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The condensation of homophthalic acid (**1**) with 3-methoxybenzoyl chloride, followed by demethylation gave 3-(3-hydroxyphenyl)isocoumarin (**3b**). Reaction of (**3b**) with α -tetraacetobromo glucose yielded tetraacetylhomalicine (**3d**), which was deacetylated to homalicine (**3e**).

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Isocoumarins and 3,4-dihydroisocoumarins are secondary metabolites of a wide variety of fungi, lichens, molds, bacteria, higher plants and insects [1]. A number of reviews have appeared on the isocoumarins [2-4]. A survey of the literature, covering the later period, shows that the isocoumarins display a wide range of biological activities *e.g.*, antifungal [5], bactericidal [6], vitamin K like [7] activities, and are also useful industrially as anti-corrosive agents [8]. In view of the importance of isocoumarins and 3,4-dihydroisocoumarins and in continuation of our previous reports [9-10], it was planned to synthesize a naturally occurring isocoumarin, homalicine and its related 3,4-dihydro aglycon.

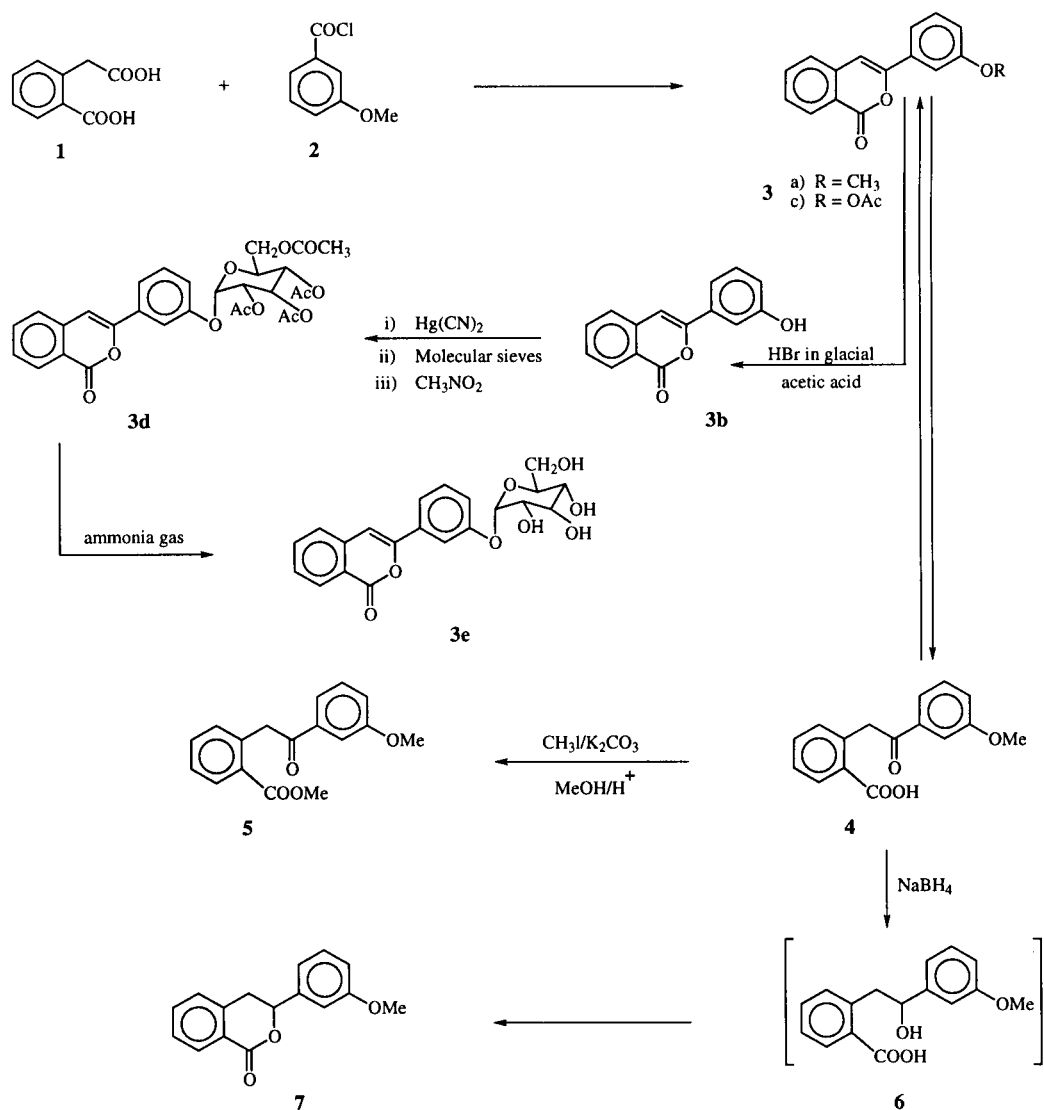
Homalium zeylanicum (Samydaceae) is a lofty tree commonly found in the evergreen forests from north Kanara southwards. In 1975, Govindachari *et al.*, [11] isolated two new isocoumarin glycosides from the roots of *Homalium zeylanicum* benth., named homalicine and dihydrohomalicine. The plan of the work is illustrated in Scheme 1.

Results and Discussion.

Direct condensation of 3-methoxybenzoyl chloride (**2**) with homophthalic acid (**1**) at 200 °C [12] afforded 3-(3-methoxyphenyl)isocoumarin (**3a**). Alkaline hydrolysis of isocoumarin (**3a**) afforded the 2-(3-methoxybenzoyl)methylbenzoic acid (**4**). Isocoumarin (**3a**) was also obtained on refluxing of compound (**4**) with acetic anhydride. Methylation of compound (**4**) with excess of methyl iodide or with dry acidic methanol for 8 hours yielded the methyl ester (**5**). Sodium borohydride reduction of compound (**4**) afforded the racemic hydroxy derivative (**6**) (not isolated) that was dehydrated with acetic anhydride to produce (dl)-3-(3-methoxyphenyl)-3,4-dihydroisocoumarin (**7**). The 3,4-dihydroisocoumarin (**7**) exhibited the carbonyl absorption at 1720 cm⁻¹ in the IR spectrum. The typical ABX pattern of the C_{3-H} and C_{4-H} protons was observed in the ¹H-nmr spectrum of this compound. Thus, each of the C_{4-H} proton signals observed as double doublet at δ 3.10-3.15 and 3.29-3.36 and the C_{3-H} proton signal was

observed as double doublet at δ 5.15-5.25. In the mass spectrum of dihydroisocoumarin (**7**) the molecular ion peak was observed at *m/z* 254 as the base peak. The loss of hydroxyl radical from the molecular ion gave a cation at *m/z* 237 (72.3%). High Resolution Electron Impact Mass Spectrometry (HREIMS) of the dihydroisocoumarin (**7**) is in good agreement with the calculated value. Demethylation of the 3-methoxy group using hydrobromic acid in glacial acetic acid afforded the 3-(3-hydroxyphenyl)isocoumarin (**3b**). The hydroxyl derivative (**3b**) was converted into the acetyl derivative (**3c**). Tetraacetylhomalicine (**3b**) were synthesized [13] from reaction of 3-(3-hydroxyphenyl)isocoumarin (**3b**) and α -tetraacetobromo glucose in nitromethane. The formation of *O*-glycosides was indicated by the appearance of a sharp band at 1758 cm⁻¹ for the carbonyl stretching in IR spectra and 1720 cm⁻¹ for the lactone carbonyl stretching of compounds (**3d**). In the ¹H-nmr spectra of compound (**3d**) the protons of the acetyl groups appeared as singlets in the region 1.99-2.64 ppm. Protons 5" and 6"a/6"b resonated in the region 4.13-4.25 ppm as a multiplet. The anomeric protons showed doublets at 5.88-5.90 ppm with a coupling constant of 3.93 Hz. The aromatic protons are observed at 6.97-8.17 ppm. In the ¹³C-nmr of this compound (**3d**), the methyl carbons of the acetyl groups resonated in the region 20.7-29.7 ppm. The carbonyl group of acetyl resonated at 169.9-170.8 ppm. The anomeric carbons resonated at 92.5 ppm and the carbonyl of lactone ring appeared at 214.5 ppm. The C-4 carbon resonated at 95.6 ppm, however C-3 appeared at 156.5 ppm. The required aromatic carbons resonated in the region 116.6-131.7. The deacetylation of compounds (**3d**) was carried out successfully in methanolic ammonia to yield (**3e**). The IR spectra of this compounds showed free OH stretching vibrations in the region 3200-3300 cm⁻¹. The aromatic ring stretching vibration was observed at 1584 cm⁻¹. The IR spectra of this compound did not show any signals at 1758 cm⁻¹ due to the carbonyl vibration of acetyl group, however the carbonyl of lactone ring appeared at 1720 cm⁻¹. The absence of the singlets due to the methyl group

Scheme 1



in ¹H-nmr of this compound and elimination of carbonyl carbon of acetyl group in IR indicated complete deacetylation of sugar moiety. The anomeric proton was observed as a doublet which resonated at 5.45-5.46 ppm with a coupling constant 3.5 Hz.

EXPERIMENTAL

3-(3-Methoxyphenyl)isocoumarin (3a, R = Me).

A mixture of homophthalic acid (1) (5.0 g, 0.0277 mole) and 3-methoxybenzoyl chloride (2) (15.6 g, 0.11 mole) was heated at 200 °C for 4 hours. The residue after concentration was chromatographed on a silica gel column in petroleum-ether (60-80 °C)

to give (3a) clearly separated from 3-methoxybenzoyl chloride. Compound 3 was further purified by recrystallization from methanol, mp 116-118 °C (lit [11], 120-123 °C) (4.6 g, 65.7%); IR $\nu_{\max}$ (potassium bromide): 1720, 1675 cm⁻¹; ¹H-nmr (CDCl₃): δ 3.87 (3H, s, OMe), 6.92 (1H, s, H-4), 6.97 (1H, dd, J = 0.9, 2.5 Hz, H-4'), 7.26-7.50 (5H, m, H-5,5',2',6',7), 7.70 (1H, ddd, J = 1.3, 7.7, 9.3 Hz, H-6), 8.28 (1H, dd, J = 0.7, 8.1 Hz, H-8); ms: (70 ev): m/z (%) = 252 (M⁺, 100), 224 (32.8), 208 (1.9), 177 (3.9), 145 (6.9), 135 (36.91); Calcd. for C₁₆H₁₂O₃: 252.0786. Found: 252.0804 (MS).

2-(3-Methoxyphenyl)methylbenzoic Acid (4).

A suspension of 3-(3'-methoxyphenyl)isocoumarin (3a) (2.0 g, 7.94 mmol) in ethanol (15 ml) and potassium hydroxide (5%, 15 ml) was refluxed for 4 hours. After cooling, the reaction mixture was evaporated to remove ethanol under reduced pressure. Cold water (20 ml) was added, and the reaction mixture was

acidified with 5% hydrochloric acid. The reaction mixture was then extracted with dichloromethane (2 x 20 ml), dried with sodium sulfate (Na_2SO_4) and the solvent was evaporated to yield a crude solid which was recrystallized to give (**4**), mp 127-129 °C, (1.7 g, 91.1%), IR ν_{max} (potassium bromide): 3370, 1700, 1685 cm^{-1} ; ^1H -nmr (CDCl_3): δ 3.84 (3H, s, OMe), 4.70 (2H, s, CH_2), 7.12 (1H, ddd, $J = 0.8, 2.6, 9.8$ Hz, H-3), 7.24-7.26 (2H, m, H-2',4'), 7.35-7.41 (3H, m, H-4,5',6'), 7.54 (1H, dt, $J = 1.4, 7.5$ Hz, H-5), 8.11 (1H, dd, $J = 1.3, 7.8$ Hz, H-6), 10.7 (1H, bs, COOH, D_2O exchanged); ms (70 ev): m/z (%) = 270 (M^+ , 10.7), 242 (3.58), 135 (100); Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_4$: 270.0892. Found: 270.0892 (MS).

Anal. Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_4$: C, 71.15; H, 5.22. Found: C, 71.12; H, 5.20.

Synthesis of 3-(3-Methoxyphenyl)isocoumarins (**3a**) from Compound (**4**).

Compound (**4**) (0.15 g, 0.55 mmole) was refluxed with acetic anhydride (1 ml) for twelve hours. After cooling, the reaction mixture was poured into ice water (10 ml), and extracted with ethyl acetate (2 x 15 ml). The combined extract was washed with sodium bicarbonate solution (2 x 10 ml, 5%), then with water (10 ml), dried (Na_2SO_4) and concentrated to give an oily product which solidified on standing. The solid was recrystallized to afford (**3a**). Melting point, R_f values, EIMS, IR and ^1H -nmr spectral data are in good agreement with already synthesized (**3a**).

Methyl 2-(3-Methoxyphenyl)methylbenzoate (**5**).

Method A.

Compound (**4**) (0.15 g, 0.55 mmole), methyl iodide (0.05 ml) and anhydrous potassium carbonate (1.5 g) in dry acetone (15 ml) were heated under reflux for 4 hours. The reaction mixture was filtered while hot. The cake was washed with warm dry acetone (10 ml) and the solvent was evaporated leaving an oil which solidified on standing. The solid was recrystallized to afford (**5**), mp 112-114 °C, (0.123 g, 78.2%), IR ν_{max} (potassium bromide): 1715, 1685 cm^{-1} ; ^1H -nmr (CDCl_3): δ 3.76 (3H, s, COOCH_3), 3.89 (3H, s, OCH_3), 4.02 (2H, s, CH_2), 7.26 (1H, d, $J = 7.5$ Hz, Ar-H), 7.35-7.53 (5H, m, Ar-H), 7.73 (1H, dt, $J = 1.3, 7.7$ Hz, H-5), 8.32 (1H, dd, $J = 2.8, 7.5$ Hz, H-6); ms (70 ev): m/z (%) = 284 (M^+ , 33.83), 252 (100), 224 (47.70), 181 (23.43), 135 (22.33); Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_4$: 284.1049. Found: 284.1071 (MS).

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{O}_4$: C, 71.87; H, 5.68. Found: C, 71.85; H, 5.64.

Method B.

A solution of compound (**4**) (0.15 g, 0.55 mmole) in dry methanol (30 ml) and concentrated sulfuric acid in catalytic amount (one drop) was refluxed for eight hours. Water (30 ml) was then added, and methanol was removed under reduced pressure. The reaction mixture was extracted with ether (2 x 20 ml). The combined extract was dried (Na_2SO_4) and the solvent was removed under reduced pressure to leave an oil which solidified on standing. The crude solid was recrystallized and further purified by preparative thin layer chromatography to furnish (**5**). Melting point, R_f values, EIMS, IR and ^1H -nmr spectral data are in good agreement with already synthesized (**5**).

(dl)-3-(3-Methoxyphenyl)-3,4-dihydroisocoumarin (**7**).

A solution of compound (**4**) (0.5 g, 1.85 mmole) in absolute ethanol (25 ml) and sodium borohydride (0.4 g) was heated under reflux for four hours. Ethanol was then rotary evaporated. The residue was diluted with cold water (20 ml) and acidified with 5% sulfuric acid to give a precipitate that was extracted with ethyl acetate (2 x 10 ml). The solvent was evaporated to leave a solid residue of racemic hydroxy derivative (**6**). This crude compound was dissolved in acetic anhydride (1 ml) and heated under reflux for two hours. The reaction mixture was then cooled, water (15 ml) added and stirred till separation of a solid. This was extracted with dichloromethane (2 x 10 ml). The combined extract was treated with sodium bicarbonate (2 x 10 ml, 5%), washed with water (10 ml), dried (Na_2SO_4) and filtered. The filtrate was subjected to the removal of solvent to leave a crude solid. This solid was recrystallized from methanol to yield (**7**), mp 94-95 °C (lit [11], 95 °C), (0.35 g, 74.5%), IR ν_{max} (potassium bromide): 1720, 1610 cm^{-1} ; ^1H -nmr (CDCl_3): δ 3.10 (AB, 1H, dd, $J_{\text{vic}} = 3.2, J_{\text{gem}} = 16.5$ Hz, H-4), 3.29 (AB, 1H, dd, $J_{\text{vic}} = 12.0, J_{\text{gem}} = 16.4$ Hz, H-4), 3.83 (3H, s, OCH_3), 5.51-5.52 (1H, dd, $J = 3.1, 12.0$ Hz, H-3), 6.90 (1H, dd, $J = 1.8, 5.0$ Hz, H-4'), 7.03 (2H, dd, $J = 2.3, 4.3$ Hz, H-5,5'), 7.26-7.32 (2H, m, H-2',6'), 7.35 (1H, ddd, $J = 1.8, 2.3, 7.6$ Hz, H-7), 7.57 (1H, ddd, $J = 1.2, 7.5, 8.7$ Hz, H-6), 8.12 (1H, d, $J = 7.7$ Hz, H-8); ms (70 ev): m/z (%) = 254 (M^+ , 100), 237 (72.3), 118 (82.8); Calcd. for $\text{C}_{16}\text{H}_{14}\text{O}_3$: 254.0943. Found: 254.0955 (MS).

3-(3-Hydroxyphenyl)isocoumarin (**3b**).

A solution of freshly distilled HBr (47%, 5.5 ml) was added to a stirred solution of isocoumarin (**3a**) (0.5 g, 1.98 mmole) in glacial acetic acid (8 ml). The reaction mixture was then refluxed for 4 hours, cooled and poured on crushed ice. The mixture treated with solid sodium carbonate (Na_2CO_3) till pH~7 and then extracted with diethyl ether (2 x 15 ml). The organic layer was dried (Na_2SO_4) and concentrated. The crude solid obtained, purified by column chromatography and recrystallized from methanol, (**3b**), mp 184-186 °C (lit [11], 186-187 °C), (0.25 g, 53.2%), IR ν_{max} (potassium bromide): 3390, 1718, 1680 cm^{-1} ; ^1H -nmr (CDCl_3): δ 6.90 (1H, s, H-4), 6.96-7.71 (6H, m, Ar-H), 7.72 (1H, dd, $J = 1.1, 4.2$ Hz, H-4'), 8.29 (1H, d, $J = 8.1$ Hz, H-8), 11.1 (1H, bs, D_2O exchanged, OH); ms (70 ev): m/z (%) = 238 (M^+ , 100), 210 (7.3), 194 (3.1), 122 (15.8); Calcd. for $\text{C}_{15}\text{H}_{10}\text{O}_3$: 238.0626. Found: 238.0617 (MS).

3-(3-Acetoxyphenyl)isocoumarin (**3c**).

A solution of (**3b**) (100.0 mg, 0.4 mmole) and acetic anhydride (0.401 g, 0.4 mmole) in dry pyridine (5 ml) was stirred overnight, water was then added and the resulting mixture was extracted with dichloromethane. The organic layer was washed with 5% sodium bicarbonate solution, 5% hydrochloric acid (2%), saturated sodium chloride solution and finally dried over sodium sulfate. Evaporation of the dichloromethane afforded (**3c**). The solid obtained was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give (**3c**), mp 128-130 °C (lit [11], 137 °C), (0.085 g, 68.3%), IR ν_{max} (potassium bromide): 1772, 1746, 1699 cm^{-1} ; ^1H -nmr (CDCl_3): δ 2.13 (3H, s, OCOCH_3), 6.97 (1H, s, H-4), 7.15 (1H, dd, $J = 1.3, 3.4$ Hz, H-2'), 7.26-7.99 (6H, m, Ar-H), 8.32 (1H, d, $J = 8.2$ Hz, H-8); ms (70 ev): m/z (%) = 280 (100), 265 (8.2), 252 (12.1), 236 (4.3); Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_4$: 280.0776. Found: 280.0770 (MS).

Anal. Calcd. for $\text{C}_{17}\text{H}_{12}\text{O}_4$: C, 72.90; H, 4.32. Found: C, 72.87; H, 4.30.

Tetraacetylhomalicine (**3d**).

To a mixture of α -tetraacetobromo glucose (2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide) (2 mmoles) and mercuric cyanide (0.5 g, 2 mmoles) and anhydrous calcium sulfate (2 g) in nitromethane (30 ml), was added (**3c**) (0.24 g, 1 mmole). The reaction mixture was refluxed and monitored by TLC. The completion of the reaction occurred within 6 hours. Then, the reaction mixture was filtered while still hot in order to remove any insoluble residue. The residue was washed thoroughly with more hot nitromethane. The filtrate was evaporated to dryness *in vacuo*, and to the residue obtained was added dichloromethane (10 ml) and filtered to separate a solid (a complex formed by mercuric halide and the heterocycle). The dichloromethane extract was washed with aqueous potassium iodide (30%), then with water and dried over anhydrous sodium sulfate. The solution was filtered, and the solvent was evaporated to dryness. The crude solid thus obtained was purified with column chromatography, and the solid obtained was recrystallized from absolute ethanol to yield (**3d**); mp 152-154 °C (lit [11], 153-155 °C), (0.17 g, 43.1%), IR $\nu_{\max}$ (potassium bromide): 1758, 1720, 1697, 1603 cm^{-1} ; ^1H -nmr (CDCl_3): δ 1.99, 2.01, 2.06, 2.64 (4 x 3H, s, CH_3), 4.14-4.26 (3H, m, H-5", H-6"a, H-6"b), 5.30 (1H, dd, $J = 2.0, 9.1$ Hz, H-3"), 5.47 (1H, dd, $J = 8.2, 11.0$ Hz, H-4"), 5.56 (1H, dd, $J = 4.5, 10.0$ Hz, H-2"), 5.89 (1H, d, $J = 3.9$ Hz, H-1"), 6.21 (1H, s), 6.97-7.14 (3H, m, Ar-H), 7.26-7.63 (4H, m, Ar-H), 8.16 (1H, dd, $J = 0.9, 8.2$ Hz, H-8). ^{13}C -nmr (CDCl_3): 20.7, 20.8, 29.4, 29.7 (4 CH_3), 61.5 (C-6"), 67.2 (C-3"), 68.0 (C-2"), 71.2 (C-4"), 73.3 (C-5"), 92.5 (C-1"), 95.6 (C-4), 105.2 (C-5), 116.6 (C-2'), 117.4 (C-4'), 121.5 (C-8a), 123.2 (C-4a), 123.7 (C-6'), 129.1 (C-8), 129.6 (C-7), 130.0 (C-1'), 130.9 (C-5'), 131.7 (C-6), 156.5 (C-3), 164.5 (C-3'), 169.9 (CO), 170.3 (CO), 170.3 (CO), 170.8 (CO), 214.5 (CO); ms (70 ev): m/z (%) = 568 (3.7%), Calcd. for $\text{C}_{29}\text{H}_{28}\text{O}_{12}$: 568.0200. Found: 568.0209 (MS).

Homalicine (**3e**).

The compound (**3d**) (0.2 g, 3.5×10^{-4} mol) was dissolved in dry methanol, and stream of dry ammonia gas was passed through the stirring solution for 3 hours. The reaction progress

was monitored by TLC, and the reaction was run to completion. The solution was stirred overnight and concentrated to the crude solid. This solid was purified by column chromatography on silica gel and recrystallized from methanol-ether to give (**3e**), mp 240-242 °C (lit [11], 241-243 °C), (0.11g, 77.8%), IR $\nu_{\max}$ (potassium bromide): 3200-3300 (b), 1718, 1680, 1603, 1584 cm^{-1} ; ^1H -nmr (CDCl_3): δ 3.72-3.81 (3H, m, H-5", H-6"a, H-6"b), 4.15 (1H, dd, $J = 3.5, 6.4$ Hz, H-3"), 4.8 (1H, dd, $J = 6.2, 9.6$ Hz, H-4"), 5.05 (1H, dd, $J = 4.8, 9.7$ Hz, H-2"), 5.46 (1H, d, $J = 3.5$ Hz, H-1"), 5.57 (1H, s, H-4), 7.26-7.51 (7H, m, Ar-H), 8.13 (1H, dd, $J = 1.7, 6.9$ Hz, H-8); ms (70 ev): m/z (%) = 400; Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_8$: 400.0144. Found: 400.0137 (MS).

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