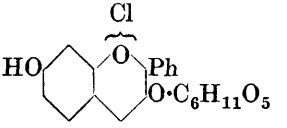
XXXVIII.—*Experiments on the Synthesis of Anthocyanins. Part II. The Synthesis of* 3- *and* 7-*Glucosidoxyflavylium Salts.*

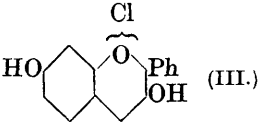
By Alexander Robertson and Robert Robinson.

In the first part of this series (J., 1926, 1713) it was shown that certain glucosides of pyrylium salts of anthocyanidin type may be prepared by relatively simple applications of the general method. In these cases, however, the carbohydrate group was associated with the position 4′ in the flavylium nucleus, whereas in the natural anthocyanins the available evidence shows that the sugar is attached to one of the positions 3, 5, and 7. Thus Willstätter and his collaborators found that all the anthocyanins derived from cyanidin gave a strong ferric chloride reaction and hence bear hydroxyl groups in positions 3′ and 4′. We have accordingly carried our investigation to a further stage by applying the processes already developed to the synthesis of flavylium salt glucosides which should,

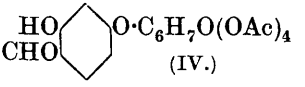
in respect of the position of the glucose residues, be more closely allied to the anthocyanins than any as yet obtained. ω-O-*Tetra-acetylglucosidoxyacetophenone*, $Ph{\cdot}CO{\cdot}CH_2{\cdot}O{\cdot}C_6H_7O(OAc)_4$ (I), prepared from benzoylcarbinol and tetra-acetylglucosidyl bromide with the help of silver carbonate, condensed with β-resorcylaldehyde in ethereal solution in presence of hydrogen chloride to a product which was not crystallised but was at once hydrolysed by means of methyl-alcoholic ammonia. The recovered pyrylium salt was difficult to purify, but, ultimately, 3-β-*glucosidoxy*-7-*hydroxyflavylium chloride* (II) was isolated. On hydrolysis, this yielded glucose and 3 : 7-dihydroxyflavylium chloride (III), which has also been obtained by a direct condensation of β-resorcylaldehyde and benzoylcarbinol, or its acetate. The salt has been previously obtained by demethylation of its 3-methyl ether (Pratt and Robinson, J., 1924, **125**, 191).

(II.)

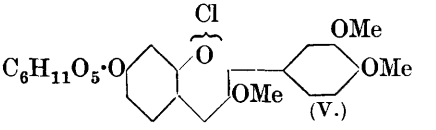




(III.)



(IV.)



(V.)

Similarly, the *tetra-acetylglucoside* (IV) has been prepared by the interaction of β-resorcylaldehyde and tetra-acetylglucosidyl bromide in acetone solution in presence of aqueous potassium hydroxide; in this case, condensation with ω-methoxyacetoveratrone was effected. The resulting flavylium chloride was deacetylated in the usual manner and 7-*glucosidoxy*-3 : 3′ : 4′-*trimethoxyflavylium chloride* (V) was then isolated in a satisfactory condition of purity. On boiling with hydrochloric acid, the glucose was detached and fisetinidin chloride trimethyl ether (Pratt and Robinson, J., 1925, **127**, 170) was obtained.

Experimental.

ω-O-*Tetra-acetyl*-β-*glucosidoxyacetophenone* (I).—Freshly-precipitated silver carbonate (6 g.) was added to a solution of *O*-tetra-acetyl-α-glucosidyl bromide * (6 g.) and anhydrous benzoyl-

* Hudson (*J. Amer. Chem. Soc.*, 1924, **46**, 466, 979, 2501) indicated that this substance, the so-called acetobromoglucose, is probably an α-glucose derivative and yields β-glucosides through a Walden inversion.

carbinol * (5 g.) in dry ether (70 c.c.), which was then gently refluxed for 14 hours. The filtered solution was freed from ether under diminished pressure, a solution of the syrupy residue in acetone (50 c.c.) poured in a fine stream into cold water, and the precipitated viscous mass triturated with fresh water until it crystallised. The dried material was crystallised several times from 86% methyl alcohol (charcoal) and finally obtained in white, prismatic needles, m. p. 104—105° (yield of pure product, 4 g.) (Found: C, 56·4; H, 5·7. $C_{22}H_{26}O_{11}$ requires C, 56·6; H, 5·6%). The substance is moderately readily soluble in cold methyl or ethyl alcohol and is easily soluble in the hot solvents. At room temperature, 100 c.c. of dry ether dissolve about 1·2 g. of the glucoside. The condensation may also be effected in the cold and without a solvent and, though the process is slower than that described above, the yield is about the same.

3-β-*Glucosidoxy*-7-*hydroxyflavylium Chloride* (II).—Condensation of tetra-acetylglucosidoxyacetophenone and β-resorcylaldehyde in presence of hydrogen chloride occurs in absolute formic acid solution, but the product is contaminated with the sugar-free pyrylium salt. Trials showed, however, that in ethereal solution the hydrolysis of the glucoside does not occur in 96 hours, although in this case the reaction is very sluggish. A cooled solution of tetra-acetylglucosidoxyacetophenone (1 g.) and β-resorcylaldehyde (1·5 g.) in dry ether (100 c.c.) was saturated with hydrogen chloride and allowed to remain for 96 hours. The dark brown, viscous mass obtained on the addition of light petroleum was separated, washed with ether, and dried in a vacuum; it became a brittle solid which could not be crystallised. Deacetylation was effected by means of saturated methyl-alcoholic ammonia at 0° during 14—15 hours, the ammonia and methyl alcohol being then removed below 25° under diminished pressure. The residue was dissolved in 2% methyl-alcoholic hydrogen chloride (40 c.c.), and the glucoside precipitated from the filtered solution by the addition of ether (300 c.c.). The amorphous products from several experiments were combined and dried in a vacuum. A mixture of the crude material (4 g.), methyl alcohol (50 c.c.), and 12% hydrochloric acid (5 c.c.) was heated to the boiling point for 1 minute, a large proportion of the impurities being thus dissolved, and filtered hot.

* Benzoylcarbinol was prepared by the method of O. Fischer and Busch (*Ber.*, 1891, **24**, 2680) from ω-bromoacetophenone, the yield being 80%. The hydroxyketone was not, however, isolated by means of ether, but was separated from an aqueous solution by the addition of potassium carbonate. It was dehydrated by distillation of a solution in a large volume of benzene and finally crystallised from light petroleum in glistening plates, m. p. 85—86°.

The orange-red residue was easily soluble in 2% hydrochloric acid and in 2% methyl-alcoholic hydrogen chloride. The glucoside (2 g.) was dissolved in a hot mixture of methyl alcohol (15 c.c.) and 2% hydrochloric acid (10 c.c.), and the filtered solution allowed to remain for 24 hours. Most of the alcohol evaporated and crystals were deposited; the process was thrice repeated, and the salt obtained in bundles of microscopic, pointed rods which matted together on the filter and when dry exhibited a golden reflex. The salt was dried for 3 hours, powdered, and again dried in a vacuum for 15 hours (Found: C, 56·6; H, 5·0; Cl, 8·2, 7·8. $C_{21}H_{21}O_8Cl,0{\cdot}5H_2O$ requires C, 56·6; H, 4·9; Cl, 8·0%). The substance is readily soluble in 2% and 4% hydrochloric acid and in the simple alcohols to orange solutions which become red on the addition of sodium acetate. Pseudo-base formation was observed and the salt is only partly extracted from an aqueous acid solution by means of *iso*amyl alcohol. On boiling with 15% hydrochloric acid for 5 minutes, hydrolysis occurred and, after cooling, 3 : 7-dihydroxyflavylium chloride separated from the solution in orange-brown prisms. The salt was identified by comparison with an authentic specimen.

3 : 7-*Dihydroxyflavylium Chloride* (III).—(A). A solution of β-resorcylaldehyde (1·0 g.) and ω-acetoxyacetophenone (1·2 g.) in formic acid (20 c.c.) was saturated with hydrogen chloride. A week later, the crude product was isolated after precipitation by ether and boiled with 0·2% hydrochloric acid, and the solution filtered. Concentrated hydrochloric acid was then added, bringing the acid concentration to about 8%, and, on cooling, the salt crystallised in deep orange-brown, elongated, rhombic, pointed prisms (yield, 0·3 g.) (Found in material dried in a vacuum: C, 61·6; H, 4·4. Calc. for $C_{15}H_{11}O_3Cl,H_2O$: C, 61·5; H, 4·5%).

(B). The condensation of β-resorcylaldehyde (0·5 g.) and benzoylcarbinol (0·5 g.) in formic acid (20 c.c.) by means of hydrogen chloride occupied 72 hours and the yield of the pure salt was 0·35 g., about twice as great as that obtained from ω-acetoxyacetophenone. The properties of the salt were in agreement with those described by Pratt and Robinson (*loc. cit.*).

4-O-*Tetra-acetylglucosidoxy*-2-*hydroxybenzaldehyde* (IV).—A solution of potassium hydroxide (2·6 g.) in water (25 c.c.) cooled to 10° was gradually added to one of β-resorcylaldehyde (6 g.) and *O*-tetra-acetylglucosidyl bromide (18 g.) in pure acetone (55 c.c.), the temperature being maintained below 16° by cooling in ice-water. Two layers appeared and, after 30 minutes, acetone (20 c.c.) was added and the homogeneous solution was allowed to remain for 12 hours. The liquid was rendered faintly acid by the addition of

a little dilute acetic acid, and the acetone removed in a vacuum below 25°. The thick residual syrup, which became semi-solid on trituration with cold water, was several times crystallised (charcoal) from 85% methyl alcohol; it was finally obtained in almost colourless, silky, prismatic needles, m. p. 134—135° (Found: C, 53·5; H, 5·1. $C_{21}H_{24}O_{12}$ requires C, 53·8; H, 5·1%). (A mixture with β-resorcylaldehyde, also m. p. 135°, had m. p. 90—100°.) This acetylglucoside is moderately readily soluble in methyl or ethyl alcohol, sparingly soluble in cold 85% methyl alcohol, and very readily soluble in hot alcohol. 100 C.c. of dry ether dissolve about 1 g. at room temperature. Ferric chloride added to an alcoholic solution gives a dark red coloration identical with that developed by 2-hydroxy-4-methoxybenzaldehyde under similar conditions. The residues from this preparation were examined, but an isomeric compound could not be isolated.

7-*Glucosidoxy*-3 : 3′ : 4′-*trimethoxyflavylium Chloride* (V).—A solution of tetra-acetylglucosidoxyhydroxybenzaldehyde (2 g.) and ω-methoxyacetoveratrone (3 g., an excess) in dry ether (200 c.c.) was saturated with hydrogen chloride at 16—18° and allowed to remain for 72 hours. Almost the whole of the product crystallised in compact clusters of slender, prismatic needles which were dark brown in mass (yield, 2 g.). Recrystallisation from 0·5% hydrochloric acid could not be satisfactorily accomplished owing to the tendency of the substance to give a crystalline, colourless pseudobase, whilst with more concentrated acid deacetylation appeared to occur; moreover, in 2% to 4% hydrochloric acid the salt was only sparingly soluble to an orange-red solution. A solution of the acetylglucoside (2 g.) in methyl alcohol (150 c.c.) was saturated at 0° with ammonia and allowed to remain at 0° for 14 hours; the ammonia and methyl alcohol were then removed under diminished pressure and below 20° until the volume was about 15 c.c. Hydrochloric acid (30 c.c. of 4%) at 50° was added and, on cooling, the chloride separated in crimson, rhombic plates (yield, 1·5 g.) which exhibited a brilliant golden reflex. Recrystallisation in a similar form was effected by dissolving 1 g. in hot methyl alcohol (15 c.c.), adding warm 4% hydrochloric acid (30 c.c.), heating the mixture to 60—70° (it must not be boiled) and filtering it. The salt was dried in a high vacuum for 48 hours (Found: C, 54·2; H, 5·7; Cl, 6·7. $C_{24}H_{27}O_{10}Cl,H_2O$ requires C, 54·5; H, 5·5; Cl, 6·8%). Concentrated acid solutions are crimson and dilute solutions are orange-red. This glucoside is readily hydrolysed, even by 4% hydrochloric acid, and on being treated in the usual way with boiling 15% hydrochloric acid it yielded fisetinidin chloride trimethyl ether, which was identified by comparison with an authentic specimen (Pratt

and Robinson, *loc. cit.*). The *picrate* of the glucoside separated from a warm alcoholic solution of the chloride and picric acid in fine needles and crystallised from 85% ethyl alcohol, containing a little picric acid, in balls of bright red, very slender, prismatic needles which filled the liquid. On heating, decomposition commenced at 240—243° and was complete at 250—252°. In contrast, the acetylated glucoside did not yield a stable picrate.

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