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Synthesis of 6-*C*-(3,3-Dimethyl-2-propen-1-yl) Norwogonin

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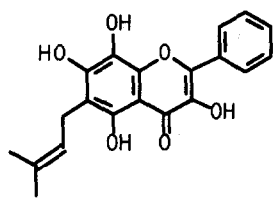
Key Words: Flavonoids; Prenyl flavones; Synthesis; 6-*C*-(3,3-Dimethyl-2-propen-1-yl) norwogonin.

Abstract: 6-*C*-(3,3-Dimethyl-2-propen-1-yl) norwogonin was synthesized in 34% yield by direct *C*-prenylation of 5,7-dihydroxy-8-sulfooxy flavone using 4-bromo-2-methyl-2-buten in aqueous tetramethylammonium hydroxide. Among the minor products of the reaction, 6-*C*-(1,1-dimethyl-2-propen-1-yl) norwogonin, and traces of 7-O-(3,3-dimethyl-2-propen-1-yl) norwogonin were identified as well.

Platanetin **1** is one of the naturally occurring *C*-prenylated flavonols isolated from *Platanus* buds[1], and acting as an inhibitor of the external NADH dehydrogenase of the inner mitochondrial membrane[2].



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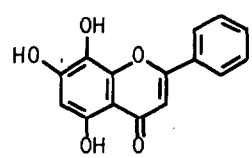

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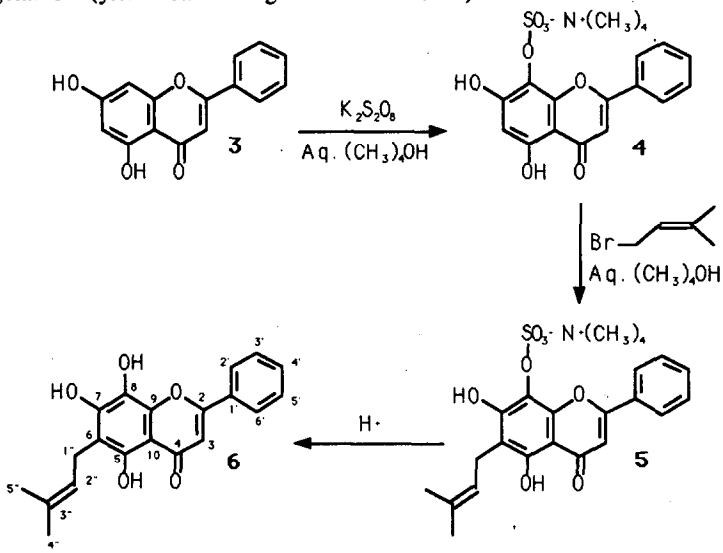
The design of a QSAR study, however, was conditioned to the obtention of series of structural analogues of platanetin, only a few of them being easily accessible from natural sources. Thus the chemical synthesis of prenylated flavones and flavonols was undertaken.

Until now, only very few publications have described the synthesis of prenylated flavonoids[3-6]. When we tried to apply the 3-buten-2-ol/BF_3-etherate method[3] to the direct prenylation of 5,7,8-trihydroxyflavone (norwogonin) **2**, no formation of 6-*C*-prenyl norwogonin **6** was detected[7]. Beside the fact that direct prenylation with prenyl bromide/NaOMe in methanol yields a mixture of *O*- and *C*-prenylated products[4], it cannot be applied to the prenylation of norwogonin since the strong alkaline medium would induce extensive degradation of the 5,7,8-trihydroxyflavone. Similar problems are expected in the Claisen rearrangement[6] of a norwogonin derivative since the last deacylation step involves alkaline conditions as well. Direct prenylation of norwogonin **2**

using prenyl bromide in presence of freshly prepared silver oxide[8] yielded 7-*O*-prenyl norwogonin **7** as major product, and only traces of the desired *C*-prenyl norwogonin **6**.

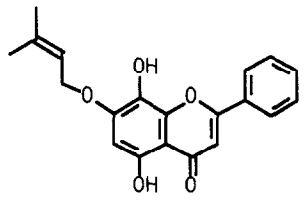
In the present paper, we wish to report that direct prenylation of norwogonin-8-sulfate **4** does not lead to degradation of the flavonoid compound, due to the protection of the 8-hydroxyl by sulfation. Furthermore, when prenylation was carried out in aqueous medium, *C*-prenylation was favoured over *O*-prenylation and the expected 6-*C*-prenyl norwogonin was the major product of the reaction.

Thus oxidation of 5,7-dihydroxyflavone (chrysin) **3** with potassium persulfate[9] directly yielded norwogonin-8-sulfate **4** (43%) which was subsequently prenylated with prenyl bromide in aqueous tetramethylammonium hydroxide to yield **5**. Acid hydrolysis of **5** at room temperature gave 6-*C*-(3,3-dimethyl-2-propen-1-yl) norwogonin **6**[10] (yield from norwogonin-8-sulfate: 34%).



Synthesis of 6-*C*-(3,3-dimethyl-2-propen-1-yl) norwogonin.

Among the minor products of the reaction, 7-*O*-(3,3-dimethyl-2-propen-1-yl norwogonin **7**[11], 6-*C*-(1,1-dimethyl-2-propen-1-yl) norwogonin **8**[12], as well as some unreacted norwogonin **2** were identified.



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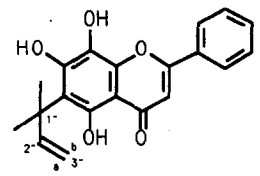

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Identification of the compounds was carried out by ^1H and ^{13}C NMR spectroscopy. This is the first report of a successful synthesis of a 5,7,8-trihydroxy-6-*C*-prenyl flavone.

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8. Direct prenylation of norwogonin using prenyl bromide and silver oxide:
To a stirred solution of 250 mg norwogonin **2** (0.93 mmoles) in 10 ml Me_2CO were successively added 0.5 ml of prenyl bromide (4.27 mmoles) and 1g of freshly prepared Ag_2O (4.3 mmoles). After one hour the reaction medium was filtered, the acetone evaporated to dryness and the residue taken in MeOH. The MeOH suspension was centrifugated and the supernatant purified by gel filtration on Sephadex® LH-20 using MeOH as solvent. Final purification of compounds was carried out by LPLC on diol bonded silica using Hex-BuOH-EtOH 85:10:5 as solvent, yielding 40 mg of 7-*O*-prenyl norwogonin **7** (0.12 mmoles; 13%), 4.7 mg of 6-*C*-prenyl norwogonin **6** (0.014 mmoles; 1.5%) and 22 mg of unreacted norwogonin **2** (0.08 mmoles; 8.6%).

9. Synthesis of 6-*C*-(3,3-dimethyl-2-propen-1-yl) norwogonin **6**:
To 1g of 5,7-dihydroxy flavone (chrysin; 3.94 mmoles) in solution in 50 ml of 5% aq. tetramethylammonium hydroxide were added 2 g (7.41 mmoles) of $K_2S_2O_8$ dissolved in 100 ml H_2O, dropwise with stirring. Oxidation was allowed to proceed under stirring for 1.5 h. The solution was neutralized to pH 7.0 with saturated aq. KH_2PO_4. Unreacted chrysin was removed by extraction with Et_2O. Norwogonin-8-sulfate (yield: 43%) was subsequently extracted with BuOH.
The BuOH extract was evaporated to dryness under reduced pressure and the residue was taken in 30 ml of 5% aq. tetramethylammonium hydroxide. To this alkaline aqueous solution was added 1.5 ml of 4-bromo-2-methyl-2-butene (13 mmoles) dropwise under stirring at room temperature. Prenylation was allowed to take place for 3.5 h. The solution was acidified to pH 1 (HCl 6N) in order to hydrolize the sulfate groups. After standing 4 h at room temperature the products of the reaction were extracted with EtOAc.

The EtOAc extract was evaporated to dryness under reduced pressure, taken in MeOH and purified by gel filtration on Sephadex® LH-20 using MeOH as solvent. Subsequent purification of the Sephadex® fractions by LPLC on diol bonded silica using Hex-BuOH-EtOH 85/10/5 as solvent yielded 195.6 mg (34%) of 6-*C*-(3,3-dimethyl-2-propen-1-yl) norwogonin **6**, 1.4 mg of 7-*O*-(3,3-dimethyl-2-propen-1-yl norwogonin **7** and 2.4 mg of 6-*C*-(1,1-dimethyl-2-propen-1-yl) norwogonin **8**.

10. Spectral data for 6-*C*-(3,3-dimethyl-2-propen-1-yl) norwogonin **6**:
^{13}C NMR (Bruker AC 200, 50 MHz, DMSO-d_6, δ ppm/TMS): 17.71 (C-5"); 21.37 (C-1"); 25.48 (C-4"); 102.99 (C-10); 104.64 (C-3); 111.15 (C-6); 122.23 (C-2"); 124.07 (C-8); 126.69 (C-2'/6'); 128.97 (C-3'/5'); 130.67 (C-3")*; 130.92 (C-1')*; 131.69 (C-4'); 144.13 (C-9); 150.94 (C-5); 152.48 (C-7); 162.74 (C-2); 182.19 (C-4). *Assignments may be reversed.
^{1}H NMR (Bruker AC 200, 200 MHz, DMSO-d_6, δ ppm/TMS): 1.61 (s, 3H, H-4"); 1.72 (s, 3H, H-5"); 3.25 (d, 2H, J = 6.8 Hz, H-1"); 5.18 (br t, 1H, J = 6.8 Hz, H-2"); 6.93 (s, 1H, H-3); *c.a.* 7.56-7.59 (m, 3H, H-3'/5' and H-4'); *c.a.* 8.20-8.23 (m, 2H, H2'/6'); 9.10 (s, 1H, 8-OH); 9.96 (s, 1H, 7-OH); 12.59 (s, 1H, 5-OH).

11. Spectral data for 7-*O*-(3,3-dimethyl-2-propen-1-yl norwogonin **7**:
^{13}C NMR (Bruker AC 200, 50 MHz, DMSO-d_6, δ ppm/TMS): 18.09 (C-5"); 25.46 (C-4"); 65.63 (C-1"); 96.61 (C-6); 104.04 (C-10); 104.65 (C-3); 119.47 (C-2"); 122.28 (C-8); 126.54 (C-2'/6'); 129.06 (C-3'/5'); 130.68 (C-1'); 132.01 (C-4'); 137.69 (C-3"); 144.68 (C-9); 152.97 (C-5); 153.72 (C-7); 163.32 (C-2); 182.44 (C-4).
^{1}H NMR (Bruker AC 200, 200 MHz, DMSO-d_6, δ ppm/TMS): 1.71 (s, 1H, H-4"); 1.73 (s, 1H, H-5"); 4.66 (d, 2H, J = 6.6 Hz, H-1"); 5.46 (br t, 1H, J = 6.6 Hz, H-2"); 6.54 (s, 1H, H-6); 6.92 (s, 1H, H-3); *c.a.* 7.52-7.58 (m, 3H, H-3'/5' and H-4'); *c.a.* 8.09-8.14 (m, 2H, H-2'/6'); 8.82 (br s, 1H, 8-OH); 12.30 (br s, 1H, 5-OH).

12. Spectral data for 6-*C*-(1,1-dimethyl-2-propen-1-yl) norwogonin **8**:
^{13}C NMR (Bruker AC 200, 50 MHz, DMSO-d_6, δ ppm/TMS): 28.64 (C-4"/5"); 102.83 (C-10); 104.65 (C-3); 107.75 (C-3"); 123.79 (C-8); 126.71 (C-2'/6'); 129.01 (C-3'/5'); 130.77 (C-1'); 131.98 (C-4'); 149.68 (C-2"); 153.30 (C-5); 154.19 (C-7); 162.47 (C-2); 182.59 (C-4).
^{1}H NMR (Bruker AC 200, 200 MHz, DMSO-d_6, δ ppm/TMS): 1.56 (s, 6H, H-4"/5"); 4.78 (dd, 1H, J = 10.6 and 1.4 Hz, H-3"a); 4.83 (dd, 1H, J = 17.4 and 1.4 Hz, H-3"b); 6.29 (dd, 1H, J = 17.4 and 10.6 Hz, H-2"); 6.92 (s, 1H, H-3); *c.a.* 7.56-7.60 (m, 3H, H-3'/5' and H-4'); *c.a.* 8.19-8.24 (m, 2H, H-2'/6'); 9.22 (br s, 1H, 8-OH); 9.65 (br s, 1H, 7-OH); 13.41 (s, 1H, 5-OH).

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