258. *Synthesis of the 7-Chloro-derivatives of Chromone, Flavone, and Isoflavone.*

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7-Chloro-chromone and -flavone have been synthesised from 4-chloro-2-hydroxyacetophenone; 7-chloroisoflavone has been synthesised from benzyl 4-chloro-2-hydroxyphenyl ketone.

3-Chloroxanthone [1] reacts quantitatively with methoxide ion in refluxing methanol but is inert towards toluene-*p*-sulphonamide in refluxing pentanol. The 7-chloro-derivatives of chromone, flavone, and isoflavone possess the same mesomeric system as 3-chloroxanthone and were required for a similar examination of their activities with nucleophiles.

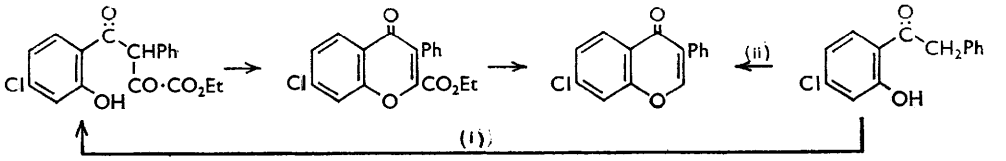
The necessary intermediate for two syntheses was 4-chloro-2-hydroxyacetophenone. This was obtained by Fries rearrangement of *m*-chlorophenyl acetate; the constitution of the product was proved by methylation and oxidation to 4-chloro-2-methoxybenzoic acid.

Reaction of 4-chloro-2-hydroxyacetophenone with diethyl oxalate gave the ω-ethoxalyl derivative which on treatment with hydrochloric acid gave 7-chlorochromone-2-carboxylic acid. Pyrolysis of the latter yielded 7-chlorochromone.

O-Benzoylation of 4-chloro-2-hydroxyacetophenone and rearrangement of the product with potassium hydroxide gave the ω-benzoyl derivative which was cyclised by warm sulphuric acid to 7-chloroflavone.

Fries rearrangement of *m*-chlorophenyl phenylacetate gave benzyl 4-chloro-2-hydroxyphenyl ketone, conveniently isolated *via* its sparingly-soluble sodium salt. Two routes to the isoflavone were successfully employed in which $C_{(2)}$ of the heterocycle was supplied by (i) ethoxalyl chloride [2] and (ii) formamide.[3]

[1] Goldberg and Wragg, *J.*, 1958, 4234.
[2] Baker, Chadderton, Harborne, and Ollis, *J.*, 1953, 1852; Baker, Harborne, and Ollis, *J.*, 1953, 1860.
[3] Gowan, Lynch, O'Connor, Philbin, and Wheeler, *J.*, 1958, 2495.



Experimental

4-Choro-2-hydroxyacetophenone.—The following method is more convenient than that recently described by Chen and Chang.[4] *m*-Chlorophenyl acetate was obtained in 91% yield by addition of acetic anhydride (1·6 moles) to a stirred mixture of *m*-chlorophenol (1 mole) and N-sodium hydroxide (1·6 moles) at 0°; it had b. p. 105—107°/13 mm. *m*-Chlorophenyl acetate (102 g.) was added dropwise during 15 min. to a mixture of powdered aluminium chloride (101 g.) and carbon disulphide (600 c.c.) stirred at 15°. After the mixture had been stirred at 15° for a further 1¼ hr. the solvent was distilled off and the viscous residue heated at 135° (bath temp.) for 3 hr. Water (1200 c.c.) and 10N-hydrochloric acid (60 c.c.) were added, and the mixture was distilled in steam. The distillate (3 l.) was extracted with ether (4 × 300 c.c.), the ethereal solution dried (Na_2SO_4), and ether distilled off. The residual oil (91 g.) was dissolved in warm water (105 c.c.) and 5N-sodium hydroxide and set aside to cool. The precipitated sodium salt (92 g.) was collected and washed with a little acetone; the filtrate was concentrated at reduced pressure and another crop (12 g.) collected. The combined crops were added to water (500 c.c.) and 10N-hydrochloric acid, and the whole extracted with ether (3 × 300 c.c.). Distillation gave 4-chloro-2-hydroxyacetophenone (76 g.; 74%), b. p. 120—122°/10 mm. (Found: Cl, 21·4. Calc. for $C_8H_7O_2Cl$: Cl, 20·8%). The 2,4-*dinitrophenylhydrazone* crystallised from aqueous pyridine in orange-red needles, m. p. 244—246° (Found: N, 15·8. $C_{14}H_{11}O_5N_4Cl$ requires N, 16·0%); the *semicarbazone*, needles, had m. p. 218° (Found: N, 18·3; Cl, 15·6. $C_9H_{10}O_2N_3Cl$ required N, 18·5; Cl, 15·6%).

The anhydrous sodium derivative of this phenol (6·5 g.) was refluxed for 20 hr. with acetone (50 c.c.) and methyl iodide (10 c.c.). Solvent was distilled off, water (50 c.c.) and 5N-sodium hydroxide (5 c.c.) were added, and the mixture was heated on the water-bath for 10 min. and cooled. The insoluble solid on crystallisation from ligroin (b. p. 60—80°) gave *4-chloro-2-methoxyacetophenone* (4·5 g.) as needles, m. p. 58—60° (Found: C, 57·8; H, 4·8. $C_9H_9O_2Cl$ requires C, 58·6; H, 4·9%).

The foregoing compound (2·7 g.), potassium permanganate (12·4 g.), and water (200 c.c.) were stirred on the water bath for 2½ hr. The mixture was filtered, and the filtrate adjusted to pH 8, evaporated to small volume, and acidified with hydrochloric acid. The precipitate gave 4-chloro-2-methoxybenzoic acid (0·6 g.) (from aqueous alcohol), m. p. 138—140° alone and admixed with material obtained by methylation of 4-chlorosalicylic acid (Found: C, 51·5; H, 3·6; Cl, 18·9. Calc. for $C_8H_7O_3Cl$: C, 51·5; H, 3·8; Cl, 19·1%). The m. p. was depressed by admixture with 6-chloro-2-methoxybenzoic acid.

7-Chlorochromone.—A warm solution of 4-chloro-2-hydroxyacetophenone (8·53 g.) in diethyl oxalate (40 g., 37 c.c.) was added to a solution from sodium (4·6 g.) in ethanol (80 c.c.). The mixture became yellow, and solidified when warmed for ½ hr. After cooling, the solid was drained, washed with ether and partitioned between N-acetic acid and chloroform; the chloroform extract was dried and evaporated. The pale yellow residue was refluxed for 4 hr. with acetic acid (30 c.c.) and hydrochloric acid (1 c.c.). After cooling and the addition of water (50 c.c.), the solid was filtered off, washed, and dried *in vacuo*. Crystallisation from ethanol–water gave *7-chlorochromone-2-carboxylic acid* as needles (8·0 g., 71%), m. p. 248—250° (decomp.) (Found: Cl, 15·7. $C_{10}H_5O_4Cl$ requires Cl, 15·8%).

The acid (2·25 g.) was heated at 250°/760 mm. for *ca.* ½ hr. under a cold-finger condenser. Collection of the sublimate was continued at *ca.* 150°/12 mm.; *7-chlorochromone* (1·26 g., 70%) was obtained as needles (from ethanol), m. p. 100—102° (Found: C, 59·7; H, 2·8; Cl, 20·0. $C_9H_5O_2Cl$ requires C, 59·9; H, 2·8; Cl, 19·7%).

7-Chloroflavone.—Benzoyl chloride (17·4 c.c.) was added portionwise with shaking to a solution of 4-chloro-2-hydroxyacetophenone (17 g.) in dry pyridine (25 c.c.). After 1 hr. the

[4] Chen and Chang, *J.*, 1958, 146.

mixture was poured into ice–water (800 c.c.) and 5N-hydrochloric acid (100 c.c.). *2-Benzoyloxy-4-chloroacetophenone* was collected, washed with water, and crystallised from methanol; it formed white needles (25 g.), m. p. 77° (Found: C, 65·0; H, 3·9; Cl, 12·7. $C_{15}H_{11}O_3Cl$ requires C, 65·6; H, 4·0; Cl, 12·9%). A solution of the ester (25 g.) in dry pyridine (80 c.c.) was stirred at 50° and powdered potassium hydroxide (7·6 g.) added. After ½ hr. the mixture was chilled and acidified with 10% acetic acid (110 c.c.) and the yellow *ω-benzoyl-4-chloro-2-hydroxyacetophenone* (20 g.; m. p. 130°) collected. Crystallisation from alcohol gave pale yellow needles, m. p. 132° (Found: C, 65·5; H, 4·0. $C_{15}H_{11}O_3Cl$ requires C, 65·6; H, 4·0%).

This ketone (19·2 g.), acetic acid (110 c.c.), and sulphuric acid (4·5 c.c.) were heated (steam-bath) for 1½ hr., and the mixture then poured into ice–water (600 c.c.). The precipitate was washed with water and crystallised from alcohol and then from ethyl acetate; 7-chloroflavone (13 g.) formed needles, m. p. 158° (Found: Cl, 13·8. Calc. for $C_{15}H_9O_2Cl$: Cl, 13·8%).

7-Chloroisoflavone.—*m*-Chlorophenol (25·8 g.; 0·2 mole) and phenylacetyl chloride (31 g.; 0·2 mole) were refluxed with dry benzene (120 c.c.) for 2½ hr. The chilled mixture was washed with water (20 c.c.), saturated sodium hydrogen carbonate solution (2 × 20 c.c.), and again with water (20 c.c.). After being dried (Na_2SO_4) the liquid was distilled to give *m*-chlorophenyl phenylacetate (44·5 g.), b. p. 210—212°/25 mm.

A mixture of this ester (43 g.), powdered aluminium chloride (29·3 g.), and carbon disulphide (250 c.c.) was stirred at room temperature for 1 hr. The solvent was distilled off and the residual oil heated at 100° for 5 hr. and then kept overnight at room temperature. The resinous mass was heated with 2N-hydrochloric acid (250 c.c.) to 60° and then the whole extracted with ether (2 × 150 c.c.). The ethereal solution was washed with water (2 × 20 c.c.), dried (Na_2SO_4), and distilled, the fraction of b. p. 196—198°/2 mm. being collected. This was boiled with 2N-sodium hydroxide (90 c.c.) and water (40 c.c.) for a few minutes and the solution set aside to cool. The sodium salt was filtered off, washed with cold saturated aqueous sodium chloride and then added to excess of 2N-hydrochloric acid and the mixture extracted with ether (2 × 150 c.c.). The ethereal solution was dried and the ether removed, leaving *benzyl 4-chloro-2-hydroxyphenyl ketone* (25 g., 58%), m. p. 62—64° (Found: C, 68·7; H, 4·7; Cl, 14·0. $C_{14}H_{11}O_2Cl$ requires C, 68·2; H, 4·5; Cl, 14·4%).

A solution of this ketone (9·86 g.; 0·04 mole) in dry pyridine (100 c.c.) was stirred at 0° and ethoxalyl chloride (13·2 g.; 0·08 mole) added dropwise during 20 min. The dark solution was kept for 20 hr., then poured into water (600 c.c.), and the liberated oil extracted with chloroform (4 × 80 c.c.). The extract, after being washed with N-hydrochloric acid (2 × 50 c.c.) and then water, was dried (Na_2SO_4), and evaporated. The residue, which was 7-chloro-2-ethoxycarbonylisoflavone or 7-chloro-2-ethoxycarbonyl-2-hydroxyisoflavanone or a mixture thereof (compare Baker *et al.*[2]), was heated at 100° for ¾ hr. with acetic acid (60 c.c.) and 10N-hydrochloric acid (10 c.c.) in order to effect complete dehydration. The mixture was diluted with water and extracted with ether (3 × 70 c.c.), the extract washed with water and dried, and the ether evaporated. The residual ester was hydrolysed with sulphuric acid (120 c.c.) on the steam-bath for 1½ hr. The solution was quenched in ice–water and extracted with ether (3 × 30 c.c.), and the ethereal solution extracted with 2N-sodium hydroxide (3 × 20 c.c.). The combined aqueous alkaline extracts were acidified and extracted with chloroform (3 × 50 c.c.). Evaporation of the dried chloroform solution left a residue of *7-chloroisoflavone-2-carboxylic acid*; a sample formed small prisms, m. p. 214—216° (decomp.) from chloroform–light petroleum (b. p. 40—60°) (Found: *M*, 302. $C_6H_9O_4Cl$ requires *M*, 300·5).

The crude acid was heated at 220—230° until the evolution of carbon dioxide ceased (20 min.). The residue on crystallisation twice from ethanol gave *7-chloroisoflavone* (4·4 g.; 43% overall) as pale cream plates, m. p. 149—150° (Found: C, 70·6; H, 3·6; Cl, 13·6. $C_{15}H_9O_2Cl$ requires C, 70·2; H, 3·5; Cl, 13·8%).

7-Chloroisoflavone.—Benzyl 4-chloro-2-hydroxyphenyl ketone (3·52 g.; 0·014 mole) and formamide (3·9 g.; 0·084 mole) were refluxed for 1½ hr. The liquid was cooled, ether (150 c.c.) added, and the whole extracted with 0·5N-potassium hydroxide (2 × 40 c.c.). The ethereal solution was dried and evaporated; crystallisation of the residue from ethanol gave 7-chloroisoflavone (0·45 g.; 12%) as pale cream plates, m. p. 149—150° alone and in admixture with the material obtained by the Baker synthesis.

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