ISOPIMARIC ACID[1]

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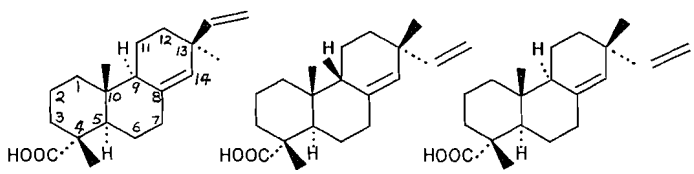
Dedicated to Professor R. B. Sandin on the Occasion of his Sixty-Eighth Birthday

ABSTRACT

Evidence is presented for the epimeric character of the C-13 substituents in pimaric and isopimaric acids and for the nuclear double bond location in isopimaric acid. This work, coupled with recent synthetic work and rotatory dispersion evidence, permits assignment of the structure and stereochemistry IV to isopimaric acid. Hydroboration and selenium dioxide oxidation of the acid are described.

In 1948 Harris and Sanderson suggested structures for two diterpenoid constituents of pine oleoresin, pimaric and isopimaric acids (1). Extensive chemical work (2–6) appeared to confirm their assignments. In combination with arguments based on optical rotation (7) and optical rotatory dispersion (8), this led to general acceptance of the structure and stereochemistry shown in I for pimaric acid and in II for isopimaric acid. Another isomer, sandaracopimaric acid, was assigned configuration III (9). The elegant



I II III

total synthesis by Ireland and Schiess of *dl*-pimaradiene and *dl*-sandaracopimaradiene confirmed the structure of the corresponding acids (10). With reasonable assumptions regarding the steric course of the reactions, supplemented by evidence from ultraviolet absorption spectra and relative adsorption, this work provided strong support for the stereochemistry shown in I and III. Further confirmation of the structure and absolute configuration was given by Milne and Smith, who transformed a steroid degradation product into pimar-8-ene (11).[3] Finally, transformation of testosterone into sandaracopimaradiene by Bose and Harrison (12) and of 3β-hydroxyandrost-5-ene-17-one into the same diene by Fetizon and Golfier (12*a*) established beyond question the configuration at C-13 for all three acids. Thus, pimaric and sandaracopimaric acids are correctly represented in every detail by I and III.

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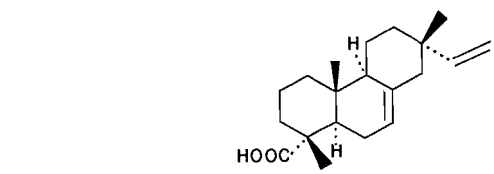
[3]*It seems logical to use the phenanthrene numbering system for the pimaric acids. However, because of the widespread familiarity with the steroid numbering system, most North American groups have applied this to the resin acids. For this reason we also use the latter in this paper.*

The chemistry and optical rotatory dispersion (2, 8) of isopimaric acid seemed perfectly consistent with the structure and stereochemistry denoted by II. However, Church and Ireland synthesized the corresponding pimaradiene (13) and found it to be different from isopimaradiene. This observation proved that the double bond of isopimaric acid was not in the 8,14 position. They pointed out that, since the nuclear vinyl hydrogen signal for isopimaric acid (14) was a broadened doublet, it must be coupled with adjacent hydrogens. Since the double bond migrates easily to the 8,9 position, the most logical location for it, on this and biogenetic grounds, was the 7,8 position. They hence postulated that isopimaric acid had the structure and stereochemistry illustrated in IV. This expression was also consistent with all the previous evidence except that of Harris and Sanderson.

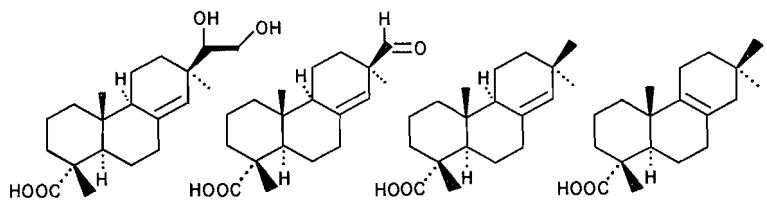
We now amplify our preliminary report on work which interrelated pimaric and isopimaric acids and proved that they are epimeric at C-13 (6), and on the experiments which proved Church and Ireland's structure IV to be correct for the latter (15).

A direct and unequivocal way of interrelating the acids and settling whether or not they were isomeric at C-13 proved to be the conversion of both to the 13,13-dimethyl compounds (6). Pimaric acid reacted with 1 mole of osmium tetroxide in dry ether to give an osmate which was decomposed by alkaline mannitol solution. A diol acid V was obtained in poor yield.[4]

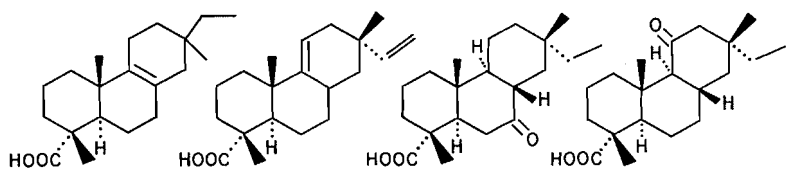
This was cleaved in aqueous dioxane solution by periodic acid to a rather sensitive aldehydo acid VI. Wolff–Kishner reduction of VI (preforming the hydrazone) gave the 13,13-dimethyl acid VII. This could be quantitatively isomerized by hydrogen chloride in chloroform to the Δ^8 acid VIII.



IV



V VI VII VIII



IX X XI XII

[4]*This diol acid does not correspond to either of the acids previously described as arising by permanganate oxidation of pimaric acid (16).*

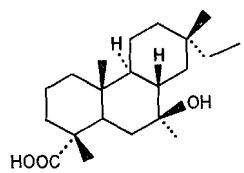
Hydroxylation of isopimaric acid in the same way gave a mixture of sparingly soluble products. Two isomeric diol acids and a triol acid were separated by fractional crystallization. The major diol acid gave an aldehydo acid when treated with periodic acid. Wolff–Kishner reduction of this gave a 13,13-dimethyl acid distinct from the one from pimaric acid. When exposed to dry HCl in $CHCl_3$ this acid was isomerized to the $\Delta^{8,9}$ isomer, which proved identical with VIII derived from pimaric acid. This confirmed the earlier conclusion (2–5) that pimaric and isopimaric acids had identical skeletons and stereochemistry at C-4, C-5, and C-10. Since the $\Delta^{8,9}$ acids (IX) derived from dihydro pimaric and isopimaric acids were different, it followed that the parent acids were epimeric at C-13.

Although structure IV for isopimaric acid seemed the most plausible one on biogenetic grounds, the chemical evidence did not exclude the $\Delta^{9,11}$ isomer X from consideration. We hence sought experiments which would clearly distinguish between these. One possibility was that of converting the acid via the keto acids XI or XII to 1,7,9- or 1,5,7-trimethyl phenanthrene or to the phenols 1,7-dimethyl-9-phenanthrol or 1,7-dimethyl-5-phenanthrol. Hydroboration of the double bond of dihydroisopimaric acid gave a mixture of alcohols[5] which on oxidation with Jones's reagent (17) have one keto acid. Since this was stable to base, the ring fusion at this point was in its most stable configuration. The nuclear magnetic resonance (n.m.r.) spectrum of the keto acid had signals between τ 7.5 and τ 8.2 corresponding to three hydrogens alpha to the ketone carbonyl. This was consistent with either XI or XII. An indication that the carbonyl was at C-7 (XI) was given by the facile formation of a 2,4-dinitrophenylhydrazone. An 11-ketone as in XII should (if the ring fusion were *trans*–anti–*trans*) be inert to the reagent by analogy to the behavior of 11-keto steroids.

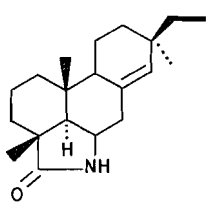
The keto acid was treated with methyl magnesium iodide to give the methyl carbinol (probably configuration XIII if structure XI is correct). This, however, gave only small amounts of phenanthrenes which could not be purified when it or its sodium salt was heated with selenium. Dehydrogenation of the keto acid (XI or XII) did give a phenolic product very similar to 1,7-dimethyl-9-phenanthrol, but identity could not be rigorously established.

The second approach to location of the double bond of isopimaric acid proved more definitive. It had already been shown that photolysis of the azide of dihydropimaric acid gave a mixture of the corresponding isocyanate and the γ-lactam XIV (18). It appeared likely that the same course would be followed with isopimaric acid, and experiment confirmed this expectation. A 9% yield of γ-lactam ($\nu_{max}^{CHCl_3}$ 1 685 cm^{-1}) was produced when the azide was photolyzed in hexane solution. On the basis of structure IV this should be XV, while structure X would give rise to XVI. Only in structure XV is the amide nitrogen allylic to the double bond. Inspection of the geometry of this structure (see XVII) indicated that the 6-hydrogen should be weakly coupled, if at all, to the 7-hydrogen ($\phi \simeq 90°$) and hence should give a fairly clean doublet in the n.m.r. spectrum of the compound. In contrast, the 6-hydrogen in XVI and XVIII should give rise to a complex signal, since it should be coupled with the 5-hydrogen and the two on C-7 (see XVIII). In fact, the 6-hydrogen of the lactam from pimaric acid XVIII gave a very broad and complex signal between τ 5.95 and 6.65. The corresponding signal for the γ-lactam from isopimaric acid was a doublet centered at τ 6.17 (J = 10 c.p.s.). This observation excludes structure XV from consideration and proves that isopimaric acid has the sekeleton shown in IV.

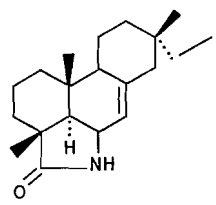
[5]*In most experiments the carboxyl group was partially reduced by the diborane simultaneously with hydroboration of the double bond.*



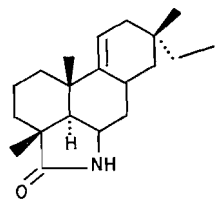
XIII



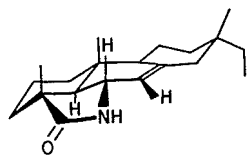
XIV



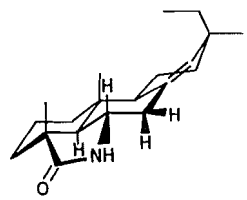
XV



XVI

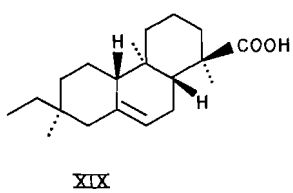


XVII

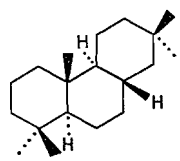


XVIII

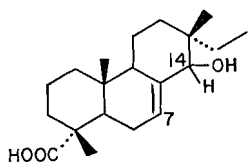
The stereochemistry of isopimaric acid can be deduced on the following grounds. C-13: The configuration at C-13 has been shown above to be epimeric to that of pimaric acid (I) whose stereochemistry is established by the syntheses of Ireland (10), Smith (11), and Bose (12). C-9: If dihydropimaric acid had a 9-α-hydrogen, it is clear from the orientation shown in XIX that its rotatory dispersion curve should be very similar to



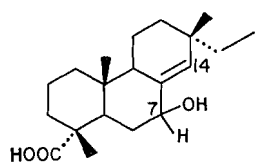
XIX



XX



XXI



XXII

that of cholest-5-ene. The O.R.D. curve for dihydroisopimaric acid is plain and negative (8), almost identical with that of the steroid (19); hence this is the correct stereochemistry.

Proof of this configuration was also provided by Ireland and Newbould (20). They converted pimaradiene to the pentamethyl *trans*–anti–*trans* perhydrophenanthrene XX.

By a similar sequence which left the asymmetry at C-9 untouched, they converted isopimaric acid to the same hydrocarbon, proving that it has a 9-α-hydrogen. Thus, no doubt is left that the structure and absolute stereochemistry of isopimaric acid is that shown in IV.

Ukita's acid, for which a $\Delta^{7,8}$ structure was suggested (2), has since proved to be a mixture of isopimaric and sandaracopimaric acids (21). Our interest in Ukita's report that the dihydro compound derived from this mixture gave a 7-hydroxy-$\Delta^{8,9}$ derivative on oxidation with selenium dioxide led us to examine the reaction of methyl dihydroisopimarate with this reagent. In ethanol at room temperature a very complex mixture of products resulted. These appeared to be mainly dienes ($\lambda\lambda_{max}$ 235, 244, and 253 mμ). However, careful chromatography on alumina enabled isolation of small quantities of two alcohols. These appeared to be allylic, since in each case manganese dioxide oxidized them to α–β unsaturated ketones (λ_{max} 242 mμ). The n.m.r. spectrum of the first, which melted at 84°, contained a vinyl hydrogen signal as a very broad doublet (J = 4 c.p.s.) centered at τ 4.42. This appeared identical with the 7-hydrogen signal of isopimaric acid (14). A second hydrogen resonating at τ 6.44 was a singlet. These observations accord with structure XXI, the second deshielded hydrogen being the one on C-14.

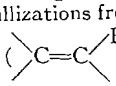
The second alcohol, m.p. 92°, had a n.m.r. signal at τ 4.55 (one hydrogen, half band width 4 c.p.s.). This is consistent with structure XXII.

EXPERIMENTAL

Rotations were of solution in absolute ethanol. Infrared spectra were determined on a Perkin–Elmer model 21 spectrometer and were of Nujol mulls unless otherwise stated. Nuclear magnetic resonance spectra were obtained with Varian HR-60 and A-60 spectrometers, in chloroform or deuterochloroform with tetramethylsilane as internal standard. Melting points were determined on a Kofler hot stage unless otherwise stated.

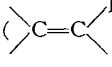
Diol V from Pimaric Acid

Pure pimaric acid (9.17 mg, m.p. 211–214°, $[\alpha]_D$ +79°) was suspended in 5 ml of dry ether. A solution of 876 mg of osmium tetroxide in 5 ml of ether was added followed by 5 ml of ether washings. The mixture was shaken for 10 min to dissolve the pimaric acid. The dark solution was left at 5 °C for 65 h. The black precipitate recovered by filtration weighed 1.53 g. Evaporation of the filtrate gave 450 mg of dark residue. The precipitate was heated on the steam bath for 1 h with a mixture of 1 g of sodium hydroxide and 5 g of mannitol in 15 ml of water. The solution was then cooled, acidified with acetic acid, and the precipitate collected by filtration. The solid was dissolved in chloroform, the solution was washed with water, and the water layer back-extracted with chloroform. The chloroform solution was combined with a chloroform extract of the aqueous filtrate from the reaction, dried, and distilled, giving 842 mg of solid. The ether-soluble osmate, when treated similarly, gave 268 mg of solid acid. These were fractionally crystallized separately from ether, giving in each case unchanged pimaric acid, crude diol, and a small quantity of prisms, m.p. 252–257°, which gave analytic figures between those of a diol and a monohydroxy acid.

The crude diol (m.p. up to 165°) was purified by chromatography on a 20-fold ratio of silica gel, from which the main component was eluted with 50% benzene–ether mixture. After three recrystallizations from ether this had m.p. 160–163°, $[\alpha]_D^{23}$ +3 ± 2° (c, 1.11), ν_{max} 1 681 cm^{-1} (COOH) and 821 cm^{-1} (). Yield was approximately 17%.

Anal. Found: C, 71.56; H, 9.50. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59.

Aldehydo Acid VI

Diol acid V (70 mg) was dissolved in 5 ml of pure dioxane. A solution of 108 mg of paraperiodic acid in 1 ml of water was added, and the solution left at room temperature in the dark for 1 h. The bulk of the solvent was then removed under reduced pressure, water added, and the product extracted into methylene chloride. The organic layer was back-washed with water, dried, and distilled, giving 70 mg of crystalline residue, m.p. 195–204°. After four recrystallizations from ether this melted at 215–217° (evacuated capillary) and had $[\alpha]_D^{23}$ +119° (c, 1.60); ν_{max} 2 700, 1 720 cm^{-1} (—CHO), 1 693 cm^{-1} (COOH), 824 cm^{-1} (). A form melting at 174–177° (evacuated capillary) was obtained once.

Anal. Found: C, 75.09; H, 9.10. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27.

13,13-Dimethyl Acid VII

A solution of 55 mg of the aldehydo acid VI in 2 ml of triethylene glycol containing 0.5 ml of 95% hydrazine was heated on the steam bath for 30 min, then at 140° for 30 min. After cautious addition of 0.64 g of potassium hydroxide the bath temperature was raised slowly to 205° under a slow nitrogen stream, then maintained at this temperature for 3 h. The mixture was cooled, diluted with water, and extracted with methylene chloride. The organic layer was back-washed with dilute alkali. The combined aqueous layers were acidified with sulfuric acid, and extracted with methylene chloride. The 54 mg of acid recovered crystallized spontaneously, m.p. 228–235°. After several recrystallizations from methanol it melted at 232–238° and had $[\alpha]_D^{22}$ +17 ± 2° (*c*, 1.0), ν_{max} 1 692 and 823 cm^{-1}.

Anal. Found: C, 78.41; H, 10.10. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.

Δ^8-13,13-Dimethyl Acid VIII

The 13,13-dimethyl acid VII (26 mg) was dissolved in 5 ml of dry ethanol-free chloroform and the solution cooled to 0°. Dry hydrogen chloride was then bubbled into the solution for 3.5 h. The hydrogen chloride was then removed from the chloroform by a water wash. An attempt to extract the acid into dilute sodium hydroxide failed, since the sodium salt was more soluble in moist chloroform than in water. The free acid (23 mg) crystallized from aqueous methanol as thick hexagonal plates, m.p. 156.5° after preliminary sintering at 147°, $[\alpha]_D^{24}$ +67 ± 4° (*c*, 0.725), ν_{max} 1 693 cm^{-1} (COOH).

Osmylation of Isopimaric Acid

A solution of 1.21 g of isopimaric acid (m.p. 160–163°, $[\alpha]_D$ 0° (*c*, 2.1)) in 10 ml of dry ether containing 1.0 g of osmium tetroxide quickly turned dark and deposited a precipitate. After 17 h at 5 °C the suspension was filtered and the solid washed with ether, leaving 2.28 g. This was suspended in 15 ml of water containing 1 g of sodium hydroxide and 5 g of mannitol; then the mixture was heated on a steam bath for 1 h. After cooling, the solution was acidified with acetic acid. The solid which separated was collected by filtration, and then washed with hot methylene chloride. The insoluble residue weighed 1.17 g, while the methylene chloride dissolved 14 mg.

The solid was recrystallized from absolute ethanol, giving 407 mg of diol 1, m.p. 205–223°. After four more recrystallizations this melted at 222–228° and had $[\alpha]_D^{22}$ +1° (*c*, 1.14); ν_{max} 3 420, 3 160, 2 520 cm^{-1} (OH's), 1 695 cm^{-1} (C=O), and 825 cm^{-1} (vinyl hydrogen).

Anal. Found: C, 71.66; H, 9.59. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59.

The main mother liquor crystallized slowly, giving blades, m.p. 205–218°, and soft feathery crystals, which were mechanically separated. After two recrystallizations from methanol the blades melted at 208–218°, markedly depressed on admixture with the above diol. Found: C, 71.75; H, 9.56. Hence, this is a second diol acid. The feathery crystals from the mother liquor were separated by crystallization into diol 1 and a new compound. The latter, when recrystallized from methanol, melted at 283°.

Anal. Found: C, 68.33; H, 8.92. Calcd. for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. This appears to be a triol acid.

Aldehydo Acid from Diol 1 (from Pimaric Acid)

To a solution of 80 mg of diol 1 in 5 ml of pure dioxane was added a solution of 122 mg of paraperiodic acid in 2 ml of water. After 1.5 h in the dark the solution was concentrated to ca. 1 ml *in vacuo*, diluted with water, and extracted with methylene chloride. The organic layer was washed with sodium thiosulfate solution, dried, and distilled, giving 78 mg of nearly pure aldehydo acid. An ether solution of this was diluted with hexane, clarified by filtration, and then concentrated. The aldehydo acid crystallized and had m.p. 145–185° on a hot stage, 166–168° in an evacuated capillary. One recrystallization from ether–hexane raised the melting point to 168–169° (evacuated capillary); $[\alpha]_D^{24}$ −3° (*c*, 1.97); ν_{max} 2 725, 1 721 cm^{-1} (CHO), 1 693 cm^{-1} (COOH), and 825 cm^{-1} (vinyl hydrogen).

Anal. Found: C, 74.85; H, 9.23. Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27.

13,13-Dimethyl Acid (from Isopimaric Acid)

Pure aldehydo acid (69 mg) was dissolved in 2 ml of triethylene glycol containing 0.5 ml of 95% hydrazine. This was left overnight at room temperature, and then heated to 150°. After cautious addition of 0.6 g of potassium hydroxide the bath temperature was raised to 200 ± 5° and held there for 4.5 h. The mixture was cooled, diluted with water, acidified, and extracted with methylene chloride. The 80 mg of material from the methylene chloride crystallized spontaneously. After three recrystallizations from aqueous methanol the product melted at 149–154° and had $[\alpha]_D^{24}$ −7° (*c*, 1.38); ν_{max} 2 820, 1 695 cm^{-1} (COOH), and 824 cm^{-1} (vinyl hydrogen).

Anal. Found: C, 78.55; H, 10.24. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.

Isomerization of the 13,13-Dimethyl Acid (from Isopimaric Acid)

Dry hydrogen chloride was bubbled through an ice-cold solution of 25 mg of the dimethyl acid in 5 ml of dry ethanol-free chloroform for 4 h. The solution was then extracted twice with cold water, dried, and distilled. The residue was dissolved in hexane and the acid extracted into dilute sodium hydroxide solution. The aqueous solution was acidified and the liberated acid extracted into methylene chloride, giving 26 mg

of product. This was recrystallized twice from aqueous methanol, giving 14 mg of flat needles, m.p. 146–156°, $[\alpha]_D$ +69° (*c*, 0.83). This did not depress the melting point of the Δ^8-13,13-dimethyl acid from pimaric acid, and the mull spectra of the two acids were identical.

Anal. Found: C, 78.59; H, 10.29. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41.

Photolysis of the Azide of Dihydroisopimaric Acid

This azide was prepared as described previously (18). The hydrazide formed prisms from aqueous methanol, m.p. 153°; $[\alpha]_D$ +3° (*c*, 0.97); ν_{max} 3 380 cm^{-1} (>NH), 1 620 cm^{-1} and 1 590 cm^{-1} (amide).

Anal. Found: C, 75.29; H, 10.67; N, 8.73. Calcd. for $C_{20}H_{34}N_2O$: C, 75.42; H, 10.76; N, 8.80.

A hexane solution of the acyl azide prepared from this hydrazide (800 mg), which showed infrared absorption at 2 125 cm^{-1} and 1 700 cm^{-1}, was photolyzed as described previously (18). After 16 h all the azide absorption in the infrared spectrum had disappeared, and the solution was then evaporated to dryness and chromatographed on alumina (grade IV). Hexane eluted the isocyanate (510 mg) as a colorless oil showing infrared absorption at 2 245 cm^{-1}. Elution with benzene yielded a crystalline product (66 mg, 9%) which was purified by sublimation (160° at 10^{-4} mm pressure), yielding small prisms, m.p. 178°, $[\alpha]_D$ 32° (*c*, 0.75).

Anal. Found: C, 79.91; H, 10.17; N, 4.52. Calcd. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37; N, 4.65.

Infrared spectrum: ν_{max} 3 250 cm^{-1} (>NH), 1 690 and 1 645 cm^{-1} (γ-lactam), or 1 685 cm^{-1} (γ-lactam in chloroform). Nuclear magnetic resonance spectrum: τ 1.73, one-hydrogen singlet (NH); τ 4.20, broad one-hydrogen signal, half band width 6 c.p.s. (vinyl hydrogen); τ 6.17, one-hydrogen doublet with J = 10 c.p.s. and half band width for each branch of 6 c.p.s. (hydrogen on C-6). Dihydroisopimaric acid (300 mg) in hexane (100 ml) was unchanged after photolysis for 24 h.

Hydroboration of Methyl Dihydroisopimarate

Freshly distilled boron trifluoride etherate (5 ml) in tetrahydrofuran (70 ml) was treated with sodium borohydride (5.9 g) during 10 min and the mixture was stirred overnight at room temperature before being filtered through glass wool. The diborane solution was made up to 100 ml and used as a standard solution for hydroboration. A solution of methyl dihydroisopimarate (1.5 g) in tetrahydrofuran (50 ml) at 0° under nitrogen was treated with 30 ml of the above diborane solution with vigorous stirring for 3 h. Water (20 ml) was added to the reaction mixture and the mixture evaporated under reduced pressure to about 10 ml. Ethanol (30 ml of 95%), containing sodium hydroxide (1 g), and hydrogen peroxide (2.5 ml of 10%) were added, and the mixture was heated on a steam bath for 15 min and then evaporated to dryness under reduced pressure. The residue was extracted with ether and the ether layer washed with water, dried, and evaporated to yield a colorless oil (1.6 g) which was oxidized directly with Jones's reagent (17). The oxidation product obtained by dilution of the reaction mixture with water and ether extraction was chromatographed on alumina (grade IV). Ether–benzene (1:3) eluted a crystalline solid (600 mg), m.p. 79–80°, raised to 83° on crystallization from aqueous methanol. An analytical sample was sublimed at 120° under 10^{-3} mm pressure, giving colorless prisms, m.p. 83°, $[\alpha]_D$ +10.0° (*c*, 0.37).

Anal. Found: C, 75.62; H, 10.16. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25.

Its infrared spectrum had a broad peak at 1 720 cm^{-1} (—COOMe and >C=O) and its n.m.r. spectrum contained complex signals integrating for three hydrogens between τ 7.5 and 8.2. The keto ester reacted immediately with 2,4-dinitrophenyl hydrazine at room temperature. The product formed orange needles from ethyl acetate – methanol, m.p. 193°.

Equilibrium of Keto Ester XI with Base

The keto ester XI (30 mg) in methanol (10 ml) was refluxed with 20% aqueous potassium hydroxide (2 ml) for 3 h. The mixture was cooled, acidified, and ether extracted. Evaporation of the dried extract yielded an acid (25 mg) which crystallized from benzene–hexane as prisms, m.p. 238–240°, $[\alpha]_D$ +2° (*c*, 1.0).

Anal. Found: C, 74.85; H, 9.80. Calcd. for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06.

Infrared spectrum: ν_{max} at 3 150 cm^{-1} and 1 690 cm^{-1} (—COOH) and 1 725 cm^{-1} (>C=O). Nuclear magnetic resonance spectrum: three-hydrogen signals between τ 7.5 and 8.1. Methylation of this acid with ethereal diazomethane gave the same keto ester, m.p. and mixed m.p. 83°, $[\alpha]_D$ +10°, with its infrared spectrum and thin-layer mobility identical with those of the original ester described above.

Dehydrogenation of the Keto Ester

The keto ester (500 mg) and selenium (2 g) were intimately mixed and heated at 300° for 14 h. The mixture was cooled and the black solid was extracted several times with boiling benzene. The benzene extract was refluxed with freshly precipitated silver for 1 h, filtered, and refluxed again with fresh silver. The benzene extract was washed 4 times with 5-ml portions of 2 *N* sodium hydroxide. The aqueous solution was acidified and extracted with ether. The ether extract was dried and evaporated to yield a yellow oil

(15 mg) which showed phenanthrene-like absorption in its ultraviolet spectrum. Methylation of the crude product with dimethyl sulfate and potassium carbonate in boiling acetone yielded a neutral product which gave one spot on a thin-layer chromatogram after purification by chromatography on alumina. Despite the fact that its ultraviolet spectrum and R_f in two solvents were identical with those of authentic 1,7-dimethyl-9-methoxyphenanthrene,[6] it would not crystallize when seeded with this. The infrared spectrum of the oil was nearly superimposable on that of the authentic sample.

Methyl Carbinol XIII

A solution of 400 mg of keto acid X in 40 ml of dry ether was added slowly to methyl Grignard reagent prepared from methyl iodide and 300 mg of magnesium in 10 ml of ether. The mixture was stirred overnight at room temperature, and then poured into 40 g of ice and 20 ml of 4 *N* sulfuric acid. The ether layer was washed with sodium hydrogen sulfite solution, dried, and distilled, giving 440 mg of residue. The residue was adsorbed on a column of silica gel (20 g). Hexane eluted 123 mg, but the main product (301 mg) was eluted by 30% ether in benzene. The strongly adsorbed material was converted to its methyl ester, which was distilled over a short path at 110–120°, 2×10^{-3} mm pressure. It then melted at 100–103°. After purification by chromatography on alumina the methyl ester of XIII melted at 105° and had $[\alpha]_D$ +6° (*c*, 3.0).

Anal. Found: C, 75.53; H, 10.76. Calcd. for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93.

Dehydrogenation of XIII and Its Salt

A mixture of XIII (500 mg) and 2 g of selenium was heated at 300° for 17 h. The product extractable into benzene was refluxed in this solvent with freshly precipitated silver for 1 h. The filtrate gave a product showing phenanthrene-like ultraviolet absorption, but no pure product was obtained.

An intimate mixture of 800 mg of the sodium salt of XIII with selenium was covered with more selenium (total 8 g) and heated at 260° for 16 h and at 300° for 7 h. Extraction of the reaction mixture as described above did not give any pure products.

Selenium Dioxide Oxidation of Methyl Dihydroisopimarate

To a solution of methyl dihydroisopimarate (500 mg) in ethanol (20 ml) was added freshly sublimed selenium dioxide (200 mg) in ethanol (10 ml) and water (2 ml). The solution was stirred at room temperature for 8 h, after which the yellow solution was filtered to remove precipitated selenium. The solution on evaporation left a yellow oil (510 mg) which was redissolved in ethanol and filtered through active charcoal (Darco G 60). Evaporation gave a colorless oil (470 mg) showing hydroxyl absorption in its infrared spectrum. Thin-layer chromatography indicated the presence of at least seven components. The oxidation product was chromatographed on alumina (Woelm grade III). Benzene eluted a crystalline compound (40 mg) which, on rapid crystallization from the minimum amount of pentane at 0 °C, yielded colorless prisms, m.p. 84°.

Anal. Found: C, 75.16; H, 10.00. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25.

Infrared spectrum: ν_{max} at 3 510 cm^{-1} (hydroxyl), 1 710 cm^{-1} (ester), and 830 cm^{-1} (trisubstituted double bond). Nuclear magnetic resonance spectrum: a broad one-hydrogen doublet at τ 4.42, J = 4 c.p.s. (vinyl hydrogen), a three-hydrogen singlet at τ 6.36 (carbomethoxyl), and a one-hydrogen singlet at τ 6.44 (carbinol hydrogen). Chloroform eluted a further crystalline product (57 mg) which on sublimation furnished colorless prisms, m.p. 92°.

Anal. Found: C, 75.51; H, 10.13. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25.

Infrared spectrum: ν_{max} at 3 650 cm^{-1} (hydroxyl), 1 725 cm^{-1} (ester), and 820 cm^{-1} (trisubstituted double bond). Nuclear magnetic resonance spectrum: 4.55 τ (one-hydrogen singlet, half-band width 4 c.p.s., vinyl hydrogen), 5.94 τ (one-hydrogen broadened singlet, half-band width 7 c.p.s., carbinol hydrogen), 6.36 τ (three-hydrogen singlet, carbomethoxyl).

The other components of the reaction mixture could not be obtained pure but appeared to be other allylic alcohols and dienes (based upon spectra).

Oxidation of the two alcohols by manganese dioxide in chloroform yielded, in both cases, products with ultraviolet absorption at λ_{max} 242 mμ, log ϵ 3.5 (assuming molecular weight of 300) and infrared absorption at 1 665 cm^{-1}. These products could not be purified nor were derivatives obtained. Dehydration experiments with hydrochloric acid in ethanol on the allylic alcohols gave an inseparable mixture of dienes.

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