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The Phenolic Constituents of *Semecarpus anacardium* Linn.*

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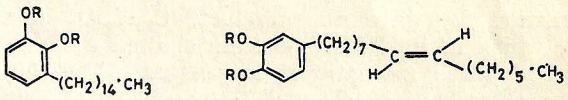
Bhilawanol, isolated by previous authors [*J. Indian chem. Soc.*, 3 (1931), 517] from *S. anacardium* Linn. is shown to be a mixture of phenolic compounds consisting mainly of 1,2-dihydroxy-3-(pentadecenyl-8′)-benzene (Va) and 1,2-dihydroxy-3-(pentadecadienyl-8′,11′)-benzene (VIIa). These results are also at variance with those reported by Rao and Row [*Curr. Sci.*, 39 (1970), 207].

THE marking nut, *Semecarpus anacardium* Linn. (Fam: Anacardiaceae) (Hindi: *Bhilawan*) has found use in Indian medicine in the treatment of rheumatism[1]. From the vesicant oil of its fruit pericarp, Pillay and Siddiqui[2] isolated an unidentified monophenol called semecarpol and a catechol named bhilawanol. The latter analysed for the formula $C_{21}H_{32}O_2$, formed a diacetate, a dimethyl ether and on catalytic reduction gave 3-pentadecylcatechol (Ia). On the basis of this, bhilawanol was regarded as a catechol with a $C_{15}H_{27}$ side chain at position-3.

The biological activity of the oil[1,3,4] and a recent communication by Rao and Row[5] have prompted us to reinvestigate the structure of bhilawanol. Rao and Row[5] methylated the phenolic oil and obtained three fractions separated by chromatography. Fraction-1 which was the major constituent (70%), gave a product which analysed for $C_{23}H_{38}O_2$. This was assigned structure IIb on the basis of its mass and NMR spectra. Oxidation of this gave *n*-heptanoic acid and a second acid assigned structure IIIa on the basis of the mass and NMR spectra of its methyl ester, assigned structure IIIb. Fraction-2 (10%) gave a product, $C_{23}H_{36}O_2$, which was considered to differ from that obtained from fraction-1 in possessing a side chain with two double bonds. Fraction-3 (10%) was not studied further. Rao and Row had without adequate reasons rejected the 1,2,3-trisubstitution pattern assigned earlier by Pillay and Siddiqui in favour of a 1,2,4-substitution pattern and assigned structure IIa to the main constituent of the oil (Fr. 1). We find in the present work that the 1,2,3-substitution is indeed correct.

In our hands, both commercial samples of the oil as well as hexane extracts of the pericarp of freshly collected fruits were used and found to have the same constituents. Purification of the oil by distillation *in vacuo* followed by chromatography over silica gel yielded bhilawanol as a light yellow oil which turned brown on exposure to air. Although TLC and GLC indicated it to be homogeneous, methylation studies showed it to be a mixture of closely related phenolic constituents. TLC on silica gel impregnated with sodium tetraborate[6] showed that bhilawanol was a catechol. Catalytic reduction of bhilawanol gave 3-pentadecylcatechol (Ia), m.p. 57-58°, identical with an authentic sample. This was in agreement with the findings of Pillay and Siddiqui. Prolonged hydrogenation resulted in the saturation of the ring and yielded compound (IV), m.p. 78-80°. Methylation of hydrobhilawanol yielded 3-pentadecylveratrole (Ib) whereas ethylation yielded the diethyl ether (Ic)

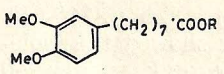


I

a : R = H
b : R = Me
c : R = Et

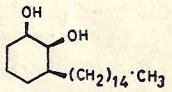
II

a : R = H
b : R = Me



III

a : R = H
b : R = Me



IV

Methylation of bhilawanol by the method of Symes and Dawson[7], using methyl iodide and sodium ethoxide, and chromatography of the product over silca gel yielded two main fractions — A (60%) and B (30%)— apparently identical with fractions 1 and 2 respectively of Rao and Row[5]. Both fractions, on hydrogenation, yielded 3-pentadecylveratrole. Fraction A gave a product $C_{23}H_{38}O_2$ (M^+ 346), which in its NMR spectrum, showed the presence of three aromatic hydrogens as a complex multiplet at δ 6·4-7·0, two vinyl hydrogens as a triplet at δ 5·3 (J=5 Hz) and two methoxyls at δ 3·71. Its mass spectrum showed significant peaks (a-d) at m/e 121, 123, 136 and 151 arising from the dimethoxybenzyl portion. Hydroxylation of the product obtained from fraction A with osmium tetroxide yielded a crystalline diol, m.p.

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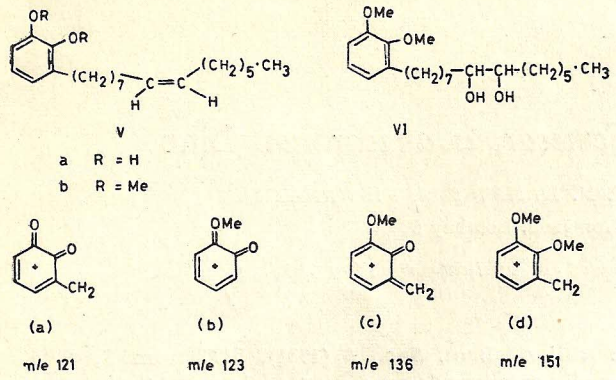
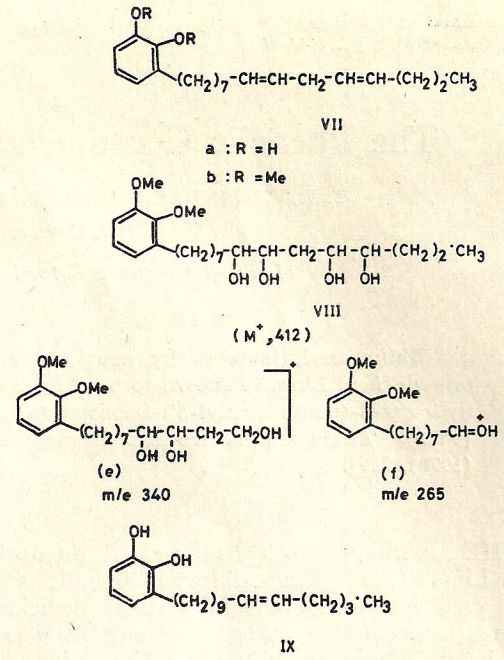


100-101°, identical in its properties with the *erythro*-diol (VI)[8] and showed that the product from A is the *cis*-monoolefin (Vb). The major constituent of bhilawanol is hence the corresponding catechol (Va).

Fraction B, gave the product, $C_{23}H_{36}O_2$ (M^+ 344), which in its NMR spectrum showed the presence of three aromatic hydrogens at δ 6·4-7·0, two methoxyls at δ 3·72 and 3·74 and four vinylic hydrogens as a triplet at δ 5·3 (J=5 Hz). Evidently this product differs from that obtained from fraction A in having two double bonds in the side chain. The absence of UV absorption showed that these were not in conjugation. Hydroxylation of the product obtained from fraction B with osmium tetroxide yielded a crystalline tetraol, m.p. 160-61°. The mass spectrum of the latter showed the molecular ion peak at m/e 412. The peak at m/e 340 (M—72) due to the fragment (e) arising by loss of a $CH_3CH_2CH_2CHO$ fragment[9] indicated that one of the double bonds in fraction B is at C_{11}-C_{12}. The base peak at m/e 265, which is also very significant in the diol (VI), is assigned to the fragment (f) and indicates that the other double bond in fraction B is at C_8-C_9. The tetraol can hence be assigned structure (VIII) and fraction B the structure (VIIb). The second major constituent of bhilawanol is therefore the diolefin (VIIa).

The mass spectrum of fraction B showed the presence of small peaks at m/e 360 and 374 indicating the presence (*ca.* 5% each) of higher homologues with $C_{16}H_{31}$ and $C_{17}H_{33}$ side chains respectively. The compounds could not however be obtained pure.

The major constituents of the oil are hence compounds (Va) and (VIIa) as in Poison ivy (*Rhus toxicodendron radicans*)[7], Japanese lac urushiol (*Rhus vernicifiora*)[10] and *Rhus striata*[11]. The triene, 1,2-dihydroxy-3-(pentadecatrienyl-8′,11′,14′)-benzene, which occurs in the *Rhus* species, seems to be absent in *Semecarpus anacardium*. Renghol[12], isolated from *Semecarpus heterophylla* Bl. has been reported to have structure IX, isomeric with (Va).



Experimental Procedure

The relative intensities of the mass spectral fragmentation peaks are given in parentheses.

Isolation — Mature nuts of *S. anacardium* Linn. were dried in the sun and the seeds removed. The pericarp (6 kg) was extracted with hexane and the solvent evaporated to get a dark viscous oil (3 kg). Distillation of this oil (50 g) *in vacuo* in a molecular distillation apparatus yielded a pale brown oil (12 g), b.p. 200°/1 mm, giving a dark green ferric colour. Chromatography of the distillate over silica gel in benzene, yielded a light yellow oil (6 g) which became brown on exposure to air. This product, bhilawanol, was homogeneous in TLC (silica) in three different solvent systems.

Catalytic reduction of bhilawanol —(1) A solution of bhilawanol (2 g) in ethanol (100 ml) was hydrogenated in an Ente apparatus in the presence of platinum oxide (0·25 g) at atmospheric pressure. After 4 hr, the solution was filtered, evaporated and the product chromatographed over silica gel in benzene to yield hydrobhilawanol (1·8 g), needles (from hexane), m.p. 57-58°, undepressed by admixture with an authentic sample of 3-pentadecylcatechol (Ia). R_f: 0·3 (silica, $CHCl_3$), <0·01 (silica containing 2% sodium tetraborate, $CHCl_3$); NMR ($CDCl_3$): δ 6·70 (*s*, 3H), 5·35 (br, 2H, OH), 2·6 (*t*, 2H), 1·26 (br *s*, 26H), 0·88 (*t*, 3H) ppm (Found: C, 79·2; H, 11·5. Calc. for $C_{21}H_{36}O_2$: C, 78·7; H, 11·3%). Its IR (KBr) and NMR spectra were identical with those of an authentic sample of 3-pentadecylcatechol.

(2) A solution of bhilawanol (2 g) in ethanol (100 ml) was shaken with hydrogen at atmospheric pressure in the presence of platinum oxide (0·25 g) for 24 hr. Chromatography of the product over silica gel in benzene yielded 3-pentadecylcatechol (0·5 g). Subsequent elution of the column with ether yielded 1,2-dihydroxy-3-pentadecylcyclohexane (IV) (1 g), m.p. 78-80° (from hexane), which had no UV absorption and gave no ferric colouration; NMR (CCl_4): δ 3·77 (*m*, 2H), 3·07 (br *s*, 2H, OH), 1·26 (br *s*, 35 H), 0·9 (*t*, 3H) ppm (Found: C, 77·1; H, 13·1. $C_{21}H_{42}O_2$ requires C, 77·2; H, 13·0%).

Methylation of hydrobhilawanol — A solution of hydrobhilawanol (2 g) obtained by the controlled hydrogenation of bhilawanol, was refluxed in acetone (60 ml) with dimethyl sulphate (2 g) and anhydrous

potassium carbonate (15 g) for 24 hr. Chromatography of the product over alumina in hexane followed by crystallization from hexane yielded 3-pentadecylveratrole (Ib) (1 g), m.p. 35-36°; NMR ($CDCl_3$): δ, 6·5-7·3 (*m*, 3H), 3·86 (*s*, 3H), 3·84 (*s*, 3H), 2·65 (*m*, 2H), 1·26 (br *s*, 26H), 0·9 (*t*, 3H); mass spectrum: *m/e* 348 (M^+, 100), 151 (40), 136 (50) (Found: C, 79·3; H, 11·4. Calc. for $C_{23}H_{40}O_2$: C, 79·3; H, 11·6%).

Methylation of hydrobhilawanol with diazomethane was found to result in incomplete methylation.

Ethylation of hydrobhilawanol — A solution of hydrobhilawanol (1·5 g) was refluxed in acetone (50 ml) with ethyl iodide (2 g) and anhydrous potassium carbonate (10 g) for 24 hr and the product chromatographed over alumina in hexane to yield the diethyl ether (Ic) (0·9 g), m.p. 37-40° (from hexane) (Found: C, 80·3; H, 11·9. $C_{25}H_{44}O_2$ requires C, 79·7; H, 11·8%).

Methylation of bhilawanol — A solution of sodium (22 g) in absolute ethanol (700 ml) was added to bhilawanol (100 g). Methyl iodide (300 g) was then added and the solution refluxed in nitrogen for 12 hr. A solution of sodium (12 g) in ethanol (400 ml) was again added followed by methyl iodide (300 g). After refluxing for 24 hr more, the solution was evaporated, water added and the oil extracted with ether. The reddish oil obtained was refluxed for 1 hr with 3NKOH (300 ml) in 70% aqueous ethanol, diluted with water and extracted with hexane. The oil (60 g) obtained was chromatographed over alumina (1 kg) in hexane to yield a colourless oil (15 g). Repeated chromatography over silica gel yielded fraction A (5 g) (Vb) (M^+ at m/e 346) and fraction B (2·5 g) (VIIb) (M^+, m/e 344).

Catalytic reduction of methylbhilawanols — A solution of the above fraction A (1·2 g) in ethanol (40 ml) was reduced with hydrogen at atmospheric pressure in the presence of platinum oxide (0·3 g) to yield 3-pentadecylveratrole (1·2 g), m.p. 35-36° (from hexane), undepressed by an authentic sample. Reduction of fraction-B also yielded 3-pentadecylveratrole in quantitative yield.

Hydroxylation of methylbhilawanols — (1) A solution of fraction A (0·5 g) in dioxane (30 ml) was treated with osmium tetroxide (0·5 g) and a few drops of pyridine. After 3 days at 30°, the solution was saturated with hydrogen sulphide, filtered and evaporated. The residue was chromatographed over silica gel in benzene. Elution with benzene containing 1% methanol yielded the diol (VI) (0·4 g), m.p. 100-101° (from methylene chloride-hexane) (Found: C, 72·6; H, 10·8. Calc. for $C_{23}H_{40}O_4$: C, 72·6; H, 10·6%), mass spectrum: m/e 380 (M^+, 100), 362 (9), 266 (100), 265 (81), 152 (50), 151 (9), 137 (62), 136 (64), 121 (25).

(2) Fraction B (0·5 g) was treated similarly with osmium tetroxide (1 g) and the product chromatographed over silica gel. Elution with benzene containing 10% methanol yielded the tetraol (VIII) (0·3 g), m.p. 160-61° (from methanol) (Found: C, 67·1; H, 10·0. $C_{23}H_{40}O_6$ requires C, 67·0; H, 9·8%); mass spectrum: *m/e* 412 (M^+, 16), 340 (5), 304 (29), 303 (70), 266 (54), 265 (100), 264 (87), 205 (22), 191 (23), 177 (46), 152 (66), 151 (92), 137 (60), 136 (66), 121 (32).

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