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SYNTHESIS OF ROBUSTIC ACID AND RELATED 4-HYDROXY-3-PHENYLCOUMARINS[a]

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Abstract—2,4-Dihydroxy-6,4'-dimethoxydesoxybenzoin **1a** with 2-hydroxy-2-methyl-3-butene in the presence of BF_3-etherate yielded 3-C-prenyl- **2a** and 5-C-prenyl **3** derivatives. However, reaction with prenyl bromide in the presence of methanolic potash afforded 3-C-prenyl **2a** and 4-O-prenyl **1b** derivatives. The C-prenyl derivatives **2a** and **3** readily underwent cyclodehydrogenation with DDQ to form phenacyl chromenes **7** and **9** respectively. The latter on condensation with ethyl chloroformate gave robustic acid **10** identical in all respects with natural sample. The desoxybenzoins **2b**, **3** and **7** have also been converted into the corresponding 4-hydroxy-3-phenyl coumarins **11**, **12** and **8**.

Robustic acid was first isolated by Krishna[1] from the roots of *Derris robusta* and studied by a number of workers.[2-7] Robustic acid, 4-hydroxy-5,4'-dimethoxy-6",6"-dimethyl-3-phenylpyrano (2",3":7,6)-coumarin **10**, has not yet been synthesised.

Its biogenesis could involve introduction of the pyran ring either at the coumarin stage or before the formation of the coumarin ring. The former approach for the synthesis of robustic acid proved to be a failure because direct prenylation of two 4,5,7-trihydroxy-3-phenylcoumarins gave tetra-C- and tri-C-prenyl derivatives.[8] Since model experiments on introducing the pyran ring at the desoxybenzoin stage,[9] followed by coumarin ring formation, succeeded,[8] this approach has now been adopted for the synthesis of robustic acid.

2,4-Dihydroxy-6,4'-dimethoxydesoxybenzoin,[10] **1a** reacted with 2-methyl-2-hydroxy-3-butene in the presence of BF_3-etherate to give a mixture from which two crystalline compounds were obtained by column chromatography. The major compound was identified as the 3-C-prenyl derivative, on the basis of its elemental analysis, solubility in aq. Na_2CO_3, and NMR spectrum showing one doublet of only two protons of one benzylic methylene group at δ3·35 and only one aromatic proton of phenyl ring A at δ6·30 as a singlet, in addition to other expected signals; formic acid cyclisation yielded two isomeric chromans, one of which was sparingly soluble in alkali and gave a positive ferric reaction and the other was easily soluble in alkali and showed a negative ferric reaction. Hence the former could be 2,2-dimethyl-5-hydroxy-6-(p-methoxyphenacyl)-7-methoxychroman **4** and the latter 2,2-dimethyl-5-hydroxy-7-methoxy-8-(p-methoxyphenacyl) chroman **5a**, both of which had been obtained earlier during degradation experiments.[6] The location of the prenyl group in 3-posi-

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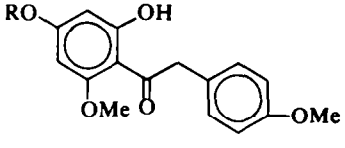
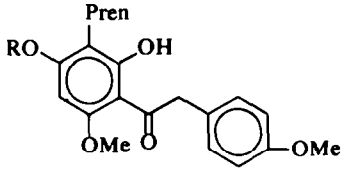


1
a: R = H
b: R = Pren



2
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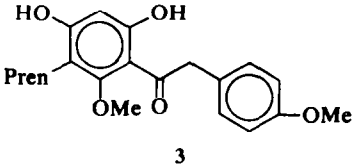
b: R = Me



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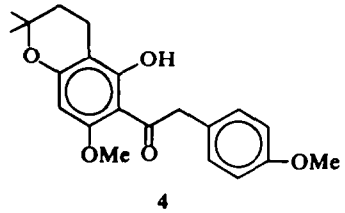

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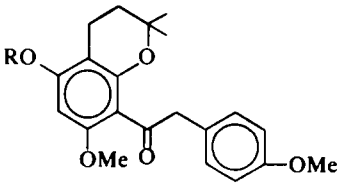
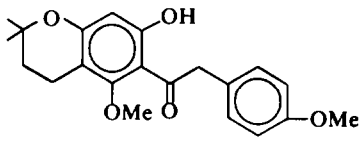


5
a: R = H
b: R = Me



6

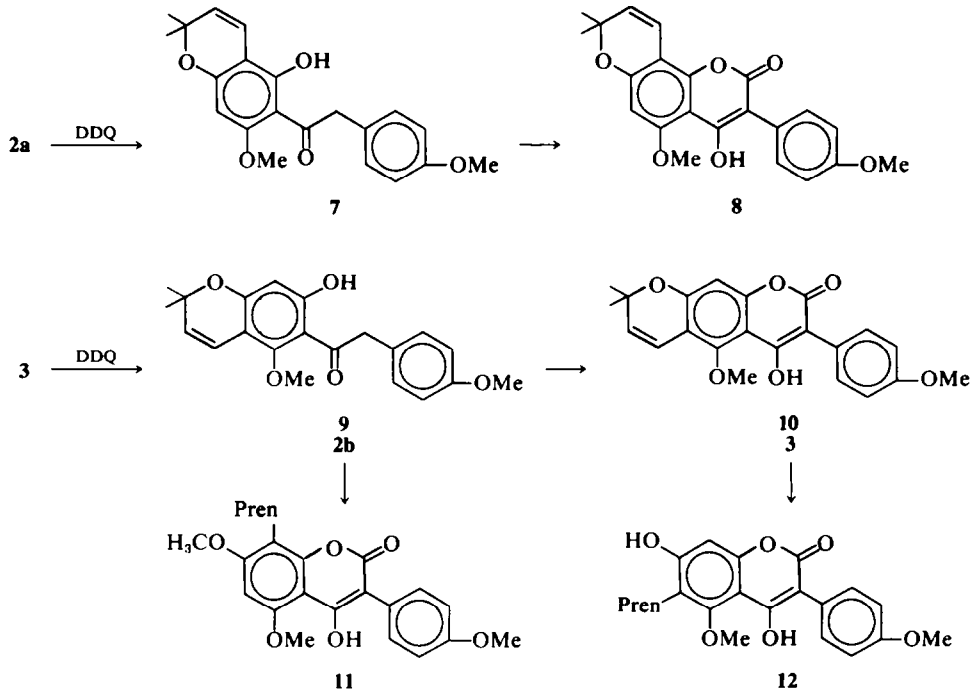
tion was confirmed by partial methylation of the prenylated desoxybenzoin with 1 mole of Me_2SO_4 in the presence of K_2CO_3 and acetone and subsequent formic acid cyclisation of the resulting ketone **2b** when only one chroman **5b**[6] with a negative ferric reaction was obtained. Thus the structure of the first prenylation product is 3-C-prenyl-2,4-dihydroxy-6,4′-dimethoxydesoxybenzoin, **2a**; the second prenylation product was considered as the 5-C-prenyl isomer **3** which was supported by its NMR spectrum and acid cyclisation to give only one chroman **6** when a positive ferric reaction resulted.

In the second method of prenylation, the desoxybenzoin **1a** was reacted with prenyl bromide in the presence of K_2CO_3 and acetone when the 4-prenyl ether **1b** formed exclusively as shown by its insolubility in aq. Na_2CO_3, and by NMR (one doublet of two protons of a methylene-oxy group at δ4·48, (J = 7 Hz) and two meta-coupled protons of ring A at δ5·92 and 6·05 (J = 2 Hz)). However, when prenylation was carried out in the presence of methanolic KOH, a mixture of three compounds was obtained. The first product was identified as the 3-C-prenyl-derivative **2a**, the second as homoanisic acid and the third as 4-phenyl ether **1b**.

Both 3-C-prenyl-**2a** and 5-C-prenyl-**3** desoxybenzoins were cyclodehydrogenated with DDQ to give phenacyl chromenes **7** and **9** respectively. These chromenes were characterized by their NMR spectra which showed characteristic doublets of two olefinic protons at δ5·42 and 6·65 ppm in the former case and at δ5·62 and 6·53 ppm in the latter case, J being 10 Hz in each case.

When the chromene **9** was condensed with ethyl chloroformate in the presence of K_2CO_3 and acetone, robustic acid **10** resulted, identical in all respects with the natural product. The other phenacyl chromene **7** yielded 3-phenyl-4-hydroxy-5,4′-dimethoxy-6″,6″-dimethylpyrano(2″,3″:7,8)coumarin, **7**, which may be called isorobustic acid.

The C-prenylated desoxybenzoins **2b** and **3** have



7 8

9 10
2b 3

11 12

also been converted into corresponding 3-phenyl-4-hydroxycoumarins **11** and **12** respectively, and the products have been characterized.

EXPERIMENTAL

Unless otherwise stated, all m.ps are uncorrected; light petroleum had b.p. 60–80°; IR spectra were determined using KBr matrix; NMR spectra were taken in $CDCl_3$ on a Varian 60 MHz spectrometer using TMS as internal standard; J values are reported in Hz; silica gel was used for column chromatography; TLC was carried out on silica gel G plates using either (a) Benzene : ethyl acetate (85 : 15) or (b) benzene : methanol (19 : 1) as solvent systems; and spraying agents for TLC were either 3% alcoholic $FeCl_3$ or 10% dil. H_2SO_4.

Nuclear prenylation of 2,4-dihydroxy-6-methoxyphenyl-4-methoxybenzylketone. (a) *Using 2-methyl-2-hydroxy-3-butene.* To an ice-cooled solution of 2,4-dihydroxy-6-methoxyphenyl 4-methoxybenzyl ketone[10] (3·5 g) in dry dioxan (25 ml) was added BF_3 etherate (1·65 ml) slowly while shaking, followed by 2-methyl-2-hydroxy-3-butene (1·5 ml) in dioxane (10 ml) in one lot. The whole mixture was shaken for 1 hr at room temp, diluted with moist ether (300 ml), washed with ice-cooled water, 1% Na_2CO_3 aq and finally with water. The alkaline solution gave unchanged 2,4-dihydroxy-6-methoxyphenyl-4-methoxybenzyl ketone (0·55 g). The ethereal extract was dried and examined by TLC (solvent a) when it showed the presence of several compounds. It was, therefore, subjected to column chromatography. The column was eluted successively with (i) benzene : light petroleum (3 : 1) and (ii) benzene alone when the following two fractions were obtained. *Fraction A*; crystallised from benzene yielding 3-C-prenyl-2,4-dihydroxy-6-methoxyphenyl-4-methoxybenzyl ketone (**2a**, 0·4 g) as yellow plates, m.p. 153–154°; R_f 0·46 (solvent a), light green ferric reaction; NMR: δ1·76 and 1·78 (2s, 6H, one $(CH_3)_2C=$), 3·35 (1d, J = 7 Hz, 2H, one $-CH_2-$), 5·27 (1t, J = 7 Hz, one H, $-CH=$), 3·76 (1s, 6H, two $-OCH_3$), 4·27 (1s, 2H, $-CO-CH_2-$), 6·30 (1s, 1 aromatic H in position 5), 6·82 and 7·15 ppm (2d, J = 8 Hz, 4 aromatic H at positions 2', 3', 5' and 6'). Found: C, 71·3; H, 6·9. $C_{21}H_{24}O_5$ requires: C, 70·8; H, 6·8%. *Fraction B*; crystallised from benzene : light petroleum yielding 5-C-prenyl-2,4-dihydroxy-6-methoxyphenyl-4-methoxybenzyl ketone (**3**, 0·3 g) as white silky needles, m.p. 91–92°; R_f 0·49 (solvent a); green ferric reaction; NMR: δ1·76 and 1·80 (2s, 6H, one $(CH_3)_2C=$), 3·35 (1d, J = 7 Hz, 2H, one $-CH_2-$), 3·75 and 3·78 (2s, 6H, two $-OCH_3$), 4·34 (1s, 2H, $-CO-CH_2-$), 5·25 (1t, J = 7 Hz, 1H, one $-CH=$), 6·47 1s, 1 aromatic H at position 3), 6·83 and 7·17 ppm (2d, J = 8 Hz, 4 aromatic H at positions 2', 3', 5' and 6'). Found: C, 70·4; H, $C_{21}H_{24}O_5$ requires: C, 70·8; H, 6·8%.

(b) *Using prenyl bromide, potassium carbonate and acetone.* To an acetone solution of 2,4-dihydroxy-6,4'-dimethoxydesoxybenzoin (**1**, 0·2 g) was added prenyl bromide (0·1 ml) and K_2CO_3 (1 g) and the solution refluxed for 3 hr. 2-Hydroxy 4-prenyloxy-6,4'-dimethoxydesoxybenzoin (**1b**) was obtained by crystallisation from light petroleum (0·2 g), m.p. 76–77°; R_f 0·65 (solvent a); brown ferric reaction; NMR: δ1·72 and 1·76 (2s, 6H, one $(CH_3)_2C=$), 3·76 and 3·80 (2s, 6H, two $-OCH_3$), 4·23 (1s, 2H, $-CO-CH_2-$), 4·48 (1d, J = 8 Hz, 2H, $-O-CH_2-$), 5·42 (1t, J = 7 Hz, 1H of $-CH=$), 5·92 and 6·05 (2d, J = 2 Hz, 2 aromatic H at positions 3 and 5) and 6·81, 7·12 ppm (2d, J = 8 Hz, 4 aromatic H at positions 2', 3', 5' and 6'). Found: C, 70·7; H, 7·0. $C_{21}H_{24}O_5$ requires C, 70·8; H, 6·8%.

(c) *Using prenyl bromide and methanolic KOH.* 2,4-Dihydroxy-6,4'-dimethoxydesoxybenzoin (**1**, 4 g) was dissolved in absolute methanolic KOH (3·7 g in 35 ml) and the solution was cooled and treated with prenyl bromide (5·3 ml). After keeping the reaction mixture for 20 hr at room temp, it was diluted with ice-cold water, acidified and extracted with ether. The ethereal solution showed several spots on TLC. Hence it was separated by column chromatography. Elution was done successively with (i) benzene : light petroleum (1 : 9), (ii) benzene : light petroleum (1 : 1) and (iii) with benzene when the following three main fractions were obtained. *Fraction A*; crystallised from light petroleum yielding 4-prenyloxy-2-hydroxy-6,4'-dimethoxydesoxybenzoin (**1b**, 0·1 g) as colourless shining crystals, m.p. and m.m.p. with the above authentic sample, 76–77°. *Fraction B*; crystallised from benzene yielding 3-C-prenyl-2,4'-dihydroxy-6,4'-dimethoxydesoxy-benzoin (**2a**, 0·6 g): m.p. and m.m.p. with the sample prepared above 153–54°. *Fraction C*; crystallised from benzene-light petroleum mixture and afforded homoanisic acid (50 mg), m.p. 83–84° (lit.[11] m.p. 84–85°); soluble in aq. $NaHCO_3$. Found: C, 65·3; H, 6·1, calculated for $C_9H_{10}O_3$; C, 65·1; H, 6·0%.

3-C-Prenyl-2-hydroxy-4,6,4'-trimethoxydesoxybenzoin **2b**. 3-C-Prenyl-2,4-dihydroxy-6,4'-dimethoxydesoxybenzoin (**2a**, 0·35 g) was refluxed for 3·5 hr with Me_2SO_4 (0·1 ml) in the presence of K_2CO_3 and acetone (30 ml). Acetone was distilled off, water was added and the solid filtered off. The product **2b** crystallised from alcohol as yellow needles, m.p. 94–95° it gave a green ferric reaction. Found: C, 71·6; H, 7·1. $C_{22}H_{26}O_5$ requires: C, 71·3; H, 7·0%.

Formic acid cyclisation of 3-C-prenyl-2,4-dihydroxy-6,4'-dimethoxydesoxybenzoin **2a**. **2a** (0·3 g) was warmed with formic acid (10 ml) for 5 min and then left at room temp for 1 hr. The resulting yellow solution was then poured over ice and extracted with chloroform and dried. The chloroform residue on TLC showed two compounds which were separated by column chromatography and eluting successively with (i) benzene : light petroleum (1 : 3) and (ii) chloroform. *Fraction A*; crystallised from alcohol yielding 2,2-dimethyl-5-hydroxy-6-(p-methoxy) phenacyl-7-methoxychroman (**4**, 0·1 g) as colourless crystals, m.p. 120–21° (lit.,[6] m.p. 120–21°), reddish brown ferric reaction. *Fraction B*; crystallised from methanol yielding 2,2-dimethyl-5-hydroxy-7-methoxy-8-(p-methoxyphenacyl) chroman as colourless needles (**5a**, 0·15 g), m.p. 149–50° (lit.,[6] m.p. 149–51°), negative ferric reaction, soluble in aq. Na_2CO_3.

2,2-Dimethyl-5,7-dimethoxy-8-(p-methoxyphenacyl) chroman **5b**. 3-C-Prenyl-2-hydroxy-4,6,4'-trimethoxydesoxybenzoin (**2b**, 120 mg) was dissolved in warm formic acid (10 ml) and then left at room temp for 1 hr. The product crystallised from methanol as colourless crystals (0·1 g), m.p. 105° (lit.,[6] m.p. 105°).

2,2-Dimethyl-5-methoxy-6(p-methoxyphenacyl) 7-hydroxychroman **6**. 5-C-Prenyl 2,4-dihydroxy-6,4'-dimethoxydesoxybenzoin (**3**, 0·1 g) was dissolved in warm formic acid (15 ml) and then left at room temp for 1 hr. The product crystallised from alcohol as white needles (**6**, 80 mg), m.p. 114–15° (lit.,[6] m.p. 113–15°); reddish brown ferric reaction.

2,2-Dimethyl-5-hydroxy-6-(p-methoxyphenacyl)-7-methoxychromene 7. 3-C-Prenyl-2,4-dihydroxy-6,4'-dimethoxydesoxybenzoin (**2a**, 0·2 g) was dissolved in dry

benzene (20 ml) and the solution heated with DDQ (160 mg) on a water bath for 1 hr when colourless hydroquinone separated out. It was filtered while hot and the residue washed with dry benzene. The filtrate was evaporated and the residue chromatographed. Elution with benzene-light petroleum mixture (1:3) gave a solid which on crystallisation from benzene-light petroleum gave 2,2-dimethyl-5-hydroxy-6-(p-methoxy)phenacyl-7-methoxychromene **7** as yellow crystals (0·15 g), m.p. 155–56°; light green ferric reaction; R_f 0·83 (solvent a): NMR: δ1·42 (1s, 6H, $(C\underline{H}_3)_2C$), 3·77 and 3·82 (2s, 6H, two $-OC\underline{H}_3$), 4·22 (1s, 2H, $-CO-C\underline{H}_2-$), 5·42 and 6·65 (2d, J = 10 Hz, 2H, $-C\underline{H}=C\underline{H}-$), 5·88 (1s, 1 aromatic H at position 8), 6·82 and 7·14 ppm (2d, J = 8 Hz, 4 aromatic H at positions 2′, 3′, 5′, and 6′). Found: C, 71·4; H, 6·3. $C_{21}H_{22}O_5$ requires: C, 71·2; H, 6·2%.

2,2-*Dimethyl-5-methoxy-6-(p-methoxyphenacyl)-7-hydroxychromene* **9**. 5-C-Prenyl-2,4-dihydroxy-6,4′-dimethoxydesoxybenzoin (**3**, 0·1 g) in dry benzene (20 ml) was heated with DDQ (0·1 g) for 1 hr. The product on chromatography and elution with benzene:light petroleum mixture (1:9) gave 2,2-dimethyl-5-methoxy-6-(p-methoxyphenacyl)-7-hydroxychromene **9** as yellow plates (40 mg), m.p. 86–87°; green ferric reaction; R_f 0·61 (solvent a); NMR: δ1·42 (1s, 6H, $(CH_3)_2C$), 3·79 (1s, 6H, 2-$OC\underline{H}_3$), 4·32 (1s, 2H, $-CO-C\underline{H}_2-$), 5·62 and 6·53 (2d, J-10 Hz, 2H, $-C\underline{H}=C\underline{H}-$), 6·21 (1s, 1 aromatic H at position 8), 6·88 and 7·21 ppm (2d, J = 8 Hz, 4 aromatic H at 2′, 3′, 5′, 6′ positions). Found: C, 71·2 H, 6·5. $C_{21}H_{22}O_5$ requires: C, 71·2; H, 6·2%.

5,4′-*Dimethoxy-3-phenyl-4-hydroxy-6″,6″-dimethylpyrano* (2″,3″:7,8)*coumarin* (*isorobustic acid*) **8**. 2,2-Dimethyl-5-hydroxy-6-(p-methoxyphenacyl)-7-methoxychromene (**7**, 0·1 g) was refluxed with ethyl chloroformate (0·1 ml), K_2CO_3 (1 g) and acetone (15 ml) for 4·5 hr. Acetone was distilled off and water added to the residue and filtered. The solid was crystallised from acetone yielding isorobustic acid **8** as white shining plates, (80 mg), m.p. 220–21°; R_f 0·32 (solvent b); soluble in sodium bicarbonate; ν_{max} 1705 cm^{-1}. Found: C, 70·3; H, 5·6. $C_{22}H_{20}O_6$ requires: C, 69·5; H, 5·3%.

5,4′-*Dimethoxy-3-phenyl-4-hydroxy-6″,6″-dimethylpyrano*(2″,3″:7,6)*coumarin*, *Robustic acid* **10**. A solution of 2,2-dimethyl-5-methoxy-6-(p-methoxyphenacyl)-7-hydroxychromene (**11**, 20 mg) was refluxed with ethyl chloroformate (0·01 ml), K_2CO_3 (0·5 g) and acetone (5 ml) for 4·5 hr. The product crystallized from acetone yielding 5,4′-dimethoxy-3-phenyl-4-hydroxy-6″,6″-dimethylpyrano(2″,3″:7,6)coumarin **10** as white shining plates, m.p. 208–9°, R_f 0·55 (solvent b), soluble in aq. $NaHCO_3$, ν_{max} 1704 cm^{-1} (C=O), MS: molecular ion peak at 380. In all these properties it agrees with natural robustic acid and direct comparison with natural sample revealed complete identity in m.m.p., TLC, IR and mass spectra.

8-C-*Prenyl-3-phenyl-4-hydroxy-5,7,4′-trimethoxycoumarin* **11**. 3-C-Prenyl-2-hydroxy-4,6,4′-trimethoxydesoxybenzoin (**2b**, 150 mg) was refluxed with ethyl chloroformate (0·15 ml), K_2CO_3 (0·5 g) and acetone (10 ml) for 4·5 hr. The product crystallised from benzene yielding 8-C-prenyl-3-phenyl-4-hydroxy-5,7,4′-trimethoxycoumarin (**11**, 150 mg) as white shining needles, m.p. 170–71°, R_f 0·42 (solvent a), soluble in aq. $NaHCO_3$, ν_{max} 1700 cm^{-1} (C=O). Found: C, 70·2; H, 5·7. $C_{23}H_{24}O_6$ requires: C, 69·7; H, 6·1%.

6-C-*Prenyl-3-phenyl-4,7-dihydroxy-5,4′-dimethoxycoumarin* **12**. 5-C-Prenyl-2,4-dihydroxy-6,4′-dimethoxydesoxybenzoin (**3**, 0·4 g) was refluxed with ethyl chloroformate (0·45 ml), K_2CO_3 (3 g) and acetone (20 ml) for 4·5 hr. Acetone was distilled and water added to the residue and solid filtered. Solid was heated with 4% NaOH for 1 hr, filtered and acidified. The solid was collected and crystallised from methanol when 6-C-prenyl-3-phenyl-4,7-dihydroxy-5,4′-dimethoxycoumarin (**12**, 0·2 g) was obtained as white shining needles, m.p. 209–10°; R_f 0·20 (solvent a); soluble in aq. $NaHCO_3$; ν_{max} 1670 cm^{-1} (C=O). Found: C, 69·4; H, 6·3. $C_{22}H_{22}O_6$ requires: C, 69·1; H, 5·8%.

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