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CONSTITUENTS OF *TABEBUIA GUAYACAN*—II

THE STRUCTURE OF GUAYIN

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Abstract—A unique oxalactone dibenzxanthone, guayin, has been isolated from the heartwood of *T. guayacan* and structurally identified. A biomimetic synthesis of the dihydro derivative of guayin, based upon the probable biosynthetic origin of guayin from the dibenzxanthene guayacanin, has been successfully achieved.

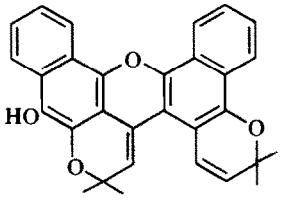
Previous studies[1-3] on the heartwood constituents of the marine borer resistant[4] Central American tree, *Tabebuia guayacan* Hemsl., have led to the isolation of a number of naphthaquinones, tectol, and a novel dibenzxathene derivative, guayacanin **1**. Further investigation of the heartwood has yielded a second novel constituent, now called *guayin* and shown to be the oxalactone dibenzxanthone **2**.

Guayin (m.p. 277–278°, $C_{30}H_{22}O_6$), separated from the ether extract of *T. guayacan* heartwood, is non-phenolic and contains one highly conjugated ketonic group (IR 1660 cm^{-1}) and an ester or lactone (aryl or vinyl) carbonyl group (IR 1785 cm^{-1}). The 100 MHz NMR spectrum in $CDCl_3$ shows the presence of a chromene *gem* dimethyl group (singlet at δ 1·56) with two coupled vicinal vinylic (chromene) protons (1H, doublets, J = 10 Hz, δ 5·75 and δ 8·01). A second *gem* dimethyl group resonates at δ 1·77 and the signals of eight aromatic protons occur as multiplets at δ 7·60–δ 7·76 (4H), δ 8·10–δ 8·36 (2H), and at δ8·56–δ 8·74 (2H), respectively.

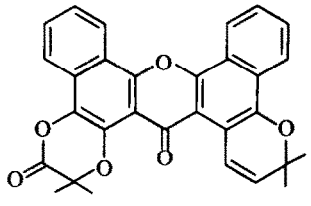
Guayin was successfully reduced with 1,3,6,8-tetrahydroxyxanthene in glacial acetic acid to yield dihydroguayin **3**, $C_{30}H_{24}O_6$, m.p. 272–273°. The 100 MHz NMR spectrum of **3** reveals the successful reduction of the chromene ring of guayin to a chroman with the two chroman methylene groups resonating as triplets (J = 7 Hz) at δ 1·91 and δ 3·58 while the chroman *gem* dimethyl group occurs as a singlet at δ 1·44. The NMR signals for the aromatic protons and the isolated *gem* dimethyl group remain essentially unchanged with respect to guayin.

The occurrence of a 6-membered aryl lactone in guayin was established through an alkaline methylation of **2** to produce an 00-dimethyl derivative **4** of an hydroxy acid, $C_{32}H_{28}O_7$, m.p. 188–189°. Subsequent alkaline hydrolysis of **4** yields the corresponding carboxylic acid **5**, $C_{31}H_{26}O_7$, m.p. 217–218°, whose NMR spectrum shows a paramagnetic shift (10 Hz) of the isolated *gem* dimethyl group to δ 1·66, a single aromatic OMe at δ 4·03, and a carboxylic acid proton as a broad singlet at δ 13·57. Subtle differences in chemical shift were observed for the chromene and aromatic protons of **5** compared to **4**.

Mass spectral analysis of the acid shows no expected parent ion at *m/e* 510. However, the appearance of prominent ions at *m/e* 424 ($C_{27}H_{20}O_5$) and *m/e* 86 ($C_4H_6O_2$) indicates **5** undergoes thermal decomposition readily with concomitant loss of a C_4 unit. This observation was confirmed in the attempted decarboxylation of **5** by heating above its m.p. The product **6a**, m.p. 208–210°, has molecular formula $C_{27}H_{20}O_5$, forms a monoacetate, **6b**, $C_{29}H_{22}O_6$, m.p. 232–233°, and is therefore formed from **5** with the loss of $C_4H_6O_2$. The NMR spectrum of the thermal product (**6a**) shows the chromene *gem* dimethyl group as a singlet at δ 1·54 and the vinylic chromene protons as doublets (J = 10 Hz) at δ 5·75 and δ 7·97. The aromatic OMe group resonates as a singlet at δ 4·10, and a chelated OH group appears as a sharp singlet at δ 12·63. This compound also gives a positive ferric



1



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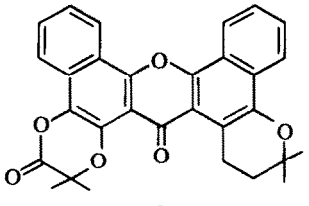
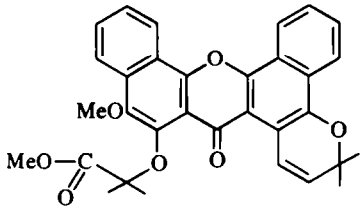


3

Guayin (m.p. 277–278°, $C_{30}H_{22}O_6$), separated from the ether

reaction and exhibits a 24 nm bathochronic shift in the UV λ_{max} upon addition of $AlCl_3$.[5] These data indicate the presence of a free phenolic hydroxyl *peri* to a CO group. The general character of the UV spectral bands of **6a** and its precursors were similar to those reported[6] for xanthones, while the low field resonances of the vinyl chromene protons (δ 5·75 and δ 7·97) were identical with 1,6 - dihydroxy - 6',6' - dimethylpyrano - (2',3':7,8) xanthone as described by Gabriel and Gottlieb.[7] On the basis of these data, compound **6a** was considered to be 1 - hydroxy - 2 - methoxy - (3,4:5,6) - dibenz - 6',6' - dimethylpyrano - (2',3':7,8) - xanthone. Thus, the carboxylic acid from which **6a** is derived can be formulated as **5** and the carbomethoxy derivative as **4** and therefore structure **2** can be assigned for guayin.



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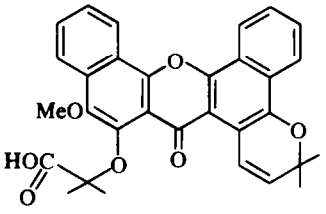

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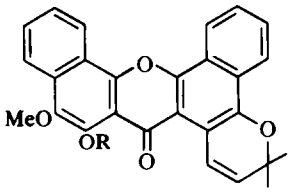


6

a: R = H
b: R = Ac

The structural assignment for guayin was confirmed by the determination of its crystal structure. The schematic drawing (Fig. 1) designates the atom numbering system and interatomic bond distances determined for the guayin crystal. The bond distances of the crystal are at a larger than usual variance from expected values, for reasons similar to those postulated for guayacanin.[8] The crystal contains solvate molecules whose location can not be determined from the X-ray data presumably because they do not occupy definite crystallographic positions.

The dihedral angles between the fused rings of the nearly planar guayin molecule are shown in Table 1. Rings 2, 3, 4, 5 and 7 (Fig. 1) are nearly parallel; the largest dihedral angle between adjacent rings is only 3·9°. On the other hand, rings 1 and 6 are bent out of the molecular plane by a greater degree as indicated by the dihedral angles between rings 1 and 2 and rings 5 and 6 of 8·5° and 13·1°, respectively.

Table 1. Dihedral angle between planes illustrated in Fig. 1

Planes	Dihedral angle
1–2	8·5°
2–3	1·5°
2–4	3·9°
4–5	3·6°
5–6	13·1°
5–7	3·3°

A comparison of the structure of guayin with that of guayacanin suggests that guayin may be derived biosynthetically from guayacanin through an oxidative cleavage of the benzylically substituted chromene double bond and subsequent lactonization of the resultant oxa-isobutanoic acid fragment with the free phenolic hydroxyl (Scheme 1).

On the basis of this proposal and the prior successful synthesis[2] of tetrahydroguayacanin, a synthesis of dihydroguayin was devised involving (a) sequential oxidative cleavage and lactonization of isodihydroguayacanin **11** (Scheme 2) or (b) by the prenylation of an oxa-lactone monophenol obtained in an acid catalyzed condensation of dehydro-α-lapachone diol with naphthalene-1,4-diol (Scheme 3).

The latter of these synthetic approaches proved to be the most successful with the initial condensation of dehydro-α-lapachone diol **7b** and naphthalene-1,4-diol in 80% aqueous formic acid to yield **9** (23%), $C_{25}H_{18}O_4$, m.p. 274–278°. In addition, an 8% yield of the oxalactone **10a** (guayol) was obtained directly by aerial oxidation during this synthetic step. Subsequent oxidative cleavage (peroxide/formic acid) of the xanthene **9** yielded **10a** (39%), m.p. > 350°. The overall yield of **10a** in the synthetic sequence was 17%.

Guayol **10a** formed a monoacetate **10b**, $C_{27}H_{18}O_7$, m.p. 295–297°. The NMR spectrum of the acetate shows the isolated *gem* dimethyl group as a singlet at δ 1·76 while the phenolic acetate protons resonate at δ 2·49. Eight of the nine aromatic protons occur as three multiple resonances (5H), m, δ 7·60–7·78; (1H), m, δ 8·08–8·20; and (2H), m, δ 8·66–8·84, and the single aromatic proton ortho to the aromatic acetate appears as a singlet at δ 7·86.

Synthetic guayol **10a** was successfully prenylated with 2 - methyl - 3 - butene - 2 - ol in aqueous formic acid to yield (59%) synthetic dihydroguayin, $C_{30}H_{22}O_6$, m.p. 272–273°, identical in all respects (m.m.p., IR, NMR) with dihydroguayin obtained from the natural guayin **2**.

Guayin represents an unusually substituted xanthone with biosynthetic origins closely related to guayacanin. The facile biomimetic synthesis of dihydroguayin introduces a novel synthetic approach to xanthones and the applicability of this method for the synthesis of other, more common, natural xanthones is currently under investigation.

EXPERIMENTAL

All m.ps are uncorrected. Unless otherwise stated, NMR spectra were determined on a modified HA-100 instrument in $CDCl_3$ with a TMS internal standard. Mass spectral analysis were determined on a CEC 110 high solution spectrophotometer. IR data were obtained on a Perkin Elmer model 237B grating infrared spectrophotmeter. UV spectra wer obtained on a Cary Model 15 recording spectrophotometer.

Extraction. Hammermilled *Tabebuia guayacan* Hemsl. heartwood (5 kg) was successively extracted with petrolcum ether 30–60°, ethyl ether, acetone and methanol. Only the ethyl ether extract will be discussed.

Ethyl ether extract. The hot ether extraction yielded 90 g of ether solubles and 35 g of ether insolubles upon cooling. The ether insoluble portion was boiled in 500 ml of benzene and filtered.

Guayin (**2**). The hot benzene filtrate was concentrated and preparatively chromatographed on a 2 × 8 in. silica column with benzene. The benzene eluent was concentrated to dryness, acetone was added, concentrated and cooled to form crude yellow orange crystals. The crystals were collected and crystallized from

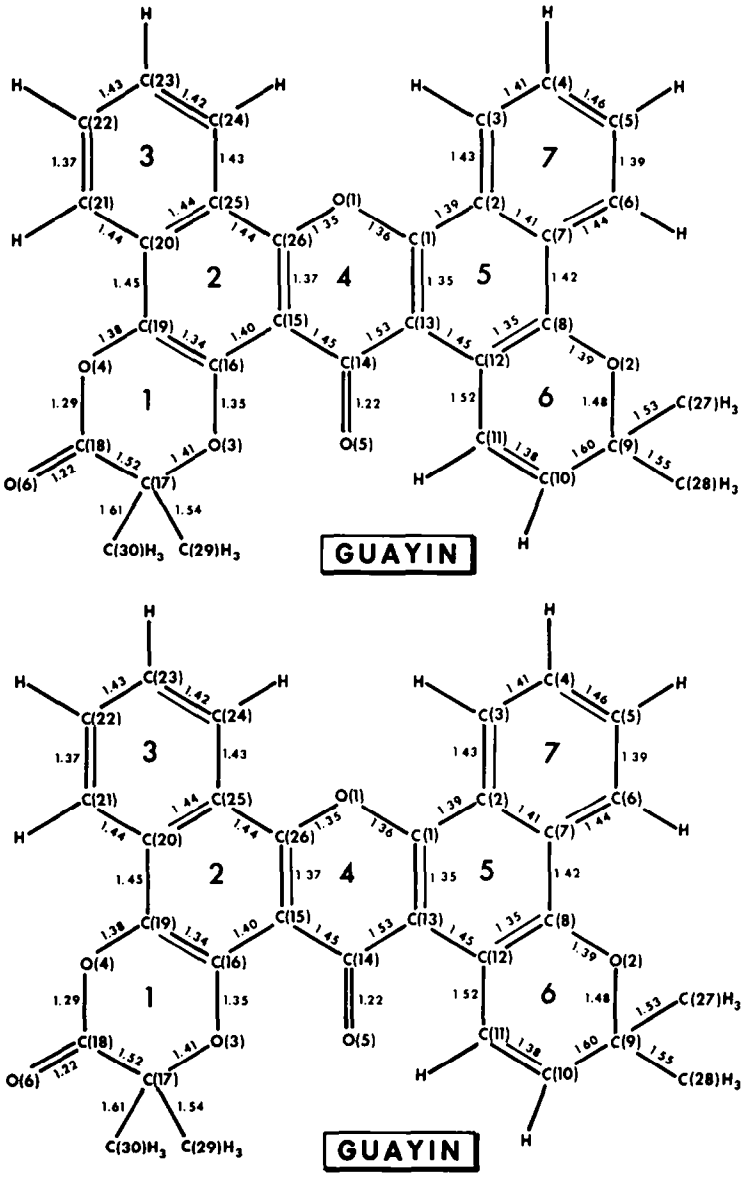
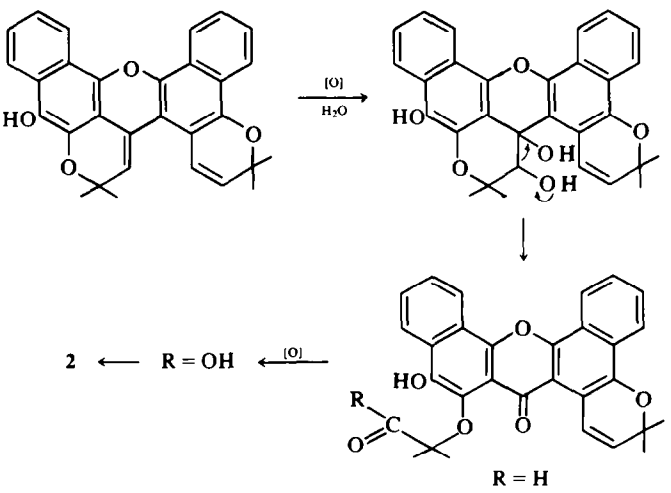
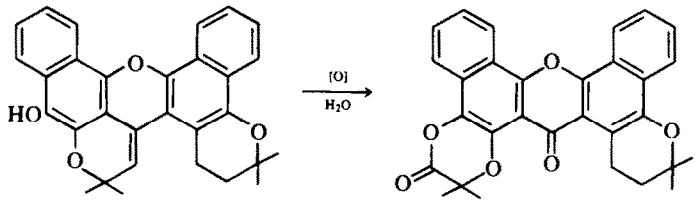


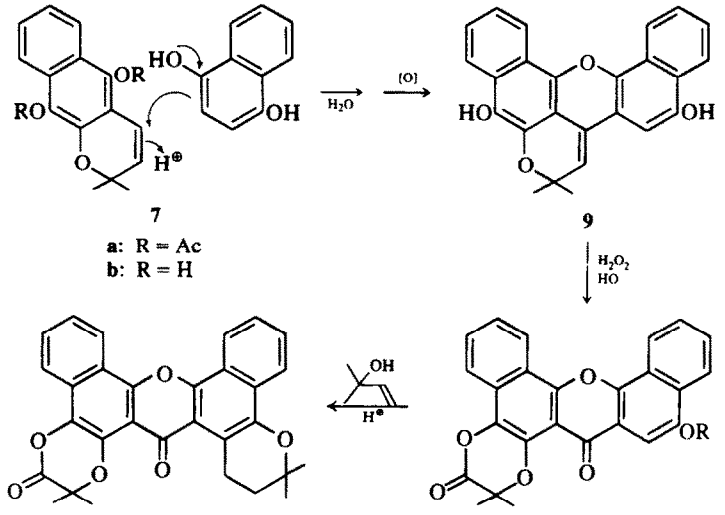
Fig. 1.



Scheme 1.



Scheme 2.



Scheme 3.

a large volume of acetone and recrystallized from a large volume of tetrahydrofuran to yield **2**, fine yellow needles, m.p. 277–278° (1·03 g, 3%). (Found: C, 75·4; H, 4·80. Calc. for $C_{30}H_{22}O_6$: C, 75·3; H, 4·63%); UV spectrum λ_{max}^{EtOH} nm (log ϵ), 414 (3·84), 323 (4·22), ~294 (4·53), 282 (4·57), ~250 (4·51), 226 (4·81). IR spectrum (Nujol): 1785, 1660, 1640, 1460, 1440, 1400, 1385, 1380, 1174, 1090, 1020, 900, 775, 725 cm^{-1}; NMR spectrum: 6H, s, δ 1·56; 6H, s, δ 1·77; 1H, d, J = 10 Hz, δ 5·75; 1H, d, J = 10 Hz, δ 8·01; 4H, m, δ 7·60–7·76; 2H, m, δ 8·10–8·36; 2*H*, *m*, δ 8·56–8·74.

Dihydroguayin (**3**). **2** (0·1 g) in glacial AcOH (30 ml), was treated with 10% HCl aq (2 ml) and 1,3,6,8-tetrahydroxyxanthene (0·3 g) and warmed until solid precipitated. Water was added and the mixture was extracted with ether. The ether soln was washed with water, sat. $NaHCO_3$ aq, water, dried and concentrated with acetone to yield **3**, pale yellow needles, m.p. 272–273°. (Found: C, 75·1; H, 5·23. Calc. for $C_{30}H_{24}O_6$: C, 75·1; H, 5·24%); NMR spectrum: 6H, s, δ 1·44; 6H, s, δ 1·77; 2H, t, J = 7 Hz, δ 1·91; 2H, t, J = 7 Hz, δ 3·58; 4H, m, δ 7·54–7·80; 2H, m, δ 8·04–8·36; 2H, m, δ8·53–8·70.

Compound **4** (*Alkaline methylation of* **2**). Methylation of **2** in $MeSO_4$/acetone with K_2CO_3 (4 hr) yielded **4**, red needle clusters, m.p. 188–189°. (Found: m^+ *m/e* 524·1855. Calc. for $C_{32}H_{28}O_7$, m^+ *m/e* 524·1836). NMR spectrum: 6H, s, δ 1·56; 6H, s, δ 1·72; 3H, s, δ 3·95; 3H, s, δ 3·96; 1H, d, J = 10 Hz, δ 5·75; 1H, d, J = 10 Hz, δ 7·96; 4H, m, δ 7·70–7·80; 2H, m, δ 8·10–8·38; 2H, m, δ 8·60–8·82.

Compound **5** (*Alkaline hydrolysis of* **4**). **4** was dissolved in MeOH and hydrolyzed in 50% KOHaq for 20 min. The mixture was acidified and extracted with ether. The dried ether extract was diluted with MeOH and concentrated to yield **5** as yellow needles, m.p. 217–218°. Mass spectral analysis shows no m^+ *m/e* 510 ion for $C_{31}H_{26}O_7$ (**5**). Analysis of *m/e* 424 ion (Found : *m/e* 424·1317. Calc. for $C_{27}H_{20}O_5$: *m/e* 424·1313) and *m/e* 86 ion (Found: *m/e* 86·0363. Calc. for $C_4H_6O_2$: *m/e* 86·0368) indicate the facile loss of $C_4H_6O_2$ fragment from parent compound **5**. MS: mass (rel. ab.); 463 (1·3), 426 (3·2), 424 (55·8), 409 (100), 393 (29·8), 391 (6·9), 204 (8·4), 197 (17·1), 183 (13·6), 86 (7·3). NMR spectrum: 6H, s, δ 1·53; 6H, s, δ 1·66; 3H, s, δ 4·03; 1H, d, J = 10 Hz, δ 5·75; 1H, d, J = 10 Hz, δ7·91; 4H, m, δ 7·60–7·88; 2H, m, δ 8·18–8·35; 2H, m, δ 8·60–8·80; 1H, br.s, δ 13·57.

Compound **6a** (*Thermal cleavage of* **5**). **5** (0·1 g) was heated to 230° in an oil bath and held at temp. for 3 min. The melted product was cooled and recrystallized from acetone/MeOH to yield **6a**, pale yellow needles, m.p. 208–210°. (Found: m^+ *m/e* 424·1316. Calc. for $C_{27}H_{20}O_5$; m^+ *m/e* 424·1313.) MS: mass (rel. ab.); 424 (41·4), 409 (100), 394 (18·5), 391 (8·0), 204 (6·6), 197 (14·4), 183 (14·3). NMR spectrum: 6H, s, δ 1·54, 3H, s, δ 4·10; 1H, d, J = 10 Hz, δ 5·75; 1H, d, J = 10 Hz, δ 7·97; 4H, m, δ 7·42–7·76; 2H, m, δ 8·06–8·34; 2H, m, δ 8·46–8·70; 1H, s, δ 12·63. UV spectrum: λ_{max}^{EtOH} nm (log ϵ), 427 (3·78), ~339 (4·04), 303 (4·56), 280 (4·53), 267 (4·49), 241 (4·58), 215 (4·86); $\lambda_{max}^{EtOH-AlCl_3}$ nm (log ϵ), ~357 (4·31), 327 (4·76), ~287 (4·43), ~270 (4·51), 246 (4·78), ~238 (4·77), 218 (4·85). IR spectrum (Nujol): 3500–3700, 1665, 1600, 1580, 1475, 1410, 1390, 1360, 1330, 1300, 1105, 1080, 805, 775, 774 cm^{-1}.

Acetylation of **6a** with Ac_2O-pyridine yielded **6b** as yellow needles from MeOH, m.p. 232–233°. (Found: m^+ *m/e* 466·1409. Calc. for $C_{29}H_{22}O_6$: m^+ *m/e* 466·1416). NMR spectrum: 6H, s, δ 1·55; 3H, s, δ 2·61; 3H, s, δ 4·05; 1H, d, J = 10 Hz, δ 5·76; 1H, d, J = 10 Hz, δ8·00; 4H, m, δ 7·42–7·62; 2H, m, δ 8·16–8·38; 2H, m, δ 8·64–8·84.

Dehydro-α-lapachone diacetate (**7a**). **7a** was synthesized from lapachol according to the method of Hooker,[8] yielding **7a** as white needle clusters, from MeOH, m.p. 131–132°. All physical and spectral properties of **7a** were in agreement with recorded values.

Dehydro-α-lapachone diol (**7b**). A soln of **7a** (2·4 g) in the minimum amount of MeOH (10 ml) was treated with 10% NaOHaq (50 ml) containing sodium dithionite (3 g), and warmed on a steam bath for 3 min. Water (30 ml) was added and the soln was acidified (dil HClaq), and cooled to yield **7b** as a white solid.

This product was collected, washed well with water and used immediately without further purification (to minimize oxidation) in the synthesis of **9**.

Compound **9** (*Condensation of* **7a** *and naphthalene*-1,4-diol). **7b** (2 g) was dissolved in hot 80% aqueous formic acid (50 ml), and naphthalene-1,4-diol (2 g) was added to the soln in 0·25 g portions over 10 min. The mixture was heated on a steam bath (2·5 hr), diluted with water, and extracted with ether. After washing with water and sat $NaHCO_3$ aq, the dried ether soln was concentrated, diluted with benzene and reconcentrated to give a benzene soln of the product. The benzene concentrate was applied to a silica column (3 × 8 in.) and eluted with benzene. A major brown colored band (approx. 8·1 of eluent) was collected and evaporated to dryness. Fractional crystallization first yielded **10a** as yellow crystals, which after recrystallization from tetrahydrofuran, was obtained as yellow needles, m.p. >350° (0·25 g, 8%). **9** then crystallized as crude brown needles which were treated with charcoal and recrystallized (acetone/benzene) to give fine gray needles, m.p. 274–277°, (0·73 g; 23%). (Found: m^+ *m/e* 382·1210. Calc. for $C_{24}H_{18}O_4$ m^+ *m/e* 382·1205). NMR spectrum: (Acetone D_6): 6H, s, δ 1·58; 1H, s, δ 5·95; 1H, s, δ 7·19; 4H, m, δ 7·40–7·80; 1H, br. s, δ 7·97; 2H, m, δ 8·12–8·38; 2H, m, δ 8·42–8·71; 1H, br. s, δ 8·91.

Guayol (**10a**). **9** (0·1 g) was dissolved in hot 88% formic acid (3 ml). The soln was cooled and 30% H_2O_2 (3 ml) was added. The mixture was heated, thereby initiating an exothermic reaction with the formation of a yellow brown solid. Water was added; the solid was collected. After washing with ether the solid was recrystallized from a large volume (300 ml) of tetrahydrofuran to yield **10a** as fine yellow needles, m.p. >350° (0·05 g). IR spectrum (Nujol): 3300, 1785, 1650, 1625, 1602, 1595, 1395, 1270, 1210, 1170, 1080, 1025, 874, 790, 785, 770 cm $^{-1}$. **10a** was acetylated (Ac_2O/pyridine) to yield **10b** as fine yellow needles, from MeOH, m.p. 295–297°. (Found: C, 71·2; H, 3·96. Calc. for $C_{27}H_{18}O_7$: C, 71·36; H, 3·99%); NMR spectrum: 6H, s, δ 1·76, 3H, s, δ 2·49; 5H, m, δ 7·60–7·78; 1H, s, δ 7·86; 1H, m, δ 8·08–8·20; 2H, m, δ 8·66–8·84.

Synthetic dihydroguayin (**2**). **10a** (0·1 g) in 88% formic acid (150 ml) was heated just below reflux. 2-Methyl-3-butene-2-ol (0·05 g) was added initially and 0·03 g was added every 2 hr for an 8 hr total reaction time. The mixture was poured into water, extracted with ether, concentrated with benzene, filtered, applied to a silica column (2 × 10 in.) and eluted with benzene. The column was monitored by TLC, the desired product collected, evaporated to dryness and recrystallized (acetone/MeOH) to yield in **2**, (0·07 g, 59%) as yellow needles, m.p. 272–273°. All physical and spectral properties were identical with dihydroguayin obtained from the natural guayin.

X-Ray data. The space group of guayin was determined from precession and Weissenberg photographs. The unit cell dimensions were obtained by averaging the data obtained from high angle $\theta/2\theta$ scans at a 1° take-off angle. The crystal data are summarized below:

$a = 24{\cdot}126$ Å	F.W. = 478·50
$b = 5{\cdot}946$ Å	space group = $P2_1/n$
$c = 17{\cdot}968$ Å	$Z = 4$
$\beta = 98{\cdot}03°$	$v = 2552{\cdot}26$ Å^3.

The intensity data were collected with an automated GE XRD6 four circle diffractometer at 23°C. The crystal was orange in color with dimensions 0·094 × 0·132 × 0·235 mm. Ni-filtered copper radiation (λ = 1·5418 Å) was detected with a scintillation counter coupled to a single-channel pulse height analyzer. The $\theta/2\theta$ scan technique was used at a scan rate of 1° per min. One quarter of the reciprocal sphere was recorded in the range $0° < 2\theta \leq 100°$. The scan range varied with θ to include both the α_1 and α_2 peaks. Two backgrounds were measured at 0·5° before and after the scan limits. 3106 reflections were measured; of these 2603 were unique and 2006 had $I > \sigma(I)$. The structure was determined by direct methods with the programs Normal[10] and Multan.[11] With anisotropic temperature factors, the 34 heavy atoms refined to only $R_1 = \Sigma|F_o - F_c|/\Sigma|F_o| = 0{\cdot}14$, and it was decided to discontinue the refinement. A Fournier difference synthesis indicated that there were four residual peaks with electron densities of 1·34, 1·28, 1·28 and 1·11, respectively. The position of these peaks is not compatible with the geometry of possible solvate molecules, although both the NMR spectrum and the observed density indicate that a solvate is present in the crystal. A similar situation was observed for guayacanin;[8] in both cases the solvent molecules can not be located in the crystal.

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