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TERPENOIDS—CVIII

ISOLATION OF AN OXIDODIOL FROM *ZANTHOXYLUM RHETSA**

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Abstract—A crystalline oxido-diol, m.p. 171°, has been isolated from *Zanthoxylum rhetsa*, and found to be identical with one of the oxidation products of sabinene. The vicinal hydroxyls of the oxido-diol are *trans* oriented, since cyclic derivatives such as carbonate, sulphite and acetonide can not be prepared from it. This is supported by its IR and NMR spectra and its reaction with lead tetra-acetate.

Zanthoxylum rhetsa commonly known as mullilam belongs to the Rutecae family and is widely distributed in India.[1] The plant exhibits antibiotic activity and is prescribed in dyspepsia and diarrhoea. The fruit rind has aromatic properties and is used for its stimulant and an extract is active against several pathogenic micro-organisms.[2]

The fruits of *Zanthoxylum rhetsa* on steam distillation yield a volatile oil which has been examined[3,4] and several constituents isolated. In the present investigation the essential oil of *Zanthoxylum rhetsa* was subjected to systematic fractionation to identify the lower boiling components. The major monoterpenic component has been identified as sabinene by its IR and NMR spectra and confirmed by its conversion to sabina ketone on ozonolysis. The presence of α-pinene and β-pinene has been established by GLC analysis. The essential oil was subjected to chromatography to identify the highly oxygenated constituents and this has led to the isolation of a crystalline solid, m.p. 171°, which we propose to name as mullilam diol.

The elemental analysis and mol wt of mullilam diol suggests the molecular formula $C_{10}H_{18}O_3$. The IR spectrum shows the presence of an OH group (3350 cm^{-1}) and absence of ketone, aldehyde, ester or lactone group (no absorption in the CO region). Active hydrogen determination indicates the presence of two OH groups. It forms a diacetate, $C_{14}H_{22}O_5$, which does not contain a OH group (no IR absorption in the OH region). Thus only two oxygen atoms are in the form of OH groups, the third oxygen atom may exist in the form of an ether linkage.

The mullilam diol is saturated since it does not absorb hydrogen on catalytic hydrogenation and gives no colouration with tetranitromethane. The absence of unsaturation is further supported by its inertness towards perbenzoic acid and absence of absorption in the 210–340 mμ region.

With a view to finding the carbon skeleton of mullilam diol an attempt was made

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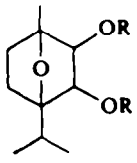
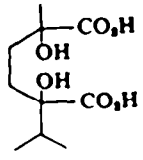
[1] J. D. Hooker, *Flora of British India* Vol. 1; p. 495 (1875).
[2] C. G. Joshi and N. G. Magar, *Ind. J. Pharm.* 15, 312 (1953).
[3] B. S. Rao, J. J. Sudborough and H. E. Watson, *J. Indian Inst. Sci.* 8A, 174 (1925).
[4] Y. R. Naves, *Perf. and Essent. oil Rec.* 441 (1950); *Bull. Soc. Chim. Fr.* 673 (1950).

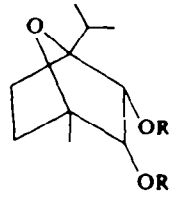
to remove the oxygen functions. Treatment of the diol with *p*-toluenesulphonyl chloride in the cold followed by LAH reduction of the tosylation product furnishes a monohydroxy compound $C_{10}H_{18}O_2$ m.p. 110°. Oxidation of the diol with alkaline potassium permanganate yields a dihydroxy acid, $C_{10}H_{18}O_6$ m.p. 186°, identified as (±)αα′-dihydroxy-α-methyl-α′-isopropyladipic acid (III), previously described.[5] This suggests that mullilam diol may be identical with the oxido-diol m.p. 172° obtained by the action of peracetic acid on sabinene. This was confirmed by comparison with an authentic sample.[5] It is of interest that sabinene occurs simultaneously with mullilam diol in the essential oil of *Zanthoxylum rhetsa*. The NMR spectrum of the diol which exhibits signals at 8·4 τ (singlet; 3H; $CH_3—\overset{C}{\underset{C}{\diagup\diagdown}}—O$) and at 9·0 τ (doublet; 6H, $C—\overset{CH_3}{\underset{CH_3}{\diagup\diagdown}}CH$) is in agreement with the structure I. Its IR spectrum in very dilute solution in dichloromethane exhibits bands at 3632 cm (sh) and 3605 cm^{-1} (m). These bands are comparable with those of *trans*-cyclohexane-1,2-diol[6] which exhibits bands at 3634 and 3602 cm^{-1} suggesting that the vicinal hydroxyls of mullilam diol are *trans* oriented. This is further supported by its inability to form cyclic derivatives



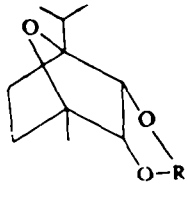
I R = H
II R = —Ac

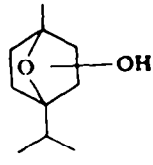


III



IV R = H
V R = —Ac





VIII

VI R = $\overset{\diagup}{\underset{\diagdown}{S}}$ = O

VII R = $\overset{Me}{\underset{Me}{\diagup\diagdown}}$C

[5] G. G. Henderson and A. Robertson, *J. Chem. Soc.* 1849 (1923).
[6] L. P. Kuhn, *J. Am. Chem. Soc.* 76, 4323 (1954).

such as carbonate, sulphite and isopropylidine derivative under conditions which are favourable for the conversion of ascaridole-glycol IV[7] to cyclic derivatives. It has been shown[8] that the rate of glycol-fission with lead tetraacetate in *trans*-1,2-diols is slower than in the *cis*-1,2-diols in rigid systems of bicyclo(2,2,1)heptane. A comparative study of the rate of glycol fission of mullilam diol I with ascaridole-glycol (IV) and camphane-2-exo-3-exo-diol* with lead tetraacetate was made and it was found that mullilam diol reacts very slowly indicating the *trans* nature of the OH groups.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer infracord spectrophotometer (Model 137B). NMR spectra were recorded on a Varian A 60 spectrometer operating at 60 MC, in CCl_4 soln (unless otherwise stated) using TMS as internal reference. Microanalyses were carried out in the microanalytical section of this Laboratory. GLC analysis were carried out on a Griffin-George model MK-II apparatus using a polyester column and H_2 as the carrier gas.

Isolation of mullilam diol (I). Mullilam oil (19·5 g) was chromatographed over alumina (Gr. III; neutral; 320 g) and fractions eluted with pet. ether (13·5 g), benzene (2·8 g), and ether (0·210 g) were collected successively. The ether-eluted fraction solidified. Sublimation and repeated crystallizations from EtOH furnished crystals of mullilam diol, m.p. 171°, $[\alpha]_D$ ±0° (*c*, 2·5, EtOH). (It is also possible to isolate mullilam diol directly by crystallization of the residue left in the flask after removal of the lower boiling constituents by careful distillation through a fractionating column.)

IR spectrum (in nujol) exhibited bands at: 3350, 1471, 1384, 1332, 1217, 1149, 1096, 1075, 1036, 1008, 978, 948, 928, 924, 897, 877 and 850 cm^{-1}.

UV spectrum: no absorption in the region 210-340 mμ. NMR spectrum (pyridine): signals at 9·04 τ (doublet; 6H; $-CH(CH_3)_2$) and 8·4 τ (singlet; 3H; $O-C(C)_2-CH_3$). (Found: C, 64·3; H, 9·9; mol. wt. (Rast) 187. $C_{10}H_{16}O_3$ requires: C, 64·49; H, 9·74%; mol. wt. 186.)

Diacetate II *of mullilam diol* I. The diol (0·332 g) on refluxing with Ac_2O (5 ml) furnished the diacetate II (0·29 g), m.p. 67–68°. IR spectrum: bands at 1730, 1469, 1435, 1364, 1235, 1190, 1149, 1087, 1063, 943, 925, 900, 869, 833, 806 and 751 cm^{-1}.

NMR spectrum: signals at 9·15 τ (doublet; 6H; $-C(CH_3)_2-CH$) 8·57 τ (singlet; 3H; $-O-C(C)_2-CH_3$) and at 8·06 and 8·00 τ (6H; $CH-O-COCH_3$). (Found: C, 61·89; H, 8·33. $C_{14}H_{22}O_4$ requires: C, 62·20; H, 8·20%.)

Tosylate of I *and* LAH *reduction of the tosylate.* A soln of *p*-toluenesulphonyl chloride (0·8 g) in pyridine (20 ml) was added to a cooled (0)° soln of the diol (0·326 g) in pyridine (10 ml) and the reaction mixture kept at 0° for 72 hr. The resulting viscous liquid (0·37 g) in anhyd ether (20 ml) was added dropwise to a stirred slurry of LAH (0·3 g) in ether (30 ml) at 0°. The reaction mixture was refluxed for 3 hr. Excess of LAH was destroyed, and the product extracted with ether. The

* The terms exo and endo are used to indicate a substituent to be *cis* or *trans* respectively to the bridge of bicyclo (2,2,1)heptane system.

[7] G. Jacob and G. Ourission, *Bull. Soc. Chim. Fr.* 734 (1958).

[8] S. J. Angyal and R. J. Young, *J. Am. Chem. Soc.* **81**, 5467 (1959).

ether layer was washed with water and dried (Na_2SO_4). Evaporation of ether left a viscous liquid (0·202 g) which was chromatographed over alumina (gr. II; 15 g). The fractions eluted with pet. ether (0·040 g), benzene (0·115 g) and ether (0·020 g) were collected. The benzene fraction solidified and crystallized from EtOH, m.p. 110°.

IR spectrum (nujol): bands at 3448, 1481, 1412, 1376, 1316, 1269, 1244, 1188, 1139, 1096, 1070, 1054, 1034, 1025, 1005, 993, 961, 952 and 932 cm^{-1}. (Found: C, 70·6; H, 10·8. $C_{10}H_{16}O_8$ requires: C, 70·54; H, 10·66%.) The compound presumably is a monohydroxy alcohol (VIII).

$KMnO_4$ *oxidation of mullilam diol.* The diol on oxidation with alkaline $KMnO_4$[6] furnished an acid, m.p. 188°, which was identified as (±)αα′-dihydroxy-α-methyl-α′-isopropyl adipic acid by comparison of the IR spectra and determination of m.p. and mixed m.p. 186–187°.

Oxidation with lead tetraacetate. The AcOH used in these runs was purified by refluxing and distillation over lead tetraacetate.

A. A soln of diols was prepared by dissolving the diol in AcOH. (Conc. 0·0005M to 0·001M.)

B. Solns of the oxidizing reagent was prepared by dissolving lead tetraacetate in AcOH. (Conc. 0·0125M to 0·02M.)

C. Stopping soln was made by dissolving KI (50 g) and AcONa (250 g) in water (1 l.).

Solns of the diol and the oxidizing reagent (5 ml each) were mixed at a particular temp for a definite period. Then the stopping soln (10 ml) was added and the liberated I was titrated against 0·02N $Na_2S_2O_3$. The results are indicated below:

TABLE 1. LEAD TETRAACETATE OXIDATION OF DIOLS

Diol	temp	period (min)	Reacted diol
Oxido diol (I) m.p. 171°	27·5°	15·0	2·65%
Oxido diol (I) m.p. 171°	50·0°	10·0	4·40%
Ascaridole-glycol (IV)	27·5°	5·0	92·5%
Ascaridole-glycol (IV)	27·5°	15·0	106·3%
Camphane-2-exo-3-exo-diol	27·5°	5·0	106·0%

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