Vol. 6 No. 1
Winter 1995

SYNTHESIS OF 8-HYDROXY-6-METHOXY-3-UNDECYLISOCOUMARIN AND 2-HYDROXY-4-METHOXY-6-(2-OXOTRIDECYL) BENZOIC ACID

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Abstract

Straightforward conversion of (±)-6,8-dimethoxy-3,4-dihydro-3-undecylisocoumarin (3) to the title isocoumarin was carried out. Hydrolytic ring opening of (3) afforded the hydroxy acid (4) which was immediately oxidized to keto acid (5) using chromic acid. Cyclodehydration of (5) afforded the 6,8-dimethoxy-3-undecylisocoumarin (6) which on selective demethylation of 8-methoxy group furnished the title isocoumarin (2). The title keto acid (1, R=H) which was obtained by hydrolytic ring opening of title isocoumarin (2) was esterified to keto ester (1, R=Me).

Introduction

Ononis natrix is a small flowering plant of the family Leguminosae, known for its medicinal properties. The infusion of its roots has diuretic and antirheumatic properties and has been used for the treatment of certain disturbances of the urinary tract [1]. The chemical composition of *Ononis natrix* has recently been studied and a number of important compounds have been isolated and identified [2].

In 1990, during further studies [3] on the composition of *Ononis natrix*, in addition to a number of dihydroisocoumarins isolated from the acid fraction of the n-hexane extract, the presence of an aromatic acid (1, R=H) was also detected in the most polar chromatographic fraction. However, the separation of acid was found to be impossible by further chromatography. When the fraction containing the acid was treated with diazomethane-ethyl lether, the keto ester (1, R=Me) was obtained. On treatment of keto ester (1, R=Me) with 5% methanolic potassium hydroxide, 8-hydroxy-6-methoxy-3-undecylisocoumarin (2) was obtained.

We have previously carried out the synthesis of the principal dihydroisocoumarins of *Ononis natrix* [4]. In this article we wish to report the conversion of dihydroisocoumarin (3) to the corresponding isocoumarin (6) followed by selective demethylation to (2) and the hydrolysis of the latter to keto acid (1, R=H) which on esterification afforded the keto ester (1, R=Me).

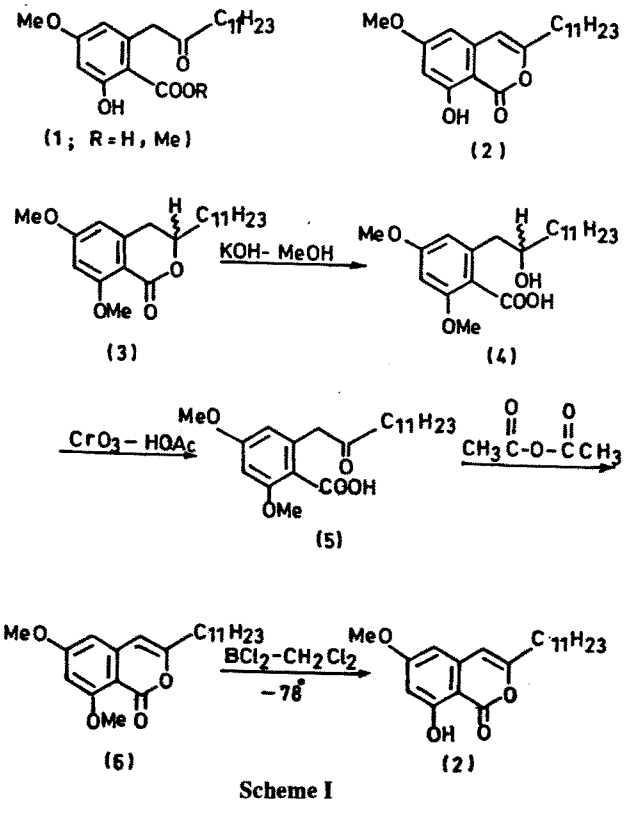
Thus, hydrolysis of the (±)-6,8-dimethoxy-3,4-dihydro-3-undecylisocoumarin (3) with 5% methanolic potassium hydroxide [5] resulted in the opening of lactone ring to afford the hydroxy acid (4) m.p. 50-51°C, characterized by low R_f value in TLC and the IR spectrum which showed the characteristic envelope of carboxylic OH, at 3000-2500 cm^{-1} and a change of carbonyl absorption from 1662 cm^{-1} in (3) to 1716 cm^{-1}. The acid was immediately subjected to chromic acid oxidation since it slowly undergoes spontaneous recyclization to the parent lactone on standing.

Keywords: Isocoumarins; 3,4-dihydro-; Orsellinic acid; *Ononis natrix*

Chromic acid oxidation [6] of the hydroxy acid (4) in glacial acetic acid afforded the corresponding keto acid (5) m.p. 49°C having a markedly higher R_f value.

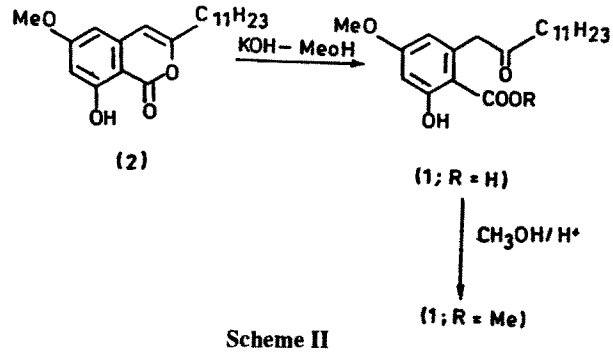
Cyclodehydration of keto acid (5) with acetic anhydride [7] at 50°C for 12 hours, resulted in the 6,8-dimethoxy-3-undecylisocoumarin (6) m.p. 44-45°C. The IR spectrum showed the absorptions at 1716, 1660, 1590 cm^{-1} and in the PMR spectrum the characteristic 1H singlet for C-4 proton at δ 6.08 ppm was evident.

The 8-0-methyl group of (6) was selectively cleaved using boron trichloride to furnish the 8-hydroxy-6-methoxy-3-undecylisocoumarin (2) m.p. 67-68°C (lit. [3] 69-70°C). The carbonyl absorption was lowered from 1716 cm^{-1} to 1685 cm^{-1}, due to chelation with 8-hydroxylic group (Scheme 1).



Scheme I

Alkaline hydrolytic ring opening of isocoumarin (2) in a manner similar to dihydroisocoumarin (3), afforded the *2-hydroxy-4-methoxy-6-(2-oxotridecyl) benzoic acid* (1, R=H) m.p. 113-115°C which is the natural keto acid (1, R=H) actually present in acid fraction of n-hexane extract of *Ononis natrix*. The keto acid was characterized by acid catalysed esterification using absolute methanol to furnish the keto ester (1, R=Me) (Scheme 2).



Scheme II

Experimental Section

Melting points were determined using a MEL-TEMP MP-D apparatus and are uncorrected. IR spectra were recorded on a Hitachi spectrophotometer Model-270 as KBr discs or as neat liquids. PMR (360 MHz) was recorded on a Bruker AM-350 instrument and the EIMS on a MAT-112-S machine.

(±)-2,4-Dimethoxy-6-(2-hydroxytridecyl)benzoic acid (4)

A solution of *(±)-6, 8-dimethoxy-3-undecyl-3,4-dihydroisocoumarin (3)* (0.5 g, 0.0014 mol) in methanolic potassium hydroxide (5%, 20 ml) was refluxed for 2 hours. After cooling, the reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted with ether (3×100 ml) dried and concentrated to leave the hydroxy acid (4) as an oil which solidified on standing m.p. 50-51°C (spot at the base line in TLC).

IR ν_{max}: 3000-2500, 1705, 1635, 1615 cm^{-1}.

2,4-Dimethoxy-6-(2-oxotridecyl)benzoic acid (5)

A solution of the hydroxy acid (4) (0.5 g, 0.0013 mol) in glacial acetic acid (5 ml) was treated with a solution of chromium trioxide (0.4 g, 0.004 mol), water (0.5 ml) and glacial acetic acid at 35° for 3 hours. Extraction with chloroform afforded the keto acid (5) (0.33 g, 0.0008 mol, 68%) m.p. 49-50°C.

IR: 2848, 2500, 1705, 1650, 1575 cm^{-1}.

6,8-Dimethoxy-3-undecylisocoumarin (6)

The crude keto acid (5) (0.30 g, 0.0008 mol) was heated with acetic anhydride (4.3 ml, 0.043 mol) at 50°C for 12 hours. The reaction mixture was poured into ice-water, extracted with ether, dried, concentrated and the oily product was purified by thick layer chromatography. Elution with ether afforded *6,8-dimethoxy-3-undecylisocoumarin (6)* (0.26 g, 0.0007 mol) as colourless crystals m.p. 44-

45°C.
IR(KBr): 1730, 1665, 1600 cm^{-1}.
$\delta(CDCl_3)$: 0.86(3H, t, H11', J=6, 5Hz), 1.25 (18H, brs, H2'-H10'), 1.71 (2H, t, H1', J=4.5Hz), 3.85 (3H, s, 8-OCH_3), 3.87(3H, s, OCH_3), 6.08(1H, s, H4, 6.32 (1H, d, H5 J=2.3Hz), 6.29 ppm (1H, d, H7, J=2.2Hz).
MS m/z: 360 (M^+), 291, 207 (base), 177.

8-Hydroxy-6-methoxy-3-undecylisocoumarin (2)

A solution of boron trichloride in dichloromethane (0.42 ml, 0.0026 mol) was added dropwise to a stirred solution of *6,8-dimethoxy-3-undecylisocoumarin (6)* (0.25 g, 0.00069 mol) at -78°C for 4 hours. After stirring overnight, the mixture was poured into ice-water, filtered, and extracted with dichloromethane (3×20 ml). The combined extracts were washed, dried and concentrated. Thick layer chromatography gave *8-hydroxy-6-methoxy-3-undecylisocoumarin (2)* (0.18 g, 0.0005 mol, 80%) as colourless scales m.p. 67-68°C (lit. [3] 69-70°C).
IR: 1685, 1625, 1584 cm^{-1}.
δ ($CDCl_3$): 0.87 (3H, t, H11', J=6.5Hz), 1.25 (18H, brs, H2'-H10'), 1.72 (2H, t, H1' J=4.5Hz), 3.85(3H, s, 6-OCH_3), 6.21 (1H, s, H4), 6.30 (1H, d, H5 J=2.3Hz), 6.40 (1H, d, H7, J=2.2Hz), 11.21 ppm (1H, s, 8-OH).
MS m/z: 346 (M^+), 191 (base), 163, 137, 55.

2-Hydroxy-4-methoxy-6-(2-oxotridecyl)benzoic acid (1, R=H)

A solution of *8-hydroxy-6-methoxy-3-undecylisocoumarin (2)* (0.35 g, 0.001 mol) in methanolic potassium hydroxide (5%, 25 ml) was refluxed for 2 hours. After cooling, the reaction mixture was diluted with water and extracted with ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted with ether (3×100 ml) dried and concentrated to afford *2-hydroxy-4-methoxy-6-(2-oxotridecyl)benzoic acid* (1, R=H) m.p. 113-115°C.
IR ν_{max}: 3456, 2950, 2500, 1705, 1635, 1615 cm^{-1}.

Methyl 2-hydroxy-4-methoxy-6-(2-oxotridecyl) benzoate (1, R=Me)

A solution of *2-hydroxy-4-methoxy-6-(2-oxotridecyl)benzoic acid* (1, R=H) (0.36 g, 0.001 mol) in dry methanol, and concentrated sulfuric acid (3 drops) was refluxed for 13 hours. The methanol was rotary evaporated, neutralization and the work-up afforded an oil which solidified on standing. Recrystallization from methanol afforded the *methyl 2-hydroxy-4-methoxy-6-(2-oxotridecyl)benzoate* (1, R=Me) as colourless prisms m.p. 86-87°C (lit. [3] 88-89°C).
IR: 1710, 1662, 1593 cm^{-1}.
δ ($CDCl_3$): 0.86(3H, t, H13', J=6.5Hz), 1.25 (18H, brs, H4'-H12'), 1.55 (2H, t, H3' J=4.5Hz), 3.80(3H, s, OCH_3), 3.82(3H, s, 4-OCH_3), 3.87 (2H, s, H1'), 6.25(1H, d, H5, J=6.5Hz), 6.40 ppm. (1H, d, H3, J=2.2Hz).
MS m/z: 378(M^+), 346, 206, 196, 164 (base).

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