381. *Syntheses of Glycosides.* Part X. The Synthesis of Primeverin.*

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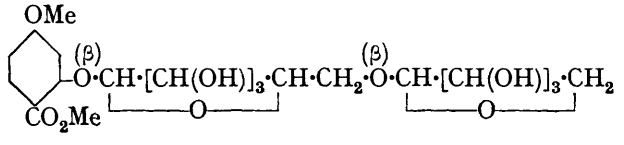
THE bioside primeverin which occurs along with its isomeride primulaverin in the root of *Primula officianalis* has been shown by Goris and his co-workers (*Bull. Sci. Pharm.*, 1909, **16**, 695; 1912, **19**, 577; 1920, **27**, 13) to be a primeveroside of methyl 4-methoxysalicylate. The synthesis of this compound has now been achieved by the general method developed by Robertson and Waters (J., 1931, 1881) for the synthesis of monotropitoside.

In the following, the Roman numerals are those in the scheme already given (*loc. cit.*, p. 1882), but R is now $\cdot C_6H_3(OMe)\cdot CO_2Me$.

By the interaction of methyl 4-methoxysalicylate and *O*-tetra-acetyl-α-glucosidyl bromide in the presence of silver oxide and quinoline the *tetra-acetate* of (I) was obtained in excellent yield, and on deacetylation with methyl-alcoholic ammonia this compound yielded the *glucoside* (I). The *triphenylmethyl ether* (II) was obtained from (I) in the usual manner and converted into the *triacetate* (III), which on subsequent removal of the triphenylmethyl group with hydrogen bromide in acetic acid furnished the 2 : 3 : 4-O-*triacetyl*-β-*glucoside* of methyl 4-methoxysalicylate (IV). The condensation of (IV) and *O*-triacetyl-α-xylosidyl bromide gave rise to an amorphous product which appeared to

(VI.)



consist mainly of (V), since on deacetylation it gave rise to a syrup from which the crystalline β-primeveroside (VI) was eventually isolated and found to be identical with a specimen

* The general term " glycoside " has been substituted for " glucoside," used in Parts I—IX (compare this vol., p. 1167).

of the natural bioside kindly presented to us by Professor Goris. Acetylation of the natural and the synthetic glycoside gave rise to the same crystalline ***hexa-acetate*** (V).

Experimental.

O-Tetra-acetyl-β-glucoside of Methyl 4-Methoxysalicylate.—Esterification of 4-methoxysalicylic acid, m. p. 156° (Kostanecki and Tambor, *Ber.*, 1895, **28**, 2308) with methyl-alcoholic sulphuric acid gave the methyl ester, m. p. 52° (compare Herzig, Wenzel, and Batscha, *Monatsh.*, 1903, **24**, 881, and Mutschler, *Annalen*, 1877, **185**, 222, who respectively record m. p. 48—50° and 49°).

Silver oxide (5 g.) was stirred into a paste of this ester (4 g.), *O*-tetra-acetyl-α-glucosidyl bromide (10 g.), and quinoline (10 c.c.), occasionally cooled in tap-water. The mixture was agitated for 10 minutes, kept in a desiccator for ½ hour, and extracted with warm acetic acid (50 c.c. at 45°). The filtered (charcoal) extract was poured into ice-water (500 c.c.), and the *tetra-acetate* well washed and crystallised from methyl alcohol, forming elongated prisms (11·5 g.), m. p. 138—139°, $[\alpha]_{5461}^{20°}$ — 66·0° in acetone (*c*, 0·83), readily soluble in acetone, chloroform, or benzene (Found: C, 53·9; H, 5·5. $C_{23}H_{28}O_{13}$ requires C, 53·9; H, 5·5%).

β-Glucoside of Methyl 4-Methoxysalicylate (I).—Methyl alcohol (45 c.c.) containing a suspension of the foregoing tetra-acetate (2 g.) was saturated at 0° with dry ammonia. The solid quickly dissolved and 6 hours later the removal of the ammonia and methyl alcohol in a vacuum left the *glucoside* as a colourless crystalline solid, which separated from warm water as a *hemihydrate* in slender needles, m. p. 124—126°, $[\alpha]_{5461}^{21°}$ — 82·36° in acetone (*c*, 0·41) (Found: C, 50·9; H, 6·0. $C_{15}H_{20}O_9,0{\cdot}5H_2O$ requires C, 51·0; H, 5·9%). Dried in a high vacuum at 110°, a specimen had m. p. 134—136° (Found: C, 52·2; H, 6·0. $C_{15}H_{20}O_9$ requires C, 52·3; H, 5·8%).

6-O-*Triphenylmethyl-β-glucoside of Methyl 4-Methoxysalicylate* (II).—A mixture of the afore-mentioned glucoside (1·2 g.), triphenylmethyl chloride (0·95 g.), and pyridine (8 c.c.) was heated on the steam-bath for 1 hour, kept at room temperature for 3 days, diluted with sufficient water to form a slight turbidity, and 1 hour later poured into ice-water (200 c.c.). The *product* was triturated with water until it solidified, and crystallised from dilute methyl alcohol, forming microscopic plates, m. p. 120° after sintering at 87°, $[\alpha]_{5461}^{21°}$ — 36·72° in acetone (*c*, 0·31), readily soluble in chloroform or warm alcohol (Found: C, 69·9; H, 5·5. $C_{34}H_{34}O_9$ requires C, 69·6; H, 5·8%).

6-O-*Triphenyl*-2 : 3 : 4-O-*triacetyl-β-glucoside of Methyl 4-Methoxysalicylate* (IV).—Treatment of the triphenyl ether (1 g.) with acetic anhydride (2 c.c.) and pyridine (25 c.c.) at room temperature for 18 hours gave rise to the *triacetate*, which separated from methyl alcohol in elongated hexagonal plates, m. p. 168—169°, $[\alpha]_{5461}^{21°}$ — 103·41° in acetone (*c*, 0·49) (Found: C, 67·4; H, 5·6. $C_{40}H_{40}O_{12}$ requires C, 67·4; H, 5·6%).

This acetate was also prepared directly without isolation of the ether (II). A solution of the glucoside (I) (5 g.) and triphenylmethyl chloride (4·4 g.) in pyridine (40 c.c.) was warmed on the steam-bath for 1 hour, kept at room temperature for 24 hours, and mixed with acetic anhydride (40 c.c.). 3 Days later the triacetate (8 g.) was isolated in the usual manner, m. p. and mixed m. p. 168° after purification.

2 : 3 : 4-O-*Triacetyl-β-glucoside of Methyl 4-Methoxysalicylate* (IV).—Scission of the triphenylmethyl ether (5 g.), dissolved in acetic acid (12 c.c.), was effected with a saturated solution of hydrogen bromide in acetic acid (1·5 c.c.) in the course of 1 minute. The rapidly filtered solution was immediately poured into ice-water, and a solution of the product in chloroform (200 c.c.) washed with ice-water until free from acetic and hydrobromic acids, dried with sodium sulphate, and evaporated in a vacuum at 30°, leaving the *triacetyl glucoside* as a crystalline solid, which separated from ethyl acetate–light petroleum in rectangular prisms, m. p. 136°, $[\alpha]_{5461}^{21°}$ — 40·82° in acetone (*c*, 0·29), readily soluble in alcohol or benzene (Found: C, 53·6; H, 5·7. $C_{21}H_{26}O_{12}$ requires C, 53·6; H, 5·5%). Treatment of this compound with acetic anhydride and pyridine gave the tetra-acetyl-β-glucoside of methyl 4-methoxysalicylate, m. p. and mixed m. p. 138—139°.

Primeverin (VI).—Active silver oxide (3·5 g.) was added to a solution of the foregoing triacetate (1·5 g., well dried) and *O*-triacetylxylosidyl bromide (Levene and Sobotka, *J. Biol. Chem.*, 1925, **65**, 465) (5 g.) in warm dry benzene (25 c.c. at 35°), and the mixture vigorously agitated for 1 hour and refluxed for 5 minutes. Excess of benzene was added, the silver salts filtered off, the solvent distilled in a vacuum, a solution of the residue in acetone (200 c.c.) evaporated in a vacuum, the benzene-free product dissolved in methyl alcohol (100 c.c.), and

the solution diluted with excess of water. The resulting precipitate was triturated with water and finally obtained as an amorphous solid, which separated from solvents as a viscous syrup. This material, which gave the phloroglucinol and orcinol reactions for a pentose and did not reduce Fehling's solution, appeared to consist mainly of primeverin hexa-acetate. Repetition of the condensation under slightly modified conditions always gave rise to the same product.

Treatment of the amorphous substance (4 g.) with methyl-alcoholic ammonia (250 c.c.) at 0° for 6 hours and subsequent removal of the ammonia and solvent in a vacuum left a viscous syrup, which did not immediately crystallise and on acetylation re-formed the original material. A solution of this syrup in methyl alcohol (20 c.c.) was allowed to evaporate at room temperature in the course of 5—6 days. This procedure was twice repeated, and the residue dissolved in the same solvent (40 c.c.) contained in a loosely stoppered vessel. On slow evaporation in the course of 2 months crystalline primeverin gradually separated; it was filtered off from the accompanying syrup, washed with a little methyl alcohol, and recrystallised from the same solvent or from ethyl alcohol, forming prismatic needles, m. p. 205° alone or mixed with a natural specimen, $[\alpha]_D^{20°}$ — 76·75° in water (*c*, 1·06) (Found in material dried in a high vacuum at 105° : C, 50·3; H, 6·0. Calc. for $C_{20}H_{28}O_{13}$: C, 50·4; H, 5·9%) (Goris and co-workers, *loc. cit.*, record $[\alpha]_D$ — 71·53° in water). On one occasion a specimen separated from 96% alcohol which on heating melted at 188—189°, solidified about 195—197°, and then remelted at 205° (compare Goris and co-workers, *loc. cit.*). Recrystallised from methyl alcohol, this material melted at 205°.

Acetylation of the pure synthetic primeverin (both forms) with acetic anhydride and pyridine at room temperature gave rise to the *hexa-acetate* (V), which separated from dilute methyl or ethyl alcohol in slender needles and was identical in every way with a specimen similarly prepared from the natural glycoside, m. p. and mixed m. p. 125° (Found : C, 52·8; H, 5·7. $C_{32}H_{40}O_{19}$ requires C, 52·7; H, 5·5%). This derivative is readily soluble in absolute methyl or ethyl alcohol, acetone, or benzene and separates from warm ligroin in microscopic needles.

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