

Complex Flavonoids from *Pityrogramma* Frond Exudates: Synthesis of Two Flavones with C–C-Linked Dihydrocinnamoyl Substituents

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Pityrogramma calomelanos var. *aureoflava* (Pteridophyta, Polypodiales, Pteridaceae), Complex Flavonoids, Synthesis, β -(5,7,4'-trihydroxy-8-yl)- β -phenylpropionic Acid

Complex flavonoids that are typical for the frond exudate in ferns of the genus *Pityrogramma* are surveyed to demonstrate their close structural relation. Two such compounds, isolated earlier from the exudate of *Pityrogramma calomelanos* var. *aureoflava* are prepared by an unambiguous synthesis. Direct comparisons of the synthetic products, namely β -(5,7,4'-trihydroxy-8-yl)- β -phenylpropionic acid and its methyl ester, show them to be identical with the natural products. The structures deduced previously for these compounds by spectroscopic methods are thus confirmed.

Detailed studies on the “farinose” frond exudates produced by several species of the fern genus *Pityrogramma* led to the isolation of several complex flavonoids [1]. They represent a new type of carbon skeleton, where a flavonoid moiety is linked with a phenyldihydrocoumarin (neoflavanoid) moiety. Compounds designated **D-1**, **D-2a** and **D-2b** are characteristic features in the flavonoid pattern of *Pityrogramma argentea*, *P. aurantiaca*, *P. calomelanos* and *P. tartarea* (only **D-1** in the latter) [1]. **D-1** was found to contain a dihydrochalcone as flavonoid moiety, while compounds **D-2a/b** contain the corresponding flavone and flavonol, respectively [2]. Three further compounds, called **T-1**, **T-2** and **T-3**, are characteristic for the frond exudate of *P. trifoliata* (L.) Tryon (syn: *Trismeria trifoliata* (L.) Diels) and were found also in a hybrid of this species with *P. calomelanos*, along with **D-1** and **D-2a/b** [1]. They were determined by spectroscopic studies to consist of a chalcone moiety and a phenyldihydrocoumarin moiety [3], the phenyldihydrocoumarin being linked via 6'-O and 5'-C of the flavonoid, as is the case in **D-1**, too. Reduction of **T-1** yielded indeed **D-1** [3]. **T-1**, **T-2** and **T-3** differ by the number of OH-groups in the B-ring of the chalcone. Finally, two rather

polar flavonoids designated **X-1** and **X-2** were isolated from cultivated plants of *P. calomelanos* var. *aureoflava*; **X-2** occurs also in some specimens of *P. sulphurea* [1]. In these two complex flavonoids there is no additional γ -pyron ring present; they bear dihydrocinnamoyl substituents [4].

Unfortunately, these closely related complex flavonoids have been reported under different abbreviations, and chemical nomenclature has not been consistent. Thus, **D-1** was called a dihydrochalcone in [1], described as 8-dihydrocinnamoyl-5,7-dihydroxy-4-phenyl-2-H-1-benzopyran-2-one in [2] (compound **A**, structure **1**), and reported as 5,7-dihydroxy-8-(3-phenylpropionyl)-4-phenyldihydrocoumarin in [5], p. 342. Compounds **D-2a/b** were regarded as flavone and flavonol derivatives in [1] and in [6], p. 233, but reported as phenylbenzopyran-2-one derivatives with additional 2-phenyl- γ -pyron(ol) ring systems [2] (compounds **B₁** and **B₂**, structures **3**). Compounds **T-1**, **T-2** and **T-3** were designated chalcone derivatives [1] and also 5,7-dihydroxy-8-cinnamoyl-4-phenyl-dihydrocoumarins [3]. Compounds **X-1** and **X-2**, cited as flavone derivatives with dihydrocinnamoyl substituents in [6], p. 233, were originally reported as β -(5,7,4'-trihydroxy-8-yl)- β -phenylpropionic acid (compd. **2**) and its methyl ester (compd. **1**) in [4]. The different ways in which the structural formulae have been presented still increased the confusion. We therefore deem it desir-

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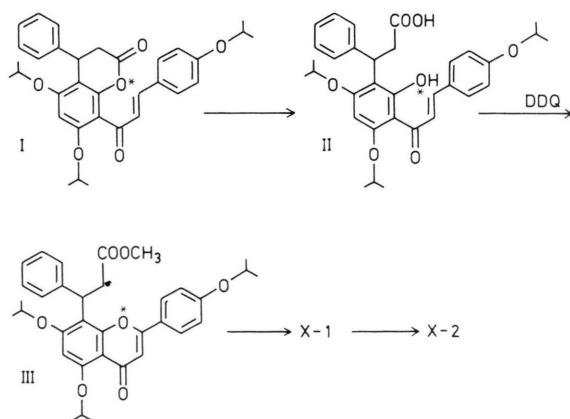
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able to reproduce here a survey of all these complex flavonoid structures (Fig. 2), denoting them by the abbreviations used in the chemotaxonomic study on flavonoid patterns in *Pityrogramma* frond exudates [1]. We thus hope to facilitate the understanding of these structures.

D-1 was synthesized some years ago and the structure proposed in [2] was confirmed also by X-ray analysis [7]. Compounds **T-1**, **T-2** and **T-3** were also synthesized [8] and shown, by direct comparisons, to be identical with the natural products. In the present paper we report the unambiguous synthesis of compounds **X-1** and **X-2**.

Materials and Methods

5,7,4'-Triisopropoxy-8-cinnamoyl-4-phenyldihydrocoumarin (**I**) (synthesis described in [8]) was hydrolyzed to give β -phenyl-3-(4-isopropoxy)-cinnamoyl-2-hydroxy-4,6-diisopropoxyphenylpropionic acid (**II**). This product was esterified with methyl iodide and potassium carbonate in dry acetone to give a methyl ester, *m/z* 560 (M^+), which was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dry dioxane to give a flavone, compound **III**, as yellow oil in 45% yield; ^1H NMR (CCl_4) δ : 6.30, 6.39 (1H each, s, H-3,6); *m/z* 558 (M^+ , 3%), 544 (100%). This flavone was de-isopropylated with boron trichloride in dichloromethane at -50°C to afford compound **X-1** after purification by CC on silica gel (eluent: ethyl acetate/n-hexane 1:1). Usual saponification of synthetic **X-1** with 10% potassium hydroxide in aqueous alcohol yielded the other derivative, **X-2**.



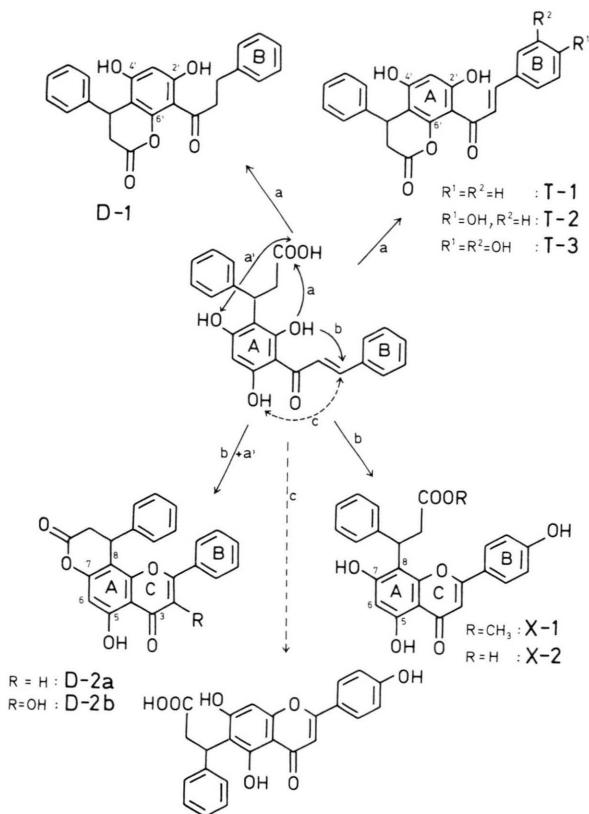
The flavonoids thus obtained have the following physical and spectral properties. **X-1**: Yellow powder, m. p. 305–307 °C. MS *m/z* (rel. int.): 400 (88), 383 (37), 372 (22), 341 (22), 323 (100), 239 (15), 205 (74). UV λ_{max} (MeOH) nm (log ϵ): 273 (4.2), 305sh (4.0), 327 (4.1); + AlCl_3 280, 308, 349, 390; + AlCl_3+HCl 281, 308, 345, 390; + NaOMe 283, 335, 394; + NaOAc 277, 284sh, 305sh, 388; + $\text{NaOAc}+\text{H}_3\text{BO}_3$ 274, 330. ^1H NMR (DMSO- d_6) δ : 3.32 (2H, d, *J* = 7.0 Hz, CHCH_2CO_2), 3.52 (3H, s, COOCH_3), 5.31 (1H, t, *J* = 7.0 Hz, ArCHCH_2), 6.28, 6.60 (1H, each s, H-3, H-6), 6.90 (2H, d, *J* = 8.8 Hz, H-3',5'), 7.26 (5H, br. s, Ar), 7.73 (2H, d, *J* = 8.8 Hz, H-2',6'), 10.06 (1H, br. s, OH), 10.60 (1H, s, C_5-OH), 12.97 (1H, br. s, OH).

X-2: Yellow powder, m. p. 280–285 °C. MS *m/z* (rel. int.): 400 (41), 383 (26), 372 (9), 341 (15), 323 (100), 239 (6), 205 (54). UV λ_{max} (MeOH) nm: 274, 301, 327; + AlCl_3 281, 309, 347, 393; + AlCl_3+HCl 283, 308, 344, 393; + NaOMe 284, 337, 397; + NaOAc 275, 303, 330, 360; + $\text{NaOAc}+\text{H}_3\text{BO}_3$ 276, 300sh, 329. ^1H NMR (DMSO- d_6) δ : 3.35 (2H, d, *J* = 7.2 Hz, CHCH_2CO_2), 5.35 (1H, t, *J* = 7.2 Hz, ArCHCH_2), 6.26, 6.63 (1H, each s, H-3, H-6), 6.90 (2H, s, *J* = 8.8 Hz, H-3',5'), 7.30 (5H, s, Ar), 7.72 (2H, d, *J* = 8.8 Hz, H-2',6'), 10.66 (1H, s, C_5-OH).

Results and Discussion

The structure in the centre of Fig. 2 is the hypothetical intermediate in the formation of the complex flavonoids. Compound **T-1** would be built by lactonization according to the direction of (a). Compounds **X-1** and **X-2** are derived from the intermediate by dehydrogenative cyclization according to direction (b). By the present synthesis, structures **X-1** and **X-2** are distinguished from their isomers with the dihydrocinnamoyl moiety linked to C-6 of the flavone, which could be built from the intermediate by the reaction corresponding to (c). It is a characteristic feature of the synthesis described here that a bridge oxygen belonging to the dihydronaphthalene (indicated with an asterisk in Fig. 1) is transformed into that of a flavone by DDQ oxidation after opening of the ring. This method has the great advantage that a CC_3 -unit is exclusively retained at C-8 of a flavone, and as a result the desired complex flavonoids are selectively synthesized.

By direct comparisons (m. p., UV, MS, ^1H NMR) the synthetic flavonoids were shown to be identical



with the relevant natural products. Therefore, the structures of the flavonoids **X-1** and **X-2** are confirmed by the present synthesis. So the earlier claim [5] that the structures of the complex *Pityrogramma* flavonoids should be corroborated by synthesis is now completely answered. — It may be mentioned that further compounds of this type have not been found till now.

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