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Synthesis of some new 3-(chlorophenyl)isocoumarins and their conversion to 3,4-dihydro derivatives

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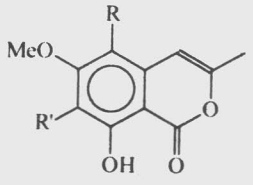
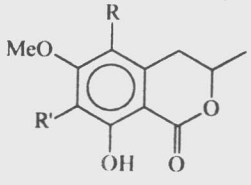
Condensation of homophthalic acid **4** with chlorobenzoyl chlorides **5a-c** yields 3-(chlorophenyl)isocoumarins **6a-c** which on alkaline hydrolysis give the keto-acids **7a-c**. (*dl*)-3-(Chlorophenyl)-3,4-dihydroisocoumarins **10a-c** have been obtained by the reduction of **7a-c** to racemic hydroxyacids **9a-c** followed by cyclodehydration using acetic anhydride.

Two types of chlorine containing isocoumarins and 3,4-dihydroisocoumarins are found in nature. In the first type, chlorine atom is attached to the nucleus as in isocoumarins **1a, b**, isolated from *Swartzia laevicarpa*[1], *Tavimita brasillensis*[2], and in 3,4-dihydroisocoumarins **2a-c**, isolated from *Periconia macrospinosa*[3-4] and *Sporomia affinis*[5]. In the second type, chlorine atom is present in the side chain of isocoumarins. These include bactobolins A, C and B' isolated from *Pseudomonas yoshitomiensis*[6] and LL-Z1640-5 **3** isolated from lederale culture Z1640 of unidentified fungus[7]. Ochratoxin A is nephratoxin metabolite of several *Aspergillus* and *Penicillium* species[8] and also inhibits protein synthesis[9]. Analogues of bactobolin A possess antileukemic activity whereas bactobolin A and its related metabolites have been reported[10] to be active against bacteria and viruses. These reports prompted us to synthesize 3-(chlorophenyl)isocoumarins **6a-c** and (*dl*)-3-(chlorophenyl)-3,4-dihydroisocoumarins **10a-c** which contain chlorine atom in the side chain at 3-position of the phenyl ring. So far such compounds have not been reported to occur in Nature.



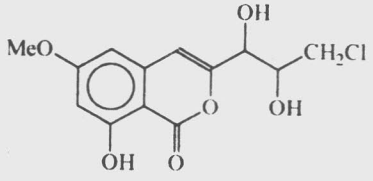
(1)

a) R= Cl, R' = H
b) R = H, R' = Cl



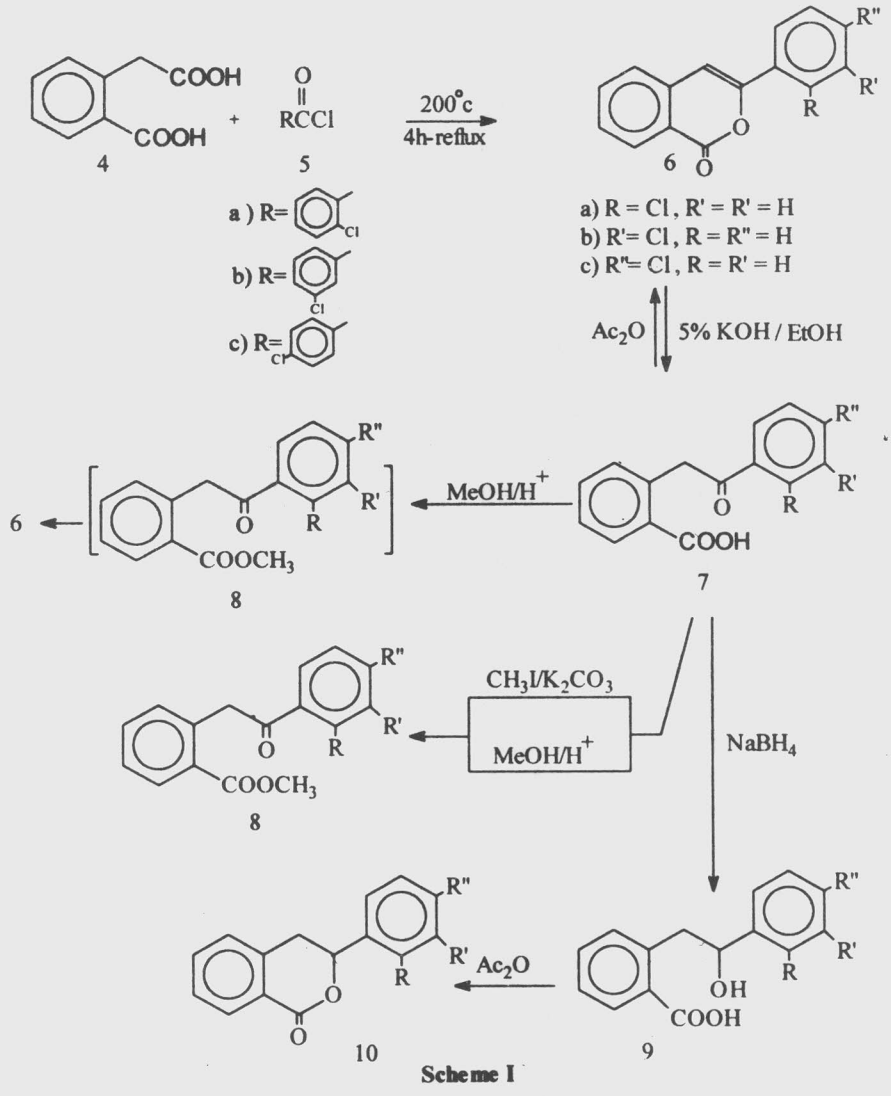
(2)

a) R = Cl, R' = H
b) R = H, R' = Cl
c) R = R' = Cl



(3)

Direct condensation[11] of chlorobenzoyl chlorides **5a-c** with homophthalic acid **4** at 200°C afforded 3-(chlorophenyl)isocoumarins **6a-c**. These isocoumarins showed characteristic 1H singlets at δ 6.93, 6.89 and 6.91 respectively for C_4-H and lactonic carbonyl absorption at 1718 and 1735 cm^{-1}. Alkaline hydrolysis yielded the keto-acids **7a-c** (Scheme I) which showed a 2H singlets at δ 4.63, 4.60 and 4.66 respectively for benzylic $-CH_2$ in their ^1H NMR spectra, while ketonic and carboxyl carbonyl groups absorption in IR were observed at 1680 and 1716 cm^{-1} respectively. Isocoumarins **6a-c** were obtained back on refluxing of **7a-c** with acetic anhydride. Following an already reported procedure[12], keto-acids **7a-c** were refluxed with dry acidic methanol for 8 hr to furnish the keto-esters **8a-c** as indicated by TLC. It may be pointed out that the work-up of this reaction mixture involved the use of sodium bicarbonate which might have hydrolyzed the keto-esters **8a-c** to the corresponding keto-acids **7a-c** which under the work-up conditions were converted to the lactones



Scheme I

6a-c identical in all respect with those prepared earlier. Methylation of **7a-c** with excess of methyl iodide or acidic dry methanol yielded the methyl keto-esters **8a-c**. These esters showed 3H singlets for CH_3 at δ 3.71, 3.70 and 3.72 respectively in their ^{1}H NMR spectra, while ketonic and ester carbonyl absorptions in IR spectra appeared at 1680 and 1735 cm^{-1} in each case. Sodium borohydride reduction of **7a-c** furnished the corresponding racemic hydroxyacids **9a-c** which were treated in the crude form with acetic anhydride to produce the (*dl*)-3-(chlorophenyl)-3, 4-dihydriisocoumarins **10a-c**. The dihydroisocoumarins **10a-c** showed a typical *AB* pattern for C_3-H and a typical *ABX* pattern for C_4-H protons in their ^{1}H NMR spectra, and carbonyl absorption at 1718 cm^{-1} in IR spectra. The structures of the synthesized compounds were further confirmed by HREIMS data which were in good agreement with the calculated values.

Experimental Section

General. Melting points were determined using a MELTEMP MP-D apparatus and are uncorrected. The IR spectra were recorded on a Hitachi model 270-50 Infrared spectrophotometer as KBr discs or as neat liquids. ^{1}H-NMR (500 MHz) spectra were recorded on a Bruker AM-500 as $CDCl_3$ solution, using TMS as internal standard and EIMS were recorded on a MAT-112-S machine.

Preparation of 3-(chlorophenyl)isocoumarins 6: General procedure. The following procedure is representative for the synthesis of **6a-c**. The melting points, mixed melting points, % yields and solvents for recrystallisation are listed in Table I.

3-(4′-Chlorophenyl)isocoumarin 6c: A mixture of homophthalic acid **4** (8.33 mmoles) and 4-chlorobenzoyl chloride **5c** (35 mmoles) was heated using an oil bath at 200°C for 4 hr. The residue after concentration was chromatographed on silica gel column in pet. ether (60-80°) to give **6c** which clearly separated out from 2-chlorobenzoyl chloride. It was further purified by recrystallization; (KBr): 1735, 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 6.91 (1H, s, H-4), 7.42 (2H, d, *J*=8.7 Hz, H-3′,5′), 7.49 (2H, m, H-5,7), 7.71 (1H, dt, *J*=1.3, 7.6 Hz, H-6), 7.80 (2H, d, *J*=8.7 Hz, H-2′,6′), 8.29 (1H, d, *J*=6.9 Hz, H-8); MS (70 eV): m/z 256 (M^+, 100%), 258 (M+2, 34.99), 228, (67), 193 (41); Calcd. M^+ for $C_{15}H_9O_2Cl$: 256.02910 (Found: 256.02950).

^1H NMR, IR, EIMS and HREIMS data of **6a** and **6b** were in good agreement with the proposed structures.

2-(Chlorobenzoylmethyl)benzoic acids 7: General procedure. The following procedure is representative for the synthesis of **7a-c**. The melting points, mixed melting points, % yields and solvents for recrystallisation are listed in Table I.

2-(4′-Chlorobenzoylmethyl)benzoic acid 7c: A suspension of 3-(4′-chlorophenyl)isocoumarin **6c** (2 mmoles) in ethanol (15 mL) and potassium hydroxide (5%, 25 mL) was refluxed for 4 hr. After cooling, the reaction mixture was evaporated to remove ethanol under reduced pressure. Cold water (20 mL) was then added and the reaction mixture acidified with dil. hydrochloric acid, and extracted with dichloromethane (2×20 ml). The extract was dried (Na_2SO_4) and the solvent rotary evaporated to yield a crude solid residue which was recrystallized to give **7c**; (KBr): 3370, 1716, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.66 (2H, s, CH_2), 7.25 (2H, dd, *J*=1.5, 7.6 Hz, H-3,5), 7.44 (2H, m, H-3′,5′), 7.54 (1H, dt, *J*=1.5, 7.6 Hz, H-4), 7.95 (2H, d, *J*=8.5 Hz, H-2′,6′), 8.12 (1H, dd, *J*=1.4, 7.8 Hz, H-6), 10.2 (1H, bs, COOH, D_2O exchangable); MS (70 eV): m/z 274 (M^+, 1.2%), 276 (M+2, 0.41), 256 (2.0), 139 (100), Calcd. M^+ for $C_{15}H_{11}O_3Cl$: 274.03967 (Found: 274.03967).

^1H NMR, IR, EIMS and HREIMS data of **7a** and **7b** were in good agreement with the proposed structures.

3-(Chlorophenyl)isocoumarins 6: General procedure. The following procedure is representative for the synthesis of **6a-c**. The melting points, mixed melting points, % yields and solvents for recrystallisation are listed in Table I.

Table I—Physical data of various compounds prepared

Compd	m.p. °C	Mixed m.p., °C	Yield (%)	Crystallized from
6a	121-2	—	62	MeOH
6a*	121	122	82	MeOH
6a**	121-2	122	76	MeOH
6b	158-9	—	60	MeOH
6b*	159	158-9	79	MeOH
6b**	159	158-9	73	MeOH
6c	141-2	—	69	MeOH
6c*	141-2	142	83	MeOH
6c**	141	142	71	MeOH
7a	107-8	—	80	Et_2O
7b	108-9	—	82	Et_2O
7c	162-3	—	85	CH_2Cl_2
8a	106-7	—	95	Et_2O
8b	138-9	—	92	Et_2O
8c	86-7	—	98	Et_2O
10a	86-7	—	62	Et_2O
10b	88-9	—	58	Et_2O
10c	78	—	65	EtOH

*Prepared by Method A.
**Prepared by Method B.

3-(4′-Chlorophenyl)isocoumarin 6c. Method A: Keto-acid **7c** (0.73 mmole) was refluxed with acetic anhydride (1 mL) for 12 hr. After cooling, the reaction mixture was poured into ice-water(10 mL) and extracted with ethyl acetate (2×15 mL). The combined extract was washed with sodium bicarbonate (2×10 mL, 5%), then with water (10 mL), dried (Na_2SO_4) and concentrated to give an oily product which solidified on standing. It was recrystallized to afford **6c**. R_f values, EIMS, HREIMS, IR and ^1H NMR spectra data were in good agreement with already synthesized **6c**.

Method B: A solution of the keto-acid **7c** (0.73 mmole) in dry methanol (20 mL) and conc. sulphuric acid (as a catalyst) was refluxed for 8 hr. The reaction mixture was neutralized with solid sodium bicarbonate, filtered and methanol rotary evaporated to afford an oil which solidified on cooling. It was recrystallized to furnish **6c**. R_f values, EIMS, HREIMS, IR and ^1H NMR spectral data were found in good agreement with already synthesized **6c**.

Compounds **6a** and **6b** were synthesized by the same procedures and were identical in all respect with those synthesised earlier.

Methyl 2-(chlorobenzoylmethyl)benzoates 8: General procedure. The following procedure is representative for the synthesis of **8a-c**. The melting points, mixed melting points, % yields and solvents for recrystallisation are listed in Table I.

Methyl 2-(4′-chlorobenzoylmethyl)benzoate 8c. Method A: The keto-acid **7c** (0.73 mmole), methyl iodide in excess and anhydrous potassium carbonate (1.5 g) in dry acetone (15 mL) were heated under reflux for 4 hr. The reaction mixture was filtered while hot. The cake was washed with warm dry acetone (10 mL) and the solvent evaporated leaving an oil which solidified on standing. The solid was recrystallized to afford **8c**; (KBr): 1735, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.72 (3H, s, OCH_3), 4.67 (2H, s, CH_2), 7.24 (1H, d, *J*=7.5 Hz, H-3), 7.37 (1H, dt, *J*=1.2, 7.7 Hz, H-5), 7.45 (2H, d, *J*=8.5 Hz, H-3′,5′), 7.50 (1H, dt, *J*=1.5, 7.5 Hz, H-4), 8.05 (2H, d, *J*=8.5 Hz, H-2′,6′), 8.06 (1H, dd, *J*=1.3, 7.8 Hz, H-6); MS (70 eV): m/z 288 (M^+, 10%), 290 (M+2, 3), 139 (100); Calcd M^+ for $C_{16}H_{13}O_3Cl$: 288.05532 (Found: 288.05590).

Method B: A solution of the keto-acid **7c** (0.73 mmole) in dry methanol (30 mL) and conc. sulphuric acid in catalytic amount (one drop) was refluxed for 8 hr. Water (30 mL) was then added and methanol removed under reduced pressure. The reaction mixture was extracted with ether (2×20 mL). The combined extract was dried (Na_2SO_4) and the solvent removed under reduced pressure to leave an oil which solidified on standing. The crude solid was recrystallized and further purified by thick layer chromatography to furnish **8c**. R_f values, EIMS, HREIMS, IR and ^1H NMR spectral data are in good agreement with already synthesized **8c**.

Compounds **8a** and **8b** were synthesised by the same procedures and were identical in all respect with these synthesised earlier.

***(dl)*-3-(4′-Chlorophenyl)-3, 4-dihydroisocoumarins 10: General procedure.** The following procedure is representative for the synthesis of **10a-c**. The melting points, mixed melting points, % yields and solvents for recrystallization are listed in Table I.

***(dl)*-3-(Chlorophenyl)-3, 4-dihydroisocoumarin 10c.** A solution of the keto-acid **7c** (0.73 mmole) in absolute ethanol (15 mL) and sodium borohydride (0.2 g) was heated under reflux for 4 hr. Ethanol was rotary evaporated, and the residue diluted with cold water (20 mL) and acidified with dil. sulphuric acid to give a precipitate which was extracted with ethyl acetate (2×10 mL). The solvent was evaporated to leave a solid residue of racemic hydroxyacid **9c**. This crude compound was dissolved in acetic anhydride (1 mL) and heated under reflux for 2 hr. The reaction mixture was cooled, water (15 mL) added and stirred till separation of a solid. This solid was extracted with dichloromethane (2×10 mL). The combined extract was treated with sodium bicarbonate (2×10 mL, 5%), washed with water (10 mL), dried (Na_2SO_4) and filtered. The filtrate was subjected to removal of solvent to leave a crude solid which was recrystallized to yield **10c**; (KBr): 1718 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.11 (1H, dd, *J*=3.3, 16.5 Hz, H-4), 3.28 (1H, dd, *J*=11.9, 16.4 Hz, H-4), 5.52 (1H, dd, *J*=3.3, 11.9 Hz, H-3), 7.27 (2H, d, *J*=7.6 Hz, H-3′,5′), 7.39 (2H, m, H-5,7), 7.42 (2H, d, *J*=6.9 Hz, H-2′,6′), 7.56 (1H, dt, *J*=1.4, 7.5 Hz, H-6), 8.13 (1H, dd, *J*=1.3, 7.8 Hz, H-8); MS (70 eV): m/z 258 (M^+, 7.3), 260 (M+2, 2.4), 118 (100); Calcd M^+ for $C_{15}H_{11}O_2Cl$: 258.04475 (Found: 258.04566).

^1H NMR, IR, EIMS and HREIMS data of **10a** and **10b** were in good agreement with the proposed structures.

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