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SANTALIN PIGMENTS: ON THE STRUCTURE OF SANTALIN A

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As a part of our programme of research on natural phenolics and quinone-methides[1], we have investigated the pigments of Pterocarpus santalinus, that have been known for more than a century[2].

The very recent[3] communication by Ravindranath and Seshadri on the structure of the fully methylated derivative santalin permethylether prompts us to communicate immediately our present results on the same subject. These results not only bring independent evidence to support conclusions similar to those reached by Seshadri, but moreover provide new information on the structure of the natural pigment santalin A itself.

Santalin A (I) was isolated as a chromatographically pure, crystalline substance, $C_{33}H_{26}O_{10}$, m.p. $>300°$ (dec.), from $CHCl_3$-MeOH, λ_{max}(EtOH): 242, 269.5, 279, 307, 319, 455sh, 472 and 505nm (ε 50000, 40600, 41800, 15300,16900,23200, 37000, 37000), ir (nujol): 3.1 (OH, strong), 6.15 μ (conj.CO), mass: 582, NMR (DMSO, 100 MHz): 3 OMe (3.60, 3.66, 3.93 δ), one Aryl-CH_2-Aryl ($\sim$3.9 δ, shifted to 4.42 in TFA), 9 arom. H (6.2-7.2 δ), one H singlet (9.54 δ). Thus, according to Seshadri's nomenclature[3], santalin A is santalin trimethylether.

Exhaustive methylation with MeI and K_2CO_3 gave santalin octamethylether (II), which shew the same properties reported by Seshadri[3]. Particularly, if the NMR spectrum of II is run in benzene/$CDCl_3$, the benzylic group appears as an AB system at 4.13 δ (J = 14 Hz). The quinone--methide nature of II became apparent by the easy reduction with $NaBH_4$[Ia] to a dihydroderivative III, and by addition of other nucleophiles, like acetone and acetic acid. In the NMR of III the singlet at low field was absent, whereas a new signal of 2 H appeared at 4.80 δ (benzene); this signal was two singlets (1/2 H each) when the reduction was carried on with $NaBD_4$.

The reduction produced a new OH group, which could be acetylated. The same results were obtained by reducing I, thus confirming the presence in I and II of a carbonyl group, on the other hand supported by the presence of a singlet at 175.5 δ in the ^{13}C NMR spectrum of II ($CDCl_3$). Analogously, addition of acetone gave an adduct which shew the new signal of one H as the X part of an ABX (5.75 δ, acetone), due to the coupling with the methylene (2.86 δ) of a CH_2COMe group (confirmed by decoupling). All these data, together with other NMR evidence, andthe results of alkali degradation, already obtained by Robertson and Whalley[2], and confirmed by Seshadri[3] (see later), indicated a quinone-methide fragment (A) where the singlet at 9.54 δ in the NMR spectrum of I is assigned to H_6, and where the nucleophilic

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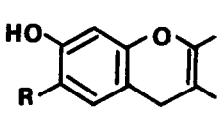
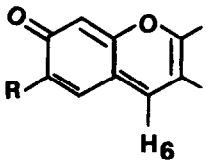
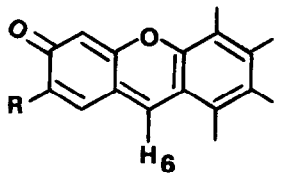


III



A

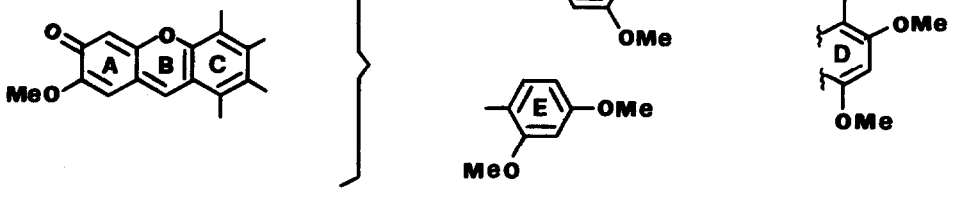


B

attack occurs at C_6. This latter fact, and particularly the reduction to a dihydro and not to a tetrahydroderivative[1a] with $NaBH_4$, suggested that the double bond ε, ζ to the carbonyl was part of an aromatic ring (B).

Methanolic KOH degradation of II afforded two main compounds, IV, $C_{31}H_{32}O_9$, that is the same (compound C) obtained by Seshadri[3], and V, $C_{30}H_{32}O_8$. From spectral data, it appears that V has the same structure of IV, except for the absence of the formyl group[+]. IV is an aromatic hydroxyaldehyde. Its NMR spectrum (100 MHz, benzene), shows, besides the CHO (11.29 δ) and the chelated OH (15.10 δ), 7 separated OMe, the benzylic methylene (4.18δ) and 7 aromatic protons, one singlet (6.82 δ) and two groups of three protons, each on a different nucleus, and arranged in a 1,2,4 pattern (δ_1= 6.95; δ_2= 6.56; δ_3= 6.45; $J_{1,2} \simeq 0$; $J_{1,3}$= 8.20; $J_{2,3}$= 2.3; δ_4= 6.79; δ_5= = 6.70; δ_6= 6.58; $J_{4,5}$= 2.0; $J_{4,6}$= 8.2; $J_{5,6} \simeq 0$).

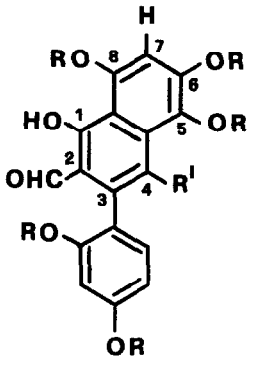
All these data, coupled with the known chemical evidence, i.e. the formation of veratraldehyde and 2,4-dihydroxy-5-methoxybenzaldehyde in the same degradation[2,3] and of 2,4-dimethoxybenzoic acid in $KMnO_4$ oxidation of II[2,3], brought to the partial formula:



The substitution on ring D shown here is based on an important result by Seshadri[3], i.e. the isolation of 2,4,6-trimethoxyphthalic acid. On this basis he concluded also that the fragments E and F must be ortho on the ring C. We had independent evidence (see VI) for this latter statement.

Two formulae (IVa and IVb) could now be assigned to IV and two correspondent IIa and IIb to II:

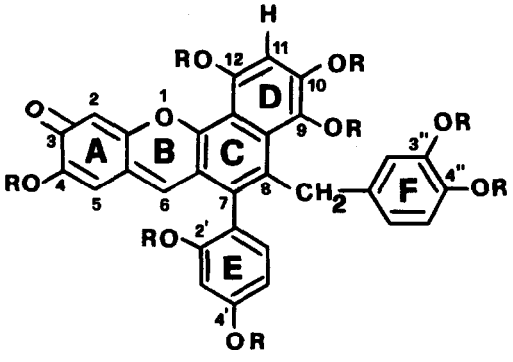
[+]The formation of both IV and V by alkali degradation of II can be easily rationalized.



IV
R = Me
R' = $-CH_2$ (OMe, OMe)
VI
R = H or Me
R' = H

IV a
VI a

IV b
VI b



IIa R = Me IIb

VIIa | R(4,3",4") = H; R(9,10,12,2',4') = H or Me | VII b

Both these formulae are consistent with the results so far obtained by ourselves. Seshadri's[3] preference for IIa is based on the high-field chemical shift of the acetoxy methyl group in a 6-acetoxyderivative of II, attributed to the shielding by the phenyl ring E, and on biogenetical grounds. It must be noted that IIb is also consistent with biogenetical arguments, being derived from the coupling of an isoflavonoid (instead of a flavonoid) unit with another C_{15} moiety. In both cases the substitution on ring D (9,10,12 and not 9,11,12) is assigned only on biogenetical hypotheses.

Alkali degradation of santalin A afforded a new compound (VI), $C_{20}H_{18}O_7$, m.p.=180° , λ_{max}(EtOH), 222, 270sh, 276, 342 and 410 nm, (ε 24000,28000, 30000, 11900, 2600), mass=370; NMR(acetone): 3 OMe (3.67, 3.68, 3.97δ), 2 arom. H (singlets 6.65, 7.33 δ), 3 arom. H (ABX, δ_A6.73, δ_B6.67, δ_X 7.09; J_{AX} 0.7, J_{AB} 2.3, J_{BX} 7.9), 2 OH (broad, 8.5 δ, 1 CHO (9.73 δ), 1 OH chel. (11.13 δ).

This compound is clearly a degradation product, where not only the quinone-methide system, but also the benzyl residue (ring F) have been eliminated, most probably via oxidation and retro--aldol reaction. In fact, the NMR spectrum shows only one 1,2,4 aromatic pattern, no benzylic methylene, and two singlets; one of them (7.33 δ) shows a long-range coupling of 0.7 Hz with the aldehydic proton, which is consistent with a meta position[4]. As the singlet must occupy the same position held by the benzyl residue in I, this must be also placed on ring C.
The compound VI contains all the three OMe groups already present in santalin A. It follows immediately that in I the substituent on ring A and the two ones on ring F are all OH. (formula VIIa or VIIb). Acetylation of VI gave a triacetate (VIII), the NMR of which shows (acetone, 100 MHz): 3 OMe, 3 OAc, 1 CHO (9.78 δ), 2 arom. H (singlets, 7.78δ H_4; $J_{H_4,CHO}$=0.7, 6.69 H_7) and 3 arom. H (ABX, δ_A=7.07, δ_B=6.97, δ_X=7.32). As all the three latter protons show a paramagnetic shift on acetylation, whereas H_7 is not substantially affected, we suspect that at least one substituent on ring E is an OH, and the substituents at 10 and 12 on ring D are OMe. Finally, the isolation of a small amount of the 2,4,-dihydroxybenzaldehyde by alkali degradation of I, suggests that the three methoxy-groups in I are in the D ring.

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