274. *A Synthesis of Flavone Glycosides.*

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Previous methods for the synthesis of flavone glycosides are briefly reviewed. The possibility has been investigated of preparing such compounds from tetra-acetyl glucosyloxy-*o*-aroyloxyacetophenones by molecular rearrangement to the related 1 : 3-diketones and thence by cyclisation and hydrolysis to the glucosyloxyflavone. 7-β-D-Glucosyloxyflavone has been thus prepared, but the method is of very limited scope.

Although the flavones have for long been intensively investigated in many laboratories, very little work is recorded on the preparation of flavone glycosides, and only two essentially different methods have been used.

The first, which consists in the formation of a glycoside of a preformed hydroxyflavone, using, for example, tetra-acetyl α-glucosyl bromide followed by deacetylation, is unsuitable in the general case of di- and poly-hydroxylated flavones. Hattori (*Acta Phytochim.*, 1928, **4**, 63; *A.*, 1928, 1020) used it to prepare 7- and 4′-β-D-glucosyloxyflavones, and Zemplén, Bognár, and Mechner (*Ber.*, 1944, **77**, 99) were able to synthesise 7-β-D-glucosyloxy-5-hydroxyflavone (toringin) from 5 : 7-dihydroxyflavone (chrysin) by taking advantage of the known inhibiting effect of the carbonyl group on alkylation of the hydroxyl group in position 5.

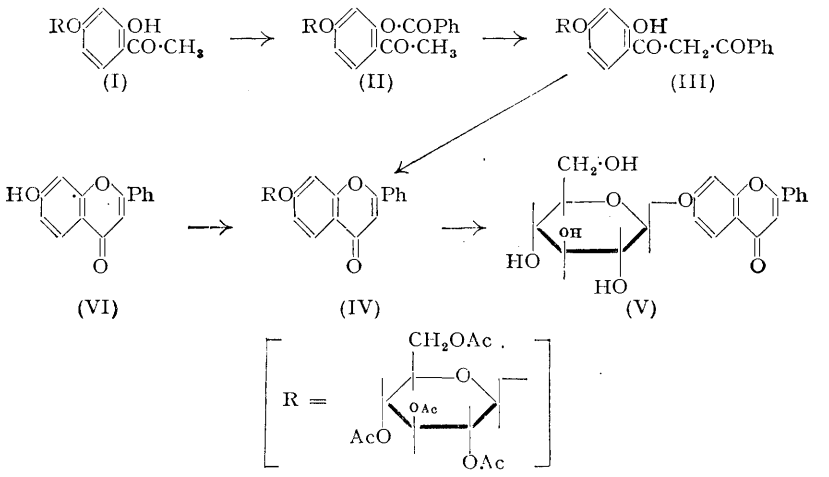
The second method, which is of much wider application but gives very poor yields in the final stage, starts from a fully acetylated flavanone glycoside which is brominated in position 3 and then treated with alkali, to give the flavone glycoside. This method has been used in the preparation of 5 : 3′-dihydroxy-4′-methoxy-7-rutinosyloxyflavone (diosmin) from the related flavanone (hesperidin) (Zemplén and Bognár, *Ber.*, 1943, **76**, 452), and of 5-glucosyloxy-7 : 4′-dihydroxyflavone from the flavanone salipurposide (Zemplén and Mester, *Ber.*, 1943, **76**, 776). A considerable improvement was introduced by Narasimhachari and Seshadri (*Proc. Indian Acad. Sci.*, 1949, **30**, 151) who found that flavanone glycosides, preferably those containing a free phenolic group in position 5, are smoothly oxidised to flavone glycosides by iodine in boiling ethanol in presence of sodium acetate.

Before the publication by Narasimhachari and Seshadri we had begun experiments to see if the Baker–Venkataraman base-catalysed rearrangement of *o*-aroyloxyacetophenones to *o*-hydroxydibenzoylmethanes could be adapted to the synthesis of flavone glycosides (see Baker, *J.*, 1933, 1382; Mahal and Venkataraman, *Current Sci.*, 1933, **2**, 214). An account of this work is now given, but the method is of limited scope and inferior to the potentially versatile synthesis from a flavanone glycoside which may be either natural (cf. Zemplén *et al.*, *loc. cit.*) or synthetical (Reichel and Steudel, *Annalen*, 1942, **553**, 83), followed by oxidation with iodine according to Narasimhachari and Seshadri.

Preliminary experiments with 2 : 4-dibenzoyloxyacetophenone showed that the most suitable basic reagent which might be used in the case of an acetylated glycoside for bringing about molecular rearrangement to a *o*-hydroxydibenzoylmethane [cf. conversion of (II) into (III)] was anhydrous potassium carbonate in pyridine, although the yield of the pure product was only 30% (cf. Doyle, Gógan, Gowan, Keane, and Wheeler, *Proc. Roy. Dublin Soc.*, 1948, **24**, 291, who have discussed the mechanism of this reaction and the different bases which may be used). The next step, cyclodehydration of the 1 : 3-diketone to the flavone [cf. conversion of (III) into (IV)] cannot, in the case of a glycoside, be carried out in the usual way with hydrochloric acid in acetic acid, but it was found that the reaction could be satisfactorily effected by heating the diketone in xylene with a trace of toluene-*p*-sulphonic acid. In this manner 4-benzoyloxy-2-hydroxydibenzoylmethane gave 7-benzoyloxyflavone in good yield.

The preparation of 7-β-D-glucosyloxyflavone (V) was then achieved as follows. 2-Hydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone (I) reacted with benzoyl chloride in pyridine to give the *O*-benzoyl derivative (II), and this underwent rearrangement, when heated with potassium carbonate in pyridine, to the 1 : 3-diketone (III).

Cyclisation in boiling xylene with toluene-*p*-sulphonic acid yielded 7-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)flavone (IV) which was identical with a specimen prepared from



7-hydroxyflavone (VI) and 2 : 3 : 4 : 6-tetra-acetyl α-D-glucosyl bromide. Finally deacetylation with a trace of sodium methoxide in methanol–chloroform gave, from both specimens of (IV), 7-β-D-glucosyloxyflavone (V). Molecular rearrangement of the benzoyl derivative (II) with potassium hydroxide in pyridine gave an isomeride of the diketone (III); this is probably an enolic form. Similar phenomena were obtained by molecular rearrangement of resacetophenone dibenzoate which, on occasion, gave a 1 : 3-diketone whose initial melting point of 210° fell to 167° on storage (this paper), and by 2-benzoyloxy-4-methoxypropiophenone which reacted with potassium hydroxide in pyridine to give a diketone, m. p. 166° falling to 144° after being kept (Mr. D. Weight, unpublished observation).

Attempts to apply these reactions to the synthesis of 7-β-D-glucosyloxy-5-hydroxyflavone (toringin) were not successful. Treatment of 2 : 6-dihydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone with two equivalents of benzoyl chloride gave only the monobenzoyl derivative, 2-benzoyloxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)-acetophenone, and treatment of this with potassium carbonate and pyridine led to the isolation of only the debenzoylated product (note that the Baker–Venkataraman transformation had not been effected with a compound containing a free phenolic group).

Experimental

4-Benzoyloxy-2-hydroxydibenzoylmethane.—Resacetophenone dibenzoate (5 g.), anhydrous potassium carbonate (4 g.), and dry pyridine (10 c.c.) were heated on the steam-bath for 1 hour, cooled, poured into water, and acidified to pH 6 with glacial acetic acid. The solid benzoyl-(4-benzoyloxy-2-hydroxybenzoyl)methane crystallised from benzene–methanol as yellow needles (1·37 g., 27%), m. p. 165—167° (Baker, *loc. cit.*, gives m. p. 167°). In some preparations the material, when first isolated, had m. p. *ca.* 210°, but after some time the m. p. had dropped to 167°; this phenomenon is probably due to prototropic change.

7-Benzoyloxyflavone.—4-Benzoyloxy-2-hydroxydibenzoylmethane (1·5 g.) was boiled under reflux in a Soxhlet apparatus in xylene (50 c.c.) containing a trace of toluene-*p*-sulphonic acid; the cup contained anhydrous magnesium sulphate. After 10 hours the xylene was removed under diminished pressure and the residue was crystallised from ethanol, giving 7-benzoyloxyflavone (1·12 g., 79%), m. p. 155—157° (Baker, *loc. cit.*, gives m. p. 157—158°).

2-Benzoyloxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone (II).—Benzoyl chloride (5 c.c.) was added to a solution of 2-hydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)-acetophenone (I) (20 g.; Reichel and Steudel, *loc. cit.*) in anhydrous pyridine, and after 24 hours the solid was collected, dried, and crystallised from ethanol, giving *2-benzoyloxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone* (16 g., 66%) as platelets, m. p. 186—187°, $[\alpha]_D^{17}$ −18·6° (*c*, 2·5 in acetone) (Found: C, 59·4; H, 5·3. $C_{29}H_{30}O_{13}$ requires C, 59·4; H, 5·2%).

2-*Hydroxy*-4-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyloxy*)*dibenzoylmethane* (III).—The foregoing compound (II) (1 g.) and anhydrous potassium carbonate (0·24 g.) in anhydrous pyridine (5 c.c.) were heated under reflux with stirring for 1 hour, cooled, poured into water (100 c.c.), and neutralised with 20% acetic acid. The precipitate was collected, dried, and crystallised from ethanol, giving 2-*hydroxy*-4-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyloxy*)*dibenzoylmethane* (III) (0·46 g., 46%) as clusters of minute, yellow needles, m. p. 142—143°, $[\alpha]_D^{23}$ −32·2° (*c*, 1·1 in acetone) (Found: C, 59·4; H, 4·8. $C_{29}H_{30}O_{13}$ requires C, 59·4; H, 5·2%). It gave a red-brown colour with ferric chloride.

Reaction of 2-*Benzoyloxy*-4-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyloxy*)*acetophenone* (II) *with Potassium Hydroxide in Pyridine.*—Powdered potassium hydroxide was added to a solution of the acetophenone (II) (1 g.) in anhydrous pyridine (5 c.c.) and, after being shaken at room temperature for 2 hours, the mixture was acidified to pH 6 with 20% acetic acid and then diluted with water (50 c.c.). The precipitate was collected, dried, and crystallised from aqueous ethanol, giving a compound (0·32 g.) as small, pale yellow needles, m. p. 135—136°, $[\alpha]_D^{19}$ −29·2° (*c*, 1·2 in acetone) (Found: C, 59·6; H, 5·5. $C_{29}H_{30}O_{13}$ requires C, 59·4; H, 5·2%). This material, which may be an enol *form* of (III), gave an intense reddish-purple colour with ferric chloride; in very dilute solution the colour was green.

7-(2 : 3 : 4 : 6-*Tetra-acetyl* β-D-*glucosyloxy*)*flavone* (IV).—(*a*) 2-Hydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)dibenzoylmethane (III) (1·75 g.), xylene (50 c.c.), and a trace of toluene-*p*-sulphonic acid were heated under reflux in a Soxhlet apparatus as previously described. After 9 hours, the xylene was removed under diminished pressure and the residue was crystallised (charcoal) from methanol, giving 7-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)flavone (1·1 g., 65%) as long, colourless needles, m. p. 180—181°, $[\alpha]_D^{22}$ −30·8° (*c*, 0·9 in acetone). This m. p. was not depressed when mixed with the material prepared in the following manner.

(*b*) 7-Hydroxyflavone (0·75 g.) and 2 : 3 : 4 : 6-tetra-acetyl α-D-glucosyl bromide (1·4 g.) (Bárczai-Martos and Korösy, *Nature*, 1950, **165**, 369) were dissolved in acetone (5 c.c.), and 5% aqueous sodium hydroxide (2·6 c.c.) was added. After 48 hours at room temperature the mixture was poured into water (100 c.c.), and the precipitate collected, washed repeatedly with sodium carbonate solution and then with water, and dried. Crystallisation from methanol gave the flavone (0·42 g. 33%) as long needles, m. p. 180—181°, $[\alpha]_D^{23}$ −30·7° (*c*, 1·1 in acetone) (Hattori, *loc. cit.*, gives m. p. 183°).

7-β-D-*Glucosyloxyflavone.*—Both specimens of 7-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)-flavone were hydrolysed as follows. The tetra-acetyl compound (200 mg.) was dissolved in pure chloroform (3 c.c.), and a dilute solution of sodium methoxide in methanol (1·5 c.c.) added. After being kept at 0—5° for 96 hours, the solid was collected, washed with a small amount of water, and crystallised from methanol, giving 7-β-D-glucosyloxyflavone (115 mg., 81%) as long, colourless needles, m. p. 256—257°, $[\alpha]_D^{25}$ −61·5° (*c*, 0·28 in pyridine) [from preparation (*a*)], $[\alpha]_D^{24}$ −63·1° (*c*, 0·46 in pyridine) [from preparation (*b*)]. Hattori (*loc. cit.*) gives m. p. 255°.

4-O-(2 : 3 : 4 : 6-*Tetra-acetyl* β-D-*glucosyl*)*phloracetophenone.*—This compound was prepared by Zemplén and Bognár (*Ber.*, 1942, **75**, 647), but it was not analysed.

To phloracetophene (30 g.) and 2 : 3 : 4 : 6-tetra-acetyl α-D-glucosyl bromide (84 g.) in acetone (150 c.c.) was slowly added 10% aqueous sodium hydroxide (80 c.c.), and after being shaken for 48 hours the solution was poured into iced water (1800 c.c.), methanol (125 c.c.) was added, and the whole extracted with chloroform (some phloracetophenone separated at the interface). The chloroform layer yielded an oil which was crystallised twice from methanol (*ca.* 400 c.c.) at 0—5°, giving 4-O-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyl*)*phloracetophenone* (7·6 g.) as needles, m. p. 218—219°, $[\alpha]_D^{19}$ −35·4° (*c*, 0·37 in pyridine) (Found: C, 53·0; H, 5·3. $C_{22}H_{26}O_{13}$ requires C, 53·0; H, 5·2%). It gave a faint orange colour with ferric chloride. Zemplén and Bognár (*loc. cit.*) record m. p. 215—216°, $[\alpha]_D^{20}$ −52·7° (in pyridine).

2-*Benzoyloxy*-6-*hydroxy*-4-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyloxy*)*acetophenone.*—2 : 6-Dihydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone (7·6 g.) was dissolved in dry pyridine (40 c.c.) and benzoyl chloride (4·3 g.) was slowly added. After 24 hours at room temperature the mixture was poured into iced water, and the sticky solid dissolved in hot ethanol, giving 2-*benzoyloxy*-6-*hydroxy*-4-(2 : 3 : 4 : 6-*tetra-acetyl* β-D-*glucosyloxy*)*acetophenone* (7·3 g., 68%) as needles, m. p. 153° (Found: C, 55·8; H, 5·3. $C_{29}H_{30}O_{14}$,H_2O requires C, 56·1; H, 5·2%). It gave no colour with ferric chloride, and in an attempted rearrangement with potassium carbonate in dry pyridine the only isolable product was 2 : 6-dihydroxy-4-(2 : 3 : 4 : 6-tetra-acetyl β-D-glucosyloxy)acetophenone.

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