Ebenaceae Extractives. Part 10.[1] Macassaric Acid, an *o*-Methoxycarbonylcinnamic Acid from Macassar Ebony

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Macassaric acid is shown to be the *cis*-cinnamic acid derivative (**3**). The corresponding methyl ester (**4**) is synthesised from the *o*-naphthoquinone (**9**) *via* the cyclic unsaturated anhydride (**8**). Related reactions give the isochromenone (**10**), the methoxy anhydride (**13**), and the *trans*-cinnamic acid (**15**) and its methyl ester. Macassaric acid appears to be a catabolic product of macassar II (**1**).

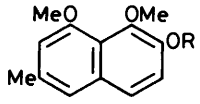
The extractives from macassar ebony, the heartwood of *Diospyros celebica* Bakh, so far reported include the dimethoxynaphthol macassar II (**1**) and its methyl ether macassar III (**2**),[2] and several naphthoquinones[1] and binaphthoquinones.[1,3] We now describe the acid $C_{13}H_{14}O_5$ which is the most polar product obtained from the chloroform extract[1] of the wood. We propose the name 'macassaric acid' for this compound.

The IR spectrum of macassaric acid indicates that it contains an α,β-unsaturated carboxylic acid and an ester group, while its UV absorption is typical of a benzenoid rather than a naphthalenoid system. Macassaric acid contains two oxygen atoms more than does macassar II (**1**) and this suggested to us that the acid might be a product of the oxidative ring cleavage of the latter and would in consequence have the structure (**3**). The NMR signals proved to be in full agreement with this formula. Singlets (3 H) at δ 2.33, 3.82, and 3.83 correspond to the protons of the aryl methyl, methoxy, and methoxycarbonyl groups respectively, while an AB quartet (2 H) centred at δ 5.98 and 7.13 results from the olefinic protons, the coupling constant (*J* 12 Hz) of which establishes their *cis* relationship (*cf. cis*-cinnamic acid,[4] *J* 12.3 Hz). Finally, the broad singlets (1 H) at δ 6.71 and 6.78 correspond to the *meta*-coupled aryl protons. There is no distinct signal from the carboxy proton, presumably because of a rapid exchange process. We confirmed the presence of the carboxy group by treating macassaric acid with ethereal diazomethane to give the methyl ester (**4**) which showed a new singlet (3 H) at δ 3.62.

The above data do not establish conclusively the position of the ester methyl group in macassaric acid and we therefore compared its NMR and mass spectra with those of two simple possible analogues, 2-methoxybenzoic acid (**5**), and the corresponding methyl ester (**6**). The protons of the hydrogen-bonded methoxy group of the acid (**5**) give rise to a signal at δ 4.05, while, in contrast, the methyl groups of the methoxy ester (**6**) appear as a singlet (6 H) at δ 3.86, in excellent agreement with those shown by macassaric acid. The methoxy acid (**5**) gives the mass spectral fragment ions *inter alia* $(M - 18)^+$ (4%) and $(M - 19)^+$ (4.5%), the latter of which may be represented by the cyclic structure (**7**). The methoxy ester (**6**) behaves differently giving a fragment ion $(M - 33)^+$ [*i.e.* $(M - Me - H_2O)^+$] (32%) which however can also be represented by structure (**7**). The mass spectrum of macassaric acid shows the absence of $(M - 18)^+$ and $(M - 19)^+$ ions but does include a relatively abundant $(M - 33)^+$ ion (9%). We conclude that it is not the carboxy group but the methoxycarbonyl group in macassaric acid which is adjacent to the aryl methoxy group, as shown in structure (**3**).

The cyclic anhydride (**8**) is an obvious precursor in a synthesis of macassaric acid or its methyl ester and we sought to prepare it by the Baeyer–Villiger oxidation[5] of the *o*-naphthoquinone (**9**) which we had previously isolated[1] from macassar ebony. No reaction occurred between the *ortho*-quinone and *m*-chloroperbenzoic acid using benzene, methanol, or ether as solvent but in chloroform solution the quinone reacted with an excess (2.55 mol. equiv.) of the peracid to give a neutral compound $C_{14}H_{14}O_5$. The IR absorption bands at 1 743 and 1 730 cm^{-1} suggested that the product contained an unsaturated lactone and an α,β-unsaturated ester group while the NMR signals indicated the presence of an ethoxycarbonyl group, an aryl methyl and an aryl methoxy group, two *meta*-coupled aromatic protons, and one olefinic proton. Our formulation of the compound as the ethoxycarbonylisochromenone (**10**) is supported by the close resemblance of its UV absorption to that[6] of the acid (**11**). The ethoxy group must of course originate in the ethanol which is present in chloroform as a stabiliser. The formation of the isochromenone presumably involves an initial Baeyer–Villiger reaction and the resulting unsaturated anhydride (**8**) then undergoes epoxidation. The addition of ethanol and the opening of the oxirane ring as in (**12**) gives a 4-hydroxyisochromanone which finally undergoes dehydration producing the isochromenone (**10**). When we repeated the peracid oxidation of the *o*-naphthoquinone (**9**) using chloroform which was free from ethanol, and a smaller excess (1.4 mol. equiv.) of *m*-chloroperbenzoic acid, we obtained the desired anhydride (**8**) without difficulty; it exhibits the expected spectral properties.

The opening of the seven-membered ring of the anhydride (**8**) proved to be unexpectedly difficult to control. The reaction of the pure compound with methanol either with or without the addition of sulphuric acid or pyridine produced a neutral compound $C_{13}H_{14}O_5$ which gave IR bands at 1 766 and 1 741 cm^{-1} showing that the anhydride system remained intact. Its NMR spectrum showed a general resemblance to that of the parent unsaturated anhydride (**8**) except that signals attributable to $-CH(OMe)CH_2-$ replaced the olefinic AB quartet of the latter. The product is therefore the dimethoxyanhydride (**13**) and results from the conjugate addition of methanol to the α,β-unsaturated carbonyl system of the anhydride (**8**). Brief treatment of the anhydride (**8**) at 0 °C with a stronger nucleophile, methanolic potassium hydroxide, followed by acidification and methylation of the product using diazomethane was successful in leading to anhydride ring opening. The products however proved to be the *trans*-cinnamic acid (**15**) (*J* 16 Hz[4]) and its methyl ester (**16**). The NMR signals of the *trans*-acid confirm that, as with macassaric acid (**3**), the free carboxy group is attached to the olefinic system, as in (**15**), and not to the aromatic ring. Thus the *trans*-ester (**16**) shows methoxy proton



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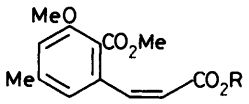

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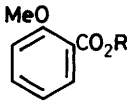

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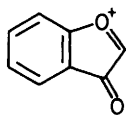

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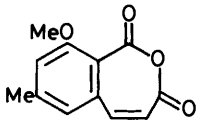

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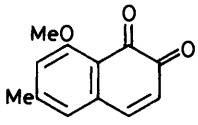

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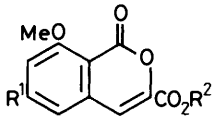

(10) R^1 = Me; R^2 = Et
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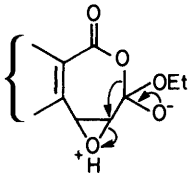

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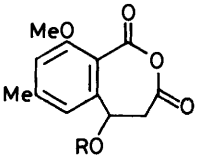

(13) R = Me
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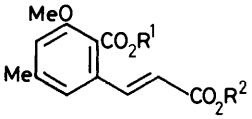
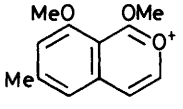


(15) R^1 = Me; R^2 = H
(16) R^1 = R^2 = Me
(17) R^1 = R^2 = H



(18)

signals at δ 3.78, 3.83, and 3.93, two of which are almost identical with the signals at δ 3.84 and 3.94 shown by the corresponding protons of the *trans*-acid (15). The third such signal given by the *trans*-ester, at δ 3.78, resembles closely that at δ 3.76 from the methyl protons of methyl *trans*-cinnamate itself. It follows that the *trans*-acid (**15**) must contain a cinnamic acid grouping.

The acid-catalysed isomerisation of *cis*-cinnamic acid is known[7,8] to occur *via* the conjugate addition of water to the α,β-unsaturated carbonyl system followed by dehydration to give the more stable *trans*-isomer and the formation of the *trans*-acid (**15**) from the *cis*-anhydride (**8**) would appear to involve a related reaction sequence. We suggest that the conjugate addition of hydroxide ion to the *cis*-anhydride leads to the formation of the adduct (**14**) which then undergoes hydroxide-induced opening of the anhydride ring to give the dicarboxylate anion. Acidification of the latter is accompanied by dehydration to give the *o*-carboxy-*trans*-cinnamic acid (**17**). The subsequent preferential esterification of the aromatic carboxy group by diazomethane to give the mono-ester (**15**) may be a consequence of the donor properties of the methoxy group which would help to stabilise the intermediate methanediazonium cation and thereby favour reaction with the nearer of the two adjacent carboxy groups.

The reported[9] formation of a monomethyl ester of *o*-carboxycinnamic acid by the oxidation of *o*-naphthoquinone with monoperphthalic acid in ethereal methanol suggested to us that the presence of a carboxylic acid might promote the ring-opening of an *o*-carboxycinnamic anhydride in the desired manner, *i.e.* without isomerisation. Accordingly we oxidised the *o*-naphthoquinone (**9**) with *m*-chloroperbenzoic acid in ethanol-free chloroform and then treated the resulting mixture of the anhydride (**8**), *m*-chlorobenzoic acid, and the excess of the peracid, with methanol. The mass spectrum of the crude product indicated the presence of macassaric acid, or an isomer, but we were unable to isolate this component. Methylation with diazomethane produced a mixture of esters which on separation by TLC gave the methyl ester of macassaric acid (**4**).

The ion at *m/z* 205 which is by far the most abundant in the mass spectra of both macassaric acid and its *trans*-isomer (**15**) results from the loss of OH$^{\bullet}$ and CO from the molecular ions concerned. The corresponding methyl esters (**4**) and (**16**) also give a base peak with *m/z* 205. We suggest that the fragment having *m/z* 205 is the 3,4-benzopyrylium ion (**18**), in which the mesomeric effects of the two methoxy groups assist in the delocalisation of the positive charge.

Catalin models of the *trans*-acid (**15**) and its methyl ester (**16**) reveal that in these compounds the unsaturated side chain can adopt a conformation in which the –CH=CHCO$_2$R group is coplanar with, and therefore conjugated with, the aromatic system. In both macassaric acid (**3**) and its methyl ester (**4**), however, the *cis*-configuration of the groups attached to the double bond prevents the attainment of such coplanarity and in each case the –CH=CHCO$_2$R group now lies in a plane approximately perpendicular to that of the aromatic ring. The resulting decrease in the extent of conjugation accounts for the higher carbonyl frequencies in the IR spectrum for the unsaturated acid and ester groups of these compounds and also for the shift to shorter wavelengths of their UV absorption. The Catalin model of the methyl ester of macassaric acid (**4**) shows that the *cis*-CH=CHCO$_2$Me side-chain curls over the aromatic ring in the same way as the tail of a scorpion curls over its body. This scorpioid conformation results in the protons of the ester methyl group being within the shielding cone of the aromatic ring and consequently resonating at higher field than do the corresponding protons of the *trans*-ester (**16**). The difference in the chemical shifts of the two esters (0.16 ppm) is close to that observed (0.19 ppm) for the methyl protons of the non-planar *cis*- and the planar *trans*-isomers of methyl *o*-cyanocinnamate.[10]

The two methoxy groups in macassaric acid (**3**) are in positions which correspond to those of the methoxy groups in macassar II (**1**). This provides strong evidence that the acid results from the *ortho*-cleavage of macassar II by an oxygen/dioxygenase system present in the wood.[11,12]

Experimental

General instructions are given in Parts 4[13] and 5.[14] Mass spectra were obtained using an AEI MS-30 spectrometer at 70eV. UV absorption spectra were measured for methanolic solutions.

Macassaric Acid (**3**).—The most polar fraction from the chloroform extract[1] of *D. celebica* Bakh heartwood (1.4 kg) crystallised from chloroform–light petroleum to give *macassaric acid* as needles (833 mg), m.p. 140–141 °C (Found: M^+, 250.0842. $C_{13}H_{14}O_5$ requires M^+, 250.0841); ν_{max} 3 200–2 600 (carboxylic OH), 1 729 (aromatic ester C=O), 1 710 (α,β-unsaturated acid C=O), and 1 643 and 1 606 cm^{-1} (conjugated *cis* –CH=CH–); λ_{max} 257 nm (log ε 3.63), λ_{infl} 296 nm (log ε 3.15); δ 2.33 (3 H, s, ArMe), 3.82 and 3.83 (each 3 H, s, ArOMe and $ArCO_2Me$), 5.98 and 7.13 (2 H, ABq, *J* 12 Hz, *cis* Ar*CH*=*CH*CO_2H), and 6.71br and 6.78br (each 1 H, s, 4- and 6-H); *m/z* 250 (10%, M^+), 219 [4, $(M - MeO)^+$], 217 [9, $(M - Me - H_2O)^+$], 205 [100, $(M - HO - CO)^+$], 191 [20, $(M - MeO - CO)^+$], 175 (11, 205 – CH_2O), and 173 (8, 205 – MeO – H). It is soluble in hot water and in aqueous sodium hydrogen carbonate.

Treatment of macassaric acid (25 mg) with an excess of ethereal diazomethane gave an oil which after TLC and crystallisation from light petroleum gave *methyl 3-methoxy-2-methoxycarbonyl-5-methyl*-cis-*cinnamate* (**4**) (21 mg), as prisms, m.p. 52 °C (Found: M^+, 264.0998. $C_{14}H_{16}O_5$ requires M^+, 264.0997); ν_{max} 1 730 (aromatic ester and α,β-unsaturated ester C=O), and 1 642 and 1 607 cm^{-1} (conjugated *cis* –CH=CH–), λ_{infl} 265 nm (log ε 3.71); δ 2.36 (3 H, s, ArMe), 3.62 (3 H, s, ArCH=CHCO$_2$*Me*), 3.83 (6 H, s, $ArOCH_3$ and $ArCO_2Me$), 5.98 and 7.04 (2 H, ABq, *J* 12 Hz, *cis* Ar*CH*=*CH*CO_2Me), and 6.71br and 6.80br (each 1 H, s, 4- and 6-H); *m/z* 264 (7%, M^+), 233 [7, $(M - MeO)^+$], 217 [6, $(M - Me - MeOH)^+$], 205 [100, $(M - MeO - CO)^+$], 190 (4, 205 – Me), 189 (4, 217 – CO), and 173 (4, 205 – MeO – H).

Oxidation of 8-*Methoxy*-6-*methyl*-1,2-*naphthoquinone with* m-*Chloroperbenzoic Acid*.—(*a*) A solution of the quinone[2] (**9**) (0.11 g) and *m*-chloroperbenzoic acid (0.24 g, 2.55 mol. equiv.) in chloroform (10 ml) was kept at 10 °C for 2 days and then shaken with aqueous sodium hydrogen carbonate. The chloroform layer was evaporated and the residue, after TLC and crystallisation from light petroleum–chloroform, gave 3-*ethoxycarbonyl*-8-*methoxy*-6-*methylisochromenone* (**10**) as needles (35 mg), m.p. 143–144 °C (Found: M^+, 262.0842. $C_{14}H_{14}O_5$ requires M^+, 262.0841); ν_{max} 1 743 (unsaturated lactone C=O), 1 730 (α,β-unsaturated ester C=O), and 1 653 cm^{-1} (conjugated C=C); λ_{max} 246 (log ε 4.27), 265 (3.99), and 334 nm (3.56), λ_{infl} 273 nm (log ε 3.96); δ 1.42 (3 H, t, *J* 7 Hz, –CO_2CH_2*Me*), 2.44 (3 H, s, ArMe), 3.99 (3 H, s, ArOMe), 4.46 (2 H, q, *J* 7 Hz, –CO_2CH_2Me), 7.01br and 7.51br (each 1 H, s, 7- and 5-H), and 7.08 (1 H, s, 4-H); *m/z* 262 (100%, M^+), 234 [32, $(M - CO)^+$], and 219 (18, 234 – Me).

(*b*) A similar reaction between the quinone (**9**) (0.5 g) and *m*-chloroperbenzoic acid (0.6 g, 1.40 mol. equiv.) in chloroform which had been washed with concentrated sulphuric acid to remove ethanol gave the anhydride 9-*methoxy*-7-*methyl*-2-*benzoxepine*-1,3-*dione* (**8**) (240 mg) which crystallized from benzene as needles, m.p. 141–142 °C (Found: M^+, 218.0576. $C_{12}H_{10}O_4$ requires M^+, 218.0579); ν_{max} 1 772 and 1 735 cm^{-1} (unsaturated cyclic anhydride C=O); λ_{max} 246 (log ε 4.08), and 325 nm (3.55), λ_{infl} 287 nm (log ε 3.74); δ 2.41 (3 H, s, ArMe), 3.90 (3 H, s, ArOMe), 6.28 and 7.10 (2 H, ABq, *J* 12 Hz, *cis* Ar*CH*=*CH*CO–), and 6.76br and 6.90br (each 1 H, 4- and 6-H); *m/z* 218 (100%, M^+), 190 [10, $(M - CO)^+$], 174 [7, $(M - CO_2)^+$], 145 (63, 174 – CHO), and 115 (79, 145 – CH_2O).

Reactions of the Anhydride (**8**).—(*a*) A solution of the anhydride (**8**) (20 mg) in methanol (20 ml) was kept at 20 °C for 2 days. Evaporation and TLC of the residue gave 5,9-*dimethoxy*-7-*methyl*-4,5-*dihydro*-2-*benzoxepine*-1,3-*dione* (**13**) as a liquid (20 mg) (Found: M^+, 250.0844. $C_{13}H_{14}O_5$ requires M^+, 250.0841); ν_{max} 1 766 and 1 741 cm^{-1} (unsaturated cyclic anhydride C=O); λ_{max} 244 nm (log ε 3.96) and 297 (3.66), λ_{infl} 292 nm (log ε 3.62); δ 2.44 (3 H, s, ArMe), 2.82 [2 H, d, *J* 7 Hz, –CH(OMe)C*H*$_2$–], 3.73 (3 H, s, =CHO*Me*), 3.94 (3 H, s, ArOMe), 5.70 [1 H, t, *J* 7 Hz, –C*H*(OMe)CH_2–], and 6.72 and 6.76 (each 1 H, s, 4- and 6-H); *m/z* 250 (50%, M^+), 191 [11, $(M - MeO - CO)^+$], 190 [50, $(M - MeO - CHO)^+$], 177 [100, $(M - MeO - CH_2CO)^+$], and 173 (10, 190 – OH).

(*b*) A mixture of the anhydride (**8**) (60 mg) and methanolic potassium hydroxide (2%; 2.5 ml) was kept at 0 °C for 15 min, the solvent was evaporated off, and the residue was shaken with 0.5M sulphuric acid (2 ml) and ether (35 ml). The dried (Na_2SO_4) ethereal solution was added to ethereal diazomethane (0.25%; 9 ml) and kept at 20 °C for 1 h. Evaporation gave an oil which was separated by TLC into two fractions. Fraction 1 crystallised from light petroleum–chloroform to yield *methyl* 3-*methoxy*-2-*methoxycarbonyl*-5-*methyl*-trans-*cinnamate* (**16**) as needles (19 mg), m.p. 95–96 °C (Found: M^+, 264.0998. $C_{14}H_{16}O_5$ requires M^+, 264.0997); ν_{max} 1 734 (aromatic ester C=O), 1 718 (alkyl cinnamate C=O), and 1 647 cm^{-1} (*trans* –CH=CH–); λ_{max} 237 (log ε 4.19), 278 (4.13), and 316 nm (3.52); δ 2.37 (3 H, s, ArMe), 3.78, 3.83, 3.93 (each 3 H, s, –CO_2CH_3, $ArCO_2Me$, and ArOMe), 6.35 and 7.62 (2 H, ABq, *J* 16 Hz, *trans* –Ar*CH*=*CH*CO_2–), and 6.76br and 7.02br (each 1 H, s, 4- and 6-H); *m/z* 264 (2%, M^+), 233 [2.5, $(M - MeO)^+$], 217 [2, $(M - Me - MeOH)^+$], and 205 [100, $(M - MeO - CO)^+$]. Fraction 2 crystallised from light petroleum–chloroform to yield 3-*methoxy*-2-*methoxycarbonyl*-5-*methyl*-trans-*cinnamic acid* (**15**) as needles (33 mg), m.p. 187 °C (Found: M^+, 250.0842. $C_{13}H_{14}O_5$ requires M^+, 250.0841); ν_{max} 3 100–2 550 (carboxylic OH), 1 734 (aromatic ester C=O), 1 680 (cinnamic acid C=O), and 1 634 cm^{-1} (*trans* –CH=CH–); λ_{max} 230 (log ε 4.29), 270 (4.17), and 313 nm (3.43); δ 2.39 (3 H, s, ArMe), 3.84 and 3.94 (each 3 H, s, $ArCO_2Me$ and ArOMe), 6.38 and 7.73 (2 H, ABq, *J* 16 Hz, *trans* Ar*CH*=*CH*CO_2H), 6.79br and 7.06br (each 1 H, s, 4- and 6-H); *m/z* 250 (4%, M^+), 217 [3, $(M - Me - H_2O)^+$], 205 [100, $(M - OH - CO)^+$], 191 [6, $(M - MeO - CO)^+$], and 175 (8, 205 – CH_2O).

(*c*) A solution of 8-methoxy-6-methyl-1,2-naphthoquinone (**9**) (0.10 g) and *m*-chloroperbenzoic acid (0.15 g, 1.75 mol. equiv.) in ethanol-free chloroform was kept at 10 °C for 2 days and then evaporated. The residual solid was treated with methanol at 20 °C for 2 days, the solvent was again evaporated off, and the residue was treated with an excess of ethereal diazomethane at 20 °C for 1 day. Separation of the resulting mixture of methyl esters by repeated TLC gave methyl 3-methoxy-2-methoxycarbonyl-5-methyl-*cis*-cinnamate (**4**) (22 mg), m.p. 52 °C (from light petroleum–chloroform), which was identical with the product obtained by the methylation of macassaric acid.

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