451. *Syntheses of Glycosides. Part XIII. Primulaverin.*

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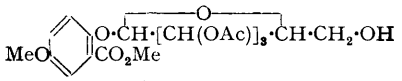
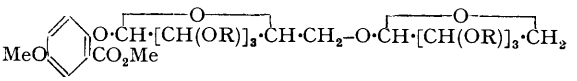
A synthesis of the β-primeveroside of methyl 5-methoxysalicylate is described and evidence has been obtained in support of the view that the mixture originally named primulaverin by Goris and his co-workers (*loc. cit.*) is a mixture of the foregoing glycoside and primeverin.

Along with primeverin (Part X, *J.*, 1933, 1618) Goris and his co-workers (*Bull. Sci. pharmacol.*, 1909, **16**, 695; 1912, **19**, 577; 1920, **27**, 13) isolated glycosidic material, m. p. 163°, which at first they considered to be an individual substance, primulaverin, but which they subsequently concluded was a mixture of the primeverosides of methyl 4-methoxysalicylate (primeverin) and 5-methoxysalicylate since on hydrolysis the purest specimens obtained invariably gave rise to mixtures of 4- and 5-methoxysalicylic acid. Further, these authors also suggested that the product, m. p. 163°, probably arose from the crystallisation of two isomorphous substances which attain a very stable equilibrium, causing their separation to be difficult, a view which seemed reasonable since the two glycosides are very similar in constitution. Though Goris continued to call the (mixed) material, m. p. 163°, by the name primulaverin, we propose to reserve this name for the β-primeveroside of methyl 5-methoxysalicylate (II, R = H), a synthesis of which was clearly an essential preliminary step in the clarification of this problem.

In the first instance two of us (H. I. K. and A. R.) in 1935 attempted the synthesis of the required primeveroside by the route adopted in the case of monotropitoside (gaultherin) (Part VIII, *J.*, 1931, 1881) and of primeverin (Part X, *J.*, 1933, 1618), a general procedure which was originally devised in order to avoid the troublesome preparation of acetylated biosidyl bromides, *e.g.*, from primeverose. Accordingly, the condensation of methyl 5-methoxysalicylate and *O*-tetra-acetyl-α-glucosidyl bromide by the quinoline–silver oxide method gave rise to *methyl* 2-O-*tetra-acetyl*-β-*glucosidoxy*-5-*methoxybenzoate* in good yield, which on deacetylation furnished *methyl* 2-β-*glucosidoxy*-5-*methoxybenzoate*. On acetylation the *trityl* ether of the latter compound yielded *methyl* 2-(2′ : 3′ : 4′-O-*triacetyl*-6′-O-*trityl*-β-*glucosidoxy*)-5-*methoxybenzoate* which on removal of the trityl group in the usual manner gave rise to the *triacetate* (I)



(I.)



(II.)

but since attempts to induce this substance to react with *O*-triacetyl-α-xylosidyl bromide so as to give the hexa-acetate of primulaverin (II, R = Ac) failed, we abandoned this route. Subsequently, Mauthner (*J. pr. Chem.*, 1940, **156**, 150) described the synthesis of the *O*-hexa-acetyl-β-primeveroside of methyl 5-methoxysalicylate, m. p. 198—199°, with the aid of Zemplen's *O*-hexa-acetyl-α-primeverosidyl bromide (*Ber.*, 1939, **72**, 49) but does not appear to have deacetylated the product. Accordingly, we have repeated the preparation of the hexa-acetate of primulaverin (II, R = Ac) which we found to have m. p. 212—214°. Deacetylation of this substance by the methyl-alcoholic ammonia process gave primulaverin (II, R = H) as a *penta-hydrate*, m. p. 195—197°, which appears to be difficult to dehydrate but which on acetylation re-formed the original hexa-acetate, m. p. and mixed m. p. 212—214°.

Having obtained primulaverin, we attempted to prepare Goris's product by recrystallising a mixture of synthetical specimens of primulaverin and primeverin from methanol; the latter compound, m. p. 205°, was obtained by repeating the synthesis of Jones and Robertson (Part X, *loc. cit.*). The solid (A), which separated, had m. p. 198—200° changing to 202° on crystallisation from the same solvent, and was apparently almost pure primeverin. Concentration of the mother-liquor from (A) gave a product which had m. p. 170—172°, unchanged on repeated recrystallisation, and appeared to be predominantly primulaverin contaminated with primeverin. In this connection it is of interest to note that the natural mixture kindly supplied to us by Professor Goris was found to have m. p. 167—169°. We then determined the melting point curve for the mixture of synthetical glycosides and found that the minimum point on the curve, which corresponds to the melting point of Professor Goris's specimen, was given by a mixture containing approximately 75% of primulaverin pentahydrate and 25% of primeverin. Thus it would appear that the evidence obtained so far serves to substantiate the suggestion made by Goris and his co-workers that the product originally named primulaverin by them is a mixture of two glycosides, but final confirmation of this must await the isolation of a substantial supply of the natural mixture to enable us to undertake the separation of the components.

Experimental.

5-Hydroxysalicylic Acid.—The following procedure for the preparation of this acid was found to be superior to those given in the literature. Sodium nitrite (29 g.), dissolved in water (100 ml.), was gradually added to a vigorously stirred mixture of aniline (36 g.), concentrated hydrochloric acid (63 ml.; *d* 1·9), and crushed ice (300 g.), and 15 minutes later a solution of salicylic acid (53·5 g.) and sodium carbonate (200 g. of hydrate) in water (1000 ml.) was introduced. The resulting azo-derivative of salicylic acid was collected, washed with water, and gradually added to a well-stirred solution of stannous chloride (172 g.) in concentrated hydrochloric acid (350 ml.) and the mixture heated on the steam-bath until a clear solution was obtained, which was then rapidly filtered through a glass-wool filter pad. After the addition of concentrated hydrochloric acid (500 ml.), the filtrate deposited in the course of 24 hours a mass of colourless prisms, and these were collected, washed with dilute hydrochloric acid (500 ml.), and recrystallised from hot water (500 ml.). The resulting 5-aminosalicylic acid was mixed with ice (300 g.) and concentrated hydrochloric acid (70 ml.) and then converted into the corresponding diazonium salt by the addition of 30% aqueous sodium nitrite (100 ml.). This product, which formed almost colourless needles, giving a red-violet ferric reaction in alcohol, was collected and washed with a little water at 0°. The moist diazonium chloride (from 53 g. of salicylic acid) was heated with 50% sulphuric acid (200 ml.) until the vigorous evolution of nitrogen had ceased (1 hour), and on being kept at room temperature the resulting solution gradually deposited 5-hydroxysalicylic acid, m. p. 200°, after recrystallisation from dilute hydrochloric acid (yield, 15 g.).

A solution of sodium hydroxide (6 g.) in water (60 ml.) was added gradually during 20 minutes to a vigorously agitated mixture of 5-hydroxysalicylic acid (12 g.) and methyl sulphate (15 ml.), and

then after the addition of more hydroxide (4 g.) in water (40 ml.) the reaction mixture was heated on the steam-bath for ½ hour, cooled, and acidified with sulphuric acid. 5-Methoxysalicylic acid was isolated from the crude product by extraction with boiling water (charcoal) and obtained in almost colourless needles, m. p. 144°, after recrystallisation, having a deep blue ferric reaction (compare Graebe and Martz, *Annalen*, 1905, **340**, 213) (yield, 12 g.). Esterification of the acid with boiling methanol and sulphuric acid for 10 hours gave the methyl ester, b. p. 143—144°/16 mm.

Methyl 2-O-*Tetra-acetyl-β-glucosidoxy-5-methoxybenzoate.*—To ensure success in this experiment it is essential that all the reactants should be pure and dry.

To a paste of methyl 5-methoxysalicylate (5 g.), *O*-tetra-acetyl-α-glucosidyl bromide (15 g.), and quinoline (6 ml.), " active " silver oxide (7 g.) was added with stirring which was continued for 15—20 minutes; the mixture was occasionally cooled by immersion in tap water. The reaction mixture was then kept in a desiccator over soda–lime for ½ hour, stirred for 10 minutes, and 3 hours later extracted with warm acetic acid (50 ml.), and the filtered extract was poured into water (500 ml.). Next day the *product* was collected, washed with water, and crystallised from a small volume of methyl alcohol, forming colourless rods (7·3 g.), m. p. 117°, $[\alpha]_D^{20°}$ −43·95° (in acetone) (Found : C, 54·0; H, 5·5. $C_{23}H_{28}O_{13}$ requires C, 53·9; H, 5·5%). The compound is soluble in alcohol, ethyl acetate, and benzene, and insoluble in light petroleum.

Methyl 2-*β-Glucosidoxy-5-methoxybenzoate.*—Methyl alcohol containing the foregoing acetate (8 g.) in suspension was saturated with ammonia at 0°, and the resulting solution kept at 0° for 6 hours. Removal of the ammonia and the solvent in a vacuum at room temperature left an oil which gradually solidified and was then extracted with methanol. Crystallisation of the residue from ethyl acetate–methanol gave the glucoside as a *hemihydrate* (3·5 g.), m. p. 170° after sintering at 115°, soluble in water and alcohol, $[\alpha]_D^{20°}$ −50·63° (in water) (Found : C, 51·1; H, 6·1. $C_{15}H_{20}O_9,0{\cdot}5H_2O$ requires C, 51·0; H, 6·0%).

Methyl 2-(2′ : 3′ : 4′-O-*Triacetyl-β-glucosidoxy*)-5-*methoxybenzoate.*—A mixture of the foregoing glucoside (3·9 g., dried in a high vacuum at 90° for 1 hour and then at 100° for 3 hours), trityl chloride (3 g.), and pyridine (25 ml.) was heated on the steam-bath for 1 hour and was treated next day with acetic anhydride (25 ml.). Three days later the mixture was poured into water (400 ml.), and the solid collected, well washed with water, and crystallised from methyl alcohol (charcoal), giving the 2-2′ : 3′ : 4′-O-*triacetyl*-6′-O-*trityl-β-glucoside* of methyl 5-methoxysalicylate in colourless rods (6 g.), m. p. 141°, $[\alpha]_D^{20°}$ −31·5° (in acetone) (Found : C, 67·0; H, 5·8. $C_{40}H_{40}O_{12}$ requires C, 67·3; H, 5·6%). Scission of this trityl ether (1 g.), dissolved in acetic acid (4 ml.), was effected with a saturated solution of hydrogen bromide in acetic acid (0·5 ml.) in the course of 1 minute, and the rapidly filtered mixture immediately poured into ice-water (100 ml.). A solution of the gummy precipitate in chloroform (150 c.c.) was washed several times with ice-water, dried over calcium chloride, and evaporated in a vacuum at 30°. Crystallisation of the residue from ethyl acetate–light petroleum (b. p. 40—60°) gave the 2-2′ : 3′ : 4′-O-*triacetyl-β-glucoside* of methyl 5-methoxysalicylate as a *hemihydrate* in tiny colourless prisms (0·6 g.), m. p. 160°, $[\alpha]_D^{20°}$ −54·93° (in acetone), soluble in benzene, alcohol, and chloroform (Found, in material dried in air : C, 52·7; H, 5·6. $C_{21}H_{26}O_{17},0{\cdot}5H_2O$ requires C, 52·6; H, 5·6%. Found, in material dried in a high vacuum at 90° : C, 53·3; H, 5·4. $C_{21}H_{26}O_{12}$ requires C, 53·6; H, 5·5%).

O-*Hexa-acetyl-β-primeveroside of Methyl* 5-*Methoxysalicylate* (II, R = Ac).—" Active " silver oxide (5 g.) was gradually added with stirring to a paste of methyl 5-methoxysalicylate (1·8 g.), *O*-hexa-acetyl-α-primeverosidyl bromide (Zemplen, *Ber.*, 1939, **72**, 49) (6·4 g.), and anhydrous quinoline (10 ml.), and the mixture stirred for 20 minutes. Next day the product was extracted with warm acetic acid (80 ml.), the filtered extract (charcoal) diluted with water (400 ml.), and the precipitate crystallised from methyl alcohol, giving the hexa-acetate (4·5 g.) in rectangular prisms, m. p. 212—214°, $[\alpha]_D^{20°}$ −31·2° (*c*, in chloroform, 1·28) (Found : C, 52·5; H, 5·7. Calc. for $C_{32}H_{40}O_{19}$: C, 52·7; H, 5·5%) (compare Mauthner, *loc. cit.*, who gives m. p. 198—199°).

β-Primeveroside of Methyl 5-*Methoxysalicylate* (II, R = H).—Methyl alcohol (200 ml.), containing the foregoing hexa-acetate (2·5 g.), was saturated with ammonia at 0° and 6 hours later the clear solution was evaporated in a vacuum at room temperature. Slow evaporation of a solution of the residual syrup in methyl alcohol (10 ml.) in the course of several days gave the crystalline primeveroside, which was collected, washed with a little ice-cold methyl alcohol, and dissolved in the minimum amount of warm water. This solution was diluted with four times its volume of alcohol and in the course of a week deposited the *pentahydrate* of the glycoside in colourless slender needles, m. p. 195—197°, unchanged after repeated purification, $[\alpha]_D^{20°}$ −20·0° (*c* in water, 0·8) (Found : C, 42·6; H, 6·5. $C_{20}H_{28}O_{13},5H_2O$ requires C, 42·4; H, 6·5%).

Acetylation of the synthetical pentahydrate with acetic anhydride and sodium acetate on the steam-bath for 2 hours regenerated the hexa-acetate, m. p. 212—214°, identical in every way with the original material. Under the same conditions acetylation of a small specimen of natural mixed glycosides supplied by Professor Goris gave rise to a product which formed needles, m. p. 178—180°, from methyl alcohol. A mixture of the two acetates melted at 176—178°.

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