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

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Recommended Citation

A NEW TWO-POSITION PROTECTING GROUP: PREPARATION AND

PROPERTIES OF GLUCOPYRANOSIDO-[1,2:4',5'] -2'-

OXAZOLIDONE AND SYNTHESES OF D-GLUCOSAMINIDES

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A Dissertation

Presented to

the Faculty of the Graduate School

The University of the Pacific

————

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

————

by

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August 1964

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Dated _August 1964_

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ACKNOWLEDGEMENTS

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 (48,58).

D-glucosamine and D-galactosamine are the two amino-sugars which are found mainly in the animal kingdom, where their most usual occurrence is as constituents of carbohydrate polymers--amino polysaccarides 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 I

OCCURRENCE OF AMINOSUGARS IN ANTIBIOTIC SUBSTANCES

Antibiotic	Aminosugar Trivial Name	Aminosugar Systematic Name
Kanamycine	Kanosamine	3-amino-3-deoxy-D-glucose
Nystatin	Mycosamine	3-amino-3,6-dideoxy-mannose
Magnamycin	Mycaminose	3-dimethylamino-3,6-dideoxy-D-glucose
Erythromycins Methmycins Narbomycin Olandomycin Picormycin		3-dimethylamino-3,4,6-trideoxy-D-hexopyranose
Puromycin		3-amino-3-deoxy-D-ribose
Rhodomycins	Rhodosamine	3-dimethylamino-2,3,6-trideoxy-lyxo-hexopyranose
Amicetin	Amosamine	4-dimethylamino-4,6-dideoxy-D-glucose
Racemomycins Streptothricins		2-amino-2-deoxy-D-gulose
Monomycin		2-amino-D-deoxy-D-glucose
Zygomycins	Neoamine-C	2,6-diamino-2,6-dideoxy-D-glucose
Neomycins Paromomycin	Neosamine-B Paromose	2,6-diamino-2,6-dideoxy-L-idose
Streptomycin	N-methyl-L-glucosamine	2-methylamino-2-deoxy-L-glucose

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-0-acetyl-2-deoxy-D-glucosyl-bromide with 1,2,3,4-tetra-0-acetyl-D-glucose or the corresponding D-galactose derivatives in benzene solution in the presence of mercuric cyanide as catalyst, followed by de-0-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

$$Hg(CN)_2 + C_6H_6$$

$$AC = CH_3CO-$$

$$CH_3OH + NH_3$$
at $0^{\circ}C.$
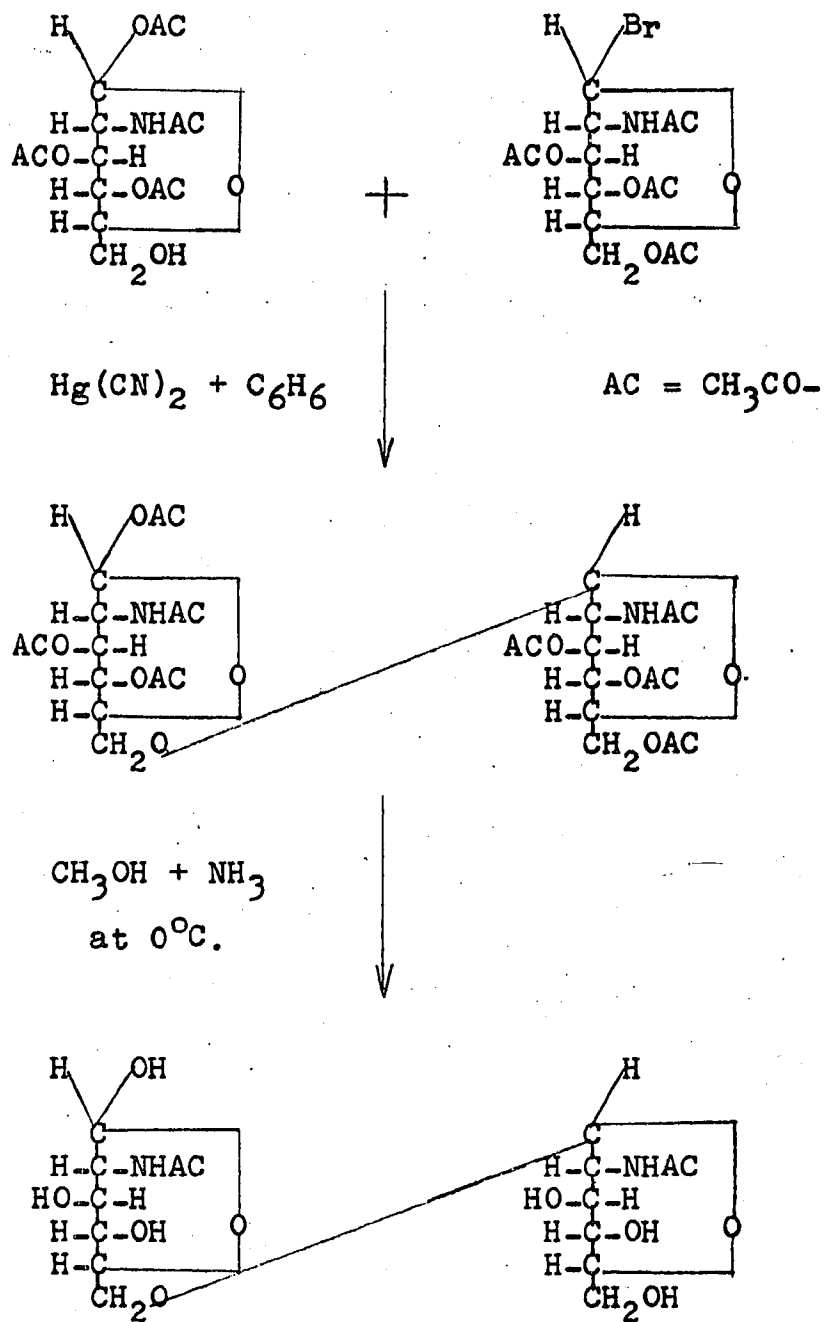
CHART 1

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 pro-
tecting 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) crystaliza-
bility, 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

S U M M A R Y   O F   P R O P E R T I E S   O F

Function	Protecting Group	Stability Towards		
		Acid	Base	Heat
Hydroxyl	Acetyl	Low	Low	Inter.*
	Ether	Inter.	High	High
	Benzoyl	Inter.	Low	High
	Methyl Sulfonyl	Low	Low	Inter.
	p-Toluene Sulfonyl	Low	Low	Inter.
Amino	Acetyl	Inter.	High	High
	2,4-dinitro-phenyl	Inter.	High	High
	Benzyloxy-carbonyl	Inter.	High	High

*Inter. = Intermediate

I I

V A R I O U S   P R O T E C T I N G   G R O U P S

Solubility in Organic Solvents	Crystallizability	Removeability
High	Difficult	Easy
Inter.	Easy	Difficult
Inter.	Easy	Easy
Inter.	Easy	Easy
Inter.	Easy	Easy
High	Easy	Difficult
Inter.	Easy	Easy
Inter.	Easy	Easy

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 crystal-
lize (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). Sul-
fonyl 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
benzyloxycarbonyl (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 benzyloxycarbonyl
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 aminosugar derivatives (55,44).

It is known that hydroxy groups at C_4 and C_6 can be protected by benzylidine, 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-α-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

β-D-glucosaminides. The products thus obtained can be used
to prepare new disaccharides. In addition new aminosugar
derivatives have been prepared.

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C_1 and C_2 can be protected by 3,4,6-tri-0-acetyl-D-glucopyranosido-[1,2:4',5']-2'-oxazoline (40) and 3,4,6-tri-0-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-0-acetyl-α-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.

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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 β-D-glucosaminides it was neces-
sary to react α-bromo-3,4,6-tri-0-acetyl-glucosamine hydro-
bromide (XV) with alcohols in the presence of pyridine (12).
Later the method was improved by treating α-bromo-3,4,6-
tri-0-acetyl-N-carbobenzoxy-D-glucosamine (I) with alcohols
in chloroform using mercuric cyanide (21) or silver carbon-
ate (41,62,13).

α-bromo-3,4,6-tri-0-acetyl-D-glucosamine-hydrobromide
(XV) was prepared by heating D-glucosamine with acetyl bromide
(42,6). Later it was obtained by reacting α,β-1,3,4,6-
tetra-0-acetyl-N-carbobenzoxy-D-glucosamine and glacial
acetic acid solution saturated with hydrobromic acid (29).
It was, however, found that α-bromo-3,4,6-tri-0-acetyl-D-
glucosamine-hydrobromide is unstable.

α-Bromo-3,4,6-tri-0-benzyl-D-glucosamine-hydrobromide
(VI) (55) was prepared from α,β-1,3,4,6-tetra-0-benzoyl-N-
carbobenzoxy-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 pro-
tected by an acetyl or benzoyl group, as in the preceding two
cases, bromine replaces only benzoyl or acetyl at C_1, without

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 α-bromo compound was obtained (29,55).

Recently it has been found (17) that α-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. α-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 pre-
pare α-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-β-D-
glucosaminide (IIa) was prepared by heating α-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 = $C_6H_5CH_2O-CO-$

HO   H
|
H-C-NBCBZ
HO-C-H
H-C-OH
H-C
CH$_2$OH

XXII*

2MHCl in

$(CH_3CO)_2O$

ACO   H
|
H-C-NHCBZ
ACO-C-H
H-C-OAC
H-C
CH$_2$OAC

+

H   OAC
|
H-C-NHCBZ
ACO-C-H
H-C-OAC
H-C
CH$_2$OAC
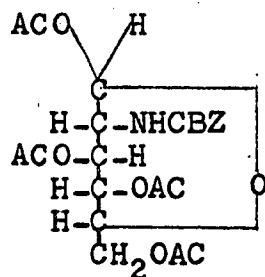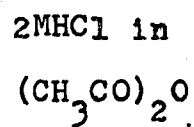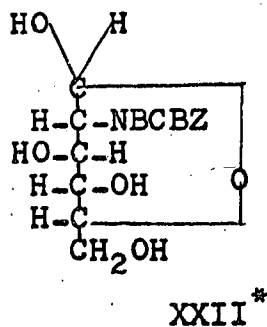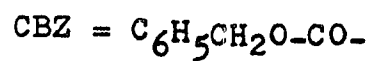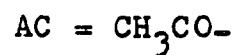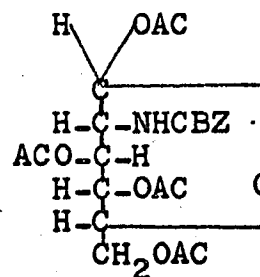
AC = CH_3CO- XXIII*

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

$Hg(CN)_2$ + $CHCl_3$

$Cbz = C_6H_5CH_2O\text{-}CO\text{-}$

$Bzl = C_6H_5CO\text{-}$

C_5H_5N: + ROH

ROH + $CHCl_3$ + $Hg(CN)_2$

$R\text{-}\ddot{O}H$

$Hg(CN)_2$

+ $C_6H_5CH_2Br$ + HCN

II_a*:R = n-C_3H_7-

II_a*:R = n-C_3H_7-
II_b*:R = 1 C_3H_7-
II_c*:R = n-C_4H_9-
II_d:R = ter.C_4H_9-
II_e*:R = $C_6H_5CH_2$-
II_f*:R = cyclo.C_6H_{11}-

*Compounds are known.

oxazolidone can be obtained from certain β-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 4.4×10^{-3} mole to 0.5×10^{-3} mole per 4.4×10^{-3} mole of α-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-D-glucosamine (I) (56). It was found that the yield of the β-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 β-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 GLYCOSIDATION REACTIONS USING 4.4×10^{-3} MOLE OF COMPOUND (I)

Alcohol 17.4×10^{-3} mole	Mercuric Cyanide (moles)	Yield of Compound (II) (moles)	Yield of Compound (III) (moles)
n-Propanol	4.4×10^{-3}	3.4×10^{-3}	0.19×10^{-3}
n-Propanol	2.2×10^{-3}	3.3×10^{-3}	0.19×10^{-3}
n-Propanol	1.1×10^{-3}	1.8×10^{-3}	0.19×10^{-3}
n-Propanol	0.5×10^{-3}	0.75×10^{-3}	0.19×10^{-3}
n-Butanol	4.4×10^{-3}	3.4×10^{-3}	0.19×10^{-3}
Benzyl alcohol	4.4×10^{-3}	3.0×10^{-3}	0.19×10^{-3}
Cyclohexanol	4.4×10^{-3}	3.0×10^{-3}	0.19×10^{-3}
Isopropanol	4.4×10^{-3}	3.1×10^{-3}	0.29×10^{-3}
Tertiary butanol	4.4×10^{-3}	1.6×10^{-3}	0.96×10^{-3}

be increased. It was found that the yield of the corresponding β-D-glucosaminide (IId) 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-β-D-glucosaminide (IId) can be attributed to the steric effect of the bulky methyl groups in the 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 α-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, SN_2 and SN_1 (where 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 $\Delta\Delta E_{s\ddagger}^{+}$ 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 alco-

hols (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 β-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:

$$Br^- + R-X \longrightarrow R-Br + X^-,$$
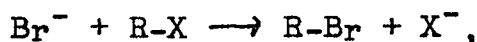
where R = n-propyl, isopropyl, t-butyl and neopentyl. They

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 α or β -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 β-substituted compounds, besides the steric

effect, the inductive effect also plays an important role in

the transition state (15). The inductive effect may hinder

Total Steric Energy of Activation $\Delta\Delta E_s^{\ddagger}$
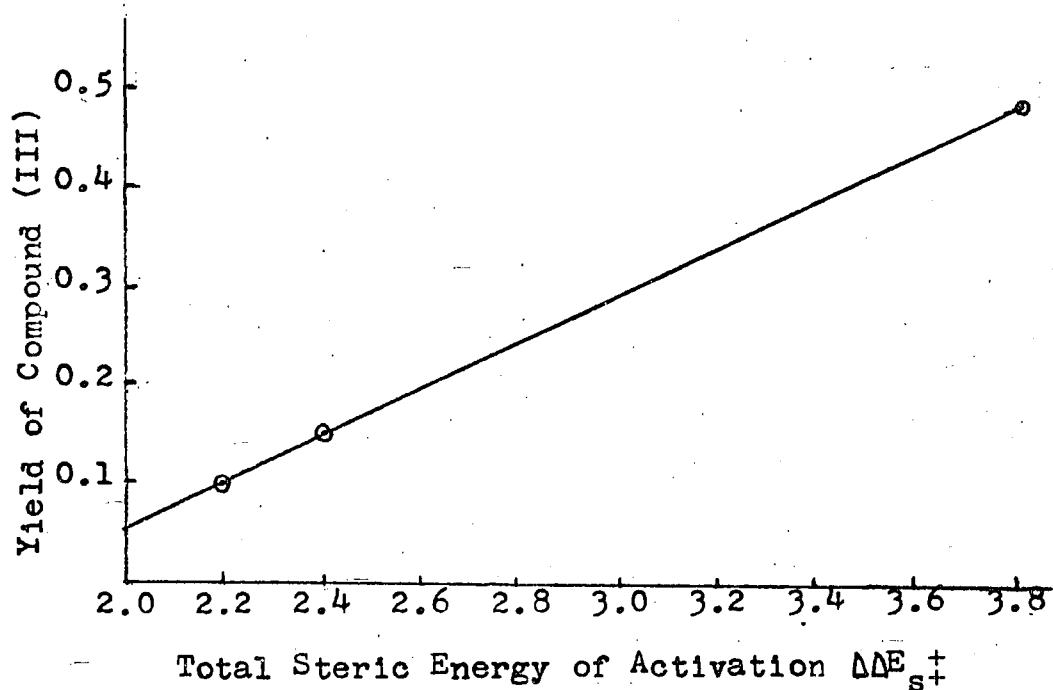
Substituent R	Total Steric Energy of Activation at 30°C. in K. Cal.	Yield of Compound (III) in grams
n-C$_3$H$_7$	2.2	0.10
n-C$_4$H$_9$	2.2	0.10
C$_6$H$_5$CH$_2$	2.2	0.10
i-C$_3$H$_7$	2.4	0.15
t-C$_4$H$_9$	3.8	0.50

FIGURE 1

RELATION BETWEEN THE YIELD OF COMPOUND (III) AND
THE TOTAL STERIC ENERGY OF ACTIVATION $\Delta\Delta E_s^{\ddagger}$

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_α-C_β 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 -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-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone (33).

S. Konstas, I. Photaki, and L. Zervas (32) obtained 3,4,6-tri-O-acetyl-D-glucopyranosido-[1,2:4',5']-2'-oxazolidone by treating 1,3,4,6-tetra-O-acetyl-N-carbobenzoxy-β-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 C_2. Recently T. Ito prepared the above oxazolidone by heating 1,3,4,6-tetra-O-acetyl-N-carbobenzoxy-β-D-glucosamine with trifloroacetic acid and proposed a similar SN_1 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 boro-hydride 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 pal-ladium 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-glucopyzanosido-$\left[2,3:4',5'\right]$-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 attribut-able to the fact that the compound (III) is insoluble in hydrochloric acid solution.

Bzl = C$_6$H$_5$CO-

$$\begin{array}{c} H \underset{|}{\overset{Br}{C}} \\ H-\overset{+}{\underset{|}{C}}-NH_3\bar{B}r \\ Bzl O-\underset{|}{C}-H \\ H-\underset{|}{C}-OBzl \\ H-\underset{|}{C} \\ CH_2OBzl \end{array}$$

VI*

CH$_3$COOH
+
HBr
⟶
① CHCl$_3$ +
NaHCO$_3$ soln.
+
C$_6$H$_5$CH$_2$O-COCl
② Hg(CN)$_2$ + CHCl$_3$

IV ← C$_5$H$_5$N:
+
C$_6$H$_5$COCl

III*

V

Dioxane
Ag . KOH

C$_5$H$_5$N:
+
(CH$_3$CO)$_2$O

VII*

*Compounds are known.

CHART 4

PROPERTIES OF 3,4,6-TRI-O-BENZOYL-D-GLUCOPYRANOSIDO-[1,2:4',5']-2'-OXAZOLIDONE
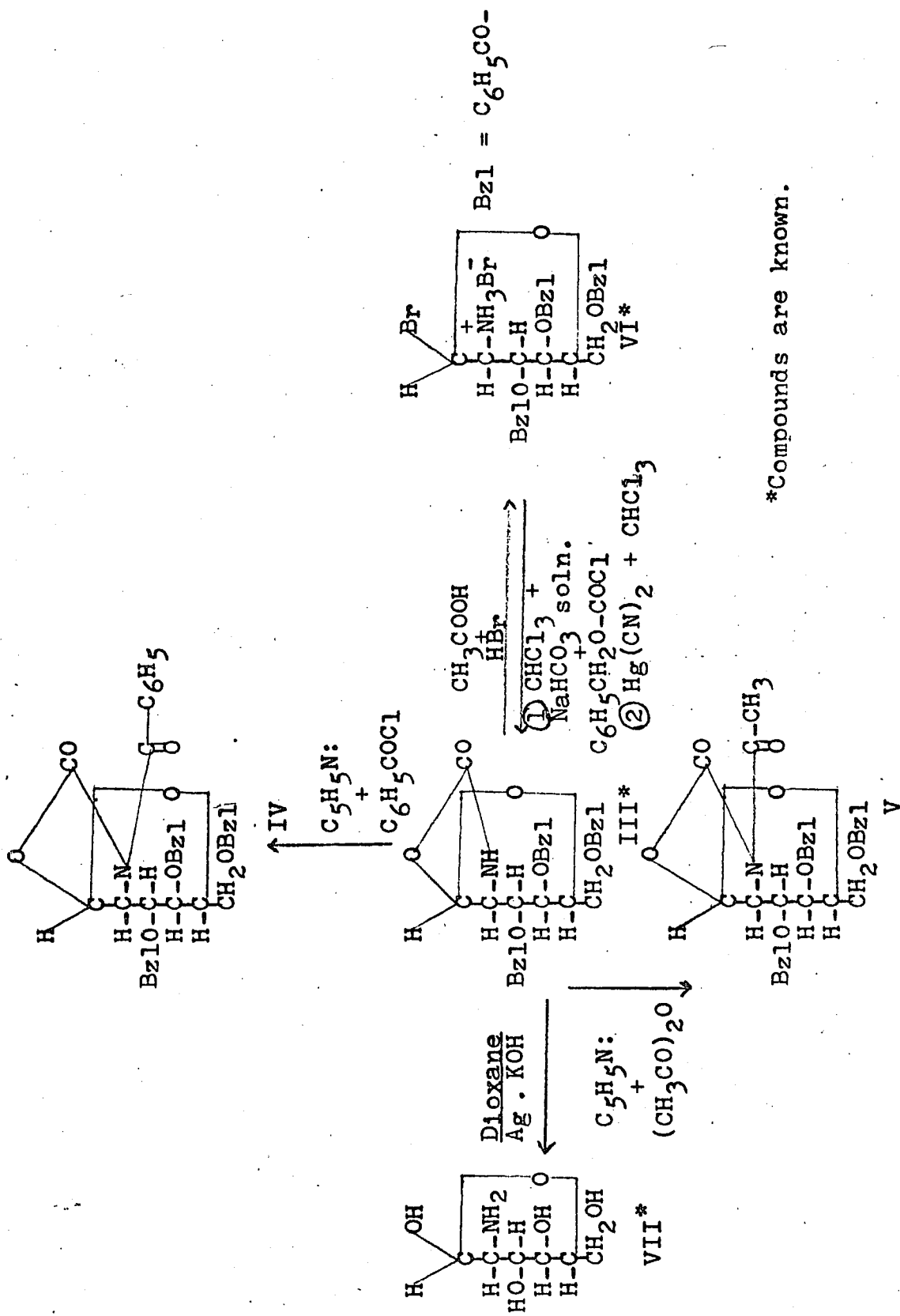
Benzyl-4,6-di-O-acetyl-α-D-glucopyranoside-[2,3:4',5'] -
2'-oxazolidone, when heated with 75 per cent acetic acid solu-
tion, was found stable (17). The compound (III), when
treated with 75 per cent acetic acid under similar condi-
tions, also was found stable.

α-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 fre-
quently hinder the latter reaction. O-Acetate groups may be
removed preferentially without affecting the N-acetyl func-
tion (39,51). Deacetylation with methanolic sodium or barium
methoxide in catalytic amounts depends upon transesterifica-
tion (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 cata-
lytic amount of 0.1 N sodium methoxide solution (57). No
reaction product was obtained. However the compound (III)
$(3.34 \times 10^{-3}$ moles), when treated with sodium methoxide solu-
tion $(3.8 \times 10^{-3}$ 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 following 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 compound (III) when treated with methanolic ammonia solution (11,61), gave a product which was found to be very hygroscopic.

3,4,6-tri-O-benzoyl-D-glucopyranosido- [1,2:4',5'] -2'-oxazolidone (III), unlike benzyl-4,6-di-O-acetyl-α-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.

D-GLUCOSAMINIDE SYNTHESES

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 (II$_c$), 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 (II$_c$) in solution in chloroform and methanol for twenty-four hours at room temperature, n-butyl-N-carbobenzoxy-β-D-glucosaminide (VIIIc) 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 C_3 or the C_4, 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 C_4
(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 saponifi-
cation with aqueous potassium hydroxide in dioxane for twenty-
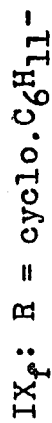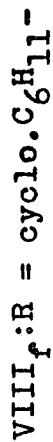four hours at room temperature. The completely de-O-benzoylated

Bzl = C$_6$H$_5$CO

Cbz = C$_6$H$_5$CH$_2$O-CO

II$_c$:R = n-C$_4$H$_9$- *

II$_f$:R = cyclo-C$_6$H$_{11}$- *

VIII$_c$:R = n-C$_4$H$_9$-

VIII$_f$:R = cyclo.C$_6$H$_{11}$-

IX$_c$: R = n-C$_4$H$_9$-

IX$_f$: R = cyclo.C$_6$H$_{11}$-

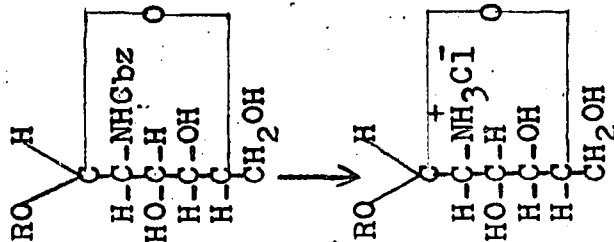Aq. KOH + Dioxane

H$_2$ / Pd. Black / 1 M HCl in C$_2$H$_5$OH
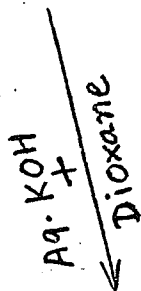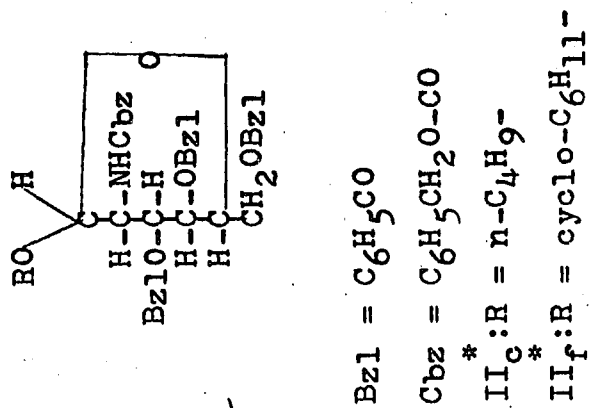
CHART 5

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

*Compounds are known.

XXIVa

$$\begin{array}{l} RO \quad H \\ \text{H–C–NHCbz} \\ \text{Bzl0–C–H} \quad O \\ \text{H–C–O} \\ \text{CH}_2\text{–O} \end{array} \quad \text{CHC}_6\text{H}_5$$

$$\xrightarrow[\text{CH}_3\text{COOH}]{\substack{C_6H_5CHO \\ + \\ ZnCl_2}}$$

$$\begin{array}{l} RO \quad H \\ \text{H–C–NHCbz} \\ \text{Bzl0–C–H} \quad O \\ \text{H–C–OH} \\ \text{CH}_2\text{OH} \end{array}$$

VIIIa : R = n-C$_3$H$_7$–

$\xleftarrow{\text{Aq. KOH} + \text{Dioxane}}$

$$\begin{array}{l} RO \quad H \\ \text{H–C–NHCbz} \\ \text{Bzl0–C–H} \quad O \\ \text{H–C–OBzl} \\ \text{CH}_2\text{OBzl} \end{array}$$

Bzl = C$_6$H$_5$CO

Cbz = C$_6$H$_5$CH$_2$O–CO

IIa : R = n-C$_3$H$_7$– *

$$\xrightarrow[\text{1M HCl in C}_2\text{H}_5\text{OH}]{\substack{H_2 \\ \text{Pd. Black}}}$$

$$\begin{array}{l} RO \quad H \\ \text{H–C–}\overset{+}{\text{N}}\text{H}_3\overset{-}{\text{Cl}} \\ \text{Bzl0–C–H} \quad O \\ \text{H–C–OH} \\ \text{CH}_2\text{OH} \end{array}$$

IX$_a$: R = n-C$_3$H$_7$

CHART 5 (continued)
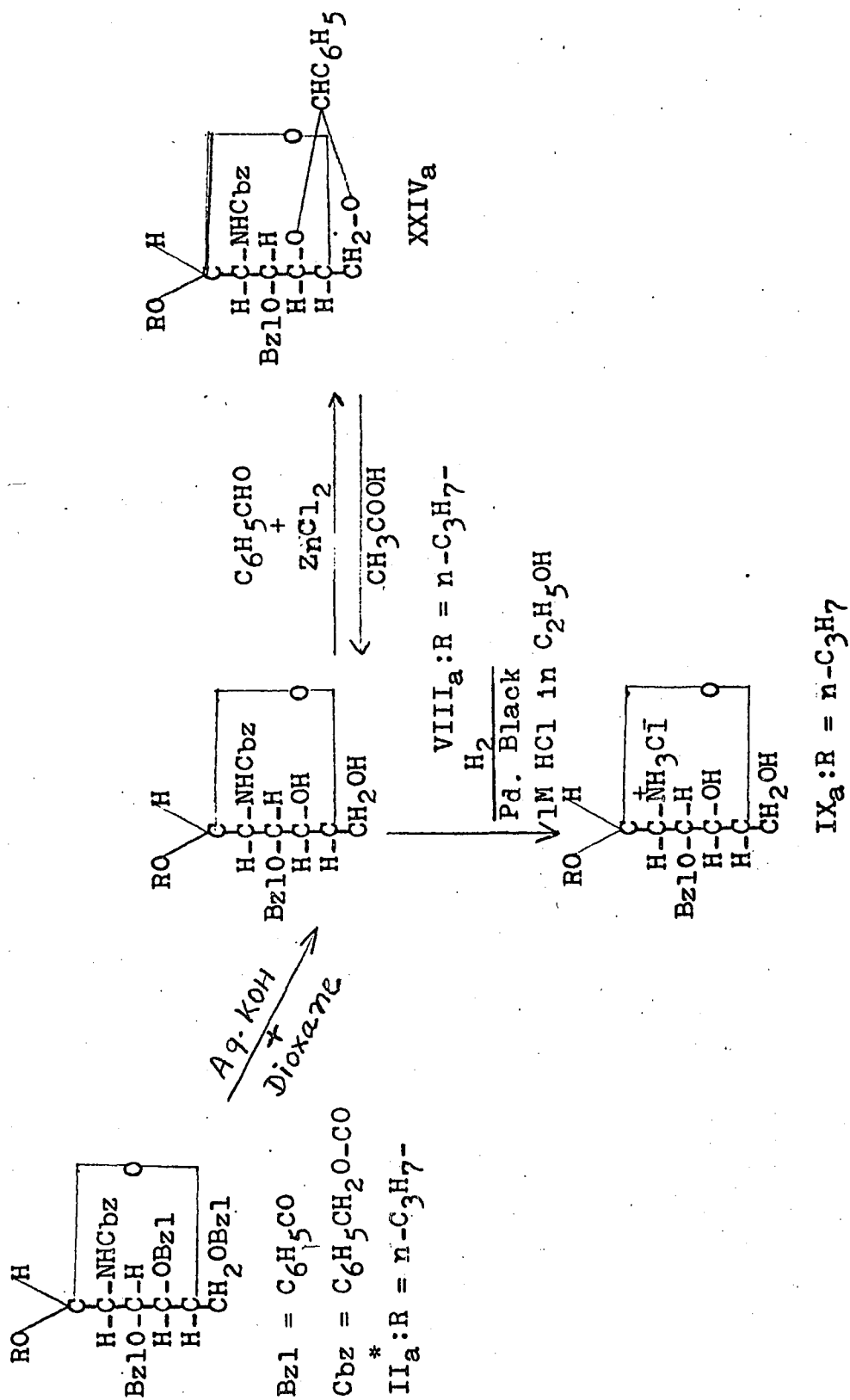
*Compound is known.

compound (VIIIc) and (VIIIf) show similar solubility proper-
ties (Chart 5). Infrared spectra show bands at 3500 (hydroxyl):
745, 700 (phenyl).

De-O-benzoylated compound (VIIIa), (VIIIc), and
(VIIIf) 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)
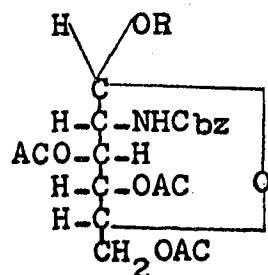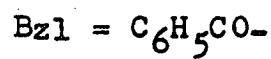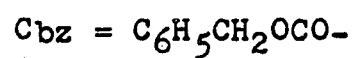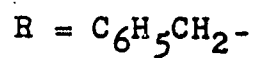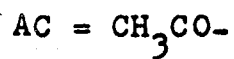and 3500 (hydroxyl).

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

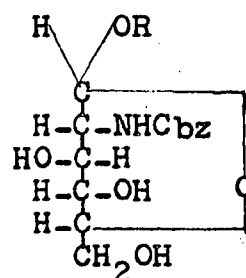(44), gave pure benzyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-α-D-glucosaminide (XX) (See Chart 6).

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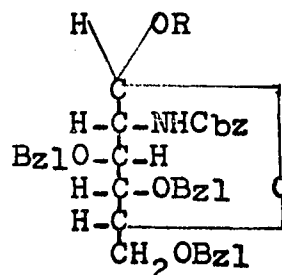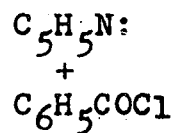
Isopropyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (XVI) was prepared with isopropanol in the presence of pyridine as base. Isopropyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (XVI), when treated with ethyl chlorformate in chloroform and aqueous sodium bicarbonate solution at 0°C., gave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

AC = CH$_3$CO-

R = C$_6$H$_5$CH$_2$-

Cbz = C$_6$H$_5$CH$_2$OCO-

Bzl = C$_6$H$_5$CO-

$$
\begin{array}{c}
\text{H} \quad \text{OR} \\
\text{C} \\
\text{H--C--NHCbz} \\
\text{ACO--C--H} \\
\text{H--C--OAC} \quad \text{O} \\
\text{H--C} \\
\text{CH}_2\text{OAC}
\end{array}
$$

XVIII*

$\dfrac{\text{Ag} \cdot \text{KOH}}{\text{Dioxane}}$

$$
\begin{array}{c}
\text{H} \quad \text{OR} \\
\text{C} \\
\text{H--C--NHCbz} \\
\text{HO--C--H} \\
\text{H--C--OH} \quad \text{O} \\
\text{H--C} \\
\text{CH}_2\text{OH}
\end{array}
$$

XIX*

C$_5$H$_5$N:
+
C$_6$H$_5$COCl

$$
\begin{array}{c}
\text{H} \quad \text{OR} \\
\text{C} \\
\text{H--C--NHCbz} \\
\text{BzlO--C--H} \\
\text{H--C--OBzl} \quad \text{O} \\
\text{H--C} \\
\text{CH}_2\text{OBzl}
\end{array}
$$

XX

CHART 6

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

*Compounds are known.

$R = C_6H_5CH_2-$

$$
\begin{array}{c}
RO \quad H \\
| \\
C \\
H-C-NH_3^+ Br^- \\
ACO-C-H \\
H-C-OAC \\
H-C \quad \quad O \\
CH_2OAC
\end{array}
\qquad X^*
$$

$CHCl_3 + NaHCO_3$ soln. +

$Cl-CO-OC_2H_5$

$AC = CH_3CO-$

$$
\begin{array}{c}
RO \quad H \\
| \\
C \\
H-C-NH-Cbe \\
ACO-C-H \quad O \\
H-C-OAC \\
H-C \\
CH_2OAC
\end{array}
\qquad XI
$$

$\underline{Ag \cdot KOH}$
Dioxane

$Cbe = -CO-OC_2H_5$

$$
\begin{array}{c}
RO \quad H \\
| \\
C \\
H-C-NH-Cbe \\
HO-C-H \quad O \\
H-C-OH \\
H-C \\
CH_2OH
\end{array}
\qquad XII
$$

$C_5H_5N: + C_6H_5COCl$

$Bzl = C_6H_5CO-$

$$
\begin{array}{c}
RO \quad H \\
| \\
C \\
H-C-NH-Cbe \\
BzlO-C-H \quad O \\
H-C-OBzl \\
H-C \\
CH_2OBzl
\end{array}
\qquad XIII
$$
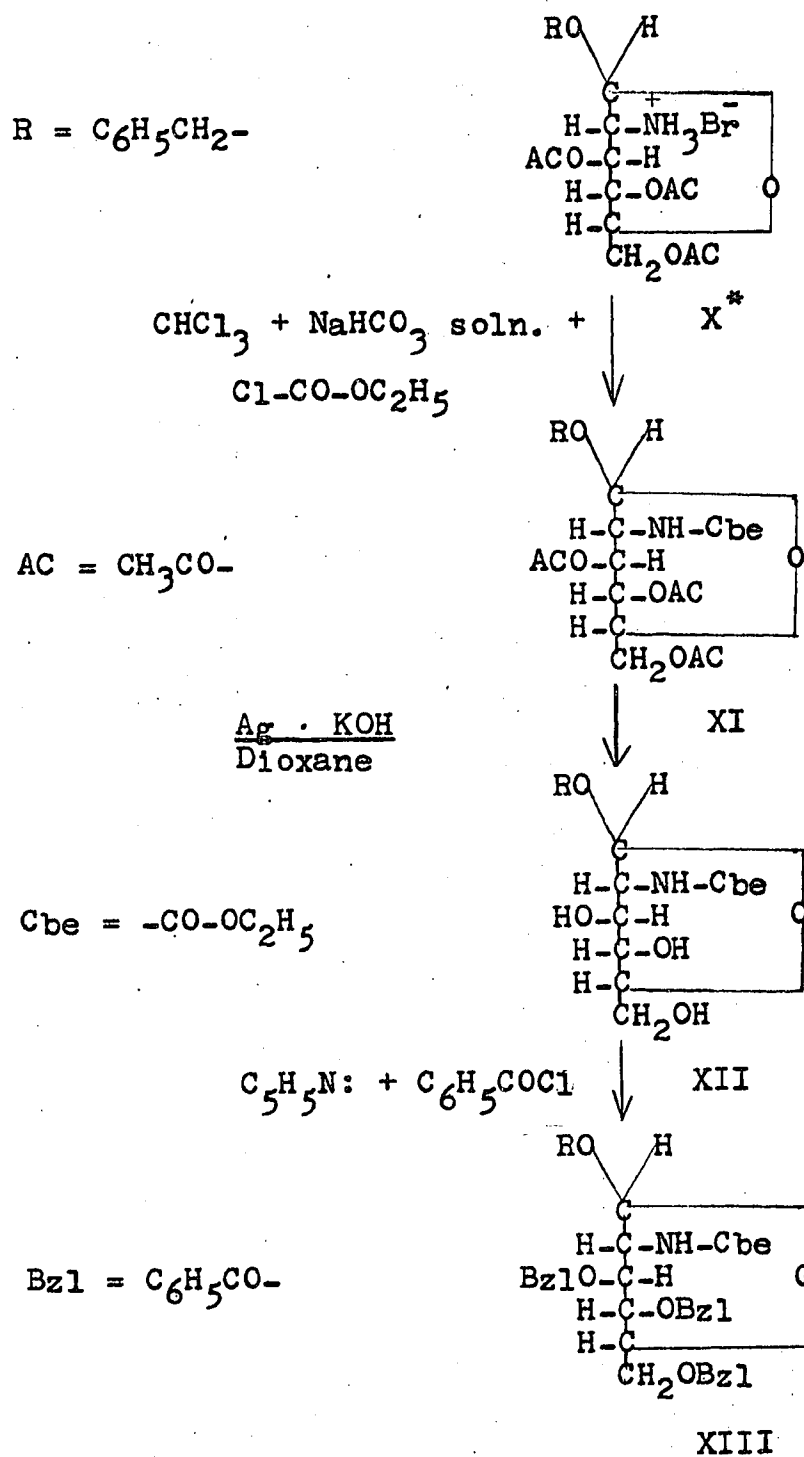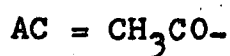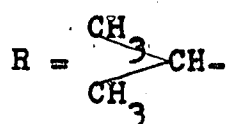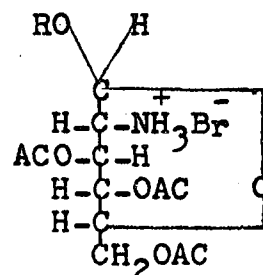
CHART 7

SYNTHESIS OF BENZYL-3,4,6-TRI-O-BENZOYL-
N-CARBOETHOXY-β-D-GLUCOSAMINIDE

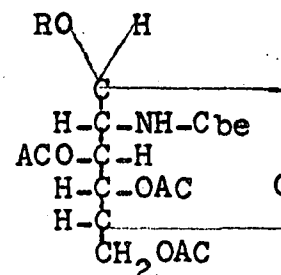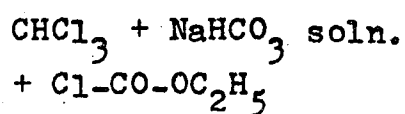*Compound is known.

$$R = \begin{array}{c} CH_3 \\ CH_3 \end{array} CH-$$

$$AC = CH_3CO-$$

$$Cbe = -CO-OC_2H_5$$

XV*

$C_5H_5N:$
$\overset{+}{ROH}$

XVI

$CHCl_3 + NaHCO_3$ soln.
$+ Cl-CO-OC_2H_5$
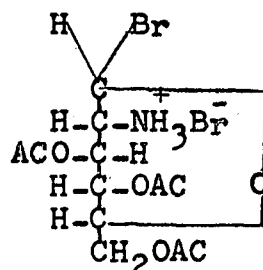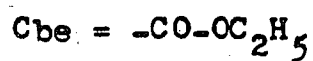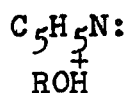
XVII

CHART 8

ISOPROPYL-3,4,6-TRI-O-ACETYL-N-CARBOETHOXY-β-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 AARAU, Sursee,
Switzerland.

n-Propyl-3,4,6-tri-O-benzoyl-N-carbobenzoxy-β-D-
glucosaminide (IIa). Three grams (4.4 x 10^{-3} mole) of
α-bromo-3,4,6-tri-O-benzoyl-N-carbobenzoxy-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} mole) and mercuric cyanide
1.1 g. (4.4 x 10^{-3} 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 char-
coal, m. p. 142-43°; yield 2.3 g. 3.4 x 10^{-3} mole (79 per
cent). The mother liquor was concentrated to small volume
and cooled to 0°C., whereupon a substance melting at 204-05°
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:

$C_{38}H_{37}NO_{10}$
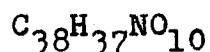
	% C	% H	% N
Found	68.53	5.71	2.20
Calculated	68.50	5.60	2.10

Rotation:

$$[\alpha]_D^{25} = -4.5^\circ (C = 2\% \text{ in } CHCl_3)$$

3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-
oxazolidone (III). Three grams (4.4 x 10^{-3} mole) of α-
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°; yield 1.8 g.
(3.48 x 10^{-3} mole) (80 per cent). The mother liquor, on
removal of alcohol, gave lacrymetory liquid benzyl bromide.

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

Analysis:

$C_{28}H_{23}NO_9$ (517.2)

	% C	% H	% N
Found	64.70	4.63	2.92
Calculated	65.0	4.47	2.70

Rotation:

$[\alpha]_D^{25}$ = -39.2 (1.344% in pyridine)

$[\alpha]_D^{25}$ = + 3.25 (2% in chloroform)

3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-N-acetyl-2'-oxazolidone (V). Two grams (3.34×10^{-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. (1.5×10^{-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. (3.4×10^{-3} mole) (76 per cent).

Properties: (V) is soluble in chloroform and dioxane, but insoluble in petroleum ether and cyclohexane. The infrared spectra of (V) show bands at 3350, 1750 (oxazolidone), 1250 (acetate), and 1730, 1280 ('O-benzoyl).

<u>Analysis</u>:

$C_{30}H_{25}O_{10}N$ (559.538)

	% C	% H	% O
<u>Found</u>	63.76	4.48	29.29
<u>Calculated</u>	64.20	4.52	28.70

<u>Rotation</u>:

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

<u>3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-</u>
<u>N-benzoyl-2'-oxazolidone</u> (<u>IV</u>). Two grams $(3.34 \times 10^{-3}$ mole)
of 3,4,6-tri-O-benzoyl-D-glucopyranosido-[1,2:4',5']-2'-
oxazolidone (III) were dissolved in pyridine (8 ml.) and
cooled to $0^\circ C$. Benzoyl chloride 0.8 ml. $(6.7 \times 10^{-3}$ mole)
was added while stirring at $0^\circ C$. 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. $160\text{-}61^\circ C$.;
yield 2.1 g. $(3.4 \times 10^{-3}$ mole) (87 per cent).

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

<u>Analysis</u>:

$C_{35}H_{27}O_{10}N$ (621.609)

	% C	% H	% O
Found	67.34	4.50	26.06
Calculated	67.50	4.35	25.80

Rotation:

$$[\alpha]_D^{25} = -39.4^\circ \ (C = 1.34\% \text{ in pyridine})$$

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 anhyride (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 $50^\circ C$. The residue was washed with ice cold water (15 ml.) and then recrystallized from alcohol after treatment with charcoal, M. P. $204-05^\circ C$., 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 (1.94×10^{-3} mole) of compound (III) was dissolved in dry tetrahydrofuran (15 ml.) and was stirred in the presence of sodium borohydride 0.12 g. (3.16×10^{-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. $203-04^\circ C$., 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. $87^\circ C$. It reduced Fehling solution and gave D-glucosamine hydrochloride,

M. P. 195-97°C., when treated with aqueous hydrochloric acid solution.

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

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.

$[\alpha]_D^{25} = -140°C.$ (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-carboethoxy-β-D-glucosaminide (XI). Four grams (8.4 x 10^{-3} mole) of benzyl-3,4,6-tri-O-acetyl-β-D-glucosaminide hydrobromide (X) (7) were suspended in dry chloroform (30 ml.). The mixture was shaken with ethyl chloroformate 1.9 ml. (16.8 x 10^{-3} mole) in the presence of saturated sodium bicarbonate solution (30 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 x 10^{-3} mole) (89.5 per cent).

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

<u>Analysis</u>:

$C_{22}H_{29}O_{10}N$ (467.480)

	% C	% H	% O
<u>Found</u>	56.20	6.14	34.39
<u>Calculated</u>	56.50	6.25	34.20

<u>Rotation</u>:

$$[\alpha]_D^{25} = -22.6^\circ C. \quad (C = 1.54\% \text{ in pyridine})$$

<u>Benzyl-N-carboethoxy-β-D-glucosaminide</u> (<u>XII</u>). Two grams (4.3 x 10^{-3} mole) of benzyl-N-carboethoxy-3,4,6-tri-O-acetyl-β-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°C. The solid thus obtained was washed with water and recrystallized from alcohol, M. P. 195-96°C.; yield 1.1 g. (3.2 x 10^{-3} mole) (78.5 per cent).

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

<u>Analysis</u>:

$C_{16}H_{23}O_7N$ (341.362)

	% C	% H	% O
<u>Found</u>	55.12	6.72	32.07
<u>Calculated</u>	55.50	6.80	32.52

Rotation:

$$[\alpha]_D^{25} = -47^\circ C. \ (C = 1.38\% \text{ in pyridine})$$

Benzyl-3,4,6-tri-O-benzoyl-N-carboethoxy-β-D-glucosaminide (XIII). Two grams (5.8×10^{-3} mole) of benzyl-N-carboethoxy-β-D-glucosaminide (XII) were dissolved in pyridine (10 ml.), and the solution was cooled to $0^\circ C$. Benzoyl chloride 1.6 ml. (23.2×10^{-3} mole) was added dropwise while stirring at $0^\circ C$. 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. (4.3×10^{-3} mole) (81.5 per cent).

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

Analysis: $C_{37}H_{35}O_{10}N$ (653.695)

	% C	% H	% O
Found	69.49	5.17	25.14
Calculated	69.90	5.20	25.40

Rotation:

$$[\alpha]_D^{25} = -29.2^\circ C. \ (C = 1.2\% \text{ in pyridine})$$

Tertiary butyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-β-D-glucosaminide (IId). Three grams (4.4×10^{-3} mole) of

α-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. (17.6×10^{-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. (1.6×10^{-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'-oxazolidene (III) by mixed
melting point with authentic sample. Yield 0.5 g. (0.96 x
10^{-3} mole) (16.7 per cent).

Properties: (IId) is soluble in dioxane, acetic acid,
and chloroform, but insoluble in petroleum ether and cyclo-
hexane.

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

	% C	% H	% O
Found	69.91	5.75	24.61
Calculated	69.50	5.75	24.10

Rotation:

$$[\alpha]_D^{25} = +15.7°C. \quad (C = 1.43\% \text{ in pyridine})$$

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 dropwise 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.

Rotation:

$$[\alpha]_D^{25} = -21.0^oC. \quad (C = 0.96\% \text{ in water})$$

n-Butyl-N-carbobenzoxy-β-D-glucosaminide (VIIIc);
Ten grams (1.47 x 10^{-3} mole) of n-butyl-N-carbobenzoxy-3,4,6-
tri-O-benzoyl-β-D-glucosaminide (IIc) were dissolved in
dioxane (180 ml.). Ninety milliliters of 0.5N aqueous potas-
sium 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°C. The residue
thus obtained was washed with water and recrystallized from
alcohol-ether mixture, M. P. 175-76°C.; yield 4.4 g. (1.2 x
10^{-3} mole) (81.5 per cent).

Properties: (VIIIc) is soluble in acetic acid and
methanol, but insoluble in ether, petroleum ether, cyclo-
hexane, and chloroform.

Analysis: $C_{18}H_{27}O_7N$ (369.422)

	% C	% H	% O
Found	59.14	7.35	33.56
Calculated	58.70	7.50	33.00

Rotation:

$$[\alpha]_D^{25} = -35^oC. \quad (C = 1.43\% \text{ in pyridine})$$

50

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: $C_{10}H_{22}O_5NCL$ (271.665)

	% C	% H	% O	% Cl
Found	41.73	8.24	31.97	13.11
Calculated	41.40	8.20	31.6	13.10

Rotation:

$[\alpha]_D^{25}$ = - 21.4°C. (C = 1.4% in water)

Cyclohexyl-N-carbobenzoxy-β-D-glucosaminide (VIIIf). Ten grams (1.3 x 10^{-3} mole) of cyclohexyl-N-barbobenzoxy-3,4,6-tri-O-benzoyl-D-glucosaminide (IIf) were dissolved in dioxane (180 ml.). Ninety ml. of 0.5N aqueous potassium

hydroxide (4.0 x 10^{-3} 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 x 10^{-3} mole) (80 per cent).

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

Analysis: $C_{20}H_{29}O_7N$ (395.460)

	% C	% N	% O
Found	61.42	7.57	27.52
Calculated	61.00	7.40	27.30

Rotation:

$[\alpha]_D^{25}$ = -45.6°C. (C = 1.374% in pyridine)

Cyclohexyl-β-D-glucosamine hydrochloride (IXf).
Three grams (7.6 x 10^{-3} mole) of cyclohexyl-N-carbobenzoxy-β-D-glucosaminide (VIIIf) 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 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: $C_{12}H_{24}O_5NCl$ (297.665)

	% C	% H	% O	% Cl
Found	43.70	7.65	27.59	15.06
Calculated	43.5	7.15	27.00	14.80

Rotation:

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

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: $C_{15}H_{26}O_8NBr$ (428.124)

	% C	% H	% O	% Br
Found	40.71	5.99	28.83	20.86
Calculated	40.80	6.15	28.70	20.60

Rotation:

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

Isopropyl-N-carboethoxy-3,4,6-tri-O-acetyl-β-D-glucosaminide (XVII). Two grams (4.7×10^{-3} mole) of isopropyl-3,4,6-tri-O-acetyl-β-D-glucosamine hydrobromide (XVI) were suspended in chloroform (25 ml.) and ethyl chloroformate 0.8 ml. (9.4×10^{-3} 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. (3.35×10^{-3} 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)

	% C	% N	% O
Found	52.01	6.72	37.31
Calculated	51.60	7.00	37.20

Rotation:

$[\alpha]_D^{25}$ = - 10.8°C. (C = 1.39% in pyridine)

1,3,4,6-tetra-O-acetyl-N-carbobenzoxy-α-β-D-glucosamine (XXIV) (46). Ten grams (3.2 x 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 x 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)

	% C	% H	% O	% Cl
Found	54.70	5.66	36.50	0.0
Calculated	54.80	5.60	36.60	0.0

Rotation:

$$[\alpha]_D^{25} = +24.0°C. \quad (C = 1.252\% \text{ in chloroform})$$
$$[\alpha]_D^{25} = +22.2°C. \quad (C = 1.354\% \text{ in pyridine})$$

Benzyl-N-carbobenzoxy-3,4,6-tri-O-benzoyl-α-D-glucosaminide (XX). Four grams (1×10^{-3} mole) of benzyl-N-carbobenzoxy-α-D-glucosaminide (XIX) (16) were dissolved in pyridine (20 ml.) and cooled to $0°C$. Benzoyl chloride 1.6 ml. (3.5×10^{-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. (0.78×10^{-3} mole) (79 per cent).

Properties: (XX) is soluble in alcohol, ether dioxane and acetic acid but insoluble in water.

<u>Analysis</u>: $C_{42}H_{37}O_{10}N$ (715.766)

	% C	% H	% O
<u>Found</u>	69.49	5.17	25.14
<u>Calculated</u>	70.00	5.20	25.40

<u>Rotation</u>:

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

n-<u>Propyl-N-carbobenzoxy-3-O-benzoyl-4,6-O-benzylidene</u>-
β-<u>D-glucosaminide</u> (<u>XXIVa</u>). Freshly fused zinc chloride 0.7
g. (5.15 x 10^{-3} mole) was dissolved in benzaldehyde (40 ml.).
n-Propyl-3-O-benzoyl-N-carbobenzoxy-β-D-glucosaminide 0.7 g.
(1.52 x 10^{-3} 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 recrystallized from tetrahydrofuran-ether
mixture, M. P. 230-31°C.; yield 0.75 g. (0.37 x 10^{-3} 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°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 (SN_2) and nucleophilic substitution of bromide by the neighboring benzyloxy carbonyl group intramolecularly (SN_1).

In the presence of alcohol, the SN_2 reaction predominates over SN_1. 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 SN_2 reaction. The decrease

in the rate of the 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, $\Delta\Delta E_s^{\ddagger}$, 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 com-
pound (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 SYNTHESES

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 (VIIIf) 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 α-anomer (XX) has a low melting point, high optical rotation, and high solubility in organic solvents. However the β-anomer (IIe) has a high melting point, low optical rotation, and low solubility in organic solvents.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. H. C. Brown. *Hydroboration*. New York: W. A. Benjamin, Inc., 1962.

2. F. M. Burnet. *Annu. Rev. Microbiol.* 6, 229 (1952).

3. Chaikin and W. G. Brown. *J. Am. Chem. Soc.* 71, 122 (1949).

4. E. Chargaff and M. Bovarnick, *J. Biol. Chem.* 118, 421 (1937).

5. W. R. C. Crimmin. *J. Chem. Soc.* 2838 (1957).

6. W. O. Cutler, W. N. Haworth, and S. Peat. *J. Chem. Soc.* 1979 (1937).

7. W. O. Cutler and S. Peat. *J. Chem. Soc.* 274 (1939).

8. _____. *J. Chem. Soc.* 782 (1939).

9. P. B. D. De la Mare, E. D. Hudges, C. K. Ingold, and J. D. H. Mackie. *J. Chem. Soc.* 3169-3187 (1955).

10. R. C. Elderfield. *Heterocyclic Compounds 5.* New York: John Wiley & Sons, 1957.

11. E. Fischer and M. Bergmann. *Ber.* 50, 1047 (1917).

12. G. Fodor and L. Otvos. *Chem. Ber.* 89, 701 (1956).

13. A. B. Foster, D. Horton, and M. Stacey. *J. Chem. Soc.* 81 (1957).

14. A. B. Foster, M. Stacey, and S. Verdheim. *Acta. Chem. Scand.* 13, 281 (1959).

15. E. S. Gould, *Mechanism and Structure in Organic Chemistry.* New York: Holt, Rinehart and Winston, 1962.

16. P. Gross, K. Brendel, and H. K. Zimmerman. "Aminozuckersynthesen XIII" *Liebigs Ann.* in press.

17. _____. "Aminozuckersynthesen VIII," *Liebigs Ann.* in press.

18. _____. *Angewandte Chemie,* 76, 377 (1964).

19. W. N. Haworth, W. H. G. Lake, and S. Peat. *J. Chem. Soc.* 271 (1931).

20. W. N. Haworth and S. Peat. *J. Chem. Soc.* 3094 (1926).

21. B. Helferich and K. Weis. *Chem. Ber.* 89, 314 (1956).

22. K. Heyns and H. Paulsen. *Chem. Ber.* 88, 188 (1955).

23. A. C. Hill. *J. Chem. Soc.* 83, 589 (1903).

24. C. S. Hudson (ed.). *Advances in Carbohydrate Chemistry,* 7. New York: Academic Press, 1952.

25. C. K. Ingold. *Structure and Mechanism in Organic Chemistry.* Ithaca, New York: Cornell University Press, 1953.

26. T. Ito. *Chem. Pharm. Bull. Japan,* 12, 499-501 (1964).

27. S. P. James, F. Smith, M. Stacey, and L. F. Wiggins. *J. Chem. Soc.* 625 (1946).

28. R. W. Jeanloz. *J. Am. Chem. Soc.* 76, 555 (1954).

29. _____, H. G. Fletcher, and C. S. Hudson. *J. Am. Chem. Soc.* 70, 4052 (1948).

30. E. A. Kabat. *Annu. Rev. Biochem.* 15, 505 (1946).

31. P. W. Kent and M. W. Whitehouse. *Biochemistry of Amino-sugars.* London: Butterworths Scientific Publications, 1955.

32. S. Konstas, I. Photaki, and L. Zervas. *Chem. Ber.* 92, 1288 (1959).

33. S. R. Kulkarni and H. K. Zimmerman. *Liebigs Ann. Chem.* 663, 174-77 (1963).

34. R. Kuhn and W. Kirschenlohr. *Chem. Ber.* 86, 1331 (1953).

35. G. Ledderhose. *Z. Physiol. Chem.* 2, 213 (1878).

36. P. A. Levene. *J. Biol. Chem.* 26, 143 (1916).

37. _____ and F. B. LaForge. *J. Biol. Chem.* 18, 123 (1914).

38. P. F. Loyd and M. Stacey. *Chem. and Ind.* 917 (1955).

39. F. J. McEvoy, B. R. Baker, and M. J. Weis. _J. Am. Chem. Soc._ _82_, 205-09 (1960).

40. F. Michael and H. Kochling. _Chem. Ber._ _90_, 1597 (1957).

41. F. Michael, F. P. Van De Kamp, and H. Wulf. _Chem. Ber._ _88_, 2011 (1955).

42. R. C. G. Moggridge and A. Neuberger. _J. Chem. Soc._ 745 (1938).

43. C. J. Morel. _Helv. Chim. Acta_, _41_, 1501 (1958).

44. R. K. Ness, H. G. Fletcher, and C. S. Hudson. _J. Am. Chem. Soc._ _72_, 2200 (1950).

45. A. Neuberger. _J. Chem. Soc._ 50 (1941).

46. _____ and R. P. Rivers. _Biochem. J._ _33_, 1580 (1939).

47. M. S. Newman. _Steric Effects in Organic Chemistry._ New York: John Wiley & Sons, Inc., 1956.

48. W. Pigman. _The Carbohydrates: Chemistry, Biochemistry, Physiology._ New York: Academic Press, Inc., 1957.

49. H. Pringsheim, J. Bondi, and J. Leibwitz. _Chem. Ber._ _59_, 1983 (1926).

50. M. Stacey (ed.). _Advances in Carbohydrate Chemistry_, _2_, 216 (1946).

51. P. J. Stoffyn and R. W. Jeanloz. _J. Am. Chem. Soc._ _80_, 5690 (1958).

52. R. W. Taft, Jr. _J. Am. Chem. Soc._ _74_, 4534 (1953).

53. S. Umezawa, S. Koto, and Y. Ito. _Bull. Chem. Soc. Japan_ 36, 183-86 (1963).

54. H. Weidman and H. K. Zimmerman. _Chem. Ber._ _92_, 2828-32 (1959).

55. _____. _Chem. Ber._ _92_, 1523-26 (1959).

56. _____. _Liebigs Ann. Chem._ 633, 198 (1960).

57. R. L. Whistler (ed.). _Methods in Carbohydrate Chemistry_, _2_. New York: Academic Press, Inc., 1963.

58. M. L. Wolfrom (ed.). _Advances in Carbohydrate Chemistry_, _14_. New York: Academic Press, Inc., 1959.

59. M. L. Wolfrom (ed.). *Advances in Carbohydrate Chemistry*, *15*. New York: Academic Press, Inc., 1960.

60. G. Zemplén and R. Bognár. *Ber.* *72*, 1160 (1939).

61. G. Zemplén and E. Pacsu. *Ber.* *72*, 1613 (1929).

62. L. Zervas and S. Konstas. *Chem. Ber.* *93*, 435 (1960).