The Structure of Lapachenole, a Hardwood Extractive.

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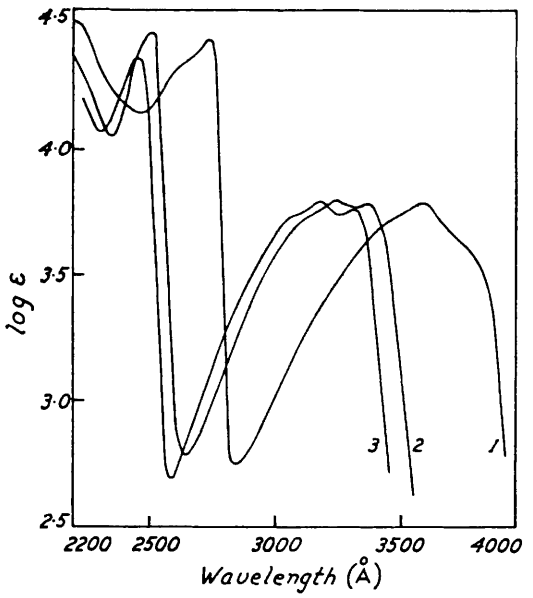
The name " lapachenole " is proposed for a substance present in the wood of " Brazilian white peroba." Its structure has been elucidated as 4′-methoxy-6 : 6-dimethylnaphtho(1′ : 2′-2 : 3)pyran (III), and confirmed by the total synthesis of its dihydro-compound.

BECAUSE of reports that use of the hardwood " Brazilian white peroba " (*Paratecoma alba*) was causing dermatitis, an attempt was made to isolate the active constituent. The (active) neutral fraction of the light petroleum extract yielded a compound, $C_{16}H_{16}O_2$, m. p. 62°, which appeared to be identical with a substance isolated by Manuelli (*Atti Acad. Lincei*, 1900, **9**, 102, 314; 1913, **22**, 686, see *Chem. Zentr.*, 1900, II, 727; 1901, I, 114; 1914, I, 984) from " lapacho wood," probably the same species and given the Italian trivial name " lapachonon." The structure (III) now established for this compound, for which we propose the less confusing English name " lapachenole," is related to 1-methoxynaphthalene, which Katz (see *Chem. Abs.*, 1946, **40**, 7525) found to cause a similar dermatitis; it may therefore be the active factor, though tests were inconclusive.

Lapachenole proved to be inert towards lithium aluminium hydride, whence both of the oxygen atoms must be present in ether groupings. A Zeisel determination indicated one methoxyl group, and catalytic hydrogenation gave a crystalline dihydro-compound, which had an ultraviolet absorption spectrum considerably different from that of lapachenole and generally similar to that of some naphthalene derivatives. Distillation of lapachenole with zinc dust gave naphthalene, the yield (3%) being, if anything, higher than that obtained from lapachol in a comparable experiment. Lapachenole was therefore believed to have an ethylenic linkage in conjugation with a naphthalene nucleus; this view was confirmed when more vigorous hydrogenation gave a liquid, but apparently homogeneous, hexahydro-derivative with an absorption spectrum ($\lambda_{max.}$ 2950 Å, $\varepsilon = 3600$) very like that of quinol ($\lambda_{max.}$ 2880 and 3000 Å, $\varepsilon = 2300$), allowance being made for nuclear alkylation. Resemblances to catechol, resorcinol, and phenol, and their ethers were less pronounced. Accordingly, 1 : 4-dimethoxynaphthalene was prepared for comparison with dihydrolapachenole, with results which leave no doubt about the chromophore present in the latter (see Figure). Hydrogenation of 1 : 4-dimethoxynaphthalene also gave a (crystalline) tetrahydro-derivative (5 : 8-dimethoxytetralin) which in its ultraviolet absorption spectrum closely resembled hexahydrolapachenole.

Ultraviolet spectra of (1) *lapachenole,* (2) *dihydrolapachenole, and* (3) 1 : 4-*dimethoxynaphthalene.*



Oxidative degradation of lapachenole had been extensively employed by Manuelli (*locc. cit.*), who used nitric acid and bromine in most of his experiments, obtaining products involving nuclear substitution, together with oxalic and phthalic acid.

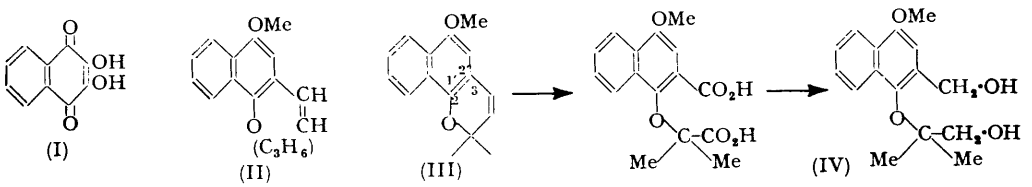
Treatment of lapachenole with potassium permanganate in acetone gave a dibasic acid $C_{16}H_{16}O_6$ (yield *ca.* 40%), in addition to phthalic acid and a trace of pigment identified almost with certainty as *iso*-naphthazarin (I). This reaction can only be explained plausibly as the oxidation of –CH:CH– to two carboxyl groups. Whereas lapachenole and its dihydro-compound (and also 1 : 4-dimethoxynaphthalene) had given deep red syrups on treatment with hydrogen bromide in acetic acid, the acid $C_{16}H_{16}O_6$ underwent smooth dealkylation at 60°, giving, however, a mixture of 1 : 4-dihydroxynaphthalene-2-carboxylic acid and its 4-monomethyl ether which were not easily separable. After further transformations the latter was isolated as such and as its methyl ester, and the former as 1 : 4-diacetoxynaphthalene. Partial structure (II) could now be written.

The nature of the C_3H_6 bridge—for biogenetic reasons an *iso*propylidine grouping was of course suspected—was proved by reduction of the methyl ester of the acid $C_{16}H_{16}O_6$ to the diprimary glycol with lithium aluminium hydride. In hot 30% sulphuric acid this underwent a pinacolinic rearrangement, giving *iso*butaldehyde in 75% yield, isolated as its 2 : 4-dinitrophenylhydrazone. The only *primary* aryloxy-alcohol which could have given this aldehyde is (IV), derived from (III) as the structure for lapachenole.

Attention was now directed to the confirmation of this structure (III) by synthesis of the dihydro-compound. Preliminary attempts to condense 4-methoxy-1-naphthol with isoprene in the presence of zinc chloride (cf. Smith, Ungnade, Hoehn, and Wawzonek, *J. Org. Chem.*, 1939, **4**, 311) proved unsuccessful. Condensation with 1-bromo-3-methylbut-2-ene (Smith and Denyes, *J. Amer. Chem. Soc.*, 1936, **58**, 304; Smith and Dobrovolny, *ibid.*, 1926, **48**, 1693) was then attempted in benzene at 80° in the presence of zinc chloride. From the syrupy neutral fraction a picrate was readily obtained which

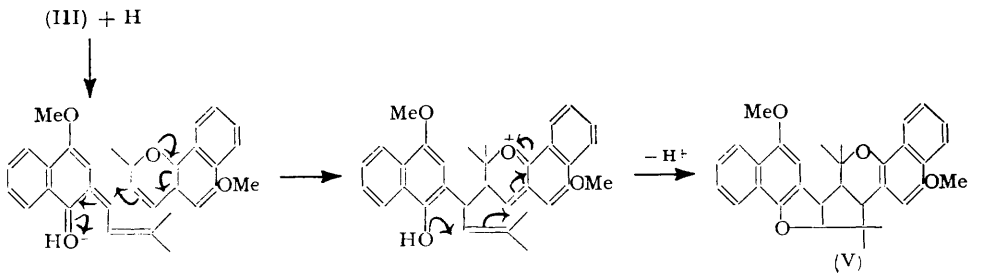
proved to be identical with that of dihydrolapachenole, and this substance was obtained from it on chromatography.

Subsequently to the investigations described, more complete infrared data became available for lapachenole and its dihydro-derivative which confirm the relation between them here postulated. Bands common to both spectra include those at 1645 cm.$^{-1}$, similar



to one in the spectrum of quinol dimethyl ether, and at 760 cm.$^{-1}$, characteristic of benzenoid rings with four adjacent positions unsubstituted. The chief differences were in the intensity of absorption at 3050 cm.$^{-1}$, significantly greater for lapachenole than its dihydro-compound, and in the strong band at 684 cm.$^{-1}$ in the spectrum of lapachenole but absent in that of the dihydro-compound. Both may be attributed to the *cis*-CH:CH grouping.

The high-melting substance, m. p. 258°, formed on treatment of lapachenole with acids was stated by Manuelli (*locc. cit.*) to be dimeric, on the basis of both cryoscopic and ebullioscopic measurements which gave molecular weight values between 350 and 500. On the other hand, molecular weights of 245, 290, 296, and 255 (cf. 240 required by $C_{16}H_{16}O_2$) were obtained in replicate determinations (ebullioscopic, in benzene) using the accurate method of Menzies (*J. Amer. Chem. Soc.*, 1921, **43**, 2309); a monomeric formula was therefore assumed during much of the present work. It could be explained with the assumption that a Wagner–Meerwein rearrangement had given a 2 : 3-dimethyl-2-chromen system, provided that considerable stabilising influences were ascribed to C–H hyperconjugation and crystal-lattice forces—the substance is almost insoluble in common solvents. In a conversation with one of us (M. C. W.), Professor R. B. Woodward criticised this formulation, and, since no other monomeric structure was plausible, suggested that it must be dimeric. The use of both isothermal distillation (Niederl *et al.*, *Science*, 1940, **92**, 225; 1944, **100**, 228) and ebullioscopic measurements in benzene by Pregl's method ("Die quantitative organische Mikroanalyse," Springer, Berlin, 1930, p. 237) then clearly indicated that the compound was indeed dimeric. No evidence could be obtained for the presence of an ethylenic linkage; thus its ultraviolet and infrared absorption spectra closely resemble those of dihydrolapachenole, it was inert to potassium permanganate in acetone at 56°, and on hydrogenation it absorbed four mols. of hydrogen (assuming $M = 480$) very slowly to give a high-melting product resembling hexahydrolapachenole in its ultraviolet absorption. These facts suggest a heptacyclic structure; Professor Woodward's formula, (V), represents the most satisfactory of several alternatives, being the only heptacyclic dimer whose formation can be envisaged without the intervention of carbonium ions.



A 2 : 4-dinitrophenylhydrazone was obtained from lapachenole by Professor D. H. R. Barton (personal communication); it is formed only under forcing conditions, and then

in small yield. Subsequent experiments (Livingstone, unpublished work) have shown that comparable reactions occur with authentic chromens, and the formation of this derivative, whose structure will be discussed later, therefore need not be considered as evidence for, *e.g.*, a vinyl ether grouping in the molecule.

Experimental

Ultraviolet absorption spectra were determined with a Beckman DU or Unicam SP 500 spectrophotometer, in ethanol.

Isolation.—From the finely-ground sapwood the lapachenole was isolated by steam-distillation (yield 0·5%) or by prolonged shaking with light petroleum, washing with sodium carbonate solution, and recrystallisation of the residue from pentane (0·4%). From the darker heartwood the yield of the crude neutral fraction was larger and that of the purified lapachenole smaller (about 0·35%). Lapachol was present in quantity only in the heartwood. Lapachenole formed plates, m. p. 62°, from light petroleum (Found: C, 80·2, 80·45; H, 6·55, 6·65. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·65%). When adsorbed on alumina lapachenole becomes photosensitive, giving initially an orange colour which later becomes deep blue-green.

Lapachenole picrate was prepared from methanolic solutions of the components; it formed violet needles, m. p. 141° [Found: C, 56·5; H, 4·1; *M* (by titration), 470, 472, 468. $C_{22}H_{19}O_9N_3$ requires C, 56·3; H, 4·05; *M*, 469].

Dihydrolapachenole.—Lapachenole (5·0 g.), platinic oxide (0·1 g.), and ethanol (100 c.c.) were shaken in hydrogen until absorption (1 mol.) was complete. Filtration, evaporation, and recrystallisation from aqueous ethanol gave *dihydrolapachenole* (3·75 g.), m. p. 78° (Found: C, 79·0; H, 7·25. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·45%). It formed a *picrate* (in methanol), violet needles, m. p. 141° (Found: C, 56·45; H, 4·3; N, 8·75. $C_{22}H_{21}O_9N_3$ requires C, 56·1; H, 4·45; N, 8·9%).

Hexahydrolapachenole.—Lapachenole (0·50 g.), platinic oxide (0·08 g.), and glacial acetic acid (25 c.c.) were shaken together under hydrogen until (after 33 hr.) the rate of absorption became negligible; the uptake was about 3 mols. Filtration, addition of water, and isolation of the neutral fraction gave a syrup which was distilled at 10^{-5} mm., to give *hexahydrolapachenole* (0·39 g.), $n_D^{17\cdot5}$ 1·5668 (Found: C, 77·9; H, 8·75. $C_{16}H_{22}O_2$ requires C, 78·0; H, 8·95%). Light absorption: flat maximum, 2910—2980 Å (ε = 3640).

In another experiment equal weights of lapachenole and platinic oxide were shaken in hydrogen in acetic acid for 60 hr., whereafter uptake ceased (total, *ca.* 5 mols.). The product was a heterogeneous liquid which still absorbed appreciably around 2600 Å (Found: C, 79·0; H, 10·3; OMe, 8·8. Calc. for $C_{16}H_{28}O_2$, *i.e.*, a dodecahydro-derivative: C, 76·2; H, 11·1; OMe, 12·3%).

Oxidation of Lapachenole.—(*a*) A solution of lapachenole (2 g.) in acetone (50 c.c.) was treated with potassium permanganate (13 g.). After 24 hr. at 20° acetone (450 c.c.) was added and the mixture was heated under reflux for 3 hr., cooled, and filtered. The residue was suspended in water (350 c.c.), acidified with dilute sulphuric acid, and treated with sulphur dioxide to give a clear yellow solution. This was extracted continuously with ether, and the ether was evaporated, giving an orange gum (1·54 g.) from which, after addition of ether, phthalic acid (0·11 g.; m. p. and mixed m. p. 190—196°) was separated. When the ethereal solution was washed with aqueous sodium hydroxide it was decolorised, a blue-green colour appearing in the lower layer; acidification of the latter gave a bright red solid (40 mg.) which sublimed at 258—260° after recrystallisation from ethyl acetate (Found: C, 62·15; H, 3·5; OMe, nil. Calc. for $C_{10}H_6O_4$: C, 63·15; H, 3·15%). Light absorption in EtOH: max. at 2680, 3300, 4400 Å (log ε 4·32, 3·32, and 3·26, respectively). For *iso*naphthazarin (I), Macbeth, Price, and Winzor (*J.*, 1935, 327) give m. p. 280°, and $\lambda_{max.}$ 2700, 3350, and 4400 Å (log ε 4·12, 3·31, and 3·25, respectively).

Methylation. The pigment was treated with diazomethane in ethereal solution, and the solvent was allowed to evaporate slowly. Sublimation of the residue at 10^{-5} mm. gave a yellow solid, m. p. 112—114° (Zinke and Ossenbecke, *Annalen*, 1899, **307**, 11, give m. p. 112—114° for 2 : 3-dimethoxy-α-naphthaquinone).

(*b*) Oxidation of lapachenole with nitric acid (*d* 1·12) under reflux gave phthalic acid in 80% yield, identified as phthalic anhydride, m. p. and mixed m. p. 131°.

(*c*) Lapachenole (6·0 g.), powdered potassium permanganate (17·4 g.), and acetone (150 c.c.) were heated under reflux for 6 hr., cooled, and filtered, the residue being washed with acetone and dried. Water (200 c.c.) was added and sulphur dioxide was introduced until the manganese

dioxide had dissolved. An orange residue remained, and was filtered off, dried, washed with benzene, and crystallised from aqueous ethanol, giving α-(2-*carboxy*-4-*methoxy*-1-*naphthoxy*)iso-*butyric acid* (2·2 g.) as prisms, m. p. 163—164° (Found: C, 63·0; H, 5·3%; equiv., 151. $C_{16}H_{16}O_6$ requires C, 63·1; H, 5·25%; equiv., 152). Light absorption: max. at 2470, 3060, and 3380 Å (log ε 4·46, 3·72, and 3·60 respectively). Decomposition at 170° in nitrogen liberated 1·03 mol. of carbon dioxide, estimated gravimetrically.

Dealkylation of this acid was effected with hydrogen bromide in acetic acid (25 c.c.; 50%) under reflux at 60—65° under nitrogen in 3 hr. On cooling, a grey solid (0·6 g.), m. p. 190—193° (decomp.), separated; crystallisation from aqueous ethanol gave needles (*A*), m. p. 200° (decomp.), displaying a blue fluorescence in ethanol and yielding a green colour with ferric chloride (Found: C, 64·7; H, 4·2; OMe, 4·95. Calc. for a mixture of 1 : 4-dihydroxy-2-naphthoic acid and its monomethyl ether (ratio 2 : 1): C, 65·15; H, 3·95; OMe, 4·9%).

1 : 4-*Diacetoxynaphthalene*.—The above mixture (*A*) (200 mg.), acetic anhydride (5 c.c.), and sodium acetate (100 mg.) were heated under reflux for 2 hr. Addition of water, isolation of the neutral fraction, and crystallisation from aqueous ethanol gave 1 : 4-diacetoxynaphthalene (40 mg.), m. p. and mixed m. p. 130·5—131·5°.

Methyl 1-*Hydroxy*-4-*methoxy*-2-*naphthoate*.—(*a*) The above mixture (*A*) (100 mg.) in ether (7 c.c.) and methanol (2 c.c.) was treated with an excess of diazomethane. The solution was washed with dilute hydrochloric acid and sodium hydroxide solution (to remove the dihydroxy-ester), then evaporated, and the residue (10 mg.) was crystallised from aqueous ethanol, then acetone, giving the hydroxy-ester, m. p. 136—137° (Homeyer and Wallingford, *J. Amer. Chem. Soc.*, 1942, **64**, 801, give m. p. 137—138°).

(*b*) The mixed acids (85 mg.) were dissolved in methanol (5 c.c.), and the solution was saturated with hydrogen chloride. The mixture was heated under reflux for 90 min. and poured into water, and the precipitate was collected; this was shaken with ether and sodium hydrogen carbonate solution. Acidification of the aqueous layer and isolation with ether gave 1-hydroxy-4-methoxy-2-naphthoic acid (50 mg.), m. p. 196—200° [Homeyer and Wallingford, *loc. cit.*, give m. p. 196—198° (decomp.)]. The neutral fraction was crystallised from aqueous acetone, giving the corresponding methyl ester (20 mg.), m. p. 137—138°.

2-(2-*Hydroxymethyl*-4-*methoxy*-1-*naphthyloxy*)-2-*methylpropan*-1-*ol* (IV).—The C_{16} acid (1·2 g.) was dissolved in ether (20 c.c.) and methanol (15 c.c.), and treated with an excess of diazomethane in ether for 60 min. The solvent was removed, and the residue was dissolved in dry ether and added with stirring to an excess of ethereal lithium aluminium hydride. After 2 hours' heating under reflux the excess of hydride was decomposed and the neutral fraction was isolated with ether; crystallisation from light petroleum (b. p. 80—100°) gave the *diol* (0·81 g.) as needles, m. p. 105—106° (Found: C, 69·3; H, 7·5. $C_{16}H_{20}O_4$ requires C, 69·55; H, 7·25%).

iso*Butaldehyde*.—The above glycol (153 mg.) and 30% sulphuric acid (55 c.c.) were heated under reflux while a stream of nitrogen was passed through the boiling liquid and up the condenser into a methanolic solution of 2 : 4-dinitrophenylhydrazine sulphate. After chromatography and crystallisation the derivative which separated (102 mg., 75%) formed yellow needles, m. p. 183—184°, undepressed on admixture with *iso*butaldehyde 2 : 4-dinitrophenylhydrazone.

Lapachenole Dimer (V ?).—This substance is obtained whenever lapachenole is subjected to acidic conditions. Conveniently, lapachenole (5·0 g.) and formic acid (150 c.c.; *d* 1·12) were heated to 90°; the ether dissolved and, after a few minutes, the dimer began to separate. After 30 min. the mixture was cooled and the *product* collected and crystallised from ethyl acetate, giving needles (4·25 g.), m. p. 258° (Found: C, 79·7; H, 6·7; OMe, 13·85. $C_{32}H_{32}O_4$ requires C, 80·0; H, 6·65; OMe, 12·9%). Light absorption: max. at 2500, 3220, 3330 Å (ε 37,900, 6290, and 5660, respectively, in $CHCl_3$).

Octahyrod-derivative of Lapachenole Dimer.—The dimer (190 mg.) was dissolved in a mixture of chloroform (7 c.c.), ethyl acetate (25 c.c.), and glacial acetic acid (25 c.c.), added in that order. Platinic oxide (330 mg.) was added and the mixture was shaken in hydrogen until uptake (*ca.* 4 mols.) was complete (24 hr.). Filtration and isolation of the neutral *product* gave a solid which crystallised from ethyl acetate as prisms, m. p. 248—249°, depressed to 224—225° on admixture with the dimer (Found: C, 78·65; H, 8·15. $C_{32}H_{40}O_4$ requires C, 78·7; H, 8·2%). Light absorption: max. 2900 Å (ε 6500).

1 : 2 : 3 : 4-*Tetrahydro*-5 : 8-*dimethoxynaphthalene*.—1 : 4-Dimethoxynaphthalene (467 mg.), glacial acetic acid (40 c.c.), and platinic oxide (42 mg.) were shaken in hydrogen until absorption (uptake *ca.* 2 mols.) was complete (24 hr.). Isolation of the neutral fraction and recrystallisation from methanol gave the *tetrahydro-ether* (370 mg.) as plates, m. p. 43—44° (Found: C,

75·1; H, 8·2. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). Light absorption: max. at 2870 Å (ε 3250). A shoulder at 3180 Å indicated the presence of 7% of unreduced dimethoxynaphthalene.

4-*Methoxy*-1-*naphthol*.—1 : 4-Dihydroxynaphthalene (from 1 : 4-naphthaquinone, cf. *Org. Synth.*, Coll. Vol. I, 2nd Edn., 49, 383) (12·1 g.) in methanol (40 c.c.) was refluxed in nitrogen with sodium hydroxide (3·4 g.) and methyl iodide (12·1 g.) for 4 hr. Evaporation of the solvent gave a brown solid which darkened rapidly in air; it was at once sublimed at 10^{-5} mm., giving at 90° a fraction (2·1 g.) consisting mainly of 1 : 4-dimethoxynaphthalene, and at 90—112° a solid (5·47 g.), m. p. 120—125°, which was crystallised from light petroleum (b. p. 80—100°), giving 4-methoxy-1-naphthol (3·15 g., 24%), m. p. 124—125°. Russig (*J. prakt. Chem.*, 1900, **62**, 50) gives m. p. 124—125°.

Synthesis of Dihydrolapachenole.—The above phenol (0·2 g.), 1-bromo-3-methylbut-2-ene (170 mg.), zinc chloride (170 mg.), and benzene (6 c.c.) were heated under reflux for 3 hr. The cooled benzene solution was washed with dilute hydrochloric acid, sodium hydroxide, and sodium hydrosulphite (dithionite) solution, and finally water, then evaporated. The residue was treated with saturated methanolic picric acid, and the precipitate was crystallised from methanol, giving dihydrolapachenole picrate (160 mg.), m. p. and mixed m. p. 141—142·5°. This was dissolved in ether and decomposed chromatographically, giving dihydrolapachenole (56 mg.), m. p. and mixed m. p. 78°. The greater part of the methoxynaphthol used was recovered from the alkaline hydrosulphite washings.

At an early stage in this work Professor D. H. R. Barton, F.R.S., informed us that he also had begun investigations on what proved to be lapachenole, and had obtained from it a 2 : 4-dinitrophenylhydrazone and a picrate; we thank him for resigning the problem to us and giving us his preliminary results. We thank Professor E. R. H. Jones, F.R.S., for practical assistance and valuable advice. We are indebted to Dr. Robert Murray, H.M. Inspector of Factories, for directing our attention to this problem and helping us to obtain peroba wood, to the Forest Products Research Laboratory for a generous gift of lapachenole, to Messrs. E. M. Morton and H. Swift for microanalyses, to Mrs. E. B. Bates for ultraviolet spectroscopic data, and to Dr. D. Meakins for infrared data.

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