Koenigs-Knorr Synthesis of Galactofuranosides of Estrone, Androstanolone, 11α-Hydroxyprogesterone and Prednisolone

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Galactofuranosylation has been accomplished with 1-bromo-1-deoxy-2,3,5,6-tetra-O-benzoyl-α-D-galactofuranoside in the presence of cadmium carbonate as promotor. Glycosylation agent has been prepared by bromination of penta-O-benzoyl-αβ-D-galactofuranoside with a solution of hydrogen bromide in glacial acetic acid. The precursor of the latter reaction has been produced by benzoylation of D-galactose that had been heated in pyridine while still warm. The following hydroxysteroids have been selected as being representative in terms of configuration, type of hybridization of carbon bearing hydroxyl, position on cyclopentenoperhydrophenantrene nucleus and, implicitly, the degree of shielding: estrone, androstanolone, 11-α-hydroxyprogesterone, prednisolone. The synthesized galactofuranosides have been characterized by ^{1}H and ^{13}C NMR as well as by chromatographic and chemical means.

Key words: galactofuranosides, estrone, androstanolone, 11-α-hydroxyprogesterone, prednisolone, ^{1}H, ^{13}C NMR spectra

Sterol glycosides are natural compounds having a relatively wide distribution in living tissues [1]. Cholesterol and sitosterol were among the first complex aglycones used as glycosyl acceptor in Koenigs-Knorr synthesis [2]. Subsequently, cholesterol became a model acceptor in a series of alternatives to this glycosylation reaction. By using acetobromoglucose as glycosylating agent and silver oxide as promotor, Lettre and Hagedorn obtained glucosides with the following aglycones: cholesterol, dihydroergosterol, dehydroergosterol, cholestan 3,5,6-triol [3]; by a similar method, they obtained cholesteryl lactoside [3]. The same glycosyl donor was used to prepare the glucosides of estrone and estradiol [4]. Woolf et al., [5] glycosylated tigogenin alternatively with bromoglucopyranose, bromogalactopyranose, bromoarabinopyranose; then they changed the aglycone and synthesized the glucosides of cholesterol, 4-cholesten 3-ol, digitoxigenin, 3β-hydroxy-14α-cardadien-(4,20(22))-olide. A series of new promotors were tested on this occasion and they found out that the silver salts of 2-, 3-, and 4-hydroxyalkanoic acids as well as of 1,3- and 1,4-dicarboxylic acids proved to be superior to the commonly used silver carbonate or silver oxide [5]. In order to avoid formation of othoesters, esters and hydrolysis products, Kunz and Harreus [6] used 2,3,4,6-tetra-O-pivaloyl-α-D-glucopyranosylbromide for cholesterol glycosylation in the presence of three promotors: silver carbonate, silver oxide, silver trifluoromethane sulfonate. Subsequently, they extended the advantage of stability of pivaloyl group to xylopyranosyl bromide and glycosylated a series of steroids [7]. In the last two decades, spectacular biochemical functions have been attributed to glycosterols. β-D-Glucopyranosyl cholesterol is the molecule of stress for vertebrates: when added to a culture of human fibroblasts, it evokes the whole suite of events as the stress factors themselves - producing of heat shock factors and heat shock proteins [8]. β-D-Glucopyranosyl sitosterol is the primer molecule for cellulose biosynthesis in plants [9].

In this paper some hydroxysteroids - estrone, androstanolone, 11-α-hydroxyprogesterone, prednisolone - have been galactofuranosylated by using 1-bromo-1-deoxy-2,3,5,6-tetra-O-benzoyl galactofuranoside as glycosyl donor and cadmium carbonate as chemical condensing agent.

Experimental part

^{1}H and ^{13}C NMR spectra of all intermediates, including galactofuranosylated steroids, were registered in peracylated form in $CDCl_3$ containing TMS. Methyl β-D-galactofuranoside was synthesized as Haworth et al., [10]. Thin-layer chromatography (TLC) was performed on ready-to-use glass plates covered with silica gel 60 (E. Merck). The following solvent systemes (SS) were used: chloroform-methanol-water, 50:10:1 (v/v, SS I) and toluene-methanol, 7:1 (v/v, SS 2). Visualisation was made by dipping the plates in a solution of amonium molybdate, sulfuric acid and cerium(IV) sulfate, followed by heating.

Hydrolysis of sterol glycosides and determination of their constituents. 0.1-0.5 mg of glycosterol was heated to reflux in a solution of ethanol-water, 1:1 (v/v) containing 0.3 N hydrochloric acid. Hydrolysis was monitored by TLC in SS I. Solvents were evaporated to dryness and the residue partitioned between chloroform and water. The two phases were separated, in water phase D-galactose was determined by anthrone reaction [11], while in chloroformic phase the respective steroid was determined by Liebermann-Burchardt reaction [12].

1,2,3,5,6-penta-O-benzoyl-αβ-D-galactofuranoses. D-Galactose (10 g, 55,5 mmoles) that had been dried in a dessicator on P_2O_5 was suspended in 150 mL pyridine in a 500 mL flask ($CaCl_2$ tube). The suspension was then heated at 100-105^{0}C for one hr, cooled to 60^{0}C and 40 mL benzoylchloride was added portionwise with stirring, a clear solution being obtained [13, 14]. Heating to 60 ^{0}C was continued for 1,5 hrs and then the flask was left to cool gradually to room temperature overnight. Next day the content of the flask was cooled on ice and ice was added in the flask too. Supernatant solution was decanted from the heavy syrup that appeared and the residue was solved in chloroform and washed repeatedly with a saturated solution of sodium bicarbonate, water, 2 N sulfuric acid, water. Chloroformic phase was then dried on magnesium sulfate, filtered, evaporated to dryness and the residue repeatedly crystallized from methanol; m. p. 133-144 ^{0}C;

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$[\alpha]_D^{23}$ = +18.1 (c 1.3, chloroform) yield 23.45 g (33.5 mmole, 60 %).

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 6.860 (d, 4.4, H-α of D-Gal), 6.849 (s, H-1β of D-Galf), 6.126 (dd, H-2), 6.301 (t, H-3), 4.813 (dd, H-4), 5.918 (m, H-5), 4.880 (dd, H-6a), 4.782 (dd, H-6b), 7.253-7.268 and 7.902-8.123 (aromatic rings of benzoyl moieties).

^{13}C-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 99.765 (C-1β), 94.120 (C-1α), 81.015 and 76.095 (C-2), 73.816 and 77.348 (C-3), 79.547 and 84.315 (C-4), 70.329 and 70.303 (C-5), 63.058 and 63.594 (C-6), 128.214-133.737 (aromatic rings of benzoyl fragments), 164.468-165.772 (C=O groups of benzoyl).

1-bromo-1-deoxy-2,3,5,6-tetra-O-benzoyl-α-D-galactofuranoside. 2.1 g (3 mmoles) pentabenzoyl galactofuranoses was cooled and stirred on ice for 3 h with 3 mL hydrogen bromide (33 % in glacial acetic acid) and 10 mL 1,2-dichloroethane [15]. The reaction mixture was then left to reach gradually the room temperature and stirred to this temperature for 2 hrs. Then ice was added in the flask and reaction product was extracted with chloroform. Chloroformic solution was washed two times with sodium hydrogencarbonate then with water. After drying the chloroformic solution on magnesium sulfate, it was filtered, the solvent removed and the residue dried overnight in a vaccum dessicator on phosphorus pentoxide. As the vacuum increased, the product expanded as a white foam; yield 1.7260 g (2.61 mmoles, 87.3 %).

General procedure for Koenigs-Knorr synthesis. In a flask protected against moisture, the following were added: 12-15 mL of dry toluene (Na), 0.3-0.4 g (1.0-1.5 mmole) hydroxysteroid, 3 g of dry calcium sulfate and 3 g of cadmium carbonate [14, 16]. Constantly, the molar ratio between glycosylation donor and acceptor was 1.2-1.3/1. The suspension was stirred for one hr at room temperature and then a solution of tetra-O-benzoyl-α-D-galactofuranosyl bromide in dry toluene was added; the suspension was heated to boiling under stirring for 7-8 hrs. Boiling was interrupted and 2 vols of chloroform were added to the reaction mixture while warm. Suspension was filtered on Celite and the filtrate concentrated to dryness by rotavapor. Residue was resumed in methanol and enough sodium methoxide was added so as its final concentration was 0.2 M. The course of Zemplen saponification was followed in SS I and SS II and when it reached the final, solution was neutralized, evaporated to dryness and the residue partitioned between chloroform and water. Chloroformic solution was dried with magnesium sulfate, filtrated and concentrated to dryness. Residue was solved in a small volume of chloroform-methanol 2/1 (v/v) and chromatographed on a column of silica gel, the elution being made with a gradient of methanol in chloroform (0-40 %, v/v). The course of separation was followed by TLC in SS I by comparison with the whole glycosylation mixture as well as by colorimetric determination of lipophilic sugar after acidic hydrolysis. A portion (30-40 mg) of the purified glycosterol was peracetylated, the kinetics of esterification being followed in SS II, and its ^{1}H and ^{13}C NMR spectra registered. Constantly, the spectra of peracetylated glycosterol have been referred to the spectra of peracetylated aglycone.

β-*D-Galactofuranosyl-estrone*. Wax-like material, gave D-galactose and estrone by hydrolysis, 1:1 (molar ratio).

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 5.656 (s, H-1ß), 5.321 (d, 2.2, H-2), 5.113 (d, 5.5, H-3), 4.407 (t, 3.5, H-4), 5.428 (m, 7.6, H-5), 4.357-4.316 (m H-6a), 4.232-4.185 (m, H-6b), 0.909 (s, H-18'), 7.217-7.196 (d, 8.4, H-1'), 6.842-6.820 (d, 8.8, H-2'), 6.785 (s, H-4'), 1.627-1.412 (m, H-11').

^{13}C-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 103.915 (C-1), 81.349 (C-2), 77.017 (C-3), 80.642 (C-4), 69.107 (C-5), 62.504 (C-6), 220.841 (C-17'), 170.420 (C-3'), 58.220 (C-14'), 38.128 (C-12'), 25.571 (C-15').

β-*D-Galactofuranosyl-androstanolone*. Solid, wax-like material, produced D-galactose and androstanolone in the molar ratio 1:1, by acidic hydrolysis.

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 5.059 (H-1), 5.050 (H-2), 4.981 (H-3), 4.279 (H-4), 5.363 (H-5), 4.345 (H-6a), 4.217 (H-6b), 0.710 (H-18' m), 0.750 (m, H-19') 1.442 (H-8'), 0.910 (H-14'), 1.589 (H-15'a), 1.555 (H-15b).

^{13}C-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 105.77 (C-1), 79.25 (C-2), 74.91 (C-3), 81.51 (C-4), 68.95 (C-5), 62.58 (C-6), 211.75 (C-3'), 31.159 (C-8'), 23.462 (C-11'), 38.433 (C-12'), 23.462 (C-15').

β-*D-Galactofuranosyl-11α-hydroxyprogesterone*. Solid, glassy material, contained D-galactose and hydroxyprogesterone, as was revealed by acidic hydrolysis.

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 5.249 (H-1), 5.064 (H-2), 4.966 (H-3), 4.289 (H-4), 5.372 (H-5), 4.319 (H-6a), 4.190 (H-6b), 1.816 (H-16'α), 1.527 (H-15'α), 1.499 (H-6'), 1.245 (H-16'β), 1.155 (H-15'β), 0.705 (H-18').

^{13}C-NMR ($CDCl_3$; δ ppm; *J*, Hz): 103.37 (C-1), 81.66 (C-2), 77.33 (C-3), 80.77 (C-4), 69.58 (C-5), 62.33 (C-6), 208.74 (C-20',C-3'), 29.34 (C-16'), 24.21 (C-15').

β-*D-Galactofuranosyl-prednisolone-21-yl*. Amorfous solid, contained D-galactose and prednisolone in the molar ratio 1:1.

^{1}H-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 5.129 (H-1), 5.170 (H-2), 5.530 (H-3), 4.723-4.590 (H-4), 5.479 (H-5), 4.370-4.340 (H-6a), 4.271-4.173 (H-6b), 5.394 (H-1'), 1.480 (H-6'α), 0.962 (H-19'), 0.941 (H-14), 0.842 (H-18').

^{13}C-NMR ($CDCl_3$; δ, ppm; *J*, Hz): 105.743 (C-1), 81.288 (C-2), 69.875 (C-3), 80.724 (C-4), 68.640 (C-5), 63.428 (C-6), 206.791 (C-3',C-20'), 156.491 (C-2',C-5'), 122.357 (C-1',C-4').

Periodic acid oxidation. Glycosterol (10-15 mg) was solved in a solution of methanol-water 1:1 containing 0.05 M periodic acid and kept in the dark for 30 min [17]. Then formaldehyde was determined by reaction with chromotropic acid [18].

Results and discussions

Benzoylation reaction of D-galactose could be monitored chromatographically by TLC in SS I: R_F D-galactose = 0.05, R_F benzoylated galactose = 0.55. Specific rotation value $[\alpha]_D^{23}$ = +18,1 indicated the presence of D-galactofuranosic ring in α and β-configuration [13]. ^{1}H NMR Spectra indicated that the product of benzoylation was a mixture consisting of penta-O-benzoyl-α- and penta-O-benzoyl-β-D-galactofuranose: 6.860 (d, 4.4, H-1α of D-Gal), 6.849 (s, H-1β of D-Galf), 4.880 (dd, H-6a), 4.782 (dd, H-6b), 7.253-7.268 and 7.902-8.123 (aromatic rings of benzoyl moieties). ^{13}C NMR Spectra indicated the same results: 99.765 (C-1β), 94.120 (C-1α), 63.058 and 63.594 (C-6), 128.214-133.737 (aromatic rings of benzoyl fragments), 164.468-165.772 (C=O groups of benzoyl).

Bromination reaction could be followed by TLC in SS I (R_F pentabenzoate galactofuranose 0.55; R_F tetrabenzoyl-α-D-galactofuranosyl bromide 0.65). By treating bromination product with silver carbonate [19] a reducing compound (Fehling) was obtained, 2,3,5,6-tetra-O-benzoyl-αβ-D-galactofuranoses.

Succeeding of glycosylation reaction was proved by two simultaneous conditions: (A) appearance in glycosylation mixture of a compound that, after being submitted to

Zemplen saponification, migrates in the zone of neutral glycolipids [11] by TLC in SS I, or in other words it has a lower R_F value in comparison with aglycone (fig. 1); (B) the compound formed by glycosylation produces D-galactose and aglycone in the molar ratio 1:1 by acidic hydrolysis. Two remarks have to be made: (i) some steroids, due to a relatively higher degree of hydroxylation (prednisolone) migrate themselves in the region of glycolipids by TLC; (ii) phenolic aglycones (estrone) give rise to Friedel-Crafts products (C-glycosyl derivative) [20] and such compounds, although contain both defining moieties, D-galactose and hydroxysteroid, are not cleaved by acidic hydrolysis.

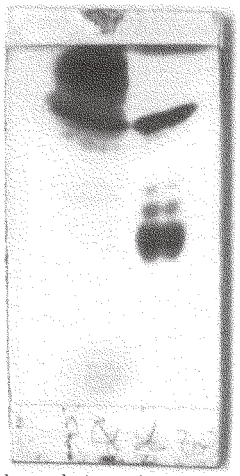

Fig. 1. TLC analysis of glycosylation mixture; start 1, before Zemplen saponification; start 2, after. The lowest spot on start 2 is a glycosterol. Migration with SS I, chloroform-methanol-water, 50:10:1 (v/v); visualization by mostain

Glycosterols produced by Zemplen saponification of glycosylation mixture have been separated by column chromatography and the course of separation was followed by TLC in SS I by comparison with the whole glycosylation mixture (fig. 2).

Furanosic ring of D-galactose in β-configuration was disclosed in ^{1}H NMR spectra by δ value of H-1 (5.656, β-D-galactofuranosyl-estrone; 5.059, β-D-galactofuranosyl-

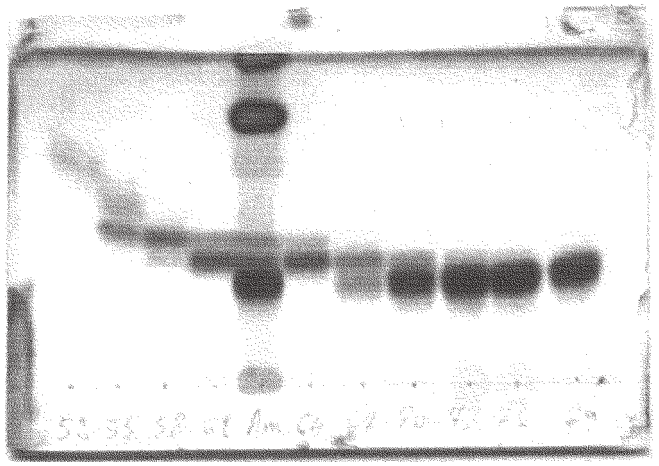

Fig. 2. TLC of fractions obtained by separation of glycosylation mixture that had been submitted to Zemplen saponification (start labelled *Am* represents the whole mixture). Migration with SS I, chloroform-methanol-water, 50:10:1 (v/v); visualization by mostain

androstanolone; 5.249, β-D-galactofuranosyl-11α-hydroxyprogesterone; 5.129, β-D-galactofuranosyl-prednisolone-21-yl) as well as by a constant characteristic of this signal - singlet. ^{13}C NMR Spectra confirmed this aspect by a relatively high value of δ for C-1:

103.915, β-D-galactofuranosyl-estrone; 105.77, β-D-galactofuranosyl-androstanolone;

103.37, β-D-galactofuranosyl-11α-hydroxyprogesterone; 105.743 β-D-galactofuranosyl-prednisolone-21-yl. Production of formaldehyde by periodic acid oxidation constituted a suplimentary argument for furanosic ring of D-galactose.

Undoubtfully, a glycosterol was produced by galactofuranosylation of prednisolone. It contained D-galactose and prednisolone in the molar ratio 1:1, as revealed by acidic hydrolysis of the purified glycoconjugate. As is evident from its structure - 11β, 17α,21-trihydroxy 3,20-diketo 1,4-pregnadien - prednisolone has three hydroxyl groups (fig. 3). So, one raises the question of their relative chemical reactivity. Methylation of prednisolone indicated that exclussively C-21 methoxy prednisolone was obtained [21]. N-Acetyl glucosaminidation of this steroid produced

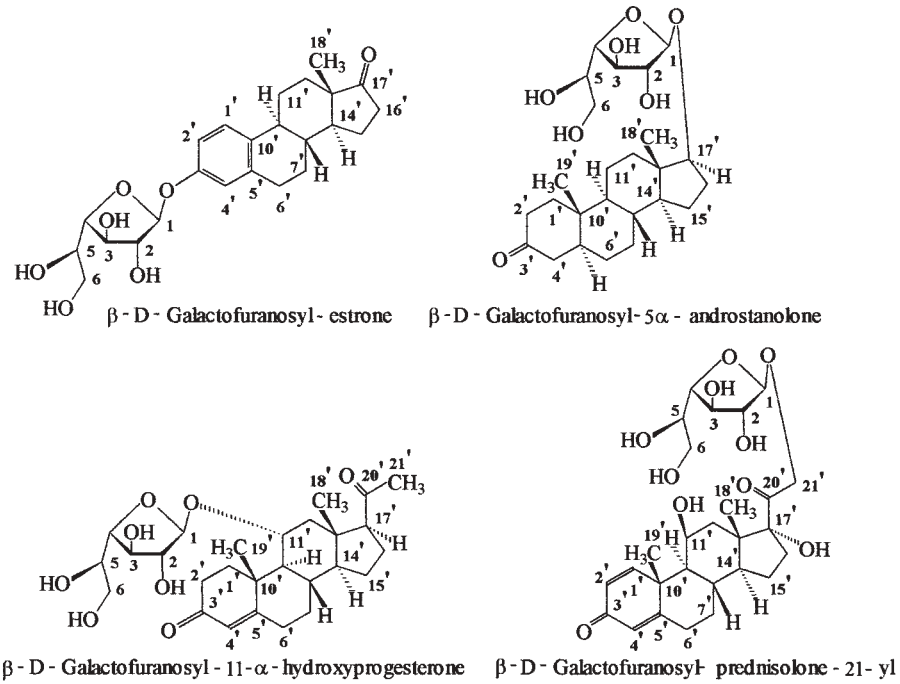

Fig.3. Structure of synthesized sterylgalactofuranosides

β-D-N-acetylglucosaminide prednisolone 21-yl [22]. A suplimentary proof that galactofuranosylation had been accomplished exclussively on C-21, was produced as follows: the synthesized prednisolone galactofuranoside was submitted to oxidation with periodic acid and the formaldehyde was determined by reaction with chromotropic acid in comparison with 1-O-methyl β-D-galactofuranoside; the same amount of formaldehyde per mole of compound was obtained in both cases.

The widespread distribution of glycosterols as well as their important biochemical and physiological functions constituted serious reasons for the synthesis of glycosterols and neoglycosterols as well as for improving of Koenigs-Knorr synthesis. Koenigs and Knorr used silver carbonate and silver oxide as promotors [23]. Other authors used mercury salts [24] or cadmium salts, especially cadmium carbonate [14, 16, 20]. Field's bromosugar/N-iodosuccinimide alternative to the Koenigs-Knorr reaction has been evaluated in the glucuronic acid series with very interesting results. Both α and β glucuronides became accessible and the products could be transformed into other useful glycosides [25]. For many years, bromine and chlorine were the preferred leaving groups. Acyl groups - acetate, benzoate, p-nitrobenzoate - in the presence of Lewis acids were largely used as leaving groups. An advantage of the 1-O-acylated glycosyl donors in glycosylation method is easiness of their preparation. Several Lewis acids have appeared effective promotors in the glycosylation, for instance tin tetrachloride, ferric chloride, [26]. An extremely widespread method of glycosylation activates glycosyl donor by a reaction of C-1 with trichloroacetonitrile; a very reactive trichloro-acetimidate is produced, borontrifluoride etherate being used as promotor [26]. The method that uses pentenyl glycosides as glycosyl donors, was introduced by Fraser-Reid [27]. The activation of the leaving group is based on an electrophilic addition to the double bond of the aglycone, followed by an intramolecular displacement by the ring oxygen and eventual expulsion of the pentenyl chain to form an oxonium species. Trapping with a glycosyl acceptor, then leads to the desired glycoside [27]. The access to galactofuranosic ring has been facillitated by submitting a mixture of di-isopropylidene galacto-furanoside and –pyranoside to tritylation; only di-isopropylidene galactofuranoside suffered the respective reaction [28]. Synthesis of glycosteroids disclosed important biochemical functions: ß-lactosyl-cholesterol proved to be a better acceptor for sialyltransferase from rat liver Golgi vesicles than lactosylceramide [29].

Conclusions

Heating of D-galactose in pyridine, followed by benzoylation produces penta-O-benzoyl-galactofuranoses.

Bromo-perbenzoylated-α-D-galactofuranose constitutes an excellent galactofuranosyl donor by using cadmium carbonate as chemical condensing agent.

Hydroxysteroids being representative in terms of configuration, type of hybridization of carbon bearing hydroxyl, position on cyclopentenoperhydrophenantrene nucleus and, implicitly, the degree of shielding could be galactofuranosylated.

The synthesized galactofuranosides of estrone, androstanolone, 11-α-hydroxyprogesterone, prednisolone have been characterized by ^{1}H and ^{13}C NMR as well as by chromatographic and chemical means.

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