SYNTHESIS OF TRITERPENE GLYCOSIDES

II. Synthesis of Acyl Glycosides of 18β- and 18α-Glycyrrhetic Acids

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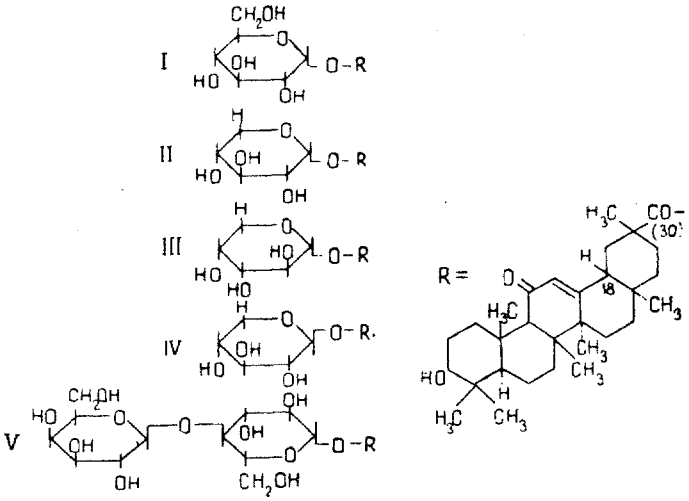
We have previously [1] reported the synthesis of acyl glycosides of oleanolic and ursolic acids, showing the normal course of the Koenigs-Knorre reaction. Using the same method we have attempted to prepare an acyl β-D-glucopyranoside of 18β-glycyrrhetic acid via its acetate. As a result, we obtained a mixture of the anomeric acetates of the acyl-D-glucopyranosides. However, when the acetate of α-D-glucopyranosyl bromide was replaced by the corresponding benzoate the main product was the acyl tetra-O-benzoyl-α-D-glucopyranoside of 18β-glycyrrhetic acid.

The shift of the reaction in the direction of the α-anomer can be explained by the comparative stability of the acylated acyl α-D-glucopyranoside of 18β-glycyrrhetic acid under the reaction conditions and the high stability of the benzoylated glucopyranosyl cation [2]. A similar behavior with respect to 18β-glycyrrhetic acid is exhibited by tri-O-benzoyl-α-D-xylopyranosyl bromide. The condensation of D- and L-tri-O-acetyl-β-arabinopyranosyl bromides with 18β- and 18α-glycyrrhetic acids takes place normally and gives the corresponding acetates of the acyl D- and L-α-arabinopyranosides.

When hepta-O-acetyl-α-D-lactosyl bromide was used, both acids formed sirupy acetates of acyl β-D-lactosides. After the acetates and benzoates had been purified on a column of silica gel [1] with subsequent deacylation with sodium methoxide [3] in a mixture of methylene chloride and methanol, the acyl α-D-glucopyranoside (I), the acyl α-D-xylopyranoside (II), the acyl α-D-arabinopyranoside (III), and the acyl α-L-arabinopyranoside (IV) of 18β-glycyrrhetic acid were obtained. The deacetylation of the corresponding crude acetates gave the acyl β-D-lactosides of 18β- and 18α-glycyrrhetic acids (V) and (VI), differing only in the configuration of the H at C-18 of the aglycone R.



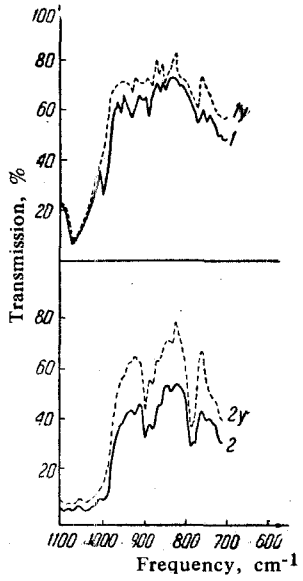
The deacetylation of the mixture of anomeric acetates of the acyl D-glucopyranosides of 18β-glycyrrhetic acid with sodium methoxide in methanol forms I contaminated with a small amount of its anomer. In addition to this, a considerable amount of the methyl ester of 18β-glycyrrhetic acid is obtained. The acetates of the acyl D- and L-α-arabinopyranosides of 18α-glycyrrhetic acid rapidly undergo methanolysis under these conditions to give the methyl ester of 18α-glycyrrhetic acid and the monosaccharide.

On being treated with methanolic alkali or sodium methoxide in methanol, the acylated and free acyl glycosides of 18β-glycyrrhetic acid give the methyl ester of this acid and the corresponding sugar. In addition, on hydrolysis with 1% potassium hydroxide in aqueous methanol they give 18β-glycyrrhetic acid and the monosaccharide. This behavior of the acyl glycosides in the presence of methoxide and hydroxyl ions, namely the cleavage of the O-glycosidic bond at the oxygen/aglycone position is similar to that described in the literature [4]. The acid hydrolysis of the acyl glycosides with 1% hydrochloric acid in aqueous dioxane or aqueous methanol gives 18β-glycyrrhetic acid and the monosaccharide. On acid and alkaline hydrolysis in 50% methanol, the acyl β-D-lactosides of 18β- and 18α-glycyrrhetic acids give the methyl ester of the corresponding acid and lactose.

The structure of the acyl glycosides was confirmed by their synthesis from the silver salt of 18β-glycyrrhetic acid

and the benzoates of the glycopyranosyl bromides in benzene–acetonitrile solution [5]. The acetates of the glycopyranosyl bromides hardly take part in this reaction.

The configuration of the glycosidic bond follows from the satisfactory correspondence of the values of the specific rotations calculated according to Klyne [6] and the experimental figures. For I and V it can be substantiated by an analysis of the differential spectrograms of their carbohydrate moieties in the IR region of the spectrum (figure) according to Kovalev and Litvinenko [7]. The spectrum of V has a band at 895 cm^{-1} which is characteristic for the β-glycosidic bond [8] and lacks a band at 840 ± 10 cm^{-1}. Under these conditions, I gives only a band at 844 cm^{-1}, which is due to the presence of an α-glucosidic bond in it [8].



IR spectra of the acyl α-D-glucopyranoside [1] and the acyl β-D-lactoside [2] of 18β-glycyrrhetic acid and the corresponding spectograms of their carbohydrate moieties (1y, 2y).

Experimental

All the melting points were determined on a Boetius micro heating stage and have been corrected. The angles of rotation were measured (the acyl glycosides in 95% ethanol and their benzoates and acetates in chloroform) on a Carl Zeiss polarimeter with a sodium spectroscopic lamp. The IR spectra were taken on a Nippon Bunko DS-301 instrument (4–6 mg of substance in 800 mg of potassium bromide, in tablets).

The chromatography was carried out with type KSK silica gel (100–200 mesh for columns and 200–250 mesh for plates). In the production of the free acyl glycosides, the columns were subjected to gradient elution with benzene–ether in ratios of 9:1, 4:1, 7:3, 1:1, 2:3, and 1:4 and then with benzene–methanol in the same ratios (100 ml of each mixture). In the case of the acetates and benzoates of the acyl glycosides, the columns were eluted only with benzene–ether, as above. Chromatographic monitoring was carried out on plates (9 × 12 cm) with a thin layer of silica gel fixed with gypsum in the following systems: 1) benzene–ether (7:3); 2) benzene–methanol (7:3); 3) butanol–ethanol–18% ammonia (18:3.5:18); and on plates with gypsum in system 4) chloroform–methanol (19:3). The chromatograms were revealed with antimony pentachloride. Analytical samples were dried in a vacuum gun over phosphorus pentoxide at 83° C.

The 18β-glycyrrhetic acid used in the synthesis we obtained as described by Drefahl and Suneck [9], mp 291–293° C, $[\alpha]_D^{20}$ +170 ± 1° (c 1.51; chloroform) and $[\alpha]_D^{20}$ +150 ± 1° (c 1.06; 95% ethanol). The 18α-glycyrrhetic acid was prepared as described by Beaton and Spring [10], mp 329–332° C and $[\alpha]_D^{20}$ +98 ± 3° (c 0.41; methanol–chloroform).

Acyl 2, 3, 4, 6-tetra-O-benzoyl-α-D-glucopyranoside of 18β-glycyrrhetic acid

A. Condensation was carried out by the procedure described previously [1]. To 0.6 g of 18β-glycyrrhetic acid in pyridine (5 ml) were added 3.2 g of 2, 3, 4, 6-tetra-O-benzoyl-α-D-glucopyranosyl bromide [11] and 1 g of active silver oxide. The mixture was stirred, initially at 10° C (15 min), and then at room temperature (4 hr). The reaction product was diluted with acetic acid (20 ml) and poured into water (500 ml). The precipitate was filtered off and dried, and its solution in benzene (100 ml) was chromatographed on a column of silica gel (40 g). The separation was checked in system 1. The fractions collected, after treatment with ether (20 ml) and recrystallization from methylene chloride–methanol of the precipitate that deposited, gave 0.94 g (70% of theory) of the acyl glucoside benzoate with mp 256–257° C and $[\alpha]_D^{20}$ +124 ± 1° (c 2.06). Calculations according to Klyne gave $[\alpha]_D$ +125.5°. In the calculations, a value of $[\alpha]_D^{20}$ +84° was taken for the benzoate of methyl α-D-glucopyranoside.

Found, %: C 73.01; 72.80; H 6.88; 6.97. Calculated for $C_{64}H_{72}O_{13} \cdot (1/2)CH_3OH$, %: C 72.72; H 7.00.

B. To 0.74 g of finely ground silver 18β-glycyrrhetate (obtained by precipitation from a 10% solution of the sodium salt with a 10% solution of silver nitrate) in a mixture of dry benzene and acetonitrile was added 3.2 g of 2, 3, 4, 6-tetra-O-benzoyl-α-D-glucopyranosyl bromide, and the mixture was stirred for 24 hr at room temperature. After chromatography on a column of silica gel as above, 0.51 g (38% of theory) of a substance with mp 254–256° C and $[\alpha]_D^{21}$ +123 ± 1° (c 2.02) was obtained. The substance gave no depression of the melting point in admixture with a sample of the benzoate of the acyl α-D-glucopyranoside of 18β-glycyrrhetic acid from the previous experiment, and it had an IR spectrum similar to that of this sample.

Mixture of anomeric acetates of the acyl D-glucopyranosides of 18β-glycyrrhetic acid

A mixture of 0.6 g of 18β-glycyrrhetic acid in pyridine (5 ml) and 2 g of 2, 3, 4, 6-tetra-O-acetyl-α-D-glucopyranosyl bromide [12] was condensed in the presence of active silver oxide (1 g) as in the preceding experiment. Chromatography on a column of silica gel (40 g) and subsequent crystallization from ether (30 ml) yielded 0.7 g (7% of theory)

of a substance with mp 227–229° C, $[\alpha]_D^{20}$ +111 ± 1° (c 2.01). The calculated figure for the acetate of the acyl α-D-glucopyranoside of 18β-glycyrrhetic acid was $[\alpha]_D$ +161° and that for its anomer $[\alpha]_D$ +91°. In the calculations, the specific rotation of methyl tetra-O-acetyl-α-D-glucopyranoside was taken as $[\alpha]_D^{20}$ +134° [13] and that of its anomer $[\alpha]_D^{20}$ −18.2° [13].

Found, %: C 66.09; 65.98; H 7.83; 7.89. Calculated for $C_{44}H_{64}O_{13}$, %: C 65.98; H 8.05.

The acyl α-D-glucopyranoside of 18β-glycyrrhetic acid (I)

A. 0.62 g of the benzoate of the acyl α-D-glucopyranoside was deacylated with 0.1 N sodium methoxide in methanol (3 ml) in a mixture of 6 ml of absolute methanol and 2 ml of freshly purified methylene chloride at room temperature (10 min). The solution was acidified with acetic acid, stirred with silica gel (10 g), dried, and transferred to a column of silica gel (30 g). After chromatography and subsequent treatment of the fractions collected with ethyl acetate, 0.33 g of the substance was obtained. The separation was monitored by thin-layer chromatography in system 2. After recrystallization from ethyl acetate containing 1% of ethanol, 0.31 g was obtained of the acyl glucoside (82% of theory) with mp 132–134° C, $[\alpha]_D^{21}$ +155 ± 2° (c 1.37). Calculated: $[\alpha]_D$ +160° C. In the calculations, $[\alpha]_D^{20}$ +158° was used for methyl α-D-glucopyranoside [14].

Found, %: C 67.51; 67.36; H 9.50; 9.28. Calculated for $C_{36}H_{56}O_9 \cdot C_2H_5OH$, %: C 67.23; H 9.20.

B. A suspension of 0.55 g of a mixture of anomeric acetates of acyl α-D-glucopyranosides of 18β-glycyrrhetic acid in 10 ml of absolute methanol was deacetylated with 0.1 N sodium methoxide in methanol (3 ml) at room temperature (4 hr). After chromatography on a column of silica gel and subsequent treatment as in the preceding experiment, 0.14 g (30% of theory) of a substance with mp 230–232° C, $[\alpha]_D^{20}$ +144 ± 2° (c 0.62) was obtained. It was identical with the acyl α-D-glucopyranoside (I) of the preceding experiment in respect of the melting point of a mixture and its IR spectrum but was apparently contaminated with a small amount of the β-anomer.

In addition, from the benzene-ether eluates was isolated 0.15 g of the methyl ester of 18β-glycyrrhetic acid with mp 250–251° C $[\alpha]_D^{20}$ +161 ± 1° (c 0.83; chloroform). It was identical with an authentic sample [9] according to a mixed melting point, its IR spectrum, and its chromatographic behavior in systems 1 and 2. Data relating to the other acyl glycosides of 18β- and 18α-glycyrrhetic acids are given in the table.

Acid hydrolysis of the acyl glycosides of 18β-glycyrrhetic acid

A. A mixture of 0.0598 g of the acyl α-D-glucopyranoside (I) and 10 ml of 0.2 N hydrochloric acid in 50% aqueous methanol was stirred for 2 hr at room temperature. The methanol was distilled off in vacuum and the precipitate that deposited was recrystallized from aqueous ethanol. This gave 0.0395 g of 18β-glycyrrhetic acid with mp 288–290° C (mixture with an authentic sample), $[\alpha]_D^{20}$ +167 ± 2° (c 0.63; chloroform). The filtrate of the hydrolyzate was passed through a column of Dowex-2 anion-exchanger (CO_3^{2-} form). The eluates were concentrated and chromatographed on a plate with gypsum in system 4. After staining with α-naphthol [18], only glucose was detected. The behavior of the acyl α-D-xylopyranoside (II) and of the acyl D- and L-α-arabinopyranosides (III) and (IV) were similar under these conditions.

B. 0.1029 g of the acyl β-D-lactoside (V) was treated with methanolic hydrochloric acid as above. This gave 0.0582 g of methyl 18β-glycyrrhetate with mp 247–249° C (mixture with an authentic sample), $[\alpha]_D^{20}$ +156 ± 2° (c 0.81; chloroform).

The chromatography of the hydrolyzate on a gypsum plate in system 4 showed the presence of lactose and traces of glucose.

The acyl β-D-lactoside (VI) of the 18α-glycyrrhetic acid was subjected to methanolysis similarly.

Alkaline hydrolysis of the acyl glycosides of 18β-glycyrrhetic acid

A mixture of 0.050 g of the acyl α-D-glucopyranoside (I) and 10 ml of a 0.2 N solution of potassium hydroxide in 50% aqueous methanol was stirred at room temperature for 2 hr. Methanol (10 ml) was added to the solution and it was passed through a column of KU-2 ion exchange resin (H^+ form). The eluates were evaporated in vacuum to small bulk and the precipitate that deposited was recrystallized from aqueous ethanol. This gave 0.028 g of 18β-glycyrrhetic acid with mp 287–289° C (mixture with an authentic sample), $[\alpha]_D^{20}$ +165 ± 3° (c 0.43; chloroform). The filtrate of the hydrolyzate was investigated chromatographically on a plate with gypsum in system 4. After staining with α-naphthol, glucose was detected. The other acyl glycosides of 18β- and 18α-glycyrrhetic acids were also hydrolyzed under these conditions, except for their acyl β-D-lactosides (V) and (VI), which underwent methanolysis.

Methanolysis of the acyl glycosides of 18β- and 18α-glycyrrhetic acids

One milliliter of a 10% solution of potassium hydroxide in methanol was added to 0.043 g of the acyl α-D-glucopyranoside (I) of 18β-glycyrrhetic acid in absolute methanol (15 ml), and the mixture was left at room temperature (0.5

Acylated glycosyl bromide	Acyl glycoside	Yield, % of theory	$[\alpha]_D$, deg		mp, °C	Solvent	Composition	Analysis, %			
			found	calculated				found		calculated	
								C	H	C	H
18β-glycyrrhetic acid											
Tri-O-benzoyl-α-D-xylopyranosyl bromide [15]	Acyl α-D-xylopranoside (II)		+147±2 (c 0.48)	+159	202 204°	EtAc EtOH	$C_{35}H_{54}O_8 \cdot C_2H_5OH$	68.55	9.32	68.47 68.35	9.36 9.15
	Tri-O-benzoyl	63	+117±1 (c 1.42)	—	sirup		$C_{56}H_{66}O_{11}$	73.50	7.27	73.29 73.37	7.21 7.19
Tri-O-benzoyl-β-D-arabinopyranosyl bromide [16]	Acyl α-D-arabinopyranoside (III)		+141±1 (c 1.21)	+112	amorphous	Moist EtAc	$C_{35}H_{54}O_8 \cdot H_2O$	67.71	9.09	67.59 67.53	8.85 8.81
	Tri-O-benzoyl	59	−36±1 (c 2.03)	−17	164 167°	CH_2Cl_2 +MeOH	$C_{56}H_{66}O_{11} \cdot 1/2\ CH_3OH$	72.87	7.36	72.69 72.81	7.17 7.09
Tri-O-acetyl-β-D-arabinopyranosyl bromide [12]	Tri-O-acetyl	53	+90±1 (c 1.24)	+104	216 217°	MeOH	$C_{41}H_{60}O_{11} \cdot 1/2\ CH_3OH$	66.91	8.38	67.01 66.86	8.36 8.38
Tri-O-benzoyl-β-L-arabinopyranosyl bromide [17]	Acyl-α-L-arabinopyranoside (IV)		+130±2 (c 0.97)	+122	amorphous	Moist EtAc	$C_{35}H_{54}O_8 \cdot H_2O$	67.71	9.09	67.51 67.47	9.24 9.08
	Tri-O-benzoyl	31	+217±2 (c 0.62)	—	160— 163°	CH_2Cl_2 +MeOH	$C_{56}H_{66}O_{11}$	73.50	7.27	73.44 73.59	7.39 7.17
Penta-O-acetyl-α-D-lactosyl bromide [12]	Acyl β-D-lactoside (VI)	57	+95±4 (c 0.22) (pyridine)	—	248—251	EtOH	$C_{42}H_{66}O_{14}$	63.46	8.36	63.31 63.29	8.27 8.30
18α-Glycyrrhetic acid											
Tri-O-acetyl-β-D-arabinopyranosyl bromide	Acyl tri-O-acetyl-α-D-arabinopyranoside	48	+76±2 (c 1.47)	+60	257—258°	MeOH	$C_{41}H_{60}O_{11} \cdot 1/2\ CH_3OH$	66.91	8.39	66.99 66.77	8.23 8.23
Tri-O-acetyl-β-L-arabinopyranosyl bromide [12]	Acyl tri-O-acetyl-α-L-arabinopyranoside	37	+72±2 (c 1.04)	+67	253—255°	MeOH	$C_{41}H_{60}O_{11} \cdot 1/2\ CH_3OH$	66.91	8.39	67.06 67.17	8.27 8.35
Hepta-O-acetyl-α-D-lactosyl bromide	Acyl β-D-lactoside (VI)	60	+70±4 (c 0.4) (pyridine)	—	243—244°	EtOH	$C_{42}H_{66}O_{14}$	63.46	8.36	63.24 63.33	8.32 8.22

Note. The following abbreviations are used in the table: MeOH—methanol, EtOH—ethanol, EtAc—ethyl acetate.

hr). It was then passed through a column of KU-2 resin (H^+ form) and the eluates were evaporated to 1 ml. This gave 0.0298 g of methyl 18β-glycyrrhetate with mp 248–249° C (mixture with an authentic sample), $[\alpha]_D^{20}$ +157 ± 3° (c 0.53, chloroform).

The mother liquor was investigated on a plate with gypsum in system 4, and glucose was detected. The other acylated and free acyl glycosides of 18β-glycyrrhetic acid were also subjected to methanolysis under these conditions. The acetates of the acyl D- and L-α-arabinopyranosides of 18α-glycyrrhetic acid underwent complete methanolysis in 1 min at room temperature.

Summary

The acyl α-D-glucopyranoside, the acyl α-D-xylopyranoside, the acyl D- and L-α-arabinopyranosides, and the acyl β-D-lactoside of 18β-glycyrrhetic acid, and also the acyl β-D-lactoside of 18α-glycyrrhetic acid have been synthesized. The acid and alkaline hydrolysis of the compounds obtained has been studied.

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