H, singlet); 6·31 (3H, singlet). (Found: 70·21; H, 9·29. Calc. for $C_{14}H_{22}O_3$: C, 70·55; H, 9·31%).

*Copaol* (VII, R = H).† A solution of copaene (0·50 g) in dry tetrahydrofuran (6 ml) was treated with diborane and the intermediate borane oxidised with basic $H_2O_2$ according to the procedure of Brown.[27] The crude product was chromatographed on alumina (20 g, Woelm, neutral, grade III) and yielded a crystalline solid (0·46 g) which was recrystallised from hexane and sublimed (bath temp 60°, 1 Torr) to give the pure alcohol (VII, R = H) m.p. 84–85°, $[\alpha]_D^{25}$ +32° (*c*, 4·76), $\nu_{max}^{CHCl_3}$ 3590 (sharp), 3415 (broad), 1385, 1375, 1370 and 1040 $cm^{-1}$. NMR spectrum: 9·12 (6H, broad doublet, J ~ 7·0 c/s); 9·07 (3H, singlet); 8·88 (3H, doublet, J ~ 7 c/s), 8·75–7·80 (11H, many lines); 7·53 (1H, multiplet); 6·77 (1H, broad singlet); 5·99 (1H, doublet of triplets, J ~ 9·0 and 6·5 c/s). (Found: C, 80·91; H, 11·82. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79%).

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*Copaone* (VIII, R = H).† A solution of copaol (420 mg) in acetone (10 ml) was oxidised by titration with Jones' reagent.[28] After dilution and isolation of the product with ether a yellow oil was obtained on evaporation of the solvent. Distillation (short path, temp 80–90°, 0·15 Torr) then gave copaone, $[\alpha]_D^{27}$ +2° (*c*, 6·46), $\nu_{max}$ (liquid film) 1715, 1410, 1390, 1375, 1370 $cm^{-1}$. (Found: C, 81·57; H, 10·98. Calc. for $C_{15}H_{24}O$: C, 81·76; H, 10·98%).

*Epicopaone* (VIII, R = H, *epimeric at* $C_4$).† Copaone (310 mg) was refluxed in a solution of MeONa (from ca. 50 mg Na) in MeOH (6·5 ml) for 20 hr under $N_2$. After dilution and isolation with ether followed by evaporation of the solvent an oil (0·27 g) was obtained which was a mixture of copaone and epicopaone (1:3). Epicopaone (170 mg) was isolated by VPC and distilled as an oil, $[\alpha]_D^{26}$ −64° (*c*, 3·75), $\nu_{max}$ (liquid film) 1710, 1405, 1390, 1385, 1370 $cm^{-1}$. (Found: C, 81·87; H, 11·04. Calc. for $C_{15}H_{24}O$: C, 81·76; H, 10·98%). Epicopaone could be converted to the epimeric mixture of copaone and epicopaone (1:3) by reequilibration in the MeONa solution. Under the same conditions, replacement of the MeOH by MeOD gave trideuterio-copaone and epicopaone, M.W. (mass spectrum) 223.

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