CHEMICAL CONSTITUENTS OF *EVODIA MICROCOCCA*

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[*Manuscript received September* 9, 1960]

Summary

Leaf constituents of two varieties of *Evodia micrococca* have been investigated. Both varieties contained palmitic acid and n-hentriacontane but while *E. micrococca* F. Muell. var. *micrococca* yielded pinoresinol dimethyl ether and a trace of essential oil, *E. micrococca* var. *pubescens* Fraser & Vickery yielded (+)-sesamin and a larger quantity of a very different essential oil.

By the nitration of pinoresinol dimethyl ether, a 5,5′,6,6′-tetranitro derivative has been prepared and the structure of Freudenberg and Dietrich's (1953) lactone has been clarified. The ultraviolet absorption spectra of the four dinitroveratroles are included.

I. INTRODUCTION

Two varieties of *Evodia micrococca* are observed in the field and are distinguished as *E. micrococca* var. *pubescens* Fraser & Vickery (which retains the leaf hairs of the juvenile form in maturity) and *E. micrococca* F. Muell. var. *micrococca*, the mature leaves of which are free from hairs. A sample of each variety was examined for the presence of the chromenes characteristic of most other *Evodia* species (Kirby and Sutherland 1956) with negative results. The first smooth-leaf sample investigated was found to contain much pinoresinol dimethyl ether. Examination of additional samples, however, showed only traces of this lignan but revealed differences in composition between the two varieties which show an interesting chemical facet to the botanical variation.

II. DISCUSSION

Single samples of the two varieties were worked up by the procedure previously employed for the isolation of chromenes from other *Evodia* species—glycerol distillation of the ether extract of the dried leaves. Both varieties yielded considerable ether extracts (8·86 and 7·96% of dry leaf weight) but minor proportions of glycerol-volatile oil (0·26 and 0·87%), consisting of neutrals (0·12 and 0·47%), phenols (0·10 and 0·13%), and acids (0·03 and 0·17%) for var. *microrocca* and var. *pubescens* respectively. The ether extract of the former deposited a considerable quantity (2·9%) of crystalline pinoresinol dimethyl ether which was filtered off before commencing the glycerol distillation. Treatment of the various fractions by extraction, chromatography, and seeding yielded no phenolic or methoxylated chromenes as was also the case with *E. bonwickii* (Kirby and Sutherland 1956). Both varieties yielded palmitic acid and a paraffin

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or mixture of paraffins (Chibnall and Piper 1934), the melting point of which agrees most closely with that of n-hentriacontane. Only trace quantities of other crystalline substances could be isolated and none of these were identified.

The well-known lignan, pinoresinol dimethyl ether (I; $R_1=R_2=H$) is the enantiomorph of (−)-eudesmin, a constituent of the kinos of several *Eucalyptus* species (Maiden and Smith 1896; Robinson and Smith 1914), but was only recently first reported (Dryselius and Linberg 1956) as a plant constituent. Indeed, lignans have not previously been isolated from *Evodia* species. The identity of the isolate as pinoresinol dimethyl ether was confirmed by melting point, analysis, optical rotation, and ultraviolet spectrum and by conversion to the known 6,6′-dibromo-(I; $R_1=Br$ and $R_2=H$) and 6,6′-dinitro-(I; $R_1=NO_2$ and $R_2=H$) derivatives and to the diastereoisomeric epipinoresinol dimethyl ether. Pinoresinol dimethyl ether shows an *in vitro* bacteriostatic activity towards *Mycobacterium tuberculosis* (Ramaswamy and Sirsi 1957).

At this stage it appeared that var. *micrococca* leaves constituted a rich source of pinoresinol dimethyl ether whereas var. *pubescens* leaves contained little or no lignan. To provide a firmer basis for this conclusion, two further samples of each variety from a different locality were examined specifically for lignan content. Neither var. *micrococca* sample yielded crystals of pinoresinol dimethyl ether directly in the ether extract. By partitioning the ether extract between hexane and 90% methanol, saponifying the hypophase, and chromatographing the unsaponifiable fraction, small yields only (0·6 and 0·5%) of pinoresinol dimethyl ether were obtained from the var. *micrococca* samples. There was thus a surprisingly large variation (from >2·9 to 0·5%) in pinoresinol dimethyl ether content between the samples.

By the same procedure, the var. *pubescens* samples yielded by contrast, crystalline (+)-sesamin (0·3 and 0·25%), a lignan of identical structure and stereochemistry (Erdtman and Pelchowicz 1958) apart from the substitution of two methylenedioxy groups in place of the four methoxy groups of pinoresinol dimethyl ether. A trace of unidentified crystalline material isolated from the glycerol distillate from the first sample of var. *pubescens* proved to be (+)-sesamin also.

(+)-Sesamin is well known as a constituent of sesame oil, of *Asarum sieboldii* roots, and as a synergist with other insecticides (Hearon and MacGregor 1955). The identity of the isolate from *E. micrococca* var. *pubescens* was concluded from melting point, mixed melting point, analysis, optical rotation, ultraviolet spectrum, and conversion to the known dibromo derivative.

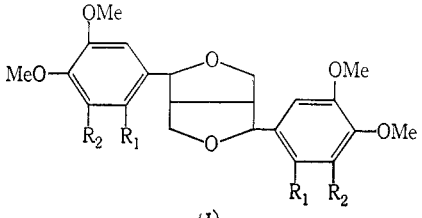
A comparison of the essential oils of the two varieties was made by submitting a combined sample of each variety to steam distillation for 6 hr and subjecting the oil obtained to gas chromatography on an Apiezon M column at 170 °C. The var. *micrococca* leaves yielded less than 0·03% of essential oil, the chromatogram of which showed 26 peaks and 3 shoulders indicating at least 29 constituents. The var. *pubescens* material yielded 0·22% of oil which showed 27 peaks and 3 shoulders. However only 11 relatively minor peaks were possibly common to both oils, which differed also in that the var. *pubescens* oil was rich in monoterpenes whereas the var. *micrococca* oil was substantially composed of

higher-boiling substances. The essential oils must thus be regarded as distinctive since they differ in yield, in general character, and in identity of most constituents.

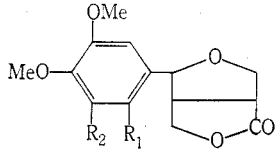
Even with the limited data presented above, it would seem very probable that the slight botanical difference between the two varieties, suggested by Mr. L. Smith (1958, personal communication) as probably the consequence of a one gene difference, is reflected in chemical differences in more than two classes of natural products. The present results require confirmation by examination of a much greater number of samples and preferably using a wider range of isolates. A similar examination of a suitable pair of Penfold's (1954) " physiological forms " (plants botanically identical but with differing essential oils) is also planned for evidence of differences concomitant with that of essential oil composition.

III. The Nitration of Pinoresinol Dimethyl Ether

According to the literature, mild nitrating conditions yield 6,6′-dinitropinoresinol dimethyl ether (Robinson and Smith 1914) and 6-nitropinoresinol dimethyl ether (Gripenberg 1946), whereas vigorous conditions result in cleavage of the veratrole-furan linkages with the formation of 4-nitro-, 4,5-dinitro- and 3,4,5-trinitroveratrole (Erdtman 1935), and bis(hydroxymethyl)succinic dilactone (Erdtman and Gripenberg 1947). The nitration conditions used by Robinson and Smith (1914) for the preparation of the dinitroveratrole yielded in our hands, however, a mixture of products separable by fractional crystallization or chromatography on alumina or by treatment with alkali, into neutral substances, mainly 4,5-dinitroveratrole, and an alkali-soluble fraction. This latter yielded a crystalline lactone, $C_{14}H_{14}N_2O_9$, m.p. 185–186 °C, presumably identical with that (m.p. 180 °C) previously obtained by Freudenberg and Dietrich (1953) by prolonged fractional crystallization of nitration products. This substance was designated as (II ; $R_1=R_2=H$) substituted by two nitro groups, the positions of which were not determined.



(I)



(II)

Since the formation of compounds such as 6-nitro-, 6,6′-dinitro-, and 6,6′-dibromopinoresinol dimethyl ether indicates position-6 is the most readily substituted, 5,6- or 2,6-disubstitution is more likely than 2,5-disubstitution. Reduction of the two nitro groups of the lactone and condensation of the resulting diamine with phenanthraquinone to yield a yellow crystalline phenanthraphenazine, confirmed the lactone as (II ; $R_1=R_2=NO_2$).

The presence of two nitro groups in the veratrole ring of this lactone suggested that a tetranitrolignan should also be produced in the nitration reaction, although no record of such compounds from this or similar lignans appears in the literature.

A search by chromatography of the residual neutral mother liquors remaining after the crystallization of the 4,5-dinitroveratrole, yielded a small quantity (1%) of the expected 5,5′,6,6′-tetranitropinoresinol dimethyl ether (I; $R_1=R_2=NO_2$) as pale yellow crystals, m.p. 221 °C. The assigned structure was confirmed by conversion to a bisphenanthraphenazine.

The nitration of pinoresinol dimethyl ether is thus analogous to the nitration of 3,4-dimethoxytoluene in yielding 6-(and 6′-)nitro and 5,6-(and 5′,6′-)dinitro substitution (Oberlin 1925; Oxford 1927) but shows in addition an alternative cleavage reaction promoted presumably by the electron-releasing properties of the furan oxygens of the lignan (de la Mare and Harvey 1957) since nitrodealkylation does not appear to have been observed in the nitration of homo-

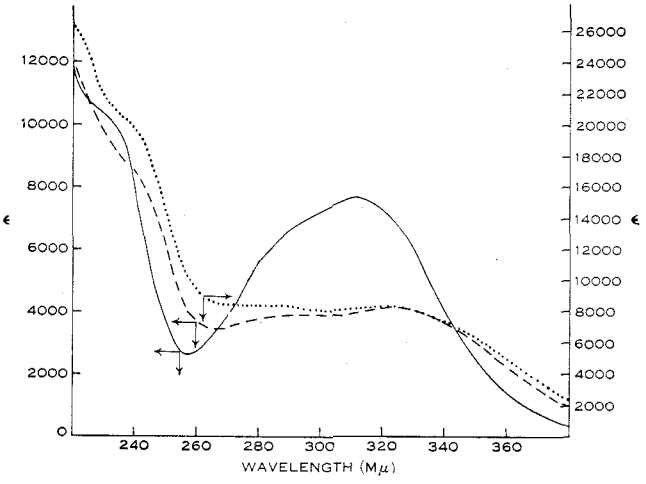


Fig. 1.—Ultraviolet absorption spectra in ethanol.
—— 3,4-Dinitroveratrole.
---- Dinitrolactone.
.... 5,5′,6,6′-Tetranitropinoresinol dimethyl ether.

veratrole or lignans lacking α-oxygenated side chains. The isolation of the dinitrolactone and the tetranitrolignan and the absence of trinitroveratrole from the nitration products formed under Robinson and Smith's conditions suggests, however, that the second (5- or 5′-) nitro group to enter the veratrole ring effectively suppresses cleavage of the veratrole-furan link. The resistance of the 5,6-dinitro compounds to cleavage at C_1 and to further nitration at C_2 was further demonstrated by refluxing the dinitro lactone in conc. nitric acid for 4 hr. The products were largely unchanged lactone and 5,6-dinitroveratric acid.

Evidence for the structures of the tetranitrolignan and the dinitrolactone was first sought by comparing their ultraviolet absorption spectra with those of the four dinitroveratroles, synthesized for this purpose. Both the lactone and tetranitrolignan can be regarded as alkylsubstituted 3,4-dinitroveratroles. Inspection of Figure 1 shows their spectra to be similar in gross features to that of 3,4-dinitroveratrole with the bathochromic shift expected from alkyl substitu-

tion. However, the extinction coefficients and wavelengths of maxima are probably influenced by steric interaction between the furan rings and the adjacent nitro group aggravating the crowding known to exist between *ortho*-nitro groups (Abe 1960). A study of molecular models supports this view and discourages attempts to draw structural conclusions from the absorption data. The spectra (see Table 1) for the 3,5-, 4,5-, and 3,6-dinitroveratroles on the other hand, afford even less satisfactory comparisons with the substances in question.

TABLE 1

ULTRAVIOLET ABSORPTION SPECTRA OF VARIOUS DINITROVERATROLES

3,4-Isomer		3,5-Isomer		3,6-Isomer		4,5-Isomer	
λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε	λ (mμ)	ε
220	11800	220	14600	220	13500	220	10500
225	10760(s)*	245·5	8500(n)	240	5755	240·5	14100(m)
257·5	2650(n)*	255	8680(m)	245	5630(s)	265·5	6140(s)
280	5430	280	5260	250	5560	285	4450(n)
300	7180	307·5	4080(n)	287·5	1960(n)	307	4850(s)
312	7650(m)*	328	4630(m)	311	2320(m)	333	5160(m)
340	4110	340	3900	340	1610	380	2280
380	380	380	274	380	270	400	650

* (m), maximum ; (n), minimum ; (s), inflection point.

IV. EXPERIMENTAL

(*a*) *Extraction of* E. micrococca *var.* pubescens.—Dried leaves (SN 5558 ; 2·35 kg) gathered in February from Brookfield, Brisbane, on ether extraction yielded 187 g of dark oil. Working up in the same manner as in the previous paper (Kirby and Sutherland 1956) resulted in 20·4 g of glycerol-volatile oil, consisting of 11·5 g neutrals, 3·5 g phenols, and 4·0 g acids. Both the phenol fraction and the acid fraction crystallized to yield palmitic acid. The neutral fraction deposited waxy crystals which after several recrystallizations from ethyl acetate gave colourless platelets, m.p. 66·8–67·7 °C. These were optically inactive and did not dissolve in conc. H_2SO_4 (Found : C, 85·6 ; H, 14·9%. Calc. for $C_{31}H_{64}$: C, 85·3 ; H, 14·7%). Distillation of the neutrals at 0·7 mm resulted in no homogeneous fraction and the residue (1·1 g) was chromatographed on an alumina column. The first fraction yielded more crystalline paraffin. Three other crystalline substances were obtained in quantity too small for analysis, including one crystallizing from methanol as colourless needles, m.p. 121·5–122 °C. This was later shown by mixed melting point test and crystalline habit to be (+)-sesamin.

(*b*) *Extraction of* E. micrococca *var.* micrococca.—Air-dry leaves (SN 5552 ; 1·52 kg) gathered in January at Springbrook, Qld., were extracted with ether. The crude extract deposited crystals of pinoresinol dimethyl ether (44 g). Washing with ether and crystallization from ethanol and from ethyl acetate yielded colourless chunky crystals, m.p. 106·3–106·9 °C, $[\alpha]_D^{20}$ +63·8° (*c*, 4·6% in $CHCl_3$), light absorption in ethanol : $\lambda_{max.}$ (mμ) 232, 279 ; log ε 4·29, 3·76 (Found : C, 68·6 ; H, 6·9 ; OMe, 31·2% ; mol. wt., 370. Calc. for $C_{22}H_{26}O_6$: C, 68·4 ; H, 6·8 ; OMe, 32·0% ; mol. wt., 386). Robinson and Smith (1914) report m.p. 107 °C, $[\alpha]_D^{21}$ —64·3° for eudesmin, and Erdtman and Erdtman (1944) find $\lambda_{max.}$ 230 and 280 mμ.

The lignan was brominated (Robinson and Smith 1914) to yield the 6,6′-dibromo derivative, m.p. 171·5–172·5 °C, $[\alpha]_D^{21}$ —68·3° (*c*, 1·2% in $CHCl_3$) and nitrated to the 6,6′-dinitro derivative, m.p. 212–213 °C, $[\alpha]_D^{19}$ —122·8° (*c*, 0·8% in $CHCl_3$).

The remaining oil (91 g) yielded 4·0 g of glycerol-volatiles consisting of 1·8 g neutrals, 1·6 g phenols, and 0·5 g acids. Palmitic acid and the paraffin were isolated and identified as above. Chromatography of the neutrals on alumina yielded in addition to oils only minute amounts of the following crystalline materials in order of elution (i) paraffin, (ii) colourless crystals, m.p. 234–240 °C, (iii) colourless crystals from methanol, m.p. 75·6–77·6 °C, (iv) colourless crystals from methanol, m.p. 124–130 °C, and (v) colourless crystals from ethyl acetate, m.p. 226·5–228 °C; of these (ii) was not identical with aromadendrin and (iii) was not identical with *allo*evodione.

(*c*) *Examination of Leaf Samples for Lignan Content.*—Two leaf samples of both varieties (SN6206 and SN6207) gathered at Whian Whian, N.S.W., in June, were oven-dried and finely ground. Samples of 50 g were extracted with ether in a Soxhlet for 24 hr. The green oily residues obtained did not yield crystals directly as in (*b*) above. They were each dissolved in a mixture of 100 ml each of mutually saturated " Stanvac " hexane and 90% methanol and were equilibrated. (The distribution coefficient of pinoresinol dimethyl ether in this system is 0·06.) Each layer was then washed with 25 ml of the other solvent and the two wash layers were later equilibrated with each other. The two hypophases were combined and refluxed for 1 hr in the water-bath with the addition of KOH (5 g). After removal of the methanol, dilution with water, extraction with ether, and washing, drying, and evaporation of the ether layers, orange to red gums resulted.

The gums were dissolved in benzene and chromatographed on alumina (grade II, alkaline) columns (20 × 2·5 cm) until benzene (1 l.) had passed through. The solvent was changed to a mixture of 20% by volume of commercial chloroform in benzene. Both pinoresinol dimethyl ether and sesamin eluted after 300 ml and before 500 ml of this eluant. Rechromatography was necessary in one case where the saponification had been omitted. The crude products after one recrystallization from ethanol, melted at 102–105 °C and 102–104 °C for var. *micrococca* and 115–118 °C and 114–117 °C for var. *pubescens*. Only traces of other crystalline products were observed.

(*d*) *Identification of Sesamin.*—Mixed var. *pubescens* leaf was extracted with ether and crude sesamin, m.p. 118–121 °C isolated as in (*c*). Recrystallization from ethanol yielded laths which occasionally formed large rafts of crystals 2–3 cm long and 0·5 cm wide, of m.p. 121–122 °C, $[\alpha]_D^{22}$ +60° (*c*, 4% in $CHCl_3$), light absorption in 95% ethanol; $\lambda_{max.}$ (mμ) 235·5, 287; ε 9450, 8300 (Found: C, 67·7; H, 5·2%; OMe, nil. Calc. for $C_{20}H_{18}O_6$: C, 67·8; H, 5·1). The dibromide formed needles, m.p. 181–182 °C from ethanol. For literature values see Hearon and MacGregor (1955). There was no depression of melting point on mixing with a sample of (+)-sesamin prepared from (+)-asarinin (Davenport and Sutherland 1954).

(*e*) *Isomerization of Pinoresinol Dimethyl Ether.*—Pinoresinol dimethyl ether (7·5 g) in 675 ml ethanol and 75 ml HCl were refluxed 17 hr, diluted with 500 ml water, and then extracted with chloroform. The first crops from slow crystallization from ethanol consisted of epipinoresinol dimethyl ether, m.p. 129–130 °C, $[\alpha]_D^{29}$ +140·3° (*c*, 2·2% in $CHCl_3$) (Found: C, 68·4; H, 7·0%. Calc. for $C_{22}H_{26}O_6$: C, 68·4; H, 6·8%. The literature records m.p. 130–131 °C, $[\alpha]_D$ +141° for this substance.

(*f*) *Nitration of Pinoresinol Dimethyl Ether.*—Pinoresinol dimethyl ether (5 g) was refluxed with 50 ml conc. HNO_3 for 10 min (Robinson and Smith's conditions) and then poured into water. The crude product was filtered and shaken vigorously for several hours with separate batches of 5% aqueous KOH. Filtration and acidification of the filtrate precipitated the lactone (1·1 g) which crystallized from methanol as fine, pale yellow needles, m.p. 185–186 °C, $[\alpha]_D^{24·5}$ −93·7° (*c*, 2·2% in $CHCl_3$); light absorption in ethanol: $\lambda_{max.}$ 293, 323 mμ, ε 3900, 4150. Freudenberg and Dietrich (1953) record m.p. 180 °C (Found: C, 47·7; H, 4·1; N, 8·1; OMe, 17·5%. Calc. for $C_{14}H_{14}N_2O_9$: C, 47·5; H, 4·0; N, 7·9; OMe, 17·5%).

The alkali-insoluble material (3·9 g) was crystallized from ethanol to yield yellow crystals (3·8 g) of 4,5-dinitroveratrole, m.p. 129–130 °C (Found: C, 42·1; H, 3·4; N, 12·2; OMe, 27·8%. Calc. for $C_8H_8N_2O_6$: C, 42·1; H, 3·5; N, 12·3; OMe, 27·2%).

The mother liquors from this crystallization were chromatographed on alumina to yield more 4,5-dinitroveratrole and also 5,5′,6,6′-tetranitropinoresinol dimethyl ether in low yield (50 mg). This crystallized from ethyl acetate as pale yellow crystals, m.p. 221–221·5 °C (Found: C, 46·6;

H, 4·1; N, 9·6; OMe, 21·7%. Calc. for $C_{22}H_{22}N_4O_{14}$: C, 46·6; H, 4·0; N, 9·9; OMe, 21·9%); light absorption in ethanol: $\lambda_{max.}$ 322 mμ; ε 8300.

(*g*) *Nitration of Dinitropinoresinol Dimethyl Ether.*—6,6′-Dinitropinoresinol dimethyl ether (104 mg) on refluxing with conc. HNO_3 (1 ml) for 10 min, yielded crude 4,5-dinitroveratrole (67 mg, m.p. 125–130 °C) as the neutral product and the C_{14}-lactone from the alkali extracts as in (*f*).

(*h*) *Phenanthraphenazine Derivatives.*—5,5′,6,6′-Tetranitropinoresinol dimethyl ether (22 mg) was dissolved in 2 ml hot acetic acid and 1 ml conc. HCl. Zinc dust (1 g) was then added and the mixture filtered. A solution of phenanthraquinone (18 mg) in aqueous sodium bisulphite/sodium acetate was then added, the mixture boiled for 15 min, and then added to water. Crystallization of the precipitate from pyridine yielded the bisphenanthraphenazine as yellow crystals, which did not melt below 400 °C and at that temperature decomposed slowly in the melting point tube (Found: C, 75·4; H, 5·2%. Calc. for $C_{50}H_{38}N_4O_6$: C, 75·9; H, 4·8%).

The C_{14}-lactone (60 mg) was treated as above with the substitution of ethanol for acetic acid. The product was crystallized from glacial acetic acid to yield yellow crystals, m.p. 284 °C, with a yellow-green fluorescence in benzene (Found: C, 71·1; H, 4·9; N, 6·3%. Calc. for $C_{28}H_{22}N_2O_5$: C, 72·1; H, 4·7; N, 6·0%).

(*i*) *Action of Nitric Acid on the Lactone.*—The C_{14}-lactone (270 mg) was refluxed with 3 ml conc. HNO_3 for 4 hr. The diluted reaction mixture was extracted with ether after filtering off unchanged lactone, and from the ether was obtained 160 mg of bicarbonate-soluble material. Crystallization of this from methanol yielded a further small quantity of lactone. The mother liquors after evaporation were crystallized from water to yield pale yellow crystals (30 mg) of 5,6-dinitroveratric acid, m.p. 192–192·5 °C (Found: C, 39·8; H, 3·15; N, 9·5; OMe, 22·8%. Calc. for $C_9H_8N_2O_8$: C, 39·7; H, 2·9; N, 10·3; OMe, 22·8%). The literature (Klemenc 1912) gives m.p. 193 °C. The acid gives a white precipitate with ferric chloride solution and depresses the melting point of the lactone.

(*j*) *Ultraviolet Absorption Spectra of the Dinitroveratroles.*—These were synthesized by known procedures (Jones and Robinson 1917; Oxford 1926; Baker and Robinson 1929). The intermediate nitroguaiacols, being rather strongly acidic, were methylated satisfactorily by using diazomethane rather than the reagents previously employed. Chromatography on alumina in light petroleum, benzene, etc. was found satisfactory for separating the various products, the order of elution being 3,6-, 3,5-, and 3,4-dinitroveratroles.

The data obtained from the examination of the ultraviolet spectra in 95% ethanol is summarized in Table 1.

V. Acknowledgments

We wish to thank the staff of the Phytochemical Survey, C.S.I.R.O., Brisbane, for provision of plant material, and Mr. L. S. Smith of the Queensland Herbarium, for botanical advice.

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