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ACACETIN 7-*O*-β-D-GALACTOPYRANOSIDE FROM *CHRYSANTHEMUM INDICUM*

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Abstract—From the yellow flowers of *Chrysanthemum indicum*, a new flavone glycoside, acacetin 7-*O*-β-D-galactopyranoside was isolated and its structure established from spectral evidence and synthesis.

The chemical investigation of the yellow flowers of *Chrysanthemum indicum* L. (= *Dendranthema indicum* (L.) Desmoulins), which are known to be stomachic and aperient [1], led to the isolation of a new flavone glycoside, acacetin 7-*O*-β-D-galactopyranoside (**1**). In this communication we report on the chemistry and synthesis of this compound.

The colour reactions and spectral properties indicated that **1** is a flavone glycoside. **1**, $C_{22}H_{22}O_{10}$ (M^+ 446), showed UV absorption maxima characteristic of a 5-hydroxyflavone [2] and gave a bathochromic shift with $AlCl_3$. Several structural features could be ascertained from its 80 MHz ^1H NMR spectrum in DMSO-d_6. Thus, it exhibited an A_2B_2 system in the aromatic region at δ 7.96 ($C_{2'}$–H + $C_{6'}$–H) and 7.03 ($C_{3'}$–H + $C_{5'}$–H) (J = 8.0 Hz each) indicating the presence of a *para*-substituted B-ring. The two *meta*-coupled protons at C_6 and C_8 appeared at 6.75 and 6.85 (J = 2.0 Hz each), while the C_3–H resonated as a singlet at 6.38. The other singlet at 3.79 was attributed to the $C_{4'}$–OMe. Gal-H-1 resonated at 5.30 while other galactosyl protons appeared in the region 3.0–3.70. The exchangeable proton signal was observed at 12.78 for C_5–OH.

Acid hydrolysis gave acacetin, 5,7-dihydroxy-4′-methoxyflavone, which was identified from spectral studies. The sugar was characterized as galactose.

The structure of **1** was confirmed by synthesis. Wagner *et al.* [3] previously synthesized it by the coupling of 5,7-dihydroxy-4′-methoxyflavanone (isosakuranetin) and α-acetobromogalactose. We, however, prepared this compound using phloroacetophenone involving a different route. On treatment with anisoyl chloride in the presence of dry C_5H_5N, phloroacetophenone afforded 2,4,6-trianisoylphloroacetophenone which underwent Baker–Venkataraman transformation [4, 5] in powdered KOH and dry C_5H_5N to give the dibenzoylmethane derivative **2**. This, on dehydrocyclization [5] with fused NaOAc in glacial HOAc, gave acacetin. Galactosylation of acacetin was achieved by treatment with pentaacetyl-β-D-galactopyranose in the presence of BF_3/Et_2O at room temperature [7]. The 5-hydroxy-4′-methoxyflavone 7-*O*-β-D-galactopyranoside tetraacetate (**3**) thus produced was deacetylated with methanolic $KHCO_3$ solution to afford **1**. The synthetic compound was identical with the naturally occurring glycoside (co-TLC, mmp, superimposable IR spectra).

EXPERIMENTAL

The plant material was collected from the Indian Botanic Garden, Howrah, W.B., India and verified by Professor P. C. Dutta, Department of Botany, Ballygunge Science College, Calcutta. A voucher specimen has been deposited at the Department of Pure Chemistry, Calcutta University. The mps are uncorr. The UV spectra were measured in MeOH and the NMR spectra were recorded using TMS as internal standard. Column chromatography was carried out with Si gel (Gouri Chemical Works, 60–100 mesh) and TLC with Si gel G (Merck). Appropriate drying agents were used to dry organic solvents and samples were routinely dried over P_2O_5 for 24 hr.

Isolation of acacetin 7-O-β-D-*galactopyranoside* (**1**). On concentrating the EtOH extract of the dry petals of *C. indicum* (1 kg), a pale yellow solid separated out. The hot MeOH soluble fraction of the solid was concd and the residue cryst. × 3 from MeOH–Me_2CO to afford **1** (60 mg), mp 258–260°, R_f 0.56 ($CHCl_3$–MeOH, 3:1); $[\alpha]_D^{25}$ −60° (MeOH); λ_{max}^{MeOH} nm: 269 and 325 (log ε 4.28 and 4.32); + $AlCl_3$: 277, 300 and 343.5 (log ε 4.24, 4.18 and 4.32); ν_{max}^{KBr} cm^{-1}: 3360 (br., −OH), 1650 (flavone >CO), 1600, 1485 (aromatic), 1160 (ether linkage), 820 (*p*-substituted phenyl ring); MS *m/z* (rel. int.): 446 (M^+, 5), 284 (100), 241 (17.2), 152 (12) and 132 (29.3).

Acid hydrolysis of **1**. **1** (40 mg) was heated with 6 N ethanolic HCl (8 ml) for 2 hr on a steam bath to give acacetin (18 mg) and galactose (PC *n*-BuOH–HOAc–H_2O 4:1:2; aniline hydrogen phthalate). Acacetin, R_f 0.67 (MeOH); λ_{max}^{MeOH} nm: 269.5 and 328 (log ε 4.22 and 4.21), $AlCl_3$: 278, 302 and 344 (log ε 4.19, 4.18 and 4.23); + NaOAc: 276 and 362 (log ε 4.37 and 4.08); ν_{max}^{KBr}: 3000 (br), 1670 (flavone >CO), 1600 (aromatic), 1160 (ether linkage) and 820 (*p*-substituted phenyl ring) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 3.80 (3 H, *s*, $C_{4'}$–OMe), 6.12 (1 H, *d*, J = 2 Hz, C_6–H), 6.42 (1 H, *d*, J = 2 Hz, C_8–H), 6.76 (1 H, *s*, C_3–H), 7.02 (2 H, *d*, J = 8 Hz, $C_{3'}$–H + $C_{5'}$–H), 7.93 (2 H, *d*, J = 8 Hz, $C_{2'}$–H + $C_{6'}$–H) and 12.79 (1 H, *s*, exchangeable, C_5–OH).

Synthesis of 2-*hydroxy*-4,6-*anisoyloxy*-4′-*methoxydibenzoylmethane* (**2**). A mixture of phloroacetophenone (1.0 g) (prepared from phloroglucinol and BF_3–HOAc) [6] and anisoyl chloride (3 equiv.) in dry C_5H_5N (8 ml) was heated on a steam bath for 3 hr. The reaction mixture was cooled, treated with cold dil. aq. HCl, extracted with $CHCl_3$, washed with H_2O, dried and concd. The ester thus obtained was a semi-solid product. It was dissolved in dry C_5H_5N (5 ml) and treated with powdered KOH (1.0 g) at 60° with stirring for 2 hr. The reaction mixture was worked up as above. The concd extract was chromatographed over Si gel. The C_6H_6–EtOAc (5:1) eluate afforded the diketone **2**, cryst. as colourless needles (EtOAc–petrol) (700 mg), mp 94–97° (Found: C, 67.32; H, 4.59; $C_{32}H_{26}O_{10}$ requires: C, 67.36; H, 4.56%); ν_{max}^{KBr} cm^{-1}: 2940, 1730 (ester >CO), 1680 (>CO), 1150, 1110 (–C–O–C); ^{1}H NMR ($CDCl_3$): δ 3.75 (< 2 H (for enolization), *s*, $-\overset{\overset{O}{\|}}{C}-CH_2-\overset{\overset{O}{\|}}{C}-$), 3.82 (9 H, *s*, −OMe × 3), 6.86 (6 H, *d*, J = 10 Hz, $C_{3'}$–H + $C_{5'}$–H of three anisoyl units), 8.0 (6 H, *d*, J = 10 Hz, $C_{2'}$–H + $C_{6'}$–H of three anisoyl units), 7.10 (< 1 H, *s* (olefinic proton of the enol form of β-diketone)), 7.15 (2 H, *s*, C_3–H + C_5–H of phloroglucinol nucleus).

Synthesis of 5,7-*dihydroxy*-4′-*methoxyflavone*. The diketone **2** (500 mg) was dissolved in glacial HOAc (20 ml) and refluxed with fused NaOAc (2 g) on an oil bath for 3 hr. The cooled soln was diluted with H_2O and the pptd product purified by column chromatography over Si gel. The C_6H_6–EtOAc (4:1) eluate yielded acacetin, which cryst. from an Me_2CO–petrol mixture as pale yellow needles (110 mg), mp 254–256°. The compound was identical with the natural aglycone (co-TLC, mmp, superimposable IR spectra).

Synthesis of 5-*hydroxy*-4′-*methoxyflavone* 7-O-β-D-*galactopyranoside tetraacetate* (**3**). A mixture of acacetin (1 equiv. 70 mg) and pentaacetyl-β-D-galactopyranose (1 equiv. 80 mg) was dissolved in dry CH_2Cl_2 (20 ml). BF_3/Et_2O (0.2 ml) in dry CH_2Cl_2 (5 ml) was added dropwise at 25° with stirring. The reaction mixture was kept for 24 hr, poured into crushed ice, extracted with $CHCl_3$ (3 × 25 ml), washed with $NaHCO_3$ soln then H_2O and dried. The concd extract was chromatographed over Si gel and the C_6H_6–EtOAc (5:1) eluate furnished **3** (65 mg), mp 189–190° (Found: C, 57.60; H, 4.76. $C_{30}H_{30}O_{14}$ requires: C, 58.47; H, 4.88%), showed positive $FeCl_3$ reaction; ν_{max}^{KBr} cm^{-1}: 1740 (ester >CO), 1640 (flavone >CO), 1600 (aromatic), 1200 (–C–O–C–); ^{1}H NMR ($CDCl_3$): δ 2.0–2.35 (12 H, –COMe × 4), 3.81 (3 H, *s*, $C_{4'}$–OMe), 4.14 (3 H, gal H-5 and H-6 (two)), 5.0–5.35 (4 H, gal H-1, H-2, H-3 and H-4), 6.45 (1 H, *s*, C_3–H), 6.58 (1 H, *d*, J = 2 Hz, C_6–H), 6.90 (1 H, *d*, J = 2 Hz, C_8–H), 6.93 (2 H, *d*, J = 8 Hz, $C_{3'}$–H + $C_{5'}$–H) and 7.72 (2 H, *d*, J = 8 Hz, $C_{2'}$–H + $C_{6'}$–H).

Synthesis of 5-*hydroxy*-4′-*methoxyflavone* 7-O-β-D-*galactopyranoside* (**1**). A soln of **3** (30 mg) and $KHCO_3$ (60 mg) in MeOH (4 ml) and H_2O (1 ml) was kept at room temp. for 20 hr. The ppt. obtained after removal of MeOH *in vacuo* and dilution with H_2O was collected. Crystallization from MeOH gave **1** (12 mg), mp 258–259°.

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