846. *Thermal Cyclization of* o-*Aroyloxyacetoarones. Part III.* Synthesis in the Chromone Series.*

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The method for the preparation of flavones and flavonol ethers based on thermal cyclization of aroyl esters of *o*-hydroxyacetoarones * has been extended to the synthesis of chromonol ethers. It is confirmed that this method involves a thermal Baker–Venkataraman transformation.

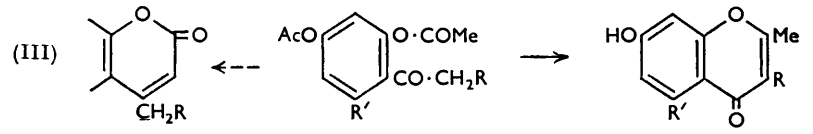
It was shown in Part I [1] that *o*-aroyloxyacetoarones yield flavones when heated in glycerol; in some instances the yield is excellent.[2] Flavonol 3-methyl ethers can also be synthesised in this way.[3] The method has now been extended to the synthesis of 7-hydroxy- and 5 : 7-dihydroxy-3-methoxy-2-methylchromone (IIa and b) from the corresponding acetoxy-ω-methoxyacetophenones (Ia) and (Ib), respectively.

In view of the possibility of coumarin formation (see III), the identity of each chromone derivative was confirmed by comparison with an authentic specimen prepared by Kostanecki–Robinson acylation of the related *o*-hydroxyacetophenones.[4] These chromonol ethers were also synthesized by the Baker–Venkataraman method, spontaneous cyclization of the intermediate diketone occurring in the transformation. No useful result was obtained by application of the glycerol cyclization technique to 2-acetoxy-4-benzyloxyacetophenone, 2 : 4-diacetoxyacetophenone (Ic) or 2 : 4 : 6-triacetoxyacetophenone (Id). Also, it was not found possible to obtain 2-styrylchromones from *o*-cinnamoyloxyacetophenone, 4-benzyloxy-2-cinnamoyloxyacetophenone, or 2 : 4 : 6-tricinnamoyloxyacetophenone, by thermal cyclization in glycerol, although these esters undergo the Baker–Venkataraman transformation to form the corresponding 2-styrylchromones, and *o*-cinnamoyloxyacetophenones had previously been cyclized by the glycerol method, though in poor yield.[1] Two of the styrylchromones were oxidized to chromonecarboxylic acids.

* Parts I and II, *J.*, 1950, 1252; 1952, 2063.

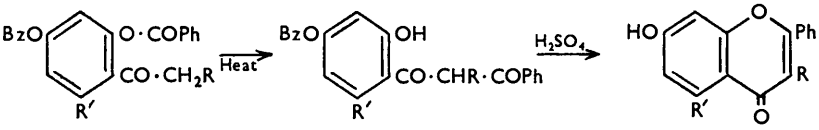
[1] Dunne, Gowan, Keane, O'Kelly, O'Sullivan, Roche, Ryan, and Wheeler, *J.*, 1950, 1252.
[2] Cf. Wheeler, *Org. Synth.*, 1952, **32**, 72.
[3] Lynch, O'Toole, and Wheeler, *J.*, 1952, 2063.
[4] (*a*) Allan and Robinson, *J.*, 1924, 2192; (*b*) Kalff and Robinson, *J.*, 1925, 1968.

Thermal Baker–Venkataraman Transformation.—The suggestion [1,3] that the glycerol cyclization involves a thermal Baker–Venkataraman transformation receives support from the observation that 2 : 4-dibenzoyloxyacetophenone (IVa), and 2 : 4 : 6-tribenzoyloxy-ω-methoxyacetophenone (IVb) are transformed, when heated, into the diketones, ω-benzoyl-4-benzoyloxy-2-hydroxyacetophenone (Va), and ω-benzoyl-4 : 6-dibenzoyloxy-2-hydroxy-ω-methoxyacetophenone (Vb), respectively. The diketones cyclized to the corresponding



(I) (a) R = OMe, R′ = H; (b) R = OMe, R′ = OAc; (c) R = R′ = H; (d) R = H, R′ = OAc

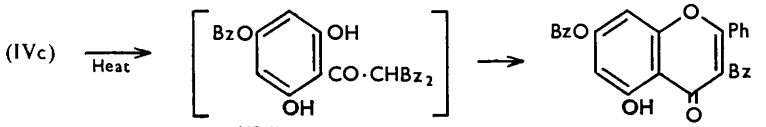
(II) (a) R = OMe, R′ = H; (b) R = OMe, R′ = OH



(IV) (V) (VI)

(IV)&(V) (a) R = R′ = H; (b) R = OMe, R′ = OBz; (c) R = H, R′ = OBz

(VI) (a) R = R′ = H; (b) R = OMe, R′ = OH



(VIII) (VII)

hydroxyflavones (VIa and b) on treatment with sulphuric acid in the usual way. 2 : 4 : 6-Tribenzoyloxyacetophenone (IVc) gave, on heating, 3-benzoyl-7-benzoyloxy-5-hydroxyflavone (VII) with, presumably, intermediate formation of the triaroylmethane (VIII). Baker [5] observed a similar double Baker–Venkataraman transformation with cyclization when he treated 2 : 6-dibenzoyloxyacetophenone with potassium carbonate in toluene and obtained 3-benzoyl-5-hydroxyflavone. The structure of compound (VII) was confirmed by the identity of its 5-*O*-benzoyl derivative with the product of Allan–Robinson benzoylation of phloracetophenone with omission of the normal alkaline after-boil.

Experimental

Crystallization was from ethanol unless otherwise stated.

Preparation of Chromonols.—*3 : 7-Dihydroxy-2-methylchromone.* 2 : 4-*Diacetoxy-ω-methoxyacetophenone* (Ia), needles, m. p. 54° (Found: C, 58·7; H, 5·3. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%), which was prepared by the pyridine–acetic anhydride method, was heated in anhydrous glycerol (10 parts) at 250° in an atmosphere of nitrogen for 30 min. The product was diluted with water (100 parts), and the resulting precipitate was chromatographed from ethanol on alumina. The yellow band of 7-hydroxy-3-methoxy-2-methylchromone (IIa) was extracted by boiling ethanol. It separated from aqueous ethanol in needles (0·1 part), m. p. 214° (Found: C, 63·8; H, 4·7. Calc. for $C_{11}H_{10}O_4$: C, 64·1; H, 4·9%), not depressed by addition of an authentic sample obtained by Kostanecki–Robinson acylation of ω-methoxyresacetophenone.[4a]

The hydroxymethoxymethylchromone was also prepared by the Baker–Venkataraman

[5] Baker, *J.*, 1934, 1953.

method. A solution of 2 : 4-diacetoxy-ω-methoxyacetophenone (1 g.) in pyridine (10 ml.) was shaken with powdered potassium hydroxide (0·2 g.) for 2 hr., and the product was acidified to yield the crude chromone which, after crystallization (0·1 g.), did not depress the m. p. of an authentic sample. Demethylation of this chromone by hydriodic acid gave 3 : 7-dihydroxy-2-methylchromone, m. p. 249° (decomp.) (Found : C, 62·6; H, 4·5. Calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). Allan and Robinson [4a] give the same m. p.

3 : 7-*Dimethoxy-2-styrylchromone*. A mixture of 3 : 7-dimethoxy-2-methylchromone (1 g.), benzaldehyde (2 ml.), and ethanolic sodium ethoxide (Na, 0·5 g.; EtOH, 10 ml.) was refluxed for 30 min. 3 : 7-*Dimethoxy-2-styrylchromone* crystallized in yellow needles, m. p. 157—158° (Found : C, 73·8; H, 5·2. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%).

3 : 5 : 7-*Trihydroxy-2-methylchromone*. 2 : 4 : 6-*Triacetoxy-ω-methoxyacetophenone* (Ib), plates, m. p. 115—116° (Found : C, 55·7; H, 5·1. $C_{15}H_{16}O_8$ requires C, 55·6; H, 5·0%), gave 5 : 7-dihydroxy-3-methoxy-2-methylchromone (IIb), m. p. 223—224° (Found : C, 59·4; H, 4·6. Calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%), by both the glycerol dehydration and the Baker–Venkataraman method, in about 50% yield (crystallized material). The products did not depress the m. p. of an authentic sample of the dihydroxymethoxychromone.[4b] For demethylation the chromone (1 g.) was refluxed with hydriodic acid (*d* 1·7; 20 ml.) for 45 min., and the product was poured into aqueous sodium hydrogen sulphite. The precipitate of 3 : 5 : 7-*trihydroxy-2-methylchromone* separated from aqueous ethanol in needles (0·5 g.), m. p. 224° (Found : C, 57·3; H, 4·0. $C_{10}H_8O_5$ requires C, 57·7; H, 3·9%). The m. p. was depressed by addition of 5 : 7-dihydroxy-3-methoxy-2-methylchromone, m. p. 224°.

2-*Acetoxy-4-benzyloxyacetophenone*, plates, m. p. 111—112° (Found : C, 71·9; H, 5·7. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%), was prepared by the pyridine–acetic anhydride method from 2-hydroxy-4-benzyloxyacetophenone.[6]

Attempted Cyclization in Glycerol of o-*Cinnamoyloxyacetophenones*.—The following esters were prepared by the pyridine–acid chloride method : *o*-cinnamoyloxyacetophenone, needles, m. p. 73° (Found : C, 76·1; H, 5·4. Calc. for $C_{17}H_{14}O_3$: C, 76·7; H, 5·3%) (Doyle *et al.*[7] give the same m. p.); 4-*benzyloxy-2-cinnamoyloxyacetophenone*, needles, m. p. 102—103° (Found : C, 77·6; H, 5·4. $C_{24}H_{20}O_4$ requires C, 77·4; H, 5·4%); 2 : 4 : 6-*tricinnamoyloxyacetophenone*, m. p. 178—180° (Found : C, 75·1; H, 4·5. $C_{35}H_{26}O_7$ requires C, 75·3; H, 4·7%). No useful result was obtained by the application of the glycerol dehydration method to these esters.

Synthesis of 2-Styrylchromones by the Baker–Venkataraman Method.—4-Benzyloxy-2-cinnamoyloxyacetophenone was heated with pyridine and potassium hydroxide in the usual way. The product, 7-benzyloxy-2-styrylchromone, had m. p. 162—163° (from benzene or acetic acid), not depressed by addition of an authentic sample.[6] Similarly, 2 : 4 : 6-tricinnnamoyloxyacetophenone gave 5 : 7-dicinnamoyloxy-2-styrylchromone, m. p. 232°, not depressed by addition of an authentic sample.[8]

Oxidation of 2-Styrylchromones to Chromone-2-carboxylic Acids.—A solution of 7-benzyloxy-2-styrylchromone (1 g.) in pyridine (10 ml.) and water (100 ml.) was treated with aqueous potassium permanganate (1 g. in 50 ml.).[9] The product was decolorized by sulphur dioxide, concentrated to half-volume under reduced pressure, acidified, and extracted with ethyl acetate. 7-*Benzyloxychromone-2-carboxylic acid* was removed from the extract by aqueous sodium carbonate and recovered by acidification. It separated in needles (0·2 g.), m. p. 237° (Found : C, 68·7; H, 4·3. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

Decarboxylation and debenzylation was effected by refluxing the benzyloxychromone-carboxylic acid in glacial acetic acid saturated with hydrogen bromide for 2 hr.[9] Dilution of the product with water afforded 7-hydroxychromone, m. p. 218°. Kostanecki *et al.*[10] give the same m. p.

2-Styrylchromone when similarly oxidized gave chromone-2-carboxylic acid, m. p. 247—248° (Found : C, 63·4; H, 3·5. Calc. for $C_{10}H_6O_4$: C, 63·2; H, 3·2%). Heywang and Kostanecki [11] give m. p. 252°. Gomberg and Cone [12] give m. p. 258°. Decarboxylation by the method of Ruhemann and Stapleton [13] gave, as they describe, chromone, m. p. 59°.

Thermal Baker–Venkataraman Reaction.—The *o*-aroyloxyacetophenone was heated for 30 min.

[6] Gulati, Seth, and Venkataraman, *J.*, 1934, 1765.
[7] Doyle, Gógan, Gowan, Keane, and Wheeler, *Sci. Proc. Roy. Dublin Soc.*, 1948, **24**, 291.
[8] Cheema, Gulati, and Venkataraman, *J.*, 1932, 925.
[9] Cf. Baker, Robinson, and Simpson, *J.*, 1937, 805.
[10] Kostanecki, Paul, and Tambor, *Ber.*, 1901, **34**, 2475.
[11] Heywang and Kostanecki, *Ber.*, 1902, **35**, 2887.
[12] Gomberg and Cone, *Annalen*, 1910, **376**, 229.
[13] Ruhemann and Stapleton, *J.*, 1900, **77**, 1179.

at 280°/3 mm., and the diketone formed was extracted from the residue with ethanol. 2 : 4-Dibenzoyloxyacetophenone (IVa) [14] (2 g.) gave ω-benzoyl-4-benzoyloxy-2-hydroxyacetophenone (Va), yellow needles (0·25 g.), m. p. 167°, not depressed by addition of an authentic sample.[14] Cyclization by sulphuric acid gave 7-hydroxyflavone (VIa) (mixed m. p.).

2 : 4 : 6-Tribenzoyloxy-ω-methoxyacetophenone (IVb) [3] (3 g.) gave *ω-benzoyl-4 : 6-dibenzoyloxy-2-hydroxy-ω-methoxyacetophenone* (Vb), yellow needles (0·5 g.) (from ligroin), m. p. 152—154° (Found: C, 70·8; H, 4·2. $C_{30}H_{22}O_8$ requires C, 70·6; H, 4·3%). The ethanolic ferric reaction was red. This diketone on cyclization by sulphuric acid yielded 5 : 7-dihydroxy-3-methoxyflavone (galangin 3-methyl ether) (VIb), m. p. 297°, not depressed by addition of an authentic sample.[3]

2 : 4 : 6-Tribenzoylacetophenone (IVc) [15](3 g.) gave, when heated, *3-benzoyl-7-benzoyloxy-5-hydroxyflavone* (VII) as a microcrystalline powder (0·2 g.), m. p. 154° (from ligroin) (Found: C, 75·3; H, 3·9. $C_{29}H_{18}O_6$ requires C, 75·3; H, 3·9%). The first fraction from ligroin separated as a yellow powder which melted indefinitely from 58° to 128° (?cyclization), and gave analytical figures for the triketone, *dibenzoyl-4-benzoyloxy-2 : 6-dihydroxybenzoylmethane* (VIII) (Found: C, 72·5, 72·5; H, 4·4, 4·3. $C_{29}H_{20}O_7$ requires C, 72·5; H, 4·2%). Benzoylation (pyridine–benzoyl chloride) of the benzoylflavone, m. p. 154°, gave 3-benzoyl-5 : 7-dibenzoyloxyflavone as a microcrystalline powder (Found: C, 76·6, 76·7; H, 4·2, 4·0. Calc. for $C_{36}H_{22}O_7$: C, 76·3; H, 3·9%), m. p. and mixed m. p. with authentic sample, 173—175°. Dunne *et al.*[1,16] give m. p. 169°.

5 : 7-*Dibenzoyloxyflavone* (Found: C, 75·1; H, 4·0. $C_{29}H_{18}O_6$ requires C, 75·3; H, 3·9%) separated as a crystalline powder, m. p. 194—196°.

UNIVERSITY COLLEGE, DUBLIN. [*Received, June 8th*, 1956.

[14] Baker, *J.*, 1933, 1381.
[15] Canter, Curd, and Robertson, *J.*, 1931, 1245.
[16] Cf. Trivedi, Sethna, and Shah, *J. Indian Chem. Soc.*, 1943, **20**, 171.