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SYNTHESIS OF DERRUBONE AND ROBUSTONE

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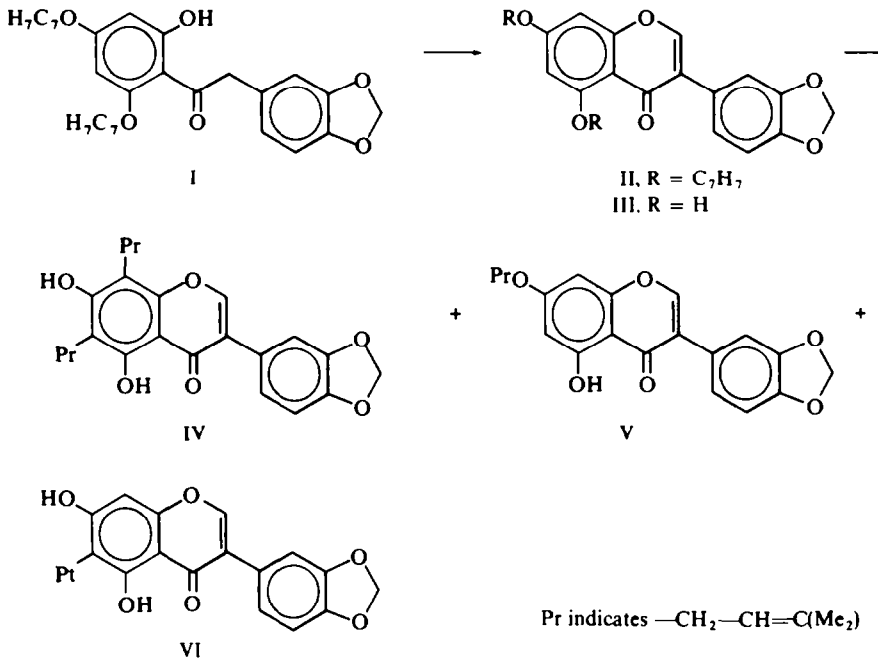
Abstract—5,7-Dihydroxy-3',4'-methylenedioxyisoflavone(III) has been synthesised by condensation of 2-hydroxy-4,6-dibenzyloxyphenyl-3,4-methylenedioxybenzyl ketone (I) with ethyl formate in the presence of sodium, followed by catalytic debenzylation. Treatment of this isoflavone with prenyl bromide in the presence of methanolic sodium methoxide yields a mixture of 6,8-di-C-prenyl(IV), 7-O-prenyl(V) and 6-C-prenyl(VI) derivatives, constitutions of which have been established by a study of their NMR and mass spectra. The last compound agrees with derrubone which on cyclodehydrogenation with DDQ affords robustone (IX). Since natural robustone has already been converted into robustone methyl ether which in turn has been transformed into the corresponding 3-phenyl-4-hydroxycoumarins robustin and its methyl ether, the present work constitutes the synthesis of all these natural products.

FROM the roots of the Indian tree *Derris robusta*, nine pure compounds have recently been isolated.[1] Of these, four are isoflavones and the rest 3-phenyl-4-hydroxycoumarins. Among the isoflavones, derrubone (VI), robustone (IX) and its methyl ether(X) possess the same oxygenation pattern and are isopentenylated in the same position. Obviously they are biogenetically interrelated. Derrubone(VI) seems to be first formed by C-prenylation of 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(III). Subsequent cyclodehydrogenation may yield robustone(IX) which on further O-methylation affords robustone methyl ether(X). Among the five 3-phenyl-4-hydroxycoumarins which may also be called isoflavonols, robustin(XII) and its methyl ether(XIII) have also the same oxygenation and isopentenylation pattern as robustone methyl ether (X). In fact the latter has been degraded to its desoxybenzoin (XI) and then reconverted into robustin(XII) and its methyl ether (XIII). Synthesis of derrubone and robustone has now been accomplished on the pattern of their biogenesis.

The synthesis of derrubone starts with the preparation of 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(III) which is described by Baker *et al.*[2] to result in very low field by the ethoxalylation method. Although 2-carbethoxy 5,7-dihydroxy-3',4'-methylenedioxyisoflavone could be obtained in satisfactory yields, all attempts to decarboxylate it in reasonable yields failed. Hence an alternative method was explored. Ethyl formate was used to obtain the isoflavone from 2-hydroxy-4,6-dibenzyloxy 3',4'-methylenedioxydesoxybenzoin[3](I). The resulting 5,7-dibenzyloxy 3',4'-methylene dioxyisoflavone(II) could be obtained in good yields, and its structure confirmed by NMR which showed a characteristic singlet of one hydrogen in 2-position at δ 7·69 ppm. The above dibenzyloxyisoflavone was hydrogenolysed with hydrogen in the presence of palladium deposited on charcoal when 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(III) was obtained identical with the one described by Baker *et al.*[2]



Nuclear prenylation of 5,7-dihydroxy-3′,4′-methylene-dioxyisoflavone(III) was carried out by treatment with prenyl bromide in the presence of methanolic sodium methoxide. A mixture of three compounds, separable by column chromatography, was obtained.

The first component eluted with benzene–light petroleum (1:3) appeared to be the di-prenyl derivative on the basis of its mass ion(M^+ 434). Its positive ferric reaction and solubility in aqueous sodium carbonate showed that both the hydroxyls were free. That the two prenyl units had entered the two available nuclear positions in the ring A was shown by its NMR spectrum which had the expected resonance signals of two C-prenyl units [δ 1·73 and 1·82(2s, 12H, 2$(CH_3)_2C$=), 3·46 (1d, J = 8 Hz, 4H, 2—CH_2—), 5·25 (1t, J = 8 Hz, 2H, 2—CH=)] but no signal of the aromatic proton of the condensed benzene ring. Hence the first prenylated product is 6,8-di-C,C-prenyl-5,7-dihydroxy-3′,4′-methylenedioxyisoflavone(IV). This structure is supported by its typical mass spectrum.

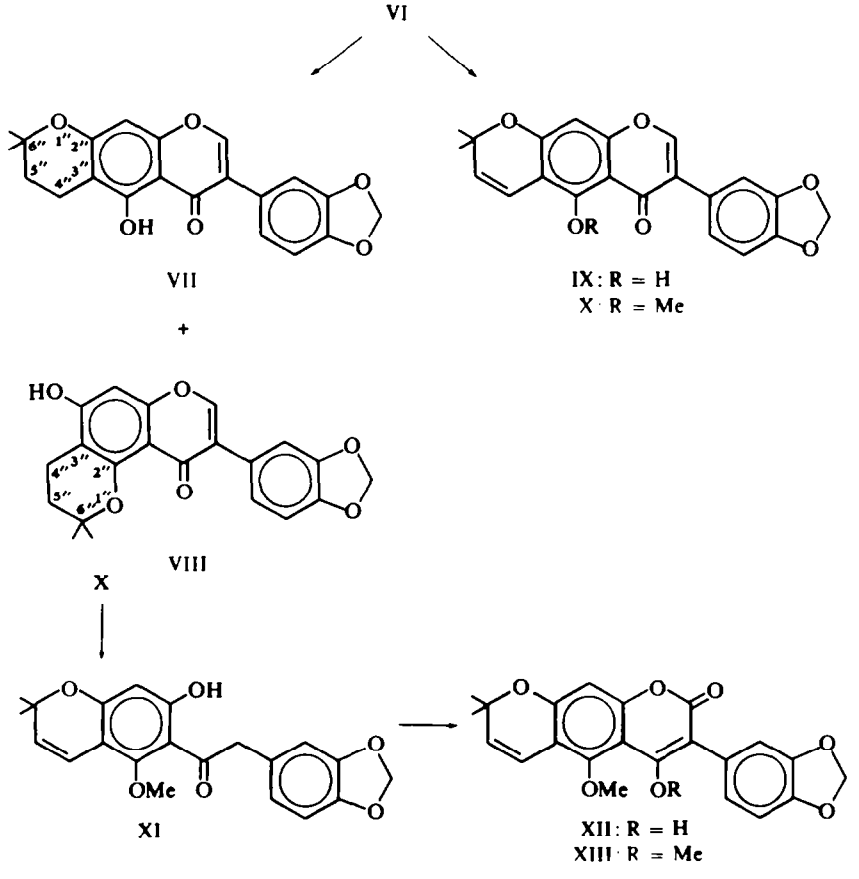
The second product eluted with benzene–light petroleum (1:1) was obtained in a very small amount. It was identified as 7-prenyloxy-3′,4′-methylenedioxy-5-hydroxyisoflavone(V) on the basis of its elemental analysis and NMR data which showed resonance signals of one prenyloxy protons [δ 4·60(1d, J = 6·5 Hz, 2H, O—CH_2—), 1·78(1s, 6H,$(CH_3)_2C$=), 5·53 ppm(1t, J = 6·5 Hz, 1H, —CH=)] in addition to other signals. The structure V finally was confirmed by direct comparison with an authentic sample synthesized by O-prenylation of 5,7-dihydroxy-3′,4′-methylenedioxyisoflavone(I).

The third component eluted with benzene: ethyl acetate (9:1) gave a solid which was soluble in aqueous sodium carbonate and gave positive ferric reaction indicating that both the hydroxyls of the parent compound are free. Its mass ion(M^+ 366)

showed that it is a mono-prenyl derivative. On acid catalysed cyclization, it gave two mono-chromans, one (VII) showing positive ferric reaction and the other (VIII) negative ferric reaction. Hence the third prenylated product is 6-C-prenyl-5,7-dihydroxy-3',4'-methylenedioxyisoflavone(VI) which is the structure given to derrubone. Although direct comparison could not be made with the natural sample because of its nonavailability; m.p. of the synthetic sample agrees with that of natural sample and the m.p. of synthetic monochromans are identical with β-(VII) and α-(VIII) isoderrubones respectively obtained from the natural sample.[1]

Finally the mass spectrum of synthetic derrubone showed main peaks at 366, 351, 323, 311, 165 and 146 which is in accordance with the given structure. Hence the structure of derrubone is now established by synthesis.

The above synthetically prepared derrubone (VI) has now been cyclodehydrogenated with DDQ in dry benzene medium. The only product formed was identified as the linear pyrano derivative (IX), because it gave a positive ferric reaction. It agrees in m.p. with the natural compound robustone. In view of the fact that natural robustone has earlier been converted into robustone methyl ether which in turn has also been converted into robustin (XII) and its methyl ether(XIII) via the desoxybenzoin (XI); this synthesis constitutes the synthesis of robustone, its methyl ether, robustin and its methyl ether.



EXPERIMENTAL

Unless otherwise stated, mps are uncorrected; NMR spectra were recorded on a Varian A-60 spectrophotometer; TMS was used as internal reference standard, mass spectra were recorded using AEI MS12 spectrometer; light petroleum had boiling range 60–80°; silica gel was used for column chromatography and TLC. Solvent systems for TLC were (A) chloroform (B) toluene:ethyl formate: formic acid (5:4:1); R_f values are those taken on TLC.

5,7-Dibenzyloxy-3',4'-methylenedioxyisoflavone(II)

Compound I[3](2·5 g) in dry ethyl formate (20 ml) was added, slowly while shaking during 2 hr, to a freshly prepared powdered suspension of Na (2·5 g) in ethyl formate(60 ml). The mixture was left overnight in an ice chest. It was treated with ice-cold water, extracted with ether and the ethereal soln dried over Na_2SO_4. The ethereal residue was refluxed with Ac_2O (50 ml) for 1 hr and then poured over ice. The solid was crystallized from benzene when 5,7-dibenzyloxy-3',4'-methylenedioxyisoflavone was obtained as a colourless solid(1·3 g), m.p. 142–43°; R_f 0·62 (solvent A); NMR: δ 5·08 and 5·19(2s, 4H, 2—O—CH_2—Ph), 5·95(1s, 2H,1—O—CH_2—O—), 6·52 (1s, 2 aromatic H at 6 and 8 positions), 7·25(1 broad m, 13H, 10 aromatic H of two phenyl rings and three aromatic H at 2',5' and 6' positions) and 7·69 ppm(1s, 1H at 2 position) (Found: C, 75·3; H, 4·9. $C_{30}H_{22}O_6$ requires C, 75·3; H, 4·6%).

5,7-Dihydroxy-3',4'-methylenedioxyisoflavone(III)

A soln of the above isoflavone (3 g) in glacial AcOH (300 ml) was treated with 10% Pd-C (3 g) and hydrogenated at room temp. When the required amount of H_2 had absorbed, the mixture was filtered and the filtrate concentrated *in vacuo*. The isoflavone(III) crystallized from EtOAc as cream-coloured crystals (1·1 g), m.p. 227–28°C(lit.,[3] m.p. 227°).

5-Hydroxy-7-prenyloxy-3',4'-methylenedioxyisoflavone(V)

To an acetone soln of 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(150 mg) was added prenyl bromide (0·08 ml) and ignited K_2CO_3 (0·5 g) and the resulting mixture refluxed for 3 hr. Acetone was distilled and water added to the residue. The solid was filtered, dried and crystallized from benzene–light petroleum mixture when 7-prenyl ether was obtained as colourless small needles(150 mg), m.p. 142–43°; R_f 0·65 (solvent A); reddish brown ferric reaction; NMR ($CDCl_3$); δ 1·78(1s, 6H, 1-(CH_3)$_2$C=), 4·60(1d, J = 6·5 Hz, 2H of —O—CH_2—), 5·53(1t, J = 6·5 Hz, 1H, —CH=), 6·03(1s, 2H, —O—CH_2—O), 6·41(1s, 2 aromatic H at 6 and 8 positions), 7·12(broad m, 3 aromatic H at 2',5',6' positions) and 7·87 ppm(1H at 2 position) (Found: C, 68·9; H, 5·4. $C_{21}H_{18}O_6$ requires: C, 68·9; H, 4·9%).

Nuclear prenylation of 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(III) *and synthesis of derrubone* (VI)

To a soln of III(0·8 g) in anhyd MeOH(30 ml) was added methanolic soln of NaOMe(1·4 g Na/20 ml MeOH). The soln was cooled, treated with prenyl bromide (1·9 ml) and refluxed for 3 hr. After removal of the solvent the mixture was treated with crushed ice and acidified with dil HCl. The solid product was collected and examined on TLC using solvent A which showed the presence of a number of compounds. It was therefore, subjected to column chromatography over silica gel and the column eluted successively with (i) benzene:light petroleum(1:3) (ii) benzene:light petroleum(1:1) and (iii) EtOAc:benzene (1:9) thus giving the following three fractions A to C.

Fraction A crystallized from benzene–light petroleum mixture yielding IV(120 mg) as pale yellow plates, m.p. 119–20°; soluble in Na_2CO_3 aq; green ferric reaction; R_f 0·65(solvent A); NMR; δ 1·73 and 1·82 (2s, 12H of two (CH_3)$_2$C=), 3·46(1d, J = 8·0 Hz, 4H, 2—CH_2—), 5·25(1t, J = 8·0 Hz, 2H, 2—CH=), 5·98(1s, 2H, 1—O—CH_2—O—), 7·08(1 broad m, 3 aromatic H at 2',5',6'-positions) and 7·91 ppm (s, 1H at 2 position); MS ions; 434, 419, 391, 379, 336, 324, 178 and 146.

Fraction B crystallized from benzene:light petroleum yielding V as cream-coloured solid(10 mg), m.p. and mmp with the authentic sample described above 142–43°.

Fraction C crystallized from MeOH affording VI as pale yellow needles(90 mg); m.p. 210–11 (derrubone,[1] m.p. 210–11°); R_f 0·26(solvent A): soluble in Na_2CO_3 aq, green ferric reaction, MS ions 366, 351, 323, 311, 165 and 146.

Acid cyclization of 6-C-prenyl-3',4'-methylenedioxy-5,7-dihydroxyisoflavone(VI)

6-C-Prenyl-5,7-dihydroxy-3',4'-methylenedioxyisoflavone (20 mg) was dissolved in warm formic acid and left at room temp for 2 hr, extracted with chloroform and the organic layer tested on TLC (solvent B) which showed two compounds. Hence it was separated by column chromatography, elution being carried

out successively with benzene:light petroleum (1:3) and (ii) chloroform when the following two fractions were obtained:

Fraction A was crystallized from MeOH yielding VII as colourless crystals(7 mg), m.p. 195–6°(lit.,[1] m.p. 195–96°), green ferric reaction; R_f 0·77(solvent B).

Fraction B crystallized from MeOH yielding VIII as colourless crystals(4 mg) m.p. 324–326°(lit.[1] m.p. 324–26°), no ferric reaction; R_f 0·42(solvent B).

5-Hydroxy-3',4'-methylenedioxy-6'',6''-dimethylpyrano(2'',3'':7,6)isoflavone(Robustone IX)

A soln of 6-C-prenyl 5,7-dihydroxy-3',4'-methylenedioxyisoflavone(14 mg) in dry benzene(5 ml) and added DDQ(14 mg) was heated on a water bath for 30 min and yielded colourless hydroquinone. This was filtered while hot and the residue washed with dry benzene. The filtrate was distilled to remove the solvent and the residue chromatographed Elution with benzene:light petroleum MeOH (1:3) gave a solid which on crystallization from MeOH gave 5-hydroxy 3',4'-methylenedioxy 6'',6''-dimethylpyrano(2'',3'':7,6)-isoflavon(8 mg) as yellow crystals, m.p. 172–73° (lit.[1] 172–73°), intense dark green ferric reaction, R_f 0·61(solvent A). These properties agree with those of natural robustone.

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