The Chemistry of the ' Insoluble Red ' Woods. Part XI.[1] Revised Structures of Santalin and Santarubin

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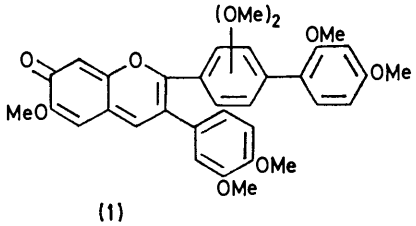
Revised structures for the pigments santalin and santarubin, from the ' insoluble red ' woods are reported. These complex benzopyran-7-ones are derivatives of C_{30} skeletal structures and constitute novel, additional examples of plant products arising from the dimerisation of C_{15} flavonoid units.

DURING our previous investigation [2] into the constitution of santalin and santarubin, isolated from the ' insoluble red ' woods sandalwood, camwood, and barwood, we proposed partial structures for these pigments, of type (1), derived from a C_{27} parent nucleus. We have



(1)

become increasingly aware of the unsatisfactory features of these partial formulae, especially their incompatibility with current biogenetic concepts. Additionally, our original investigations of these complex products, which were difficult to isolate and purify, were performed without the aid of currently available spectroscopic and purification techniques. We have therefore carried out a comprehensive reinvestigation of this topic and now report revised structures for these pigments, the nature of which constitutes one of the remaining structural legacies of ' classical ' organic chemistry. During the completion of this work for publication, Ravindranath and Seshadri [3] reported conclusions similar to our own, in an essentially complementary investigation, concerning the constitution of santalin.

The mass spectrum of fully methylated santalin, has M^+ 652·2284 in agreement with a molecular formula of $C_{38}H_{36}O_{10}$ (M^+ 652·2308), and exhibits an intense peak at m/e 151 ($C_9H_{11}O_2$, accurate mass measurement), which may be attributed to a dimethoxybenzyl residue. The analytical figures for fully methylated santalin correspond [2] to a hydrate, $C_{38}H_{36}O_{10},H_2O$, in keeping with our observation (*cf.* Ravindranath and Seshadri [3]) that this ether has m.p. 155° (decomp.) [2] and then resolidifies before remelting at *ca.* 250°. If fully methylated santalin is analysed after heating to the temperature of resolidification (*ca.* 200°) the analytical figures are in agreement with the molecular formula derived from mass spectral observations.

The i.r. spectrum of fully methylated santalin is devoid of hydroxy-absorption. The n.m.r. spectrum shows signals at τ (C_6D_6) 0·80 (1H, s), 2·9—3·9 (m, aromatic), 5·8br (2H, s, ArCH_2), and 6·16, 6·30, 6·53, 6·57, 6·62, 6·65, 6·71, and 6·78 (each 3H, s, 8 × OMe). Thus fully methylated santalin is the octa-*O*-methyl ether of a C_{30} nucleus, *i.e.* two C_{15} units. The elemental analytical results in conjunction with the n.m.r. spectrum of santalin [methoxy-signals at τ 6·0, 6·30, and 6·38 in $(CD_3)_2CO$–$(CD_3)_2SO$ (1 : 1)] show that santalin contains three methoxy-groups. Thus fully methylated santalin is penta-*O*-methylsantalin. We propose to retain the names santalin and santarubin for the natural pigments

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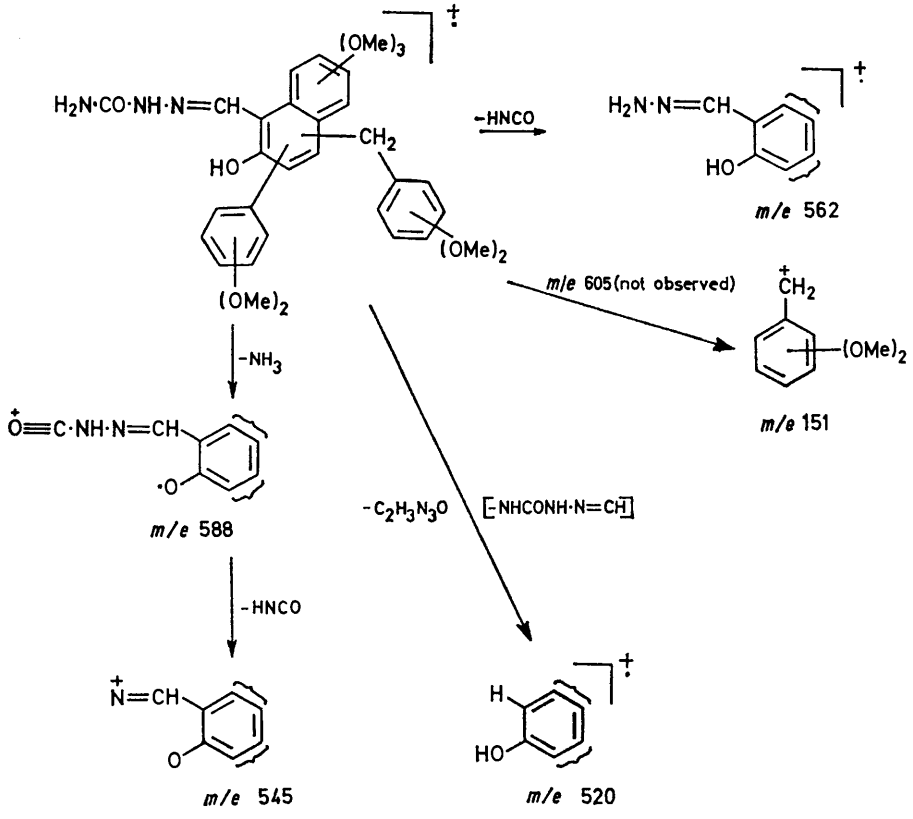
[1] Part X, C. A. Anirudhan, W. B. Whalley, and M. M. E. Badran, *J. Chem. Soc.*, 1966, 629.

[2] A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1954, 2794.

[3] B. Ravindranath and T. R. Seshadri, *Tetrahedron Letters*, 1972, 1201.

because of long historic precedent (at least 100 years; see ref. 2) and not to adopt the name santalin for the parent C_{30} nucleus (contrast Ravindranath and Seshadri [3]).

This clarification of the properties of santalin confirmed our earlier view [2] that the semicarbazone, of m.p. 202°, and the corresponding 2,4-dinitrophenylhydrazone, of m.p. 203°, were derived from the portion of penta-*O*-methylsantalin remaining after hydrolytic fission of the pyran ring. The spectral data are in accordance with eliminates ammonia in the mass spectrometer we examined other semicarbazones, including those of benzaldehyde and *o*-hydroxybenzaldehyde. Salicylaldehyde semicarbazone shows a molecular ion at *m/e* 179 (6% of base peak at *m/e* 61) and an $M^+ - 17$ ion at *m/e* 162 (20%), due to the loss of ammonia (accurate mass measurement) as in Scheme 2. With benzaldehyde semicarbazone the molecular ion appears at *m/e* 163 and the ion (*m/e* 146) corresponding to loss of ammonia is negligible (<1% of the base peak at *m/e*

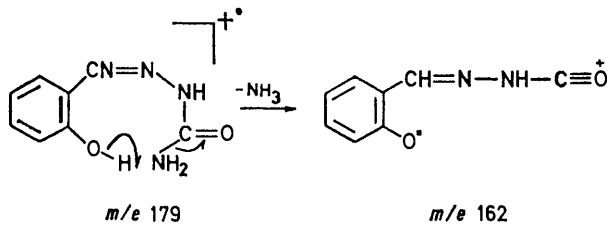


SCHEME 1

this suggestion. The n.m.r. spectrum of the semicarbazone has signals at τ −1·70 (1H, s, OH, exchangeable with D_2O), 0·3 (1H, s, NH, exchangeable), 0·42 (1H, s, −CH=N), 3·0—3·52 (7H, m, aromatic), 4·50br (2H, s, $CO{\cdot}NH_2$, not quickly exchangeable with D_2O), and 6·06, 6·10, 6·13, 6·24, 6·28, 6·38, and 6·48 (each 3H, s, 7 × OMe). The methoxy-envelope integrates for 23 protons; the extra protons appear as a broad singlet at τ 6·0 in $CDCl_3$–C_6D_6 (1 : 1) and thus correspond to the benzylic methylene group detected in penta-*O*-methylsantalin by n.m.r. and mass spectral examination. The total proton count in this semicarbazone is thus 35. The mass spectrum does not show a molecular ion but contains a peak at $M^+ - 17$ (*m/e* 588·2118; $C_{32}H_{32}N_2O_9$ requires 588·2108). Additional significant ions at *m/e* 562, 520, 545, and 151 (accurate mass measurements) agree with fragmentation as in Scheme 1.

To substantiate the implication that our semicarbazone

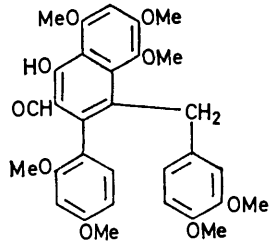
119). The mass spectral data therefore support the view that the semicarbazone (m.p. 202°) derived from the degradation of penta-*O*-methylsantalin with alkali, is an



SCHEME 2

o-hydroxy-semicarbazone, in agreement with the intense colour produced by Fe^{III} [2] and its parent molecule. In accord with these views the 2,4-dinitrophenylhydrazone which corresponds to the semicarbazone shows M^+

728·2285 ($C_{37}H_{36}N_4O_{12}$ requires 728·2330). Hence the carbonyl precursor of these derivatives has the molecular formula $C_{31}H_{32}O_9$, which may be expanded to



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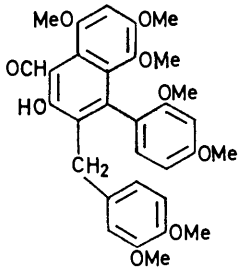

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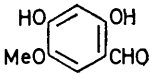

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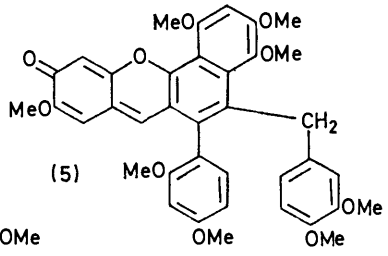

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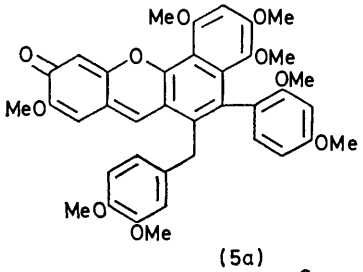
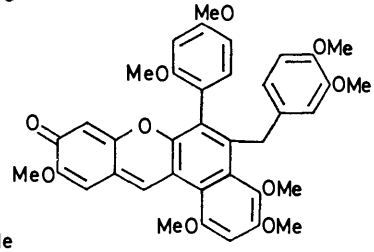
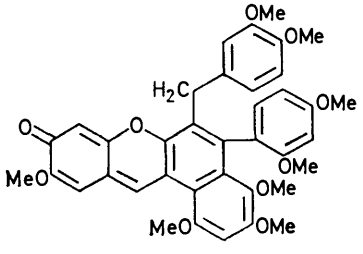


(5a)



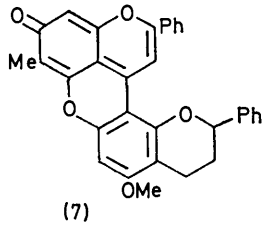
(6a)



(6)

$C_{24}H_{10}O(OH)(OMe)_7$. This residue must contain the 2,4-dimethoxyphenyl and 3,4-dimethoxyphenyl residues, which furnish 2,4-dimethoxybenzoic acid, veratric acid, and veratraldehyde from oxidation of penta-*O*-methylsantalin,[2] together with the benzylic methylene system; two protons remain to be allocated and of these only one is aromatic. These results may thus be combined in terms of an *o*-hydroxy-aldehyde of type (2) or (3). This conclusion, in conjunction with the formation of 2,4-dihydroxy-5-methoxybenzaldehyde (4) during the alkali degradation of penta-*O*-methylsantalin,[2] indicates a structure of type (5) or (6) [or less likely (see later) (5a) or (6a)] for the parent pigment. We provisionally assign the orientation of the trimethoxylated ring on the basis of the apparent formation [3] of 3,4,6-trimethoxyphthalic acid in the degradation of penta-*O*-methylsantalin. Work to clarify this point and the nature of the other degradation products [2] of penta-*O*-methylsantalin is in progress.

The C_{30} skeletal structure for santalin is compatible with its derivation by oxidative coupling of two C_{15} flavonoid fragments, by yet another variant upon a process which is now recognised as providing many other 'bisflavonoids,' such as dracorubin (7) [4] and ginkgetin (8).[5] The formation of veratraldehyde during the oxidation of penta-*O*-methylsantalin with potassium permanganate has hitherto been a puzzling feature of the chemistry of this pigment and one which initially seemed irreconcilable with much spectral and chemical information. The interpretation of this unusual feature is however now reasonably clear and provides additional evidence for the structure of penta-*O*-methylsantalin. Thus the oxidation of penta-*O*-methylsantalin may well proceed through an intermediate similar in structure to the alkaline fission product of type (2). Under the



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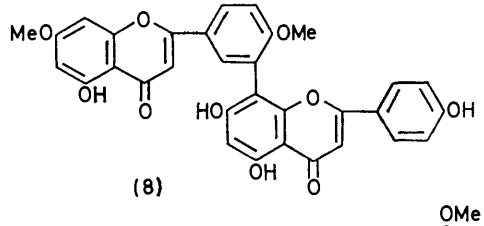

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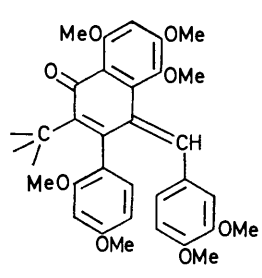

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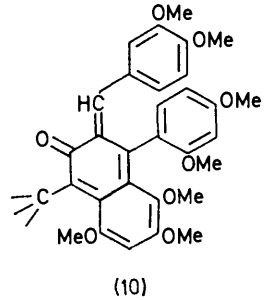


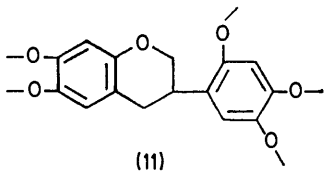
(10)

alkaline conditions developing during the oxidation with potassium permanganate [2] a partial 'rottlerone'-

[4] A. Robertson, W. B. Whalley, and J. Yates, *J. Chem. Soc.*, 1950, 3117.

[5] F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, p. 314.

type rearrangement [6] could furnish veratryl alcohol (or its equivalent) as an intermediate and hence (by oxidation) veratraldehyde. Alternatively, and perhaps more probably, an intermediate of type (2) or (3) could be oxidised to a quinone methide of type (9) or (10) and



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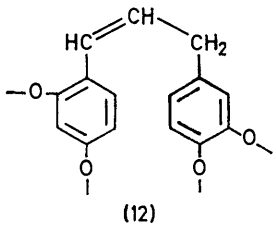

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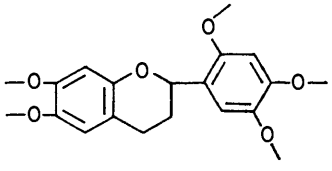


(13)

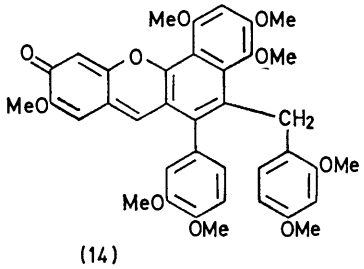
thence to 3,4-dimethoxybenzaldehyde. In either case this view of the genesis of veratraldehyde requires that the 3,4-dimethoxybenzyl system be located *ortho* or *para* to the phenolic hydroxy-group. Only formulae (2) and (3) are compatible with these requirements. Hence penta-*O*-methylsantalin may be represented as (5) or (6) rather than as (5a) or (6a). Structure (5) could arise biogenetically from the oxidative coupling of a flavonoid of type (13) with a second C_{15} unit of type (12); the coupling of an isoflavonoid unit of type (11) with the C_{15} unit (12) would lead to the alternative structure (6) for penta-*O*-methylsantalin. Since only isoflavonoids,[7] namely santal, homopterocarpin, and pterocarpin have been isolated from the ' insoluble red ' woods, we provisionally favour formula (6) for penta-*O*-methylsantalin. Work to clarify this point is in progress.

The nature of santarubin follows. The mass spectrum of fully methylated santarubin,[2] shows M^+ 652 (accurate mass) and hence this ether has the molecular formula, $C_{38}H_{36}O_{10}$, and, as previously adumbrated [2] is isomeric with penta-*O*-methylsantalin. The n.m.r. spectrum of fully methylated santarubin has signals at τ 0·39 (1H, s, aromatic), 2·9—3·9 (9H, m, aromatic), and 5·94 (3H), 5·99 (3H), 6·04 (6H), 6·24 (3H), 6·29 (6H), and 6·34 (3H) (each s, 8 × OMe). The total integral under the methoxy-envelope indicates the presence of 26 protons. The benzylic nature of the two extra protons (as in santalin) was clarified by the n.m.r. spectrum [in C_6D_6–$CDCl_3$ (1 : 1)] of tetra-*O*-methylsantarubin: τ 0·56 (1H, s, aromatic), 5·75 (2H, s, ArCH_2), and 6·00 (3H), 6·02 (3H), 6·34 (3H), 6·36 (3H), 6·46 (3H), 6·48 (3H), and 6·52 (6H) (each s, 8 × OMe).

Elemental analyses show that santarubin contains four methoxy-groups (the insolubility precluded a determination of the n.m.r. spectrum); hence the fully methylated derivative is tetra-*O*-methylsantarubin. The 2,4-dinitrophenylhydrazone obtained from the ' second half ' of this ether by alkali degradation [2] is isomeric [M^+ 728·2285 ($C_{37}H_{36}N_4O_{12}$)] with the corresponding derivative from penta-*O*-methylsantalin. The n.m.r. spectrum (in $CDCl_3$) shows methoxy-singlets at τ 6·03 (3H), 6·12 (3H), 6·13 (3H), 6·35 (6H), 6·42 (3H), and 6·52 (3H); the methoxy-envelope contains a benzylic proton signal which appears downfield at τ 6·03br (2H, d) with the methoxy-signals at τ 6·15, 6·28, 6·46, 6·59, 6·62 (6H), and 6·70 in $CDCl_3$–C_6D_6 (1 : 1). Since oxidation of tetra-*O*-methylsantarubin furnishes 2,4-dimethoxybenzaldehyde,[2] the pigment must contain a 2,4-dimethoxybenzyl system, and hence by analogy with santalin, tetra-*O*-methylsantarubin may be formulated as (14) or (15), on the assumption that the substitution pattern of the trimethoxylated ring is the same in both fully methylated pigments.

For the reasons already discussed in connection with santalin we prefer formula (15) for tetra-*O*-methylsantarubin.

Our structures for santalin and santarubin are thus compatible with their derivation by minor, unexceptional variants of the same general biosynthetic route, in which the isoflavonoid of type (11) couples with one of the double-bond isomers of type (12) to give santalin and



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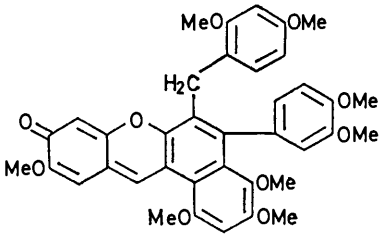


(15)

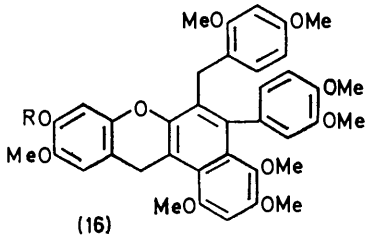
with the alternative double-bond isomer of type (12) to yield santarubin.

In accord with its structure, reduction of tetra-*O*-methylsantarubin with sodium borohydride gives the dihydro-derivative of type (16; R = H), which is extremely susceptible to oxidation and which was characterised as the *O*-acetate (16; R = Ac) and the *O*-methyl ether (16; R = Me). The n.m.r. spectrum of

[6] A. McGookin, A. Robertson, and T. H. Simpson, *J. Chem. Soc.*, 1951, 2021.

[7] A. McGookin, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1940, 787; A. Robertson, C. W. Suckling, and W. B. Whalley, *ibid.*, 1949, 1571.

(16; R = Ac) showed signals at τ 3·0—4·0 (9H, m, aromatic), 5·13br (2H, s, ArCH_2), 5·95 (3H), 6·00 (3H), 6·05 (3H), 6·15 (3H), 6·25 (6H), 6·32 (3H), 6·43 (3H) (each s, 8 × OMe), and 7·70 (3H, s, OAc). In C_6D_6 this acetate had signals at τ 3·0—4·0 (9H, m, aromatic), 5·10br (2H, s, ArCH_2), 5·58br (2H, s, ArCH_2), 6·10 (3H), 6·17 (3H), 6·61 (6H), 6·67 (3H), 6·69 (3H), and 6·75 (6H)



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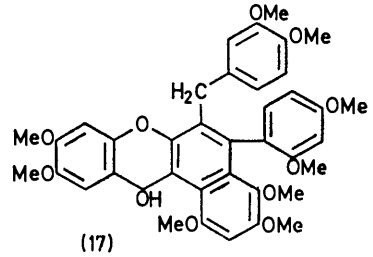

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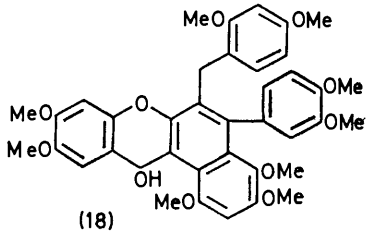

(18)

(each s, 8 × OMe), 6·69 (3H), and 6·75 (6H) (each s, 8 × OMe), and 8·17 (3H, s, OAc). The methoxy-envelope integrated for 24 protons. The methyl ether (16; R = Me) gave n.m.r. signals at τ 2·9—3·9 (8H, m, aromatic), 5·20br (2H, s, ArCH_2), and 5·95 (3H), 6·00 (3H), 6·05 (3H), 6·10 (3H), 6·20 (3H), 6·27 (6H), 6·32 (3H), and 6·42 (3H) (each s, 9 × OMe). In C_6D_6 the n.m.r. spectrum had signals at τ 5·06br (2H, s, ArCH_2), 5·52br (2H, s, ArCH_2), and 6·12, 6·19, 6·57, 6·64, 6·71, 6·74, 6·78, 6·79, and 6·80 (each 3H, s, 9 × OMe). These spectra clearly show the presence of two benzylic methylene groups.

The structures for other derivatives [2] of these pigments follow, so that *e.g.* methylation of penta-*O*-methylsantalin gives a pyranol, hexa-*O*-methylsantalanol (17). The analogous derivative of santarubin is penta-*O*-methylsantarubanol (18).

The elemental analyses [2] for the various derivatives of these pigments * are in satisfactory agreement with the revised structural assignments.

EXPERIMENTAL

Mass spectra were determined on an A.E.I. MS 902 spectrometer provided by the S.R.C. Unless otherwise stated n.m.r. spectra were observed for solutions in $CDCl_3$ with a Perkin-Elmer R-12A spectrometer.

Penta-O-methylsantalin.—Prepared as previously [2] this compound had m.p. 155° (decomp.); when the temperature was raised to 200° the material resolidified, and then re-melted at about 225° [Found: (for a specimen heated to 200°) C, 69·8, 69·5, 69·8; H, 5·6, 5·4, 5·5. $C_{33}H_{26}O_{10}$ requires C, 70·0; H, 5·5%].

Reduction of Tetra-O-methylsantarubin.—Sodium borohydride (100 mg) was added to a stirred solution of the pigment (253 mg) in ethanol (25 ml). The red colour was discharged after 5 min; the mixture was then poured into water (100 ml) and rapidly extracted with chloroform, and the extract was evaporated *in vacuo* at as low a temperature as possible to yield an almost colourless gum which rapidly re-oxidised. The gum was acetylated (acetic anhydride–pyridine) during 24 h at room temperature under nitrogen. The *acetate* formed prisms (100 mg), m.p. 164—167° (decomp.) (from ethanol) (Found: C, 69·0; H, 5·9%; M^+, 696. $C_{40}H_{40}O_{11}$ requires C, 69·0; H, 5·9%; *M*, 696).

Methylation of dihydrotetra-*O*-methylsantarubin with diazomethane in methanol at room temperature during 24 h gave *dihydropenta-O-methylsantarubin* in prisms, m.p. 166° [Found: M^+ 668. $C_{30}H_{13}O(OMe)_9$ requires *M*, 668].

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* Available as Supplementary Publication No. SUP 20599 (2 pp.); for details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue 20.