

Note

A convenient synthesis of xyridin A metabolite from *Xyris indica* L.

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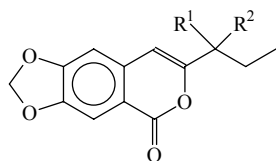
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A convenient synthesis of xyridin A (isocoumarin) isolated from *Xyris indica* L. has been carried out. 4,5-Dimethoxyhomophthalic acid is condensed with butanoyl chloride to yield 3-*n*-propyl-6,7-dimethoxyisocoumarin which on demethylation with aluminium chloride followed by reaction with dibromomethane and Adogen 464 as a catalyst affords xyridin A.

Keyword: Isocoumarins, synthesis, Xyridin A, *Xyris indica* L

IPC: Int.Cl.⁷ C 07 D

Two new isocoumarins named xyridin A and B¹ were isolated by Ruangrunsi *et al.* in 1995 from the non-polar fraction of the chloroform extract of the flowering heads of a weed *Xyris indica* L. *Xyris indica* L is one of the five species of genus *Xyris* found throughout Thailand and is known locally as 'Krathin thung'. In Bengal the plant has been used in folklore medicine as a cure for ringworm, itch and leprosy. 5,6-Dimethoxyindan-1, 2-dione **4**, which is an intermediate product in our synthetic scheme, has shown evaluated performance in fingerprint work². The structures of xyridin A and B have been established by modern spectroscopic techniques as 3-*n*-propyl-6,7-(methylenedioxy)isocoumarin **1a** and 3-(1'-oxopropyl)-6,7-(methylenedioxy)isocoumarin **1b**, respectively.



1a R¹ = R² = H

1b R¹R² = O

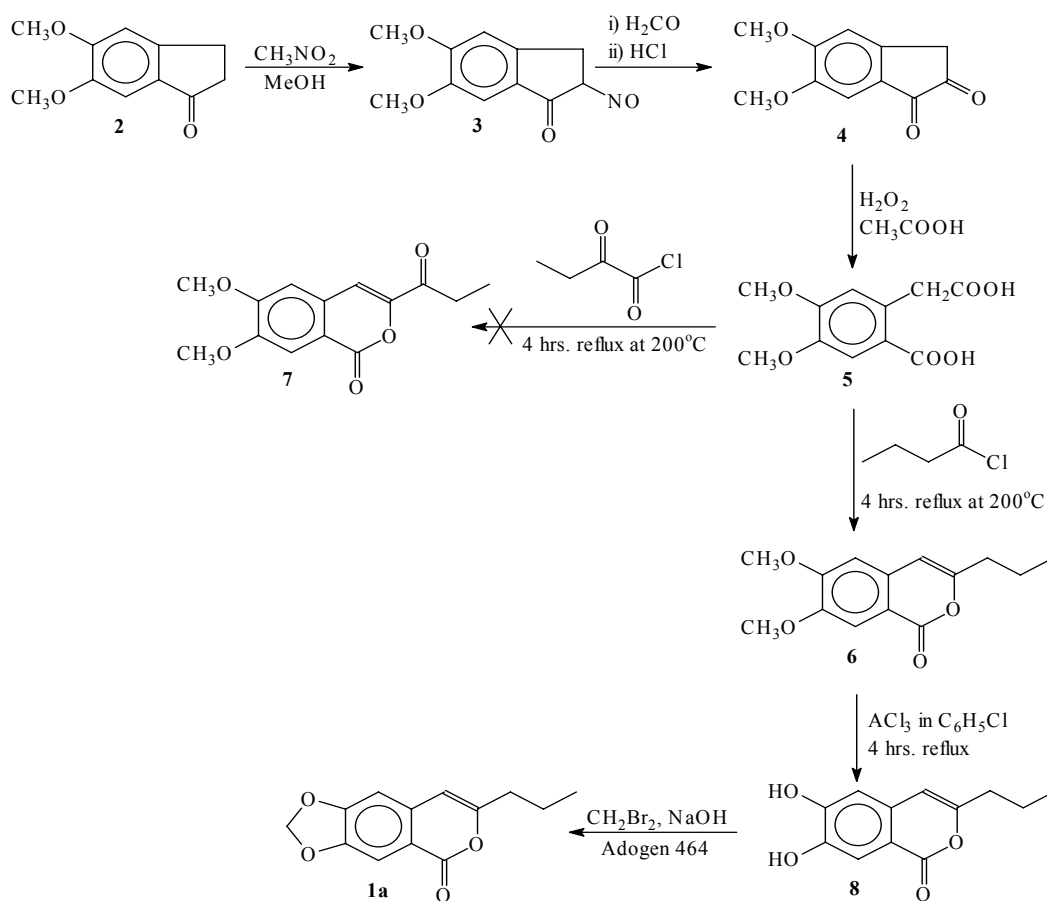
In continuation of our previous efforts towards synthesis of naturally occurring isocoumarins³⁻⁵ and dihydroisocoumarins⁶, which show a wide range of biological activities, we report herein the total synthesis of Xyridin A **1a** which confirms the structural assignment but also makes it available for biological evaluation.

Results and Discussion

4,5-Dimethoxyhomophthalic acid **5** was prepared in two steps from 5,6-dimethoxy-indan-1-one according to the literature procedure⁷. Condensation of 4,5-dimethoxyhomophthalic acid **5** with a butanoyl chloride (which is commercially available) was carried at 200°C to yield 3-*n*-propyl-6,7-dimethoxyisocoumarin **6** which showed characteristic ¹H singlet of isocoumarin at δ 6.16 for C-4 proton while characteristic lactonic carbonyl absorption appeared at 1725 cm⁻¹ in the IR spectrum. The mass spectrum showed the molecular ion peak at m/z 248 while HREIMS molecular ion was found to be in good agreement with the calculated value. This isocoumarin **6** was demethylated with aluminium chloride in chlorobenzene to yield 3-*n*-propyl-6, 7-dihydroxyisocoumarin **8**, which without purification was used in the next step. The demethylated isocoumarin **8** was dissolved in sodium hydroxide solution and then added to the stirred solution of dibromomethane using Adogen 464 as a catalyst to afford the xyridin A **1a** whose physical and spectroscopic properties are in good agreement with the xyridin A **1a** isolated from the natural source. In the synthetic scheme of xyridin **1b**, condensation of 4,5-dimethoxyhomophthalic acid **5** with 2-oxobutanoyl chloride (which was prepared from commercially available 2-oxobutanoic acid on reaction with oxalyl chloride at room temperature) at 200°C did not take place to afford 3-(1'-oxopropyl)-6,7-dimethoxyisocoumarin **7** as shown by IR, ¹H NMR and EIMS spectra, which may be due to the instability of the 2-oxobutanoyl chloride as shown in the Scheme I.

Experimental Section

Melting points of the compounds were determined in open capillaries on Gallenkamp melting point



Scheme I

apparatus and are uncorrected. The IR spectra were recorded on Bio-Rad Merlin FTIR spectrophotometer as KBr discs or as neat liquids. ^1H NMR (400 MHz) spectra were recorded on a Bruker AM-400 as CDCl_3 solution using TMS as internal standard and EIMS were recorded on a MAT-311 machine.

2-Nitroso-5,6-dimethoxyindan-1-one 3: Commercially available 5,6-dimethoxyindan-1-one **2** (2.0 g, 0.0104 mole) was dissolved in methanol (25 mL) and concentrated hydrochloric acid (7 mL). Nitro methane gas was passed for 15 min through the reaction mixture, nitroso-derivative precipitated out, which was filtered, dried and recrystallized with pet. ether (40–80°C) to give 2-nitroso-5,6-dimethoxyindan-1-one **3** (1.8 g, 0.008 mole, 78%). m.p. 182°C; IR (ν_{max} , KBr): 1780, 1717 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.75 (2H, d, $J = 7.2$ Hz, H-3), 3.91 (3H, s, $-\text{OCH}_3$), 3.98 (3H, s, $-\text{OCH}_3$), 4.3 (1H, t, $J = 7.3$ Hz, H-2), 6.90 (1H, s, H-4), 7.3 (1H, s, H-7) ppm; EIMS: m/z (%) = 221(73.51) [M^+], 204(100), 192(16.23), 176(46.56), 159.9(13.61), 131.9(33.87), 117.9(17.14), 77(27.55), 63(55.26).

5,6-Dimethoxyindan-1,2-dione 4: 2-Nitroso-5,6-dimethoxyindan-1-one **3** (1.5 g, 0.0067 mole) was mixed with formaldehyde (50 mL) and tritrated with concentrated hydrochloric acid. The reaction mixture was treated with hot water and extracted with chloroform. The organic layer was separated and rotary evaporated to afford 5,6-dimethoxyindan-1,2-dione **4** (1.2 g, 0.0058 mole, 80%). m.p. 154°C; IR (ν_{max} , KBr): 1710, 1680 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.49 (2H, s, H-3), 3.91 (3H, s, $-\text{OCH}_3$), 4.0 (3H, s, $-\text{OCH}_3$), 6.91 (1H, s, H-4), 7.29 (1H, s, H-7) ppm; EIMS: m/z (%) = 206(19.09) [M^+], 178(84.93), 163(1.68), 150(100), 135(20.52), 118.9(3.32), 107(15.54), 91.9(24.52), 77(14.05), 63(18.50).

4,5-Dimethoxyhomophthalic acid 5: 5,6-Dimethoxyindan-1,2-dione **4** (1.2 g, 0.0058 mole) was mixed with glacial acetic acid (30 mL) and hydrogen peroxide (4 mL, 10%) was added dropwise. The reaction mixture was cooled for 15 min and crude 4,5-dimethoxyhomophthalic acid **5** precipitated out which was filtered and washed with cold water to remove excess of acetic acid and was recrystallized from hot

water (1.0 g, 0.004 mole, 72%). m.p. 212°C (lit. [8] m.p. 215°C); IR (ν_{\max} , neat), 1628 and 1577 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.70 (3H, s, $-\text{OCH}_3$), 3.72 (3H, s, $-\text{OCH}_3$), 3.76 (2H, s, H-1'), 6.57 (1H, s, H-3), 7.40 (1H, s, H-6), 11.0 (2H, broad s, $-\text{COOH}$, exchangeable with D_2O); EIMS: m/z (%) = 240(42.06) [M^+], 222(26.37), 196(100), 194(70.88), 181(26.18), 152(3.71), 151(26.42), 150(41.60), 135(26.96), 120(2.06), 119(3.99), 89(6.02).

3-*n*-Propyl-6,7-dimethoxyisocoumarin 6: A mixture of 4,5-dimethoxyhomophthalic acid **5** (1.0 g, 0.004 mole) and butanoyl chloride (1.7 g, 0.016 mole) was heated at 200°C under reflux for 4 hr. The reaction mixture was dissolved in ethyl acetate (25 mL), extracted with sodium carbonate solution (3×25 mL). The organic layer was separated, concentrated and chromatographed on silica gel using pet.ether (40-80°C) as an eluent to afford 3-*n*-propyl-6,7-dimethoxyisocoumarin **6** (0.7 g, 0.0028 mole, 70%) as an oil. IR (ν_{\max} , neat): 1725 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.96 (3H, t, H-3', $J = 7.31$ Hz), 1.70 (2H, m, H-2', $J = 7.45$, 7.48 Hz), 2.47 (2H, t, H-1', $J = 7.38$ Hz), 3.93 (3H, s, $-\text{OCH}_3$), 3.95 (3H, s, $-\text{OCH}_3$), 6.16 (1H, s, H-4), 6.70 (1H, s, H-5), 7.60 (1H, s, H-8) ppm; EIMS: m/z (%) = 248 (100) [M^+], 220 (9.2), 219 (56.7), 191 (64.7), 149 (38.2), 119 (25.9), 117 (18.26), 89 (11.8), 63 (59.0); HREIMS: 248.0900 (Calcd. for $\text{C}_{14}\text{H}_{16}\text{O}_4$, 248.1045).

3-*n*-Propyl-6, 7-(methylenedioxy)isocoumarin (xyridin A) 1a: 3-*n*-Propyl-6,7-dimethoxyisocoumarin **6** (2.0 g, 0.008 mole) was dissolved in dry chlorobenzene (20 mL) and refluxed with powdered anhydrous aluminium chloride (2.0 g, 0.015 mole) for 4 hr to give 3-*n*-propyl-6,7-dihydroxyisocoumarin **8**. The reaction mixture was cooled, poured into ice-cold hydrochloric acid (15%) and extracted with diethyl ether (3×50 mL). The combined ethereal extract was extracted with aq. sodium hydroxide (1%), acidified with dilute hydrochloric acid and the reaction mixture was extracted with dichloromethane (3×50 mL) (it showed a positive FeCl_3 test). The crude demethylated isocoumarin **8** was used without purification in the next step. A mixture of water (10 mL), dibromomethane (5 mL) and one drop of Adogen 464 were stirred vigorously and heated to reflux and air was replaced by Argon. 3-*n*-Propyl-6,7-dihydroxyisocoumarin **8** (1.32 g, 0.006 mole) was dissolved in sodium hydroxide (0.1 mole in 20 mL water) and slowly added dropwise to the stirred solution of

dibromomethane. The addition was completed in 2 hr and the reaction mixture was stirred for further 1 hr to furnish 3-*n*-propyl-6, 7-(methylenedioxy)isocoumarin (xyridin A) **1a**. The reaction mixture was extracted (lit. [1] m.p. 67-68°C); IR (ν_{\max} , neat): 3092, 2960, 1725, 1600 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.93 (3H, t, H-3', $J = 7.35$ Hz), 1.66 (2H, tq, H-2', $J = 7.30$, 7.48 Hz), 2.78 (2H, t, H-1', 7.31 Hz), 6.14 (2H, s, OCH_2O), 6.39 (1H, s, H-5), 7.41 (1H, s, H-8) ppm; EIMS: m/z (%) = 232 (100) [M^+], 204 (2.6), 203 (6.9), 175 (5.5), 133 (14.9), 75 (3.9); HREIMS: 232.0667 (Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}_4$, 232.0735).

Attempted synthesis of 3-(1'-Oxopropyl)-6,7-dimethoxyisocoumarin 7: A mixture of 4,5-dimethoxyhomophthalic acid **5** (1.0 g, 0.004 mole) and 2-oxobutanoyl chloride (which was prepared by the reaction of 2-oxobutanoic acid with oxalyl chloride at room temperature (1.93 g, 0.016 mole) was heated at 200°C under reflux for 4 hr. The reaction mixture was dissolved in ethyl acetate (25 mL), extracted with sodium carbonate solution (3×25 mL). The organic layer was separated, concentrated and chromatographed on silica gel using pet.ether (40-80°C) as an eluent did not afford 3-(1'-oxopropyl)-6,7-dimethoxyisocoumarin as indicated by IR, ^1H NMR and HREIMS. Reaction did not take place and 4,5-dimethoxyhomophthalic acid was recovered. This may be due to the instability of the 2-oxobutanoyl chloride.

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