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CONSTITUTION OF THE SANTALIN PIGMENTS A AND B*

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Key Word Index—*Pterocarpus santalinus*, Leguminosae, santalin pigments, santalin-A and santalin-B, mixed ethyl methyl ethers, 9,10,12-tri-*O*-methylsantalin and 9,10,12,4′-tetra-*O*-methylsantalin

Abstract—The heartwood of *Pterocarpus santalinus* contains two major red pigments, santalin-A and santalin-B which are partial methyl ethers of the same polyphenol (santalin) For locating the position of the methoxyl groups, alkali fission and permanganate oxidation of the mixed ethyl methyl ethers are the most convenient By this method santalin-A has been shown to be 9,10,12-tri-*O*-methylsantalin and santalin-B, 9,10,12,4′-tetra-*O*-methylsantalin

IT HAS now been possible to locate unequivocally the position of methoxyls in santalin-A [$C_{30}H_{17}O_7(OMe)_3$] and santalin-B [$C_{30}H_{16}O_6(OMe)_4$], the two major red pigments of heartwood of *Pterocarpus santalinus* (red sandal). The isolation and the properties of these two compounds have already been reported by Ravindranath and Seshadri.[1]

There are difficulties in the alkali fission as well as in the oxidative degradation with permanganate of flavonoids having a number of free hydroxyls; usually the decomposition is complex and gives poor yields of the products. On the other hand, the method of ethylation and fission of the mixed methyl ethyl ethers is smoother and gives better yields and has therefore been adopted in the present study.

Santalin-A pentaethyl ether was prepared by the ethylation of santalin-A using EtI–K_2CO_3–acetone. Its fission with aqueous methanolic potash yielded four products just as in the case of santalin permethyl ether.[1] They were identified as 2,4-dihydroxy-5-ethoxybenzaldehyde, 4-ethoxyresorcinol, a naphthaldehyde and the corresponding 1,2-naphthaquinone. The first two products showed that ring A in santalin-A has a free hydroxyl at position C_4. This is in agreement with its stability, colour and capacity to stain the skin red (c.f. carajurin and carajurone[2]). The third compound, the naphthaldehyde, was converted into the fourth compound by Dakin's oxidation; both contained 3 methoxyls and 4 ethoxyls as determined by NMR and gave information about rings C, D, E and F.

Permanganate oxidation of the pentaethyl ether gave three acids, viz, 3,4-diethoxybenzoic, 2,4-diethoxybenzoic and 3,4,6-trimethoxyphthalic, whose identity was confirmed by comparison with synthetic samples. Thus, santalin-A should have all the 3 methoxyls in ring D and its structure would be 9,10,12-tri-*O*-methylsantalin (**1**). Arnone *et al*[3] suggested

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* Part III in the series "Chemistry of santalin pigments" For Part II, see ref 1

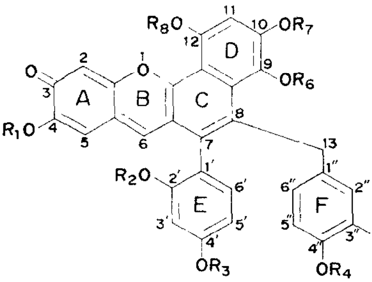
[1] RAVINDRANATH, B and SESHADRI, T R (1973) *Phytochemistry* **12,** 2781

[2] PERKIN, A G (1914) *Proc Chem Soc* **30,** 212

[3] ARNONE, A, MERLINI, L and NASINI, G (1972) *Tetrahedron Letters* 3503

the same structure, from the spectral properties of the alkali fission products and isolation of a small amount of 2,4-dihydroxybenzaldehyde as one of the products

Santalin-B tetraethyl ether was prepared by the method of ethylation already mentioned. Its alkali fission also yielded 2,4-dihydroxy-5-ethoxybenzaldehyde and 4-ethoxyresorcinol, as in the case of santalin-A pentaethyl ether, showing absence of methoxyls in ring A, but the naphthaldehyde and the 1,2-naphthaquinone were different from those obtained from santalin-A pentaethyl ether. However, these two were closely related, since the naphthaldehyde was convertible into the 1,2-naphthaquinone by alkaline H_2O_2. The NMR spectrum revealed the presence of 4 methoxyls and 3 ethoxyls in each, showing that these are present in rings C, D, E and F. The details of these rings were obtained by permanganate oxidation of the tetraethyl ether giving three acids which were identified as 3,4,6-trimethoxyphthalic and 3,4-diethoxybenzoic as in the case of santalin-A pentaethyl ether, and the third was different, being 2-ethoxy-4-methoxybenzoic acid. Santalin-B should therefore have the structure 9,10,12,4′-*O*-methylsantalin (**2**)



(**1**) $R_1 = R_2 = R_3 = R_4 = R_5 = H$; $R_6 = R_7 = R_8 = Me$

(**2**) $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = R_6 = R_7 = R_8 = Me$

EXPERIMENTAL

NMR spectra were recorded in Varian A-60 with $CDCl_3$ as solvent and TMS internal standard.

Santalin-A pentaethyl ether. Santalin-A (500 mg) in dry acetone (50 ml) was refluxed for 6 hr with EtI (5 ml) and anhyd. K_2CO_3 (5 g). The acetone soln was filtered and evaporated; the residue crystallized from EtOAc–petrol in orange yellow needles m.p. 172–173°, ν_{max}^{KBr} 1634 cm^{-1} (Found: C, 71.4; H, 6.6. $C_{43}H_{46}O_{10}$ requires C, 71.5; H, 6.4%); NMR (δ): 1.39–1.60 (m, 15H, OCH_2CH_3), 3.60, 3.66 and 4.06 (s, 9H, OMe), 3.70–4.30 (m, 12H, $OC\underline{H}_2CH_3$ and $C\underline{H}_2$-Ar), 6.50–7.20 (m, 9H, Ar H) and 9.50 (s, 1H, C_{11} H).

Alkali fission. The pentaethyl ether (200 mg) in methanol (5 ml) was refluxed with aq. KOH (3 g in 2 ml H_2O) for 3 hr. The mixture was diluted with H_2O and extracted with ether (neutral fraction). The aq. soln was acidified and extracted with ether (acidic fraction). This fraction on column chromatography over silica gel using $CHCl_3$–MeOH yielded two components; the first formed pale yellow plates from methanol m.p. 139–140° and was identified as 2,4-dihydroxy-5-ethoxybenzaldehyde by comparison with a synthetic sample (IR and NMR). The second compound crystallized from aq. alcohol in colourless needles, m.p. 72–73° and agreed fully with 4-ethoxyresorcinol (IR and NMR). The neutral fraction was chromatographed on silica gel column using C_6H_6–$CHCl_3$ (1:1) whereby two neutral compounds, the naphthaldehyde and the corresponding 1,2-naphthaquinone were obtained. The first was a pale yellow semi-solid and could not be crystallized. It gave green colour with $FeCl_3$ and formed a DNP derivative having m.p. 228–230°; ν_{max}^{Nujol} 1725 cm^{-1}; NMR (δ): 1.26–1.60 (m, 12H, OCH_2CH_3), 3.56, 3.61 and 3.96 (s, 9H, OCH_3), 3.80–4.40 (m, 10H, $OC\underline{H}_2Me$ and $C\underline{H}_2$ Ar), 6.50–7.00 (m, 7H, Ar H), 11.40 (s, 1H, CHO) and 14.40 (s, 1H, OH). It was dissolved in MeOH (10 mg in 2 ml) and a drop of 10% aq. NaOH added. Further addition of a few drops of 30% H_2O_2 immediately turned the soln red which was diluted with H_2O and extracted with ether. The red gummy product was found identical with the 1,2-naphthaquinone (TLC, IR); the second neutral product mentioned above ν_{max}^{Nujol} 1678 cm^{-1}, λ_{max}^{EtOH} 245 and 380 nm.

Permanganate oxidation. The pentaethyl ether (100 mg) in acetone (5 ml) was treated with $KMnO_4$ (1 g in 10 ml H_2O) and allowed to stand at room temperature for 24 hr. It was then diluted with H_2O, decolourized with $NaHSO_3$ and HCl and extracted with ether. The ether soln was extracted with satd. aq. bicarbonate (5 ml × 3). The extract was acidified and re-extracted with ether. The ether soln gave a residue (55 mg) which was chromatographed on silica gel using 1–4% MeOH in $CHCl_3$ to get three crystalline compounds. One was identical with 3,4-diethoxybenzoic acid, m.p. 165–166°, the second with 2,4-diethoxybenzoic acid m.p. 99°, and the third with

3,4,6-trimethoxyphthalic acid,[4] m p 180–181° and their identities were confirmed by comparison with synthetic samples (TLC, m m p, IR)

Santalin-B tetraethyl ether Santalin-B was ethylated by the method described earlier The tetraethyl ether crystallized from EtOAc–petrol in orange yellow needles, m p 176–177°, ν_{max}^{KBr} 1634 cm^{-1} (Found C, 71 0, H, 6 3 $C_{42}H_{44}O_{10}$ requires C, 71 2, H, 6 2%) NMR (δ) 1 23–1 66 (*m*, 12H, $-OCH_2C\underline{H}_3$), 3 60, 3 68, 3 73 and 4 06 (*s*, 12H, $-OC\underline{H}_3$), 3 70–4 30 (*m*, 10H, $-OC\underline{H}_2Me$ and $-C\underline{H}_2Ar$), 6 50–7 20 (*m*, 9H, Ar–H) and 9 50 (*s*, 1H, C_6–H)

Alkali fission of the tetraethyl ether The tetraethyl ether (200 mg) was subjected to fission with aq methanolic potash as described earlier Of the four products that were isolated, two were identical with 2,4-dihydroxy-5-ethoxybenzaldehyde m p 139–140° and 4-ethoxyresorcinol m p 72–73° (m m p, IR). The third compound was a pale yellow semi-solid, gave green colour with $FeCl_3$ and formed a DNP derivative having m p 235–236° ν_{max}^{Nujol} 1726 cm^{-1}, NMR (δ) 1 26–1 60 (*m*, 9H, $OCH_2C\underline{H}_3$), 3 52, 3 63, 3 75 and 3 96 (*s*, 12H, OMe), 3 80–4 40 (*m*, 8H, $-OC\underline{H}_2Me$ and $-OC\underline{H}_2Ar$), 6 50–7 00 (*m*, 7H, Ar–H), 11 40 (*s*, 1H, CHO) and 14 40 (*s*, 1H, OH) This naphthaldehyde (10 mg) was treated with alkaline H_2O_2 as described earlier which turned the solution red The product was extracted with ether and on evaporation of ether a red semi-solid was obtained which compared fully with the 1,2-naphthaquinone (TLC and IR) produced as the fourth compound in the above alkali fission ν_{max}^{Nujol} 1678 cm^{-1}, λ_{max}^{EtOH} 245 and 380 nm

Permanganate oxidation To a soln of the tetraethyl ether (100 mg) in acetone (5 ml) 10% aq $KMnO_4$ (5 ml) was added at room temperature and allowed to stand for 24 hr It was worked up as described earlier to get a residue (50 mg) which on silica gel column chromatography using $CHCl_3$–MeOH (99 1 and 97 3) mixture yielded 3 crystalline compounds One was identical with 3,4-diethoxybenzoic acid, 165–166°, the second with 2-ethoxy-4-methoxybenzoic acid, 114–115° and the third with 3,4,6-trimethoxyphthalic acid, 180–181°, their identity was confirmed by comparison with synthetic samples (TLC, m m p and IR)

Synthetic samples 4-Ethoxyresorcinol and 5-ethoxy-2,4-dihydroxybenzaldehyde Protocatechuic aldehyde (1 4 g) in dry ether (20 ml) was refluxed with Et_2SO_4 (0 7 ml) over anhyd K_2CO_3 (2 g) for 2 hr The mixture was filtered and the ethereal soln was extracted 4% aq Na_2CO_3 (10 ml × 3) The aqueous extract was acidified and re-extracted with ether The residue from ether soln was chromatographed over silica gel Elution with $CHCl_3$ yielded 4-ethoxy-3-hydroxybenzaldehyde which crystallized from aq methanol in colourless prisms, m p 125–126° (yield 0 75 g) (lit [5] m p 125) The monoethyl ether (50 mg) was methylated using MeI–K_2CO_3– ether The product had m p 62° and was found identical with a synthetic sample of 4-ethoxy-3-methoxybenzaldehyde obtained from ethylation of vanillin using EtI–K_2CO_3–ether (m m p and IR) 4-Ethoxy-3-hydroxybenzaldehyde (0 6 g) in 10 ml $CHCl_3$ was stirred with performic acid (5 ml, 30% H_2O_2 HCO_2H, 4 1) at 40° for 30 min and then kept overnight at room temperature, The $CHCl_3$ layer was separated, dried and the solvent distilled off under reduced pressure The residue was refluxed with 15 ml of 4% ethanolic KOH for 1 hr, acidified and extracted with ether The ethereal soln on removal of solvent gave 4-ethoxyresorcinol that crystallized from alcohol in needles m p 71–72° (0 35 g) (Found C, 62 1, H, 6 6 $C_8H_{10}O_3$ requires C, 62 3, H, 6 5) 4-Ethoxyresorcinol (0 2 g) was dissolved in DMF (1 ml) and $POCl_3$ (4 ml) added dropwise while cooling the mixture in an ice bath The mixture was kept at 50–60° for 30 min and then at room temperature for 2 hr It was poured over ice when a pale yellow solid separated 2,4-Dihydroxy-5-ethoxybenzaldehyde crystallized from alcohol in pale-yellow plates m p 138–140° (Found C, 58 9, H, 5 7 $C_9H_{10}O_4$ requires C, 59 3, H, 5 5)

3,4-*Diethoxybenzoic acid* Protocatechuic aldehyde (0 7 g) in acetone (10 ml) was refluxed with Et_2SO_4 (0 7 ml) over anhyd K_2CO_3 (1 g) for 4 hr The product was an oil (0 75 g) To a soln of the diethyl ether in acetone (0 5 g in 5 ml) aq $KMnO_4$ (10%, 5 ml) was added and the mixture allowed to stand at room temperature for 24 hr Then on working up as described in an earlier case, 3,4-diethoxybenzoic acid was obtained in colourless needles from aq alcohol m p 165–166° (lit [6] m p 166°)

2,4-*Diethoxybenzoic acid* β-Resorcylic aldehyde (0 7 g) was ethylated using Et_2SO_4–acetone–K_2CO_3 The product that crystallized from methanol had m p 70–71° The diethyl ether (0 5 g) was oxidized with aq $KMnO_4$ as given earlier to get 2,4-diethoxybenzoic acid, colourless needles from alcohol m p 98–99° (lit [7] m p 99°)

2-*Ethoxy*-4-*methoxybenzoic acid* β-Resorcylic aldehyde (1 4 g) in ether (25 ml) was refluxed with Me_2SO_4 (0 5 ml) over anhyd K_2CO_3 (2 g) for 2 hr The product was taken up on a column of silica gel and eluted with $CHCl_3$ First dimethyl ether was obtained, m p 71–72° (0 1 g), then the 4-methyl ether, crystallized from methanol in needles, m p 87–88° (yield 0 8 g) (lit [8] m p 88–89°) The 4-methyl ether (0 5 g) was ethylated by refluxing with EtI (0 2 ml), K_2CO_3 (0 8 g) and acetone (10 ml) for 3 hr The product that came as an oil was directly oxidized with $KMnO_4$ (10%, 5 ml) The acid crystallized from aq alcohol in colourless needles m p 113–114° (Found C, 61 0, H, 6 3 $C_{10}H_{12}O_4$ requires C, 61 2, H 6 1) 4-Ethoxy-2-methoxybenzoic acid prepared by a similar method involving ethylation β-resorcylic aldehyde first, followed by methylation and oxidation had a m p 122–123° (Found C, 60 8, H, 6 4 $C_{10}H_{12}O_4$ requires C 61 2, H 6 1)

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[7] Tiemann, F and Lewy, L (1877) *Ber* **10,** 2215

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