CCLIII.—*Syntheses of Glucosides. Part VIII. The Synthesis of Monotropitoside (Gaultherin).*

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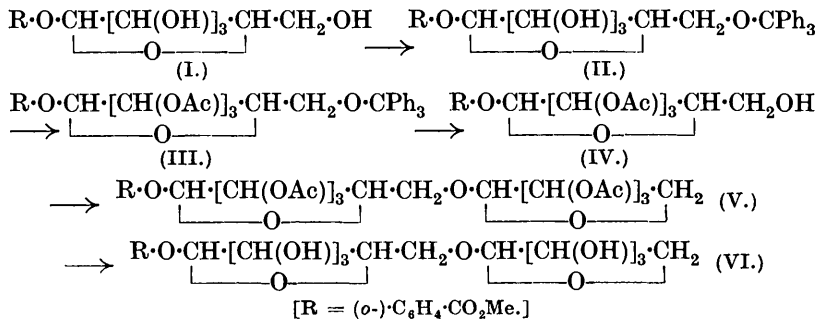
The glucoside monotropitoside * was first isolated in the pure state by Bridel (*Compt. rend.*, 1923, **177**, 642; 1924, **179**, 991; 1925, **180**, 1421), who showed it to be a primeveroside of methyl salicylate which is hydrolysed by the specific enzyme primeverosidase, yielding primeverose. With mineral acids the hydrolytic decomposition proceeds further, resulting in the decomposition of the biose into glucose and xylose. In collaboration with his co-workers, Bridel (*J. Pharm. Chim.*, 1924, **30**, 400; *Compt. rend.*, 1925, **180**, 1864; 1928, **187**, 609) has found that this bioside, which he obtained in the first instance from *Monotropa hypopitys*, also occurs in *Betula lenta*, *Gaultheria procumbens*, and in the three species of *Spiræa*, *S. ulmaria*,

* The name monotropitin, first given to the bioside by Bridel, was subsequently changed to monotropitoside (*Bull. Soc. Chim. biol.*, 1925, **7**, 52).

S. filipendula, and *S. gigantea*. As a result, therefore, it is considered that monotropitoside is identical with the glucoside gaultherin (Procter, *Amer. J. Pharm.*, 1844, **15**, 249; Schneegans and Gerock, *Arch. Pharm.*, 1894, **232**, 437; Bourquelot, *J. Pharm. Chim.*, 1896, **3**, 577). The latter compound, which apparently had not been obtained in a pure condition, was generally believed to be a simple α-glucoside of methyl salicylate.

In attempting the synthesis of monotropitoside, the most obvious method was to prepare hexa-acetylprimeverosidyl bromide from synthetic primeverose hepta-acetate (Helferich and Rauch, *Annalen*, 1927, **455**, 168) and to condense this bromide with methyl salicylate. In view of the difficulties involved in preparing a sufficient quantity of the hepta-acetate, and as the required bromide had not been described, we decided to effect the synthesis in the first instance by a route analogous to that used by Helferich and Rauch in their preparation of primeverose. This method seemed to be all the more feasible since the procedure described in Part VI of this series (J., 1930, 2739) rendered possible the preparation of the starting material (the β-glucoside of methyl salicylate) in quantity.

The tetra-acetyl β-glucoside of methyl salicylate was obtained in excellent yield by the quinoline–silver oxide method (compare Mauthner, *J. pr. Chem.*, 1918, **97**, 217), and on deacetylation with methyl-alcoholic ammonia it afforded the β-glucoside (I). Although deacetylation of methyl 3-tetra-acetyl-β-glucosidoxyindole-2-carboxylate by means of this reagent gave rise to a mixture of the corresponding glucoside and 3-β-glucosidoxyindole-2-carboxylamide (J., 1927, 1937), yet in the present instance amide formation was almost completely avoided by reducing the time of contact with the reagent to 6 hours. This glucoside (I), m. p. 196—197°, is probably identical with the compound, m. p. 105°, described by Karrer and Weidmann (*Helv. Chim. Acta*, 1920, **3**, 252), which they obtained by an indirect method. Both compounds appear to yield the same tetra-acetate.



The glucoside (I) on treatment with triphenylmethyl chloride in presence of pyridine formed the 6-*triphenylmethyl ether* (II), which was converted into the *triacetate* (III). Removal of the triphenylmethyl residue from the latter by careful treatment with hydrogen bromide in acetic acid gave rise to the 2 : 3 : 4-*triacetyl* β-*glucoside* of methyl salicylate (IV). The conclusion that in (II) and (III) the triphenylmethyl group is attached at the 6-position in the glucose residue, and consequently that in (IV) the 6-hydroxyl group is free, depended mainly on the behaviour of analogous compounds (Helferich and co-workers, *Annalen*, 1924, **440**, 1; 1926, **447**, 19; Haworth and co-workers, J., 1927, 2443). The ultimate success of our synthesis, however, affords confirmation of this view.

The interaction of (IV) and *O*-triacetylxylosidyl bromide (Levene and Sobotka, *J. Biol. Chem.*, 1925, **65**, 465) in the presence of silver oxide in chloroform solution gave only traces of *monotropitoside hexa-acetate* (V). When the reaction was carried out in benzene solution at 33—35° (excess of the bromide being used), a comparatively good yield of (V) was obtained (compare Robertson and Robinson, J., 1928, 1460; Robertson, J., 1929, 1820). The synthetic hexa-acetate was directly compared with a specimen prepared from the natural glucoside and found to be identical in all respects. The crystallisation and purification of synthetic monotropitoside (VI), which was obtained as a gum on deacetylating (V), caused a considerable loss of material. A specimen was ultimately obtained which was identical with the natural product. Sufficient material was not available to enable us to make an accurate determination of the rotation of synthetic monotropitoside, but the rotations of the natural and the synthetic hexa-acetate were found to be identical.

Since it is a general rule that acetobromo-sugars always furnish β-glucosides when silver oxide or caustic alkali is used as the condensing agent (compare Levene and Sobotka, *loc. cit.*), the synthesis of primeverose by Helferich and Rauch (*loc. cit.*) indicates that in monotropitoside and in other primeverosides the xylose is present as a β-xylopyranose residue. The present synthesis affords confirmation of this, and proves that in monotropitoside the glucose residue has the normal pyranose structure and that the biose is united to the aglucone by a β-linking.

The preparation of the *rhamnoside* and *xyloside* of methyl salicylate is described. The former is unaffected by emulsin (supplied by British Drug Houses, Ltd.), but the latter is partially hydrolysed in aqueous solution at 37°. After three days this solution, which had the smell of methyl salicylate, gave a positive ferric chloride reaction but a control was unchanged. This result is in agreement with the

experiments of Bridel (*Compt. rend.*, 1925, **181**, 523), who found that monotropitoside is slowly hydrolysed by emulsin with simultaneous decomposition of the biose into glucose and xylose. Since both α- and β-methylxylosides (Fischer, *Ber.*, 1895, **28**, 1429, 1158) and β-α-naphthylxyloside (Ryan and Ebrill, *Sci. Proc. Roy. Dublin Soc.*, 1908, **11**, 247) are unaffected by emulsin, the action of enzymes on other synthetic xylosides is being investigated.

Experimental.

O-*Tetra-acetyl* β-*Glucoside of Methyl Salicylate*.—Dry "active" silver oxide (5 g.) was added with stirring to a paste of methyl salicylate (4 g.), *O*-tetra-acetyl-α-glucosidyl bromide (10 g.), and quinoline (10 c.c.), and the vigorous reaction was controlled by cooling the vessel in tap water. The mixture, which at first became less viscous, was agitated for 10 minutes, and the resulting stiff paste was then kept in a desiccator for ½ hour. A solution of the product in acetic acid (30 c.c.) was filtered from silver salts and poured into water (500 c.c.). The solid tetra-acetate was collected, washed with water, and crystallised from methyl alcohol (charcoal), forming colourless, rectangular prisms (12 g.), m. p. 158—160°, $[\alpha]^{21°}_{5461}$ — 48·35° in acetone (*c*, 1·72) (Found : C, 54·7; H, 5·7. Calc. for $C_{22}H_{26}O_{12}$: C, 54·8; H, 5·4%) (Mauthner, *loc. cit.*, gives m. p. 154—155°, and Karrer and Weidmann, *loc. cit.*, m. p. 154°).

β-*Glucoside of Methyl Salicylate* (I).—A solution of the foregoing tetra-acetate (5 g.) in methyl alcohol (50 c.c.) cooled to 0° was saturated with ammonia and then kept in ice-water for 6 hours. After removal of the ammonia and alcohol in a vacuum, the residue was dissolved in warm moist ethyl acetate, and on cooling, the glucoside gradually separated in clusters of colourless prisms (2·5 g.). Recrystallised from the same solvent, it had m. p. 196—197°, $[\alpha]^{21°}_{5461}$ — 68·83° in water (*c*, 1·61) (Found, in air-dried material : C, 52·0; H, 5·9. Calc. for $C_{14}H_{18}O_8,\frac{1}{2}H_2O$: C, 52·0; H, 5·9. Found, in specimen dried at 130° : C, 53·7; H, 5·7. Calc. for $C_{14}H_{18}O_8$: C, 53·5; H, 5·7%). The compound is readily soluble in alcohol or water, and does not give a ferric chloride reaction. It is rapidly hydrolysed by emulsin at 37°.

6-O-*Triphenylmethyl*-β-*glucoside of Methyl Salicylate* (II).—Triphenylmethyl chloride (0·9 g.) was added to a solution of the β-glucoside of methyl salicylate (1 g.) in dry pyridine (6 c.c.), and the mixture was heated on the steam-bath for 1 hour, and then kept at room temperature for 3 days. Sufficient water was added to form a slight turbidity, and after 1 hour the reaction mixture was poured into ice-water (200 c.c.) (agitate). Next day the aqueous solution was decanted, and the residual gum was washed with water

and dissolved in chloroform (200 c.c.). The chloroform solution was once washed with water and, on keeping, gradually deposited the *triphenylmethyl ether* as a mass of voluminous, slender needles (1 g.), m. p. 149° after recrystallisation, $[\alpha]_{5461}^{20°}$ — 5·14° in acetone (*c*, 0·49) (Found, in specimen dried at 110°: C, 71·1; H, 6·0. $C_{33}H_{32}O_8$ requires C, 71·2; H, 5·8%). The compound is readily soluble in methyl or ethyl alcohol and is insoluble in water.

6-O-*Triphenylmethyl* 2 : 3 : 4-O-*Triacetyl* β-*Glucoside of Methyl Salicylate* (III).—The foregoing triphenylmethyl ether (1 g.) was acetylated by means of acetic anhydride (1 c.c.) and pyridine (2 c.c.) during 18 hours at room temperature. Addition of ice-water (30 c.c.) to the mixture precipitated the *triacetate* as a colourless amorphous solid which crystallised from methyl alcohol in colourless, hexagonal prisms (1 g.), m. p. 125°, $[\alpha]_{5461}^{20°}$ — 34·84° in acetone (*c*, 0·61) (Found, in specimen dried at 110°: C, 68·7; H, 5·6. $C_{39}H_{38}O_{11}$ requires C, 68·6; H, 5·6%). The compound is easily soluble in alcohol and is quickly decomposed by warm, 10% hydrochloric acid.

In subsequent experiments the triacetate was prepared directly without isolation of the triphenylmethyl ether (II). A mixture of the β-glucoside of methyl salicylate (5 g.), triphenylmethyl chloride (4·5 g.), and pyridine (40 c.c.) was heated on the steam-bath for one hour. Next day acetic anhydride (40 c.c.) was added and the mixture kept at room temperature for 3 days. Isolated by means of ice-water (500 c.c.), the triacetate crystallised from methyl alcohol in prisms (7 g.), m. p. 125°.

2 : 3 : 4-O-*Triacetyl* β-*Glucoside of Methyl Salicylate* (IV).—A solution of the foregoing glucoside (1 g.) in acetic acid (6 c.c.) was cooled to 0°. A saturated solution of hydrobromic acid in acetic acid (1 c.c.) was then introduced with stirring, and after 2 minutes the mixture was filtered and poured into ice-water. A solution of the gummy precipitate in chloroform (100 c.c.) was washed several times with water and dried, and the solvent removed in a vacuum at 30°. The residual solid was dissolved in ethyl acetate–ligroin and, on cooling, the *triacetate* separated in colourless, rectangular prisms, m. p. 152—153°, $[\alpha]_{5461}^{20°}$ — 50·87° in acetone (*c*, 0·8) (Found: C, 54·6; H, 5·7. $C_{20}H_{24}O_{11}$ requires C, 54·5; H, 5·5%). The substance is readily soluble in alcohol (ethyl or methyl), acetone, chloroform, and benzene. Acetylated by means of pyridine and acetic anhydride, it gave the tetra-acetate, m. p. 158—160°.

Hexa-acetyl Monotropitoside (V).—To a solution of 2 : 3 : 4-triacetyl β-glucoside of methyl salicylate (3 g., dried in a high vacuum at 90° for 5 hours), and *O*-triacetylxylosidyl bromide (10 g.) in dry benzene (50 c.c. at 33°), active silver oxide (7 g.) was added, and the mixture

vigorously agitated for ½ hour. After refluxing for 15 minutes, the solution was filtered from silver salts (wash with benzene), and the solvent removed in a vacuum at 30—35°. To remove the last traces of benzene, the almost colourless syrup was triturated with light petroleum and (after the solvent had been decanted) was dissolved in acetone (200 c.c.). The acetone was distilled under diminished pressure, and a solution of the residue in the same solvent (100 c.c.) was poured into water (400 c.c.). The crude product was triturated with water until it became semi-solid, and a solution of this material in warm methyl alcohol deposited the *hexa-acetate* in colourless needles (1·4 g.), m. p. 189°, $[\alpha]_{5461}^{20°}$ — 85·8° in chloroform (*c*, 0·46) (Found : C, 53·1; H, 5·4. $C_{31}H_{38}O_{18}$ requires C, 53·3; H, 5·4%). The compound is readily soluble in chloroform or acetone, and sparingly soluble in cold alcohol. It was rapidly hydrolysed by warm 10% alcoholic hydrochloric acid, and the resulting mixture, which smelt of methyl salicylate, gave positive orcinol and phloroglucinol reactions for a pentose.

A specimen of the hexa-acetate was prepared from the natural glucoside by acetylation with acetic anhydride and pyridine at room temperature for 24 hours. It crystallised from methyl alcohol in colourless needles, m. p. 189°, $[\alpha]_{5461}^{20°}$ — 85·67° in chloroform (*c*, 0·46) (Found : C, 53·3; H, 5·6%). A mixture of the natural and the synthetic compound gave an undepressed m. p.

Monotropitoside (VI).—Dry methyl alcohol (300 c.c.) containing the finely powdered hexa-acetate (2 g.) in suspension was saturated at 0° with ammonia. The glucoside quickly dissolved and the solution was kept at 0° for 6 hours. After removal of the ammonia and methyl alcohol in a vacuum, the gummy residue was dissolved in warm 90% aqueous acetone, and on slow evaporation of the solvent, monotropitoside gradually separated in clusters of slender needles. Recrystallised twice from 99% acetone, it formed colourless needles, m. p. 180° alone or mixed with a specimen of the natural compound (Found, in material dried at 110° in a high vacuum : C, 51·1; H, 6·0. Calc. for $C_{19}H_{26}O_{12}$: C, 51·1; H, 5·8%) [Bridel and Piccard, *Compt. rend.*, 1925, **180**, 1864, give m. p. 179·5° (bloc Maquenne)]. The properties of the synthetic glucoside were identical with those of the natural compound described by Bridel and his co-workers (*loc. cit.*). Examined under the microscope, the appearance and habit of crystallisation were identical.

O-*Triacetyl* β-*Xyloside of Methyl Salicylate.*—The vigorous interaction between methyl salicylate (1 g.) and *O*-triacetylxylosidyl bromide (2·4 g.) in the presence of quinoline (5 c.c.) and silver oxide (1·5 g.) was moderated by cooling under tap water. The reaction mixture, having been kept in a desiccator for 15 minutes, was ex-

tracted by grinding with cold 20% acetic acid (150 c.c.), and the extract rejected. The solid was dissolved in hot methyl alcohol, and the solution filtered to remove silver salts (charcoal). Addition of water (200 c.c.) precipitated the *triacetate*, which crystallised from 60% methyl alcohol in colourless, elongated, rhombic prisms (2·5 g.), m. p. 109—110°, $[\alpha]_{5461}^{21°}$ — 62·3 in acetone (*c*, 1·61) (Found : C, 55·8; H, 5·4. $C_{19}H_{22}O_{10}$ requires C, 55·6; H, 5·4%).

β-*Xyloside of Methyl Salicylate.*—Removal of the acetyl groups was effected by means of methyl-alcoholic ammonia at 0° during 6 hours. The *xyloside* (yield, 90% of the theoretical) separated from moist ethyl acetate in colourless prisms, m. p. 173°, $[\alpha]_{5461}^{21°}$ — 46·01° in water (*c*, 2·05) (Found, in air-dried material : C, 53·2; H, 5·5. $C_{13}H_{16}O_7,\frac{1}{2}H_2O$ requires C, 53·2; H, 5·8. Found, in specimen dried at 130° : C, 54·9; H, 5·7. $C_{13}H_{16}O_7$ requires C, 54·9; H, 5·6%). The compound is very soluble in alcohol and insoluble in benzene or chloroform. From concentrated aqueous solutions it separates in fine needles. The xyloside does not reduce ammoniacal silver nitrate solution, but it is decomposed by boiling Fehling's solution.

O-*Triacetyl Rhamnoside of Methyl Salicylate.*—The semi-solid obtained from methyl salicylate (7 g.), triacetylrhamnosidyl bromide (Fischer, Bergmann, and Rabe, *Ber.*, 1920, **53**, 2372) (10 g.), silver oxide (6 g.), and quinoline (10 c.c.) was extracted with chloroform, and the extract filtered from silver salts. After being washed with 0·5*N*-sulphuric acid to remove quinoline and then with water, the chloroform solution was dried over calcium chloride. Distillation of the solvent in a vacuum left a syrup which on keeping at 0° gradually solidified. Recrystallised from benzene–ligroin, the *triacetate* formed colourless, rod-like prisms, m. p. 109°, $[\alpha]_{5461}^{21°}$ — 11·36° in acetone (*c*, 2·29) (Found : C, 56·6; H, 5·8. $C_{20}H_{24}O_{10}$ requires C, 56·6; H, 5·7%).

Rhamnoside of Methyl Salicylate.—Deacetylation of the foregoing acetate (5 g.) was effected by means of methyl-alcoholic ammonia at 0° during 6 hours. The *trihydrate* of the *rhamnoside* separated from moist ethyl acetate in colourless slender needles (3·2 g.), m. p. 233° (decomp.), $[\alpha]_{5461}^{21°}$ + 22·64° in water (*c*, 1·23) (Found, in air-dried material : C, 47·7; H, 6·8. $C_{14}H_{18}O_7,3H_2O$ requires C, 47·7; H, 6·8. Found, in specimen dried at 130° : C, 56·4; H, 6·1. $C_{14}H_{18}O_7$ requires C, 56·4; H, 6·4%). The compound is readily soluble in water or warm alcohol and is quickly hydrolysed by warm 10% hydrochloric acid. It is unaffected by boiling Fehling's solution.

We have pleasure in acknowledging our indebtedness to Professor M. Bridel, who kindly sent us a specimen of monotropitoside isolated

from *Gaultheria procumbens*. Our thanks are due to the Chemical Society for grants in aid of this investigation, and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (R. B. W.).

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EAST LONDON COLLEGE. [*Received, June 18th*, 1931.]