Carbohydrate Research
Elsevier Publishing Company, Amsterdam
Printed in Belgium

Note

2-Deoxy sugars
Part XVIII. The anomers of 3β-(2-deoxy-D-*lyxo*-hexopyranosyloxy)-14β-hydroxy-5β-card-20(22)-enolide*

W. WERNER ZORBACH, SILVANO L. DEBERNARDO, AND K. VENKATRAMANA BHAT

Department of Bio-Organic Chemistry, Gulf South Research Institute, New Iberia, Louisiana 70560 (U. S. A.)

(Received May 20th, 1969)

The work described constitutes an extension of our earlier studies[1] designed to obtain a series of cardiac glycosides having minimal structural variations in the sugar component in the hope of clarifying the relation between the structure of the carbohydrate residue and the cardiotonic activity of the cardiac glycoside. In particular, we have shown that the 2-deoxy-β-D-*arabino*-hexoside and the 2-deoxy-β-D-*ribo*-hexoside of digitoxigenin [3β,14β-dihydroxy-5β-card-20(22)-enolide, **1**] have approximately the same potency, and it appears, therefore, that a reversal of the configuration at C-3 of the carbohydrate residue has no effect. However, for all of the glycosides of digitoxigenin (**1**) thus far studied (see Table I, Ref. 1), the hydroxyl group on C-4 of the sugar residue is an equatorial substituent, and it is for this reason that we undertook the synthesis of the title glycoside (4-OH axial), differing from the 2-deoxy-β-D-*arabino*-hexoside only with respect to a reversal of configuration at this carbon atom.

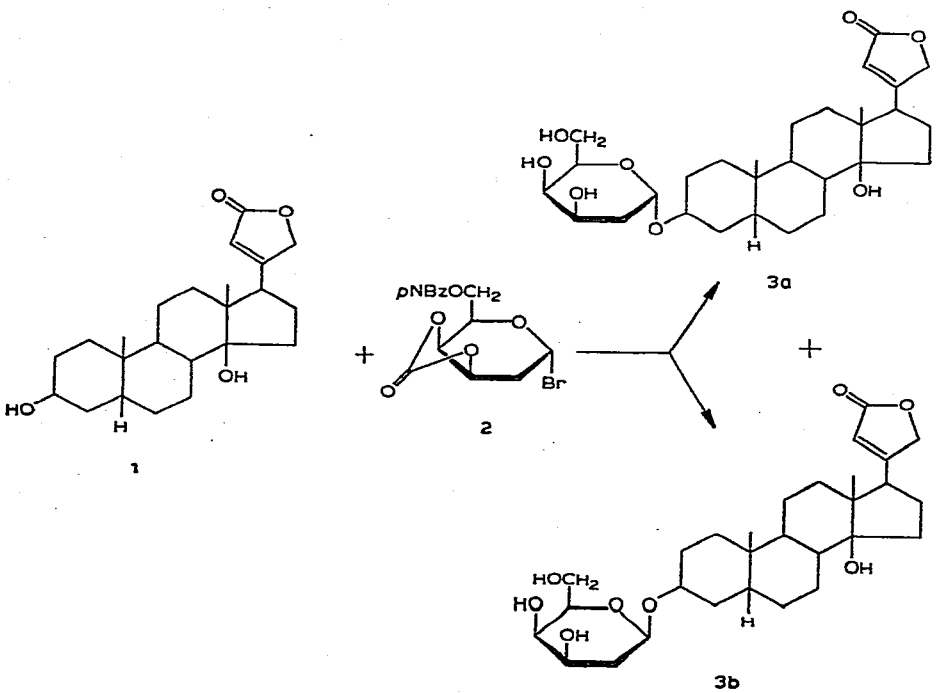
To this end, and also with a view to synthesizing some pyrimidine nucleosides containing 2-deoxy-β-D-*lyxo*-hexopyranose residues, we undertook, and were successful in, the preparation of crystalline 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide[2]. In contrast to similarly constituted halides of other 2-deoxyhexoses[2], the new halide failed to condense with dialkoxypyrimidines, even at elevated temperatures, and, because of this situation, it appeared unlikely that the bromide would have utility in the synthesis of cardiac glycosides.

We have attributed the failure of the *p*-nitrobenzoylated halide to form *N*-glycosyl derivatives to the axially oriented *p*-nitrobenzoyloxy group on C-4, which, apparently, causes C-1 to become a hindered position[2]. Accordingly, we sought to prepare a halide of 2-deoxy-D-*lyxo*-hexose in which the substituent at C-4 would have the smallest possible bulk, and, subsequently, were successful in converting the sugar, in six steps, into crystalline 3,4-*O*-carbonyl-2-deoxy-6-*O*-*p*-nitrobenzoyl-α-D-*lyxo*-hexosyl bromide[3] (**2**). The latter halide readily underwent reaction with dialkoxy-

*This work was supported by Grant No. GSRI-NS257, from the Louisiana State Science Foundation.

pyrimidines at room temperature, and, from these results, it appeared that the halide would have utility in the preparation of some new cardiac glycosides.

Digitoxigenin (**1**) was treated with the new bromide (**2**) under conditions of a modified Koenigs–Knorr synthesis (see Ref. 1, pp. 307–308), affording an anomeric mixture in low yield. The acylated intermediates were not isolated, but were saponified in aqueous methanol with sodium hydrogen carbonate to give the unsubstituted glycosides (**3a** and **3b**). The anomeric configuration of each was determined by the method of molecular rotational additivities[4].



EXPERIMENTAL

Melting points were determined with a Kofler hot-stage, and optical rotations were measured with a Rudolph Model 80 polarimeter. T.l.c. was performed on 250-μm silica gel (Camag DF-5) plates with 1:1:8 butyl alcohol–2,2,4-trimethylpentane–ethyl acetate. The spots were visibilized by spraying either with Kedde reagent[5] or with 80% sulfuric acid, followed by heating the plates at 110° for 5 min.

*3β-(2-Deoxy-α and β-*D*-*lyxo*-hexopyranosyloxy)-14β-hydroxy-5β-card-20(22)-enolide* (**3a** *and* **3b**). — Dry, freshly prepared silver carbonate (1.4 g), 740 mg (2 mmoles) of digitoxigenin (**1**), and 70 ml of dry 1,2-dichloroethane were placed in a 100-ml, 2-necked flask equipped with a dropping funnel and a condenser. The mixture was heated, with magnetic stirring, in an oil bath (105°), and about 20 ml of the solvent was distilled off. A solution of 1.61 g (4 mmoles) of the bromide (**2**) in 100 ml of dry

1,2-dichloroethane (contained in the dropping funnel) was added, with efficient stirring, during 2 h, distillation of the solvent from the reaction flask being maintained at a rate equal to that of the addition of the solution of the bromide. An additional 100 ml of 1,2-dichloroethane was added during 2 h, under the same conditions as those for the addition of the solution of the bromide. To the reaction mixture was added 30 ml of acetone, the mixture was filtered, and the silver salts were thoroughly washed with acetone. The filtrate was evaporated almost to dryness, the residue was dissolved in 50 ml of tetrahydrofuran, and the solution was diluted with 500 ml of methanol, followed by the addition of 200 ml of 1.65% aqueous sodium hydrogen carbonate. The solution was kept for 6 days at room temperature, and then concentrated to about 200 ml by evaporation under diminished pressure at 40°. The mixture was extracted with four 150-ml portions of chloroform, and the aqueous layer (*A*) was preserved. The chloroform extracts were combined, dried with sodium sulfate, and evaporated to dryness under diminished pressure at 40°. The resulting residue was extracted with three 50-ml portions of ether, which were discarded, and the residue was dissolved in 3 ml of absolute ethyl alcohol, followed by the addition of 15 ml of ether. Pentane was added to incipient turbidity, and the mixture was kept in a refrigerator overnight. The crystals that formed were filtered off, giving 85 mg (8.2%, based on **1**) of the α-D-glycoside (**3a**), m.p. 238–248°. Two recrystallizations from ethyl alcohol–ether–pentane afforded 46 mg of pure **3a**, m.p. 248–250°, $[\alpha]_D^{23}$ +73.4° (*c* 0.46, ethyl alcohol), λ_{max}^{EtOH} 217 nm (log ε 4.27), homogeneous by t.l.c. (R_F 0.19). Calc. for [M] (digitoxigenin + methyl 2-deoxy-α-D-*lyxo*-hexopyranoside)[6]: +71° + 292° = +363°. Found for [M] (**3a**): +382°. The glycoside has, therefore, the α-D configuration.

Anal. Calc. for $C_{29}H_{44}O_8$: C, 66.89; H, 8.52. Found: C, 66.74; H, 8.57.

The aqueous layer (*A*) was extracted with five 150-ml portions of 1:4 ethyl alcohol–chloroform and five 150-ml portions of 1:3 ethyl alcohol–chloroform. The extracts were combined, dried with sodium sulfate, and evaporated to dryness under diminished pressure at 40°. The resulting residue was chromatographed on a column (5 × 40 cm) of 220 g of Silica Gel (E. Merck, Darmstadt; 0.05–0.2 mm) premixed with 100 ml of water. Elution was conducted with water-saturated ethyl acetate, and the first 100 ml of eluate was discarded. Collection was made in 6-ml fractions, and, from fractions 64–84, an additional 35 mg of the α-D glycoside was secured, bringing the total yield of **3a** to 11.5%. Fractions 85–145 were combined, and evaporated to dryness under diminished pressure, and the residue was dissolved in 1 ml of absolute ethyl alcohol, followed by the addition of 8 ml of ether and 5 ml of pentane, affording 35 mg (3.4%) of the β-D-glycoside (**3b**), m.p. 195–200° $[\alpha]_D^{23}$ +23.7° (*c* 0.20, ethyl alcohol), λ_{max}^{EtOH} 217 nm (log ε 4.27), homogeneous by t.l.c. (R_F 0.15). Calc. for [M] (digitoxigenin + methyl 2-deoxy-β-D-*lyxo*-hexopyranoside)[6]: +71° −83° = −12°. Found for [M] (**3b**): +123°. The glycoside has, therefore, the β-D configuration.

Anal. Calc. for $C_{29}H_{44}O_8 \cdot H_2O$: C, 64.66; H, 8.61. Found: C, 64.82; H, 8.54.

REFERENCES

1 W. W. ZORBACH AND K. V. BHAT, *Advan. Carbohyd. Chem.*, 21 (1966) 273.
2 W. W. ZORBACH, C. C. BHAT, AND K. V. BHAT, *Advan. Chem. Ser.*, 74 (1968) 1.
3 W. W. ZORBACH, S. L. DEBERNARDO, AND K. V. BHAT, *Carbohyd. Res.*, 11 (1969) 413.
4 W. KLYNE, *Biochem. J.*, 47 (1950) xli.
5 D. L. KEDDE, *Pharm. Weekblad*, 82 (1947) 741.
6 C. C. BHAT, K. V. BHAT, AND W. W. ZORBACH, *Carbohyd. Res.*, 10 (1969) 197.