Synthesis of 4-(Glycosyl)isoxazoline *N*-Oxides and Related Substances[1)]

Eisuke KAJI,* Hiromi ICHIKAWA, and Shonosuke ZEN

School of Pharmaceutical Sciences, Kitasato University, Shirokane, Minato-ku, Tokyo 108

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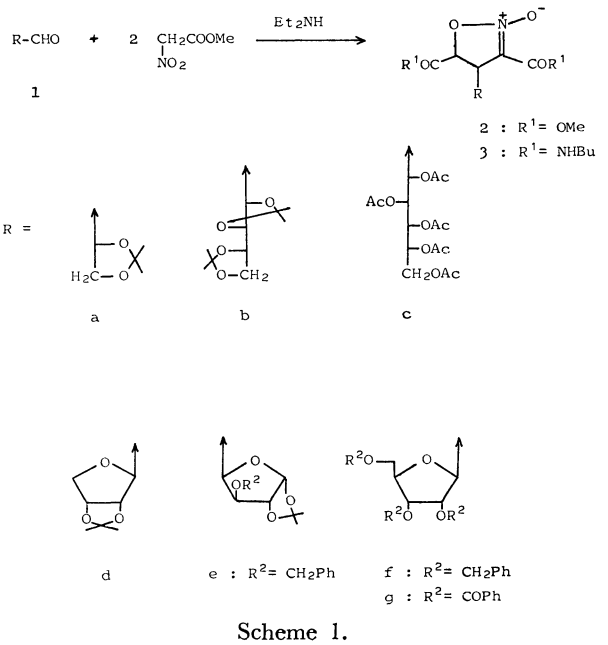
4-(Glycosyl)isoxazoline *N*-oxides were synthesized directly from *aldehydo* sugars by one-step cyclization with double mole of methyl nitroacetate in a satisfactory yield. 2,3-*O*-Isopropylidene-D-glyceraldehyde reacted with methyl nitroacetate to give 4-(1,2-*O*-isopropylidene-D-*glycero*-dihydroxyethyl)-3,5-bis(methoxycarbonyl)isoxazoline *N*-oxide. The same treatment of 2,3: 4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose and penta-*O*-acetyl-*aldehydo*-D-glucose also gave the corresponding homologs. From the corresponding cyclic *aldehydo* sugars, 4-aldofuranosyl-3,5-bis(methoxycarbonyl)isoxazoline *N*-oxides, *e.g.* 4-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-, 4-[(4*R*)-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-threofuranos-4-yl]-, 4-(2,3,5-tri-*O*-benzyl-β-D-ribofuranosyl)-, and 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-derivatives were synthesized. The latter was converted into 3,5-dicarbamoyl-4-(β-D-ribofuranosyl)isoxazoline by deoxygenation followed by carbamoylation and deprotection.

Recently numerous reports have appeared on the synthesis of *C*-glycosyl heterocycles related to *C*-nucleoside antibiotics and their analogs in the quest of potential chemotherapeutic compounds,[2)] such as polyhydroxyalkyl-[3)] or *C*-glycosyl[4)] isoxazolines and isoxazoles, and their carbocyclic analogs.[5)] The heterocyclic moiety was obtained mostly by 1,3-dipolar cycloaddition of olefinic or acetylenic dipolarophiles to sugar nitrile oxides, or by that of olefinic sugars to some nitrile oxides, affording 3- or 5-(glycosyl)isoxazolines or isoxazoles. However, no 4-(glycosyl)isoxazoline or isoxazole appears to have been prepared. A previous work[6)] on the synthesis of 4-substituted isoxazoline *N*-oxide led us to develop a new route to the above-mentioned *C*-nucleoside. In the present paper we give syntheses of some 4-(polyhydroxyalkyl)- and 4-(glycosyl)isoxazoline *N*-oxides by means of one-step cyclization of *aldehydo* sugars with double mole of methyl nitroacetate.

First we examined the condensation of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1a**) with methyl nitroacetate in order to confirm the reaction conditions. It was found that **1a** reacts with two equivalents of methyl nitroacetate in the presence of one equivalent of diethylamine in *N*,*N*-dimethylacetamide (DMA) to afford 4-(1,2-*O*-isopropylidene-D-*glycero*-dihydroxyethyl)-3,5-bis(methoxycarbonyl)isoxazoline *N*-oxide (**2a**) in 74% yield. The structure of **2a** was confirmed by its IR, UV, and ^{1}H-NMR spectra and elemental analysis. Fractional recrystallization of **2a** from hexane resulted in the isolation of two diastereomers (**2a**$_1$: mp 121.5—124 °C and **2a**$_2$: mp 86.5—87.5 °C) in a *ca.* 3: 2 ratio. The relatively small $J_{4,5}$ value (3.5—4.0 Hz) shows the 4,5-*trans* configuration of **2a**$_1$ and **2a**$_2$.[6,7)] The opposite sign of CD spectra centered at 270 nm might be attributed to a symmetric relationship on the configuration of the isoxazoline ring as shown is Scheme 3. Accordingly (4*R*,5*S*) and (4*S*,5*R*) configuration could fit both isomers. However, we can offer no convincing argument as to the assignment of each isomer.



Scheme 1.

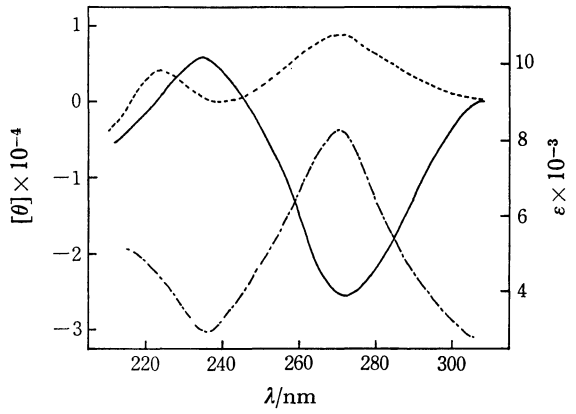


Fig. 1. CD and UV spectra of **2a**$_1$ and **2a**$_2$ in MeOH
——: CD (**2a**$_1$), – – –: CD (**2a**$_2$), ——: UV (**2a**$_1$ and **2a**$_2$).

The same treatment of 2,3,: 4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose (**1b**) and penta-*O*-acetyl-*aldehydo*-D-glucose (**1c**) also gave the corresponding homologs (**2b** and **2c**) in 48 and 64% yields, respectively, their diastereomers not being detected. 3,5-Bis(butylcarbamoyl) derivatives (**3a**$_1$ and **3b**) were prepared by treatment of **2a**$_1$ and **2b** with butylamine in methanol. Deisopropylidenation of **2a**$_1$ and **2b** by Dowex 50 W in methanol gave **5a**$_1$ and **5b**, respectively. The latter

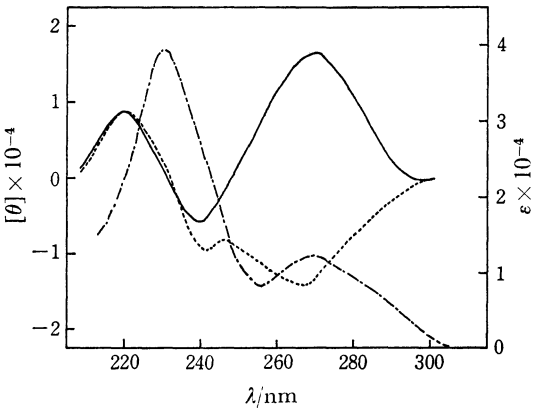
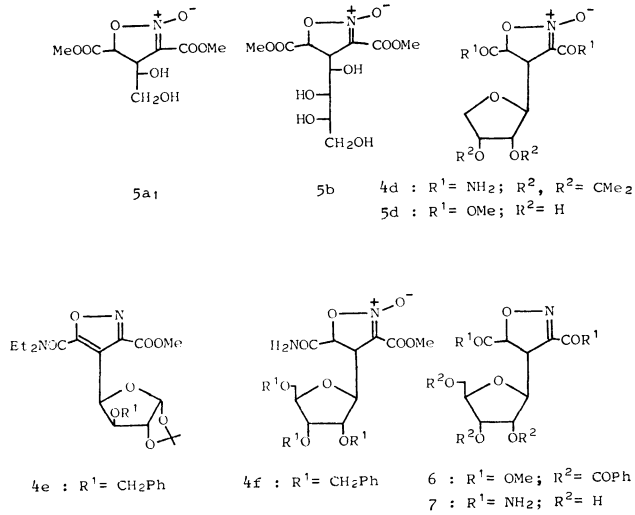


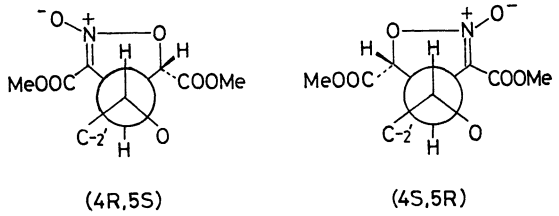
Fig. 2. CD and UV spectra of **2g**$_1$ and **2g**$_2$ in MeOH. ——: CD (**2g**$_1$), – – –: CD (**2g**$_2$), ——: UV (**2g**$_1$ and **2g**$_2$).

seems to have been formed through the 3,4-deprotected intermediate which was isolated. Deacetylation and carbamoylation of **2c** led to a mixture of products which could not be characterized.

It is of interest to explore a route to 4-aldofuranosylisoxazolines, since naturally occurring *C*-nucleosides contain a D-ribofuranosyl moiety. For synthesis of 4-aldofuranosylisoxazolines, 2,5-anhydro-aldoses and 1,4-pentodialdofuranose were employed. 2,5-Anhydro-3,4-*O*-isopropylidene-D-ribose (**1d**), 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**1e**), 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**1f**) and its 3,4,6-tri-*O*-benzoyl analog (**1g**) were condensed with methyl nitroacetate by the above-mentioned procedure, affording the corresponding 4-aldofuranosylisoxazoline *N*-oxides (**2d**—**2g**) in a satisfactory yield except **2e** (6%). *C*-Glycoside **2f** was obtained as a mixture of two diastereomers indicated by two sets of singlet for the methyl of the methoxycarbonyl groups of **2f** in its ^{1}H-NMR spectrum. With regard to compound **2g**, two diastereomers (**2g**$_1$: mp 97.5—99 °C and **2g**$_2$: mp 68—71 °C) were isolated through column chromatography on silica gel in a *ca.* 1 : 3 ratio. The ^{1}H-NMR



Scheme 2.



Scheme 3.

and CD spectra (Fig. 2) of **2g**$_1$ and **2g**$_2$ also indicate that the isomers have either (4*R*,5*S*)- or (4*S*,5*R*)-isoxazoline moiety as described for compound **2a**.

In view of biological activities of several nucleosides possesing carbamoyl groups in the heterocyclic portion, carbamoylation of **2d**—**2f** with methanolic ammonia or butylamine in methanol was carried out, affording mono- or dicarbamoyl derivatives (**3d**, **4d**, and **4f**). On the other hand carbamoylation of **2e** with diethylamine in methanol gave 5-diethylcarbamoyl-3-methoxycarbonylisoxazole (**4e**), the structure of which was confirmed by its spectral and elemental analysis. The formation of **4e** would have resulted from a base catalyzed transformation of isoxazoline *N*-oxide into isoxazole.[6,8] In other cases, however, no isoxazole derivative was observed.

Deisopropylidenation of **2d** was achieved using Dowex 50 W resin in aqueous methanol, giving **5d**. Since direct debenzoylation of **2g**$_2$ (major isomer) with saturated methanolic ammonia was unsuccessful because of the lability of **2g**$_2$ in such a medium, it was subsequently deoxygenated with triethyl phosphite, leading to an isoxazoline (**6**) in 49% yield. Debenzoylation and carbamoylation of **6** was accomplished with saturated methanolic ammonia, giving **7** in 55% yield, biological assay of which is now in progress.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded with a 60 MHz Varian T-60 and a 100 MHz JEOL PS-100 spectrometer with a spin decoupler using tetramethylsilane as an internal standard in chloroform-*d*, acetone-d_6 and methanol-d_4 solution, and sodium 2,2-dimethyl-2-silapentane-5-sulfonate in deuterium oxide. IR, UV, CD, and MS were measured with JASCO IRA-1, Hitachi 340, JASCO J-20, and JMS D-100 spectrometers, respectively. TLC was carried out on Kiesel gel G (Merck), spots being detected with iodine vapor or 10% sulfuric acid on a hot plate. Silica gel (Kanto Kagaku, up to 100 mesh) was used for column chromatography. For preparation of *aldehydo* sugars, reported procedures were applied to 2,3-*O*-isopropylidene-D-glyceraldehyde (**1a**),[9] 2,3:4,5-di-*O*-isopropylidene-*aldehydo*-L-arabinose (**1b**),[10] penta-*O*-acetyl-*aldehydo*-D-glucose (**1c**),[11] 2,5-anhydro-3,4-*O*-isopropylidene-D-ribose (**1d**),[12] 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**1e**),[13] 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (**1f**),[14] and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose (**1g**).[14]

*4-(1,2-O-Isopropylidene-*D-glycero-*dihydroxyethyl)-3,5-bis(methoxycarbonyl)isoxazoline* N*-Oxide (2a) (A Typical Procedure for Condensation).* To a solution of **1a** (0.69 g, 5.3 mmol) in 30 ml of anhydrous DMA were added methyl nitroacetate (1.2 g, 10.6 mmol) and an equivalent of diethylamine (0.52

ml, 5.3 mmol). The mixture was stirred at room temperature for 16 h. After the starting materials had been almost consumed by TLC (silica gel, ethyl acetate–hexane (1:1)) analysis, the mixture was poured into a mixture of benzene (40 ml) and ice–water (80 ml), and the aqueous phase was extracted with benzene (3×40 ml). The combined extract was washed with water (3×80 ml) and dried over anhydrous sodium sulfate. Evaporation gave a yellowish syrup, which was purified by column chromatography on silica gel eluted with ethyl acetate–hexane (1:1), giving 1.2 g (74%) of **2a**. Fractional recrystallization of **2a** from ethyl acetate–hexane resulted in isolation of two diastereomers (**2a**$_1$ and **2a**$_2$) in a ratio of *ca.* 3:2. **2a**$_1$: mp 122.5—123.5 °C; $[\alpha]_D^{20}$ −117° (*c* 2.5, $CHCl_3$); UV_{max} (MeOH) 270 nm (ε 8400); IR (KBr) 1760—1740 (ester C=O), 1630—1620 (C=N), 1380 and 1150 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.37 and 1.50 (each 3 H, s, CMe_2), 3.87 and 3.90 (each 3 H, s, ester Me), 3.97—4.07 (3H, m, H-1′,2′), 4.57 (1H, dd, $J_{4,1'}$=6 Hz, H-4), 5.08 (1H, d, $J_{4,5}$=3.5 Hz, H-5); CD (MeOH) $[\theta]_{273}$ −26000 (negative maximum).

Found: C, 47.52; H, 5.58; N, 4.59%; M$^+$, 303. Calcd for $C_{12}H_{17}NO_8$: C, 47.52; H, 5.65; N, 4.62%; M, 303.

2a$_2$: mp 86.5—87.5 °C; $[\alpha]_D^{20}$ −23° (*c* 2.5, $CHCl_3$); UV_{max} (MeOH) 270 nm (ε 8300); IR (KBr) 1760—1740 (ester C=O), 1630—1620 (C=N), 1380 and 1150 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.37 and 1.50 (each 3H, s, CMe_2), 3.90 and 4.07 (each 3H, s, ester Me), 4.65 (1H, m, H-4), 5.21 (1H, d, $J_{4,5}$=4 Hz, H-5); CD (MeOH) $[\theta]_{268}$+8140 (positive maximum).

Found: C, 47.28; H, 5.60; N, 4.48%; M$^+$, 303.

*4-(1,2: 3,4-Di-*O*-isopropylidene-*L*-*arabino*-tetrahydroxybutyl)-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide (**2b**) from **1b***. Reaction time 2.5 h; Yield 48%; mp 86—87 °C (hexane); $[\alpha]_D^{20}$ −36° (*c* 2.6, $CHCl_3$); IR (KBr) 1755 and 1710 (ester C=O), 1635 (C=N), 1380 and 1150 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.40 (12H, m, CMe_2), 3.87 (6H, s, ester Me), 3.5—4.2 (5H, m, H-4,2′,3′,4′), 4.52 (1H, m, H-1′), 5.05 (1H, d, $J_{4,5}$=2 Hz, H-5).

Found: C, 50.89; H, 6.34; N, 3.49%; M$^+$, 403. Calcd for $C_{17}H_{25}NO_{10}$: C, 50.61; H, 6.25; N, 3.47%; M, 403.

*3,5-Bis(methoxycarbonyl)-4-(*D*-gluco-pentaacetoxypentyl)-isoxazoline* N-*Oxide (**2c**) from **1c***. Yield 64% (yellowish syrup); $[\alpha]_D^{25}$ +6° (*c* 3.4, $CHCl_3$); IR (liq. film) 1750 (ester C=O), 1640 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=2.10—2.16 (15H, m, OAc), 3.83 and 3.95 (each 3H, s, ester Me), 4.0—4.3 (3H, m, H-4,5′), 5.08 (2H, d, $J_{4,5}$=2.5 Hz, H-5,1′), 5.0—5.6 (3H, m, H-2′,3′,4′).

*4-(2,3-*O*-Isopropylidene-β-*D*-erythrofuranosyl)-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide (**2d**) from **1d***. Reaction time 3 days. Solvent system for chromatography, ethyl acetate–hexane (1:2); Yield 32% (yellowish syrup); $[\alpha]_D^{20}$ −41° (*c* 1.0, $CHCl_3$); IR (liq. film) 1740 (ester C=O), 1630 (C=N), 1380 and 1160 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.37 and 1.53 (each 3H, s, CMe_2), 3.88 and 3.92 (each 3H, s, ester Me), 3.65—4.38 (3H, m, H-4,4′), 4.6—5.0 (3H, m, H-1′,2′,3′), 5.11 (1H, d, $J_{4,5}$=1.5 Hz, H-5).

Found: C, 48.28; H, 5.71; N, 3.58%. Calcd for $C_{14}H_{19}NO_9$: C, 48.69; H, 5.55; N, 4.06%.

*4-[(4R)-3-*O*-Benzyl-1,2-*O*-isopropylidene-β-*L*-threofuranos-4-yl]-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide (**2e**) from **1e***. Solvent system for chromatography, chloroform–ethyl acetate (5:1); yield 6% (yellowish syrup); $[\alpha]_D^{20}$ −64.9° (*c* 2.0, $CHCl_3$); IR (liq. film) 1760—1735 (ester C=O), 1620 (C=N), 1380 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.33 and 1.50 (each 3H, s, CMe_2), 3.77 and 3.83 (each 3H, s, ester Me), 3.95—4.8 (4H, m, H-4,2′,3′,4′), 4.53 (2H, broad, CH_2Ph), 5.30 (1H, m, H-5), 5.99 (1H, d, H-1′), 7.37 (5H, s, Ph).

Found: C, 55.71; H, 5.81; N, 2.96%; M$^+$, 451. Calcd for $C_{20}H_{25}NO_{10}$: C, 55.87; H, 5.58; N, 3.10%; M, 451.

*4-(2,3,5-Tri-*O*-benzyl-β-*D*-ribofuranosyl)-3,5-bis-(methoxycarbonyl)isoxazoline* N-*Oxide (**2f**) from **1f***. Solvent system for chromatography, ethyl acetate–hexane (2:1) followed by acetone–hexane (1:3); yield 60% (a syrupy mixture of two diastereomers); $[\alpha]_D^{20}$ −21.3° (*c* 2.1, $CHCl_3$); IR (liq. film) 1760 and 1740 (ester C=O), 1630 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=3.45 (1H, dd, $J_{4,1'}$=4.7 Hz, $J_{1',2'}$=4.3 Hz, H-1′), 3.67, 3.70, 3.78, and 3.80 (6H, s, ester Me), 3.85—4.0 (4H, m, H-3′,4′,5′), 4.14 (1H, dd, $J_{4,5}$=2.5 Hz, $J_{4,1'}$=4.7 Hz, H-4), 4.46—4.58 (7H, m, CH_2Ph, H-2′), 5.30 (1H, d, $J_{4,5}$= 2.5 Hz, H-5).

Found: C, 65.19; H, 5.88; N, 2.29%; M$^+$, 604. Calcd for $C_{33}H_{35}NO_{10}$: C, 65.44; H, 5.83; N, 2.31%; M, 604.

*4-(2,3,5-Tri-*O*-benzoyl-β-*D*-ribofuranosyl)-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide (**2g**) from **1g***. Reaction time 3 days. By column chromatography on silica gel eluted with ethyl acetate–hexane (1:2), two diastereomers of **2g** (**2g**$_1$: R_f 0.35 and **2g**$_2$: R_f 0.25) were isolated in a *ca.* 1:3 ratio in a combined yield of 67%. **2g**$_1$: mp 97.5—99 °C; $[\alpha]_D^{20}$ +62.9° (*c* 0.45, MeOH); UV_{max} (MeOH) 230 nm (ε 40000), 269 nm (ε 12000); IR (KBr) 1725 (ester C=O), 1640 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=3.65 and 3.71 (each 3H, s, ester Me), 4.18 (1H, dd, $J_{4,5}$=3.0 Hz, $J_{4,1'}$=5.3 Hz, H-4), 4.53—4.77 (4H, m, H-1′,4′,5′), 5.19 (1H, d, $J_{4,5}$=3.0 Hz, H-5), 5.59 (1H, dd, $J_{2',3'}$=5.9 Hz, $J_{3',4'}$=7.7 Hz, H-3′), 5.78 (1H, dd, $J_{1',2'}$=3.5 Hz, $J_{2',3'}$=5.9 Hz, H-2′), 7.5—8.0 (15H, m, Ph); CD (MeOH) $[\theta]_{269}$ +16200 (positive maximum).

Found: C, 61.19; H, 4.54; N, 2.13%; M$^+$, 647. Calcd for $C_{33}H_{29}NO_{13}$: C, 61.20; H, 4.51; N, 2.16%; M, 647.

2g$_2$: mp 68—71 °C; $[\alpha]_D^{20}$ −61.4° (*c* 0.51, MeOH); UV_{max} (MeOH) 230 nm (ε 39000), 270 nm (ε 1100); IR (KBr) 1725 ester C=O), 1640 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=3.68 and 3.73 (each 3H, s, ester Me), 4.27 (1H, dd, $J_{4,5}$=2.3 Hz, $J_{4,1'}$=5.5 Hz, H-4), 4.5—4.7 (3H, m, H-4′,5′), 4.76 (1H, m, H-1′), 5.14 (1H, d, $J_{4,5}$=2.3 Hz, H-5), 5.55—5.70 (2H, m, H-2′,3′), 7.3—8.1 (15H, m, Ph); CD (MeOH) $[\theta]_{266}$ −13000 (negative maximum).

Found: C, 60.99; H, 4.59; N, 2.10%; M$^+$, 647.

*3,5-Bis(butylcarbamoyl)-4-(1,2-*O*-isopropylidene-*D*-glycero-dihydroxyethyl)isoxazoline* N-*Oxide (**3a**$_1$) (A Typical Procedure for Butylcarbamoylation)*. A solution of **2a**$_1$ (200 mg, 0.66 mmol) in methanol (5 ml) was refluxed in the presence of excess butylamine (480 mg, 6.6 mmol) for 1 h. After evaporation the residue was chromatographed on silica gel eluted with ethyl acetate–hexane (1:1), giving 85 mg (34%) of **3a**$_1$ as colorless needles: mp 109—110 °C (hexane); $[\alpha]_D^{25}$ +8° (*c* 1.7, $CHCl_3$); IR (KBr) 3300 (NH), 1680 and 1650 (amide I), 1615 (C=N), 1540 (amide II), 1380 and 1160 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.33 and 1.48 (each 3H, s, CMe_2), 3.93—4.23 (3H, m, H-4, 2′), 4.77 (1H, m, H-1′), 4.98 (1H, d, $J_{4,5}$=3 Hz, H-5), 6.70 and 8.00 (each 1H, broad, NH).

Found: C, 56.09; H, 8.11; N, 10.90%; M$^+$, 385. Calcd for $C_{18}H_{31}N_3O_6$: C, 56.16; H, 8.04; N, 10.88%; M, 385.

*3,5-Bis(butylcarbamoyl)-4-(1,2: 3,4-di-*O*-isopropylidene-*L*-arabino-tetrahydroxybutyl)isoxazoline* N-*Oxide (**3b**) from **2b***. Yield 38%; mp 137.5—139 °C (hexane); $[\alpha]_D^{20}$ −2° (*c* 2.5, $CHCl_3$); IR (KBr) 3300 (NH), 1680 and 1650 (amide I), 1610 (C=N), 1530 (amide II), 1380 and 1160 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=1.38—1.50 (6H, m, CMe_2), 3.8—4.3 (5H, m, H-4,2′,3′,4′), 4.73 (1H, m, H-1′), 4.92 (1H, d, $J_{4,5}$ =3 Hz, H-5), 6.6 and 8.0 (each 1H, broad, NH).

Found: C, 56.91; H, 8.12; N, 8.60%. Calcd for $C_{23}H_{39}N_3O_8$: C, 56.89; H, 8.10; N, 8.65%.

*3,5-Bis(butylcarbamoyl)-4-(2,3-*O*-isopropylidene-β-*D*-erythrofuranosyl)isoxazoline* N-*Oxide (**3d**) from **2d***. Reaction time 20

min. Solvent system for chromatography, ethyl acetate–hexane (1: 3); yield 12%; mp 141.5—142 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ +0.5° (*c* 0.2, $CHCl_3$); IR (KBr) 3340 and 3300 (NH), 1645 (amide I), 1620 (C=N), 1550 (amide II), 1380 and 1155 cm^{-1} (CMe_2); ^{1}H-NMR ($CDCl_3$) δ=0.93 (6H, t, $CH_2C\underline{H}_3$), 1.32—1.48 (14H, m, CMe_2, CH_2), 3.25—3.38 (4H, m, $NHC\underline{H}_2$), 3.88—4.3 (4H, m, H-4,1′,4′), 4.89—4.98 (2H, m, H-2′,3′), 5.13 (1H, d, $J_{4,5}$=3 Hz, H-5), 6.56 and 7.95 (each 1H, broad, NH).

Found: C, 55.97; H, 7.79; N, 9.80%; M^+, 427. Calcd for $C_{20}H_{33}N_3O_7$: C, 56.19; H, 7.78; N, 9.83%; M, 427.

3,5-Dicarbamoyl-4-(2,3-O-isopropylidene-β-D-erythrofuranosyl)-isoxazoline N-*Oxide* (**4d**). A solution of **2d** (100 mg, 0.29 mmol) in saturated methanolic ammonia (1 ml) was stored at room temperature for 0.5 h and then evaporated to dryness. The residue was crystallized from ethyl acetate, giving 14 mg (15%) of **4d**: mp 222 °C (dec); $[\alpha]_D^{20}$ −4.3° (*c* 0.47, MeOH); IR (KBr) 3460—3400 (NH), 1685 and 1655 (amide I), 1615 (C=N), 1385 and 1150 cm^{-1} (CMe_2); ^{1}H-NMR (acetone-d_6) δ=1.32 and 1.45 (each 3H, s, CMe_2), 3.81 (1H, dd, J_{gem}=10 Hz, $J_{3,4'a}$=2 Hz, H-4′a), 4.00 (1H, d, $J_{4,1'}$=6 Hz, H-1′), 4.08 (1H, dd, H-4′b), 4.34 (1H, dd, $J_{4,5}$=3 Hz, H-4), 4.84—5.08 (3H, m, H-5,2′,3′), 6.84—7.88 (4H, m, $CONH_2$).

Found: C, 45.71; H, 5.42; N, 13.24%; M^+, 315. Calcd for $C_{12}H_{17}N_3O_7$: C, 45.71; H, 5.44; N, 13.33%; M, 315.

4-[(4R)-3-O-Benzyl-1,2-O-isopropylidene-β-L-threofuranos-4-yl]-5-diethylcarbamoyl-3-methoxycarbonylisoxazole (**4e**). A solution of **2e** (74 mg, 0.16 mmol) in methanol (5 ml) was kept with diethylamine (0.17 ml, 1.6 mmol) at room temperature for 5 h. After evaporation the residue was crystallized from methanol–diethyl ether to give 26 mg (35%) of **4e**: mp 174—179.5 °C; $[\alpha]_D^{20}$ −189° (*c* 0.32, $CHCl_3$); IR (KBr) 1760 (ester C=O), 1710 cm^{-1} (amide); ^{1}H-NMR ($CDCl_3$) δ=1.19 (6H, t, $CH_2C\underline{H}_3$), 1.32 and 1.50 (each 3H, s, CMe_2), 2.96 (4H, q, $C\underline{H}_2CH_3$), 3.82 (3H, s, ester Me), 4.35 (1H, d, H-3′), 4.46 (2H, d, $C\underline{H}_2Ph$), 4.58 (1H, d, $J_{1',2'}$=4 Hz, $J_{2',3'}$=0 Hz, H-2′), 5.42 (1H, d, $J_{3',4'}$=4 Hz, H-4′), 5.82 (1H, d, $J_{1',2'}$=4 Hz, H-1′), 7.16 (5H, s, Ph).

Found: C, 60.35; H, 6.50; N, 5.69%; M^+, 475. Calcd for $C_{24}H_{30}N_2O_8$: C, 60.75; H, 6.37; N, 5.90%; M, 475.

4-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)-5-carbamoyl-3-methoxycarbonylisoxazoline N-*Oxide* (**4f**). A solution of **2f** (208 mg, 0.34 mmol) in saturated methanolic ammonia (1 ml) was stored at room temperature for 1 h and then evaporated to dryness. The residue was chromatographed on silica gel eluted with ethyl acetate–hexane (3: 2). A fraction of R_f 0.3 was collected and crystallized from ethyl acetate–hexane, giving 44 mg (22%) of **4f**: mp 128.5—129.5 °C; $[\alpha]_D^{20}$ +1.4° (*c* 0.3, $CHCl_3$); IR (KBr) 3415 (NH), 1730 (ester C=O), 1680 (amide), 1615 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=3.3—3.65 (3H, m, H-1′,5′), 3.79 (3H, s, ester Me), 3.85—4.18 (3H, m, H-2′,3′,4′), 4.11 (1H, dd, H-4), 4.4—4.62 (6H, m, $C\underline{H}_2Ph$), 5.14 (1H, d, $J_{4,5}$=3.3 Hz, H-5), 5.60 and 6.45 (each 1H, broad, $CONH_2$), 7.2—7.3 (15H, m, Ph).

Found: C, 65.10; H, 5.79; N, 4.73%; M^+, 590. Calcd for $C_{32}H_{34}N_2O_9$: C, 65.07; H, 5.80; N, 4.74%; M, 590.

*4-(*D-glycero-*Dihydroxyethyl)-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide* (**5a$_1$**) *(A Typical Procedure for Deisopropylidenation)*: A solution of **2a$_1$** (major isomer, 726 mg, 2.4 mmol) in aqueous methanol (50 ml) was treated with acidic resin (Dowex 50 W-X8, 4 g) under stirring at room temperature for 4 h. After evaporation the residue was crystallized from ethyl acetate–hexane, giving 630 mg (quantitative) of **5a$_1$**: mp 145.5—147 °C; $[\alpha]_D^{20}$ −124° (*c* 0.2, MeOH); IR (KBr) 3430 and 3320 (OH), 1730 (ester C=O), 1615 cm^{-1} (C=N); ^{1}H-NMR (acetone-d_6) δ=3.6—3.7 (3H, m, H-1′,2′), 3.80 (6H, s, ester Me), 4.06 (1H, m, H-4), 5.28 (1H, d, $J_{4,5}$=2 Hz, H-5).

Found: C, 40.91; H, 4.97; N, 5.16%. Calcd for $C_9H_{13}NO_8$: C, 41.07; H, 4.98; N, 5.32%.

*4-(*L-arabino-*Tetrahydroxybutyl)-3,5-bis(methoxycarbonyl)isoxazoline* N-*Oxide* (**5b**) *from* **2b**. The reaction mixture obtained after stirring for 0.5 h was chromatographed on silica gel eluted with ethyl acetate–chloroform (3: 1), giving 3,4-diol (colorless syrup, R_f 0.4); yield 36%; $[\alpha]_D^{20}$ −93.7° (*c* 2.7, MeOH); IR (liq. film) 3460 (OH), 1760—1735 (ester C=O), 1630 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=1.42 and 1.45 (each 3H, s, CMe_2), 2.4—3.2 (2H, broad, OH), 3.87 and 3.90 (each 3H, s, ester Me), 3.75 (4H, m, H-2′,3′,4′), 4.18 (1H, dd, H-4), 4.58 (1H, dd, H-1′), 5.12 (1H, d, $J_{4,5}$=2.5 Hz, H-5) and 1,2,3,4-tetrol (**5b**, R_f 0.1); yield 17%; mp 66 °C (dec); $[\alpha]_D^{20}$ +39.7° (*c* 3.0, MeOH); IR (KBr) 3360 (OH), 1735 and 1700 (ester C=O), 1630 cm^{-1} (C=N); ^{1}H-NMR (methanol-d_4) δ=3.83 and 3.87 (each 3H, s, ester Me), 3.70—4.03 (5H, m, H-4,2′,3′,4′), 4.37 (1H, m, H-1′), 5.68 (1H, d, $J_{4,5}$=3 Hz, H-5).

Found: C, 40.46; H, 5.08; N, 3.98%. Calcd for $C_{11}H_{17}NO_{10}$: C, 40.87; H, 5.30; N, 4.33%.

4-(β-D-Erythrofuranosyl)-3,5-bis(methoxycarbonyl)isoxazoline N-*Oxide* (**5d**) *from* **2d**. Reaction time 10 h. Solvent system for chromatography, ethyl acetate–acetone–benzene (4: 5: 3); yield 29%; mp 167—169.5 °C (ethyl acetate–hexane); $[\alpha]_D^{20}$ +14.7° (*c* 0.2, MeOH); IR (KBr) 3480 (OH), 1765 and 1730 (ester C=O), 1620 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=2.9—3.3 (2H, broad, OH), 3.71 and 3.84 (each 3H, s, ester Me), 5.02 (1H, d, $J_{4,5}$=2 Hz, H-5), 3.8—4.35 (6H, m, other protons).

Found: C, 42.89; H, 4.91; N, 4.33%; M^+ 306. Calcd for $C_{11}H_{15}NO_9$: C, 43.28; H, 4.95; N, 4.59%; M 306.

4-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-3,5-bis(methoxycarbonyl)isoxazoline (**6**). A mixture of **2g$_2$** (major isomer, 970 mg, 1.5 mmol) and triethyl phosphite (300 mg, 1.8 mmol) in anhydrous toluene (4 ml) was refluxed for 5 h under nitrogen atmosphere. The solvent was evaporated and the residue was chromatographed on silica gel eluted with ethyl acetate–hexane (1: 1), giving 632 mg of amorphous solid. Recrystallization from benzene–hexane gave 461 mg (49%) of **6** as colorless prisms: mp 92.5—93.5 °C; $[\alpha]_D^{20}$ −134° (*c* 0.25, $CHCl_3$); UV_{max} (MeOH) 230 nm (ε 42000), 272^{sh} nm (ε 4600); IR (KBr) 1720 (ester C=O), 1630 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) δ=3.60 and 3.68 (each 3H, s, ester Me), 4.36 (1H, dd, $J_{4,5}$=5.0 Hz, $J_{4,1'}$=5.0 Hz, H-4), 4.48—4.66 (3H, m, H-4′,5′), 4.77 (1H, dd, $J_{4,1'}$=5.0 Hz, $J_{1',2'}$=7.8 Hz, H-1′), 5.23 (1H, d, $J_{4,5}$=5.0 Hz, H-5), 5.43 (1H, dd, $J_{1',2'}$=7.8 Hz, $J_{2',3'}$=5.8 Hz, H-2′), 5.65 (1H, dd, $J_{2',3'}$=5.8 Hz, $J_{3',4'}$=3.5 Hz, H-3′).

Found: C, 62.48; H, 4.54; N, 2.15%. Calcd for $C_{33}H_{29}NO_{12}$: C, 62.76; H, 4.63; N, 2.22%.

3,5-Dicarbamoyl-4-(β-D-ribofuranosyl)isoxazoline (**7**). A solution of **6** (200 mg, 0.32 mmol) in saturated methanolic ammonia (15 ml) was stored at room temperature for 7 h, when TLC (silica gel, ethyl acetate–hexane (1: 1)) showed complete consumption of **6**. The syrupy residue on evaporation was dissolved in methanol and chromatographed on silica gel eluted with methanol–ethyl acetate (1: 3), giving 51 mg (55%) of **7** as colorless prisms: mp 198—198.5 °C; $[\alpha]_D^{20}$ −173° (*c* 0.14, MeOH); UV_{max} (MeOH) 225 nm (ε 5400); IR (KBr) 3400—3280 (NH, OH), 1655 (amide), 1605 cm^{-1} (C=N); ^{1}H-NMR (D_2O) δ=3.5—3.8 (2H, m, H-5′), 3.9—4.1 (3H, m, H-1′,2′,4′), 4.16 (2H, m, H-4,3′), 5.25 (1H, d, $J_{4,5}$=3.7 Hz, H-5).

Found: C, 41.58; H, 5.23; N, 14.32%. Calcd for $C_{10}H_{15}N_3O_7$: C, 41.52; H, 5.23; N, 14.53%.

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