THE ABSOLUTE STEREOCHEMISTRY OF HARDWICKIIC ACID AND ITS CONGENERS R. Misra, R.C. Pandey and Sukh Dev

National Chemical Laboratory, Poona (India)

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IN an earlier communication¹, we reported on the structure elucidation of hardwickic acid (I) and some other related diterpencids, all constituents of the oleo-resin of <u>Hardwickia pinnata</u>. However, biogenetic considerations were invoked for the placement of the angular methyls as shown in I. We now describe degradation work, designed to provide experimental support for the location of these quaternary methyls, as also to elucidate the absolute stereochemistry at the various asymmetric centres. This work provides conclusive evidence for the absolute stereostructure II for (-)-hardwickiic acid.



Evidence for the location of methyls at C_5^* and C_9

Ozonolysis of hardwickiic acid, followed by oxidative (H_2O_2) work-up of the ozonide, furnished two major products (isolated as Me esters), formulated on the basis of their analytical and spectroscopic data, as III and IV, in terms of structure I for hardwickiic acid. Oxidation of IV with NaOBr gave, after esterification (CH_2N_2) , III. The methyl ketone ester (IV) could be prepared more expeditiously by the ozonolysis of kolavic acid¹ (V).

The PMR spectra² of both III and IV show one of the quaternary methyls downflue (at 72 c/s and 71 c/s respectively) as required³ for a methyl group of to a carbomethoxy function, thus supporting the presence of a quaternary methyl at C_5 in I.

The location of a quaternary methyl at C₂ is evident from its chemical shift data collected for several derivatives of hardwickiic acid, in which the olefinic linkage and/or the carboxyl group had been chemically modified. This aspect will be discussed in the detailed communication to be published later.



Bromination of IV with NBS (in CCl₄) or with Br_2 -Et₂O complex⁴ (in ether) yielded a bromo derivative which on dehydrohalogenation with CaCO₃-DMF⁵ gave an $\alpha\beta$ unsaturated ketone: $\lambda_{max}^{\text{EtOH}}$ 227 mL (ϵ 6200); IR: -C=C-C=O 1695, 1645 cm⁻¹. Its FMR spectrum shows two olefinic protons as an AB quartet centred at 380 c/s J_{AB} = 16 c/s and $J_{AB}/(\delta_B - \delta_A) = 0.47$, a finding consistent only with fully substituted C₉, as shown in VI. This placement of a Me at C₉ is further supported by the position of its PMR signal (in VI), which as required by its being on an allylic carbon has now suffered a downfield shift (57 c/s as compared to 50 and 49 c/s in III and IV respectively; the other quaternary Me signal remains essentially unchanged, i.e. at 73 c/s).

These conclusions are further corroborated by the transformations described below.

Ring-fusion

The triester III on Dieckmann cyclisation (NaH, xylene) gave a β -keto ester (yield ~ 78%; deep blue colour with FeCl₃), which on acid hydrolysis (HCl-AcOH aq.) gave, as expected, the cyclopentanone derivative VII (after esterification with CH₂N₂): n_D^{30} 1.4923, [α] D^{32} -82.4° (CHCl₃), $\nu_{1iq}^{c=0}$ 1740 cm⁻¹; 2,4-DNP, orange-yellow needles, m.p. 173-174°. This ketone shows in its circular dichroism (CD) a strong negative Cotton effect ($\Delta \epsilon_{301}^{-2.49}$, T = 36 mµ; dioxane), which is almost a mirror image (except for reduced intensity) of that observed for a normal 17-keto-steroid, e.g., 3β -hydroxy-5 α -androstan-17-one⁶ ($\Delta \epsilon_{300}^{-3.26}$, T = 34 mµ; dioxane). Thus, the two rings in VI must be trans-locked, like the C/D rings of an androstan-17-one, but



with opposite absolute stereochemistry, as shown in VII.

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Configuration at Co

The above keto ester (VII) was ketalized (2-methyl-2-ethyl-1,3-dioxalane and p-toluene sulphonic acid), the ketal exposed to excess C_6H_5MgBr and the resulting carbinol dehydrated with HCOOH to give VIII ([d] $_D^{29}$ -12.7°, CHCl₃): λ_{max}^{EtOH} 252 m μ ,



 ϵ 12900; $\nu_{\text{liq.}}^{\text{c=0}}$ 1740 cm⁻¹; PMR: $C_{11}-CH_2$ (2H doublet centred at 131 c/s, J= 8 c/s), $C_{12}-CH$ (1H, triplet centred at 362 c/s, J = 8 c/s). The ketal derived from VIII, on treatment with NBS gave the allylic bromide, which was solvolysed in buffered aq. dioxane to yield a hydroxy derivative. The latter was directly oxidised with Ru04⁷ to give an acid, which was isolated as its methyl ester (IX): n_D^{30} 1.4870, [d] 27-64°; 2,4-DNF, yellow needles, m.p. 173-174°. The positions of the quaternary Me resonances for this bisnor-keto ester (IX), as well as the related compounds III, VII and VIII, are given in Table 1; the assignments are obvious from the respective structures. It is clear from this comparison that the carbomethoxy group at C₉ in IX has no shielding effect on the C₅-methyl and hence it must be β -oriented as shown in X, as in the alternative \propto -configuration it will have 1,3-diaxial relationship with the C₅-methyl which will then be subject to the shielding cone of the carbonyl group⁸.

Compound	Quaternary methyl		
	° ₅	с ₉	
III	72	50	
VII	58	50	
VIII	54	47	
IX	55	64	

TABLE 1. QUATERNARY METEYL RESONANCES IN IX AND RELATED COMFOUNDS

As expected X, like its parent ester VII, shows a strong negative Cotton effect in its CD: ΔE_{302} -2.91, Γ = 37 m (dioxane). <u>Configuration at C₈</u>

The unsaturated keto diester VI was oxidised with RuO_4 and the product hydrolysed with 1% KOH-MeOH (1 hr) to give a monoester dicarboxylic acid, which in view of our previous conclusions, can be formulated as XI. This, on being refluxed with Ac_2O ,







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followed by distillation at ~200°/2 mm gave the required ketone XII: $n_D^{30}1.4839$, [s] $\frac{31}{D}$ +20°(CHCl₃). Its CD shows a positive Cotton effect (ΔE 296-306 +2.10, T = 38 mm; dioxane)⁴ as expected for XII (cf. X); this provides further evidence for the configuration at C₉, as already deduced. The PMR spectrum of XII shows the C₀-methyl resonance (C₅ and C₉ quaternary Me signals occur at 53 and 72 c/s respectively) as a doublet centred at 71.5 c/s (J = 7 c/s). In all other compounds described so far, the C₀-Me doublet is usually centred ~50 c/s. This large paramagnetic shift in XII must have been caused by the keto group, with which it has a 'peri' relationship. Since the carbonyl group can deshield only those protons which lie in its plane, the C₀-methyl must be equatorial, as shown in XIII.

These experiments enable us to uniquely describe the absolute stereostructure of (-)-nardwickiic acid as II. The absolute stereochemistry of kolavic acid (V), kolavenic acid and kolavenol follow from their relationship with hardwickiic acid. <u>Acknowleugement</u> - The authors are grateful to Frof. 7. Ourisson for providing the CD data.

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