CCLXXXVIII.—*Synthesis of Glucosides. Part III. Synthesis of Glucosides of Hydroxyxanthones.*

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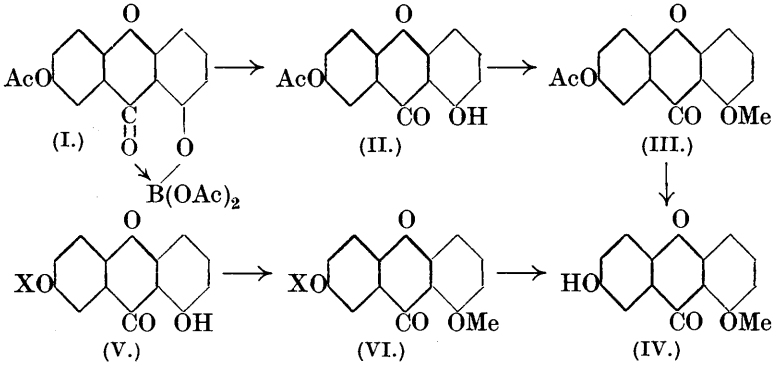
The preparation of the glucosides described in this communication was undertaken as a preliminary step in the investigation of the naturally occurring hydroxyxanthone derivatives euxanthic acid, gentiin (Tanret, *Compt. rend.*, 1905, **141**, 207), and mangiferin (Boorsma, *Bull. Dep. Agric. Ind. Néerl.*, 1908, **16**). The O-*tetra-acetyl* β-*glucosides* of 2- and 4-hydroxyxanthone (Ullmann and Zlokasoff, *Ber.*, 1905, **38**, 2111) and of euxanthone (Ullmann and Panchaud, *Annalen*, 1906, **350**, 108) have been prepared. Removal of the acetyl groups was best effected by means of warm methyl-alcoholic potassium hydroxide solution and 2- and 4-β-*glucosidoxy-xanthone* and 7-β-*glucosidoxy*-1-*hydroxyxanthone*, which corresponds to the naturally occurring glycuronate euxanthic acid, were thus obtained. These glucosides are readily hydrolysed by emulsin as well as by mineral acids.

Since euxanthone when methylated with methyl iodide and alkali (von Kostanecki, *Ber.*, 1894, **27**, 1992) gives rise to the 7-methyl ether, it appeared likely that the glucose residue of (V) was also attached at the same position. 1-Hydroxyxanthone (Dimroth, *Annalen*, 1925, **446**, 97) and 1-hydroxythioxanthones (Roberts and Smiles, this vol., p. 1322) form boroacetates, and hence it seemed probable that a substance of formula (V) would yield a derivative on treatment with boroacetic anhydride. Although the pale yellow solution of either euxanthone glucoside or its acetyl derivative in acetic anhydride assumed a deep orange colour on the addition of boroacetic anhydride, a solid boroacetate could not be isolated; the deep orange-coloured solutions became pale yellow on the addition of water. Euxanthone itself on treatment with this reagent undergoes simultaneous acetylation with the formation of the *diacetoborate* of *acetyl euxanthone* (I). This substance undoubtedly possesses a chelate structure (compare Dimroth, *loc. cit.*; Smiles and Roberts, *loc. cit.*).

The boroacetate is readily decomposed by warm water and is thus a convenient source of pure 1-*hydroxy*-7-*acetoxyxanthone* (II). Methylation of (II) by means of methyl iodide and silver oxide afforded the *methyl* ether (III), which on hydrolysis gave 7-*hydroxy*-1-*methoxyxanthone* (IV). The latter, unlike the isomeric ether described by von Kostanecki (*loc. cit.*), is readily soluble in dilute aqueous alkali. Attempts to methylate (II) in ethereal solution with diazomethane failed, but the reaction proceeded in the normal

manner when a mixture of nitrobenzene and ether was used as the solvent. The crude product on deacetylation gave the methyl ether (IV). The isolation of the substance (IV) as a product of the hydrolysis of the ether (VI), obtained by methylation of the glucoside (V), finally afforded conclusive proof of the structure of (V).



[X = $C_6H_7O(OAc)_4$·]

As the glucosides were not sufficiently soluble in ordinary solvents at room temperature, their specific rotations could not be determined; the constants of the acetyl derivatives in acetone are recorded.

As the yields in the synthesis of euxanthone by Ullmann's method are somewhat disappointing, this substance was also obtained by the hydrolysis of euxanthic acid, for which a convenient method (avoiding the use of a sealed tube) is described.

EXPERIMENTAL.

2-O-*Tetra-acetyl*-β-*glucosidoxyxanthone*.—To a solution of 2-hydroxyxanthone (3·5 g.) in a mixture of acetone (90 c.c.) and 0·7% aqueous sodium hydroxide solution (85 c.c.) cooled to 10°, *O*-tetra-acetyl-α-glucosidyl bromide (5 g.) was added in one portion. The solution was maintained at 10—12° for 8 hours and then 6% sodium hydroxide solution (7·5 c.c.) and a further quantity of the bromide (4 g.) were added with vigorous agitation for ½ hour. After 12 hours at room temperature, the *glucoside*, mixed with unchanged 2-hydroxyxanthone, had separated. The mixture was acidified with dilute acetic acid and the solid was collected, washed with water, and recrystallised from methyl alcohol, from which 2-O-*tetra-acetyl*-β-*glucosidoxyxanthone* (3·5 g.) separated in colourless needles, m. p. 173°, $[\alpha]_D^{20°}$ — 36·4° in acetone (Found : C, 59·7; H, 4·8. $C_{27}H_{26}O_{12}$ requires C, 59·8; H, 4·8%). This substance is moderately easily soluble in alcohol and insoluble in ether.

Unchanged 2-hydroxyxanthone was recovered from the reaction mixture after separation of the glucoside and removal of the acetone.

2-β-*Glucosidoxyxanthone*.—The tetra-acetyl glucoside (2 g.), suspended in methyl alcohol (10 c.c.), was treated with 5% methyl-alcoholic sodium hydroxide solution (40 c.c.) at 60° for 5 minutes. The cooled mixture after acidification with glacial acetic acid was kept at room temperature for 48 hours; 2-β-*glucosidoxyxanthone* (1·4 g.) then separated as a solid. Recrystallised from methyl alcohol, it formed colourless needles, m. p. 237° (Found in material dried at 110°: C, 60·9; H, 4·8. $C_{19}H_{18}O_8$ requires C, 61·0; H, 4·8%). On acetylation with acetic anhydride and sodium acetate the glucoside was quantitatively converted into the tetra-acetyl derivative, m. p. and mixed m. p. 173°. It is readily hydrolysed by warm 15% hydrochloric acid and by emulsin in aqueous solution at 37—38° to 2-hydroxyxanthone and glucose.

4-O-*Tetra-acetyl*-β-*glucosidoxyxanthone*.—This was prepared in the same way as the 2-isomeride and separated gradually when the homogeneous solution was kept at 10—12° for 24 hours. After acidification with dilute acetic acid the solid (4 g.) was collected, washed with water, and crystallised from warm methyl alcohol, from which it separated in colourless elongated prisms, m. p. 199—200°, $[\alpha]_D^{20°}$ — 31·8° in acetone (Found: C, 59·8; H, 4·8%). The *substance* is slightly soluble in alcohol and in ether. Unchanged 4-hydroxyxanthone was recovered from the acetone–water residues.

4-β-*Glucosidoxyxanthone*.—The tetra-acetyl glucoside was de-acetylated, and the product isolated, in the way described above. The 4-β-*glucosidoxyxanthone* obtained crystallised from 60% acetic acid in colourless needles (4 g.), m. p. 274° (decomp.) (Found: C, 60·9; H, 4·8%). This substance is slightly soluble in cold alcohol and readily soluble in warm alcohol or water. It is hydrolysed by warm 15% hydrochloric acid and by emulsin in aqueous solution at 37—38° to 4-hydroxyxanthone and glucose. Acetylation gave the tetra-acetyl derivative, m. p. and mixed m. p. 199—200°.

Hydrolysis of Euxanthic Acid.—The acid (10 g.), suspended in 25% sulphuric acid, was heated under reflux for 5 hours. The mixture was then kept in the ice-chest for 24 hours; after the addition of ice-water (200 c.c.), the euxanthone was collected and recrystallised from toluene, forming orange needles (5 g.), m. p. 240°.

7-O-*Tetra-acetyl*-β-*glucosidoxy*-1-*hydroxyxanthone* (V).—*O*-Tetra-acetyl-α-glucosidyl bromide (5 g.) was added to a solution of euxanthone (3·5 g.) in a mixture of acetone (75 c.c.) and 1·3% aqueous sodium hydroxide (50 c.c.) cooled to 12°. After 48 hours, 6% aqueous sodium hydroxide (7 c.c.) and a further quantity of the bromide (3·5 g.) were added to the reaction mixture (agitation),

which was then kept at room temperature for 24 hours. The *tetra-acetyl glucoside* (V) separated and, on recrystallisation from alcohol, formed pale yellow, elongated prisms, m. p. 176—177°, $[\alpha]_D^{20°}$ — 33·4° in acetone (Found : C, 58·0; H, 4·7. $C_{27}H_{26}O_{13}$ requires C, 58·1; H, 4·7%). This tetra-acetyl derivative on acetylation with acetic anhydride and sodium acetate gave 7-O-*tetra-acetyl*-β-*glucosidoxy*-1-*acetoxyxanthone*, which separated from warm 80% acetic acid in colourless slender needles, m. p. 211°, $[\alpha]_D^{20°}$ — 34·2° in acetone (Found : C, 58·0; H, 4·7. $C_{27}H_{28}O_{14}$ requires C, 58·0; H, 4·7%). When synthetic euxanthone (Ullmann and Panchaud, *loc. cit.*) was used, the same tetra-acetyl glucoside was obtained, m. p. 176—177°, which on acetylation gave the penta-acetyl derivative, m. p. 211°.

Unchanged euxanthone was recovered from the acetone–water residues.

7-β-*Glucosidoxy*-1-*hydroxyxanthone*.—De-acetylation was effected by the addition of warm 10% methyl-alcoholic sodium hydroxide (20 c.c.) to a suspension of the tetra-acetyl derivative (2 g.) in warm methyl alcohol (10 c.c.). The solid rapidly dissolved and the bright orange solution was maintained at 60° for 5 minutes. After acidification with glacial acetic acid and addition of water (30 c.c.) the solution slowly deposited 7-β-*glucosidoxy*-1-*hydroxyxanthone* as a solid, which separated from warm methyl alcohol in yellow needles, m. p. 218—219° (Found : C, 58·5; H, 4·7. $C_{19}H_{18}O_9$ requires C, 58·5; H, 4·6%). This glucoside is readily soluble in hot alcohol and in warm water. Acetylation with acetic anhydride and sodium acetate gave the penta-acetyl derivative, m. p. 211°. It is hydrolysed by warm 15% hydrochloric acid and by emulsin in aqueous solution at 37—38° to glucose and euxanthone.

1-*Hydroxy*-7-*acetoxyxanthone Diacetoborate* (I).—A mixture of euxanthone (2 g.) and boroacetic anhydride (3 g.) in acetic anhydride (10 c.c.) was heated under reflux for 5 minutes, and on cooling the *diacetoborate* of 7-*acetyl euxanthone* (I) separated in golden needles, which were collected, washed with anhydrous ether, and dried over sulphuric acid for 2 hours. The substance was decomposed by boiling water, yielding 1-*hydroxy*-7-*acetoxyxanthone* (II), which crystallised from warm alcohol in elongated yellow prisms, m. p. 160° (Found : C, 66·7; H, 3·8. $C_{15}H_{10}O_5$ requires C, 66·8; H, 3·7%). Analysis of the diacetoborate was made by decomposing it with warm water and weighing the acetyl euxanthone [Found : $C_{15}H_{10}O_5$, 67·5. $C_{15}H_9O_5{\cdot}B(O{\cdot}CO{\cdot}CH_3)_2$ requires $C_{15}H_{10}O_5$, 67·7%].

7-*Hydroxy*-1-*methoxyxanthone* (IV).—(A) A suspension of 1-*hydroxy*-7-*acetoxyxanthone* (1 g.) and active silver oxide (2 g.) in a mixture of acetone (15 c.c.) and methyl iodide (2 g.) was heated

under reflux for 12 hours. After filtration the residue was extracted with warm acetone (15 c.c.), and on addition of ice-water (200 c.c.) to the combined filtrates 7-*acetoxy*-1-*methoxyxanthone* (III) separated. Crystallisation from 50% methyl alcohol gave the substance (1 g.) in almost colourless plates, m. p. 176° (Found : C, 67·7; H, 4·3. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·2%). A solution of this acetyl derivative (1 g.) in 10% methyl-alcoholic potassium hydroxide was kept at room temperature during 3 hours and then acidified with glacial acetic acid. Water (150 c.c.) was added and 7-*hydroxy*-1-*methoxyxanthone* (IV) (0·8 g.) separated, which on recrystallisation from 50% methyl alcohol and then from benzene was obtained in pale straw-coloured, rectangular plates, m. p. 235° (Found : C, 69·4; H, 4·4. $C_{14}H_{10}O_4$ requires C, 69·4; H, 4·1%). This ether is readily soluble in aqueous alkali, forming an orange solution.

(B) To a solution of 1-hydroxy-7-acetoxyxanthone (0·5 g.) in pure anhydrous nitrobenzene (30 c.c.), diazomethane (0·2 g.) in ether (15 c.c.) was added; a brisk evolution of nitrogen followed. After 12 hours, the ether and nitrobenzene were removed in a current of steam, the solid residue was dissolved in 10% methyl-alcoholic potassium hydroxide (20 c.c.), and the solution kept at room temperature for 3 hours. On acidification with glacial acetic acid and addition of water (150 c.c.) 7-hydroxy-1-methoxyxanthone (IV) separated, which on crystallisation from 50% methyl alcohol and then from benzene was obtained in pale straw-coloured plates, m. p. and mixed m. p. 235°.

7-O-*Tetra-acetyl*-β-*glucosidoxy*-1-*methoxyxanthone* (VI).—Silver oxide (0·5 g.) and methyl iodide (0·5 g.) were added to a solution of 7-*O*-tetra-acetyl-β-glucosidoxy-1-hydroxyxanthone (V) (0·7 g.) in acetone (20 c.c.), and the mixture heated under reflux for 12 hours. After separation from silver salts (washing with acetone) the solvent was removed by distillation, and the residue triturated with water. The solid obtained, on crystallisation from warm 60% methyl alcohol, gave the *methyl* ether (VI) (0·7 g.) in colourless plates, m. p. 166—168° (Found : C, 58·8; H, 5·0. $C_{28}H_{28}O_{13}$ requires C, 58·7; H, 4·9%). A solution of this substance (0·6 g.) in a mixture of methyl alcohol (10 c.c.) and concentrated hydrochloric acid (10 c.c.) was heated under reflux for 3 hours. Water (150 c.c.) was added to the cooled solution and 7-hydroxy-1-methoxyxanthone (IV) gradually separated, m. p. 235° after crystallisation from benzene.

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