

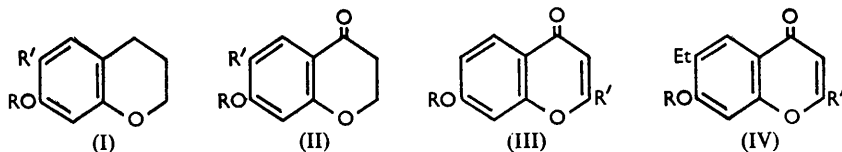
235. 7-Hydroxychroman and its 6-Acetyl Compound.

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Resorcinol and β -chloropropionyl chloride gave 7-hydroxychroman-4-one which was reduced to 7-hydroxychroman. This formed a 6-acetyl compound as was shown by reduction to the 6-ethyl compound, which was also prepared from 4-ethylresorcinol.

6-ACETYL-7-HYDROXYCHROMAN (I; R = H, R' = Ac) was required for the synthesis of various dihydropyranochromones. Several routes to 7-hydroxychroman were examined, one of which involved many stages and was an extension of the route to 7-hydroxychromone-2-carboxylic acid (III; R = H, R' = CO₂H) reported by Jacobson, Brower, and Amstutz.¹ Recently Gregory and Tomlinson² prepared the 7-benzyloxy-compound (II; R = CH₂Ph, R' = H) but failed with the debenzylation stage.

7-Hydroxychroman-4-one (II; R = R' = H) was conveniently obtained from resorcinol and β -chloropropionyl chloride in nitrobenzene by the action of aluminium chloride. The initial product was extracted with aqueous sodium hydroxide and this brought about the necessary ring closure, forming 7-hydroxychroman-4-one, and not the alternative coumarin or 5-membered ring compound. The chromanone was characterised



by derivatives and reduced, by hydrogen and a Raney nickel catalyst, to 7-hydroxychroman (I; R = H, R' = H). This gave the 6-acetyl compound (I; R = H, R' = Ac)

¹ Jacobson, Brower, and Amstutz, *J. Org. Chem.*, 1953, **18**, 1117.

² Gregory and Tomlinson, *J.*, 1956, 795.

when treated with acetic anhydride and aluminium chloride under Friedel-Crafts conditions, or by a Fries rearrangement of its *O*-acetyl derivative (I; R = Ac, R' = H). The position of the acetyl group was established by its reduction to an ethyl group and the identity of the resulting product (I; R = H, R' = Et) with that derived from 4-ethyl-resorcinol.

For the alternative synthesis, the slightly modified route of Jacobson *et al.*¹ was used. A Claisen condensation with ethyl oxalate and 4-benzyloxy-5-ethyl-2-hydroxyacetophenone gave ethyl 4-benzyloxy-5-ethyl-2-hydroxybenzoylpyruvate, which was converted into 6-ethyl-7-hydroxychromone (IV; R = H, R' = H) by cyclisation, hydrolysis, debenzoylation, and decarboxylation. The resulting chromone (IV; R = H, R' = H) was reduced in two stages and gave the chroman-4-one (II; R = H, R' = Et) and then 6-ethyl-7-hydroxychroman (I; R = H, R' = Et). This route was also used to prepare 7-hydroxychroman-4-one and in this way the identity of the product from resorcinol and β -chloropropionyl chloride was confirmed.

EXPERIMENTAL

4-Benzyloxy-5-ethyl-2-hydroxyacetophenone.—5-Ethyl-2 : 4-dihydroxyacetophenone³ (49 g.) and powdered anhydrous potassium carbonate (42 g.) were added to a cold solution of sodium iodide (50 g.) in dry acetone (300 c.c.), followed by benzyl chloride (43 c.c.), and the mixture gently refluxed with stirring for 5 hr. After removal of the acetone, the mixture was digested with warm water (500 c.c.) and the product filtered. Crystallisation from ethanol (charcoal) gave 4-benzyloxy-5-ethyl-2-hydroxyacetophenone (66 g., 90%) as needles, m. p. 106° (Found: C, 76.1; H, 6.8. Calc. for C₁₇H₁₈O₃: C, 75.5; H, 6.7%). Jacobson *et al.*¹ gave 50%.

Ethyl 7-Benzyloxychromone-2-carboxylate (III; R = CH₂Ph, R' = CO₂Et).—Ethyl 4-benzyloxy-2-hydroxybenzoylpyruvate¹ (27 g.) was refluxed for 1 hr. with ethanolic hydrogen chloride (250 c.c.; 12% w/v), cooled, and filtered. On crystallising the residue from ethanol, *ethyl 7-benzyloxychromone-2-carboxylate* (III; R = CH₂Ph, R' = CO₂Et) was obtained as needles (24 g., 94%), m. p. 172° (Found: C, 70.3; H, 4.9. Calc. for C₁₉H₁₆O₅: C, 70.4; H, 5.0%).

A similar preparation from ethyl 4-benzyloxy-5-ethyl-2-hydroxybenzoylpyruvate¹ gave *ethyl 7-benzyloxy-6-ethylchromone-2-carboxylate* (IV; R = CH₂Ph, R' = CO₂Et) (22 g., 86%) as needles (from ethanol), m. p. 111–112° (Found: C, 71.4; H, 5.4. C₂₁H₂₀O₅ requires C, 71.6; H, 5.7%).

7-Hydroxychromone-2-carboxylic Acid (III; R = H, R' = CO₂H).—Concentrated hydrochloric acid (100 c.c.) was added to a solution of the ester (III; R = CH₂Ph, R' = CO₂Et) (10.5 g.) in ethanol (100 c.c.), and the suspension was refluxed for 6 hr. and then cooled. Water (200 c.c.) was added and the mixture filtered. The residue was purified by dissolving it in, and reprecipitating it from, dilute sodium hydroxide solution, followed by washing with water and crystallisation from methanol. *7-Hydroxychromone-2-carboxylic acid* (5 g., 75%) formed needles, m. p. 312° (decomp.) (Found: C, 58.2; H, 3.3. C₁₀H₆O₅ requires C, 58.3; H, 2.9%).

7-Hydroxychromone (III; R = R' = H).—The acid (III; R = H, R' = CO₂H) (2 g.) was heated at 300–310° for 5 min. and cooled. The product was extracted with boiling water, and 7-hydroxychromone (0.8 g., 50%) recovered on cooling as colourless needles, m. p. 221° (Found: C, 66.6; H, 3.9. Calc. for C₉H₆O₃: C, 66.7; H, 3.7%).

7-Hydroxychroman-4-one (II; R = R' = H).—(a) Raney nickel catalyst (10 c.c.; settled suspension in ethanol) was shaken with a solution of 7-hydroxychromone (3 g.) in methanol (150 c.c.) in hydrogen until the hydrogen uptake reached 470 c.c. (*ca.* 3 hr.). The catalyst was filtered off and washed with methanol. Evaporation, at low temperature and pressure, of the combined filtrate and washings left a residue which on crystallisation from water gave 7-hydroxychroman-4-one (2.4 g., 79%) as needles, m. p. 149°.

(b) A solution of resorcinol (11 g.) in dry nitrobenzene (120 c.c.) was cooled below 8° and β -chloropropionyl chloride (12.7 g., 9.6 c.c.) added. The solution was stirred and anhydrous resublimed aluminium chloride (31 g.) added in four portions during 30 min., while the temperature of the mixture was kept below 15°. Then the mixture was stirred for 15 min., finally

³ Shah and Mehta, *J. Univ. Bombay*, 1935, **4**, 109.

at 40—45° for 3 hr., and next day poured on crushed ice (200 g.) and concentrated hydrochloric acid (10 c.c.) with stirring. The mixture was extracted with ether (220 c.c. and 2 × 80 c.c.), and the combined ethereal extracts were shaken with 5% aqueous sodium hydroxide (3 × 100 c.c.). The combined extracts were washed with ether (80 c.c.), before being added to concentrated hydrochloric acid (80 c.c.) and ice (100 g.), with stirring. The resulting tar was filtered off and crystallised from water (charcoal), and gave 7-hydroxychroman-4-one (7.5 g., 46%) as colourless needles, m. p. 149°, identical with the above material.

7-Hydroxychroman-4-one formed a *semicarbazone*, m. p. 237—238° (decomp.), which crystallised from 50% aqueous ethanol as prisms (Found: C, 54.8; H, 5.0. $C_{10}H_{11}O_3N_3$ requires C, 54.3; H, 5.0%).

7-Hydroxychroman (I; R = R' = H).—Raney nickel catalyst (10 c.c.; settled suspension in ethanol) was shaken with a solution of 7-hydroxychroman-4-one (3 g.) in ethanol (150 c.c.) at 40—45° in hydrogen. When the uptake had ceased (*ca.* 24 hr.) the mixture was cooled and filtered and the catalyst washed with ethanol. Removal of the ethanol under reduced pressure left a brown residue which was distilled (100—120°/0.3 mm.) on to a cold finger. The resulting 7-hydroxychroman (2.13 g., 77%) crystallised from *cyclohexane* as colourless plates, m. p. 91° (Found: C, 72.2; H, 6.5. Calc. for $C_9H_{10}O_2$: C, 72.0; H, 6.7%).

7-Acetoxychroman (I; R = Ac, R' = H).—A solution of 7-hydroxychroman (4.5 g.) in acetic acid (6 c.c.) and acetyl chloride (2.4 g.) was warmed for 2 min. and then poured into water (35 c.c.). When shaken, the product solidified and was then filtered off and crystallised from aqueous ethanol, to yield 7-acetoxychroman (4.7 g., 82%), m. p. 50° (Found: C, 69.0; H, 6.2. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

6-Acetyl-7-hydroxychroman (I; R = H, R' = Ac).—(a) 7-Acetoxychroman (1.0 g.) was ground with resublimed anhydrous aluminium chloride (0.85 g.) and heated slowly to 120°, kept thereat for 15 min., and then cooled. The complex was decomposed with ice (9 g.) and concentrated hydrochloric acid (1 c.c.), and the product filtered off, dried, and crystallised from light petroleum (b. p. 40—60°), to yield 6-acetyl-7-hydroxychroman (0.62 g., 62%) as prisms, m. p. 93° (Found: C, 68.7; H, 6.5. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

(b) A similar experiment at room temperature, using 7-acetoxychroman (1.0 g.), resublimed anhydrous aluminium chloride (0.85 g.), and dry nitrobenzene (2 c.c.), yielded 6-acetyl-7-hydroxychroman (0.31 g., 31%) identical with the above material.

(c) A solution of 7-hydroxychroman (8.5 g.) in dry nitrobenzene (85 c.c.) and acetic anhydride (6 c.c.) was stirred at 0° and resublimed anhydrous aluminium chloride (16.5 g.) was added in four portions during 30 min., as described for the preparation of 7-hydroxychroman-4-one. The product was filtered off, dried, and extracted with light petroleum (b. p. 40—60°), to yield 6-acetyl-7-hydroxychroman (5.02 g., 46%) as prisms, m. p. 93°.

6-Acetyl-7-hydroxychroman formed a *semicarbazone*, prismatic needles (from ethanol), m. p. 304° (decomp.) (Found: C, 58.5; H, 5.9. $C_{12}H_{15}O_3N_3$ requires C, 57.8; H, 6.1%), and a 2:4-dinitrophenylhydrazone, orange needles (from dioxan), m. p. 304° (decomp.) (Found: C, 54.0; H, 4.3. $C_{17}H_{16}O_6N_4$ requires C, 54.8; H, 4.3%).

7-Benzoyloxy-6-ethylchromone-2-carboxylic Acid (IV; R = CH_2Ph , R' = CO_2H).—The ester (IV; R = CH_2Ph , R' = CO_2Et) (10 g.) was refluxed with 5N-hydrochloric acid (200 c.c.) for 5 hr., and the cooled product, in the form of a hard ball, was removed mechanically. Crystallised from ethanol, 7-benzoyloxy-6-ethylchromone-2-carboxylic acid was obtained as flocculent needles (7.4 g., 80%), m. p. 248° (decomp.) (Found: C, 69.8; H, 4.8. $C_{18}H_{16}O_5$ requires C, 70.4; H, 5.0%). A small amount of 6-ethyl-7-hydroxychromone-2-carboxylic acid (0.7 g., 11%) was isolated from the dilute hydrochloric acid, and crystallised from ethanol as needles, m. p. 293—294° (decomp.) (Found: C, 61.6; H, 4.3. Calc. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3%).

7-Benzoyloxy-6-ethylchromone (IV; R = CH_2Ph , R' = H).—A solution of the acid (IV; R = CH_2Ph , R' = CO_2H) (5 g.) in pure dry quinoline (25 c.c.) was refluxed with copper bronze powder (2.5 g.) for 20 min., cooled, and acidified with dilute hydrochloric acid. The mixture was extracted with ether (2 × 100 c.c.), and the combined extracts were washed with 5% sodium carbonate solution (100 c.c.) and then water (50 c.c.). Evaporation of the dried (Na_2SO_4) ethereal solution left a residue which on crystallisation from *cyclohexane* gave 7-benzoyloxy-6-ethylchromone (2.5 g., 58%) as pale yellow needles, m. p. 105° (Found: C, 77.3; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.8%).

6-Ethyl-7-hydroxychromone (IV; R = R' = H).—(a) The benzoyloxy-compound (IV; R = CH_2Ph , R' = H) (5 g.) was refluxed for 5 hr. with 5N-hydrochloric acid (200 c.c.), filtered

hot, and cooled. The product was removed by filtration and on crystallisation from ethanol gave 6-ethyl-7-hydroxychromone (2.0 g., 60%) as needles, m. p. 230° (Found: C, 69.3; H, 5.3. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%).

(b) The acid (IV; R = H, R' = CO₂H) (2.34 g.) was heated for 5 min. at 300°. Distillation of the residue under reduced pressure gave 6-ethyl-7-hydroxychromone (1.04 g., 55%) as a yellow solid which crystallised from ethanol as colourless needles, m. p. 230°, identical with the above material.

6-Ethyl-7-hydroxychroman-4-one (II; R = H, R' = Et).—(a) Raney nickel catalyst (5 c.c.; settled suspension in ethanol) was added to a solution of 6-ethyl-7-hydroxychromone (2.5 g.) in ethanol (100 c.c.). The mixture was shaken at 45° in hydrogen until the uptake reached 360 c.c. (ca. 3½ hr.); it was then cooled and filtered and the catalyst washed with ethanol. The filtrate and washings were concentrated to about 25 c.c., hot water (25 c.c.) was added, and the solution cooled. 6-Ethyl-7-hydroxychroman-4-one (2.2 g., 88%) formed plates, m. p. 159° (Found: C, 68.8; H, 6.4. $C_{11}H_{12}O_3$ requires C, 68.7; H, 6.3%).

(b) 4-Ethylresorcinol⁴ (13.8 g.) was subjected to a Friedel-Crafts reaction as described for the preparation of 7-hydroxychroman-4-one. 6-Ethyl-7-hydroxychroman-4-one (6 g., 31%) crystallised from water (charcoal) as plates, m. p. 159°, identical with the above material.

6-Ethyl-7-hydroxychroman-4-one formed a *semicarbazone*, m. p. 258° (decomp.), which was crystallised from water (Found: C, 57.8; H, 5.9. $C_{12}H_{15}O_3N_3$ requires C, 57.8; H, 6.1%).

6-Ethyl-7-hydroxychroman (I; R = H, R' = Et).—(a) A solution of 6-ethyl-7-hydroxychroman-4-one (1.0 g.) in ethanol (100 c.c.) and 10% palladium-charcoal catalyst (0.5 g.) were shaken together at 45° in hydrogen until the uptake ceased (ca. 24 hr.). The mixture was filtered and the catalyst washed with ethanol. Evaporation of the filtrate and washings under reduced pressure left a brown oil which was distilled (105–115°/0.9 mm.) on to a cold finger. 6-Ethyl-7-hydroxychroman crystallised from light petroleum (b. p. <40°) as colourless prismatic needles (0.8 g., 86%), m. p. 69–70° (Found: C, 74.2; H, 8.0. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

(b) 6-Acetyl-7-hydroxychroman (1.0 g.) and amalgamated zinc (10 g.) were refluxed gently with 4N-hydrochloric acid (30 c.c.) for 4 hr. and cooled. The mixture was extracted with ether (2 × 15 c.c.), and the combined extracts were washed with water (15 c.c.) and dried (Na₂SO₄). Evaporation of the ether left a brown oil which on purification as above gave 6-ethyl-7-hydroxychroman (0.75 g., 81%), identical with the above material.

6-Ethyl-7-hydroxychroman formed an *O-carboxymethyl derivative* (I; R = •CH₂•CO₂H, R' = Et), m. p. 161–162°, which crystallised from benzene as needles (Found: C, 66.0; H, 6.5. $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%).

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⁴ Clemmensen, *Ber.*, 1914, **47**, 54.