Synthesis of Isoponcimarin

P. Rodighiero, A. Guiotto*, P. Manzini, and G. Pastorini
Istituto di Chimica Farmaceutica dell’Università di Padova,
Centro di Studio della Chimica del Farmaco e dei Prodotti Biologicamente attivi del CNR,
Via Marzolo 5, I-35100 Padova, Italy
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Synthesis of isoponcimarin, 7-(3’-methyl-2’,3’-epoxy-butyl)oxy)-8-(3’’-methyl-2’’-oxo-buty1) coumarin, a natural coumarin isolated from Poncirus trifoliata L., was obtained starting from acetyl osthenol. From the intermediate 7-acetoxy-8-(3’-methyl-2’-oxobuty1) coumarin, the coumarin derivatives isomeranzin and dihydrooroselone were also prepared.

In a previous paper [1] we reported the isolation and identification from unripe fruits of Poncirus trifoliata L. (fam. Rutaceae; subfam. Aurantioideae) of a new coumarin, which was named isoponcimarin.

This compound is a neutral coumarinic derivative, optically active [a]D29 = 6.94° (CHCl3), m.p. 85 °C (from n-hexane), violet-blue fluorescent to UV light (365 nm) and has molecular formula C18H22O5. On the basis of the chemical and spectroscopical evidences to isoponcimarin was assigned the structure 7-(3’-methyl-2’,3’-epoxy-butyloxy)-8-(3’’-methyl-2’’-oxo-buty1) coumarin (6) [1, 2]; therefore isoponcimarin is a structural isomer of poncimarin, 7-(3’-methyl-2’,3’-epoxy-butyloxy)-8-(3’-methyl-2’-oxo-buty1) coumarin (10), isolated from the same natural source [3] and confirmed by total synthesis [4].

A number of natural coumarins were known, in which isopentenyl and geranyl side chains are present at various oxidation level [5]. The oxygenated function may be an epoxy group, a diol, a ketonic or an aldehydic group. It has been suggested a biogenetic pathway (not tested up to now) which from the epoxide derivative, via the diol derivative, give rise to the formation of the keto- or formyl-derivative by a pinacol-type rearrangement [6].

In this way poncimarin (10) will be hydrolyzed to a diol derivative, which so far failed to be identified from extracts of Poncirus trifoliata. On the other hand a direct rearrangement of the epoxide group may also be assumed: in this hypothesis poncimarin (10) may be considered the direct precursor of the isoponcimarin (6).

* Reprint requests to Dr. A. Guiotto.
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In this paper we describe the synthesis of isoponcimarin obtaining a definite confirmation of the proposed structure 6 of this substance; in addition, we describe the synthesis of two other chemically correlated compounds.

The preparation (see Fig. 1) started from osthenol, 7-hydroxy-8-(3’-methyl-but-2-enyl) coumarin, in which an isopentenyl residue branched from the 8-position of the coumarin nucleus is already present; osthenol was prepared in good yield by Claisen rearrangement of 7-(1,1-dimethyl-prop-2-enyloxy) coumarin [7] in boiling diethylaniline [4, 8].

Osthenol was acetylated and then epoxidated by treatment with perbenzoic acid in chloroformic solution. The phenolic group ortho to the isopentenyl moiety must be protected before the epoxidation, because it was proved [9] that the direct epoxidation of osthenol affords to products of an oxidative cyclisation, i.e. the dihydrofuranocoumarin, (±)-columbianetin, when the treatment with peracid was conducted under neutral conditions and the dihydropyranocoumarin, (±)-lomatin, by treatment in acidic medium.

The rearrangement with boron trifluoride in ethereal solution of the 7-acetoxy-8-(3’-methyl-2’,3’-epoxy-buty1) coumarin (3) gave the desired ketodervative, 7-acetoxy-(3’-methyl-2’-oxo-buty1) coumarin (4), as the major product other than a minor amount of the formyl isomer, 7-acetoxy-(2’-formyl-2’-methyl-propyl) coumarin (7). It is well known [10] that the course of the rearrangement process of the epoxide ring is governed by two main factors: the direction of ring opening and the relative migratory aptitude of the different substituent groups; other factors however, i.e. the steric effects or the solvent, must be important, as we have observed in the present case. It was reported [11] in
fact that the rearrangement of the epoxidate osthol, 7-methoxy-8-(3’-methyl-2’,3’-epoxy-butyl) coumarin, with boron trifluoride etherate in dioxan solution, instead of ethereal solution as used by us, afforded as a major product the formyl derivative, 7-methoxy-8-(2’-formyl-2’-methyl-propyl) coumarin, other than a small amount of the keto derivative, 7-methoxy-8-(3’-methyl-2’-oxo-buthyl) coumarin (isomeranzin).

The 7-acetoxy-8-(3’-methyl-2’-oxo-buthyl) coumarin was directly isoprenylated with isoprenyl bromide in acetonic solution and in the presence of K₂CO₃ to the 7-isoprenyloxy-analogue, which by epoxidation with perbenzoic acid in chloroformic solution gave the (±)-isoponcimarin. Synthetic isoponcimarin is necessarily a racemate, the m.p. of which (90 °C; from n-hexane) is slightly different from that of the natural optically active compound (85 °C; from n-hexane): Spectroscopical data (UV, IR, ¹H NMR) of both synthetic and natural isoponcimarin are superimposable.

The availability of synthetic isoponcimarin allowed us to reconfirm the unexpected resistance to the acid hydrolysis, conc. H₂SO₄ in AcOH solution, of the ethereal linkage between the epoxidate isopentenyl moiety and the 7-position of the coumarin nucleus [2].

Under these conditions the epoxide group underwent rearrangement giving the diketo derivative 7-(3’-methyl-2’-oxo-butyloxy)-8-(3’’-methyl-2’’-oxo-butyl) coumarin and acetolysis giving the monoacetate 7-(2’-acetoxy-3’-hydroxy-3’-methylbutfyloxy)-8-(2’’-oxo-3’’-methyl-butyl) coumarin and the dehydration product of the last compound, 7-(2’-acetoxy-3’-methyl-but-3’-enyloxy)-8-(2’’-oxo-3’’-methyl-butyl) coumarin.

The reaction of 4 with methyl iodide in acetonic solution and in the presence of K₂CO₃ easily gave isomeranzin (isoauraptene), 7-methoxy-8-(2’-oxo-3’-methyl-butyl) coumarin (8).

Isomeranzin is a natural coumarin [12] and was previously prepared both by treatment of auraptene
(meranzin), 7-methoxy-8-(2',3'-epoxy-3'-methylbutyl) coumarin, with 20% sulfuric acid [13] and by treatment of auraptenol, 7-methoxy-8-(2'-hydroxy-3'-methyl-but-3'-enyl) coumarin, in the same conditions [14], as well as by total synthesis [11]. Compound 4 refluxed with hydrochloric acid in acetic acid solution underwent cyclisation giving dihydrooroselone, 8-(methyl-ethyl)-2H-furo[2,3-h]-[1]-benzopyran-2-one (9). This compound is not a naturally occurring coumarin and was previously obtained by other ways, that is by treatment with hydrobromic acid of the epoxidated osthol [15] and by acid catalyzed dehydration of lomatins [16], 9,10-dihydro-9-hydroxy-8-(3'-methyl-2'-enyl) coumarin (3) by treatment of auraptenol, 7-methoxy-8-(2'-hydroxy-3'-methyl-but-3'-enyl) coumarin, in the same conditions [14], as well as by total synthesis [11].

Experimental

Mps, determined in open capillary, are uncorrected. Silica gel plates 60 F-254 (Merck cat. 5715) were used for TLC, using as developing solvent a mixture of CHCl₃. The first fractions containing only the component with higher Rf were put together and by elimination of the solvent an oily residue was obtained.

1H NMR spectra were recorded at 60 MHz on Hitachi-Perkin Elmer R-24A or Bruker WP-60 spectrometer and are given in δ relative to TMS as internal standard, coupling constants are given in Hz; all assignments are in agreement with relative peak areas and were applicable with decoupling.

Rearrangement of the 7-acetoxy-8-(3'-methyl-2',3'-epoxy-butyl) coumarin

Into a dry ether solution of 7-acetoxy-8-(3'-methyl-2',3'-epoxy-butyl) coumarin (0.350 g; 1.2 mmoles) a stream of BF₃ was bubbled as long as the solution became pale-yellow persistent in colour, while heat was developed. The mixture was allowed to stand at room temperature 2 h. After this time the starting material appeared to be absent from the mixture by TLC, while a main product was formed other than a minor derivative with higher Rf value; both spots reacted when sprayed with the di-N0₂-phenyl-hydrazine reagent.

a) 7-Acetoxy-8-(3'-methyl-2'-oxo-butyl) coumarin (4): The mixture was diluted to 200 ml with moist ether and extracted two times with water. The organic phase was dried (Na₂SO₄) and the solvent eliminated under vacuum. A white crystalline solid was obtained (0.198 g; 57.5%). The solid was recrystallized from a EtOAc-n-hexane (20/80) mixture giving white crystals of 7-acetoxy-8-(3'-methyl-2'-oxo-butyl) coumarin, m. p. 114-115 °C; 1H NMR(CDC1₃): δ 7.67 (1H; d; J = 9.5 Hz; -CHMe²); δ 7.41 (1H; d; J = 8.5 Hz; -CHMe²); δ 7.06 (1H; d; J = 8.5 Hz; -CHMe²); δ 6.32 (1H; d; J = 9.5 Hz; -CHMe²); δ 3.96 (2H; s; Ph-CH₂-CO); δ 2.82 (1H; s; septet; J = 7 Hz; -CHMe₂); δ 2.28 (3H; s; Acetyl group); δ 1.20 (6H; s; Acetyl group); δ 1.82 and δ 1.67 (each 3H; ss; two Me).

b) 7-Acetoxy-8-(2'-formyl-2'-methyl-propyl) coumarin (7): The mother liquors of crystallization of the keto derivatives (4) were deprived of the solvent and chromatographed in a silica gel column by eluting with CHCl₃. The first fractions containing only the component with higher Rf were put together and by elimination of the solvent an oily...
A number of fractions containing both the keto and the formyl derivative were then eluted. In the next fractions a further crop of pure 7-acetoxy-8-(3'-methyl-2'-oxo-butyl) coumarin, keto derivative (4) was obtained.

7-(3'-Methyl-but-2'-enyl-oxy)-8-(3''-methyl-2''-oxo-butyl) coumarin (5)

The 7-Acetoxy-8-(3'-methyl-2'-oxo-butyl) coumarin (0.200 g; 0.69 mmoles) was dissolved in MeCO (5 ml). To the acetonitrile solution an excess of finely powdered K2CO3, a catalytic amount of KI, few drops of H2O and an excess of 3-methyl-but-2-enylchloride (5 ml) were added and the mixture refluxed under neergical stirring. More 3-methyl-but-2-enylchloride was added after 5 min. After 30 min the mixture monitored by TLC appeared to be devoid of the starting material. The mixture was cooled and K2CO3 was eliminated by filtration, washing it with fresh MeCO. Filtrate and washings were evaporated under vacuum. The residue was purified in a silica gel column by eluting with CHCl3. Fractions containing the main component were collected, the next fractions a further crop of pure 7-acetoxy-8-(3'-methyl-2'-oxo-butyl) coumarin (0.0035 g; 10%) was obtained, which failed to crystallize from several solvents; H NMR; δ 7.63 (1H; d; J = 9.5 Hz; H-4); δ 7.39 (1H; d; J = 8.5 Hz; H-5); δ 7.00 (1H; d; J = 8.5 Hz; H-6); δ 6.26 (1H; d; J = 9.5 Hz; H-3); δ 2.98 (2H; s; Ph-CH=C); δ 2.32 (3H; s; -CHMe2); δ 1.36 (6H; d; J = 7 Hz; -CHMe2).