# Synthesis of 8-Hydroxy-6-methoxy-3-undecylisocoumarin and 2-Hydroxy-4-methoxy-6-(2-oxotridecyl)benzoic acid

AAMER SAEED, RASHID IQBAL AND NASIM HASAN RAMA*
*Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan*

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## Introduction

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

In 1990, during further studies [3] on the composition of *Ononix nitrix*, 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 ether, 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 [4] the synthesis of the principal dihydroisocoumarins of *Ononix nitrix*. In this article we wish to report the conversion of dihydroisocoumarin (3) to corresponding isocoumarin (6) followed by selective demethylation to (2) and the hydrolysis of latter to keto acid (1, R=H) which on electrification afforded the ketoester (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 envelop of carboxylic OH, at 3000-2500 $cm^{-1}$ and 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.

Chromic acid oxidation [6] of the hydroxy acid (4) in glacial acetic acid afforded the corresponding keto acid (5) m.p. 47°C having 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 $\delta$ 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

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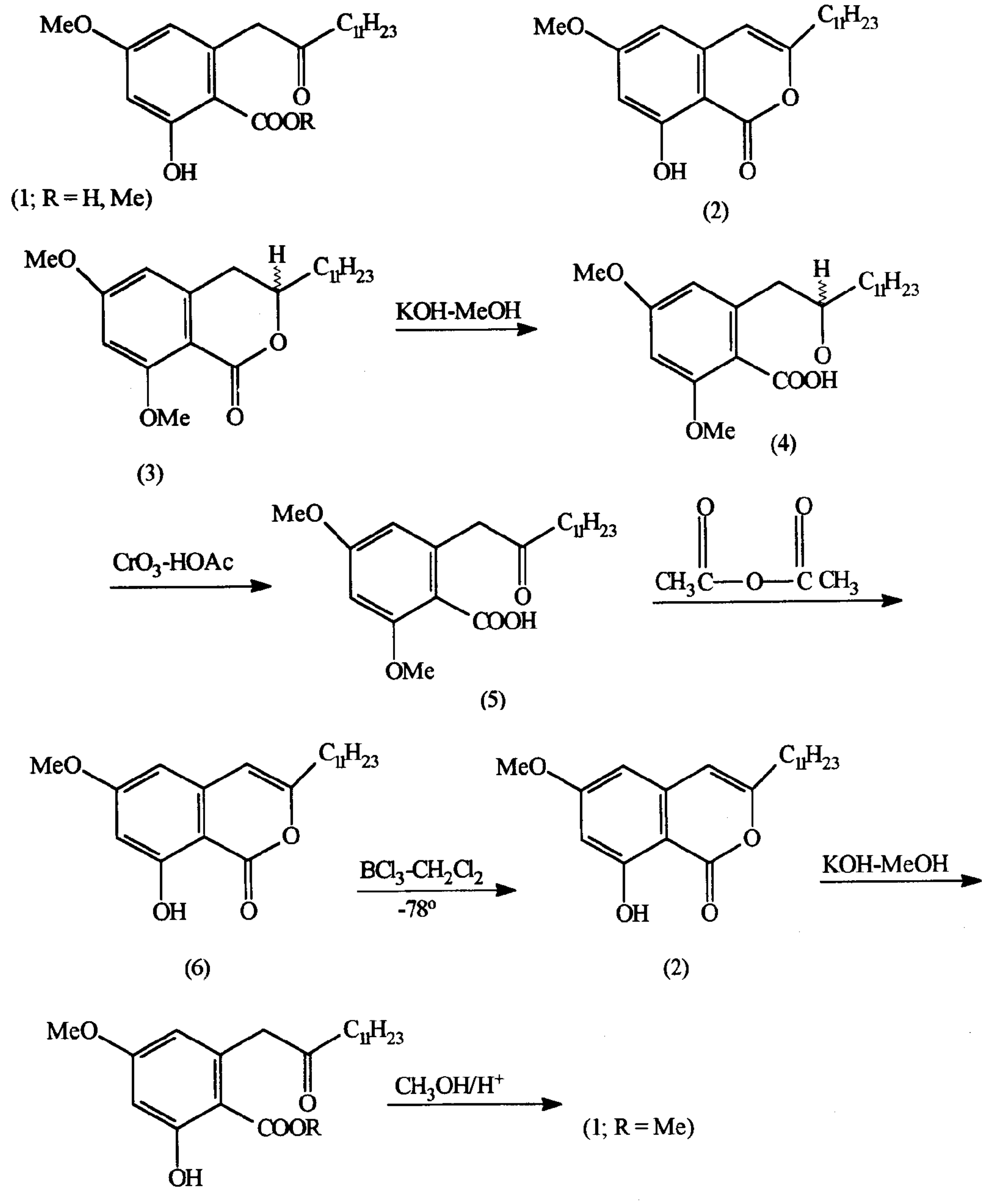
*To whom all correspondance should be addressed.



SYNTHETIC SCHEME

chelation with 8-hydroxylic group (Synthetic Scheme).

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). (Synthetic Scheme).

## Experimental

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. P.M.R (360 MHz) recorded on a Bruker AM-350 instrument and the E.I.M.S. 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 extracted with ether. The aqueous layer was acidified with dil. hydrochloric acid and extracted with ether (3x100 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 $\nu_{max}$: 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, 1575 cm$^{-1}$.

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

The crude keto acid (5) (0.30g, 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, 91%) as colourless crystals. m.p. 44-45°C. IR (KBr): 1730, 1665, 1600 cm$^{-1}$ δ($CDCl_3$): 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 (1H, d, H7, J=2.2Hz) ppm. MS m/z: 360 ($M^+$), 291, 207 (base), 177.

### *8-hydroxy-6-methoxy-3-undecylisocoumarin (2)*

1.0 Molar solution in dichloromethane of boron trichloride (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) in dichloromethane at -78° for 4 hours. After stirring overnight at room temperature, the mixture was poured onto ice-water, filtered, and extracted with dichloromethane (3x20 ml). The combined extracts 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, br, s, 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), 6.4.0(1H, d, H7, J=2.2Hz), 11.21 (1H, s, 8-OH) ppm. 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 extract with ether. The aqueous layer was acidified with dil. hydrochloric acid and extracted with ether (3x100 ml), dried and concentrated to afford 2-Hydroxy-4-methoxy-6-(2-oxotridecyl)benzoic acid (1, R=H) IR $\nu_{max}$: 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-methyoxy-6-(2-oxotridecyl)benzoic acid (1, R=H) (0.36g, 0.001 mol) in dry methanol, and conc. sulfuric acid (3 drops) was refluxed for 13 hours. The methanol was rotary evaporated, neturalization 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$^{-1}$. PMR δ: 0.86 (3H, t, H13′, J=6.5Hz), 1.25 (18H, br s, 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 (1H, d, H3, J=2.2Hz) ppm. MS m/z: 378 ($M^+$), 346, 206, 196, 164 (base).

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