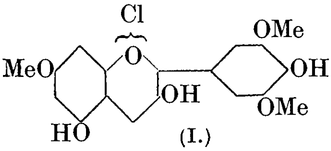
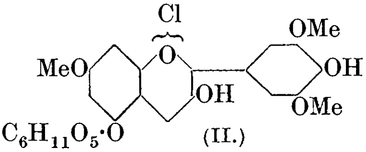
CCCLXXIX.—*Experiments on the Synthesis of Anthocyanins. Part XIII. 5-β-Glucosidyl- and 5-Lactosidyl-hirsutidin Chlorides.*

By Leopold Ferdinand Levy and Robert Robinson.

Karrer and Widmer (*Helv. Chim. Acta*, 1927, **10**, 758) isolated a diglucosidic anthocyanin termed hirsutin from *Primula hirsuta* and showed that the related hirsutidin is a methylmalvidin, since it could be oxidised to syringic acid. The synthesis of hirsutidin was accomplished by Bradley, Robinson, and Schwarzenbach (J., 1930, 793) and in this way it was shown to be malvidin 7-methyl ether (I). The present communication is concerned with the preparation of the 5-glucoside (II) and 5-lactoside derived from this anthocyanidin and it may be noted that the latter bioside is the first synthetic diglucosidic anthocyanin to be prepared. The methods which we have employed offer no new feature, and indeed the requisite glucoside had already been obtained by Karrer, Lichtenstein, and Helfenstein (*Helv. Chim. Acta*, 1929, **12**, 991). A point of interest in connexion with the lactoside is the very great ease with which it passes into a crystalline pseudo-base, a property which is apparently not shared by hirsutin. Anthocyanins of this group are also characterised by their remarkably sparing solubility in dilute aqueous and alcoholic hydrochloric acid. It is proposed to continue the investigation and attempt a synthesis of hirsutin by condensing the glucoside employed in this communication with the intermediate for œnin (Part VIII).



(I.)



(II.)

Experimental.

2 - O - *Benzoyl - 4 - O - methylphloroglucinaldehyde.*—The method of Bradley, Robinson, and Schwarzenbach (*loc. cit.*) for the preparation of this substance has been modified and improved mainly by the substitution of silver carbonate for the silver oxide previously employed.

A mixture of 2-*O*-benzoylphloroglucinaldehyde (5·0 g.), methyl iodide (8·8 g.), finely divided silver carbonate (8 g.), and pure acetone (50 c.c.) was mechanically shaken for 48 hours, and after filtration the precipitate was washed with acetone. The light orange *crystalline* residue obtained by evaporation to dryness under reduced pressure was dissolved in ether (about 250 c.c.), filtered from a trace of insoluble flocculent material, and washed with 10% aqueous sodium carbonate. On acidification of the aqueous layer, unchanged aldehyde (0·2 g.) was recovered. The ethereal solution was twice shaken with 5% aqueous potassium hydroxide (20 c.c. and 10 c.c.) and the alkaline solutions were acidified at once with dilute acetic acid. After a short time, a pink crystalline precipitate (3·75 g.), m. p. 97—100°, was obtained. This monomethyl ether crystallised from ethyl alcohol in colourless plates, m. p. 109° as stated by Bradley, Robinson, and Schwarzenbach (*loc. cit.*). The ethereal mother-liquor yielded the dimethyl ether (0·35 g.).

When a dry ethereal solution of *O*-benzoylphloroglucinaldehyde was treated with diazomethane, only a small yield of monomethyl ether was obtained (0·6 g. from 2·5 g., 1·8 g. of unchanged material being recovered). No dimethyl ether was produced.

3-*Hydroxy*-5-O-*tetra-acetyl*-β-*glucosidoxy*-4′-*acetoxy*-7 : 3′ : 5′-*trimethoxyflavylium Chloride*.—2-*O*-Tetra-acetyl-β-glucosidyl-4-*O*-methylphloroglucinaldehyde (1·7 g., m. p. 177°; Found: C, 53·0; H, 5·3; MeO, 6·6. Calc. for $C_{22}H_{26}O_{13}$: C, 53·0; H, 5·3; MeO, 6·2%) was obtained from 4-*O*-methylphloroglucinaldehyde (2·0 g.) by the method of Karrer, Lichtenstein, and Helfenstein (*loc. cit.*).

The tetra-acetyl glucoside (1·35 g.) and ω-hydroxy-4-acetoxy-3 : 5-dimethoxyacetophenone (1·05 g.) were dissolved in dry ethyl acetate (40 c.c.), and the solution was cooled with ice-water and saturated with dry hydrogen chloride; in 1 hour it became deep red. After 48 hours, dry ether (500 c.c.) was added, and the dark red precipitate collected, well washed with ether, and dried (1·8 g.) [Found: C, 49·8; H, 5·2; Cl, 6·35; MeO, 12·9. $C_{34}H_{37}O_{17}Cl,3·5H_2O$ (penta-acetyl derivative) requires C, 50·0; H, 5·4; Cl, 4·35; MeO, 11·4%].

$C_{24}H_{27}O_{12}Cl,2H_2O$ (completely de-acetylated substance) requires C, 49·8; H, 5·4; Cl, 6·14, MeO, 16·1%. These figures indicate partial loss of acetyl groups.

5-β-*Glucosidylhirsutidin Chloride* (II).—The crude flavylium salt (1·8 g.) was treated with 8% cold aqueous sodium hydroxide (50 c.c.), and the solution allowed to remain for 90 minutes under hydrogen. The substance dissolved slowly to a deep blue solution, turning after a few minutes to yellowish-green. Hydrochloric acid (80 c.c. of 7%) was added, and the 2% acid solution so obtained was heated to 60° and filtered from a trace of insoluble material. When the deep red solution was cooled, 5-β-glucosidylhirsutidin chloride separated (0·95 g.). The mother-liquor, after being extracted twice with amyl alcohol and washed with ether, furnished a little more of the pure glucoside (0·07 g.). When the powdered material was stirred with 5% methyl-alcoholic hydrogen chloride (150 c.c.) and warmed to about 30°, it dissolved, but was quickly deposited in a finely divided condition, leaving a light pink mother-liquor. When again stirred with a like quantity of the solvent, the substance, without dissolving, crystallised in fine slender needles (0·68 g.), which were purple by transmitted light and beetle-green in mass (Found : C, 49·2; H, 5·5; Cl, 6·3; CH_3O, 15·9; loss on heating at 105° in a high vacuum over phosphoric anhydride, 7·7, 7·5, 7·1. $C_{24}H_{27}O_{12}Cl,2{\cdot}5H_2O$ requires C, 49·0; H, 5·5; Cl, 6·1; CH_3O, 15·8; 2·5H_2O, 7·7%. Found in anhydrous material: C, 53·3; H, 5·2; Cl, 5·45; CH_3O, 16·2. $C_{24}H_{27}O_{12}Cl$ requires C, 53·1; H, 5·0; Cl, 6·5; CH_3O, 17·1%). The low figures for Cl and MeO after drying may be due to loss of methyl chloride on heating.

The substance is very sparingly soluble in cold 0·5% hydrochloric acid to a very faint pink solution. On warming, the substance dissolves to a reddish solution, but, on cooling, it separates almost completely. For this reason the distribution numbers could not be determined. The salt dissolves in aqueous sodium carbonate to a rich-coloured solution, violet in thick layers and blue in thin layers, permanganate by artificial light. The addition of sodium hydroxide changes the colour through green to yellow. With aqueous sodium acetate a blue-violet solution is obtained and this becomes blue on the addition of acetone.

2-O-*Hepta-acetyl*-β-*lactosidyl*-4-O-*methylphloroglucinaldehyde*.—A solution of 4-*O*-methylphloroglucinaldehyde (2·3 g.) and *O*-hepta-acetyl-α-lactosidyl bromide (10·7 g.) (E. Fischer and H. Fischer, *Ber.*, 1910, **43**, 2521) in pure acetone (30 c.c.) was cooled to 5—10°, and aqueous potassium hydroxide (0·8 g. in 8 c.c.) added dropwise with shaking. After 30 minutes, more acetone (30 c.c.) was introduced and the mixture kept for 12 hours. After removal of the acetone in a vacuum, the brown gummy residue was well washed with cold water; it crystallised from ethyl alcohol in colourless needles, m. p. 163—164°, and 164° after several recrystallisations (yield, 3·4 g.) (Found: C, 51·9; H, 5·3; CH_3O, 3·95. $C_{34}H_{42}O_{21}$ requires C, 51·8; H, 5·4; CH_3O, 4·25%). The substance is very sparingly soluble in water, but is freely soluble in most organic solvents.

3 : 4′-*Dihydroxy*-5-O-*hepta-acetyl*-β-*lactosidoxy*-7 : 3′ : 5′-*trimethoxyflavylium Chloride*.—A solution of the hepta-acetyl lactoside (3·26 g.) and ω : 4-dihydroxy-3 : 5-dimethoxyacetophenone (1·20 g.) (see Part VIII, p. 2706) in dry ethyl acetate (60 c.c.) was cooled to 0° and saturated with dry hydrogen chloride. After 2 hours the flavylium salt began to crystallise, and after 20 hours the mixture was filled with crystals. The salt was collected after the addition of dry ether (400 c.c.), well washed with ether, and dried (3·90 g. or 90%) [Found : C, 46·8; H, 5·6; CH_3O, 10·6. $C_{34}H_{41}O_{19}Cl,4{\cdot}5H_2O$ (diacetate) requires C, 46·9; H, 5·75; CH_3O, 10·7%].

5-β-*Lactosidylhirsutidin Chloride*.—The above flavylium salt (3·9 g.) was hydrolysed by treatment with cold 8% aqueous sodium hydroxide (90 c.c.) in a stream of hydrogen for 90 minutes; the greenish-yellow solution was then acidified with 18% hydrochloric acid (60 c.c.). The 2% acid solution obtained was heated to 60° in a water-bath, a deep red solution being obtained. On cooling, the 5-β-lactosidylhirsutidin chloride, mixed with some of the related pseudo-base, separated; it was collected after a few days (2·3 g.). When a small portion was warmed with 0·5% hydrochloric acid, it dissolved to a reddish solution, and, on cooling, the almost colourless pseudo-base crystallised. This was recrystallised from water, forming clusters of needles which darkened at 102°, lost water of crystallisation, and decomposed at 150—165° (Found: C, 45·1; H, 6·2; CH_3O, 12·3. $C_{30}H_{38}O_{18},6H_2O$ requires C, 45·3; H, 6·3; CH_3O, 11·7%). A chlorine estimation gave a negative result. The pseudo-base was reconverted into the oxonium salt when warmed with 5% hydrochloric acid or on treatment with cold 5% ethyl-alcoholic hydrogen chloride, from which the chloride separated on keeping.

The major portion of the substance was converted into the chloride by the latter method and then crystallised from hot 5% methyl-alcoholic hydrogen chloride. Microscopic flat needles were obtained which were reddish by transmitted light and dark beetle-green in mass (Found: C, 45·5; H, 5·9; MeO, 12·1; loss at 105° in a high vacuum, 12·1, 11·1, 12·6. $C_{30}H_{37}O_{17}Cl,5H_2O$ requires C, 45·5; H, 5·9; MeO, 11·7; $5H_2O$, 11·3%. Found in substance dried over phosphoric oxide in a high vacuum at 105°: C, 51·3; H, 5·35; Cl, 6·0; MeO, 14·8. $C_{30}H_{37}O_{17}Cl$ requires C, 51·1; H, 5·3%). Different estimations of chlorine gave divergent results and the same was true of the micro-Zeisel estimations of the anhydrous material.

This salt is soluble in hot 5% hydrochloric acid but separates, on cooling, in an amorphous condition.

The rather stable bluish-violet solution in aqueous sodium carbonate (which fades rapidly to yellowish-green on the addition of sodium hydroxide) has a bluer tone than that given by 5-glucosidylhirsutidin chloride in the same circumstances. This has a bearing on the contrast between pelargonenin and pelargonin (Part VII, p. 2696), the former being the bluer in alkaline solution. Mecocyanin (3-bioside) gives a bluer solution than chrysanthemin (3-monoside) and now this lactoside (5-bioside) has a similar relation with respect to the corresponding glucoside (5-monoside). If, therefore, pelargonenin and pelargonin were 5-monoside and 5-bioside respectively, the effect would be reversed. There is no anomaly if the 3 : 5-

dimonoside configuration is accepted. The distribution number of this anthocyanin is very low, definitely diglucosidic.

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UNIVERSITY OF OXFORD.
UNIVERSITY COLLEGE, LONDON.

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