Structures of the Red Sandalwood Pigments Santalins A and B

By **Alberto Arnone, Lorenzo Camarda, Lucio Merlini,* and Gianluca Nasini,** Istituto di Chimica,† Politecnico di Milano, 20133 Milano, Italy

The red sandalwood (*Pterocarpus santalinus*) pigment santalin A has been identified as 6-(3,4-dihydroxybenzyl)-2,10-dihydroxy-5-(4-hydroxy-2-methoxyphenyl)-1,3-dimethoxybenzo[*a*]xanthen-9-one (2) on the basis of degradative and spectroscopic evidence. Santalin B (3) is the corresponding 6-(4-hydroxy-3-methoxybenzyl) derivative. N.m.r. data, particularly those obtained by use of the shift reagent $Eu(dpm)_3$, have led to the assignment of a revised structure (24) to per-*O*-methylsantarubin. A common biogenetic scheme for santalins and santarubin is suggested.

THE pigments of red sandalwood (*Pterocarpus santalinus*) and of related red woods have attracted the interest of natural products chemists for more than a century since the first report by Pelletier.[1,‡] Despite much effort, it was not until 1954 that two pure compounds, santalin and santarubin, were isolated by Robertson and Whalley,[2] who performed extensive and difficult degradative work and put forward the first structural proposal for these colouring matters. Santalin is the main pigment of red sandalwood (*Pterocarpus santalinus*), and was found also in commercial samples of camwood and barwood, where-

† Centro del C.N.R. per la Chimica delle Sostanze Organiche Naturali.

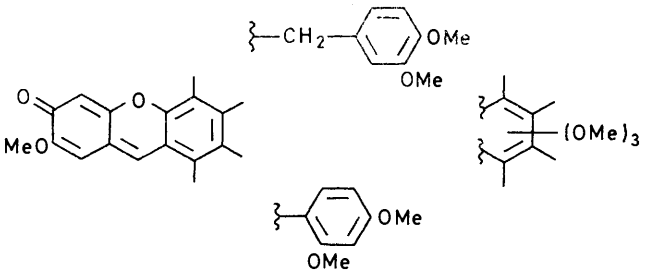
‡ See refs. 2 and 3 for a summary of the earlier work.

[1] J. Pelletier, *Annalen*, 1833, **6**, 28.
[2] A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1954, 2794.
[3] D. W. Mathieson, B. J. Millard, J. W. Powell, and W. B. Whalley, *J.C.S. Perkin I*, 1973, 184.

as santarubin was isolated only from the latter two types of wood.[2] The 'anhydrobenzopyranol' structure of both pigments was firmly established.[2]

Yet, owing to difficulties encountered in the isolation of the pigments, the English workers abandoned their work and left the complete structures unsolved. As a part of our programme of research on natural phenolic compounds and quinone methides,[4] and also since we were attracted by the problem, which has been referred to recently as 'one of the remaining legacies of classical organic chemistry,'[3] we began in 1971 to reinvestigate the colouring matters of the heartwood of botanically identified *Pterocarpus santalinus*, collected in India. When our work was already in an advanced stage, a communication appeared by Ravindranath and Seshadri,[5] who reported the presence in *Pterocarpus santalinus* of two pigments, santalins A and B, which both give the same per-*O*-methyl derivative, $C_{38}H_{36}O_{10}$.

The results obtained by degradative and spectroscopic work on this per-*O*-methyl derivative by ourselves [6] and by the Indian group are summarized in the partial formulae shown in Scheme 1. On this basis, Ravindranath and Seshadri [5] proposed the structure (1) for per-*O*-methylsantalin. The C_{30} skeleton is consistent with a biflavanoid system, derived by the coupling of a flavanoid unit with another C_{15} system. However we claimed, in our preliminary communication,[6] that the same evidence could equally well support another structure which could be derived from the combination of an isoflavanoid unit, instead of a flavanoid one, with another C_{15} system. Afterwards, a paper by Whalley and his co-workers [3] appeared where the same structural proposal as ours was preferred to (1) on the basis of new spectral data and of

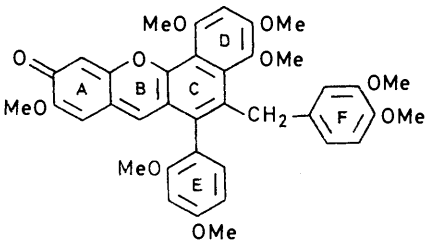


SCHEME 1

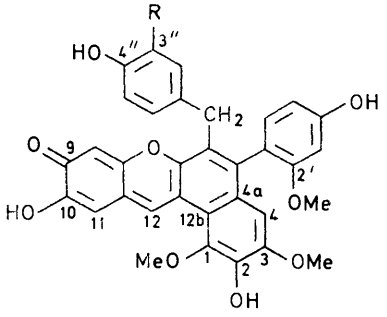
reinterpretation of the former [2] degradative results.* An isomeric structure was also proposed for per-*O*-methylsantarubin.

The present paper reports the isolation of the true natural pigments, santalins A, B, and C, and gives fully detailed evidence, which rules out the structure (1), and demonstrates the structures (2) and (3) for santalins A and B respectively.

Extracts of *Pterocarpus santalinus* heartwood were separated by polyamide column chromatography, and purified to give pure crystalline santalins A and B, and a small amount of santalin C. As expected, we found no



(1)



(2) R = OH
(3) R = OMe

santarubin in our material. Methylation of all the three santalins gave the same per-*O*-methyl derivative, thus establishing that each contained the same skeleton. Direct comparison with a sample of per-*O*-methylsantarubin supplied by Professor Whalley clearly indicated that this was different from per-*O*-methylsantalin.

Spectral data already reported [6] for santalin A and given in the Experimental section for santalins B and C indicated that these are, respectively, a trimethyl ether, $C_{33}H_{26}O_{10}$, and two tetramethyl ethers, $C_{34}H_{28}O_{10}$, of the same parent phenol. Evidence for the quinone methide structure of ring A has been given already by us [6] and others.[2,3,5,7] In particular, the n.m.r. spectrum of per-*O*-methylsantalin shows a one-proton signal at δ 9·51, assigned to H-12, with two couplings, of 1·3 Hz with H-8 [8] and 0·5 Hz with H-11. The 11-proton shows also a small coupling with an *O*-methyl group (at C-10). The absence of coupling between H-8 and -11 is consistent with their relative positions.[9]

As one of the main problems concerning the elucidation of the structures of the pigments was the location of the OH and OMe groups on the aromatic backbone, we prepared the *O*-ethylated derivative of santalin B, instead

* Surprisingly, in their recent full paper,[7] which contains no new evidence, Ravindranath and Seshadri not only do not take account of our [6] and Whalley's [3] new structural proposal, but claim that both these papers support their findings.

[4] G. Cardillo, L. Merlini, G. Nasini, and P. Salvadori, *J. Chem. Soc.* (*C*), 1971, 3967; A. Gennaro, L. Merlini, and G. Nasini, *Phytochemistry*, 1972, **11**, 1515.

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

[6] A. Arnone, L. Merlini, and G. Nasini, *Tetrahedron Letters*, 1972, 3503.

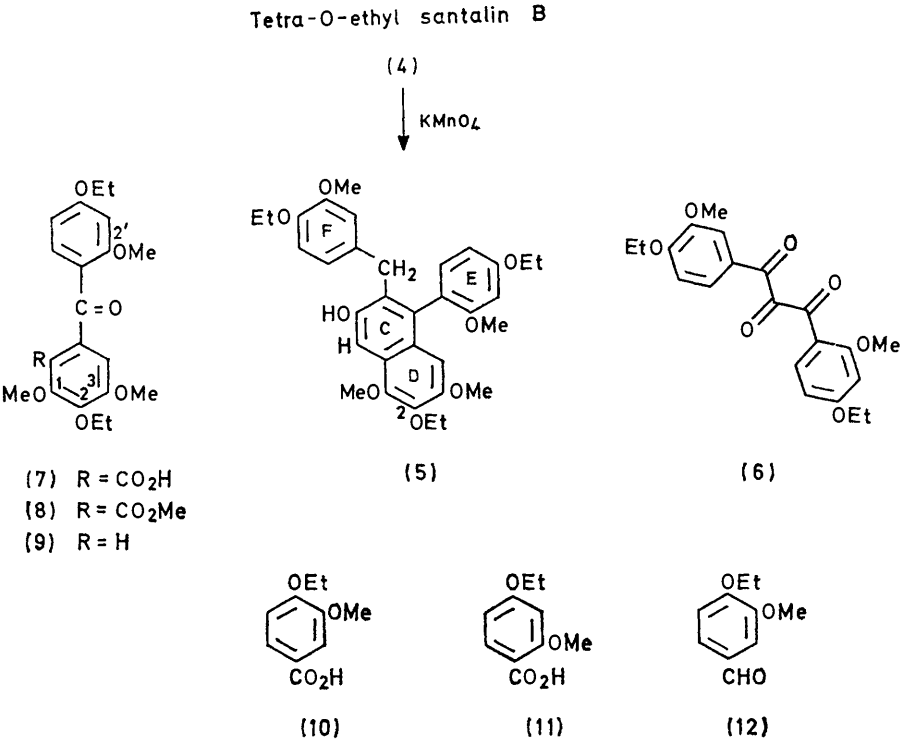
[7] B. Ravindranath and T. R. Seshadri, *Phytochemistry*, 1973, **12**, 2781.

[8] K. Nakanishi, Y. Takahashi, and H. Budzikiewicz, *J. Org. Chem.*, 1965, **30**, 1729.

[9] W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, 1969, **52**, 1354.

of the previously used per-*O*-methyl derivative. Ethylation with ethyl iodide and potassium carbonate gave pure tetra-*O*-ethylsantalin B (4). Permanganate oxidation of the ether (4) for 3 days afforded the compounds shown in Scheme 2.

The isolation of the acids (10) and (11) and of the aldehyde (12) establishes the 3-OMe,4-OH substitution of ring F and the 2-OMe,4-OH substitution of ring E of



SCHEME 2

structure of which indicates the nature of the link between rings D and E. The acid (7) was converted into the methyl ester (8), the phenone structure of which was apparent from its i.r., mass, and n.m.r. spectra. In particular, the n.m.r. spectrum showed the presence of three methoxy- and two ethoxy-groups (apart from the ester), and a 1,2,4-pattern of aromatic protons, with only one at low field (*ortho* to the carbonyl). This requires that santalin B. Since the same reaction carried out on pent-*O*-ethylsantalin A gave a mixture of (7), (11), and 3,4-diethoxybenzoic acid, santalin A differs from santalin B in having a 3,4-$(OH)_2$ substitution pattern on ring F. Compound (5) comes from the oxidative destruction of rings A and B. The presence of only three ethoxy-groups confirms the already established [6] presence of a hydroxy-group on ring A (position 10). The two substituents on ring C, *viz.* 4-ethoxy-2-methoxyphenyl- and 4-ethoxy-3-methoxybenzyl-, could be *ortho* or *para* to each other. That they are indeed *ortho*, as is most reasonable on biogenetic grounds, is supported by the isolation of the trione (6). The structure of this compound is shown by the n.m.r. spectrum (two patterns due to 1,2,4-arrangements of aromatic protons, in which in one case two and in the other one proton is *ortho* to a carbonyl group), the mass spectrum (highest mass peak at *m/e* 179, common to both ArCO units), and the i.r. spectrum (CO bands at 5·70 and 6·00 μm). Therefore the two rings of (6) must be derived from rings E and F of structure (5), and the structure of (6) shows their relative orientation. The remaining uncertainty, *i.e.* which position the two substituents occupy on ring C of (5), is resolved by the isolation of (7), the one of the two rings of structure (8) must be E. The substitution pattern on the other ring (D) was ascertained by decarboxylation of (7) with copper chromite to give the ketone (9). This compound shows, in the n.m.r. spectrum, a singlet corresponding to the two protons on ring D, thus requiring a symmetrical substitution pattern as shown. Confirmation of this assignment and also of the relative positions of the two methoxy-groups and the ethoxy-group on ring D was given by the solvent-induced shift in the n.m.r. spectrum [10] (Figure 1): only the signal of the OCH_2 group in position 2 of ring D is not shifted, and therefore this group must be adjacent to two *ortho*-substituents (*i.e.* to no hydrogen atoms). The positions of the alkoxy-groups were all verified from the results of decoupling experiments.* Independent support for the structure (9) was obtained by similar degrad-

* This result, which gives proof for the substitution of ring D in santalins, is in contrast with Seshadri's contention [7] that permanganate degradation of per-*O*-methylsantalin gives 3,4,6-trimethoxyphthalic acid. However, this claim is based on insufficient experimental evidence: the only proof given for the alleged structure is ' difference in m.p. from 3,4,5-trimethoxyphthalic acid.'

[10] A. Pelter and P. I. Amenechi, *J. Chem. Soc.* (*C*), 1969, 887.

ation of per-*O*-methylsantalin. The product corresponding to (9), which contains five methoxy-groups, again gave a singlet in the n.m.r. spectrum corresponding to the protons on ring D, and moreover was identical (spectra

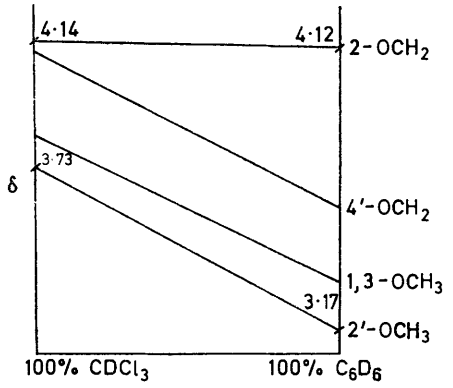
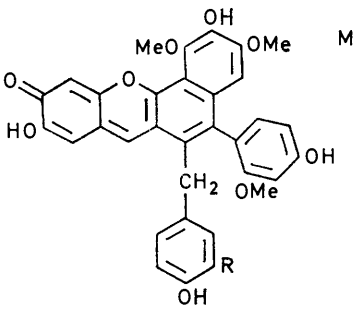


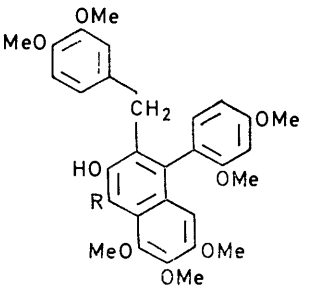
FIGURE 1 Solvent-induced shifts in the n.m.r. spectrum of the ketone (9)

and t.l.c. comparison) with authentic 2,3',4,4',5'-pentamethoxybenzophenone. Further confirmation of

potassium hydroxide [6] afforded two main products: (15) $C_{31}H_{32}O_9$, and (16), $C_{30}H_{32}O_8$, both containing seven

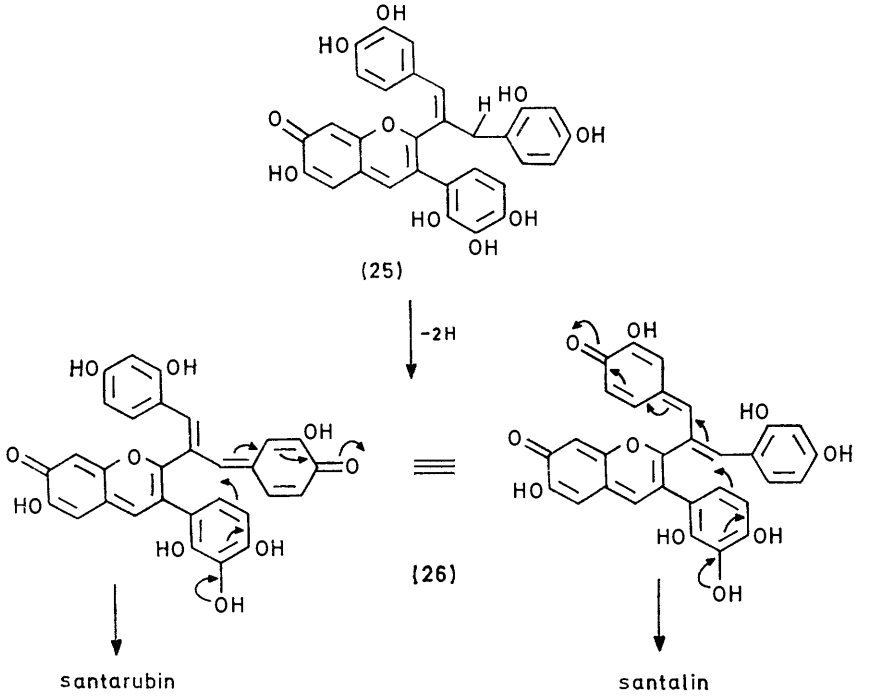


(13) R = OH
(14) R = OMe



(15) R = CHO
(16) R = H

methoxy-groups. Compound (15) is an aromatic *o*-hydroxy-aldehyde, whereas (16) lacks the formyl group. Their formation from per-*O*-methylsantalin is easily explained in terms of nucleophilic attack of OH^- at position 12, in the quinone methide ring, followed by retro-aldol



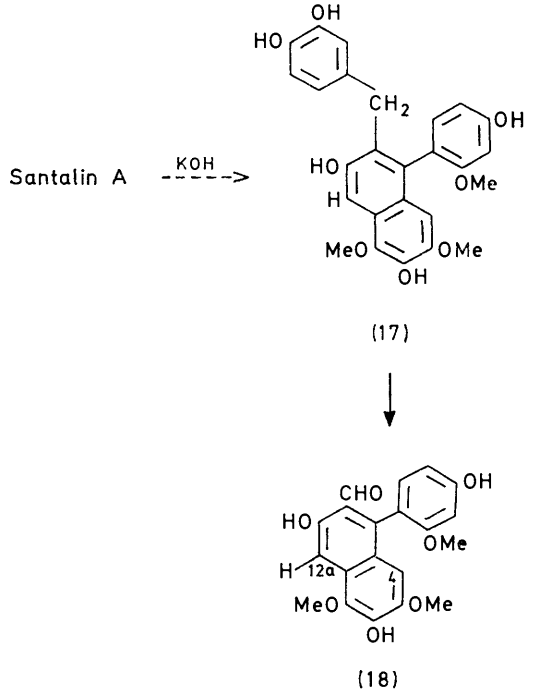
SCHEME 4

the substitution pattern on ring D comes from the n.m.r. spectrum of per-*O*-methylsantalin in the presence of the shift reagent $Eu(dpm)_3$ (see later). All these results establish the structure of the *O*-ethylated santalin (4), except for the reciprocal positions of the H and OH on ring C, rule out Seshadri's formula (1), and leave (2) and (3), and (13) and (14) as the only possible structures for santalins A and B, respectively.*

Degradation of per-*O*-methylsantalin with methanolic cleavage of the 11a,12-bond [to give (15)], or the 12,12a-bond [to give (16)] and rupture of the ether bond. Complete analysis of the n.m.r. spectrum of (15) (Figure 2) provides further proof of the substitution on rings E and F. The spectrum shows two systems of substituted benzene rings each with three protons in a 1,2,4-arrangement. Those numbered 2'' and 6'' are coupled to the

* As santalin A and B give the same per-*O*-methyl derivative these conclusions hold for both compounds.

methylene group, and must therefore be on ring F, whereas the other three (on ring E) are not decoupled by irradiation at the CH_2 frequency. Of particular interest is

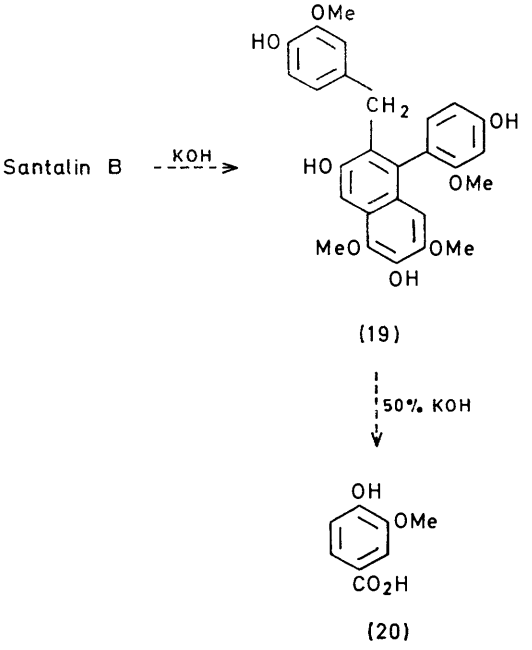


SCHEME 3

the result of the irradiation at the 1-OMe frequency, which induces a nuclear Overhauser effect (n.O.e.) of 15% in the CHO signal. This requires a close relationship (*peri*) between these two groups and thus provides a strong indication in favour of the structures (15) and (16), and consequently of (2) and (3) for the santalins.

The choice between the structures (2) and (3), and (13) and (14) could be made with certainty by examining the products of the alkaline degradation of santalin A (Scheme 3). Compound (17) is obtained from santalin A by the same mechanism of degradation that leads to the ether (16), and its identification is based on similar evidence. The presence of two hydroxy-groups on ring F is established by further degradation of (17) to (18), which still retains the three methoxy-groups of santalin A. The step (17) ⟶ (18) can be explained in terms of oxidation of the *p*-hydroxybenzylic unit of (17) to a *p*-quinone methide and addition of water, or direct radical oxidation,[11] followed by retro-aldol cleavage of the benzyl alcohol. This step establishes unequivocally that the formyl group of (18) is derived from the benzylic methylene group attached to ring F and not from C-12 (ring B) of santalin A.* As (18) is an *o*-hydroxy-aldehyde (chelated OH indicated by the n.m.r. spectrum), and the mode of attachment of rings F (from which the aldehyde is derived) and E to ring C is known from Scheme 2, the position of the hydroxy-group, and thus the structure of (18) is established. Consistent with this interpretation are the couplings of H-12a and the chemical shift of both the formyl and the chelated hydroxy-groups in the n.m.r. spectrum of (18), which clearly indicates the presence of a 2-hydroxy-3-naphthaldehyde system. The 12a-proton shows two couplings, both 0·7 Hz, with the formyl group and with H-4. This requires a *meta*-relationship with the aldehyde [12] and a 1,5-relationship between the two protons on the naphthalene ring.[13] In (18) the CHO and the OH signals appear, respectively, at δ 9·66 and 10·2 (in $CDCl_3$), positions very similar to those of the same groups in 2-hydroxy-3-naphthaldehyde (δ 9·98 and 10·28 [14]), whereas 2-hydroxy-1-naphthaldehyde shows the corresponding signals at δ 10·66 and 13·02.[14,†] Moreover, the 12a-proton shows a n.O.e. of 17% on irradiation at the 1-methoxy-group frequency in the acetate of (18); this provides further proof of the *peri*-position of H-12a (the position of the methoxy-group is assigned by decoupling of all the other methoxy-groups from the adjacent protons).

The analogous degradation of santalin B gave a mixture, from which only the compound (19) could be isolated. Further degradation of (19) gave only vanillic acid (20). Conjunction of the results obtained from



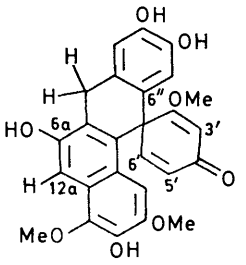
degradations of santalin A and B, in particular the combination of structures (18) and (5), excludes the formulae (13)

* In our preliminary communication [6] we assigned this incorrect position to the formyl group; this would also be consistent with the mechanism of degradation of santalin A, in which both products could be produced.

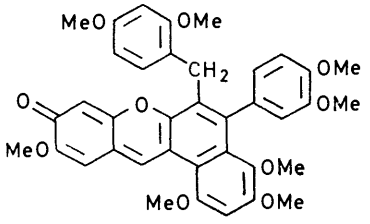
† Also 1-hydroxy-2-naphthaldehyde has a different value for the OH shift (δ 12·60), whereas the aldehyde signal is at δ 9·85.[15]

[11] G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, in ' Oxidation of Organic Compounds, vol. 1,' A.C.S. Advances in Chemistry Series, no. 75, Washington, 1968, p. 174.
[12] D. G. de Kowalewski and V. J. Kowalewski, *Mol. Phys.*, 1965, **9**, 319.
[13] R. W. Crecely and J. H. Goldstein, *Org. Magnetic Resonance*, 1970, **2**, 613.
[14] G. O. Dudek, *Spectrochim. Acta*, 1963, **19**, 691.
[15] D. C. Nonhebel, *Tetrahedron*, 1968, **24**, 1869.

and (14), and leaves (2) and (3) as the only possible structures for santalins A and B.



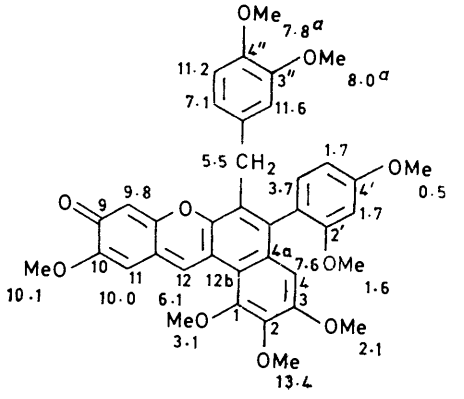
(21)



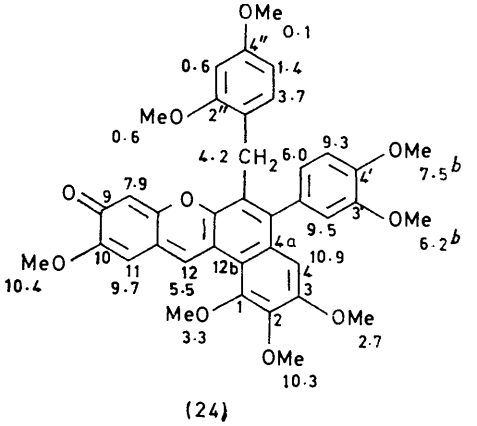
(22)

A side product (21) formed during the alkaline degradation of santalin A is apparently a product of oxidative phenolic coupling of (17), probably as a result of oxidation by air, since it contains two hydrogen atoms less than (17). Since the n.m.r. spectrum of (21) does not show a signal due to the 6″-proton on ring F, the coupling reaction must involve the C-6″ and the OH on ring D, or the same carbon atom and another on ring E (*para* to OH). This second possibility would lead to a spiro-dienone, and is more consistent with some features of the n.m.r. spectrum of (21), particularly the value of $J_{5',6'}$ (10 Hz), which is too high for an aromatic structure, and consistent with a dienone structure.[15] The same holds for the chemical shift of H-3′ (δ 5·94), which is consistent with a position α to a carbonyl group, and for the shift to lower field (Δδ +0·4 p.p.m.) of the H-12a signal on acetylation, which indicates the presence of a free OH in position 6a.

The structure (22) was assigned by Whalley and his coworkers [3] to tetra-*O*-methylsantarubin on the basis of mass spectra, previous degradative results (particularly the isolation of 2,4-dimethoxybenzaldehyde after oxidation), and Seshadri's proposal [5] for the substitution on ring D. The 100 MHz n.m.r. spectrum of tetra-*O*-methylsantarubin shows coupling between the protons of the benzylic methylene group and one proton only of one of the two 1,2,4-substituted aromatic systems, and confirms the substitution on rings E and F proposed by Whalley. Moreover, this proton (H-6″) is not decoupled (as well as H-6′) on irradiation over the range of methoxy-frequencies. Owing to the similarity of structure and the close biogenetic relationship between the santalins and santarubin, it appears likely that santarubin has the same vicinal tri-OR substitution on ring D as the santalins. Although this has not been proved by chemical degradation, a strong indication has been obtained from the n.m.r. spectra of per-*O*-methylsantarubin (24) and per-*O*-methylsantalin (23) in the presence of the shift reagent $Eu(dpm)_3$. The figures on the formulae give the induced shifts of the signals (solvent 1 : 1 CCl_4–$CDCl_3$) when $Eu(dpm)_3$ (100 mg) was added to a solution containing 20 mg of compound in 0·5 ml. The two compounds show a striking similarity in the induced shifts of all the aromatic and methoxy-signals. In particular, the methoxy-shifts agree closely with the results obtained recently by Wright and Tang Wei [16] for differently substituted methoxybenzenes and prove that the substitutions on rings E, F, and (particularly) D are those shown in the formulae (23) and (24). The difference in the shift of H-4 could be explained in terms of a stronger bond between the europium and the *ortho*-dimethoxy-system, which is on ring E in santarubin, and thus nearer to H-4



(23)



(24)

Eu(dpm)$_3$-induced shifts (p.p.m.) in $CDCl_3$–CCl_4 (1 : 1). [a,b] These values may be interchanged

than in santalin. These results indicate that the use of shift reagents might also be useful for the assignment of substitution in polymethoxylated aromatic molecules such as biflavonoids. We therefore propose formula

[16] G. E. Wright and T. Y. Tang Wei, *Tetrahedron*, 1973, **29**, 3775.

(24) for tetra-*O*-methylsantarubin. The respective positions of the methoxy- and hydroxy-groups in santarubin itself remain unknown.

As the santalins and santarubin differ only in having opposite substitution on rings E and F, a common biogenetic origin is likely. A possible pathway, requiring thetical intermediate (25) could be formed by radical coupling, consistent with attack on the central carbon atom of the chain of the cinnamylphenol unit. Such a carbon radical would be a mesomeric form of the phenoxyl radicals available by oxidation of each of the *para*-hydroxy-groups. A further oxidative step would give

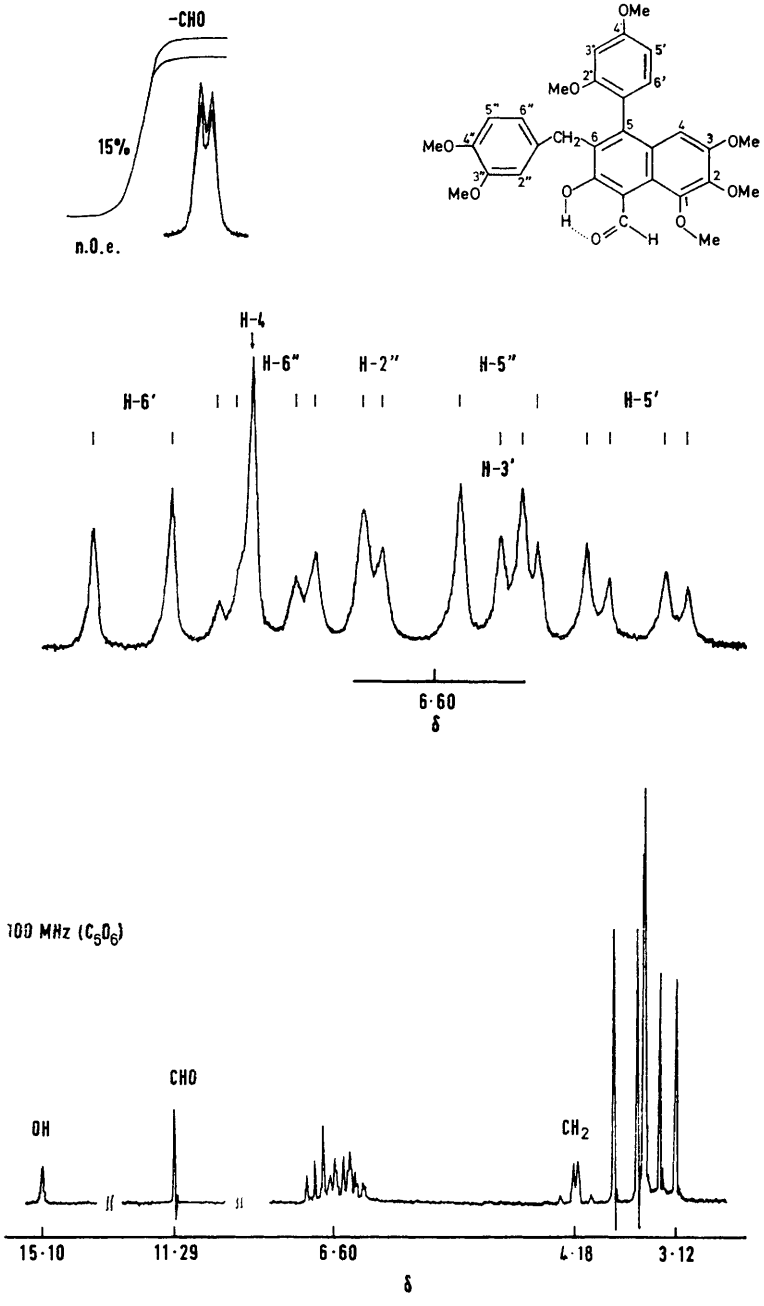


FIGURE 2 N.m.r. spectrum of compound (15)

coupling of a preformed isoflavanoid unit with a cinnamylphenol unit, is outlined in Scheme 4. The presence of simple isoflavans in the heartwood of *Pterocarpus santalinus* is in agreement with this Scheme. The hypothe the quinone methide (26), and vinylogous nucleophilic attack of the hydroxy-group on ring D in both rotamers of (26) would give santalins or santarubin. We note that coupling of two cinnamylphenol units, followed by oxid-

ation and ring closure, would lead to structural types such as (13). So far, however, no condensed biflavonoid other than the santalins and santarubin has been isolated from natural sources.

EXPERIMENTAL

U.v. spectra were measured for solutions in 95% EtOH ($\lambda_{max.}$ in nm) with a Beckman DK-2 apparatus, and n.m.r. spectra with Varian XL-100 instrument. Where not otherwise stated, column chromatography was performed with Merck silica gel (0·05—0·20 mm), and t.l.c. with Merck HF_{254} silica gel.

Isolation of the Pigments.—The heartwood shavings were extracted with hexane, then with chloroform and ethyl acetate. The ethyl acetate extract was concentrated and the residue chromatographed through a Woelm polyamide column ($CHCl_3$–MeOH), to give red products, of which santalins A and B were the major constituents. The fractions were separated on a second column to give pure santalins A and B and a small amount of santalin C. *Santalin A* (2) crystallized from $CHCl_3$–MeOH as orange needles, m.p. 300° (decomp.), $\lambda_{max.}$ 242, 269, 279, 307, 318, 445sh, 472, and 505 (ε 50,000, 40,600, 41,800, 15,700, 17,510, 23,200, 37,400, and 36,900), $\lambda_{max.}$ (Nujol) 3·05 (OH) and 6·15 μm (conj. CO), *m/e* 582, δ [$(CD_3)_2SO$] 3·60, 3·66, and 3·93 (OMe), 3·9 (shifted to 4·2 in $CF_3{\cdot}CO_2H$; $ArCH_2Ar$), 6·2—7·2 (9 aromatic H), and 9·54 (H-12). *Santalin B* (3) crystallized from $CHCl_3$–MeOH as orange needles, m.p. 180°, second m.p. 290—291°, $\lambda_{max.}$ 242, 271, 279, 308, 320, 445sh, 472, and 505 (ε 50,000, 38,150, 41,800, 14,380, 19,500, 23,200, 37,400, and 36,900), $\lambda_{max.}$ (Nujol) 3·05 (OH) and 6·15 μm (conj. CO), *m/e* 596, δ [$(CD_3)_2SO$] 3·64, 3·70, 3·70, and 3·94 (OMe), *ca.* 4·0 ($ArCH_2Ar$), 6·2—7·2 (9 aromatic H), and 9·54 (H-12). *Santalin C*, obtained as orange needles from $CHCl_3$–MeOH, had m.p. >300° (decomp.), $\lambda_{max.}$ 242, 269, 320, 449, 478, and 510 (ε 46,300, 14,350, 19,150, 20,000, 33,700, and 33,500), $\lambda_{max.}$ (Nujol) 3·07 (OH) and 6·15 μm (conj. CO), *m/e* 596, δ [$(CD_3)_2SO$] 3·60, 3·65, 3·86, and 3·94 (OMe), 3·9 ($ArCH_2Ar$), 6·2—7·2 (9 aromatic H), and 9·54 (H-12).

Ethylation of Santalin A.—Santalin A (1 g) dissolved in dry acetone (50 ml) was refluxed for 12 h with ethyl iodide (3 ml) over anhydrous potassium carbonate (2 g). Filtration, evaporation, and t.l.c. of the residue with ethyl acetate yielded *penta-O-ethylsantalin A* as orange needles, m.p. 117—118°, $\lambda_{max.}$ 238, 269, 278, 322, 420, 445, 473, and 507 (ε 37,400, 43,600, 45,300, 16,450, 14,850, 21,600, 34,200, and 29,900), $\lambda_{max.}$ (Nujol) 6·2 μm (CO conj.), *m/e* 724 (*M* + 2) (Found: C, 70·3; H, 5·65. $C_{43}H_{46}O_{10}$ requires C, 71·45; H, 6·4%).

Ethylation of Santalin B.—Santalin B was ethylated as described for santalin A and the *tetraethyl ether* (4), purified by t.l.c. (AcOEt) (yield 40%), had m.p. 115°, $\lambda_{max.}$ 237, 269, 278, 322, 420, 448, 475, and 510 (ε 52,000, 39,700, 42,600, 15,200, 13,000, 19,100, 31,000, and 27,400), $\lambda_{max.}$ (Nujol) 6·2 μm (conj. CO) (Found: C, 69·4; H, 5·9. $C_{42}H_{44}O_{10}$ requires C, 71·15; H, 6·25%), δ ($CDCl_3$) 3·61, 3·68, 3·70, and 4·06 (OMe), 3·99, 4·10, 4·13, and 4·22 ($O{\cdot}CH_2Me$), 1·36, 1·46, 1·48, and 1·56 ($O{\cdot}CH_2\mathit{Me}$), 4·0 ($ArCH_2Ar$), 6·5—7·0 (9 aromatic H), 7·02 (H-6′), and 9·51 (H-12).

Methylation of Santalin A.—Santalin A (1 g) was dissolved in dry acetone (50 ml) and refluxed for 6 h with methyl iodide (3 ml) over anhydrous potassium carbonate (2 g). Filtration, evaporation, and crystallization from MeOH gave penta-*O*-methylsantalin A, orange needles (80%), m.p. 145°, second m.p. 220°, $\lambda_{max.}$ 235, 268, 277, 321, 472, and 505 (ε 34,200, 26,500, 28,300, 10,700, 21,100, and 18,800), $\lambda_{max.}$ (Nujol) 6·2 μm (CO conj.), *m/e* 652, δ [$(CD_3)_2CO$] 3·66 (4 OMe), 3·84, 3·90, 3·96, and 4·06 (OMe), 4·1 ($ArCH_2Ar$), 6·7—6·8 (5 aromatic H), 6·27 (H-8), 6·76 (H-4), 6·98 (H-11), 7·14 (H-6′), and 9·51 (H-12), $J_{8,12}$ 1·3, $J_{11,12}$ 0·5, $J_{11,10\text{-OMe}}$ 0·1 Hz.

Methylation of Santalin B.—Santalin B (1 g) was methylated as described for santalin A, and the tetramethyl ether was crystallized from MeOH to give orange-yellow needles (80%), m.p. 145°, second m.p. 220°, u.v., i.r., and n.m.r. spectra and t.l.c. behaviour identical with those of penta-*O*-methylsantalin A.

Methylation of Santalin C.—Santalin C (100 mg) was methylated as described for santalin A, to give the same methyl ether (t.l.c., u.v., and i.r. comparison).

Oxidation of Tetra-O-ethylsantalin B with Permanganate.—Tetra-*O*-ethylsantalin B (4) (0·2 g) in acetone (50 ml) was treated with saturated aqueous potassium permanganate and stirred for 3 days at room temp. Filtration, concentration, and extraction with ether gave a mixture, which was separated by preparative t.l.c. (hexane–ethyl acetate, 2 : 1) into the products (5), (6), and (12). The aqueous layer was acidified and extracted with ethyl acetate; preparative t.l.c. of the extract (benzene–ether–formic acid, 50 : 50 : 1, then chloroform–methanol, 9 : 1) gave the products (7), (10), and (11). Compound (5) was a solid, m.p. 68°, *m/e* 562, δ ($CDCl_3$) 3·56, 3·64, 3·73, and 4·00 (OMe), 4·06, 4·10, and 4·15 ($O{\cdot}C\mathit{H}_2{\cdot}CH_3$), 1·40, 1·40, and 1·46 ($O{\cdot}CH_2{\cdot}C\mathit{H}_3$), 3·9 ($ArCH_2$-Ar), 6·5—7·0 (6 aromatic H), 7·46 (H-12a), and 6·44 (H-4). Compounds (10)—(12) appeared to be, respectively, 4-ethoxy-3-methoxybenzoic acid, 4-ethoxy-2-methoxybenzoic acid, and 4-ethoxy-3-methoxybenzaldehyde, as shown by t.l.c. and spectral comparison with authentic samples. The substance (6) was a solid, m.p. 70°, *m/e* 179 and 151, $\lambda_{max.}$ 228, 252, 279, and 315 (ε 24,800, 12,100, 16,400, and 14,950), $\lambda_{max.}$ (neat) 5·7, 6·0, and 6·1 μm, δ [$(CD_3)_2CO$] 1·40 and 1·40 ($O{\cdot}CH_2{\cdot}C\mathit{H}_3$), 3·60 and 3·90 (OMe), 4·16 and 4·20 ($O{\cdot}C\mathit{H}_2{\cdot}CH_3$), 6·61 (H-3′), 6·73 (H-5′), 7·94 (H-6′), 7·04 (H-5″), 7·35 (H-6″), and 7·50 (H-2″). The acid (7) was a solid, m.p. 150° (decomp.), which, treated with diazomethane in ether, afforded the methyl ester (8) as a glass, *m/e* 418·1650 ± 0·004 (Calc. for $C_{22}H_{26}O_8$: *M*, 418·1628), 359, 195, 179, 165, and 151, $\lambda_{max.}$ 281 and 309 (ε 11,120 and 960), $\lambda_{max.}$ (neat) 5·80 and 6·06 μm, δ ($CDCl_3$) 1·40 and 1·43 ($O{\cdot}CH_2{\cdot}C\mathit{H}_3$), 3·60, 3·70, 3·82, and 3·93 (OMe), 4·10 and 4·15 ($O{\cdot}C\mathit{H}_2{\cdot}CH_3$), 6·47 (H-3′), 6·52 (H-5′), 7·53 (H-6′), and 6·84 (H-4) (numbering as in santalin). Decarboxylation of (7) (10 mg), with copper chromite (100 mg) and quinoline (2 ml) at 150° gave 4,4′-diethoxy-2,3′,5′-trimethoxybenzophenone (9), as a glass, *m/e* 360, 343, 315, 303, 179, and 151, $\lambda_{max.}$ 210 and 306 (ε 3500 and 1315), $\lambda_{max.}$ (Nujol) 6·1 μm, δ (benzene) (numbering as in santalin) 1·10 and 1·30 ($O{\cdot}CH_2{\cdot}C\mathit{H}_3$), 3·17 (2′-OMe), 3·33 (1- and 3-OMe), 3·58 (2-OCH_2), 4·12 (4′-OCH_2), 6·35 (H-5′), 6·38 (H-3′), 7·50 (H-6′), and 7·35 (H-4 and -12b).

Oxidation of Per-O-methylsantalin with Permanganate.—The methyl ether was oxidized as described for the ethyl ether. Acidification of the reaction mixture (dil. HCl), extraction (AcOEt), and preparative t.l.c. (benzene–ether–formic acid 50 : 150 : 1, then chloroform–methanol 9 : 1) gave 6-(2,4-dimethoxybenzoyl)-2,3,4-trimethoxybenzoic acid. This compound (10 mg) was treated with copper chromite (100 mg) and quinoline (2 ml) at 150° to give 2,3′,4,4′,5′-pentamethoxybenzophenone, identical (t.l.c., n.m.r.) with an authentic sample.

2,3′,4,4′,5′-Pentamethoxybenzophenone.— 3,4,5-Trimethoxybenzoic acid (2·12 g) in dry benzene (50 ml) was refluxed for 2 h with *m*-methoxyphenol (1·24 g) and toluene-*p*-sulphonic acid (150 mg). Evaporation, addition of water, neutralization, and extraction with ethyl acetate gave *m*-methoxyphenyl 3,4,5-trimethoxybenzoate (1·1 g). This ester (200 mg) was treated with aluminium chloride (250 mg) for 45 min at 160°. Addition of hydrochloric acid and extraction with ethyl acetate gave a crude product which was refluxed in dry acetone (10 ml) with methyl iodide (0·2 ml) and potassium carbonate (200 mg) for 1 h. Filtration, evaporation, and preparative t.l.c. (hexane–ethyl acetate, 4 : 1) gave 2,3′,4,4′,5′-pentamethoxybenzophenone (50 mg), m.p. 82°, *m/e* 332, 315, 287, 195, 182, and 165, $\lambda_{max.}$ 207 and 300 (ε 4150 and 1425), $\lambda_{max.}$ (Nujol) 6·08 μm, δ ($CDCl_3$) 3·72, 3·83, 3·83, 3·85, and 3·90 (OMe), 6·53 (H-3 + H-5), 7·05 (H-2′ + H-6′), and 7·33 (H-6).

Oxidation of Penta-O-ethylsantalin A with Permanganate.—The oxidation and work-up were performed as described for santalin B ethyl ether. The acid fraction afforded the acid (7), 4-ethoxy-2-methoxybenzoic acid (11), and 3,4-diethoxybenzoic acid, m.p. 165° (lit.,[17] 164—165°), δ [$(CD_3)_2CO$] 1·40 ($O{\cdot}CH_2{\cdot}CH_3$), 4·10 and 4·15 (OMe), 7·03 (H-5), 7·55 (H-2), and 7·65 (H-6).

4-Ethoxy-2-methoxybenzoic Acid.—4-Ethoxy-2-hydroxybenzoic acid (100 mg) was refluxed for 30 min with methyl iodide (0·2 ml) and potassium carbonate (0·2 g) in dry acetone (10 ml). Refluxing the ester thus obtained with 10% sodium hydroxide for 30 min gave 4-ethoxy-2-methoxybenzoic acid, m.p. 125° (from H_2O), δ ($CDCl_3$) 1·44 ($O{\cdot}CH_2{\cdot}CH_3$), 4·11 ($O{\cdot}CH_2{\cdot}CH_3$), 4·02 (OMe), 6·53 (H-3), 6·63 (H-5), and 8·12 (H-6).

4-Ethoxy-3-methoxybenzoic Acid.—Vanillic acid was treated with ethyl iodide as described for the preceding acid. Hydrolysis of the ester gave 4-ethoxy-3-methoxybenzoic acid, m.p. 193° (from H_2O), δ ($CDCl_3$) 1·50 ($O{\cdot}CH_2{\cdot}CH_3$), 4·18 ($O{\cdot}CH_2{\cdot}CH_3$), 6·90 (H-5), 7·60 (H-2), 7·64 (H-6), and 3·92 (OMe).

Degradation of Santalin A with Alkali.—Santalin A (2 g) was refluxed for 12 h with 20% potassium hydroxide (100 ml). Dilution, neutralization, extraction with ethyl acetate, and preparative t.l.c. of the residue with hexane–ethyl acetate (2 : 1) gave three compounds, (17), (18), and (21). *3,6-Dihydroxy-1-(4-hydroxy-2-methoxyphenyl)-5,7-dimethoxy-2-naphthaldehyde* (18) (200 mg) formed yellow needles, m.p. 170° (from benzene–petroleum) (Found: C, 65·6; H, 5·4. $C_{20}H_{18}O_7$ requires C, 64·85; H, 4·9%), $\lambda_{max.}$ 222, 270sh, 276, 342, and 410 (ε 24,000, 28,000, 30,000, 11,900, and 2600), $\lambda_{max.}$ (KBr) 3·05 (OH) and 6·1 μm (conj. CO), *m/e* 370, 355, 233, and 137, δ ($CDCl_3$) (numbering as in santalin) 3·95 [1-OMe, Δδ ($CDCl_3 - C_6H_6$) +27 Hz], 3·66 [3-OMe, Δδ ($CDCl_3 - C_6H_6$) +64 Hz], 3·56 [2′-OMe, Δδ ($CDCl_3 - C_6H_6$) +58 Hz], *ca.* 6·5 (H-3′, -5′, and -4), 6·96 (H-6′), 7·42 (H-12a), 9·66 (CHO), and 10·2 (OH). Acetylation of (18) with pyridine and acetic anhydride gave its triacetate, δ [$(CD_3)_2CO$] 2·30, 2·31, and 2·35 (AcO), 4·02 (1-OMe), 3·71 (2′-OMe), 3·67 (3-OMe), 6·97 (H-5′), 7·07 (H-3′), 7·32 (H-6′), 6·69 (H-4), 7·78 (H-12a), and 9·78 (CHO); n.O.e. 1-OMe/H-12a 17%, 2′-OMe/H 30%.

Compound (17) (15 mg) was a solid, m.p. 160°, *m/e* 464 and 339, $\lambda_{max.}$ 241, 285, 340, 453, and 477sh (ε 17,100, 4680, 1990, 3520, and 2800), δ [$(CD_3)_2CO$] 3·50, 3·61, and 3·93 (OMe), 3·75 ($ArCH_2Ar$), 7·36 (H-12a), 6·80 (H-6′), and 6·2—6·7 (6 aromatic H). Refluxing (17) for 3 h with 30% potassium hydroxide afforded (18).

Compound (21) was a glassy solid, $\lambda_{max.}$ 6·06 and 6·35 μm, δ [$(CD_3)_2CO$] 3·53, 3·69, and 3·94 (OMe), 4·15 ($ArCH_2Ar$), 5·94 (H-3′), 6·28 (H-5′), 6·77 (H-6′), 6·83 and 6·87 (H-2″ and -5″), 7·47 (H-4), and 7·50 (H-12a). Acetylation of (21) with pyridine and acetic anhydride gave its tetra-acetate, *m/e* 630, 629, 587, 545, 503, and 461, $\lambda_{max.}$ (neat) 5·66 and 6·05 μm, δ (benzene) 1·74, 1·82, 1·94, and 1·96 (AcO), 2·58 (2′-OMe), 3·60 (3-OMe), 3·62 (1-OMe), 4·12 ($ArCH_2Ar$), 5·78 (H-3′), 6·17 (H-6′), 6·27 (H-5′), 6·97 and 7·44 (H-5″ and -2″), 7·63 (H-4), and 8·11 (H-12a), $J_{5',6'}$ 10·0, $J_{3',5'}$ 1·5, $J_{4,12a}$ 0·7, $J_{CH_2,2''}$ 0·4, $J_{CH_2,5''}$ 0·2 Hz; n.O.e. 3-OMe/H-4 35%, 1-OMe/H-12a 20%, 2′-OMe/H-3′ 30%.

Degradation of Santalin B with Alkali.—Santalin B (2 g) was refluxed for 6 h with 20% potassium hydroxide. Dilution, neutralization, and extraction with ethyl acetate, and t.l.c. with hexane–ethyl acetate (2 : 1) gave compound (19), m.p. 180°, *m/e* 478 and 339 (*M* − 137), $\lambda_{max.}$ 241, 284, 301sh, 325, and 339 (ε 21,700, 10,680, 6200, 4050, and 5070), $\lambda_{max.}$ (KBr) 3·0 (OH), δ [$(CD_3)_2CO$] 3·50, 3·60, 3·66, and 3·92 (OMe), 3·75 ($ArCH_2Ar$), 7·40 (H-12a, $J_{4,12a}$, 0·7 Hz), 6·45 (H-4), and 6·5—6·7 (6 aromatic H). Treatment of (19) with 50% potassium hydroxide gave vanillic acid, identical with an authentic sample.

Degradation of Per-O-methylsantalin with Alkali.—Per-*O*-methylsantalin (0·5 g) was refluxed for 6 h with methanolic 2N-potassium-hydroxide (25 ml) under nitrogen. Concentration, treatment with dilute acid, extraction with ethyl-acetate and preparative t.l.c. (hexane–ethyl acetate, 2 : 1) gave two main products, (15) and (16). Compound (15) had *m/e* 548, m.p. 71°, $\lambda_{max.}$ 233, 277, 347, and 386sh (ε 22,800, 11,500, 10,000, and 7600), δ (benzene) 3·12 (2′-OMe), 3·29 (3-OMe), 3·45 (4′-, 3″-, and 4″-OMe), 3·53 (1-OMe), 3·79 (2-OMe), 4·18 ($ArCH_2Ar$), 6·45 (H-5′), 6·56 (H-3′), 6·95 (H-6′), 6·58 (H-5″), 6·70 (H-2″), 6·79 (H-6″), 6·82 (H-4), 11·29 (CHO), and 15·10 (OH), $J_{CH_2,H\text{-}2''} = J_{CH_2,H\text{-}6''} = 0{\cdot}4$ Hz; n.O.e. 1-OMe/CHO 15%.

Compound (16) had *m/e* 520, $\lambda_{max.}$ 235, 276, 345, and 381 (ε 334,150, 20,200, 4650, and 3100), m.p. 67—68°, $\lambda_{max.}$ (neat) 3·02 (OH), δ (benzene) 3·13, 3·34, 3·44, 3·44, 3·44, 3·84, and 3·84 (OMe), 4·20 ($ArCH_2Ar$), 5·78 (OH), 6·43 (H-5′), 6·58, (H-3′), 7·09 (H-6′), 6·59 (H-5″), 6·75 (H-2″), 6·7 (H-6″), 6·75 (H-4), and 7·60 (H-12a), $J_{4,12a}$ 0·7 Hz.

We thank Professor W. B. Whalley for the sample of tetra-*O*-methylsantarubin and for exchange of information, and Mr. E. Barlesi for technical help.

[4/1134 *Received*, 11*th June*, 1974]

[17] F. E. King, L. Jurd, and T. J. King, *J. Chem. Soc.*, 1952, 21.