Heterocyclic Amino Sugar Derivatives. V. *N*-Alkyloxazolidinones Derived from Vicinal Trans Diequatorial Amino Hydroxy Groups[1]

FRED R. SEYMOUR AND PAUL H. GROSS*

Department of Chemistry, University of the Pacific, Stockton, California 95204

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A series of carbamate, carbonate, and trans diequatorially fused *N*-alkyloxazolidinone derivatives have been prepared from benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides (I). The base-catalyzed equilibria and irreversible reactions between these species have been studied in dialkyl carbonate solutions. This has resulted in a direct synthesis of N-substituted oxazolidinones derived from D-glucosamine. In the course of these reactions the reversal of an ester condensation has been observed under very mild conditions.

The synthesis of a morpholinedione ring-fused trans diequatorially to benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib)[2] by a two-step reaction of Ib with dimethyl oxalate was described in the preceding paper.[3]

It appeared interesting to study reactions of I also with dialkyl carbonates. Such reactions could lead to an improved and more direct route to trans diequatorially fused oxazolidinones which were previously reported.[4]

However, the reaction between benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (I) and dialkyl carbonates under basic conditions was shown to yield several products (Scheme I).[2] The ratio of yields of these products is temperature dependent. Dimethyl carbonate or diethyl carbonate was the solvent, with the base, potassium *tert*-butoxide, present in slight molar excess to the sugar. At low temperature (90 or 115°) a mixture of the *N*-alkoxycarbonyl compound (II or VI) and the *N*,*O*-dialkoxycarbonyl compound (III or VII) was formed. At high temperatures (130 or 145°) the N-alkylated oxazolidinone (V or VIII) was formed. These compounds were readily identifiable by ir spectra because II and VI show the –NH, –OH, amide I, and amide II bands; III and VII show the –NH, ester, amide I, and amide II bands; and V and VIII show only the characteristic oxazolidinone band. The oxazolidinone band is at the same frequency as the amide I band, but no amide II or –NH band appears.

The oxazolidinone IV, previously synthesized by Miyai and Gross,[4] was postulated as an intermediate due to the presence of the N-substituted product. Further evidence was found by substituting IVb for Ib and using the same high temperature reaction conditions. This reaction, with diethyl carbonate, gave mostly the N-substituted oxazolidinone, VIIIb, with some VIb and VIIb. The equilibrium between VIb, VIIb, and IVb was more clearly established by substituting IVb for Ib using the same low temperature conditions, the product being a mixture of VIb and VIIb. No VIIIb was found in this low temperature reaction, a fact which was further emphasized when VIIIb was substituted for Ib under low temperature conditions and no reaction occurred.

The above indicates that VIb, VIIb, and IVb exist at low temperature as an equilibrium mixture with the equilibrium shifted strongly toward VIb and VIIb. The N-alkylation of the oxazolidinone occurs only at high temperatures and is irreversible.

The "high temperature" reaction can be used to prepare mono-N-alkylated oxazolidinones in good to excellent yield without a chromatographic purification, as shown in the Experimental Section. This reaction may have considerable biochemical interest, since a number of antibiotics[5] contain N-methylated amino hexoses in their structure. The oxazolidinone protective group could be quite useful in the synthesis of antibiotics with a modified *N*-alkyl group.

In an attempt to form a seven-membered ring, by bridging the malonate methylene group and the hydroxyl at C-3 with a carbonyl group, benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (IXb)[3] was then used in place of Ib. For both high temperature and low temperature reaction conditions, the products obtained from diethyl carbonate and IXb were the same as those obtained from Ib. These products can be explained by postulation that the oxazolidinone IVb is formed by an internal hydroxyl attack on the amide carbonyl with subsequent loss of the remainder of the malonyl group (Scheme II). This leaves the oxazolidinone intermediate which can immediately undergo the same reactions as when Ib was the starting material.

The above reaction is of interest in that it shows the preference of the hydroxyl group to attack the amide carbonyl (and form a five-membered ring) rather than to attack the carbonic ester carbonyl, forming a seven-membered ring. The apparent ease of reaction shows the stability of the five-membered ring system and suggests that any attempt to form a larger ring system using an amide under alkaline conditions will meet with failure. The reaction is unusual in that this is an example of a reversal of an ester condensation ("ester elimination") which apparently has not been reported before. That such an elimination occurs so readily with these substances under mild conditions is readily explained by the favorable anchimeric assistance of the adjacent hydroxyl group.

The conditions for the above reaction are in marked contrast to the normal "ester elimination" or decarboxylation of malonic *esters* (not malonic acids) first observed by Dieckmann.[6] Quantitative studies by Cope and McElvain[7] showed that even the most easily

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(2) Throughout this article, a roman numeral *without* an arabic letter refers to *both* anomeric compounds. A roman numeral with an arabic letter is used to describe a particular anomer (a for α, b for β).

(3) Part IV: F. R. Seymour and P. Gross, *J. Org. Chem.*, **36**, 1079 (1971).

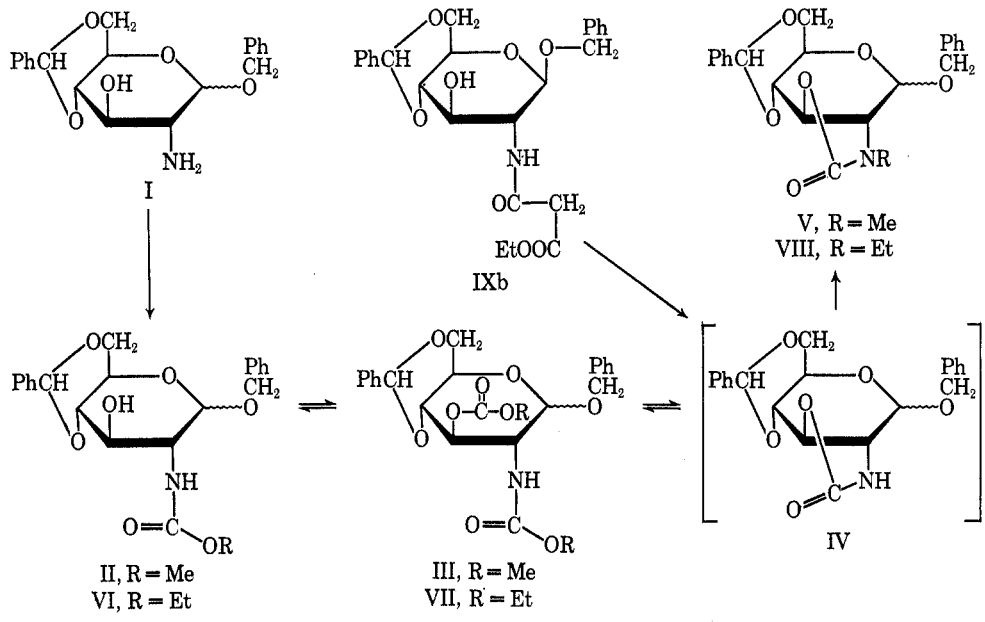
(4) Part II: K. Miyai and P. Gross, *ibid.*, **34**, 1683 (1969).

(5) J. P. Dutcher, *Advan. Carbohyd. Chem.*, **18**, 259 (1963).

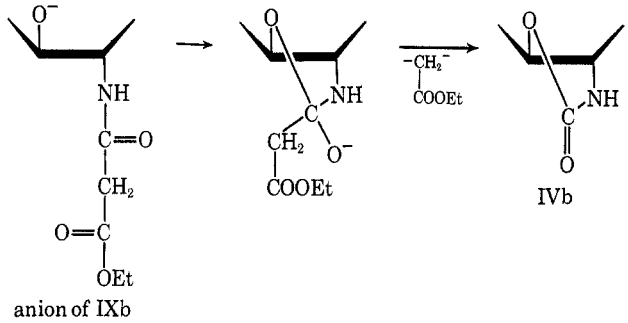
(6) W. Dieckmann, *Ber. Deut. Chem. Ges.*, **33**, 2670 (1900).

(7) A. Cope and S. McElvain, *J. Amer. Chem. Soc.*, **54**, 4319 (1932).

SCHEME I[2]



SCHEME II[2]



decarboxylated malonate ester, the diethyl substituted, required 30 min with sodium ethoxide in ethanol at 250° and 1000 psi for 81% of the starting material to be decarboxylated.

Experimental Section

The infrared spectra have been taken with a Perkin-Elmer 337 spectrophotometer using potassium bromide pellets. The tlc studies have been done with a mixture of two parts Merck silica gel G with one part Merck silica gel GF_{254}, the plates being activated by heating at 120° for 2 hr. The plates were developed with chloroform, containing lesser amounts of either ethanol or petroleum ether. The compounds were visualized by extinction of the uv fluorescence and by spraying with a 20% sulfuric acid in methanol solution and heating for 10 min at 250°. As absolute R_f values for tlc are difficult to determine, comparative studies have been made. Unless otherwise stated, all compounds reported herein are chromatographically homogeneous and distinguishable from their starting materials and by-products. The preparative tlc separations were made on Merck precoated silica gel plates, 2-mm thick. The melting points are uncorrected and were taken on a Thomas-Hoover Uni-melt apparatus. The rotations were taken with a Rudolph polarimeter, Model 956, in pyridine at *c* 1. The elemental analyses were determined by Alfred Bernhardt Mikroanalytisches Laboratorium, Engelskirchen, Germany. The commercial solvents and reagents were purified by fractional distillation.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (Ia) and Dimethyl Carbonate.—A solution of Ia (1.00 g, 0.0028 mol) in warm dimethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and refluxed for 12 hr, and then filtered hot leaving a white residue (precipitate 1, 0.47 g). Petroleum ether (200 ml) was added to the filtrate, which was again filtered after 1.5 hr at 0° (precipitate 2, 0.69 g). The resulting filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.23 g), and precipitates 2 and 3 were separated by preparative tlc; precipitate 2 yielded 0.23 g of a fast fraction and 0.27 g of a slow fraction, and precipitate 3 yielded 0.15 g of a fast fraction and 0.03 g of a slow fraction.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonyl)amino-α-D-glucopyranoside (IIa).—The slowest moving fractions were combined and recrystallized from 2-propanol to give 0.31 g (27%): mp 195–196°; $[\alpha]^{20}D$ +114°; ν_{max} 3380 (OH), 3310 (NH), 1670, 1530 (amide C=O), 740, 691 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_7$ (415.41): C, 63.59; H, 6.07; N, 3.37; O, 26.96. Found: C, 63.30; H, 6.16; N, 3.35; O, 26.79.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methoxycarbonyl-2-(methoxycarbonyl)amino-α-D-glucopyranoside (IIIa).—The fastest moving fractions were combined and recrystallized from 2-propanol–diisopropyl ether to give 0.25 g (19%): mp 169–170°; $[\alpha]^{20}D$ +71°; ν_{max} 3300 (NH), 1790 (amide C=O), 1680, 1520 (amide C=O), 732, 695 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.52): C, 60.88; H, 5.75; N, 2.96; O, 30.41. Found: C, 60.80; H, 5.58; N, 2.87; O, 30.65.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Dimethyl Carbonate.—A solution of Ib (1.00 g, 0.0028 mol) in warm dimethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and refluxed 7 hr, and filtered hot leaving a white basic residue (precipitate 1, 0.37 g). Petroleum ether (200 ml) was added to the filtrate. After 45 min at 0° precipitate 2 (0.96 g) was filtered out. The resulting filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.13 g). Analytical tlc showed that precipitate 2 contained only two components and that precipitate 3 was a mixture of these same two components and two minor components with R_f values identical with IVb and Vb. Only precipitate 2 was separated by preparative tlc giving two fractions.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(methoxycarbonyl)amino-β-D-glucopyranoside (IIb).—The slowest moving fraction from the above separation was recrystallized from 2-propanol to give 0.36 g (31%): mp 206–207°; $[\alpha]^{20}D$ −89°; ν_{max} 3400 (OH), 3320 (NH), 1680, 1530 (amide C=O), 745, 692 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_7$ (415.41): C, 63.59; H, 6.07; N, 3.37; O, 26.96. Found: C, 63.49; H, 6.25; N, 3.23; O, 27.05.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-methoxycarbonyl-2-(methoxycarbonyl)amino-β-D-glucopyranoside (IIIb).—From the above tlc separation of precipitate 2, the fastest moving component was recrystallized from 2-propanol–diisopropyl ether to give 0.31 g (24%): mp 204–205°; $[\alpha]^{20}D$ −101°; ν_{max} 3320 (NH), 1750 (ester C=O), 1690, 1530 (amide C=O), 749, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.52): C, 60.88; H, 5.75; N, 2.96; O, 30.41. Found: C, 60.79; H, 5.67; N, 3.02; O, 30.44.

Benzyl 4,6-*O*-Benzylidene-β-D-glucopyranosido[2,3:4′,5′]-2′-oxazolidinone (IVb).—This compound was prepared by the method of Miyai and Gross.[4]

Benzyl 4,6-*O*-Benzylidene-2-deoxy-β-D-glucopyranosido-[2,3:4′,5′]-*N*-methyl-2′-oxazolidinone (Vb).—A solution of Ib (0.50 g, 0.0014 mol) in warm dimethyl carbonate (12 ml) was treated with potassium *tert*-butoxide (0.20 g, 0.0018 mol), stirred in an autoclave 15 hr at 130°, and filtered hot leaving a white crystalline precipitate (precipitate 1, 0.42 g). Petroleum ether (100 ml) was added to the filtrate which after 1 hr at 0° was again filtered (precipitate 2, 0.16 g). The resulting filtrate was evaporated *in vacuo* to dryness and on tlc showed approximately equal portions of IIb, IIIb, and IVb (precipitate 3, 0.20 g). The solution of precipitate 1 and precipitate 2 in chloroform was extracted twice with ice-cold 0.5 *M* HCl and once with 5% sodium bicarbonate, dried for 1 hr over anhydrous sodium carbonate, and evaporated *in vacuo* to dryness. The solid residue (0.32 g) was recrystallized from ethanol to give 0.30 g (54%): $[\alpha]^{20}D$ −101°; mp 258–259°; mixture melting point and ir spectra confirmed the identity of Vb with a sample prepared by N-methylation of IVb;[3] ν_{max} 1740 (oxazolidinone).

Anal. Calcd for $C_{22}H_{23}NO_6$ (397.4): N, 3.53. Found: N, 3.46.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (Ia) and Diethyl Carbonate.—A solution of Ia (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and heated 9 hr at 115°, and then filtered hot leaving a white basic residue (precipitate 1, 0.47 g). Petroleum ether (200 ml) was added to the filtrate which was again filtered after 45 min at 0° (precipitate 2, 0.52 g). The resulting filtrate was evaporated to dryness (precipitate 3, 0.23 g).

Analytical tlc showed that both precipitates 2 and 3 were mixtures of the same two components. However, in precipitate 2 the major component was slow moving; in precipitate 3 the major was fast moving. Precipitates 2 and 3 were separated by preparative tlc: precipitate 2 gave 0.12 g of a fast fraction and 0.32 g of a slow fraction; precipitate 3 gave 0.22 g of a fast fraction and 0.13 g of a slow fraction.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethoxycarbonyl)amino-α-D-glucopyranoside (VIa).—The slowest moving fractions were combined and recrystallized from 2-propanol to give 0.40 g (35%): mp 197–198°; $[\alpha]^{20}D$ +89°; ν_{max} 3390 (OH), 3300 (NH), 1670, 1530 (amide C=O), 745, 691 (C_6H_5).

Anal. Calcd for $C_{23}H_{27}NO_7$ (429.46): C, 64.31; H, 6.33; N, 3.27; O, 26.08. Found: C, 63.60; H, 6.36; N, 3.24; O, 26.74.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-ethoxycarbonyl-2-(ethoxycarbonyl)amino-α-D-glucopyranoside (VIIa).—The fastest moving fractions were combined and recrystallized from 2-propanol–diisopropyl ether to give 0.29 g (22%): mp 138–139°; $[\alpha]^{20}D$ +59°; ν_{max} 3290 (NH), 1730 (ester C=O), 1670, 1520 (amide C=O), 746, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_9H_2O$ (519.5): C, 60.10; H, 6.40; N, 2.70. Found: C, 59.94; H, 6.14; N, 2.93.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-α-D-glucopyranosido-[2,3:4′,5′]-*N*-ethyl-2′-oxazolidinone (VIIIa).—A solution of Ia (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), refluxed with stirring for 48 hr, and filtered hot leaving a basic precipitate (precipitate 1, 0.32 g). Petroleum ether (200 ml) was added to the filtrate, which was filtered again after 2 hr at 0° (precipitate 2, 0.30 g). Immediately after filtering, white crystalline material came out of solution which, after 1 hr at 0°, yielded precipitate 3 (0.53 g). The solution was then evaporated to dryness *in vacuo* (precipitate 4, 0.31 g) which proved to be a mixture of VIa, VIIa, and VIIIa. Precipitates 1 and 2 proved to be strongly basic. Precipitate 3 was found to be pure VIIIa. It was recrystallized from 2-propanol-diisopropyl ether and gave 0.49 g (45%): mp 181–182°; $[\alpha]^{20}D$ +46°; ν_{max} 1740 (oxazolidinone), 750, 696 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_6$ (411.44): C, 67.13; H, 6.12; N, 3.41; O, 23.33. Found: C, 67.35; H, 6.17; N, 3.15; O, 23.52.

"Low Temperature" Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Diethyl Carbonate.—A solution of Ib (1.00 g, 0.0028 mol) in warm diethyl carbonate (25 ml) was treated with potassium *tert*-butoxide (0.40 g, 0.0036 mol), stirred and heated 24 hr at 115°, and then filtered hot leaving a basic residue (precipitate 1, 0.44 g). Petroleum ether (200 ml) was added to the filtrate, which was again filtered after 1 hr at 0° (precipitate 2, 0.55 g). The filtrate was evaporated *in vacuo* to dryness (precipitate 3, 0.53 g). When the oxazolidinone, IVb, or benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (IXb)[3] was substituted for Ib in the above procedure, the results were similar.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethoxycarbonyl)amino-β-D-glucopyranoside (VIb).—Precipitate 2, on recrystallization from dioxane–2-propanol, gave 0.50 g (43%): mp 230–232°; $[\alpha]^{20}D$ −87°; ν_{max} 3430 (OH), 3300 (NH), 1680, 1530 (amide C=O), 749, 692 (C_6H_5). The above was identical with an authentic sample.[4]

Benzyl 4,6-*O*-Benzylidene-2-deoxy-3-*O*-ethoxycarbonyl-2-(ethoxycarbonyl)amino-β-D-glucopyranoside (VIIb).—Precipitate 3, on recrystallization from ethanol, gave 0.43 g (32%): mp 164–165°, $[\alpha]^{20}D$ −85°; ν_{max} 3320 (NH), 1730 (ester C=O), 1690, 1520 (amide C=O), 750, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_9$ (501.52): C, 62.26; H, 6.23; N, 2.80; O, 28.71. Found: C, 61.81; H, 6.41; N, 3.08; O, 28.49.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-β-D-glucopyranosido-[2,3:4′,5′]-*N*-ethyl-2′-oxazolidinone (VIIIb).—A solution of Ib (0.50 g, 0.0014 mol) in warm diethyl carbonate (12 ml) was treated with potassium *tert*-butoxide (0.20 g, 0.0018 mol), refluxed with stirring for 62 hr, and filtered hot leaving a precipitate (precipitate 1, 0.05 g). Petroleum ether (200 ml) was added to the filtrate, which was filtered again after 1 hr at 0° (precipitate 2, 0.15 g). The solution was then evaporated *in vacuo* to dryness (precipitate 3, 0.49 g).

Precipitate 3, shown by tlc to be VIIIb with some VIIb, was recrystallized from methanol (0° for 16 hr) to give 0.41 g (75%): mp 200–201°; $[\alpha]^{20}D$ −105°; ν_{max} 1750 (oxazolidinone), 760, 646 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_6$ (411.44): C, 67.13; H, 6.12; N, 3.41; O, 23.33. Found: C, 67.24; H, 6.15; N, 3.45; O, 23.30.

When IVb or benzyl 4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-β-D-glucopyranoside (IXb)[3] was substituted for Ib in the above procedure, the results were similar.

Registry No.—IIa, 27909-16-6; IIb, 27909-17-7; IIIa, 27909-18-8; IIIb, 27909-19-9; Vb, 27909-20-2; VIa, 27909-21-3; VIb, 19359-04-7; VIIa, 27909-23-5; VIIb, 27909-24-6; VIIIa, 27909-25-7; VIIIb, 27909-26-8.

(8) K. Miyai and P. Gross, unpublished results.