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CUPARENE AND CUPARENIC ACID, TWO SESQUITERPENIC COMPOUNDS WITH A NEW CARBON SKELETON

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Abstract—An aromatic sesquiterpene, cuparene (IV), has been isolated from *Chamaecyparis thyoides*, *Biota orientalis* and *Widdringtonia*. Cuparene gives terephthalic acid on oxidation with dilute nitric acid and (+)-camphonic acid (III) on prolonged treatment with ozone and is therefore 1-(4-methylphenyl)-1:2:2-trimethylcyclopentane. Oxidation of cuparene with chromium trioxide gives the corresponding substituted benzoic acid, cuparenic acid (V). This acid has been found to be identical with one of the sesquiterpene acids ("acid III") previously isolated from *Widdringtonia* species and now also from *Chamaecyparis thyoides*.

EARLIER studies on the heartwood constituents of conifers belonging to the family Cupressaceae have shown the presence of a high boiling, dextrorotatory sesquiterpene fraction, "widdrene II", in the South African *Widdringtonia* species *W. dracomontana*, *W. juniperoides*, *W. Schwarzii* and *W. Whytei*¹ and in the East Asian *Arbor vitae*, *Biota orientalis*.² A similar fraction has now been obtained from the North American *Chamaecyparis thyoides*³ and it contained, according to gas chromatographic results and spectroscopic data, about 60 per cent of an aromatic hydrocarbon. The present investigation was devoted to the isolation and structural elucidation of this aromatic compound.

The low hydrogen consumption of this high boiling fraction on hydrogenation with a palladium catalyst indicated that the ethylenic linkages present are not in the aromatic component. The non-aromatic unsaturated components can be removed after treatment with ozone at low temperature. The remaining hydrocarbon, which according to gas chromatographic examination and sorption analysis is a pure compound, has the composition C₁₅H₂₂. The same compound was isolated, by the same procedure from *Biota orientalis* and from a mixture of sesquiterpene fractions from the *Widdringtonia* species mentioned. (mainly from *W. juniperoides* and *W. Whytei*).

The ultra-violet and infra-red (Fig. 1) absorption spectra of the compound showed the presence of a *para*-disubstituted benzene nucleus. The mass spectrum, kindly determined by R. Ryhage, Stockholm, confirmed the molecular weight (202) and showed peaks corresponding to a benzyl fragment and to fragments formed by successive removal of 1, 3, 4, 5 . . . carbon atoms from the parent molecule.

The presence of a *para*-disubstituted benzene nucleus was confirmed by the isolation of terephthalic acid on oxidation of the compound with dilute nitric acid.

* Part XX. *Acta Chem. Scand.* **12**, 267 (1958).

¹ H. Erdtman and B. R. Thomas, *Acta Chem. Scand.* **12**, 267 (1958).

² H. Erdtman and Z. Polchowicz, *Chem. Ber.* **89**, 341 (1956).

³ C. Enzell. To be published.

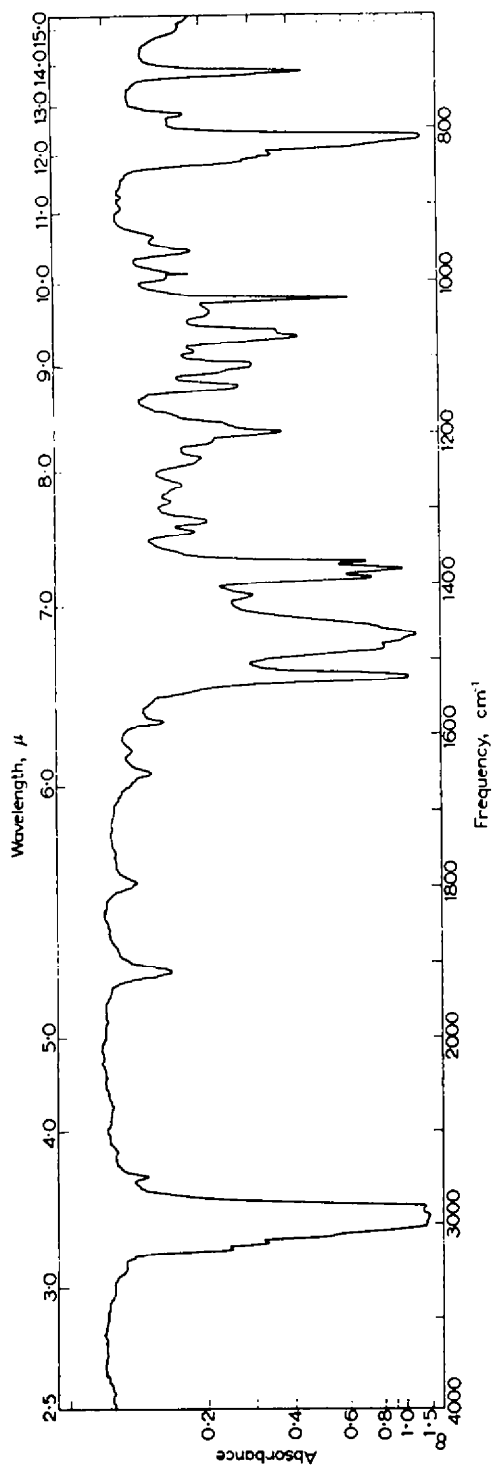
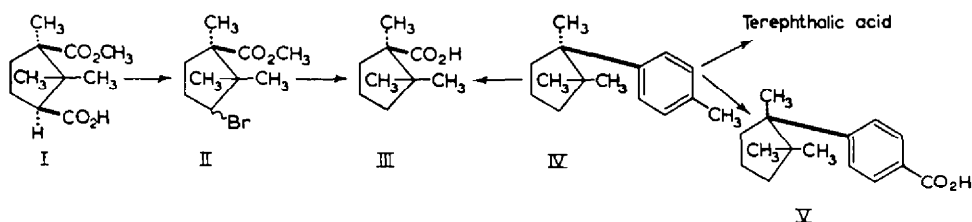


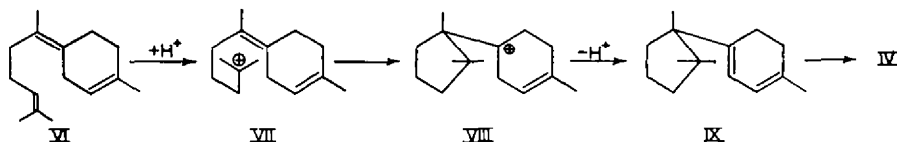
FIG. 1. Infra-red spectrum of cuparenc.

Since the hydrocarbon has the composition $C_{15}H_{22}$ and does not react with ozone or hydrogen under the above conditions it must be bicyclic in agreement with the high density. Prolonged ozonisation at room temperature followed by oxidation with alkaline hydrogen peroxide furnishes an acid with the properties of (+)-camphononic acid⁴ (III) and an infra-red spectrum identical with that of (\pm)-camphononic acid. The racemic acid⁵ was kindly supplied by Dr. H. L. Lochte, Austin, Texas. (+)-Camphononic acid has been obtained from (+)-camphononic acid⁴ but is more conveniently prepared by a Hunsdiecker degradation of the β -monomethyl ester of (+)-camphoric acid (I) followed by reductive removal of the bromine atom and saponification of the ester. The identity of the degradation product with the synthetic specimen was established by mixed melting point, infra-red spectra and optical rotations. These degradation products account for all the carbon atoms present in the molecule and the hydrocarbon must therefore be 1-(4-methylphenyl)-1:2:2-trimethylcyclopentane. The absolute configuration at C_1 is the same as that at the corresponding atom in (+)-camphor.⁶ The name cuparene is proposed for this new sesquiterpene hydrocarbon, since it is aromatic and apparently occurs widely in the Cupressaceae.



In the communication on the *Widdringtonia* genus Erdtman and Thomas¹ reported the presence of a *para*-substituted benzoic acid, "acid III". This acid has now also been found in *Chamaecyparis thuyoides*³ and it appears highly probable that it is related to cuparene. Oxidation of cuparene with chromium trioxide in acetic acid gives an acid, which is shown to be identical with "acid III", by mixed melting point, infra-red spectra (Fig. 2) and optical rotations. The name cuparenic acid is now proposed for this compound (V).

The novel type of sesquiterpene carbon skeleton found in cuparene and cuparenic acid obeys the farnesol rule and may have a biogenetic relationship to γ -bisabolene (VI) as indicated in formulae VI-IX. (Compare also ref. 7)



The only aromatic sesquiterpene hydrocarbons previously reported are the α -curcumenes, which occur in *Curcuma aromatica* together with their dihydroderivatives, the β -curcumenes.⁸ Dihydrocuparenes, *e.g.* (IX) might similarly be expected to occur

⁴ H. Appel, *Z. physiol. Chem.* **218**, 202 (1933).

⁵ K. Hancock and H. L. Lochte, *J. Amer. Chem. Soc.* **61**, 2448 (1939).

⁶ W. Klyne, *Progress in Stereochemistry* Vol. 1, p. 189. Butterworths Scientific Publications, London (1954).

⁷ L. Ruzicka, *Experientia* **9**, 357 (1953).

⁸ J. Simonsen and D. H. R. Barton, *The Terpenes* (2nd Ed.) Vol. III, p. 18. Cambridge (1951); J. Simonsen and W. C. J. Ross, *The Terpenes* Vol. V, p. 514. Cambridge (1957).

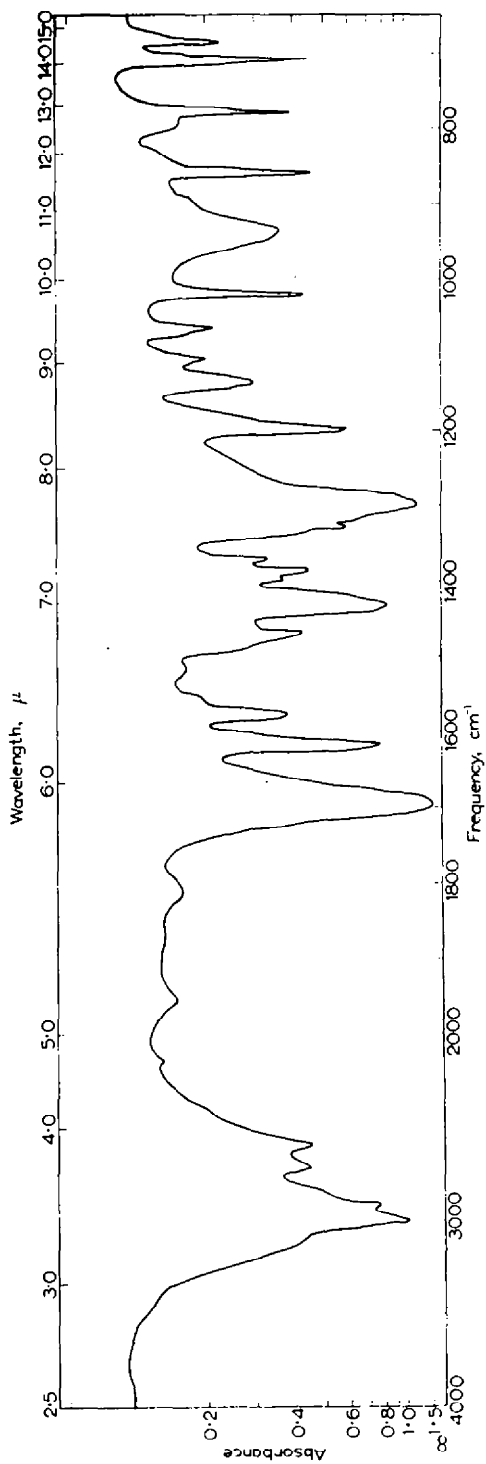


FIG. 2. Infra-red spectrum of cuparenic acid.

associated with cuparene, but attempts to isolate cuparene from the selenium dehydrogenation products of the lower boiling sesquiterpene fractions of *Chamaecyparis thuyoides* and *Biota orientalis* failed, although cuparene is stable under the conditions employed.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage, unless otherwise stated. The infra-red spectra were recorded on a Perkin-Elmer No. 21 instrument (NaCl-prism; solids, KBr-disks; liquids, pure oils in 0.025 mm NaCl-cell). The ultra-violet spectra were measured in absolute ethanol on a Beckman DU spectrophotometer. Light petroleum refers to a fraction b.p. 35–60°. Microanalyses by Dr. A. Bernhardt, Mülheim.

*Isolation of the fractions containing cuparene from the neutral oil of Chamaecyparis thuyoides.*³ The main part (85%) of the neutral oil (3.5% air dry wood basis) from the heart-wood extract of *Chamaecyparis thuyoides*, after a quick preliminary distillation, was fractionally distilled through a vacuum jacketed, packed column. Pressure 50 mm; back pressure 10 mm; reflux ratio 30 : 1. In the section of the distillation data given, temperatures were taken at the end of each fraction and the rotations were measured in chloroform.

Fraction *a*, b.p. 170°, 23.8 g, $[\alpha]_D +12^\circ$, n_D^{25} 1.5098; *b*, 171°, 6.4 g, $+41^\circ$, 1.5121; *c*, 171°, 5.1 g, $+53^\circ$, 1.5135; *d*, 173°, 11.0 g, $+51^\circ$, 1.5142; *e*, 183°, 4.9 g, $+53^\circ$, 1.5126.

Investigation of fraction d. This showed two strong aromatic bands (1518 and 813 cm^{-1}) in the infra-red and two absorption maxima (265, 272 $\text{m}\mu$) in the ultra-violet. A comparison with the similar spectra of *p*-tert.-butyltoluene indicated the presence of approximately 60 per cent aromatic material.

Gas chromatographic examination of fraction *d* was made with a Perkin-Elmer vapour fractometer model 154 B. (Two metre column; 2:4-dinitrophenyl-2-naphthyl ether (20%) on celite⁹; column temp. 162°; flow rate 50 ml/min of helium; charge 5 μ l). Two peaks were found with elution times 19 and 27 min. The area of the latter was about 60 per cent of the total.

Fraction *d* (1.23 g) was hydrogenated in ethanol solution (20 ml) in the presence of a palladium on charcoal catalyst (10%, 70 mg) at room temperature and atmospheric pressure. Hydrogenation ceased after 54 ml (0.37 mole, calculated for $\text{C}_{15}\text{H}_{24}$) of hydrogen had been absorbed in 10 hr.

Isolation of cuparene from Chamaecyparis thuyoides. Fraction *d* (1.3 g) dissolved in methylene chloride (12 ml) was ozonised at -70° until excess ozone was present. The solvent was evaporated under reduced pressure and the product refluxed with hydrogen peroxide (30%, 2 ml) and aqueous potassium hydroxide (10%, 10 ml) for 30 min. The mixture was steam distilled and the ether extract of the distillate dried (Na_2SO_4) and concentrated. The residue was dissolved in light petroleum and filtered through alumina (100 g). Distillation of the concentrated eluate gave pure cuparene (0.7 g), b.p. 138°/19 mm, d_{21}^{25} 0.9374, n_D^{25} 1.5202, $[\alpha]_D +65.3^\circ$ (pure oil), $+65^\circ$ (CHCl_3 , *c*, 5.9), $[R_L]_D$ found: 65.9, calculated 65.7 (Found: C, 89.1; H, 11.2. $\text{C}_{15}\text{H}_{22}$ requires C, 89.0; H, 11.0%).

The higher boiling fraction (2.4 g) of fraction *a* and fractions *b*–*e* were all treated

⁹ A. B. Groth, *Svensk Papperstidn.* 61, 311 (1958).

in the same way. The amount of cuparene obtained was 13 g or 0.14 per cent of the air-dry wood.

Isolation of cuparene from the sesquiterpene fractions of Biota orientalis and Widdringtonia oils. A sesquiterpene fraction (b.p. 123°/10 mm, 9 g) had previously been obtained in this laboratory from the heartwood of *Biota orientalis*.¹ This, after purification as described, gave cuparene (3.5 g or 0.1% of the air-dried wood), identified by its infra-red spectrum and physical constants.

Fractional distillation of an available sesquiterpene fraction (120 g) from the heartwoods of several *Widdringtonia* species² (mainly *W. juniperoides* and *W. whytei*) gave a high boiling fraction. (b.p. 138–141°/18 mm, 10 g) This, after purification as above, gave cuparene (4 g), identified by its infra-red spectrum and physical constants. An approximate calculation on the basis of the data given for the "widdrene II"-fractions in the communication on the *Widdringtonia* genus³ gave the following percentages (air-dried wood basis) of cuparene in the different species: *W. dracomontana* (present), *W. juniperoides* (0.5%), *W. Schwarzii* (0.1%), *W. Whytei* (0.1%).

Sorption analysis of cuparene (Blohm¹⁰) gave the following results. Sample n_D^{25} 1.5199. Fractions as removed from the silica gel column: (1) n_D^{25} 1.5202, (2) n_D^{25} 1.5202, (3) n_D^{25} 1.5202, (4) n_D^{25} 1.5202, (5) n_D^{25} 1.5199, (6) n_D^{25} 1.5142.

Gas chromatographic examination of cuparene under the same conditions as before showed only one peak (elution time 27 min).

The ultra-violet absorption spectrum of cuparene, λ_{\max} 259 m μ (ϵ 260), 265 m μ (ϵ 360), 273 m μ (ϵ 350), cf. *p*-tert.-butyltoluene, λ_{\max} 259 m μ (ϵ 270), 264 m μ (ϵ 360), 272 m μ (ϵ 330).

The mass spectrum was recorded on an instrument with an all-glass, heated inlet system.¹¹ Major peaks at $m/e = 203$ (5), 202 (20), 187 (4), 159 (6), 146 (8), 145 (30), 133 (14, bt), 132 (100), 131 (44), 130 (6), 129 (10), 128 (10), 120 (10), 119 (25), 117 (22, bt), 116 (7), 115 (16, bt), 105 (20, bt), 92 (5), 91 (20, bt), 83 (5), 77 (8, bt), 69 (6, cp), 65 (7, bt), 53 (4), 41 (4, bt, cp), 39 (9, bt, cp), 27 (4, bt) and 25 (4).

The figures in brackets give peak intensity as a percentage of the strongest peak (132) and show peaks in common with *p*-tert.-butyltoluene (bt) and 1:2:2-trimethylcyclopentane (cp).¹² The peak (69) appears to be due to the five membered ring in cuparene.

Nitric acid oxidation of cuparene. Cuparene (0.5 g) and dilute nitric acid (30%, 4 ml) were heated overnight in a sealed tube at 170°. The white crystalline material (0.3 g) obtained, was collected by filtration, washed and treated with an ethereal solution of diazomethane to give the dimethyl ester of terephthalic acid, m.p. and mixed m.p. 141–142°.

Ozonolysis of cuparene. Ozone was passed through a solution of cuparene (0.9 g) in methanol (20 ml) for 24 hr at room temperature. Most of the methanol was removed by evaporation and the residue was refluxed with a mixture of aqueous sodium hydroxide (5%, 5 ml) and hydrogen peroxide (30%, 1 ml) for 1 hr, cooled and extracted with ether. The alkaline solution was acidified with dilute sulphuric acid and extracted with ether. The ether solution was dried (Na₂SO₄) and the solvent

¹⁰ S. G. Blohm, *Ark. Kemi* 6, 317 (1953).

¹¹ R. Ryhage, To be published.

¹² *Amer. Petroleum Inst. Res. Proj.* 44, *Nat. Bur. Standards*. Catalog of Mass Spectral Data No. 443 (1949) and No. 194 (1948) resp.

removed yielding crude (+)-camphonanic acid (0.5 g), which after sublimation (80°/2 mm) and successive crystallisations from water, aq. methanol and nitromethane, melted at 191–192° (sealed tube, uncorr.), $[\alpha]_D + 21^\circ$ (CHCl₃, c, 1.3), +17° (benzene, 1.3). (Found: C, 69.2; H, 10.3. C₉H₁₆O₂ requires C, 69.2; H, 10.3%). The toluide melted at 116–117°. These constants agree with those given for (+)-camphoanic acid.⁴ The infra-red spectrum was identical with that of (±)-camphonanic acid.

β-Methyl ester of (+)-camphoric acid. (+)-Camphoric acid (60 g) was esterified with diazomethane and the neutral ester (68 g) obtained was partially saponified to give the *β*-methyl ester¹³ (42 g), m.p. 87–88°.

(+)-Camphonanic acid. *β*-Methyl hydrogen (+)-camphorate (10.7 g) was dissolved in aqueous potassium hydroxide (3.1 g, 150 ml) and a solution of silver nitrate (8.5 g) in water (50 ml) was added with stirring. The silver salt was filtered off, washed successively with water, acetone and ether and dried (80°/mm) over phosphorus pentoxide for 15 hr.

The dry silver salt (13 g) and dry carbon tetrachloride (400 ml) were placed in a three-neck flask, fitted with condenser, dropping funnel and stirrer and half the amount of solvent was distilled off. The mixture was heated under reflux and bromine (7.8 g) dissolved in dry carbon tetrachloride (30 ml) was added over a period of 30 min. The heating was continued for another 30 min and the mixture was then cooled. The silver bromide was removed by filtration and the filtrate was extracted with aqueous sodium carbonate (5%), dried (Na₂SO₄) and concentrated. A quick distillation of the remaining material gave the bromo-ester (b.p. 75–85°/0.2 mm, 5 g), which was not purified further.

Sodium (6 g) was added to a boiling solution of the bromo-ester (3 g) in absolute ethanol (200 ml) over a period of one hour. Most of the ethanol was removed by distillation and the residue, mixed with water (30 ml), was refluxed for 18 hr. The ether-extracted alkaline solution was acidified with dilute sulphuric acid and extracted with ether. The ethereal solution was dried (Na₂SO₄) and concentrated to give a semi solid product, which was dissolved in aqueous ethanol, filtered and allowed to crystallise. Colourless needles (0.4 g) were deposited which on recrystallisation and sublimation gave pure (+)-camphonanic acid, $[\alpha]_D + 21^\circ$ (CHCl₃, c, 1.5), m.p. and mixed m.p. with the degradation product of cuparene 191–192° (sealed tube, uncorr.). The infra-red spectra of the two acids were identical.

Cuparenic acid. Cuparene (0.70 g) was dissolved in acetic acid (20 ml) and a solution of chromium trioxide (2.4 g) in acetic acid (18 ml) was added. The mixture was left at room temperature overnight and was then heated on a water-bath for 1 hr. It was poured into water (600 ml), extracted with ether and the ether extract repeatedly shaken with aqueous sodium hydroxide (10%). The alkaline solution was acidified with dilute sulphuric acid, extracted with ether and the ether extract was dried (Na₂SO₄) and concentrated to give crude cuparenic acid (0.33 g) which was purified by sublimation and crystallisation from light petroleum, m.p. and mixed m.p. with the *Widdringtonia* acid, "acid III", 158–160°, $[\alpha]_D + 63^\circ$ (CHCl₃, c, 2.4). The infra-red spectra of the two acids were identical. (Found: C, 77.8; H, 8.9; equiv. w. 235; C₁₅H₂₀O₂ requires C, 77.5; H, 8.7% equiv. w. 232.)

Cuparene was recovered unchanged in 80% yield after treatment with selenium at

¹³ W. A. Noyes and L. R. Littleton, *J. Amer. Chem. Soc.* 35, 78 (1913).

300° for 60 hr and in 50% yield after treatment with sulphuric acid in acetic acid (1:10) for 24 hr.

Attempts to obtain crystalline nitro-derivatives of cuparene by treatment with nitric acid or a mixture of nitric acid and sulphuric acid failed.

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