Notes

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Tetrahydropyranyl Ether Derivatives of Digitoxigenin and Strophanthidin[*4]

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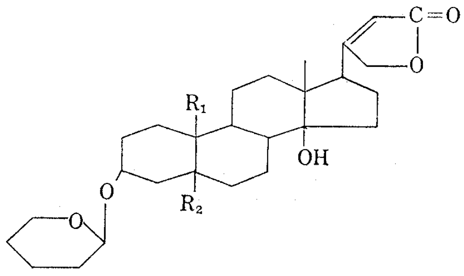
As part of a program dealing with the effect of subtle changes in the carbohydrate component of a cardenolide on its cardiotonic activity, we became interested in the effect of deoxygenating certain positions in the sugar portion of the molecule. To this end we have also "oxygenated" the potent convallatoxin by coupling L-mannose with strophanthidin, and the resulting 6′-hydroxyconvallatoxin[1)] was shown to be even more potent than convallatoxin itself. The results we have thus far obtained point clearly to the fact that, in general, deoxygenation in the sugar component leads to a decrease in potency.

As a further test of this hypothesis, we considered the preparation of 3-O-(tetrahydro-2-pyranyl) digitoxigenin (3β-(tetrahydro-2-pyranyloxy)-14β-hydroxy-5β-card-20(22)-enolide (I) and 3β-O-(tetrahydro-2-pyranyl)strophanthidin (3β-(tetrahydro-2-pyranyloxy)-19-oxo-5β,14β-dihydroxycard-20(22)-enolide (II).[2)] Such derivatives would, in effect, be pentopyranosides completely devoid of oxygen function. In each case, I and II were prepared by dissolving the aglycone in dry dihydropyran and adding a small quantity of *p*-toluenesulfonic acid.



I : R_1=CH_3, R_2=H

II : R_1=CHO, R_2=OH

Chart 1.

A comparison of the potencies of some selected cardenolides is found in Table I and, with the digitoxigenin hexosides the adverse effect of removing oxygen function from the carbohydrate component is clearly demonstrated. Unfortunately, strophanthidin cardenolides do not lend themselves well for providing this kind of information; this is likely due to interaction between the carbohydrate portion and the C5 hydroxyl group or C19 oxo group of the steroid fragment, or both. Such interactions would not obtain with digitoxigenin hexosides owing to the fact that C5 and C19 of the aglycone carry only hydrogen atoms.

As expected, the completely deoxygenated tetrahydropyranyl derivatives (I) and (II) show a low order of activity; however, it was surprising to note in each case that the

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1) *a*) W. W. Zorbach, S. Saeki : Naturwiss., **50**, 93 (1963). *b*) W. W. Zorbach, S. Saeki, W. Bühler : J. Med. Chem., **6**, 298 (1963).

2) During the course of our inyestigation, this compound was independently prepared by K. Lingner, K. Irmscher, W. Küssner, R. Hotovy, J. Gillisen : Arzneimittel Forschung, **13**, 142 (1963).

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Table I. Cardiotonic Activity of Selected Hexosides of Digitoxigenin and of Strophanthidin as Measured Intravenously in Cats

	LD/mg.[*6]	LD/μmole
Hexosides of digitoxigenin (LD/mg. = 2.2)		
β-D-Glucoside[3]	8.0	4.3
2-Deoxy-β-D-glucoside[4]	5.3	2.8
2-Deoxy-β-D-alloside[5]	5.1	2.7
2,6-Dideoxy-β-D-alloside[3]	4.6	2.3
"2,3,4-Trideoxy-β-D-pentoside"[*7] (3-Tetrahydropyranyl deriyative (I))	0.4	0.2
Hexosides of strophanthidin (LD/mg. = 3.4)		
α-L-Mannoside[1]	14.5	8.2
6-Deoxy-α-L-mannoside (convallatoxin)[3]	12.6	6.9
β-D-Glucoside[3]	11.0	6.2
2,6-Dideoxy-β-D-alloside[3]	12.5	6.7
"2,3,4-Trideoxy-β-D-pentoside"[*7] (3-Tetrahydropyranyl derivative (II))	1.8	0.9

potency was lower than that of the corresponding aglycone. It may be reasoned, therefore, that the pyranose *per se* makes no contribution in terms of cadiotonic enhancement, but merely acts as a vehicle for carrying hydroxy function. The results disclosed herein suggest that the tetrahydropyranyl ring in I and II serves only to "dilute" the cardiotonic activity of the aglycone.

Experimental

General Directions for Forming the Tetrahydropyranyl Derivatives (I) and (II)——One millimole of the aglycone was dissolved in 80 ml. of dry dichloromethane and 20 ml. of the solvent was distilled off to remove traces of water. After cooling to room temperature, 180 mg. (2.2 mmoles) of absolute dihydropyran and 2 mg. of *p*-toluenesulfonic acid were added. The solution was allowed to stand at room temperature overnight and was then washed with 5% aqueous sodium bicarbonate. The dichloromethane layer was dried over magnesium sulfate and evaporated to dryness, leaving a solid, non-crystalline residue.

3β-O-(Tetrahydro-2-pyranyl)digitoxigenin (I)——The crude product was dissolved in 70% aqueous ethanol and decolorized with Darco G-60. The crystalline material separating from the filtrate was recrystallized again from the same solvent, giving 256 mg. (56%) of I, m.p. 161~165°, $[\alpha]_D^{26}$ +31.9° (c=1.138, $CHCl_3$). *Anal.* Calcd. for $C_{28}H_{42}O_5$: C, 73.32; H, 10.82. Found : C, 73.25; H, 10.85.

3β-O-(Tetrahydro-2-pyranyl)strophanthidin (II)——The crude product was placed on a column (3×26 cm.) of 100 g. of Fisher reagent grade silicic acid (activated by heating for one hour at 105°). Elution was carried out in 2.5 ml. fractions using methanol-chloroform (1:99). Fractions 200~220 contained 150 mg. of crystalline material which, when recrystallized from a small amount of methanol, gave 130 mg. (27%) of II, m.p. 179~182°, $[\alpha]_D^{20}$ +46.0° (c=1.00, $CHCl_3$).

When chromatographed on paper by an ascending technique, using 1-butanol saturated with water, II had Rf 0.79 (in the same system strophanthidin had Rf 0.72). *Anal.* Calcd. for $C_{28}H_{40}O_7$: C, 68.82; H, 8.25. Found : C, 68.67; H, 8.14.

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[*6] LD/mg. refer to the number of lethal doses per mg. and may be obtained simply by taking the reciprocal of the MLD mean (geometric) lethal dose in mg./kg., as measured in 10 cats.

[*7] Assays on the two new cardenolides (I and II) were carried out by Prof. K.K. Chen, Department of Pharmacology, Indiana University Medical School, Indianapolis. The authors wish to thank Prof. Chen for this valued co-operation.

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