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# STUDIES OF THE CLEAVAGES AND STABILITIES OF CARBOHYDRATE EPOXIDES AND EPIMINES

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A Dissertation

Presented to

the Faculty of the Graduate School

University of the Pacific

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

---

by

Curtis Alvin Johnson

September 1971

This dissertation, written and submitted by

Curtis A. Johnson,

is approved for recommendation to the Graduate Council, University of the Pacific.

Department Chairman or Dean:

Dissertation Committee:

Paul Groß.

Donald K. Wedegaertner

Dated 9-10-71

# STUDIES OF THE CLEAVAGES AND STABILITIES OF CARBOHYDRATE EPOXIDES AND EPIMINES

## Abstract of Dissertation


A novel epoxide ring opening of benzyl 3,4-anhydro-2-benzyloxcarbonylamido-2-deoxy-β-D-allopyranoside(I) was effected by phenylboronic anhydride in toluene. One of the products was demonstrated to be benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulopyranoside. Another product isolated, while not identified, had the properties of an anhydro-sugar different from the starting compound(I). Benzyl 6-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside(II) also underwent epoxide ring opening in a reaction with phenylboronic acid. An isolated product had the properties of a benzyl 2-benzyloxycarbonylamido-2-deoxy-D-hexoside different from compounds isolated in the reaction of I with the phenylboronate. This indicated the necessity for an unsubstituted 6-OH group in order for the boron compound to be involved in the ring opening. Supporting this view is the lack of reaction between the blocked benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside and phenylboronic anhydride.

The 2,3-epoxide ring of benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside(III) was shown to be remarkably stable in a reaction with boron acetate in nitromethane. The product had retained the 2,3-epoxide ring under conditions that removed the benzylidene group.

Trimethylsilyl azide was prepared in good yield in a mild and direct method. The azide was then used to prepare a new, low-melting, compound by silation of the 6-OH group of I. The epoxide ring remained stable under these conditions.

The epimine ring of benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside(IV) was found to be unreactive with phenylboronate. However IV was deaminated with $HNO_2$ to give the 2,3-unsaturated derivative of IV. This derivative was then cis-hydroxylated with $KMnO_4$ to give benzyl 4,6-O-benzylidene-α-D-mannopyranoside.

## ACKNOWLEDGMENTS

The author wishes to express his sincere appreciation to the members of the Department of Chemistry of the University of the Pacific for their assistance during his period of study. He especially wishes to express appreciation to Dr. Paul H. Gross whose wide knowledge of carbohydrate research, and creative assistance was invaluable in completing the research and dissertation.

The author is indebted to his wife, Louise, whose forbearance and encouragement enabled him to see this work through.

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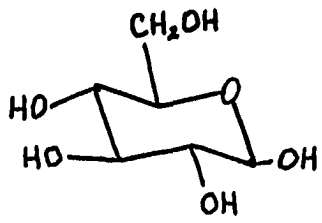
# CHAPTER I

## INTRODUCTION

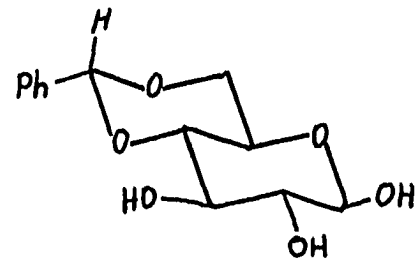
The ring opening reactions which epoxy-sugars undergo make them versatile and valuable intermediates for the preparation of epimeric sugars. The epoxide rings are usually opened by reagents that are either strongly basic or strongly acidic. In many cases the particular sugar derivative contains functional groups that would be cleaved by strong acids or bases. It would be convenient to have reagents that are effective in cleaving epoxides and at the same time unreactive toward other functional groups.

The purpose of this study was to test the reactivity of sugar epoxides toward novel, ring-opening reagents. The study is especially concerned with the opening of the epoxide ring of benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside, which has been found to be quite stable.[1] These reagents were also used in a comparative study of the reactivity of epimino rings of sugars. Epimino rings react in a manner analogous to epoxide rings. They have also been found to be quite stable in sugars.[2,15]

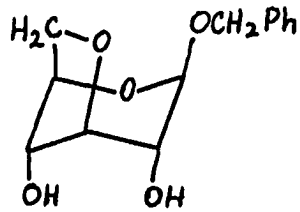
When sugar epoxides with pyranoid rings are cleaved the possible products depend upon the configuration of the sugar molecule and the conformation in the transition state of the reaction. Generally the preferred conformation in the ground state is the C 1 chair conformation which can be represented by β-D-glucopyranose in which all substituents other than H are equatorial in the stable conformation (Figure 1). The pyranoid ring has two chair conformations, but may be locked in one



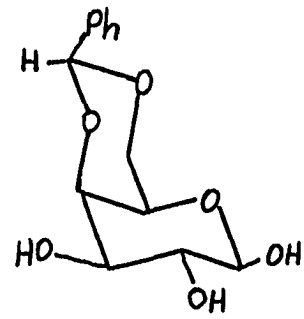

β-D-glucopyranose



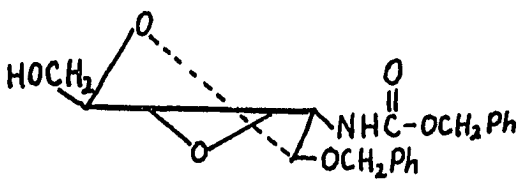

4,6-O-Benzylidene
β-D-glucopyranose




Benzyl 3,6-anhydro
β-D-glucopyranoside




4,6-O-Benzylidene
β-D-galactopyranose

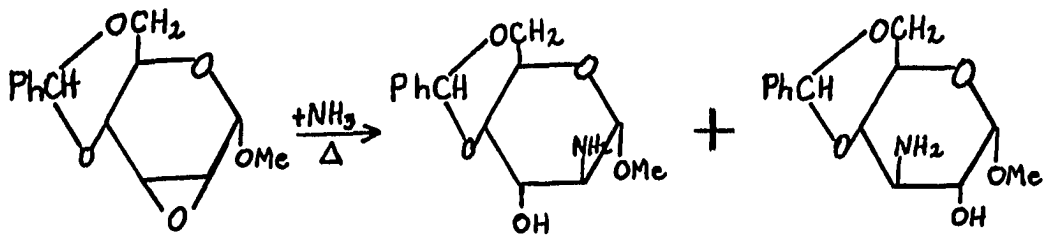



Benzyl 3,4-anhydro-2-benzyl-
oxycarbonylamido-2-deoxy-
β-D-allopyranoside

FIGURE 1.
Conformational Formulas of
Various Carbohydrate Compounds

chair conformation by fusion trans to another ring system. The pyranoid ring of 4,6-O-benzylidene-β-D-glucopyranose is fixed in the C 1 chair conformation by fusion to the benzylidene group. In benzyl 3,6-anhydro-β-D-glucopyranoside the conformation is also fixed. In this case the chair conformation is 1 C, and all substituents other than H are axial. If the pyranoid ring is fused cis to another ring then steric factors favor the C 1 conformation. The pyranoid ring in this type of system is somewhat restricted in flexibility, but not to one conformation, and 4,6-O-benzylidene-β-D-galactopyranose illustrates this case.[3] An epoxide ring is always fused cis to the pyranoid ring, and the pyranoid ring is then considered to be in a "half-chair" conformation.[4] Our starting material, benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside, has such a half-chair conformation.

When ammonia is used to cleave sugar epoxides, amino sugars are formed. The ammonia will always add in such a way as to give a trans-related amino alcohol as a result of Walden inversion at the point of cleavage. Thus, there is a possibility of formation of two isomeric amino sugars. For example, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside gives a mixture of methyl 2-amino-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside and methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-glucopyranoside[5] (Figure 2, Reaction 1). This result is an illustration of the Fürst-Plattner rule:[6] "When an epoxide is attached to a rigid six member ring, which is fixed in one conformation, C 1 in this case, the epoxide opens so that the new groups are predominantly in axial positions". Thus the altro compound is the main product. The pyranoid

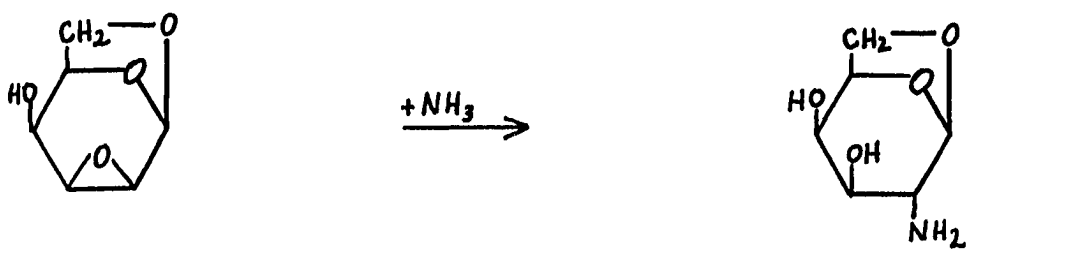



Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside

Methyl 2-amino-4,6-O-benzylidene-2-deoxy-α-D-altropyranoside

Methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D glucopyranoside

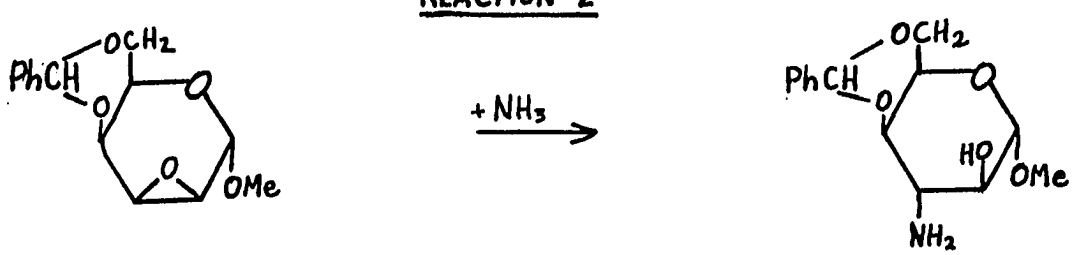
**REACTION 1**




1,6:2,3-Dianhydro β-D-talopyranose

2-Amino-1,6-anhydro-2-deoxy-β-D-galactopyranose

**REACTION 2**




Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-talopyranoside

Methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-idopyranoside

**REACTION 3**

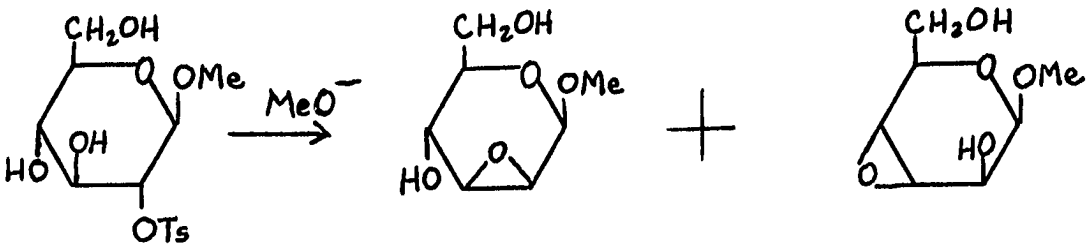
FIGURE 2.
Stereochemical Course of
Sugar Epoxide Cleavages

ring of 1,6:2,3-dianhydro-β-D-talopyranose is forced into the 1 C chair conformation. Ammonolysis of this 2,3 epoxide ring also gives the diaxial isomer, 2-amino-1,6-anhydro-2-deoxy-β-D-galactopyranose as the major product[7] (Figure 2, Reaction 2). The pyranoid ring of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-talopyranoside is in the C 1 conformation. Ammonolysis of its epoxide ring gives the diaxial isomer, methyl 3-amino-4,6-O-benzylidene-3-deoxy-α-D-idopyranoside[8] (Figure 2, Reaction 3).

In a flexible pyranoid sugar ring system, however, it is more difficult to predict which isomer will predominate.[9]

Intramolecular reactions of epoxides are well-known. When methyl 2,3-anhydro-β-D-mannopyranoside is formed by the reaction of sodium methoxide with methyl 2-O-toluene-p-sulfonyl-β-D-glucopyranoside it is always accompanied by some methyl 3,4-anhydro-β-D-altropyranoside[10] (Figure 3, Reaction 1). Presumably an alkoxy anion, formed at the 4-position, attacks the 3-position of the initially formed 2,3-epoxide forming the 3,4-epoxide. A neighboring group-assisted opening of the epoxide ring of benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-α-D-galactopyranoside was accomplished by heating in an acidic medium[1] (Figure 3, Reaction 2). The benzyl α-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone was formed. The formation of an oxanium ion is believed to induce ring-closure across the 2-and 3- positions.

The epoxide ring of benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside is not subject to a neighboring group-assisted opening from the benzyloxycarbonyl group. There is a cis relationship

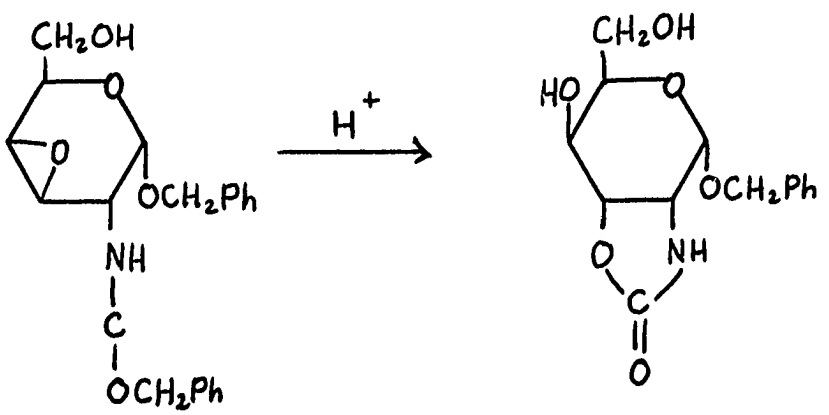



Methyl 2-O-toluene p-sulfonyl β-D-glucopyranoside

Methyl 2,3-anhydro-β-D-mannopyranoside

Methyl 3,4-anhydro-β-D altropyranoside

REACTION 1




Benzyl 3,4-anhydro-2-benzyloxycarbonyl-2-deoxy-α-D-galactopyranoside

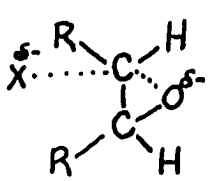
Benzyl α-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone

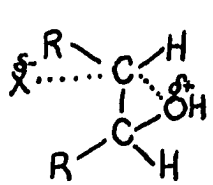
REACTION 2

FIGURE 3.
Intramolecular Reactions of
Sugar Epoxides

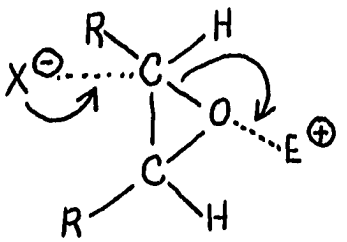
between the 2- and 3-positions. However, it is possible that a group at the 6-position could attack the 3-position forming a 3,6-anhydro gluco derivative. The product would have the 1 C chair conformation. Another possibility is an intermolecular trans ring opening of the 3,4 epoxide ring of the allo derivative by reagents to be discussed in this chapter. This could lead to a gluco or a gulo derivative.

The cleavages of epoxides are generally considered as nucleophilic substitution reactions. The C—O bond in epoxy compounds is much more easily broken than the normal ether C—O bond. This abnormal behavior of the epoxy function is considered to be caused by ring strain. Many reagents can be used to open the ring.[11] Water and alcohols are effective, with an acid catalyst, as well as alkoxide, phenoxide, and alkylsulfide ions. As mentioned previously ammonia also opens epoxides. Primary and secondary alkyl and aryl amines also substitute on epoxides. The addition of organometallic compounds to ethylene oxide is a well-known method of lengthening a carbon chain by two carbon atoms. Reduction of epoxides by lithium hydride can also be classified as a nucleophilic substitution of an oxygen by a hydride ion. The mechanism of these substitutions is probably of the $S_N2$ kind,[11] although acid-catalyzed hydrolyses of simpler epoxides in water may proceed through carbonium-ion intermediates.[12] The transition states may be represented as:





In the absence of acid other cations are likely to be involved in the ring opening simultaneously with the nucleophile.[13] A generalized way of representing the transition state according to this view is as follows:




This view would help to explain why the nucleophile can displace such a poor leaving group as the alkoxy anion. The cation coordinates with the epoxide and helps to reduce the charge separation during the actual ring cleavage. Support for this view can be found in the fact that acid catalyzed opening of epoxides occurs usually under much milder conditions than base catalyzed opening. The transition state of a cation-catalyzed species should be much lower in energy than that of the uncatalyzed species. Consequently there should be a considerable cation effect in nucleophilic epoxide openings.

The above mentioned ideas led us to the investigation of a number of new potential epoxide cleaving reagents, especially boron and silicon compounds. The reactivity and stability of epoxides with respect to these new cleavage reagents was investigated. As substrates we chose mostly sugar epoxides and epimines which have become available by earlier work in this laboratory,[1,14,15] or closely analogous compounds.

The synthetic uses of carbohydrate epoxides are numerous and varied.[16] Sugar epoxides are commonly used for the synthesis of new sugars. The

conditions for opening sugar epoxides are usually fairly harsh. Use of good electrophiles such as $Li^+$, $R-\overset{R}{\underset{R}{Si}}{}^+$, and such Lewis acids as boron compounds should assist cleavage of epoxides under mild conditions. Lithium iodide has been found to cleave sugar epoxides.[17] Trimethylsilyl chloride has been found to cleave simple aliphatic epoxides.[18] Trimethylsilyl azide could react in an analogous way and introduce $-N_3$ instead of chlorine into the molecule. Boron trichloride is commonly known to cleave ethers, but probably would cause rearrangement and polymerization along with introduction of chlorine into the sugar molecule. Boric acids and boric esters should be good electrophiles, and yet be milder than boron chloride. Also, chlorine would not be introduced into the sugar molecule if boric acids or boric esters were usable.

Solvents for the epoxide cleavages should be chosen that leave the electrophile free to attach to the epoxide. Chloroform, benzene, or toluene are good solvents for many sugar derivatives and should not form complexes with cations. If the cleaving reagent were not soluble in these solvents more polar solvents may be needed.

The proposed investigation made necessary:

(a) The preparation of suitable starting materials,

(b) The preparation of materials for comparison with possible products of the epoxide cleavages,

(c) Investigation of the reaction of sugar epoxides and epimines with boron compounds of low acidity,

(d) Investigation of the reaction of sugar epoxides and epimines with silicon compounds, e.g., trimethylsilylazide,

(e) Reaction with other possible reagents, with electron deficiency, e.g., $HNO_2$ and carbonyl compounds.

# CHAPTER II

## METHODS AND DISCUSSION OF RESULTS

### I. PREPARATION OF SUITABLE STARTING MATERIALS

The sugar compounds used for this study are generally rare compounds of very limited supply and are not available commercially. The general procedures for their preparation are presented in this section. More detailed preparation procedures and the properties of the substances are presented in Chapter III. Come of them had been prepared earlier in this laboratory. Others were new compounds prepared during this study. Comparison to similar compounds from this laboratory, and the use of ir spectra and optical rotation allowed easy characterizations of these new compounds.

Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) was prepared from chitin (poly-N-acetyl-glucosamine) following procedures developed or applied in this laboratory. Chitin was hydrolyzed with hydrochloric acid to give 2-amino-2-deoxy-D-glucopyranose hydrochloride,[19] the amino group of which was then protected by reaction with carbobenzoxy chloride.[20,21] The resulting 2-benzyloxycarbonylamido-2-deoxy-D-glucose was reacted with benzyl alcohol in the presence of hydrochloric acid to form an α, β anomeric mixture of benzyl 2-benzyloxycarbonylamido-2-deoxy-D-glucose.[22] By reaction with benzaldehyde/$ZnCl_2$, followed by methanesulfonylation, benzyl 4,6-benzylidene-2-benzyloxycarbonylamido-2-deoxy-3-O-methanesulfonyl-D-glucopyranoside was obtained as an anomeric mixture, which was separated by fractional

crystallization as described by Gross and Zimmerman.[22]

Cleavage of the benzylidene function of the pure benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside with aqueous acetic acid, gave benzyl 2-benzyloxycarbonylamido-2-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside (Ib).[22] The α-anomer (Ia)[22] was obtained analogously. When Ia or Ib were reacted with aqueous base the α or β anomer of benzyl 2-benzyloxycarbonylamido-3,4-anhydro-2-deoxy-D-allopyranoside (IIa or IIb) was obtained (Figure 5). The procedure used here varies somewhat from the previous methods.[1] The 3,4-anhydro derivatives were prepared with base directly from Ia and Ib without intermediate acetylation of the hydroxyl groups, as described before.[1]

In order to assess the influence of the 6-OH group on ring opening of the 3,4-epoxides (IIa and IIb) three other new compounds were prepared (Figure 5). Two of these compounds, benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) and its α anomer (IIIa) were formed by the reaction of acetic anhydride with IIa or IIb in pyridine. It is of interest that the 3,4-epoxide ring is stable under these conditions. Epoxy sugars are normally acid-labile and do not withstand acetolysis.[23] The third compound with the 6-position substituted was benzyl 3,4-anhydro-6-O-benzyl-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IVb). It was prepared by an adaption of the methylation method of Kuhn, Low and Trischmann.[24] This possibility to alkylate an epoxy sugar in a basic medium with $Ba(OH)_2/DMF/PhCH_2Br$, with the retention of the epoxy function, is also a novelty. The study

| | | |
|---|---|---|
| Ac- | : | $-COCH_3$ |
| Bz- | : | $-COC_6H_5$ |
| Cbz- | : | $-COOCH_2C_6H_5$ |
| Ms- | : | $-SO_2CH_3$ |
| Ph- | : | $-C_6H_5$ |
| Ts- | : | $-SO_2C_6H_5CH_3$ |
| a | : | $\alpha$ anomer |
| b | : | $\beta$ anomer |

Explanation of Symbols

Figure 4

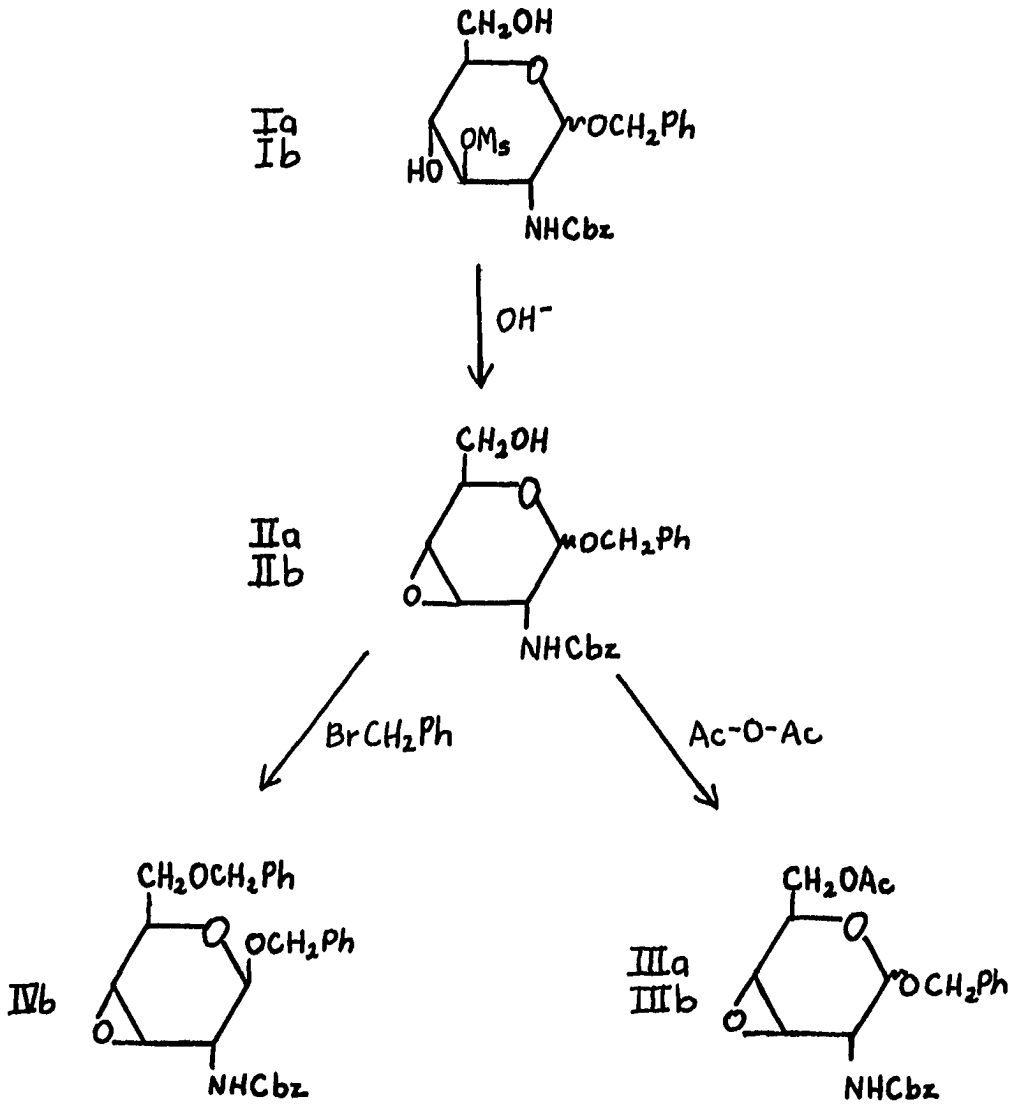



FIGURE 5. Preparation of Benzyl 3,4-anhydro-2-benzyloxycarbonyl-amido-2-deoxy α and β-D-Allopyranoside Acetyl Derivatives

of these compounds which were substituted at $C_6$ was not followed through since the reaction of IIIb with phenylboronate gave several products.

The epimino ring of carbohydrates was studied in order to provide a comparison to the epoxy ring. Two epimino sugars were available by direct means from materials available in this laboratory. Following the procedures of Rhoads and Gross, benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-β-D-allopyranoside (VIb) was prepared by heating benzyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-O-mesyl-β-D-glucopyranoside (Vb) with sodium isopropoxide in isopropanol.[15] The α anomer (VIa) was prepared by treating benzyl 4,6-benzylidene-2-benzyloxycarbonylamido-3-O-mesyl-α-D-glucopyranoside[22] (Va) in a like manner (Figure 6).

Benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (XVII) was needed to make studies comparative to the reactions of the 3,4-anhydro derivative. It had been prepared by Chiu and Gross.[14]

## II. PREPARATION OF MATERIALS FOR COMPARISON TO PRODUCTS

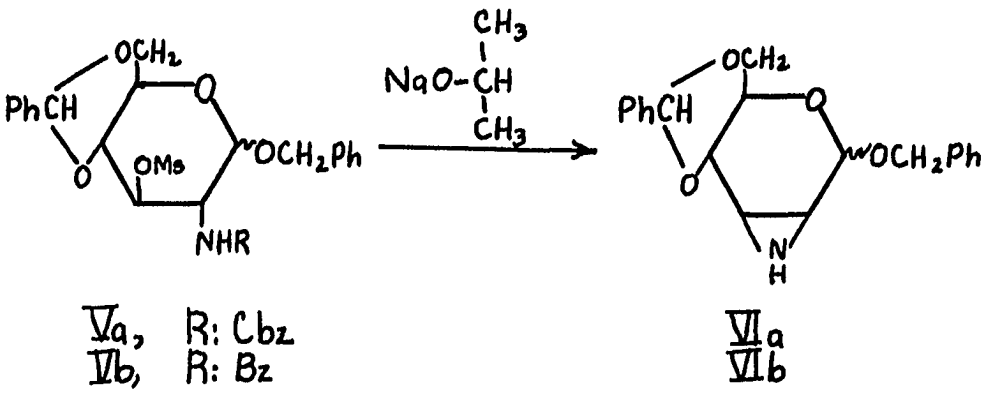
One of the most conclusive means of identification of new products is the synthesis of substances with identical properties by unequivocal routes. Many synthetic routes to known substances were available starting with the compounds previously prepared in this laboratory. This section describes, in general, the syntheses used for that purpose in this study. A more detailed description of experimental procedures is given in Chapter III.

Two new compounds prepared were benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (VIII) and its debenzylidinated

derivative, benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IX)(Figure 7). Compound IX was needed as a comparative compound for identification of possible products. It was considered possible that the epoxide ring of IIb could coordinate with phenylboronic anhydride and undergo a cis opening producing IX. While a cis opening of an epoxide ring is unlikely, stabilization of the leaving oxide ion, by coordination with the boron compound, could lead to cis addition to the resulting carbonium ion. Compound VIII was prepared by reaction of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside[58](VII) with benzyloxycarbonyl chloride in a mixture of chloroform and aqueous-$KHCO_3$. The benzylidene group of VIII was removed by slow addition of water to its hot acetic acid solution giving IX.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV) was also a possible product of the epoxide ring opening of IIb. It was prepared from benzyl β-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone[25] (X)(Figure 8). Compound X was changed to the benzylidene compound, benzyl 4,6-O-benzylidene-β-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone (XI) by reaction with benzaldehyde in the presence of $ZnCl_2$. Compound XI was changed to the free amino compound benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-gulopyranoside (XII) by heating in an aqueous-ethanol-KOH solution. Carbobenzoxy chloride was then added to XII to give benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIII). Finally the benzylidene group was removed from XIII by acetic acid and water to give XIV.

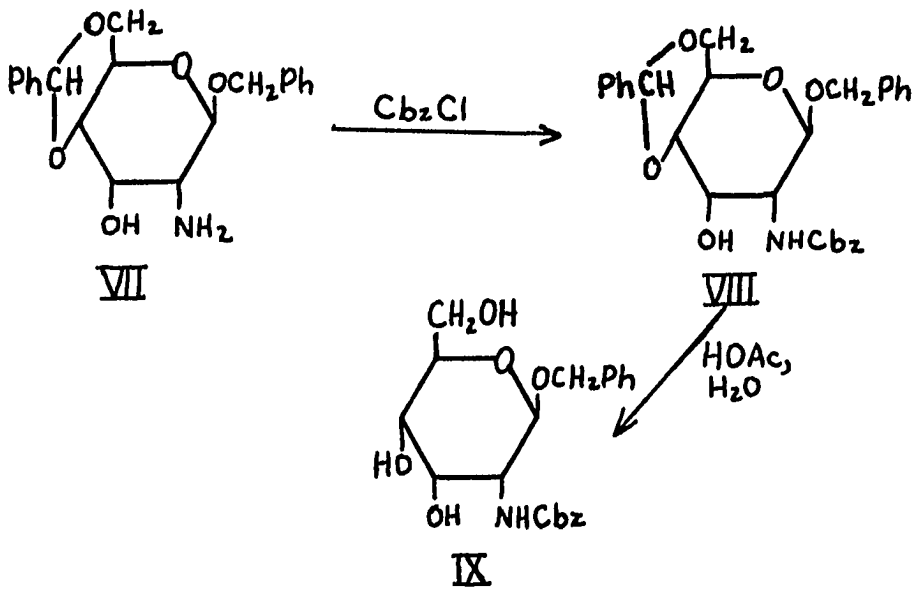
Ring opening reactions of the 2,3-anhydro allopyranoside derivative




Va, R: Cbz
Vb, R: Bz

VIa
VIb

FIGURE 6. Preparation of Benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino- and β-D-Allopyranoside




VII

VIII

IX

FIGURE 7. Preparation of Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-Allopyranoside

(XVII) could lead to either altropyranoside or glucopyranoside derivatives. Benzyl 4,6-O-benzylidene-α-D-glucopyranoside (XV) was available in this laboratory.[14] It was reacted with glacial acetic acid and water to give the debenzylidenated derivative (XVI)(Figure 9). Benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside[14](XVII) was heated with hot KOH solution to give benzyl 4,6-O-benzylidene-α-D-altropyranoside (XVIII) which was debenzylidenated with acetic acid and water to give XIX (Figure 10).

A possible product from the ring opening reactions of the 3,4-anhydro-allo derivative (IIb) is benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXVII). Two procedures were available for the synthesis of 3,6-anhydro derivatives of glucosamines.

One of these procedures, described by Foster, Stacey, and Vardheim[26] used methyl 2-benzyloxycarbonylamido-2-deoxy-6-O-tosyl-β-D-glucopyranoside in reaction with base to form methyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside.[26] Under these conditions no inversion occurs at $C_3$. The tosyl group at $C_6$ is readily displaced and the 3,6-anhydro ring is unequivocally formed, the formation of other rings being sterically impossible. The second procedure described by Reckendorf and Bonner used methyl 2-benzamido-2-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside as starting material for the preparation of a 3,6-anhydro derivative.[27] In this case there are other possible products. The OH group at $C_4$ could attack with inversion at $C_3$ to form a 3,4-anhydro derivative of the allo configuration. Also the benzamido group at $C_2$ could attack at $C_3$ to form either an oxazoline or epimine derivative of the allo configuration. The 3,6-anhydro derivative which Reckendorf and Bonner

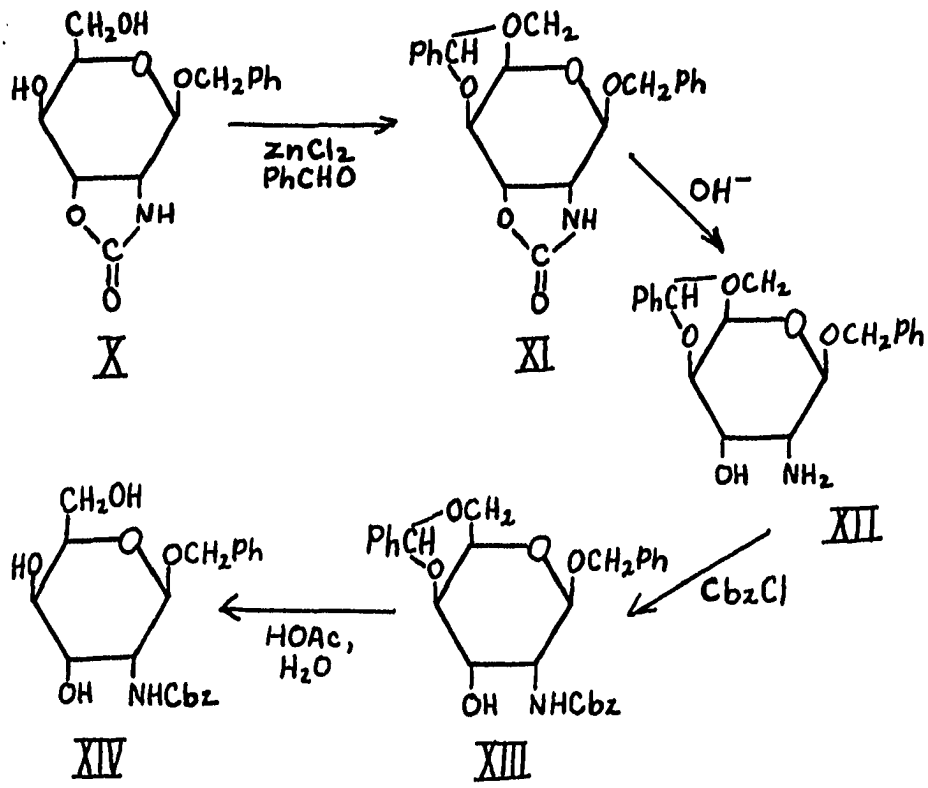



FIGURE 8. Preparation of
Benzyl 2-benzyloxycarbonylamido-2-deoxy-
β-D-Gulopyranoside

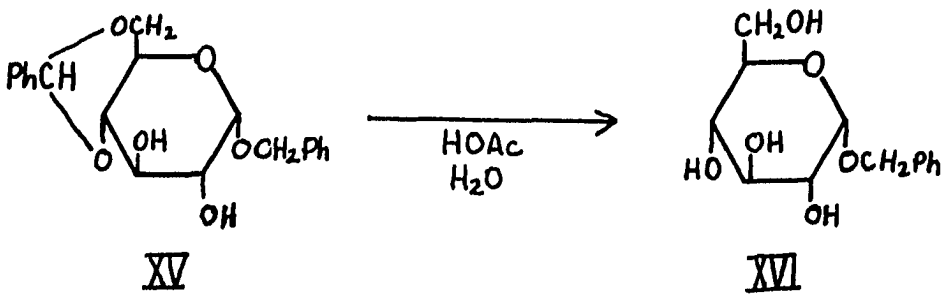



FIGURE 9. Preparation of
Benzyl α-D-Glucopyranoside

obtained in fact was assumed to result from a second inversion at $C_3$ by attack of the $C_6$ hydroxyl on an intermediate oxazoline.

Following the procedures of Reckendorf and Bonner[27] a similar compound was treated in like manner. This similar compound, benzyl 2-benzamido-2-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside (XXI), was reacted with $NaOCH_3$ to give benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (XXII)(Figure 11). Compound XXII decomposed in methanolic-aqueous KOH at room temperature. The 3,6-anhydro derivative (XXVII), prepared by the unequivocal procedure to be described later, was stable under these conditions. The ir spectrum of XXII was not the same as that of benzyl 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXX) prepared from XXVI. The ir spectrum of XXII had absorptions ascribed to an amide group at 1638 and 1536 $cm^{-1}$. This indicated that it was not an epimine or an oxazoline derivative. Being bulkier than in the methyl glycoside analogue, the β-benzyl glyoside in compound XXI probably makes attainment of the 1 C conformation in the transition state leading to XXX less favorable.

Following the experimental procedure of Foster, et. al.,[26] the tosylation of benzyl 3-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside[28](XXIII)(Figure 12) gave the 6-O-tosyl derivative benzyl 3-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluenesulfonyl-β-D-glucopyranoside (XXIV). Some of the 4,6-di-O-tosyl derivative (XXIX) was also formed. The reaction of XXIV with methanolic-aqueous KOH gave the carbonyl compound benzyl 3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside (XXV). Especially characteristic for this structure

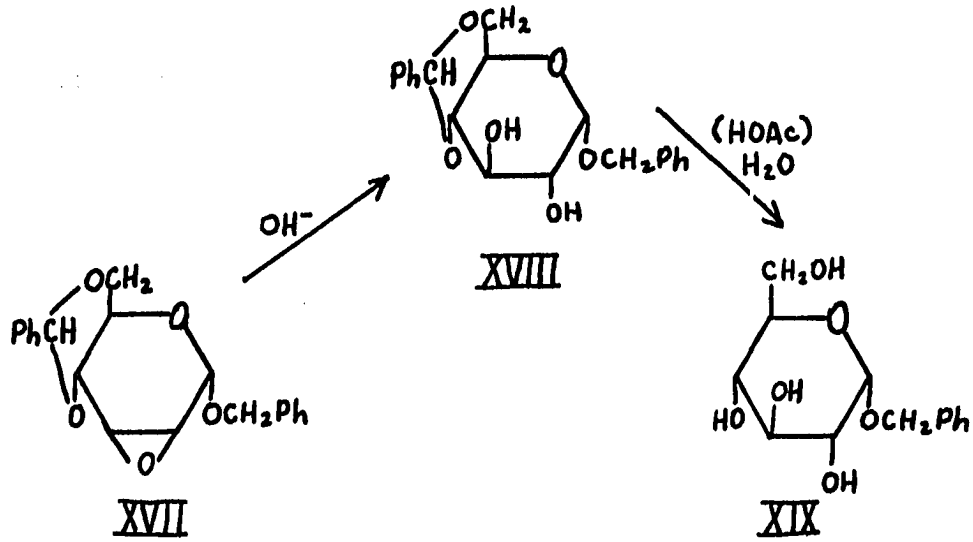



FIGURE 10. Preparation of
Benzyl α-D-Altropyranoside

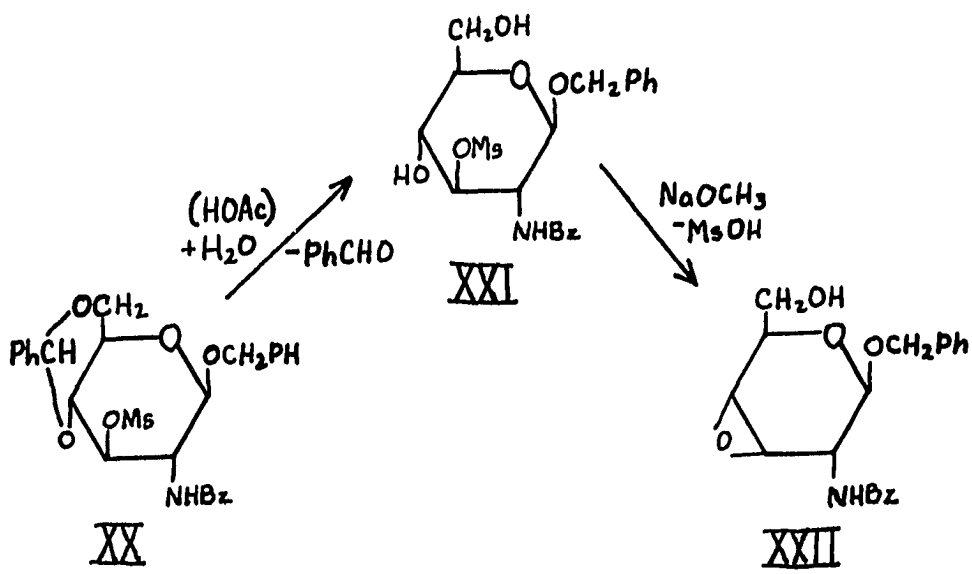



FIGURE 11. Preparation of
Benzyl 3,4-anhydro-2-benzamido-2-
deoxy-β-D-Allopyranoside

was the ir absorption for the ring carbonyl amide 3322 $cm^{-1}$(NH) and 1722 $cm^{-1}$(C=O) and the absence of the amide II band.

Continuing beyond the procedure of Foster et. al.,[26] compound XXV was heated (15 hr) at 70°C in aqueous-methanolic KOH to give benzyl 2-amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XXVI). Treatment of XXVI with carbobenzoxy chloride gave the desired N-carbobenzoxy 3,6-anhydro derivative (XXVII).

A more direct route for the preparation of XXVII was also developed. This route led to the resolution of a mechanistic question in the preparation of the carbonyl compound (XXV). For the synthesis of the methyl glycoside analogue of XXV by Foster, et. al.,[26] the sequence of ring closures of the 3,6-anhydro ring and the 2,4-carbonyl ring was hypothetical. In this study, it was found that the 3,6-anhydro ring is closed before the formation of the 2,4 carbonyl ring. The more direct route developed here formed benzyl 2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluene sulfonyl-β-D-glucopyranoside (XXVIII) from the 3-O-acetyl derivative (XXIV) by addition of XXIV to methanolic-aqueous KOH at room temperature. Deacetylation occurs easily under these conditions and XXVIII precipitated immediately before the 3,6-anhydro ring could be formed. The presence of the p-toluenesulfonyl group in compound XXVIII was determined by a positive sulfur test and the presence of the sulfonate absorption at 1366 $cm^{-1}$ in the ir spectrum. Compound XXVIII left three days in methanolic-aqueous KOH at room temperature gave the benzyloxycarbonylamido-3,6-anhydro derivative XXVII. Upon standing longer in the methanolic-aqueous KOH the carbonyl ring was formed to give XXV.

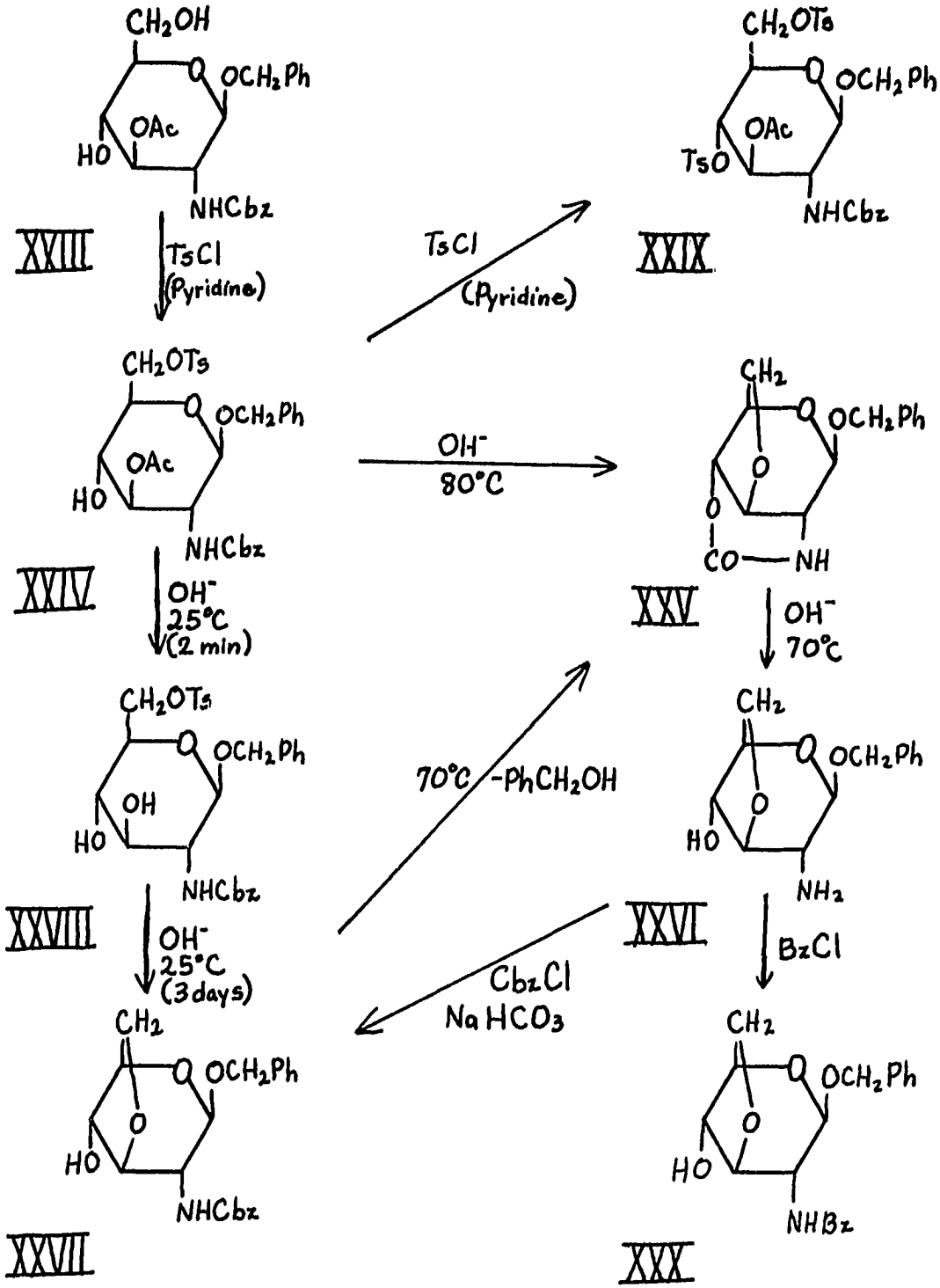



FIGURE 12. Preparation of
Benzyl 3,6-anhydro-2-benzyloxycarbonylamido-
2-deoxy-β-D-Glucopyranoside

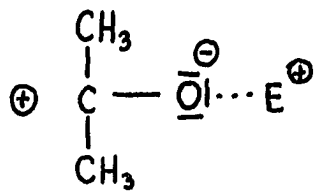
## III. REACTIONS OF EPOXIDES WITH BORON COMPOUNDS

The reagents chosen to react with the epoxide ring of 3,4-anhydro-allopyranoside derivatives have been discussed in general in the introduction of this thesis. They should contain good electrophiles as well as nucleophiles. The electrophile should reduce charge separation as the oxide anion parts from the carbon atom in epoxide ring opening. Positive ions such as $Li^+$ or $Ag^+$ display electrophilic nature when coordinating with Lewis bases, such as ammonia or methanol. Compounds containing "electron deficient" boron atoms with six valence electrons are also electrophilic and coordinate with Lewis bases such as ammonia and diethyl ether.[29]

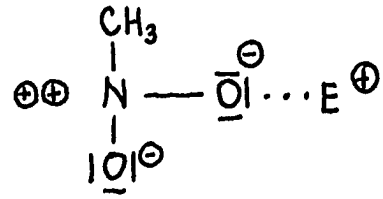
Boron triacetate and phenylboronic acid or its anhydride (triphenylboroxole) seemed to meet the above qualifications. They coordinate with many nitrogen or oxygen containing compounds. Phenylboronic acid has been used to increase the mobilities of carbohydrate derivatives in chromatographic separations.[30] Yabroff and Branch prepared a complex with pyridine and phenylboronic acid.[31] More recently phenylboronic acid has been used to complex with a variety of amines.[32] Ferrier and workers have prepared many cyclic esters with phenylboronic acid and cyclic hexo- and pento- side sugars.[33] They have also used phenylboronic acid as a protecting group in disaccharide synthesis.[34]

Solvents that would not complex with the electrophile were selected for the reactions. The nonpolar solvents benzene, toluene, and xylene

and the moderately polar chloroform and dioxane were used and found to be good solvents for the benzyl sugar derivatives. The triphenylboroxole was also very soluble in these solvents. Boron acetate was much less soluble in the above solvents. It was more soluble in acetone and nitromethane. Acetone and nitromethane complex with electrophiles, but still expose an electron deficiency at the outside of the complex:



ACETONE



NITROMETHANE

When benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) was heated with boron acetate in dioxane at 100°C for two hours, the boron compound dissolved only partially. Analysis of the reaction mixture by tlc (thin layer chromatography) indicated an incomplete reaction with some degradation. As was found out by comparison with materials later isolated by preparative tlc, there was material corresponding to an anhydro sugar, along with some other compounds. Refluxing the IIb with boron acetate for 7.5 hours in acetone dissolved the boron acetate, but the final results were similar to that for the reaction in dioxane. Heating a solution of IIb with boron acetate and boric acid in a mixture of acetone and benzene to 80°C for an hour gave a complete reaction. Again there was material corresponding to an anhydro sugar. In this case there was more degradation than in the

preceeding cases.

The least degradation was encountered when phenylboronic anhydride was refluxed with IIb in benzene overnight. Part of the benzene was distilled off during the first part of the reaction to remove water. Six days of refluxing was required to drive the reaction to completion. Changing the solvent to toluene or to xylene and increasing the temperature to 100°C led to a complete reaction in three hours.

Addition of petroleum ether to the reaction solution gave an oil that gradually solidified. The solid was separated and the filtrate was evaporated leaving a residue. This residue was dissolved in a hot methanol and water solution and extracted with chloroform. After evaporation of the chloroform, the remainder was recrystallized from methanol to give a high melting crystalline substance, containing boron. It was stable in a boiling water-methanol solution.

Heating the crystalline substance for two hours in 1,3-propanediol and acetic acid (10%) removed phenylboronic acid and gave hydrated benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV)(Figure 13) that melted at 61°C. When dried overnight at 80°C in a vacuum desicator, it melted at 92°C. Compound XIV was independently synthesized for comparison as described in Part II of this chapter.

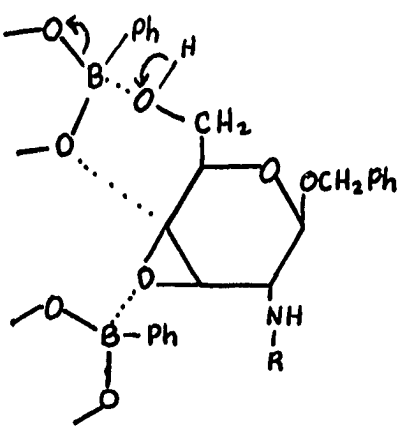
It was noticed that the ir spectra of the hydrated and non-hydrated forms of compound XIV differed. The hydrated form absorbed at 1237, 1092, 1048, and 728 $cm^{-1}$ while the non-hydrated form absorbed at 1313, 1247, 1096, 1072, and 750 $cm^{-1}$.

The high melting crystalline substance which contains boron is

therefore benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulopyranoside (XXXI). Its ir spectrum gives strong absorption at 1313 $cm^{-1}$ and sharp absorption at 1430 $cm^{-1}$. Literature values are recorded with this kind of absorption at 1350-1310 $cm^{-1}$ for the B—O stretching and at 1440 $cm^{-1}$ for B-aryl systems.[35] The fact that the phenylboronate is only removed with difficulty from XXXI is consistent with a six-membered ring phenylboronate structure. Surprisingly, however, the substance decomposed somewhat on silica gel. Bowie and Musgrave found six-membered ring phenylboronates much more resistant to hydrolysis than five membered rings.[36] The six-membered ring is free from ring-strain and the coordination of water to boron is hindered by axial interactions from the ring. Other evidence that supports assignment of the boron ester to the 4- and 6-positions is the ir amide absorption. It is nearly identical to that of the product (XIV) resulting after removal of the phenylboronate. Therefore coordination of the boron to the 2-position is not likely. Involvment of the 3- and 4-positions in the boron ester is highly unlikely because of preference for a six-membered ring over a diequatorially fused five membered ring. Elemental analysis does not support a seven membered pyroboronate ring formed by vicinal hydroxyl groups as found by Ferrier in the preparation of a 2,3-(diphenyl-pyroboronate) in a reaction of phenylboronic acid and methyl α-D-gluco-pyranoside.[37]

The opening of the 3,4-epoxide ring of the allo sugar probably involves subsequent coordination of boron atoms, from two different triphenyl-boroxole molecules, to the epoxide ring oxygen and the

C-6 hydroxyl. To give a gulo derivative, an oxygen atom from the triphenylboroxole molecule coordinated to the C-6 hydroxyl must attack the C-4 position from the rear. This would give inversion at the C-4 position leading to the gulo derivative. Formation of the 4,6-O-phenylboronate ester would result from cission of the triphenylboroxole. A possible transition state would have the following structure:




The oil that came out upon addition of petroleum ether to the reaction solution of phenylboronic acid and IIb in benzene gave a crystalline material that melted at 163°C. Although not identified, its elemental analysis (Part III, Chapter III) is consistent with a benzyl anhydro-2-benzyloxycarbonylamido-2-deoxy-hexoside derivative. Its ir spectrum shows absorptions for an amide I and an amide II band indicating no cyclization of the amide group. There is no absorption at 825 or 878 $cm^{-1}$. This indicates that the substance does not have a furanose structure.[38] Lack of formation of a cyclic 4,6-O-phenylboronate ester is evidence that either the four or six hydroxyl group is not available for esterification. It seemed reasonable that the compound could be

benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXVII). The oxygen in the 6-position could attack the epoxide ring with inversion at the 3-position forming the diaxial 3,6-anhydro-gluco derivative in the 1 C conformation. Coordination of the epoxide with boron may facilitate the opening of the 3-member ring in this process. However, benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXVII) was prepared as described earlier (Part II of this chapter) and the properties of the two substances were different.

Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) reacted to completion with boric acid and boron acetate or phenylboronic anhydride in acetone or toluene under conditions similar to those used for the reaction of the non-acetylated 3,4-anhydro-allo derivative. Some material, separated by preparative tlc, was eluted with an ethanol-chloroform solution. (70:30). Flat crystals were formed upon air evaporation of the eluent solution. An ir spectrum of these crystals showed a shoulder on the amide I absorption band at 1728 $cm^{-1}$. The shoulder is apparently due to the ester absorption of the acetate group. There were ir absorptions at 1694 and 1528 $cm^{-1}$ attributable to the amide I and II absorptions. Elemental analysis (Part III, Chapter III) agrees with the formula of a monohydrated benzyl 6-O-acetyl-2-benzyloxycarbonyl-2-deoxy-hexoside sugar. Treatment of the crystals with dioxane-water-KOH solution under deacetylation conditions gave a material that moved slower than the original crystalline material on tlc. It moved differently on tlc than the 3,4-anhydro-allo derivative (IIb) or the gulo derivative (XIV), but the same as benzyl-2-benzyl-

oxycarbonylamido-2-deoxy-β-D-allopyranoside (IX). This result indicates that the 3,4-anhydro compound (IIIb) may have undergone a cis-opening of the epoxy ring. Such an opening is highly unusual and its confirmation requires further study. A complex neighboring group effect from the acetyl group may be involved. The fact that the crystalline material differs from the products isolated from the reaction of compound IIb with phenylboronate indicates that the 6-position plays an important role in the 3,4 epoxide ring opening. This is also evidenced by the lack of reaction between benzyl 2,3-anhydro-4,6-O-benzylidene- -D-allopyranoside and phenylboronate.

Making a comparative study it was found that benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (XVII) did not react with phenylboronic anhydride. However, when heated with boron acetate in nitromethane at 70°C, for eight hours, it reacted completely. The melting point and ir spectrum of the product was identical to benzyl 2,3-anhydro-α-D-allopyranoside which was prepared by heating starting material (XVII) in glacial acetic acid with slow addition of water (Figure 14). The melting point and ir spectra of XXXIII obtained by both routes differed also from those of benzyl α-D-altropyranoside (XIX) and benzyl α-D-glucopyranoside (XVI), which were prepared as reference compounds.

It is remarkable that the epoxide ring is stable under these conditions. The possibility of removing a benzylidene group in a sugar epoxide with retention of the epoxy function opens up a possible route for unprotected

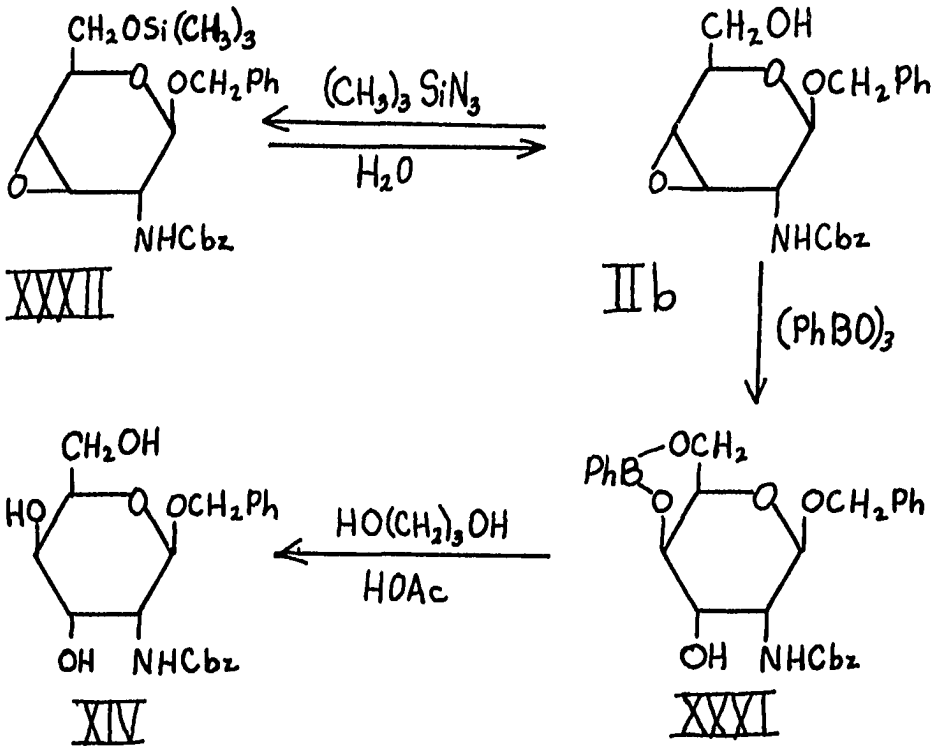



FIGURE 13. Reactions of
Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-Allopyranoside

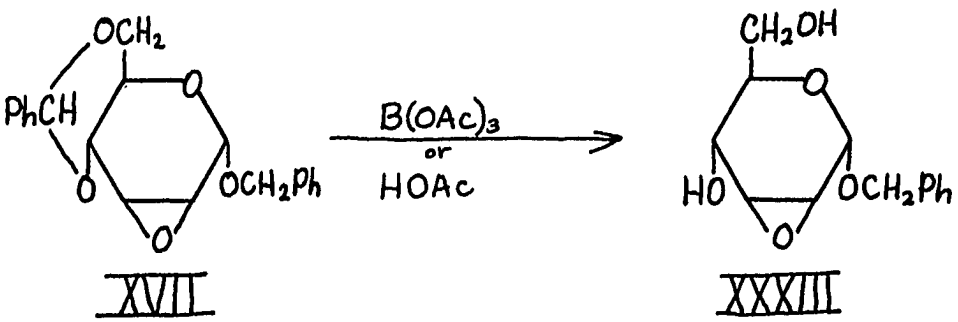



FIGURE 14. Reactions of
Benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-Allopyranoside

epoxy sugars, if the glycosidic function can be selectively removed by catalytic hydrogenation. Since metabolism of sugars involves cleavage between $C_3$ and $C_4$, and the epoxy group is very reactive, giving stable linkages with -OH and $-NH_2$ groups, such free epoxy sugars could be convenient, irreversibly blocking substrates for enzymes. These may become important in the study of metabolic pathways. Studies of the influence of such derivatives on the gluconeogenesis in perfused rat liver are being carried out in cooperation with the Department of Pharmacology, College of Medicine, Tucson, Arizona.[39]

## IV. TRIMETHYLSILYLATION OF BENZYL 3,4-ANHYDRO-2-BENZYLOXYCARBONYLAMIDO-2-BENZYLOXYCARBONYLAMIDO-2-DEOXY-B-D-ALLOPYRANOSIDE

Continuing the study of the 3,4 epoxide ring, benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-B-D-allopyranoside (IIb) was reacted with trimethylsilyl azide. It was thought that the silyl group would be an effective electrophile for attacking the oxygen in the epoxide ring. Trimethylsilyl chloride is known to cleave epoxides.[18] It cleaves propyleneoxide as is shown in the following reaction:

$$CH_2\text{—}\underset{\diagdown\,O\,\diagup}{CH}\text{—}CH_3 + (CH_3)_3SiCl \qquad (CH_3)_3SiO\text{--}CH_2\text{--}\underset{Cl}{CH}\text{--}CH_3$$

It was expected that substitution of the azide group for chloride in trimethylsilyl chloride would give a reagent that would lead to compounds carrying $-N_3$ instead of -Cl. The trimethylsilyl group in such compounds could easily be hydrolyzed by $H_2O$ at room temperature giving a hydroxyl-group. Reduction of the azido function to an amino group by catalytic hydrogenation has been done by W. Sundermeyer[40] and others. Concurrent

reductive cleavage of the protective benzyl and benzyloxycarbonyl groups would make possible a fast route to new amino sugars.

A search of the literature revealed that trimethylsilyl azide is prepared directly from sodium azide and trimethylsilyl chloride. The substances are either fused in anhydrous $ZnCl_2$-KCl at 230-250°C,[40] refluxed in tetrahydrofuran for 48 hours,[41] or refluxed in bis-(2-methoxyethyl) ether in the presence of aluminum chloride.[42] It was found that heating the trimethylsilyl chloride and sodium azide without a catalyst in bis-(2-ethoxyethyl) ether at 85°C for three hours gave a good yield of trimethylsilyl azide.

Reaction of trimethylsilyl azide and epoxide IIb in refluxing chloroform for four hours gave an incomplete reaction. When the solvent was changed to the higher boiling bis-(2-ethoxyethyl) ether and the temperature raised to 120°C for three hours the reaction went to completion. Refluxing IIb in excess trimethylsilyl azide for seven and one half hours also gave a complete reaction.

Evaporation of trimethylsilyl azide from the reaction mixture <u>in vacuo</u> gave an oil that was soluble in hot hexane. At room temperature crystals which melted sharply at 81-82°C, separated from the hexane. The substance (XXXII) decomposed when analyzed by tlc. Refluxing the crystalline material (XXXII) in a small volume of equal parts of methanol and water for an hour gave starting material (IIb)(Figure 13).

Obviously the epoxide ring of IIb had not been opened. An examination of the ir spectrum of XXXII showed that the open hydroxyl group in the 6-position of IIb had been silylated in XXXII. There was no

absorption peak in the spectrum of XXXII for the hydroxyl group, whereas the starting material (IIb) had broad absorption at 3440 $cm^{-1}$.

While it is possible that either the oxygen or the nitrogen of the carboxamide could be silylated[43] the ir spectrum does not support either of these possibilities. There are strong absorption peaks at 3294, attributed to the N-H absorption, and at 1683 and 1539, attributed to the amide I and II absorptions. Silylation of the nitrogen would remove the hydrogen. Silylation of the carbonyl oxygen would give an O-silyl imino-ether structure.

Silylation of hydroxyl groups of carbohydrates has been done mainly to form a blocking group or to increase the volatility of the compound. Glucose has been selectively silylated by N-trimethylsilylacetamide in pyridine.[44] The resulting compound was reacted with acetobromoglucose to form a disaccharide. A variety of carbohydrates and related polyhydroxy compounds were silylated in pyridine containing hexamethyldisilazane and trimethylsilyl chloride at temperatures varying from room temperature to 85°C.[45] These compounds were used in gas-liquid chromatography.

The method developed here for the silylation of carbohydrates is relatively mild and does not have the disadvantages of a base as a solvent. Pyridine probably causes anomerizations in simple sugars and affects base-labile groups.[45]

## V. REACTION OF BENZYL 4,6-O-BENZYLIDENE-2,3-DIDEOXY-2,3-EPIMINO-α-D-ALLOPYRANOSIDE WITH $HNO_2$

Benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-β-D-allopyranoside

(VIb) was studied as a compound analogous to I. The epimine ring, like the 2,3-epoxide ring, has proven to be quite stable, although it is labile in mineral acid.[2] Buss, Hough, and Richardson report the epimine ring resistant to prolonged treatment with lithium aluminum hydride and ethanolic sodium ethoxide.[2] Guthrie and Murphy were able to deacylate N-acetyl and N-benzoylepimines of mannosamine in hot aqueous KOH without opening the ring, but they did effect an opening with sodium azide in a slightly acidic medium.[46]

It was found that the 2,3-epimino-β-D-allo derivative (VIb) failed to react with trimethylsilyl azide at 130°C for 18 hours or with methyl borate in refluxing toluene. Refluxing with hexachloro-2-propanone in toluene also gave no reaction, but addition of a small amount of p-nitro-phenol or ethyl-diisopropyl amine to this solution gave several products as revealed by tlc. The α anomer (VIa) failed to react with phenylboronic anhydride in refluxing toluene. Refluxing VIa in $CH_3NO_2$ gave only starting material.

The epimino ring of VIa did react with nitrous acid and acetic acid in dioxane to give the 2,3-unsaturated derivative benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (XXXIV)(Figure 15).

Such 2,3-unsaturated glycosides have been prepared by direct introduction of a 2,3-olefinic double bond, as is the case with $HNO_2$, or by double bond shifts in glycal derivatives. Newth reacted methyl 4,6-O-benzylidene-3-iodo-3-deoxy-2-O-p-toluenesulfonyl-α-D-glucoside with sodium iodide in acetone to obtain methyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside.[47] Ferrier, Overend, and Sankey

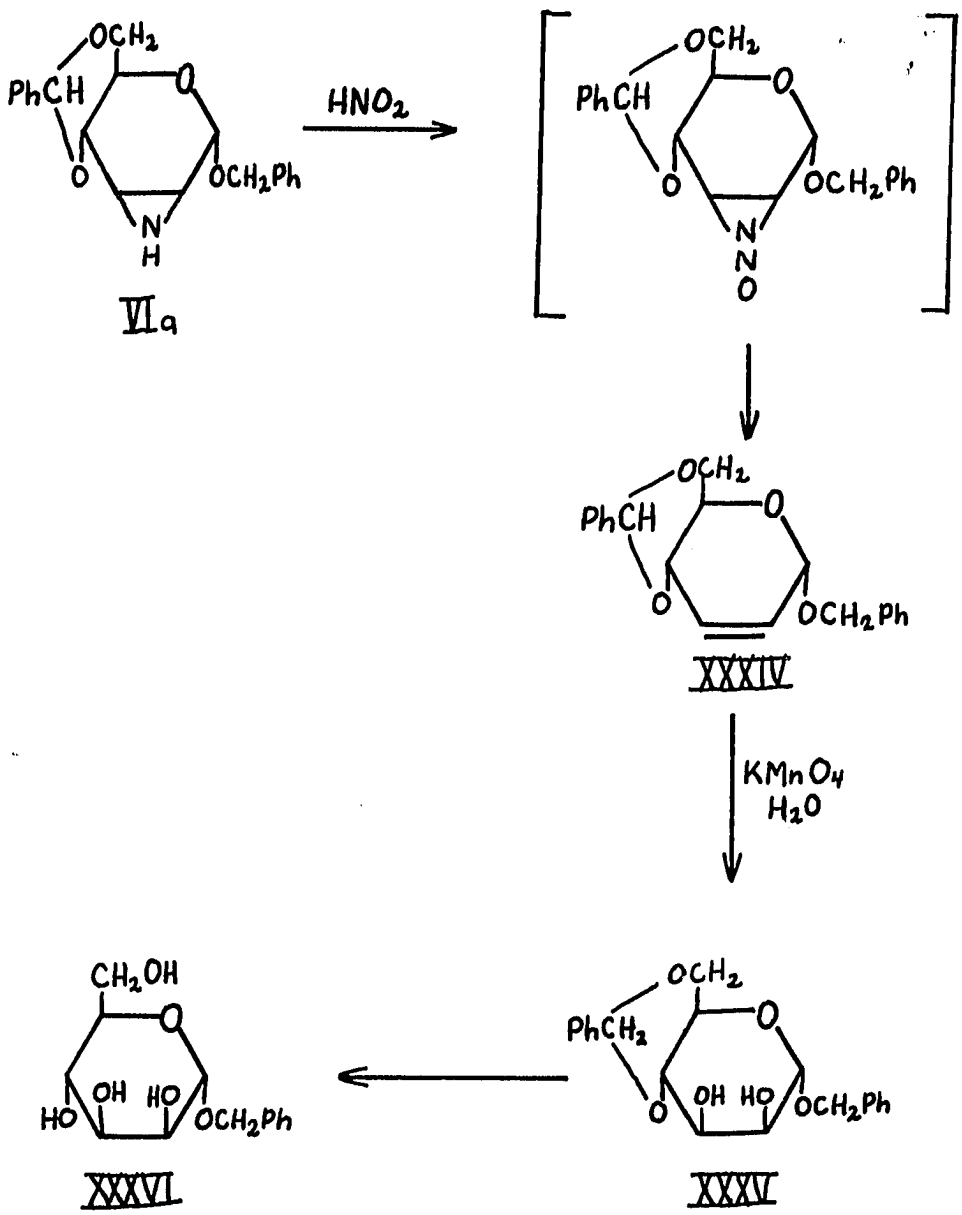



FIGURE 15. Reaction of
Benzyl 4,6-O-benzylidene-2,3-dideoxy-
2,3-epimino-α-D-Allopyranoside with $HNO_2$

have caused tetra-O-acetyl-2-hydroxy-D-glucal to rearrange to the α and β anomers of 1,2,4,6-tetra-O-acetyl-2,3-didehydro-3-deoxy-D-erythro-hexoses.[48] Nitrous acid has been used in the deamination of amino alcohols. Elphimoff-Felkin and Gault formed heptanones, glycols, or alkenes from amino(1-hydroxycyclohexyl)(tert-alkyl)methanes.[49] Defaye used $HNO_2$ to form 2,5-anhydro-D-talose from 2-amino-D-galactose.[50]

The nitrosating agent is believed to be either the nitrosyl ion $NO^+$ or dinitrogen trioxide $N_2O_3$. At low concentrations of nitrous acid the nitrosyl ion is formed while at higher concentrations dinitrogen trioxide is formed.[51] In acetic acid the nitrosyl ion is probably the nitrosating agent.

Although rate studies of the reaction have not been made, a possible mechanism of the deamination of the nitroso compound would involve elimination of two equivalents of nitroxyl (HNO)(Figure 16). While the oxygen of the nitroso compound would no doubt be protonated, protonation of the nitrogen would lead to a species that could eliminate nitroxyl. Nitroxyl is known to be a common elimination product of similar organic reactions where C--NO or N--NO bonds are broken.[52] It is also considered to be a product in the Nef reaction.[53] The secondary carbonium ion of the pyranoid ring (Figure 16) would be a relatively stable intermediate[54] for elimination of the epimine nitrogen through the formation of a second nitroxyl molecule.

A literature search revealed that the corresponding methyl derivative of XXXIV as well as the methyl 4,6-O-benzylidene-α-D-mannopyranoside had been prepared in a similar manner.[55] While the nitroso

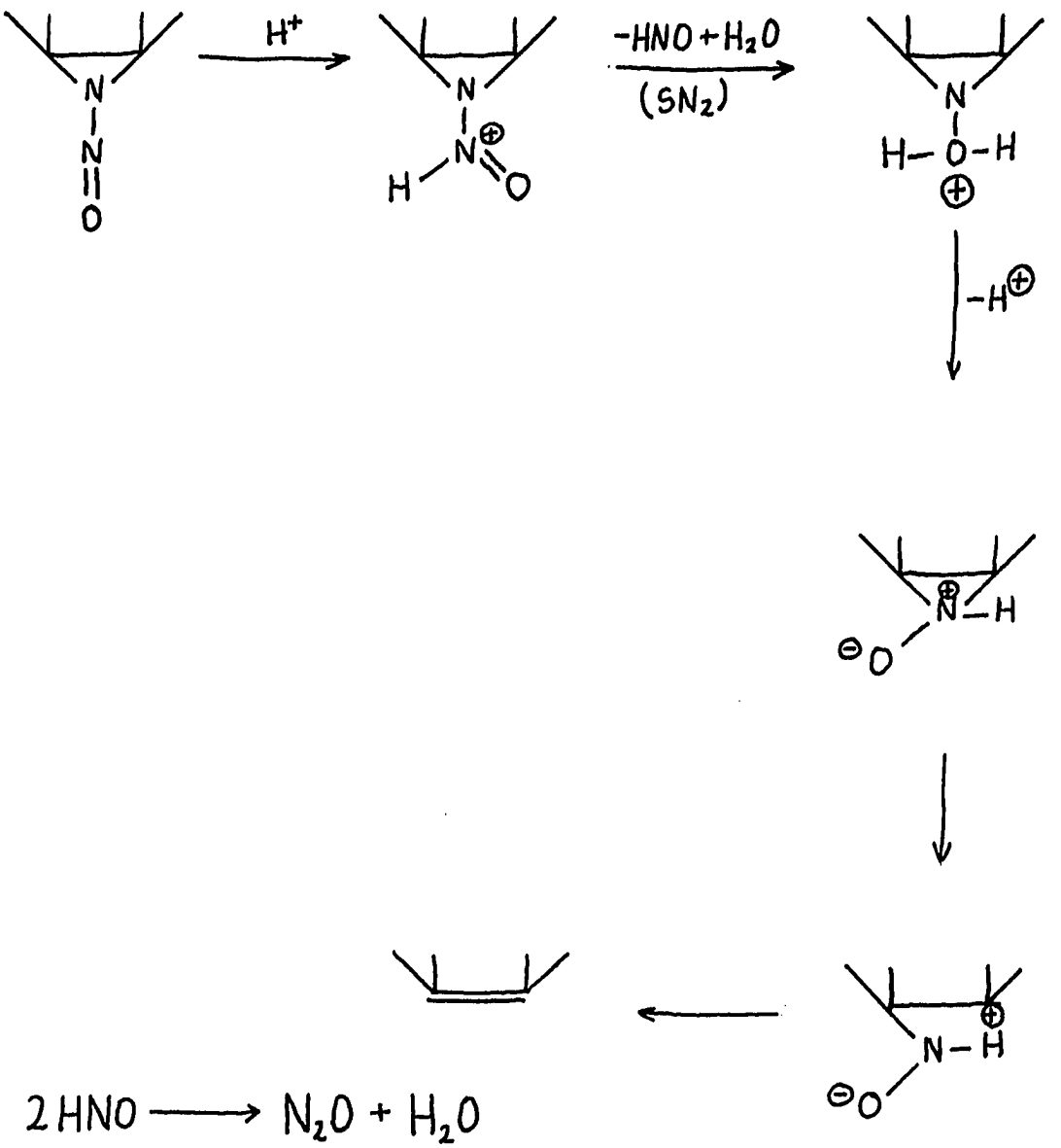



FIGURE 16. Possible Deamination Mechanism of a Nitroso-Epimino Sugar

intermediate of the benzyl derivative (XXXIV) was not isolated, the reaction solution was temporarily yellow as is characteristic for nitroso-epimines.[55] The benzyl derivative was easily separated from the reaction solution by addition of water. Its ir spectrum showed no absorption characteristic of a compound containing nitrogen functions.

The 2,3-unsaturated glycosides are of interest as intermediates in metabolic pathways.[17] They could also lead to a variety of derivatives through addition to the double bond. Albano, Horton, and Lauterbach have shown that addition to such compounds have high stereospecificity and can be used as models for the study of addition reactions to carbon-carbon double bonds.[56]

Thus, in our case, treatment of compound XXXIV in dioxane with a 2% aqueous solution of $KMnO_4$ led to cis hydroxylation of the double bond, mostly on the sterically less hindered side. The only characterized product was demonstrated to be benzyl 4,6-O-benzylidene-$\alpha$-D-mannopyranoside (XXXV). Removal of the benzylidene group with acetic acid and water gave benzyl $\alpha$-D-mannopyranoside XXXVI with melting point and rotation agreeing to literature values.[57] Some material from the $KMnO_4$ hydroxylation of the unsaturated compound was water soluble and remained an oil upon drying. It was not moved from the starting point on tlc plates using 10% ethanol in chloroform. It probably resulted from over-oxidation of the double bond.

# CHAPTER III

## EXPERIMENTAL PROCEDURES

Melting points were taken in a Thomas-Hoover melting point apparatus model No. 6404H. All melting points reported herein are uncorrected. Optical rotations were measured at the sodium D line with an O.C. Rudolph and Sons Inc., Model No. 956 polarimeter, at C=1. Ir spectra were recorded with a Perkin-Elmer spectrophotometer (model 337) using the KBr pellet technique. The homogeneity of the compounds synthesized was determined by thin layer chromatography using a mixture of two parts Merk Silica Gel G with one part Merk Silica Gel $GF_{254}$, the plates being activated by heating at 120°C for two hours. The plates were developed with chloroform containing sufficient ethanol to produce $R_f$ values between 0.2 and 0.7. The compounds were detected by extinction of the ultraviolet fluorescence of a zinc-silicate indicator and also by subsequent spraying with sulfuric acid (10%)-methanol and heating about 15 minutes at 120°C. The preparative tlc separations were made on Merk precoated silica gel plates, $F_{254}$, 2mm thick. The microanalyses were performed by Alfred Bernhardt of Mikroanalytisches Laboratorium in West Germany.

## I. PREPARATION OF SUITABLE STARTING MATERIALS

Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-α-D-allopyranoside (IIa):

Benzyl 2-benzyloxycarbonylamido-2-deoxy-3-O-mesyl-α-D-glucopyranoside (Ia)[22](5.0 g, 0.0104 mol) was dissolved in dioxane (90 ml) and 0.5N KOH (60 ml) and kept at room temperature (24 hr). The dioxane was evaporated in vacuo. The remaining oil solidified when shaken with water (200 ml). The crystals were recrystallized from toluene to give 2.74 g (65%): mp 92-95°, $[\alpha]_D^{25}$ + 57 (C=1, Pyridine); $\bar{\nu}_{max}$ 3332 (NH), 1683, 1654, 1522 (amide C=O), 736, 693 ($C_6H_5$).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.422): C, 65.44; H, 6.02; N, 3.64. Found: C, 65.31; H, 6.02; N, 3.33.

Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb):

This compound was prepared from Ib[22] (5 g, 0.0104 mol) by a procedure identical to that used for the preparation of the α anomer to give 3.1 g (73%) of IIb: mp 109-110°, $[\alpha]_D^{25}$ - 143 (C=1, Pyridine)(Literature[1] mp 108-110° $[\alpha]_D^{20}$ -142).

Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-α-D-allopyranoside (IIIa):

Starting from Compound IIa (0.5 g, 0.0013 mol), the procedure given for IIIb gave 0.39 g (70%); mp 106.5-107.5°, $[\alpha]_D^{25}$ + 40.5 (C=1, Pyridine); $\bar{\nu}_{max}$ 3339 (NH), 1731 (ester C=O), 1693, 1529 (amide C=O), 738, 696 ($C_6H_5$).

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.44): C, 64.62; H, 5.90; N, 3.28. Found: C, 64.33; H, 6.07; N, 3.25.

Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-Allopyranoside (IIIb):

A solution of compound IIb (3.0 g, 0.0078 mol) in pyridine (4 ml) was treated with acetic anhydride (1.5 ml) at -5°C (2 hr). The solution was kept overnight at room temperature and was poured on ice (25 g). The resulting precipitate was filtered and recrystallized from methanol to give 2.95 g (86%): mp 120.5-121°, $[\alpha]_D^{25}$ - 148° (C=1, Pyridine); $\bar{\nu}_{max}$ 3285 (NH), 1740 (ester C=O), 1690, 1545 (amide C=O), 757, 697 ($C_6H_5$).

Anal. Calcd for $C_{23}H_{25}NO_7$ (427.44: C, 64.62; H, 5.90; N, 3.28; O, 26.20. Found: C, 64.65; H, 6.01; N, 2,86; O, 26.69.

Benzyl 3,4-anhydro-6-O-benzyl-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IVb):

Benzyl bromide (2.3 ml, 0.019 mol), compound IIb (1 g, 0.0026 mol) BaO (2.75 g), and $Ba(OH)_2 \cdot 8H_2O$ (0.1 g), were stirred in dry dimethylformamide (5.0 ml) at room temperature (96 hr). The barium salts were removed by centrifuging. The supernatant liquid was filtered through cellulose and poured into ice and water (30 ml). The resulting precipitate was filtered, washed with water and recrystallized twice from anhydrous ethanol (5 ml) to give 0.18 g (14.5%): mp 128.5-129°, $[\alpha]_D^{25}$ - 123 (C=1, Pyridine); $\bar{\nu}_{max}$ 3280 (NH), 1683, 1545 (amide C=O), 738, 692 ($C_6H_5$).

Anal. Calcd for $C_{28}H_{29}NO_6$ (475.52): C, 70.72; H, 6.14; N, 2.94. Found: C, 70.30; H, 6.11; N, 2.79.

Trimethylsilyl Azide:

Sodium azide (15 g, 0.23 mol), bis (2-ethyoxyethyl) ether (10 ml) and trimethylsilyl chloride (30 g, 0.28 mol) were heated at 85° for 3 hr. The mixture was distilled and the fraction boiling at 93-97° was collected and redistilled to give 22 g (83%), bp 93-94° (Literature[41] bp 95°).

Benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (VIa):

Benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-3-O-mesyl-α-D-glucopyranoside[22](Va) (2.3 g, 0.0043 mol) was dissolved in dioxane (40 ml) and 0.65M sodium isopropoxide (20 ml. 0.013) was added. The solution was refluxed for 30 hr and evaporated in vacuo to dryness. The residue was shaken with water, filtered, and recrystallized from methanol to give 1.0 g (68%): mp 185-186°, $[\alpha]_D^{25}$ + 114 (C=1, Pyridine); $\nu_{max}$ 3300 (NH), 737, 693 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{22}NO_4$ (340.404): C, 70.57; H, 6.51; N, 4.12. Found: C, 70.42; H, 6.53; N, 4.18.

Benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-β-D-allopyranoside (VIb):

This compound described previously by Rhoads and Gross[15] was prepared according to their procedure from benzyl 2-benzamido-4,6-O-benzylidene-2-deoxy-3-O-mesyl-β-D-glucopyranoside[15](Vb) by a procedure identical to that used for the preparation of the α-anomer (VIa) mp 148-150° (Literature[15] mp 149°).

## II. PREPARATION OF MATERIALS FOR COMPARISON TO PRODUCTS

Benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (VIII):

Benzyl 2-amino-4,6-O-benzylidene-2-deoxy-B-D-allopyranoside (VII)[58] (0.5 g, 0.0014 mol), $CHCl_3$ (50 ml), 3% aqueous $KHCO_3$ (50 ml) and carbobenzoxy chloride (0.25 ml), were stirred vigorously overnight at room temperature. The $CHCl_3$ layer was separated, washed with water and dried by filtering through two layers of fluted filter paper. The resulting solution was concentrated *in vacuo*. Addition of diethyl ether gave 0.45 g (65%): mp 204-206°, $[\alpha]_D^{25}$ - 64.5(C=1, Chloroform); $\tilde{\nu}_{max}$ 3311 (NH), 1694, 1544 (amide C=O) 741, 694 ($C_6H_5$).

Anal. Calcd for $C_{28}H_{29}NO_7$ (491.52): C, 68.42; H, 5.94; N, 2.85. Found: C, 68.16; H, 6.10; N, 2.93.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IX):

Benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (VIII) (0.4 g, 0.0008 mol) was dissolved in glacial acetic acid (15 ml) at 90°C and $H_2O$ (8 ml) was added by drops over 20 min. The solvent was removed at 40°C *in vacuo*. The residue was dissolved in toluene and the toluene was evaporated under the same conditions. The process was repeated until no acetic acid remained. Recrystallization of the product from methanol and diisopropyl ether gave 0.24 g (73%); mp 134-135°, $[\alpha]_D^{25}$ - 70.0 (C=1,Pyridine ); $\tilde{\nu}_{max}$ 3303 (NH), 1689, 1533 (amide C=O) 729, 693 ($C_6H_5$).

Anal. Calcd for $C_{21}H_{25}NO_7$ (403.42): C, 62.49; H, 6.25; N, 3.48. Found: C, 62.40; H, 6.23; N, 3.42.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV):

Following the method Noorzad[59] used to prepare benzyl 4,6-O-benzylidene-α-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone, the β anomer was prepared in an analogous manner by dissolving benzyl β-D-gulopyranosido-[2.3:4'.5']-2'-oxazolidinone[25](X)(5.9 g, 0.020 mol) in benzaldehyde (60 ml). Fused, powdered zinc chloride (6 g) was added to the mixture. It was shaken at room temperature for 72 hr and the solution was poured into a mixture of diethyl ether, hexane, and ice water (3:1:3)(140 ml). The product was filtered and recrystallized from ethanol to yield 7 g, presumably benzyl 4,6-O-benzylidene-β-D-gulopyranosido[2,3:4'.5']-2'-oxazolidinone (XI): mp 227-228°, homogeneous on tlc.

Compound XI (5 g, 0.013 mol) was dissolved in a solution of KOH (20 g) in 95% ethanol (75 ml) and refluxed for 6 hr. The solution was poured into hot water (300 ml) and cooled. The precipitate was recrystallized from methanol and then from toluene and heptane to give 3 g, presumably benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-gulopyranoside (XII): mp 186-187°, homogeneous on tlc.

Compound XII (2.5 g, 0.0069 mol) was dissolved in $CHCl_3$ (100 ml) and added to 5% aqueous $NaHCO_3$ (50 ml). Carbobenzoxy chloride (1.6 g) was added and the mixture was vibrated overnight. The $CHCl_3$ layer was separated and evaporated in vacuo at room temperature. The product was recrystallized from THF and diisopropyl ether to give 2.5 g, presumably benzyl 4,6-O-benzylidene-2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIII): mp 144-145°, homogeneous on tlc.

Compound XIII (1 g, 0.002 mol) was dissolved in hot glacial acetic acid (35 ml) and $H_2O$ (20 ml) was added slowly. The solution was heated at 90° for 30 min and evaporated in vacuo three times until no acetic acid remained. The residue was dissolved in methanol and water was added to give an oil. The supernatant liquid was decanted and the oil was stirred with a mixture of methylcyclohexane (40 ml) and $H_2O$ (20 ml) to give a solid. The solid was filtered and dried in vacuo at 70° for 24 hr to give 0.15 g of (XIV): mp 100-102°, homogeneous on tlc. The ir spectrum and physical constants of XIV prepared by this route were identical to those of compound XIV formed from the hydrolysis of compound (XXXI).

Benzyl α-D-glucopyranoside (XVI):

Benzyl 4,6-O-benzylidene-α-D-glucopyranoside[14](XV)(1 g, 0.0028 mol) was dissolved in hot glacial acetic acid (40 ml) and $H_2O$ (20 ml) was added over a 20 minute period. The solution was heated at 90° for an hour and evaporated in vacuo. The residue was dissolved in an ethanol-$H_2O$ solution (5:1) and evaporated in vacuo two times. The product was recrystallized from ethanol and diisopropyl ether to give 0.5 g (66%): mp 120-121°, $[\alpha]_D^{25}$ + 136 (C=1, Pyridine); $\bar{\nu}_{max}$ 742, 697 ($C_6H_6$).

Anal. Calcd for $C_{13}H_{18}O_6$ (270.28): C, 57.76; H, 6.72. Found: C, 57.73; H, 6.82.

Benzyl 4,6-benzylidene-α-D-altropyranoside (XVIII):

Benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside[14](XVII) (0.5 g, 0.0015 mol) was dissolved in dioxane (9 ml) and KOH (1.5 g) in $H_2O$ (13 ml) was added. The solution was heated in a sealed flask at 125° for 24 hr. The product precipitated upon addition of $H_2O$. It was filtered and recrystallized from $CHCl_3$ to give 0.21 g (40%): mp 183-184°, $[\alpha]_D^{25}$ + 103 (C=1, Pyridine); $\bar{\nu}_{max}$ 743, 699 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{22}O_6$ (358.38): C, 67.02; H, 6.19. Found: C, 66.80; H, 6.11.

Benzyl α-D-altropyranoside (XIX):

Compound XVIII (0.2 g, 0.00056 mol) was dissolved in hot glacial acetic acid (7 ml) and $H_2O$ (3.8 ml) was added over a 15 minute period. The solution was heated at 90° for an hour and evaporated in vacuo. The residue was dissolved in an ethanol-$H_2O$ solution (5:1) and evaporated in vacuo two times. The product was recrystallized from $CHCl_3$ and dried in vacuo at 45° to give 0.13 g (87%): mp 101-102°, $[\alpha]_D^{25}$ + 115 (C=1, Pyridine); $\nu_{max}$ 758, 708 ($C_6H_5$).

Anal. Calcd for $C_{13}H_{18}O_6$ (270.28): C, 57.76; H, 6.27. Found: C, 57.59; H, 6.50.

Benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-allopyranoside (XXII):

Benzyl 2-benzamido-3-deoxy-3-O-methanesulfonyl-β-D-glucopyranoside[28] (XXI)(0.5 g, 0.0011 mol) and left overnight at room temperature. The solution was poured into water. The precipitate was filtered, washed with water and recrystallized from methanol/water to give 0.29 g (74%): mp 183-185°, $[\alpha]_D^{25}$ - 142.8 (C=1, $CHCl_3$); $\nu_{max}$ 3261 (NH), 1638, 1536 (amide C=O), 746, 695 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.59; H, 5.96; N, 3.95. Found: C, 67.44; H, 5.92; N, 3.89.

Benzyl 3-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluene-sulfonyl-β-D-glucopyranoside (XXIV):

Benzyl 3-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXIII)(5 g, 0.011 mol) was dissolved in pyridine (25 ml) and the solution was cooled to 0° in an ice bath. p-Toluenesulfonyl chloride (4 g) in pyridine (12 ml) was added over a 20 min period. The solution was left at room temperature for 36 hr and poured into ice water (100 ml). The resulting oil was separated and dissolved in hot ethanol. At 0° the 4,6-di-O-tosyl derivative (XXIX) precipitated and was filtered off. The filtrate was concentrated, and the resulting precipitate was recrystallized from $CHCl_3$ and diisopropyl ether to give 3.25 g (49%): mp 117-118°, $[\alpha]_D^{25}$ - 25 (C=1, Pyridine); $\bar{\nu}_{max}$ 3300 (NH), 1736 (ester C=O), 1682, 1555, 1512 (amide C=O), 1350 ($SO_2$), 744, 696 ($C_6H_5$).

Anal. Calcd for $C_{30}H_{33}NO_{10}S$ (599.63): C, 60.09; H, 5.54; N, 2.33; S, 5.35. Found: C, 60.43; H, 5.54; N, 2.39; S, 5.29.

Benzyl 3-O-acetyl-2-benzyloxycarbonylamido-2-deoxy-4,6-di-O-p-toluenesulfonyl-β-D-glucopyranoside (XXIX):

The 4,6-di-O-tosyl derivative (XXIX) separated in the preparation of XXIV was recrystallized from ethanol to give 0.97 g (11%): mp 158-159°, $[\alpha]_D^{25}$ - 8.5 (C=1, Pyridine); $\bar{\nu}_{max}$ 3397 (NH), 1755 (ester C=O), 1695, 1522 (amide C=O) 1265 ($SO_2$) 737, 697 ($C_6H_5$).

Anal. Calcd for $C_{37}H_{39}NO_{12}S_2$ (753.82): C, 58.96; H, 5.22; N, 1.86; S, 8.51. Found: C, 59.24; H, 5.03; N, 1.88; S, 8.52.

Benzyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside (XXV):

Following the procedures of Foster, et. al.,[26] for the preparation of methyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-deoxy-α-D-glucopyranoside,[26] compound XXIV (2 g, 0.0033 mol) was dissolved in ethanol (20 ml) and N KOH (10 ml) was added. The solution was refluxed for 30 min and then cooled. The precipitate was filtered off and washed with ethanol to give 0.53 g (58%): mp 235-236°, $[\alpha]_D^{25}$ - 172 (C=1, Pyridine); $\bar{\nu}_{max}$ 3322 (NH) 1722 (ester C=O) 754, 704 ($C_6H_5$).

Anal. Calcd for $C_{14}H_{15}O_5N$ (277.27): C, 60.63; H, 5.45; N, 5.05. Found: C, 60.83; H, 5.24; N, 5.07.

Benzyl 2-amino-3,6-anhydro-2-deoxy-β-D-glucopyranoside (XXVI):

Compound XXV (0.4 g, 0.0014 mol) was dissolved in methanol (10 ml) and KOH (2.17 g) in $H_2O$ (3 ml) was added. The solution was heated at 70° for 15 hr and evaporated in vacuo. The residue was crystallized from $H_2O$ to give 0.16 g (49%): mp 172-173°, $[\alpha]_D^{25}$ - 149.5 (C=1, $CH_3OH$); $\bar{\nu}_{max}$ 3301 (NH) 737, 692 ($C_6H_5$).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.28): C, 62.12; H, 6.82; N, 5.59. Found: C, 62.22; H, 6.82; N, 5.61.

Benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-gluco-pyranoside (XXVII):

Compound XXVI (0.05 g, 0.0002 mol) was dissolved in ethylenedichloride (10 ml) and added to 2.5% aqueous $NaHCO_3$ (3 ml). Carbobenzoxy chloride (0.036 g) was added and the mixture was vibrated overnight. The ethylenedichloride layer was separated and evaporated *in vacuo* at room temperature and the resulting oil solidified with addition of diisopropyl ether to give 0.04 g (52%): mp 147-148°, $[\alpha]_D^{25}$ - 98 (C=1, $CHCl_3$); $\tilde{\nu}_{max}$ 3360 (NH), 1677, 1511 (amide C = O) 744, 696 ($C_6H_5$).

Anal. Calcd for $C_{21}H_{23}NO_6$ (385.42): C, 65.44; H, 6.02; N, 3.64. Found: C, 65.11; H, 6.02; N, 3.56.

Benzyl 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXX):

Compound XXVI (0.2 g, 0.0008 mol) was dissolved in ethylenedichloride (10 ml) and added to 2.5% aqueous $NaHCO_3$ (4 ml). Benzoyl chloride (0.1 ml) was added and the mixture was vibrated overnight. The ethylene-dichloride layer was evaporated *in vacuo* and the product was recrystallized from ethanol and $CHCl_3$ to give 0.18 g (63%): mp 184-185°, $[\alpha]_D^{25}$ - 156 (C=1, Pyridine); $\tilde{\nu}_{max}$ 3238 (NH), 1633, 1522 (amide C = O) 740, 690 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{21}NO_5$ (355.38): C, 67.58; H, 5.96; N, 3.95. Found: C, 67.71; H, 5.96; N, 3.84.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluenesulfonyl-β-D-glucopyranoside (XXVIII):

Compound XXIV (3.5 g, 0.0058 mol) was dissolved in methanol (30 ml) at room temperature and KOH (1 g) in $H_2O$ (20 ml) was added. Precipitation occurred almost immediately and the precipitate was filtered off and washed with a mixture of $H_2O$ and methanol (1:1). The product was recrystallized from isopropanol to give 2.2 g (63%): mp 149-150°, $[\alpha]_D^{25}$ - 16 (C=1, Pyridine); $\tilde{\nu}_{max}$ 3416 (NH) 1688, 1525 (amide C = O) 1360 ($SO_2$) 737, 693 ($C_6H_5$). The test for sulfur was positive.

Anal. Calcd for $C_{28}H_{31}NO_9S$ (557.60): C, 60.21; H, 5.60; N, 2.51; S, 5.76. Found: C, 59.86; H, 5.22; N, 2.70; S, 5.81.

The filtrate from the above reaction was left at room temperature 3 days and precipitation occurred. The precipitate was filtered and recrystallized from toluene to give 0.16 g: mp 147-148°. It was homogenous on tlc with physical constants and an ir spectrum identical to compound XXVII.

Further precipitation from the filtrate from the above reaction gave mixtures of XXVII and XXV as shown by tlc.

## III. REACTIONS OF EPOXIDES WITH BORON COMPOUNDS

Reaction of Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) with phenylboronic acid.

Phenylboronic acid (2.94 g, 0.0241 mol) was dissolved in benzene (300 ml) and the benzene distilled off to remove water. The resulting phenylboronic anhydride and IIb (5 g, 0.013 mol) were dissolved in

toluene (50 ml) and heated at 100° for 3 hr. Petroleum ether was added to the hot reaction solution. After cooling, an oil which gradually solidified came out of the solution. The mixture was filtered to give a solid material (A, 4.38 g) and a filtrate (B). The solid A was separated by preparative tlc. The tlc plates were developed successively with petroleum ether, chloroform/petroleum ether (1:1), chloroform. One fraction (1.31 g) had the following properties: mp 162.5-164°, $[\alpha]_D^{25}$ - 97.5 (C=1, $CHCl_3$); $\tilde{\nu}_{max}$ 3486 (OH), 3303 (NH), 1689, 1522 (amide C = O), 735, 693 ($C_6H_5$).

Anal. Calcd for a benzyl anhydro-2-benzyloxycarbonylamido-2-deoxy-hexoside $C_{21}H_{23}NO_6$ (385.42): C, 65.44; H, 6.02; N, 3.64. Found: C, 65.42; H, 6.11; N, 3.64.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulopyranoside (XXXI):

The filtrate B from the reaction of IIb with phenylboronic anhydride was evaporated leaving a residue (3.65 g). It was dissolved in hot methanol and water (1:1) and extracted with chloroform. The chloroform extract was recrystallized from methanol to give 0.39 g (5.7%): mp 171.5-172.5°, $[\alpha]_D^{25}$ - 66.5 (C=1, $CHCl_3$); $\tilde{\nu}_{max}$ 3422 (NH), 1714, 1489 (amide C = O), 1430 (B-$C_6H_5$), 1313 (B-O), 741, 693 ($C_6H_5$).

Anal. Calcd for $C_{27}H_{28}BNO_7$ (489.31): C, 66.27; H, 5.77; B, 2.21; N, 2.86. Found: C, 66.89; H, 5.86; B, 1.95; N, 2.93.

Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV):

Compound XXXI (0.75 g, 0.00153 mol) was dissolved in 1,3-propanediol (8 ml) and glacial acetic acid (1 ml) was added. After refluxing for 2 hr the solution was extracted with $CHCl_3$. Evaporation of the extract gave an oil that was crystallized from methanol and water. The crystals were dried in vacuo at 80° to give 0.30 g (48%): mp 99-100°, $[\alpha]_D^{25}$ - 78 (C=1, $CHCl_3$); $\bar{\nu}_{max}$ 3317 (NH), 1687, 1511 (amide C=O), 730, 693 ($C_6H_5$).

Anal. Calcd for $C_{21}H_{25}NO_7$ (403.4): C, 62.52; H, 6.25; N, 3.48. Found: C, 62.83; H, 6.40; N, 3.55.

Reaction of Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) with phenylboronic acid.

Compound IIIb (0.8 g, 0.00187 mol) was reacted under the same conditions as compound IIb with phenylboronic acid (1.6 g, 0.013 mol). Treatment of the reaction solution with petroleum ether (20 ml) precipitated a mixture (0.8 g). By preparative tlc a fraction could be isolated which had the following properties; mp 95-97°, $[\alpha]_D^{25}$ - 58 (C=1, $CH_3OH$); $\bar{\nu}_{max}$ 3311 (NH), 1728 (ester C=O), 1694, 1528 (amide C=O), 730, 693 ($C_6H_5$).

Anal. Calcd for a benzyl O-acetyl-2-benzyloxycarbonylamido-2-deoxy-hexoside·$H_2O$ $C_{23}H_{29}NO_9$ (463.5): C, 59.60; H, 6.31; N, 3.03. Found: C, 59.87; H, 6.26; N, 3.18.

Deacetylation of this material gave a substance homogenous on tlc with an $R_f$ value equal to that of compound IX.

Benzyl 2,3-anhydro-α-D-allopyranoside (XXXIII):

Benzyl 2,3-anhydro-4,6-benzylidene-α-D-allopyranoside[14] (XVII) (0.5 g, 0.0015 mol) was dissolved in nitromethane (7 ml) and boron acetate (0.5 g) was added. The mixture was heated at 70° for 6 hr and the solution decanted from undissolved boron acetate. The solution was evaporated in vacuo to give a mixture. The mixture was separated by preparative tlc to give 0.1 g (27%): mp 108-109°, $[\alpha]_D^{25}$ + 95 (C=1, Pyridine); $\nu_{max}$ 3365 (NH) 728, 694 ($C_6H_5$).

Anal. Calcd for $C_{13}H_{16}O_5$ (252.26): C, 61.90; H, 6.39. Found: C, 61.74; H, 6.35.

The benzylidene group of XVII was also removed with $CH_3COOH$ and $H_2O$ to give a product that had physical data and an ir spectrum identical to XXXIII.

## IV. TRIMETHYLSILYLATION OF BENZYL 3,4-ANHYDRO-2-BENZYLOXYCARBONYLAMIDO-2-DEOXY-β-D-ALLOPYRANOSIDE

Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-6-O-trimethylsilyl-β-D-allopyranoside (XXXII):

A solution of compound IIb[1] (0.49 g, 0.0013 mol) in $(CH_3)_3SiN_3$ (5.0 ml) was refluxed for 7.5 hr. The excess $(CH_3)_3SiN_3$ was distilled off under reduced pressure. Hexane was added to the remaining syrup and the mixture was kept at room temperature for 2 hr. The crystals were filtered off and recrystallized from methanol and water to give 0.28 g (48%): mp 81-82°, $[\alpha]_D^{25}$ - 134 (C=1, Pyridine): $\nu_{max}$ 3294 (NH), 1683, 1539 (amide C = O), 1090 (Si — O), 752, 695 ($C_6H_5$).

Anal. Calcd for $C_{24}H_{31}NO_6Si$ (457.61): C, 62.99; H, 6.83; N, 3.06. Found: C, 62.92; H, 6.93; N, 3.44.

## V. REACTION OF BENZYL 4,6-O-BENZYLIDENE-2,3-DIDEOXY-2,3-EPIMINO-α-D-ALLOPYRANOSIDE WITH $HNO_2$

Benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (XXXIV):

Compound VIa (1 g, 0.0029 mol) was dissolved in a solution of dioxane (35 ml), $H_2O$ (3.5 ml), glacial acetic acid (4 ml), and $KNO_2$ (2 g) at room temperature. After 6 hr $H_2O$ was added and the product was filtered and recrystallized from methanol to give 0.93 g (98%): mp 143-145°, $[\alpha]_D^{25}$ + 80.5 (C=1, Pyridine); $\bar{\nu}_{max}$ 746, 692 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{20}O_4$ (324.36): C, 74.06; H, 6.21. Found: C, 73.50; H, 6.21.

Benzyl 4,6-O-benzylidene-α-D-mannopyranoside (XXXV):

Compound XXXIV (.75 g, 0.0023 mol) was dissolved in dioxane (75 ml) in an ice bath and 2% $KMnO_4$ (100 ml) was added over a two hour period. The solution was evaporated in vacuo and the residue was recrystallized from diethyl ether and petroleum ether to give 0.25 g (30%): mp 145-146°, $[\alpha]_D^{25}$ + 50 (C=1, Pyridine); $\bar{\nu}_{max}$ 748, 698 ($C_6H_5$).

Anal. Calcd for $C_{20}H_{22}O_6$ (358.38): C, 67.02; H, 6.19. Found: C, 66.73; H, 6.07.

Benzyl α-D-mannopyranoside (XXXVI):

Compound XXXV (0.15 g, 0.0004 mol) was dissolved in glacial acetic acid (6 ml) and $H_2O$ (3 ml) was added over a 20 min period. The solution was heated at 90° for 30 min and evaporated *in vacuo*. The residue was dissolved in toluene and the solution evaporated *in vacuo* three times. The product was recrystallized from isopropanol and diisopropyl ether to give 0.09 g (79%): mp 132-133°, $[\alpha]_D^{25}$ + 71 (C=1, $H_2O$); (Literature[57]: mp 131-132°, $[\alpha]_D^{20}$ + 74 (C=1.3, $H_2O$).

# CHAPTER IV

## SUMMARY

Carbohydrate epoxides and epimines are often intermediate substances in the preparation of epimeric sugars. The usual methods of opening the epoxide or epimine rings of these intermediate substances involve the use of a strong base or acid. Protective groups may be removed under these conditions. The reactivity of epoxides and epimines was investigated with reagents that were neither strongly basic nor acidic.

A novel epoxide ring opening of benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) was effected by phenylboronic anhydride in toluene. One of the products was demonstrated to be benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulopyranoside. Another isolated product, while not identified, has the properties of an anhydro-sugar different from the starting material.

Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) also underwent epoxide ring opening in reaction with phenylboronic acid. An isolated product had the properties of a benzyl 2-benzyloxycarbonylamido-2-deoxy-hexoside with properties different from the properties of the compounds isolated from the reaction of IIb with phenylboronate. This indicated that the substituent at the 6-position played an important role in the 3,4-epoxide ring opening.

Deacetylation of the product isolated from the reaction of IIIb gave another substance that had an $R_f$ value on tlc identical to benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IX). This product

could have resulted from a cis-opening of the epoxide ring by assistance from coordination with the boron compound. Such an opening is highly unusual and its confirmation requires further study. A complex neighboring group effect from the acetyl group may be involved.

The 2,3-epoxide ring of benzyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (XVII) was shown to be remarkably stable in a reaction with boron acetate in nitromethane. The product retained the epoxide ring under conditions that removed the benzylidene group.

The order of ring closure of the carbonyl- and anhydro- rings of benzyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside (XXV) was determined. An intermediate with the 3,6-anhydro structure was isolated (XXVII). This intermediate was then changed to the carbonyl compound XXV.

Trimethylsilyl azide was prepared in good yield in a mild, direct method. The azide was then used to prepare a new, low-melting compound by trimethylsilation of the 6-OH group of IIb. The epoxide function remained unchanged under the conditions of this new trimethylsilylation method.

The epimine ring of benzyl 4,6-O-benzylidene-2,3-dideoxy-2,3-epimino-α-D-allopyranoside (VIa) did not react with phenylboronate. However, VIa was deaminated by $HNO_2$ to give the 2,3-unsaturated derivative (XXXIV). This derivative was then cis-hydroxylated with $KMnO_4$ to give benzyl 4,6-O-benzylidene-α-D-mannopyranoside.

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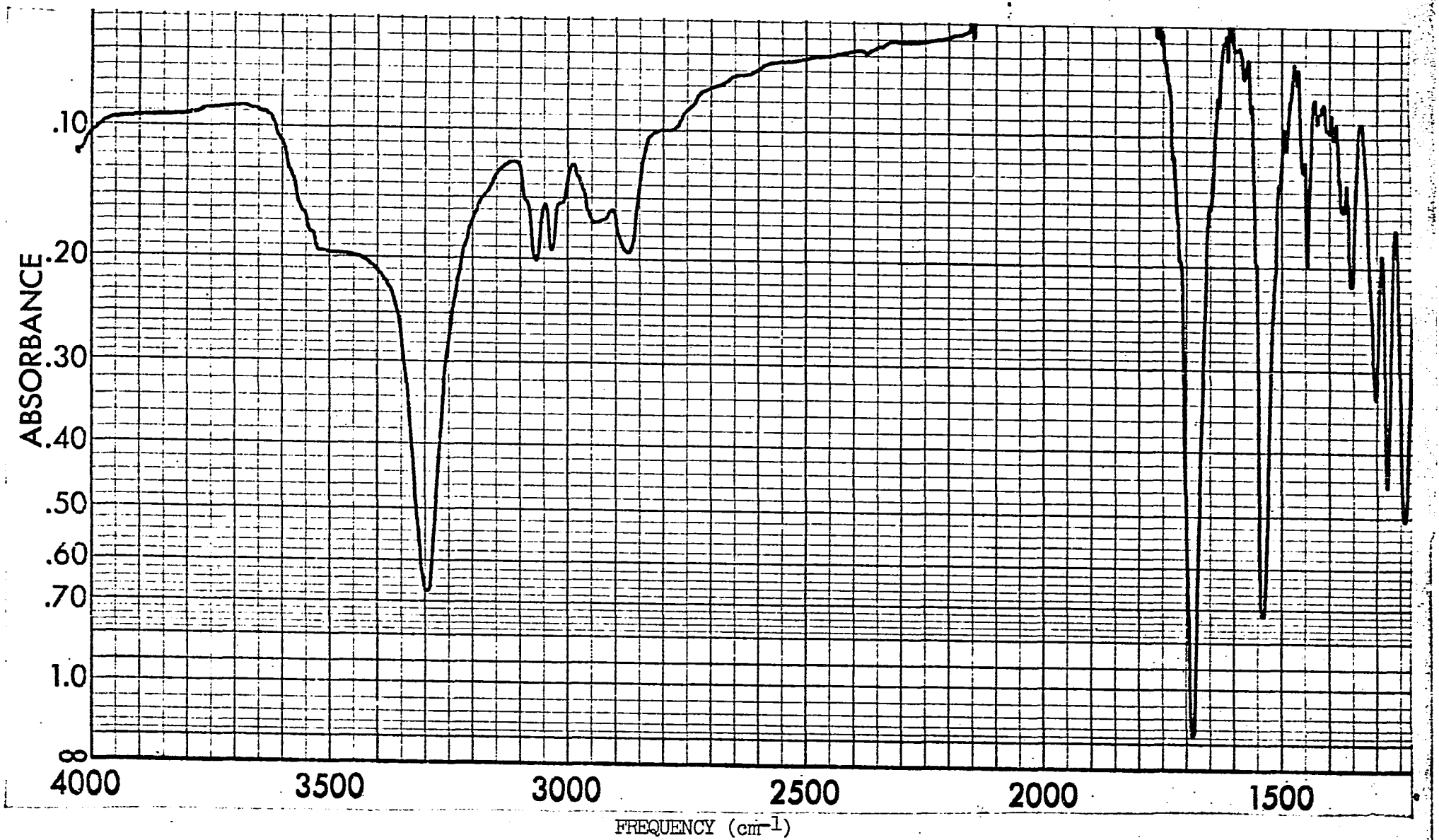


Figure 17. Infrared Spectra of Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) Part 1

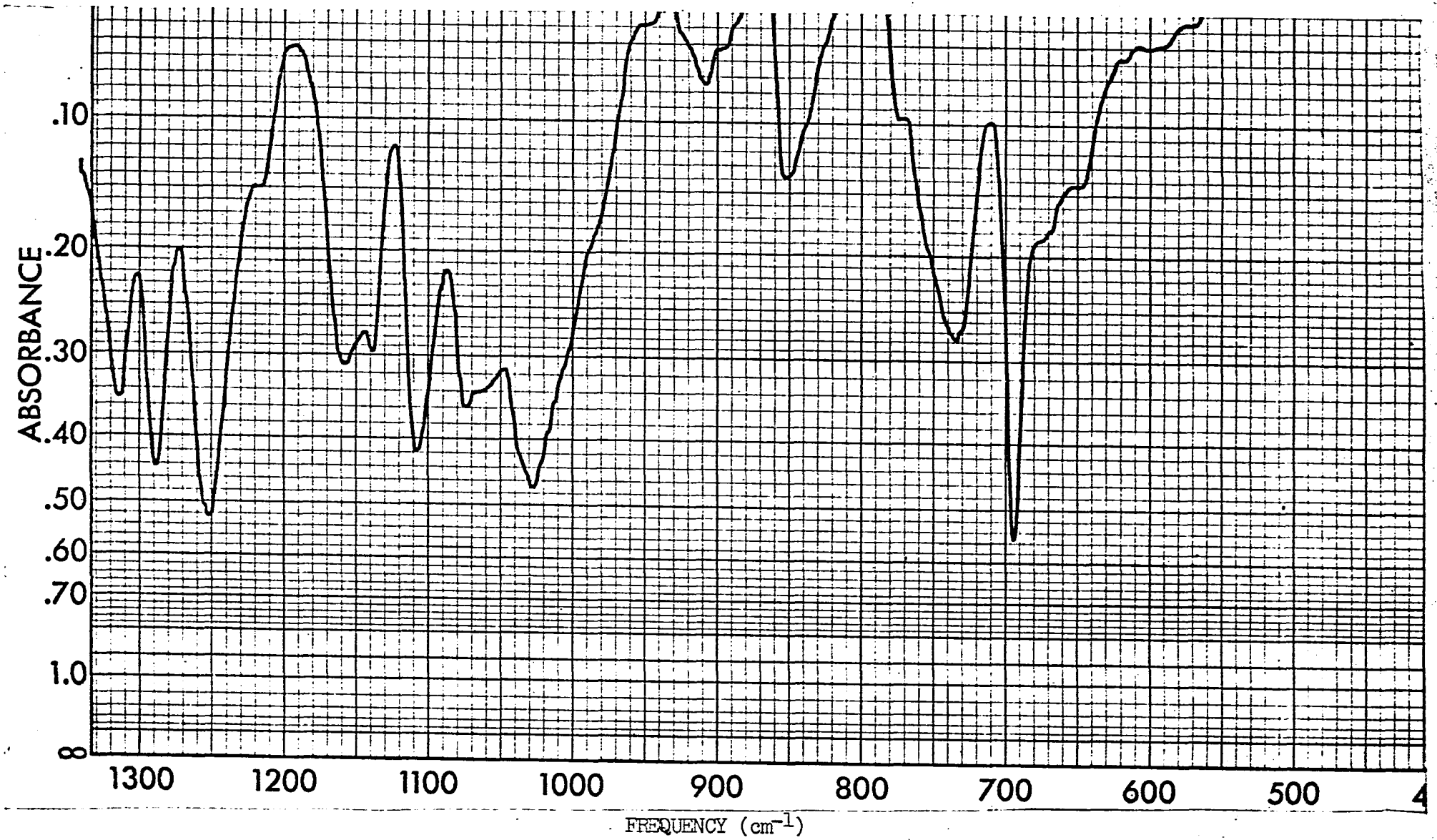


Figure 17. Infrared Spectra of Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) Part 2

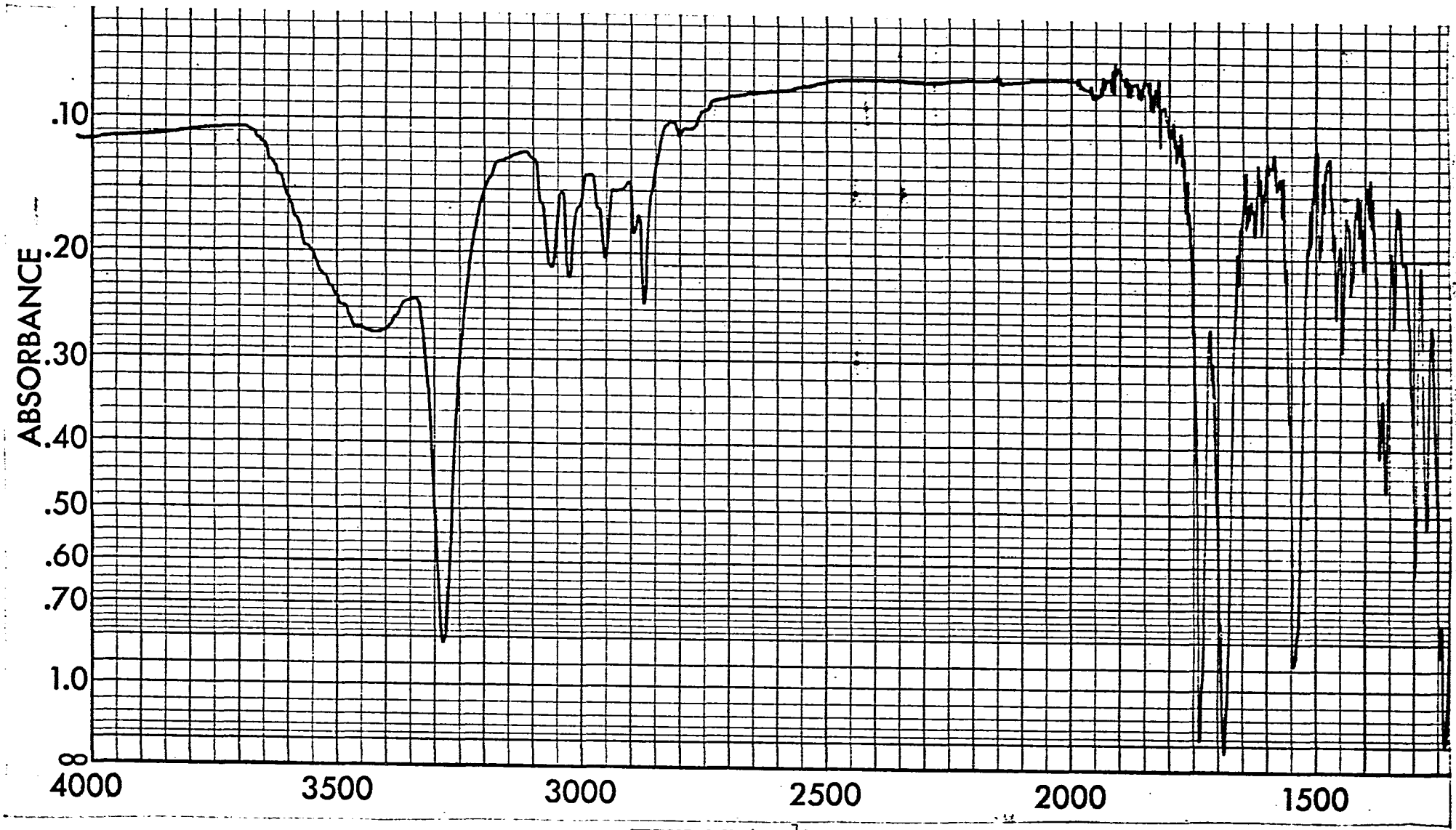


Figure 18. Infrared Spectra of Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxy-carbonylamido-2-deoxy-β-D-allopyranoside (IIIb) Part 1

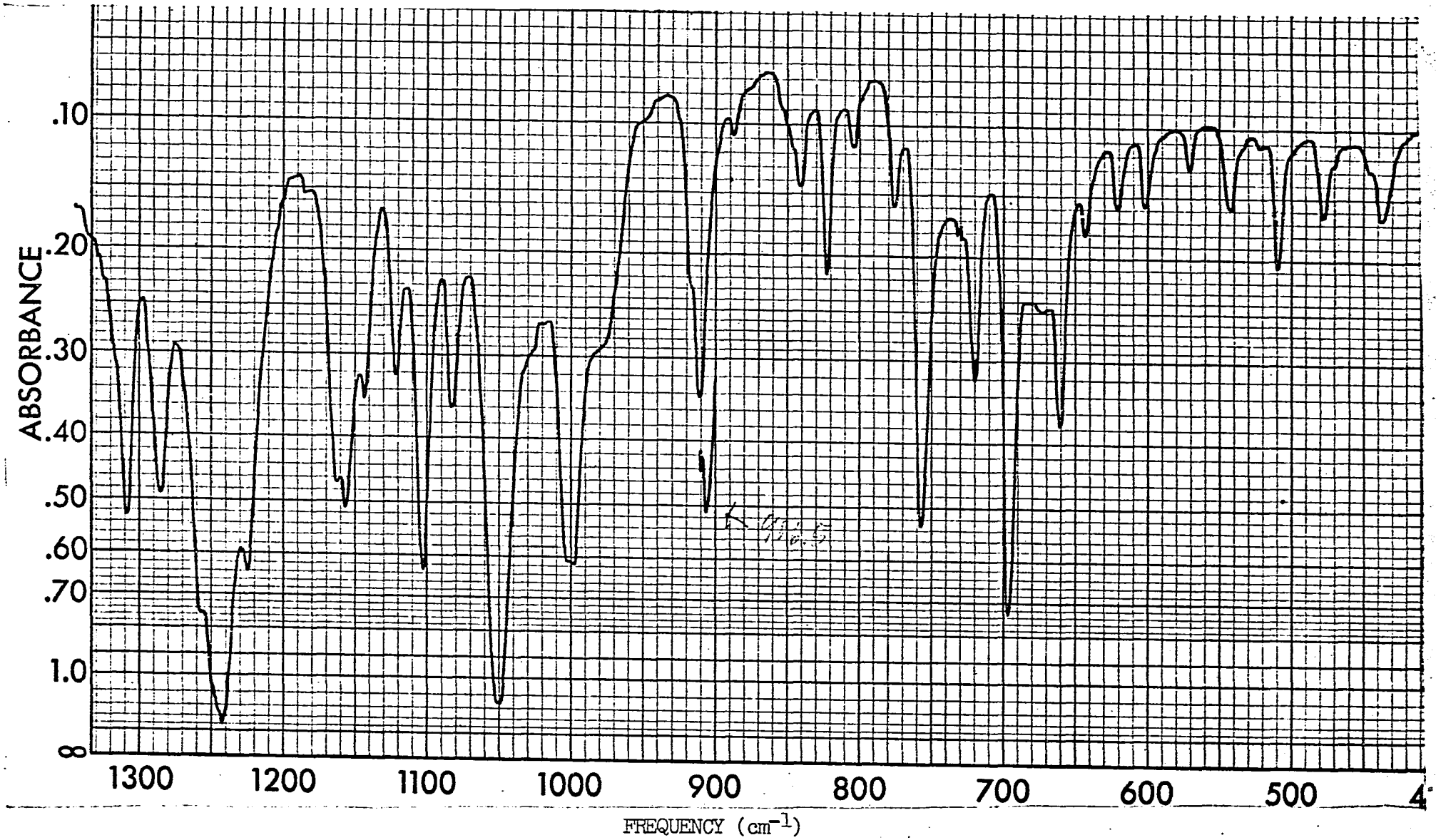


Figure 18, Infrared Spectra of Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxy-carbonylamido-2-deoxy-β-D-allopyranoside (IIIb) Part 2

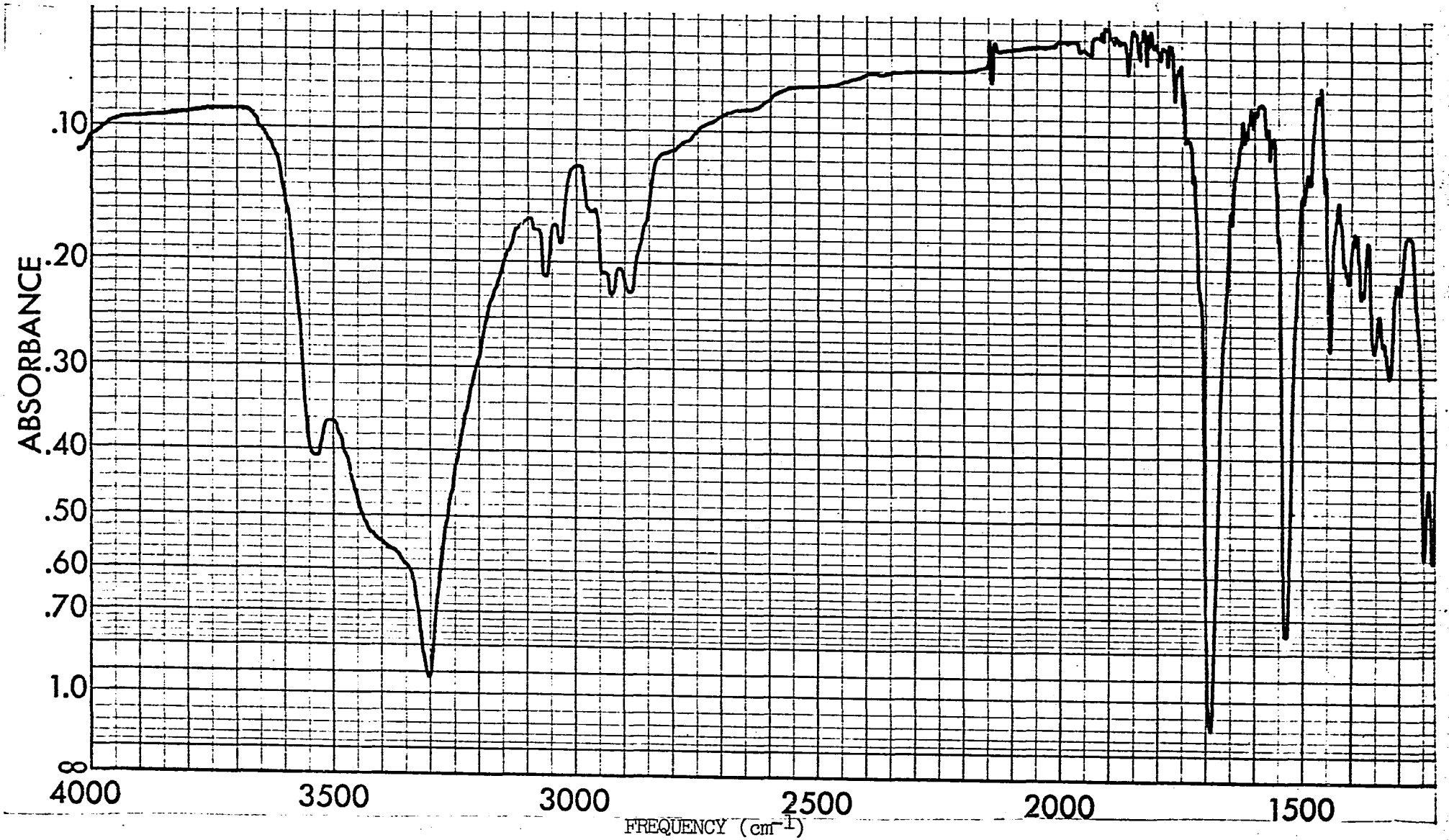


Figure 19. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IX) Part 1

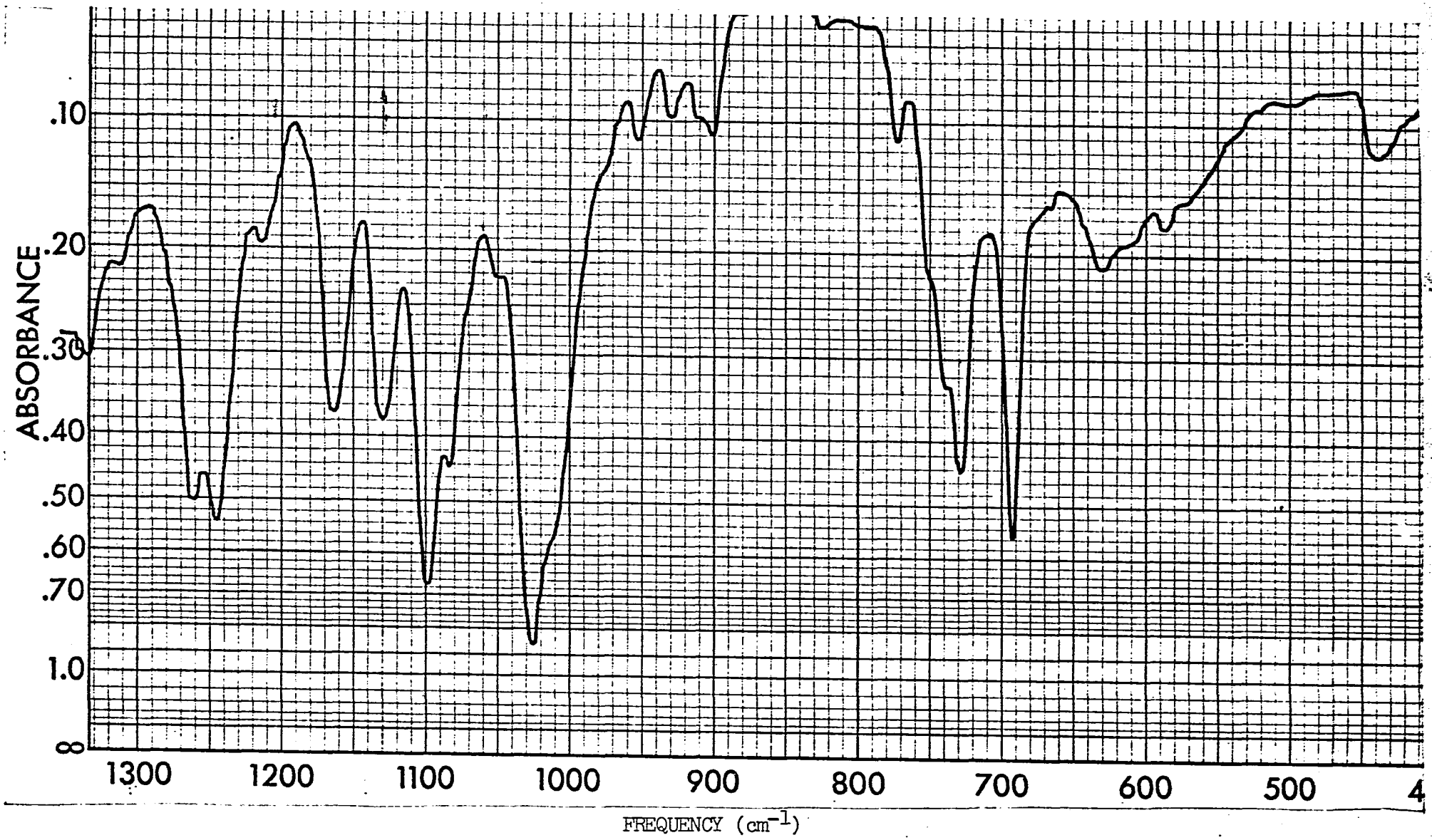


Figure 19. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IX) Part 2

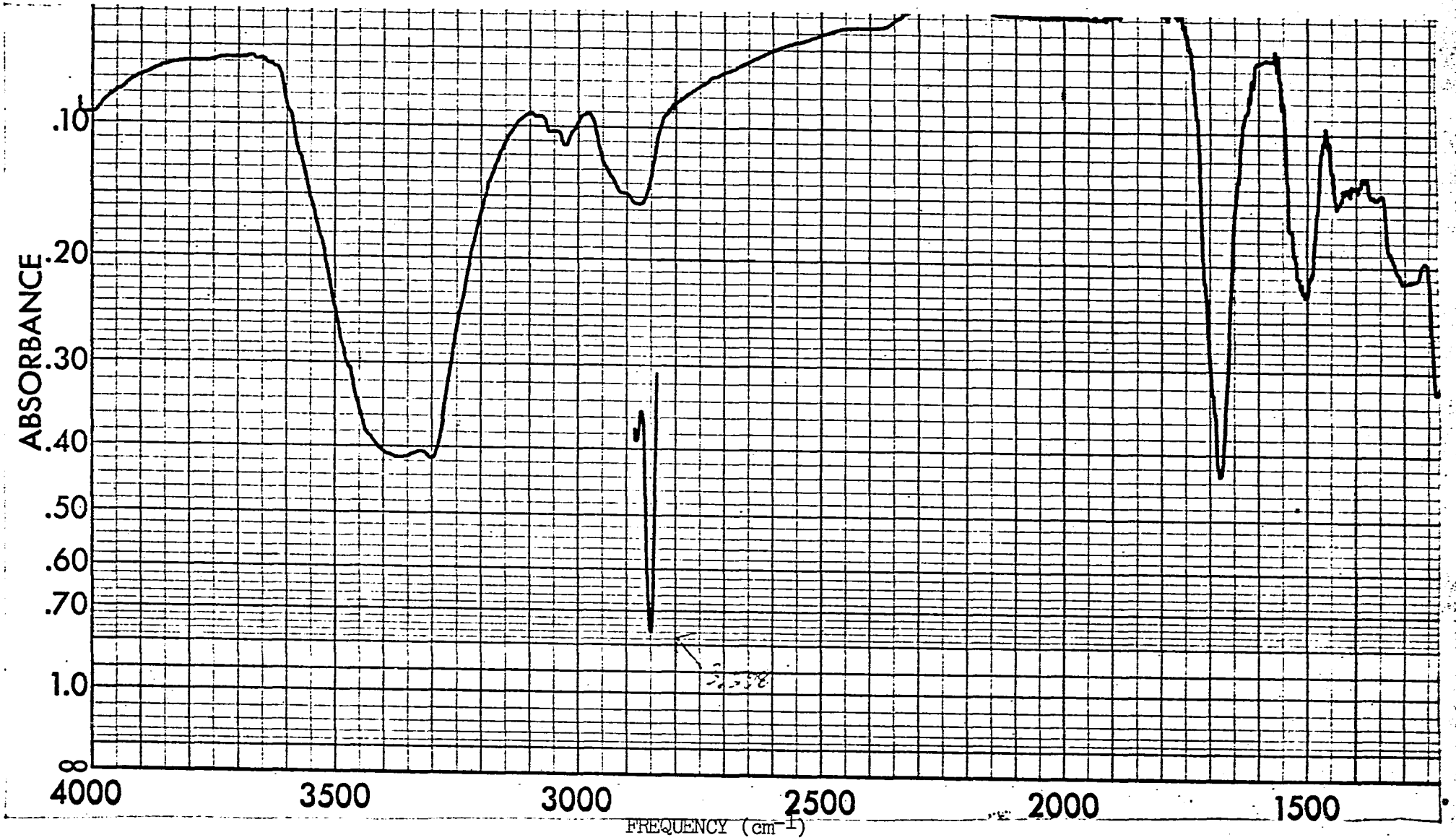


Figure 20. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV) Part 1

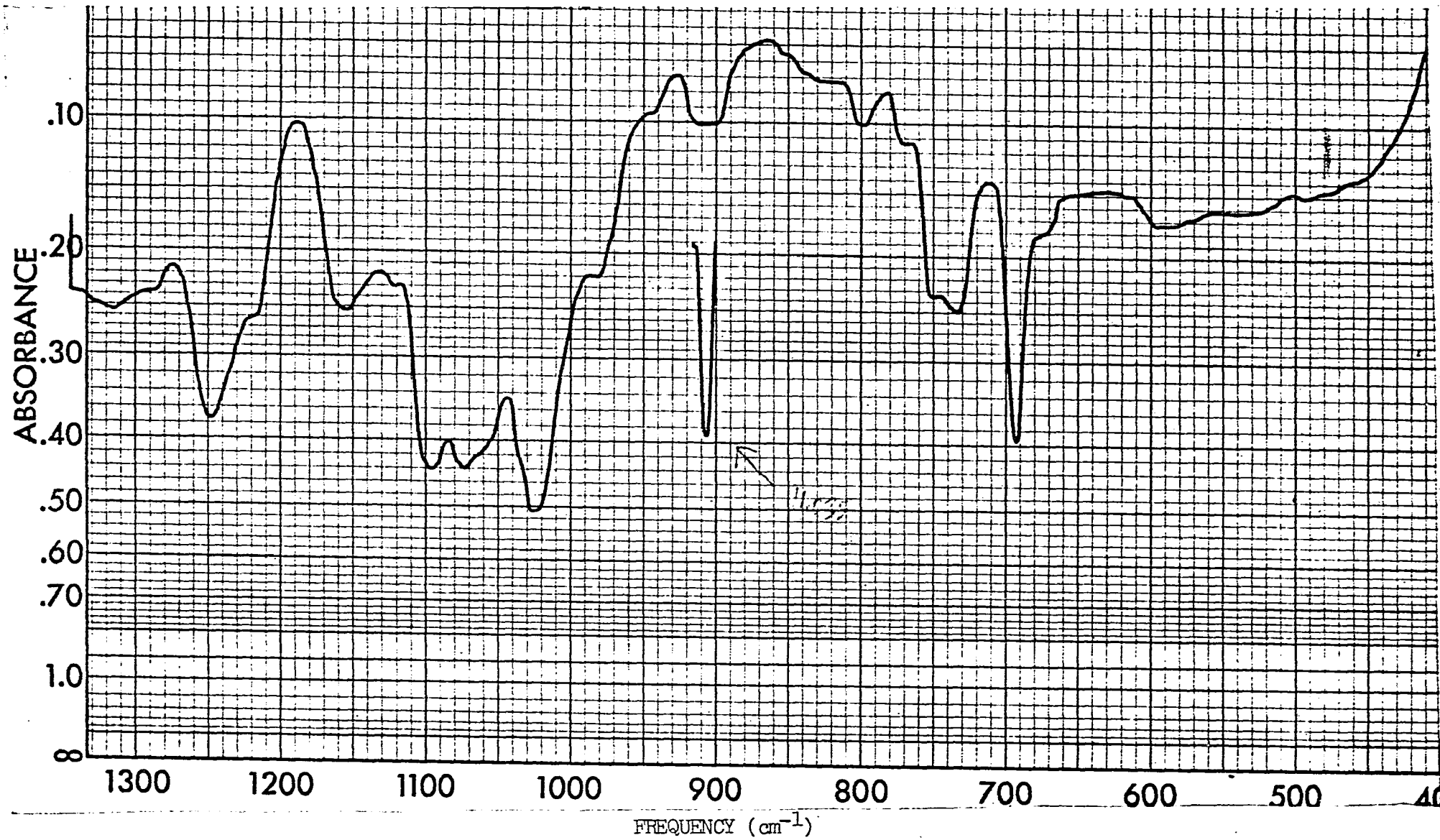


Figure 20. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside (XIV) Part 2

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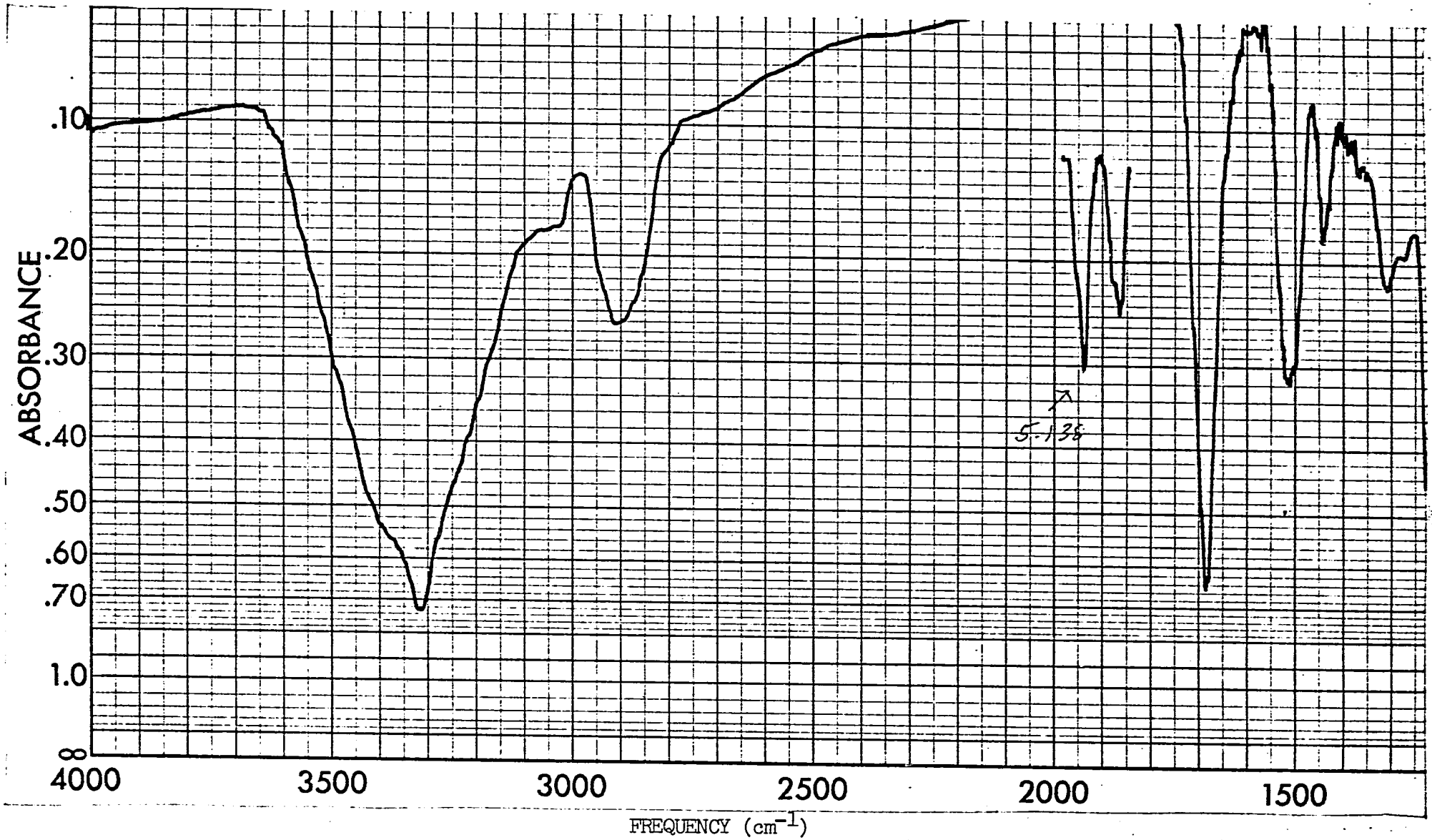


Figure 21. Infrared Spectra of Hydrated Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside Part 1

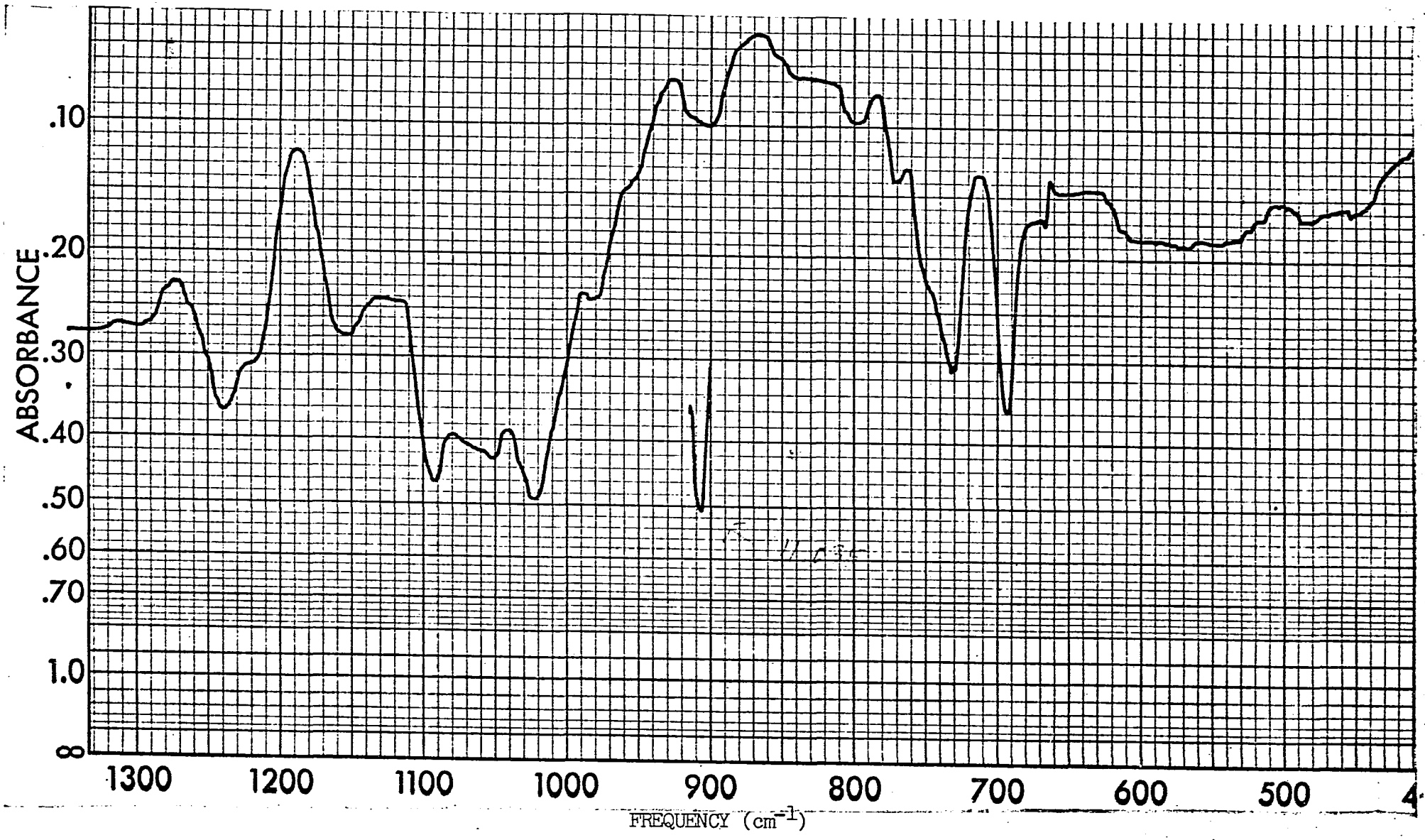


Figure 21. Infrared Spectra of Hydrated Benzyl 2-benzyloxycarbonylamido-2-deoxy-β-D-gulopyranoside Part 2

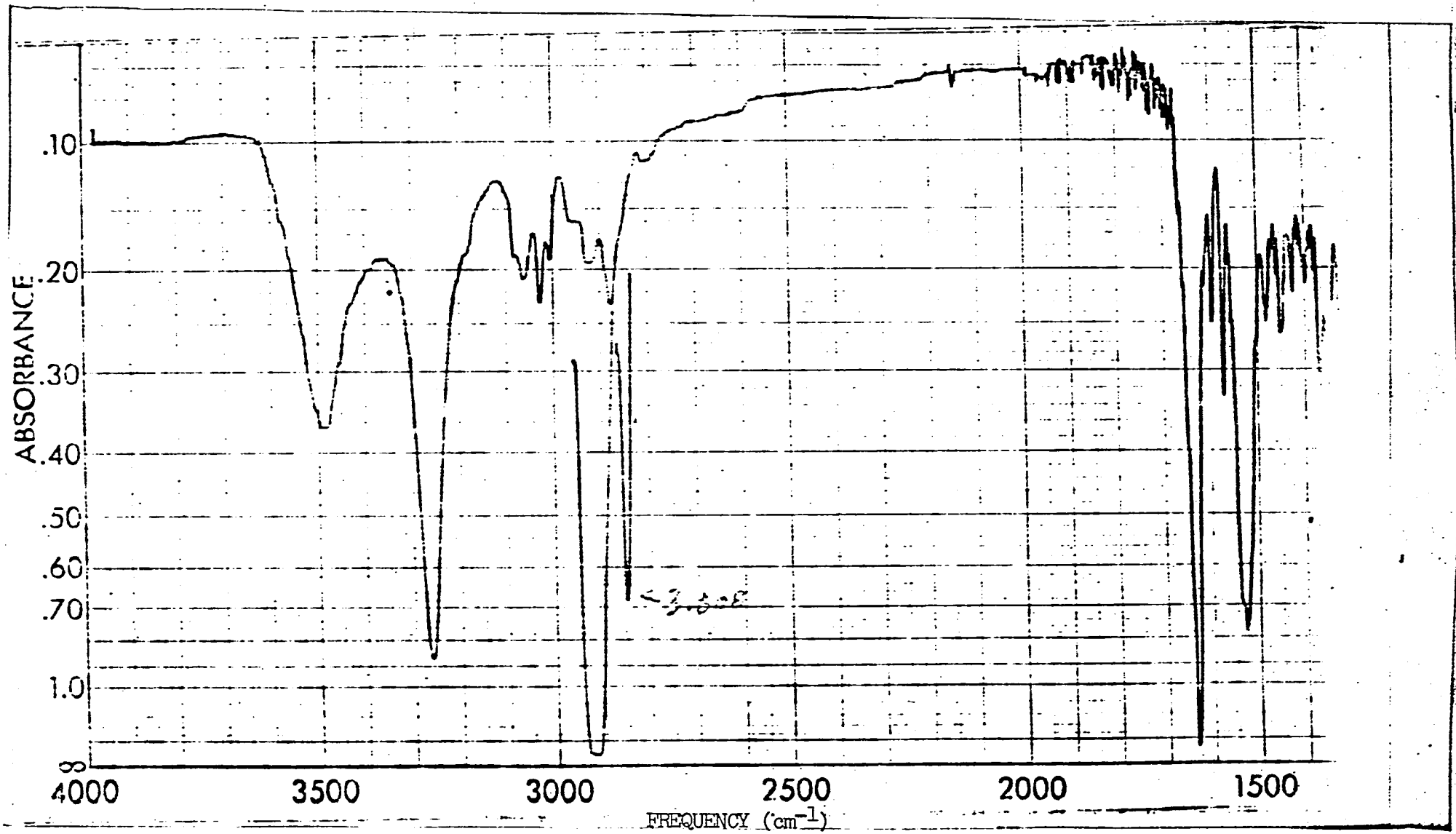


Figure 22. Infrared Spectra of Benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXII) Part 1

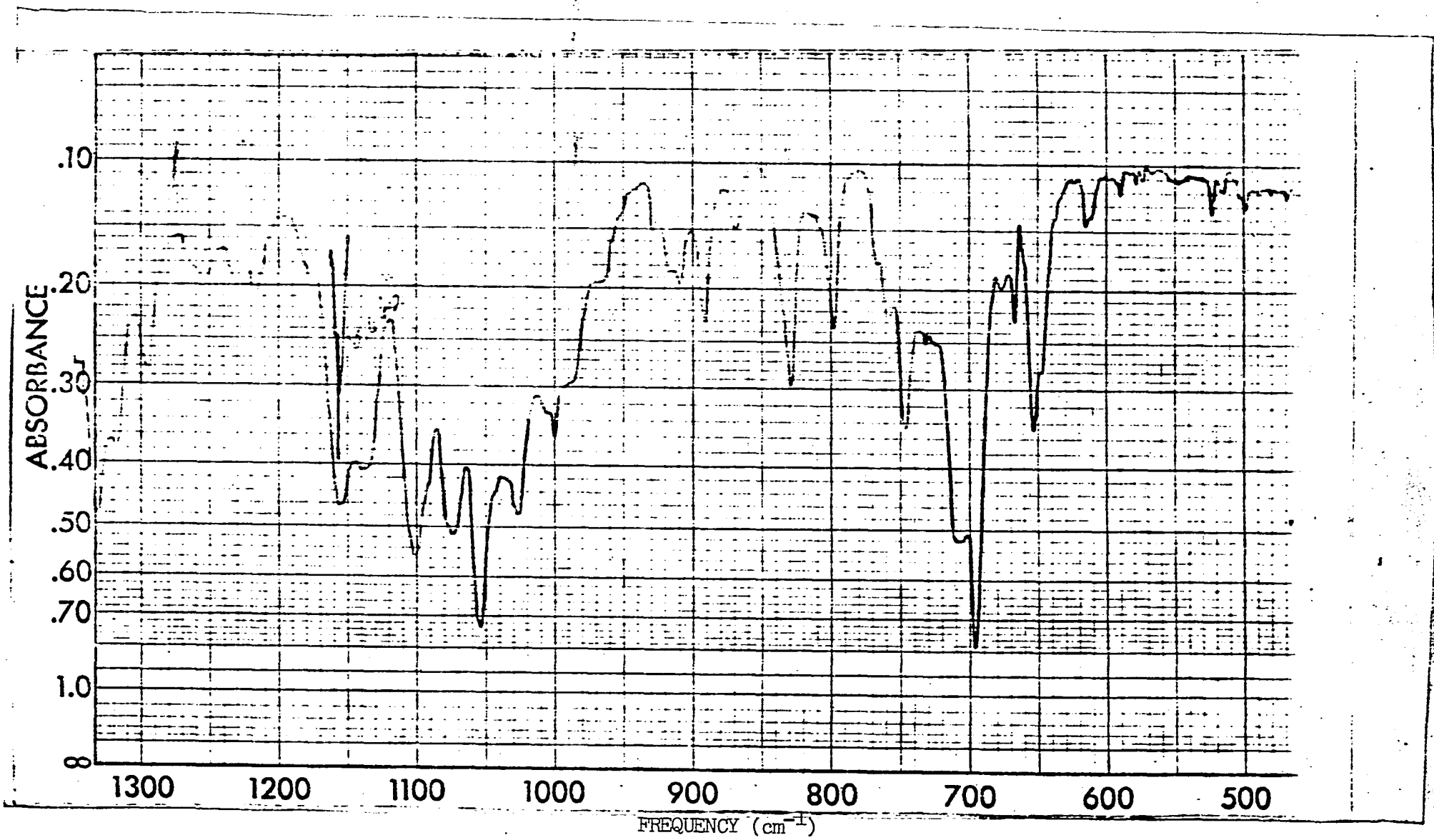


Figure 22. Infrared Spectra of Benzyl 3,4-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXII) Part 2

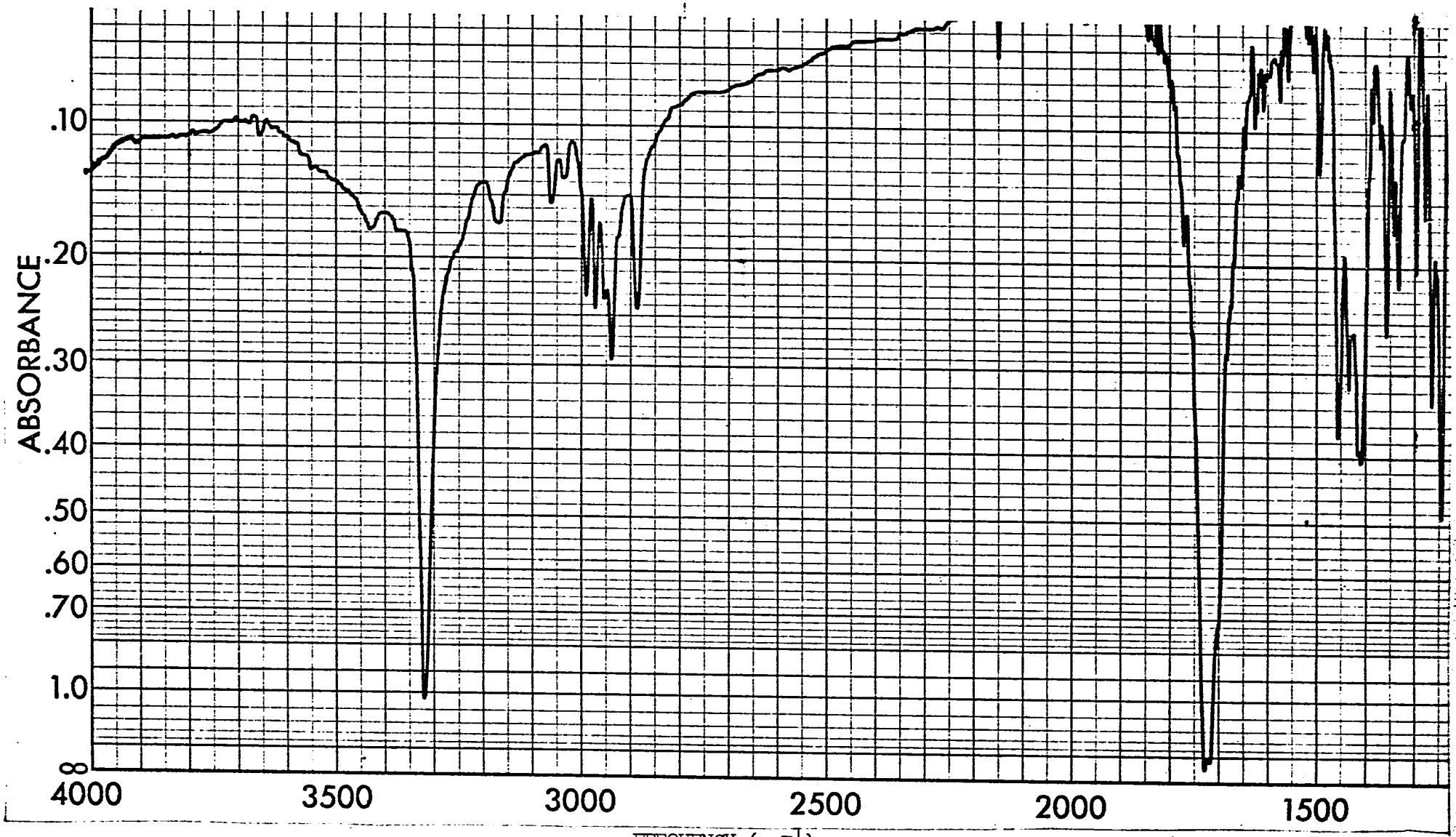


Figure 23. Infrared Spectra of Benzyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside (XXV) Part 1

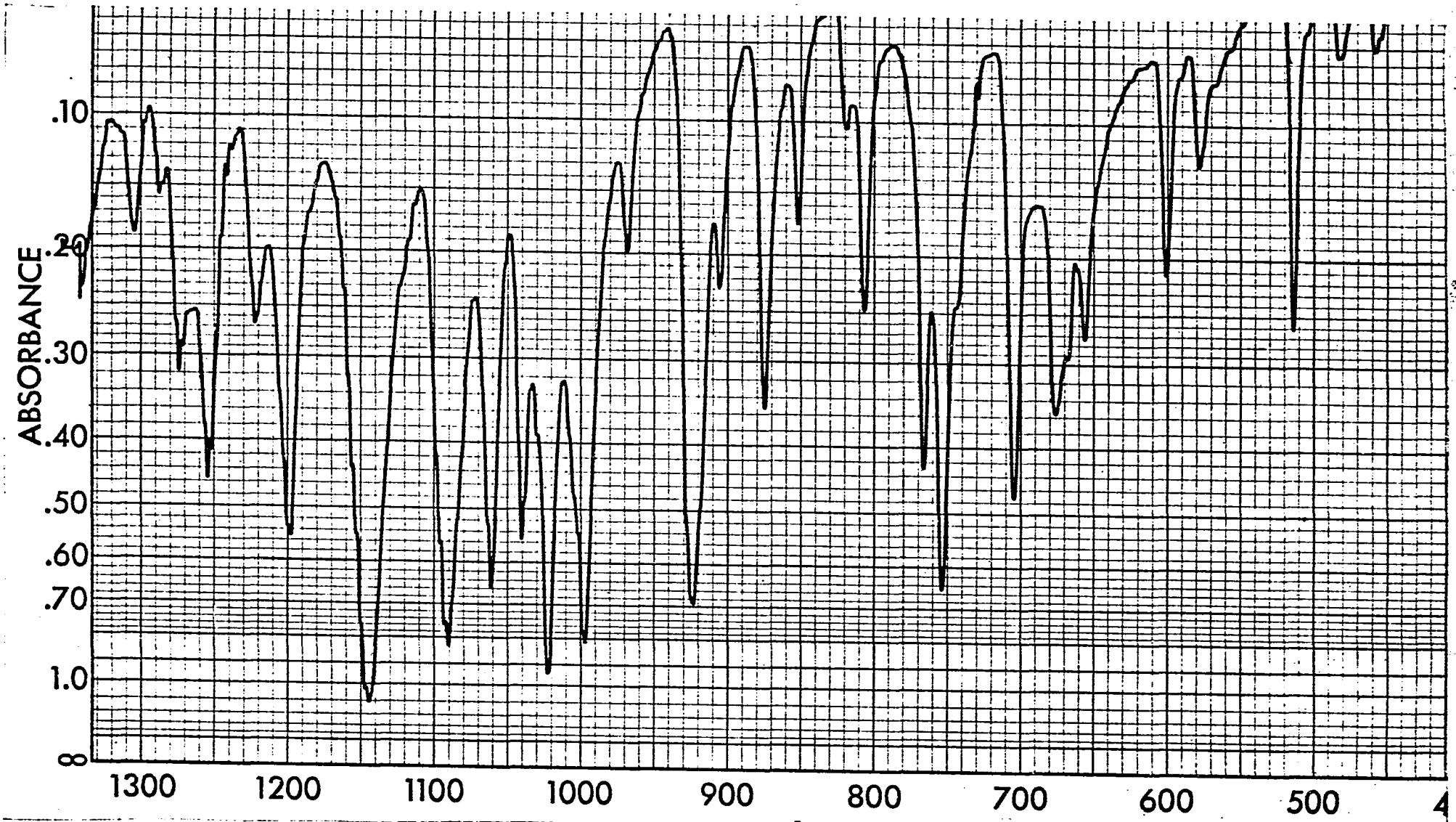


Figure 23. Infrared Spectra of Benzyl 2-amino-3,6-anhydro-2-N:4-O-carbonyl-2-deoxy-β-D-glucopyranoside (XXV) Part 2

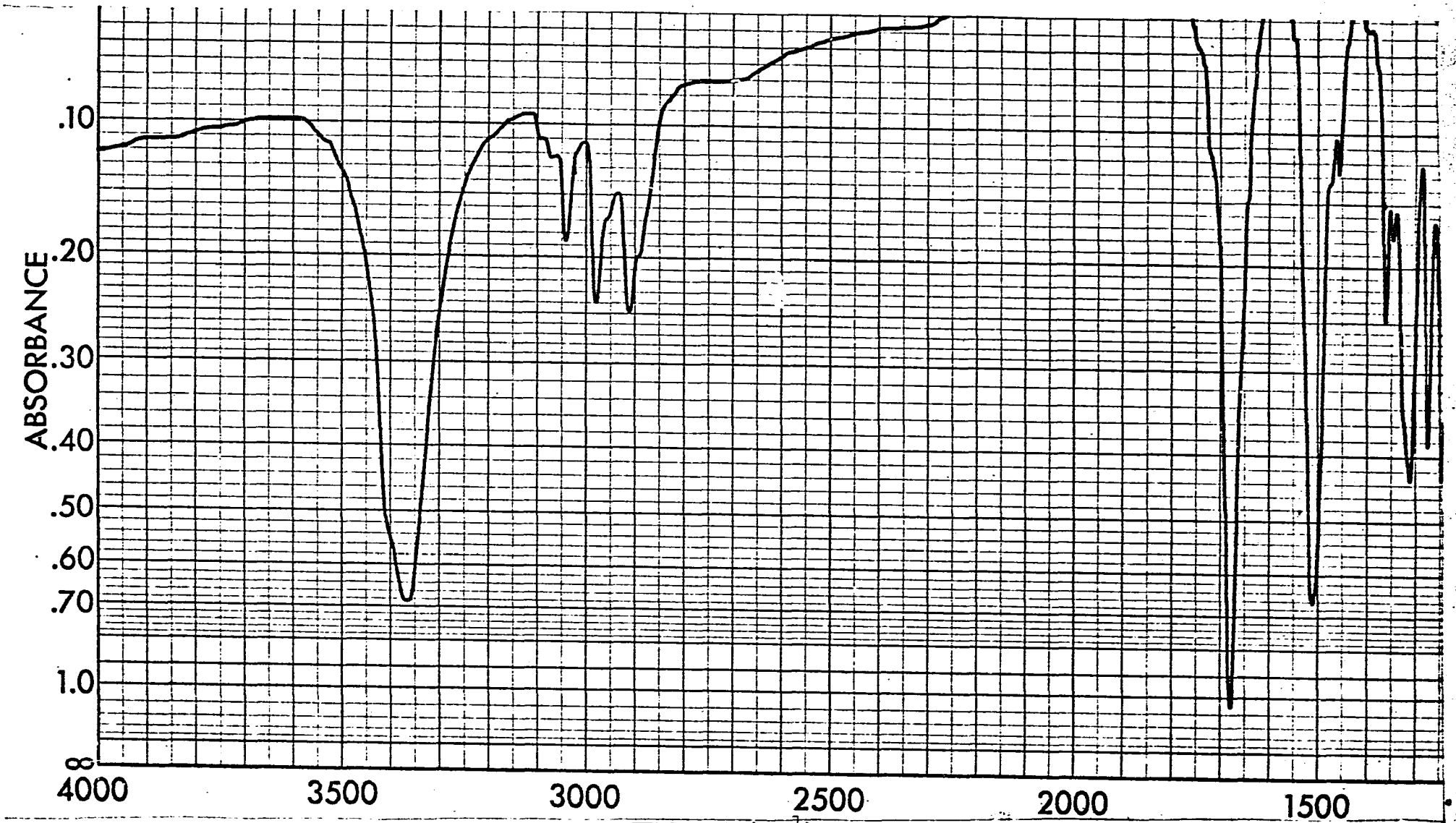


Figure 24. Infrared Spectra of Benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXVII) Part 1

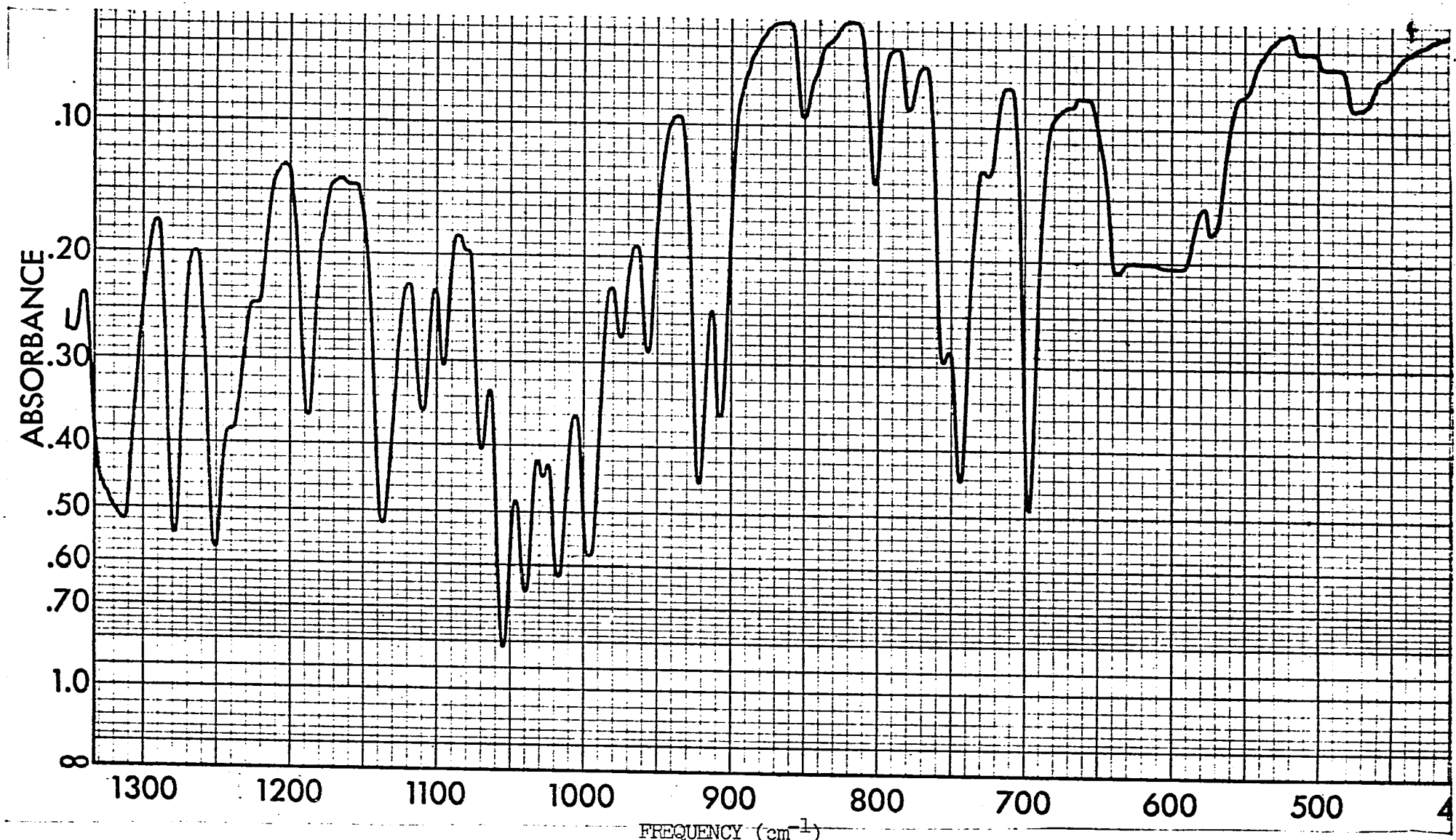


Figure 24. Infrared Spectra of Benzyl 3,6-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-glucopyranoside (XXVII) Part 2

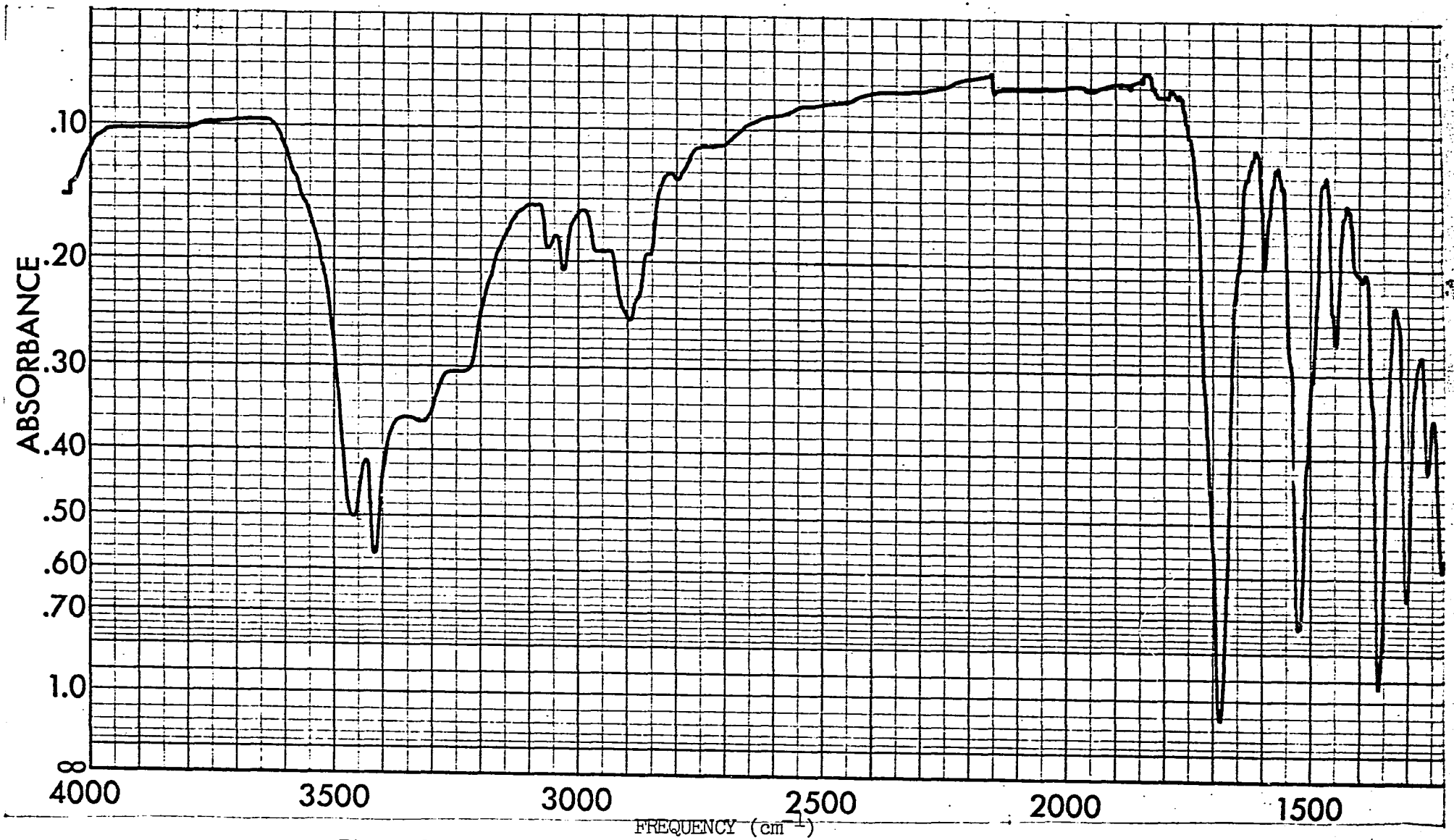


Figure 25. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluenesulfonyl-β-D-glucopyranoside (XXVIII) Part 1

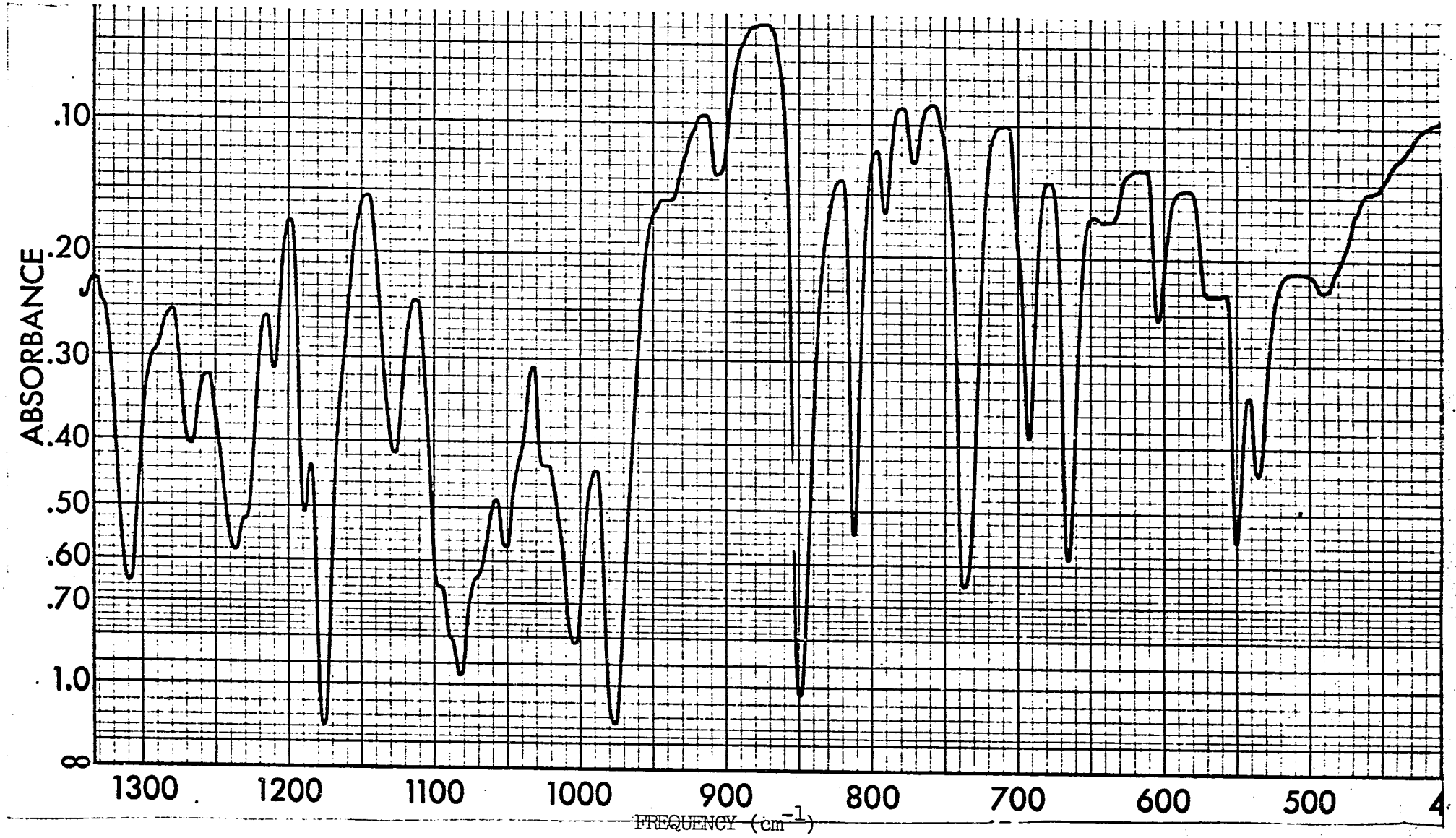


Figure 25. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-6-O-p-toluenesulfonyl-β-D-glucopyranoside (XXVIII) Part 2

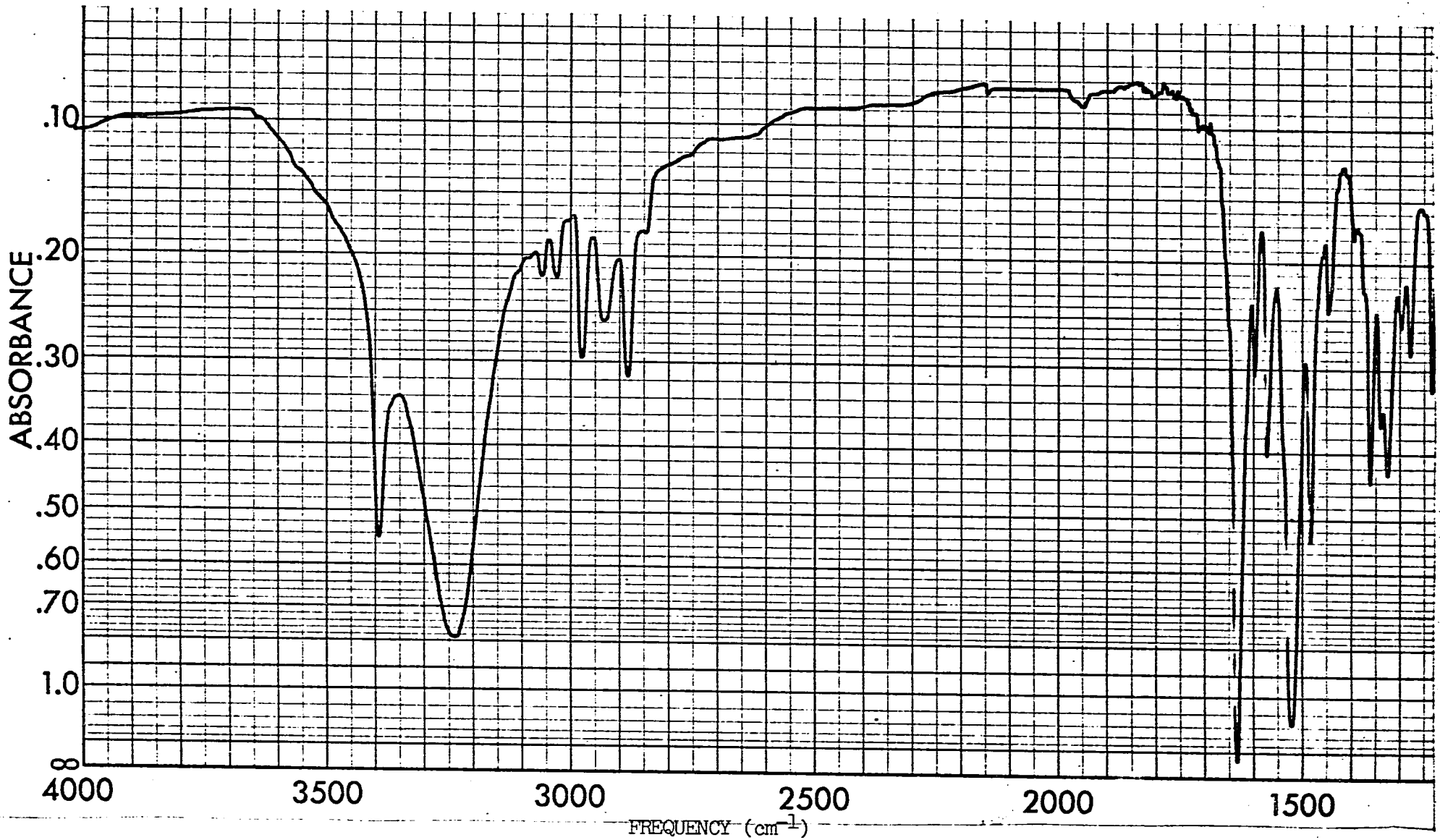


Figure 26. Infrared Spectra of Benzyl 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXX) Part 1

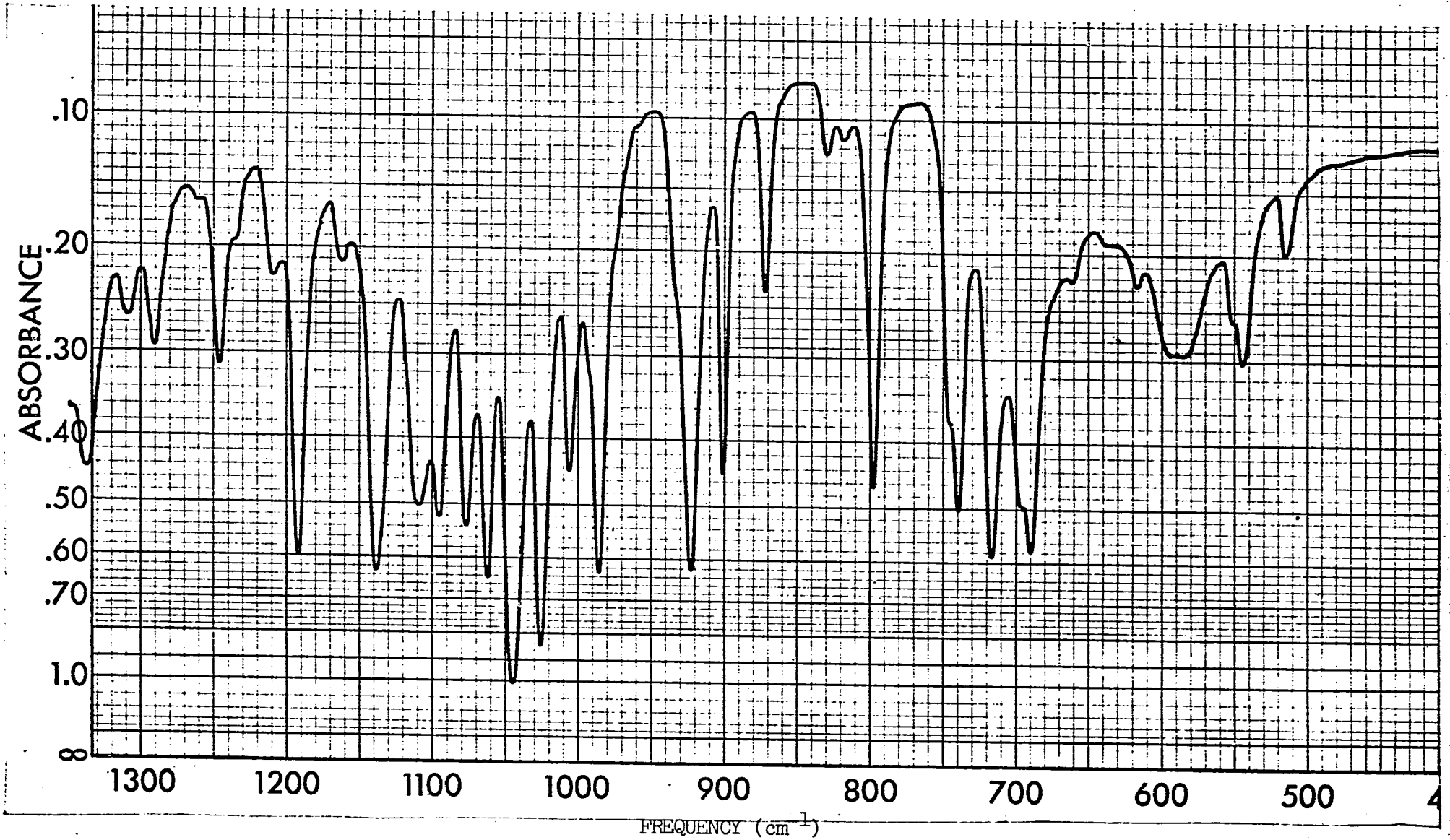


Figure 26. Infrared Spectra of Benzyl 3,6-anhydro-2-benzamido-2-deoxy-β-D-glucopyranoside (XXX) Part 2

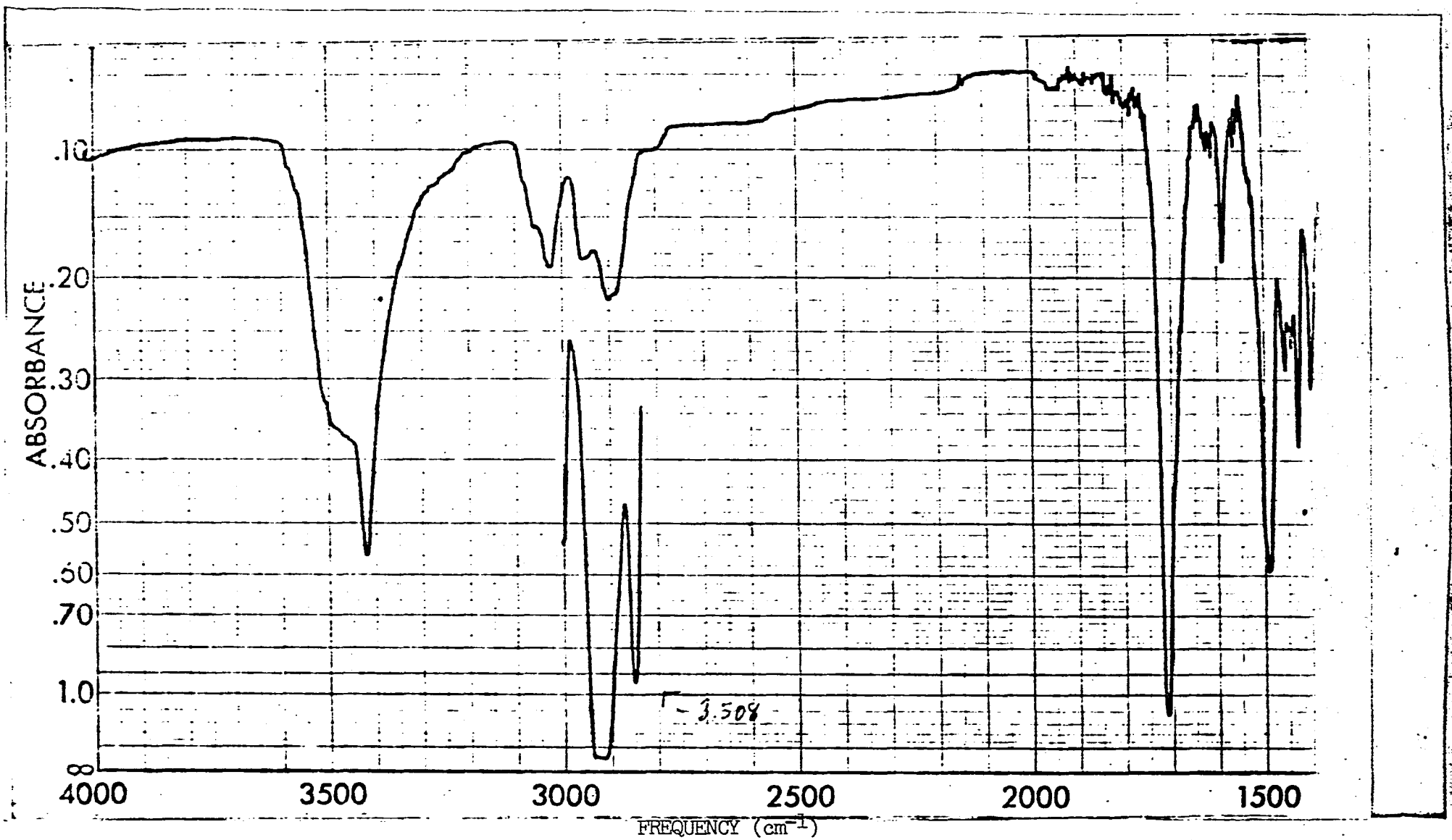


Figure 27. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulopyranoside (XXXI) Part 1

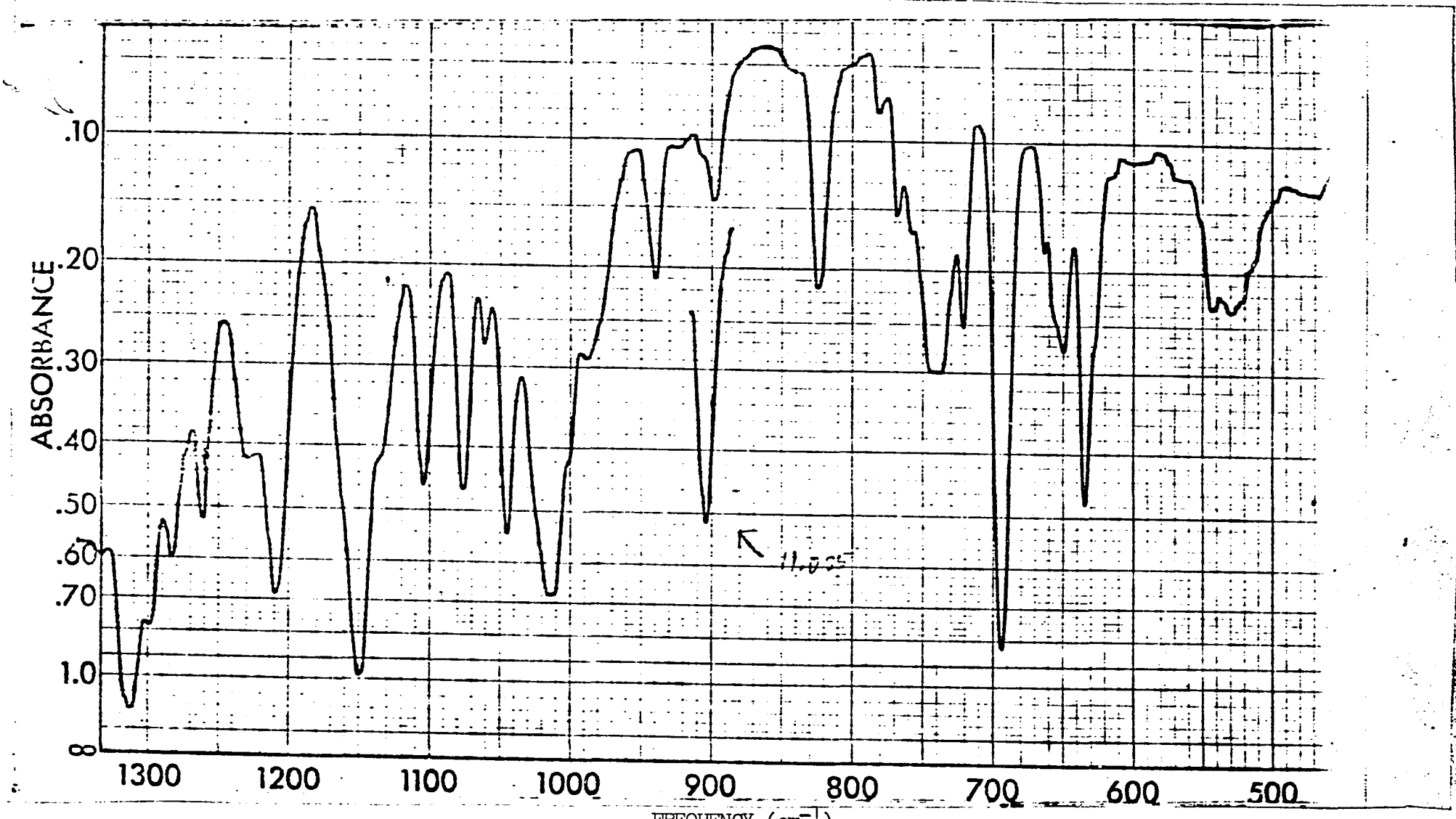


Figure 27. Infrared Spectra of Benzyl 2-benzyloxycarbonylamido-2-deoxy-4,6-O-phenylboronate-β-D-gulppyranoside (XXXI) Part 2

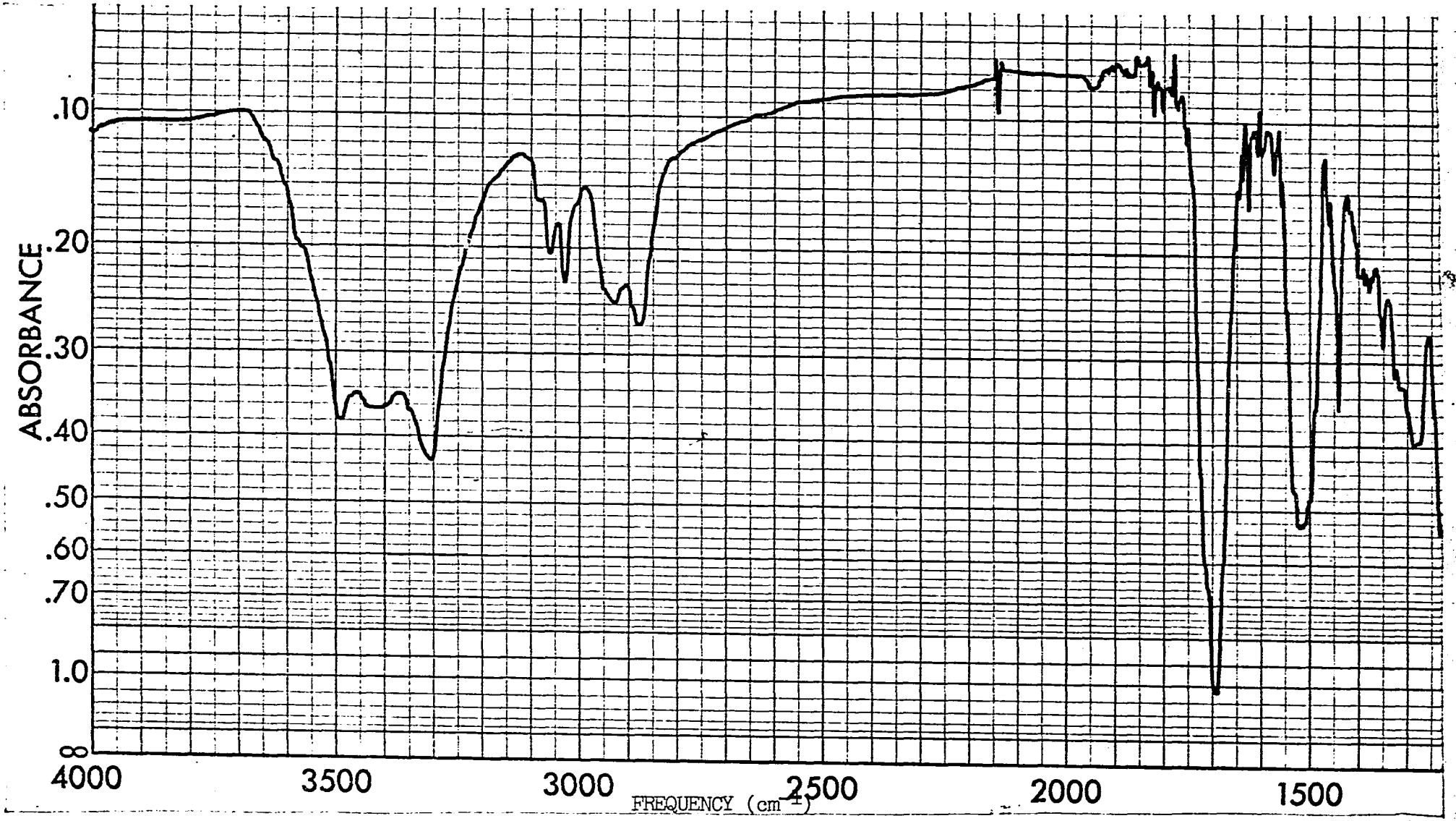


Figure 28. Infrared Spectra of Product Separated by Preparative tlc from Reaction of Phenylboronic Anhydride and Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) Part 1

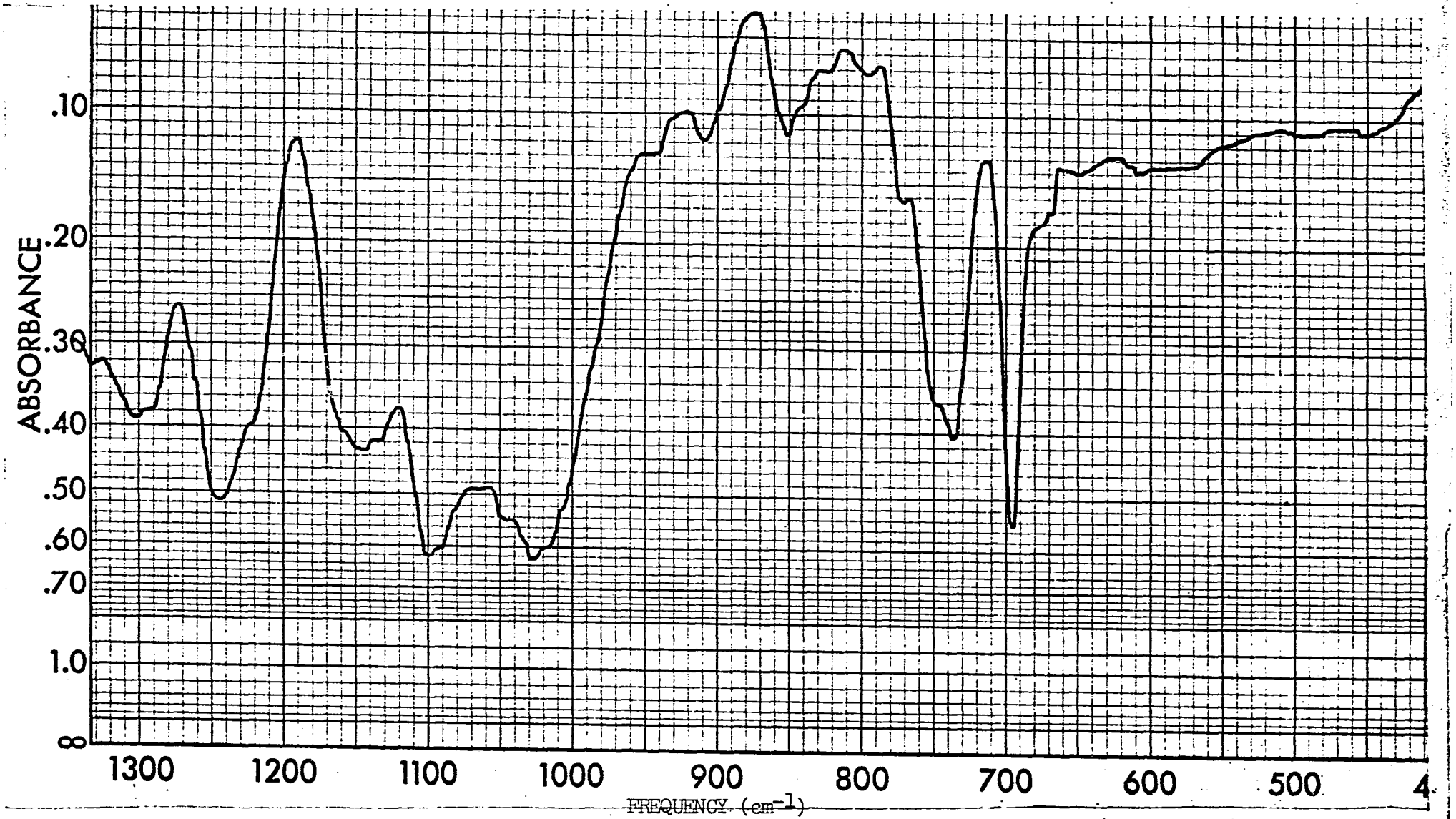


Figure 28. Infrared Spectra of Product Separated by Preparative tlc from Reaction of Phenylboronic Anhydride and Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIb) Part 2

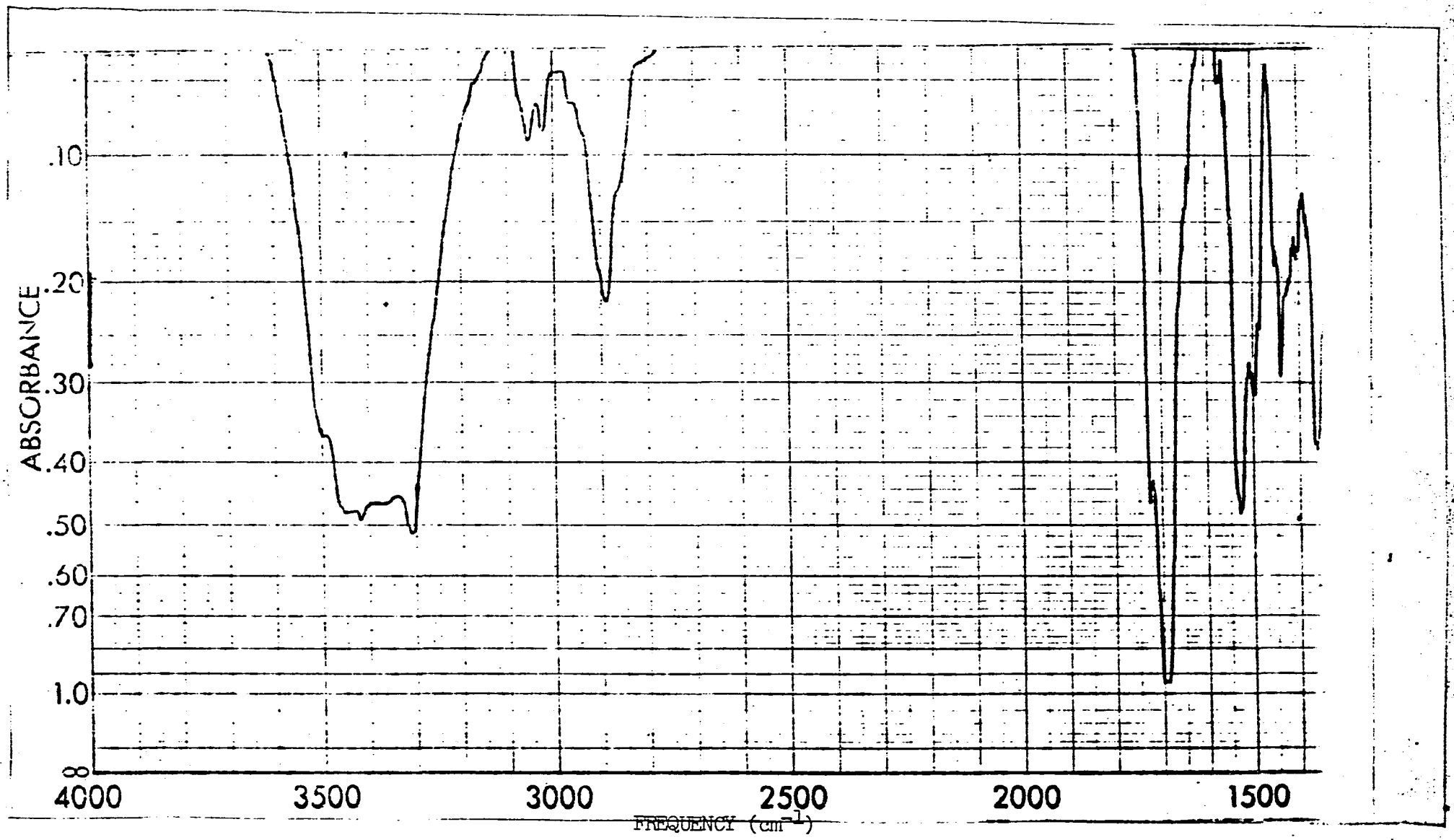


Figure 29. Infrared Spectra of Product Separated by Preparative tlc from Reaction of Phenylboronic Anhydride and Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) Part 1

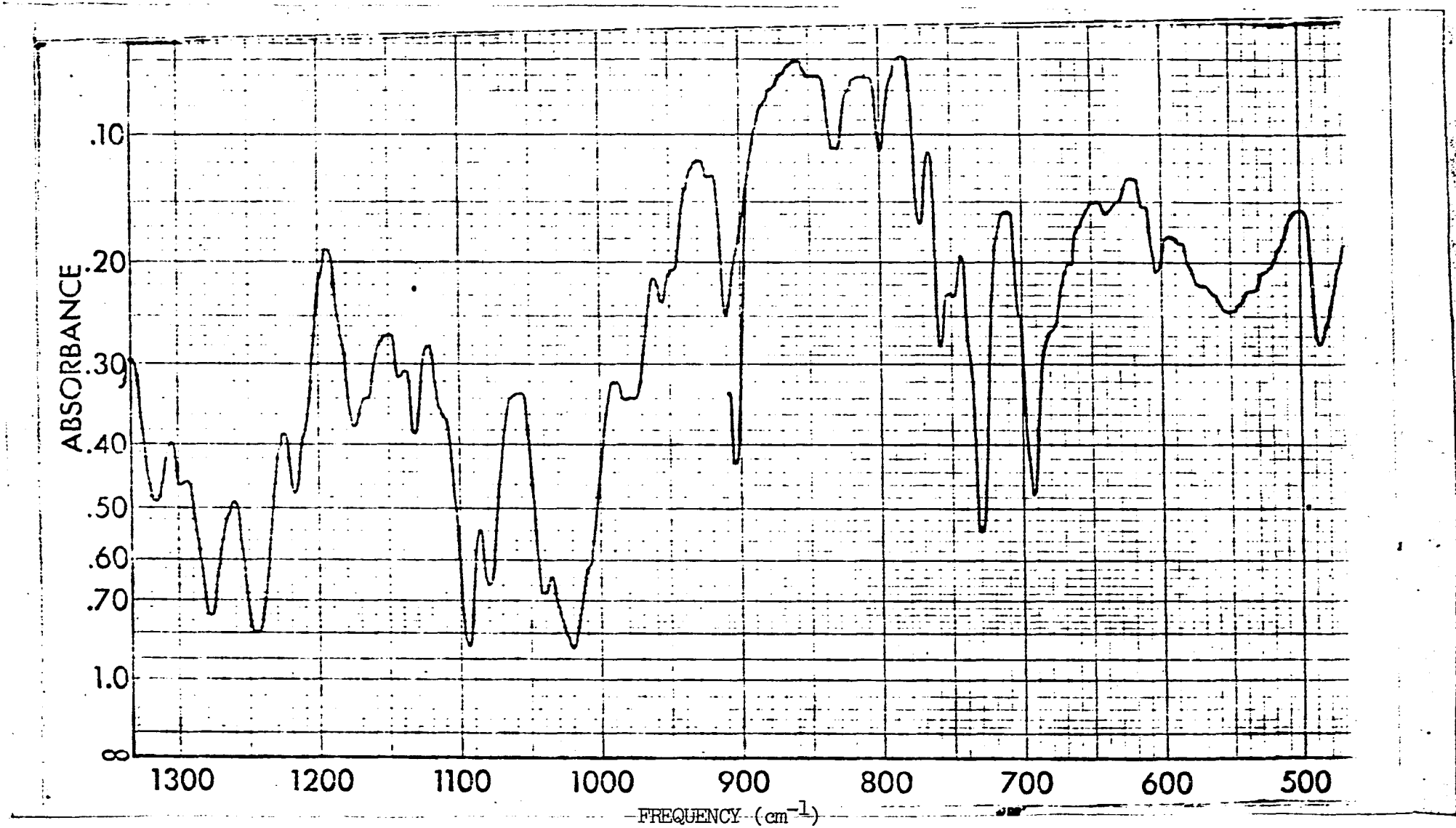


Figure 29. Infrared Spectra of Product Separated by Preparative tlc from Reaction of Phenylboronic Anhydride and Benzyl 6-O-acetyl-3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-β-D-allopyranoside (IIIb) Part 2

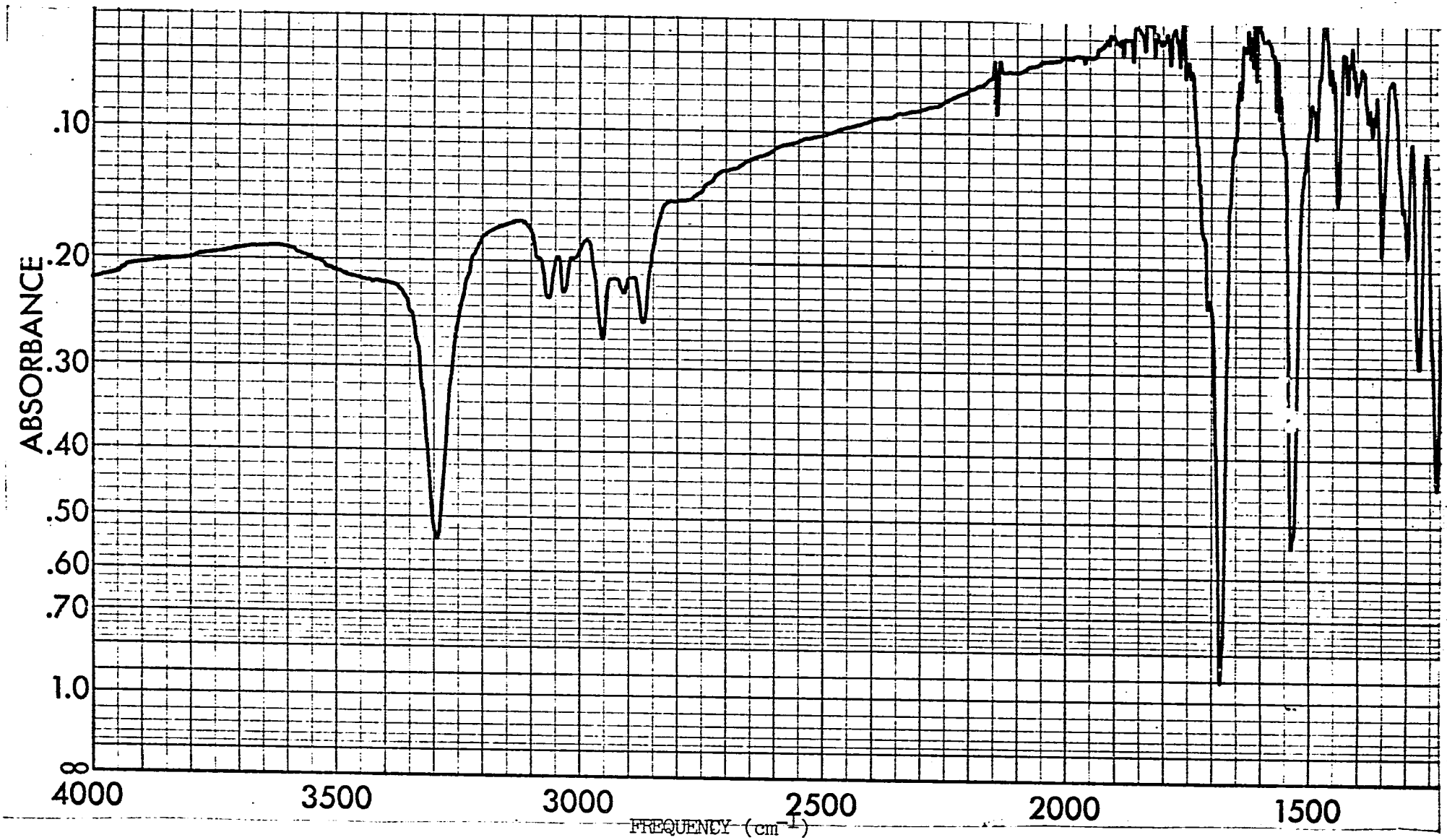


Figure 30. Infrared Spectra of Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-6-O-trimethylsilyl-β-D-allopyranoside (XXXII) Part 1

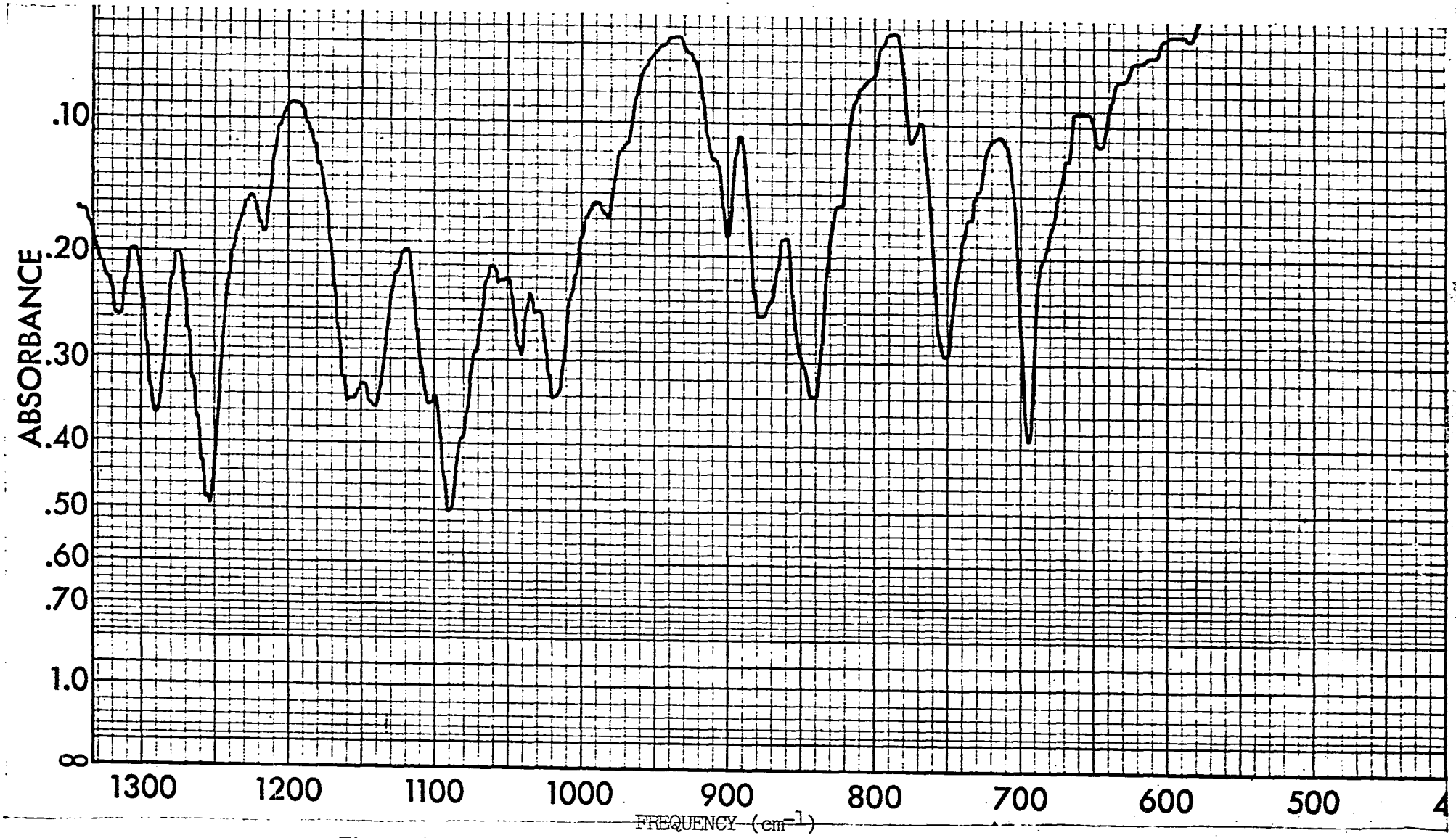


Figure 30. Infrared Spectra of Benzyl 3,4-anhydro-2-benzyloxycarbonylamido-2-deoxy-6-O-trimethylsilyl-β-D-allopyranoside (XXXII) Part 2

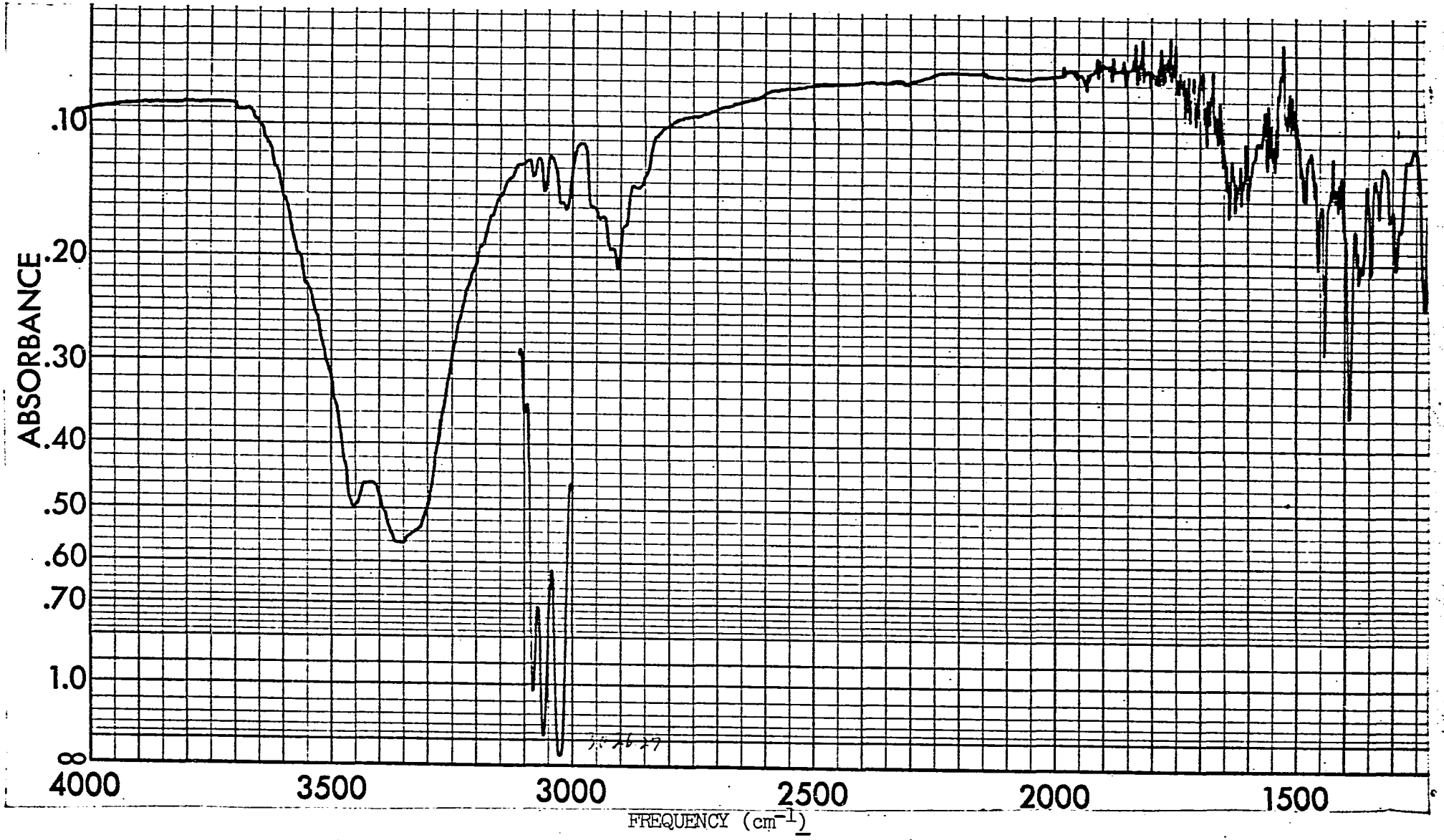


Figure 31. Infrared Spectra of Benzyl 2,3-anhydro-α-D-allopyranoside (XXXIII) Part 1

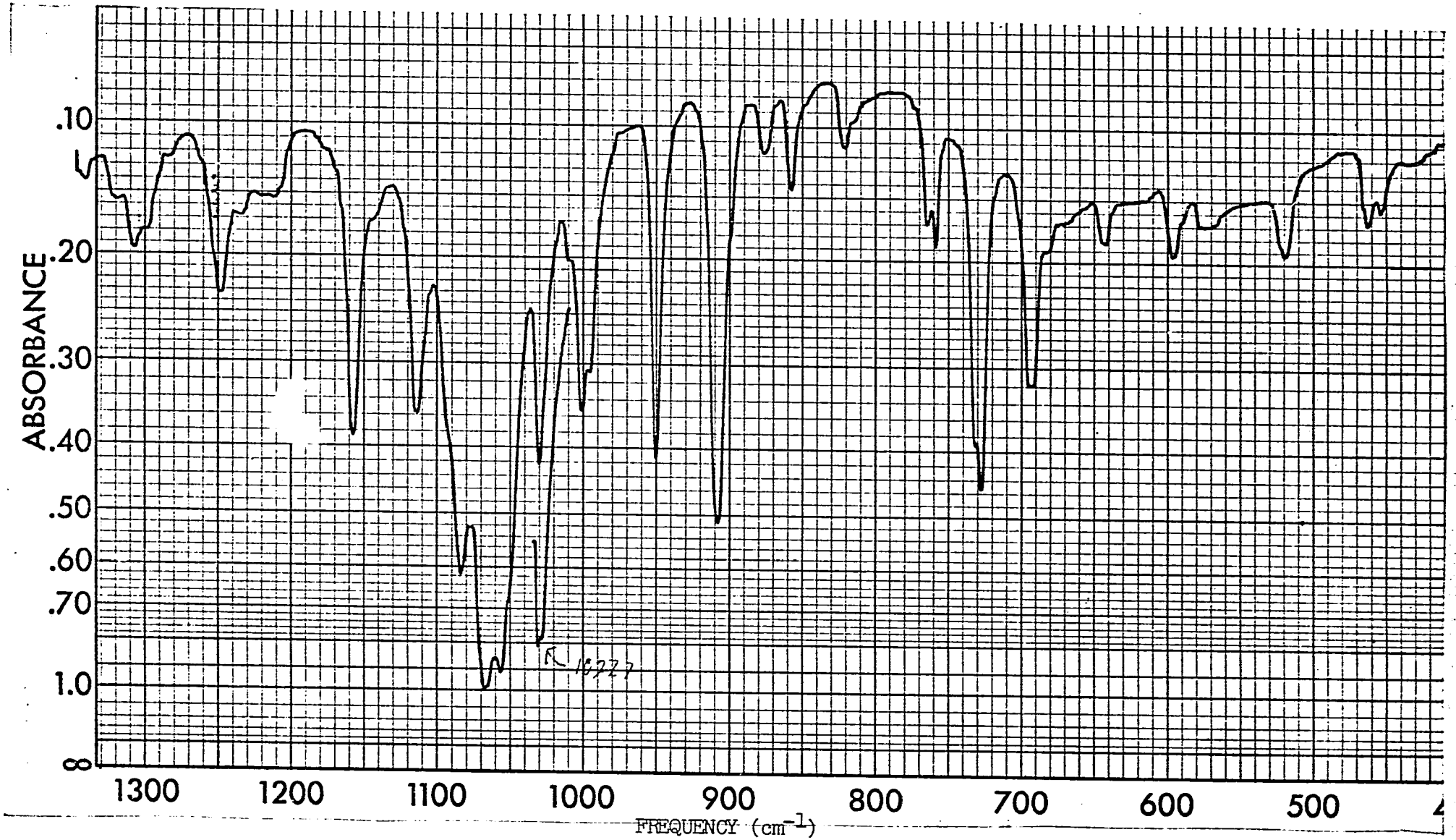


Figure 31. Infrared Spectra of Benzyl 2,3-anhydro-α-D-allopyranoside (XXXIII) Part 2

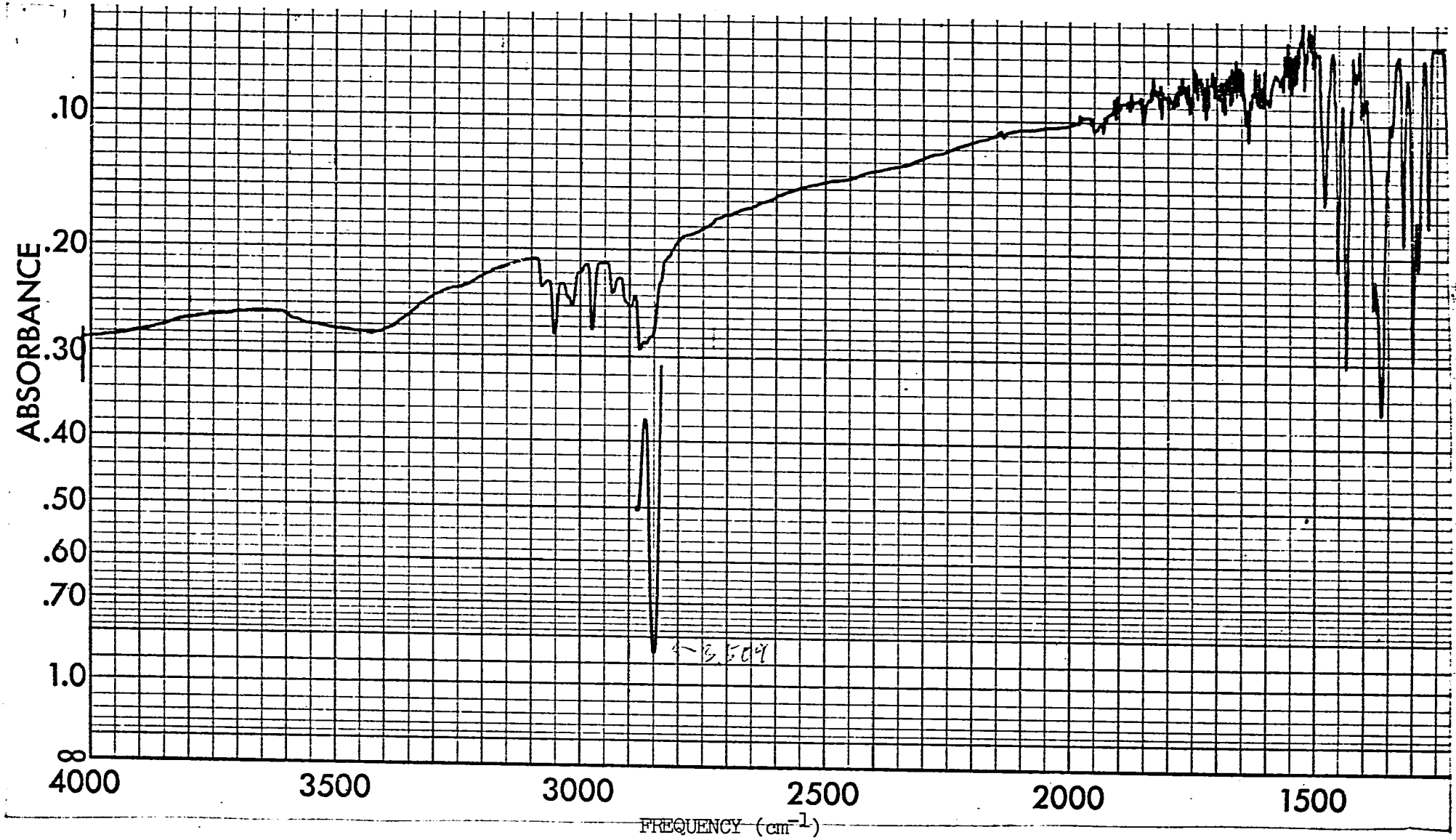


Figure 32. Infrared Spectra of Benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erythrohex-2-enopyranoside (XXXIV) Part 1

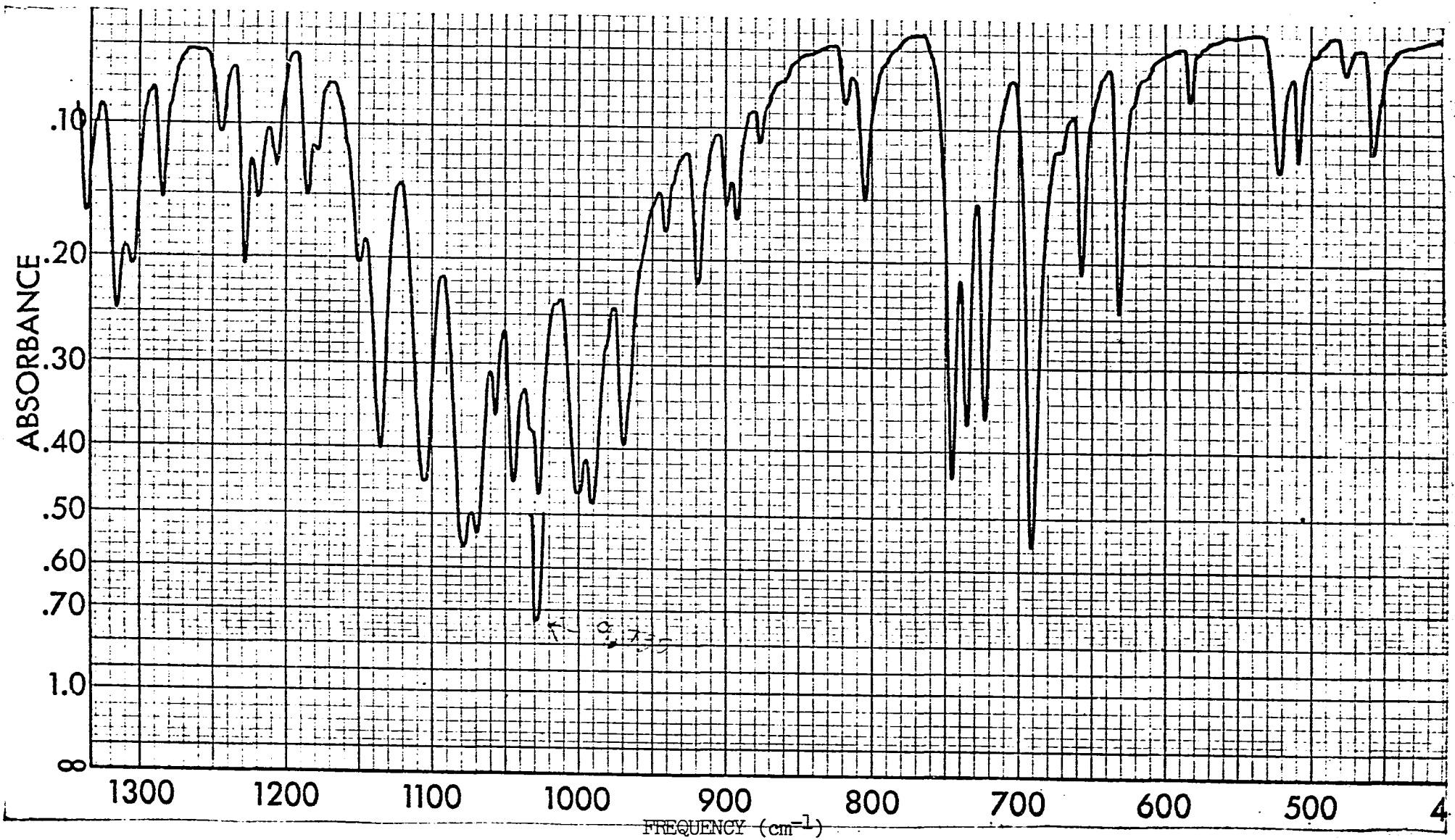


Figure 32. Infrared Spectra of Benzyl 4,6-O-benzylidene-2,3-dideoxy-α-D-erthrohex-2-enopyranoside (XXXIV) Part 2