SYNTHESIS OF GLYCOSIDES OF GYPSOGENIN AND OF GYPSOGENIC ACID BY THE ORTHOESTER METHOD

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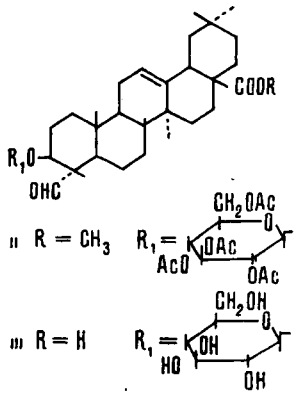
Glycosides of gypsogenin have been found in many plants of the family Caryophyllaceae [1-5]. However, not even the simplest of these compounds has been synthesized. This is possibly due to the lability of gypsogenin [6]. We have attempted to synthesize gypsogenin glucoside by the orthoester method, which has been applied successfully to the synthesis of steroid and triterpene glycosides [7-9]. The glycosylation of gypsogenin methyl ester and of free gypsogenin was performed with glucose (ethyl orthoacetate) (I) in the presence of catalytic amounts of mercuric bromide in nitromethane.

The acetate of the glucoside of gypsogenin methyl ester (II) was synthesized by the reaction of gypsogenin methyl ester with glucose (ethyl orthoacetate) (I) with a yield of ~20%. Gypsogenin 3-glucopyranoside (III) was obtained after the halolysis of compound (II) with lithium iodide [10]. In addition to this, it was isolated by the direct condensation of gypsogenin with compound (I) followed by alkaline saponification of the condensation product.

The acid hydrolysis of substance (III) formed gypsogenin and glucose. Calculations by Klyne's method showed the existence of a β-glycosidic bond in the glycoside synthesized.



We have recently for the first time isolated from the plant Saponaria officinalis L. a gypsogenic acid glycoside which we called saponaroside [11]. It was shown that the latter is gypsogenic acid 3-β-D-xylopyranoside. In the present paper we give the synthesis of this glycoside by the orthoester method. We obtained the initial gypsogenic acid by the oxidation of gypsogenin with potassium dichromate [12]. In order to synthesize the xyloside of gypsogenic acid, the dimethyl ester of this acid was condensed with xylose (ethyl orthobenzoate) (IV) in the presence of a 0.02 M solution of mercuric bromide in nitromethane.

The use of the ethyl orthobenzoate instead of the ethyl orthoacetate of xylose for synthesis in this case was due to the greater reactivity of the former [13]. Compound (IV) is readily obtained from benzoylated xylosyl bromide. The condensation performed led to the benzoate of the xyloside of gypsogenic acid dimethyl ester (V).

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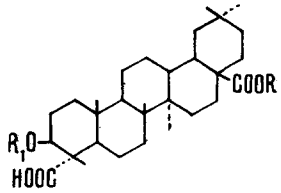
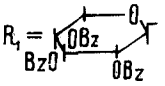
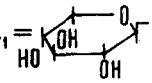


V R=CH3 R1= 

VI R=H R1= 

After the halolysis of compound (V) with lithium iodide in collidine, gypsogenic acid 3-xylopyranoside (VI) could not be isolated. This compound was obtained by the direct reaction of gypsogenic acid with xylose (ethyl o-benzoate) (IV) followed by the alkaline saponification of the resulting product. In its constants and chromatographic behavior, the glycoside synthesized coincided completely with an authentic sample of gypsogenic acid 3-β-D-xylopyranoside (saponaroside).

EXPERIMENTAL METHOD

For column chromatography we used type KSK silica gel. Thin-layer chromatography (TLC) was performed on "Silufol" plates with a fixed layer of silica gel. The following solvent systems were used for chromatography: 1) chloroform–methanol (98 : 2) chloroform–methyl ethyl ketone (98.5 : 1.5); 3a) benzene–ether (3 : 1); 3b) benzene–ether (1 : 3); 4) ether–ethyl acetate (3 : 1); 5) butan-1-ol–acetic acid–water (4 : 1 : 5); 6) ethyl acetate–methanol (95 : 5).

The sugars and the sugar orthoesters were revealed with a solution of aniline phthalate, and the glycosides with a saturated solution of $SbCl_3$ in chloroform. The melting points were determined on a Kofler block. The nitromethane was redistilled over urea and twice over P_2O_5. The elementary analyses of the substances given corresponded to the calculated figures.

3,4,6-Tri-O-acetyl-1,2-O-(ethyl orthoacetyl)-α-D-glucopyranose (I). A solution of 2.4 g of acetobromoglucose [14] in 10 ml of nitromethane, 2 ml of absolute ethanol, and 5 ml of freshly distilled 2,6-lutidine was kept at 37° C for 2 days. Then the mixture was diluted twofold with chloroform and was washed with a cold saturated solution of sodium carbonate (2 × 10 ml) and with cold water (5 × 10 ml). The chloroform layer was dried over $MgSO_4$ and evaporated at 60° C in vacuum. This gave 2.1 g of crude product, which was transferred to a column (3 × 30 cm) of silica gel and eluted with 150 ml of system 1. The yield of product chromatographically homogeneous in system 2 was 1.5 g (68%), mp 91-92° C, $[\alpha]_D^{20}$ + 40° (c 1.2; chloroform). Literature data: mp 92-94° C, $[\alpha]_D^{20}$ + 36° (chloroform) [15].

2,3,4,6-Tetra-O-acetyl-β-D-glucopyranoside of Gypsogenin Methyl Ester (II). A solution of 0.48 g (1 mmole) of gypsogenin methyl ester and 0.38 g (1 mmole) of 3,4,6-tri-O-acetyl-1,2-O-(ethyl orthoacetyl)-α-D-glucopyranose (I) in 10 ml of nitromethane was heated in a flask with a condenser for direct distillation at the boiling point of the solvent. After 5 ml of nitromethane had distilled off, 0.5 ml of a 0.02 M solution of mercuric bromide in benzene was added to the falsk and the mixture was heated for 4 h with the addition of fresh nitromethane as it distilled off so that the volume of the reaction mixture remained constant. Then the solution was cooled, a few drops of pyridine was added, and it was evaporated at 60-70° C in vacuum. The residue was transferred to a column (3 × 30 cm) of silica gel and was eluted in system 3a with the collection of 15-ml fractions. Separation was monitored by TLC in system 3b. Fraction 1 contained 0.14 g of compound (I), fractions 2 and 3 contained 0.37 g of gypsogenin methyl ester, and fractions 4 and 5 contained 0.16 g of compound (II). The yield of the latter was 20%, mp 164-167° C (from ethanol), $[\alpha]_D^{20}$ + 17° (c 1.1; chloroform).

Gypsogenin 3-β-D-Glucopyranoside (III). A. Compound (II) (0.16 g) was added to a solution of 2.5 g of anhydrous lithium iodide in 8 ml of dry collidine, and the mixture was heated in a nitrogen-filled tube at 160° C for 7 h. Then the collidine was distilled off at 70° C, the residue was dissolved in 15 ml of water, and the solution was acidified with acetic acid and extracted with butan-1-ol (4 × 10 ml). Teh butanolic extracts were washed with water, and evaporated, and the residue (0.12 g) was transferred to a column (2.5 × 15 cm) of silica gel and eluted in system 4. This gave 50 mg of compound (III), mp 237-241° C (from ethanol), $[\alpha]_D^{20}$ + 21° (c 1.3; pyridine).

B. The condensation of 0.3 g (0.62 mmole) of gypsogenin and 0.31 g (0.83 mmole) of 3,4,6-tri-O-acetyl-1,2-O-(ethyl orthoacetyl)-α-D-glucopyranose was performed in 10 ml of nitromethane under the conditions described above. The residue after the evaporation of the reaction mixture was dissolved in 5 ml of a 10% solution of KOH in methanol and the solution was kept at room temperature for a day and was then neutralized with KU-2 cation-exchange resin and evaporated. The resulting residue (0.45 g) was transferred to a column (3 × 30 cm) of silica gel and was eluted in system 4, 20-ml fractions being collected. The process was monitored by TLC in the same solvent system. Fractions 1-3 contained 0.2 g of gypsogenin, fraction 4 contained 30 mg of a mixture of gypsogenin and gypsogenin β-D-glucopyranoside, and fractions 5-7 contained 50 mg of gypsogenin β-D-glucopyranoside with mp 239-244° C, $[\alpha]_D^{20} \pm 22°$ (c 1.0; pyridine).

Gypsogenin β-D-glucopyranoside (III) (20 mg) was dissolved in 3 ml of 5% hydrochloric acid in aqueous methanol and the solution was heated in the boiling-water bath for 6 h. The precipitate was filtered off, dried in vacuum, and was shown by TLC on silica gel in system 3b to be identical with an authentic sample of gypsogenin. The filtrate was neutralized with ÉDÉ-10P anion-exchange resin, and in it glucose was shown to be identical with a marker by paper chromatography in system 5.

3,4-Di-O-benzoyl-1,2-O-(ethyl orthobenzoyl)-α-D-xylopyranose (IV). A solution of 2 g of 2,3,4-tri-O-benzoyl-α-D-xylopyranosyl bromide [16] in 8 ml of nitromethane, 1.5 ml of absolute ethanol, and 4 ml of freshly distilled 2,6-lutidine was kept at 37° C for 2 days. Then the reaction mixture was diluted twofold with ice water and was extracted with chloroform (4 × 10 ml). The chloroform extracts were washed with cold saturated sodium carbonate solution (3 × 10 ml) and then three times with water, dried over $MgSO_4$, and evaporated in vacuum at 60° C. Of the resulting mixture, 2.5 g was transferred to a column (3 × 30 cm) containing silica gel and was eluted with 150 ml of system 1. This gave 1.45 g of substance (IV) with mp 180-181° C (from methanol), $[\alpha]_D^{20} +33°$ (c 1.5; chloroform). Yield 78%.

The orthoester (IV) was hydrolyzed by dilute acids under the conditions described by Kochetkov et al. [13] and it feebly reduced Fehling's solution.

2,3,4-Tri-O-benzoyl-β-D-xylopyranoside of Gypsogenic Acid Dimethyl Ester (V). A mixture of 0.51 g (1 mmole) of gypsogenic acid dimethyl ester, 0.49 g (1 mmole) of 3,4-di-O-benzoyl-1,2-O-(ethyl orthobenzoyl)-α-D-xylopyranose (IV) in 10 ml of nitromethane, and 0.5 ml of 0.02 M mercuric bromide was heated at the boiling point of nitromethane with the simultaneous distillation and additional fresh portions of the solvent for 4 h. Then the solution was cooled, a few drops of pyridine was added, and it was evaporated in vacuum at 60° C. The residue after evaporation was transferred to a column (3 × 30 cm) of silica gel and was eluted in system 4, 20-ml fractions being collected.

The process was monitored by TLC in system 3b. Fraction 1 contained 0.33 g of substance (IV), fractions 2 and 3 contained 0.41 g of gypsogenic acid dimethyl ester, and fractions 4-6 contained 0.16 g of substance (V). The yield of (V) was 16%, mp 217-219° C (from ethanol), $[\alpha]_D^{20} -3°$ (c 1.0; chloroform).

Gypsogenic Acid 3-β-D-Xylopyranoside (VI). The condensation of 0.48 g (1 mmole) of gypsogenic acid and 0.49 g (1 mmole) of 3,4-di-O-benzoyl-1,2-O-(ethyl orthobenzoyl)-α-D-xylopyranose in 10 ml of nitromethane was performed as described above. The reaction mixture was evaporated in vacuum at 70° C, the residue was dissolved in 3 ml of 10% KOH in methanol, and the solution was kept for a day at room temperature, neutralized with KU-2 cation-exchange resin, and evaporated. This gave 0.8 g of a mixture which was deposited on a column (3 × 30 cm) containing silica gel. Elution was performed in system 6, 15-ml fractions being collected. The separation was monitored by TLC in system 4. Fractions 1 and 2 contained 0.3 g of substance (IV), fractions 3 and 4 contained 0.32 g of gypsogenic acid, and fractions 5-8 contained a mixture of gypsogenic acid and gypsogenic acid 3-β-D-xylopyranoside (VI) – 0.15 g. After rechromatography, fractions 5-8 yielded 70 mg of gypsogenic acid 3-β-D-xylopyranoside (VI). Yield 11%, mp 216-220° C (from methanol). It gave no depression of the melting point with an authentic sample of gypsogenic acid 3-β-D-xylopyranoside (saponaroside) [11]. $[\alpha]_D^{20} -11°$ (c 1.0; pyridine).

SUMMARY

1. Gypsogenin 3-β-D-glucopyranoside has been obtained for the first time.
2. The natural 3-(β-D-xylopyranoside) of gypsogenic acid (saponaroside) has been synthesized.

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