Heterocyclic *N*-Glycosides. VIII. Anomerisation and Rearrangement of 2′,3′-Unsaturated *N*-Glycosides.

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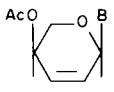
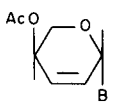
The acid catalyzed transformation of either 1-(4′-*O*-acetyl-2′,3′-dideoxy-α- or β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole gave the same mixture of unsaturated glycosides. The main three components of this mixture were the above α and β anomers and a glycal-type compound which results from the allylic rearrangement of the 5,6-dichlorobenzotriazole moiety to the C-3 position of the carbohydrate. Evidence is presented that these results can be rationalized as proceeding through an allylic carbonium ion. Preliminary experiments on transglycosidation reactions using 2′,3′-unsaturated *N*-glycosides are reported.

In previous papers on the synthesis of heterocyclic *N*-glycosides for further testing as anticancer agents, the preparation of a series of 2′,3′-unsaturated *N*-glycosides was reported (1,2). The synthesis of those unsaturated compounds was achieved by the reaction of glycal derivatives (3,4-di-*O*-acetyl-D-xylal and 3,4-di-*O*-acetyl-L-arabinal) with 6-chloropurine (I) and benzotriazoles (2) dissolved in a proper solvent, and in the presence of a catalytic amount of trifluoroacetic acid.

In all the experiments carried out so far a mixture of several components was obtained being generally present in this reaction mixture the following three compounds which were separated by preparative tlc: the anomeric pair of the corresponding 2′,3′-unsaturated *N*-glycosides which can be represented as in I and II, and a glycal type compound (3) (III) in which the heterocyclic base is joined to C-3 position of the sugar moiety.



I



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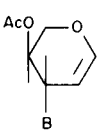


III

In order to gain information about the stability of these compounds and if possible about how they are produced, a sample of each of them was treated under similar reaction conditions as those used in their preparation. The reactions were monitored by NMR spectroscopy and the resulting products of each experiment were isolated and identified.

In this way, when the anomeric compounds 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (IV) and 1-(4′-*O*-acetyl-2′,3′-dideoxy-α-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (V) (5) were dissolved in chloroform with a catalytic amount of trifluoroacetic acid, and heated in a sealed tube both gave the same mixture of compounds. The main three components of this mixture were the two anomers (IV) and (V) (Chart I) and the glycal type compound VI which results from an allylic rearrangement of IV or V. In addition, two minor components were also isolated, and their structures were shown to be from the spectroscopy data (UV, IR and NMR) VII and VIII, respectively.

The only difference observed so far during the above experiments was that the conversion of the β-anomer (IV) to the reaction mixture began first than in the case of the α-anomer (V), although the final mixture composition was sensibly the same in both cases.

On the other hand, no reaction took place when 1,2,3-trideoxy-4-*O*-acetyl-3-(5′,6′-dichloro-1′-benzotriazolyl)-L-threo-pent-1-enopyranose (VI) (7) was submitted under exactly the same experimental conditions as the above *N*-glycosides, the starting material being recovered in about 80% yield.

The importance of the acid catalyst in those experiments was demonstrated from the fact that when the reactions were carried out in a sealed tube in the absence of trifluoroacetic acid, and using degasified solutions of the reactants, no reaction was observed.

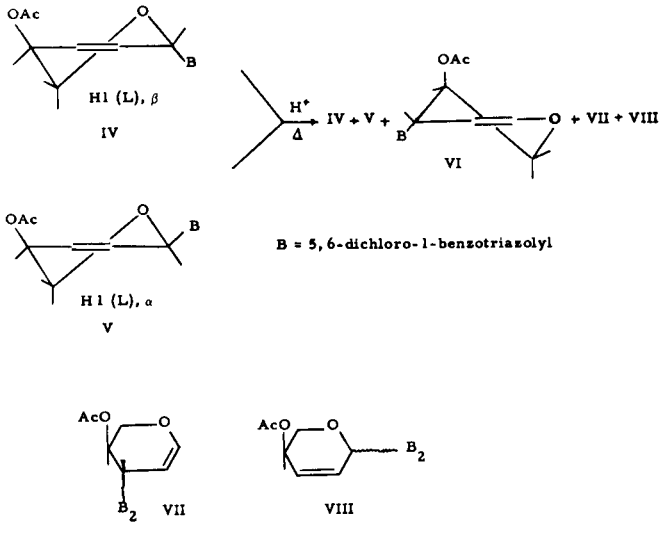
These results can be rationalized on the basis of formation of the stabilized carbonium ion (IX) which has previously been invoked by Ferrier (8) to explain other glycal reactions. However, the anomerisation of 2′,3′-unsaturated

TABLE I

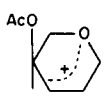
Compounds	$[\alpha]_D$ (chloroform) D-series	$[\alpha]_D$ (chloroform) L-series	Parcially racemized compounds (amount obtained)
A	-164.7 c ≅ 1.5	+167.3 c ≅ 1.2	+14° c ≅ 0.25 (5 mg.)
B	+22.4 c ≅ 1	-25.8 c ≅ 1	-4° c ≅ 1.8 (80 mg.)
C	-7.4 c ≅ 1	+9 c ≅ 0.5	0° c ≅ 0.5 (23 mg.)
D	-216 c ≅ 0.5		-20° c ≅ 0.4 (8 mg.)
E	+120.7 c ≅ 1	-122.4 c ≅ 0.8	+2.9° c ≅ 0.5 (54 mg.)

A - 1,2,3-Trideoxy-4-*O*-acetyl-3-(5′,6′-dichloro-1′-benzotriazolyl)-*threo*-pent-1-enopyranose
B - 1-(4′-*O*-acetyl-2′,3′-dideoxy-*β*-*glycero*-pent-2′-enosyl)5,6-dichlorobenzotriazole
C - 1-(4′-*O*-acetyl-2′,3′-dideoxy-*α*-*glycero*-pent-2′-enosyl)5,6-dichlorobenzotriazole
D - 1,2,3-Trideoxy-4-*O*-acetyl-3-(1′-benzotriazolyl)-*threo*-pent-1-enopyranose
E - 1-(4′-*O*-acetyl-2′,3′-dideoxy-*β*-*glycero*-pent-2′-enosyl)benzotriazole.

Chart I



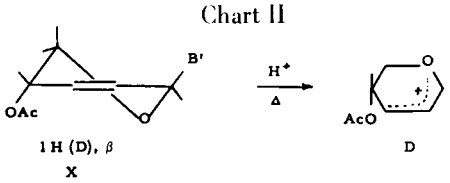
N-glycosides might proceed as well through similar mechanisms to those occurring in the anomerisation of furanosides and pyransides (9).

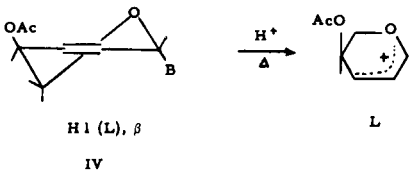


In order to obtain any evidence for the existence of this carbonium ion (IX) as an intermediate in the above reactions, it was decided to carry out an experiment similar to the preceding formerly described, using a mixture of equimolecular amount of two different 2′,3′-unsaturated *N*-glycosides (one from benzotriazole and the other one from 5,6-dichlorobenzotriazole) having the same anomeric configuration and sugar moiety, but this belonging to the D- and L-series, respectively.

If the reaction goes through a carbonium ion, as represented in Chart II, this would now be a mixture of a D-carbocation with a L-carbocation, and the resulting compounds would therefore have to be racemic or parcially racemized compounds.

Chart II





According to it a mixture of 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enosyl)benzotriazole (X) and 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (IV) was dissolved in chloroform and heated in a sealed tube in the presence of trifluoroacetic acid as catalyst. On work up, a mixture of compounds was obtained from which the expected anomers of the starting *N*-glycosides, the corresponding derivatives from the allylic rearrangement of the heterocyclic moieties, and the starting materials were isolated by thick-layer chromatography and identified. All the compounds so obtained showed specific optical rotation values close to 0°. In Table I are collected these values along with those of the corresponding optically active derivatives.

This almost total racemization can not be attributed to any cause acting upon the chiral C-4′ center, because as it was shown before the products obtained from the decomposition of IV or V are optically active.

A possible explanation to the fact that these compounds have some optical activity could be that they were contaminated with a small amount of the corresponding optically active compound which in turn could also have been produced if one of the carbocation intermediates (Chart II) was formed faster than the other and therefore some anomerisation and rearrangement process has taken place before the racemization.

The evidence so obtained is taken as support for the existence of the allylic carbonium ion (IX) which is not much different from the cyclopropylcarbinyl-oxo-carbonium ion (XI) proposed by Fraser-Reid *et al.*, (10) to explain the unusually high solvolytic reactivity of 4,6-*O*-benzylidene-1,2,3-trideoxy-3-*C*-iodomethyl-D-*ribo*-hex-1-enopyranose. On the other hand, the case of the acid-catalyzed hydrolysis of methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside has been considered by Horton *et al.* (11) as attributable to allylic stabilization of an intermediate C-1 carboxonium ion.

XI

As a consequence of the work above described the possibility of using 2′,3′-unsaturated *N*-glycosides in transglycosidation reactions (glycosyl transfer from a preformed *N*-glycoside to a heterocyclic compound) is being studied. In this way 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (IV) has been converted in rather satisfactory yield to 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)benzotriazole.

Although this procedure has not been assessed for its general utility it would appear to offer a new approach to the synthesis of 2′,3′-unsaturated *N*-glycosides. Experiments in this way are now being conducted in our laboratory.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a 60 Mc Perkin-Elmer R-12 spectrometer and the ultraviolet spectra on a Perkin-Elmer 350 spectrophotometer. Specific rotations were determined with a Perkin-Elmer 141 polarimeter. Tlc was performed with 0.25 mm chromatoplates of silica gel GF_{254} (Merck) and spots were visualized with UV light of 254 mμ.

Decomposition of 1-(4′-*O*-Acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (IV).

A solution of 139 mg. of IV (6) (m.p. 184-185° from benzene, $[\alpha]_D$ -25.8°, (c ~ 1, chloroform) in deuteriochloroform (0.7 ml.) with a trace of trifluoroacetic acid was heated, in a sealed NMR tube, at 100° for 130 hours. After this, the resulting mixture of compounds was applied to one preparative tlc plate (20 x 20 cm and 2 mm thickness, silica gel, Merck PF_{254}) and the plate was developed several times with a mixture of ether-petroleum ether 1:3.

From the faster moving band it was obtained 15 mg. of a syrupy compound to which the structure VII was tentatively assigned.

NMR (deuteriochloroform, τ) 1.94 singlet (2H, aromatic), 3.19 doublet (1H, vinylic H-1), 4.91 multiplet (1H, vinylic H-2), 4.54 multiplet (2H, H-3 and H-4), 5.72 multiplet (2H, H-5), 7.88 singlet (3H, acetoxy group). IR, 1650 cm^{-1} and 1230 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_3 \cdot H_2O$: C, 45.08; H, 3.75; N, 12.13. Found: C, 44.66; H, 3.53; N, 12.48.

The following band gave 14 mg. of a colourless solid, m.p. 163-165° (from ethyl acetate-petroleum ether), $[\alpha]_D$ -281.9° (c 0.5, chloroform); U.V. λ max (chloroform), 296 (ε, 13,500), 306 mμ (ε, 11,500). The compound was identified as 2-(4′-*O*-acetyl-2′,3′-dideoxy-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (VIII) by comparison with a sample obtained from the reaction of 3,4-di-*O*-acetyl-L-arabinal with 5,6-dichlorobenzotriazole (6).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_3$: C, 47.56; H, 3.35; N, 12.80; Cl, 21.64. Found: C, 47.34; H, 3.39; N, 12.94; Cl, 21.68.

The next band gave 11 mg. of a syrup identified as 1,2,3-trideoxy-4-*O*-acetyl-3-(5′,6′-dichloro-1′-benzotriazolyl)-L-threo-pent-1-eropyranose (VI), $[\alpha]_D$ +167.3° (c 1.2, chloroform), U.V. λ max (ethanol), 267 (ε, 7,500), 297 mμ (ε, 5,100). This product was shown to be identical to that obtained from the reaction between 3,4-di-*O*-acetyl-L-arabinal and 5,6-dichlorobenzotriazole (6).

The next band gave 38 mg. of the starting compound IV. Finally, the slower moving band gave 30 mg. of a solid which was recrystallized from ethyl acetate-petroleum ether, m.p. 117-118°, $[\alpha]_D$ +9° (c 0.5, chloroform), U.V. λ max (chloroform), 263.5 (ε, 7,200), 298 mμ (ε, 4,975). This compound was identified as 1-(4′-*O*-acetyl-2′,3′-dideoxy-α-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (V) by comparison with that obtained from the direct condensation of 3,4-di-*O*-acetyl-L-arabinal and 5,6-dichlorobenzotriazole (6).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_3$: C, 47.56; H, 3.35; N, 12.80; Cl, 21.64. Found: C, 47.30; H, 3.33; N, 12.92; Cl, 21.67.

Decomposition of 1-(4′-*O*-Acetyl-2′,3′-dideoxy-α-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole (V).

A solution of 122 mg. of V, m.p. 117-118° (from ethyl acetate-petroleum ether), $[\alpha]_D$ +9° (c ~ 0.5, chloroform) in 0.7 ml. of

deuteriochloroform was heated under the same experimental conditions used in the preceding case. The reaction mixture was chromatographed as before resulting in the separation and identification of exactly the same compounds as above.

Decomposition of 1,2,3-Trideoxy-4-*O*-acetyl-3-(5′,6′-dichloro-1′-benzotriazolyl)-L-*threo*-pent-1-enopyranose (VI).

A solution of 0.12-mg. of VI, $[\alpha]_D$ +167.3° (c ≅ 1.2, chloroform) in 0.7 ml. of deuteriochloroform was treated as above. No reaction took place and VI was recovered unchanged in ~ 80% yield.

Mixed Decomposition of 1-(4′-*O*-Acetyl-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enosyl)benzotriazole and 1-(4′-*O*-Acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole.

A equimolecular mixture of 103 mg. of 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-D-*glycero*-pent-2′-enosyl)bnezotriazole (X) and 131 mg. of IV in 1 ml. of pure chloroform with a catalytic amount of trifluoroacetic acid was heated in a NMR sealed tube at 100° for 4 days. After this time the solution was applied to two preparative tlc plates (20 x 20 cm and 2 mm thickness silica gel, Merck PF_{254}). The plates were developed several times in a mixture of ether-petroleum ether 1:2, resulting in the separation of the four major spots which were detected by a UV lamp (254 mμ). The original No. 3 spot (from top) was shown to be formed by two compounds which were separated by tlc using ethyl acetate-petroleum ether 1:1 as developing system.

In Table 1 are listed the parcially racemized products separated in the order they appeared in the tlc from top to bottom, along with the amounts obtained. Also are collected the specific rotations data for these and the corresponding optically active compounds.

Transglycosidation Reaction of 1-(4′-*O*-Acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)-5,6-dichlorobenzotriazole with Benzotriazole.

A solution of IV (150 mg.) and benzotriazole (150 mg.) in chloroform (1 ml.) was heated in a NMR tube at 100° for 24 hours. After this time the reaction mixture was diluted with ethyl acetate and the products were separated by thick-layer chromatography (silica gel PF_{254}, Merck, 20 x 20 cm and 2 mm thickness, ethyl acetate-chloroform 1:4). The faster moving band afforded 64 mg. of the starting *N*-glycoside IV. The next band furnished 55 mg. of 1-(4′-*O*-acetyl-2′,3′-dideoxy-β-L-*glycero*-pent-2′-enosyl)benzotriazole, m.p. 144-145° (from ethyl acetate-petroleum ether); $[\alpha]_D$ -122° (c 0.5, chloroform); U.V. λ max (ethanol), 254 (ε, 7,040), 280 mμ (ε, 3,910). This compound was shown to be identical to that obtained from the reaction of 3,4-di-*O*-acetyl-L-arabinal and benzotriazole (6).

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.02; N, 16.21. Found: C, 60.04; H, 4.97; N, 16.16.

Acknowledgment.

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(2) M. Fuertes, G. García-Muñoz, M. Lora-Tamayo, R. Madroñero and M. Stud, *Tetrahedron Letters*, 4089 (1968).

(3) Compounds like III *i.e.*, 1,2,3-trideoxy-4-*O*-acetyl-3-(6′-chloro-9′-purinyl)-D-*threo*-pent-1-enopyranose (1) (obtained from the reaction of 6-chloropurine with 3,4-di-*O*-acetyl-D-xylal) along with that recently reported by Townsend *et al.*, (4), 3-deoxy-3-(6-chloro-2-methylthio-9-purinyl)-D-erythro-hex-1-enopyranoses, represent a new class of nucleoside analogs.

(4) E. E. Leutzinger, R. K. Robins and L. B. Townsend, *Tetrahedron Letters*, 3751 (1970).

(5) These compounds have been previously obtained from the reaction of 3,4-di-*O*-acetyl-L-arabinal with 5,6-dichlorobenzotriazole. Their structure and conformation were established by NMR studies (6).

(6) M. Fuertes, G. García-Muñoz, R. Madroñero, M. Stud and M. Rico, work to be published.

(7) This product was also obtained from the reaction of 3,4-di-*O*-Acetyl-L-arabinal and 5,6-dichlorobenzotriazole (6).

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