UDC 547.918

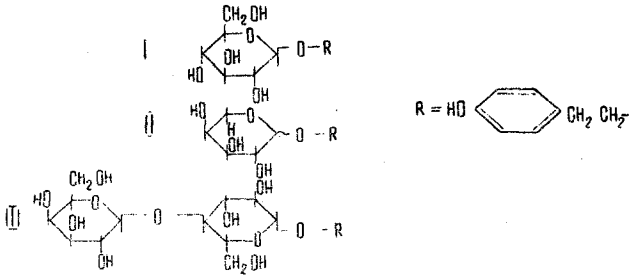
SYNTHESIS OF GLYCOSIDES OF 2-(p-HYDROXYPHENYL)ETHANOL(TYROSOL)

A. T. Troshchenko and A. M. Yuodvirshis

Khimiya Prirodnykh Soedinenii, Vol. 5, No. 4, pp. 256-260, 1969

One of us has previously reported the isolation of a new glycoside from the roots of Rhodiola roseum L. and Rhodiola quadrifida (Pall. Fish. et Mey) for which the structure 2-(p-hydroxypheny)ethyl β-D-glycopyranoside has been established [1]. In view of the physiological activity of this compound, we have attempted to synthesize it.

There is no literature information on the synthesis of glycosides of 2-(p-hydroxyphenyl)ethanol. We have succeeded in obtaining some glycosides with respect to the alcoholic hydroxyl of this compound. Synthesis was effected by condensing 2-(p-hydroxyphenyl)ethanol with the corresponding acetylglycosyl bromide in ether or in ether–dichloroethane in the presence of silver carbonate—a modification of Helferich's method for the synthesis of isosalicin [2]. After chromatographic purification of the crude glycoside acetates on a column of silica gel and their subsequent deacetylation with sodium methoxide in methanol [3], 2-(p-hydroxyphenyl)-ethyl β-D-glycopyranoside (I) was obtained via its crystalline acetate and the (α + β)-L-arabinopyranoside (II) and the β-D-lactoside (III) via their syrupy acetates. In aqueous solutions, all the glycosides were characterized by a blue coloration with ferric chloride, which shows the presence of the free phenolic hydroxyl of the aglycone.



When the glycosides were methylated with methyl iodide in dimethylformamide and the methylated product was then hydrolyzed with hydrochloric acid in methanol [1], 2-(p-methoxyphenyl)ethanol and the corresponding partially methylated monosaccharides for substances I and III were identified. We were able to show the configuration of the glycosidic bond on the basis of the good agreement of the specific rotations calculated according to Klyne [4] and those found experimentally, and also from the agreement of the IR spectra in which both glycosides showed absorption bands at 900 cm^{-1}, characteristic for a β-glycosidic link [5], and the absence of absorption bands at 844 ± 8 cm^{-1}, characteristic for an α-glycosidic link; the configuration of the glycosidic bond was not confirmed spectroscopically for substance II. The magnitude of the specific rotation of II, calculated according to Klyne, did not agree with that found experimentally, occupying a position intermediate between the calculated values for the α- and β-anomers of this glycoside. The structures of the glycosides were confirmed definitely by the results of a direct comparison of I with natural 2-(p-hydroxyphenyl)ethyl β-D-glucopyranoside, with which it was completely identical in respect of the IR spectra and the melting point of a mixture.

To obtain a glycoside at the phenolic hydroxyl of 2-(p-hydroxyphenyl)ethanol, the latter was condensed with tetra-O-benzoyl-α-D-glucopyranosyl bromide in pyridine in the presence of silver oxide [6]. Instead of the expected benzoate of p-(2-hydroxyethyl)phenyl β-D-glucopyranoside a product was isolated which gave no characteristic reactions for either an alcoholic or a phenolic hydroxyl group. From its elementary analysis and molecular weight, this compound was probably the benzoate of the bis-β-D-glucoside of 2-(p-hydroxyphenyl)ethanol. When it was treated with 10% caustic potash in methanol, debenzoylation took place with simultaneous hydrolysis of the glucoside. The reaction mixture yielded potassium benzoate and 2-(p-hydroxyphenyl)ethanol. The fate of the sugar residue remains obscure.

Experimental

The melting points were determined on a "Boëtius" micro heating stage and have been corrected. The angles of rotation were measured (the glycosides in water and the acetates or benzoates in chloroform) on a "Karl Zeiss" polarimeter. The IR spectra were recorded on a UR-10 instrument (4 mg of the substance with 800 mg of potassium bromide in tablets). Chromatography was carried out with type KSK silica gel (100–200 mesh for columns and 200–250 mesh for plates). The chromotographs were monitored on plates (9 × 12 cm) with a thin fixed layer of silica gel in the following systems: 1) benzene–ether (9:1), 2) benzene–ether–methanol (13:4:1), 3) benzene–methanol–ether

(7:2:1), and 4) butanol–acetic acid–water (4:1:1). The chromatograms were revealed with antimony pentachloride in chloroform and a 1% solution of ferric chloride in water. Analytical samples were dried in a vacuum pistol over phosphorus pentoxide at 83° C.

The tyrosol was synthesized from 2-(p-aminophenyl)ethanol [7] as described by Ferber [8]. Mp 92–93° C (from chloroform).

Acetate of 2-(p-hydroxyphenyl)ethyl β-D-glucopyranoside. A mixture of 1.33 g of 2-(p-hydroxyphenyl)ethanol (tyrosol), 2 g of silver carbonate, and 4 g of Drierite in absolute ether (20 ml) was stirred at room temperature for 0.5 hr. Then a solution of 4 g of tetra-O-acetyl-α-D-glucopyranosyl bromide [9] in 40 ml of ether was slowly added dropwise over 1.5 hr and the mixture was stirred at room temperature for 3 hr. The ethereal solution was filtered from the silver salt, washed with water (3 × 50 ml), and dried over calcium chloride, and the solvent was distilled off under reduced pressure. The residue was taken up in benzene (40 ml) and deposited on a column of silica gel (30 g) which was eluted with benzene–ether (9:1, 700 ml), 100-ml fractions being collected. The separation of the fractions was checked in system 1. The fractions collected were combined and distilled in vacuum. The residue was crystallized from 50% ethanol, giving 2.3 g of the crystalline glucoside acetate (50% of theory) with mp 112-117° C (needles), $[\alpha]_D^{20}$ −18 ± 2° (c 2.09). The specific rotation calculated according to Klyne is $[\alpha]_D^{20}$ −12.3°. For methyl β-D-glucopyranoside, $[\alpha]_D^{20}$ −18.7° (chloroform [10]).

Found, %: C 56.14, 56.43; H 6.13, 6.08. Calculated for $C_{22}H_{28}O_{11}$, %: C 56.40; H 6.35.

2-(p-Hydroxyphenyl)ethyl β-D-glucopyranoside* (I). The glucoside acetate (6.5 g) in methanol (20 ml) was deacetylated with 0.1 N sodium methoxide in methanol (10 ml) at 20° C for 24 hr. The reaction mixture was neutralized with acetic acid (0.3 ml), diluted with benzene (30 ml), and filtered through a layer of silica gel (15 g). The solvent was distilled off under reduced pressure. The residue was dissolved in methanol (50 ml) and benzene (100 ml) was added. The mixture of solvents was distilled off until crystallization began (in the form of bundles of needles) and the residue was left at 20° C for 12 hr. The amount of substance separating was 3.5 g. After recrystallization from the same solvent, the pure glycoside (3.1 g) was obtained with mp 160–161° C and $[\alpha]_D^{20}$ −26 ± 2° (c 0.35). The specific rotation according to Klyne is $[\alpha]_D$ −22.1°. For methyl β-D-glucopyranoside $[\alpha]_D^{20}$ −34.2° (water) [11]. Literature data for tyrosol glucoside: mp 164–165° C, $[\alpha]_D$ −32.38° (water) [1]. The natural and synthetic glycosides had similar IR spectra and the melting point of the mixture was 161–163° C.

Found, %: C 54.95, 55.02; H 6.67, 6.63. Calculated for $C_{14}H_{20}O_7 \cdot 0.5(CH_3OH)$, %: C 55.05; H 7.01.

2-(p-Hydroxyphenyl)ethyl β-D-lactoside (III). A mixture of 1 g of tyrosol and 6 g of Drierite in 40 ml of a mixture of ether and dichloroethane (1:1) was stirred at room temperature for 0.5 hr. Hepta-O-acetyl-α-D-lactosyl bromide (4 g) [9] in 40 ml of ether–dichloroethane (1:1) was slowly added dropwise, and stirring was continued at 20° C for 5 hr. The reaction mixture was filtered and the filtrate was washed with water (3 × 150 ml) and dried over calcium chloride. The solvent was distilled off under reduced pressure. The residue was taken up in benzene (50 ml) and transferred to a column of silica gel (50 g). The column was eluted with 300 ml of 9:1 benzene–ether and 500 ml of 1:1 benzene–ether, 100-ml fractions being collected. The separation of the fractions was monitored in system 2. The solvent was distilled off from the fractions collected at reduced pressure. The residue was dissolved in methanol (10 ml) and deacetylated with 0.1 N sodium methoxide in methanol (10 ml) on the steam bath for 30 min. After treatment as described above, 0.77 g of an amorphous hygroscopic powder (30% of theory) was obtained with $[\alpha]_D^{20}$ +11 ± 3° (c 1.17). The specific rotation calculated according to Klyne was $[\alpha]_D$ +5°. For methyl β-D-lactoside $[\alpha]_D^{20}$ +5.6° [12].

Found, %: C 50.43, 50.51; H 6.66, 6.67. Calculated for $C_{20}H_{30}O_{12} \cdot CH_3OH$, %: C 51.00; H 6.85.

2-(p-Hydroxyphenyl)ethyl (α+β)-D-arabinopyranoside (II). This was obtained in a similar manner to the preceding experiment from 1 g of tyrosol, 2 g of acetyl-β-L-arabinopyranosyl bromide [9] and 1.3 g of silver carbonate. The yield of amorphous powder (from a mixture of ethanol and benzene) was 88 g (39% of theory), $[\alpha]_D^{20}$ +80° ± 2° (c 1.04). The specific rotation was determined according to Klyne; for the α-anomer of this arabinoside $[\alpha]_D$ +10° and for the β-anomer $[\alpha]_D$ +140°. In the calculations we took $[\alpha]_D^{20}$ +17.3° for methyl α-L-arabinpyranoside [13] and $[\alpha]_D^{20}$ +245.6° for its β-anomer.

Found, %: C 56.29, 56.40; H 6.98, 6.91. Calculated for $C_{13}H_{18}O_6 \cdot 0.5(CH_3OH)$, %: C 56.63; H 7.03.

Methylation and subsequent hydrolysis of 2-(p-hydroxyphenyl)ethyl β-D-glucopyranoside. A mixture of 0.5 g of the glucoside, 1.6 g of ground barium oxide, and 2.4 ml of methyl iodide in dimethylformamide (1.2 ml) was stirred at 30° C for 5 hr. The reaction mixture was filtered and was treated again with 1.2 ml of methyl iodide and 1 g of silver oxide at 20° C for 24 hr. A chromatographic check was carried out in systems 1 and 2. The yellow solution was filtered and poured into chloroform (100 ml). The extract was washed with water (30 × 50 ml) and dried over sodium

*Preliminary experiments on the synthesis of tyrosol β-glucoside were carried out by apprentice G. A. Kutikova.

sulfate, and the solvent was distilled off under reduced pressure. The residue (a bright yellow oil, 0.45 g) was hydrolyzed with a mixture of methanol (10 ml) and 2 N HCl (10 ml) on the steam bath (2 hr). The methanol was distilled off and the hydrolysis was repeated. The methanolic solution was neutralized with sodium bicarbonate to a weakly alkaline reaction and was passed through a column of KU-2 cation-exchange resin (H^+ form).

The eluates were distilled and the residue was taken up in benzene (40 ml) and transferred to a column of silica gel (50 g). The column was eluted with benzene–ether (9:1, 400 ml) and then with benzene–methanol (8:2, 500 ml), 100-ml fractions being collected. The separation of the fractions was monitored in systems 2 and 3.

The elution with benzene–ether yielded a syrupy substance which, by its chromatographic behavior in systems 1 and 2 and its IR spectrum was identified as 2-(p-methoxyphenyl)ethanol. Yield 0.2 g. The phenylurethane of this substance had mp 127–128° C (from methanol). Literature data: mp 127–128° C [14]. When the column was eluted with a mixture of benzene and methanol, a substance with mp 90–92° C (from a mixture of ether and petroleum ether, bp 70–100° C) was obtained. It was identical with an authentic sample of 2,3,4,6-tetra-O-methyl-D-glucose according to a mixed melting point, its IR spectrum, and its chromatographic behavior in system 4. The chromatogram was revealed with α-naphthol [15].

2-(p-Hydroxyphenyl)ethyl(α + β)-L-arabinopyranoside and the β-D-lactoside were methylated and subsequently hydrolyzed similarly. After working up as in the preceding experiment, in the first case 2-(p-methoxyphenyl)ethanol and a syrupy substance with $[\alpha]_D^{20}$ +122 ± 2° (c 0.7; water) identical with an authentic sample of 2,3,4-tri-O-methyl-L-arabinose by its specific rotation, IR spectrum, and chromatographic behavior in system 4, were obtained.

In the case of the lactoside, 2-(p-methoxyphenyl)ethanol, 2,3,4,6-tetra-O-methyl-D-galactose (syrup) with $[\alpha]_D^{21}$ +118 ± 2° (c 0.62; water), and 2,3,6-tri-O-methyl-D-glucose with mp 118–121° C, $[\alpha]_D^{20}$ +67 ± 2° (c 0.54; water) were isolated and shown to be identical with authentic samples. In this experiment, all the angles of rotation of the partially methylated monosaccharides were measured 12 hr after the preparation of the solutions.

Product of the condensation of 2-(p-hydroxyphenyl)ethanol with tetra-O-benzoyl-α-D-glucopyranosyl bromide. A mixture of 0.27 g of tyrosol, 3.2 g of benzoyl-α-D-glucopyranosyl bromide [16], and 1 g of active silver oxide in pyridine (8 ml) was stirred at 20° C for 6 hr. The reaction mixture was diluted with acetic acid (25 ml) and poured into water (500 ml). The solid precipitate that deposited was washed with water and dried in the air. Then it was dissolved in benzene (40 ml) and transferred to a column of silica gel (50 g) which was eluted with benzene–ether (9:1, 500 ml). The separation of the fractions was monitored in system 1. The solvent was distilled off from the fractions collected and the residue was crystallized from methanol (bundles of needles); 1.9 g of a substance with mp 92–94° C $[\alpha]_D^{20}$ −84 ± 2° (c 2.12), was obtained.

Found, %: C 70.96, 71.04; H 4.51, 4.48. Calculated for $C_{76}H_{62}O_{20}$, %: C 70.47; H 4.71.

Alkaline saponification of the condensation product. Five grams of the condensation product from the preceding experiment in methylene chloride (20 ml) was treated with 10% caustic potash in methanol (10 ml) at 20° C for 12 hr. The potassium benzoate that deposited was filtered off and the filtrate was passed through a column of KU-2 cation-exchanger (H^+ form). The column was washed with methanol. The eluates were distilled under reduced pressure. The residue was taken up in benzene (60 ml) and transferred to a column of silica gel (80 g), which was washed with benzene–ether (8:2), 100-ml fractions being collected. The separation of the fractions was monitored in systems 2 and 3. After the solvent had been distilled off from the fractions collected, 0.45 g of tyrosol was obtained with mp 89–92° C (from chloroform). Its dibenzoyl derivative had mp 109–110° C. Literature data: mp 111° C [17]. The molecular weight of the condensation product, from the yield of tyrosol in this experiment, was 1534 ± 20%. Calculated for $C_{76}H_{62}O_{20}$: mol. wt. 1295.33.

Conclusions

1. 2-(p-Hydroxyphenyl)ethyl β-D-glucopyranoside, (α±β)-L-arabinopyranoside, and β-D-lactoside have been synthesized for the first time.

2. The glycosidation reaction has been studied with respect to the phenolic and alcoholic hydroxyls of 2-(p-hydroxyphenyl)ethanol.

REFERENCES

1. A. T. Troshchenko and G. A. Kutikova, KhPS [Chemistry of Natural Compounds], 3, 244, 1967.
2. B. Helferich and H. Lisen, Ann., 570, 148, 1950.
3. G. Zemplen and E. Pascu, Ber., 62, 1613, 1929.
4. W. Klyne, "Optical rotation," in: A. F. Braude and F. C. Nachod, Determination of Organic Structures by Physical Methods, Acad. Press., NY, 73, 1955.
5. S. Barker et al., J. Chem. Soc., 3468, 1954.
6. A. M. Yudvirshis and A. T. Troshchenko, KhPS [Chemistry of Natural Compounds], 2, 405, 1966.

7. H. Woodburn and C. Stuntz, J. Am. Chem. Soc., 72, 1361, 1950.
8. E. Ferber, Ber., 62, 189, 1929.
9. M. Barczai-Martos and F. Korosy, Nature, 165, 369, 1950.
10. T. Harris, E. Hirst, and C. Wood, J. Chem. Soc., 2108, 1932.
11. W. Koenigs and E. Knorr, Ber., 34, 957, 1901.
12. R. Ditmar, Ber., 35, 1951, 1902.
13. C. S. Hudson, J. Am. Chem. Soc., 47, 265, 1925.
14. R. Fuchs and C. A. Van der Werf, J. Am. Chem. Soc., 76, 1631, 1954.
15. N. Albon and D. Gross, Analyst, 77, 410, 1952.
16. R. Ness, H. Fletcher, and C. S. Hudson, J. Am. Chem. Soc., 72, 2200, 1950.
17. F. Ehrlih, Ber., 44, 139, 1911.

11 August 1967

Novosibirsk Institute or Organic Chemistry, Siberian Division AS USSR

Lensovet Leningrad Technological Institute