acetoxy at C-3 (*i.e.*, the *gulo* isomer II) should show a small splitting (*ca.* 2 c.p.s.) for the H-3 doublet, whereas the isomer having an equatorial C-3 acetoxy substituent (*i.e.*, the *altro* isomer III) should show H-3 as a doublet with a large splitting (*ca.* 10 c.p.s.). Additional proof of these assignments should follow from the measurements of the splittings of the H-5 resonance if these could be observed. It was indeed fortunate that the downfield shift of H-3 and H-5, caused by the adjacent acetoxy substituents, was sufficient for both these hydrogens to be resolved, and hence for II and III to be distinguished. One isomer exhibited a doublet, which could only be H-3, at τ 4.71 (splitting, 4.6 c.p.s.) and three lines of a partially concealed quartet, which must be H-5, at τ 4.89 (splittings, 3.5 and 10.4 c.p.s.); clearly, this must be the *gulo* isomer II. The remaining isomer showed the H-3 doublet at τ 4.89 (splitting, 9.9 c.p.s.) and a partially concealed quartet for H-5 at τ 4.97 (splittings, 2.1 and 4.4 c.p.s.), all of which is consistent with the *altro* configuration (III).

Although the ring hydrogens of the *allo* isomer I were not well resolved, they were consistent with the assigned configuration. H-3 occurred as a poorly resolved doublet at τ 4.77 (splitting, *ca.* 4 c.p.s.), and while H-5 overlapped with the resonances of two other hydrogens the total band width was insufficient to accommodate an axial–axial coupling of *ca.* 10 c.p.s.

Also included in Table I are the acetoxy resonances of fully acetylated 2,7-anhydro-β-D-altroheptulopyranose (sedoheptulosan, IV), although this product could not be obtained in crystalline condition. However, the resonances were as expected, showing one axial and three equatorial substituents.

Experimental

The 60-Mc./sec. p.m.r. spectra were measured in a Varian V-4302B spectrometer for chloroform solutions. A Varian V-3521 integrator was used for base line stabilization. Calibration was by the usual side-band technique with tetramethylsilane as internal reference. The chemical shifts and multiplet splittings in Table I are averaged values from at least three spectra.

Acetylation of Aminodeoxyheptulosans.—Aminodeoxyheptulosan (about 100 mg.) in pyridine (2 ml.) was treated with acetic anhydride (2 ml.) at room temperature for 2 days. Excess anhydride was destroyed by the addition of methanol and the solution was evaporated *in vacuo*. The sirupy residue was taken up in 15 ml. of chloroform which was then extracted once with 6 ml. of *N* sulphuric acid and twice with 6 ml. of a saturated sodium hydrogen carbonate solution. After drying over anhydrous sodium sulfate and evaporation of the chloroform solution, the crystalline acetylated aminodeoxyheptulosan was obtained from, and recrystallized with, chloroform–ether. The three isomers were obtained in yields of 50–65% and had the following properties: **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-alloheptulopyranose** (I, from compound IVa[1]), oblong flat platelets, m.p. 213–214° dec., $[\alpha]^{22}D$ −60.9° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-guloheptulopyranose** (II, from compound IVb[1]), thin prisms, m.p. 128–129°, $[\alpha]^{22}D$ +43.7° (*c* 1, chloroform); **4-acetamido-4-deoxy-1,3,5-tri-*O*-acetyl-2,7-anhydro-β-D-altroheptulopyranose** (III, from compound IVc[1]), fine needles, m.p. 189–190°, $[\alpha]^{22}D$ −145.5° (*c* 1, chloroform).

Anal. Calcd. for $C_{15}H_{21}NO_9$ (359.3): C, 50.13; H, 5.89. Found for I: C, 50.07; H, 5.72. Found for II: C, 49.74; H, 5.78. Found for III: C, 50.36; H, 5.56.

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2-Deoxy Sugars. VI. Concurrent One-Step Formation of Both Anomeric Monodigitoxosides of Digitoxigenin[1]

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This paper deals with the direct coupling of digitoxose (2,6-dideoxy-β-D-*ribo*-hexose, I) with digitoxigenin [3β,14β-dihydroxy-5β-card-20(22)-enolide, II] to give not only the α-monodigitoxoside (III) but the β-anomeric form (IV) as well. The β-, or "natural," anomer was obtained originally by a controlled, partial hydrolysis of digitoxin,[3] but when we attempted to synthesize the material by coupling 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride with digitoxigenin (II), we obtained the alternate anomeric form (III) instead (see Scheme I).[4]

The presently described reaction was carried out by treating a solution of digitoxigenin (II) and an excess of digitoxose (I) in pure dioxane with a small quantity of hydrogen chloride–dichloromethane solution. After neutralizing the acid, the reaction products were dissolved in aqueous methanol and were extracted with chloroform to remove all extraneous carbohydrate materials. Thin-layer chromatograms disclosed two major spots corresponding chromatographically to the α- and β-monodigitoxosides III and IV, respectively.

The extracted material was resolved by first chromatographing on formamide–cellulose powder[5] which brought about an incomplete separation of II, III, and IV. The fractions containing the latter were recombined and were chromatographed on silicic acid giving a complete separation, from which the monosides III and IV were obtained in a combined yield of 10% based on the genin II.

The formation of an α-glycoside (III) is of interest and may be accounted for satisfactorily in terms of the "anomeric" effect (structure A)[6] which allows for an attraction between the axially oriented α-glycosidic oxygen atom and C-5 which carries a partial positive charge. Such an attraction would overcome, at least in part, the conformational instability imposed by the erected oxygen atom. In the case of pyranosides which are not deoxygenated at C-6, the added electron-

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(2) (a) To whom all enquiries concerning this paper should be addressed; (b) U. S. Public Health Service Predoctoral Fellow; (c) visiting scientist, Georgetown, University, 1961–1963.

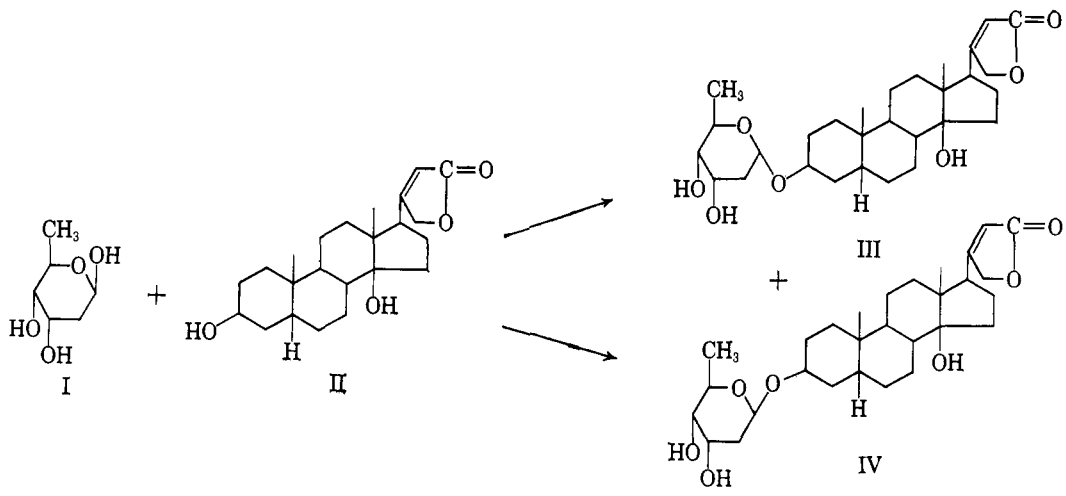
(3) F. Kaiser, E. Haack, and H. Spingler, *Ann. Chem.*, **603**, 75 (1957).

(4) (a) W. W. Zorbach and T. A. Payne, *J. Am. Chem. Soc.*, **81**, 1519 (1959); (b) **82**, 4079 (1960).

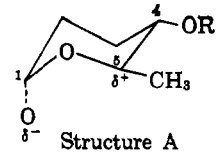
(5) E. Haack, F. Kaiser, and H. Spingler, *Chem. Ber.*, **89**, 1353 (1956).

(6) R. U. Lemieux and P. Chu, Abstracts, 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April, 1958, p. 31N. The suggestion that the formation of α-cardenolides is due most likely to this effect was communicated privately by Professor Lemieux to whom the authors are most grateful.

SCHEME I



withdrawing power of the C-5 hydroxymethyl (or acyloxymethyl) group should increase the charge on C-5, thus favoring even more α-glycoside formation.[7] In the present case (structure A, R = H) this attraction is not strong enough to offset to a large degree the conformational instability with the result that substantial amounts of the conformationally more stable β-digitoxoside (IV) were formed.



Structure A

Support for this argument is given in the coupling of 2,6-dideoxy-3,4-di-*O*-*p*-nitrobenzoyl-β-D-*ribo*-hexosyl chloride with digitoxigenin (II)[4] which was carried out under equilibrating conditions in the absence of an acid acceptor. Under these conditions, an α-glycoside was formed exclusively, and it is suggested that the powerful electron-withdrawing capacity of the C-4 *p*-nitrobenzoyl group (structure A, R = p-$O_2NC_6H_4\overset{O}{\overset{\|}{C}}$–) was sufficient to offset conformational instability to a point where β-glycoside formation was excluded.

Experimental

All melting points were determined using a Kofler hot stage. Diagnostic thin-layer chromatograms were carried out on Fluka No. D5 TLC silica gel and were developed employing the upper phase separating from an ethyl acetate–pyridine–water (5:1:4) mixture as described by Steinegger and van der Walt.[8]

α- and β-Monodigitoxosides (III and IV) of Digitoxigenin (II).—To a solution of 748 mg. (2.0 mmoles) of digitoxigenin (II) and 592 mg. (4.0 mmoles) of digitoxose (I) in 10 ml. of anhydrous dioxane was added 2 ml. of a solution of dichloromethane containing 0.1 mequiv./ml. of anhydrous hydrogen chloride. After standing for 24 hr., the solution was neutralized by stirring for a short time with an excess of silver carbonate. The filtered solution was then evaporated to dryness at 30° and the sirup was dissolved in 400 ml. of methanol followed by the addition of 1 l. of water. The aqueous solution was shaken thoroughly with 60 ml. of chloroform and, after separating, the chloroform extract was washed three times with small portions of water. After drying over sodium sulfate, the extract was evaporated to dryness at 30°, giving 1.0 g. of sirup containing only Kedde-positive material.

The latter material was placed on a column (4 × 40 cm.) of 200 g. of cellulose powder (Whatman No. 1) previously treated with a 40% (v./v.) solution of formamide in acetone and which was thoroughly dried to remove the acetone prior to packing. Elution was carried out in 2.5-ml. fractions using tetrahydrofuran–cyclohexane (2:3) saturated with formamide. Fractions 62–130, amounting to 330 mg., were combined and were placed on a column (3 × 35 cm.) of 250 g. of silicic acid. The column was eluted with tetrahydrofuran–cyclohexane (2:3), 2.5-ml. fractions being collected. Fractions 241–280 contained 90 mg. of material which, on recrystallization from ether–tetrahydrofuran, gave pure digitoxigenin (II), m.p. 250–254°, $[\alpha]^{30}D$ +20.2° (*c* 0.962, methanol). Fractions 291–360 contained 40 mg. (5.4%) of the α-monodigitoxoside (III) which, after recrystallization from ether–tetrahydrofuran, gave pure III, m.p. 252–256°, $[\alpha]^{30}D$ +87.0° (*c* 0.361, methanol); lit.[4b] m.p. 251–255°, $[\alpha]^{20}D$ +85.1° (in methanol). Fractions 441–500 amounted to 34 mg. (4.5%) of material which, after recrystallization from absolute ether, gave pure β-monodigitoxoside (IV), m.p. 204–209°,[9] $[\alpha]^{30}D$ −7.1° (*c* 0.446, methanol). The ultraviolet and infrared absorption spectra of the two monosides (III and IV) were identical in all respects with the spectra prepared from corresponding authentic samples. Because the analytical data thus presented for III and IV were unambiguous, combustion analyses were considered unnecessary.

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(7) J. T. Edward, P. E. Morand, and I. Puskas [*Can. J. Chem.*, **39**, 2069 (1961)] suggest, for hexopyranoses not deoxygenated at C-6, that through an inductive effect both the C-4 and C-6 hydroxyl groups serve to augment the positive charge on C-5.

(8) E. Steinegger and J. H. van der Walt, *Pharm. Acta Helv.*, **36**, 599 (1961).

(9) The melting point recorded herein does not agree with the value of 181–184° originally reported[8] by Kaiser and co-workers. In a private communication Dr. F. Kaiser pointed out that, when larger amounts of the β-monoside are isolated from *D. lanata*, he obtains m.p. 205–208° which agrees closely with m.p. 202–208° of some material he had sent us previously. The authors wish to take this opportunity to thank Dr. Kaiser for his generous gift of β-monodigitoxoside.