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COUMARINS FROM UNRIPE FRUITS OF *PONCIRUS TRIFOLIATA*

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Key Word Index—*Poncirus trifoliata*; Rutaceae; coumarins; poncimarin; isoponcimarin.

Abstract—Petrol extracts of unripe fruits of *Poncirus trifoliata* L. were found to contain 7-geranyloxycoumarin, bergapten, imperatorin, 6-methoxy-7-geranyloxycoumarin and two new coumarins which were shown by chemical and spectroscopic means to be 7-(3′-methyl-2′,3′-epoxybutyloxy)-8-(3″-methyl-2″,3″-epoxybutyl)coumarin and 7-(3′-methyl-2′,3′-epoxybutyloxy)-8-(3″-methyl-2″-oxobutyl)coumarin respectively.

INTRODUCTION

During a current project dealing with the coumarin derivatives of *Poncirus trifoliata* L., an investigation of the whole unripe fruit demonstrated that it is a very rich source of coumarins but not furocoumarins, as opposed to seeds from ripe fruit in which furocoumarins largely predominate. Previously the furocoumarins imperatorin, bergapten, isopimpinellin, prangenin and prangenin hydrate, and a small quantity of the two coumarins 7-geranyloxycoumarin (aurapten) and 6-methoxy-7-geranyloxycoumarin were isolated from seeds [1, 2]. This paper describes the isolation from a petrol extract of unripe fruit of two new isoprenylated coumarinic derivatives, which we called with the trivial name poncimarin (**5**) and isoponcimarin (**6**), as well as a large amount of the above mentioned coumarins.

A number of coumarins and alkaloids of rutaceous plants are known in which isopentenyl and geranyl side chains are present. These are at various oxidation levels and the question is raised if the oxidation levels of such terpenoid residues can be correlated with their taxonomic distribution [3]. The new extractives were identified as 7, 8 disubstituted coumarin [4, 5], with two oxidised isopentenylic chains linked to an O atom in the 7 position and to a C atom in the 8 position respectively, and can be regarded as osthenol (7-hydroxy-8-(3′-methyl-2′-butenyl)coumarin derivatives.

Brown *et al.* [6] established that osthenol and 7-demethylsuberosin (7-hydroxy-6-(3′-methyl-2′-butenyl)-coumarin are intermediates in angular and linear furocoumarin biosynthesis respectively, osthenol being much less rapidly metabolized than 7-demetylsuberosin. Therefore it is possible that poncimarin and isoponcimarin also may be implicated in the angular furocoumarin or pyranocoumarin pathways and from this point of view it is significant that these compounds, which are well represented in unripe fruits, are not detectable even by TLC in extracts of ripe fruits or seeds. Up to now however, only the angular pyranocoumarin seselin has been isolated from *P. trifoliata* roots [7], while in fruit neither derivatives of the angelicine nor seselin type have been detected.

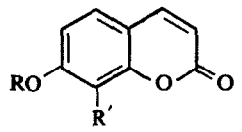
RESULTS

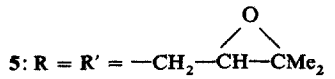
As described in the Experimental Section, the isolation of the various coumarinic and furocoumarinic compounds was achieved by extraction of the unripe fruits of *P. trifoliata* with petrol and by subsequent chromatography of the extract on a silica gel column.

The first compound eluted from the column was 7-geranyloxycoumarin (**1**) (aurapten), which has been found in many rutaceous plants and identified by acid hydrolysis to umbelliferone and further methylation to herniarin and by comparison of physical and spectral data (UV, IR, PMR) with those of an authentic sample. In the next fractions a mixture was eluted of the two furocoumarins bergapten (**2**) and imperatorin (**3**), which were separated by further column chromatography. Further elution of the column gave 6-methoxy-7-geranyloxycoumarin (**4**) identified from spectral data and by acid hydrolysis to scopoletin. Up till now, this coumarin has been found in *Feronia elephantum* [8], *Haplaophyllum hispanicum* (*H. linifolium*) [9] and *H. pedicellatum* [10] in the Rutaceae.

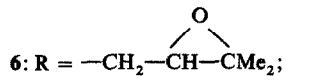
In subsequent fractions two compounds were eluted which had a small difference in R_f values. The combined oily residues were dissolved in EtOAc and after long standing furnished a substantial quantity of a solid, which crystallized from MeOH and gave the first new coumarin, poncimarin (**5**). The compound showed a blue fluorescence in UV light, $C_{19}H_{22}O_5$ from elemental analysis and MW determination, typical UV spectrum of a 7-alkoxycoumarin, very similar to that of osthenol and auraptenol [11]. The PMR spectrum of **5** showed doublets centered at δ 6.26 and 7.65 assigned to the coumarinic system protons at H-3 and H-4 and doublets centered at δ 6.9 and 7.37 for H-6 and H-5 *ortho* aromatic protons respectively. A 4 line signal centered at δ 4.23 was assigned to the O-methylene. A broad multiplet from δ 3 to 3.4 was assigned to the benzylic methylene and to the two epoxide protons. Four singlets at δ 1.30; 1.39; 1.41; 1.51 occurred for the two gem-diMe groups.

Acid hydrolysis carried out by adding a small quantity of conc H_2SO_4 to a HOAc solution of **5** gave a mixture of products, the major of which was purified by column





5: R = R' = —CH_2—CH(O)—CMe_2



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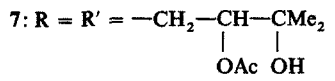

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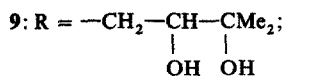
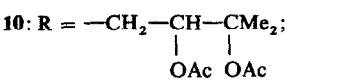
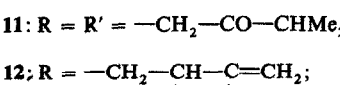


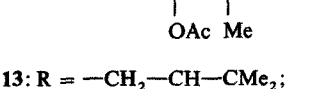
9: R = —CH_2—CH(OH)—CMe_2(OH); R' = —CH_2—CO—$CHMe_2$



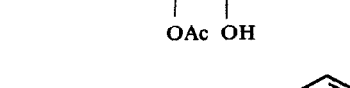
10: R = —CH_2—CH(OAc)—CMe_2(OAc); R' = CH_2—CO—$CHMe_2$



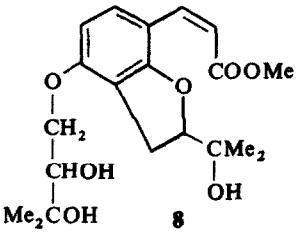
11: R = R' = —CH_2—CO—$CHMe_2$



12: R = —CH_2—CH(OAc)—C(Me)=CH_2; R' = —CH_2—CO—$CHMe_2$



13: R = —CH_2—CH(OAc)—CMe_2(OH); R' = —CH_2—CO—$CHMe_2$



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chromatography and identified as the *bis*-acetate **7**. It would be expected to obtain a monoacetate of the 2',3' diol derivative of osthenol and/or (±) lomatin (3'-hydroxy-3',4'-dihydroseselin) derived from an acid catalysed cyclization [12] and/or dihydrooroselone, the dehydration derivative of lomatin [13] from acid hydrolysis of **5**, but none of the hydrolysis products showed a R_f value corresponding to that of synthetic samples of the anticipated compounds. The unexpected resistance to acid hydrolysis of the C-7 ethereal linkage in poncimarin was later confirmed under the same conditions with isoponcimarin (**6**) and with synthetic 7-(3'-methyl-2',3'-epoxybutyloxy) coumarin.

Confirmation of the branching from the 8 position of the coumarin skeleton of an epoxidate isopentenylic residue followed from treatment of **5** with methanolic KOH, when the compound **8** was formed; the structure of this compound was deduced from PMR analysis. Such transformation, well known in the coumarin series [14], involves the opening of the lactone ring followed by intramolecular reaction between the phenolic and the epoxide groups forming a new ring. Unequivocal confirmation of the structure **5** for poncimarin followed from a synthesis achieved by isoprenylation of osthenol and PBA epoxidation of the isoprenylated derivative [15].

Rechromatography of the combined residue from which poncimarin was obtained gave the second new coumarin, isoponcimarin (**6**). It showed a blue fluorescence in UV light, $C_{19}H_{22}O_5$ from elemental analysis and MW determination, a UV spectrum virtually superimposable on that of poncimarin and typical therefore of a 7-alkoxycoumarin chromofore. The PMR spectrum of **6** confirmed the presence of a 7,8 disubstituted coumarin system showing doublets centered at δ 6.23 and 7.64 for the H-3 and H-4 protons and doublets centered at δ 6.87 and 7.38 for the H-6 and H-5 *ortho* aromatic protons respectively. A sharp singlet at δ 4.07 was assigned to the benzylic protons of the C-8 branched isoprenylic moiety, because of the combined diamagnetic effects of the aromatic nucleus and contiguous carbonyl group [11], while a septet at δ 2.86 and doublet at 1.23 were assigned to the isopropyl group of the same chain. A 4 line signal centered at δ 4.19 and a triplet centered at δ 3.08 was

assigned to *O*-methylene and to epoxide proton respectively, while two singlets at δ 1.35 and 1.37 were assigned to the terminal Mes.

Isoponcimarin is not an artefact from the rearrangement of an epoxide group of poncimarin, since the latter compound did not undergo isomerization under the condition of isolation and the crude extracts showed the presence of both coumarins on TLC. Isoponcimarin by treatment with $(COOH)_2$ in boiling H_2O underwent opening of the epoxide ring to give the diol **9**, which by acetylation gave the diacetate **10**.

Like poncimarin, the ethereal linkage also appeared to be resistant to acid hydrolysis. Under these conditions the epoxide group of **6** underwent rearrangement giving the diketo derivative **11** and acetolysis to the monoacetate **13** of the diol **9**, which by elimination of H_2O gave the compound **12**.

The downfield shift of the methyne proton of the monoacetate **13** by comparison with the diol **9** confirmed the proposed structure in accordance with Krassusky rule [16], with attachment of the acetyl group to the carbon atom bearing the greater number of free H atoms.

EXPERIMENTAL

PMR spectra were recorded at 60 MHz unless otherwise specified and are given in δ (Hz) relative to TMS; all assignments are in agreement with relative peak areas and where applicable with decoupling experiments. UV spectra were obtained in EtOH and IR spectra as KBr discs. Mps, determined in open capillary, are uncorr.

Isolation. Fruits of *P. trifoliata* were collected from plants growing in Padua or its surroundings in June, *ca* 3 months before ripeness. They were dried at 60° to constant wt (5.85 kg), finely ground and exhaustively extracted with petrol. Solvent was removed and the oily residue (572.5 g) chromatographed on 5% H_2O deactivated Si gel. Fractions from the column were monitored by Si gel TLC using cyclohexane–EtOAc (13:7). Initial petrol fractions contained trace amounts of a compound with a violet fluorescence (R_f 0.9) which was not isolated. The next fractions, eluted with petrol–C_6H_6 (17:3), contained a blue fluorescent compound (R_f 0.75) and yielded **1** (19.5 g), mp 71°, from *n*-hexane. Found: C, 76.39; H, 7.37. Calc. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%. Hydrolysis of **1** in HOAc soln by addition of few drops of conc H_2SO_4 gave umbelliferone (7-hydroxycoumarin) which by treatment with CH_2N_2 in Et_2O gave herniarin (7-methoxycoumarin). UV, IR and PMR spectra were identical with those of an authentic specimen. Petrol–C_6H_6 (7:3) fractions containing two yellow fluorescent components (R_f 0.57 and 0.52) gave after rechromatography a small amount of bergapten (**2**) and imperatorin (**3**). Workup of the subsequent C_6H_6–EtOAc (9:1) eluate gave 6-methoxy-7-geranyloxycoumarin (**4**) (1.6 g), mp 88°; after recrystallization from EtOH 95°. Found: C, 73.19; H, 7.28; —OMe, 9.49. Calc. for $C_{19}H_{24}O_4$: C, 73.14; H, 7.37; —OMe, 9.44%. Acid hydrolysis of **4** in HOAc soln gave scopoletin (6-methoxy-7-hydroxycoumarin) identical to a synthetic specimen. Fractions eluted with C_6H_6–EtOAc (17:3) contained 2 compounds (R_f 0.25 and 0.23) both with a pale blue fluorescence. Solvent was removed and the residue dissolved in EtOAc. After a long standing poncimarin (**5**) crystallized (5.7 g), mp 140°, after recrystallization from MeOH, $[\alpha]_D^{25}$ −56.2° ($CHCl_3$); λ_{max} nm (log ε) 320 (4.19), 255.5 (3.61), 246 (3.6), 235 (3.57), 216 (shoulder; 4.14), λ_{min} 262 (3.28), 250.5 (3.55), 240.5 (3.54), 233 (3.56); ν 1725, 1600, 1500, 1390, 1380, 1250, 830; PMR ($CDCl_3$, 90 MHz) δ 7.65 (1H, *d*, *J* = 9.5 Hz) H-4; 7.37 (1H, *d*, *J* = 8.6 Hz) H-5; 6.9 (1H, *d*, *J* = 8.6 Hz) H-6; 6.26 (1H, *d*, *J* = 9.5 Hz) H-3; 4.23 (2H, 4 line signal) —OCH_2—; 3.4–3 (4H, *m*) epoxide ring protons and benzylic methylene; 1.51; 1.41; 1.39; 1.3 (each 3H, *s*) C-Me. Found: C, 69.10; H, 6.89. $C_{19}H_{22}O_5$ requires: C, 69.07; H, 6.71%. Workup of the mother liquors by Si gel chromatography gave a further crop of crystalline **5** (2.3 g) and isoponcimarin (**6**) (7.04 g), mp 85°, from *n*-hexane, $[\alpha]_{465}^{20}$ −6.94 ($CHCl_3$), λ_{max} nm (log ε) 320 (4.20); 255 (3.63); 217 (shoulder 4.16), λ_{min} 264 (3.38); ν 1720, 1600, 1500, 1395, 1375, 1280, 1250, 1110, 1050, 875, 830, 760; PMR ($CDCl_3$) δ 7.64 (1H, *d*, *J* = 9.5 Hz) H-4; 7.38 (1H, *d*, *J* = 8.6 Hz) H-5; 6.87 (1H, *d*, *J* = 8.6 Hz) H-6; 6.23 (1H, *d*, *J* = 9.5 Hz) H-3; 4.19 (2H, 4 line signal) —OCH_2—; 4.07 (2H, *s*) ϕ—CH_2—CO—; 3.08 (1H, *t*) epoxide ring proton; 2.86 (1H, septet, *J* = 7 Hz) and 1.23 (6H, *d*, *J* = 7 Hz) —$CHMe_2$; 1.37 and 1.35 (each 3H, *s*) C-Me. Found: C, 69.01; H, 6.71. $C_{19}H_{22}O_5$ requires: C, 69.07; H, 6.71%.

Acid hydrolysis of poncimarin. To a soln of **5** (540 mg) in HOAc (5 ml) 5 drops of conc H_2SO_4 were added and the mixture kept at room temp. for 4 hr. The mixture was diluted with H_2O, neutralized with $NaHCO_3$ and extracted with EtOAc. After removal of solvent, chromatography of the syrupy residue led to isolation of the major from several products. This compound, which failed to crystallize, was the diacetate **7**, PMR ($CDCl_3$) δ 7.62 (1H, *d*, *J* = 10 Hz) H-4; 7.32 (1H, *d*, *J* = 8.6 Hz) H-5; 6.76 (1H, *d*, *J* = 8.6 Hz) H-6; 6.15 (1H, *d*, *J* = 10 Hz) H-3; 5.45–4.9 (2H, *bm*) two —CH(OAc)-groups; 4.4–4.15 (2H, *m*) —OCH_2—; 3.3–3.05 (2H, *m*) benzylic protons; 2.0 (6H, *s*) acetyl groups; 1.43 (12H, *bs*) C-Me. Found: C, 61.68; H, 6.68. $C_{23}H_{30}O_9$ requires: C, 61.32; H, 6.71%.

Alkaline hydrolysis of poncimarin. **5** (1.035 g) was dissolved in MeOH (20 ml) and a soln of methanolic KOH (15 ml) added. The mixture was allowed to stand 18 hr at room temp. H_2O added and the MeOH removed. The aq. soln was acidified with dil H_2SO_4 and extracted with Et_2O, the organic phase washed with $NaHCO_3$ soln and the solvent evaporated. From the residue the main component was isolated by Si gel chromatography and identified as **8** uncrystallizable, PMR ($CDCl_3$; 90 MHz) δ 7.45 (1H, *d*, *J* = 8.5 Hz) and 6.42 (1H, *d*, *J* = 8.5 Hz) *ortho* benzenic protons; 6.94 (1H, *d*, *J* = 12.5 Hz) and 5.89 (1H, *d*, *J* = 12.5 Hz) β and α protons respectively of the *cis*- coumarinate system; 4.64 (1H, *t*, *J* = 9 Hz) α proton of the dihydro furan ring; 4.22–4.07 (2H, 4 line signal) —OCH_2—; 3.72 (3H, *s*) —OMe; 3.27–3.03 (3H, *m*) β protons of the dihydro furan ring and —CH(OH)—; 2.9–2.4 (*brs*; displaced by D_2O addition) —OH; 1.40, 1.36, 1.34, 1.20 (each 3H, *s*) C-Me. Found: C, 62.78; H, 7.48. $C_{20}H_{28}O_7$ requires: C, 63.14; H, 7.42%.

Hydrolysis of isoponcimarin. (a) A H_2O soln of **6** (300 mg) and $(CO_2H)_2$ (300 mg) was boiled for 10 min and after cooling extracted with EtOAc. After removal of solvent, the residue was purified by Si gel chromatography and elution with EtOAc. The pure diol **9**, which could not be crystallized, had PMR ($CDCl_3$) δ 7.62 (1H, *d*, *J* = 9.5 Hz) H-4; 7.33 (1H, *d*, *J* = 9 Hz) H-5; 6.85 (1H, *d*, *J* = 9 Hz) H-6; 6.2 (1H, *d*, *J* = 9.5 Hz) H-3; 4.45–3.9 (2H, *m*) —OCH_2—; 4.03 (2H, *s*) ϕ—CH_2—CO—; 3.95–3.65 (1H, *t*, being each peak split into doublets) —CH(OH)—; 3.5–2.9 (*ca* 2H, *brs*; displaced by D_2O addition) —OH; 2.83 (1H, septet, *J* = 9 Hz) and 1.19 (6H, *d*, *J* = 7 Hz) —$CHMe_2$; 1.25 (6H, *s*) C-Me. Found: C, 65.78; H, 7.02. $C_{19}H_{24}O_6$ requires: C, 65.50; H, 6.94. The diol **9** was refluxed with Ac_2O and few drops of C_5H_5N. H_2O was added and after cooling, the mixture was neutralized with $NaHCO_3$ and extracted with EtOAc. After removal of solvent the diacetate **10** was crystallized from cyclohexane, mp 118.5–119°, PMR ($CDCl_3$): δ 7.57 (1H, *d*, *J* = 9.5 Hz) H-4; 7.31 (1H, *d*, *J* = 9 Hz) H-5; 6.75 (1H, *d*, *J* = 9 Hz) H-6; 6.14 (1H, *d*, *J* = 9.5 Hz) H-3; 5.6–5.35 (1H, 4 line signal) —CH(OAc)—; 4.30–4.50 (2H, *m*) —OCH_2—; 3.95 (2H, *s*) ϕ—CH_2—CO—; 2.92 (1H, septet, J = 7 Hz) and 1.24 (6H, *d*, *J* = 7 Hz) —$CHMe_2$; 2.08 and 2 (3H, each; *s*) acetyl groups; 1.55 (6H, *s*) C-Me. Found: C, 63.81; H, 6.55. $C_{23}H_{28}O_8$ requires: C, 63.88; H, 6.53%. (b) A soln of **6** (580 mg) in HOAc (2 ml) was added to conc H_2SO_4 (0.15 ml) and kept at room temp. for 4 hr. After a further addition of conc H_2SO_4 (0.15 ml) the mixture was allowed to stand 2 hr, and then diluted with H_2O, neutralized by addition of a $NaHCO_3$ soln and extracted with Et_2O. The residue (626 mg) obtained from the dried Et_2O extract was chromatographed on anhydrous Si gel and eluted with $CHCl_3$. Two compounds

(R_f 0.22 and 0.31) were eluted in the first fraction. The residue was dissolved in $CHCl_3$, *n*-hexane added and the mixture cooled in a solid CO_2–Me_2CO bath. A white ppt. of **11** was collected and twice crystallized from $CHCl_3$–*n*-hexane (1:20) (52.2 mg), mp 109°, PMR ($CDCl_3$) δ 7.60 (1H, *d*, J = 9 Hz) H-4; 7.34 (1H, *d*, J = 8.5 Hz) H-5; 6.67 (1H, *d*, J = 8.5 Hz) H-6; 6.21 (1H, *d*, J = 9 Hz) H-3; 4.72 (2H, *s*) —OCH_2CO; 4.1 (2H, *s*) ϕ—CH_2—CO—; 2.85, 2.8 (1H each, septets, J = 7 Hz) and 1.2, 1.1 (6H, each, *d*, J = 7 Hz) —$CHMe_2$ groups. Found: C, 68.69; H, 6.61. $C_{19}H_{22}O_3$ requires: C, 69.07; H, 6.71. By rechromatography of the mother liquors from **11**, pure **12** was obtained but it could not be crystallized. PMR ($CDCl_3$): δ 7.63 (1H, *d*, J = 9 Hz) H-4; 7.37 (1H, *d*, J = 8 Hz) H-5; 6.73 (1H, *d*, J = 8 Hz) H-6; 6.21 (1H, *d*, J = 9 Hz) H-3; 5.56 (1H, *t*, J = 6 Hz) —CH(OAc)—; 5–5.18 (2H, *m*) —CMe=CH_2; 4.18 (2H, *d*, J = 6 Hz) —O—CH_2—; 4.01 (2H, *s*) ϕ—CH_2—CO—; 2.83 (1H, septet, J = 7 Hz) and 1.24 (6H, *d*, J = 7 Hz) —$CHMe_2$; 2.1 (3H, *s*) acetyl group; 1.83 (3H, *brs*) —C(=CH_2)Me. Found: C, 67.48; H, 6.61. $C_{21}H_{24}O_6$ requires: C, 67.73; H, 6.50%. Further elution of the column of the rearrangement mixture gives **13** (171 mg) mp 104° from EtOAc–*n*-hexane, PMR ($CDCl_3$) δ 7.56 (1H, *d*, J = 9 Hz) H-4; 7.29 (1H, *d*, J = 8.5 Hz) H-5; 6.78 (1H, *d*, J = 8.5 Hz) H-6; 6.15 (1H, *d*, J = 9 Hz) H-3; 5.3–5.05 (1H, 4 line signal) —CH(OAc)—; 4.5–4.1 (2H, *m*) —O—CH_2—; 3.94 (2H, *s*) ϕ—CH_2—CO—; 2.83 (1H, septet, J = 7 Hz) and 1.22 (6H, *d*, J = 7 Hz) —$CHMe_2$; 2.56 (1H, *bs*, displaced by D_2O addition) —OH; 1.27 (6H, *s*) C—Me. Found: C, 64.76; H, 6.78. $C_{21}H_{26}O_7$ requires: C, 64.60; H, 6.71%.

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