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SYNTHESIS OF (±)-7,3′- AND 7,4′-DI-*O*-METHYLERIODICTYOL AND OF VELUTIN AND PILLOIN

AMOLAK CHAND JAIN and BHOLA NATH SHARMA
Department of Chemistry, University of Jammu, Jammu-1, India

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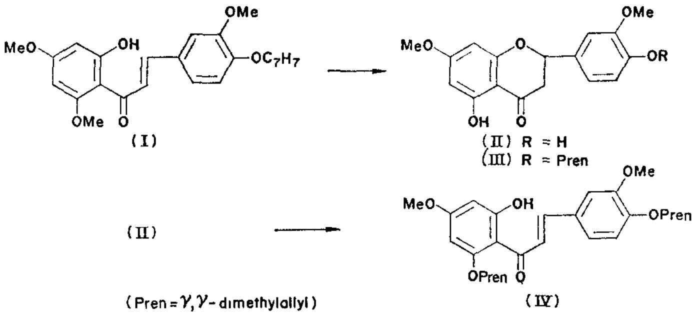
Key Word Index—Flavanone and flavone syntheses; structures of velutin and pilloin.

Abstract—Synthetic 2′-hydroxy-3,4′,6′-trimethoxy-4-benzyloxychalcone (I) affords (±)-7,3′-di-*O*-methyleriodictyol (II) and 7,3′-di-*O*-methylluteolin (or velutin, VII) identical with natural samples. Similarly synthetic 2′-hydroxy-4,4′,6′-trimethoxy-3-benzyloxychalcone (X) gives natural (±)-7,4′-di-*O*-methyleriodictyol (XI) and 7,4′-di-*O*-methylluteolin (or pilloin, IX). However, attempts to partially etherify II with one mole of prenyl bromide to obtain the natural prenyl ether failed; only the corresponding diprenyloxychalcone (IV) was obtained.

FROM THE bark of *Melicope sarcococca* Laut. (Rutaceae), two optically active flavanones, viz. (—)-7,3′-di-*O*-methyleriodictyol (II) and its 4′-prenylether (III) were isolated by Geissman.[1] The structure of the former compound was established by analytical data, colour reactions, UV shifts in alkali, non-identity with the known[2] 7,4′-di-*O*-methyleriodictyol (XI), formed by partial methylation of hesperetin (4′-*O*-methyleriodictyol), and finally by dehydrogenation to a flavone (7,3′-di-*O*-methyl-luteolin) which was different from 7,4′-di-*O*-methyl-luteolin formed by dehydrogenation of 7-*O*-methylhesperetin.[2] The nature and location of the prenyl residue in III was established by smooth deprenylation with a trace of mineral acid to 7,3′-di-*O*-methyleriodictyol, chromic acid oxidation and positive ferric reaction. However, no synthetic evidence for these structures was obtained; hence their syntheses were projected.



2′-Hydroxy-3,4′,6′-trimethoxy-4-benzyloxychalcone[3] (I) with HBr/HOAc gave 7,3′-di-*O*-methyleriodictyol (II) in nearly 30% yield. The flavanone structure was established by its NMR spectrum which showed methine and methylene protons of the oxygen heterocylic

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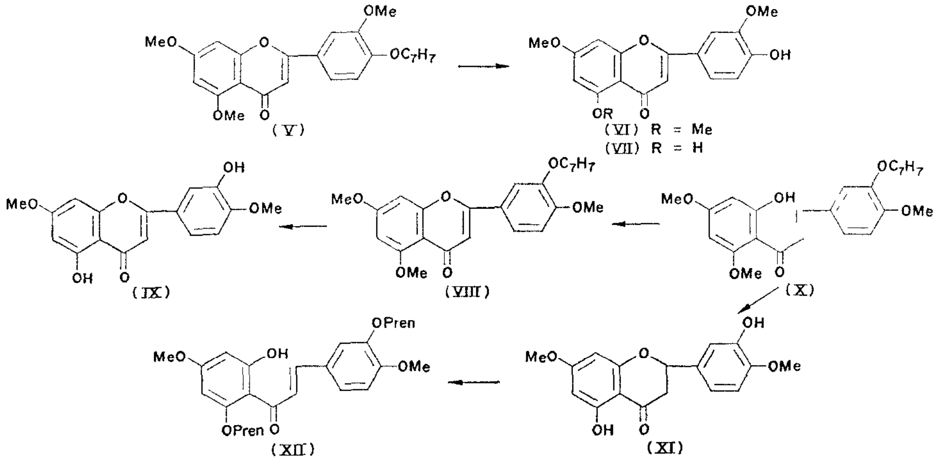
[1] GEISSMAN, T. A. (1958) *Australian J. Chem.* **11**, 376.
[2] GUPTA, S. R., NARASHIMHACHARI, N. and SESHADRI, T. R. (1953) *J. Sci. Ind. Res.* **12B**, 229.
[3] NORDSTRÖM, C. G. and SWAIN, T. (1953) *J. Chem. Soc.* 2764.

ring at δ 5·26 ppm as a quartet ($J = 5{\cdot}5$ Hz) and at δ 2·80 ppm as a doublet ($J = 5{\cdot}5$ Hz) respectively. This compound agrees in m.p. with the racemized product of natural 7,3′-di-*O*-methyleriodictyol (II). It readily gave a 4′-monoacetate as shown by one singlet at δ 2·26 ppm of $O\text{–}CO\text{–}C\underline{H}_3$ group in its NMR spectrum and positive ferric reaction.

The above synthetic 7,3′-di-*O*-methyleriodictyol was etherified with one mole of prenyl bromide in the presence of K_2CO_3 and acetone.[4] However, only 2′-hydroxy 3,4′-dimethoxy-4,6′-diprenyloxychalcone (IV) was obtained as shown by analysis and NMR spectrum (see Experimental). Obviously, the flavanone ring opens and two hydroxy groups in the resulting chalcone are prenylated and one remains free due to chelation. An attempt to avoid ring opening by the use of dry benzene instead of acetone, gave a complex mixture of products. Thus III could not be synthesized.



Recently, a new flavone velutin was isolated by Das *et al.*[5] from the leaves of *Ceanothus velutinus* (Rhamnaceae). Available chemical and spectral data led them to postulate two alternative structures, 7,3′-di-*O*-methyl-(VII) or 7,4′-di-*O*-methylluteolin (IX). Since velutin agreed in m.p. with the dehydrogenation product of 7,3′-di-*O*-methyleriodictyol (II), it was considered to be 7,3′-di-*O*-methylluteolin (VII). However, 7,4′-di-*O*-methylluteolin,[2,6] is recorded to melt very close to 7,3′-di-*O*-methylluteolin. Hence a direct comparison of synthetic and natural samples is necessary. Further, the structure of 7,4′-di-*O*-methylluteolin (IX) was recently given to the compound pilloin isolated from a South Chilean plant *Ovidia pillo-pillo* Meisner[7] (Thymelaeaceae) and *Alnus japonica*.[8] Here also a direct comparison with the synthetic sample was not made. Hence, the synthesis of the isomers (VII) and (IX) has now been carried out.

7,3′-Di-*O*-methylluteolin (VII) was synthesized from 5,7,3′-trimethoxy-4′-benzyloxyflavone[3] (V) by debenzylation with HCl in HOAc and partial demethylation of the resulting product (VI) with HBr in HOAc. This synthetic sample was found to be completely identical with natural velutin (mixed m.p., TLC, UV and IR spectra, and acetates). Hence this establishes the structure of velutin unambiguously as VII.

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[4] Seshadri, T. R. and Vishwa, Paul (1970) *Indian J. Chem.* **8**, 1041.

[5] Das, K. C., Farmer, W. J. and Weinstein, B. (1970) *J. Org. Chem.* **35**, 3989.

[6] Perkin, A. G. and Horsfall, L. H. (1900) *J. Chem. Soc.* **77**, 1314.

[7] Nunez-Alarcon, J. (1971) *J. Org. Chem.* **36**, 3829.

[8] Wollenweber, E. and Wassum, M. (1972) *Tetrahedron Letters* 797.

7,4′-Di-*O*-methylluteolin (IX) was similarly made by debenzylation and partial demethylation of 5,7,4′-trimethoxy-3′-benzyloxyflavone[3] (VIII) in one step. The structure of the resulting compound was established by the NMR spectrum of its diacetate which showed 2 singlets at δ 2·35 and 2·42 ppm of two acetoxyl groups, and 1 singlet at δ 6·47 ppm of 1 hydrogen atom in position 3. The synthetic 7,4′-di-*O*-methylluteolin (IX) agrees completely with natural pilloin in m.m.p., TLC, UV and IR spectra. However, the m.p. (237–41°) of the natural sample of the German workers[8] is slightly higher than ours (236°).

7,4′-Di-*O*-methyleriodictyol (XI) was isolated from the bark of peach tree (*Prunus persica* L.) by Christiansen and Boll[9] and was compared directly with the sample prepared from hesperetin by the method of Gupta *et al.*[2] This has now been synthesized from 2′-hydroxy-4,4′,6′-trimethoxy-3-benzyloxychalcone (X) by treatment with HBr in HOAc. The structure of the product as (XI) was established by its NMR spectrum and that of its 3′-acetate. The latter shows a quartet of methine at δ 5·44 ppm, a doublet of methylene at δ 2·96 ppm ($J = 5$ Hz) and a singlet of one acetoxyl group at δ 2·38 ppm.

Attempts to prepare 3′-prenyl ether of (XI) again failed and the product isolated was 2′-hydroxy-4,4′-dimethoxy-3,6′-diprenyloxychalcone (XII), as established by its positive ferric reaction and NMR spectrum (see Experimental).

EXPERIMENTAL

Unless otherwise stated, mps are uncorrected; UV data are in EtOH: IR spectra are measured using KBr disc; NMR spectra are those recorded with a 60 Mc spectrometer in $CDCl_3$ solution; light petrol. had b.p. 60–80°; silica gel was used for column chromatography and TLC was carried out on silica gel G plates using (A) C_6H_6–EtOAc (3:1) and (B) C_6H_5Me–HCO_2Et–HCO_2H (5:4:1) and either, (a) alcoholic $FeCl_3$, or (b) dil. H_2SO_4 as spraying reagent.

(±)-7,3′-*Di-O-methyleriodictyol* (II). 2′-Hydroxy-3,4′,6′-trimethoxy-4-benzyloxychalcone (I) was prepared according to procedure of Nordström *et al.*[3]; m.p. 136°; R_f 0·85 (solvent A), NMR. δ 3·75, 3·84 and 3·88 (3*s*, 9H, 3-OC$\underline{H}_3$), 5·14 (*s*, 2H, O–C$\underline{H}_2$), 5·88 and 6·03 (2*d*, *J* 3 Hz, 2 *meta* coupled aromatic H at 3′ and 5′ positions), 6·81 (*d*, *J* 8·5 Hz, 1 H in 5 position), 7·05 (*q*, *J* 8 and 2 Hz, 1H in 6 position), 7·25 (*d*, *J* 2 Hz, 1 H in 2 position), 7·34 (*s*, 5 H of phenyl) and δ 7·67 ppm (*s*, 2 olefinic H in α- and β-positions). I (3 g) was refluxed with HBr–HOAc (50 ml) for 3 hr, cooled and added to ice-cold water. The resulting viscous mass was steam-distilled to remove benzyl bromide, dried and subjected to column chromatography. Elution with C_6H_6–EtOAc (49:1), gave 7,3′-di-*O*-methyleriodictyol (II) as needles (1 g), m.p. 149° (lit.[1] m.p. 148–9°): purple–red colour with Mg–HCl (alc.); brown ferric reaction; purplish–blue colour with conc. HNO_3; R_f 0·60 (solvent A); NMR δ 2·80 (*d*, *J* 5·5 Hz, 2 H, –C$\underline{H}_2$– in 3 position), 3·75 and 3·85 (2*s*, 6H, 2–OC$\underline{H}_3$), 5·26 (*q*, *J* 5·5 Hz, 1H, –C$\underline{H}$< in 2 position), 6·0 (1*s*, 2 aromatic *meta* coupled H in 6 and 8 positions) and δ 6·87 ppm (m, 3 aromatic H in 2′,5′ and 6′ positions). (Found: C, 64·6; H, 4·7. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%). The 4′-monoacetate crystallized from MeOH as prisms, m.p. 146°; R_f 0·80 (solvent *A*); reddish–brown ferric reaction; NMR: δ 2·26 (*s*, 3H, 1–O.CO.C$\underline{H}_3$), 2·80 (*d*, *J* 5 Hz, 2H, –C$\underline{H}_2$ in 3 position), 3·73 and 3·82 (2*s*, 6H, 2-OC$\underline{H}_3$), 5·27 (*q*, *J* 6 Hz, 1H, –C$\underline{H}$< in 2 position), 6·0 (1*s*, 2 aromatic *meta* coupled H in 6 and 8 positions) and δ 7·0 ppm (*m*, 3 aromatic H in 2′, 5′ and 6′ positions). (Found: C, 63·4; H, 5·5. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·1%).

O-*Prenylation of* (±)-7,3′-*di*-O-*methyleriodictyol.* A solution of 7,3′-di-*O*-methyleriodictyol (II, 300 mg) in acetone (30 ml) was refluxed with prenyl bromide (0·1 ml) and K_2CO_3 (1·5 g) for 3 hr. The product crystallized from C_6H_6–light petrol, when diprenyloxychalcone (IV) was obtained as yellow needles (150 mg), m.p. 118–9°; brown ferric reaction: R_f 0·85 (solvent *A*); NMR. δ 1·70 (*s*, 12H, 2(C$\underline{H}_3$)$_2$ C=), 3·80 and 3·88 (2*s*, 6H, 2-OC$\underline{H}_3$), 4·58 (*m*, 4H, 2-OC$\underline{H}_2$), 5·46 (*m*, 2H, 2-C$\underline{H}$ <), 5·92 and 6·08 (*d*, *J* 3 Hz, 2 aromatic *meta* coupled H in 3′ and 5′ positions), 6·92 (*m*, 3 aromatic H in 2, 5 and 6 positions) and δ 7·83 ppm (*d*, *J* 4 Hz, 2 olefinic H in α- and β-positions). (Found: C, 71·3; H, 7·5 $C_{27}H_{32}O_6$ requires: C, 71·7; H, 7·1%).

5,7,3′-*Tri*-O-*methyl-luteolin* (VI). 5,7,3′-Trimethoxy-4′-benzyloxyflavone (V) was first prepared from 2′-hydroxy-3,4′,6′-trimethoxy-4-benzyloxy chalcone (I, 5 g) by oxidation with SeO_2 (5 g) in amyl alcohol (50 ml).[3] However, the product on working up was always found to contain selenium. Hence it was extracted 4 × with CS_2 (20 ml) and the remaining solid subjected to column chromatography. Elution with C_6H_6–MeOH (19:1) gave 5,7,3′-trimethoxy-4′-benzyloxyflavone (V) as light yellow needles (3 g), m p. 208° (lit.[3]

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[9] Christiansen, K. and Boll, P. M. (1966) *Tetrahedron Letters* 1293.

208–9°); R_f 0·56 (solvent B); NMR. δ 3·90; 3·92 and 3·94 (3*s*, 9H, 3-OC$\underline{H}_3$), 5·20 (*s*, 2H, -OC$\underline{H}_2$), 6·39 and 6·58 (2*d*, *J* 3 Hz, 2 aromatic *meta* coupled H in 6 and 8 positions), 7·05 (*s*, 1H in 3 position), 7·30 (1*s*, 5H of phenyl) and δ 7·50 ppm (m, aromatic H in 2′,5′ and 6′ positions). The above flavone (V, 1 g) was refluxed with HCl (10 ml) and HOAc (14 ml) at 130° for 3 hr and the product crystallized from MeOH when 5,7,3′-tri-*O*-methyl-luteolin (VI) was obtained as light yellow needles (0·7 g), m.p. 224° (lit[3] 223–4°); negative ferric reaction; R_f 0·50 (solvent *B*); NMR in d$_6$-DMSO. δ 3·75 (*s*, 9H, 3-OC$\underline{H}_3$), 6·38 and 6·72 (2*d*, *J* 3 Hz, 2 *meta* coupled aromatic H at 6 and 8 positions), 6·52 (*s*, 1H in 3 position), 6·82 (*d*, *J* 8·5 Hz, 1 aromatic H at 5′ position), 7·40 (*m*, 2 aromatic H at 2′ and 6′ positions).

7,3′-*Di*-O-*methyl-luteolin* (*velutin*, *VII*). The above flavone (VI, 0·7 g) was refluxed with HBr–HOAc (14 ml) at 115–6° for 2 hr. 7,3′-Di-*O*-methylluteolin crystallized from EtOAc as yellow crystals (0·5 g), m.p. 225° (lit.[5] 225–7°); brown with alc. FeCl$_3$; R_f 0·46 (solvent *B*); λ_{max} 252, 270 and 348 nm (log ε 4·19, 4·15 and 4·29); λ_{max} in EtOH–NaOEt 400 nm (log ε 4·34); ν_{max} 3440 (OH), 1660 cm^{-1} (C=O) (Found C, 65·4; H, 5·0; $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). This sample is completely identical with velutin[5] in m.p., m.m.p., TLC, UV and IR. Further their diacetates agreed in m.p. (207°).

7,4′-*Di*-O-*methyl-luteolin* (*Pilloin*, IX). 2′-Hydroxy-4,4′,6′-trimethoxy 3-benzyloxychalcone (X) was first prepared according to the procedure of Nordstrom and Swain,[3] m.p. 107° (lit.[3] 106–7°); R_f 0·80 (solvent *A*); NMR: δ 3·80 and 3·89 (2*s*, 9H, 3OC$\underline{H}_3$), 5·17 (*s*, 2H–OC$\underline{H}_2$), 5·92 and 6·09 (*d*, *J* 3 Hz, 2 *meta* coupled aromatic H at 3′ and 5′ positions), 6·9 (*d*, *J* 8·5 Hz, 1H in 5 position), 7·17 (*m*, 2 aromatic H in 2 and 6 positions), 7·30 (*s*, 5H of phenyl) and δ 7·67 ppm (*s*, 2 olefinic H in α- and β-positions). This chalcone (5 g) was oxidized with SeO$_2$ according to the earlier procedure[3] and the product was purified by chromatography. Elution with C$_6$H$_6$–EtOAc (3:2) gave 5,7,4′-trimethoxy-3′-benzyloxyflavone (VIII) as needles (3 g), m.p. 190° (lit[3] 190–1°), R_f 0·50 (solvent *B*), NMR: δ 3·93 and 3·96 (2*s*, 9H, 3-OC$\underline{H}_3$), 5·26 (*s*, 2H, –OC$\underline{H}_2$), 6·39 and 6·55 (2*d*, *J* 3 Hz 2 *meta* coupled aromatic H in 6 and 8 positions), 6·51 (1*s*, 1H in 3 position), 7·01 (*d*, *J* 8 Hz, 1H in 5′ position), 7·34 (1*s*, 5H of phenyl), 7·50 (*q*, *J* 8 and 2 Hz, 1H in 6′ position) and 7·62 (*d*, *J* 2 Hz, 1 H in 2′ position). The above flavone (VIII, 1 g) was refluxed with HCl (10 ml) and HOAc (14 ml) at 130° for 5 hr. The product crystallized from EtOAc to give 7,4′-di-*O*-methylluteolin (IX) as deep yellow needles (0·6 g), m.p. 236°, brown ferric reaction; R_f 0·42 (solvent *B*), λ_{max} 254, 270 and 342 nm (log ε 4·2, 4·3, 4·3), ν_{max} 3300 (OH), 1660 cm^{-1} (C=O) (Found: C, 64·8, H, 4·5, Calc. for $C_{17}H_{14}O_6$ C, 65·0, H, 4·5%) This product is identical with pilloin in m.p. (lit.[7] 235·5–6·5°), m.m.p., TLC, UV and IR. The m.p. of the German sample[8] is 237–41°. The diacetate crystallized from EtOAc light petroleum as crystals, m.p. 185° (lit.[6] 182°), R_f 0·35 (solvent *B*) NMR. δ 2·35 and 2·42 (2*s*, 6H, 2-O–CO–C$\underline{H}_3$), 3·88 (*s*, 6H, 2-OC$\underline{H}_3$), 6·47 (*s*, 1H in 3 position), 6·58 and 6·80 (2*d*, *J* 3 Hz, 2 *meta* coupled aromatic H in 6 and 8 positions), 7·0 (*d*, *J* 8·5 Hz, 1H at 5′ position), 7·52 (*q*, *J* 8·5 and 2 Hz, 1H at 6′ position), 7·67 (*d*, *J* 2 Hz, 1H at 2′ position).

(±)-7,4′-*Di*-O-*methyleriodictyol* (XI) The chalcone (X, 3 g) was refluxed with HBr in HOAc The product on column chromatography and elution by C$_6$H$_6$ gave (±)-7,4′-di-*O*-methyleriodictyol (XI) as crystals, m.p. 160° (lit.[9] 163–4°), red–purple colour with Mg–HCl (alcohol); reddish–brown ferric reaction; purplish-blue colour with conc. HNO$_3$; R_f 0·64 (solvent *A*); NMR: δ 2·85 (*d*, *J* 5 Hz, 2H, –C$\underline{H}_2$ in 3 position), 3·79 and 3·90 (2*s*, 6H, 2-OC$\underline{H}_3$), 5·33 (*q*, *J* 6 Hz, 1H, –CH< in 2 position); 6·05 (1*s*, 2 aromatic *meta* coupled H at 6 and 8 positions) and δ 6·95 ppm (*m*, 3H, 3 aromatic H in 2′, 5′ and 6′ positions) (Found. C, 64·6, H, 5·4 Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%). 3′-Monoacetate crystallized from EtOAc—light petrol as needles, m.p. 150°, brown ferric reaction; R_f 0·84 (solvent *A*); NMR: δ 2·38 (*s*, 3H, 1-O-CO C$\underline{H}_3$), 2·96 (*d*, *J* 5·5 Hz, 2H, –C$\underline{H}_2$ in 3 position), 3·88 and 3·94 (2*s*, 6H, 2-OC$\underline{H}_3$), 5·95 (*q*, *J* 5·5 Hz, 1H, –C$\underline{H}$< in 2 position), 6·12 (1*s*, 2H, 2 *meta* coupled aromatic H in 6 and 8 positions) and δ 7·10 ppm (*m*, 3H, 3 aromatic H in 2′, 5′ and 6′ positions) (Found: C, 63·9; H, 5·2. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·1%).

2′-*Hydroxy*-4,4′-*dimethoxy*-3,6′-*diprenyloxychalcone* (XII) A solution of the above flavanone (XI, 300 mg) in acetone (30 ml) was refluxed with prenyl bromide (0·1 ml) and K$_2$CO$_3$ (1·5 g) for 3 hr The product when crystallized from C$_6$H$_6$–light petrol. afforded 2′-hydroxy-4,4′-dimethoxy-3,6′-diprenyloxychalcone (XII) as yellow needles (150 mg), m.p. 130°, dark brown with FeCl$_3$; R_f 0·88 (solvent *A*); NMR: δ 1·78 (1*s*, 12H, 2(C$\underline{H}_3$)$_2$C=), 3·82 and 3·90 (2*s*, 6H, 2-OC$\underline{H}_3$), 4·60 (*m*, 4H, 2-OC$\underline{H}_2$), 5·56 (*m*, 2H, 2-C$\underline{H}$=), 5·95 and 6·08 (*d*, *J* 3 Hz, 2 *meta* coupled aromatic H in 3′ and 5′ positions); 7·00 (*m*, 3 aromatic H in 2, 5 and 6 positions) and 7·80 ppm (*d*, *J* 4 Hz, 2 olefinic H in α- and β-positions) (Found: C, 71·4; H, 7·0 $C_{27}H_{32}O_6$ requires: C, 71·7, H, 7·1%)

Acknowledgements—The authors thank Drs. B. Weinstein and J. Nunez-Alarcon for supplying natural samples of velutin and pilloin respectively.