61. *Hopeaphenol, an Extractive of the Heartwood of* Hopea odorata *and* Balanocarpus heimii.

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The heartwoods of *Hopea odorata* and *Balanocarpus heimii* give, by ether extraction, a crystalline phenol, $C_{56}H_{42}O_{12}$, containing ten hydroxyl groups. Oxidative degradations show the presence of at least two 4-hydroxybenzyl units in the molecule.

The extraction of the heartwood of *Hopea odorata* (thingan) was first carried out in 1951. Boiling light petroleum removed waxy materials which were not further investigated, and subsequent ether extraction gave a brown solid (7%) which was best purified by crystallisation from acetone–acetic acid and then gave hopeaphenol (*ca.* 1%) as colourless crystals. The same material was later obtained by a similar extraction of *Balanocarpus heimii* (chengal). Both of these plants are *Dipterocarpaceae* indigenous to South East Asia, and there has been dispute [1] as to whether chengal should be merged with the *Hopea* genus. Chengal and various *Hopea* species are the source of dammar resins which have been extensively investigated in recent years. The occurrence of the same very unusual extractive in chengal and in a *Hopea* might reinforce the view [1a] that there is little justification for a separate *Balanocarpus* genus.

Since the original isolation in 1951, there has been intermittent work on hopeaphenol but progress has been hindered by the inability of classical methods of combustion analysis and molecular weight determinations to define the molecular formula of the phenol or its derivatives. Very recently mass spectrometry showed conclusively that hopeaphenol has the formula $C_{56}H_{42}O_{12}$, and that ten of the oxygen atoms are present as hydroxyl groups. Investigations are proceeding but, in view of the complexity of the problem, it seems proper to report now the existence of the compound, which appears to be of a unique type, and the results of the earlier investigations.

Hopeaphenol is fairly stable and only slowly becomes coloured on exposure to air even in alkaline solution. It is insoluble in water but soluble in alkali. Its solubility is high in the lower alcohols and ketones but very low in acetic acid, ether, hydrocarbons, and chlorinated hydrocarbons. It gives no colour with ferric chloride and has $[\alpha]_D$ −407°. Its ultraviolet spectrum ($\lambda_{max.}$ 283 mμ) is very similar in shape to that of a simple phenol, and the intensity of the absorption is compatible with a molecule possessing several unconjugated benzene rings. The infrared spectrum is not very informative but it establishes the absence of carbonyl groups; thus, the two non-hydroxylic oxygen atoms are present in ether groups [but not as methoxy- (Zeisel) or methylenedioxy-groups (colour tests negative)]. The phenol is relatively stable to acids, being only slowly degraded by boiling hydrochloric acid; however, it is rapidly resinified by boiling hydrobromic or hydriodic

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[1] (*a*) Desch, *Malayan Forest Records*, 1941, **14**, 83; (*b*) Symington, *ibid.*, 1941, **16**, 147.

acid. In the absence of air it is also stable to alkali under conditions milder than alkali fusion. It was resistant to catalytic reduction under neutral conditions but hydrogen was absorbed slowly over Adams catalyst in the presence of mineral acid. Under these conditions, reduction of aromatic rings is possible, and even after prolonged hydrogenation unchanged hopeaphenol was recovered as the sole purifiable product.

Hopeaphenol was characterised as the methyl ether, ethyl ether, and acetate. The benzoate, *p*-nitrobenzoate, and toluene-*p*-sulphonate were amorphous. The elemental compositions and molecular weights (*X*-rays, thermistor drop method) of these derivatives were consistent with a range of formulæ for hopeaphenol containing 50 ± 2 or 54 ± 2 carbon atoms together with 11 or 12 oxygen atoms, respectively, with more recent results favouring the higher molecular-weight range. The uncertainty has been resolved by the determination of the molecular weight of the methyl ether by mass spectrometry (by courtesy of Dr. J. Beynon, Imperial Chemical Industries Limited, Dyestuffs Division); the value of 1046·42 is compatible only with a molecular formula of $C_{66}H_{62}O_{12}$. The molecular weight of the ethyl ether (by courtesy of Dr. R. I. Reed, University of Glasgow) is 1186, establishing that the ethers contain ten alkoxyl groups.

Several unsuccessful attempts have been made to prepare partially alkylated or acylated derivatives of hopeaphenol. For example, methylation with a limited amount of diazomethane affords a complex mixture (thin-layer chromatography) from which only the fully methylated material has been isolated pure.

Many degradative experiments have been carried out with hopeaphenol and its methyl ether (see Experimental section), but these have been mostly uninformative, and the only fragments isolated have been derivatives of phenol and of *p*-methoxytoluene. Thus, alkali fusion of hopeaphenol gives *p*-hydroxybenzoic acid, zinc dust distillation affords phenol, and nitric acid oxidation yields picric acid. Deca-*O*-methylhopeaphenol is not oxidised under mild conditions, *e.g.*, cold potassium permanganate in acetone, and new products have been isolated only when the molecule has been largely destroyed; permanganate in boiling aqueous acetone afforded anisic acid, chromium trioxide in boiling acetic acid gave anisic acid and a little anisaldehyde, and boiling nitric acid gave nitroanisic acid and dinitroanisole. The yields in some cases suggest that the molecule has at least two 4-methoxybenzyl residues.

Reduction of the methyl ether with sodium–ammonia gives a new product containing phenolic hydroxyl groups, presumably formed by hydrogenolysis of one or both of the ethereal links of hopeaphenol. It is characterised as the methyl ether, ethyl ether, and acetate, and present evidence suggests that its formula is $C_{66}H_{66}O_{12}$ with ten methoxyl groups and two new hydroxyl groups. There is some doubt about the purity of this reduction product and its derivatives because, although they can be crystallised easily to constant melting point, light absorption, and optical rotation, and are homogenous on thin-layer chromatography in several solvent systems, the n.m.r. spectrum of, for example, the acetate shows two peaks for the acetate methyl resonance which integrate to a total of $1\frac{1}{2}$ methyl groups. This feature of the spectrum persists in all samples of this acetate, however purified, even when it has been made from reduction products prepared under widely different conditions of reduction.

The n.m.r. spectra of hopeaphenol and its derivatives are complex and cannot yet be completely interpreted. Gross features confirm the presence of ten methoxyl groups in the methyl ether and show the probable presence of twenty aromatic protons and the absence of protons in an environment in which they would resonate at $\tau >$ *ca.* 6·0. Although there are some resonances in the olefinic region, we do not believe that olefinic double bonds are present and prefer to attribute these resonances to the presence of deshielded protons perhaps of the type in benzhydryl ethers.

The mass spectra of the methyl and ethyl ethers show one very important feature, namely, that a very easy fission (second most intense peak) leads to an ion of precisely half the mass of the parent. The base peak has a mass corresponding to (P/2 — PhOR).

These facts indicate that hopeaphenol must be, formally at least, a dimer, and thus simplify the problem.

The formula of hopeaphenol seems to require the presence of eight aromatic rings. Olefinic bonds in conjugation with the aromatic rings are unlikely to be present (ultraviolet spectra, relative resistance to oxidation and reduction), and isolated double bonds are also probably absent for chemical reasons and because it is difficult to include them in structures within the limitations imposed by the molecular formula and the absence of proton resonance at $\tau > 6{\cdot}7$. We therefore believe that the double bonds are confied to isolated benzene rings, and our present working hypotheses are based on this assumption.

EXPERIMENTAL

Alumina was Spence Grade H throughout. Rotations are, except where otherwise stated, for chloroform solutions at room temperature using the sodium D wavelength. Known compounds were identified by mixed m. p. and comparison of infrared spectra.

Isolation of Hopeaphenol.—The powdered heartwood of *Hopea odorata* or *Balanocarpus heimii* (2·5 kg.) was exhaustively extracted with boiling light petroleum (b. p. 60—80°) to remove fatty material, and then similarly with ether. Removal of ether left a viscous brown gum (*ca.* 240 g.) which was dissolved in acetone (250 c.c.), filtered, and treated with acetic acid (500 c.c.). The mixture was evaporated to *ca.* 500 c.c., and crystals of *hopeaphenol* appeared. The phenol (20—25 g.) was collected from the cold solution and crystallised by dissolving it in methanol, adding acetic acid, and evaporating the solution until crystallisation began. Hopeaphenol crystallises in colourless plates, m. p. 351° (evac. cap.), $[\alpha]$ −407° (in ethanol) (Found, on a sample dried to constant weight at 150°, C, 73·8; H, 4·9. $C_{56}H_{42}O_{12}$ requires C, 74·3; H, 4·65%), $\lambda_{max.}$ 281 mμ (ε 14,500); it is soluble in sodium hydroxide and sodium carbonate solutions, and gives no colour with ferric chloride or with magnesium in hydrochloric acid.

Degradations of Hopeaphenol.—(*a*) Hopeaphenol (0·5 g.) was heated at 230° with a mixture of sodium hydroxide (4 g.), potassium hydroxide (4 g.), and water (1 c.c.) for 10 min. The cooled melt was dissolved in water, acidified, and extracted with ether. The extract was separated into acidic and phenolic fractions in the usual way. The acidic fraction afforded a small quantity of *p*-hydroxybenzoic (comparison with an authentic sample). The phenolic fraction did not yield any identifiable fragment.

(*b*) Hopeaphenol (2 g.) and zinc dust (20 g.) were thoroughly mixed and heated together at 15 mm. to a dull red heat, and the volatile products were trapped at −10°. Redistillation of the volatile product gave phenol (0·4 g.), identified as the toluene-*p*-sulphonate.

(*c*) Hopeaphenol (1 g.) and concentrated nitric acid (15 c.c.) were heated together at 100° for 1 hr. The solution was diluted and extracted with ether, and the extract extracted with aqueous sodium hydrogen carbonate. The latter extract was acidified, and extraction with ether yielded picric acid (comparison with an authentic sample). Thin layer chromatography did not reveal any other nitrophenols.

*Deca-*O*-methylhopeaphenol.*—Hopeaphenol (2 g.) was boiled in acetone (75 c.c.) with dimethyl sulphate (3·5 c.c.) and potassium carbonate (7 g.) for 16 hr. The solution was filtered and evaporated, and the residue was triturated with concentrated ammonia and dissolved in ether. The washed and dried extract was filtered through a short column of alumina, the solvent was removed, and the residue gave *the ether* as colourless needles (2·0 g.), m. p. 162—164° (from benzene–methanol), $[\alpha]$ −378° [Found: C, 75·3; H, 6·1; OMe, 28·0. $C_{56}H_{32}O_2(OMe)_{10}$ requires C, 75·7; H, 6·0; OMe, 29·6%], $\lambda_{max.}$ 283 mμ (ε 15,000). The same compound was obtained when the phenol was treated during several days with diazomethane, but the major product was a complex mixture of partially methylated substances.

Hopeaphenol Deca-acetate.—The *acetate*, prepared from the phenol with acetic anhydride in pyridine or in the presence of a catalytic amount of sulphuric acid, formed needles, m. p. 249—250° (from methanol), $[\alpha]$ −338° [Found: C, 69·0; H, 4·7. $C_{56}H_{32}O_2(OAc)_{10}$ requires C, 68·9; H, 4·7%].

*Deca-*O*-ethylhopeaphenol.*—The *ethyl ether*, prepared as for the methyl ether, formed plates, m. p. 192—193°, $[\alpha]$ −332° [Found: C, 76·6; H, 6·9. $C_{56}H_{32}O_2(OEt)_{10}$ requires C, 76·9; H, 6·9%].

Oxidations of the Methyl Ether.—(*a*) The ether (300 mg.) was heated at 100° with concentrated nitric acid (15 c.c.) for 2 hr. The solution was diluted and extracted with ether. The acid fraction of the extract was isolated with sodium hydrogen carbonate, to give a total acid fraction of 188 mg. of which 101 mg. were soluble in hot benzene. The benzene extract, purified by careful recrystallisation from water, afforded a total of 63 mg. of pure 3-nitroanisic acid (a yield of 56·3 mg. would correspond to 1 mole of acid from 1 mole of phenol). On one occasion the neutral fraction of the oxidation was examined and gave a small amount of 2,4-dinitroanisole.

(*b*) The ether (0·5 g.) was boiled in aqueous acetone (30 c.c.; 1 : 4) with potassium permanganate (3 g.) for 5 hr. Water (50 c.c.) was added, the acetone was evaporated, and the aqueous solution was decolorised with sulphur dioxide and extracted with chloroform. The acid part of the extract was removed by aqueous sodium hydroxide and liberated with hydrochloric acid. Recrystallisation of this fraction from water afforded anisic acid (5mg.) identified by comparison with an authentic sample. From the neutral fraction the unchanged ether (385 mg.) was recovered.

(*c*) The ether (0·5 g.) was heated in boiling acetic acid (25 c.c.) containing chromium trioxide (1 g.) for 1 hr. The mixture was diluted and the acid fraction of the product isolated. Crystallisation from water gave anisic acid (0·1 g.). The neutral oxidation product afforded a red 2,4-dinitrophenylhydrazone which was purified on alumina and identified as the anisaldehyde derivative (0·02 g.).

Deca-O-*methyltetrahydrohopeaphenol*.—The above methyl ether (1 g.) in refluxing liquid ammonia (150 c.c.) was treated with sodium (0·5 g. in small pieces) with stirring. After 30 min., more sodium (1 g.) was added, stirring was continued for 90 min., and excess of sodium was destroyed by ammonium chloride. The ammonia was allowed to evaporate, and the residue was treated with water, neutralised, and extracted with chloroform. The extract was passed down an alumina column which was eluted with the same solvent until the eluent was nearly colourless, and then with 1 : 10 ethanol–chloroform. The removed *product* crystallised from ethanol as needles (0·5 g.) which soon turned red in light, m. p. 165—167°, [α] −245° [Found: C, 74·4; H, 6·4; OMe, 28·0. $C_{56}H_{34}(OH)_2(OMe)_{10},H_2O$ requires C, 74·2; H, 6·4; OMe, 28·0%], $\nu_{max.}$ 3400 and 3600 cm.$^{-1}$ (OH). The product is soluble in aqueous sodium hydroxide; oxidation with permanganate in hot aqueous acetone gave anisic acid, and with chromium trioxide in acetic acid gave anisic acid accompanied by traces of anisaldehyde. The fully methylated derivative, *dodeca*-O-*methyltetrahydrohopeaphenol*, prepared with methyl sulphate–potassium carbonate in acetone, easily formed needles, m. p. 249—251 (from ethanol), [α] −254° [Found: C, 75·8; H, 6·8; OMe, 33·7. $C_{56}H_{34}(OMe)_{12}$ requires C, 75·9; H, 6·5; OMe, 34·5%]; no infrared absorption corresponding to OH stretching. The ethyl derivative, *di*-O-*ethyldeca*-O-*methyltetrahydrohopeaphenol*, prepared similarly, crystallised from ethanol as plates, m. p. 164—167°, [α] −246° [Found: C, 75·7; H, 6·9. $C_{56}H_{34}(OEt)_2(OMe)_{10}$ requires C, 76·0; H, 6·8%]. The *diacetate* formed needles from methanol, m. p. 270—272°, [α] −220° [Found: C, 73·8; H, 6·3. $C_{56}H_{34}(OAc)_2(OMe)_{10}$ requires C, 74·3; H, 6·2%].

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