

An Efficient and New Synthesis of (\pm)-8-Hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin

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Summary: The title compound (Ia: $R^1 = \text{Me}$; $R^2 = \text{H}$) which corresponds to the (-)-8-hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin, a mold metabolite from carrots has been synthesized by a new and efficient method. The method involved the reaction of the acid chloride obtained from 3,5-dimethoxyphenylacetic acid with magnesium metal and diethylmalonate to yield 1-(3,5-dimethoxyphenyl)propanone (IIa). The propanone was reduced and the acetylated to (\pm)-1-(3,5-dimethoxyphenyl)propan-2-ylacetate (IIc). Vilsmeier reaction of latter followed by oxidation and hydrolysis yielded (\pm)-6,8-dimethoxy-3-methyl-3,4-dihydroisocoumarin (Ib) which on selective demethylation with boron trichloride furnished the title compound (Ia)

Introduction

(\pm)-8-hydroxy-6-methoxy-3,4-dihydroisocoumarin (Ia) also called (\pm)-6-methoxymellein corresponds to (-)-8-hydroxy-6-methoxy-3-methyl-4-dihydroisocoumarin, a mold metabolite from carrots which have been stored for sometime after harvest [1,2]. The isolation and identification of the metabolite by chemical and spectroscopic method was first reported by Sondheimer [1].

Later, Condon *et al.* [3] reported a biosynthesis of the naturally occurring (-)-8-hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin. The only synthesis of (Ia) found in the literature [4] is from 3,5-dimethoxyhomophthalic acid which was itself prepared from 3,5-dimethoxyphenylpropanoic acid using a cumbersome long route. This report, however, neither includes the percentage yield nor the spectroscopic data of the final product (Ia).

We now wish to report a new and convenient synthesis of (Ia) starting from 3,5-dimethoxyphenylacetic acid which was synthesized by an authenticated route [5] from commercially available 3,5-dihydroxybenzoic acid. 1-(3,5-dimethoxyphenyl)propan-2-one (IIa) was prepared from 3,5-dimethoxyphenylacetic acid by adopting the method of Hauser and Walker [6]. Reduction of the ketone (IIa) with sodium borohydride yielded the carbinol (IIb) which was converted to the acetate (IIc) using pyridine-acetic anhydride method. Aldehyde (IIIa) was obtained by subjecting the acetate (IIc) to Vilsmeier reaction [7]. Oxidation of (IIIa) with potassium permanganate in neutral aque-

ous acetone [8] to yield the intermediate carboxylic acid (IIIb) was followed by alkaline hydrolysis of the acetate residue. As a result (\pm)-6,8-dimethoxy-3-methyl-3,4-dihydroisocoumarin (Ib) was obtained as white crystals. Selective demethylation [9] of the latter with boron trichloride furnished (\pm)-8-hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (Ia) in good yield. No attempt was made to resolve the racemic mixture.

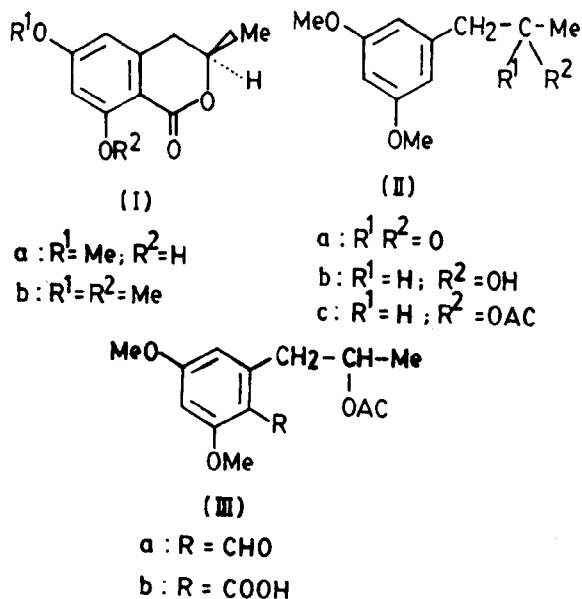
Experimental

Melting points which were determined using MEL-TEMP MP-D apparatus are uncorrected. Infrared spectra were recorded with Hitachi infrared spectrophotometer Model-270. $^1\text{H-NMR}$ spectra were obtained with a Bruker AM-300 machine (300 MHz) in deuteriochloroform (with tetramethylsilane as an internal standard) as solvent. The following abbreviations have been used for the description of the signals: s = singlet, d = doublet, dd = doublet of doublet, t = triplet and m = an unresolved multiplet. A MAT 1125 was used for recording mass spectra at H.E.J. Research Institute of Chemistry, Karachi. The term petroleum ether refers to the fraction (bp 35-60°).

1-(3,5-Dimethoxyphenyl)propan-2-one

Oxalyl chloride (12.0 g; 0.09 mol) was added to a solution of 3,5-dimethoxyphenylacetic acid (9.0 g; 0.045 mol) in dry benzene (60 ml). The solution turned yellow with vigorous effervescence. After 24

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hours, the solvent was evaporated *in vacuo* to give the corresponding acid chloride. More benzene (50 ml) was added and the solvent was again evaporated *in vacuo*. This process was repeated several times till there was no more smell of oxalyl chloride. The residue (9.6 g) was taken up in dry ether and used as such.

Diethyl acylmalonate was prepared by a modification of the procedure of Lund [10,11]. Magnesium turnings (1.2 g; 0.05 mol) and absolute ethanol (1.12 ml) were placed in a round bottom flask and carbon tetrachloride (0.1 ml) was added. The reaction which started almost immediately (an iodine crystal was added to enhance the reaction) was allowed to proceed for a few minutes and then absolute diethyl ether (17 ml) was added cautiously with stirring. The resulting mixture was placed on an oil bath and a solution of diethyl malonate (8.0 g; 0.05 mol) absolute ethanol (4.5 ml) and absolute ether (5.5 ml) was added at such a rate that rapid refluxing was maintained. The mixture was refluxed till all the magnesium metal had dissolved. To the clear solution was added with vigorous stirring an ethereal solution of the acid chloride (0.045 mol) and the mixture refluxed for 2 1/2 hours. The reaction mixture was cooled and acidified with dilute sulphuric acid. The ether phase (with which an ether extract of the aqueous phase was combined) was washed with water and the solvent evaporated *in vacuo*. To the crude diethyl acylmalonate was added a mixture of glacial acetic acid (13.5 ml),

concentrated sulphuric acid (2.0 ml) and water (10.0 ml). This reaction mixture was refluxed for five hours to complete the decarboxylation reaction. The reaction mixture was chilled in an ice bath, made alkaline with sodium hydroxide solution (20 %) and then extracted with ether (3 x 150 ml). The combined ethereal extracts were washed with water, dried over anhydrous sodium sulphate and the solvent evaporated *in vacuo*. The residual material containing the ketone was adsorbed on silica (150g) and eluted with ethyl acetate and petroleum ether (1:19) to yield 1-(3,5-dimethoxyphenyl)propan-2-one (5.0g; 56.2% from acid) as light yellow oil. ν_{\max} film 1716 (m) and 1599 (s) cm^{-1} δ (CDCl₃) 6.35 (3H, m, Ar-H); 3.77 (6H, s, 2-OMe); 3.60 (2H, s, Ar-CH₂-); 2.13 (3H, s, -COCH₃). M.S.: m/z 194 (M⁺) 151, 137, 121, 108, 91 and 77.

(±)-1-(3,5-Dimethoxyphenyl)propan-2-ol

1-(3,5-Dimethoxyphenyl)propan-2-one (5.0 g; 0.025 mol) and sodium borohydride (3.0 g; 0.079 mol) in absolute ethanol (250 ml) were heated under reflux for 1 1/2 hours. The solution was cooled, treated with water and acidified carefully with dilute sulphuric acid. The reaction mixture was extracted with ether (3 x 125 ml) and the combined extract was dried (Na₂SO₄) and solvent evaporated *in vacuo* to leave a light yellow oil which was adsorbed on silica (100 g). Elution with ethyl acetate and light petroleum (3:7) gave (±)-1-(3,5-dimethoxyphenyl)propan-2-ol (4.2 g; 83.2%) as a colourless oil. ν_{\max} film 3412(w) and 1599(s) cm^{-1} δ (CDCl₃) 6.30 (3H, m, Ar - H); 3.96 (1H, m, ArCH₂ - CH-); 3.72 (6H, s, 2-OMe); 2.56 - 2.62 (1H, dd, Ar-CH-, J_{gem} = 12.3 Hz, J_{trans} = 7.4 Hz, J_{cis} = 5.3 Hz); 2.62-2.68 (1H, dd, Ar-CH-J_{gem} = 12.3 Hz, J_{trans} = 5.5 Hz, J_{cis} = 3.4 Hz); 2.51 (1H, s, -OH, exchangeable); 1.18 (3H, d, -CH(OH)-CH₃, J = 6.1 Hz). M.S.: m/z 197, 196 (M⁺), 195, 152, 151, 137, 91, 78 and 77.

(±)-1-(3,5-Dimethoxyphenyl)propan-2-ylacetate

A mixture of (±)-1-(3,5-dimethoxyphenyl)propan-2-ol (4.2 g; 0.021 mol) and acetic anhydride (4.3 g; 3.98 ml; 0.042 mol) in pyridine (10.0 ml) was stirred overnight. Water was added and the reaction mixture was extracted with ether (3 x 100 ml). The combined ether extract was washed with sodium bicarbonate (5%, 3 x 100 ml), hydrochloric

acid (2%: 150 ml), saturated brine solution (100 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give (\pm)-1-(3,5-dimethoxyphenyl)propan-2-ylacetate (4.3 g; 84.3%) as yellow oil. $\nu_{\text{max}}^{\text{film}}$ 1740 (s) and 1602 (s) cm^{-1} . δ (CDCl_3) 6.30 (3H, m, Ar-H); 5.07 (1H, m, $\text{ArCH}_2\text{-CH}$); 3.72 (6H, s, 2 x -OMe); 2.59-2.65 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 6.6$ Hz); 2.80-2.87 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 6.7$ Hz); 1.96 (3H, s, -OCOCH₃); 1.18 (3H, d, -CH-CH₃, $J = 6.3$ Hz). M.S.: m/z 238 (M^+), 178, 150, 121, 91, 79, 78 and 77.

(\pm)-1-(2-Formyl-3,5-dimethoxyphenyl)propan-2-ylacetate

Phosphorous oxychloride (8.9 g; 5.3 ml; 0.058 mol) was added to a stirred solution of (\pm)-1-(3,5-dimethoxyphenyl)propan-2-ylacetate (4.2 g; 0.018 mol) in dimethylformamide (7.5 g; 8.0 ml) under nitrogen. After heating the reaction mixture at 55° for 30 minutes and then at 100° for 10 minutes, sodium acetate (21.5 g) and ice were added. The reaction mixture was extracted with methylene chloride (3 x 125 ml). The combined extracts were dried (Na_2SO_4) and the solvent was evaporated *in vacuo*, leaving a yellow oil which was adsorbed on silica (75 g). Elution with ethyl acetate and light petroleum (3:7) gave (\pm)-1-(2-formyl-3,5-dimethoxyphenyl)propan-2-ylacetate (2.5 g; 53.25%) as a light brown oil which was recrystallized from aqueous methanol, m.p. 50-51°. $\nu_{\text{max}}^{\text{KBr}}$ 1740(s), 1680(s), 1608(s) and 1578 (m) cm^{-1} . δ (CDCl_3) 10.43 (1H, s, Ar-CHO); 6.31 (1H, d, Ar-H, $J = 2.3$ Hz); 6.33 (1H, d, Ar-H, $J = 2.3$ Hz); 5.09 (1H, m, $\text{ArCH}_2\text{-CH}$); 3.82 (6H, s, 2-OMe); 2.87-2.94 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.1$ Hz, $J_{\text{vic}} = 8.5$ Hz); 3.44 - 3.50 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.1$ Hz, $J_{\text{vic}} = 4.1$ Hz); 1.90 (3H, s, -OCOCH₃); 1.26 (3H, d, -CH-CH₃, $J = 6.3$ Hz). M.S.: m/z 266 (M^+), 238, 208, 206, 191, 179, 177, 165, 121, 91 and 77.

(\pm)-6,8-Dimethoxy-3-methyl-3,4-dihydroisocoumarin

Potassium permanganate (0.9 g; 0.005 mole) in neutral acetone (125 ml) was added dropwise for half an hour to a stirred solution of (\pm)-1-(2-formyl-3,5-dimethoxyphenyl)propan-2-ylacetate (1.2 g; 0.004 mol) in neutral aqueous acetone (125:125 ml) at 60-70°. The reaction mixture was heated at 60-70° until the completion of reaction as followed by t.l.c. (9h). The reaction mixture was then stirred

overnight at room temperature, filtered and the residual manganese dioxide was washed with warm acetone. The filtrate was subjected to evaporation of acetone *in vacuo*. Aqueous sodium bicarbonate (5%, 40 ml) was then added the mixture was extracted with methylene chloride (3 x 100 ml): the extract being discarded. The aqueous layer containing sodium salt was acidified with dilute hydrochloric acid, extracted with methylene chloride (3 x 50 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* leaving (\pm)-1-(2-carboxy-3,5-dimethoxyphenyl)propan-2-ylacetate (0.82 g; 0.003 mol) in ethanol (60 ml) was refluxed for two hours with 10% aqueous potassium hydroxide solution (20 ml). The mixture was concentrated to 20 ml *in vacuo*, diluted with water, acidified, extracted with ether (3 x 50 ml) and dried over anhydrous sodium sulphate. Ether was evaporated *in vacuo*, leaving a brown oil of (\pm)-6,8-dimethoxy-3-methyl-3,4-dihydroisocoumarin (0.4 g; 62.5%) which was purified by preparative t.l.c. m.p. 105-107°; 125-128° ([4]). $\nu_{\text{max}}^{\text{KBr}}$ 1704(s), 1602(s), and 1584 (m) cm^{-1} . δ (CDCl_3) 6.27 (1H, d, Ar-H, $J = 2.3$ Hz); 6.37 (1H, d, Ar-H, $J = 2.3$ Hz); 4.42-4.53 (1H, m, $\text{ArCH}_2\text{-CH}$); 3.82 (3H, s, -OMe); 3.88 (3H, s, -OMe); 2.72-2.78 (1H, dd, Ar-CH-, $J_{\text{gem}} = 16.1$ Hz, $J_{\text{vic}} = 3.7$ Hz); 2.79-2.88 (1H, dd, Ar-CH-, $J_{\text{gem}} = 16.0$ Hz, $J_{\text{vic}} = 10.5$ Hz); 1.42 (3H, d, -CH-CH₃, $J = 6.3$ Hz). M.S.: m/z 222 (M^+), 221, 179, 178, 151, 121, 91, 79, 78 and 77.

(\pm)-8-Hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin

(\pm)-6,8-Dimethoxy-3-methyl-3,4-dihydroisocoumarin (0.3 g; 0.001 mol) was dissolved in dry dichloromethane (35 ml), cooled to -70° and boron trichloride in dichloromethane (10%, 15 ml) was added. The solution was stirred for 30 minutes, brought to room temperature and allowed to stand for 3 hours. The reaction mixture was then poured into ice cooled aqueous sodium acetate (10%, 30 ml), shaken and extracted with dichloromethane (3 x 50 ml). The extracts were combined, washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo* to give a yellow oil which was chromatographed on silica. Elution with ether and light petroleum (1:20) followed by recrystallisation from methanol gave (\pm)-8-hydroxy-6-methoxy-3-methyl-3,4-dihydroisocoumarin (0.2 g; 80%), m.p. 90-91°; 95-97° ([4]). An ethanolic solution of the isolated product gave a red brown colouration with

acid (2%: 150 ml), saturated brine solution (100 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give (\pm)-1-(3,5-dimethoxyphenyl)propan-2-ylacetate (4.3 g; 84.3%) as yellow oil. $\nu_{\text{max}}^{\text{film}}$ 1740 (s) and 1602 (s) cm^{-1} . δ (CDCl_3) 6.30 (3H, m, Ar-H); 5.07 (1H, m, $\text{ArCH}_2\text{-CH}$); 3.72 (6H, s, 2 x -OMe); 2.59-2.65 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 6.6$ Hz); 2.80-2.87 (1H, dd, Ar-CH-, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 6.7$ Hz); 1.96 (3H, s, - OCOCH_3); 1.18 (3H, d, - CH-CH_3 , $J = 6.3$ Hz). M.S.: m/z 238 (M^+), 178, 150, 121, 91, 79, 78 and 77.

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overnight at room temperature, filtered and the residual manganese dioxide was washed with warm acetone. The filtrate was subjected to evaporation of acetone *in vacuo*. Aqueous sodium bicarbonate (5%, 40 ml) was then added the mixture was extracted with methylene chloride (3 x 100 ml); the extract being discarded. The aqueous layer containing sodium salt was acidified with dilute hydrochloric acid, extracted with methylene chloride (3 x 50 ml) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* leaving (\pm)-1-(2-carboxy-3,5-dimethoxyphenyl)propan-2-ylacetate (0.82 g; 0.003 mol) in ethanol (60 ml) was refluxed for two hours with 10% aqueous potassium hydroxide solution (20 ml). The mixture was concentrated to 20 ml *in vacuo*, diluted with water, acidified, extracted with ether (3 x 50 ml) and dried over anhydrous sodium sulphate. Ether was evaporated *in vacuo*, leaving a brown oil of (\pm)-6,8-dimethoxy-3-methyl-3,4-dihydroisocoumarin (0.4 g; 62.5%) which was purified by preparative t.l.c. m.p. $105\text{-}107^\circ$; $125\text{-}128^\circ$ ([4]). $\nu_{\text{max}}^{\text{KBr}}$ 1704(s), 1602(s), and 1584 (m) cm^{-1} . δ (CDCl_3) 6.27 (1H, d, Ar-H, $J = 2.3$ Hz); 6.37 (1H, d, Ar-H, $J = 2.3$ Hz); 4.42-4.53 (1H, m, $\text{ArCH}_2\text{-CH}$); 3.82 (3H, s, -OMe); 3.88 (3H, s, -OMe); 2.72-2.78 (1H, dd, Ar-CH-, $J_{\text{gem}} = 16.1$ Hz, $J_{\text{vic}} = 3.7$ Hz); 2.79-2.88 (1H, dd, Ar-CH-, $J_{\text{gem}} = 16.0$ Hz, $J_{\text{vic}} = 10.5$ Hz); 1.42 (3H, d, - CH-CH_3 , $J = 6.3$ Hz). M.S.: m/z 222 (M^+), 221, 179, 178, 151, 121, 91, 79, 78 and 77.

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ferric chloride solution. ν_{\max} film 3430(w), 1685(s), 1605(m) and 1518(m) cm^{-1} δ (CDCl_3) 11.21 (1H, s, -OH, exchangeable); 6.20 (1H, d, Ar - H, $J = 2.3$ Hz); 6.32 (1H, d, Ar - H, $J = 2.3$ Hz), 4.56-4.67 (1H, m, ArCH_2 - CH -); 3.73 (3H, s, -OMe); 2.84-2.90 (1H, dd, Ar - CH -, $J_{\text{gem}} = 16.1$ Hz, $J_{\text{vic}} = 3.7$ Hz); 1.47 (3H, d, -CH - CH_3 , 6.3 Hz). (Found: C, 63.1; H, 5.6, $\text{C}_{11}\text{H}_{12}\text{O}_4$ requires C, 63.4; H, 5.8%).

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