Indian Journal of Chemistry
Vol. 36B, October 1997, pp. 860-863

Synthesis of novel tetraoxygenated homoisoflavanones

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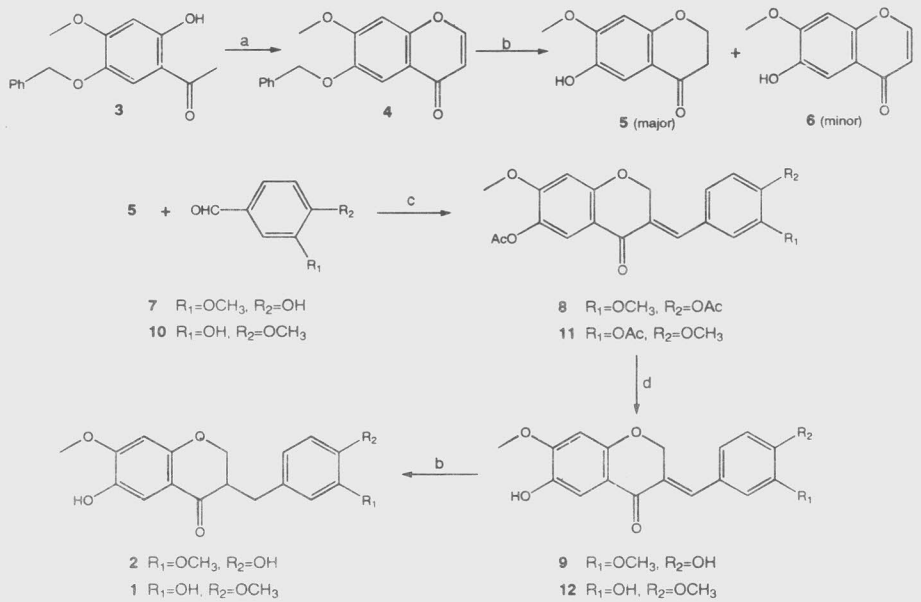
Received 10 June 1997; accepted (revised) 8 September 1997

Two novel isomeric tetraoxygenated homoisoflavanones, 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methylbenzyl) chroman-4-one **1** and 6-hydroxy-7-O-methyl-3-(4-hydroxy-3-O-methylbenzyl) chroman-4-one **2** have been synthesised and the structure of a new homoisoflavanone, reported from *Pterocarpus marsupium* Roxb, has been confirmed as **1** by direct comparison with synthetic samples.

A new homoisoflavanone (pteromarsupone) has been recently isolated by Jain *et al.*[1] from *Pterocarpus marsupium* Roxb. Its structure was proposed as 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methylbenzyl) chroman-4-one **1** based on spectral data. However, there was some ambiguity about the positions of methoxy and hydroxy groups in the benzyl moiety. The NMR of **1** indicated the presence of 3,4-dioxygenation pattern[2]. The methoxy group was fixed at C-4 on the basis of NOE studies and consequently the hydroxy group was placed at C-3. Since there was no direct proof for such assignments, therefore it became necessary to synthesise both the possible isomeric homoisoflavanones **1** and **2** in order to confirm the assigned constitution by direct comparison. Further literature survey revealed that homoisoflavanone bearing 6,7,3',4'-tetraoxygenation pattern is novel and not known. Some of the naturally occurring homoisoflavanones are found to possess antibacterial[3], antimutagenic[4] and antiinflamatory[5,6] activities and are of chemotaxonomic[7] interests also. In view of these facts, we undertook the synthesis of **1** and its isomer 6-hydroxy-7-O-methyl-3-(4-hydroxy-3-O-methylbenzyl) chroman-4-one **2** starting from the intermediate 6-hydroxy-7-O-methyl chroman-4-one **5**, prepared from **4** by hydrogenation. **4** in turn was obtained by reacting 5-O-benzyl- 2-hydroxy-4-O-methyl acetophenone[8] **3** and ethyl formate in presence of pulvarized sodium. The chromanone **5** on condensation separately with vanillin **7** and isovanillin **10** in boiling acetic anhydride gave 6-O-acetyl-7-O-methyl-3-(4-O-acetyl-3-O-methylbenzylidene) chroman-4-one **8** and 6-O-acetyl-7-O-methyl-3-(3-O-acetyl-4-O-methylbenzylidene) chroman-4-one **11** respectively. Saponification of **8** and **11** separately, followed by hydrogenation using calculated amount of H_2/Pd-C in ethyl acetate afforded 6-hydroxy-7-O-methyl-3-(4-hydroxy-3-O-methylbenzyl) chroman-4-one **2** and 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methylbenzyl) chroman-4-one **1** respectively. On direct comparison, the natural sample of pteromarsupone was found to be different from 6-hydroxy-7-O-methyl-3-(4-hydroxy-3-O-methylbenzyl) chroman-4-one **2** but identical (Co-TLC, Co-IR and mmp) with the synthetic sample of 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methylbenzyl) chroman-4-one **1**. Also the ^{1}H NMR and ^{13}C NMR spectras and the mass spectral fragmentation patterns agreed well for both the synthetic and natural samples, thereby confirming the assigned constitution. This is the first report on the synthesis of 6,7,3',4'-tetraoxygenated homoisoflavanones in literature.

Experimental Section

General. All melting points are uncorrected and were determined in a sulphuric acid bath. UV spectra were recorded on Beckman DU-64 spectrophotometer in methanol, IR spectra on Shimadzu model-435 spectrophotometer, ^{1}H NMR spectra on either Brucker or Perkin-Elmer model (300 MHz) (250 MHz), (90 MHz) and (60 MHz) and ^{13}C NMR on Brucker (62.89 or 75.42 MHz) using TMS as internal standard. Chemical shifts



a= HCOOEt/Na; b= H_2/Pd-C/EtOAc; c= Anhydrous Ac_2O; d= NaOH/ MeOH

were quoted in δ ppm and *J* values in Hz. Mass spectra were recorded on a Varian MAT 311A instrument. Silica gel 60-120 mesh was used for column chromatography and TLC was performed using silica gel G.

6-O-Benzyl-7-O-methylchromone 4. A solution of 5-O-benzyl-2-hydroxy-4-O-methyl acetophenone[8] **3** (5.5 g, 19.0 mmol) in dry ethyl formate (120 mL) was added to pulvarized sodium (6.4 g, 278.0 mmol) under dry conditions and the contents stirred for 24 hr. The resulting reaction mixture was then decomposed with ice cold 10% HCl and the ethyl formate from the mixture was evaporated on the steam bath. The oily residue was left, which on cooling gave 6-O-benzyl-7-O-methylchromone **4** as a solid. It was filtered and crystallised from chloroform-petrol as colourless crystals, yield 2.82 g, m.p. 129°, R_f=0.18 (benzene/ethyl acetate, 95:5). IR(KBr): 3020, 1650, 1625, 1605, 1510, 1480, 1455, 1400, 1305, 1270, 1245, 1230, 1180, 1050, 970, 865, 815, 755, 700; ^{1}H NMR ($CDCl_3$): 3.96 (s, 3H, OCH_3), 5.20 (s, 2H, $-CH_2-C_6H_5$), 6.29 (d, *J*=6 Hz, 1H, H-3), 6.87 (s, 1H, H-8), 7.42 (m, 5H, $-C_6H_5$), 7.62 (s, 1H, H-5), 7.80 (d, *J*=6 Hz, H-2); ^{13}C NMR($CDCl_3$): 176.81, 154.98, 154.51, 152.76, 146.76, 136.09, 128.61, 128.15, 127.61, 118.16, 112.39, 106.14, 99.83, 70.95, 58.36, 56.35.

6-Hydroxy-7-O-methylchroman-4-one 5. A solution of **4** (4.0 g, 14.0 mmol) in dry ethyl acetate (50 mL) and palladized charcoal (12.0 g, 10%) was stirred in the atmosphere of hydrogen at rt for 30 min. Absorption of hydrogen was rapid in the beginning but stopped completely at the end of this period. The catalyst was filtered and washed with ethyl acetate. The solvent was removed from the combined filtrate under reduced pressure when **5** along with small amount of 6-hydroxy-7-O-methylchromone **6** was obtained. The separation of these compounds was carried out by column chromatography using silica gel as an adsorbent. Elution of the column with benzene : ethyl acetate (98:2) and (95:5) afforded compound **5** (major) and **6** (minor) respectively.

Compound **5** was crystallised from chloroform-petrol as colourless solid, yield 1.59 g, m.p. 147°, R_f 0.46 (benzene: ethyl acetate, 95:5) (Found: C, 61.15; H, 5.11 $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.15%); IR (KBr): 3000, 2960, 1628, 1550, 1520, 1480, 1450, 1418, 1280, 1180, 1020, 980, 936, 860, 810, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.73 (t, 2H, H-3), 3.91 (s, 3H, OCH_3), 4.48 (t, 2H, H-2), 6.42(s, 1H, H-8), 7.37 (s, 1H, H-5); ^{13}C NMR($CDCl_3$): 190.78, 157.59, 153.61, 140.69, 114.47, 110.47, 99.38, 67.45, 56.16, 37.36.

Compound **6** was also crystallised from chloroform-petrol as colourless needles, yield 0.198 g,

m.p. 208°, R_f 0.24 (benzene: ethyl acetate, 95:5) (Found: C, 62.43; H, 4.19. $C_{10}H_8O_4$ requires C, 62.50; H, 4.17%); ^{1}H NMR(DMSO-d_6): 3.90 (s, 3H, OCH_3), 6.11 (d, J= 6Hz, 1H, H-3), 6.80 (s, 1H, H-8), 7.20 (s, 1H, H-5), 8.0 (d, J=6 Hz, 1H, H-2).

6-O-Acetyl-7-O-methyl-3- (4-O-acetyl-3-O-methylbenzylidene) chroman-4-one 8. A mixture of **5** (1.0 g, 5.2 mmol) and vanillin **7** (1g, 6.6 mmol) in dry acetic anhydride (15 mL) was refluxed for 80 hr. The contents were cooled and diluted with excess of water. The solid that separated was filtered, washed with water and crystallised from chloroform-petrol as light yellow solid, yield 1.02 g, m.p. 185°, R_f 0.41(benzene: ethyl acetate, 90:10). ^{1}H NMR ($CDCl_3$): 2.31 and 2.34 (2s, 6H, 2×$COCH_3$), 3.86 (s, 6H, 2×-OCH_3) 5.34 (d, J=1.8 Hz, 2H, H-2), 6.48 (s, 1H, H-8), 6.85 (d, J_o=9 Hz, 1H, H-5'), 7.11 (m, 2H, H-2' and H-6'), 7.67 (s, 1H, H-5), 7.79 (s, 1H, H-9); ^{13}C NMR($CDCl_3$): 180.10, 169.21, 161.35, 136.30, 122.99, 122.12, 121.15, 113.88, 100.62, 67.84, 56.21, 55.89, 20.57, 20.41; EIMS *m/z* 413 (M^++1), 412(M^+), 371, 370, 330, 329, 328, 327, 194, 168, 167, 165, 163, 162, 161, 147, 123, 91, 83, 69, 59, 43.

6-Hydroxy-7-O-methyl-3- (4-hydroxy-3-O-methylbenzylidene) chroman-4-one 9. Compound **8** (0.5 g, 1.2 mmol) was treated with methanolic NaOH (2.5 mL, 10%) and contents refluxed with stirring for an hour. The solvent was then removed under reduced pressure and water added. The resulting solution was neutralised by dilute HCl and contents extracted with ether. The ether solution was dried over anhyd. magnesium sulphate and inorganic salt filtered. The solvent was distilled off from the filtrate and the residue thus left was crystallised from ethanol to give **9** as yellow solid, yield 0.3 g, m.p. 209°, R_f 0.2 (benzene: ethyl acetate, 90:10). ^{1}H NMR($CDCl_3$): 3.93 and 3.94 (2s, 6H, 2×OCH_3), 5.34 (d, J=1.8 Hz, H-2), 6.45 (s, 1H, H-8), 6.80 (d, J_o=9 Hz, 1H, H-5'), 6.96 (d, J_o=9 Hz, 2H, H-2' and H-6'), 7.51 (s, 1H, H-5), 7.80 (s, 1H, H-9); EIMS *m/z*: 329 (M^++1), 328 (M^+), 297, 168, 167, 166, 163, 162, 148, 147, 123, 119, 99, 77, 69, 65.

6-Hydroxy-7-O-methyl-3- (4-hydroxy-3-O-methylbenzyl) chroman-4-one 2. To a solution of **9** (0.2 g, 0.06 mmol) in dry ethyl acetate (5 mL), palladized charcoal (0.5 g, 10%) was added and contents stirred in atmosphere of hydrogen at rt. The progress of reaction was monitored on TLC. Examination of TLC after 40 min. showed the absence of compound **9** and the presence of a new compound at higher R_f. The reaction was worked up as usual. The residue left was crystallised to give **2** as colourless solid, yield 0.12 g, m.p 195°, R_f 0.44 (benzene: ethyl acetate, 90:10). ^{1}H NMR (DMSO-d_6): 2.49 and 2.93 (2dd, 1H each, H-9), 2.69 (m, 1H, H-3), 3.68 and 3.75 (s, 6H, 2×OCH_3), 4.14 (dd, J = 1.8 Hz, 2H, H-2), 6.39 (s, 1H, H-8), 6.69 (dd, J_m=1.8 Hz and J_o=8.5 Hz, 1H, H-6'), 6.76 (d, J_m = 1.8 Hz, 1H, H-2'), 6.80 (d, J_o = 8.5 Hz, 1H, H-5'), 7.40 (s, 1H, H-5); EIMS *m/z*: 330(M^+), 313, 194, 167, 149, 138, 122, 94, 72, 55, 28.

6-O-Acetyl-7-O-methyl-3- (3-O-acetyl-4-O-methylbenzylidene) chroman-4-one 11. A mixture of **5** (1.0 g, 5.2 mmol) and isovanillin **10** (1g, 6.6 mmol) in the acetic anhydride (15 mL) was refluxed for 80 hr. The contents were cooled and reaction was worked up as in the synthesis of **8** earlier. The residue left was crystallised from chloroform-petrol to give **11** as light yellow solid, yield 1.01 g, m.p. 173-74°, R_f=0.38 (benzene: ethyl acetate, 90:10). ^{1}H NMR($CDCl_3$): 2.20 and 2.25 (2s, 6H, 2×$COCH_3$), 3.80 (s, 6H, 2×OCH_3), 5.32 (s, 2H, H-2), 6.50 (s, 1H, H-8), 6.92 (d, J_o=9 Hz, 1H, H-5'), 7.18 (m, 2H, H-2' and H-6'), 7.71 (s, 1H, H-5), 7.81(s, 1H, H-9); EIMS *m/z*: 412(M^+), 397, 370, 329, 328, 194, 167, 162, 147, 123, 91, 63, 43.

6-Hydroxy-7-O-methyl-3- (3-hydroxy-4-O-methylbenzylidene) chroman-4-one 12 . Compound **11** (0.5 g, 1.2 mmol) was treated with methanolic NaOH (2.5 mL, 10%) and contents refluxed with stirring for an hour. The solvent was removed under reduced pressure and water added. The reaction mixture was worked up as described earlier in the synthesis of **9**. The residue obtained was purified by column chromatography. Elution with benzene/ethyl acetate (90:10) gave yellow mass containing **12** only which could not be crystallised, yield 0.90 g. R_f 0.18 (benzene: ethyl acetate, 90:10); ^{1}H NMR (CD_3COCD_3): 3.90 (s, 6H, 2×OCH_3), 5.43 (s, 2H, H-2), 6.50 (s, 1H, H-8), 6.30 (d, J_o=9 Hz, 1H, H-5'), 7.12 (m, 2H, H-2' and

H-6'), 7.44 (s, 1H, H-5), 7.80 (s, 1H, H-9); EIMS *m/z*: 328(M^+), 313, 298, 297, 167, 162, 147, 123, 119, 102, 91, 69, 65.

6-Hydroxy-7-O-methyl-3- (3-hydroxy-4-O-methylbenzyl) chroman-4-one 1. To a solution of **12** (0.15 g, 0.40 mmol) in ethyl acetate (5 mL), palladized charcoal (0.4 g, 10%) was added and contents stirred in the atmosphere of hydrogen at rt. The progress of reaction mixture was monitored by TLC and the reaction mixture was worked up as usual when it showed the presence of a new compound at a higher R_f value. The crude residue thus obtained was purified by column chromatography to yield **1** as dirty white solid. It was crystallised from chloroform-methanol as colourless needles, yield 0.10 g, m.p. 186-87°, UV(CH_3OH): 276 nm; IR (KBr): 3400, 1640 cm^{-1}; ^1H NMR(CD_3COCD_3): 2.6 and 3.1 (2dd, 1H each, H-9), 2.8 (m, 1H, H-3), 3.8 (s, 6H, 2×OCH_3), 4.1 and 4.4 (2dd, 1H each, H-2), 6.5 (s, 1H, H-8), 6.7 (dd, J=1.8 and 8.1 Hz, 1H, H-6'), 6.7 (d, J_m=1.8 Hz, 1H, H-2'), 6.8 (d, J_o=8.1 Hz, 1H, H-5'), 7.2 (s, 1H, H-5); ^{13}C NMR(CD_3COCD_3): 191.8, 157.2, 152.2, 146.3, 132.0, 120.2, 116.1, 116.0, 112.0, 110.5, 100.0, 70.2, 55.9, 55.7, 47.4, 31.8; EIMS *m/z*: 330(M^+), 313, 194, 193, 167, 149, 138, 137, 122, 94, 72, 55, 28.

Acknowledgement

The authors express their sincere gratitude to UGC and CSIR, New Delhi for financial assistance.

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