Heterocyclic Amino Sugar Derivatives. IV. Reactions of Difunctional Esters with Vicinal Trans Diequatorial Amino Hydroxy Groups[1]

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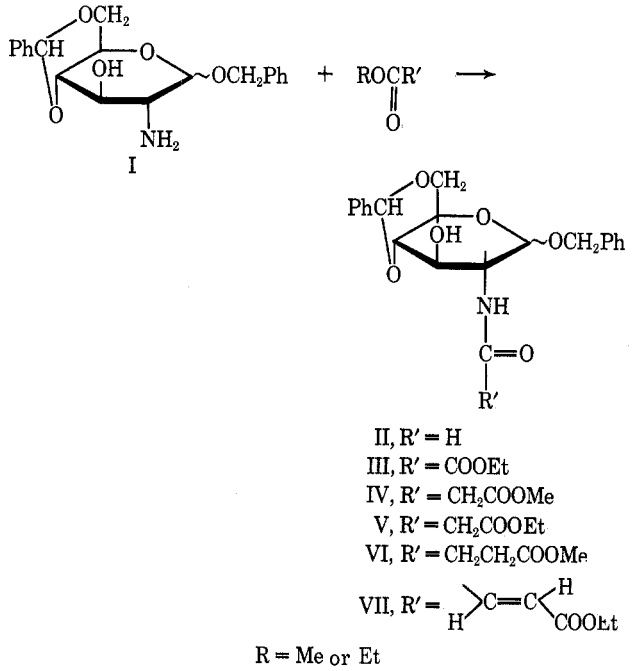
A wide variety of *N*-acyl derivatives has been synthesized from reaction between benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides (I) and carboxylic esters by methods not previously used for sugars. Increasing difficulty in producing derivatives with bulky acyl groups has been noted. The ir spectra amide I and amide II bands of the α anomers of 3 position unsubstituted glucopyranosides are of lower wave number than the corresponding β anomers. The competition between aminolysis of ester, to form amides, and amine addition to double bonds, to form secondary amines, has been studied. This latter reaction has resulted in novel amino acid derivatives. The stability of the formamide, oxamide, and malonamide groups with regard to acylations and acidic debenzylidenations has been studied. The formamide and malonamide have been found to be quite stable, with the oxamide much less so. An exception with the formamides is methanesulfonylation, which gives rise to the dehydration of the formamide group with formation of novel isocyanide derivatives. On treatment of the *O*-ethylmalonyl derivative of I with base, formation of a *C*-sodium salt occurs rather than hydrolysis of the ester. Malonyl dichloride and diethyl malonate yield α,α, β,β, and α,β dimers with 2 mol of I. Dimers of this type have not been reported before. Diethyl oxalate and 1 equiv of I in a two-step reaction give a derivative which has a morpholinedione ring trans diequatorially fused to the sugar.

The reaction between the two anomers of benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-glucopyranoside (I) and various difunctional esters has been studied (Scheme I).[2] As compounds I[2] have a single alcohol and a single amine group available as reaction sites and these groups are on adjacent carbons of the sugar ring, it was felt that the nature of these reactions might provide insight into possible blocking groups for the 2 and 3 positions.

SCHEME I[2]



Amide derivatives have been made by reaction of I with acyl chlorides or the free acid in the presence of a carbodiimide.[3] However, esters had not been employed for the purpose of N-acylation of I.

Analogous to similar compounds prepared by Meyer zu Reckendorf and Bonner,[4] both formamide anomers II were produced using methyl formate in a methanolic methoxide solution. The ethyl oxamide anomers III were prepared by the method of Drefahl, Hartmann, and Skurk[5] previously used for making amides of 1-hydroxy-2-aminocyclohexane with diethyl oxalate in ethanol.

The above methods failed completely in reacting more complicated difunctional esters with I. It was found that compound I could form amides with some other esters by using the ester itself as the solvent and employing elevated temperatures. It should be noted that the times and temperatures for the reaction are critical. For example, the conditions for the reaction of Ib and diethyl malonate to form Vb are 150° for 4 hr. A reaction temperature 20° higher for 1 hr results in tars and no product, this also being the case for 150° and 6-hr reaction time. A reaction temperature 25° lower resulted in no noticeable reaction after 12 hr. Using the "correct" conditions, the product often starts to crystallize directly from the reaction mixture.

The methyl esters are considerably more reactive than the ethyl esters. For example, the reaction temperature for dimethyl malonate, in the preparation of IV, is 35° lower and the reaction time 2 hr less than for the corresponding diethyl malonate in the preparation of V.

As the ester increases in size, the reactivities and yields decrease or are nonexistent. Even though the methyl esters are the most reactive, reaction conditions have not been found which will yield the methyl adipate amide. Dimethyl succinate resulted in tars before the corresponding amide was formed. Similarly, ethyl cinnamate does not undergo reaction. Also, the products of the reaction of I with bulky esters may have a solubility in nonpolar solvents, not different enough from the ester, which is removed by precipitation of the product with petroleum ether. As the larger esters have

(1) A preliminary communication was presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstracts, CARB 10. Taken from the doctoral thesis of F. R. Seymour, University of the Pacific, 1969. This work was partially supported by Grant No. GP12222 of the National Science Foundation. For the previous paper in this series see W. D. Rhoads and P. H. Gross, *Carbohyd. Res.*, **11**, 561 (1969).

(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) P. H. Gross and R. W. Jeanloz, *J. Org. Chem.*, **32**, 2759 (1967).

(4) W. A. Bonner and W. Meyer zu Reckendorf, *Chem. Ber.*, **94**, 3293 (1961).

(5) G. Drefahl, M. Hartmann, and A. Skurk, *ibid.*, **99**, 1174 (1966).

quite high boiling points, they cannot be removed by distillation.

Of ten comparable pairs of amide derivatives of I (Table I),[2] the amide I and amide II bands in the ir

TABLE I[a]

RELATIVE IR SPECTRA OF AMIDE I AND AMIDE II SHIFTS BETWEEN α AND β ANOMERS OF *N*-ACYL DERIVATIVES OF BENZYL 2-AMINO-4,6-*O*-BENZYLIDENE-2-DEOXY-D-GLUCOPYRANOSIDES

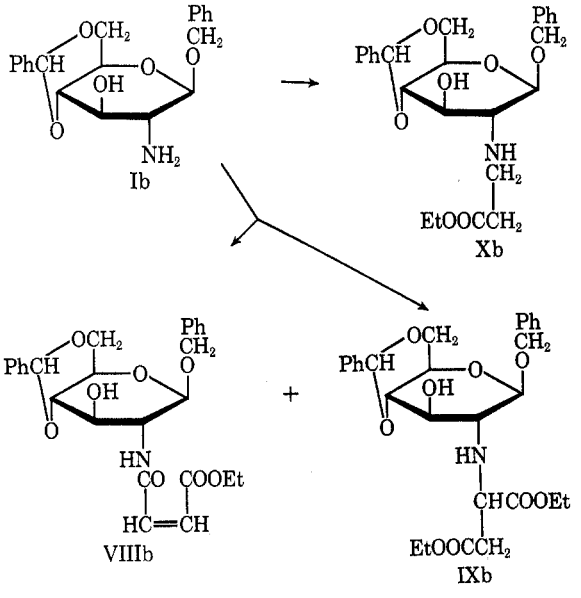
	α anomer Amide band, cm⁻¹		β anomer Amide band, cm⁻¹	
Acyl group	I	II	I	II
-CHO	1650	1530	1670	1550
-CHO[b]	1630	1530	1650	1540
-COCOOEt	1670	1540	1690	1550
$-COCH_2COOMe$	1620	1540	1650	1540
$-COCH_2COOEt$	1640	1540	1650	1540
$-COCH_2COOEt$[b]	1630	1540	1660	1540
trans-COCH=CHCOOEt	1630	1530	1650	1540
-COOMe[c]	1670	1530	1680	1530
-COOEt[c]	1670	1520	1680	1530
$-COCH_3$[d]	1630	1530	1640	1540

[a] Reference 2. [b] After removal of the 4,6-*O*-benzylidene group (XII or, respectively, XX). [c] From part V: F. R. Seymour and P. H. Gross, *J. Org. Chem.*, **36**, 1085 (1971). [d] Benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-D-glucopyranosides previously prepared by Gross and Jeanloz.[3]

spectra of the α anomers are of lower wave number than the bands of the corresponding β anomers. The average shift is 15 cm^{-1}. For this shift to occur, the hydroxyl at C-3 has to be free. The amide shift in α,β anomers may prove to be useful in distinguishing α and β linkages in disaccharides.

A relationship of interest with some compounds lies in the competition between aminolysis of an ester and addition to a double bond. The first route gives the expected amide and the second results in a secondary amine (Scheme II).[2] With fumaric esters, only the

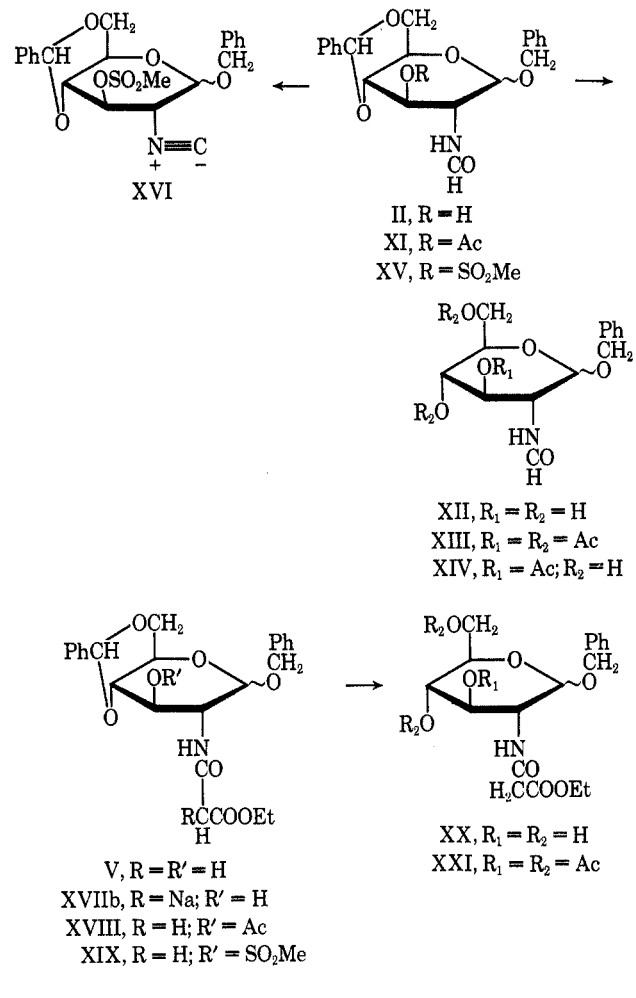
SCHEME II[2]



amides VII are produced, while with maleic esters both the amide VIIIb and aspartic acid derivative IXb are produced. This provides evidence that the sterically strained double bond of maleic esters is more reactive than the fumaric double bond. With ethyl acrylate only the β-alanine derivative Xb was found. This represents the extreme case in the competition between the two reaction routes.

The anomers of II gave a number of normal products resulting from acetylation (XI), debenzylidenation (XII), or both (XIII, XIV) as shown in Scheme III.[2]

SCHEME III[2]



However, the methanesulfonylation gave two reaction products for each anomer. The ir spectrum of one of the compounds showed that it was the expected 3-*O*-mesyl product XV of the starting material. The second compound, XVI, was a sugar with an ir spectrum showing no -OH, -NH, or amide bands, clearly a completely substituted product. The prominent feature of the spectrum was a sharp band at 2140 cm^{-1}, indicating the isocyanide group. Also, cyclohexyl isocyanide has been reported[6] with ir absorption at 2138 cm^{-1}.

Recently, acid halides, in the presence of tertiary amines, have been used to dehydrate monosubstituted formamides.[7] For example, benzenesulfonyl chloride and toluenesulfonyl chloride[8] in pyridine have been used for this purpose. The use of methanesulfonyl chloride for isocyanide synthesis has not previously been reported, nor has the introduction of an isocyanide group into a sugar.

(6) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).
(7) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem., Int. Ed. Engl.*, **4**, 476 (1965).
(8) W. Hertler and E. Corey, *J. Org. Chem.*, **23**, 1221 (1958).

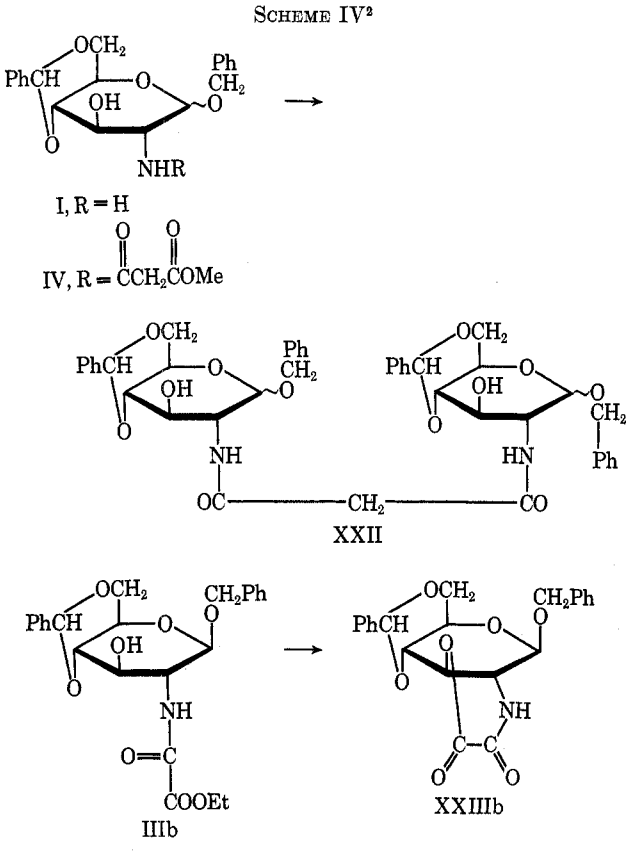
The malonate group in IV and V can be modified without affecting the rest of the molecule (Scheme III). On treatment with sodium hydroxide in an aqueous medium, a sodium salt of compound Vb is formed (XVIIb). Its ir spectrum shows all the functional groups of Vb remaining, and acidification of XVIIb yields the starting material Vb. Therefore, XVIIb is the C–Na malonate salt. This is surprising when contrasted to diethyl malonate, which when subjected to analogous reaction conditions does hydrolyze to form the half ester salt of the acid.[9] The different results with Vb may be due partly to the amide group replacing one of the ester groups, partly to chelation by the many oxygen atoms of the molecule.

A series of derivatives of V were prepared to explore the possibility of C-acylation at the malonamide group of these compounds. However, both anomers of V smoothly underwent O-acylation (yielding XVIII) and methanesulfonylations (yielding XIX), with the N substituent remaining intact. The debenzylidenation product XX similarly underwent O-acylation to give XXI.

The ethyloxamide group in III proved to be unstable under the reaction and/or work-up conditions of the usual acylations and debenzylidenations.

A difunctional reagent, such as malonyl dichloride, could react with both the alcohol and amine functional groups of compound I to form a heterocyclic ring fused into the sugar, or it could react with the amino groups of two molecules of I to form a dimer, such as XXII (Scheme IV). After removal of the benzylidene and/or

SCHEME IV[2]



benzylglycoside protective groups by mild acid or hydrogenation and the linkage to a high molecular protein carrier by means of the reactive methylene group of the malonamide, such dimers may become of interest as synthetic antigens.

Both Ia and Ib yielded products (Scheme IV)[2] with malonyl dichloride which showed no ester band in their ir spectrum, but showed amide I and amide II bands, along with an –OH band, indicating that the amide group was not in a cyclic structure.[10] The above data were in accord with dimerization having occurred. However, the ir evidence cannot be considered as definitive, as rings with *two* carbonyl groups present (*e.g.*, barbituric acid derivatives) may have an amide II band, and the possible heterocyclic structure being considered would be a seven-membered ring. Thus, compounds XXII were synthesized by an independent method. An equimolar mixture of Ia and IVa was refluxed in xylene, yielding a single product identical with XXIIa having $[\alpha]^{20}D$ +109°. Similarly, Ib and IVb gave a single product identical with XXIIb having $[\alpha]^{20}D$ −101°. Also, as expected, reaction between Ia and IVb gave a product XXIIa,b, identical with that obtained from Ib and IVa. The specific rotation of this product, $[\alpha]^{20}D$ +3°, is halfway between those of XXIIa and XXIIb.

The reactions between the acid dihalides and the glucosamine anomers (I) were carried out under a range of temperatures from −15 to 60° and in the solvents chloroform and tetrahydrofuran. The concentration of both reactants in the reaction mixture was kept to a minimum by the dropwise addition of solutions of both the acid dihalide and the sugar over a period of several hours. At all times the acid halide was in excess to the sugar. In none of these reactions was any product other than the dimer observed. In view of this, it may be said that the possibility is very low of forming a protective heterocyclic group between positions 2 and 3 of glucosamine in a single reaction resulting in a seven-member ring.

For such heterocyclic groups a two-step procedure is indicated in which a difunctional compound is first reacted selectively with the amine, the resulting compound is separated and purified, and finally the remaining functional group is reacted with the sugar's alcohol group. As in the final reaction there are no amine groups present; the competition is simply between an intraalcohol attack (to form a heterocycle) and an interalcohol attack (to form an oxygen–nitrogen linked dimer). In dilute solutions, the intramolecular attack should be favored and the heterocyclic formed.

By refluxing in xylene, with a catalytic amount of base, it has been possible to convert IIIb into a six-membered heterocyclic fused sugar, XXIIIb. However, this compound degrades on silica gel to give a compound which has an extremely low R_f value. Due to this lack of tlc migration, the degradation product is interpreted as the oxalate half-acid. That XXIIIb has actually been formed can be demonstrated in two ways. The ir spectra of XXIIIb shows strong, sharp ester and amide I bands but no trace of an –OH or amide II band. On cellulose tlc, with pure chloroform as the solvent, XXIIIb has an R_f value of 0.7, much greater than IIIb, indicating that no polar functional groups, such as an amine or alcohol, are present. The instability of the

(9) D. Breslow and E. Baumgarten, *J. Amer. Chem. Soc.*, **66**, 1287 (1944).

(10) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958.

compound is attributed to ring strain plus the inductive effect of the adjacent consecutive carbonyl groups weakening the O–C bond in the ring. This morpholinedione ring is not new, having recently been reported by Drefahl, Hartmann, and Skurk as fused into the cyclohexane ring.[5] The method of preparation is analogous to their reported method. Their cyclohexane fused heterocyclic compound is apparently more stable than XXIIIb.

A similar heterocyclic product could not be formed with IIIa. Also, similar conditions with Va and Vb resulted in no reaction. Possible explanations for this are that the malonyl esters are much less reactive than the oxalyl esters or that a seven-membered ring is formed much less readily.

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.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (IIa).—A solution of Ia[3] (5 g, 0.014 mol) and methyl formate (6 ml, 0.1 mol) in 0.1 *N* methanolic sodium methoxide (350 ml) was refluxed and stirred 5 hr, and the resulting solution kept 8 hr at 0°. The resulting crystals were filtered and recrystallized from dioxane–2-propanol to give 5.1 g (94%): mp 267–268°; $[\alpha]^{20}D$ +99°; ν_{max} 3390 (OH), 3290 (NH), 1650, 1530 (amide C=O), 749, 697 (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.4): C, 65.51; H, 6.02; N, 3.64. Found: C, 64.57; H, 6.43; N, 3.75.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (IIb).—Compound Ib,[3] by the same procedure as for IIa, gave 5.05 g (93%): mp 257–258°; $[\alpha]^{20}D$ −70°; ν_{max} 3390 (OH), 3270 (NH), 1670, 1550 (amide C=O), 750, 697 (C_6H_5).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.4): C, 65.51; H, 6.02; N, 3.64. Found: C, 65.51; H, 6.16; N, 3.51.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethyl)oxamido-α-D-glucopyranoside (IIIa).—A solution of Ia[3] (4 g, 0.011 mol) and diethyl oxalate (12 ml, 0.08 mol) in anhydrous ethanol (120 ml) was refluxed 12 hr, filtered hot, and kept 12 hr at −15°. The resulting crystals were filtered and recrystallized from anhydrous ethanol to give 4.15 g (84%): mp 223–224°, $[\alpha]^{20}D$ +88°; ν_{max} 3470 (OH), 3300 (NH), 1740 (ester C=O), 1670, 1540 (amide C=O), 745, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.96; N, 3.07. Found: C, 63.65; H, 5.94; N, 2.92.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(ethyl)oxamido-β-glucopyranoside (IIIb).—Compound Ib,[3] by the same procedure as described for IIIa, gave 3.8 g (76%): mp 214–215°; $[\alpha]^{20}D$ −89°; ν_{max} 3530, 3495 (OH), 3300 (NH), 1730 (ester C=O), 1690, 1550 (amide C=O), 750, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.96; N, 3.07. Found: C, 63.68; H, 5.80; N, 3.07.

Below we show the general preparation of the benzyl 4,6-*O*-benzylidene-2-deoxy-2-(acyl)amino-D-glucopyranosides (IVa through Xb).

The carboxylic ester and Ia (or Ib)[3] were stirred and heated for the time and temperature given below. The resulting hot solution was treated with petroleum ether–diethyl ether 1:1 (20 ml/g of starting sugar) and kept 12 hr at −15°. The precipitate was filtered off and recrystallized from dioxane–2-propanol. The resulting yields and properties as well as deviations from the general procedure are listed under the individual compounds. Only one ester group reacted to form the amide.

Benzyl 4,6,*O*-Benzylidene-2-deoxy-2-(*O*-methyl)malonamido-α-D-glucopyranoside (IVa).—Dimethyl malonate (10 ml, 0.06 mol) and Ia (3 g, 0.009 mol) at 115° for 75 min gave 3.47 g (93%): mp 224–225°; $[\alpha]^{20}D$ +118°; ν_{max} 3450 (OH), 3280 (NH), 1730 (ester C=O), 1620, 1540 (amide C=O), 750, 691 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.95; N, 3.07; O, 27.98. Found: C, 62.68; H, 6.07; N, 3.10; O, 28.10.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-methyl)malonamido-β-D-glucopyranoside (IVb).—Dimethyl malonate (5 ml, 0.03 mol) and Ib (1 g, 0.003 mol) at 115° for 85 min gave 1.1 g (89%): mp 243–244°; $[\alpha]^{20}D$ −82°; ν_{max} 3480 (OH), 3250 (NH), 1740 (ester C=O), 1650, 1540 (amide C=O), 752, 691 (C_6H_5).

Anal. Calcd for $C_{24}H_{27}NO_8$ (457.5): C, 63.00; H, 5.95; N, 3.07; O, 27.98. Found: C, 63.89; H, 6.16; N, 3.13; O, 27.31.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (Va).—Diethyl malonate (45 ml, 0.3 mol) and Ia (7 g, 0.02 mol) at 110° for 3 hr gave 7.24 g (80%): mp 188–189°; $[\alpha]^{20}D$ +102°; ν_{max} 3450 (OH), 3280 (NH), 1730 (ester C=O), 1620, 1540 (amide C=O), 740, 690 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8H_2O$ (489.5): C, 61.34; H, 6.38; N, 2.86; O, 29.42. Found: C, 61.63; H, 6.25; N, 3.03; O, 29.44.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (Vb).—Diethyl malonate (8 ml, 0.048 mol) and Ib (8 g, 0.024 mol) at 115° for 3 hr gave 8.46 g (82%): mp 181–182°; $[\alpha]^{20}D$ −75°; ν_{max} 3450 (OH), 3270 (NH), 1740 (ester C=O), 1650, 1540 (amide C=O), 750, 692 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8$ (471.5): C, 63.86; H, 6.20; N, 2.79; O, 27.15. Found: C, 63.69; H, 6.19; N, 2.81; O, 27.10.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-methyl)succinamido-α-D-glucopyranoside (VIa).—Dimethyl succinate (3.0 ml, 0.017 mol) and Ia (1.0 g, 0.0027 mol) were kept at 155° for 9 hr; petroleum ether (20 ml) was added. After 3 hr at 20° (at lower temperature the dimethyl succinate crystallizes out) the mixture was filtered to yield 0.65 g of precipitate containing approximately 25% Ia. The precipitate was purified by preparative tlc. The major fraction was recrystallized from 2-propanol to give 0.40 g (30%): mp 201–202°; $[\alpha]^{20}D$ +96°; ν_{max} 3380 (OH), 3290 (NH), 1720 (ester C=O), 1630, 1530 (amide C=O), 691 (C_6H_5).

Anal. Calcd for $C_{25}H_{29}NO_8$ (471.5): C, 63.68; H, 6.20; N, 2.97; O, 27.15. Found: C, 63.28; H, 6.47; N, 3.01; O, 27.22.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)fumaramido-α-D-glucopyranoside (VIIa).—Diethyl fumarate (3 ml, 0.02 mol) and Ia (0.60 g, 0.002 mol) at 155° for 4 hr gave 0.44 g, which when separated by preparative tlc gave a major component which recrystallized from dioxane–2-propanol gave 0.27 g (34%): mp 206–207°; $[\alpha]^{20}D$ +104°; ν_{max} 3400 (OH), 3270 (NH), 1690 (ester C=O), 1630, 1530 (amide C=O), 745, 690 (C_6H_5), 690 (s) → C_6H_5.

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 65.40; H, 5.66; N, 3.00; O, 25.93.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)fumaramido-β-D-glucopyranoside (VIIb).—Diethyl fumarate (5 ml, 0.03 mol) and Ib (1 g, 0.003 mol) at 115° for 53 min gave 0.64 g (48%): mp 235–236°; $[\alpha]^{20}D$ −75°; ν_{max} 3450 (OH), 3280, 3240 (NH), 1740 (ester C=O), 1640, 1540 (amide C=O), 751, 691 (C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 65.64; H, 5.66; N, 3.00; O, 25.93.

Reaction between Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (Ib) and Diethyl Maleate.—Diethyl maleate (5 ml, 0.03 mol) and Ib (1.0 g, 0.003 mol) were stirred at 155° for 5 hr. The product was precipitated by first adding 15 ml of diethyl ether and then adding 15 ml of petroleum ether. After 6 hr at 0°, 0.45 g was filtered out and separated by preparative tlc to give two fractions.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)maleamido-β-D-glucopyranoside (VIIIb).—The slowest moving fraction, recrystallized from dioxane-2-propanol, gave 0.17 g (13%): mp 203–205°; ν_{max} 3420 (OH), 3280 (NH), 1710 (ester C=O), 1640, 1510 (amide C=O), 743, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8$ (483.5): C, 64.59; H, 6.04; N, 2.90; O, 26.47. Found: C, 64.95; H, 6.40; N, 3.54; O, 24.66.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(1,2-diethoxycarbonyl)-ethylamino-β-D-glucopyranoside (IXb).—The fastest component, recrystallized from diisopropyl ether–petroleum ether, gave 0.11 g (8%): mp 74–96°, two slightly separated components on tlc due to the new asymmetric carbon at the amino group; ν_{max} 3550 (OH), 3210 (NH), 1710, 1700 (ester C=O), 750, 690 (C_6H_5).

Anal. Calcd for $C_{28}H_{35}NO_9$ (529.6): C, 63.51; H, 6.66; N, 2.64; O, 27.19. Found: C, 63.30; H, 6.59; N, 2.96; O, 27.22.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(2-ethoxycarbonyl)ethylamino-β-D-glucopyranoside (Xb).—Ethyl acrylate (6.0 ml, 0.06 mol) and Ib (0.80 g, 0.0022 mol) at 115° for 2.5 hr yielded 0.57 g. Purified by preparative tlc and recrystallized from 2-propanol the major fraction gave 0.42 g (41%): mp 114–115°; $[\alpha]^{20}D$ −68°; ν_{max} 3450 (OH), 3300 (NH), 1720 (ester C=O), 761, 698 (C_6H_5).

Anal. Calcd for $C_{25}H_{31}NO_7$ (457.5): C, 65.63; H, 6.83; N, 3.06; O, 24.48. Found: C, 65.27; H, 6.60; N, 3.42; O, 24.78.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (XIa).—To a solution of IIa (1.5 g, 0.0039 mol) in dry pyridine (33 ml) was added acetic anhydride (1.8 ml, 0.017 mol). After 14 hr at 20°, ice–water (100 ml) was added to the reaction mixture. After 3 hr the precipitate was filtered off and recrystallized from dioxane–diisopropyl ether to give 1.37 g (77%): mp 194–195°; $[\alpha]^{20}D$ +72°; ν_{max} 3270 (NH), 1730 (ester C=O), 1650, 1530 (amide C=O), 751, 697 (C_6H_5).

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.4): C, 64.69; H, 5.90; N, 3.28. Found: C, 64.41; H, 6.02; N, 3.12.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (XIb).—The above procedure was repeated with IIb (1.5 g) to give 1.32 g (74%): mp 287–288°; $[\alpha]^{20}D$ −100°; shows the same ir bands as given for XIa.

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.4): C, 64.69; H, 5.90; N, 3.28. Found: C, 64.53; H, 6.07; N, 3.08.

Benzyl 2-Deoxy-2-formamido-α-D-glucopyranoside (XIIa).—To a mixture of IIa (0.92 g, 0.0024 mol) and acetic acid (35 ml) at 75° was added water (8 ml) dropwise over a 15-min interval. After the solution became clear it was evaporated *in vacuo* to dryness. To the residue was added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated *in vacuo* to dryness. The residue was recrystallized from dioxane–benzene to give 0.51 g (72%): mp 148–149°; $[\alpha]^{20}D$ +221°; ν_{max} 3450, 3320 (OH), 3200 (NH), 1630, 1530 (amide C=O), 750, 691 (C_6H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$ (297.3): C, 56.61; H, 6.45; N, 4.72; O, 32.32. Found: C, 56.50; H, 6.51; N, 4.78; O, 32.47.

Benzyl 2-Deoxy-2-formamido-β-D-glucopyranoside (XIIb).—The above procedure was repeated with IIb (0.90 g) to give 0.47 g (66%): mp 163–165°; $[\alpha]^{20}D$ −56°; ν_{max} 3450, 3340 (OH), 3210 (NH), 1650, 1540 (amide C=O), 750, 695 (C_6H_5).

Anal. Calcd for $C_{14}H_{19}NO_6$ (297.3): C, 56.61; H, 6.45; N, 4.72. Found: C, 56.53; H, 6.51; N, 4.72.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-formamido-α-D-glucopyranoside (XIIIa).—To a solution of XIIa (0.25 g, 0.00059 mol) in dry pyridine (2.0 ml) was added acetic anhydride (0.5 ml, 0.005 mol). After 12 hr at 25°, ice–water (20 ml) was added to the reaction mixture. After 4 hr the precipitate was filtered off and recrystallized from 2-propanol to give 0.33 g (92%): mp 113–114°; $[\alpha]^{20}D$ +89°; ν_{max} 3220 (NH), 1730 (ester C=O), 1660, 1530 (amide C=O), 740, 696 (C_6H_5).

Anal. Calcd for $C_{20}H_{25}NO_9$ (423.4): C, 56.78; H, 5.96; N, 3.31. Found: C, 56.47; H, 6.15; N, 2.82.

Benzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-formamido-β-D-glucopyranoside (XIIIb).—The above procedure was repeated with XIIb (0.25 g) to give 0.31 g (87%): mp 170–171°; $[\alpha]^{20}D$ −34°; ν_{max} 3210 (NH), 1730 (ester C=O), 1660, 1510 (amide C=O), 750, 698 (C_6H_5).

Anal. Calcd for $C_{20}H_{25}NO_9$ (423.4): C, 56.78; H, 5.96; N, 3.31. Found: C, 56.51; H, 5.95; N, 2.98.

Benzyl 3-*O*-Acetyl-2-deoxy-2-formamido-α-D-glucopyranoside (XIVa).—To a solution of XIa (1.06 g, 0.0022 mol) in acetic acid (20 ml) at 75° were added water (8 ml), dropwise over a 30-min interval. The solution was then evaporated *in vacuo* to dryness. To the residue were added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated to dryness *in vacuo*. The residue was then recrystallized from dioxane–benzene to give 0.62 g (77%): mp 101°; $[\alpha]^{20}D$ +82°; ν_{max} 3380 (OH), 3290 (NH), 1720 (ester C=O), 1640, 1540 (amide C=O), 730, 692 (C_6H_5).

Anal. Calcd for $C_{16}H_{21}O_7N$ (339.3): C, 56.68; H, 6.24; N, 4.13; O, 33.04. Found: C, 56.61; H, 6.47; N, 4.05; O, 33.13.

Benzyl 3-*O*-Acetyl-2-deoxy-2-formamido-β-D-glucopyranoside (XIVb).—The above procedure was repeated with XIb (1.06 g) to give 0.62 g (77%): mp 193°; $[\alpha]^{20}D$ −66°; ν_{max} 3420 (OH), 3290 (NH), 1700 (ester C=O), 1660, 1530 (amide C=O), 740, 693 (C_6H_5).

Anal. Calcd for $C_{16}H_{21}O_7N$ (339.3): C, 56.68; H, 6.24; N, 4.13; O, 33.04. Found: C, 56.69; H, 6.25; N, 3.74; O, 33.44.

Reaction between Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-α-D-glucopyranoside (IIa) and Methanesulfonyl Chloride.—To a mixture of IIa (1.5 g, 0.0039 mol) in dry pyridine (12 ml) at −10° was added methanesulfonyl chloride (1.2 ml, 0.01 mol) dropwise over a 10-min interval. After 11 hr at 0° a clear solution with a deep red color resulted. Ice–water (40 ml) was added to the reaction mixture and a reddish precipitate resulted. After 4 hr at 5° the precipitate was filtered off, air-dried, and recrystallized from dioxane–diisopropyl ether to give 1.13 g. Analysis of this precipitate on tlc showed three major components, the red material which did not move from the origin plus two moving fractions. The mixture was then separated by preparative tlc using 2% ethanol in chloroform.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-3-*O*-mesyl-α-D-glucopyranoside (XVa).—The slowest moving fraction to leave the origin, recrystallized from 2-propanol, gave 0.69 g (35%): mp 195–196°; $[\alpha]^{20}D$ +67°; ν_{max} 3270 (NH), 1650, 1530 (amide C=O), 741, 695 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_8S$ (463.49): C, 57.07; H, 5.44; S, 6.93. Found: C, 57.07; H, 5.56; S, 7.00.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-isonitryl-3-*O*-mesyl-α-D-glucopyranoside (XVIa).—The fastest moving fraction, recrystallized from 2-propanol–diisopropyl ether, gave 0.21 g (12%): mp 176–177°; $[\alpha]^{20}D$ +106°; ν_{max} 2140 (N≡C), 747, 696 (C_6H_5).

Anal. Calcd for $C_{22}H_{23}NO_7S$ (445.48): C, 59.31; H, 5.20; N, 3.15; O, 25.14. Found: C, 60.10; H, 5.30; N, 3.02; O, 25.49.

Reaction between Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-β-D-glucopyranoside (IIb) and Methanesulfonyl Chloride.—The procedure was the same as for the above α anomer, however, using a 7-hr reaction time instead of 11 hr. The reaction mixture also gave a reddish precipitate (0.99 g) with two moving components on tlc.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-formamido-3-*O*-mesyl-β-D-glucopyranoside (XVb).—The slowest moving fraction, recrystallized from 2-propanol, gave 0.72 g (37%): mp 180–181°; $[\alpha]^{20}D$ −54°; ν_{max} 3340 (OH), 1660, 1520 (amide C=O), 745, 698 (C_6H_5).

Anal. Calcd for $C_{22}H_{25}NO_8S$ (469.49): C, 57.07; H, 5.44; N, 3.03; S, 6.93. Found: C, 57.00; H, 5.62; N, 2.83; S, 6.51.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-isonitryl-3-*O*-mesyl-β-D-glucopyranoside (XVIb).—The fastest moving fraction, recrystallized from 2-propanol–diisopropyl ether, gave 0.17 g (9%): mp 160–163°; $[\alpha]^{20}D$ −46°; ν_{max} 2140 (N≡C), 741, 692 (C_6H_5). As both tlc and ir showed a trace of XVIIb, estimated at 5%, this compound has not been sent for analysis.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl-*C*-sodium)malonamido-β-D-glucopyranoside (XVIIb).—A solution of Vb (2.35 g, 0.005 mol), water (20 ml), methanol (20 ml), and dioxane (100 ml) was treated with a solution of sodium metal (0.127 g, 0.0055 g-atom) in methanol (11 ml) at 25°. The resulting solution was evaporated *in vacuo*. Dioxane and toluene were added to the residue and reevaporated *in vacuo*. The residue was dried for 1 hr at 80°, washed with chloroform–ether, and dried for 12 hr at 50°, to give 2.31 g (98%): mp 264–265°; ν_{max} 3410 (OH), 3280 (NH), 1710 (ester C=O), 1640, 1530 (amide C=O), 742, 691 (C_6H_5); very slow migration on tlc compared to Vb when using chloroform–ethanol solution.

The starting material Vb, used in the above reaction, was regenerated in the following manner. To a mixture of XXIIIb (0.94 g, 0.002 mol) with methanol (100 ml) were added 0.23 *N* HCl (8 ml, 0.002 mol) and glacial acetic acid (2 drops). The suspension was stirred rapidly for 5 hr, and the precipitate was dried azeotropically with ethanol–toluene, and recrystallized from dioxane–2-propanol to yield 0.80 g (84%). Physical constants are identical with Vb (rotation, R_f value, ir spectrum) with the exception that this product melts at 231–232°. A mixture melting point is halfway between the new and old melting points. This is interpreted as being a new crystal form.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-α-D-glucopyranoside (XVIIIa).—To a solution of Va (0.90 g, 0.0019 mol) in dry pyridine (8 ml) was added acetic anhydride (1.5 ml, 0.014 mol). After 10 hr at 25°, ice and water (40 ml) were added to the reaction mixture. After 6 hr the precipitate was filtered off, air-dried, and recrystallized from 2-propanol to give 0.77 g (79%): mp 166–169°; $[\alpha]^{20}D$ +210°; ν_{max} 3280 (NH), 1730 (ester C=O), 1640, 1530 (amide C=O), 751, 694 (C_6H_5).

Anal. Calcd for $C_{27}H_{31}NO_9$ (514.53): C, 62.97; H, 6.07; N, 2.72. Found: C, 63.13; H, 5.90; N, 2.91.

Benzyl 3-*O*-Acetyl-4,6-*O*-benzylidene-2-deoxy-2-(*O*-ethyl)-malonamido-β-D-glucopyranoside (XVIIIb).—The above procedure was repeated with Vb (0.90 g) to give 0.73 g (74%): mp 188–189°; $[\alpha]^{20}D$ −93°; ν_{max} 3280 (NH), 1730 (ester C=O), 1640, 1530 (amide C=O), 751, 694 (C_6H_5).

Anal. Calcd for $C_{27}H_{31}NO_9$ (514.53): C, 62.97; H, 6.07; N, 2.72. Found: C, 62.66; H, 6.52; N, 2.38.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-3-*O*-mesyl-α-D-glucopyranoside (XIXa).—To a solution of Va (1.5 g, 0.0032 mol) in dry pyridine (12 ml) at −10° was added methanesulfonyl chloride (1.2 ml, 0.01 mol) dropwise over a 15-min interval. After 14 hr at 0°, ice and water (80 ml) were added to the reaction mixture. After 4 hr at 5° the precipitate was filtered off, air-dried, and recrystallized from dioxane–diisopropyl ether to give 1.51 g (86%): mp 190–191°, $[\alpha]^{20}D$ +198°; ν_{max} 3290 (NH), 1730 (ester C=O), 1650, 1540 (amide C=O), 747, 691 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_{10}S$ (549.58): C, 56.77; H, 5.68; N, 2.55; S, 5.83. Found: C, 56.74; H, 5.61; N, 2.50; S, 6.02.

Benzyl 4,6-*O*-Benzylidene-2-deoxy-2-(*O*-ethyl)malonamido-3-*O*-mesyl-β-D-glucopyranoside (XIXb).—The above procedure was repeated with Vb (1.5 g). Recrystallization from ethanol gave 1.00 g (57%): mp 168–169°; $[\alpha]^{20}D$ −48°; ν_{max} 3260 (NH), 1730 (ester C=O), 1650 (amide C=O), 749, 690 (C_6H_5).

Anal. Calcd for $C_{26}H_{31}NO_{10}S$ (549.58): C, 56.77; H, 5.68; N, 2.55; S, 5.83. Found: C, 56.93; H, 5.61; N, 2.42; S, 6.01.

Benzyl 2-Deoxy-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (XXa).—To a solution of Va (0.81 g, 0.0017 mol) and acetic acid (25 ml) at 75° was added water (12 ml, 0.7 mol) dropwise over a 45-min interval. The solution was then evaporated *in vacuo* to dryness. To the residue were added water (two 10-ml portions) and then toluene (two 10-ml portions). After each solvent addition the solution was again evaporated *in vacuo* to dryness. The residue was then recrystallized from dioxane–benzene to give 0.39 g (59%): mp 147–148°; $[\alpha]^{20}D$ +157°; ν_{max} 3530, 3380 (OH), 3280 (NH), 1730 (ester C=O), 1630, 1530 (amide C=O), 740, 692 (C_6H_5).

Anal. Calcd for $C_{18}H_{25}NO_8$ (383.39): C, 56.44; H, 6.58; N, 3.66. Found: C, 56.26; H, 6.73; N, 2.64.

Benzyl 2-Deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (XXb).—The above procedure was repeated with Vb (0.80 g) to give 0.56 g (85%): mp 177–178°; $[\alpha]^{20}D$ −27°; ν_{max} 3360 (OH), 3270 (NH), 1730 (ester C=O), 1660, 1540 (amide C=O), 742, 693 (C_6H_5).

Anal. Calcd for $C_{18}H_{25}NO_8H_2O$ (401.39): C, 53.85; H, 6.78; N, 3.49. Found: C, 54.26; H, 6.73; N, 3.58.

Benzyl 3,4,6-*O*-Triacetyl-2-(*O*-ethyl)malonamido-α-D-glucopyranoside (XXIa).—To a solution of XXa (0.25 g, 0.0016 mol) and dry pyridine (2 ml) was added acetic anhydride (0.5 ml, 0.005 mol). After 10 hr at 25°, ice and water (20 ml) were added to the reaction mixture. First crystals developed, then oil. A system could not be found to crystallize the oil: 0.27 g (81%); uniform on tlc; ν_{max} 3340 (NH), 1740 (ester C=O), 1670, 1530 (amide C=O), 750, 695 (C_6H_5).

Benzyl 3,4,6-*O*-Triacetyl-2-deoxy-2-(*O*-ethyl)malonamido-β-D-glucopyranoside (XXIb).—The above procedure was repeated with XXb (0.25 g) to give a precipitate, which recrystallized from 2-propanol–diisopropyl ether and gave 0.22 g (67%): mp 159–160°; $[\alpha]^{20}D$ −22°; ν_{max} 3310 (NH), 1730 (ester C=O), 1660, 1520 (amide C=O), 752, 692 (C_6H_5).

Anal. Calcd for $C_{24}H_{31}NO_{11}$ (509.50): C, 56.52; H, 6.13; N, 2.75. Found: C, 56.53; H, 6.23; N, 2.66.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)malonamide (XXIIa). A.—To a solution of dry, alcohol-free chloroform (100 ml) and collidine (1.17 g, 0.007 mol) at −10° were added dropwise two separate solutions: Ia (0.98 g, 0.0027 mol) in chloroform (50 ml), and malonyl dichloride (0.46 g, 0.0033 mol) in chloroform (50 ml). At the start, 5 ml of the malonyl dichloride solution was added and the two solutions were then added at an equal rate over a 2-hr period. The reaction mixture was stirred for 4 hr (the temperature slowly rising to 20°) and extracted successively with 5% aqueous $KHCO_3$, 5% citric acid, and distilled water. The chloroform phase was then filtered and evaporated *in vacuo*. The solid residue was recrystallized from dioxane–diisopropyl ether to give 0.92 g (90%): mp 306–307° dec; $[\alpha]^{20}D$ +109°; ν_{max} 3580 (OH), 3280 (NH), 1650, 1520 (amide C=O), 734, 691 (C_6H_5).

B.—A solution of Ia (0.20 g, 0.00056 mol) and IVa (0.25 g, 0.00056 mol) in xylene (30 ml) was refluxed with stirring for 14 hr. The precipitate formed was filtered hot from the solution, air-dried, and recrystallized from dioxane–diisopropyl alcohol to give 0.36 g (79%), physical constants identical with the product from procedure A.

Bis(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosido)malonamide (XXIIb). A.—This was identical with procedure A of XXIIa except that Ib was used in place of Ia to give 0.87 g (85%): mp 280–281° dec; $[\alpha]^{20}D$ −101°; ν_{max} 3480 (OH), 3270 (NH), 1640, 1520 (amide C=O), 745, 692 (C_6H_5).

B.—This was identical with procedure B of XXIIa using the β anomers rather than the α anomers to give 0.32 g (72%). The physical constants are identical with the product XXIIb of procedure A.

(Benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranosido)(benzyl 2-amino-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranosido)malonamide (XIIa,b). A.—This was identical with procedure B of XXIIa using Ib and IVa to give 0.36 g (79%): mp 292–293° dec; $[\alpha]^{20}D$ +3°; ν_{max} 3380 (OH), 3270 (NH), 1640, 1540 (amide C=O), 748, 692 (C_6H_5).

B.—This was identical with procedure B of XXIIa, using Ia and IVb to give 0.28 g (62%). The physical constants are identical with the product from procedure A.

Benzyl 4,6-*O*-Benzylidene-β-D-glucopyranosido[2,3:5′,6′]-2′,3′-morpholinedione (XXIIIb).—A solution of potassium *tert*-butoxide (0.02 g, 0.0002 mol) and IIIb (0.51 g, 0.0012 mol) in xylene (20 ml) was refluxed for 6 hr. After 24 hr at 20°, Dry Ice was added. The reaction mixture was filtered through a short cellulose column, evaporated to dryness *in vacuo*, and recrystallized from chloroform–diisopropyl ether to give 0.15 g (32%): mp 127–128°; $[\alpha]^{20}D$ −79°; ν_{max} 3480 (NH), 1770 (ester C=O), 1720 (amide C=O), 755, 700 (C_6H_5).

Anal. Calcd for $C_{22}H_{21}NO_7$ (411.39): C, 64.21; H, 5.15; N, 3.41; O, 27.22. Found: C, 64.18; H, 5.40; N, 3.30; O, 27.31.

Registry No.—IIa, 27915-45-3; IIb, 27915-46-4; IIIa, 27915-47-5; IIIb, 27915-48-6; IVa, 27915-49-7; IVb, 27915-50-0; Va, 27915-51-1; Vb, 27915-52-2; VIa, 27915-53-3; VIIa, 27915-54-4; VIIb, 27915-55-5; VIIIb, 27915-56-6; IXb, 27915-57-7; Xb, 27915-58-8; XIa, 27915-59-9; XIb, 27915-60-2; XIIa, 27915-61-3; XIIb, 27915-62-4; XIIIa, 27915-63-5; XIIIb, 27915-64-6; XIVa, 27915-65-7; XIVb, 27915-66-8; XVa, 27909-34-8; XVb, 27909-35-9; XVIa, 27909-36-0; XVIb, 27909-37-1; XVIIb, 27909-38-2; XVIIIa, 27909-39-3; XVIIIb, 27909-40-6; XIXa, 27909-41-7; XIXb, 27909-42-8; XXa, 27909-43-9; XXb, 27909-44-0; XXIa, 27909-45-1; XXIb, 27909-46-2; XXIIa, 27909-47-3; XXIIb, 27909-48-4; XXIIIb, 27909-49-5.