TRITERPENE GLYCOSIDES OF Astragalus AND THEIR GENINS.

XI. CYCLOSIVERSIOSIDE G – A TRIGLYCOSIDE OF Astragalus sieversianus

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The new glycoside of the cycloartane series has been isolated from the roots of Astragalus sieversianus Pall. and has been shown to be cyclosiversigenin 3-O-[O-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranoside]-6-O-β-D-xylopyranoside.

In the present paper we consider the structure of cyclosiversioside G. (substance G) which we isolated from the roots of Astragalus sieversianus Pall. [1-3].

It was established by the GLC method [4] that cyclosiversioside G (I) contained D-xylose and L-rhamnose residues in a ratio of 2:1. In the products of the Smith degradation of the trioside (I) [5], cyclosiversigenin (II) [6] was detected, which showed that the glycoside under investigation belonged to the cycloartane series.

The Hakomori methylation [7] of glycoside (I) gave the deca-O-methyl ether (III), the acid hydrolysis of which led to 2,3,4-tri-O-methyl-D-xylopyranose, 2,3,4-tri-O-methyl-L-rhamnopyranose, and 3,4-di-O-methyl-D-xylopyranose. In addition, from products we isolated the dimethyl ether (V), shown to be identical with the authentic 16,25-dimethyl ether of siversigenin [1].

Thus, the structure of the derivatives obtained in the acid cleavage of the deca-O-methyl ether (III) shows that cyclosiversigenin G(I) is a bisdesmosidic glycoside in which the sugar residues are attached to cyclosiversigenin at the C-3 and C-6 hydroxy groups.

Hydrolysis of the glycoside (I) in 0.25% sulfuric acid yielded a diglycoside (IV), identical with the 3,6-di-O-β-D-xylopyranoside of cyclosiversigenin – cyclosiversioside E (IV) [1]. Consequently, in the glycoside (I), the disaccharide moiety contains D-xylose and L-rhamnose residues and the monosaccharide moiety D-xylose. The formation of 3,4-di-O-methyl-D-xylopyranose on the acid cleavage of the methyl ether (III) shows that the L-rhamnose is attached to the hydroxy group on the second carbon atom of one of the D-xylose molecules.

The position of the bioside residue in the genin was established on the basis of the results of a comparative analysis of the chemical shifts of the signals of the anomeric carbon atoms in the ^{13}C NMR spectra of cyclosiverioside E (IV) and the triglycoside (I) (see Scheme on following page).

It has been established previously [3] that in the ^{13}C NMR spectrum of compound (IV) the signals of the C-1' and C-1'' anomeric carbon atoms of the two xylopyranose residues appears at 107.3 and 105.3 ppm, respectively.

In the ^{13}C NMR spectrum of the triglycoside (I) under investigation, one of the three anomeric carbon atoms resonated at 101.6 ppm. From the value of its chemical shift, this signal was assigned to C-1''' of the L-rhamnose residue [8, 9].

The chemical shifts of the C-1' and C-1'' anomeric carbon atoms of the two xylopyranose residues of compound (I) are extremely close and in the spectrum a single common signal at 105.4 ppm corresponds to

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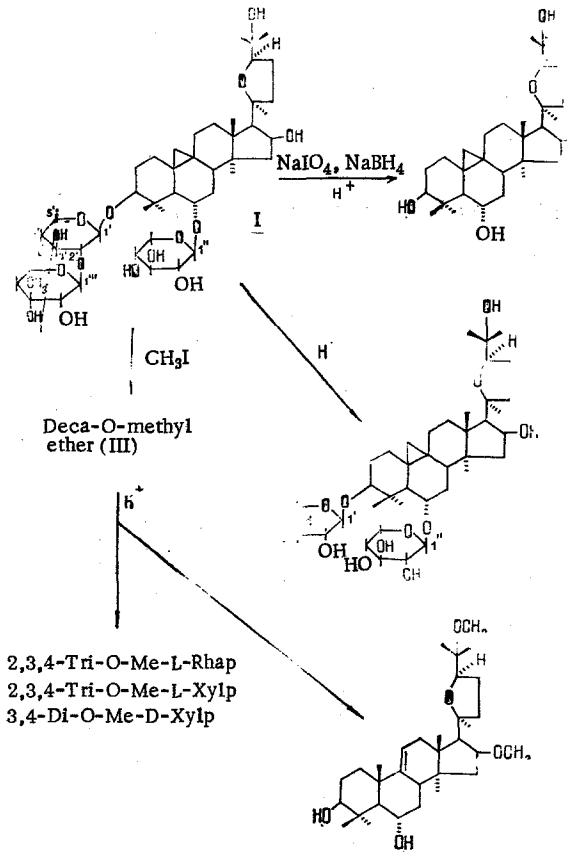

them. Consequently, in the spectrum of glycoside (I) the signal corresponding to the C-1' carbon atom has undergone a diamagnetic shift by 1.9 ppm ($\delta_{IV(C-1')} = 107.3$ ppm; $\delta_{I(C-1')} = 105.4$ ppm, $\Delta\delta = 1.9$ ppm).

The upfield shift of the C-1' anomeric carbon atom [8] shows that the molecule of L-rhamnose is attached to the C-2' atom of the D-xylose residue which, in its turn, is attached to the hydroxy group at C-3 of the aglycone.

A calculation of molecular rotation differences [10] between the triglycoside (I) and the diglycoside (IV) showed that the L-rhamnose residue has the α configuration of the glycosidic center. Thus, cyclosiversioside G (I) is cyclosiversigenin 3-O-[O-α-L-rhamnopyranosyl-(1 → 2)-β-D- xylopyranosyl]- 6-O-β-D-xylopyranoside.

EXPERIMENTAL

For general observations and methods of isolation, see [1, 6]. PMR spectra were taken in C_5D_5N on a JMN-4H-100/100 MHz instrument (δ, 0 − HMDS), and ^{13}C NMR spectra on a Varian CFT-20 instrument in C_5D_5N (0 − TMS).

The sugars were chromatographed in the form of the trimethylsilyl ethers of their methyl glycosides [4] on a column (3.7 m × 3 mm) containing Chromaton N-AW impregnated with 5% of the silicone phase SE-30. The temperature of the thermostat was 190°C and the carrier gas here and below was helium, at a rate of flow of 45 ml/min.

The methyl ethers of the sugars were identified in the form of their methyl glycosides [11]. The chromatography of the latter was carried out on a column (1.2 m × 3 mm) containing Celite impregnated with 20% of poly-(butane-1,4-diyl succinate) (phase 1) at a thermostat temperature of 180°C and on a column (1.2 m × 3 mm) containing Chromaton N-AW impregnated with 10% of poly(phenyl ether) 5 F-4 E (phase 2) at a thermostat temperature of 190°C. The retention times (T_{rel}) of the methylated methyl glycosides were calculated with respect to the retention time of methyl 2,3,4,6-tetra-O-methyl-β-D-glucopyranoside.

Cyclosiversioside G (I, substance G) [1], $C_{46}H_{76}O_{17}$, mp 222-224°C (from methanol), $[\alpha]_D^{20}$ −5.42 + 2° (c 1.34 methanol); ν_{max}^{KBr}, cm^{-1}: 3350-3430 (OH). PMR spectrum (δ, ppm): 0.49 (H at C-19, d, G = 4.0 Hz), 1.04-1.49 ($CH_3 \times 8$). By the GLC method [4], D-xylose and L-rhamnose in a ratio of 2.19 : 1.00 were detected in cyclosiversioside G.

Cyclosiversigenin (II) from (I). A solution of 150 g of cyclosiversioside G (I) in 150 ml of aqueous methanol (1:1) was treated with 150 mg of sodium periodate, and the reaction mixture was stirred at room temperature for 20 h. Then the oxidant that had not reacted was decomposed with ethylene glycol, the methanol was evaporated off, and the residue was treated with 50 ml of water. The reaction products were extracted with chloroform. The chloroform was distilled off to dryness, and the residue was heated with 200 ml of aqueous methanol (1:1) and 300 mg of sodium tetrahydroborate at 80°C for 7 h. After cooling, the reaction mixture was acidified to pH 2.0 and was then left at room temperature for 80 h. The hydrolysis products were extracted with chloroform, the solvent was evaporated off, and the residue was chromatographed on a column of silica gel. Elution with ethyl acetate gave 35 mg of cyclosiversigenin (II) with mp 239-241°C (from methanol), $[\alpha]_D^{20}$ + 49.5 ± 2° (c 1.58 methanol) [6].

The Deca-O-methyl Ether of Cyclosiversioside G (III) from (I). To a solution of 1.5 g of cyclosiversioside G (I) in 300 ml of dry dimethyl sulfoxide was added 1.5 g of sodium hydride in small portions. After 30 min, 20 ml of methyl iodide was added dropwise, and the reaction mixture was left for 5 h. All the operations were carried out at room temperature and with stirring. The reaction products were poured into 300 ml of sodium hyposulfite solution and exhaustively extracted with chloroform. The residue obtained after the evaporation of the chloroform was chromatographed on a column of silica gel with the elution first by benzene and then with benzene–ethyl acetate (1:1). This gave 300 mg of the deca-O-methyl ether of cyclosiversioside G (III), $C_{56}H_{96}O_{17}$, mp 180-182°C (from methanol), $[\alpha]_D^{20}$ +22.5 ± 2° (c 0.72 chloroform). ν_{max}^{KBr}, cm^{-1}; 3050 (>CH_2 of a cyclopropane ring); there was no absorption in the region of hydroxy groups. PMR spectrum (δ, ppm): 0.47 (H at C-19, d; J = 4.0 Hz); 0.98-1.49 (CH_3× 8); 2.97-3.58 (OCH_3× 10, s); 4.46, 4.58 (2 H, anomeric protons of D-xylose, d; J = 7.5 Hz); 5.57 (H, anomeric proton of L-rhamnose, broadened singlet). M^+ 1040.

Acid Hydrolysis of the Deca-O-methyl Ether (III). A solution of 300 mg of the methyl ether (III) in 50 ml of methanol was treated with 50 ml of 15% methanolic sulfuric acid, and the reaction mixture was heated in the boiling water bath for 1 h. After cooling, 100 ml of water was added, the methanol was distilled off and the precipitate that deposited was filtered off. Chromatography of the residue on a column of silica gel with elution by benzene–acetone (3:1) gave 16 mg of compound (V) with mp 222-224°C (from methanol) $[\alpha]_D^{20}$ +123.7 ±2° (c 0.56; chloroform), identified by comparison with an authentic sample as the 16,25-dimethyl ether of siversigenin [1].

The aqueous solution was heated on the boiling water bath for 7 h. After cooling, it was neutralized with barium acetate, and the precipitate was separated off and the filtrate was evaporated. The residue was chromatographed on a column of silica gel with elution by the benzene–acetone (2:1) system. This led to the isolation of 2,3,4-tri-O-methyl-L-rhamnopyranose (GLC: T_{rel} on phase 1, 0.43; on phase 2, 0.45); 2,3,4-tri-O-methyl-D-xylopyranose (GLC; T_{rel} on phase 1, 0.44 and 0.60; on phase 2, 0.42 and 0.51); and 3,4-di-O-methyl-D-xylopyranose (GLC: T_{rel} on phase 1, 1.31 and 1.59; on phase 2, 0.70) [11].

Partial Hydrolysis of Cyclosiversioside G (III) to the Diglycoside (IV). A solution of 300 mg of the triglycoside (I) in 200 ml of methanol was treated with 200 ml of a 0.5% aqueous solution of sulfuric acid and the mixture was heated on the boiling water bath for 4 h. After cooling, 200 ml of water was added to the reaction mixture and the excess of methanol was distilled off. The reaction products were extracted with butanol, then the solvent was distilled off, and the residue was chromatographed on a column of silica gel. Elution with chloroform–methanol–water (70:22.5:4) yielded 55 mg of compound (IV) with mp 256-258°C (from methanol), $[\alpha]_D^{20}$ +30.5 ± 2° (c 0.52; methanol), identified by comparison with an authentic sample as the 3,6,O-β-D-xylopyranoside of cyclosiversigenin [1].

SUMMARY

From the roots of the plant Astragalus sieversianus Pall. has been isolated a new glycoside of the cycloartane series, which is cyclosiversigenin 3-O-[-α-L-rhamnopyranosyl-(1 → 2)-β-D-xylopyranosyl]-6-O-β-D-xylopyranoside.

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REGIO- AND STEREOSELECTIVE GLYCOSYLATION OF 20(S),24(R)-EPOXYDAMMARANE-3,12β,25-TRIOLS WITH CHOLESTERYL (α-D-GLUCOSE ORTHOACETATE). III.

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The glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols under the conditions of the previous formation of an ion pair with a Lewis acid and subsequent treatment with cholesteryl (α-D-glucose orthoacetate) leads to the selective formation with high yields of the corresponding 12-monoglucosides having the trans configuration of the glucosidic bond. The regioselectivity of the direct glycosylation of 20(S),24(R)-epoxydammarane-3,12β,25-triols by orthoesters is determined by the influence of intramolecular hydrogen bonds in the initial triols. Details of the PMR and ^{13}C NMR spectra of the new compounds obtained are given.

The development of methods for both the selective and the exhaustive glycosylation of tetracyclic dammarane polyols of type (I) related to the panaxgenins (Scheme 1) opens up possibilities for obtaining various analogs of ginseng glycosides [1]. We have previously studied the glycosylation of the title alcohols by the orthoester method via the intermediate formation of orthoesters and their subsequent isomerization into the desired glycosides [2].

The isomerization of the 3-monoorthoesters obtained from (I) and (II) led to the anomalous selective formation of the 12-monoglucosides (III) and (V), in view of which the hypothesis was expressed that the isomerization studied takes place in actual fact as the direct intermolecular glycosylation of one molecule of a 3-monoorthoester by another. To confirm this hypothesis, we have investigated the direct glycosylation of tetracyclic dammarane polyols with a number of orthoesters. The nature of the direct glycosylation of the triols (I) and (II) with the orthoesters (XII) and (XIII) depends on the nature of the glycosylating agent and also, to an even greater degree, on the experimental conditions of glycosylation, which is probably connected with the presence of a strong intramolecular hydrogen bond (intra-HB) between the proton of the 12β-OH group and the oxygen atom of the tetrahydrofuran (THF) ring in each of the triols (I) and (II).

In the IR spectra of (I) and (II) in $CHCl_3$ solution (c 37.0 and 34.0 mg/ml, respectively), broad bands of hydroxyl absorption are observed at 3392 and 3401 cm^{-1}, respectively, which did not change their position and intensity when the solutions were diluted 25-fold. In the ^1H NMR spectra ($CDCl_3$) of (I) and (II) broad signals of unit intensity are observed at 5.62 and 5.59 ppm, respectively, which are sensitive to the temperature conditions of recording the spectra and to deuterium exchange. The intra-HBs mentioned may promote the formation of a bipolar ion of type (XIV) or (XV) on the interaction of (I) or (II) with $HgBr_2$ (scheme 2).

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