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THE SYNTHESIS OF 4-EPIDEHYDROABIETIC ACID

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The natural occurrence of (+)4-epidehydroabietic acid (Ia) (callitrisic acid) has been recently reported by a number of workers (1 - 4) and a synthesis of it is now reported.

Dimethyl agathate (II) on ozonolysis followed by reductive workup gave a mixture of diketone esters consisting principally of the compound (III), ν_{max} 1720, 1710 cm^{-1}. Hydroxy ketone (IV) crystallized out of a solution of (III) in methanolic sodium methoxide, m.p. 206° (from methanol), m.p. 211° (from hexane/acetone), $[\alpha]_D$ + 80°, ν_{max} 3500, 1715 cm^{-1}, (literature values ^{5}: m.p. 212-213°, $[\alpha]_D$ + 71°). Distillation of the alcohol (IV) at 0.1mm gave principally the unsaturated ketone (V), ν_{max} 1720, 1675 cm^{-1}, together with some of the 8(9) isomer. The semicarbazone of (V) had m.p. 231-233° in good agreement with that reported in the literature (6). The crude ketoesters in tetrahydrofuran with isopropyl magnesium bromide gave, after acid hydrolysis, acid isomerisation and chromatography, the mixture of esters (VI) giving four major peaks on gas chromatography.

This diene ester mixture (VI) was dehydrogenated with palladium on charcoal at 300° for ten minutes. The product showed numerous bands on gas chromatography but the major peak, methyl 4-epidehydroabietate (Ib), was readily isolated by chromatography over alumina and alumina-silver nitrate, and further purified by sublimation. The product, m.p. 79° with no depression on admixture with natural methyl 4-epidehydroabietate, had $[\alpha]_D$ + 140°, λ_{max}(hexane) 275, 267, 262sh mμ (log ε 2.90, 2.84, 2.66) and gave a superimposable infrared spectrum and

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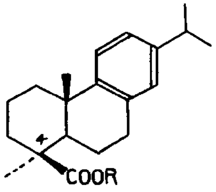
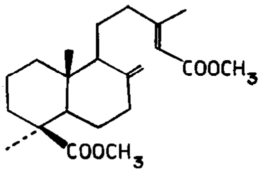
identical chromatographic behaviour with that of the methyl ester of the natural compound.

Racemic (I) has been reported previously[7,8]. A new total synthesis has now been achieved from the racemic ketone (V) by essentially the method described above. Racemic (V)[9] with isopropyl magnesium bromide followed by ammonium chloride hydrolysis and methanolic hydrochloric acid isomerisation gave crude (±) ester (VI). Dehydrogenation over palladium on charcoal at 230-240° for 1.5 hours gave (±) ester (Ib), m.p. 92-93° (literature[7,8]: 91-92°, 98-99°) with an infrared spectrum in CS_2 superimposable on that of the natural (+) ester, and showing the characteristic ultraviolet spectrum. Methyl (±)-desoxypodocarpate (Ib, H instead of C-13 isopropyl)[9], m.p. 126-127°, was obtained as a by-product from the dehydrogenation. The acid (± Ia) was obtained from the ester (± Ib) by hydrolysis with potassium t-butoxide in dimethyl sulphoxide, m.p. 198-200° (literature[7,8]: 202-203°), with λ_{max} (ethanol) 276, 268, 262sh mμ (log ε 2.80, 2.74, 2.56).



Ia R = H

Ib R = CH_3



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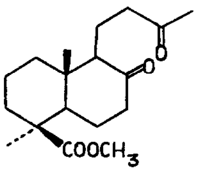
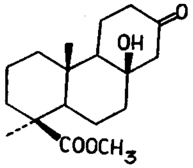


III



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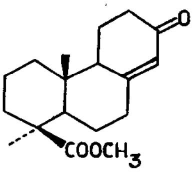
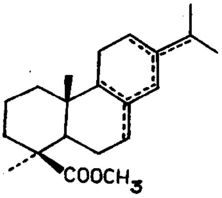


V



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ACKNOWLEDGMENT

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