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C-Glycosyl Nucleosides. VI. Synthesis of Several 3- and 5-(β-D-Ribofuranosyl)isoxazoles

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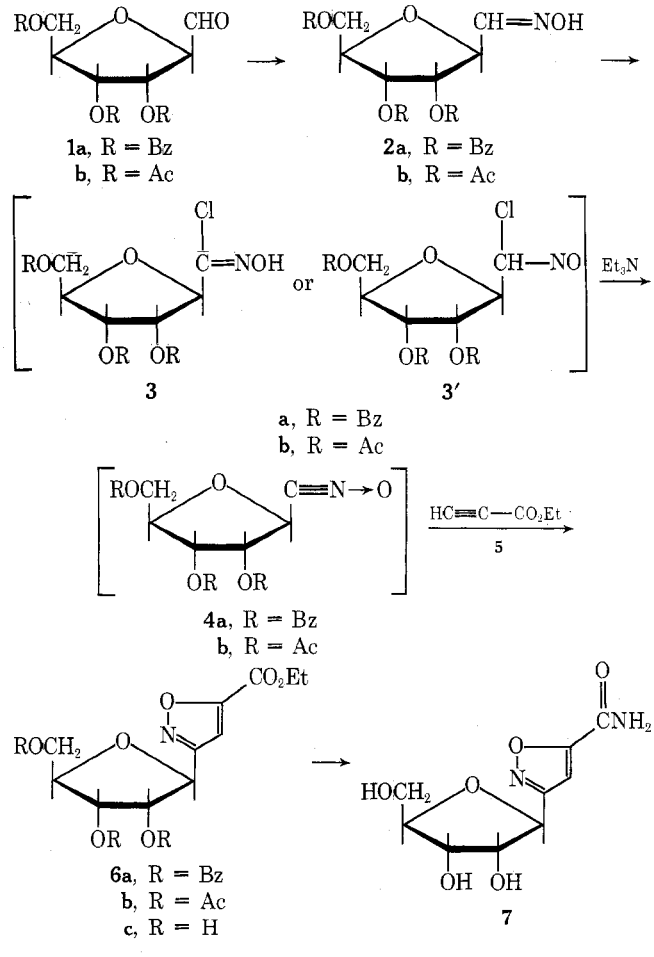
The oximes of several derivatives of 2,5-anhydro-D-allose were chlorinated at low temperature and then treated with triethylamine to generate nitrile oxides. The latter underwent 1,3-dipolar cycloaddition reactions with ethyl propiolate and with dimethyl acetylenedicarboxylate to form 3-(β-D-ribofuranosyl)isoxazolecarboxylates in good yield. Various sequences of deblocking then gave rise to several substituted isoxazole C-glycosyl nucleosides. Condensation of 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose with acetonylidenetriphenylphosphorane gave the unsaturated ketone (**13a**) which was converted to its oxime and oxidatively cyclized with iodine. Deblocking of the resulting product then gave 3-methyl-5-(β-D-ribofuranosyl)isoxazole.

In a previous paper in this series we have described the synthesis of a number of variously substituted derivatives of 2,5-anhydro-D-allose (e.g., **1, 9a**).[1] Such compounds provide versatile starting materials for the synthesis of C-glycosyl nucleosides through elaboration of the aldehyde function into heterocyclic systems. In this vein we have already described a facile synthesis of the antibiotic showdomycin[2] and of a number of 4-(β-D-ribofuranosyl)pyrazoles.[3] In the present paper we describe the conversion of suitable 2,5-anhydro-D-alloses into several 3- and 5-(β-D-ribofuranosyl)isoxazoles.

Of the various methods available for the synthesis of isoxazoles[4] the most convenient for our purpose appeared to be the 1,3-dipolar cycloaddition of nitrile oxides to activated acetylenes.[5] With this in mind 2,5-anhydro-3,4,6-tri-O-benzoyl-D-allose (**1a**) was converted into its oxime (**2a**), which was isolated as a syrup in 91% yield as a roughly 4:1 mixture of geometrical isomers as judged by TLC. Without any further purification **2a** was converted into the α-chloro oxime **3** by reaction with chlorine in ether at −60° according to the general procedure of Casnati and Ricca.[6] During this treatment the solution assumed a greenish-blue color and deposited a precipitate, but following evaporation of the solvent the chloro oxime (**3a** or its nitroso tautomer **3'a**) was obtained as a colorless syrup with a TLC mobility somewhat greater than that of **2a**. The course of the chlorination of the oximes of several aldehydo sugars has been carefully examined by Tronchet et al.[7] and the crude product is expected to be a mixture of **3a, 3'a,** and the nitroso dimer. Without purification or further examination this product was treated with triethylamine in the presence of ethyl propiolate (**5**). The procedure is expected to convert the chloro oxime into the nitrile oxide **4,** which undergoes 1,3-dipolar cycloaddition with **5** to form 3-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (**6a**), a product that was isolated in 67% yield as a homogeneous syrup.

It is well known that in the absence of overriding steric or electronic influences, 1,3-dipolar cycloadditions of nitrile oxides to acetylenecarboxylates takes place predominantly

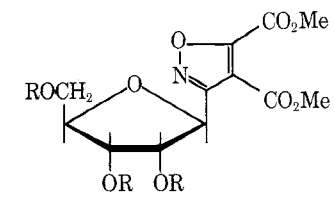


in the fashion leading to 3-substituted isoxazole-5-carboxylates similar to **6**.[5,8] Frequently, however, substantial amounts of the isomeric 3-substituted isoxazole-4-carboxylates are also formed.[8] In the present case we have observed only the formation of a single isomer which was shown by NMR spectroscopy to have the structure **6a,**

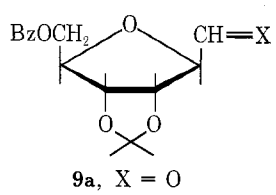
since C_4H of the isoxazole ring appeared as a singlet at 6.94 ppm. Earlier work has shown that C_4H in a variety of 5-alkoxycarbonylisoxazoles appears close to 7.0 ppm[8,9,10] while the vinyl proton adjacent to oxygen in the isomeric 4-alkoxycarbonylisoxazoles is located at 9.0 ppm.[8,9,11] During the course of our work Tronchet et al.[12] described the 1,3-dipolar cycloaddition of nitrile oxides derived from several 5-aldehydofuranoses and 6-aldehydopyranoses to acetylenes and also observed only formation of single isomers. They have not, however, examined any derivatives of 2,5-anhydroaldoses and, hence, have not prepared any D-aldofuranosyl *C*-glycosides.

The reaction of **6a** with methanolic ammonia at room temperature required 5 days to reach completion but gave crystalline 3-(β-D-ribofuranosyl)isoxazole-5-carboxamide (**7**) in 90% yield. Attempted debenzoylation of **6a** with a catalytic amount of methanolic sodium methoxide at room temperature for 16 hr, however, led to the formation of a number of unidentified products. In order to facilitate deblocking of the sugar under less vigorous conditions the above synthesis was repeated starting with 3,4,6-tri-*O*-acetyl-2,5-anhydro-D-allose (**1b**). The latter compound was readily regenerated from its previously described diphenylimidazolidene derivative[1] by brief treatment with *p*-toluenesulfonic acid. Without purification, this compound was converted in an overall yield of 76% into the oxime **2b**, which, from its NMR spectrum, appeared to be a single isomer. The oxime was chlorinated, converted to the nitrile oxide **4b**, and treated with ethyl propiolate as above to give 3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (**6b**) in an overall yield of 46% from **2b**. Once again, the direction of cycloaddition was apparent from the NMR spectrum of **6b**, which showed C_4H as a singlet at 6.97 ppm. In this case deacetylation could be readily accomplished under acidic conditions via treatment with ethanolic hydrogen chloride at room temperature. By this treatment **6b** was converted into crystalline 5-ethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (**6c**) in 49% yield. This yield was achieved by direct crystallization and could doubtless be increased by chromatography of the mother liquors.

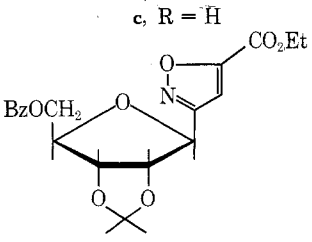
The nitrile oxides **4a** and **4b** were also generated in the presence of dimethyl acetylenedicarboxylate, giving rise to the 4,5-dimethoxycarbonyl-3-β-D-ribofuranosylisoxazole esters (**8a** and **8b**) as analytically pure syrups. Deacetyla-



8a, R = Bz
b, R = Ac
c, R = H



9a, X = O
b, X = NOH



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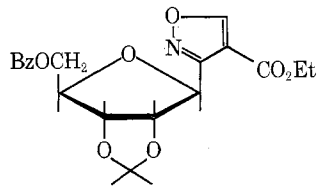

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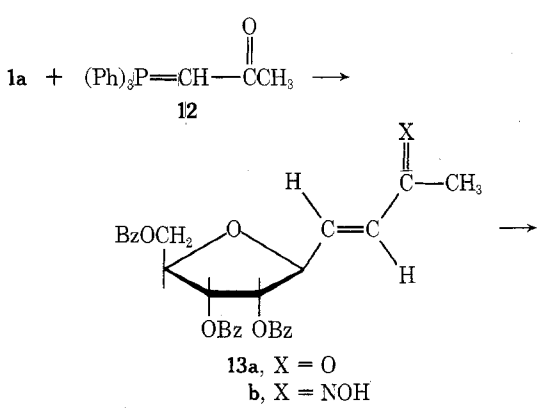
tion of **8b** under acidic conditions as above gave the crystalline *C*-glycoside **8c** without difficulty. Attempted debenzoylation of **8a** with sodium methoxide, however, gave rise to an analytically impure, syrupy compound the NMR spectrum of which was grossly similar to that of **8c** with respect to the carbohydrate moiety. The compound only appeared to contain one methyl ester group at a chemical shift quite different from those in **8c** and it once again appears that the isoxazole ring underwent degradation under the strongly basic conditions.

The previously described 2,5-anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allose (**9a**)[1] was also used as a starting material for isoxazole *C*-glycosides by routes similar to those above. Thus **9a** was converted into the crystalline oxime **9b** and thence, by chlorination and reaction with ethyl propiolate in the presence of triethylamine, into the isoxazole **10** in an overall yield of 62%. While this material gave a single spot by TLC, its NMR spectrum showed the presence of roughly 15% of an isomer, presumably **11**. The major component (**10**) showed C_4H of the isoxazole ring as a singlet at 6.88 ppm while the isoxazole proton in the putative **11** appeared at 8.84 ppm. Without purification, crude **10** was treated first with 90% trifluoroacetic acid to remove the isopropylidene group, and then with methanolic ammonia to give a 71% yield of the amide **7** identical with that obtained from **6b**. In order to characterize pure **10** the triol **6c** was converted to its 2′,3′-*O*-isopropylidene derivative and, without purification of this intermediate, then benzoylated. The product from this sequence, isolated in an overall yield of 80%, proved to be identical with the major product (**10**) obtained via the oxime **9b**.

In order to prepare a 5-ribosylisoxazole, a totally different route was explored via oxidative cyclization of an α,β-unsaturated ketoxime.[13] To this end **1a** was treated with acetonylidenetriphenylphosphorane (**12**)[14] in methylene chloride at room temperature to give, after chromatography on silicic acid, an 83% yield of *trans*-5,8-anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose (**13a**). The pure trans stereochemistry of **13a** was evident



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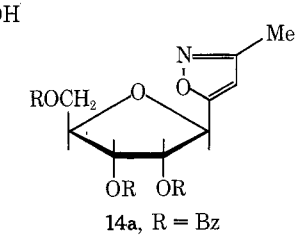
13a, X = O
b, X = NOH



14a, R = Bz
b, R = H

from its NMR spectrum, which showed the two vinyl protons as well-separated signals with $J_{3=4}$ = 16 Hz.[15] This material was then converted to the oxime **3b** and treated with iodine, potassium iodide, and sodium bicarbonate in aqueous methanol[13] to give 5-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-3-methylisoxazole (**14a**) in 51% yield. Debenzoylation of **14a** with methanolic ammonia then gave the crystalline free *C*-glycoside (**14b**) in 63% yield. The method of synthesis makes the orientation of the isoxazole substit-

uents unambiguous, and the structure and homogeneity of the product is further supported by NMR spectroscopy.

The methods described in this paper allow the synthesis of a number of differently substituted 3- and 5-(β-D-ribofuranosyl)isoxazoles for biological evaluation. Future papers in this series will extend this work to the synthesis of other heterocyclic *C*-glycosides.

Experimental Section

General Methods. Thin layer chromatography was done using 250-μ layers of Merck silica gel GF, and preparative TLC using 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF. Nuclear magnetic resonance (NMR) spectra were obtained using a Varian HA-100 spectrometer and are recorded in parts per million downfield from an internal standard of tetramethylsilane. We express our gratitude to Dr. M. L. Maddox and Mrs. J. Nelson for their help with NMR studies. Elemental analyses were obtained by Dr. A. Bernhardt, Elbach über Engelskirchen, Germany, or by the staff of the Analytical Laboratories of Syntex Research. Melting points are corrected.

2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose Oxime (2a). *p*-Toluenesulfonic acid monohydrate (7.03 g, 37 mmol) was added with stirring at 0° to a solution of1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine (10.0 g, 15 mmol)[1] in methylene chloride (150 ml) and stored for 45 min. The mixture was filtered and after addition of pyridine (3 ml) the filtrate was evaporated to a syrup. The latter was dissolved in pyridine (75 ml) and ethanol (75 ml) containing hydroxylamine hydrochloride (5.2 g, 75 mmol) and heated under reflux for 2 hr. The solvent was evaporated and the residue was dissolved in chloroform and washed with 5% aqueous sodium bisulfate, sodium bicarbonate, and water. Evaporation of the dried ($MgSO_4$) organic phase left 6.68 g (91%) of **2a** as a syrup that contained only a trace contaminant by TLC. For analytical purposes a sample was further purified by preparative TLC using ether–hexane (2:1): $[\alpha]^{23}D$ 12.9° (*c* 0.2, MeOH); λ_{max} (MeOH) 229 nm (ε 37,000), 273 (2700), 280 (2200); NMR ($CDCl_3$) 4.5–4.9 (m, 4, C_2H, C_5H, C_6H_2), 5.73 (m, 2, C_3H, C_4H), 7.25–7.45 (m, 9, Ar), 7.48 (d, 1, $J_{1,2}$ = 2 Hz, C_1H), 7.8–8.1 (m, 6, Ar), 8.19 ppm (br s, 1, NOH).

Anal. Calcd for $C_{27}H_{23}NO_8$ (489.46): C, 66.24; H, 4.74; N, 2.86. Found: C, 66.25; H, 4.90; N, 2.87.

3,4,6-Tri-*O*-Acetyl-2,5-anhydro-D-allose Oxime (2b). A solution of *p*-toluenesulfonic acid monohydrate (3.94 g, 21 mmol) in acetone (20 ml) and methylene chloride (30 ml) was added to a solution of 1,3-diphenyl-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolidine (4.0 g, 8.3 mmol).[1] After 30 min at room temperature the precipitated salt was removed by filtration and washed with methylene chloride. Evaporation of the combined filtrates left the essentially homogeneous aldehyde (**1a**), which was immediately dissolved in ethanol (100 ml) and pyridine (100 ml) containing 1.16 g (16.6 mmol) of hydroxylamine hydrochloride. The mixture was heated under reflux for 2.5 hr, cooled, and evaporated to dryness. The residue was dissolved in chloroform, washed with saturated aqueous sodium bicarbonate and with water, dried ($MgSO_4$), and evaporated. The resulting syrup was chromatographed on a column of silicic acid (250 g) using chloroform–ethyl acetate (9:1), giving 1.90 g (76%) of **2b** as a clear syrup: $[\alpha]^{23}D$ 21.7° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) 2.05, 2.07 (s, total 9, OAc), 4.20 (m, 1, C_5H), 4.20 (dd, 1, J_{gem} = 12, $J_{5,6a}$ = 3 Hz, $C_{6a}H$), 4.31 (dd, 1, $J_{5,6b}$ = 3 Hz, $C_{6b}H$), 5.54 (dd, 1, $J_{1,2}$ = 6, $J_{2,3}$ = 5 Hz, C_2H), 5.25 (m, 2, C_3H, C_4H), 7.37 (d, 1, C_1H), 8.15 ppm (br s, 1, OH).

Anal. Calcd for $C_{12}H_{17}NO_8$ (303.27): C, 47.52; H, 5.65; N, 4.62. Found: C, 47.41; H, 5.81; N, 4.59.

3-(2,3,5-Tri-*O*-benozyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (6a). Dry chlorine gas was bubbled through a solution of the oxime (**2b**, 3.0 g, 6.2 mmol) in ether (60 ml) at −60° for 15 min. The greenish-blue solution, which contained some precipitate, was evaporated to dryness and the residue was coevaporated several times with benzene, leaving crude **3, 3′** as a syrup with a TLC mobility somewhat greater than that of **2a** using CCl_4–ethyl acetate (5:1). This material was immediately dissolved in ether (100 ml) at −20° together with ethyl propiolate (2.4 g, 24.8 mmol). A solution of triethylamine (900 mg, 9 mmol) in ether (5 ml) was added dropwise and the mixture was then allowed to warm to room temperature over 1 hr. The solution was diluted to 700 ml with ether, washed twice with water, dried, and evaporated to dryness. The residue was chromatographed on a column of silicic acid using CCl_4–acetone (10:1) to give 2.4 g (67%) of **6a** as a homogeneous, colorless syrup: λ_{max} (MeOH) 229 nm (ε 44,800), 269 (3100), 274 (3300), 281 (2600); NMR ($CDCl_3$) 1.33 (t, 3, CH_3), 4.35 (q, 2, OCH_2), 4.67 (dd, 1, J_{gem} = 11.5, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 4.84 (dd, 1, J_{gem} = 11.5, $J_{4',5'b}$ = 3 Hz, $C_{5'b}H$), 4.7 (m, 1, C_4H), 5.47 (m, 1, virtual coupling to $C_{3'}H$, $C_{1'}H$), 5.85 (m, 2, $C_{2'}H$, $C_{3'}H$), 6.94 (s, 1, C_4H), 7.4 (m, 9, Ar), 7.95 ppm (m, 6, Ar).

Anal. Calcd for $C_{32}H_{27}NO_{10}$ (585.55): C, 65.63; H, 4.65; N, 2.39. Found: C, 65.87; H, 4.70; N, 2.52.

3-(β-D-Ribofuranosyl)isoxazole-5-carboxamide (7). A. A solution of **6a** (800 mg, 1.34 mmol) in saturated methanolic ammonia (300 ml) was stored at room temperature for 5 days, at which point TLC [chloroform–methanol (5:1)] showed complete conversion to **7** and benzamide. Following evaporation of the solvent the syrupy residue was dissolved in water and washed several times with ethyl acetate. The aqueous phase was evaporated, leaving 300 mg (90%) of TLC-homogeneous crystalline **7**. After recrystallization from acetonitrile **7** had mp 148–149°: λ_{max} (MeOH) 224 nm (ε 11,900); $[\alpha]^{23}D$ −36.5° (*c* 0.5, MeOH); NMR (DMSO-d_6) 3.48 (m, 2, C_5H_2), 3.8–4.1 (m, 3, $C_{2'}H$, $C_{3'}H$, $C_{4'}H$), 4.71 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_{1'}H$), 7.08 (s, 1, C_4H), 7.75 and 8.25 ppm (br s, 1, $CONH_2$).

Anal. Calcd for $C_9H_{12}N_2O_6$ (244.21): C, 44.26; H, 4.95; N, 11.47. Found: C, 44.32; H, 5.38; N, 11.61.

B. A solution of **10** (100 mg) in 90% trifluoroacetic acid (1.5 ml) was kept at room temperature for 10 min and then evaporated to dryness and coevaporated several times with ethanol and benzene. The residue was then treated with saturated methanolic ammonia for 5 days at room temperature and then purified by preparative TLC using chloroform–2-propanol (5:1), giving 41 mg (71%) of **7** identical with that from A.

3-(2,3,5-Tri-*O*-Acetyl-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (6b). The oxime **2b** (1.60 g, 5.2 mmol) was converted into the chloro oxime by treatment in ether (50 ml) with chlorine gas at −70° for 15 min as above. The reaction could be followed by TLC [ethyl acetate–chloroform (7:3)], in which the mobility of **3b** is slightly greater than that of **2b**. After evaporation of the solvent in vacuo the residue was coevaporated with benzene and dissolved in ether (50 ml). The solution was stirred at −70° while solutions of ethyl propiolate (2.08 g, 21 mmol) and then triethylamine (800 mg, 8 mmol) in ether (10 ml each) were added dropwise. The mixture was then allowed to warm to room temperature over 2 hr, diluted with ether, and washed with water. The dried organic phase was chromatographed on a column of silicic acid (150 g) using chloroform–ethyl acetate (4:1), giving 950 mg (46%) of **6b** as a homogeneous syrup: λ_{max} (MeOH) 225 nm (ε 9400); $[\alpha]^{23}D$ −32.6° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) 1.38 (t, 3, CH_2CH_3), 2.06, 2.07, and 2.08 (s, 3, OAc), 4.31 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.42 (q, 2, OCH_2CH_3), 5.15 (d, 1, $J_{2',3'}$ = 5.5 Hz, $C_{2'}H$), 5.32 (dd, 1, $J_{3',4'}$ = 9 Hz, $C_{3'}H$), 5.34 (s, 1, $C_{1'}H$), 6.97 ppm (s, 1, C_4H).

Anal. Calcd for $C_{17}H_{21}NO_{10}$ (399.37): C, 51.13; H, 5.30; N, 3.51. Found: C, 51.08; H, 5.28; N, 3.41.

5-Ethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (6c). A saturated solution of hydrogen chloride in ether (10 ml) was added to a solution of **6b** (690 mg, 1.7 mmol) in anhydrous ethanol (25 ml) and the mixture was kept overnight at room temperature. The solvent was evaporated in vacuo and the residue was coevaporated several times with ethanol, leaving a residue that was crystallized from chloroform giving 230 mg (49%) of **6c** with mp 94–95°: λ_{max} (MeOH) 226 nm (ε 10,200); $[\alpha]^{23}D$ −36.3° (*c* 0.5, MeOH); NMR (DMSO-d_6) 1.30 (t, 3, CH_2CH_3), 3.50 (m, 2, C_5H_2), 3.8–4.1 (m, 3, $C_{2'}H$, $C_{3'}H$, $C_{4'}H$), 4.34 (q, 2, OCH_2CH_3), 3.72 (d, 1, $J_{1',2'}$ = 6 Hz, $C_{1'}H$), 4.81 (t, 1, $J_{H,OH}$ = 5 Hz, $C_{5'}OH$), 4.97 (d, 1, $J_{H,OH}$ = 4 Hz, $C_{2' \text{ or } 3'}OH$), 5.17 (d, 1, $J_{H,OH}$ = 5 Hz, $C_{2' \text{ or } 3'}OH$), 7.30 ppm (s, 1, C_4H).

Anal. Calcd for $C_{11}H_{15}NO_7$ (273.25): C, 48.35; H, 5.53; N, 5.13. Found: C, 48.39; H, 5.65; N, 5.22.

3-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-4,5-dimethoxycarbonylisoxazole (8a). A solution of the oxime **2a** (3.0 g, 6.1 mmol) in ether (75 ml) was converted into the chloro oxime **3a** as in the preparation of **6a** above. It was then treated with dimethyl acetylenedicarboxylate (3.4 g, 24 mmol) and triethylamine (0.90 g, 9 mmol) at −20° and allowed to warm to room temperature over 45 min. The solution was diluted with ether, washed with water, and evaporated to dryness, leaving a syrup that was purified by preparative TLC using carbon tetrachloride–acetone (9:1), giving 1.20 g (31%) of **8a** as a homogeneous syrup: λ_{max} (MeOH) 228 nm (ε 46,000), 275 (4600), 281 (4600); $[\alpha]^{23}D$ −24.5° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) 3.83 and 3.94 (s, 3, OMe), 4.5–4.8 (m, 3, $C_{4'}H$, $C_{5'}H_2$), 5.65 (d, 1, $J_{1',2'}$ = 4.5 Hz, $C_{1'}H$), 5.90 (dd, 1, $J_{2',3'}$ = 5, $J_{3',4'}$ = 5.5 Hz, $C_{3'}H$), 6.19 (dd, 1, $C_{2'}H$), 7.4 (m, 9, Ar), 7.95 ppm (m, 6, Ar).

Anal. Calcd for $C_{33}H_{27}NO_{12}$ (629.56): C, 62.95; H, 4.32; N, 2.23. Found: C, 62.69; H, 4.48; N, 2.40.

3-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-4,5-dimethoxycarbonylisoxazole (8b). The chloro oxime **3b, 3'b** was generated as above from 1.90 g (6.27 mmol) of **2b** and evaporated to dryness, leaving a foamy residue after coevaporation with benzene. This was dissolved in ether (50 ml), cooled to −70°, and stirred while dimethyl acetylenedicarboxylate (3.54 g, 25 mmol) and then triethylamine (950 mg, 9.4 mmol) were added dropwise in ether (10 ml each). The mixture was allowed to warm to room temperature and kept for 2 hr before being diluted with chloroform and washed with water. Evaporation of the dried organic phase and chromatography of the residue on a column of silicic acid (300 g) using chloroform–ethyl acetate (9:1) gave 1.60 g (58%) of **8b** as a homogeneous syrup: λ_{max} (MeOH) 221 nm (ε 6600); $[\alpha]^{23}D$ −10.3° (*c* 1.0, $CHCl_3$); NMR ($CDCl_3$) 2.05 (s, 3, OAc), 2.09 (s, 6, OAc), 3.89 and 3.99 (s, 3, OMe), 4.3 (m, 3, $C_4'H$, $C_5'H_2$), 5.36 (d, 1, $J_{1',2'}$ = 5.5 Hz, $C_1'H$), 5.38 (dd, 1, $J_{2',3'}$ = 5.5 Hz, $C_3'H$),[16] 5.71 ppm (dd, 1, $C_2'H$).

Anal. Calcd for $C_{18}H_{21}NO_{12}$ (443.38): C, 48.76; H, 4.77; N, 3.16. Found: C, 48.58; H, 4.86; N, 3.13.

4,5-Dimethoxycarbonyl-3-(β-D-ribofuranosyl)isoxazole (8c). A solution of **8b** (1.1 g, 2.48 mmol) in anhydrous methanol (100 ml) was mixed with 6 *N* hydrogen chloride in ether (10 ml) and stored overnight at room temperature, at which point TLC [chloroform–methanol (9:1)] showed essentially complete reaction. Following evaporation of the solvent and coevaporation with methanol the syrupy residue solidified. Slow crystallization from benzene (175 ml) gave 250 mg (32%) of **8c** as needles with mp 73–74°. Chromatography of the mother liquors on a column of silicic acid using 2.5% methanol in chloroform gave a further 130 mg (total yield 48%) of crystalline **8c**: λ_{max} (MeOH) 222 nm (ε 6500); $[\alpha]^{23}D$ −7.3° (*c* 0.5, MeOH); NMR (DMSO-d_6–D_2O) 3.39 (m, 2, $C_5'H_2$), 3.8 (m, 2, $C_3'H$ and $C_4'H$), 3.82 and 3.91 (s, 3, OMe), 4.17 (dd, 1, $J_{1',2'}$ = 6.5, $J_{2',3'}$ = 5 Hz, $C_2'H$), 4.85 ppm (d, 1, $C_1'H$).

Anal. Calcd for $C_{12}H_{15}NO_9$ (317.26): C, 45.43; H, 4.77; N, 4.42. Found: C, 45.49; H, 4.85; N, 4.38.

2,5-Anhydro-6-*O*-benzoyl-3,4-*O*-isopropylidene-D-allose Oxime (9b). The free aldehyde (**9a**) was regenerated from its 1,3-diphenylimidazolidine derivative (5.0 g, 10 mmol) using *p*-toluenesulfonic acid as previously described.[1] The crude product was treated with hydroxylamine hydrochloride (1.5 g, 21.4 mmol) in pyridine–ethanol (1:1, 100 ml) under reflux for 2 hr and worked up as above for **2.** Crystallization from chloroform–hexane gave 1.55 g (53%) of **9b:** mp 120–125°; $[\alpha]^{23}D$ −4.5° (*c* 0.3, $CHCl_3$); NMR ($CDCl_3$) 1.35 and 1.55 (s, 3, CMe_2), 4.44 (m, 3, C_4H, C_5H_2), 4.59 (dd, 1, $J_{1,2}$ = 5.5, $J_{2,3}$ = 4 Hz, C_2H), 4.74 (m, 1, C_4H), 4.88 (dd, 1, $J_{3,4}$ = 6 Hz, C_3H), 7.43 (d, 1, C_1H), 7.45 (m, 3, Ar), 8.04 ppm (m, 2, Ar).

Anal. Calcd for $C_{16}H_{19}NO_6$ (321.32): C, 59.80; H, 5.96; N, 4.36. Found: C, 59.55; H, 5.95; N, 4.17.

3-(5'-*O*-Benzoyl-2',3'-*O*-isopropylidene-β-D-ribofuranosyl)-5-ethoxycarbonylisoxazole (10). A. Chlorine gas was bubbled through a solution of **9b** (315 mg, 1 mmol) in ether (30 ml) at −60° for 10 min. The resulting green solution was evaporated to dryness and the resulting white solid was coevaporated twice with benzene. The residue and ethyl propiolate (400 mg, 4 mmol) were dissolved in ether (15 ml) and cooled to −20° while triethylamine (150 mg, 1.5 mmol) in ether (5 ml) was added dropwise with stirring over 15 min. The mixture was then allowed to warm to room temperature and kept for 45 min. After dilution with chloroform the solution was washed with water, dried ($MgSO_4$), and evaporated, leaving a syrup that was purified by preparative TLC using ether–hexane (1:1), giving 260 mg (62%) of a syrup that consisted of **10** (see below) contaminated with roughly 15% of an isomer (probably **11**) which showed the isoxazole proton as a singlet at 8.84 ppm.

B. Perchloric acid (0.1 ml) was added to a solution of **6c** (50 mg) in acetone (5 ml) and 2,2-dimethoxypropane (0.2 ml). After 2 hr at room temperature the mixture was neutralized to ~pH 8 with methanolic ammonia and evaporated to dryness. The residue was partitioned between ethyl acetate and water and the dried organic phase was evaporated, leaving 60 mg of the almost pure [TLC, ether–hexane (1:1)] acetonide. This was dissolved in pyridine (5 ml) and treated with benzoyl chloride (100 mg) at 60° for 1.5 hr. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with aqueous sodium bicarbonate and with water, dried ($MgSO_4$), and evaporated. The residue was purified by preparative TLC using ether–hexane (1:1), giving 61 mg (80%) of pure **10** as a homogeneous (TLC and NMR) syrup: λ_{max} (MeOH) 228 nm (ε 21,500), 273 (1000), 280 (800); $[\alpha]^{23}D$ −59.4° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) 1.34 (t, 3, CH_2CH_3), 1.39 and 1.60 (s, 3, CMe_2), 4.36 (q, 2, CH_2CH_3), 4.4 (m, 3, $C_4'H$, $C_5'H_2$), 4.83 (m, 1, virtual coupling to $C_3'H$, $C_1'H$), 5.17 (narrow m, 2, $C_2'H$, $C_3'H$), 6.89 (s, 1, C_4H), 7.45 (m, 3, Ar), 7.90 ppm (dd, 2, J_o = 8, J_m = 1.5 Hz, Ar).

Anal. Calcd for $C_{21}H_{23}NO_8$ (417.40): C, 60.42; H, 5.55; N, 3.36. Found: C, 60.53; H, 5.67; N, 3.49.

***trans*-5,8-Anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose (13a).** 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**1a**) was regenerated from its diphenylimidazolidine derivative (5.0 g, 7.5 mmol)[1] as described for the preparation of **2a.** This material was dissolved together with 4.80 g (15 mmol) of the ylide **12** in methylene chloride (800 ml) and then stored at room temperature for 4 hr. The mixture was then washed with water and the organic phase was evaporated and chromatographed on a column of silicic acid (500 g) using ether–hexane (2:1). Concentration of the major product gave 3.2 g (83%) of **13a** as a TLC-homogeneous syrup: λ_{max} (MeOH) 229 nm (ε 48,500), 274 (3500). 281 (3000), 318 (1600); $[\alpha]^{23}D$ −21.5° (*c* 0.3, $CHCl_3$); NMR ($CDCl_3$) 2.16 (s, 3, $COCH_3$), 4.70 (m, 3, C_8H, C_9H_2), 4.88 (ddd, 1, $J_{4,5}$ = 4.5, $J_{5,6}$ = 5, $J_{3,5}$ = 1.5 Hz, C_5H), 5.47 (dd, 1, $J_{6,7}$ = 5 Hz, C_6H), 5.64 (dd, 1, $J_{7,8}$ = 5 Hz, C_7H), 6.40 (dd, 1, $J_{3,4}$ = 16 Hz, C_3H), 6.83 (dd, 1, C_4H), 7.4 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{30}H_{26}O_8$ (514.51): C, 70.03; H, 5.09. Found: C, 69.68; H, 5.12.

5,8-Anhydro-6,7,9-tri-*O*-benzoyl-1,3,4-trideoxy-D-*allo*-non-3-enulose Oxime (13b). A solution of **13a** (2.5 g, 4.86 mmol) and hydroxylamine hydrochloride (840 mg, 12 mmol) in a mixture of pyridine (30 ml) and methanol (100 ml) was stirred at room temperature for 5 hr and then evaporated to dryness. The residue was coevaporated twice with toluene and chromatographed on a column of silicic acid using ether–hexane (2:1) to give 2.1 g (82%) of **13b** as a single isomer: λ_{max} (MeOH) 229 nm (ε 58,700), 272 (sh, 4500), 280 nm (sh, 3100); $[\alpha]^{23}D$ −43.8° (*c* 0.2, $CHCl_3$); NMR ($CDCl_3$) 1.92 (s, 3, C_1H_3), 4.54 (dd, 1, J_{gem} = 13, $J_{8,9a}$ = 3 Hz, C_9aH), 4.65 (m, 2, C_8H, C_9bH), 4.82 (ddd, 1, $J_{4,5}$ = 6, $J_{5,6}$ = 5.5, $J_{3,5}$ = 1 Hz, C_5H), 5.47 (dd, 1, $J_{6,7}$ = 5.5 Hz, C_6H), 5.67 (dd, 1, $J_{7,8}$ = 5 Hz, C_7H), 6.06 (dd, 1, $J_{3,4}$ = 16 Hz, C_4H), 6.50 (dd, 1, C_3H), 7.4 (m, 9, Ar), 8.0 ppm (m, 6, Ar).

Anal. Calcd for $C_{30}H_{27}NO_8$ (529.52): C, 68.04; H, 5.14; N, 2.65. Found: C, 68.21; H, 5.14; N, 2.56.

5-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-3-methylisoxazole (14a). A solution of potassium iodide (580 mg, 3.5 mmol) and iodine (280 mg, 1.1 mmol) in water (6 ml) was added in the dark to a stirred solution of **13b** (530 mg, 1 mmol) and sodium bicarbonate (336 mg, 4 mmol) in a mixture of tetrahydrofuran (4 ml) and water (3 ml). The mixture was heated under reflux for 4.5 hr, cooled, diluted with saturated aqueous sodium bisulfite (10 ml), and extracted three times with ether. The extracts were dried ($MgSO_4$) and evaporated, leaving a residue that was chromatographed on a column of silicic acid (50 g) using chloroform–ethyl acetate (19:1) to give 270 mg (51%) of **14a** as a TLC-homogeneous clear syrup: λ_{max} (MeOH) 229 nm (ε 36,900), 274 (2800), 281 (2200); $[\alpha]^{23}D$ −32.4° (*c* 0.5, $CHCl_3$); NMR ($CDCl_3$) 2.22 (s, 3, C_3CH_3), 4.69 (dd, 1, J_{gem} = 12, $J_{4',5'a}$ = 2.5 Hz, $C_5'aH$), 4.7 (m, 1, $C_4'H$), 4.82 (dd, 1, $J_{4',5'b}$ = 2.5 Hz, $C_5'bH$), 5.40 (m, 1, with virtual coupling to $C_3'H$, $C_1'H$), 5.81 and 5.89 (dd, 1, $J_{1',2'}$, $J_{3',4'}$ = 2, $J_{2',3'}$ = 5 Hz, $C_2'H$, $C_3'H$), 6.17 (s, 1, C_4H), 7.4 (m, 9, Ar), 8.0 (m, 6, Ar).

Anal. Calcd for $C_{30}H_{25}NO_8$ (527.54): C, 68.30; H, 4.78; N, 2.66. Found: C, 68.24; H, 5.13; N, 2.67.

3-Methyl-5-(β-D-ribofuranosyl)isoxazole (14b). A solution of **14a** (390 mg, 0.74 mmol) in 25% saturated methanolic ammonia (50 ml) was kept at room temperature overnight and then evaporated to dryness. The residue was crystallized from ethyl acetate, giving 100 mg (63%) of **14b:** mp 108–109°; λ_{max} (MeOH) 216 nm (ε 6800); $[\alpha]^{23}D$ −38.3° (*c* 0.5, MeOH); NMR (DMSO-d_6) 2.20 (s, 3, C_3CH_3), 3.50 (m, 2, $C_5'H_2$), 3.9 (m, 3, $C_2'H$, $C_3'H$, $C_4'H$), 4.70 (d, 1, $J_{1',2'}$ = 6 Hz, $C_1'H$), 3.85 (t, 1, $C_5'OH$), 4.97 and 5.19 (d, 1, $C_2'OH$, $C_3'OH$), 6.35 (s, 1, C_4H).

Anal. Calcd for $C_9H_{13}NO_5$ (215.21): C, 50.23; H, 6.09; N, 6.51. Found: C, 50.40; H, 6.22; N, 6.49.

Registry No.—**1a,** 39037-99-5; **2a,** 50720-88-2; **2b,** 55267-78-2; **3a,** 50720-94-0; **3b,** 55267-79-3; (*S*)-**3b',** 55267-80-6; (*R*)-**3b',** 55331-41-4; **6a,** 50720-89-3; **6b,** 55267-81-7; **6c,** 50720-91-7; **7,** 50720-90-6; **8a,** 50720-93-9; **8b,** 55267-82-8; **8c,** 50720-96-2; **9a,** 39037-13-3; **9b,** 55267-83-9; **10,** 55267-84-0; **12,** 1439-36-7; **13a,** 55267-85-1; **13b,** 55267-86-2; **14a,** 55267-87-3; **14b,** 55267-88-4; 1,3-diphenyl-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)imidazolidine, 39038-02-3; 1,3-diphenyl-2-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazolidine, 39037-09-7.

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Approaches to Analogs of Anhydrogliotoxin. 3.[1,2] Synthesis of a Desthiomethylene Analog

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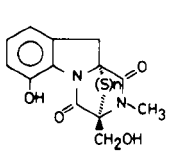
The reaction of *N*-benzyloxycarbonyl-L-cysteine (**7**) with the ethyl indolenino-2-carboxylate (**6**) gave two diastereomeric addition products, **8a** and **8b**. Deprotection of the amino group of **8a** yielded **9a**. On basification the free amine **10a** underwent ring closure by intramolecular aminolysis to yield **5**, a desthiomethylene analog of anhydrogliotoxin. The diastereomeric amine **10b** could also be converted into **5** in a reaction believed to proceed via **10a** by an autocatalyzed epimerization at C-9. Support for this mechanism was obtained by deuterium exchange studies. Recrystallization of **5** yielded a racemic and an optically active fraction. A CD spectrum of the latter supports an R_2S_9 absolute configuration, which is identical with that of gliotoxin **11**. The stereochemistry of the addition reaction is discussed: optically active product **5** results from a chiral component **7** whose configuration inverts during the reaction. The racemic, as well as the optically active compound **5**, is devoid of antiviral and antibacterial activity. This indicates that in natural products containing an epidithiodioxopiperazine moiety the disulfide bridge is essential for activity and the three-dimensional structure is of secondary importance.

Dehydrogliotoxin (**1**, n = 2) and sporidesmin (**2**, R = H) belong to a group of fungal metabolites characterized by a bridge of sulfur atoms across a dioxopiperazine ring.[3] Recently, a simple synthetic homolog, 3,6-epidithio-1,4-dimethyl-2,5-dioxopiperazine (**3**),[4-6] was found to have biological properties which are characteristic of this class of compounds.[5] On the other hand, the conversion of the complex natural products into their dithioalkylated derivatives is accompanied by complete loss of biological activity. From these observations Taylor concluded[4] that the sulfur bridged dioxopiperazine moiety, or a metabolite of it, might be responsible for the activity of these compounds. In this respect the activities of sporidesmin C, **4** (R = H),[7] having a methylene–disulfide bridge, and of monodesthiodehydrogliotoxin (**1**, n = 1)[8] are of interest. Taylor argues[3] that the low activity of the diacetate of **4** (R = $COCH_3$),[9] which is about 100 times less active than sporidesmin diacetate (**2**, R = $COCH_3$), can be accounted for by a contamination of **4** (R = $COCH_3$) with **2** (R = $COCH_3$).



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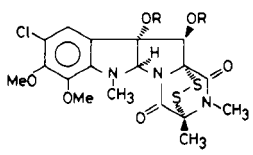

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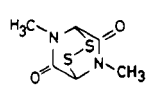

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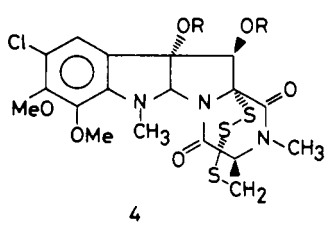

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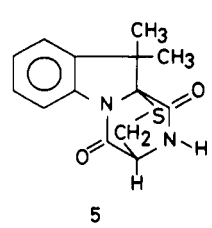

5

Here we wish to report on the synthesis of an anhydrogliotoxin analog **5** possessing a methylene sulfide bridge instead of a disulfide bridge. The three-dimensional structure will not be significantly altered by such a substitution and examination of **5** for biological activity might shed more light on the importance of the disulfide bridge in the activity of compounds such as **1–3**.

As we have previously reported,[2] β-mercaptopropionic acid reacts with the ethyl indolenino-2-carboxylate **6** to yield an indoline tetrahydrothiazone derivative. In an analogous reaction addition of *N*-benzyloxycarbonyl-L-cysteine[10] (**7**) to **6** gave in 95% yield a mixture of two compounds that could be separated by column chromatography. Both products, one an oil ($[\alpha]^{20}D$ −13.8°), the other crystalline ($[\alpha]^{20}D$ −19.2°) (ratio 5:6) were optically active. Elemental analyses and spectral data supported the diastereomeric indoline tetrahydrothiazone structures **8a** and **8b** (Scheme I). These compounds had nearly the same mass spectra, having parent peaks at m/e 454, differing only in that the oily component had a peak at m/e 408 (M − C_2H_5OH) in its spectrum which was missing in the spectrum of the crystalline material. Because intramolecular loss of C_2H_5OH seems more probable in a cis isomer, it was assumed that structure **8a** belongs to the oily material and the trans configuration **8b** to the crystalline product. This assumption could be substantiated as will be discussed below.

The *N*-benzyloxycarbonyl group was smoothly removed