

CCXXIX.—*Natural Glucosides. Part IV. The Constitution of Euxanthic Acid.*

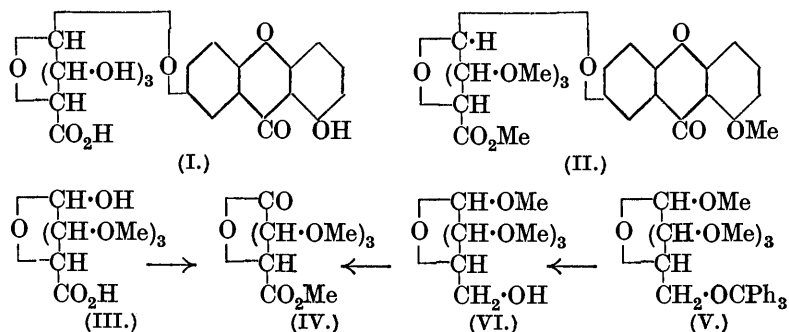
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By the interaction of a diacetylbromoglycuronolactone and the potassium derivative of euxanthone, Neuberg and Neimann (*Z. physiol. Chem.*, 1905, **44**, 114) obtained euxanthic acid, $C_{10}H_{16}O_{10} \cdot H_2O$, together with *isoeuxanthic acid*, $C_{10}H_{16}O_{10}$. This synthesis confirms the suggestion of Fischer and Piloty (*Ber.*, 1891, **24**, 521) that this glycuronate is structurally analogous to a glucoside. Evidence regarding the position of the glycuronic acid residue is afforded by the experiments of Herzig and Stanger (*Monatsh.*, 1914, **35**, 47). On treating euxanthic acid with diazomethane, these authors obtained a crystalline compound which appeared to be a dimethyl derivative containing a molecule of methyl alcohol of crystallisation. In addition they isolated an amorphous compound which had unexpectedly the composition of a tetramethyl derivative. On hydrolysis with dilute sulphuric acid both substances gave rise to 1-*O*-methyleuxanthone, a fact which

indicates that in euxanthic acid the glycuronic acid residue is attached at the 7-position. Direct experimental evidence concerning the structure of the glycuronic acid residue itself, however, does not appear to have been described.

Euxanthic acid is doubtless a product of animal metabolism and is probably formed in a manner common to all "paired glycuronates." It seemed to us of interest, therefore, to determine the exact structure of the uronic acid residue in this compound.

On methylation by means of methyl iodide and silver oxide euxanthic acid was converted into *methyl O-tetramethyleuxanthate* (II). Hydrolysis of this ester with hydrochloric acid gave rise to 1-*O*-methyleuxanthone and a trimethylglycuronic acid (III) which could not be crystallised. This uronic acid was carefully oxidised with nitric acid and the products were isolated and esterified according to the procedure of Hirst and Purves (J., 1923, **123**, 1357). Distillation of the resulting mixture afforded a small amount of an oil which appeared to consist mainly of methyl dimethoxysuccinate. The main fraction of the distillate was a crystalline solid which we consider to be the *methyl* ester of the liquid 2:3:4-trimethylsaccharolactone (IV) (Haworth and Leitch, J., 1919, **115**, 809; 1922, **121**, 1929; Irvine and Dick, J., 1919, **115**, 593). The properties of this compound are in close agreement with those of the δ -lactones derived from methylated sugars (for references, see Haworth, "Sugars," 1929, pp. 22—23).



In order to confirm the structure ascribed to this lactone it was considered essential to prepare the compound from an authentic specimen of 2:3:4-trimethyl glucose. For the preparation of the latter substance 6-triphenylmethyl α -methylglucoside (Helferich and Becker, *Annalen*, 1924, **440**, 1; Helferich, Klein, and Schäfer, *ibid.*, 1926, **447**, 19) appeared to be a convenient starting material. On methylating this compound with methyl iodide and silver oxide without the use of an extraneous solvent, we obtained 2:3:4-tri-

methyl-6-triphenylmethyl α -methylglucoside (V) as a crystalline solid (compare Helferich and Becker, *loc. cit.*). Contrary to the experience of Helferich and Becker we were able to isolate the liquid 2 : 3 : 4-trimethyl α -methylglucoside (VI) after removing the triphenylmethyl group by means of methyl-alcoholic hydrogen chloride. In addition to this glucoside a small amount of a crystalline by-product was obtained. Simultaneous hydrolysis and oxidation of (VI) with nitric acid gave, after esterification of the product, a good yield of the lactone (IV).

Since it is thus shown that the hydroxyl group taking part in the lactone formation is attached to the 5-C atom, it follows that the trimethylglycuronic acid which on oxidation gives rise to this lactone must have the pyranose structure (III). The compound (III) would thus appear to be identical with the trimethylglycuronic acid described by Challinor, Haworth, and Hirst (this vol., p. 258).

Further, methyl *O*-tetramethyleuxanthate may be represented by formula (II) and consequently euxanthic acid has formula (I). The structure (I) is analogous to the anhydro-form of the acid, $C_{10}H_{16}O_{10}$, which Graebe and his co-workers (*Ber.*, 1900, **33**, 3360; *Annalen*, 1901, **318**, 345) maintain is common only to certain derivatives—the silver salt, and the methyl and ethyl esters. For the acid itself they propose a formula of the alcoholate type, $R \cdot CH(OH) \cdot [CH(OH)]_4 \cdot CO_2H$ (where R is the euxanthone residue), and in support of this they state that the potassium salt, which they consider to have the formula $C_{10}H_{17}O_{11}K, H_2O$, lost only one molecule of water even when heated to 160—170°. On the other hand, Neuberg and Neimann (*loc. cit.*) give cogent reasons for believing that euxanthic acid exists as a stable hydrate, $C_{10}H_{16}O_{10}, H_2O$. We find that the potassium salt on drying at 120° in a high vacuum loses two molecules of water. Therefore the conclusions of Graebe and his co-workers are not supported.

With regard to the type of glucosidic linking present in euxanthic acid Neuberg and Neimann (*loc. cit.*) state that the compound is hydrolysed by emulsin and by kephir lactase, the presence of a β -linking thus being indicated. We were unable to obtain a decisive result with emulsin, but the synthesis of the compound by these authors affords strong evidence that the linking is of the β -type.

EXPERIMENTAL.

Methyl O-Tetramethyleuxanthate (II).—Euxanthic acid was methylated in three successive stages. Methyl iodide (30 c.c.) and silver oxide (60 g.) were added to a suspension of the acid (20 g.) in methyl alcohol (300 c.c.), and the mixture refluxed for 24 hours. After filtration from silver salts (wash with alcohol), the solution was

evaporated to dryness under diminished pressure, and the residue was dissolved in acetone (300 c.c.) and again methylated for 24 hours with the same quantities of the reagents. On isolation the product was soluble in methyl iodide and the methylation was completed without the aid of an extraneous solvent by means of iodide (125 c.c.) and silver oxide (30 g.) during 48 hours. After the methyl iodide had been distilled off, the residue was extracted with warm acetone (400 c.c.), the filtered extract evaporated, and the residue dissolved in warm methyl alcohol. On cooling, *methyl O-tetramethyleuxanthate* separated in colourless needles (20 g.), m. p. 168° [Found: C, 60.7; H, 5.5; OMe, 32.1. $C_{19}H_{11}O_5(OMe)_5$ requires C, 60.8; H, 5.5; OMe, 32.7%].

Hydrolysis of Methyl O-Tetramethyleuxanthate.—A suspension of the compound (5 g.) in a mixture of methyl alcohol (100 c.c.) and 20% hydrochloric acid (100 c.c.) was heated under reflux. The solid gradually dissolved and after 4 hours the reddish-brown solution was neutralised with 10% aqueous sodium hydroxide, Congo-red being used as an indicator. Next day the precipitate of 7-hydroxy-1-methoxyxanthone was collected, washed with water, and dried. Crystallised from benzene, it formed pale straw-coloured, rectangular plates, m. p. 235° alone or mixed with a synthetic specimen* (J., 1929, 2239) (Found: C, 69.4; H, 4.2. Calc. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.1%). The acetyl derivative crystallised from methyl alcohol in almost colourless plates, m. p. and mixed m. p. 176° (Found: C, 67.6; H, 4.3. Calc. for $C_{16}H_{12}O_5$: C, 67.6; H, 4.2%).

The aqueous-alcoholic filtrate from the crude 1-methyleuxanthone was evaporated at 30° in a vacuum, and the dried residue extracted several times with chloroform. Removal of the solvent left trimethylglycuronic acid as a viscid syrup which could not be crystallised. It was partially purified by being dissolved in ethyl acetate and reprecipitated with light petroleum. An aqueous solution of the purified compound was acid to litmus, liberated carbon dioxide from sodium bicarbonate, and readily reduced ammoniacal silver nitrate solution and Fehling's solution.

2 : 3 : 4-*Trimethyl-6-triphenylmethyl α -Methylglucoside* (V).—6-Triphenylmethyl α -methylglucoside (Helferich and Becker, *loc. cit.*) (3 g.) was methylated by means of methyl iodide (15 c.c.) and silver oxide (3 g.) during 10 hours in the usual manner, and the

* A specimen of the monomethyl ether, prepared by partial demethylation of *O*-dimethyleuxanthone according to the directions of Graebe and Aders (*Annalen*, 1901, 318, 365), was found to melt at 235° (these authors give m. p. 240°). This ether is identical with the synthetic compound (*loc. cit.*), m. p. and mixed m. p. 235°; acetyl derivative, m. p. 176°.

product isolated by extraction with warm acetone. The operation was repeated three times and the final product was crystallised from light petroleum. The glucoside formed colourless hexagonal plates (2.5 g.), m. p. 166—167°, $[\alpha]_{5461}^{24}$ + 88.86° in acetone ($c = 0.76$) [Found : OMe, 25.6. Calc. for $C_{25}H_{22}O_2(OMe)_4$: OMe, 25.9%].

2 : 3 : 4-Trimethyl α -Methylglucoside (VI).—A solution of the foregoing triphenyl derivative (20 g.) in methyl alcohol (400 c.c.) containing 0.5% of hydrogen chloride was heated under reflux for 5 minutes and then kept at room temperature for 3 hours. The mixture was neutralised with silver carbonate and after filtration the solvent was removed in a vacuum. The residual syrup was extracted with warm water, the filtered extract evaporated at 50° under diminished pressure, and the residue distilled in a high vacuum. The main fraction (6 g.) consisted of 2 : 3 : 4-trimethyl α -methylglucoside, b. p. 130°/0.1—0.2 mm., $[\alpha]_{5461}^{20}$ + 175.3° in methyl alcohol ($c = 1.2$) (Found : OMe, 52.3. Calc. for $C_{10}H_{20}O_6$: OMe, 52.5%). A small amount of a second fraction (b. p. 160—162°/0.2 mm.) was obtained which solidified. Recrystallised from carbon tetrachloride and then from light petroleum, this compound formed colourless hygroscopic plates, m. p. 79°, $[\alpha]_{5461}^{20}$ + 172.5° in methyl alcohol ($c = 0.41$) (Found : C, 49.4; H, 8.7; OMe, 43.9%). In moist air the crystals quickly change to a syrup. It is readily soluble in alcohol, acetone, or water. The substance does not reduce Fehling's solution, but a solution in 10% hydrochloric acid after being boiled for 5 minutes exhibits active reducing properties.

Methyl 2 : 3 : 4-Trimethyl- δ -saccharolactonate (IV).—(A) A solution of crude trimethylglycuronic acid (5 g.) in nitric acid (40 c.c., d 1.42) was cautiously warmed on the steam-bath until oxidation commenced. When the first reaction had almost ceased, the mixture was again gently heated for $\frac{1}{2}$ hour, the temperature being adjusted so that the evolution of oxides of nitrogen never became rapid, and then kept at 90° for 2 hours. The oxidation product was isolated and esterified by boiling with methyl alcohol (50 c.c.) containing 4% of hydrogen chloride according to the procedure of Hirst and Purves (*loc. cit.*). On distillation of the resulting viscous oil under diminished pressure the main fraction was a thick colourless oil, b. p. 170—180°/10 mm., which crystallised. The small first fraction had b. p. 130—150°/10 mm. and appeared to consist mainly of methyl d -dimethoxysuccinate, which was characterised by conversion into the corresponding diamide by means of methyl-alcoholic ammonia (Purdie and Irvine, J., 1901, 79, 960). This fraction did not appear to contain methyl xylotrimethoxyglutarate.

The crystalline solid was freed from traces of oil by washing with ether and then recrystallised several times from the same solvent.

Methyl trimethyl-δ-saccharolactonate formed colourless hexagonal plates (2·5 g.), m. p. 106°, $[\alpha]_{5461}^{25^\circ} + 175\cdot34^\circ$ in benzene ($c = 0\cdot762$) [Found: C, 48·2; H, 6·6; OMe, 49·6. $C_6H_4O_3(OMe)_4$ requires C, 48·4; H, 6·5; OMe, 50·0%. Titration: 0·0486 g. required 19·8 c.c. of *N*/100-NaOH; theory, 19·6 c.c.]. The lactone is readily soluble in ethyl or methyl alcohol, chloroform, and benzene. It is sparingly soluble in ether and almost insoluble in light petroleum. An aqueous solution of the substance is acid to litmus.

(B) 2 : 3 : 4-Trimethyl α -methylglucoside (5 g.) was oxidised with nitric acid (30 c.c., *d* 1·2), and the product isolated and esterified in the manner described above. On distillation of the product under diminished pressure two main fractions were obtained, (a) a colourless oil, b. p. 150—178°/10 mm., and (b) a solid, b. p. 178—184°/10 mm., which was almost pure methyl 2 : 3 : 4-trimethyl-saccharolactonate. Fraction (a) crystallised when seeded with a specimen of (b) and appeared to consist mainly of this compound. After purification the lactone had m. p. and mixed m. p. 106° (Found: C, 48·7; H, 6·7; OMe, 49·4%). Determinations of the rotation of the substance were recorded as follows :

In benzene ($c = 0\cdot984$), $[\alpha]_{5461}^{25^\circ} + 176\cdot05^\circ$.

In water ($c = 0\cdot701$):

Time in hours	0·17	0·5	1	2	4	6	24
$[\alpha]_{5461}^{25^\circ}$	+182·6°	168·4°	142·1°	107·2°	76·2°	68·9°	68·9°

Potassium Euxanthate.—A specimen of the salt was prepared by the method of Graebe (*Ber.*, 1900, **33**, 3360) (Found in air-dried material: C, 48·8; H, 3·8; K, 8·1. Calc. for $C_{19}H_{15}O_{10}K, 2H_2O$: C, 47·7; H, 4·0; K, 8·2%. Found in material dried in a high vacuum at 120° over phosphoric oxide: C, 51·4; H, 3·5. Calc. for $C_{19}H_{15}O_{10}K$: C, 51·6; H, 3·4%).

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