A New Two-Position Protecting Group: Preparation And Properties Of Glucopyranosido-(1,2: 4',5')-2'-Oxazolidone And Syntheses Of D-Glucosaminides

Sharad Ramchandra Kulkarni

University of the Pacific

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[Signature] Charles A. Matuszak

Dated August 1964
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>II. ROLE OF MERCURIC CYANIDE ON COMPETITION BETWEEN</td>
<td>11</td>
</tr>
<tr>
<td>GLYCOSIDATION AND OXAZOLIDONE FORMATION</td>
<td></td>
</tr>
<tr>
<td>III. D-GLUCOSAMINIDE SYNTHESSES</td>
<td>26</td>
</tr>
<tr>
<td>IV. EXPERIMENTAL DETAILS</td>
<td>36</td>
</tr>
<tr>
<td>V. SUMMARY</td>
<td>57</td>
</tr>
<tr>
<td>BIBLIOGRAPHY</td>
<td>61</td>
</tr>
</tbody>
</table>
## LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Occurrence of Aminosugars in Antibiotic Substances</td>
<td>2</td>
</tr>
<tr>
<td>II. Summary of Properties of Various Protecting Groups</td>
<td>6</td>
</tr>
<tr>
<td>III. Role of Mercuric Cyanide in Various Glycosidation Reactions Using $4.4 \times 10^{-3}$ Mole of Compound (I)</td>
<td>16</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Relation Between the Yield of the Compound (III) and the Total Steric Energy of Activation $\Delta\Delta E^+_s$</td>
<td>19</td>
</tr>
</tbody>
</table>

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LIST OF CHARTS

<table>
<thead>
<tr>
<th>CHART</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Synthesis of Dl-Saccharide</td>
<td>4</td>
</tr>
<tr>
<td>2. Reaction of N-Carbobenzoxy-D-Glucosamine with 2M Hydrochloric Acid in Acetic Anhydride</td>
<td>13</td>
</tr>
<tr>
<td>3. Reactions of O-Bromo-3,4,6-Tri-O-Benzoyl-N-Carbobenzoxy-D-Glucosamine with Alcohols in the Presence of Mercuric Cyanide</td>
<td>14</td>
</tr>
<tr>
<td>4. Properties of 3,4,6-Tri-O-Benzoyl-D-Glucopyranosido-[1,2;4',5']-2'-Oxazolidone</td>
<td>23</td>
</tr>
<tr>
<td>5. De-O-Benzoylation of the Compounds (IIa), (IIc), and (IIf)</td>
<td>28</td>
</tr>
<tr>
<td>6. Benzyl-3,4,6-Tri-O-Benzoyl-N-Carbobenzoxy-(\alpha)-D-Glucosaminide</td>
<td>32</td>
</tr>
<tr>
<td>7. Synthesis of Benzyl-3,4,6-Tri-O-Benzoyl-N-Carboethoxy-(\beta)-D-Glucosaminide</td>
<td>33</td>
</tr>
<tr>
<td>8. Isopropyl-3,4,6-Tri-O-Acetyl-N-Carboethoxy-(\beta)-D-Glucosamid</td>
<td>34</td>
</tr>
</tbody>
</table>
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CHAPTER I

INTRODUCTION

In 1878 Lederhose (35) isolated D-glucosamine by mineral acid hydrolysis of chitin found in lobster shell. However, it took sixty-three years to elucidate its structure and assign it an unequivocal configuration (20,19). In 1914 P. A. Leven isolated D-galactosamine (chondrosamine). Forty-one years elapsed before its structure and configuration were established conclusively (27).

Interest in aminosugar chemistry was enhanced during the past fifteen years since it was discovered that other aminosugars besides glucosamine and galactosamine are constituents of antibiotic substances synthesized by fungi (31,2). These are shown in Table I (48,5).

D-glucosamine and D-galactosamine are the two aminosugars which are found mainly in the animal kingdom, where their most usual occurrence is as constituents of carbohydrate polymers—amino polysaccharides which are known as mucopolysaccharides, mucoproteins, and mucolipids (24). They play a vital role in specific biological functions. Such polysaccharides are found in the skeletal substances of many species, as bacterial constituents, as antigens of many types, and as intercellular cementing agents and in a variety of biological lubricants (31).
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Aminosugar Trivial Name</th>
<th>Aminosugar Systematic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycine</td>
<td>Kanosamine</td>
<td>3-amino-3-deoxy-D-glucose</td>
</tr>
<tr>
<td>Nystatin</td>
<td>Mycosamine</td>
<td>3-amino-3,6-dideoxy-mannose</td>
</tr>
<tr>
<td>Magnamycin</td>
<td>Mycaminose</td>
<td>3-dimethylamino-3,6-dideoxy-D-glucose</td>
</tr>
<tr>
<td>Erythromycins</td>
<td></td>
<td>3-dimethylamino-3,4,6-trideoxy-D-hexopyranose</td>
</tr>
<tr>
<td>Methyldoses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narbomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olandomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plicomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Puromycin</td>
<td></td>
<td>3-amino-3-deoxy-D-ribose</td>
</tr>
<tr>
<td>Rhodomyccins</td>
<td>Rhodosamine</td>
<td>3-dimethylamino-2,3,6-trideoxy-lyxo-hexopyranose</td>
</tr>
<tr>
<td>Amicetin</td>
<td>Amosamine</td>
<td>4-dimethylamino-4,6-dideoxy-D-glucose</td>
</tr>
<tr>
<td>Racemomycins</td>
<td></td>
<td>2-amino-2-deoxy-D-gulose</td>
</tr>
<tr>
<td>Streptothricins</td>
<td></td>
<td>2-amino-D-deoxy-D-glucose</td>
</tr>
<tr>
<td>Monomycin</td>
<td></td>
<td>2-amino-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>Zygomyccins</td>
<td>Neosamine-C</td>
<td>2,6-diamino-2,6-dideoxy-D-glucose</td>
</tr>
<tr>
<td>Neomycins</td>
<td>Neosamine-B</td>
<td>2,6-diamino-2,6-dideoxy-L-idose</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>Paromose</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>N-methyl-L-glucosamine</td>
<td>2-methylamino-2-deoxy-L-glucose</td>
</tr>
</tbody>
</table>
Di- and oligosaccharides containing aminosugars may be conveniently divided into at least three categories: those containing (1) residues of aminosugars only, (2) non-nitrogenous and aminosugar residues, and (3) uronic acid residues and aminosugar residues. Several nitrogenous disaccharides have been synthesized enzymatically \(^{(49,23)}\). Chemical identification and definite proof of the structure of these disaccharides has been achieved \(^{(43)}\).

Alternatively, disaccharides can be synthesized by the Koenigs-Knorr procedure \(^{(48)}\). Thus 6-0-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-glucose and 6-0-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-D-galactose \(^{(60)}\) were synthesized by reacting 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-D-glucosyl-bromide with 1,2,3,4-tetra-O-acetyl-D-glucose or the corresponding D-galactose derivatives in benzene solution in the presence of mercuric cyanide as catalyst, followed by de-O-acetylation with ammonia (see Chart 1).

In order to understand how the antibiotic nature and biological activity works, it is pertinent to synthesize these naturally occurring disaccharides. The first step in this direction is the preparation of β-D-glucosaminides as model compounds. Glycosidation can be effected in two different ways. In the first method the amino group is protected and then glycosidation is undertaken with alcohol in the presence of hydrochloric acid \(^{(42,7)}\). In the second
Hg(CN)$_2$ + C$_6$H$_6$ → AC = CH$_3$CO-

CH$_3$OH + NH$_3$ at 0°C.

CHART 1
SYNTHESIS OF DI-SACCHARIDE

All compounds are known.
method the hydroxy and the amino groups are protected in a glycosyl halide, and then glycosidation is effected with alcohol in the presence of mercuric cyanide or silver carbonate (34, 62, 21). The disadvantage of the first method is that it always gives an anomeric mixture. Sometimes it is tedious to separate the mixture to get a pure anomer. The second method has the advantage that it always yields pure β-anomer.

In order to improve the method of glycosidation, the hydroxyl and amino groups have been protected by various protecting groups as shown in Table II (24, 59). These protecting groups can be examined with respect to the criteria for protecting groups: (1) stability towards acid, base, and heat, (2) solubility in organic solvents, (3) crystallizability, and (4) ease of removability by chemical methods. It is true, however, that any one protecting group cannot perfectly satisfy all the above criteria. Moreover, a property which is useful (i.e., "good") in one context may constitute a disadvantage in a different situation.

Hydroxyl protecting groups. Acetyl groups are quite satisfactory on all criteria except solubility (51). They decrease the yield of the product due to the frequently fairly high solubility of derivatives containing them. Ether groups (28) are stable and crystallize well. Their derivatives are an improvement over those of acetyl groups.
# Table

## Summary of Properties of

<table>
<thead>
<tr>
<th>Function</th>
<th>Protecting Group</th>
<th>Stability Towards</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Acid</td>
<td>Base</td>
</tr>
<tr>
<td>Hydroxyl</td>
<td>Acetyl</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Ether</td>
<td>Inter.*</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Benzyol</td>
<td>Inter.*</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Methyl Sulfonyl</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>p-Toluene Sulfonyl</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Amino</td>
<td>Acetyl</td>
<td>Inter.*</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>2,4-dinitrophenyl</td>
<td>Inter.*</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Benzyloxy-carbonyl</td>
<td>Inter.*</td>
<td>High</td>
</tr>
</tbody>
</table>

*Inter. = Intermediate*
## II
### VARIOUS PROTECTING GROUPS

<table>
<thead>
<tr>
<th>Solubility in Organic Solvents</th>
<th>Crystalizability</th>
<th>Removeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Difficult</td>
<td>Easy</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Difficult</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>High</td>
<td>Easy</td>
<td>Difficult</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Easy</td>
</tr>
<tr>
<td>Inter.</td>
<td>Easy</td>
<td>Easy</td>
</tr>
</tbody>
</table>
in that they are less soluble in organic solvents, thus increasing the yield. However, it is much more difficult to remove them. The benzoyl group fulfills all the criteria for protecting groups. Its removability is similar to that of the acetyl group and it is particularly easy to crystallize (29,55). These aminosugar derivatives have a higher melting point and are more stable than those which have the hydroxyl groups protected by acetyl groups (54,55). Sulfonyl groups are also quite good protecting groups. It has been observed that methyl sulfonyl group can be used to effect the conversion of one optical isomer to another (16,17). The primary hydroxyl group can be protected by p-toluene sulfonyl group which can be easily substituted or removed (14).

**Amino protecting groups.** Acetyl groups would be satisfactory protecting groups for amino groups except that they require mineral acid hydrolysis for their removal (24). Glycosides are fairly sensitive to acid and so the method is not very useful. More recently the amino group has been protected by groups such as 2,4-dinitrophenyl (38) and benzoyloxycarbonyl (54,55). These groups have the advantage over the acetyl group in that they satisfy all the criteria the acetyl group does and in addition are easily removable by catalytic hydrogenolysis (22,33). The benzoyloxycarbonyl group has two advantages over the 2,4-dinitrophenyl group:
It can be removed by glacial acetic acid and hydrobromic acid solution, and it increases the crystallizibility of amino-sugar derivatives (55,44).

It is known that hydroxy groups at C_4 and C_6 can be protected by benzyldine, propylidene, and boric acid (51). These groups satisfy all the criteria for protecting groups at least moderately well, including ease of removability.

C_1 and C_2 can be protected by 3,4,6-tri-O-acetyl-D-glucopyranosido-[\(1,2:4',5'\)]-2'-oxazoline (40) and 3,4,6-tri-O-acetyl-D-glucopyranosido-[\(1,2:4',5'\)]-2'-oxazolidone (26,32,53). These methods are of special interest in that they protect both the hydroxy and the amino groups. They are also interesting because their synthesis sheds light on the stereochemistry of C_1 and C_2. Recently benzyl-4,6-di-O-acetyl-\(\alpha\)-D-glucopyranosido-[\(2,3:4',5'\)]-2'-oxazolidone has been synthesized (17) and found to be useful in the preparation of new aminosugars. This synthesis reveals the configurations of C_2 and C_3.

The present work consists of two parts. The first part deals with the synthesis of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[\(1,2:4',5'\)]-2'-oxazolidone (III) and the study of its chemistry in order to determine whether it could be used as a simultaneous protecting group for C_1 and C_2 in the preparation of new aminosugars. The second part covers the synthesis and de-O-benzoylation of
\(\beta\text{-D-glucoaminides.}\) The products thus obtained can be used to prepare new disaccharides. In addition new aminosugar derivatives have been prepared.
It can be removed by glacial acetic acid and hydrobromic acid solution, and it increases the crystallizibility of amino-sugar derivatives (55,44).

It is known that hydroxy groups at C\textsubscript{4} and C\textsubscript{6} can be protected by benzylidene, propylidene, and boric acid (51). These groups satisfy all the criteria for protecting groups at least moderately well, including ease of removability.

C\textsubscript{1} and C\textsubscript{2} can be protected by 3,4,6-tri-O-acetyl-D-glucopyranosido-[1,2:4',5']-2'-oxazoline (40) and 3,4,6-tri-O-acetyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (26,32,53). These methods are of special interest in that they protect both the hydroxy and the amino groups. They are also interesting because their synthesis sheds light on the stereochemistry of C\textsubscript{1} and C\textsubscript{2}. Recently benzyl-4,6-di-O-acetyl-D-glucopyranosido-[2,3:4',5']-2'-oxazolidone has been synthesized (17) and found to be useful in the preparation of new aminosugars. This synthesis reveals the configurations of C\textsubscript{2} and C\textsubscript{3}.

The present work consists of two parts. The first part deals with the synthesis of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) and the study of its chemistry in order to determine whether it could be used as a simultaneous protecting group for C\textsubscript{1} and C\textsubscript{2} in the preparation of new aminosugars. The second part covers the synthesis and de-O-benzoylation of
β-D-glucosaminides. The products thus obtained can be used to prepare new disaccharides. In addition new aminosugar derivatives have been prepared.
CHAPTER II

ROLE OF MERCURIC CYANIDE ON COMPETITION BETWEEN GLYCOSIDATION AND OXAZOLIDONE FORMATION

In order to prepare $\beta$-D-glucosaminides it was necessary to react $\alpha$-bromo-3,4,6-tri-O-acetyl-glucosamine hydrobromide (XV) with alcohols in the presence of pyridine (12). Later the method was improved by treating $\alpha$-bromo-3,4,6-tri-O-acetyl-N-carbobenzyoxy-D-glucosamine (I) with alcohols in chloroform using mercuric cyanide (21) or silver carbonate (41,62,13).

$\alpha$-bromo-3,4,6-tri-O-acetyl-D-glucosamine-hydrobromide (XV) was prepared by heating D-glucosamine with acetyl bromide (42,6). Later it was obtained by reacting $\alpha,\beta$-1,3,4,6-tetra-O-acetyl-N-carbobenzyoxy-D-glucosamine and glacial acetic acid solution saturated with hydrobromic acid (29). It was, however, found that $\alpha$-bromo-3,4,6-tri-O-acetyl-D-glucosamine-hydrobromide is unstable.

$\alpha$-Bromo-3,4,6-tri-O-benzyl-D-glucosamine-hydrobromide (VI) (55) was prepared from $\alpha,\beta$-1,3,4,6-tetra-O-benzoyl-N-carbobenzyoxy-D-glucosamine and glacial acetic acid-hydrobromic acid solution. It was obtained in good yield and found to be stable. It was observed that when the amino function is protected by an acetyl or benzoyl group, as in the preceding two cases, bromine replaces only benzoyl or acetyl at C1, without

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splitting the N-acetyl or N-benzoyl group. When the anomeric mixture of pentaacetyl or pentabenzoyl D-glucosamine was treated with glacial acetic acid-hydrobromic acid solution, pure $\alpha$-bromo compound was obtained (29,55).

Recently it has been found (17) that $\alpha$-bromo-3,4,6-tri-O-acetyl-D-glucosamine hydrobromide (XV) can be prepared in one step by treating dry N-carbobenzoxy-D-glucosamine with 2 M hydrogen bromide in acetic anhydride, first at 0°C, and then raising the temperature by the introduction of gaseous hydrogen bromide. $\alpha$-Bromo-3,4,6-tri-O-benzoyl-D-glucosamine hydrobromide cannot be prepared in this way because benzoic acid is solid and because N-carbobenzoxy-D-glucosamine is insoluble in benzoyl chloride. An attempt was made to prepare $\alpha$-chloro-3,4,6-tri-O-acetyl-D-glucosamine hydrochloride by reacting dry N-carbobenzoxy-D-glucosamine with 2 M hydrogen chloride in acetic anhydride. It failed however (See Chart 2).

$n$-Propyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-$\beta$-D-glucosaminide (IIa) was prepared by heating $\alpha$-bromo-N-carbobenzoxy-3,4,6-tri-O-benzoyl-D-glucosamine (I) (56) with $n$-propyl alcohol in chloroform in the presence of mercuric cyanide. It was noted that 3,4,6-tri-O-benzoyl-D-glucopyranosido-$[1,2:4',5']$-2'oxazolidone (III) and benzyl bromide were obtained as byproducts (See Chart 3). It had earlier been erroneously reported (33) that the above
CBZ = C₆H₅CH₂O-CO-

2M HCl in (CH₃CO)₂O

HO
H

H-C-NHCBZ
HO-C-H
H-C-OH
H-

CH₂OH

H

OAC

H-C-NHCBZ
ACO-C-H
H-C-OAC
H-

CH₂OAC

AC = CH₃CO-

XXII* 

XXIII*

CHART 2

REACTION OF N-CARBOBENZOXY-D-GLUCOSAMINE WITH 2M HYDROCHLORIC ACID IN ACETIC ANHYDRIDE

*Compounds are known.
**Chart 3**

Reactions of α-Bromo-3,4,6 Tri-O-Benzoyl-N-Carbobenzoxy-D-Glucosamine with Alcohols in the Presence of Mercuric Cyanide

*Compounds are known.*
oxazolidone can be obtained from certain $\beta$-D-glucosaminide by treating it with sodium methoxide in methanol. Thus, it became necessary to study the reaction of glycosidation thoroughly.

In order to ascertain the role of mercuric cyanide in this reaction, the amount of mercuric cyanide was reduced in successive experiments from $4.4 \times 10^{-3}$ mole to $0.5 \times 10^{-3}$ mole per $4.4 \times 10^{-3}$ mole of $\alpha$-bromo-3,4,6-tri-O-benzoyl-N-carbobenzyoxy-D-glucosamine (I) (56). It was found that the yield of the $\beta$-D-glucosaminide went down from 78.5 per cent to 16.8 per cent without appreciably affecting the yield of the compound (III) as is shown in Table III. It seems that, in the formation of the compound (III), mercuric cyanide behaves as a catalyst.

Similar reactions were undertaken using n-butanol, benzyl alcohol, and cyclohexanol and the corresponding $\beta$-D-glucosaminides (33) were obtained, besides compound (III) and benzyl bromide (Chart 3). The yield of the compound (III) in each of the three cases was found to be equal to that obtained in the case of n-propanol. When the reaction was carried out in the case of isopropanol, it was observed that the yield of compound (III) was increased by 50 per cent as shown in Table III. This created further interest in the reaction, and so the reaction was carried out with tertiary butanol to see whether the yield of the compound (III) could
## TABLE III

**ROLE OF MERCURIC CYANIDE IN VARIOUS GLYOSIDATION REACTIONS USING 4.4x10^{-3} MOLE OF COMPOUND (I)**

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Merecuric Cyanide (moles)</th>
<th>Yield of Compound (II) (moles)</th>
<th>Yield of Compound (III) (moles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Propanol</td>
<td>4.4x10^{-3}</td>
<td>3.4x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>2.2x10^{-3}</td>
<td>3.3x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>1.1x10^{-3}</td>
<td>1.8x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>n-Propanol</td>
<td>0.5x10^{-3}</td>
<td>0.75x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>n-Butanol</td>
<td>4.4x10^{-3}</td>
<td>3.4x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>4.4x10^{-3}</td>
<td>3.0x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>Cyclohexanol</td>
<td>4.4x10^{-3}</td>
<td>3.0x10^{-3}</td>
<td>0.19x10^{-3}</td>
</tr>
<tr>
<td>Isopropanol</td>
<td>4.4x10^{-3}</td>
<td>3.1x10^{-3}</td>
<td>0.29x10^{-3}</td>
</tr>
<tr>
<td>Tertiary butanol</td>
<td>4.4x10^{-3}</td>
<td>1.6x10^{-3}</td>
<td>0.96x10^{-3}</td>
</tr>
</tbody>
</table>
be increased. It was found that the yield of the corresponding \( \beta \)-D-glucosaminide (IIId) went down and that of compound (III) was increased five fold (Table III). The low yield of tertiary butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-\( \beta \)-D-glucosaminidide (IIId) can be attributed to the steric effect of the bulky methyl groups in the \( \text{SN}_2 \) reaction.

The yields of compound (III) obtained in the case of cyclohexanol and isopropanol respectively were different (1:2), although both alcohols are secondary (Table III). The reason may be found in the lesser steric hindrance in the case of alicyclic alcohol.

Only 3,4,6-tri-O-benzoyl-D-glucopyranosido-\([1,2:4',5']\)-2'-oxazolidone (III) and benzyl bromide were obtained when \( \alpha \)-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine was heated under reflux in chloroform in the presence of mercuric cyanide. It appears that two reactions, \( \text{SN}_2 \) and \( \text{SN}_1 \) (where \( \text{SN}_1 \) represents the substitution of bromide by benzyloxycarbonyl intramolecularly), compete with each other in the presence of mercuric cyanide and alcohols and that the former predominates over the latter.

As the steric hindrance is increased in the case of isopropanol and tertiary butanol, the yield of the corresponding -D-glucosaminides decreased and that of the 3,4,6-tri-O-benzoyl-D-glucopyranosido-\([1,2:4',5']\)-2'-oxazolidone (III) increased. When a graph was plotted of
the total steric energy of activation $\Delta E^+$ against the yield of the 3,4,6-tri-O-benzyl-D-glucopyranosido-[$1,2:4',5']-2'-oxazolidone (III) obtained in the case of the various alcohols (Figure 1), a straight line was obtained (52). This tends to confirm the hypothesis that the steric effect is responsible for the decrease in the yield of $\beta$-D-glucosides when isopropanol and tertiary butanol were used. Because the two reactions, $SN_2$ and $SN_1$, compete with each other, the increase in the yield of the 3,4,6-tri-O-benzyl-D-glucopyranosido-[$1,2:4',5']-2'-oxazolidone (III) is evidently a measure of the increasing steric interference accompanying attack by the bulkier alcohols.

De la Mare and co-workers (9) have studied extensively the substitution reactions of alkyl halides by halogen in acetone. For example:

$$Br^- + R-X \rightarrow R-Br + X^-,$$

where $R = n$-propyl, isopropyl, $t$-butyl and neopentyl. They found that the rate of reaction decreases in the case of isopropyl halide, $t$-butyl halide and neopentyl halide as the number of substituents increases on the $\alpha$ or $\beta$-carbon atom. It was also observed that the rate of the reaction decreases if the size of the substituents on the attacking reagent increases. In $\beta$-substituted compounds, besides the steric effect, the inductive effect also plays an important role in the transition state (15). The inductive effect may hinder
RELATION BETWEEN THE YIELD OF COMPOUND (III) AND THE TOTAL STERIC ENERGY OF ACTIVATION $\Delta \Delta E_s$^+.

<table>
<thead>
<tr>
<th>Substituent R</th>
<th>Total Steric Energy of Activation at 30°C, in K. Cal.</th>
<th>Yield of Compound (III) in grams</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-C$_3$H$_7$</td>
<td>2.2</td>
<td>0.10</td>
</tr>
<tr>
<td>n-C$_4$H$_9$</td>
<td>2.2</td>
<td>0.10</td>
</tr>
<tr>
<td>C$_6$H$_5$CH$_2$</td>
<td>2.2</td>
<td>0.10</td>
</tr>
<tr>
<td>t-C$_3$H$_7$</td>
<td>2.4</td>
<td>0.15</td>
</tr>
<tr>
<td>t-C$_4$H$_9$</td>
<td>3.8</td>
<td>0.50</td>
</tr>
</tbody>
</table>

FIGURE 1

RELATION BETWEEN THE YIELD OF COMPOUND (III) AND THE TOTAL STERIC ENERGY OF ACTIVATION $\Delta \Delta E_s$^+.
or increase the rate of the reaction depending on whether the substituent is an electron donor or an electron withdrawer. The steric effect is called the ponderal effect (15). This effect results in the decrease in entropy of activation because of certain restrictions imposed on the degree of freedom for rotation about the $C_{\alpha}-C_{\beta}$ bond. There are more of these restrictions in the case of isopropanol and tertiary butanol than in the case of n-propanol and the other primary alcohols.

It is very difficult to determine the entropy of activation (47) in substitution reactions, especially where even more complex aminosugar molecules are involved.

In the case of isopropanol and tertiary butanol the increase in negative entropy of activation decreases the rate of glycosidation. This accounts for the low yield of $\alpha$-D-glucosaminide obtained in the case of tertiary butanol. This decrease in the rate of glycosidation improves the competitive position of the intramolecular reaction and helps to increase the yield of $3,4,6$-tri-0-benzoyl-$D$-glucopyranosido-$[1,2:4',5']-2'$-oxazolidone (33).

S. Konstas, I. Photaki, and L. Zervas (32) obtained $3,4,6$-tri-0-acetyl-$D$-glucopyranosido-$[1,2:4',5']-2'$-oxazolidone by treating $1,3,4,6$-tetra-0-acetyl-$N$-carbobenzoxy-$\beta$-D-glucosamine (46) with aluminum chloride and phosphorus pentachloride in chloroform. They suggested that, in the
formation of the oxazolidone, the reaction goes through the intermediate compound, α-chloro-3,4,6-tri-O-acetyl-N-carbobenzoxy-D-glucosamine, followed by backside attack by carbonyl oxygen at C₂. Recently T. Ito prepared the above oxazolidone by heating 1,3,4,6-tetra-O-acetyl-N-carbobenzoxy-β-D-glucosamine with trifluoroacetic acid and proposed a similar SN₁ mechanism (26). A similar observation was made in the synthesis of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III).

The study of the chemistry of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) was undertaken in terms of the following attempted processes:

I. Formation of the carbonyl derivatives with 2,4 dinitrophenyl hydrazine in acetic acid.

II. Reduction by
   A. catalytic hydrogenation
   B. sodium borohydride.

III. Formation of N-acetyl and N-benzoyl derivatives.

IV. Reaction with
   A. glacial acetic acid-hydrobromic acid
   B. 75 per cent acetic acid.

V. Saponification with
   A. aqueous mineral acid
   B. bases.

No reaction product was obtained when the compound (III) was heated with 2,4 dinitrophenyl hydrazine in acetic acid. Sodium borohydride was first used to reduce aldehyde and ketone by Chaikin and W. G. Brown (3). W. R. C. Crimmin (5) used sodium borohydride to reduce 2-acetamido-2-deoxy-D-galactitol.
The compound (III), when treated with sodium borohydride in tetrahydrofuran, gave no reaction product (1,57). However, when reduction was carried out in tetrahydrofuran and ethanol mixture, D-glucosamine and ethyl benzoate were obtained. No reaction product was obtained when the compound (III) was subjected to catalytic hydrogenation in acetic anhydride and acetic acid solution in the presence of palladium black as catalyst. The unreactivity of the carbonyl group is attributed to the fact that it is part of the cyclic urethane system. It has been reported that 2-oxazolidone exists in tautomeric form as observed by infrared spectral study (10).

Benzyl-4,6-di-O-acetyl-α-D-glucopyranosido-[2,3:4',5']-2'-oxazolidone, when heated with potassium acetate, acetic anhydride, and acetic acid, gave the N-acetyl derivative (18). The compound (III) under similar conditions also gave the N-acetyl derivative. Furthermore, the compound (III), when treated with benzoyl chloride in pyridine, gave the N-benzoyl derivative (See Chart 4).

The compound (III) was found to be stable when it was heated first with 2N aqueous hydrochloric acid and then with 6N hydrochloric acid solution. The stability may be attributable to the fact that the compound (III) is insoluble in hydrochloric acid solution.
PROPERTIES OF 3,4,6-TRI-O-BENZOYL-D-GLUCOPYRANOSIDO-[1,2:4',5']-2'-OXAZOLIDONE
Benzyl-4,6-di-O-acetyl-\(\alpha\)-D-glucopyranoside-[2,3:4',5']-2'-oxazolidone, when heated with 75 per cent acetic acid solution, was found stable (17). The compound (III), when treated with 75 per cent acetic acid under similar conditions, also was found stable.

\(\alpha\)-Bromo-3,4,6-tri-O-benzoyl-D-glucosamine hydrobromide (55) was obtained when the compound (III) was treated with glacial acetic acid-hydrobromic acid solution.

In general ester hydrolysis is acid-base catalyzed. The bases were found to be more powerful catalysts than the acids (13,42). O-Acetate groups were removed by strong acids and by bases (34). Unfavorable steric effects frequently hinder the latter reaction. O-Acetate groups may be removed preferentially without affecting the N-acetyl function (39,51). Deacetylation with methanolic sodium or barium methoxide in catalytic amounts depends upon transesterification (60). O-Acetate groups can also be removed by methanolic ammonia solution (11).

**Alkaline hydrolysis.** The compound (III) was dissolved in chloroform methanol mixture. It was treated with a catalytic amount of 0.1 N sodium methoxide solution (57). No reaction product was obtained. However the compound (III) (3.34 x 10^{-3} moles), when treated with sodium methoxide solution (3.8 x 10^{-3} moles) in a solution of chloroform and methanol, gave D-glucosamine as a reaction product (Chart 4).
A similar observation was made when saponification was
effected with aqueous potassium hydroxide in dioxane follow-
ing the method of P. Gross, K. Brendel, and H. K. Zimmerman.
(16). The compound (III), when heated with a basic ion
exchanger in methanol, gave no reaction product. The com-
 pound (III) when treated with methanolic ammonia solution
(11,61), gave a product which was found to be very hygro-
scop ic.

3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-
oxazolidone (III), unlike benzyl-4,6-di-O-acetyl-D-
glucopyranosido-[2,3:4',5']-2'-oxazolidone (17), is unstable
towards bases and hydrobromic acid in organic solvents. 
Therefore it cannot be used as the protecting group for C_1
and C_2 in the preparation of new derivatives of aminosugars.
CHAPTER III

D-GLUCOSAMINIDE SYNTHESSES

Various methods of de-O-acetylation have been discussed in Chapter II. Only two methods were selected for the purpose of de-O-benzoylation for the preparation of -D-glucosaminides obtained from n-propanol, n-butanol, and cyclohexanol, respectively.

**Method 1:** Sodium methoxide in methanol (51,57).

n-Butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-β-D-glucosaminide (IIc), when treated with a catalytic amount of 0.1 N sodium methoxide, gave no reaction product. However, when the reaction was carried out with 2 moles of sodium methoxide per mole of the compound (IIc) in solution in chloroform and methanol for twenty-four hours at room temperature, n-butyl-N-carbobenzoxy-β-D-glucosaminide (VIIc) was obtained in 70 per cent yield.

**Method 2:** Aqueous potassium hydroxide in dioxane.

P. Gross, K. Brendel, and H. K. Zimmerman (16) effected de-O-acetylation of β-D-glucosaminide with aqueous potassium hydroxide solution in dioxane. The reaction was complete in four hours and the yield of the product was found to be quantitative. When the reaction was applied to de-O-benzoylate the compound (IIa), the yield of the product...
(VIIIa) was low and unreacted substance was recovered from the homogenous solution; when the reaction was carried out for three hours, the yield of the product (VIIIa) was 71.5 per cent.

The compound (VIIIa), a partially de-O-benzoylated product, was found to be lacking in two benzoyl groups. Since the 6-O-benzoyl function is more reactive than either the 3-O-benzoyl or the 4-O-benzoyl function, it is the first to be de-O-benzoylated. Therefore, the compound (VIIIa), is propyl-N-carbobenzoxy-3 or 4-O-benzoyl-β-D-glucosaminide. In order to ascertain whether the position of the free hydroxy group is at the C₃ or the C₄, the compound (VIIIa) was reacted with benzaldehyde in the presence of anhydrous zinc chloride (28). The product thus obtained was found to be n-propyl-N-carbobenzoxy-3-O-benzoyl-4,6-O-benzylidene-β-D-glucosaminide (XXIV) by optical rotation and by reaction with hydrochloric acid whereupon benzaldehyde was obtained. This indicated that the free hydroxyl group is at the C₄ (See Chart 5).

Method (2) was chosen because of the higher yield, although method (1) would have been easier to work with.

β-D-Glucosaminides (IIc) and (IIIf), thus obtained using n-butanol and cyclohexanol, were subjected to saponification with aqueous potassium hydroxide in dioxane for twenty-four hours at room temperature. The completely de-O-benzoylated
VIII<sub>c</sub>: R = n-C<sub>4</sub>H<sub>9</sub>
VIII<sub>f</sub>: R = cyclo.C<sub>6</sub>H<sub>11</sub>

<chem>Pd. Black 1 M HCl in C<sub>2</sub>H<sub>5</sub>OH</chem>

IX<sub>c</sub>: R = n-C<sub>4</sub>H<sub>9</sub>
IX<sub>f</sub>: R = cyclo.C<sub>6</sub>H<sub>11</sub>

CHART 5

DE-O-BENZOYLATION OF THE COMPOUNDS (IIa), (IIc) AND (IIi)

*Compounds are known.
**Compound is known.**
compound (VIIc) and (VIIIf) show similar solubility properties (Chart 5). Infrared spectra show bands at 3500 (hydroxyl); 745, 700 (phenyl).

De-O-benzoylated compound (VIIa), (VIIc), and (VIIIc) were subjected to hydrogenation using palladium black as catalyst in 1 N hydrochloric acid solution in absolute ethanol (22,33). Compounds (IXa), (IXc), and (IXf) thus obtained show similar solubility properties (Chart 5). Infrared spectra show bands at 1600 (amine-hydrochloride) and 3500 (hydroxyl).

α-Benzyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-D-glucosaminide was synthesized in order to study its chemical and physical properties and compare them to those of its β-anomer. P. Gross, K. Brendel, and H. K. Zimmerman (17) obtained pure benzyl-N-carbobenzoxy-α-D-glucosaminide by first acetylating an anomeric mixture of benzyl-N-carbobenzoxy-D-glucosaminide with acetic anhydride and pyridine. Benzyl-N-carbobenzoxy-3,4,6-tri-O-acetyl-α-D-glucosaminide (pure anomer) was separated by fractional recrystallization using a toluene, petroleum ether, and pyridine mixture. This pure benzyl-N-carbobenzoxy-3,4,6-tri-O-acetyl-α-D-glucosaminide (XVIII), when subjected to de-O-acetylation with aqueous potassium hydroxide in dioxane followed by benzoylation with benzoyl chloride in pyridine
(44), gave pure benzyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-α-D-glucosaminide (XX) (See Chart 6).

The physical properties of the α- and the β-anomers of the D-glucosaminides are quite different. The α-anomer has a low melting point, high optical rotation, and high solubility in organic solvents, while the β-anomer has a high melting point, low optical rotation, and low solubility in organic solvents.

Benzyl-3,4,6-tri-O-benzoyl-N-carboethoxy-β-D-glucosaminide (XIII) was synthesized by reacting benzyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (X) (6,7) with ethyl chloroformate in chloroform and aqueous sodium bicarbonate solution. On subsequent de-O-acetylation by potassium hydroxide in dioxane, benzyl-N-carboethoxy-β-D-glucosaminide (XII) was obtained. The compound (XII), when reacted with benzoyl chloride in pyridine, gave benzyl-3,4,6-tri-O-benzoyl-N-carboethoxy-β-D-glucosaminide (XIII) (See Chart 7).

Isopropyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (XVI) was prepared with isopropanol in the presence of pyridine as base. Isopropyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (XVI), when treated with ethyl chloroformate in chloroform and aqueous sodium bicarbonate solution at 0°C., gave isopropyl-N-carboethoxy-3,4,6-tri-O-acetyl-β-D-glucosaminide (XVII) (See Chart 8).
AC = CH₃CO-

R = C₆H₅CH₂-

Cbz = C₆H₅CH₂OCo-

**CHART 6**

BENZYL-3,4,6-TRI-O-BENZOYL-N-CARBOBENZOXY-α-D-GLUCOSAMINIDE

*Compounds are known.*
**SYNTHESIS OF BENZYL-3,4,6-TRI-O-BENZOYL-\(N\)-CARBOETHOXY-\(\beta\)-D-GLUCOSAMINIDE**

*Compound is known.*
CHC$_1$ + NaHCO$_3$ →

\[
\text{v} + \text{Cl-CO-OC}_2\text{H}_5
\]

\[
\text{CH}_2\text{OAC}
\]

\[\text{RO} + \text{H} \]

AC = CH$_3$CO-

R = \[\text{CH}_3\text{CH-CH}_3\]

\[\text{XV}^*\]

\[\text{C}_5\text{H}_4\text{N}: \text{ROH}\]

\[\text{CHCl}_3 + \text{NaHCO}_3 \text{ soln.} \]

\[+ \text{Cl-CO-OC}_2\text{H}_5\]

Cbe = -CO-OC$_2$H$_5$

\[\text{XVI}\]

\[\text{CH}_2\text{OAC}\]

\[\text{XVII}\]

**CHART 8**

**ISOPROPYL-3,4,6-TRI-O-ACETYL-N-CARBOETHOXY-\(\beta\)-D-GLUCOSAMIDE**

*Compound is known.*
α-Bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) (56), when treated with tertiary butyl alcohol in chloroform using mercuric cyanide, gave tertiary butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-β-D-glucosaminide (IId) and 3,4,6-tri-O-benzoyl-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) as a byproduct (Chart 3).

n-Propyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-β-D-glucosaminide (IIa) was obtained in low yield when α-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) was heated with n-propanol in chloroform using pyridine as base. No 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) was obtained as a byproduct (Chart 3). It was observed that n-propyl-3,4,6-tri-O-benzoyl-β-D-glucosaminide hydrobromide (55) was obtained in good yield when α-bromo-3,4,6-tri-O-benzoyl-D-glucosamine hydrobromide (VI) was reacted with n-propanol in the presence of pyridine as base. The better yield in the latter case is probably due to a difference in the reaction mechanisms. In glycosidation, pyridine was found to be impractical as proton acceptor because the yield of the β-D-glucosaminide was low.
CHAPTER IV

EXPERIMENTAL DETAILS

Analyses are by Microanalytisches Laboratorium im Max-Planck-Institut, Hohenweg 17, Germany. Melting points are uncorrected. Infrared spectra are recorded using Perkin-Elmer IR 137B, Infracord, U.S.A. Optical rotations are recorded using Polarimeter by Kern ARAU, Sursee, Switzerland.

\( \text{n-Propyl-3,4,6-tri-O-benzoyl-N-carbobenzyoxyl-}\beta-\text{D-glucosaminide (}\text{IIa}\text{). Three grams (4.4 x 10}^{-3}\text{ mole) of } \alpha\text{-bromo-3,4,6-tri-O-benzoyl-N-carbobenzyoxyl-D-glucosamine (I) (56) were dissolved in dry chloroform (30 ml.). The mixture was then heated under reflux in the presence of n-propanol 1 ml. (17.6 x 10}^{-3}\text{ mole) and mercuric cyanide 1.1 g. (4.4 x 10}^{-3}\text{ mole) for two hours. The solution was to room temperature and filtered to remove mercuric salts. The filtrate, on removal of chloroform, gave a residue which was recrystallized from alcohol after treatment with charcoal, m. p. 142-43\textdegree; yield 2.3 g. 3.4 x 10}^{-3}\text{ mole (79 percent). The mother liquor was concentrated to small volume and cooled to 0\textdegree\text{C.}, whereupon a substance melting at 204-05\textdegree\text{ was obtained. It was identified as 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) by mixed} \)
melting point with authentic sample and by optical rotation. Yield 0.1 g (0.1 g x 10^{-3} mole) (4.4 per cent). The mother liquor, on removal of alcohol, gave benzyl bromide.

**Properties:** (IIa) is soluble in dioxane and acetic acid, but insoluble in petroleum ether and cyclohexane.

**Analysis:**

\[
\begin{array}{ccc}
\text{C}_{38}\text{H}_{37}\text{NO}_{10} & \% \text{C} & \% \text{H} & \% \text{N} \\
\text{Found} & 68.53 & 5.71 & 2.20 \\
\text{Calculated} & 68.50 & 5.60 & 2.10 \\
\end{array}
\]

**Rotation:**

\[
\left[\alpha\right]_{D}^{25} = -4.5^\circ \text{ (C = 2% in CHCl}_3\text{)}
\]

3,4,6-tri-O-benzoyl-D-glucopyranoside-[1,2:4',5']-2'-oxazolidone (III). Three grams (4.4 x 10^{-3} mole) of \(\alpha\)-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) (56) were heated under reflux in dry chloroform (30 ml.) in the presence of mercuric cyanide 0.3 g. (1.3 x 10^{-3} mole) for two hours. The solution was cooled to room temperature and filtered to remove mercuric salts. The residue obtained on removal of chloroform was recrystallized from alcohol after treatment with charcoal, M. P. 204-05\textdeg; yield 1.8 g. (3.48 x 10^{-3} mole) (80 per cent). The mother liquor, on removal of alcohol, gave lacrumentory liquid benzyl bromide.
Properties: (III) is soluble in dioxane and acetic acid, but insoluble in petroleum ether and cyclohexane.

Analysis:

\[ \text{C}_{28} \text{H}_{23} \text{NO}_9 \] (517.2)

<table>
<thead>
<tr>
<th></th>
<th>Found</th>
<th>% C</th>
<th>% H</th>
<th>% N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>64.70</td>
<td>4.63</td>
<td>2.92</td>
</tr>
<tr>
<td></td>
<td>Calculated</td>
<td>65.0</td>
<td>4.47</td>
<td>2.70</td>
</tr>
</tbody>
</table>

Rotation:

\[ [\alpha]_{D}^{25} = -39.2 \text{ (1.344\% in pyridine)} \]
\[ [\alpha]_{D}^{25} = +3.25 \text{ (2\% in chloroform)} \]

3,4,6-tri-O-benzoyl-D-glucopyranosido-\[1,2:4',5']-N-acetyl-2'-oxazolidone (V). Two grams (3.34 x 10^{-3} mole) of 3,4,6-tri-O-benzoyl-D-glucopyranosido-\[1,2:4',5']-2' oxazolidone (III) were heated with potassium acetate 1.5 g. (1.5 x 10^{-3} mole), acetic acid (5 ml.), and acetic anhydride (5 ml.) for six hours at 100-05°C. The solvent was removed under flash evaporator at 50°C. The residue thus obtained was washed with water and recrystallized from alcohol after treatment with charcoal, M. P. 168-69°C.; yield 1.9 g. (3.4 x 10^{-3} mole) (76 per cent).

Properties: (V) is soluble in chloroform and dioxane, but insoluble in petroleum ether and cyclohexane. The infra-red spectra of (V) show bands at 3350, 1750 (oxazolidone), 1250 (acetate), and 1730, 1280 (1'-O-benzoyl).
Analysis:
\[ C_{30}H_{25}O_{10}^N \] (559.538)

<table>
<thead>
<tr>
<th>Found</th>
<th>% C</th>
<th>% H</th>
<th>% O</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63.76</td>
<td>4.48</td>
<td>29.29</td>
</tr>
</tbody>
</table>

Calculated

\[ C_{35}H_{27}O_{10}^N \] (621.609)

Rotation:
\[ [\alpha]_D^{25} = -70^\circ \text{ (C = 1.266\% in pyridine)} \]

3,4,6-tri-O-benzoyl-D-glucopyranoside-[1,2:4',5']-N-benzoyl-2'-oxazolidone (IV). Two grams \( (3.34 \times 10^{-3} \text{ mole}) \) of 3,4,6-tri-O-benzoyl-D-glucopyranoside-[1,2:4',5']-2'-oxazolidone (III) were dissolved in pyridine (8 ml.) and cooled to 0°C. Benzoyl chloride 0.8 ml. \( (6.7 \times 10^{-3} \text{ mole}) \) was added while stirring at 0°C. The reaction mixture was kept for two hours at room temperature and then poured over crushed ice. The gummy product thus obtained was purified by acetone-water mixture. It was then recrystallized from alcohol after treatment with charcoal, M. P. 160-61°C.; yield 2.1 g. \( (3.4 \times 10^{-3} \text{ mole}) \) (87 per cent).

Properties: (IV) is soluble in chloroform, dioxane, and acetic acid, but insoluble in petroleum ether and cyclohexane. The infrared spectra of (IV) show bands at 3350, 1750 (oxazolidone) and 1730, 1280 (O-benzoyl).

Analysis:
\[ C_{35}H_{27}O_{10}^N \] (621.609)
Treatment of 3,4,6-tri-O-benzoyl-D-glucopyranosido-\([1,2:4',5']\)-2'-oxazolidone (III) with 2,4-dinitro phenyl hydrazine. One gram (1.94 x 10^{-3} mole) of 3,4,6-tri-O-benzoyl-D-glucopyranosido-\([1,2:4',5']\)-2'-oxazolidone (III) was heated with 2,4 dinitrophenyl hydrazine 0.5 g. (2.5 x 10^{-3} mole) in glacial acetic acid in the water bath for one hour. The acetic acid was removed under flash evaporator at 50°C. The residue was washed with water and recrystallized from alcohol after treatment with charcoal, M. P. 203-04°C., and was identified as compound (III) by mixed melting point with authentic substance. Yield 0.8 g.

Attempted catalytic hydrogenolysis of 3,4,6-tri-O-benzyl-D-glucopyranosido-\([1,2:4',5']\)-2'-oxazolidone (III). One gram (1.94 x 10^{-3} mole) of the compound (III) and palladium black (0.2 g.) were suspended in glacial acetic acid (5 ml.) and acetic anhydride (10 ml.). The mixture was then shaken for five hours under two atmospheres of hydrogen pressure at room temperature. The reaction mixture was filtered and the residue was washed with a small amount of acetic acid.
The solvent was removed under flash evaporator at 50°C. The residue was washed with ice cold water (15 ml.) and then recrystallized from alcohol after treatment with charcoal, M. P. 204-05°C., which was identified as the compound (III) by mixed melting point with authentic substance. Yield 0.7 g.

Treatment of 3,4,6-tri-O-benzoyl-D-glucopyranosido-\[1,2:4',5']-2'-oxazolidone (III) with sodium borohydride. One gram (1.94 x 10^{-3} mole) of compound (III) was dissolved in dry tetrahydrofuran (15 ml.) and was stirred in the presence of sodium borohydride 0.12 g. (3.16 x 10^{-3} mole) for three days at room temperature. The reaction mixture was filtered. The filtrate, on removal of tetrahydrofuran, gave a residue. It was recrystallized from alcohol, M. P. 203-04°C., and was identified as the compound (III) by mixed melting point with authentic sample.

The foregoing reaction was carried out in the presence of tetrahydrofuran and ethanol mixture (6:1) for twenty-four hours at room temperature. The mixture was treated with water (20 ml.) and extracted with chloroform. The chloroform layer was separated, dried over anhydrous sodium sulfate, and was evaporated, whereupon ethyl benzoate was obtained (1 ml.). The aqueous layer gave D-glucosamine, M. P. 87°C. It reduced Fehling solution and gave D-glucosamine hydrochloride,
M. P. 195-97°C., when treated with aqueous hydrochloric acid solution.

\[ [\alpha]_D^{25} = 100\rightarrow 73^\circ C. \; (C = 1.5\% \text{ in water}). \]

**Saponification of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III).** Two grams (3.34 x 10^{-3} mole) of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) were dissolved in dioxane (160 ml.), and the solution was cooled to 0°C. Eighty ml. of 0.5N aqueous potassium hydroxide (10 x 10^{-3} mole) were added dropwise while stirring. The homogenous reaction mixture was kept in the refrigerator for twenty hours and then neutralized with acetic acid. The solvent was removed at 50°C. under flash evaporator. The dioxane was removed with acetic acid which was then removed by toluene under flash evaporator. The residue was then washed with ether, dissolved in aqueous hydrochloric acid, and poured into methanol to give a substance melting at 194-96°C. It was identified as D-glucosamine hydrochloride.

**Saponification of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) with methanolic ammonia.** One gram (1.94 x 10^{-3} mole) of compound (III) was dissolved in saturated methanolic ammonia solution (100 ml.) at 0°C. The reaction mixture was kept for twenty hours at 0°C. The solvent was removed under flash evaporator.
at room temperature. The residue was washed with ether to remove methyl benzoate (sweet odor) and the gummy product was recrystallized from alcohol-ether mixture, M. P. 76-78°C., and found to be very hygroscopic. Yield 0.05 g.

The compound is soluble in water but insoluble in petroleum ether, tetrahydrofuran, and cyclohexane.

\[ \alpha^D_{25} = -140^\circ C \] (C = 1.698% in water)

Further work is necessary in order to determine the structure of the compound, M. P. 76-78°C.

**Benzyl-3,4,6-tri-O-acetyl-N-carboxethoxy-\(\beta\)-D-glucosaminide (XI).** Four grams \((8.4 \times 10^{-3} \text{ mole})\) of benzyl-3,4,6-tri-O-acetyl-\(\beta\)-D-glucosaminide hydrobromide (X) \((7)\) were suspended in dry chloroform \((30 \text{ ml.})\). The mixture was shaken with ethyl chloroformate \(1.9 \text{ ml.} \) \((16.8 \times 10^{-3} \text{ mole})\) in the presence of saturated sodium bicarbonate solution \((30 \text{ ml.})\) at 0°C, for one hour. The chloroform layer was separated, dried over anhydrous sodium sulfate, and was removed under flash evaporator at room temperature. The solid thus obtained was washed with n-heptane to remove unreacted ethyl chloroformate and was recrystallized from isopropanol, M. P. 163-64°C.; yield 3.5 g. \((7.5 \times 10^{-3} \text{ mole})\) \((89.5 \text{ per cent})\).

**Properties:** (XI) is soluble in ether, acetic acid, and dioxane, but insoluble in petroleum ether and cyclohexane.
Analysis:

\[
C_{22}H_{29}O_{10}N \quad (467.480)
\]

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<thead>
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<tbody>
<tr>
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<td>6.14</td>
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<tr>
<td>Calculated</td>
<td>56.50</td>
<td>6.25</td>
<td>34.20</td>
</tr>
</tbody>
</table>

Rotation:

\[
\left[\alpha\right]_{D}^{25} = -22.6^\circ C. \quad (C = 1.54\% \text{ in pyridine})
\]

**Benzyl-N-carboxethoxy-\(\beta\)-D-glucosaminide (XII).** Two grams (4.3 x 10\(^{-3}\) mole) of benzyl-N-carboethoxy-3,4,6-tri-O-acetyl-\(\beta\)-D-glucosaminide (XI) were dissolved in dioxane (70 ml.), and 35 ml. of 0.5N aqueous potassium hydroxide (13.0 x 10\(^{-3}\) mole) were added dropwise while stirring at room temperature. The reaction mixture was stirred for two hours more at room temperature. The solution was neutralized with acetic acid and the solvent was removed under flash evaporator at 50\(^\circ\)C. The solid thus obtained was washed with water and recrystallized from alcohol, M. P. 195-96\(^\circ\)C.; yield 1.1 g. (3.2 x 10\(^{-3}\) mole) (78.5 per cent).

Properties: (XII) is soluble in acetic acid and methanol, but insoluble in petroleum ether and cyclohexane.

Analysis:

\[
C_{16}H_{23}O_{7}N \quad (341.362)
\]

<table>
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<tr>
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<td>6.72</td>
<td>32.07</td>
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<tr>
<td>Calculated</td>
<td>55.50</td>
<td>6.80</td>
<td>32.52</td>
</tr>
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</table>
Rotation:
$[\alpha]_{D}^{25} = -47^\circ C$. (C = 1.38% in pyridine)

**Benzyl-3,4,6-tri-O-benzoyl-N-carboethoxy-\(\beta\)-D-glucosaminide (XIII).** Two grams (5.8 x 10^{-3} mole) of benzyl-N-carboethoxy-\(\beta\)-D-glucosaminide (XII) were dissolved in pyridine (10 ml.), and the solution was cooled to 0°C. Benzoyl chloride 1.6 ml. (23.2 x 10^{-3} mole) was added drop-wise while stirring at 0°C. The reaction was kept in the refrigerator overnight and then poured over crushed ice. The gummy product thus obtained was purified by acetone-water mixture. The yellowish-white product was recrystallized from alcohol after treatment with charcoal, M. P. 164-65°C.; yield 3.1 g. (4.3 x 10^{-3} mole) (81.5 per cent).

Properties: (XIII) is soluble in chloroform, dioxane, and ether, but insoluble in cyclohexane and petroleum ether.

**Analysis:**

\[
\begin{array}{cccc}
\text{C}_{37} \text{H}_{35} \text{O}_{10} \text{N} & (653,695) \\
\% C & \% H & \% O \\
\text{Found} & 69.49 & 5.17 & 25.14 \\
\text{Calculated} & 69.90 & 5.20 & 25.40
\end{array}
\]

Rotation:
$[\alpha]_{D}^{25} = -29.2^\circ C$. (C = 1.2% in pyridine)

**Tertiary butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-\(\beta\)-D-glucosaminide (IIa).** Three grams (4.4 x 10^{-3} mole) of
\(\alpha\)-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) (55) were dissolved in dry chloroform (25 ml.). The mixture was then refluxed with tertiary butanol 1.4 ml. (17.6 x 10^{-3} mole) in the presence of mercuric cyanide (1.1 g.) for two hours. The color of the reaction mixture turned from yellow to red. It was then cooled to room temperature and filtered to remove mercuric salts. The filtrate, on removal of chloroform, gave a solid, which was recrystallized from alcohol after treatment with charcoal, M. P. 165-66°C.; yield 1.1 g. (1.6 x 10^{-3} mole) (37.3 per cent). The mother liquor, on concentration, gave the compound melting at 203-04°C., which was identified as 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidane (III) by mixed melting point with authentic sample. Yield 0.5 g. (0.96 x 10^{-3} mole) (16.7 per cent).

Properties: (IIId) is soluble in dioxane, acetic acid, and chloroform, but insoluble in petroleum ether and cyclohexane.

Analysis: \(C_{39}H_{39}O_{10}N\) (681.749)

<table>
<thead>
<tr>
<th></th>
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<th>% H</th>
<th>% O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Found</td>
<td>69.91</td>
<td>5.75</td>
<td>24.61</td>
</tr>
<tr>
<td>Calculated</td>
<td>69.50</td>
<td>5.75</td>
<td>24.10</td>
</tr>
</tbody>
</table>

Rotation:

\([\alpha]_D^{25} = +15.7^\circ C\). (C = 1.43% in pyridine)
n-Propyl-N-carbobenzoxy-3-O-benzoyl-β-D-glucosaminide (VIIIa). Ten grams (1.5 x 10\(^{-3}\) mole) of n-propyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-β-D-glucosaminide (IIa) were dissolved in dioxane (180 ml.). Ninety ml. of 0.5N aqueous potassium hydroxide (5.0 x 10\(^{-3}\) mole) was added drop-wise while stirring during the course of one hour at room temperature. The homogenous solution was stirred for an additional one and one-half hours at room temperature and then was neutralized with acetic acid. The solvent was removed under flash evaporator at 12 mm. pressure at 50°C. Dioxane was removed by acetic acid under flash evaporator and the residue was recrystallized from alcohol after treatment with charcoal, M. P. 184-85°C. The yield of the compound (VIIIa) was 2.1 g. (0.45 x 10\(^{-3}\) mole) (45 per cent). The mother liquor, on concentration, was cooled and kept in the refrigerator, whereupon a substance melting at 142-43°C. was obtained. Yield 4.4 g. (0.65 x 10\(^{-3}\) mole). It was identified as unreacted compound (IIa) by mixed melting point with authentic sample and by optical rotation.

Properties: (VIIIa) is soluble in acetic acid and methanol, but insoluble in ether, petroleum ether, and cyclohexane.
n-Propyl-3-O-benzoyl-\(\beta\)-D-glucosaminide hydrochloride (IXa). Three grams (0.65 \(\times\) 10\(^{-3}\) mole) of n-propyl-N-carbobenzoxy-3-O-benzoyl-\(\beta\)-D-glucosaminide (Vllla) and palladium black (0.4 g.) were suspended in ethanolic 1N hydrochloric acid solution (35 ml.). The mixture was then hydrogenated under two atmospheres pressure for four hours at room temperature. The reaction mixture was filtered and the residue was washed with alcohol. The filtrate was concentrated to small volume and ether added, whereupon a white substance separated out. It was then recrystallized from alcohol-ether mixture, M. P. 165-66\(^{\circ}\)C. (decomposed). Yield 1.8 g. (0.5 \(\times\) 10\(^{-3}\) mole) (76.5 per cent).

Properties: (IXa) is soluble in water and methanol, but insoluble in petroleum ether and chloroform. The compound (IXa) shows the presence of chloride.
Rotation:
\[ \alpha_{D}^{25} = -21.0^\circ \text{C.} \] (C = 0.96% in water)

**n-Butyl-N-carbobenzoxy-\(\beta\)-D-glucosaminide (VIIc);**

Ten grams (1.47 x 10\(^{-3}\) mole) of \(n\)-butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-\(\beta\)-D-glucosaminide (IIc) were dissolved in dioxane (180 ml.). Ninety milliliters of 0.5N aqueous potassium hydroxide (4.5 x 10\(^{-3}\) mole) were added dropwise while stirring at room temperature. The homogenous solution was kept for twenty-four hours at room temperature and then neutralized with acetic acid. The solvent was removed under flash evaporator at 12 mm. pressure at 50\(^\circ\)C. The residue thus obtained was washed with water and recrystallized from alcohol-ether mixture, M. P. 175-76\(^\circ\)C.; yield 4.4 g. (1.2 x 10\(^{-3}\) mole) (81.5 per cent).

**Properties:** (VIIc) is soluble in acetic acid and methanol, but insoluble in ether, petroleum ether, cyclohexane, and chloroform.

**Analysis:** \(C_{18}H_{27}O_{2}N\) (369.422)

<table>
<thead>
<tr>
<th></th>
<th>% C</th>
<th>% H</th>
<th>% O</th>
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<tbody>
<tr>
<td>Found</td>
<td>59.14</td>
<td>7.35</td>
<td>33.56</td>
</tr>
<tr>
<td>Calculated</td>
<td>58.70</td>
<td>7.50</td>
<td>33.00</td>
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Rotation:
\[ \alpha_{D}^{25} = -35^\circ \text{C.} \] (C = 1.43% in pyridine)
n-Butyl-β-D-glucosaminide hydrochloride (IXc). Three grams (8.1 x 10⁻³ mole) of n-butyl-N-carbobenzoxy-β-D-glucosaminide (VIIIc) and palladium black (0.4 g.) were suspended in ethanolic 1N hydrochloric acid solution (35 ml.). The mixture was then hydrogenated under two atmospheres of pressure for four hours at room temperature. The reaction mixture was filtered and the palladium black was washed with ethanol (15 ml.). The filtrate was concentrated to small volume and ether was added, whereupon a white precipitate separated out. It was then recrystallized from alcohol-ether mixture, M. P. 137-38°C. (decomposed); yield 1.7 g. (6.3 x 10⁻³ mole) (77.5 per cent).

Properties: (IXc) is soluble in water and methanol, but insoluble in petroleum ether, cyclohexane, and chloroform.

Analysis: \( C_{10}H_{22}O_{5}NCL \) (271.665)

<table>
<thead>
<tr>
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<th>% C</th>
<th>% H</th>
<th>% O</th>
<th>% Cl</th>
</tr>
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<tbody>
<tr>
<td>Found</td>
<td>41.73</td>
<td>8.24</td>
<td>31.97</td>
<td>13.11</td>
</tr>
<tr>
<td>Calculated</td>
<td>41.40</td>
<td>8.20</td>
<td>31.60</td>
<td>13.10</td>
</tr>
</tbody>
</table>

Rotation:

\[ [\alpha]_{D}^{25} = -21.4^\circ C. \quad (C = 1.4\% \text{ in water}) \]

Cyclohexyl-N-carbobenzoxy-β-D-glucosaminide (VIIIc). Ten grams (1.3 x 10⁻³ mole) of cyclohexyl-N-barbobenzoxy-3,4,6-tri-O-benzoyl-D-glucosaminide (IIc) were dissolved in dioxane (180 ml.). Ninety ml. of 0.5N aqueous potassium...
hydride \((4.0 \times 10^{-3} \text{ mole})\) was added dropwise while stirring at room temperature. After addition, the homogenous solution was stirred for two hours and then kept for twenty-four hours at room temperature. The solution was neutralized with acetic acid. The solvent was removed under flash evaporator at 12 mm. pressure at 50°C. The residue was washed with water and recrystallized from alcohol-ether mixture, M. P. 166-67°C.; yield 4.4 g. \((1.1 \times 10^{-3} \text{ mole})\) (80 per cent).

**Properties**: (VIIIf) is soluble in acetic acid and methanol, but insoluble in petroleum ether, cyclohexane, and chloroform.

**Analysis**: \[ C_{20}H_{29}O_{7}N \] (395.460)

\[
\begin{array}{ccc}
\text{Found} & \% \text{C} & \% \text{N} & \% \text{O} \\
61.42 & 7.57 & 27.52 \\
\text{Calculated} & 61.00 & 7.40 & 27.30
\end{array}
\]

**Rotation**:

\[ [\alpha]_{D}^{25} = -45.6^{\circ} \text{C.} \ (C = 1.374\% \text{ in pyridine}) \]

**Cyclohexyl-β-D-glucosamine hydrochloride** (IXf). Three grams \((7.6 \times 10^{-3} \text{ mole})\) of cyclohexyl-N-carbobenzoxy-β-D-glucosaminide (VIIIf) and palladium black \((0.4 \text{ g.})\) were suspended in ethanolic 1N hydrochloric acid solution \((35 \text{ ml.})\). The mixture was then hydrogenated under two atmospheres pressure for four hours at room temperature. The reaction mixture was then filtered, and the residue was washed with ethanol.
The filtrate was concentrated to small volume, and ether was added, whereupon a white substance precipitated out. It was recrystallized from alcohol-ether mixture, M. P. 174-75°C.; yield 1.6 g. (5.4 x 10^{-3} mole) (78 per cent).

**Properties:** (IXf) is soluble in water and methanol, but insoluble in petroleum ether, cyclohexane, and chloroform.

**Analysis:** \( \text{C}_{12} \text{H}_{24} \text{O}_{5} \text{NCl} \) (297.665)

<table>
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<th></th>
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<th>% O</th>
<th>% Cl</th>
</tr>
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<tr>
<td><strong>Found</strong></td>
<td>43.70</td>
<td>7.65</td>
<td>27.59</td>
<td>15.06</td>
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<tr>
<td><strong>Calculated</strong></td>
<td>43.5</td>
<td>7.15</td>
<td>27.00</td>
<td>14.80</td>
</tr>
</tbody>
</table>

**Rotation:**

\[ [\alpha]_D^{25} = -25.9^\circ \text{C.} \] (C = 1.354% in water)

**Isopropyl-3,4,6-tri-O-acetyl-β-D-glucosamine hydrobromide (XVI).** Four grams (8.4 x 10^{-3} mole) of α-bromo-3,4,6-tri-O-acetyl-D-glucosamine hydrobromide (XV) (55) were dissolved in isopropanol (20 ml.) and tetrahydrofuran (20 ml.). Pyridine 1.5 ml. (8.4 x 10^{-3} mole) was added dropwise while stirring. The reaction mixture was stirred for two hours and kept aside for ten hours at room temperature. The solution was concentrated to small volume on the flash evaporator at room temperature. Ether was added, whereupon a yellowish product separated out. It was recrystallized from isopropanol after treatment with charcoal, M. P. 210-11°C. (decomposed). Yield 3.5 g. (8.2 x 10^{-3} mole) (76 per cent).
Properties: (XVI) is soluble in methanol, water, and acetic acid, but insoluble in isopropyl ether, petroleum ether, and chloroform.

Analysis: \[ C_{15}H_{26}O_{8}NBr \] (428.124)

\begin{align*}
\text{Found} & \quad \% C \quad \% H \quad \% O \quad \% Br \\
40.71 & \quad 5.99 & \quad 28.83 & \quad 20.86 \\
\text{Calculated} & \quad 40.80 & \quad 6.15 & \quad 28.70 & \quad 20.60
\end{align*}

Rotation:
\[
[\alpha]_D^{25} = + 5.05^\circ C. \quad (C = 1.98\% \text{ in methanol})
\]

Isopropyl-N-carboxethoxy-3,4,6-tri-O-acetyl-ß-D-glucosaminide (XVII). Two grams (4.7 \times 10^{-3} \text{ mole}) of isopropyl-3,4,6-tri-O-acetyl-ß-D-glucosamine hydrobromide (XVI) were suspended in chloroform (25 ml.) and ethyl chloroformate 0.8 ml. (9.4 \times 10^{-3} \text{ mole}) was added to it. The mixture was then shaken with saturated sodium bicarbonate solution (25 ml.) at 0°C. for one hour. The chloroform layer was separated, dried over anhydrous sodium sulfate, and the solvent was removed under flash evaporator at room temperature. The residue was washed with n-heptane to remove unreacted ethyl chloroformate. It was then recrystallized from isopropanol, M. P. 141-42°C.; yield 1.4 g. (3.35 \times 10^{-3} \text{ mole}) (71.5 per cent).

Properties: (XVII) is soluble in ether, acetic acid, and dioxane, but insoluble in petroleum ether and cyclohexane.
Analysis: $C_{18}H_{29}O_{10}N$ (419.438)

<table>
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<td>Calculated</td>
<td>51.60</td>
<td>7.00</td>
<td>37.20</td>
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Rotation:
$\left[\alpha\right]_{D}^{25} = -10.8^\circ\text{C. (C = 1.39\% in pyridine)}$

1,3,4,6-tetra-O-acetyl-$N$-carbobenzoxy-$\alpha$-$\beta$-D-glucosamine (XXIV) (46). Ten grams ($3.2 \times 10^{-3}$ mole) of dry $N$-carbobenzoxy-D-glucosamine (4) were dissolved in 2M hydrochloric acid in acetic anhydride (20 ml.) and glacial acetic acid (10 ml.) slowly in small portions while stirring in a warm water bath at 50°C. The reaction mixture was stirred for two hours more at 50°C. The solution was concentrated to small volume under flash evaporator at 12 mm. pressure at 50°C. It was cooled to room temperature and excess isopropyl ether was added, whereupon a white crystalline substance separated out. It was recrystallized from chloroform-isopropyl ether mixture, M. P. 150-51°C.; yield 7.0 g. ($1.45 \times 10^{-3}$ mole) (29.3 per cent).

Properties: (XXIV) is soluble in water and ether, but insoluble in cyclohexane and petroleum ether.
Analysis: \[ C_{22}H_{27}O_{11}N \] (481.466)

<table>
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<th>% O</th>
<th>% Cl</th>
</tr>
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<td>0.0</td>
</tr>
<tr>
<td>Calculated</td>
<td>54.80</td>
<td>5.60</td>
<td>36.60</td>
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</table>

Rotation:
\[
\left[ \alpha \right]_{D}^{25} = +24.0^\circ C. \quad (C = 1.252\% \text{ in chloroform})
\]
\[
\left[ \alpha \right]_{D}^{25} = +22.2^\circ C. \quad (C = 1.354\% \text{ in pyridine})
\]

Benzyl-N-carbobenzoxy-\(3,4,6\)-tri-O-benzoyl-\(\alpha\)-D-glucosaminide (XX). Four grams (1 x \(10^{-3}\) mole) of benzyl-N-carbobenzoxy-\(\alpha\)-D-glucosaminide (XIX) (16) were dissolved in pyridine (20 ml.) and cooled to 0°C. Benzoyl chloride 1.6 ml. (3.5 x \(10^{-3}\) mole) was added dropwise while stirring at 0°C. during the course of fifteen minutes. The reaction mixture was stirred for one hour more and kept in refrigerator overnight. The mixture was poured over crushed ice while stirring when a gummy product separated out. It was purified by acetone and water mixture. The product was recrystallized from cyclohexane after treatment with charcoal, M. P. 96-98°C. Yield 5.6 g. (0.78 x \(10^{-3}\) mole) (79 per cent).

Properties: (XX) is soluble in alcohol, ether, dioxane and acetic acid but insoluble in water.
**Analysis:**  \( C_{42}H_{37}O_{10}N \) (715.766)

<table>
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<th>% H</th>
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<td>25.40</td>
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**Rotation:**

\[ [\alpha]_D^{25} = +32.2^\circ C \] (C = 1.3% in pyridine)

**n-Propyl-N-carbobenzyoxyl-3-O-benzoyl-4,6-O-benzylidene-\( \beta \)-D-glucosaminide (XXIVa).** Freshly fused zinc chloride 0.7 g. \((5.15 \times 10^{-3} \text{ mole})\) was dissolved in benzaldehyde (40 ml.). n-Propyl-3-O-benzoyl-N-carbobenzyoxyl-\( \beta \)-D-glucosaminide 0.7 g. \((1.52 \times 10^{-3} \text{ mole})\) was added. The reaction mixture was shaken for twelve hours at room temperature, and then excess ether was added. The white product thus obtained was washed with ether and reor crystallized from tetrahydrofuran-ether mixture, M. P. 230-31°C.; yield 0.75 g. \((0.37 \times 10^{-3} \text{ mole})\) (85.5 per cent).

The compound (XXIV) when heated with hydrochloric acid gave benzaldehyde, recognized by its odor. (XXIV) is soluble in dioxane and acetic acid, but insoluble in petroleum ether and cyclohexane. \([\alpha]_D^{25} = -90.0^\circ C \] (C = 1.034% in pyridine)
CHAPTER V

SUMMARY

The present work consists of two parts. The first part contains the synthesis of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) and the study of its chemistry. The second part deals with the synthesis of new aminosugar derivatives.

I. ROLE OF MERCURIC CYANIDE ON COMPETITION BETWEEN GLYCOSIDATION AND OXAZOLIDONE FORMATION

It was observed for the first time that, during glycosidation using mercuric cyanide as Lewis base (with respect to cyanide which abstracts a proton from alcohol), 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) was obtained as a byproduct. This product resulted from the competing reactions of nucleophilic substitution of bromide by alcohol (SN₂) and nucleophilic substitution of bromide by the neighboring benzyloxy carbonyl group intramolecularly (SN₁).

In the presence of alcohol, the SN₂ reaction predominates over SN₁. The yield of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (III) increased when isopropanol and tertiary butanol were used because of the decrease in the rate of the SN₂ reaction. The decrease...
in the rate of the $\text{SN}_2$ was attributed to the increase in the negative entropy of activation resulting from imposing certain restrictions on the degree of freedom for rotation about the $C_α-C_β$ bond in the transition state. This was confirmed by the fact that a straight line was obtained when the steric energy of activation, $ΔAE^+_g$, was plotted against the yields of the 3,4,6-tri-O-benzoyl-D-glucopyranosido-$[1,2:4',5']$-2'-oxazolidone resulting from reactions using n-propanol, isopropanol, n-butanol, tertiary butanol, and cyclohexanol.

In the absence of alcohol, α-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I), when heated in chloroform in the presence of mercuric cyanide, gave 3,4,6-tri-O-benzoyl-D-glucopyranosido-$[1,2:4',5']$-2'-oxazolidone (III) and benzyl bromide.

Pyridine can be used for the proton acceptor in glycosidation, but the yield of the β-D-glucosaminide was found to be low. However, 3,4,6-tri-O-benzoyl-D-glucopyranosido-$[1,2:4',5']$-2'-oxazolidone (III) was not obtained.

3,4,6-tri-O-benzoyl-D-glucopyranosido-$[1,2:4',5']$-2'-oxazolidone (III), when reacted with 2,4, dinitrophenyl hydrazine in acetic acid gave no keto derivative. The compound (III), when subjected to catalytic hydrogenation in acetic anhydride and acetic acid in the presence of palladium black, gave no reaction product. The compound (III), when subjected to reduction by sodium borohydride in tetrahydrofuran,
gave no reaction product. The compound (III) was found to be stable when heated with 75 per cent acetic acid. However, it gave α-bromo-3,4,6-tri-O-benzoyl-D-glucosamine hydrobromide when treated with glacial acetic acid hydrobromic acid solution. The compound (III) gave D-glucosamine when treated with aqueous potassium hydroxide in dioxane.

II. D-GLUCOSAMINIDE SYNTHESSES

The corresponding β-D-glucosamides (IIa), (IIc), and (IIf) have been prepared by reacting α-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) with n-propanol, n-butanol, and cyclohexanol, respectively, in chloroform in the presence of mercuric cyanide. The compound (IIa), when de-O-benzolated with aqueous potassium hydroxide in dioxane for three hours at room temperature, gave a partially de-O-benzoylated product (VIIIa). However, when de-O-benzoylation was carried out for twenty-four hours at room temperature in the case of (IIe) and (IIf), the complete de-O-benzoylated products (VIIIc) and (VIIIff) were obtained. The de-O-benzoylated products thus obtained, when subjected to catalytic hydrogenation, gave β-substituted D-glucosamine hydrochlorides.

Benzyl-N-carbobenzoxy-3,4,6-tri-O-benzyl-α-D-glucosaminide (XX) was prepared in order to compare its properties with those of the corresponding β-anomer. It was
observed that the $\alpha$-anomer (XX) has a low melting point, high optical rotation, and high solubility in organic solvents. However the $\beta$-anomer (IIE) has a high melting point, low optical rotation, and low solubility in organic solvents.
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