Tetrahedron Letters No.49, pp. 3751-3759, 1964. Pergamon Press Ltd.
Printed in Great Britain.

THE CHEMISTRY OF THE OLEO RESIN FROM HARDWICKIA PINNATA : A SERIES OF NEW DITERPENOIDS*

R.Misra, R.C. Pandey and Sukh Dev
National Chemical Laboratory, Poona (India)

(Received 23 October 1964)

THE oleoresin of Hardwickia pinnata has been shown to consist of a series of closely related sesquiterpenoids and a series of closely related diterpenoids.

The sesquiterpene portion, which constitutes ~40% of the oleoresin has been found to consist of copaene (4.5%), caryophyllene (75%), humulene (13%), caryophyllene oxide (2.5%), humulene oxide-I (0.5%), humulene oxide-II (0.5%), β-caryophyllene alcohol (1%) and unidentified components (6, 3%).

From the diterpenoid part five new compounds (totalling ~70% of this portion) have been isolated (Table 1) and we report on the structures of four of these.

Hardwickiic acid

Hardwickiic acid, $C_{20}H_{28}O_3$ (cyclohexylamine salt, m.p. 143-144°, $[\alpha]_D$ -100.3$^+$) is a monobasic carboxylic acid

---

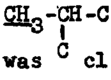
*Communication No. 733, National Chem. Lab., Poona.

$^+$All rotations have been measured in $CHCl_3$ solution, unless stated otherwise.

TABLE 1. DITERPENOIDS FROM *HARDWICKIA PINNATA*

No.	Trivial name	Mol. formula	m.p.	b.p./mm	n_D^{30}	$[\alpha]_D$
1	Hardwickiic acid	$C_{20}H_{28}O_3$	106-107°	-	-	-114.7°
2	Kolavic acid*	$C_{20}H_{30}O_4$	228-230°	-	-	-115.3° (EtOH)
3	Kolavenic acid* methyl ester	$C_{21}H_{34}O_2$	-	179-180°/ 0.4	1.5136	-65.6°
4	Kolavenol	$C_{20}H_{34}O$	-	140-150° (bath)/ 0.025	1.5151	-45.7°
5	____ (an alcohol)	$C_{20}H_{34}O$	138-139°	-	-	-34.3°

*Derived from the local name (Tamil: *Kollavu*) of the resin.

($\nu^{c=o}$ 1681, $\nu^{c=c}$ 1629 cm^{-1}. <u>Methyl ester</u>, $C_{21}H_{30}O_3$, b.p. 150-152°/0.1 mm, n_D^{30} 1.5237, $[\alpha]_D$ -113.5°; $\nu^{c=o}$ 1715, $\nu^{c=c}$ 1635 cm^{-1}, no OH stretching) having a β-monosubstituted furan ring [+ve Ehrlich test[1]; IR[2] (Me ester): 1564, 1503 and 880 cm^{-1}; NMR*[3] (Me ester): 370 (1H), 430 (1H) and 439 cps (1H, triplet) due to one β and two α,α' protons on a furan nucleus]. The presence of two quaternary methyls (sharp 3H signals at 48 and 76 cps) and a  $\underline{CH_3}-\underset{\underset{C}{|}}{CH}-C$ grouping (3H doublet centered at 51 cps, J = 6 cps) was clear from its NMR spectrum. A triplet (1H) centred at 406 cps (in Me ester at 394 cps) is assignable to a vinyl hydrogen β to the carboxyl group; this is confirmed by the NMR of the derived alcohol ($LiAlH_4$ reduction, <u>3,5-dinitrobenzoate</u>, m.p. 118-119°) when this triplet, as expected, shifted upfield (to 326 cps). The conjugation of the -COOH and the ethylenic linkage was further borne out from UV absorption of the Me ester: λ_{max} 213 mμ (ε,12,560), being a summation of furan and αβ-unsaturated ester absorptions.

On quantitative hydrogenation over Rh-C, the ester yielded a tetrahydroderivative, $C_{21}H_{34}O_3$ (n_D^{30} 1.5137, $[\alpha]_D$ -89.19; $\nu^{c=o}$ 1715, $\nu^{c=c}$ 1635 cm^{-1}) with the conjugated olefinic linkage (λ_{max} 215 mμ, ε, 6960; NMR: 1H

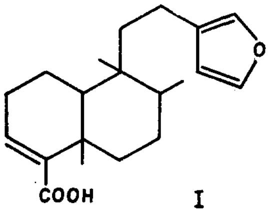
---

*The NMR spectra were taken on 10-20% solutions in CCl_4 or $CDCl_3$ on a Varian A-60 spectrometer; the signals are recorded in cps from tetramethylsilane (internal standard) as zero.

triplet at 390 cps, no furan protons) still in tact. Further hydrogenation yielded a hexahydroderivative (n_D^{30} 1.5024, $[\alpha]_D$ -56.5°), which was fully saturated (UV, NMR, tetranitromethane test). It is clear from these results that hardwickiic acid has only three C=C bonds and consequently must have two carbocyclic rings.

Hardwickiic acid on dehydrogenation with 10% Pd-c yielded 1,2-dimethyl- and 1,2,5-trimethylnaphthalenes in a ratio of 3:2.

The above results can be accommodated only in a 'rearranged' bicyclic diterpenoid skeleton and the structure I is dictated by biogenetic considerations:[4,5]



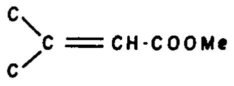
I

Kolavic acid

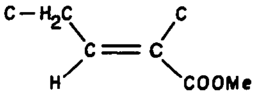
Kolavic acid, $C_{20}H_{30}O_4$, is dicarboxylic ($\nu^{C=O}$ 1680, $\nu^{C=C}$ 1650 cm^{-1}. Dimethyl ester, $C_{22}H_{34}O_4$, b.p. 193-194°/ 0.4 mm, n_D^{30} 1.5179, $[\alpha]_D$ -126°; $\nu^{C=O}$ 1720, $\nu^{C=C}$ 1650 cm^{-1}). The UV absorption of the acid (λ_{max} 216 mμ, ε 21,000) and its ester (λ_{max} 217 mμ, ε 21,400) indicated that both the carboxyl functions must be αβ-unsaturated. On catalytic hydrogenation over Pt it yielded a tetrahydro acid (m.p.

223-225°, $[\alpha]_D$ -42.3°), which gave a negative tetranitromethane test. Thus, kolavic acid must contain only two ethylenic linkages. On dehydrogenation with Pd-C, kolavic acid, like hardwickiic acid, yielded both 1,2-dimethyl and 1,2,5-trimethylnaphthalene in a 1:1 ratio and, hence, must be closely related to hardwickiic acid.

The NMR spectrum of dimethyl kolavate showed the presence of two quaternary methyls (Sharp 3H signals at 46 and 74 cps, a $\underline{\mathrm{CH_3}}\text{-}\underset{\substack{|\\ \mathrm{C}}}{\mathrm{CH}}\text{-}\mathrm{C}$ grouping (3H doublet centred at 49 cps, J = 6 cps), one methyl on an olefinic linkage (3H, doublet at 128 cps, J = 1 cps) and two -COO$\underline{\mathrm{Me}}$ (6H sharp signal at 217 cps); in the vinyl proton region a singlet (essentially) at 333 cps and a triplet centred at 392 cps serve to elaborate further the nature of the olefinic linkages, deduced earlier, to II and III respectively:

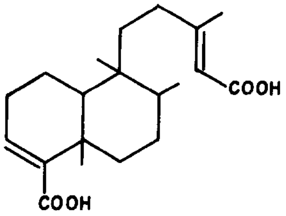


II

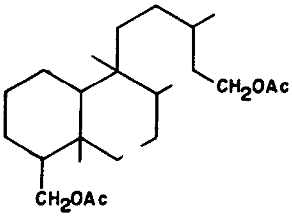


III

Keeping in mind the structure of hardwickiic acid, the above data for kolavic acid lead to its formulation as IV. The stereochemistry of the side chain has been deduced from the chemical shift of the allylic methyl group (128 cps), which must be cis to the carboxyl function[6,7].



IV

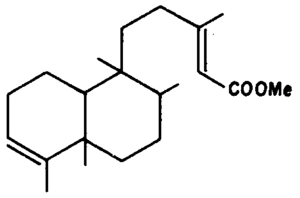


V

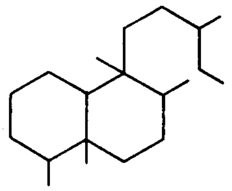
Kolavic acid was, then, correlated with hardwickiic acid as follows: Methyl hardwickiate on hydrogenation over Pt in AcOH (at 25° and 710 mm) took up 3.3 moles of hydrogen to furnish, besides other products, an ester alcohol (n_D^{30} 1.4986, $\nu^{c=o}$ 1730, ν^{OH} 3400 cm^{-1}) in 50% yield. This on $LiAlH_4$ reduction yielded a mixture of a solid (m.p. 131-133°) and a liquid glycol in approx. equal amounts; the latter was converted into its diacetate and chromatographed to yield a pure diacetate (n_D^{30} 1.4859, $[\alpha]_D$ -20.7°) which was found to be identical (physical properties, IR, NMR) with V, obtainable from tetrahydrokolavic acid.

Kolavenic acid

This could be isolated as its methyl ester. From the spectral properties of the ester [λ_{max} 219 mμ, ε 15,600; IR: $\nu^{c=o}$ 1733, $\nu^{c=c}$ 1650 cm^{-1}; NMR: two quaternary methyls (3H singlet at 44 and 59 cps), one methyl on a methine carbon (3H doublet centred at 48 cps, J = 6 cps), two vinylic methyls (3H doublet at 94 and 128 cps), one -COOMe (217 cps), one vinyl proton (broadened triplet) centred at 307 cps and, another vinyl proton (essentially a singlet) at lower field strength (334 cps)] and keeping in view the spectral characteristics of hardwickiic and kolavic acids, structure VI follows for the new acid.



VI



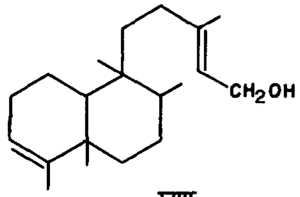
VII

The structure (VI) has been confirmed by its direct correlation with kolavic acid through the hydrocarbon VII (n_D^{30} 1.4851-1.4857; identical NMR, IR).

It may be pointed out here that the shift of a quaternary methyl signal from 76 cps in hardwickiic acid to 59 cps in kolavenic ester is in accord with the proximity of that methyl to the C_4 carboxyl function. As expected[8] the signal shifted to 47 cps in tetrahydrokolavenic ester.

Kolavenol

From spectral characteristics and biogenetic considerations, this alcohol (3,5-dinitrobenzoate, m.p. 105-106°) was assigned the structure VIII, which was confirmed by its preparation from kolavenic acid by $LiAlH_4$ reduction.

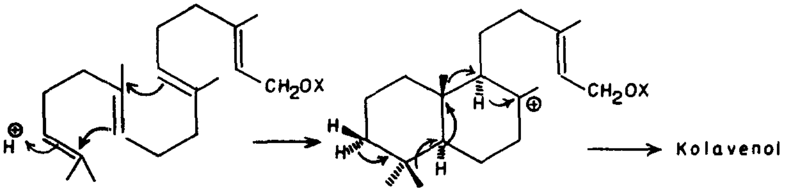


VIII

Other constituents

Evidence has also been obtained for occurrence of the β,γ-isomers of hardwickiic acid and kolavenic acid and the tertiary allylic alcohol corresponding to kolavenol. These will be discussed in the fuller communications.

The isolation of all these compounds, which represent different stages of oxidation of a "rearranged" bicyclic intermediate, is most interesting from the point of biogenesis. The simplest member of this series, viz., kolavenol can arise directly from the species IX resulting from the cyclisation of geranylgeraniol precursor:



IX

The determination of stereochemistry of these compounds should provide further support to the above scheme of concerted methyl migrations, already well-established for friedelin[9] and recognised in some diterpenoids.[10,11,12]

REFERENCES

1 T. Reichstein, Helv. Chim. Acta **15**, 1110 (1932).

2 T. Kubota, Tetrahedron **4**, 68 (1958).

3 E.J.Corey, G.Slomp, Sukh Dev, S.Tobinaga and E.R. Glazier, J. Amer. Chem. Soc. **80**, 1204 (1958).

4 L. Ruzicka, Experientia **9**, 357 (1953).

5 A.I.Scott, F. McCapra, F.Comer, S.A.Sutherland, D.W. Young, G.A.Sim and G.Ferguson, Tetrahedron **20**, 1339 (1964).

6 U.R.Nayak, T.S.Santhanakrishnan and Sukh Dev, Tetrahedron **19**, 2281 (1963) and, the references cited therein.

7 S.Bory, M. Fetizon and P.Laszlo, Bull. Soc. Chim. Fr. 2310 (1963).

8 R.F.Zürcher, Helv. Chim. Acta **44**, 1380 (1961).

9 E.J.Corey and J.J.Ursprung, J. Amer. Chem. Soc. **78**, 5041 (1956).

10 D.H.R.Barton, H.T.Cheung, A.D.Cross, L.M. Jackman and M. Martin-Smith, J. Chem. Soc. 5061 (1961).

11 D.E.Case, T.G. Halsall and A.W.Oxford, I.U.P.A.C. Symposium on Natural Products (Kyoto) 54 (1964).

12 Y. Kitahara and A. Yoshikoshi, Tetrahedron Letters 1755 (1964).