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SYNTHESIS OF POLYHYDROXY-FLAVONE METHYLETHERS WITH POTENTIAL CYTOTOXIC ACTIVITY—III

SYNTHESIS OF 5,7-DIHYDROXY 6,2',4',5'-TETRAMETHOXYFLAVONE (TABULARIN) FROM *CHUKRASIA TABULARIS A. JUSS* AND 5,6,7,2',4',5'-HEXAMETHOXYFLAVONE (TABULARIN DIMETHYLETHER)

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Abstract—5,7-dihydroxy 6,2'-4'-5'-tetramethoxyflavone (Tabularin), a naturally occurring flavone from *Chukrasia tabularis A. Juss* (Meliaceae) has been synthesised via the oxidative cyclization of the chalcone followed by removal of the 7-O-benzyl and 5-O-methyl groups in a single step on treatment with boron trichloride under very mild conditions. The dimethylether of tabularin was synthesised by independent route using standard methods. These syntheses prove the structure of tabularin.

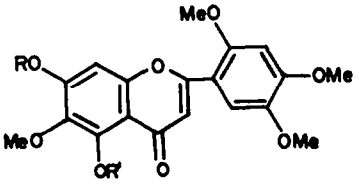
In continuation of our studies towards the synthesis of potentially cytotoxic flavonoids[1] we describe the synthesis of 5,7-dihydroxy 6,2',4',5'-tetramethoxyflavone. Synthesis of several such compounds from a variety of species have already been carried out.[2]

The leaves of *Chukrasia tabularis A. Juss* (Meliaceae) were reported[3] to contain a flavone which was assigned the structure 5,7-dihydroxy-6,2',4',5'-tetramethoxy-flavone 1. This is the third report of a flavone having a 2',4',5'-oxygenation pattern, the other two being oxyayanin A[4] and isoetin.[5] For the sake of convenience we propose the name tabularin for 1. The OMe substitution was determined by benzene induced shifts of the OMe signals in the ^{1}H-NMR spectrum of the compound. Synthesis of this compound as that of its dimethyl ether 2, by different routes, were undertaken, to prove the structure.

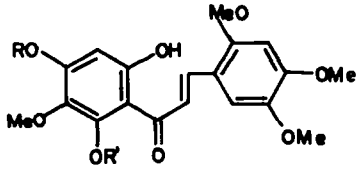
Thus condensation of 2-hydroxy-4-benzyloxy 5,6-dimethoxy-acetophenone[6] with 2,4,5-trimethoxybenzaldehyde[7] under alkaline conditions yielded the chalcone 3. The NMR spectrum of 3 showed signals for olefinic protons at 8.07 ppm (q,2H, J = 16 Hz) and the OH signal at 13.88 ppm (s,1H,OH-2'). Oxidative cyclization of the chalcone with selenium dioxide followed by preparative tlc and crystallisation yielded colourless needles of the flavone 4 giving a negative $FeCl_3$ test in alcohol, m.p. 132-34°. λ_{max} (MeOH) 350 nm, 304 nm and 252 nm. Catalytic debenzylation of the flavone 4 over Pd–C yielded the new 7-hydroxy-5,6,2',4',5'-pentamethoxy flavone 5. The NMR spectrum of this compound indicated the cleavage of the benzyl group at the 7-position. Attempts to obtain the title compound 1 by selective demethylation at position 5 in 5 by boron trichloride was not successful. The failure of the boron trichloride method[8] was probably due to the poor solubility of 5 in the usual solvents. However, treatment of the flavone 4 in dichlormethane with boron trichloride, resulted in the smooth cleavage of both the 7-O-benzyl and 5-O-methyl groups simultaneously to yield the required flavone 1, identical with authentic tabularin in all respects (TLC, m.p., m.m.p., UV, NMR and elemental analysis). To our knowledge this is the first example of simultaneous removal of 7-O-benzyl and 5-O-methyl group under such mild conditions.

The dimethyl ether of tabularin was synthesised by alkaline condensation of 2-hydroxy-4,5,6-trimethoxy-acetophenone with 2,4,5-trimethoxybenzaldehyde to yield the chalcone 6 which was oxidatively cyclized with seleniumdioxide to the flavone 2. The m.p., m.m.p., UV and NMR spectra were indistinguishable from those of authentic dimethyltabularin 2.

1. R=R'=H
2. R=R'=Me
4. R=Bz, R'=Me
5. R=H, R'=Me



3. R=Bz, R'=Me
6. R=R'=Me



EXPERIMENTAL

All m.ps are uncorrected. All NMR spectra were recorded on Varian 60 MHZ with TMS as internal Standard in $CDCl_3$ solutions unless otherwise stated. UV spectra were recorded on Beckmann DK-2A. Preparative TLC done on precoated Kieselgel F_{254} plates (Merck) of 0.5 mm thickness.

2'-Hydroxy-4'-benzyloxy 5',6',2,4,5-pentamethoxy chalcone 3. To a soln of 2,4,5-trimethoxybenzaldehyde (0.33 g) and 2-hydroxy 4-benzyloxy 5,6-dimethoxyacetophenone (0.5 g) in EtOH (100 ml) was added to an alcoholic soln of KOH (20 g) in EtOH (50 ml). The reaction was left overnight. The soln was acidified with cold 20% HCl. The yellow ppt was extracted with EtOAC, washed, dried, evaporated and crystallized from EtOH as red needles (0.23 g) of 3; m.p. 144-46°. IR KBr ν_{max} 1562, 1610 cm^{-1}. NMR δ (ppm) 3.87 (S,3H), 3.92 (S,6H), 3.96 (S,6H), 5.17 (S,2H), 6.39 (S,1H), 6.57 (S,1H), 7.19 (S,1H), 7.42 (broad S,5H), 8.07 (q,2H, J = 16 Hz), 13.88 (S,1H). (Found: C, 67.60; H, 5.83. Calc. for $C_{27}H_{28}O_8$: C, 67.78; H, 5.44%).

7-Benzyloxy-5,6,2',4',5'-pentamethoxyflavone 4. SeO_2 (1 g) was added to a soln of 3 (0.1 g) in isoamyl alcohol (75 ml) and the mixture refluxed for 5 days. The SeO_2 was filtered off and isoamyl alcohol removed by steam distillation. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed, dried and evaporated to leave a dark brown product which was chromatographed on 6 silica plates (20 × 20) which were eluted with 40% EtOAC–C_6H_6 soln. The fluorescent band on extraction with $CHCl_3$ gave colourless needles (0.037 g) from EtOH of 4, m.p. 132-34°. UV (EtOH) λ_{max} (log ϵ) 350 nm (4.29), 304 (4.10), 252 (4.31). NMR δ (ppm) 3.91 (S,9H), 3.97 (S,3H), 4.04 (S,3H), 5.23 (S,2H), 6.62 (S,1H), 6.83 (S,1H), 6.95 (S,1H), 7.37 (S,1H), 7.46 (broad S,5H). (Found: C, 67.29; H, 5.39. Calc. for $C_{27}H_{26}O_8$: C, 67.78, H, 5.44%).

7-Hydroxy-5,6,2',4',5'-pentamethoxyflavone 5. Compound 4 (11 mg) was dissolved in pure MeOH (10 ml) and a pinch of Pd/C catalyst added to the soln. The stirred mixture was kept for 3 hr in an H_2 atmosphere. The catalyst filtered off and 5 crystallised as pale microneedles (6 mg) from MeOH m.p. 220-22°. NMR (DMSO) δ (ppm) 3.85 (S,9H), 3.96 (S,6H), 6.72 (S,1H), 6.87 (S,1H), 7.13 (S,1H), 7.44 (S,1H). (Found: C, 61.57; H, 5.12. Calc. for $C_{20}H_{20}O_8$: C, 61.85. H, 5.15%).

5,7-Dihydroxy 6,2',4',5'-tetramethoxyflavone 1. Compound 4 (25 mg) was dissolved in CH_2Cl_2 and the soln brought to 0°. Excess of BCl_3 soln in CH_2Cl_2 was added and the soln kept at 0° for about 1 hr. After which it was poured into ice cold NaOAc aq. The aqueous phase was extracted with CH_2Cl_2, washed, dried and evaporated and finally crystallized as yellow micro needles of 1 from MeOH (12 mg) m.p. 210-12° (lit.[3] 212-13°). UV (EtOH) λ_{max} (log ϵ) 257 nm (4.20), 272 (4.13), 360 (4.28). NMR δ (ppm) 3.92 (S,6H), 4.0 (S,6H), 6.62 (S,1H), 6.80 (S,1H), 6.94 (S,1H), 7.45 (S,1H), 13.08 (S,1H). (Found: C, 60.87, H, 4.85. Calc. for $C_{19}H_{18}O_8$: C, 60.95, H, 4.8%).

2'-Hydroxy-4',5',6',2,4,5-hexamethoxychalcone 6. To a soln of 2,4,5-trimethoxybenzaldehyde (0.93 g) and 2-hydroxy-4,5,6-trimethoxyacetophenone (0.8 g) in EtOH (50 ml) was added a soln of KOH (30 g) in EtOH (100 ml) and left overnight at room temp. The soln was acidified with 20% ice cold HCl. The yellow ppt was filtered off, washed and crystallised from Me_2CO–Et_2O to give (0.41 g) of orange needles of 9, m.p. 128-30°. IR KBr ν_{max} 1577, 1623 cm^{-1}. NMR δ (ppm) 3.85 (S,6H), 3.93 (S,6H), 3.96 (S,6H), 6.32 (S,1H), 6.57 (S,1H), 7.18 (S,1H), 8.06 (q,2H, J = 16 Hz), 13.93 (S,1H). (Found: C, 62.26, H, 5.68. Calc. for $C_{21}H_{22}O_8$: C, 62.68. H, 5.47%).

5,6,7,2',4',5'-Hexamethoxyflavone 2. SeO_2 (0.1 g) was added to a soln of 6, (0.1 g) in isoamyl alcohol (50 ml). It was refluxed for 3 days. SeO_2 was filtered off and isoamyl alcohol removed by steam distillation to leave a sticky yellow material which was extracted with EtOAC. Evaporation of EtOAC gave a yellow product which was chromatographed on four silica gel plates (20 × 20) using 5% MeOH–$CHCl_3$. Removal of $CHCl_3$ and crystallisation with EtOH gave light pale cubes of 2, m.p. 180-82° (lit.[3] 184°) (15 mg). UV (MeOH) λ_{max} (log ϵ) 350 nm (4.32), 305 (4.11), 252 (4.32). NMR δ (ppm) 3.93 (S,6H), 3.99 (S,6H), 4.01 (S,6H), 6.64 (S,1H), 6.78 (S,1H), 6.98 (S,1H), 7.41 (S,1H). (Found: C, 62.55, H, 5.57. Calc. for $C_{21}H_{22}O_8$: C, 62.68, H, 5.47%).

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