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Advances in the Synthetic Chemistry of Aminoglycosides

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Data on the methods for the formation of the aminoglycosidic linkage in the synthesis of alkyl and aryl aminoglycosides and oligosaccharides containing 2-amino-2-deoxyglycosyl residues are reviewed systematically.
The bibliography includes 229 references.

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I. INTRODUCTION

Aminosugars and in the first place 2-amino-2-deoxyhexoses play a significant role in vital processes, being important structural components of polysaccharides and mixed biopolymers. The central problem of the chemistry of biopolymers containing aminosugar residues is that of the nature of the chemical bond joining the monomeric units of the macromolecules. Since the aminosugar residues in polysaccharides and other carbohydrate-containing polymers are as a rule linked by the aminoglycosidic linkage, the development of methods for its formation and the study of its properties constitute the most important problem in the chemistry of aminosugars.

The present review deals with methods of synthesis of aminoglycosides, including the formation of a new aminoglycosidic linkage, but not with the chemical reactions of glycosides and oligosaccharides without the formation of glycosidic linkages. The methods for the formation of the aminoglycosidic linkage are considered from the standpoint of the main requirements which must be met by glycoside synthesis in general, namely (1) the reaction must be structurally specific and stereospecific, (2) in view of the lability of the protecting groups for the "aglycone" component, the reaction must proceed under fairly mild conditions, and (3) the protecting groups of the glycosylating agent must be fairly stable under the conditions of the glycosylation reaction and at the same time must be removed easily and selectively from the final products without alteration of their structure.

From the chemical point of view, the synthesis of the glycosides of 2-amino-2-deoxysugars is of special interest, since it exhibits many important differences from glycoside synthesis with neutral sugars and other aminosugars. These differences are due to the location of the amino-group in the immediate vicinity to the glycosidic centre.

We have surveyed the studies in which the foundations were laid for the method of synthesising aminoglycosides, their reactions were investigated, or significant improvements were introduced into methods already known. Attention was concentrated on the synthesis of acetamidoglycosides, including oligosaccharides containing acetamidoglycoside residues, since in most cases aminosugars are encountered in nature as *N*-acetyl derivatives.

The problems of aminoglycoside synthesis were considered in previous reviews[1-3], but the intense development of this branch of carbohydrate chemistry, particularly the synthetic chemistry of aminosugar oligosaccharides, led us to write the present review, which covers the literature up to the middle of 1973.

II. THE SYNTHESIS OF ALKYL AND ARYL AMINOGLYCOSIDES

1. Alcoholysis of Monosaccharides

Fischer's method, which is widely used in the synthesis of alkyl glycosides of neutral sugars, is sometimes employed to obtain mixtures of anomeric glycosides of *N*-protected 2-amino-2-deoxysugars. Thus treatment of *N*-acetyl-*D*-glucosamine with alcohols in the presence of hydrogen chloride, toluene-*p*-sulphonic acid, ion-exchange resins in the H^+-form, or Lewis acids[4-13] leads to a mixture of alkyl 2-acetamido-2-deoxy-α-*D*-glucopyranosides and the corresponding β-*D*-glucopyranosides in which the α-anomers predominate. Glycosylation of benzyl alcohol with *N*-acetyl-*D*-glucosamine also leads to a mixture of anomeric glycosides from which benzyl 2-acetamido-2-deoxy-α-*D*-glucopyranoside, used in the synthesis of many 2-amino-2-deoxysugar derivatives, was isolated[14-16]. Treatment of *N*-acetyl-*D*-galactosamine (or its acetate) by lower alcohols gives analogous results[11,17-19]. Since, regardless of the nature of the aglycone, aminogalactosides are formed under the same conditions as aminoglucosides, special attention will not henceforth be devoted to their synthesis.

2-Amino-2-deoxysugars with a free amino-group do not form glycosides under the conditions of the Fischer synthesis in consequence of the electrostatic repulsion of cationic groups from the glycosidic centre by the NH_3^+ group[4].

2. The Helferich Synthesis of Aryl Aminoglycosides

The Helferich method (see the review of Conchie et al.[20]), which consists of fusing together peracetylated aminosugars with phenols in the presence of catalytic

amounts of toluene-*p*-sulphonic acid or zinc chloride, has been used in the synthesis of aryl aminoglycosides[20-25]. Toluene-*p*-sulphonic acid catalyses the preferential formation of 1,2-*trans*-aminoglycosides, while in the presence of zinc chloride a mixture of anomeric aryl aminoglycosides is formed. This method is relatively unsuitable for the synthesis of aminoglycosides with an aglycone having a complex structure and particularly for the glycosylation of labile compounds.

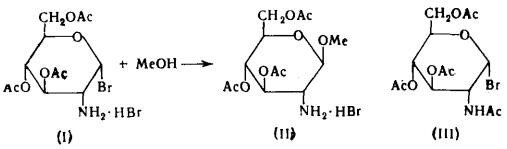
3. The Action of Alkylating Agents

N-Acetyl-D-glucosamine (or its acetate) reacts with methyl iodide in dimethylformamide (DMF) in the presence of barium oxide and hydroxide and is converted into methyl 2-acetamido-3,4,6-tri-*O*-methyl-2-deoxy-β-D-glucopyranoside[26]. When derivatives of *N*-acetyl-D-glucosamine are alkylated with dimethyl sulphate, derivatives of both α- and β-D-glycosides are formed, depending on the reaction conditions[27,28]. A very mild alkylation method was proposed by Kuhn and Baer[29], involving the treatment of *N*-acetyl-D-glycosamine and also its *N*-formyl and *N*-benzyloxycarbonyl analogues with diazomethane in aqueous methanol, which leads to methyl β-D-glycosides. The methods quoted here are specific and their preparative value is apparently small.

III. THE KOENIGS–KNORR REACTION AND ITS MODIFICATIONS IN THE SYNTHESIS OF AMINOGLYCOSIDES

1. Acylhalogeno-derivatives of Aminosugars in the Koenigs–Knorr Reaction

The Koenigs–Knorr reaction (see reviews[20,30,31]), which is based on the reaction of acylhalogenosugars with alcohols and phenols in the presence of hydrogen halide acceptors, has found extensive applications also in the synthesis of aminoglycosides. (The information about acylhalogenosugars of the 2-amino-2-deoxysugar series accumulated at the present time is summarised in Table 1.) As early as 1911, it was shown[32] that the hydrobromide of 2-amino-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl bromide (I) is converted into the glycoside hydrobromide (II) on reaction with methanol:

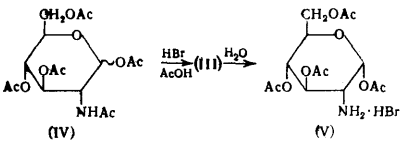


(I) (II) (III)

However, the bromides of fully acetylated 2-amino-2-deoxysugars differ significantly from the bromides of the corresponding neutral analogues[31], and for this reason the structures and properties of the acylated bromides and chlorides of 2-amino-2-deoxysugars must be specially considered.

The bromide (I) and the corresponding chloride are quite stable and resemble the acylhalogeno-derivatives of neutral hexopyranoses. Compared with tetra-*O*-acetyl-α-D-glucopyranosyl bromide, the bromide of the acetylated D-glucosamine (III) is significantly more reactive. The explanation is that in the heterolysis of the C–Br bond the acetamide group at 2-C is more involved in the formation of a stable intramolecular cyclic derivative with the 1-C atom than the acetoxy-group at 2-C in the D-glucose derivative. The reactivity can be reduced (and hence the stability and the acylhalogeno-derivatives increased) by increasing the electronegativity of the substituents in the acylamino-group.

The extreme sensitivity of the bromide (III) to moisture remained for a long time an obstacle to its isolation in a pure state. When hydrogen bromide in acetic acid was allowed to react with the acetate (IV), the expected bromide (III) was not obtained[4]; instead, as shown subsequently[33-35], the hydrobromide (V) was isolated:

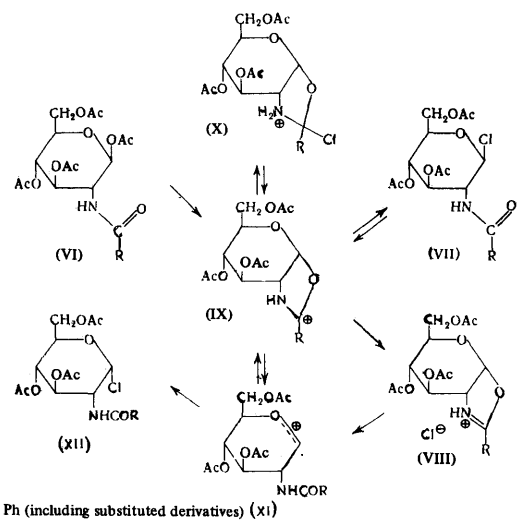


(IV) (V)

However, the bromide (III), formed in this reaction, and also the bromide of the D-galacto-series obtained under similar conditions[19], were used without purification in aminoglycoside synthesis, as will be described below. The bromide (III) was obtained much later in a pure state by treating the acetate (IV) with a limited amount of hydrogen bromide in acetic acid, taking precautions to prevent contact of the product with moisture[36] (cf. Fodor and Ötvös[37]).

Osawa[38] characterised in detail the processes occurring when hydrogen chloride, titanium tetrachloride, or aluminium chloride are allowed to act on 1,2-*trans*-acetylated derivatives of 2-amino-2-deoxysugars (VI). Initially the acetoxy-group at 1-C is eliminated rapidly with participation of the adjoining acylamino-group, which leads to the unstable β-D-glycosyl halide (VII). In this stage the *N*-aroyl derivative is rapidly stabilised as the result of the formation of a salt of the oxazoline derivative (VIII) in which the C=N bond is conjugated with the aromatic ring. If R is an alkyl group, the intermediate cation (IX) formed can react with hydrogen halide to form the oxazolidinium cation (X). Powerful electronegative acyl residues such as *p*-nitrobenzoyl or chloroacetyl favour the rapid formation of the oxonium ion (XI)—the direct precursor of the α-D-glycosyl halide (XII) (see Scheme 1). The mixture of anomeric acetates reacts with hydrogen bromide in acetic acid in a more complex manner[36].

Scheme 1



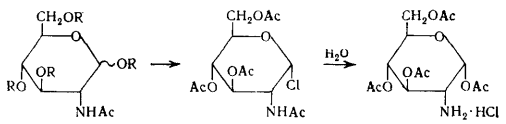
R = Me or Ph (including substituted derivatives) (XI)

The stability of the acylated bromides of 2-amino-2-deoxysugars can be enhanced not only by the introduction of electronegative substituents into the acylamino-group but also by the introduction of aryl or arylalkylidene substituents at the amino-group of the 2-amino-2-deoxysugars, since such groups at 2-C are incapable of forming the intermediate cyclic cation. *O*-Acylated α-D-glycosyl bromides were obtained in this way with the following *N*-protecting groups: benzoyl[39,40], toluene-*p*-sulphonyl[41,42], phenylmethanesulphonyl[43], 2,4-dinitrophenyl[44-46], diphenylphosphoryl[47], anisylidene[47], benzyloxycarbonyl[47], trifluoroacetyl[48,49], dichloroacetyl[50-52], and certain others[47,49,53-58]. These compounds were subsequently used in the synthesis of aminoglycosides.

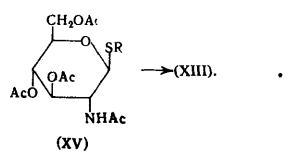
The stability of acylhalogeno-derivatives of the 2-amino-2-deoxysugar series depends also on the nature of the halogen atom and increases in the sequence Br < Cl < F. Iodides are still unknown and fluorides are so inactive that they can be deacetylated in the presence of sodium methoxide with retention of the C–F linkage[42].

Among aminosugar chlorides, the greatest interest attaches to the peracetylated 2-amino-2-deoxy-α-D-glycosyl chlorides formed when 2-acetamido-2-deoxysugars (or their acetates) are treated with hydrogen chloride[34,54,59-62], acetyl chloride[63,64], both hydrogen chloride and acetyl chloride[65], and titanium tetrachloride[19,33,34]. The chlorides of *N*-acetylated aminosugar di- and tri-saccharides were also obtained by these methods[62,65,66].

The chloride (XIII) is fairly stable and is only slowly converted into the hydrochloride (XIV), which permits its isolation even when moist solvents are employed[33,34,38]:



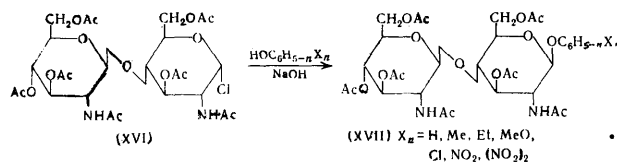
Another method for the synthesis of acetylated aminoglycosyl chlorides[67], including furanosyl chlorides[68], consists of the chlorination of *S*-substituted 1-thioanalogues (XV, R = Et, CSOEt, COMe) (cf. Bonner[69]), for example:



However, from the preparative point of view this method can hardly compete with that discussed above.

The use of the stable bromide (I) in the synthesis of aminoglycosides is restricted to the formation of glycosides from lower alcohols[32] and certain phenols[70] owing to the low solubility of (I) in solvents used in the Koenigs–Knorr reaction. When unstable bromides of acetylated aminosugars (which have as a rule not been isolated in a pure state) or stable but insufficiently reactive chlorides were used, 2-acetamido-2-deoxy-β-D-glucopyranosides and the corresponding β-D-galactopyranosides derived from lower alcohols[19,34,60,63,71,72], phenols[34,60,65,73-77], and monoterpene[78,79], steroid[80], and certain other alcohols[59,81,82] were obtained. Different monofunctional hydroxy-compounds have been glycosylated by bromides with other *N*-protecting groups[38-48,55-57,83-92]. Although the yields of the desired products increased in such cases, the employment of bromides in which the substituents at 2-C are not involved in the reaction led in a number of instances[45,89,92] to a mixture of anomeric glycosides.

The stereospecificity of the glycosylation is apparently a key problem of glycoside synthesis. The isolation of a particular anomer from the reaction mixture (which is frequently very complex, particularly in the case of glycosides with an aglycone having a complicated structure) does not alone demonstrate the stereospecificity of the reaction. Since an answer to this question can be obtained only by a detailed analysis of all the reaction products, the data on the stereospecificity of glycosylation must be treated with caution.



To obtain alkyl or aryl glycosides derived from oligosaccharides containing 2-acetamido-2-deoxy-β-D-glucopyranosyl residues at the reducing end, the Koenigs–Knorr method[62,72] or its modifications were also used. When the disaccharide chloride (XVI) was allowed to react with phenols, aryl β-chitobioside acetates (XVII) were obtained[65,66,93-98].

Scheme 2

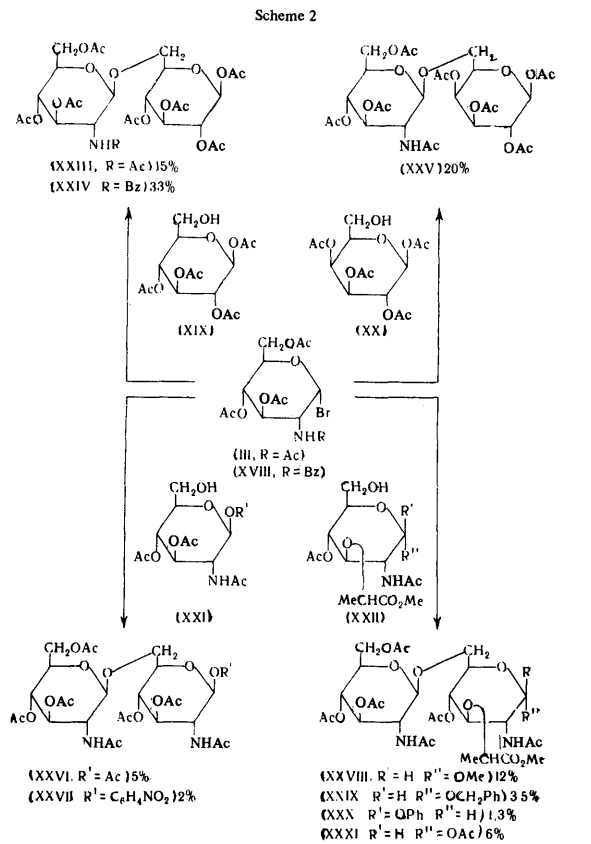


Table 1. Acylhalogeno-derivatives of 2-amino-2-deoxy-sugars.

Structure	Yield[a], %	M.p., °C	$[\alpha]_D^\beta$ and solvent[b]	Refs.
1	2	3	4	5
Glycosyl chlorides				
3,4-Di-*O*-acetyl-2-deoxy-2-nitroso-α-D--xylopyranosyl chloride, dimer	90	102–106	+164 C	171
2-Amino-2-deoxy-α-D-glucopyranosyl chloride				
[3,4,6-tri-*O*-acetyl-,				
[hydrochloride	–	161–163 d[c]	+146 C	67
[*N*-acetyl-	86	125–126 d		54
		133–134 d	+120 C	59
	69	133–134 d	+118 C	34
[β-anomer	60	syrup	+20 C	38
N-benzoyl-	53	124–127	+36 P–W	135
N-bis-(4-nitrobenzyl)phosphoryl-	80	148–149	+39 C	47
N-(3,5-dinitrobenzoyl)-	70	144	+133 C	220
N-diphenylphosphoryl-	90	125–126	+97 C	47
N-(4-methoxybenzoyl)-	11	137 d	+153 C	38
N-(4-nitrobenzoyl)-	80	129–130	+149 C	171,172
2-nitroso-analogue, dimer	64	122–124	+132 A	75
N-propionyl-	61	132–134	+21 C	38,86
NN-succinyl-, β-anomer	67	139–141	+107 C	221
N-(toluene-*p*-sulphonyl)-	80	138	+107 C	57
N-methyl-		139–140	+103 C	221
NN-phthaloyl-, β-anomer	66	149	+62 C	38,57
	86	154	+28 B	58
N-chloroacetyl-	61	143 d	+116 C	38
3,4,6-tri-*O*-benzoyl-*N*-acetyl-	45	128–130		206
2-Amino-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-galactopyranosyl chloride				
N-acetyl-	43	131–136 d	+134 C	19
		130	+138 C	73
2-nitroso-analogue, dimer	84	128–131	+128 C	171
2-Acetamido-3,4-di-*O*-acetyl-2,6-dideoxy-α-D-glucopyranosyl chloride	71	145 d	+153 C	222
2-Acetamido-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride	66	208–209 d	+41 C	93
	60	202–204 d	+34 C	65
O-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1 → 4)-*O*-(2-acetamido--3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyrano-syl)-(1 → 4)-2-acetamido-3,6-di-*O*-acetyl-2-de-oxy-β-D-glucopyranosyl chloride	34	169 d	+33 C	66
Glycosyl bromides				
2-Amino-2-deoxy-α-D-glucopyranosyl bromide				
3,4,6-tri-*O*-acetyl-		82–83	+75 C	37
hydrobromide	–	149–150 d	+148 A	32
	85	149–150	+151 A	47,223
N-acetyl-	10	116–118	+86 C	37
N-benzyloxycarbonyl-	30	90 d	+148 C	36
N-phenylmethanesulphonyl-	72	65–75	+89 C	43
N-diphenylphosphoryl-	91	126–127	+125 C	47
N-(4-methoxybenzylidene)-	64	112–114	+217 C	47
N-(toluene-*p*-sulphonyl)-	83	148	+64 C	41
	83	148 d	+134 C	42
N-trifluoroacetyl-	74	95–97		48
	92	96	+126C	49
N-phenylcarbamoyl-	70	105 d	+137 C	56
NN-phthaloyl-, β-anomer	48	136–137	+51 C	55,57
	50	130	+18 B	58
N-(2,4-dinitrophenyl)-				
3,4-di-*O*-acetyl-6-*O*-methyl-	78	135	+28 C	92
3,6-di-*O*-acetyl-4-*O*-methyl-	70	150–152	+68 C	92
4,6-di-*O*-acetyl-3-*O*-methyl-	–	amorph.	–5 C	92
3,4,6-tri-*O*-acetyl-	97	162–164 d	+46 C	44–46
3,4,6-tri-*O*-benzoyl-	70	150 d	+68 C	84
	94	143 d	+119 C	85
hydrobromide	81	163 d	+71 T	85
N-benzyloxycarbonyl-	47	102–104	+105 C	85
N-benzoyl-	86	126 d	+127 C	40
	88	128	+125 C	39,85
N-dichloroacetyl-	85	125–127	+89 C	51
2-Amino-2-deoxy-α-D-galactopyranosyl bromide				
3,4,6-tri-*O*-acetyl-, hydrobromide	76	144–148 d	+160 C	224
3,4,6-tri-*O*-benzoyl-*N*-dichloroacetyl-	–	amorph.		52

a The yields are quoted only for the stage where the halogen atom was introduced, disregarding the stage corresponding to the introduction of the *N*-substituent.

Table 1 Continued...

b The following abbreviations have been adopted in this and subsequent tables: A = acetone, B = benzene, W = water, D = dimethylformamide, M = methanol, N = nitromethane, P = pyridine, T = tetrahydrofuran, and C = chloroform.

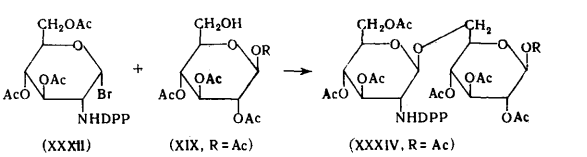
c With decomposition.

2. Synthetic Oligosaccharides†

Among the known methods for the synthesis of di- and oligo-saccharides the only ones available for oligosaccharides with 2-acetamido-2-deoxyglycopyranosyl residues remained for a long time those based on the Koenigs–Knorr reaction and its various modifications. When a freshly prepared solution of the bromide (III)[33] or its *N*-benzoyl analogue (XVIII) was allowed to react with partly substituted derivatives of D-glucose (XIX)[97,98], D-galactose (XX)[97], *N*-acetyl-D-glucosamine (XXI, R′ = acetyl or *p*-nitrophenyl)[93,99], and *N*-acetylmuramic acid (XXII)[12,100–102] under the conditions of the Koenigs–Knorr reaction, a number of disaccharide derivatives (XXIII)–(XXXI) with β-(1→6)-aminoglycosidic linkages between the monosaccharide units were synthesised. The employment of the bromide (III) resulted in a low yield also of the acetate of the non-reducing disaccharide 2,2′-diamino-2,2′-dideoxy-ββ-trehalose[33].

It is noteworthy that in all cases the yield of the desired compounds was significantly lower than in the glycosylation of the same (or similar) aglycone components of the acylhalogeno-derivatives of neutral sugars by the Koenigs–Knorr reaction.

In connection with the high lability of the bromide (III), which is the cause of the low yields of the disaccharide derivatives (XXIII)–(XXXI) (see Scheme 2), subsequently more stable glycosyl halides were used in the synthesis of disaccharides. Zervas and Konstas[47] were the first to use the stable bromide (XXXII) in the synthesis of disaccharides and, when the reaction was carried out in the presence of mercury cyanide, they obtained the protected disaccharide (XXXIV) in 60% yield. An analogous disaccharide derivative (XXXV) was synthesised subsequently[103] with the same yield by the glycosylation of (XXXIII):



† See Table 2, where the available information about synthetic oligosaccharides and their derivatives is summarised.

Table 2. Synthetic oligosaccharides containing 2-amino-2-deoxyglycosyl residues.

Oligosaccharides[a] and their derivatives	Method of synthesis and yield[b], %	M.p., °C	$[\alpha]_D^0$ and solvent	References
1	2	3	4	5
Glc*p*N-α-(1 → 3)-Glc				
N-acetyl-		212—215	+182→+158 W	180
1,2:5,6-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-, α-furanose	[c] 75	168—170	+32 C	180
2′-hydroxyamino-analogue	N 59	160—161	+66 C	176
Glc*p*N-β-(1 → 3)-Glc				
N-acetyl		amorph.	+59→+39 W	166
1,2:5,6-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-, α-furanose	Z 49	219—220	+68 C	166
N-phenylmethanesulphonyl-1,2:5,6-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-, α-furanose	K 6	219	−36 C	43
Glc*p*N-β-(1 → 4)-Glc				
N-acetyl-		190—195	+30 W	110
hepta-*O*-acetyl-, α-anomer		148—151	+24 C	110
1,6-anhydropenta-*O*-acetyl-		194—195	−29 C	110
p-nitrophenyl β-pyranoside	E 49	256—258		186
N-dichloroacetyl-1,6-anhydro-2,3-di-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-	K 10	112	−38 C	110
Glc*p*N-β-(1 → 6)-Glc				
hepta-*O*-acetyl-, hydrochloride		233 d.	+32 D	47
β-anomer		amorph.	+3 W	97,161
N-acetyl-		217—218	−9 C	47
hepta-*O*-acetyl-, β-anomer	K 16	218—219	−10 C	97
	Z 46	222—223	−7 C	161
benzyl β-pyranoside (monohydrate)		240—241	−50 M	103
hexa-*O*-acetyl-	Z 46	210—211	−26 C	103
N-benzoyl-		175—177	−6 W	137,226
hepta-*O*-acetyl-, β-anomer	K 33	252—253	−2 C	98
	Z 51	251—253	−2 C	137
methyl α-pyranoside		260—265 d.	+35 W	137
hexa-*O*-acetyl-	Z 55	214—216	+69 C	137
hexa-*O*-methyl-		196—198	+84 C	226
methyl β-pyranoside, hexa-*O*-methyl-		200—202	+14 C	226
N-diphenylphosphoryl-				
hepta-*O*-acetyl-, β-anomer	K 60	221—223	+3 C	47
benzyl β-pyranoside, hexa-*O*-acetyl-				
N-phenylmethanesulphonylhepta-*O*-acetyl-, β-anomer	K 61	202—203	−20 C	103
	K 34	246	−18 C	43
Glc*p*N-β-(1 → 3)-Gal				
N-acetyl-				
hepta-*O*-acetyl-, α-anomer		212—213	+80 C	51
1,6-anhydropenta-*O*-acetyl-		202—204	−78 C	51
N-dichloroacetyl-1,6-anhydro-2-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-4-*O*-acetyl-	K 19	235—236 syrup	−41 C	51
Glc*p*N-β-(1 → 4)-Gal				
N-acetyl-		162—165	+8 W	51
hepta-*O*-acetyl-, α-anomer		178—179	+56 C	51
1,6-anhydropenta-*O*-acetyl-		238—239	−29 C	51
N-dichloroacetyl-1,6-anhydro-2-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-	K 26	146—148	−40 C	51
3-*O*-acetyl-	K 9	235—236	−33 C	51
Glc*p*N-α-(1 → 6)-Gal				
hydrochloride (dihydrate)		50—60[d]	+112 W	106
N-acetyl-		amorph.	+126 W	180
(dihydrate)		60[d]	+126 W	106
1,2:3,4-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-	[c] 77	128—129	+23 C	180
2′-hydroxyimino-analogue	N 67	137—138	+9 C	176
N-(2,4-dinitrophenyl)-		170[d]	+103 M	106
1,2:3,4-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-	K 30	80[d] 201—202	−40 C −28 C	106 180
Glc*p*N-β-(1 → 6)-Gal				
hydrochloride		197 d.	+15 W	106
1,2:3,4-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-		245 d.	−21 M	43
N-acetyl-		amorph.	+10 W	106,161
		amorph.	+9 W	175
hepta-*O*-acetyl-	K 10	197—198	+6 C	97
β-anomer		196—197	+8 C	175
1,2:3,4-di-*O*-isopropylidene-benzyl β-pyranoside, 2,3,6-tri-*O*-benzyl-	Z 48	198 d.	+85 M	161
		213—215	+23 P	175
3′,4′,6′-tri-*O*-acetyl-	N 13	195—195.5	−28 C	175
	K 12			175
N-phenylmethanesulphonyl-1,2:3,4-di-*O*-isopropylidene-	K 50	91—100	−80 C	43
N-(2,4-dinitrophenyl)-		215—216	+33 C	106
1,2:3,4-di-*O*-isopropylidene-	K 29	198—199	−82 C	106
Glc*p*N-β-(1 → 6)-Man				
N-acetyl-		128—130 d.	−9 W	152
hepta-*O*-acetyl-, β-anomer	Z 26	187—190	−26 C	152
Glc*p*N-α-(1 → 3)-GlcN				
N-acetyl-4,6-*O*-benzylidene, benzyl α-pyranoside				
N′-dibenzylphosphoryl-		214—217	+75 P	115,117
N′-diphenylphosphoryl-3′,4′,6′-tri-*O*-acetyl-	K 5	147—149	+81 C	115,117

Table 2 continued...

1	2	3	4	5
Glc*p*N-β-(1 → 3)-GlcN				
di-*N*-acetyl-		198—199	+14 → +6 W	115,117
		180 p.	+40 → +4 W	165,166
benzyl β-pyranoside		194—195 d.		165,166
3′,4′,6′-tri-*O*-acetyl-		219—220	−8 AcOH	165,166
4,6-*O*-benzylidene	Z 81	297—298	−43 P	165,166
N-acetyl-		208—209 d.	+65 W	117
4,6-*O*-benzylidene		268—269 d.	+76 P	117
N′-dibenzylphosphoryl-		191—192	+72 M	117
4,6-*O*-benzylidene-		179—180	+38 C	117
N′-diphenylphosphoryl-3′,4′,6′-tri-*O*-acetyl-4,6-*O*-benzylidene-	K 26	102.5—103.5	+66 C	115,117
Glc*p*N-α-(1 → 4)-GlcN				
di-*N*-acetyl-[R]		150 d.	+96 M	115,116
5,6-*O*-isopropylidene-, diethyl acetal		syrup		116
di-*N*-acetyl-		177—179	+106 W	116
tetra-*O*-acetyl-		syrup	+62 C	116
2-*N*, 3-*O*-carbonate		100—102	+27 M	116
N′-dibenzylphosphoryl-		112—115	+18 C	115,116
N′-diphenylphosphoryl-3′,4′,6′-tri-*O*-acetyl	K 35	116—118	+30 C	115,116
Glc*p*N-β-(1 → 4)-GlcN				
di-*N*-acetyl-, *p*-nitrophenyl β-pyranoside				
5,6-*O*-isopropylidene-2-*N*,3-*O*-carbonate, diethyl acetal	E 62	253—256		187
N′-dibenzylphosphoryl-		syrup	−49 M	116
N′-diphenylphosphoryl-3′,4′,6′-tri-*O*-acetyl	K 10	173—176	−40 C	116
		93—95	−23 C	115,116
Glc*p*N-α-(1 → 6)-GlcN				
di-*N*-acetyl-	[f] 8	215	+140→+125 W	227
Glc*p*N-β-(1 → 6)-GlcN				
di-*N*-acetyl-	[f] 3,2	200 d.	+12→+6 W	227
		amorph.	+4 W	99
		199—201	+10 W	104
		200	+8 W	163
(monohydrate)		190—192	+22→−55 W	16
hexa-*O*-acetyl-, α-anomer	K 5,3	236—238	+12 C	99
p-nitrophenyl β-pyranoside		218—219	−43 W-M	162
(monohydrate)		220—221	−55 W-M	93
penta-*O*-acetyl-	Z 49	258.5—260	−27 C	162
(monohydrate)	K 2,4	257—258	−43 C	93
3,3′,4′,6′-tetra-*O*-acetyl-	Z 46	245—246	−25 M	162
benzyl α-pyranoside (monohydrate)		272—273	+97 M	16
penta-*O*-acetyl-	Z,K 50	254—255	+67 C	16
		242	+65 C	163
N-acetyl-				
N′-diphenylphosphoryl-				
hexa-*O*-acetyl-, β-anomer	K 41	206—207	−5 C	104
benzyl α-pyranoside, penta-*O*-acetyl-				
N′-dibenzylphosphoryl-, benzyl α-pyranoside	K 65	179—181	+68 C	104
		230—231	−15 M	104
N-acetyl-, *p*-nitrophenyl β-pyranoside	E 12			186
Glc*p*N-α-(1 → 6)-3-NH_2-3-deGlc				
dihydrochloride		amorph.	+76 W	107
N′-(2,4-dinitrophenyl)-3′,4′,6′-tri-*O*-acetyl-1,2-*O*-isopropylidene-, 3-azido-analogue, α-furanose	K 37	203—205	+58 C—M	107
Glc*p*N-β-(1 → 6)-3-NH_2-3-deGlc				
dihydrochloride		amorph.	+15 W	107
1,2-*O*-isopropylidene-, 3-azido-analogue, α-furanose				
N′-trifluoroacetyl-		amorph.	−16 M	107
3′,4′,6′-tri-*O*-acetyl-	K 65	syrup	−18 M	107
N′-(2,4-dinitrophenyl)-3′,4′,6′-tri-*O*-acetyl-	K 12	90—95	+15 M	107
Glc*p*N-β-(1 → 4)-MurNAc				
methyl ester				
N-acetyltetra-*O*-acetyl-, α-anomer		237—238	+38 C	113
N-diphenylphosphoryl-1,6-anhydro-3′,4′,6′-tri-*O*-acetyl	K 15	203—204	−29 C	113
Glc*p*N-β-(1 → 6)-MurNAc				
N-acetal-(monohydrate)		amorph.	+16→+14 W	228
benzyl α-pyranoside		227—228	+87 M	100
tetra-*O*-acetyl-, methyl ester	K 3,5	252—253 and 260	+58 C	100
methyl α-pyranoside, tetra-*O*-acetyl-, methyl ester	K 12	288—289	+54 C	12
phenyl β-pyranoside		235—237	−32 W	102
3′,4′,6′-tri-*O*-acetyl-, ester	K 1,3	261—262 d.	−7 C	102
penta-*O*-acetyl-, methyl ester	K 6	240—241	+40 C	101
Galp*N*-α-(1 → 3)-Glc				
N-acetyl-		212—215	+177 → +187 W	180
1,2:5,6-di-*O*-isopropylidene, α-furanose	[c] 35	223—224	+95 D	180
3′,4′,6′-tri-*O*-acetyl-, 2′-hydroxyimino-analogue	N 53	149—150	+62 C	176
Galp*N*-β-(1 → 3)-Glc				
N-acetyl-		208—210	+78 → +50 W	151
1,2:5,6-di-*O*-isopropylidene-3′,4′,6′-tri-*O*-acetyl-, α-furanose	Z 52	amorph.	−23 C	151,157

Table 2 continued...

1	2	3	4	5
Galp*N*-β-(1 → 6)-Glc				
N-acetyl-		186—187 p.	+36 → +18 W	151
hepta-*O*-acetyl-, β-anomer	Z 74	193—194	—12 C	151, 157
Galp*N*-β-(1 → 3)-Gal				
N-acetyl-		163—165	+56 W	118
hepta-*O*-acetyl-, α-anomer		96—97	+59 C	118
1,6-anhydropenta-*O*-acetyl-		208	—66 C	118
N-dichloroacetyl-1,6-anhydro-2-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-	K 15	139—140	+5 C	118
Galp*N*-β-(1 → 4)-Gal				
N-acetyl-		148—150	+56 W	118
hepta-*O*-acetyl, α-anomer		104—106	+43 C	118
1,6-anhydropenta-*O*-acetyl-		122—123	—27 C	118
N-dichloroacetyl-1,6-anhydro-2-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-	K 30	194—195	—2 C	118
Galp*N*-α-(1 → 6)-Gal				
N-acetyl-			+137 W	180
1,2 : 3,4-di-*O*-isopropylidene-	[c] 29	151—153	+69 D	180
3′,4′,6′-tri-*O*-acetyl-, 2′-hydroxyimino-analogue	N 80	171—172	+14 C	180
Galp*N*-β-(1 → 6)-Gal				
N-acetyl-		204—205	+38 W	52
		182—184	+38 W	153
		204—206	+44 W	151
3′,4′,6′-tri-*O*-acetyl-				
1,2,3-tri-*O*-benzoyl-, α-anomer	Z 44	209—211	+114 C	153
1,2 : 3,4-di-*O*-isopropylidene-		142—144	—62 C	52
	Z 81	141—142	—63 C	151, 157
2′-hydroxyimino-analogue	N 9	90—92	—94 C	176
N-dichloroacetyl-				
1,2 : 3,4-di-*O*-isopropylidene-				
3′,4′,6′-tri-*O*-benzoyl-	K 90	125	—4 C	52
1,2,3,4-tetra-*O*-acetyl-3′,4′,6′-tri-*O*-benzoyl-	K 76	156—157	+4 C	52
Galp*N*-β-(1 → 6)-GlcN				
di-*N*-acetyl-, *p*-nitrophenyl β-pyranoside		208—210	—41 P	151
penta-*O*-acetyl-	Z 71	226—227	—28 M	151, 157
Manp*N*-α-(1 → 6)-Glc				
N-acetyl-(dihydrate)	Z 55 [g]	amorph.	+36 W	161
Talp*N*-α-(1 → 3)-Glc				
N-acetyl-		190—195	+82 → +70 W	180
1,2 : 5,6-di-*O*-isopropylidene-, α-furanose	[c] 47	163—165	+27 D	180
Talp*N*-α-(1 → 6)-Gal				
N-acetyl-			+65 W	180
1,2 : 3,4-di-*O*-isopropylidene-	[c] 59	119—121	—10 D	180
Glcp*N*-α-(1 → 1)-α-Glc*p*	K 18 [g]	197 d.	+146 W	108
octa-acetyl-		99	+152 C	108
Glcp*N*-β-(1 → 1)-β-Glc*pN*				
octa-acetyl-	K 2,3	324—326 d.	+2 C	33
Glcp*N*-α-(1 → 1)-α-Man*f*				
2,3 : 5,6-di-*O*-isopropylidene-				
3′,4′6-tri-*O*-acetyl-, 2′-hydroxyimino-analogue	N 41	86—87	+88 C	176
Glcp*N*-β-(1 → 1)-1-*S*-β-Glc*pN*				
di-*N*-acetyl-		219—220	—37 W	61
hexa-*O*-acetyl-	K 50	314—316 d.	—146 C	61
Glcp*N*-β-(1 → 3)-Gal*p*-β-(1 → 4)-Glc				
N-acetyl-		205—209	+40 W	119
N-dichloroacetyl-, benzyl β-pyranoside		194—195	—23 M	119
2,3,6,2′, 6′-penta-*O*-acetyl-3″,4″,6″-tri-*O*-benzoyl-	K 19	125—127	—50 C	119
Glcp*N*Ac-β-(1 → 4)-Glcp*N*Ac-β-(1 → 6)-Glc	Z 29 [g]	amorph.	+1 W	162
Glcp*N*Ac-β-(1 → 3)-Glcp*N*Ac-β-(1 → 6)-GlcNAc				
p-nitrophenyl β-pyranoside		209—210	+8 W—M	166
hepta-*O*-acetyl-	Z 78	280—281	+75 C—M	166
Glcp*N*Ac-β-(1 → 4)-Glcp*N*Ac-β-(1 → 6)-GlcNAc				
p-nitrophenyl β-pyranoside (dihydrate)		239—241 d.	—48 W	162
hepta-*O*-acetyl-	Z 30	289—290 d.	—31 M—N	162
Glcp*N*Ac-β-(1 → 6)-Glcp*N*Ac-β-(1 → 4)-GlcNAc				
p-nitrophenyl β-pyranoside		257,5—259	—2 W	164
2,6,3′,3″,4″,6″-hexa-*O*-acetyl-	Z 14	273,5—275	—44 N	164
Glcp*N*Ac-β-(1 → 4)-MurNAc-β-(1 → 4)-GlcNAc	E 15		—20 W	191
Glcp*N*Ac-β-(1 → 4)-MurNac-β-(1 → 4) Xyl	E 9		—38 W	191
Glcp*N*Ac-β-(1 → 4)-MurNAc-β-(1 → 2)-Gal	E 13		—14 W	191
Glcp*N*Ac-β-(1 → 4)-Glcp*N*Ac-β-(1 → 6)-Glcp*N*Ac-β-(1 → 4)-GlcNAc				
p-nitrophenyl β-pyranoside	Z 13 [g]	248—249	—28 W	164

Table 2 continued...

[a] The following abbreviations not indicated in Ref. 225 were used: Xyl = D-xylose, GlcN = D-glucosamine, GlcNAc = *N*-acetyl-D-glucosamine, GalNAc = *N*-acetyl-D-galactosamine, ManN = D-mannosamine, MurNAc = *N*-acetylmuramic acid, TalN = D-talosamine, and 3-NH_2-3-deGlc = 3-amino-3-deoxy-D-glucose.

[b] E = enzymatic synthesis, K = Koenigs–Knorr reaction and its modifications, N = nitrosochloride method [174,176], and Z = oxazoline method. The yields are quoted only for the glycosylation stages.

[c] In the reduction stage of the corresponding hydroxyimino-derivative.

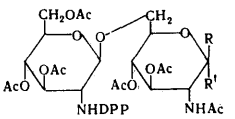
[d] Softening temperature.

[e] Solvated by ethanol.

[f] Obtained by the acid reversion of *N*-acetyl-D-glucosamine.

[g] Including the stage involving the removal of protecting groups.

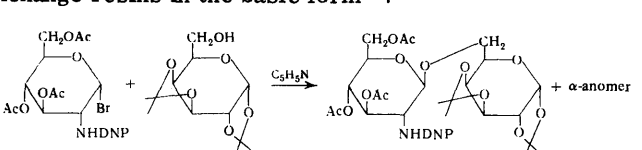
Satisfactory results in the glycosylation stage were achieved [104] when the bromide (XXXII) was allowed to react with the partly protected *N*-acetyl-D-glucosamine derivatives with a free hydroxy-group at 6-C. The yield of the glycosylation products (XXXVI) and (XXXVII) was 41–65%:



(XXXVI, R = OAc, R′ = H)
(XXXVII, R = H, R′ = OCH_2Ph)

The diphenylphosphoryl group is removed either by catalytic hydrogenation in the presence of platinum [47] or (less effectively) by alkaline hydrolysis [103].

When the bromide (XXXVIII) reacts with 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose (XXXIX), the glycosylation is non-stereospecific and depends on the nature of the solvent and the hydrogen bromide acceptor [105,106]. As in the synthesis of alkyl aminoglycosides from the bromide (XXXVIII) [89], in the presence of pyridine the α-anomer is formed preferentially (30%) and only 15% of the β-linked disaccharide (XL) is produced. When the reaction was carried out in the presence of silver carbonate, only the β-anomer (XL) was isolated in 29% yield. The dinitrophenyl group was removed by treatment with anion-exchange resins in the basic form [46]:

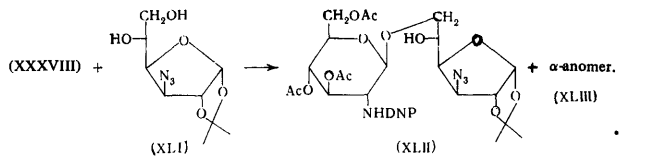


(XXXVIII) (XXXIX) (XL)

DNP = 2,4-dinitrophenyl

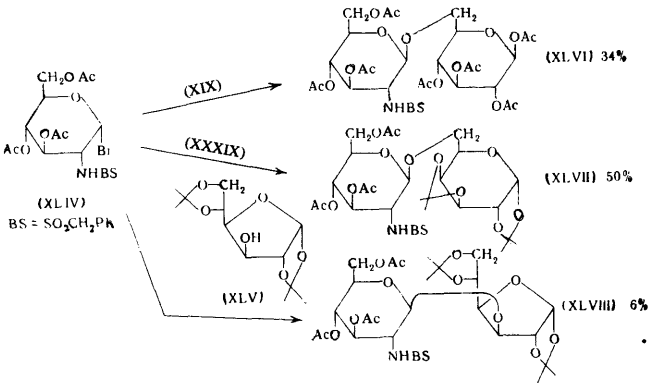
The glycosylation of compound (XLI) with the bromide (XXXVIII) in the presence of mercury salts also led [107] to a mixture of anomeric disaccharide derivatives (XLII) and (XLIII) with an overall yield of 50%, the anomers being formed in proportions of 1 : 3. On the other hand, when

compound (XLI) was glycosylated with 3,4,6-tri-*O*-acetyl-2-deoxy-2-trifluoroacetamido-α-D-glucopyranosyl bromide in the presence of mercury cyanide, only one disaccharide, analogous to (XLII), was isolated:



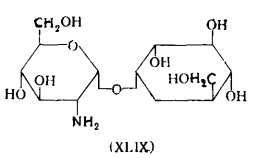
The use of the bromide (XLIV) as the glycosylating agent in the Koenigs–Knorr reaction has been described[43]. The disaccharide derivatives (XLVI)–(XLVIII), in which the phenylmethanesulphonyl group was removed by catalytic hydrogenation in the presence of Raney nickel, were obtained (Scheme 3).

Scheme 3



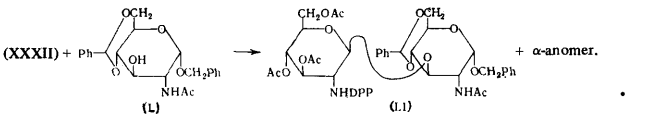
Thus the examples of the synthesis of disaccharides with the (1→6)-linkage already demonstrated the advantage of stable glycosyl bromides with electronegative and other substituents in the amino-group, which consists of a significant increase of the yield of the glycosylation products. However, the preparative value of this procedure was at the same time reduced by the large number of stages involved, particularly in the synthesis of *N*-acetylated disaccharide analogues and in many cases by the loss of stereospecificity in the glycosylation reaction.

Among the few synthetic non-reducing disaccharides containing 2-amino-2-deoxysugar moieties, mention should be made of trehalosamine (XLIX) obtained[108] by the reaction of 3,4,6-tri-*O*-acetyl-2-deoxy-2-(*p*-methoxybenzylideneamino)-α-D-glucopyranosyl bromide with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in 18% yield after the removal of protecting groups.

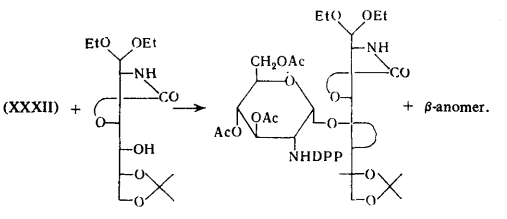

(XLIX)

In the glycosylation of secondary hydroxy-groups of sugars difficulties arose for a long time not only because of the lack of effective glycosylating agents in the amino-sugar series but also owing to the limited choice of "aglycone" components with sufficiently reactive functionable groups capable of being glycosylated. This problem was solved, on the one hand, by employing stable bromides as the glycosylating agents. On the other hand, "aglycone" components derived from pyranose[51,109–113] and acyclic[114–116] forms of monosaccharides, in which the hydroxy-groups, particularly at 4-C, are more reactive than in the pyranose form in the 1-C conformation, were proposed recently in a number of studies.

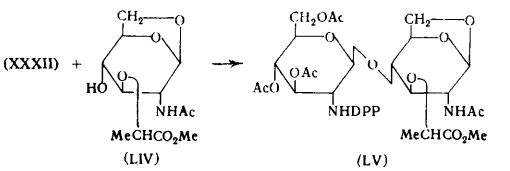
A mixture of protected disaccharides with β-(1→3)-[compound (LI)] and α-(1→3)-aminoglucosidic linkages and containing about 85% of (LI) was obtained in 31% yield by the condensation of the bromide (XXXII) with the benzylidene derivative (L)[115,117]:



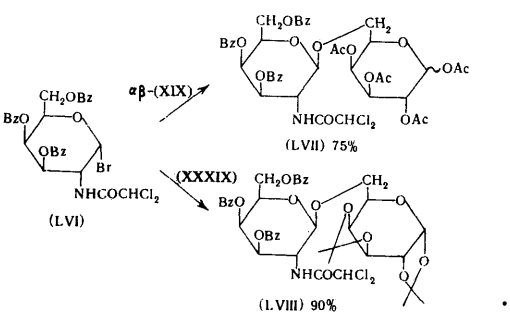
A mixture of anomers derived from disaccharides with α-(1→4)-[compound (LIII)] and β-(1→4)-glycosidic linkages was obtained similarly, in yields of 35 and 10% respectively, from the bromide (XXXII) and the acetal (LII)[115,116]:



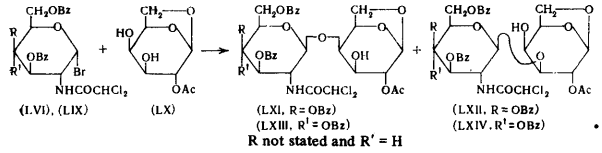
However, Merser and Sinaÿ[113] (cf. Iwamoto and Ymanaga[103] and Bundle and Shaw[104]) failed to observe the formation of a disaccharide with an α-linkage in the glycosylation of the anhydro-derivative (LIV) by the bromide (XXXII) and isolated in 15% yield the protected disaccharide (LV):



The synthesis of di- and oligo-saccharides, which form part of the carbohydrate determinants of glycoproteins and gangliosides and which contain 2-acetamido-2-deoxy-β-D-galactopyranosyl residues, was achieved recently using the reactive and relatively stable bromide (LVI)[50,52]. This version of the Koenigs–Knorr reaction leads to derivatives (LVII) and (LVIII) with a β-glycosidic linkage and with only traces of α-anomers according to infrared spectroscopic data[52]:



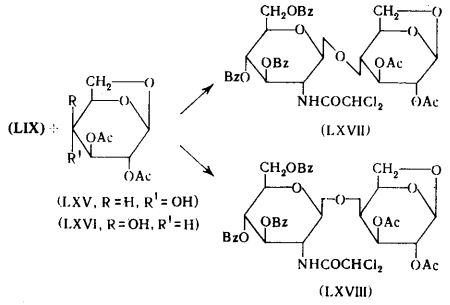
The bromide (LVI) and its D-gluco-analogue (LIX) react with the 1,6-anhydrosugar (LX) to form mixtures of isomeric disaccharide derivatives with β-(1→4)-[compounds (LXI) and (LXIII)] and β-(1→3)-glycosidic linkages [compounds (LXII) and (LXIV)] in overall yields of 45 and 47% respectively[51,118]. In both cases the isomer ratios (LXI) : (LXII) and (LXIII) : (LXIV) were close to 3 : 2. The glycosylation products (LXI) and (LXII) were separated chromatographically. In another instance the product (LXIII) was isolated from the mixture after the degradation of the (1→3)-isomer under mild alkaline conditions.



(LVI), (LIX) (LX) (LXI, R = OBz) (LXIII, R' = OBz) (LXII, R = OBz) (LXIV, R' = OBz)

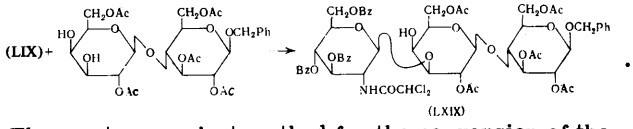
R not stated and R' = H

It is interesting to note that the glycosylation of the 2,3-di-*O*-acetates of the 1,6-anhydrosugars (LXV) and (LXVI) leads under the same conditions[51,110] to the disaccharide derivatives (LXVII) and (LXIII) in yields of only 9–10%. However, the glycosylation of the anhydride (LXV) or its analogue 1,6-anhydro-2-acetamido-3-*O*-acetyl-2-deoxy-β-D-glucopyranose with acylhalogeno-derivatives of neutral sugars is much more effective, leading to derivatives of lactose, *N*-acetyl-lactosamine, and *N*-acetylcellobiosamine in yields of 50–80%.[109,112]



(LIX) + (LXV, R = H, R' = OH) (LXVI, R = OH, R' = H) (LXVII) (LXVIII)

The same group of workers[119] achieved the synthesis of the protected trisaccharide (LXIX) in 19% yield:

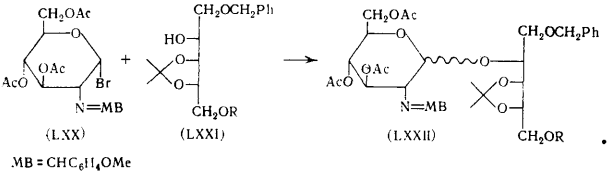


(LIX) + (LXIX)

The most convenient method for the conversion of the *N*-dichloroacetyl group into the *N*-acetyl group proved to be catalytic hydrogenation in the presence of palladium. Another procedure, involving the hydrolysis of the *N*-dichloroacetyl group to the amino-group by barium hydroxide with subsequent *N*-acetylation, is suitable only for derivatives with the β-(1→4)-aminoglycosidic linkage [for example, compounds (LXI) and (LXIII)], since the β-(1→3)-aminoglycosidic linkage in compounds (LXII) and (LXIV) is cleaved even by the action of sodium methoxide in methanol. This finding can be explained by the high electronegativity of the dichloroacetyl group, which withdraws electrons from the glycosidic centre, and this in turn facilitates the degradation of the β-(1→3)-isomer via the β-elimination mechanism.

3. Glycosylation of Polyols and Hydroxyaminoacids

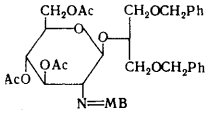
The products of the glycosylation of polyols and hydroxyaminoacids are interesting as model compounds for the investigation of the properties of glycolipids and glycoproteins. Derivatives of 2-amino-2-deoxy-D-glucopyranosyl-D-ribitol and the corresponding glycerol derivative were obtained by the Koenigs–Knorr reaction from glycosyl bromides and partly protected polyols. The glycosylation of D-ribitol derivatives (LXXI, R = CPh_3 or COPh) by the bromide (LXX) in the presence of silver carbonate led to a 15% yield of a mixture of the anomeric aminoglycosides (LXXII, R = CPh_3 or COPh), in which the α-anomers predominated[90]:



(LXX) (LXXI) (LXXII)

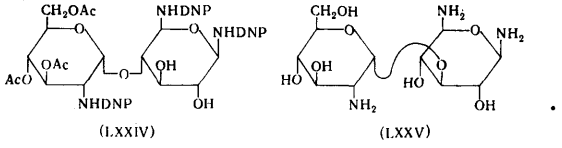
MB = CHC_6H_4OMe

The reaction of the bromide (LXX) with 1,3-di-*O*-benzylglycerol led to the formation under the same conditions[120] of the aminoglucoside (LXXIII) and its α-anomer in proportions of 1 : 0.39 and in an overall yield of 25%. In the glycosylation of 1,3-di-*O*-benzylglycerol with the bromide (XXXII) in the presence of mercury cyanide only the β-anomer, analogous to (LXXIII), was isolated in 55% yield[120].



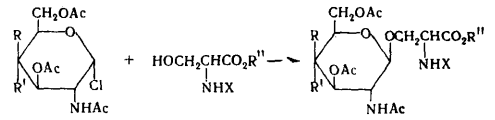
(LXXIII)

The employment of the bromide (XXXVIII) in the glycosylation of di-*N*-protected 2-deoxystreptamine resulted in the formation of a mixture of glycosides from which the isomer (LXXIV) was isolated in a low yield[121–123]. The related compound (LXXV) was also synthesised[124].



(LXXIV) (LXXV)

The Koenigs–Knorr reaction served for a long time as the main method for the synthesis of 2-acetamido-2-deoxyglycosides derived from hydroxyaminoacids. The condensation of the chloride (XIII) or its D-galacto-analogue (LXXVI) with esters of *N*-benzyloxycarbonyl- or *N*-(2,4-dinitrophenyl)-L-serine in the presence of silver carbonate or mercury cyanide led to the formation of the corresponding β-aminoglycosides [LXXVII, R and R' = H or OCOMe, R'' = Me or CH_2Ph, X = $COOCH_2Ph$ or 2,4-$(NO_2)_2.C_6H_3$] in yields up to 49%.[125–128] The glycosylation of the amide of *N*-benzyloxycarbonyl-DL-threonine with the chloride (XIII) was achieved under the same conditions[129]. It is noteworthy that the isolation of the glycosylation products is fairly laborious in many cases.

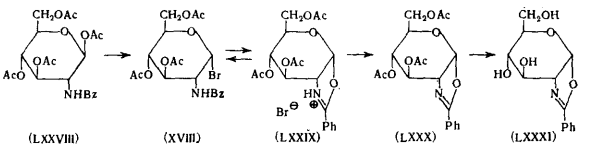


(XIII) or (LXXVI) (LXXVII)

Thus, despite the large number of studies enumerated above in which the classical version of the Koenigs–Knorr reaction or its modifications were employed, there have been virtually no systematic studies on the glycosylation by this method of partly protected saccharides and other "aglycone" components with a complex structure. Therefore, although the method can be regarded as fairly thoroughly developed, it is necessary to find special reaction conditions in each specific instance.

IV. 2-SUBSTITUTED GLYCO[2′,1′:4,5]-2-OXAZOLINES

The oxazoline derivatives of hexopyranoses, which are aza-analogues of sugar orthoesters, have been known for a long time as compounds obtained as side products when hydrogen bromide is allowed to react with acylated 2-amino-2-deoxysugars. The "oxazoline" derivative described by White[130] (cf. Micheel et al.[35]) was shown subsequently[34,131,132] to be 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-D-glucopyranose. Micheel and coworkers[63,133] succeeded for the first time in isolating the hydrobromide of 2-phenyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano) [2′,1′:4,5]-2-oxazoline (LXXIX), formed when the *N*-benzoate (LXXVIII) is treated with hydrogen bromide in acetic acid. The bromide (XVIII) formed initially is rapidly converted into the oxazoline derivative (LXXIX):

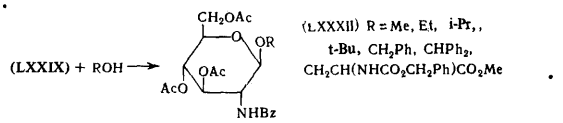


(LXXVIII) (XVIII) (LXXIX) (LXXX) (LXXXI)

Later it was established[134] that this process is reversible and that the equilibrium depends to a large extent on the solvent [as for the *O*-benzoylated analogue of the bromide (XVIII)]. In the instances described the α-chloride does not give rise to the oxazoline derivative[135]. It follows from Osawa's data[38] (see Scheme 1) that oxazoline derivatives are intermediates in the synthesis of *O*-acetylated 2-aroylamino-2-deoxy-α-D-glucopyranosyl chlorides from the corresponding β-acetates. After the acetates have been treated briefly with aluminium chloride or titanium tetrachloride in chloroform and also with hydrogen chloride in acetic anhydride, 2-arylgluco[2′,1′:4,5]-2-oxazolines were obtained in yields up to 75%; with increase of reaction time, the yield of the oxazoline derivatives fell and that of the α-chlorides increased.

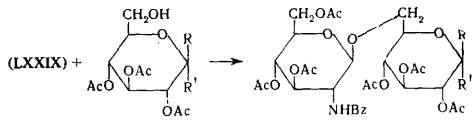
On treatment with pyridine, the hydrobromide (LXXIX) is converted into the free base (LXXX), which can be deacetylated to the oxazoline (LXXXI) without the rupture of the heterocyclic ring[135].

The oxazoline derivatives (LXXIX) and (LXXX) proved to be effective glycosylating agents in the synthesis of 1,2-*trans*-2-benzamido-2-deoxy-D-glucopyranosides. The reaction of compound (LXXIX) with primary, secondary, and tertiary alcohols and also with the methyl ester of *N*-benzyloxycarbonyl-L(D or DL)-serine in the presence of silver carbonate gave a 37–73% yield of the acetates of 2-benzamido-2-deoxy-β-D-glucopyranosides (LXXXII)[133,135,136]:



(LXXXII) R = Me, Et, i-Pr,, t-Bu, CH_2Ph, $CHPh_2$, $CH_2CH(NHCO_2CH_2Ph)CO_2Me$

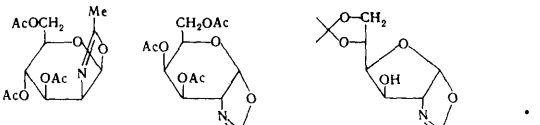
The possibility of using the oxazoline derivatives of sugars in the synthesis of disaccharides with 2-benzamido-2-deoxy-β-D-glucopyranosyl residues, for example (LXXXIV) and (LXXXV), was demonstrated for the first time in the reaction of the oxazoline (LXXIX) with glucose tetra-acetate (XIX) and the glucoside tri-acetate (LXXXIII)[137]:



(XIX, R = OAc) (LXXXIII, R′ = OMe) (LXXXIV, R = OAc), 55% (LXXXV, R′ = OMe), 51% R not specified and R′ = H

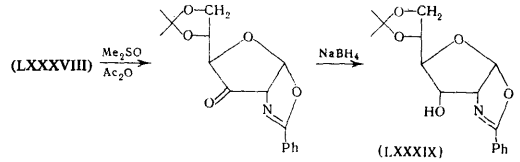
Despite the initial successes in the employment of oxazoline derivatives of sugars in the synthesis of *N*-benzoylaminoglucosides the development of the oxazoline method for the formation of the 1,2-*trans*-aminoglycosidic linkage was held back by the lack of reliable and general methods for the synthesis of the glycosylating agents themselves and in the first place of 2-methylglyco[2′,1′:4,5]-2-oxazolines which would open the way to glycosides and oligosaccharides containing 2-acetamido-2-deoxy-β-D-hexopyranosyl residues. The existing methods for the synthesis of oxazoline derivatives of sugars remained non-general for a long time.

A 2-methyl-substituted oxazoline of the D-manno-series (LXXXVI) was obtained by treating acetylated D-mannosamine with hydrogen bromide in acetic acid[133]. Fletcher and coworkers[138] observed the formation of the oxazoline (LXXXVI) and its D-galacto-analogue (LXXXVII), in yields of 11 and 26% respectively, as side products in the acetylation of *N*-acetyl-D-mannosamine and *N*-acetyl-D-galactosamine with acetic anhydride in the presence of a large amount of zinc chloride.



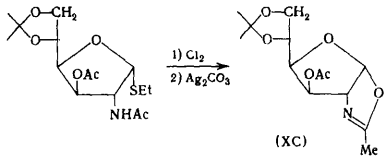
(LXXXVI) (LXXXVII) (LXXXVIII)

The oxazoline derivative of D-glucofuranose (LXXXVIII) was obtained by treating *N*-benzoyl-D-glucosamine with acetone in the presence of hydrogen chloride[139–141]. The oxazoline (LXXXVIII) was converted into the corresponding analogue of the D-allo-series (LXXXIX) by epimerisation at 3-C[142]:



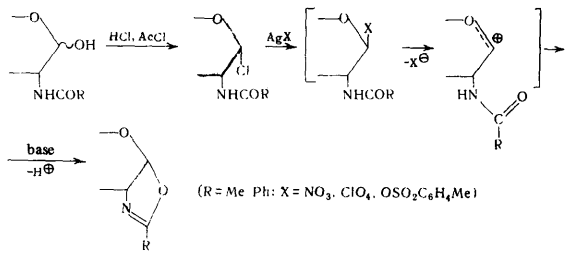
(LXXXIX)

2-Methyl-(3-*O*-acetyl-5,6-*O*-isopropylidene-1,2-dideoxy-α-D-glucofurano)[2′,1′:4,5]-2-oxazoline (XC), which is the 2-methyl analogue of the oxazoline (LXXXVIII), was obtained for the first time by Wolfrom and Winkley[143] in 56% yield:

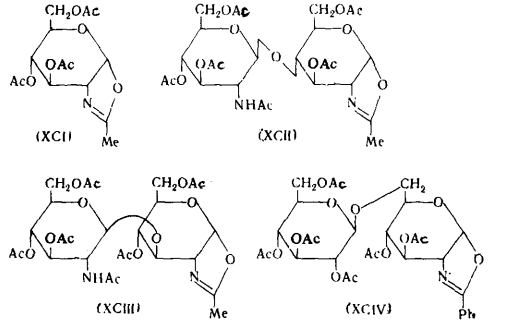


Examples of the employment of oxazoline derivatives of sugar in glycoside synthesis still remained few and were limited to the synthesis of aminoglycosides (including furanosides) derived from lower alcohols and phenol[140,142-145]. The oxazoline group was mainly used to protect the substituents at 1-C and 2-C in the synthesis of muramic acid and its derivatives[141,146-148].

A general method for the preparation of 2-substituted glyco[2′,1′:4,5]-2-oxazolines was developed in 1968 in the authors' laboratory[149,150]. The starting compounds were *O*-acetylated 2-acylamino-2-deoxyglycosyl chlorides formed in high yields when *N*-acyl derivatives of 2-amino-2-deoxysugars are treated with hydrogen chloride in acetyl chloride[65]. Treatment of the chlorides with silver salts (nitrate, perchlorate, toluene-*p*-sulphonate) in anhydrous acetone or acetonitrile[151] in the presence of organic bases (pyridine, collidine) leads to the corresponding oxazoline derivatives. The reaction probably proceeds via the intermediate formation of a carbonium ion, which is then stabilised by conversion into an oxazoline. Best results were achieved when silver nitrate and collidine were used.



Oxazoline derivatives of mono- and di-saccharides [(LXXX), (LXXXVI), (LXXXVII), and the previously unknown compounds (XCI)–(XCIV)] were obtained by this method in 50–80% yields relative to the free *N*-acylamino-sugar.



It must be emphasised that this method of synthesis rules out the isolation of the intermediate aminoglycosyl chlorides. Some of the oxazoline derivatives obtained [(LXXX), (LXXXVI) and (XCI)] were deacetylated in methanol in the presence of triethylamine[150].

Table 3. Glyco[2′,1′:4,5]-2-oxazolines.

Structure	Yield[a], %	M.p., °C	$[\alpha]_D^0$ and solvent	References
1	2	3	4	5
(1,2-Dideoxy-α-D-glucofurano)-2-oxazoline				
2-methyl-(3-*O*-acetyl-5,6-*O*-isopropylidene)-	56	96—97	+25 C	143
2-phenyl-(5,6-*O*-isopropylidene)-	61	159—160	+4 C	139
	~100	160—161,5		141
hydrochloride		125—128 d.		139
(3-*O*-acetyl)-		135—136	−16 C	139
(3-*O*-carbamoylmethyl)-		97—98,5	+0,2 C	141
(3-*O*-D-1-carbomoylethyl)-		192—193	+73 C	141
(3-*O*-L-1-carbomoylethyl)-		164.5—166	+6 C	141
(3-*O*-L-1-methoxycarbonylethyl)-		88—90	−31 C	147
(3-*O*-carboxymethyl)-		185—186	−22 C	146
		182—184	−23 C	141
(3-*O*-D-1-carboxyethyl)		163—164	+63 C	141
		163—164	+65 C	146,147
(3-*O*-L-1-carboxyethyl)		208—210	−34 C	146,147
		207—208	−38 C	141
(3-*O*-D-1-carboxypropyl)-		217—217,5	−34 C	141
(3-*O*-methyl)-		117—119	−15 C	146
(3-*O*-methanesulphonyl)-		141—142	+8 C	140
2-phenyl-(5,6-*O*-benzylidene)-		201—202	+64 C	229
(3-*O*-acetyl)-		88—89	+34 C	229
(1,2-Dideoxy-α-D-glucopyrano)-2-oxazoline				
2-methyl-		syrup	+13 C	150
(3,4,6-tri-*O*-acetyl)-	51	syrup	+10 C	149,150
	65	syrup	+7 C	154
(4,6-*O*-benzylidene)-		syrup	+3 C	229
2-*p*-methoxyphenyl-(3,4,6-tri-*O*-acetyl)-	74	106—108	+67 C	38
2-*p*-nitrophenyl-(3,4,6-tri-*O*-acetyl	76	142—143	+72 C	38
2-trifluoromethyl-(3,4,6-tri-*O*-acetyl)-	—	syrup	+5 C	107
2-phenyl		142	+48 C	135
		140—141	+48 C	150
(3,4,6-tri-*O*-acetyl)-	85	57	+45 P–W	133,135
	69	56	+52 C	38
	82	syrup		138
	98	syrup	+44 C	149,150
hydrochloride		135 d.	+39 P–W	38
hydrobromide	85	110 d.	+37 P–W	63,135
2-Methyl-(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-galactopyrano)-2-oxazoline	26	syrup	+26 C	138
	66	syrup	+26 C	153
	59	syrup	+82 C	151,157
2-Methyl-(1,2-dideoxy-β-D-mannopyrano)-2-oxazoline		166.5—167,5	+9 C	150
3,4,6-tri-*O*-acetyl)	11	133—134	−31 C	138
	82	132—133	−31 C	149,150
(4,6-*O*-benzylidene)-		172,5—174.5	−25 C	229
2-Phenyl-(1,2-dideoxy-α-D-allofurano)-2-oxazoline				
(5,6-*O*-isopropylidene)-		129—130	+76 C	142
3-keto-analogue		99—101	+380 C	142
2-Methyl-[4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-3,6-di-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano]-2-oxazoline	59	189—190	−8 C	150
2-Methyl-[3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-4,6-di-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano]-2-oxazoline	53	181—182	+8 C	166
2-Phenyl-[6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-3,4-di-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano]-2-oxazoline	60		+60 C	149

[a] The yields are quoted only for those derivatives in which the oxazoline ring is formed.

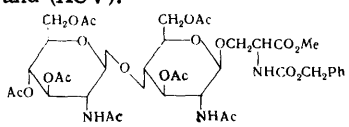
A modification of the method of Fletcher and co-workers[138], consisting of the treatment of the peracetates of 2-amino-2-deoxy-β-D-glucose and 2-amino-2-deoxy-β-D-galactose with anhydrous iron(III) chloride in methylene chloride, was proposed recently[152,153] (cf. Salo and Fletcher[154]). The high yields of the products—the oxazolines (LXXXVII) and (XCI)—and the simplicity of the process evidently make this method extremely promising.

Data for the oxazoline derivatives of sugars synthesised hitherto are summarised in Table 3.

V. OXAZOLINE SYNTHESIS OF 1,2-*trans*-2-ACETAMIDO-2-DEOXYGLYCOSIDES

2-Methylglyco[2′,1′ :4,5]-2-oxazolines, which have become available recently, were investigated as glycosylating agents mainly in the glycosylation of "aglycone" components with complex structures. A detailed study was made of the employment of oxazoline derivatives of sugars in the synthesis of acetamidoglycosides, including aminosugar oligosaccharides, in the presence of acid catalysts—mainly toluene-*p*-sulphonic acid as well as other acids[155,156]. Alkyl[135,151,153,155-157] and aryl 2-acetamido-2-deoxy-β-D-hexopyranosides[158,159] are formed in high yields when alcohols and phenols are treated with the oxazolines (LXXXVII) and (XCI) in the presence of the above catalysts. Similarly the glycosylation of monoterpene alcohols with the oxazoline (XCI) led to the formation of (-)-bornyl and (-)-menthyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosides in yields of 40–43%.[159]

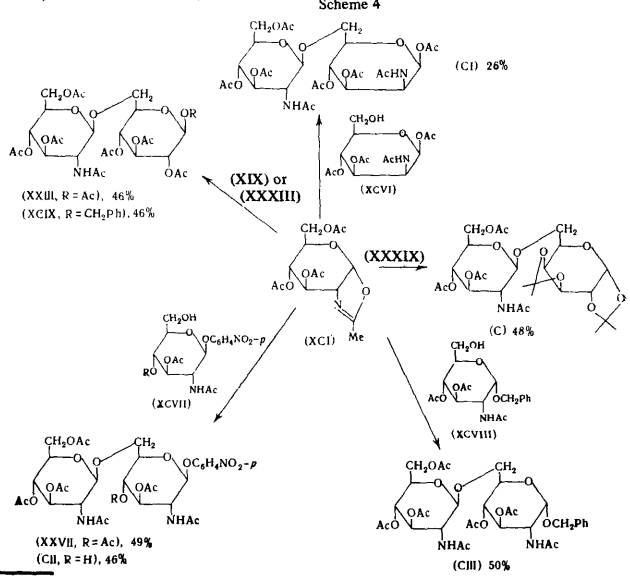
The effectiveness of the oxazoline method in the synthesis of compounds simulating the glycopeptide fragments of biopolymers was demonstrated in the glycosylation of *N*-benzyloxycarbonyl-L-serine esters by mono-[151,155] and disaccharide derivatives[160]. This led to the formation of high yields (55–75% for the monosaccharide and 40% for the disaccharide) of protected L-serine *O*-glycosides (LXXVII, R and R′ = H or OCOMe, R″ = Me or CH_2Ph, X = CO_2CH_2Ph) and (XCV).



(XCV)

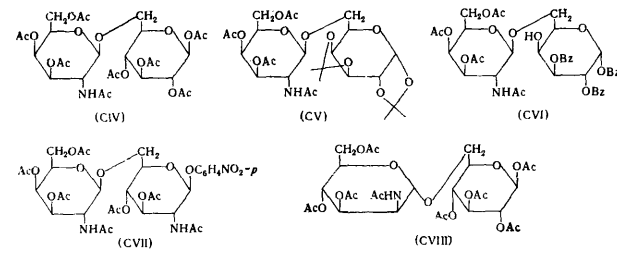
The results obtained using the oxazoline method in the synthesis of oligosaccharides ‡ are of greatest interest and value. Glycosylation of the primary hydroxy-group of derivatives of D-glucose [(XIX) and (XXXIII)][103,161], D-galactose (XXXIX)[161], D-mannose (XCVI)[152], and acetamido-D-glucose [(XCVII, R = H or COMe) and (XCVIII)][16,149,162] with the aid of the oxazoline (XCI) led to the formation of the corresponding disaccharide derivatives (XXIII), (XXVII) and (XCIX)–(CIII) in high yields—mainly about 50% (see Scheme 4).

Scheme 4

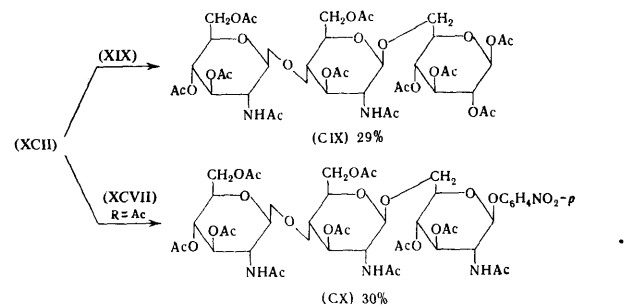


‡ See Table 2.

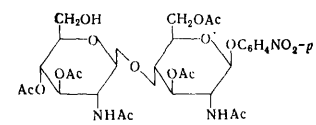
The oxazoline derivatives of the D-galacto-[151,153,157] and D-manno-series[161] proved just as effective in the synthesis of (1→6)-linked disaccharides. The protected disaccharides (CIV)–(CVIII) were obtained from them in 44–81% yield.



Glycosylation of the disaccharide (XCII) by oxazoline derivatives made it possible to increase the length of the oligosaccharide chain by two aminosugar residues in a single stage, as shown in the synthesis of the trisaccharide derivatives (CIX)[161] and (CX)[162]. This had not been achieved before by other glycosylation procedures.

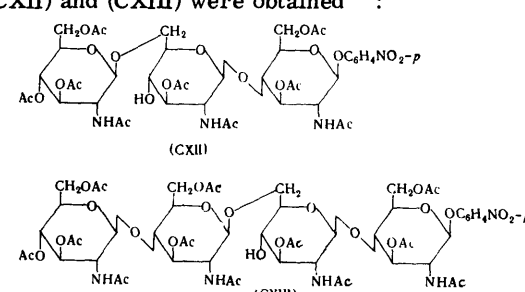


Like other glycosylating agents, oxazoline derivatives exhibit a higher reactivity in reactions with the primary hydroxy-groups of sugars than with the secondary groups, so that branched oligosaccharides, when the possibility of their formation was not ruled out altogether, were detected only in trace amounts[162,163]. This factor made it possible to employ as the glycosylated components derivatives of oligosaccharides with unprotected hydroxy-groups at 4-C and 6-C in the terminal monosaccharide residue [for example in compound (CXI)], which are readily obtained from the corresponding 4,6-*O*-benzylidene derivatives.



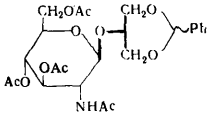
(CXI)

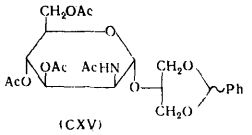
When oxazoline derivatives of the monosaccharide (XCI) and the disaccharide (XCII) were allowed to react with compound (CXI), the tri- and tetra-saccharide glycosides (CXII) and (CXIII) were obtained[164]:



The low yields of these products (not exceeding 15%) can be explained by the extremely low solubility of the glycosylated component (CXI) even in a polar solvent such as nitromethane. On the other hand, in highly polar solvents toluene-*p*-sulphonic acid catalyses the isomerisation of 2-methylglyco[2′,1′:4,5]-2-oxazolines to 2-acetamido-glycals[154], which apparently constitutes a competing process in the cases under consideration.

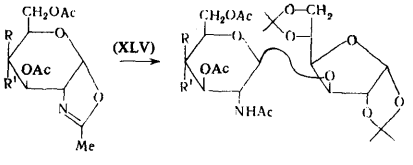
The effectiveness of the oxazoline method has been clearly demonstrated in the glycosylation of the secondary hydroxy-groups of polyols and monosaccharides. When the oxazolines (LXXXVI) and (XCI) were condensed with 1,3-*O*-benzylideneglycerol, protected 1,2-*trans*-aminoglycosides derived from benzylideneglycerol, (CXIV) and (CXV), were obtained[165,166] in yields which amounted to 34 and 31% respectively after the removal of the *O*-acetyl and benzylidene groups:


(CXIV)

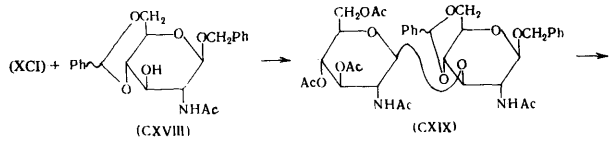

(CXV)

Derivatives of β-(1→3)-linked disaccharides (CXVI) and (CXVII) were obtained in yields of about 50% but the reaction of the oxazoline derivatives (LXXXVII) and (XCI) with diacetoneglucose (XLV)[151,157,166].

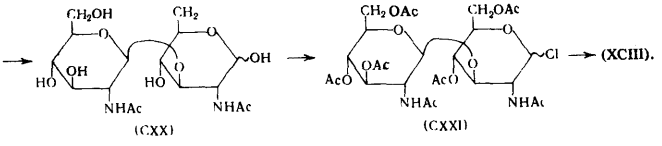
The glycosylation of the sterically hindered hydroxy-group at 3-C in the derivative (CXVIII) by the oxazoline (XCI) led to the protected disaccharide (CXIX) in 81% yield. The latter served as the starting compound in the synthesis of the oxazoline derivative of the β-(1→3)-linked disaccharide (XCIII).


(LXXXVII) or (XCI)

(CXVI, R = OAc, R′ = H)
(CXVII, R = H, R′ = OAc)


(CXVIII)

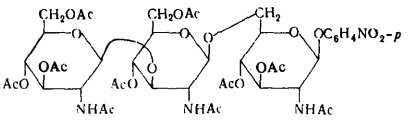
(CXIX)


(CXX)

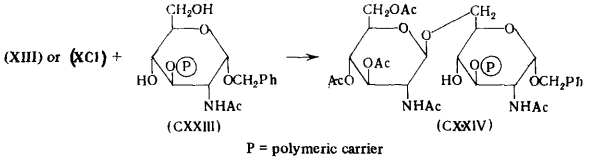
(CXXI)

(XCIII).

The disaccharide (CXX) was obtained by standard methods from (CXIX) and was then converted into the chloride (CXXI) and further into the oxazoline (XCIII) in an overall yield of 53% relative to (CXX).[166] The trisaccharide derivative (CXXII) was obtained in 78% yield by the glycosylation of *p*-nitrophenyl 2-acetamido-3,4-di-*O*-acetyl-2-deoxy-β-D-glucopyranoside by the oxazoline (XCIII).[166] The above sequence of transformations demonstrates the possibility of synthesising oligosaccharides with different combinations of 1,2-*trans*-glycosidic linkages between aminosugar residues.


(CXXII)

The recently published study of Vignon and coworkers[163], who achieved the synthesis of a disaccharide on a polymeric carrier, made a significant contribution to the development not only of the oxazoline synthesis of aminoglycosides but also to the synthesis of oligosaccharides in general. The glycosylation by the oxazoline (XCI) [or the chloride (XIII) under the conditions of the Koenigs–Knorr reaction] of the acetamido-D-glucose derivative (CXXIII) linked to a polymeric carrier via an ester bond led to a high yield of the disaccharide derivative (CXXIV) on the carrier. After the treatment of the latter with sodium methoxide in methanol, the disaccharide glycoside was liberated.


(CXXIII) (CXXIV)

P = polymeric carrier

Apart from the advantages of solid-phase synthesis, known from the synthesis of peptides, this version of the oxazoline method for the preparation of aminoglycosides will probably make it possible to solve successfully the problem of synthesising higher oligosaccharides, the difficulties of which are associated with the low solubility of the glycosylated components[164].

In summing up the discussion of the oxazoline method for the synthesis of 1,2-*trans*-2-acetamido-2-deoxyglycosides, we may note that oxazoline derivatives of sugars permit the glycosylation of various types of hydroxy-compounds—alcohols, phenols, hydroxyaminoacids, polyols, and partly protected mono- and oligo-saccharides [as well as thiols (see below)]. The general nature of the reactions has been demonstrated for a number of important classes of natural aglycones. The application of glycosylating agents with a wide variety of structures and a series of different alcoholic components makes it possible to infer the stereospecificity of the reaction. On the other hand, one can conclude on the basis of these data that all the protecting groups tested are stable under the conditions of glycosylation with oxazoline derivatives of sugars, namely the acyl, alkylidene, and benzyl glycoside groups as well as the *N*-benzyloxycarbonyl group used in peptide synthesis.

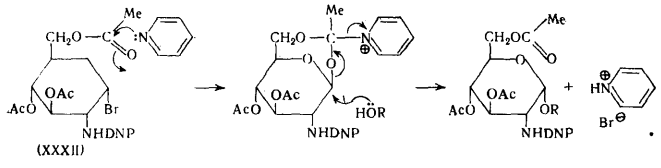
The results taken as a whole show that the oxazoline method is a general procedure for the formation of the 1,2-*trans*-aminoglycosidic linkage.

VI. STEREOSPECIFIC SYNTHESIS OF 1,2-*cis*-2-AMINO-2-DEOXYGLYCOSIDES

As in the series of neutral sugars, methods for the stereospecific synthesis of 1,2-*cis*-aminoglycosides are now in the stage of development only. Above it was stated that the formation of 1,2-*cis*-glycosides from acyl-halogeno-derivatives of sugars is prevented by the involvement of the acetoxy- or acylamino-groups. In those cases where this effect was suppressed by the introduction of "non-participating" substituents into the amino-group of the sugar, the stereospecificity of the glycosylation reaction was lost and the proportions of the anomeric glycosides formed varied within wide limits.

The separation of anomeric alkyl or aryl aminoglycosides presents no difficulties at present and is carried out by chromatographic methods[167-169]. Chromatography is also used to separate anomeric aminoglycosides with aglycones having a complex structure (including disaccharide derivatives), formed in the synthesis by different versions of the Koenigs–Knorr reaction. However, its scope is sharply reduced with increase in the length of the oligosaccharide chain, this effect being already observed for trisaccharide derivatives. For this reason, only stereospecific glycosylation permits the solution of the problem of synthesising higher oligosaccharides having the 1,2-*cis*-aminoglycosidic linkage.

The preferential formation of 1,2-*cis*-aminoglycosides was observed only in a few instances, for example in glycosylation by the bromide (XXXII) in the presence of pyridine[89,92], which the authors explain by the involvement of the acetoxy-group at 6-C:

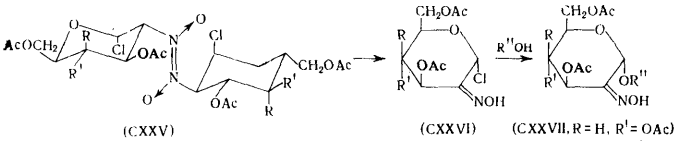


(XXXII)

Indeed, when 3,4-di-*O*-acetyl-2-deoxy-2-(2,4-dinitrophenylamino)-6-*O*-methyl-α-D-glucopyranosyl bromide was used as the glycosylating agent, the dominant reaction product was the 1,2-*trans*-glycoside[92] and in addition the reaction was significantly retarded. The replacement of the acetoxy-groups at 3-C or 4-C in the bromide (XXXII) by methyl groups does not alter the stereospecificity and rate of the reaction.

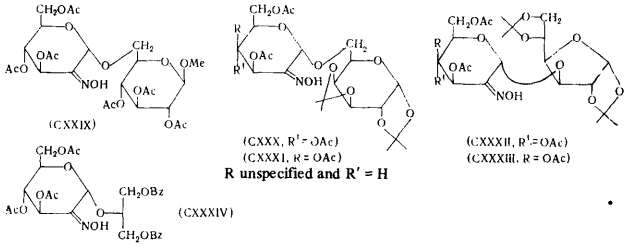
A similar effect of the involvement of the acetoxy-substituent at 4-C was observed recently[170] in a series of neutral sugars. Glycosylation by 2-*O*-benzyl-3,4-di-*O*-(*p*-nitrobenzoyl)-α-L-fucopyranosyl bromide led to α-L-fucosides with a high degree of stereospecificity.

The most promising method for the synthesis of 1,2-*cis*-aminoglycosides was proposed very recently by Lemieux and coworkers. The available[171,172] dimeric D-gluco- and D-galacto-nitrosyl chlorides (CXXV), which dissociate and isomerise in dimethyl formamide (DMF) to the corresponding hydroxyiminochlorides (CXXVI)[173], react with alcohols and phenols in the presence of pyridine to form high yields of 3,4,6-tri-*O*-acetyl-2-hydroxyimino-α-D-arabinohexopyranosides (CXXVII) and the corresponding α-D-lyxohexopyranosides (CXXVIII)[174-176]—the precursors of 2-amino-2-deoxy-α-D-glycosides:



(CXXV) (CXXVI) (CXXVII, R = H, R' = OAc)
(CXXVIII, R = OAc, R' = H)
(R'' = alkyl or aryl)

This method is suitable[174,176,177] also for the synthesis of 2'-hydroxyimino-derivatives of disaccharides [(CXXIX) – (CXXXIV)], which are formed in yields of 50–80%. The β-anomer was isolated in 9% yield only in the synthesis of (CXXXI).



(CXXIX) (CXXX, R' = OAc) (CXXXI, R = OAc) (CXXXII, R' = OAc) (CXXXIII, R = OAc)
R unspecified and R' = H
(CXXXIV)

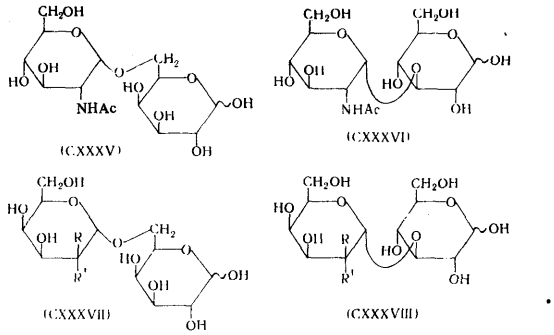
On the other hand, in the remaining cases the authors failed to observe the formation of β-anomers (but they did not rule out this possibility[176]).

The results of Miyai and Jeanloz[175] conflict with these data. They failed to observe the stereospecificity of the glycosylation of benzyl 2,3,4-tri-*O*-benzyl-β-D-galactopyranoside by the chloride (CXXV, R = H, R' = OCOMe) and obtained a mixture of α- and β-(1→6)-linked disaccharides in approximately equal amounts.

The preparative value of the method is reduced to some extent by the inadequate stereospecificity of the reduction of the hydroxyimino-derivatives to the corresponding 2-amino-2-deoxysugars. Depending on the conditions of the reduction of (CXXVII) and (CXXVIII), the ratio of the amino-α-D-glycosides formed, epimeric at 2-C, varied within a fairly wide range[175,178,179]. A high stereospecificity of the reaction was noted only in the hydrogenation of (CXXVII) on palladium in the presence of hydrazine or in the reduction of the *N*-acetate of compound (CXXVII) by diborane in tetrahydrofuran (THF), as a result of which the product contained 92–95% of the amino-α-D-glucoside and 5–8% of the amino-α-D-mannoside. The reduction of (CXXVII) or (CXXVIII) (as well as its *N*-acetate) by diborane or lithium tetrahydroaluminate in THF led to a mixture of the D-gluco- and D-manno-epimers [from (CXXVII)] and the D-galacto- and D-talo-epimers [from (CXXVIII)] in comparable amounts.

The same behaviour was noted[180] also in the reduction of the hydroxyimino-derivatives of disaccharides [(CXXX)–(CXXXIV)] by diborane in THF. The individual disaccharides (CXXXV) and (CXXXVI) were obtained in high yields only from compounds (CXXX) and (CXXXII) (after the removal of the protecting groups and *N*-acetylation). The reduction of (CXXXI) and (CXXXIII) under the same conditions led to mixtures of disaccharides [(CXXXII) and (CXXXVIII) with R = R' = H or NHCOMe) in which products with the D-talo-configuration of the aminosugar component predominated. They were separated by chromatography.

The reduction of (CXXIX) also leads to the formation of a mixture of disaccharide derivatives with the D-gluco- and D-manno-configuration of the non-reducing monosaccharide residue in proportions of approximately 1 : 1.[178]



(CXXXV) (CXXXVI)

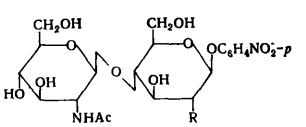
(CXXXVII) (CXXXVIII)

Despite the non-specific reduction of 2-hydroxyimino-derivatives of sugars in many cases, the method described is at present perhaps the only procedure for the synthesis of 1,2-*cis*-aminoglycosides with an aglycone having a complex structure. It is noteworthy that 2-hydroxyimino-2-deoxy-α-D-glycosides are the precursors of not only amino-α-D-glycosides but also of α-D-glycopyranosides[177,181], α-D-hexopyranosides[179], and 2-deoxy-α-D-glycosides[182], including disaccharide derivatives.

VII. ENZYMATIC SYNTHESIS OF AMINOSUGAR OLIGOSACCHARIDES

A detailed description of the synthesis of oligosaccharides containing aminosugar residues by enzymatic systems is outside the scope of this review. We wished to consider only those enzymatic methods for the formation of aminosugar oligosaccharides which are of interest from the preparative point of view. They are based on the well known transglycosylating ability of the lysozyme from hen egg protein (EC 3.2.1.17).

When lysozyme was allowed to act on di-*N*-acetylchitobiose in the presence of methanol, methyl 2-acetamido-2-deoxy-β-D-glucopyranoside was isolated[185]. Subsequently the same workers[186] obtained disaccharide glycosides (CXXXIX), which are formed when lysozyme acts on tetra-*N*-acetylchitotetraose in the presence of *p*-nitrophenyl β-glycosides derived from *N*-acetyl-D-glucosamine, D-glucose, and 2-deoxy-D-glucose as acceptors (see also van Eikeren and Chipman[187]). When penta-*N*-acetylchitopentaose was used as the donor of glycosyl residues and cellobiose as the acceptor, oligosaccharides with the formula $(GlcNAc)_nGlcGlc$§ (n = 1–3) were obtained[188,189].



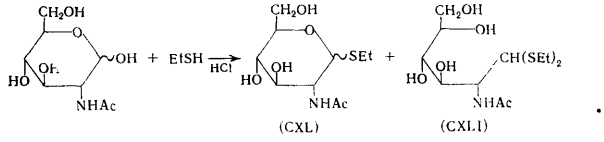
(CXXXIX, R = NHAc, OH, H)

The tetrasaccharide from the cell wall of the bacterium *Micrococcus lysodeikticus*, $(GlcNAc\text{-}MurNAc)_2$, is an active donor of glycosyl residues in lysozyme-catalysed reactions. When it was allowed to react with monosaccharide acceptors (*N*-acetyl-D-glucosamine, D-glucose, D-galactose, and D-xylose), the following trisaccharides were isolated[190–192]: GlcNAc-MurNAc-GlcNAc, GlcNAc-MurNAc-Glc, GlcNAc-MurNAc-β-(1→2)-Glc, GlcNAc-MurNAc-β-(1→2)-Gal, GlcNAc-MurNAc-Xyl, GlcNAc-MurNAc-β-(1→2)-Xyl, and GlcNAc-MurNAc-β-(1→3)-Xyl, the yield of the transglycosylation products reaching 15% (with respect to the donor). The transfer of the same glycosyl residue to oligosaccharides (di-*N*-acetylchitobiose and cellotetraose) proceeds similarly[188,192] and leads to the formation of the oligosaccharides GlcNAc-MurNAc-$(GlcNAc)_2$ and GlcNAc-MurNAc-$(Glc)_4$.

Transglycosylating activity is a characteristic property of glycosidases and endoglycanases, i.e. *O*-glycoside hydrolases, which catalyse the hydrolytic cleavage of the *O*-glycosidic linkage with retention of the configuration at the anomeric glycosidic centre of the substrate. An enhanced affinity of the active centres for the glycone part of the substrate is characteristic of enzymes of this type, and is responsible for the attachment of the activated glycosyl residue to them. The latter is then transferred to the acceptor. Apart from lysozyme, which has already been mentioned, in the preparative synthesis of aminoglycosides employing transglycosylating activity it is possible to use also other enzymes which cleave the aminoglycosidic linkage, for example α- and β-hexosaminidases. However, the available information on this subject is extremely limited.

VIII. SYNTHESIS OF *S*- AND *N*-AMINOGLYCOSIDES

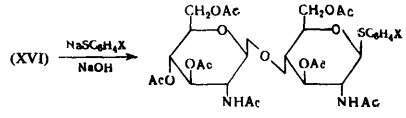
In contrast to neutral monosaccharides, *N*-acetyl-D-glucosamine is capable of giving rise to thioglycosides under the conditions of the Fischer synthesis of glycosides. Thus the anomeric ethyl 2-acetamido-2-deoxy-1-thio-D-glucopyranosides (CXL) were obtained in a low yield under controlled conditions[193], but the main reaction product was the mercaptal (CXLI):



(CXL) (CXLI)

Aminosugar *S*-glycosides are mainly synthesised by the methods used to prepare their neutral analogues[194]. The hydrolysis of the mercaptal (CXLI) in the presence of mercury(II) chloride and mercury(II) oxide gives a mixture of anomeric ethyl 2-acetamido-2-deoxy-1-thio-D-glucofuranosides, with the α-anomer predominating[195].

Different alkyl and aryl 2-amino-3,4,6-tri-*O*-benzoyl-2-deoxy-1-thio-β-D-glucopyranosides (in the form of the hydrobromides)[196] and their *N*-benzoyl analogues[39] have been obtained from the corresponding acylhalogeno-derivatives and thiols. Phenyl 1-thioglycosides of the disaccharide (CXLII, X = H, Me, or NO_2) and their 1-seleno-analogue[197] were synthesised similarly from the chloride (XVI)[197,198]:



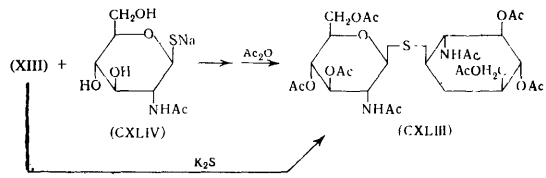
(CXLII)

§ For the significance of the abbreviations, see the footnote to Table 2. The unspecified positions of the glycosidic linkages are β-(1→4).

Ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside is formed in the mercaptolysis of α-D-glucosamine peracetate in the presence of zinc chloride[183]. In this case the stereospecificity is due to the cooperative effect.

The oxazoline method is promising for the synthesis of 1-thioaminoglycosides. Phenyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside and the thioglycoside (CXLII, X = H) were obtained in this way[158] in yields of 68 and 43% respectively.

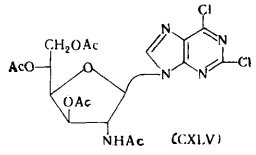
The thio-analogue of the non-reducing disaccharide (CXLIII) was obtained[61] in 50% yield by the reaction of the chloride (XIII) with the sodium salt of (CXLIV) or by treating the chloride (XIII) with potassium sulphide:



Either direct condensation of monosaccharides with aromatic amines[200-203] or aminoacids[203,204] or different versions of the Koenigs–Knorr reaction are used in the synthesis of the *N*-glycosides of 2-amino-2-deoxysugars, as for the *N*-glycosides of neutral sugars[199]. The use of acylhalogenosugars as glycosylating agents involves the same difficulties as in the synthesis of *O*-glycosides of 2-amino-2-deoxysugars.

O-Acylated glycosyl chlorides and bromides with different substituents at the nitrogen atom have been used in the synthesis of aminosugar nucleosides[205-218]. Mixtures of anomeric *N*-substituted aminoglycosides are formed as a rule from bromides with "non-participating" substituents at 2-C.

The synthesis of the nucleoside (CXLV) is so far the only instance[143] of the preparation of *N*-glycosides by the oxazoline method[135].



(CXLV)

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The data described permit the conclusion that the synthesis of 1,2-*trans*-aminoglycosides, including 2-amino-2-deoxysugar oligosaccharides, has now been developed in fair detail and there are a number of methods whereby they can be obtained on a preparative scale, among which the oxazoline method is the most convenient. Methods for the synthesis of 1,2-*cis*-aminoglycosides have been much less satisfactorily developed and the synthesis of polysaccharides made up of aminosugar residues has remained completely untouched. In this respect the synthetic chemistry of aminoglycosides still lags behind the synthetic chemistry of their neutral analogues[172,219].

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