Nuclear Oxidation in Flavones and Related Compounds. Part XLVII. A New Synthesis of Fraxetin and a Synthesis of 4-Methylfraxetin.*

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A new and convenient synthesis of fraxetin and 4-methylfraxetin has been carried out from 8-acetyl-7-methoxycoumarin and its 4-methyl derivative respectively, by nuclear oxidation in the 6-position followed by methylation to yield 8-acetyl-6 : 7-dimethoxy-compounds, partial demethylation in the 7-position, and final Dakin oxidation.

Späth and Dobrovolny (*Ber.*, 1938, **71**, 1831) synthesised fraxetin (I; R = H) in a small yield by condensing 2 : 3 : 4-trihydroxy-1-methoxybenzene with formylacetic ester; and Späth and Schmid (*Ber.*, 1941, **74**, 598) converted scopoletin through its 8-aldehyde into fraxetin, but the yield of aldehyde was very poor. Since use of a ketone might have been better than that of an aldehyde, Fries rearrangement of scopoletin acetate was attempted under different conditions (Baker and Evans, *J.*, 1938, 374; Lohfert and Rosenmund, *Ber.*, 1928, **61**, 2601), but was unsuccessful. Hence alternative routes to 8-acetyl-7-hydroxy-6-methoxycoumarin (II; R′ = R″ = H) have been explored.

First, 8-acetyl-7-methoxy-4-methylcoumarin (Limaye and Sathe, *Rasayanam*, 1936, **1**, 35) was subjected to persulphate oxidation, to give 8-acetyl-6-hydroxy-7-methoxy-4-methylcoumarin in over 50% yield. 8-Acetyl-4-methylumbelliferone similarly yielded

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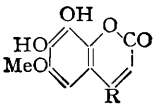
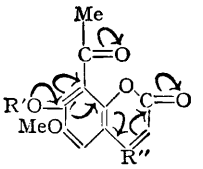
8-acetyl-6 : 7-dihydroxy-4-methylcoumarin (25% yield), but partial methylation of this dihydroxy-compound was unsuccessful. However, after initial failures, partial demethylation of 8-acetyl-6 : 7-dimethoxy-4-methylcoumarin (II; R′ = R″ = Me) by concentrated sulphuric acid gave good yields of 8-acetyl-7-hydroxy-6-methoxy-4-methylcoumarin. The product (m. p. 193—194°) was different from that reported by Baker and Evans (*loc. cit.*) (m. p. 250°). Its constitution was established by converting it into 4-methylfraxetin (I; R = Me) by Dakin oxidation and finally into the known 6 : 7 : 8-trihydroxy- and -trimethoxy-4-methylcoumarin.

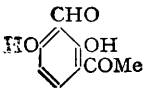
Though concentrated sulphuric acid is known to bring about demethylation, it has not been considered suitable for the partial demethylation of a methoxyl group situated *ortho* to a carbonyl; but the reagent of common choice, aluminium chloride, failed in the present case. In view of the analogy of partial demethylation, by sulphuric acid, of trimethylgallic acid to syringic acid (Bogert and Coyne, *J. Amer. Chem. Soc.*, 1929, **51**, 569), it could be suggested that demethylation of the 7-methoxyl group is encouraged by the unsaturated



(I)



(II)



(III)

carbonyl system of the α-pyrone (see II). However this influence alone is not enough since 7-methoxycoumarin does not suffer demethylation under the same conditions whereas 8-acetyl-7-methoxycoumarin is demethylated. Obviously the carbonyl group in the 8-position is also necessary.

The marked solubility of these 8-acetyl-7-hydroxycoumarins in aqueous sodium carbonate seems to be due also to the combined influence of electron-attracting groups in both the *ortho*- and the *para*-position. A closely related example is 3-formyl-2 : 4-dihydroxyacetophenone (III) which is also readily soluble in aqueous sodium hydrogen carbonate.

Fraxetin (I; R = H) has been synthesised similarly in satisfactory yield, starting from 8-acetyl-7-methoxycoumarin.

Experimental

8-Acetyl-6-hydroxy-7-methoxy-4-methylcoumarin.—8-Acetyl-7-methoxy-4-methylcoumarin (Limaye and Sathe, *loc. cit.*) (11 g.) was heated with aqueous sodium hydroxide (10%; 100 c.c.) at 100° for 1 hr. The solution was treated at 10° with stirring during 6 hr. with aqueous potassium persulphate (5%; 300 c.c.), the mixture was kept at room temperature for 24 hr. and acidified to Congo-red, and the precipitated solid (unchanged coumarin) was filtered off. The filtrate was extracted with ether thrice to remove unchanged coumarin (4 g.). The aqueous layer was treated with concentrated hydrochloric acid (80 c.c.) and sodium sulphite (2 g.) and heated for 2 hr. on a boiling-water bath and cooled. *8-Acetyl-6-hydroxy-7-methoxy-4-methylcoumarin* that separated crystallised from dilute alcohol as colourless rhombohedral tablets, m. p. 242—243° (4 g.) (Found: C, 62·9; H, 4·9. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%). The methyl ether, prepared by methyl sulphate–acetone–potassium carbonate, crystallised from alcohol as colourless elongated rectangular plates and prisms, m. p. 115—116°. It exhibited a strong bluish-green fluorescence in dry ether solution.

8-Acetyl-6 : 7-dihydroxy-4-methylcoumarin.—8-Acetyl-4-methylumbelliferone (Limaye and Sathe, *loc. cit.*) (10 g.) in aqueous sodium hydroxide (10%; 100 c.c.), oxidised as above with aqueous potassium persulphate (5%; 300 c.c.), yielded the unchanged compound (2 g.) and *8-acetyl-6 : 7-dihydroxy-4-methylcoumarin* (2 g.). The latter, pale yellow plates (from alcohol), m. p. 220—222°, gave a deep green colour with alcoholic ferric chloride and quickly dissolved to a yellow solution in aqueous sodium carbonate (Found: C, 61·2; H, 4·5. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%).

8-Acetyl-7-hydroxy-6-methoxy-4-methylcoumarin (II; R′ = H, R″ = Me).—A solution of

8-acetyl-6 : 7-dimethoxy-4-methylcoumarin (1 g.) in sulphuric acid (6 c.c.; *d* 1·8) was kept at 30° for 24 hr. and then poured into water (100 c.c.) without cooling. The solid that separated crystallised from alcohol as long yellow rectangular rods and prisms, m. p. 193—194°. The *coumarin* gave a reddish brown colour with alcoholic ferric chloride and was soluble in aqueous sodium carbonate (Found: C, 63·1; H, 4·8%).

4-*Methylfraxetin* (I; R = Me).—A solution of the preceding acetylcoumarin (1 g.) in N-sodium hydroxide (6 c.c.) at 0° was treated with hydrogen peroxide (30 c.c.; 20-vol.) all at once. The temperature rose and soon a crystalline solid separated. After 1 hr. at room temperature 4-*methylfraxetin* was filtered off. It crystallised from alcohol–benzene as colourless rhombohedral tablets, m. p. 260—261° (0·5 g.) (Found: C, 59·9; H, 5·0. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). It gave a bluish-green colour with alcoholic ferric chloride and did not fluoresce in alkaline solutions. It dissolved quickly in aqueous sodium carbonate to a yellow solution. The diacetate crystallised from alcohol–benzene as colourless needles, m. p. 220—221°.

6 : 7 : 8-*Trihydroxy-4-methylcoumarin*.—4-Methylfraxetin (0·5 g.) in acetic anhydride (5 c.c.) and hydriodic acid (10 c.c.; *d* 1·7) was refluxed for 1 hr., then poured into water, and the free iodine removed by sulphur dioxide. The solid crystallised from alcohol–benzene as colourless rectangular tablets, m. p. 278° (decomp.). Oliverio and Baroni (*Gazzetta*, 1949, **79**, 906) gave m. p. 282°; Parikh and Sethna (*J. Indian Chem. Soc.*, 1950, **27**, 369) gave m. p. 276°. The trihydroxycoumarin gave a blue colour with ferric chloride solution and a deep yellow solution with alkali which became brown in air. The triacetate crystallised from alcohol–benzene as colourless needles, m. p. 143°. The trimethyl ether prepared by methyl sulphate–acetone–potassium carbonate crystallised from dilute alcohol as colourless needles, m. p. 114°. Oliverio *et al.* (*loc. cit.*) gave the same m. p. for the derivatives.

8-*Acetyl-6-hydroxy-7-methoxycoumarin*.—8-Acetyl-7-methoxycoumarin (Limaye and Joshi, *Rasayanam*, 1941, **1**, 227) (2·2 g.) was dissolved in aqueous potassium hydroxide (14%; 20 c.c.) by heating at 100° for 1 hr. and oxidised as described above with aqueous potassium persulphate (3%; 100 c.c.). 8-*Acetyl-6-hydroxy-7-methoxycoumarin* crystallised from alcohol as plates, m. p. 196—197° (0·8 g.) (Found: C, 61·1; H, 3·9. $C_{12}H_{10}O_5$ requires C, 61·5; H, 4·3%). The methyl ether, prepared as above, crystallised from dilute alcohol as rectangular prisms, m. p. 94—95°.

8-*Acetyl-7-hydroxy-6-methoxycoumarin* (II; R′ = R″ = H).—The dimethyl ether (0·6 g.) was kept in sulphuric acid (2·5 c.c.; *d* 1·8) at 30° for 24 hr., then poured into water (50 c.c.) without cooling. The *acetylcoumarin* crystallised from alcohol as pale yellow thin rectangular plates, m. p. 180° (0·4 g.), soluble in sodium carbonate solution and giving a reddish-brown colour with alcoholic ferric chloride (Found: C, 61·6; H, 4·4%).

Fraxetin (I; R = H).—The above acetylhydroxycoumarin (0·4 g.) in N-sodium hydroxide (2·5 c.c.) was oxidised by hydrogen peroxide (25 c.c.; 20-vol.). Fraxetin crystallised from alcohol–benzene as plates, m. p. 227—228° (0·2 g.), giving a bluish-green colour with alcoholic ferric chloride (Found: C, 57·8; H, 4·3. Calc. for $C_{10}H_8O_5$: C, 57·7; H, 3·8%). The diacetate crystallised from alcohol–benzene as prisms, m. p. 192—193°. Simada (*J. Pharm. Soc. Japan*, 1937, **57**, 148) gave the same m. p.

8-*Acetyl-7-hydroxycoumarin*.—8-Acetyl-7-methoxycoumarin (0·5 g.) was demethylated with sulphuric acid (2·5 c.c.; *d* 1·8). 8-Acetyl-7-hydroxycoumarin (0·2 g.) crystallised from alcohol as pale yellow needles, m. p. and mixed m. p. 167°. It was soluble in aqueous sodium carbonate and gave a violet colour with alcoholic ferric chloride.

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