STEREOCHEMISTRY OF DESOXYPODOCARPIC ACID ISOMERS

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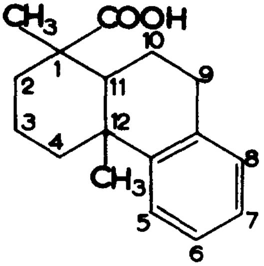
IN connexion with the assignment of definite stereochemistry to a synthetic acid (I) melting at 146-147°,[1] it became of importance to study the stereochemical behaviour of other racemates melting at 232-233°,[2] 205-207°[3] and 186-187°.[3]



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During this investigation, a new synthesis of two epimeric acids (I) m.p. 206-207° and 232-233° having an well-defined stereochemistry has been developed along with a synthesis of DL-podocarpic acid and the present communication deals with these studies.

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[1] N.N.Saha, B.K.Ganguli and P.C.Dutta, Chem. & Ind. 412 (1956).

[2] R.D.Howarth and R.L.Barker, J. Chem. Soc. 1299 (1939).

[3] W.E.Parham, E.L.Wheeler and R.M.Dodson, J. Amer. Chem. Soc. 77, 1166 (1955).

2-(β-Phenethyl)-3 methyl-3-carbomethoxycyclohexanone, b.p. 178-180°/0.6 mm. (Calc. for $C_{17}H_{22}O_3$; C, 74.45; H, 8.03; Found: C, 74.15; H, 8.06); yellow 2:4-dinitrophenylhydrazone, m.p. 163° (Calc. for $C_{23}H_{26}O_6N_4$; N, 12.33; Found: N, 12.50) was obtained in a good yield through the conjugate addition of hydrocyanic acid to 2-(β-phenethyl)-3-methyl- Δ^2-cyclohexenone,[4] followed by alkaline hydrolysis and esterification. The above ketoester was reacted with methyl-magnesium-iodide and the crude carbinol on subsequent dehydration with anhydrous oxalic acid in toluene [5] yielded a slightly yellowish liquid b.p. 150-160°/0.15 mm, which was found to be a complex mixture because of the presence of a strong γ-lactonic band (5.67μ), a strong ester band (5.77μ) and a weak hydroxyl band (2.86μ), as revealed by infra-red studies. The above mixture on cyclisation with polyphosphoric acid [6] on steam-bath for 1½hr afforded a crystalline acidic product and a liquid neutral material. The acidic product on crystallisation from ethylacetate-ethanol afforded an acid, m.p. 232-233° (Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; Found: C, 78.66; H, 8.64), methyl ester m.p. 131-132° (Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; Found: C, 79.39; H, 8.95). (Prof. R.D.Haworth was kind enough to compare the mixed melting points of the acid 232-233° and the methyl ester 131-132°, with his samples, and found no depression.) From the mother-liquor another acid was isolated, m.p. 206-207° (Calc. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; Found: C, 78.85;

[4a] G.Stork and A.W.Burgstahler, J. Amer. Chem. Soc. **73**, 3544 (1951);

[4b] N.N.Saha, P.N.Bagchi and P.C.Dutta, J.Amer.Chem.Soc. **77**, 3408 (1955).

[5] T.Weil and D.Ginsberg, J. Chem. Soc. 1291 (1957).

[6] F.E.King, T.J.King and T.G.Topliss, Chem. & Ind. 113 (1956).

H, 8.63), methyl ester m.p. 84-85° (Calc. for $C_{18}H_{24}O_2$; C, 79.41; H, 8.82; Found: C, 79.02; H, 8.90). These two acids showed a tendency to form a eutectic, melting at 190-192° and afforded 1-methylphenanthrene on dehydrogenation with 10% Pd-C. The neutral product on hydrolysis with 10% butanolic potassium hydroxide solution afforded the acid, m.p. 206-207°, besides some other low melting product, which was not further investigated. The unhydrolysed product yielded some methyl ester, m.p. 131-132°, described earlier.

The synthesis of DL-podocarpic acid has been achieved from this ester, through the introduction of the hydroxyl group in the 6-position.[7] It was allowed to react with acetyl chloride in presence of aluminium chloride in nitrobensene. The ketonic product was isolated through semicarbasone, which on decomposition yielded 6-acetyl-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, m.p. 133-134° (from methanol), λ_{max}^{alc} 259 mμ, log ϵ 4.17 (Calculated for $C_{20}H_{26}O_3$: C, 76.40: H, 8.34; Found: C, 76.41; H, 8.55), orange 2:4-dinitrophenylhydrasone m.p. 234-235° (Calculated for $C_{26}H_{30}N_4O_6$: C, 63.15; H, 6.07; Found: C, 63.16; H, 6.31). The above ketone on oxidation with perbensoic acid in chloroform yielded DL-methyl podocarpate acetate m.p. 125-126° (Calc. for $C_{20}H_{26}O_4$: C, 72.72; H, 7.87; Found: C, 72.35; H, 8.01), which on hydrolysis with ethanolic potassium hydroxide solution gave DL-methyl podocarpate m.p. 193°, (Calc. for $C_{18}H_{24}O_3$: C, 75.0; H, 8.33; Found: C, 75.02; H, 8.50). On hydrolysis with 10% ethylene glycolic potassium hydroxide the methyl ester gave DL-podocarpic acid, which crystallised from ethylacetate-petroleum ether and melted at 266-268° alone or mixed with an authenic sample (through the

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[7] E.Wenkert and B.G.Jackson, J.Amer.Chem.Soc. **80**, 217 (1958).

courtesy of Dr.T.J.King).

The methyl ester (m.p. 131-132°) on oxidation with chromic acid in acetic acid solution [8] afforded 9-keto-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, which crystallised from methanol in two polymorphic forms, m.p. 124-125°, λ^{alc}_{max} 249 mμ, log ϵ 4.07, (Calc. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; Found: C, 75.44; H, 7.97) and m.p. 146-147° (Calc. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74; Found: C, 75.07; H, 7.90); orange 2:4-dinitrophenylhydrazone m.p. 219-220° (Calc. for $C_{24}H_{26}O_6N_4$: N, 12.02; Found: N, 12.26).

On oxidation under identical conditions the methyl ester, m.p. 84-85° yielded 9:10-diketo-1:12-dimethyl-1-carbomethoxy-1:2:3:4:9:10:11:12-octahydrophenanthrene, a bright-yellow crystalline solid (from petroleum ether-benzene) m.p. 129-130°, λ^{alc}_{max} 288 mμ, log ϵ 3.87; (Calc. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.67; Found: C, 72.30; H, 6.82). The diketone was converted to the corresponding enol-acetate by refluxing with acetic-anhydride and fused sodium acetate. The crude gummy enol-acetate, λ^{alc}_{max} 259 mμ, log ϵ 4.04; on catalytic hydrogenation [8] with 10% Pd-C in acetic acid solution containing a drop of 60% perchloric acid, gave the solid methyl ester, m.p. 131-132° (Calc. for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82; Found: C, 79.16; H, 8.68) alone or mixed with the sample described before.

The formation of the mono-keto- and diketo-esters on oxidations [8] and the subsequent transformation through the enol-acetate, conclusively proved that the epimeric centres at C-1 are identical in both acids and these differ only at ring junction, i.e. the acid with m.p. 232-233°, being

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[8] E.Wenkert and B.G.Jackson, J. Amer. Chem. Soc. **80**, 211 (1958).

trans-locked [8,9] or desoxypodocarpic acid and the acid with m.p. 206-207° is cis-locked or cis-desoxypodocarpic acid.

The acid (I) with melting point 146-147° has now been proved to be cis-desisopropyldehydroabietic acid.[10] The remaining isomer, desisopropyldehydroabietic acid remains to be described and it is unlikely that the acid, melting at 186-187°, which is again derived from the 10-keto acid,[3] can be assigned this stereochemistry, because of the improbability of the epimerisation at C-1 through Wolff-Krishner reduction. The possibility of this acid being an eutectic cannot be altogether ruled out and this is being investigated.

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[9] G. Stork and W.J.Schwlenberg, J. Amer. Chem. Soc. 78, 250 (1956).

[10] N.N.Saha, B.K.Ganguli and P.C.Dutta, J. Amer. Chem. Soc. in press (1959).