SYNTHESIS OF THE α-PRIMEVEROSIDE OF METHYL SALICYLATE

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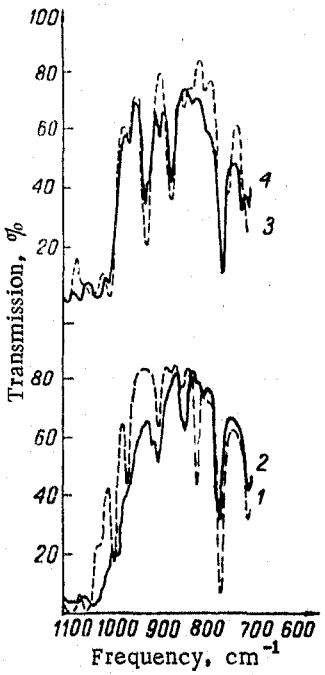
The synthesis of the β-primeveroside of methyl salicylate has been reported previously [1]. In order to compare the physiological properties of this substance, we have attempted the synthesis of its anomer. As on the previous occasion, a stepwise synthesis was chosen. First, the 2,3,4,6-tetraacetyl-α-glucoside of methyl salicylate was synthesized. There is no literature information on its preparation. Consequently, it was necessary to test the methods of synthesis of α-glucosides from acetobromoglucose using mercuric acetate [2] and pyridine [3], the decomposition of β-1-mesitoyl glucose [4], and the fusion of glucose pentaacetate with zinc chloride [5]. The latter method, as modified by Hau et al. [6], proved to be suitable for the synthesis of the 2,3,4,6-tetraacetyl-α-glucoside of methyl salicylate in 25% yield. By using catalytic amounts of perchloric acid, we increased the yield of this compound to 36% .

After the deacetylation of the tetraacetate of the glucoside with sodium methoxide in methanol [7], we isolated the α-glucoside of methyl salicylate, and obtained its triphenylmethyl derivative by condensation with triphenylchloromethane in pyridine [8]. The 2,3,4-tribenzoyl-6-O-(triphenylmethyl)-α-glucoside of methyl salicylate required for further synthesis was obtained by the benzoylation of the 6-O-(triphenylmethyl)-α-glucoside of methyl salicylate. The latter was condensed [9] with acetobromoxylose using our own modification of this method [1]. The α-primeveroside of methyl salicylate was obtained in 20% yield without preliminary isolation of the intermediate 2,3,4-tribenzoyl-2',3',4'-triacetyl-α-primeveroside of methyl salicylate.

Hydrolysis of this glycoside with dilute sulfuric acid gave xylose, glucose, and salicylic acid, as was also found in the hydrolysis of the β-primeveroside of methyl salicylate [10]. We calculated the possible specific rotation of the α-primeveroside of methyl salicylate by Klyne's method [11]. It proved to be 10° higher than the value found experimentally. The UV spectrum of the glycoside isolated agreed with the spectrum of the β-primeveroside of methyl salicylate [1]. A comparison of the IR spectrum of the glycoside with the analogous spectra of the anomeric glucosides and that of the β-primeveroside of methyl salicylate (Figure) in the range from 700 to 1000 cm^{-1} may serve as the final confirmation of its structure.

The β-glucoside and the β-primeveroside of methyl salicylate were found to have a medium-intensity absorption band at 896 cm^{-1}. In the α-primeveroside of methyl salicylate, this band was shifted to 891 cm^{-1}, and it was absent from the spectrum of the α-glucoside of methyl salicylate. An absorption band at 890 ± 7 cm^{-1} shows the β-configuration of the glycosidic bond in the glycosides, oligosides, and polysaccharides of glucose [12]. In this case, apparently, it corresponds also to the β-xylosidic bond in the primeverosides of methyl salicylate. The α-primeveroside and the α-glucoside of methyl salicylate give absorption bands at 918 and 921 cm^{-1} respectively which are characteristic for the α-anomers of glucose [12]. This band is absent from the spectra of the corresponding β-anomers. In addition, the α-primeveroside and the α-glucoside of methyl salicylate exhibit absorption bands at 868 and 866 cm^{-1} respectively which are not shown by the β-anomers.



IR spectra of the anomeric glucoside and primeverosides of methyl salicylate. 1) β-Glucoside; 2) β-primeveroside; 3) α-glucoside; 4) α-primeveroside.

Experimental

The O-tetraacetyl-α-glucoside of methyl salicylate.

With heating, 2.5 g of pure α-pentaacetyl-D-glucose was dissolved in methyl salicylate (3.8 g). Zinc chloride (0.6 g) in 2.5 ml of a mixture of acetic acid and acetic anhydride (95 : 5 by volume) containing 0.0005 g/ml of hydrochloric acid was added to the solution cooled to 40°. The reaction mixture was heated at a temperature of 131-132° for 1.5 hour under a vacuum of 25 mm Hg, and the acetic acid was distilled off continuously. The hot residue was extracted with dichloroethane (60 ml). The extract was washed twice with 2 N caustic soda solution (20-ml portions) and filtered, and was then washed again three times with water (20-ml portions). The dichloroethane extract was dried over sodium sulfate. The solvent was distilled off under reduced pressure, and the residue was dissolved in 6 ml of hot methanol. The solution was kept

for 2 hours at room temperature and was then left in the refrigerator overnight. The tetraacetate of the glucoside crystallized in clusters of rectangular prisms. The separated crystals were washed with three portions of cold methanol (1 ml each). The resulting product (1.1 g) had mp 132.5° (corr.). After recrystallization from methanol, the yield of pure glycoside tetraacetate was 0.95 g (31% of theoretical), mp 133° (corr.), $[\alpha]_D^{20}$ +168° (c 2; acetone).

Found, %: C 54.75, 54.82; H 5.54, 5.43. Calculated for $C_{22}H_{26}O_{12}$, %: C 54.77; H 5.43.

α-Glucoside of methyl salicylate.

A solution of 1 g of the O-tetraacetyl-α-glucoside of methyl salicylate in 5 ml of absolute methanol was treated with 0.2 ml of 0.1 N methanolic sodium methoxide. The mixture was heated on a steam bath for 10 min. The solvent was distilled off under reduced pressure. The residue was crystallized from 6 ml of water (active carbon), first at room temperature and then in a refrigerator at +3° (12 hours). The mass of crystals (white needles) was well pressed out on the filter, and was washed twice with cold water (0.5-ml portions). The air-dry product (0.54 g) had mp 144-145°. An additional amount of crystals (0.1 g) with the same melting point was isolated from the mother liquor by evaporating it to small bulk and treating it as described above. The substance (0.64 g) was dried in a vacuum desiccator over phosphorus pentoxide for 5 days. The loss in weight was 0.032 g (5%), which corresponds to one mole of water. The product so prepared (0.61 g) still contained 0.5 mole of water. It had mp 146°, $[\alpha]_D^{20}$ +180° ± 2 (c 1; water) calculated on the anhydrous glucoside.

Found, %: C 52.2, 51.94; H 6.05, 6.04. Calculated for $C_{14}H_{18}O_8\ 1/2\,H_2O$, %: C 52.08; H 5.92.

The α-glucoside of methyl salicylate lost water on drying in a vacuum pistol over phosphorus anhydride above 100°. The yield of dry glucoside was 0.59 g, 90% of theoretical, mp 142-143°. On dissolution in water, it partially hydrolyzed.

Found, %: C 53.21. 53.49; H 5.92, 6.07. Calculated for $C_{14}H_{18}O_8$, %: C 53.50; H 55.77.

6-O-(Triphenylmethyl)-α-glucoside of methyl salicylate.

The dry α-glucoside of methyl salicylate (3.5 g) was dissolved in absolute pyridine (12 ml), the solution was cooled to +10°, and 5 g of triphenylchloromethane was added. The mixture was stirred at room temperature until dissolution was complete. The turbid solution was allowed to stand at +3° (12 hours) and then at room temperature (2 days). The reaction mixture was diluted with water until it became turbid, allowed to stand for half an hour in the refrigerator, and poured into ice water. The mixture was left for 2 days in the refrigerator. The amorphous deposit was filtered off and was washed repeatedly with water. The air-dry product was dissolved in methanol (20 ml) and the solution was kept first at room temperature (12 hours) and then in a refrigerator (4 hours). The triphenyl carbinol which separated was filtered off and was washed with cold methanol (2 ml). The methanolic filtrate was treated with active carbon and the solvent was distilled off under reduced pressure. The residue was dissolved in ethyl acetate (8 ml). The boiling solution was treated with small portions of hot petroleum ether (70-100°) until crystallization was complete. The solution was kept at room temperature for 1 hour and was filtered. The residue on the filter was washed twice with 2-ml portions of a 1 : 1 mixture of ethyl acetate and petroleum ether. The weight of dried product was 4.4 g. A small amount of crystals was isolated from the mother liquor by evaporating it to small bulk and treating it as described above. The total yield was 4.6 g, 74% of theoretical, mp 176-177°. The product was sufficiently pure for further treatment. For analysis, the substance (0.2 g) was recrystallized from methanol (1 ml) and dried in a vacuum pistol at 105° over phosphorus pentoxide. Mp 188-189°, $[\alpha]_D^{20}$ +85° ± 2 (c 0.7; acetone).

Found, %: C 71.16, 71.18; H 5.86, 6.02. Calculated for $C_{33}H_{32}O_8$, %: C 71.2; H 5.78.

6-O-(Triphenylmethyl)-2,3,4-tribenzoyl-α-glucoside of methyl salicylate.

With continuous shaking, benzoyl chloride (7.4 g) was added to a solution of 8.3 g of the trityl ether in absolute pyridine (70 ml) cooled in an ice and salt mixture. The reaction mixture was left at room temperature for two days. With ice cooling, water was added to it until the solid matter had dissolved. The solution was poured into ice water and was left in a refrigerator (12 hr). The solid deposit was separated off and was washed repeatedly with water and then six times with methanol (20-ml portions). The residue on the filter was dissolved in 70 ml of ethyl acetate (active carbon) and was left at room temperature for 6 hr and then in a refrigerator for 4 hr. The crystalline mass was filtered off and was washed twice with cold ethyl acetate (7-ml portions). The weight of air-dry product was 10.9 g. An additional portion of crystals (1.2 g) was isolated from the mother liquor by evaporating it to small bulk (7 ml) and treating it as described above. The total yield was 12.1 g, 93% of theoretical. The substance was sufficiently pure for further use. It softened at 95° and melted at 99-101°, $[\alpha]_D^{20}$ +87° ± 2 (c 0.6; acetone).

α-Primeveroside of methyl salicylate.

With gentle heating, 2.95 g of the 2,3,4-tribenzoyl-6-O-(triphenylmethyl)-α-glucoside of methyl salicylate and 1.15 g of acetobromoxylose were dissolved in 9.5 ml of a mixture of nitromethane and benzene (2 : 1). Drierite

(1.5 g) was added to the solution and, after careful cooling to 0°C, silver perchlorate (0.705 g) in absolute nitromethane (7 ml). The reaction mixture was shaken vigorously for 7 min at the same temperature and was then filtered. The residue on the filter was washed twice with cold nitromethane (5-ml portions). The filtrate was treated rapidly with an ice-cold saturated solution of sodium bicarbonate (15 ml), and then three times with water (10-ml portions). The nitromethane extract was diluted with a small amount of chloroform and was dried over sodium sulfate. The solvent was distilled off under reduced pressure. The syrupy residue was dissolved in 15 ml of hot methanol. The solution was cooled to room temperature and treated with 3 ml of a 0.1 N solution of sodium methoxide in absolute methanol. The mixture was kept for 3 hr at room temperature and then for a day at +3°. The solvent was evaporated off under reduced pressure. The residue was extracted with water (20 ml) and ether (15 ml). The aqueous extract was again washed with ether (15 ml) and was treated with active carbon. The water was distilled off under reduced pressure at a bath temperature not exceeding 40°. The residue was treated twice with acetone (5-ml portions) at room temperature. The syrup that did not dissolve was extracted with boiling moist ethyl acetate containing 1% of methanol (1 *l*) in small portions. The solvent was distilled off under reduced pressure to small bulk. After cooling, the solid deposit was filtered off and was washed on the filter with 5 ml of acetone. The residue was crystallized from 90% acetone first at room temperature and then in the refrigerator. After recrystallization from the same solvent, 0.3 g of the glucoside, 20% of theoretical, was obtained. It had mp 142-143°, $[\alpha]_D^{20}$ +49° ± 2 (c 0.78; water), calculated on the anhydrous glycoside. By Klyne's method, a figure of $[\alpha]_D^{20}$ +59° was calculated. In the calculations, a specific rotation of $[\alpha]_D^{20}$ +118° was taken for the α-glucoside of methyl salicylate and $[\alpha]_D^{20}$ −65.5° for methyl β-xyloside [13]. 0.2177 g of the glycoside was dried in vacuum at 108° for 18 hr. The loss in weight was 0.009 g, which corresponds to 4% of the weight of the α-primeveroside of methyl salicylate containing 2 moles of water. The substance prepared in this way still contained one mole of water.

Found, %: C 49.44, 49.41; H 5.83, 6.07. Calculated for $C_{19}H_{26}O_{12} \cdot H_2O$, %: C 49.13; H 6.07.

Acid hydrolysis of the α-primeveroside of methyl salicylate.

A solution of 0.016 g of the α-primeveroside of methyl salicylate in 2 ml of 8% sulfuric acid was heated on a steam bath for 1.5 hr, after which the odor of methyl salicylate was perceived. The hydrolyzate was neutralized with 3% aqueous barium hydroxide and the barium ion was removed with carbon dioxide. The solution was filtered and was concentrated to small bulk under reduced pressure. The mixture was chromatographed on plates (12 × 12) covered with a layer of silica gel (type KSK) using butanol – acetic acid – water (4 : 1 : 5) system. The chromatogram showed the presence of xylose, glucose, and salicylic acid. On treatment with 2% perchloric acid (15°, 14 hr), the hydrolyzate was found to contain an unhydrolyzed fraction of the α-primeveroside of methyl salicylate, xylose, the α-glucoside of methyl salicylate, and salicylic acid. The xylose and glucose and the α-primeveroside and α-glucoside of methyl salicylate were detected with α-naphthol [14]. The salicylic acid spot was detected with ultraviolet light.

The IR spectra of the glucosides were recorded and interpreted by I. K. Baeva on a DS-301 instrument from the firm "Niphon Bunko" (in potassium bromide tablets – 4 mg of substance to 800 mg of potassium bromide).

Summary

1. An anomer of a natural glucoside – monotropitoside – has been synthesized for the first time.
2. This method is suitable for the synthesis of anomeric oligosides of phenols.

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