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HIGHER-ISOPRENOIDS—X

DITERPENOIDS FROM THE OLEORESIN OF *HARDWICKIA PINNATA* PART 3: KOLAVENOL, KOLAVELOOL AND A NOR DITERPENE HYDROCARBON†

Renu Misra,‡ R. C. Pandey§ and Sukh Dev*¶
National Chemical Loboratory, Poona, India

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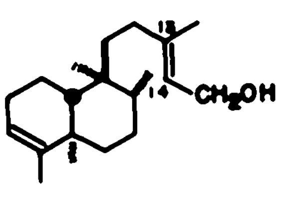
Abstract—Stereostructures of two new diterpene alcohols, which represent the simplest members of the *ent*-clerodane class of diterpenoids, are reported. Structure of a nor-diterpene hydrocarbon, possibly an artifact, is also discussed.

In an earlier communication,[1] we described the isolation of two new diterpene alcohols from the oleoresin of *Hardwickia pinnata* Roxb. We now present evidence, which enabled us to assign absolute stereostructures 1 and 2 to these alcohols which we have named kolavenol (1) and kolavelool (2). These structures[2] primarily rest on their indirect correlation with (−)-hardwickiic acid (3), the main diterpenoid from the same oleoresin.[1] Varying amounts of a C-19 hydrocarbon were invariably obtained while processing the acid fraction of the oleoresin and, in all likelihood is an artifact arising from a thermally labile acid constituent. Its structure has been elucidated to be 4.



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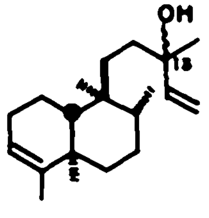

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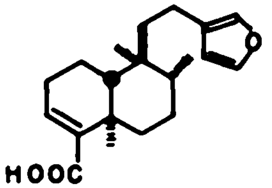

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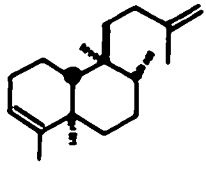

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Kolavenol (1)[2]

Kolavenol, which analyses for $C_{20}H_{34}O$ is clearly a primary alcohol (IR: 3333, 1006 cm^{-1}. PMR: 2H, d, 3.98 ppm, J = 6.5 Hz). *Acetate*, PMR: 2H, d, 4.45 ppm, J = 6.5 Hz. *3,5-Dinitrobenzoate*, m.p. 105–106°). Its PMR spectrum shows the following additional structural features: two $\mathrm{Me{-}\overset{|}{\underset{|}{C}}{-}}$ (3H singlets at 0.72 and 0.98 ppm), $\mathrm{\underline{Me}{-}CH}$ (3H, d, 0.80 ppm, J = 7 Hz), two $\mathrm{\underline{Me}{-}C{=}CH}$ (3H, d, 1.55 ppm, J = 1.5 Hz; 3H, d, 1.63 ppm, J = 1.0 Hz), two $\mathrm{C{=}C\underline{H}{-}CH_2}$ (1H, illresolved t, 5.12 ppm; 1H, t, 5.3 ppm, J = 6.5 Hz). The various Me signals in its PMR spectrum were strongly reminiscent of PMR spectra of various diterpene acids,[1,3] especially that of kolavenic acid (Me ester) 5, of this oleoresin, while the $\mathrm{C\underline{H}_2OH}$ and olefinic proton signals were suggestive of a geraniol-type structure (7). These considerations, along with biogenetic reasonings[1] suggested stereostructure 1 for the new alcohol.* This was readily confirmed, when LAH reduction of 5 furnished an alcohol indistinguishable (physical constants, IR, PMR) from the naturally occurring compound.

During LAH reduction of 5, two minor compounds formulated as 8 (epimeric at C-13) on the basis of their spectral characteristics, were also formed. The preferential reduction of the olefinic linkage during LAH reduction of αβ-unsaturated carbonyl compounds has been recorded.[6]

Kolavelool (2)[2]

Kolavelool analyses for $C_{20}H_{34}O$ and displays the following structural features: $\mathrm{{-}\overset{|}{\underset{|}{C}}{-}OH}$ (IR: 3410, 1110 cm^{-1}. PMR: no signal between 3.5–4.5 ppm), two $\mathrm{\underline{Me}{-}\overset{|}{\underset{|}{C}}{-}}$ (PMR: 3H singlets at 0.72, 0.97 ppm), $\mathrm{\underline{Me}{-}CH}$) PMR: 3H, d, 0.75 ppm, J = 6 Hz), $\mathrm{\underline{Me}{-}\overset{|}{\underset{|}{C}}{-}OH}$ (PMR: 3H, s, 1.22 ppm), $\mathrm{\underline{Me}{-}C{=}CH}$ (PMR: 3H, d, 1.54 ppm, J = 1 Hz), $\mathrm{{-}C\underline{H}{=}C\underline{H}_2}$ (IR: 1650, 1005, 927 cm^{-1}. PMR: 3H, m, 4.83–6.1 ppm), $\mathrm{{-}C{=}CH}$ (IR: 1670, 805 cm^{-1}. PMR: CH,

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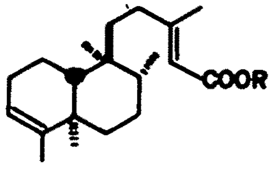
†Communication No. 2267, National Chemical Laboratory, Poona.

‡Present address: Department of Chemistry, University of Toronto, Canada.

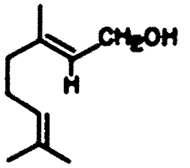
§Present address: Frederick Cancer Research Centre, Frederick, Maryland, U.S.A.

¶Present address: Multi-Chem Research Centre, Nandesari, Vadodara, India.

*Since the publication of preliminary communications,[2] (−)-kolavenol has been found to occur in *Solidago elongata* Nutt[4] and *Solidago altissima* L.[5]



5 : R = Me
6 : R = H



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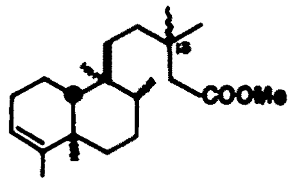

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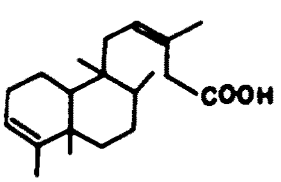
illresolved t, 5.10 ppm). These structural characters, together with the fact of its co-occurrence with kolavenol (1) strongly suggested that it may be the allylic tertiary alcohol isomer 2, corresponding to the allylic primary alcohol kolavenol (1). That this is indeed so could be demonstrated by the following conversion.

Kolavenol on MnO_2 oxidation furnished the corresponding aldehyde $\lambda_{\max}^{\text{EtOH}}$ 238 nm, ϵ 13230), which on exposure to alkaline hydrogen peroxide furnished the desired 13,14-epoxy-kolavenal. Treatment[7] of this epoxy aldehyde with hydrazine hydrate and AcOH at 0–15°, furnished a complex product of at least six components, from which the chief component could be isolated by preparative layer chromatography (PLC) and, was found to be indistinguishable[b] (IR, PMR) from the naturally occurring tertiary alcohol. This transformation, which stereospecifically converts $\alpha\beta$-epoxy ketones (or aldehydes) into allylic alcohols,[7] suffices to define the absolute stereostructure (except for the chirality at C-13) of (−)-kolavelool[c] as 2.

A nor diterpene hydrocarbon

Invariably, during the isolation/purification of hardwickiic acid (3), which involved a preliminary rapid distillation of total acids,[1] a deterpene hydrocarbon was obtained. This hydrocarbon shows the following spectral characteristics. IR: $-\underset{|}{C}=CH_2$ 3090, 1780, 1651, 889 cm^{-1}; $-\underset{|}{C}=CH$ 800 cm^{-1}. PMR: $\underline{Me}-\overset{|}{\underset{|}{C}}-$ (3H singlet at 0.73, 0.98 ppm), $\underline{Me}$–CH (3H, d, 0.81 ppm, J = 6 Hz), $\underline{Me}$–C=CH (3H, bs, 1.53 ppm; 3H, bs, 1.70 ppm), $-\underset{|}{C}=C\underline{H}_2$ (2H, bs, 4.53 ppm), $-\underset{|}{C}=C\underline{H}-CH_2$ (1H, illresolved t, 5.02 ppm). In view of these structural features and its mode of isolation, it was thought this may be a nor-hydrocarbon arising from thermal decarboxylation of a labile diterpene acid related to kolavenic acid (6), such as its $\beta\gamma$-isomer 9. If this is conceded, then the structure of the hydrocarbon should be as depicted in 4. This was confirmed, when kolavenic acid (6) on decarboxylation in quinoline in presence of copper chromite,[8] furnished a hydrocarbon which was identical in all respects (physical properties, GLC, IR, PMR) with the material "isolated" from the oleoresin.



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A careful GLC analysis[1] of the total Me esters of the total undistilled and distilled acids showed that one ester component (RRT = 0.60 with respect to methyl hardwickiate: see Table 1, Ref. 1) got considerably reduced in the esters derived from distilled acids, with significant enhancement of a component having retention time of 4. This strongly suggests that 4 is an artifact and acid 9 indeed may be a component of this oleoresin.

EXPERIMENTAL

For general directions see Ref. 1. All optical rotations were measured in $CHCl_3$, and all PMR spectra were taken in CCl_4 soln.

Kolavenol (1) IR (liq.): 3333, 1665, 1240, 1175, 1133, 1100, 1080, 1006, 865, 800 cm^{-1}. *Acetate* (Ac_2O, pyridine, room temp, 24 hr): b.p. 170–175° (bath)/0.2–0.3 mm, n_D^{30} 1.5011, $[\alpha]_D^{29}$ −45.7° (c, 2.2%). IR (liq.): 1750, 1670, 1240, 1107, 1030, 985, 960, 800 cm^{-1}. PMR: $\underline{Me}-\overset{|}{\underset{|}{C}}-$ (3H singlets at 0.72, 0.97 ppm), $\underline{Me}$–CH (3H, d, 0.80 ppm, J = 6 Hz), $\underline{Me}$–C=CH (3H, bs, 1.53 ppm; 3H, bs, 1.70 ppm). O$\underline{Ac}$ (3H, s, 1.95 ppm), –C$\underline{H}_2$OAc (2H, d, 4.45 ppm, J = 6.5 Hz), C=C$\underline{H}$ (1H, illresolved t, 5.10 ppm; 1H, t, 5.25 ppm, J = 6.5 Hz). (Found: C, 79.68; H, 10.86. $C_{22}H_{36}O_2$ requires: C, 79.46; H, 10.92%). *3,5-Dinitrobenzoate*, m.p. 105–106° (EtOH). (Found: C, 66.33; H, 7.20. $C_{27}H_{36}O_6N_2$ requires: C, 66.92; H, 7.49%).

Lithium aluminium hydride reduction of methyl kolavenate (5). Ester 5 (3.0 g) in dry ether (25 ml) was reduced with LAH (0.38 g) in ether (100 ml), with vigorous stirring at −5° for 8 hr. After destroying the excess LAH with moist ether at 0°, the complex was decomposed with 10% sodium potassium tartarate aq (50 ml) and then worked up in the usual manner to furnish a product (2.52 g), which was chromatographed on Al_2O_3/II (28.5 cm × 2.3 cm). Benzene (50 ml × 4) eluted epimeric mixture (163 mg) 8, which was further purified by PLC (solvent, C_6H_6) to give as major, one pure epimer 8 (*methyl dihydrokolavenate*): b.p. 165–175° (bath)/0.9 mm, n_D^{30} 1.4960, $[\alpha]_D^{27}$ −43° (c, 1.8%). IR (liq.): 1750, 1300, 1263, 1230, 1200, 1176, 1106, 1080, 1020, 985, 860, 840, 800 cm^{-1}. PMR: $\underline{Me}-\overset{|}{\underset{|}{C}}-$ (3H singlets at 0.70, 0.98 ppm), $\underline{Me}$–CH (3H, d, 0.77 ppm, J = 6 Hz; 3H, d, 0.92 ppm, J = 6 Hz), $\underline{Me}$–C=C (3H, d, 1.51 ppm, J = 1 Hz), COO$\underline{Me}$ (3H, s, 3.62 ppm), C=C$\underline{H}$ (1H, m, 5.1 ppm). (Found: C, 78.84; H, 11.06; $C_{21}H_{36}O_2$ requires: C, 78.69; H, 11.32%). The other epimer, which had an IR virtually identical with that of this compound was obtained in too small a quantity for further study.

Continuing the above chromatography, 1% MeOH in C_6H_6

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[b] Except for the clearly higher $[\alpha]_D$ of the semi-synthetic material. This difference is readily understood, as the semi-synthetic product is bound to be an epimeric (at C-13) mixture, as epoxidation of kolavenol cannot be expected to be stereoselective.

[c] Since the publication of the preliminary communications,[3] kolavelool has been found to occur in the roots of *Solidago elongata* Nutt.[4]

(50 ml × 12) eluted the required alcohol (2.2 g); n_D^{30} 1.5151, $[\alpha]_D^{30}$ −45.7° (c, 4.2%), IR, PMR superimposable on those of 1.

Kolavelool (2). IR (liq.): 3410, 1670, 1650, 1290, 1250, 1110, 1080, 1005, 985, 927, 806 cm^{-1}.

MnO_2 *oxidation of kolavenol.* Kolavenol (333 mg) in dry light pet. (60 ml) was stirred at room temp. (24–26°) with active MnO_2[9] for 16 hr and then worked up in the usual manner to furnish the required aldehyde (*kolavenal*) as a colourless viscous liquid (238 mg): b.p. 135–140° (bath)/7.7 × 10^{-3} mm, n_D^{30} 1.5250, $[\alpha]_D^{26}$ −64.4° (c, 2.3%). IR (liq.): 1680, 1640, 1200, 1139, 1120, 1080, 1040, 985, 860, 800 cm^{-1}. PMR: $\underline{Me}-\overset{|}{\underset{|}{C}}-$ (3H singlets at 0.75, 1.0 ppm), $\underline{Me}$–CH (3H, d, 0.80 ppm, J = 6 Hz), $\underline{Me}$–C=CH (3H, bs, 1.53 ppm; 3H, d, 2.13 ppm, J = 1 Hz), C=C$\underline{H}$ (1H, ill-resolved t, 5.1 ppm; 1H, d, 5.75 ppm, J = 7 Hz), C$\underline{H}$O (1H, d, 9.9 ppm, J = 7 Hz). (Found: C, 83.3; H, 11.53. $C_{20}H_{32}O$ requires: C, 83.27; H, 11.18%).

Epoxidation of kolavenal and Wharton reduction to kolavelool. Kolavenal (239 mg) in MeOH (15 ml) at 0–5° was treated with NaOH aq (0.48 ml; 2.65 N), followed immediately by a soln of 30% H_2O_2 aq (30 mg) in MeOH (6 ml). The mixture was held at 0–5° for 6 days and then worked up with $CHCl_3$ to give crude epoxy-kolavenal (280 mg; no UV absorption above 220 nm); IR (liq.), 1740, 1105, 1081, 1042, 1030, 1008, 980, 806, 763 cm^{-1}. This material was used as such in the next step.

The above compound (300 mg) in MeOH (7 ml) was cooled (0°) and treated with hydrazine hydrate (96 mg) and AcOH (12 mg) with good shaking. The evolution of N_2 soon started and the temp. was maintained at 5–10° for a total of 3 hr. The mixture was diluted with water and worked up with ether to furnish a product (224 mg) showing at least six spots on TLC (solvent, 10% EtOAc in C_6H_6). The major component was separated by PLC to get 24 mg of a product, b.p. 90–100° (bath)/1.2 × 10^{-3} mm, n_D^{30} 1.5131, $[\alpha]_D^{27}$ −40.4° (c, 1.3%), and identified (IR, PMR) as kolavelool (2).

Hydrocarbon 4. The total mother liquor[1] (in hexane–ether soln) from the preparation of the cyclohexylamine salt (from 94 g of the distilled acids) was shaken with a saturated aq soln of oxalic acid (100 ml × 3), the aq. part discarded and the material in the solvent layer separated into acidic (see Ref. 1) and neutral (~1.5 g) material. The neutral material was fractionated to get a cut (450 mg), b.p. 140–150°/4.0 mm. This was further purified by chromatography over Al_2O_3/II (17 cm × 1.3 cm) using light pet. as eluent to get GLC pure 4: b.p. 120–125° (bath)/0.5 mm, n_D^{30} 1.5041, $[\alpha]_D^{30}$ −51.4° (c, 3.2%). IR (liq.): 1651, 1170, 1130, 1105, 1058, 1040, 1021, 1000, 980, 889, 800 cm^{-1}. (Found: C, 87.44; H, 12.37. $C_{19}H_{32}$ requires: C, 87.62; H, 12.38%).

Decarboxylation of kolavenic acid. Methyl kolavenate (5; 1.0 g) was hydrolysed with 10% aq. alcoholic KOH (40 ml) at reflux (3 hr) and worked up to give the acid as a foam (0.95 g), which could not be crystallized.

The above acid (0.6 g), freshly distilled quinoline (8 ml) and copper chromite[8] (60 mg, freshly activated at 100–120° for 3 hr) were refluxed till evolution of CO_2 ceased (4 hr). The reaction mixture was diluted with water (20 ml), the product taken up in ether (20 ml × 4) and the ether soln washed with HCl aq, water, $NaHCO_3$ aq, water and dried (Na_2SO_4). The solvent was flashed off and the residue distilled to give a mobile liquid (400 mg), which was further purified by chromatography over Al_2O_3/I (21 cm × 0.8 cm). Light pet. (5 ml × 9) eluted a hydrocarbon, which was distilled to get pure 4 (360 mg), b.p. 135–140° (bath)/0.7 mm, n_D^{30} 1.5040, $[\alpha]_D^{32}$ −50° (c, 5.4%). (Found: C, 87.90; H, 12.49. $C_{19}H_{32}$ requires: C, 87.62; H, 12.38%).

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