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THE SYNTHESIS OF SERICETIN AND RELATED FLAVONOLS[1]

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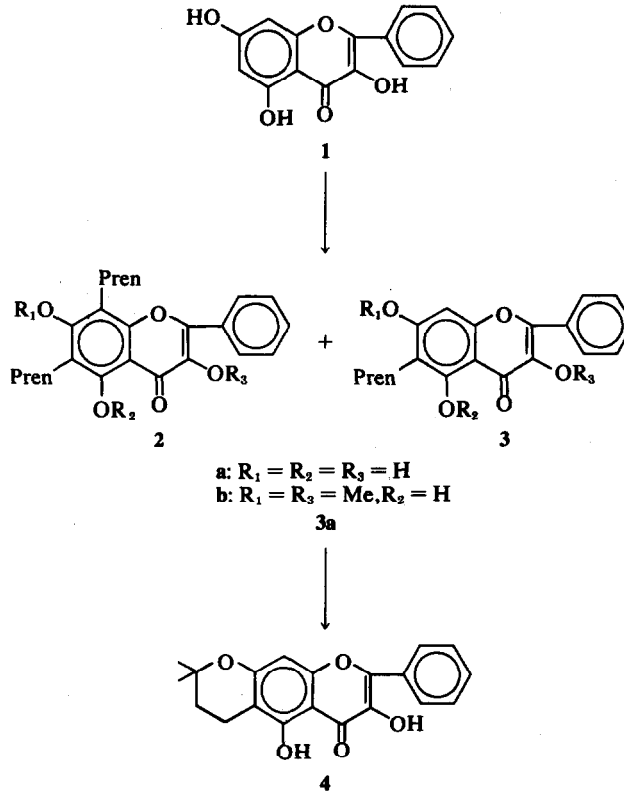
Abstract—Galangin when reacted with prenyl bromide in the presence of methanolic sodium methoxide yields 6-C-prenyl-(minor) and 6,8-di-CC-prenyl (major) derivatives. The latter on cyclodehydrogenation with DDQ yields natural sericetin along with isosericetin, and the former affords desprenyl sericetin.

Sericetin was isolated by Ollis *et al*[2] together with some structurally related compounds such as mundulone, munduserone, leaserone and sermundone from the root-bark of *Mundulea sericea* and assigned the constitution as 8-C-prenyl-3, 5-dihydroxy-6″, 6″-dimethyl pyrano (2″,3″: 7,6) flavone (**6**).[2-5] This structure has now been confirmed by synthesis.

Galangin (**1**) when reacted with excess of prenyl bromide in the presence of methanolic sodium methoxide gave a mixture from which only two crystalline products could be obtained by column chromatography. The more mobile product obtained in about 8% yield was soluble in aqueous sodium carbonate, gave positive ferric reaction and analysed for bis-prenyl derivative which was supported by NMR spectra of **1** and its acetate. Since the acetate showed three singlets of three acetoxyl groups at δ 2·28, 2·36 and 2·46 ppm, all the three



Pren indicates $\gamma\gamma$-dimethyl allyl unit.

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OH groups of galangin are free. Further as there was no resonance signal of aromatic proton of ring A and there were signals of only benzylic methylene protons (4H) in both the spectra, its constitution was given as 6,8-di-CC-prenyl galangin (**2a**). This was further confirmed by its partial methylation to 6,8-di-CC-prenyl 3,7-dimethoxy-5-hydroxy flavone[6] (**2b**).

The less mobile product (yield, 6%) was also soluble in aqueous sodium carbonate and gave positive ferric reaction but it showed only one prenyl unit in elemental analysis. NMR spectrum of its acetate showed this prenyl unit in the aromatic position of ring A, three acetoxyl groups as 3s at δ 2·26, 2·32 and 2·44 ppm and one aromatic proton of ring A at δ 6·84 ppm. Hence the constitution of the second prenylation product is either 6-C-or 8-C-prenyl galangin. The former alternative (**3a**) was established in two ways: (1) Partial methylation yielded 6-C-prenyl 3,7-dimethoxy 5-hydroxyflavone[6] (**3b**). (2) Acid cyclisation gave a mixture of two compounds as shown by TLC. Two spots appeared with dilute sulphuric acid; whereas only one appeared when the plate was sprayed with alcoholic ferric chloride. The spot with positive ferric reaction was more intense than the one with negative ferric reaction. By column chromatography only the major chroman (**4**) could be isolated. This chroman showed a characteristic pair of triplets at δ 1·86 and 2·91 ($J = 6·5$ Hz) of two methylene groups in its NMR spectrum.

6,8-Di-CC-prenylgalangin (**2a**) when subjected to oxidative cyclisation with one mole of DDQ afforded two products separable by column chromatography followed by fractional crystallisation. The major component (yield 25%) proved to be angular mono-chromene now called isosericetin (**5**). Thus NMR spectrum showed condensed 2,2-dimethylpyran signals (1s, 6H at δ 1·50; 2d, 2H at 5·58, 6·77 ppm, $J = 10$ Hz) and one C-prenyl signals and further the mass spectrum showed fragment ion at *m/e* 348 which is $(M-56)^+$ characteristic of *o*-prenyl phenols.[5] The minor component proved to be isomeric to the major one in molecular ion at *m/e* 404. Hence it is 8-C-prenyl 3,5-dihydroxy 6",6"-dimethyl pyrano (2",3": 7,6) flavone (**6**) which was supported by the lack of $(M-56)^+$ fragment ion and the presence of $(M-55)^+$ fragment ion at *m/e* 349 in its mass spectrum. This substance agrees in mmp, TLC and IR spectrum with the natural sample of sericetin (**6**). Thus it constitutes the first synthesis of sericetin.

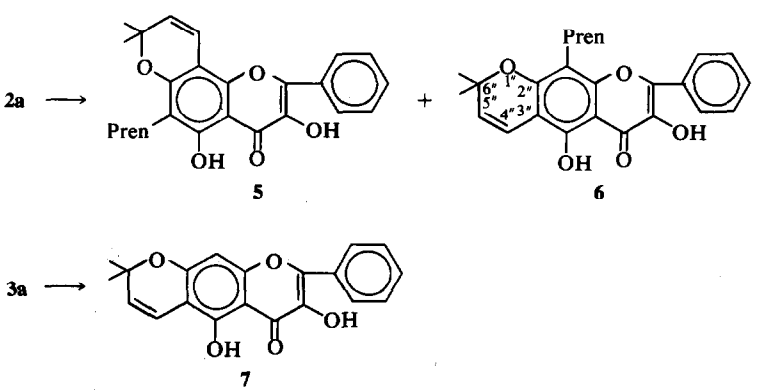
6-C-Prenyl galangin (**3a**) was also cyclised with DDQ when the corresponding chromene (**7**) was obtained. This may be called desprenyl sericetin. Its structure has been confirmed by its NMR spectrum which shows resonance signals of an aromatic proton at position 8 (δ 6·24), and proton of condensed 2,2-dimethyl pyran unit (2 doublets at δ 5·58, 6·76, $J = 10$ Hz and a singlet at δ 1·48 of a gem dimethyl group on a saturated C atom).

EXPERIMENTAL

Unless otherwise stated, all m.ps are uncorrected and were taken with a Büchi M.P. Apparatus; UV spectra were taken in MeOH, figures in parenthesis are log ϵ values; IR spectra were measured using KBr disc and Perkin-Elmer infra-cord spectrophotometer and NMR in $CDCl_3$ using 60 MHz spectrophotometer; mass spectra were determined on samples introduced through the heated inlet system using MS-72 spectrometer, 70 ev ionizing voltage, 900×10 trap current and 2·0 Kv accelerating voltage; light petroleum had boiling range 60–80°; silica gel was used for column chromatography and TLC was carried out on silica gel 'G' chromoplates using solvent systems: (A) benzene, (B) benzene: ethyl acetate (95:5), (C) benzene:ethyl acetate (90:10), (D) benzene:ethyl acetate (75:25); R_f values are those taken on TLC.

Prenylation of galangin (**1**)

A methanolic soln of NaOMe (6·2g Na/75 ml MeOH) was added to a soln of galangin (4·8g) in anhyd MeOH (150 ml). The mixture was cooled, treated with PrBr (8·2 ml) in one lot and refluxed for 3 hr. After removal of the solvent, the mixture was treated with ice and acidified in the cold with dil HCl. The solid product was examined on TLC using solvent system (B) which showed the presence of two major compounds. It was therefore subjected



to column chromatography and the column eluted successively with (i) light petroleum and (ii) benzene giving fractions A and B.

Fraction A crystallised from benzene: light petroleum mixture yielding **2a** as shining yellow needles (0·6g), m.p. 161–62°; R_f 0·8 (solvent A); soluble in Na_2CO_3 aq: green ferric reaction; λ_{max} 272 and 368 nm (4·14 and 3·47); NMR: δ 1·78, 1·83 (2d, J = 2 Hz, 12 H, 2(CH_3)$_2$C=), 3·46, 3·58 (2d, J = 6 Hz, 4H, 2-CH_2—), 5·30 (m, 2H, 2-CH=), 7·49 (m, 3H, 3 aromatic H at positions 3′, 4′ and 5′) and 8·20 ppm (m, 2H, 2 aromatic H at positions 2′ and 6′) (Found: C, 73·6; H, 6·8. $C_{25}H_{26}O_5$ requires: C, 73·9; H, 6·4%). The triacetate prepared by Ac_2O-pyridine method crystallised from EtOAc: light petroleum mixture as white needles, m.p. 149–50°; R_f 0·80 (solvent D); NMR: δ 1·70 (1s, 12H, 2(CH_3)$_2$C=), 2·28, 2·36, 2·46 (3s, 9H, 3-O—CO—CH_3), 3·24, 3·46 (2d, J = 6 Hz, 4H, 2-CH_2—), 5·04 (m, 2H, 2-CH=), 7·45 (m, 3 aromatic H at positions 3′, 4′ and 5′) and 7·75 ppm (m, 2 aromatic H at positions 2′ and 6′) (Found: C, 70·0; H, 6·5. $C_{31}H_{32}O_8$ requires: C, 69·9; H, 6·1%).

Fraction B crystallised from benzene to give **3a** as yellow plates (0·35g), m.p. 224–25°; R_f 0·41 (solvent B); soluble in Na_2CO_3 aq; violet ferric reaction; λ_{max} 212, 358 nm (4·28 and 3·30) (Found: C, 70·7; H, 5·6. $C_{20}H_{18}O_5$ requires: C, 71·0; H, 5·4%). The triacetate prepared by Ac_2O-pyridine method crystallised from EtOAc–light petroleum mixture as white flakes, m.p. 169–70°; R_f 0·30 (solvent C); NMR: δ 1·69 (s, 6H, (CH_3)$_2$C=), 2·26, 2·32, 2·44 (3s, 9H, 3-O–CO–CH_3). 3·53 (d, J = 7 Hz, 2H, —CH_2—), 5·16 (m, 1H, —CH=), 6·84 (s, 1 aromatic H in 8 position), 7·46 (m, 3 aromatic H in 3′, 4′ and 5′ positions) and 7·74 ppm (m, 2 aromatic H in 2′ and 6′ positions) (Found: C, 67·2; H, 5·4. $C_{26}H_{24}O_8$ requires: C, 67·2; H; 5·2%).

6,8-Di-CC-prenyl 3,7-di-O-methylgalangin (**2b**)

A soln of **2a** (100 mg) in acetone (10 ml) was refluxed with Me_2SO_4 (0·05 ml) and K_2CO_3 (500 mg) for 3 hr. Acetone was distilled off and water added to the residue. The solid was purified over column chromatography and crystallised from EtOAc light petroleum mixture as yellow needles (60 mg), m.p. 68–69°; R_f 0·71 (solvent B); green ferric reaction; mmp with authentic sample[6] was undepressed and TLC found identical. Its acetate prepared by Ac_2O-pyridine method crystallised from MeOH as shining white prisms, m.p. 88–89°; R_f 0·40 (solvent B) Found: C, 73·2, H, 7·0. $C_{29}H_{32}O_6$ requires: C, 73·1; H, 6·8%).

6-C-Prenyl-3,7-di-O-methyl galangin (**3b**)

A soln of **3a** (100 mg) in acetone (15 ml) was refluxed with Me_2SO_4 (0·06 ml) and anhyd K_2CO_3 (500 mg) for 3 hr. The product crystallised from EtOAc: light petroleum mixture to afford **3b** as glistening yellow crystals (60 mg), m.p. 105–6°; R_f 0·37 (solvent A); mmp with authentic sample[6] was undepressed and TLC found identical. Its acetate prepared by Ac_2O-pyridine method crystallised from MeOH as white needles, m.p. 138–39°; R_f 0·32 (solvent B) (Found: C, 70·9; H, 6·0. $C_{24}H_{24}O_6$ requires: C, 70·6; H, 5·9%).

3,5-Dihydroxy 6″,6″-dimethyl 4″,5″-dihydropyrano (2″,3″:7,6) flavone (**4**)

6-C-Prenyl galangin **3a** (120 mg) was heated with formic acid (30 ml) for 6 hr and treated with ice. The solid showed two spots on TLC, one showing positive ferric reaction and the other not. The major product obtained by column chromatography by elution with benzene: light petroleum from benzene: light petroleum mixture to give **4** as light yellow needles (75 mg), m.p. 247–48°; R_f 0·5 (solvent A); green ferric reaction: λ_{max} 272 and 358 nm (4·28 and 4·46); NMR: δ 1·39 (s, 6H, (CH_3)$_2$C<), 1·86, 2·91 (2t, J = 6·5 Hz, 4H, 2-CH_2—), 6·24 (s, 1 aromatic H in position 8), 7·45 (m, 3 aromatic H in 3′,4′ and 5′ positions) and 8·12 ppm (m, 2 aromatic H in 2′ and 6′ positions) (Found: C, 71·4; H, 5·7. $C_{20}H_{18}O_5$ requires: C, 71·0: H, 5·4%).

DDQ cyclisation of 6,8-di-CC-prenyl galangin (**2a**)

Formation of sericetin (**6**) *and isosericetin* (**5**). Soln of **2a** (250 mg) in dry benzene (25 ml) was refluxed with DDQ (180 mg) for 30 min. It was filtered hot and the residue washed with benzene. Removal of the solvent from the mother liquor gave a residue which was purified by column chromatography. Elution with light petroleum gave a solid which again proved to be a mixture. Fractional crystallisation with light petroleum (mother liquor A) yielded the sparingly soluble solid which recrystallised from benzene: light petroleum mixture to give **5** as orange yellow prisms (70 mg), m.p. 207–8°; R_f 0·62 (solvent A); light green ferric reaction; λ_{max} 275 and 354 nm (4·50 and 3·81); NMR: δ 1·50 (s, 6H, (CH_3)$_2$C<), 1·75, 1·85 (2s, 6H, (CH_3)$_2$C=), 3·39 (d, J = 6 Hz, 2H, —CH_2), 5·20 (m, 1H, —CH=), 5·58, 6·77 (2d, J = 10 Hz, 2 olefinic H of pyran ring), 7·45 (m, 3 aromatic H in 3′, 4′ and 5′ positions) and 8·16 (m, 2 aromatic H at 2′ and 6′ positions); MS: molecular ion at m/e 404 (67%) and fragment ions at m/e 389 (100%), 361 (25%), 348 (30%), 332 (13%), 105 (23%) and 77 (15%) (Found: C, 74·0; H, 6·4. $C_{25}H_{24}O_5$ requires: C, 74·2; H, 6·0%).

The mother liquor A yielded a solid which after crystallisation twice from MeOH yielded sericetin **6** as pale yellow needles (20 mg); m.p. 150–51°; R_f 0·6 (solvent A); intense green ferric reaction; MS: molecular ion at m/e 404 (75%) and fragment ions at m/e 389 (100%), 361 (21%), 349 (15%), 337 (11%), 105 (30%) and 77 (17%). The mmp with an authentic sample of sericetin was undepressed, TLC was identical and IR spectrum was superimposable with natural sericetin.

3,5-Dihydroxy 6″,6″-dimethyl-pyrano (2″,3″:7,6) flavone

Desprenyl sericetin, **7**. To a soln of **3a** (100 mg) in dry benzene (15 ml) was added DDQ (70 mg) and the resulting mixture refluxed for 10 min. The product was purified by column chromatography. Elution with light petroleum gave **7** which crystallised from benzene: light petroleum mixture as glistening pale yellow needles (50 mg), m.p. 209–10°; R_f 0·47 (solvent A); green ferric reaction; λ_{max} 268 and 341 nm (3·91 and 4·32); NMR: δ 1·48 (s, 6H, (CH_3)$_2$C<), 5·58, 6·76 (2d, J = 10 Hz, 2 olefinic H of the pyran ring), 6·24 (s, 1 aromatic H in position 8), 7·45 (m, 3 aromatic H in positions 3′, 4′ and 5′) and 8·12 ppm (m, 2 aromatic H in position 2′ and 6′) (Found: C, 71·6; H, 5·3. $C_{20}H_{16}O_5$ requires: C, 71·4; H, 4·8%).

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