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ABOUT THE EXISTENCE OF PADMAKASTEIN AND PADMAKASTIN

THE SYNTHESIS OF 4',5-DIHYDROXY-7-METHOXYISOFLAVANONE AND ITS 4'-GLUCOSIDE

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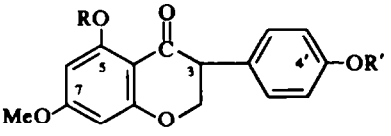
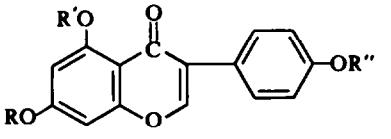
Abstract—The title compounds have been prepared by hydrogenation of the corresponding isoflavones and found to differ from padmakastein and padmakastin, isolated, from *Prunus puddum* and reported as 4',5-dihydroxy-7-methoxyisoflavanone and its 4'-glucoside.

THE isolation of the first natural isoflavanone padmakastein (1) and its glucoside, padmakastin (2) from the bark of *Prunus puddum* was reported in 1952 by Narasimhachari and Seshadri.[1] Evidence supporting the saturated nature of the pyrone ring was based on dehydrogenation and hydrogenation experiments performed on the aglycone (1). Dehydrogenation of padmakastein was reported to afford the corresponding isoflavone, prunetin (3), another constituent of *Prunus puddum* and products of the reduction of prunetin and its derivatives with sodium metabisulphite were identified with padmakastein and its derivatives. Though these results were later revised,[2] as only partial reduction had been affected by sodium metabisulphite, nevertheless the same correspondence with samples prepared by catalytic reduction of prunetin was maintained.



1: R = R' = H
2: R = H, R' = β-D-glucosyl
7: R = R' = Ac
8: R = H, R' = Me
9: R = Ac, R' = tetraacetyl-β-D-glucosyl



3: R = Me, R' = R'' = H
4: R = Me, R' = H
R'' = β D-glucosyl
5: R = R' = H, R'' = β-D-glucosyl
6: R = H, R' = Ac, R'' = tetraacetyl-β-D-glucosyl
11: R = Me, R' = R'' = Ac

The configuration of the chiral centre at C_3 was not elucidated in the original papers and thus natural padmakastin could be the glucoside of one of the enantiomers or a mixture of the two. In order to clear this ambiguity we undertook the synthesis of padmakastin.

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As no method for the resolution of isoflavanones has been elaborated, it was of interest to reduce the corresponding isoflavone glucoside prunitrin (4) and separate the mixture of diastereomers. For this purpose a synthesis of 4 had to be devised. One of the authors prepared prunitrin[3] by partial methylation of sophoricoside (5), the 4'-glucoside of genisteine, easily extractable from the fruits of *Sophora japonica*.[4] This method, however, suffered from the difficulty of purification due to small amounts of overmethylated products. Consequently, the pentaacetate of sophoricoside (6) bearing a single free OH at C_7 was methylated with diazomethane to yield directly the easily crystallizable pentaacetate of prunitrin. Sophoricoside pentaacetate (6) can be readily prepared by treating the hexaacetate[5] briefly at 60° with one equivalent of dilute sodium methoxide. The structure of the pentaacetate was supported by the negative ferric chloride reaction, diagnostic for a blocked C_5—OH, and its NMR spectrum indicating five acetoxy groups. Saponification of 6 gave in good yield pure free prunitrin.

As glycoside acetates, as a rule, can be more easily purified than the corresponding free glycosides, prunitrin pentaacetate was hydrogenated in acetic acid at room temperature with Pd–C until the uptake of one equivalent of hydrogen was complete. Before starting the tedious separation of diastereomers the product was saponified and hydrolysed to yield a product, m.p. 146–147°, clearly different from padmakastein (m.p. 238–240°). The same low melting substance was obtained by the direct hydrogenation of prunetin (3). The diacetate of our compound, prepared on the one hand by acetylation of the foregoing product and on the other by reduction of prunetin diacetate differed from padmakastein diacetate. A similar situation was encountered with the 4'-O-monomethyl ether obtained by two different methods. Consequently, the NMR spectra of our products was examined.

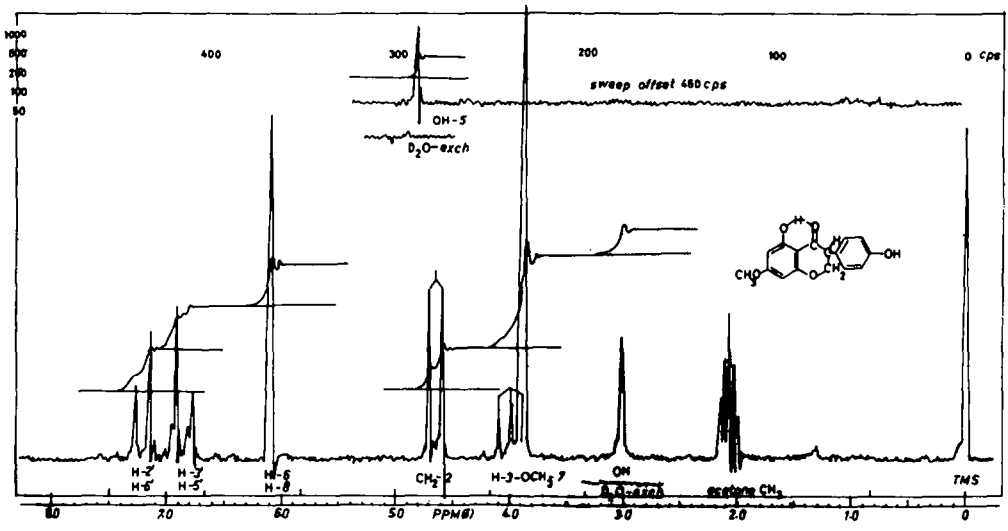
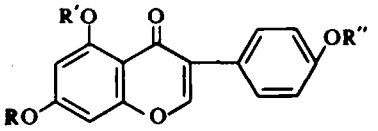
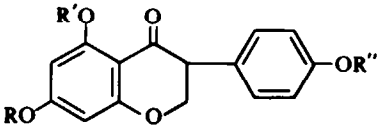


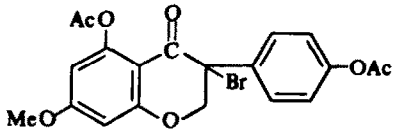
FIG. 1 NMR spectrum of 4',5-dihydroxy-7-methoxyisoflavanone.

TABLE 1

R	R′	R″	Literature data[1,2]		
CH_3	H	Gluc.	**Padmakastin**	225–230°	235–236°	115–117°
CH_3	H	H	**Padmakastein**	238–240°	239–240°[3]	146–147°
CH_3	Ac	Ac	Padmakastein diacetate	220–222°	226–227°[3]	184–185°
CH_3	H	CH_3	Padmakastein methyl ether	131–132°	138–139°	124–126°
CH_3	CH_3	CH_3	Padmakastein dimethyl ether	146–147°	160–163°[10]	156–157°[8]
H	H	H	Nor-padmakastein	270–272°	290°[10]	215–217°[9]

In the spectrum of hydrogenated prunitrin, the characteristic low field C_2—H singlet of isoflavones (7·80 ppm in prunitrin) has disappeared and instead a 2-proton doublet (J = 7 c/s), centered at δ = 4·67 and a one-proton triplet (J = 7 c/s), partly obscured by the OMe peak centered at δ = 4·00 can be observed. Since the same characteristic A_2X system is found in the spectrum of the hydrogenated prunetin diacetate and prunitrin pentaacetate, and there is no other significant change in the spectrum, the only possible structures to assign to our products are the isoflavanone structures **1**, **7**, **8** and **9** respectively.*

These structures are further supported by the conversion of the diacetate **7** to the monobromo product **10** by treatment with N-bromosuccinimide and subsequent dehydrobromination, giving prunetin diacetate (**11**). In the bromo compound, the X-part of the three proton system has disappeared and the A_2-part has given rise to a geminal AB system (J = 12 c/s).



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Thus padmakastein and its glucoside cannot be represented by formulae **1** and **2** resp.† When the hydrogenation experiments of Ramanujan *et al.*[2] were repeated, only unchanged starting material could be isolated from the reaction mixture. Examination of Table 1 reveals the close similarity between the m.ps of the prunitrin and padmakastein series suggesting, that padmakastin and padmakastein could be impure samples of the corresponding isoflavones.

In spite of these results, the separation of the diastereomeric glucosides was still of interest, as in this way we hoped to affect the resolution of racemic **1**. For this purpose the glucoside acetate **9** was recrystallized several times. The ORD curve of the constant melting product shows a negative Cotton effect. Compared with the sign of the Cotton effect of sophorol,[7] an isoflavanone of known absolute configuration, the chirality of the C_3 is R. Alkaline saponification afforded the free glucoside, which shows only a plain ORD curve, indicating complete racemization of the aglycone part during this procedure. Fractionation of the diastereomeric mixture of the free glucoside (**2**) was ineffective. After recrystallization no Cotton effect was observed for the glucoside nor for the aglycone prepared by enzymic hydrolysis.

* Private communication of T. R. Seshadri: Natural padmakastin and padmakastein are no longer available and attempts to reisolate the compounds failed.

† Apparently these same products (**1** and **2**) were obtained previously by Szabó,[6] but the discrepancy with the natural compounds had not been clarified.

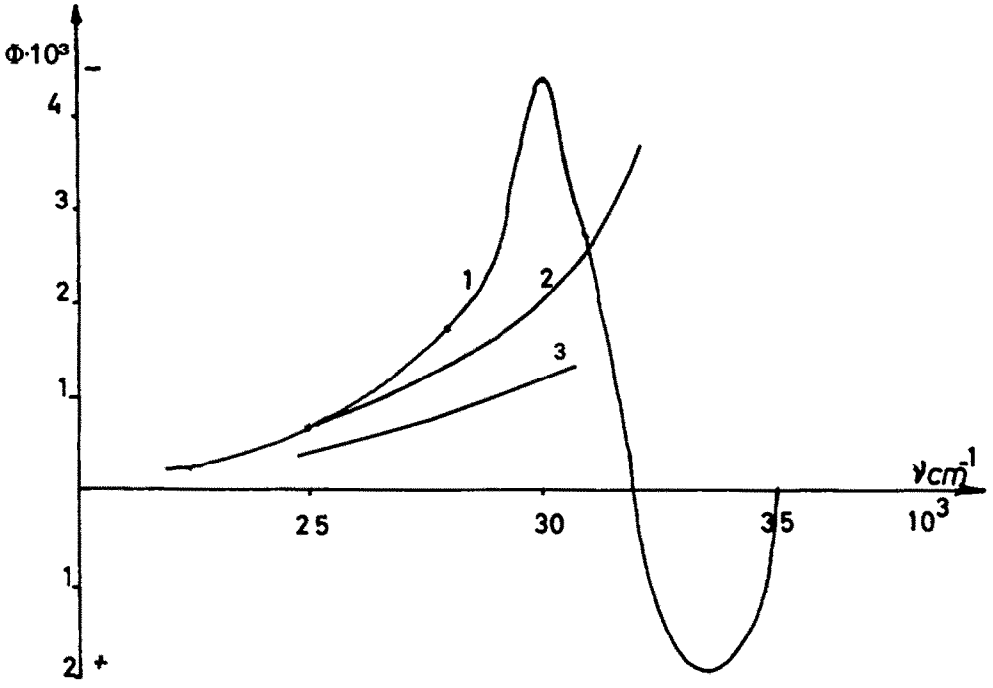

FIG. 2 ORD of *R*(−)-5-acetoxy-4′-hydroxy-7-methoxyisoflavanone-4′-tetraacetyl-β-D-glucoside (1); 5-acetoxy-4′-hydroxy-7-methoxyisoflavone-4′-tetraacetyl-β-D-glucoside (2); (±) 4′,5-dihydroxy-7-methoxyisoflavanone-4′-β-D-glucoside (3).

EXPERIMENTAL

M.ps were determined on a Koffler hot stage and are uncorrected. NMR spectra were taken on a Varian A 60 instrument at 60 Mc, with TMS as internal standard. IR spectra were recorded on a Perkin–Elmer 221 instrument, UV spectra on a Unicam Sp 700 spectrophotometer. ORD measurements were performed on an Opton REPM 12 spectropolarimeter.

5,7-Diacetoxy-4′-(tetraacetyl-β-D-glucosyloxy)-isoflavon(sophoricoside hexaacetate). This was prepared according to literature[5] and recrystallized from AcOH, m.p. 225–228°; NMR (δ, ppm): 2·1 (s, 12H, glucose acetyl); 2·34 (s, 3H, C_7—OAc); 2·41 (s, 3H, C_5—OAc); 3·8–4·1 (m, 1H, glucose C_5—H) 4·26–4·34 (m, 2H, glucose CH_2); 5·0–4·4 (m, 4H, glucose $C_{1,2,3,4}$—H); 6·90 and 7·30 (doublets, J = 2·5 c/s, C_6—H and C_8—H); 7·1 (d, 2H, J = 9 Hz, $C_{3',5'}$—H); 7·48 (d, 2H, J = 9 c/s, $C_{2',6'}$—H); 7·9 (s, 1H, C_2—H).

5-Acetoxy-7-hydroxy-4′-(tetraacetyl-β-D-glucosyloxy)isoflavone (sophoricoside pentaacetate) **6**. To a vigorously stirred suspension of sophoricoside hexaacetate[5] (3·9 g) in MeOH, 1N NaOMe (1 ml) was added in one portion at 60°. After 3 min, the clear soln was acidified with AcOH (0·4 ml) and filtered hot. The chromatographically pure product crystallized in colourless needles (0·65 g, 18%), m.p. 197° measured in a preheated apparatus. (Found: C, 58·08; H, 4·80. $C_{31}H_{30}O_{15}$ requires: C, 57·90; H, 4·70%); NMR: 2·1 (s, 12H, glucose acetyl); 2·38 (s, 3H, C_5—OAc) 3·70–4·35 (3H, glucose-CH_2 superimposed on glucose C_5—H) 4·90–5·30 (broad multiplet, 4H, glucose $C_{1,2,3,4}$—H) 6·63 and 6·85 (two doublets, J = 2·5 c/s, C_6—H and C_8—H) 7·1 (d, 2H, J = 9 c/s, $C_{3',5'}$—H) 7·49 (d, 2H, J = 9 Hz, $C_{2',6'}$—H) 7·9 (s, 1H, C_2—H).

5-Acetoxy-7-methoxy-4′-(tetraacetyl-β-D-glucosyloxy)isoflavone (prunitrin pentaacetate). A soln of **6** in $CHCl_3$ (75 ml) was treated with an excess of ethereal diazomethane. After standing overnight at 0°, the soln was evaporated and the residue recrystallized from MeOH to yield colorless needles (1·85 g, 90%) of m.p. 191–192°. (Found: C, 58·60; H, 4·95. $C_{32}H_{32}O_{15}$ requires: C, 58·60; H, 4·90%); NMR: 2·1 (s, 12H, glucose acetyl); 2·41 (s, 3H, C_5—OAc); 3·93 (4H, C_7—OCH_3 superimposed on glucose C_5—H); 4·2–4·36 (broad multiplet, glucose CH_2); 6·00–5·45 (broad multiplet, 4H, $C_{1,2,3,4}$—H), 6·66 and 6·83 (two doublets

J = 2·5 c/s, C_6—H and C_8—H); 7·08 (d, 2H, J = 9 c/s, $C_{3',5'}$—H); 7·47 (d, 2H, J = 9 c/s, $C_{2',6'}$—H); 7·87 (s, 1H, C_2—H).

(±)*4',5-Dihydroxy-7-methoxyisoflavanone*, **1**. A soln of **3** (297 mg) in AcOH (30 ml) was hydrogenated at room temp with 10% Pd–C (300 mg) until the uptake of one equiv of H_2. The crude product was recrystallized from 50% aqueous MeOH to afford colourless plates (119 mg, 40%) of m.p. 146–147°; λ_{max}^{EtOH} mμ 289 (ε: 2740) 335i (ε: 16,200); $\lambda_{C=O}^{KBr}$ 1650 cm^{-1}; NMR: 3·01 (s, 1H, C_4—OH); 3·88–4·10 (4H, C_7—OMe superimposed on C_3—H); 4·60–4·73 (d, 2H, J = 7 c/s, C_2—H_2); 6·10 (s, 2H, C_6—H; C_8—H); 6·86 (d, 2H, J = 9 c/s, $C_{3',5'}$—H); 7·22 (d, J = 9 c/s, $C_{2',6'}$—H). (Found: C, 67·11; H, 4·77. $C_{16}H_{14}O_9$ requires: C, 67·12; H, 4·93%).

(±) *4',5-Diacetoxy-7-methoxyisoflavanone*, **7**. (a) Compound **1** (119 mg) was acetylated with Ac_2O–NaOAc on the water bath. Repeated crystallization of the crude product from EtOH gave colourless rhombic plates, m.p. 184–185°.

(b) Compound **11** (375 mg) was hydrogenated as described, to afford after purification the same diacetate (300 mg, 80%); NMR: 2·30 (s, 3H, C_4—OAc); 2·39 (s, 3H, C_5—OAc); 3·78–4·00 (t, 4H, C_7—OCH_3 superimposed on C_3—H, J = 7 c/s) 4·65 (d, 2H, J = 7 c/s C_2—H_2); 6·32 and 6·43 (doublets, J = 2·5 c/s, C_6—H and C_8—H); 7·10 (d, 2H, J = 9 c/s, $C_{3',5'}$—H); 7·33 (d, 2H, J = 9 c/s, $C_{2',6'}$—H). (Found: C, 65·13; H, 4·84. $C_{20}H_{18}O_7$ requires: C, 64·86; H, 4·90%).

5-Acetoxy-4'-hydroxy-7-methoxyisoflavanone-4'-tetraacetyl-β-D-glucoside, **9**. Prunitrin pentaacetate (3·0 g) in AcOH (50 ml) was hydrogenated as described. The crude product was recrystallized from MeOH giving the mixture of diastereomers as colourless needles (2·4 g, 80%), m.p. 167–169°. This was recrystallized 5 times from MeOH and twice from acetone–MeOH. The m.p. was raised to 178–180°. $[\alpha]_D^{24}$ = −26° (c = 2·9 $CHCl_3$).

ORD in EtOH (c = 0·1) at 24°: $[\phi]_{400}$ = −658°, $[\phi]_{345}$ = −2340°, $[\phi]_{333}$ = −4350°, $[\phi]_{312}$ = 0°, $[\phi]_{298}$ = +2340°, $[\phi]_{296}$ = 0°; NMR: 2·1 (s, 12H, glucose acetyl); 2·36 (s, 3H, C_5—OAc); 3·88 (5H, C_7—OMe superimposed on glucose C_5—H and C_3—H); 4·2–1·3 (broad multiplet, glucose CH_2); 4·62 (d, 2H, J = 7 c/s C_2—H_2); 5·0–5·45 (broad multiplet, 4H, glucose $C_{1,2,3,4}$—H); 6·30 and 6·42 (doublets J = 2·5 c/s, C_6—H and C_8—H); 7·0 (d, 2H, J = 9 c/s, $C_{3',5'}$—H); 7·22 (d, 2H, J = 9 c/s, $C_{2',6'}$—H). (Found: C, 58·51; H, 5·21. $C_{32}H_{43}O_{15}$ requires: C, 58·51; H, 5·21%).

(±)*4',5-Dihydroxy-7-methoxyisoflavanone-4'-β-glucoside*, **2**. The mixture of diastereomers, obtained by the hydrogenation of prunitrin pentaacetate (0·6 g) was treated with a mixture of MeOH (10 ml) and 10% NaOH aq for 10 min while heating under reflux. After neutralization the soln was evaporated to dryness and the residue crystallized from 20% aqueous EtOH. The mixture of diastereomers crystallized as colourless plates (0·32 g), m.p. (115–117°); $[\alpha]_D^{24}$ = −32·5° (c = 1·00 EtOH). (Found: C, 55·58; H, 5·85. $C_{22}H_{24}O_{10} \cdot 1{\cdot}5\ H_2O$ requires: C, 55·57; H, 5·72%).

(±)*5-Hydroxy-4',7-dimethoxyisoflavanone*, **8**. Compound **1** (0·36 g), dry K_2CO_3 (6 g) and Me_2SO_4 (0·18 ml) was refluxed in acetone (36 ml) for 2 hr. The reaction mixture was filtered hot, evaporated and the residue crystallized twice from EtOH to afford rhomboidal plates, m.p. 124–126°. (Found: C, 67·81; H, 5·27. $C_{17}H_{16}O_5$ requires: C, 67·99; H, 5·37%).

(±)*3-Bromo-4',5-diacetoxy-7-methoxyisoflavanone*, (**10**). A soln of **7** (100 mg), N-bromo-succinimide (48 mg) and benzoyl peroxide (7 mg) was refluxed in dry CCl_4 for 3 hr. The chilled soln was filtered to remove succinimide, evaporated and the residue crystallized from EtOH to yield small colourless rods (51 mg), m.p. 158–161°; NMR: 2·3 (s, 3H, C_4—OAc); 2·4 (s, 3H, C_5—OAc); 3·83 (s, 3H, C_7—OMe); 4·67 (d, 1H, J = 12·5 c/s, C_2—H); 4·97 (d, 1H, J = 12·6 c/s, C_2—H); 6·34 (s, 2H, C_6—H, C_8—H); 7·1 (d, 2H, J = 9 c/s, $C_{3',5'}$—H) 7·55 (d, 2H, J = 9 c/s, $C_{2',6'}$—H). (Found: C, 55·18; H, 3·85. $C_{20}H_{17}BrO_7$ requires: C, 54·72; H, 3·91%).

4',5-Diacetoxy-7-methoxyisoflavone (**11**). Compound **10** (50 mg) and anhyd NaOAc (60 mg) was refluxed for 1 hr in Ac_2O (0·6 ml). The reaction mixture was poured into water, the ppt separated and recrystallized from AcOH to afford **11** m.p. 228–224° (lit. 225–226°); m.m.p. with authentic 222–225°.

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