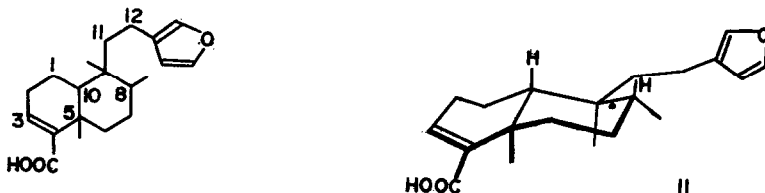


THE ABSOLUTE STEREOCHEMISTRY OF HARDWICKIIC ACID  
AND ITS CONGENERS

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IN an earlier communication<sup>1</sup>, we reported on the structure elucidation of hardwickic acid (I) and some other related diterpenoids, all constituents of the oleo-resin of Hardwickia pinnata. 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 (-)-hardwickic acid.



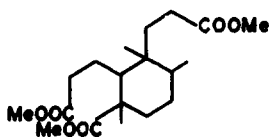
Evidence for the location of methyls at C<sub>5</sub>\* and C<sub>9</sub>

Ozonolysis of hardwickic acid, followed by oxidative (H<sub>2</sub>O<sub>2</sub>) 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 hardwickic acid. Oxidation of IV with NaOBr gave, after esterification (CH<sub>2</sub>N<sub>2</sub>), III. The methyl ketone ester (IV) could be prepared more expeditiously by the ozonolysis of kolavac acid<sup>1</sup> (V).

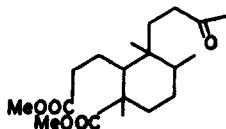
The PMR spectra<sup>2</sup> of both III and IV show one of the quaternary methyls downfield (at 72 c/s and 71 c/s respectively) as required<sup>3</sup> for a methyl group  $\alpha$  to a carbomethoxy function, thus supporting the presence of a quaternary methyl at C<sub>5</sub> in I.

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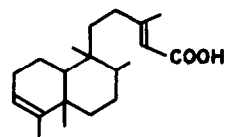
\*The location of a quaternary methyl at C<sub>5</sub> is evident from its chemical shift data collected for several derivatives of hardwickic acid, in which the olefinic linkage and/or the carboxyl group had been chemically modified. This aspect will be discussed in the detailed communication to be published later.



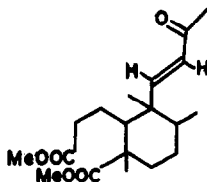
III



IV



V



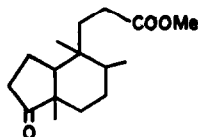
VI

Bromination of IV with NBS (in  $\text{CCl}_4$ ) or with  $\text{Br}_2\text{-Et}_2\text{O}$  complex<sup>4</sup> (in ether) yielded a bromo derivative which on dehydrohalogenation with  $\text{CaCO}_3\text{-DMF}$ <sup>5</sup> gave an  $\alpha\beta$ -unsaturated ketone:  $\lambda_{\text{max}}^{\text{EtOH}}$  227  $\text{m}\mu$  ( $\epsilon$  6200); IR:  $-\text{C}=\text{C}-\text{C}=\text{O}$  1695, 1645  $\text{cm}^{-1}$ . Its FMR spectrum shows two olefinic protons as an AB quartet centred at 380 c/s  $J_{\text{AB}} = 16$  c/s and  $J_{\text{AB}}/(\delta_{\text{B}} - \delta_{\text{A}}) = 0.47$ , a finding consistent only with fully substituted  $\text{C}_9$ , as shown in VI. This placement of a Me at  $\text{C}_9$  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).

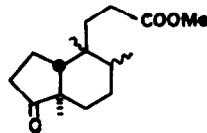
These conclusions are further corroborated by the transformations described below.

#### Ring-fusion

The triester III on Dieckmann cyclisation ( $\text{NaH}$ , xylene) gave a  $\beta$ -keto ester (yield  $\sim 78\%$ ; deep blue colour with  $\text{FeCl}_3$ ), which on acid hydrolysis ( $\text{HCl-AcOH}$  aq.) gave, as expected, the cyclopentanone derivative VII (after esterification with  $\text{CH}_2\text{N}_2$ ):  $n_{\text{D}}^{30}$  1.4923,  $[\alpha]_{\text{D}}^{32}$   $-82.4^\circ$  ( $\text{CHCl}_3$ ),  $\nu_{\text{liq.}}^{\text{C}=\text{O}}$  1740  $\text{cm}^{-1}$ ; 2,4-DNP, orange-yellow needles, m.p. 173-174 $^\circ$ . This ketone shows in its circular dichroism (CD) a strong negative Cotton effect ( $\Delta\epsilon_{301}$   $-2.49$ ,  $T = 36 \text{ m}\mu$ ; dioxane), which is almost a mirror image (except for reduced intensity) of that observed for a normal 17-keto-steroid, e.g.,  $3\beta$ -hydroxy-5 $\alpha$ -androstan-17-one<sup>6</sup> ( $\Delta\epsilon_{300}$   $+3.26$ ,  $T = 34 \text{ m}\mu$ ; dioxane). Thus, the two rings in VI must be trans-locked, like the C/D rings of an androstan-17-one, but



VI



VII

with opposite absolute stereochemistry, as shown in VII.



followed by distillation at  $\sim 200^\circ/2$  mm gave the required ketone XII:  $n_D^{30}$  1.4859,  $[\alpha]_D^{31} +20^\circ$  (CHCl<sub>3</sub>). Its CD shows a positive Cotton effect ( $\Delta \epsilon_{298-306} +2.18$ ,  $\tau = 38$  m $\mu$ ; dioxane) as expected for XII (cf. XI); this provides further evidence for the configuration at C<sub>9</sub>, as already deduced. The PMR spectrum of XII shows the C<sub>8</sub>-methyl resonance (C<sub>5</sub> and C<sub>9</sub> 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 C<sub>8</sub>-Me doublet is usually centred  $\sim 50$  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 C<sub>8</sub>-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 kolavici acid (V), kolavenic acid and kolavenol follow from their relationship with hardwickiic acid.

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#### REFERENCES

- 1 R. Misra, R.C. Pandey and Sukh Dev, Tetrahedron Letters 3751 (1964).
- 2 All PMR spectra were obtained from 10-15% solutions in CCl<sub>4</sub> using a Varian A-60 spectrometer; the signals are recorded in c/s from tetramethylsilane (internal standard) as zero.
- 3 J.C.W. Chien, J. Amer. Chem. Soc. **82**, 4762 (1960); J.W. ApSimon, O.E. Edwards and R. Howe, Can. J. Chem. **40**, 830 (1962).
- 4 R.R. Easton and S.J. Kelson, J. Amer. Chem. Soc. **75**, 640 (1953).
- 5 R. Joly, J. Garnant, G. Nomine and D. Bertin, Bull. Soc. Chim. Fr. 366 (1958); R. Joly and J. Garnant, ibid. 367 (1958).
- 6 L. Velluz and M. Legrand, Angew. Chem. **73**, 603 (1961).
- 7 S. Sarel and Y. Yanuka, J. Org. Chem. **24**, 2018 (1959); G. Stork, A. Weisels and J.E. Davies, J. Amer. Chem. Soc. **85**, 3419 (1963); H. Nakata, Tetrahedron **19**, 1959 (1963).
- 8 A.H. Zaidi and Sukh Dev, Tetrahedron Letters 1171 (1964).