One Step Synthesis of 3-(Phenylethenyl)isocoumarin as a Model of Achlisocoumarin II and III and its Conversion to 3,4-Dihydro- derivative.

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(Received 20th September, 1997, revised 7th January, 1998)

Summary:3-(Phenylethenyl)isocoumarin (**4**) which is a model of achlisocoumarin II (**2**) and achlisocoumarin III (**3**) was synthesised by the direct condensation of homophtalic acid with cinnamoyl chloride. This isocoumarin (**4**) on hydrolysis with aqueous potassium hydroxide in ethanol yielded keto-acid (**5**) which was characterized by the formation of keto-ester (**6**). Reduction of the keto-acid (**5**) with sodium borohydride followed by cyclodehydration gave (dl)-3-(phenylethenyl)-3,4-dihydro-isocoumarin (**8**). Isocoumarin (**4**) and 3,4-dihydroisocoumarin (**8**) were screened out *in vitro* for antibacterial activity.

Introduction

In 1990 Mizuno and Yoshida *et al* [1] carried out a chemical investigation of plant *Achlys triphylla* (J.E.Sm) DC family berberidaceae, to determine its chemotaxonomic relationships with other members of the subtribe Epmedinae and to look for chemicals with medicinal properties. The isolation of three phenolic compounds with novel structures, from the underground parts of *A.triphylla* were reported. The structures of the isolated compounds were established using IR, UV, PMR, CMR, and high resolution mass spectra. The isolated compounds were named as achlisocoumarin I (**1**), achlisocoumarin II (**2**) and achlisocoumarin III (**3**) (Fig.1). In continuation of our synthesis of naturally occuring isocoumarins [2] and 3,4-dihydroisocoumarins [3,4], we report in this article one step synthesis of 3-(phenylethenyl)-isocoumarin (**4**) as a model of achlisocoumarins II and III.

Results and Discussion

Thus, direct condensation [5] of cinnamoyl chloride (predominatly cis) with homophthalic acid at 200°C afforded the 3-(phenylethenyl)isocoumarin (**4**). The isocoumarin (**4**) showed characteristic 1H singlet at δ 6.94 for C_4-H and the lactonic carbonyl absorption at 1718 cm^{-1}. The coupling constants of ethenyl protons were observed as 8 Hz hence were deduced in the cis form. Alkaline hydrolysis afforded the keto-acid (**5**) which showed a 2H singlet at δ 4.65 for methylene protons. In the IR spectrum the absorption for ketonic and carbonyl groups were observed at 1683 and 1700 cm^{-1} respectively. Isocoumarin (**4**) was obtained on refluxing of keto-acid (**5**) with acetic anhydride. Methylation of (**5**) with excess of methyl iodide or by reflux with acidic dry methanol for eight hours without using sodium bicarbonate in the work up yielded the methyl keto-ester (**6**). In the IR spectrum of (**6**) carbonyl absorption at 1720 cm^{-1} and 1685 cm^{-1} were observed for ester and keto groups respectively. In the PMR spectrum of the keto-ester (**6**) 3H singlet at δ 3.74 confirmed the esterification. Sodium borohydride reduction of keto-acid (**5**) should have afforded the corresponding racemic hydroxyacid (**7**) which was not isolated and treated directly with acetic anhydride to produce (dl)-3-(phenylethenyl)-3,4-dihydroisocoumarin (**8**). The dihyroisocoumarin (**8**) exhibited carbonyl absorption at 1720 cm^{-1} in its IR spectrum and the typical ABX pattern of C_3-H and typical AB pattern of C_4-H proton in the PMR spectrum. Thus each of the C_4-H showed a doublet at δ 3.05 and 3.37 and doublet of doublet for C_3-H was observed at δ 5.51. On the basis of coupling constant between H_1' & H_2' observed as 8.0 Hz, we suggest cis configuration across the ethenyl double bond. Furthermore, relatively high coupling constant observed between H_3 and H_{4a} (12Hz) is a strong evidence of the presence of an axial hydrogen atom at C-3. Such a hydrogen would not so drastically couple with either of C-4 hydrogen atoms. Hence the structure (A) is the proposed structure of (**8**).

Antibacterial activity

Screening of the 3-(phenylethenyl) isocoumarin (**4**) and (dl)-3-(phenylethenyl)-3,4-dihydroisocoumarin (**8**) against different pathogens e.g.

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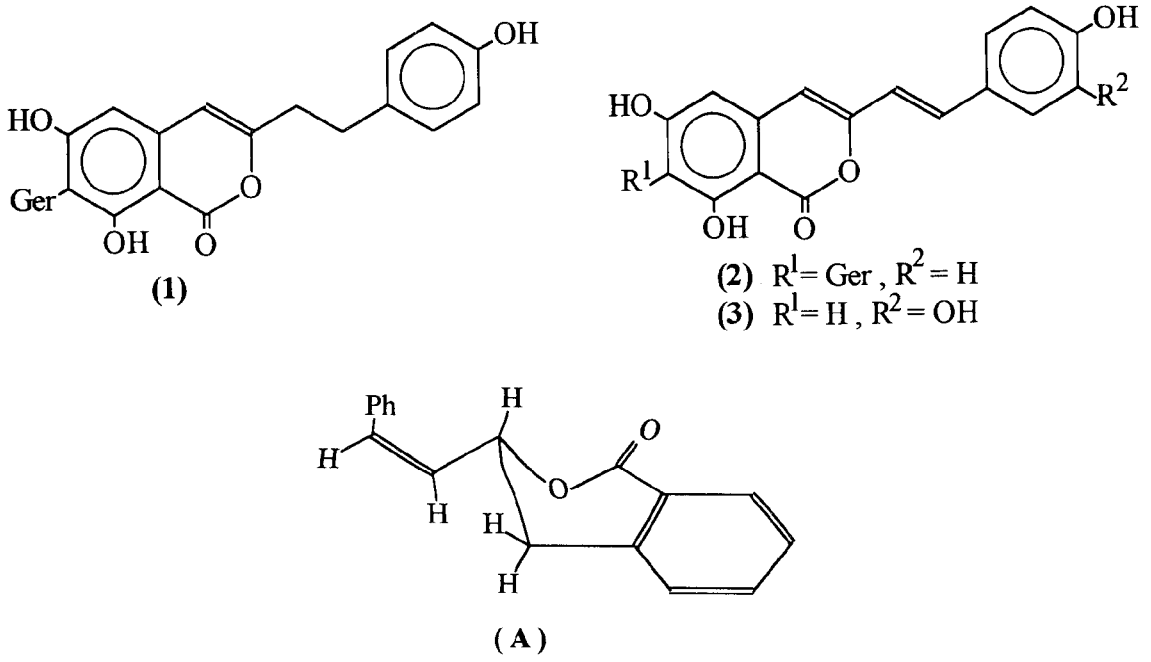


Fig.1

Bacillus cereus diphtheriae, Escherichia coli ETEC Kiebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeroginosa, Salmonella typhi, Shigella boydli, Staphylococcus aureus and Streptococcus pyogenes by Agar well diffusion protocol (1987) showed minor antibacterial activity.

Experimental

Melting point were determined on a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 270-50 Infrared spectrophotometer as KBr disc or as neat liquid. ^{1}H-NMR (500 MHz) spectra were recorded on a Bruker AM-500 as $CDCl_3$ solution , using TMS as internal standard, and EIMS on a MAT-112-S machine, 70eV.

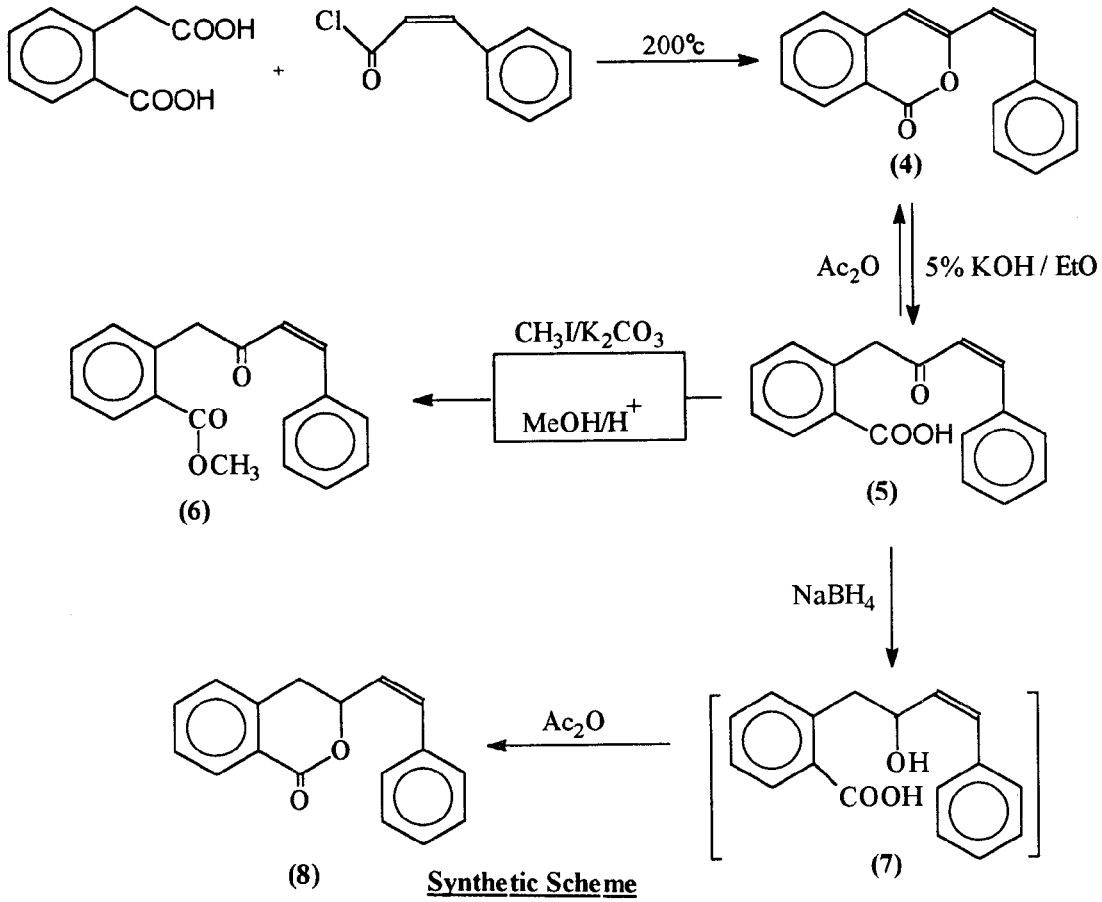
3-(Phenylethenyl)isocoumarin(4)

A mixture of homophthalic acid (1.5 g, 8.33 mmol) and cinnamoyl chloride (5.69g, 34.15 mmol) was heated at 200°c under stirring for three hours. The residue was purified by column chromatography on silica gel in pet-ether (60-80°c) and recrystallized from methanol to afford 3-(phenylethenyl) isocoumarin (**4**) (0.1.8 g, 0.0073mol, 87.4 %) mp 80-82°c. ν_{max} (KBr): 1718 , 1640 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 6.94 (1H, s, H-4), 7.30 (1H, d, J= 8.0 Hz , H-2'), 7.32 (1H, d, J= 8.0 Hz , H-1') , 7.53 (1H , ddd , J= 1.0, 2.0 , 8.0 Hz , H-5) ,7.50-7.51 (3H, m, H-7, 3") , 7.72 (1H, dt, J= 7.5, 1.5 Hz , H-6), 7.78 (1H, td , J= 8.0 , 1.5 and 1.5 Hz, H-4"), 8.02 (2H, t, J= 2.0 Hz, H-2"), 8.30 (1H , dd , J=8.0 , 1.5 Hz , H-8). MS. (70 ev): m/z (%) = 248(100)[M$^+$], 220 (60.6), 117 (0.8), 105 (19.8) .

$C_{17}H_{12}O_2$:Calcd. 248.0837 , found 248.0842 (MS).

2-[2'-Oxo-3'-butenyl-(4'-phenyl)]benzoic acid (5)

A suspension of 3-(phenylethenyl) isocoumarin (**4**) (0.6 g, 2.42 mmol) in ethanol (20 ml) and potassium hydroxide (5% ,50 ml) was refluxed for five hours. After cooling, the reaction mixture was evaporated to remove ethanol under reduced pressure. Cold water (20ml) was added and the reaction mixture was acidified with dil. hydrochloric acid. The reaction mixture was then extracted with dichloromethane (2×20ml), dried (Na_2SO_4) and the solvent was rotatory evaporated to give an oil which



Synthetic Scheme

solidified on standing and recrystallized from ethyl acetate and pet-ether (60-80°c) to afford the compound 2-[2'-oxo-3'-butenyl-(4'-phenyl)]benzoic acid (5) (0.45 g, 1.69 mmol , 69.9 %) mp 131-132°c. νmax (KBr): 1700, 1683, 1598 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.65 (2H, s , H-1') , 7.24 (2H, dd, J= 7.5, 1.0 Hz , H-3") , 7.33 (1H, d , J= 8.0 Hz , H-4'), 7.35 (1H , d , J= 8.0 Hz , H-3') ,7.40 (1H, dt , J=8.5, 1.5 Hz, H-5), 7.54 (1H, dt , J= 7.5, 1.5 Hz H-4), 7.69 (1H, ddd , J= 8.0 , 2.0 & 1.0 Hz , H-3),7.93 (2H , dd, J= 7.5, 1.0 Hz , H-3"), 8.12 (1H dd, J=8.0, 1.5 Hz, H-6), 8.14 (2H, t, J= 2.0 Hz, H-2"), 10.2 (1H, s, COOH, D_2O exchanged). MS (70 ev): m/z (%) =266 (5.4)[M^+], 248 (88.5)[M^+-H_2O], 222 (10.6), 118 (45.2),105 (100) .

$C_{17}H_{14}O_3$: Calcd. 266.0943, found 266.0938 .(MS)

3-(Phenylethenyl)isocoumarin (4)

The compound (5) (0.1g, 3.7 mmol) was refluxed with acetic anhydride (1 ml) for twelve hours. After cooling, the reaction mixture was poured into ice water and extracted with ethyl acetate (2×10 ml). The extracts were combined and washed with sodium bicarbonate (2×10 ml, 5%) dried (Na_2SO_4) and concentrated to give an oily product which was solidified on standing and recrystallized from methanol to afford 3-(phenyl-ethenyl)isocoumarin (4) (0.0639g, 0.26 mmol, 68.6 %). mp 156-157°c, mix. mp 157°c . Rf value, mass, high resolution mass, IR and ^{1}H-NMR spectral data is in good agreement with already synthesized 3-(phenylethenyl)isocoumarin (4) .

Methyl 2-[2'-oxo-3'-butenyl-(4"-phenyl)]benzoate (6)

Method A

The compound (5) (0.15 g, 5.6 mmol), methyl iodide in excess and anhydrous potassium carbonate (1.0 g) in dry acetone (10 ml) were heated under reflux for four hours. The reaction mixture was

filtered when hot, the cake was washed with warmed dry acetone (10 ml) and the solvent was evaporated *in vacuo* leaving an oil which solidified on standing and recrystallized from diethyl ether to afford methyl 2-[2'-oxo-3'-butenyl-(4'-phenyl)] benzoate (**6**). (0.085g , 0.3 mmol , 54.2 %) mp 102-103.ν_{max} (KBr): 1720, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, OMe) , 4.64 (2H, s, H-1'), 7.25 (2H, dd, J= 7.5, 1.0 Hz , H-3"), 7.33 (1H, d, J= 8.0 Hz , H-4'), 7.35 (1H, d, J= 8.0 Hz, H-3'),7.40 (1H, dt, J=8.5, 1.5 Hz , H-5), 7.54 (1H, dt , J= 7.5, 1.5 H , H-4), 7.70 (1H, ddd , J= 8.0, 2.0 & 1.0 Hz, H-3), 7.93 (2H, dd, J= 7.5 , 1.0 Hz , H-3"), 8.12 (1H dd, J=8.0, 1.5 Hz, H-6), 8.14 (2H, t , J= 2.0 Hz, H-2"), Mass (70 ev): m/z (%) = 280.1099 (3.15)[M^+],249 (9.12), 248 (40.14), 149 (11.59), 118 (2.70),105 (100)

$C_{18}H_{16}O_3$: Calcd. 280.1099, found 280.1012 (MS)

Method B

A solution of compound (**5**)(0.1 g, 3.7 mmol) in dry methanol (50 ml) and conc. sulfuric acid (one drop) was refluxed for three hours. Water (30 ml) was then added and methanol removed under reduced pressure. Extraction with ether (2×20ml), followed by removal of solvent and purification by thick layer chromatography to furnished methyl 2-[2'-oxo-3'-butenyl-(4'-phenyl)]benzoate (**6**) mp.102-103°c (0.0644 g, 0.23 mmol, 61.2%). R_f value, mass, high resolution mass, IR and ^{1}H-NMR spectral data is in good agreement with already synthesized (**6**).

(dl)-3-(Phenylethenyl)-3,4-dihydroisocoumarin (8)

The compound (**5**) (0.15 g, 5.6 mmol) was heated under reflux with sodium boronhydride (0.15 g) in absolute ethanol (30 ml) for six hours. Ethanol was rotary evaporated, cold water (25 ml) was then added and the reaction mixture was acidified with dil. sulfuric acid to give precipitate which was extracted with ethyl acetate (2×30ml). The solvent was dried (Na_2SO_4) and evaporated to leave crystals of compound (**7**)(0.12g) . This crude compound was dissolved in acetic anhydride (2 ml) and heated under reflux for two hours. The reaction mixture was cooled, water (20 ml) was added. The reaction mixture was stirred and extracted with dichloromethane (2×20ml). The extracts were combined and washed with sodium bicarbonate (2×10ml, 5%), then with water (10 ml), dried (Na_2SO_4) and rotary evaporated to leave a crude solid. The crude solid was recrystallized from methanol to furnish (dl)-3-(phenylethenyl)-3,4-dihydroisocoumarin (**8**)(0.09 g, 0.36 mmol, 63.84%) mp 107-109°c .ν_{max} (KBr): 1720, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.05 (AB ,1H, d ,d , J_{vic}=3.20, J_{gem}=16.48 Hz, H-4), 3.37 (AB ,d ,d , J_{vic}=12.06, J_{gem}=16.48 Hz, H-4), 5.51 (1H, dd, J=12.06, 3.21 Hz , H-3), 7.25 (1H, d, J=8.0Hz, H-2'), 7.28 (1H, d , J=8.0 Hz , H-1'), 7.40-7.41 (3H, m, H-7 & 3") , 7.43 (1H , tt , J=8.0 , 1.0 & 1.0 Hz , H-4"), 7.49 (1H , ddd , J=8.0 , 2.0 & 1.0 Hz , H-5), 7.54 (1H, dt, J=7.5 & 1.0 Hz, H-6), 7.65 (2H, t, J=2.0 Hz, H-2"), 8.14 (1H, dd, J=7.0 & 1.5 Hz, H-8). MS (70 ev): m/z (%) = 250 (12.0)[M^+], 222 (0.4), 118 (100), 106 (0.6), 78 (1.1) .

$C_{17}H_{14}O_2$:Calcd. 250.0994, found 250.0990 (MS)

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