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3,3-Diphenyl-2-Morpholinone Derivatives Of 2-Amino-2-Deoxy-D-Allose.

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3,3-DIPHENYL-2-MORPHOLINONE DERIVATIVES OF 2-AMINO-2-DEOXY-D-ALLOSE

A Thesis

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by

Ram Babu

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3,3'-Diphenyl-2-Morpholinone Derivatives of 2-Amino-2 Deoxy - D - Allose

Abstract of Dissertation

A new cyclic protective group has been fused to the cis amino alcohol group of benzyl 2-amino-4,6-o-benzylidene-2-deoxy β-D-Allopyranoside, by way of a unique rearrangements mechanism. To establish the 2-morpholinone structure, chemical studies, such as reduction and acetylation, were conducted.

Comparative spectroscopic studies using ir, pmr and C-13 nmr confirmed the assigned structures.

The 2-morpholinone ring was cleaved by mild alkaline hydrolysis and could be closed again with acetic anhydride in pyridine. An oxazolidinone derivative of benzyl 2-amino-4,6-o-benzylidene-2-deoxy-β-D-allopyranoside was prepared in quantitative yield by a modification of a known method.

Protective group properties of the oxazolidinone were studied prior to the examination of the 2-morpholinone cyclic protective group. The selective removal of the benzyl aglycon was achieved in excellent yield by catalytic hydrogenation, for both morpholinone and oxazolidinone protected benzyl-β-D-allopyranosides. The selective removal of the 4,6-o-benzylidene group in presence of a 2-morpholinone ring was possible in high yield. The cleavage of the 2-morpholinone protective group was accomplished in two steps. Mild alkaline hydrolysis cleaved the ester function of the ring and mild acidic hydrolysis cleaved its amine function.

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I dedicate this thesis to my wife Susan, who bore the brunt of discouragement and shared the sacrifices of graduate studies, understood my reactions and controlled them.

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INTRODUCTION

Aminosugars play diversified and important roles in biochemistry, as building blocks of homo- and heteropolymers and of complex molecules, such as microbial polysaccharides, glycoproteins, gangliosides, enzymes, glycolipids, antibiotics and nucleosides.[1] The structure of aminosugars, which shows features of both amino acids and common sugars, gives them unique lyophilicity, that demonstrates their presence in most proteins and many lipids.[2] Their presence as components of high molecular weight compounds, in the surface of cells, or in the intercellular matrix, suggests participation in mechanisms by which cells recognize other cells and large molecules. These amino sugars appear to act as letters or words in intercellular communication.[3]

The importance of cellular communication is perhaps best illustrated by its breakdown in the development of cancerous growths. The social behavior of malignant cells is different from that of normal cells. Normal cells stop growing when they touch each other, a phenomenon referred to as contact inhibition, whereas cancer cells grow without restraint. Much evidence suggests, that the transformation that makes malignant cells unresponsive to environmental cues, such as touching another cell, is related to a cell surface modification involving the sugar side chains of glycoproteins.[4]

The comprehensive treatises[5] edited by Balazs and Jeanloz review occurence, location, structure, biosynthesis and biological role of

aminosugars. Many chapters show the extensive prevalence of the (1-4) glycosidic linkage of aminosugars in natural products. The glycan component of heat-inactivated spores of B. subtilis is a polymer of alternating 2-acetamido-2-deoxy-D-glucose and muramic acid, probably all (1-4) linked with half of the muramic acid residues present in the form of lactam or 3-morpholinone structures.[6] Recent progress in the study of complex substances, containing aminosugars, is the result of work with oligosaccharides, obtained by hydrolysis, as biological useful substrates. A few naturally occurring oligosaccharides, containing aminosugars, have been synthesized.[7] Considerable problems attend the synthesis of biologically important aminosugar oligosaccharides, with some degree of complexity.

In recent years, a steadily increasing research effort has centered on the generation of the glycosidic linkage, particularly in oligo- and polysaccharides.[8] The synthetic studies are directed to glycoproteins,[9] immunoactive oligo- and polysaccharide moieties of bacterial call walls,[10] red blood cells,[11] glycolipids[12] (e.g. cerebrosides and gangliosides), and antibiotics with aminosugar constituents.[13]

Most of the synthetic work employs modifications of the Koenigs-Knorr reaction.[14] The steric course of the Koenigs-Knorr reaction of pyranosyl halides is determined, not so much by the axial or equatorial orientation of the halogen, but by the participation of the substituent on the carbon next to the anameric carbon, generally the substituent on C_2. Glycosidation of 1,2-cis pyranosyl halides generally proceeds with inversion at C_1 to give 1,2-trans glycosides,[15] whereas the

1,2-trans pyranosyl halides afford orthoesters under certain conditions[16], but also 1,2-trans glycosides under others[17] (Figure 1.0). Hence, 1,2-cis glycosides are relatively difficult to obtain from per-acetylated pyranosyl halides. The stereochemistry of C-3 may also influence the rate of Koenigs-Knorr disaccharide syntheses, and favor reactions other than those leading to a 1,4 glycosidic linkage. Steric hindrance at C_4 can be reduced considerably by the use of a cyclic protective group to protect the positions C-2 and C-3 of a 2 amino-2-deoxy-β-D-hexopyranose.

A review of the cyclic protective groups, used in general carbohydrate chemistry, is found in the treatise edited by Whistler and Wolfrom.[18] The most widely used cyclic protective groups for carbohydrates are the cyclic acetals (e.g. the 4,6-O-benzylidene group), which are very sensitive to acids, but relatively stable towards alkali, and the cyclic carbonates,[19] which are characterized by sensitivity towards alkali, and stability towards acid. These cyclic protective groups are present in numerous and diverse synthetic intermediates, and are capable of protecting two functional groups simultaneously and specifically. Cyclic blocking groups often create conformationally rigid bicyclic ring systems. The importance of these cyclic protective groups, as well as of heterocyclic protective groups for aminosugars fused to the pyranose ring, rests in the fact that they neither sterically hinder nor anchimerically influence reactions at adjacent reaction sites.

The number of useful cyclic protective groups is small for aminosugars. It would help the syntheses of complex molecules having

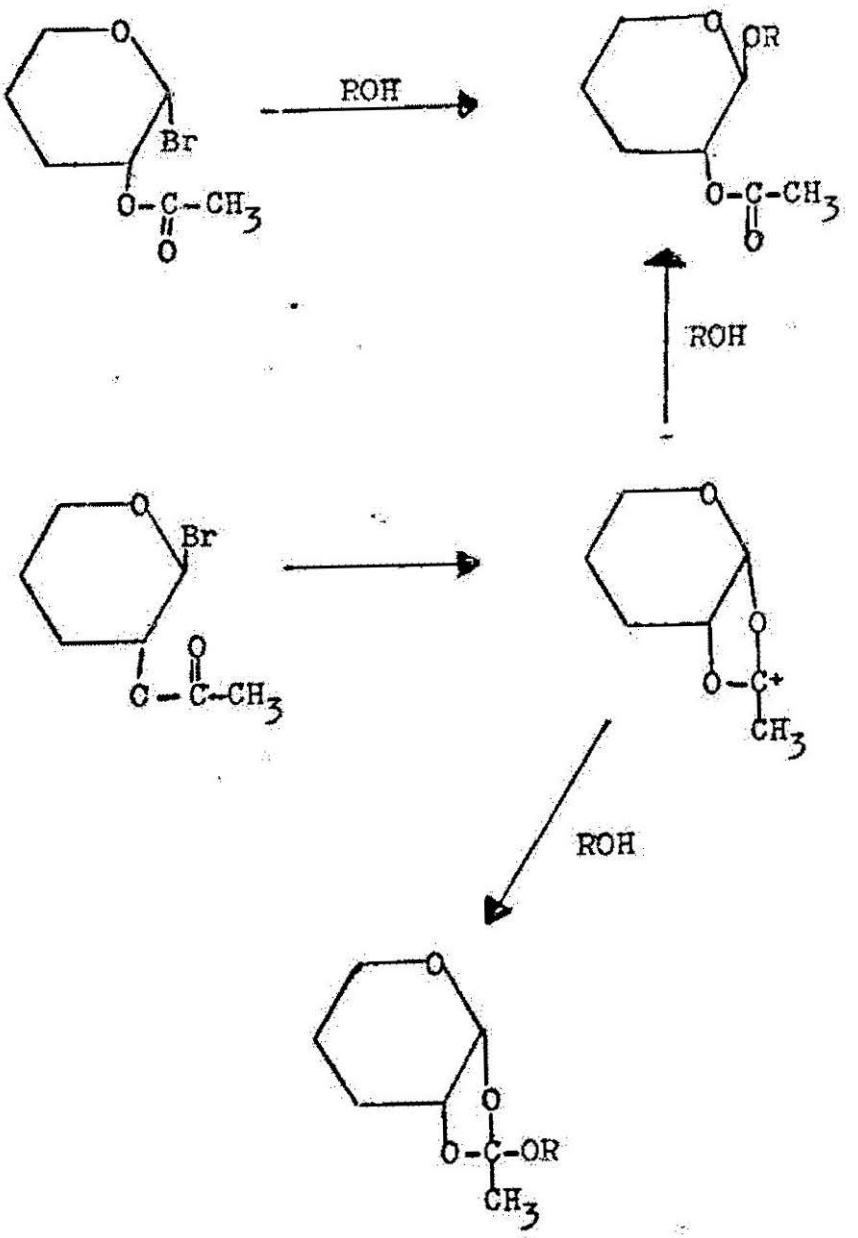


FIGURE 1.0

aminosugar moieties linked at C-1, and the syntheses of (1-4) - linked aminosugar oligosaccharides, if a variety of such cyclic blocking groups could be found that protect functional groups at C-2 and C-3 of 2-amino-2-deoxy-D-hexopyranoses and leave sites at C-1 and C-4 open for synthetic reactions. Such protecting groups should be examined with respect to the following criteria:

a)Stability towards acids, bases, hydrogenation, light and heat

b)Solubility of the protected derivatives in organic solvents

c)Ease of crystallization of derivatives

d)The selectivity of cleavage by chemical methods

e)The chemical and steric noninterference with reactions at other sites.

In this research we were looking for a protective group, to be used for blocking of the C-2 and C-3 cis amino alcohol function of 2-amino-2-deoxy-D-allose. Such a protective group should be easily removable, after it has served its purpose. Ideally, it should be possible, to deblock all positions of the aminosugar selectively. Oxazolidinone derivatives of aminosugars have been used for synthetic purposes for some time.[20] (Figure 1.1).

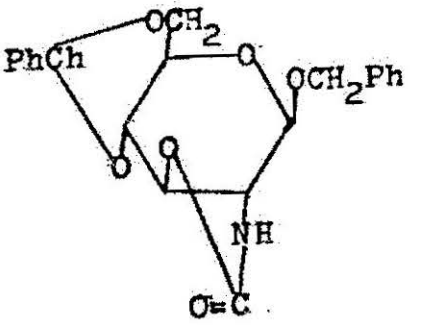


FIGURE 1.1

Unfortunately these derivatives are not very soluble in nonpolar solvents.

Muramolactam derivatives, with a six membered 3-morpholinone ring, in which the 2-amido group is trans to the oxygen function have also been prepared.[21] (Figure 1.2).

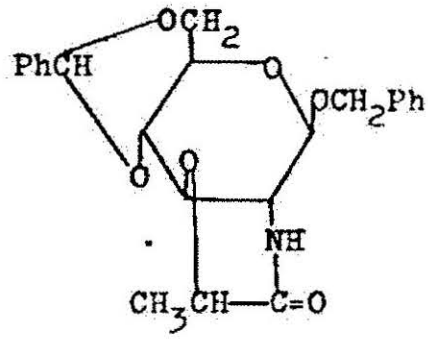


FIGURE 1.2

They do not allow the regeneration of the parent glucosamine. Similar cyclic derivatives with the allo or gulo configurations which have a cis amino alcohol group should be easy to prepare. The molecular model construction of morpholinone derivatives, fused to the cis amino alcohol group of D-allosamine showed no steric hindrance or possible participation at reaction cites C-1 and C-4. Especially diphenyl morpholinones appeared of interest to us, for two reasons: (Figure 1.3)

FIGURE 1.3

a) the influence of the phenyl groups may make it possible to cleave the corresponding ether or secondary amine bond by mild acid hydrolysis to facilitate the removal of the blocking group;

b) these derivatives may possibly show pharmacological activity.

A survey of methods for preparation of 2- and -3-morpholinones (ketotetrahydro oxazines) showed several possibilities for their synthesis.

The 2-morpholinones have a δ-lactone structure. Consequently they may be obtained from the corresponding hydroxy carboxylic acids or their salts or from δ-hydroxy carboxylic esters. In this case the parent acid would always be an ethanolamino carboxylic acid derivative. (Figure 1.4).

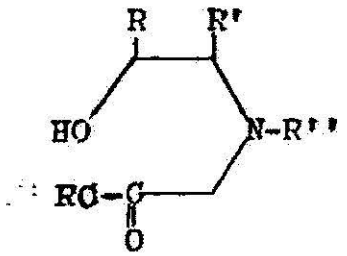


FIGURE 1.4

A large number of the available methods for synthesis of 2-morpholinones differ only in the way by which these precursors or their derivatives are obtained. They are always obtained by an alkylation process on nitrogen. The nitrogen function may be located on the molecule with the carbonyl group, or on that carrying the OH group. Thus, heating an appropriate epoxide or chlorohydrin with α-amino acids or their salts or esters, gave such ethanolamino acids and their derivatives,

which could be cyclized to give 2-morpholinones.[22] (Figure 1.5).

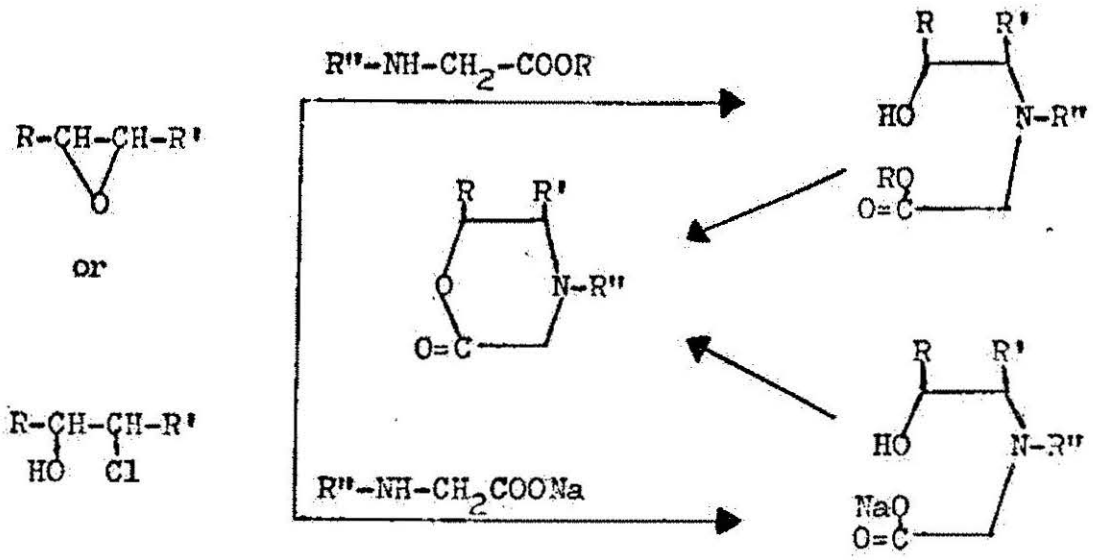


FIGURE 1.5

∝-Amino alcohols, when heated with ∝-haloester, usually give good yields of 2-morpholinones, presumably via ethanolamino carboxylic acids.[23] (Figure 1.6).

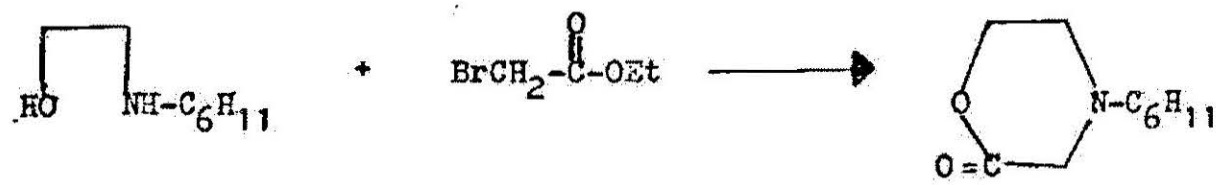


FIGURE 1.6

When a tertiary ethanolamine was used, the product was the quaternary ammonium derivative of a 2-morpholinone. (Figure 1.7)

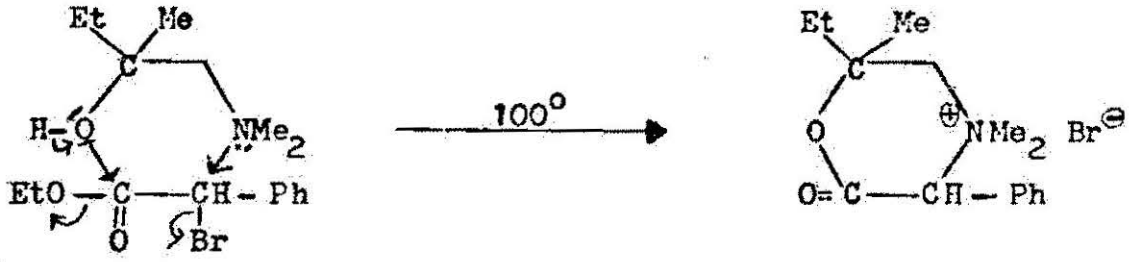


FIGURE 1.7

The quaternary ammonium salts could be converted to 2-morpholinone derivatives either by vacuum distillation or by conversion to ammonium hydroxides, followed by elimination of methanol, on heating.[24] (Figure 1.8).

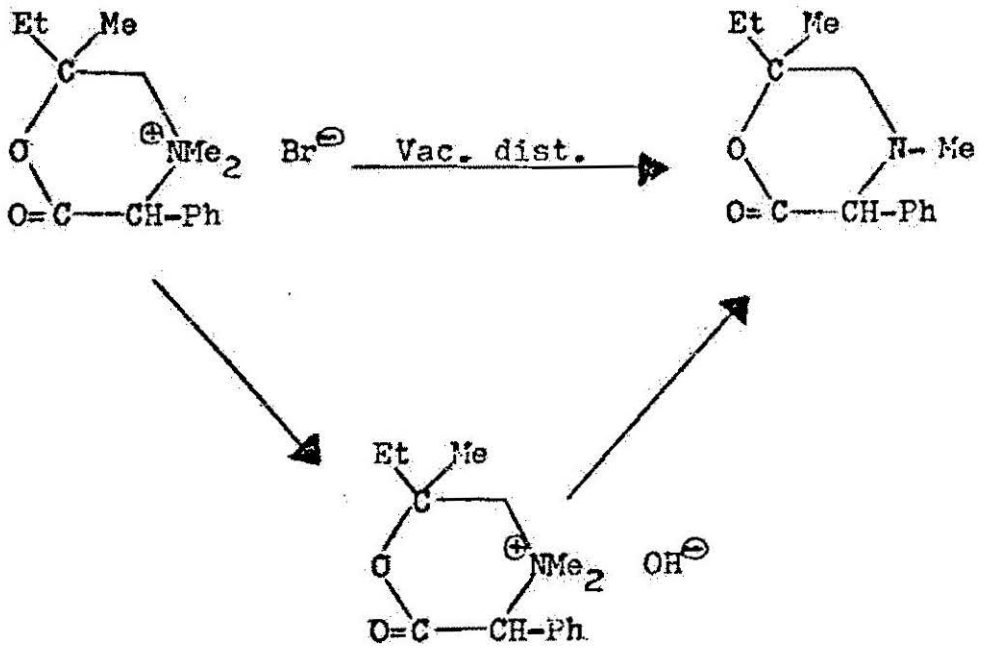


FIGURE 1.8

Mosher, Frankel and Gregory[25] prepared 3,3-diphenyl-4-methyl-2-morpholinone by heating a mixture of β-methyl amino ethanol and methyl α-bromo α,α diphenyl acetate to 40° and subsequently keeping it at 2-5°C for 3 days. (Figure 1.9).

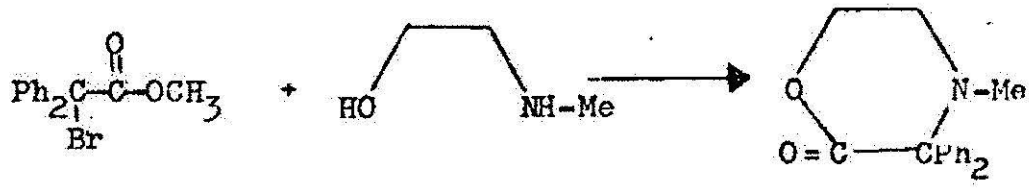


FIGURE 1.9

A method involving carboxymethylation and cyclization lead to 4-carboxymethyl 2-morpholinone.[26] Sodium cyanide, ethanolamine, and formaldehyde condensed in basic solution, and on acidification gave the morpholinone derivative. (Figure 1.10).

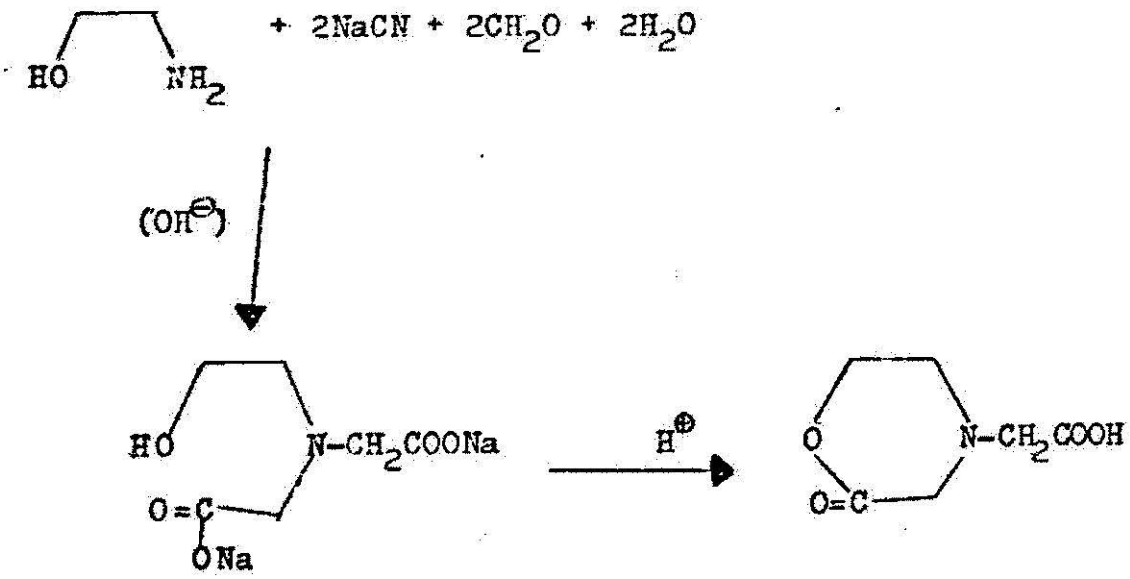


FIGURE 1.10

In a principally different way, 2-morpholinones could be obtained by the method of Biekert, Hoffman and Enslein.[27] An amino alcohol was condensed with an α-ketocarboxylic ester to a 5,6-dihydro-1,4-oxazine. By catalytic hydrogenation, the 2-morpholinone was obtained.[28] (Figure 1.11).

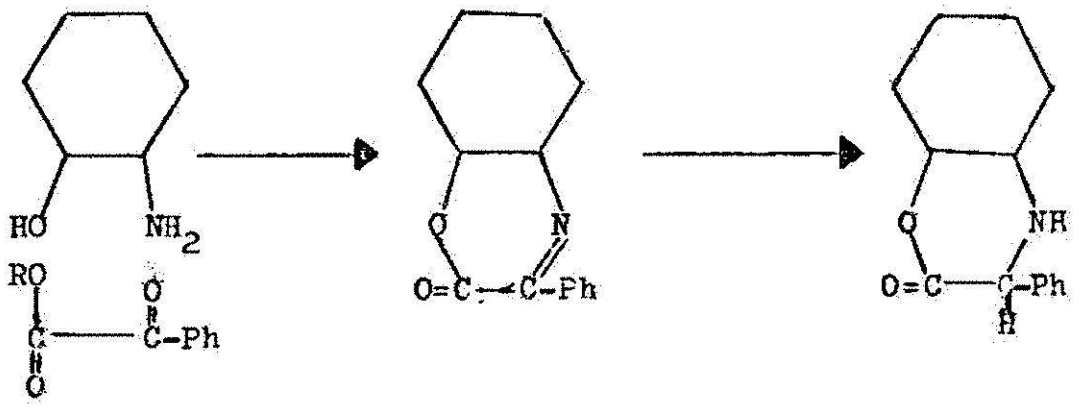


FIGURE 1.11

Similarly, for the preparation of 3-morpholinones, several methods are available. From β -chloroethoxy acetonitrile, β -aminoethoxy acetic acid was easily obtained, which cyclized on nitrogen and gave a 23% yield of 3-morpholinone.[29] (Figure 1.12).

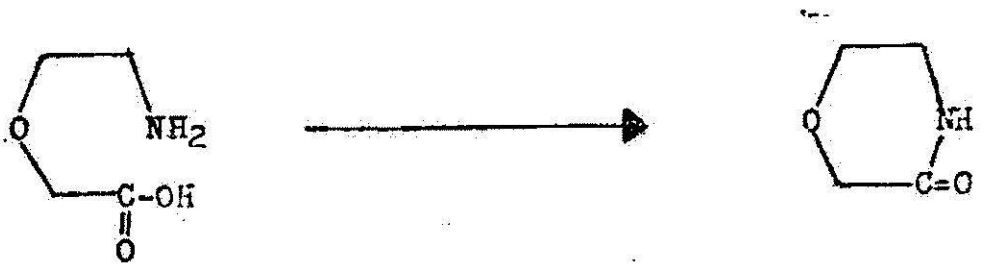


FIGURE 1.12

Vieles and Sequin[30] prepared 3-morpholinones in good yield by conversion of ethanolamine to its sodium salt with sodium in hot dioxane, followed by reaction with ethyl chloroacetate at reflux. (Figure 1.13).

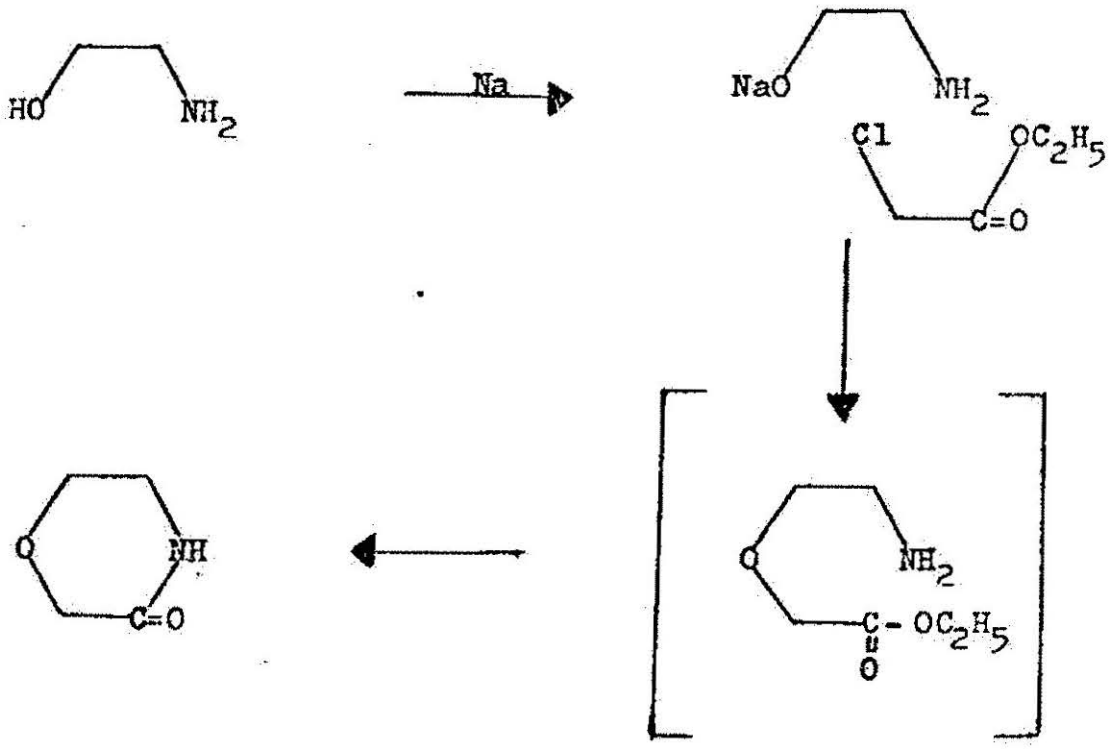


FIGURE 1.13

2,2-Diphenyl-4-methyl-3-morpholinone was prepared by two independent routes. Morrison and co-workers[31] synthesized this compound by a unique cyclization of sodium diphenyl-[(β -dimethylamino)ethoxy] acetate with thionyl chloride. The reaction proceeded with elimination of a mole of methyl chloride. (Figure 1.14).

Mosher and co-workers[25] obtained the same compound by heating diphenyl-[(β -methyl amino)ethoxy] acetic acid, which was obtained

by refluxing a benzene solution of α-bromo-α,α-diphenyl acetic acid with β-methylaminoethanol. (Figure 1.14).

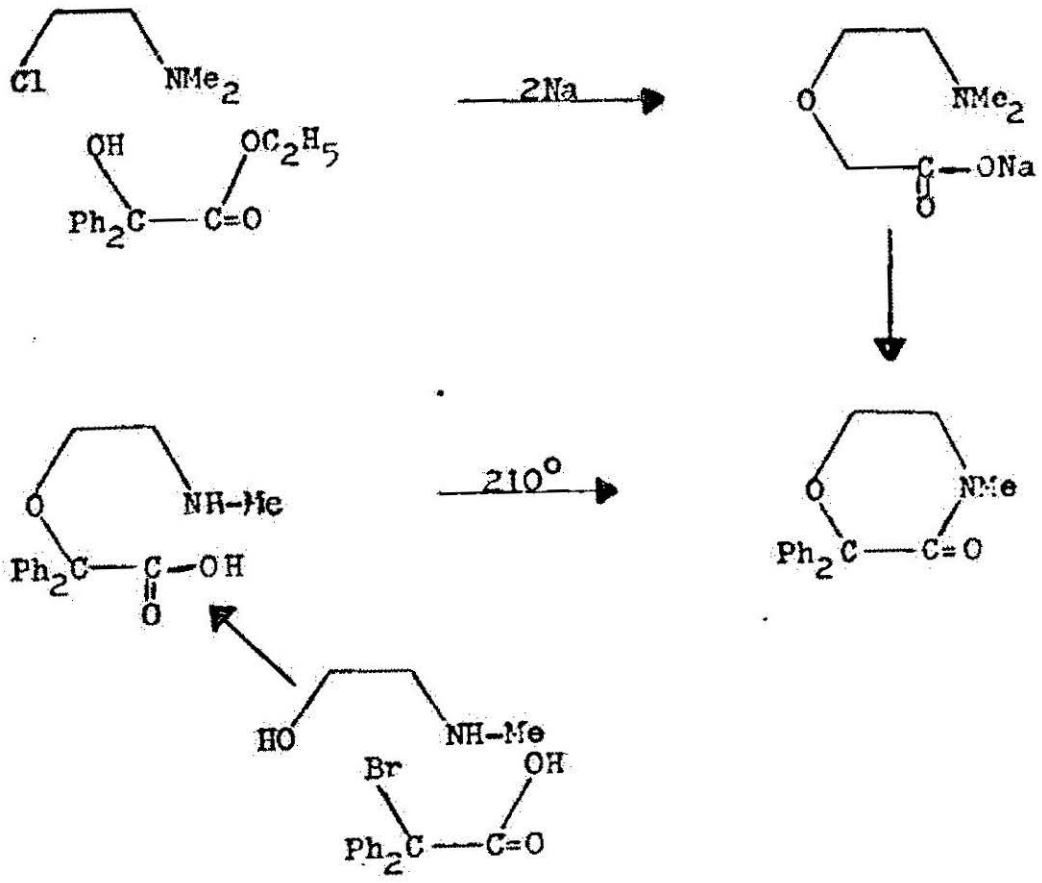


FIGURE 1.14

Pfeil and Harder[32] found a new method for the preparation of 3-morpholinones. Aziridinium tetrafluoborate (2) reacted with α-hydroxy esters (1) to give first the fluoborate salt (3) of an aminoethoxy carboxylic acid ester. Treatment with base and heating caused loss of a molecule of alcohol and cyclization to give a 3-morpholinone derivative (4). (Figure 1.15).

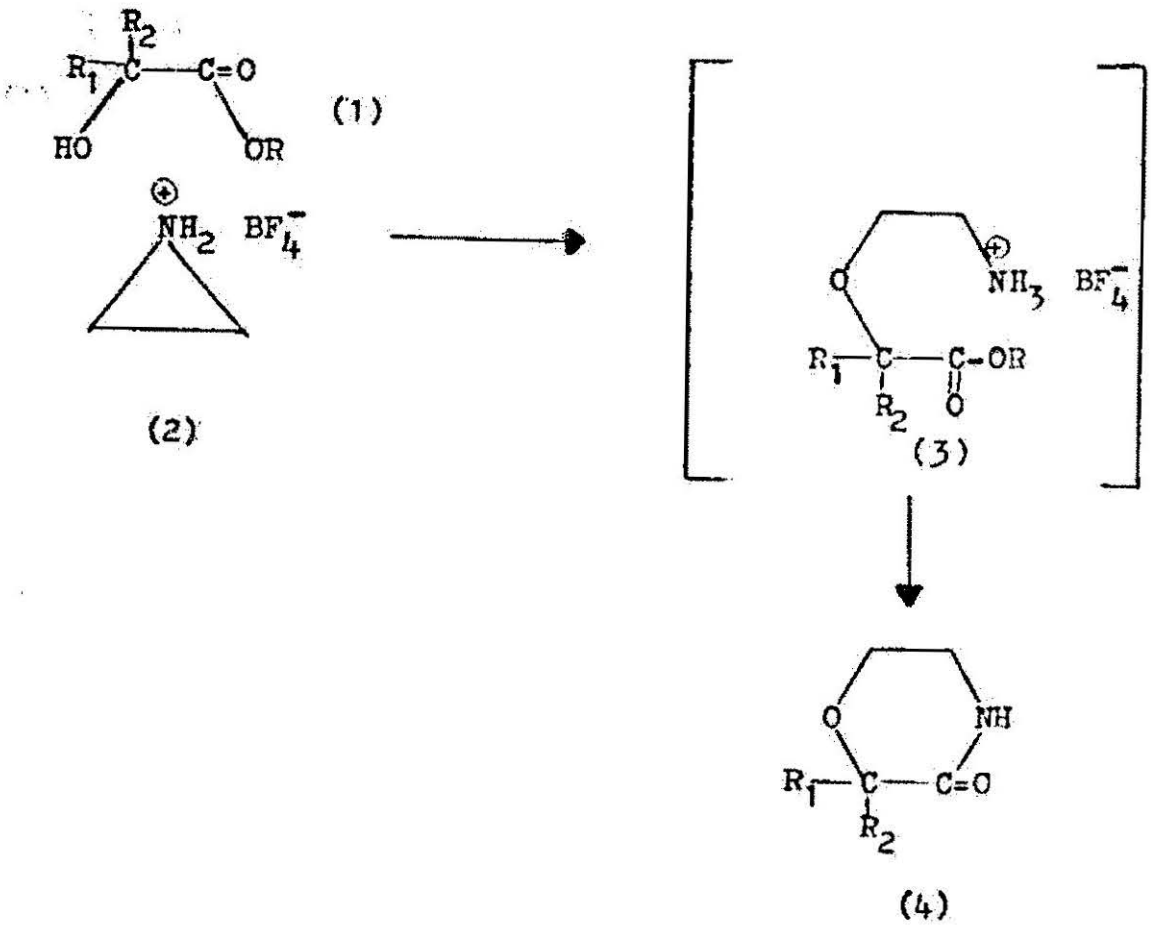


FIGURE 1.15

This survey of the preparative methods for 2- and 3-morpholinones reveals characteristic similarities and distinctions in the synthetic approaches.

The syntheses of 2-morpholinones by various methods were carried out in acidic to slightly basic media; whereas the preparations of 3-morpholinones were done under neutral to strongly basic reaction conditions. The reason for this difference most probably relates to the higher stability of amides (3-morpholinones), in basic solutions, as compared to esters (2-morpholinones). Another apparent observation

is that both, 2- and 3-morpholinones were always obtained by two step processes: Alkylation on nitrogen or oxygen preceeded ring closure by acylation at the second heteroatom. In the syntheses of 2-morpholinones, N-alkylation takes place first, followed by O-acylation. In the synthesis of 3-morpholinones, O-alkylation is the first step, followed by cyclization through N-acylation.

Infrared spectral data of 2-morpholinones have been reported by various laboratories.[23,33,34] The NH absorption appears in the region of 3100 to 3440 cm^{-1} and the carbonyl absorption at 1700-1780 cm^{-1}. For comparison, the infrared spectra of 3-morpholinones show the NH absorption at 3250 to 3400 cm^{-1} and the carbonyl absorption in the region of 1630 to 1700 cm^{-1}. Thus the carbonyl frequencies are fairly typical for esters, and amides, respectively.

The exact position of the carbonyl band in both 2- and 3-morpholinones is influenced by the physical state of the probe, by electrical and mass effects of neighboring substituents, by conjugation, by hydrogen bonding (inter-molecular and intra-molecular), by ring strain, by fusion to other ring structures, by rotational isomerism, and by mechanical coupling or interaction.

The original aim of this research project was the synthesis of substituted morpholinone derivatives, connecting C_2 and C_3 of 2-amino-2-deoxy-D-allose in a cyclic structure. The work reported in this investigation is concerned with the novel synthesis of diphenyl substituted 2-morpholinone derivatives of 2-amino-2-deoxy-D-allopyranoside. The chemistry and the physiological activity of these 2-morpholinone derivatives were also studied.

In order to obtain a comparative assessment of the utility of the 2-morpholinone derivative as a protective group, it was considered appropriate to examine the oxazolidinone of 2-amino-2-deoxy-D-allose prior to the investigation of the 2-morpholinone derivative. In the course of this examination, we aimed to demonstrate, for both protective groups, the possibility of selective cleavages of the benzyl aglycon, and of the 4,6-O-benzylidene group.

METHODS AND DISCUSSION OF RESULTS

Preparation of starting materials

The starting material for this investigation, benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (1)[35] was prepared by an eight step synthesis, originating from 2-acetamido-2-deoxy-D-glucose. Only the de-O-acetylation of benzyl 2-acetamido-3,4,6 tri-O-acetyl-2-deoxy-β-D-glucopyranoside deviated significantly from published procedures,[36] and was accomplished in almost quantitative yield, by triethyl amine in aqueous methanol, with the retention of the N-acetyl group.

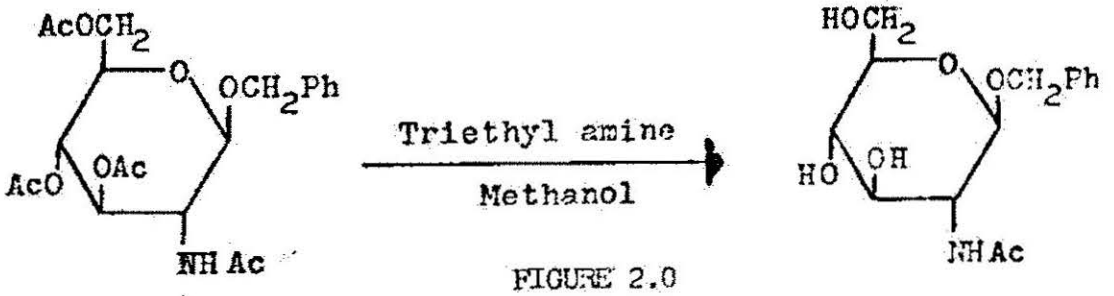


FIGURE 2.0

Two methods for the preparation of the oxazolidinone (2) are known.[37] We have developed a convenient modification of a previous method for the facile conversion of the amino alcohol (1) into the oxazolidinone derivative (2). The amino alcohol (1) is treated with an appropriate amount of phosgene gas in dioxane in presence of ethyldiisopropyl amine as acid scavenger to give a quantitative yield of 2. (Figure 2.1)

Previous attempts in our laboratory at the selective removal of the aglycon of 2 by hydrogenation in presence of 5% Pd on carbon, in

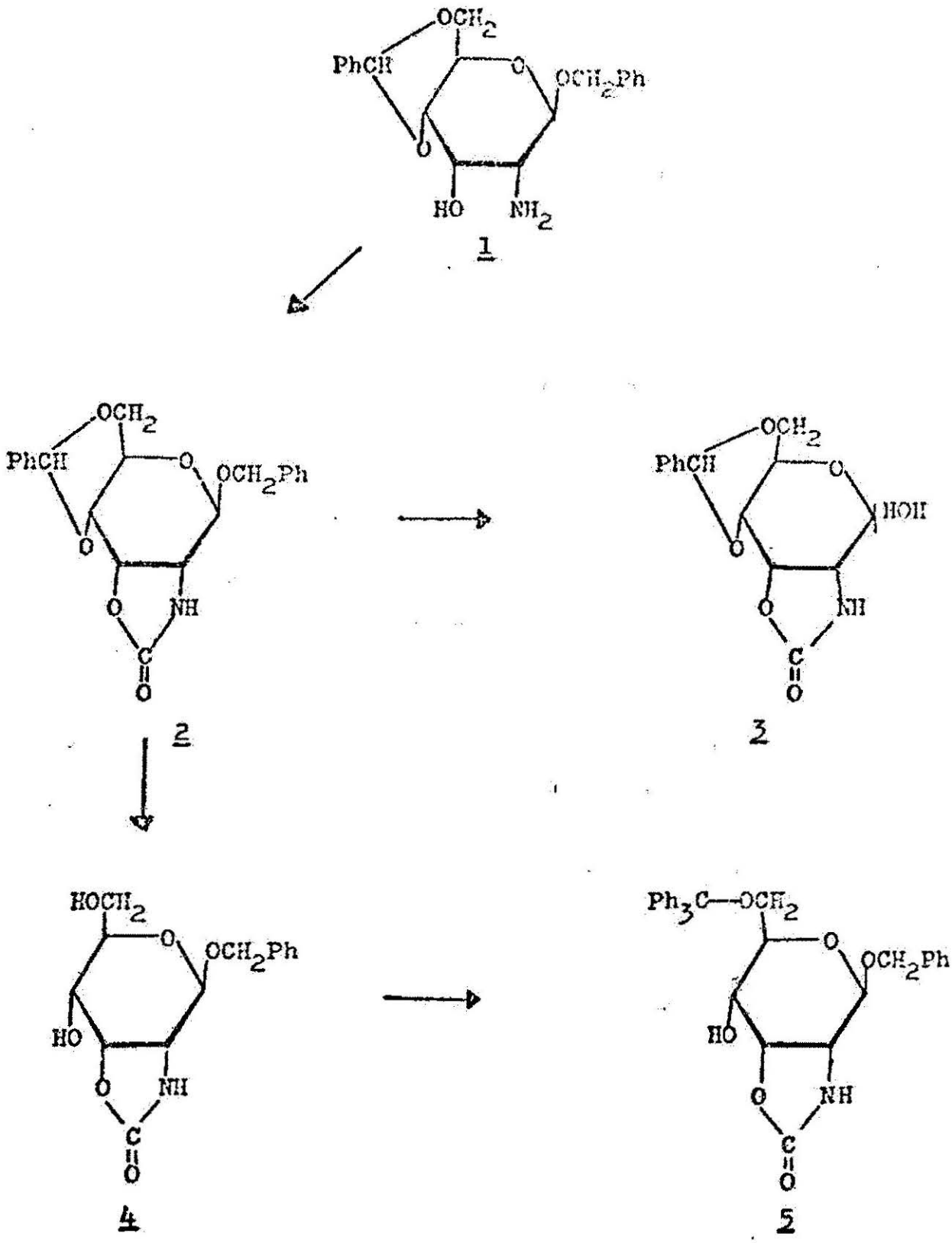
Ac : $-COCH_3$

Bz : $-COC_6H_5$

Ph : $-C_6H_5$

Explanation of Symbols

Figure 2.1
(Thin-layer chromatographic comparison on page 81)

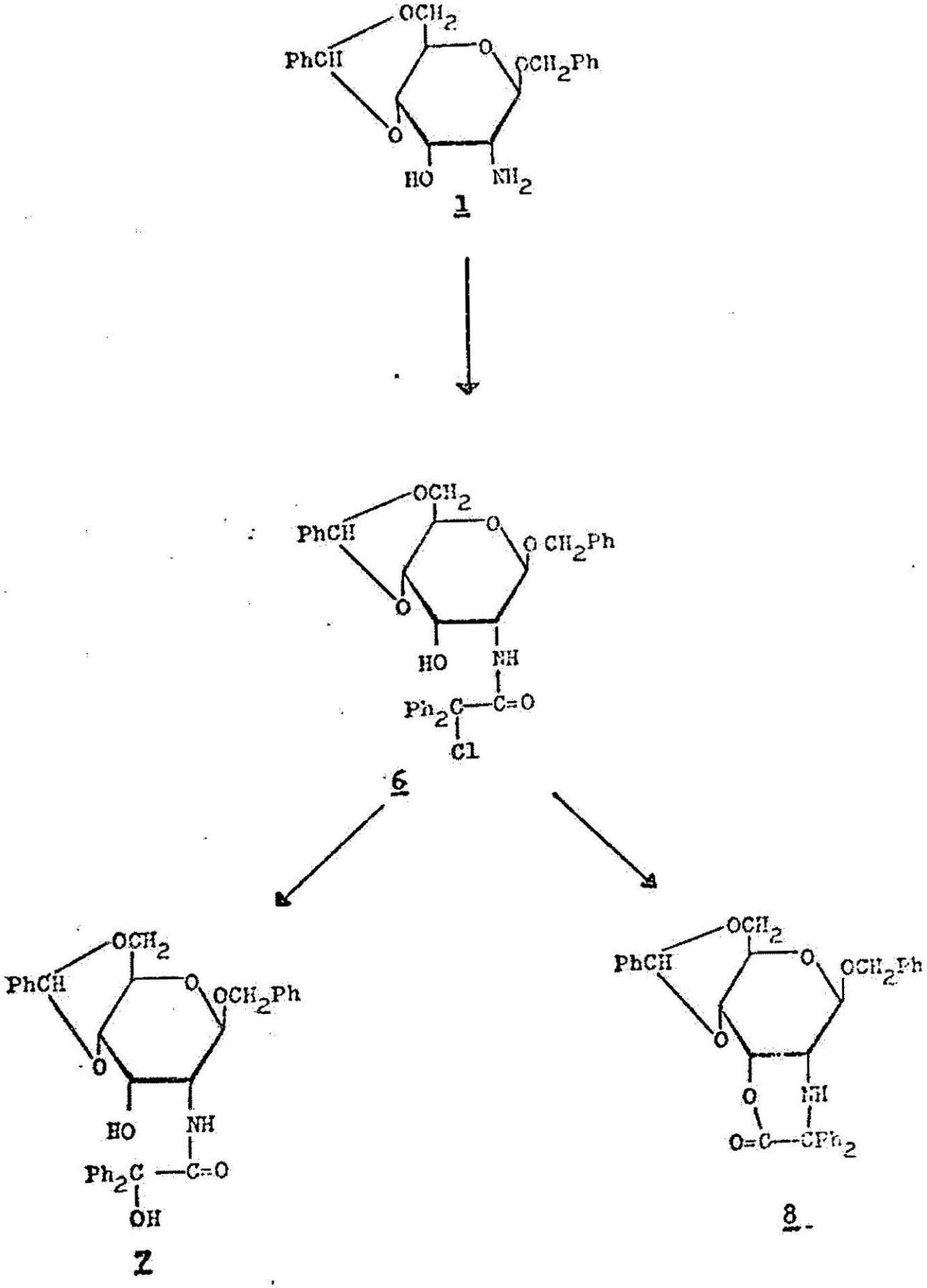


different solvents, such as dioxane, ethyl acetate, ethanol, etc. resulted in a mixture of products.[35] The analysis of the separated components of the mixture showed that the removal of the 4,6-O-benzylidene group accompanied that of the benzyl aglycon. This observation led to the investigation of benzyl glycosides, having electron withdrawing groups in the benzene ring, in recent theses.[38,39] Carpenter[38] prepared a p-nitrobenzyl 4,6-O-benzylidene-2,3-dimethoxy methyl-β-D-glucopyranoside. By catalytic hydrogenation on 5% Pd on charcoal, in methanol, this cpd gave a selective, almost quantitative removal of the benzyl aglycon, with retention of the 4,6-O-benzylidene group even with prolonged hydrogenation. The nitrobenzyl aglycon appeared as p-toluidine in the product. This observation suggested the use of p-toluidine as a catalyst poison to prevent hydrogenation of a 4,6-O-benzylidene group.

Tetrahydrofuran is a solvent of high solvating power. This is undoubtedly related to its high basicity and to its sometimes directing influence. Tetrahydrofuran has been used as a good solvent for organometallics, where it has been found to catalyze sluggish reactions.[40] Apparently,[41] tetrahydrofuran has never been used as a solvent for hydrogenation reactions in presence of Pd on charcoal. This may be due to its high flammability. Tetrahydrofuran as a solvent, in conjunction with methanol, lesser amounts of water, and one equivalent of p-toluidine gave complete and selective cleavage of the benzyl aglycon of cpd 2, by hydrogenation on 5% Pd on charcoal. (Figure 2.1).

Alternatively, when benzyl 4,6-O-benzylidene-β-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone was heated with 60% aqueous acetic acid

Figure 2.2
(Thin-layer chromatographic comparison on page 82)

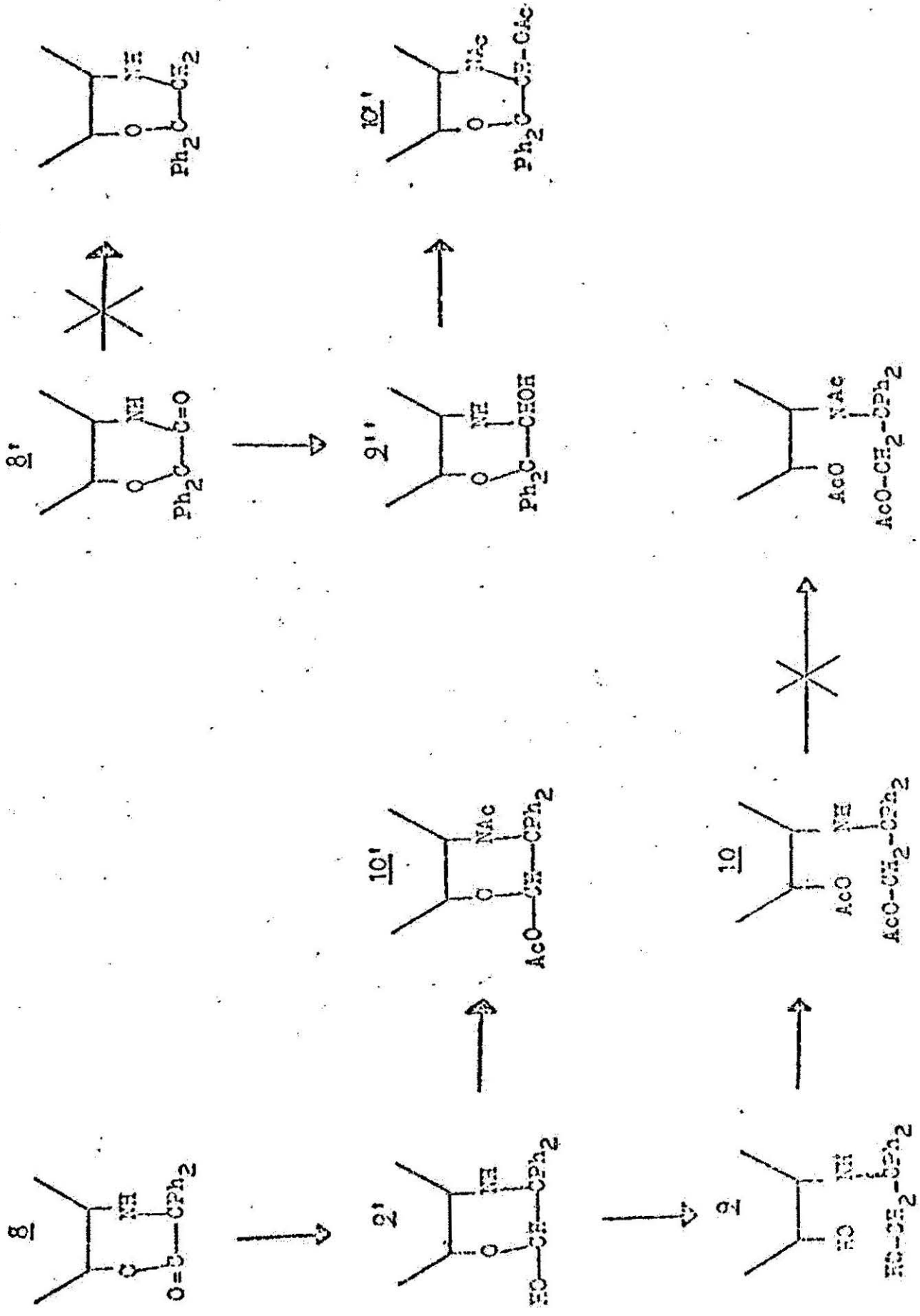


the 4,6-O-benzylidene group was selectively removed. The resulting syrupy 4 was then refluxed with triphenylchloromethane in the presence of pyridine to give the 6-O-trityl derivative 5 in much better yield than was previously reported[42] (Figure 2.1).

Following our aim to produce a new blocking group for the amino alcohol function of 1, cpd 1 was treated with α-chloro-α,α-diphenyl acetyl chloride in presence of an excess of triethyl amine. Initially, the chlorodiphenyl acetamido intermediate (6) was formed. The intermediate then cyclized, with concurrent rearrangement, in presence of an appropriate amount of sodium hydride and an excess of dimethylformamide, to give the 2-morpholinone derivative 8 which has a lactone type structure. From the literature survey of preparative methods of morpholinone derivatives, it appears that this is the first time such a rearrangement of an amide type structure to an ester type structure in strongly basic media has been observed. The reaction failed to produce any 2-morpholinone product if the starting material (1) was very dry or if sodium methoxide, sodium-t-butoxide or lithium hydride were substituted for sodium hydride. The use of only oneequivalent of triethyl amine also precluded formation of the 2-morpholinone derivative. (Figure 2.2).

The structure determination of 8 was made particularly difficult through parts of seemingly contradictory evidence. Thus, it was clear, that initially an amide linkage was formed. If no sodium hydride was added, and the intermediate (6) was treated with aq. sodium bicarbonate, the workup gave cpd 7. The elemental analysis and ir spectrum of 7 clearly showed it to be an open chain, secondary amide.[43] The ir

Figure 2.3



spectrum of 7 showed an amide I band at 1675 cm^{-1} and an amide II band at 1520 cm^{-1}.

The 2-morpholinone derivative 8 has a secondary amine group which should form a hydrochloride salt ppt in anhydrous diethyl ether or anhydrous benzene. The ppt was not observed, indicating an amide type of linkage. However, on evaporation, dissolution, and reevaporation, increased solubility of the residue in ether was observed, indicating that some change may have occurred.

On the other hand, cpd 8 showed a carbonyl band at 1750 cm^{-1}, in the ir spectrum. This high frequency is highly suggestive of a lactone structure, rather than a lactam structure. Cpd 8 could be hydrolysed with 10% alcoholic KOH under moderate conditions to give 11. (Figure 2.5). These spectral and chemical properties indicated a 2-morpholinone structure for 8 rather than a 3-morpholinone.

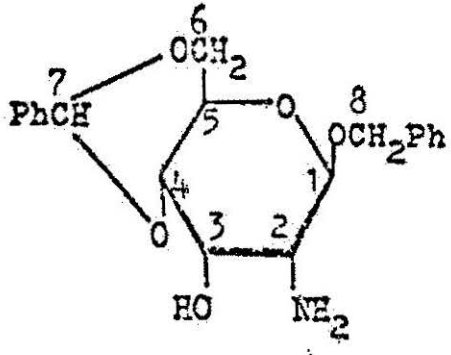
It should be pointed out, however, that normal amide carbonyl ir frequencies in the gas phase have been found as high as 1740 cm^{-1}.[44] Complete absence of amide dimerisation, caused by steric hindrance, might thus have caused an abnormally high amide carbonyl frequency. Also, some strange hydrophobic effect may have been the reason for the relatively rapid hydrolysis of a possible lactam, in base.

On reduction with lithium aluminum hydride in dry diethyl ether, cpd 8 gave a reduction product in almost quantitative yield. This product had an elemental analysis which matches best the expected cpd 9 from 2-morpholinone. (Figure 2.5). The analysis also approximately matched with two other possible reduction products, 9' derived from the 2-morpholinone 8 and 9" from the analogous 3-morpholinone 8'. (Figure 2.3).

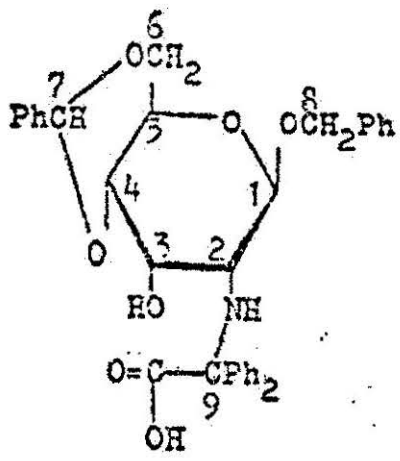
The reduction product formed a hydrochloride ppt with dry hydrogen chloride gas in anhydrous ether. To confirm the structure of the reduction product, acetylation using acetic anhydride in pyridine was carried out. The elemental analysis and the nmr spectrum of the acetylated cpd demonstrated the presence of two acetyl groups in the molecule. Theoretically cpd 9 was expected to form a triacetylated product, whereas 9' and 9" could only give diacetylated derivatives. The ir spectrum of the acetylated cpd revealed one sharp peak at 1750 cm^{-1} for the carbonyl function. In principle, these observations could be explained by all three structures (9, 9', 9"). For example, cpd 9 could have been unacetylated on N because of steric hindrance on that function. No additional explanation for nmr or ir would be necessary.

Alternatively, cpd 10' and 10" would be expected to show in the ir spectrum two different carbonyl bands, for amide, and ester, respectively. An abnormally high amide frequency, due to steric hindrance, would have to be involved.

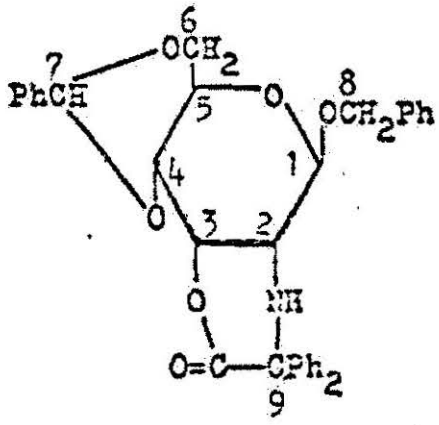
An investigation of the C-13 nmr spectra of cpds 1, 8 and 11 was carried out in order to establish the 2-morpholinone structure for cpd 8. The pyranose ring in these cpds was fixed in the C 1 conformation, by the trans diequatorially fused 4,6-O-benzylidene group. These cpds therefore allow an investigation of the correlation of chemical shifts in C-13 nmr with stereochemical changes at C-2 and C-3. An empirical comparison of diols and amino alcohols, and of the effect of substituent groups on C-13 resonances served to confirm the assignments made. The lowest field signal (172 ± 1 ppm) was assigned to the carbonyl carbon.



1

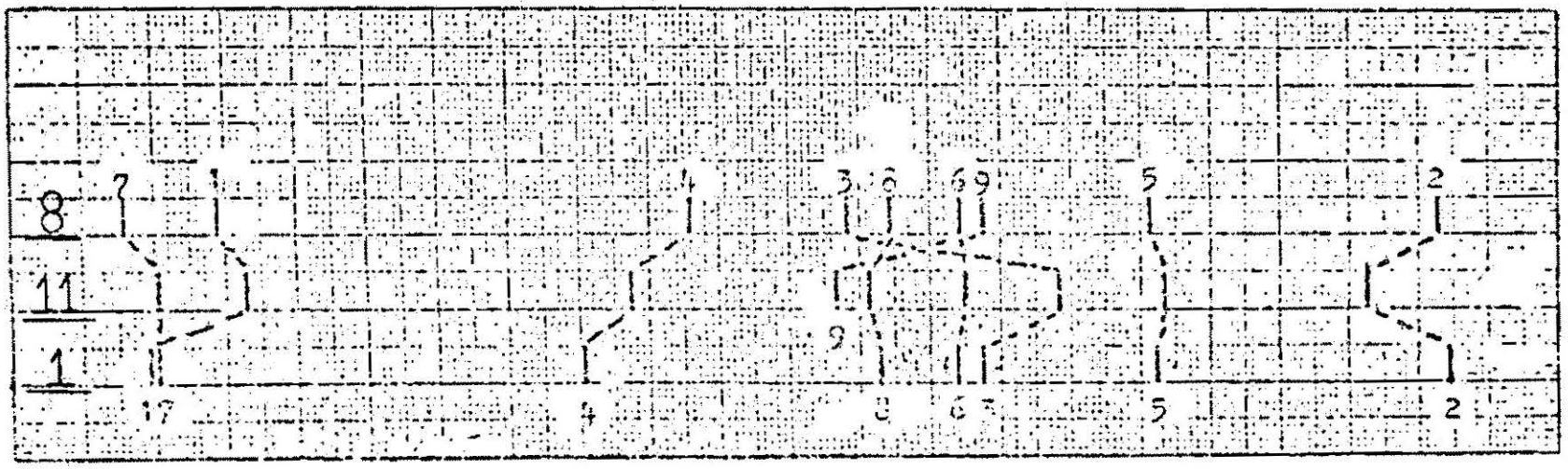


11



8

TABLE 1.

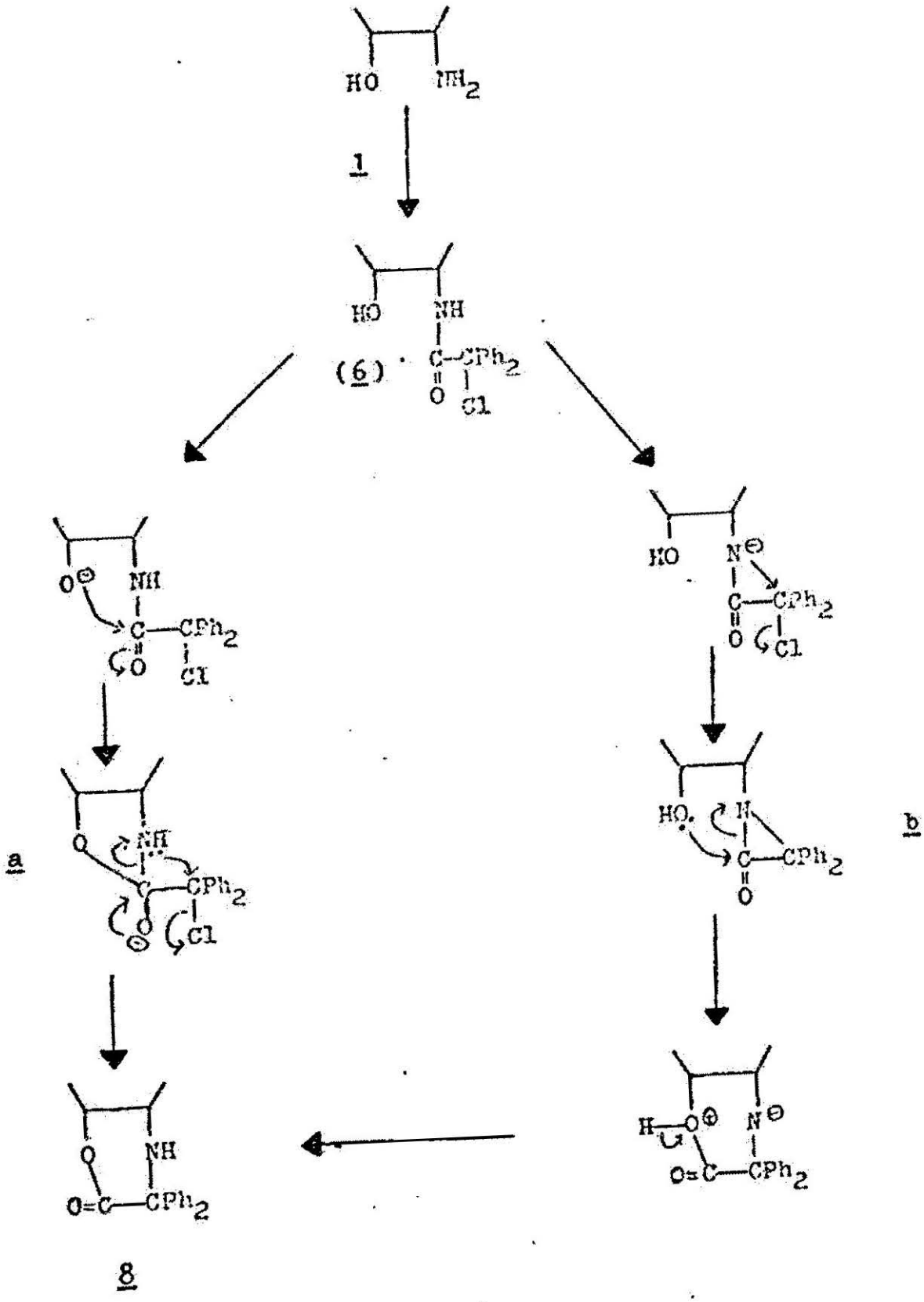


The spectra of cpds 1, 8, and 11 show many downfield peaks, due to the 12 aromatic carbons in cpd 1 and 24 aromatic carbons[45] in cpds 8 and 11. These shifts range from 143.6 to 126 ppm.

C-1 and C-7 are both attached to two oxygen atoms, and would therefore be expected to give signals at lower field than other carbon atoms which are attached only to one heteroatom. In cpd 1, C-1 and C-7 can be assigned to signals at approximately 102 ppm. Since the environment of C-7 is essentially unaltered in all three cpds, the absorption at 102.4 ± 0.4 ppm was assigned to this carbon. Because of the β -effect[46] of C-7, both C-6 and C-4 are strongly deshielded, relative to an unsubstituted glycoside. As expected, the C-6 signal varied very little in the three cpds and can be attributed to the signal at 69 ± 0.3 ppm. Similarly C-5 and C-8 are γ and δ to C-3 and C-2 and should not be affected much by stereochemical changes at these centers. These considerations lead to the assignments of the C-5 and C-8 signals to 63.5 ± 0.3 and 71.7 ± 0.3 ppm, respectively. In cpd 1 the remaining unassigned signals, those of C-2, C-3, and C-4, are composed of the unique, easily identifiable resonances of an aminomethine (C-2), a hydroxymethine (C-3), and an alkoxymethine (C-4), at 55, 68.5, and 79.9 ppm, respectively.

In N-alkylated aminosugar derivatives, such as cpd 11, the effect of an alkyl group on the α and β carbon atom signals depends on the nature of the alkyl group,[47] (i.e. primary, secondary or tertiary). Quite generally, N-alkyl substituents cause a downfield shift at the carbon of attachment and a small upfield shift at the carbons β to

Figure 2.4

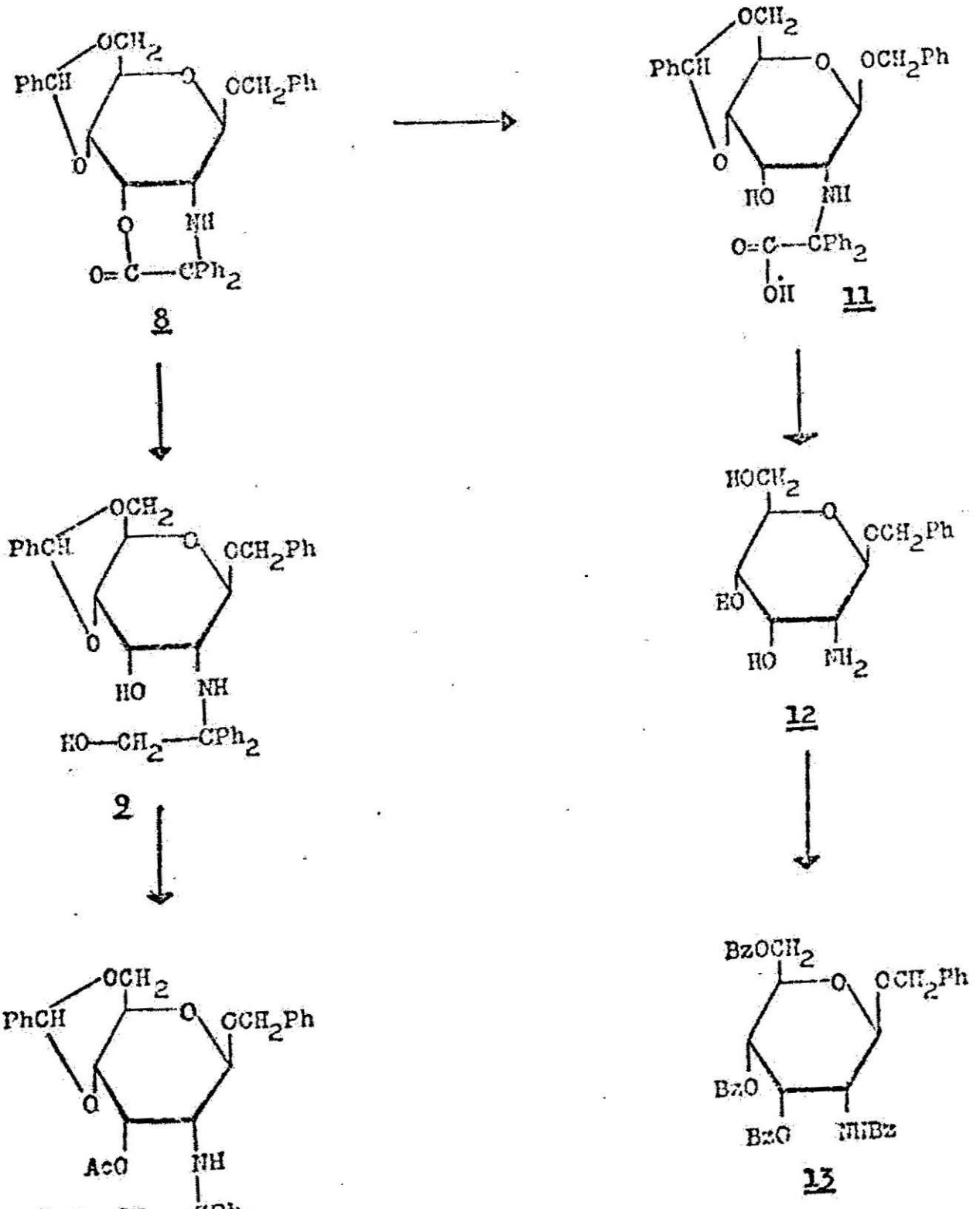


the N-atom.[48] In cpd 11 the N-alkyl group is the 1-carboxy-1,1-diphenyl methyl group. Due to its bulk, C-2 experienced a deshielding effect of only 2.5 ppm as compared to C-2 in cpd 1. Carbon atoms C-1 and C-3 were effected in the opposite way, and shielding effects of -2.7 and -2.2 ppm were observed, respectively. C-4 which is γ to the -NH group also experienced a shielding effect of -1.6 ppm. Carbon 9 was assigned the value of 72.5 ppm.

The only difference between cpds 11 and 8 was caused by the reaction of the C-3 hydroxyl group and C-9 carboxylic group of cpd 11 to form an ester linkage in cpd 8. Consequently, in cpd 8, C-3 gets deshielded by 6.1 ppm compared to cpd 11, whereas β carbons C-2 and C-4 had shielding effects of -2 and -1.8 ppm, respectively. Another carbon atom which experiences a greater magnitude of shielding is C-9. In general, whenever a carboxylic group is changed to an ester group, a shielding effect is observed on the α carbon atom. In cpd 8, C-9 absorbed at 68.4 ppm and was shielded by -4.1 ppm, compared to cpd 11. (Table 1).

If the cpd 8 would be a 3-morpholinone derivative the hydrolysis product would be an ether derivative with a free primary amino group at C-2 of the sugar molecule. The C-13 spectrum of this derivative would then be expected to have upfield chemical shift differences for carbons 2 and 4 and a downfield chemical shift difference for C-3, as compared to cpd 1, exactly opposite to the chemical shift differences between cpds 11 and 1, that were actually observed. A similar argument applies to the expected chemical shift differences between cpds 11 and 8.

Figure 2.5
(Thin-layer chromatographic comparison on page 83)



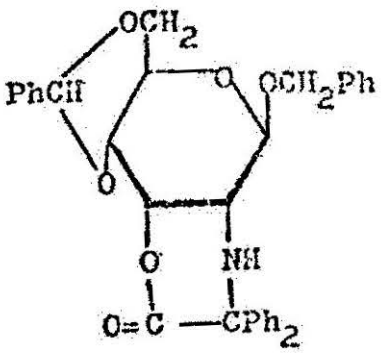
The formation of cpd 8 from the intermediate cpd 6 could be explained by two different mechanisms. The two mechanisms differ essentially only in the sequence of the two steps (Figure 2.4). In route a the hydride anion removes the hydroxylic proton leaving an alkoxide to attack the carbonyl carbon, with resultant formation of a five membered ring. A series of electronic shifts follows, that includes displacement of chloride ion by the lone pair of electrons on nitrogen, with transient formation of a 3 membered ring, and simultaneous cleavage of the previously formed 5 membered ring, to give the 2-morpholinone derivative 8.

In sequence b the proton attached to nitrogen is removed by the hydride anion leaving an amide anion to displace chloride ion, with resultant formation of a three membered ring. The lone pair of electrons on the hydroxyl group attacks the carbonyl carbon with transient formation of a 5 membered ring and subsequent or simultaneous opening of the 3 member ring to give 8.

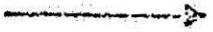
The 2-morpholinone ring, described here, after its function of protecting has been performed, can be cleaved without affecting the glycosidic bond. The removal of this new blocking group was accomplished in two steps. Mild alkaline hydrolysis cleaved the ester function of the ring, and mild acidic hydrolysis cleaved its amine function, along with the 4,6-O-benzylidene group, to give the amino alcohol 12. (Figure 2.5).

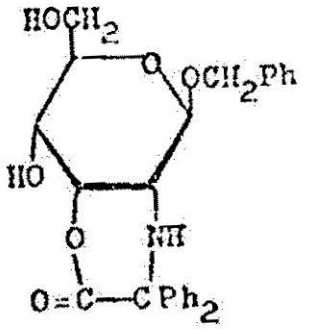
To free the anomeric carbon atom from the benzyl aglycon, in presence of the 2-morpholinone blocking group, conditions of catalytic

Figure 2.6
(Thin-layer chromatographic comparison on page 84)

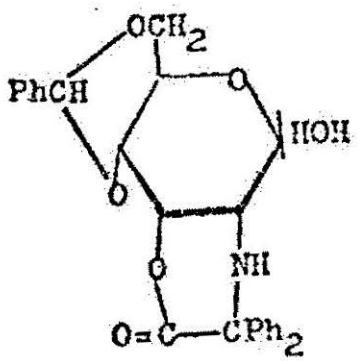


8

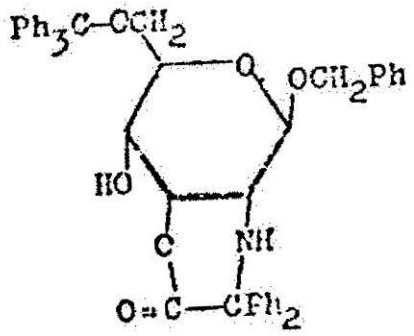




15



14



16

hydrogenation were used, identical to those for the removal of the oxazolidinone protective group. An almost quantitative selective removal of the benzyl aglycon was achieved, even after prolonged hydrogenation. Consumption of hydrogen gas stopped as soon as the anomeric position was free. The rate of hydrogenation appeared to be dependent on the reaction temperature and the speed of stirring. It was fastest at temperatures between 22-24° with very fast stirring. (Figure 2.6). When cpd 8 was heated with aqueous acetic acid until all material was just dissolved, a selective cleavage of the 4,6-O-benzylidene group occurred to give cpd 15. Prolonged heating of the reaction mixture caused decomposition of the product, presumably by cleavage at the amine, as indicated by tlc. When cpd 15 was allowed to react with chlorotriphenyl methane in pyridine, benzyl 6-O-triphenylmethyl-β-D-allopyranosido[2,3:5',6']-3',3'-diphenyl 2-morpholinone (16) was obtained in good yield. (Figure 2.6).

In view of the frequent presence of gem-diphenyl groups in physiologically active cpds such as amidone, transentin, benadryl, DDT, and methadone, the combination of such a structure with a sugar may show interesting pharmacological properties. Cpd 8 (R:B-14-C:MP 214) was tested using Hippocratic Observational Screening in Unanesthetized, Intact, Albino Rats. It demonstrated some dose-response patterns of equivocal to low-order central nervous system depression (sedation) accompanied by dehydration diuresis in the dosage range of 100-1000 mg/kg intraperitoneally. The complete report follows in the Appendix.

EXPERIMENTAL

General: The melting points are uncorrected, and were determined on a Thomas-Hoover melting-point apparatus, Model No. 6404H. Infrared spectra were recorded with a Perkin-Elmer spectrophotometer, Model 337, using potassium bromide pellets. All compounds, unless otherwise specified, were found to be homogeneous and distinguishable from their precursors and byproducts by thin layer chromatography using silica gel G (Merck) and silica gel GF (Merck). Plates were developed with chloroform, containing lesser amounts of either methanol or petroleum ether. The spots were detected by extinction of the U.V. fluorescence of a zinc silicate indicator and by spraying with 15% sulfuric acid in methanol solution and heating for 7-15 minutes at 150°C. Optical rotations were taken with a Rudolph polarimeter, Model 956. Microanalyses were performed by Beller Microanalytisches Laboratorium, 34 Gottingen, West Germany, and Alfred Bernhardt Microanalytisches Laboratorium, Engelskirchen, Germany.

Benzyl 4,6-O-benzylidene-β-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone (2). To a soln of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (5g, 0.014 M) and ethyl diisopropyl amine (5.5 ml) in abs dioxane (90 ml) was added slowly, with stirring at room temperature, a soln of phosgene (2.95 g) in dioxane (50 ml). After 12 hr of stirring, ethyl diisopropyl ammonium chloride was filtered off. The filtrate was evaporated in vacuo to a small volume (20 ml). Addition of ice water (200 ml) produced a ppt, which was filtered off, after 12 hr at 0°C, and was recrystallized from absolute ethanol, to give 2 (5 g, 95%), mp 208–209°, $[\alpha]_D^{27}$ + 17 (c 1, pyridine) [Lit.[37] mp 209°, $[\alpha]_D^{27}$ + 17.2].

4,6-O-Benzylidene-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone (3). Palladium black (10% charcoal, 0.385 g) was suspended in water (3 ml). A soln of benzyl 4,6-O-benzylidene-β-D-allopyranoside-[2,3:4',5']-2'-oxazolidinone (0.385 g, 0.001 M) and p-toluidine (0.113 g) in tetrahydrofuran (15 ml) and methanol (15 ml) was added to the reaction flask. Hydrogenation (1 atm H_2; 25°C) was started at once, and was continued until no starting material was detectable by tlc. The catalyst was removed by filtration, and the filtrate was concd in vacuo. The product, precipitated from the residual syrup by addition of diisopropyl ether, was filtered off to give 3 (0.25 g, 85%), mp 209°C, $[\alpha]_D^{25}$ + 79.57°, (c 1, pyridine); ir (cm^{-1}) 3375 (OH), 3275 (NH), 1725, 1700 (C=O).

Anal. Calcd for $C_{14}H_{15}NO_6$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.41; H, 5.12; N, 4.75.

Benzyl 2-deoxy-6-O-triphenyl-β-D-allopyranosido[2,3:4',5']-2'-oxazolidinone (5). To a soln of benzyl 4,6-O-benzylidene-β-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone (2) (0.58 g, 1.5×10^{-3}M) in glacial acetic acid (15 ml), water (10 ml) was added dropwise over a period of 10 min. The reaction mixture was then heated for 70 min at 78° to 89°C. Evaporation of the solution in vacuo was followed by repeated co-evaporations with water and finally with toluene. The residual syrup, presumably benzyl-2-deoxy-β-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone (4), was dissolved in pyridine (10 ml), and heated with chlorotriphenyl methane (0.65 g) for 2 hr at 110°-115°. The mixture was stirred for 12 hr at room temp and was poured on ice. The resultant crude crystals were filtered off, dried, and recrystallized from dioxane/petroleum ether (30-60°) to give 0.7 g (85.5%) of pale yellow crystals of 5, mp 216°C, $[\alpha]_D^{23}$ - 9° (c 1, pyridine); ir[cm^{-1}] 1753 (C=O) [Lit.[42] mp 215-217°, $[\alpha]_D^{22}$ - 9°].

Anal. Calcd for $C_{33}H_{31}NO_6$: C, 73.72; H, 5.81; N, 2.60. Found: C, 73.70; H, 5.71; N, 2.52.

Benzyl 4,6-O-benzylidene-2-deoxy-2-[(diphenyl hydroxy)acetamido]-β-D-allopyranoside (7). To a soln of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (1 g, 2.8×10^{-3}M) and ethyl diisopropyl amine (1.5 ml) in acetonitrile (15 ml) was added slowly, with stirring, α-chloro-γ,γ-diphenyl acetyl chloride (0.7 g, 2.8×10^{-3}M) in abs diethyl ether (10 ml). The mixture was stirred overnight at 25°C and the soln evaporated in vacuo. The soln in dichloromethane (40 ml)

was washed with cold aq saturated sodium bicarbonate (30 ml) and water (30 ml), was dried ($MgSO_4$), and was evaporated in vacuo. The crystallization of the residual syrup from petroleum ether (30-60°) afforded 1.3 g of a white cryst mass. This crude cpd (1.3 g) by preparative chromatography on silica gel G with acetone/chloroform (5:95), gave pure 7 (0.78 g, 50%); mp 148-53°, $[\alpha]_D^{27}$ - 119.3° (c 1, pyridine); ir[cm^{-1}] 3400 (NH), 1675 (C=O).

Anal. Calcd for $C_{34}H_{33}NO_7$: C, 71.94; H, 5.86; N, 2.46. Found: C, 72.06; H, 5.99; N, 2.43.

Benzyl 4,6-O-benzylidene-β-D-allopyranoside[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (8) (Method A). To a soln of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (1) (1.07 g, 3 x 10^{-3}M) recrystallized twice from abs ethanol and air dried) in distilled triethyl amine (3 ml), and dioxane (12 ml; 0.01% H_2O, scintillation grade) was added dropwise a soln of α-chloro-α,α-diphenyl acetyl chloride (0.8 g; mp 48-50°) in dioxane (9 ml), with stirring at 25°C. After one hr, a sodium hydride emulsion in mineral oil (59% NaH, 0.244 g) was added, and the mixture was stirred for one hr in an oil bath (95° - 98°C). Solvent (10 ml) was distilled off (bath temp 115-125°). Dimethyl formamide (20 ml) was added to the reaction mixture, which was allowed to stir for 6 hr (bath temp 95°-100°). The remainder of the dioxane (14 ml) was distilled out [distillation temp 110-115° and bath temp 140-150°]. The reaction mixture was diluted with toluene (15 ml) and allowed to cool. A

precipitate was filtered off. The filtrate was evaporated in vacuo at 60°C. The syrup was treated with methanol (50 ml). After 12 hr at -10°C crystals were filtered off. Recrystallization from dichloromethane/methanol gave pure 8 (1.1 g, 63%): mp 216°C $[\alpha]_D^{24}$ - 161°; ir [cm^{-1}] 3375 (NH), 1760 (C=O).

Anal. Calcd for $C_{34}H_{31}NO_6$ (549.60): C, 74.30; H, 5.69; N, 2.55. Found: C, 74.17; H, 5.59; N, 2.53.

(Method B)

The cpd was also prepared from benzyl 4,6-O-benzylidene-2-[(carboxydiphenyl methyl)amino]-2-deoxy-β-D-allopyranoside (11). Cpd (11) (0.05 g) was dissolved in pyridine (2 ml) and acetic anhydride (1 ml). The mixture was heated for 2 hr with gentle reflux. Addition of ice (15 g) gave a cryst ppt, which was filtered off after 12 hr at 0°C, washed with cold water, and dried, to give 8 (0.35 g, 73%).

Benzyl 4,6-O-benzylidene-2-[(1,1 diphenyl-2-hydroxyethyl)amino]-2-deoxy-β-D-allopyranoside (9). Lithium alluminum hydride (0.06 g) was added to a soln of benzyl 4,6-O-benzylidene-β-D-allopyranoside-[2,3:5',6']-3',3'-diphenyl-2-morpholinone (0.55 g) in dry diethyl ether (60 ml). The mixture was refluxed for 50 hr and cooled. Ice cold water (20 ml) was gradually added. The ethereal layer was separated, washed with water, dried (Na_2SO_4, silicagel 0.2 g) and concd in vacuo to 5 ml. Heptane (70 ml) was added to the remaining syrup and the mixture was kept at -15°C for 24 hr. The resulting slurry was filtered to give 9 (0.4 g, 72%): mp 100-107°, $[\alpha]_D^{21}$ - 42.3 (c 1 in $CHCl_3$).

Anal. Calcd for $C_{34}H_{35}NO_6$: C, 73.76; H, 6.37; N, 2.53; O, 17.34. Found: C, 73.43; H, 6.80; N, 2.57; O, 17.55. C, 73.58; H, 6.35; N, 2.97.

Benzyl 4,6-O-benzylidene-3-O-acetyl-2[(1,1-diphenyl-2-acetoxyethyl) amino]-2-deoxy-β-D-allopyranoside (10). A solution of benzyl 4,6-O-benzylidene-2[(1,1 diphenyl-2-hydroxyethyl)amino]-2-deoxy-β-D-allopyranoside (0.1 g) and acetic anhydride (0.5 ml) in pyridine (2 ml) was kept for 12 hr at room temp. Crushed ice (10 g) was added, and the mixture was kept at 0°C for 2 hr. The resultant crystals were collected, washed with water, dried, and recrystallized, first from heptane, and then from methanol/water to give 10 (0.08 g, 65%): mp 75°-90°C; ir (cm^{-1}) 1750 (C=O).

Anal. Calcd for $C_{38}H_{39}NO_8$ (679.74): C, 71.57; H, 6.16; N, 2.20; O, 20.07. Found: C, 71.41; H, 6.21; N, 2.25; O, 20.47.

Benzyl 4,6-O-benzylidene-2-[(carboxydiphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11). Benzyl 4,6-O-benzylidene-β-D-allopyranoside-(2,3:5',6')-3',3'-diphenyl-2-'-morpholinone (1.5 g, 2.73×10^{-3}M) and potassium hydroxide (2 g) were heated in ethanol (20 ml, 95%) for 3 hr, with reflux. At room temp the pH was adjusted to 7, with acetic acid. The soln was concd *in vacuo* until it became turbid. Addition of ice (20 g) produced a crystalline precipitate which was filtered off, washed with ice water and dried to give 11 (1.5 g, 96.8%): mp 173°, $[\alpha]_D^{23}$ - 94° (c 1, pyridine); ir [cm^{-1}]:

3580 (OH), 3455 (NH_2), 1760 (C=O).

Anal. Calcd for $C_{34}H_{33}NO_7$: C, 71.94; H, 5.86; N, 2.47. Found: C, 71.48; H, 6.08; N, 2.57.

Benzyl 2-N-benzoyl 3,4,6-tri-O-benzoyl-2-deoxy allopyranoside (13). A soln of benzyl 4,6-O-benzylidene-2-[(carboxydiphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11) (0.5 g, 8.8×10^{-4} M) in glacial acetic acid (7 ml) and water (5 ml) was heated for 2 hr at 90-100°C. From the cooled soln, benzylic acid and benzaldehyde were extracted with diisopropyl ether. The aqueous layer was evaporated *in vacuo* followed by repeated coevaporation, first with water, and finally with toluene. Attempts to crystallize the cpd 12 were fruitless; however, the product was uniform and identical to the sample obtained by debenzylidenation of cpd 1 by 60% acetic acid. Benzilic acid was obtained from the diisopropyl ether layer and was identified by mp, mixed melting point, and thin layer chromatography comparison with a known sample. The syrupy cpd 12 was dissolved in dry pyridine (8 ml) and the soln was cooled. Benzoyl chloride (3 ml) was added drop by drop. The mixture was shaken for 15 hr. Crushed ice (30 g) was added. A sticky mass separated and was dissolved in hot methanol. Cooling gave white crystals (0.9 g). Recrystallization from dichloromethane/ethanol gave 13 (0.7 g, 80%): mp 179-180°, $[\alpha]_D^{23}$ - 47° (c 1, pyridine) [Lit.[36] mp 180° $[\alpha]_D$ - 47°].

4,6-O-Benzylidene-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (14). Palladium black (10% on charcoal, 0.55 g) was suspended in water (5 ml) and methanol (20 ml). A soln of benzyl 4,6-O-benzylidene-β-D-allopyranosido-[2,3:5',6']-3',3'-diphenyl 2'-morpholinone (0.55 g, 10^{-3}M) in tetrahydrofuran (30 ml) and p-toluidine (0.12 g) were added. Hydrogenation (1 atm H_2; 23-25°) was continued until no starting material was detectable by tlc (8 hr). The catalyst was filtered off. The filtrate was concentrated in vacuo, and diluted with toluene, which was evaporated in vacuo. Petroleum ether (30-60°) was added to the residual syrup. After 18 hr at 0°C the resulting crystals were filtered off to give 14 (0.42 g, 91%): mp 205°C, $[\alpha]_D^{27}$ - 59°; ir (cm^{-1}) 3550 (OH), 3400 (NH), 1750 (C=O).

Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.57; H, 5.48; N, 3.05. Found: C, 70.73; H, 5.91; N, 2.98.

Benzyl β-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (15). Water (10 ml) was slowly (10 min) added to benzyl 4,6-O-benzylidene-β-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (0.5 g, 9×10^{-4}M) in glacial acetic acid (20 ml) with stirring at 70-75°. After 35 min at this temperature the mixture became clear, and was evaporated in vacuo. Acetic acid was removed from the residual syrup by repeated coevaporation with water, followed by toluene in vacuo. Heptane (30 ml) was added to the remaining syrup and the mixture was kept at 0°C for 12 hr. Crystals were filtered off and recrystallized

from toluene/petroleum ether (30-60°) to give 15 (0.35 g, 83%): mp 195-197°, $[\alpha]_D^{24}$ - 173° (c 1, pyridine); ir [cm^{-1}]: 3450 (OH), 3400 (NH), 1748 (C=O).

Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04. Found: C, 69.88; H, 5.84; N, 2.97.

Benzyl 6-O-(triphenyl)methyl-β-D-allopyranoside[2,3:5',6'] -3',3'-diphenyl-2'-morpholinone (16). Benzyl-β-D-allopyranoside [2,3:5',5']-3',3'-diphenyl-2'-morpholinone (15) (0.3 g, 6.5×10^{-4}M), absolute pyridine (5 ml) and chlorotriphenyl methane (0.3 g) were heated for 3 hr at 110°. The reaction mixture was poured on ice. The aqueous phase was decanted from the resultant tacky mass, and discarded. Methanol (20 ml), when added with stirring, produced a yellowish white ppt which was filtered off, and dissolved in dry benzene (7 ml). The solution was stirred with silica gel (0.2 g) for 20 min, filtered, and evaporated in vacuo; to the remaining syrup, petroleum ether (30-60°) was added. The mixture was kept at 0°C for 24 hr. The resulting crystals were filtered off to give 16 (0.36 g, 78.7%): mp 152-153°, $[\alpha]_D^{24}$ - 188°; (c 1, pyridine); ir [cm^{-1}]: 3500 (OH), 3400 (NH), 1750 (C=O).

Anal. Calcd for $C_{46}H_{41}NO_6$: C, 78.58; H, 5.87; N, 1.99. Found: C, 77.82; H, 5.96; N, 1.94.

SUMMARY

A new cyclic protective group has been fused to the cis amino alcohol group of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside, by way of a unique rearrangement mechanism. To establish the 2-morpholinone structure, chemical studies, such as reduction and acetylation, were conducted.

Comparative spectroscopic studies using ir, pmr and C-13 nmr confirmed the assigned structures.

The 2-morpholinone ring was cleaved by mild alkaline hydrolysis and could be closed again with acetic anhydride in pyridine. An oxazolidinone derivative of benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside was prepared in quantitative yield by a modification of a known method.

Protective group properties of the oxazolidinone were studied prior to the examination of the 2-morpholinone cyclic protective group. The selective removal of the benzyl aglycon was achieved in excellent yield by catalytic hydrogenation, for both morpholinone and oxazolidinone protected benzyl-β-D-allopyranosides. The selective removal of the 4,6-O-benzylidene group in presence of a 2-morpholinone ring was possible in high yield. The cleavage of the 2-morpholinone protective group was accomplished in two steps. Mild alkaline hydrolysis cleaved the ester function of the ring and mild acidic hydrolysis cleaved its amine function.

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BIBLIOGRAPHY

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APPENDIX

October 10, 1974 Lab Notebook 15-D, pp. 230ff.

Hippocratic Observational Screening in Unanesthetized, Intact, Albino Rats of RB-14-C:MP214

The technique used was essentially that of Malone and Robichaud(1). The 130-140 gram, Wistar-derived rats were allowed both food and water up to the time of dosage and after dosage. The test compound was suspended for dosing (5 ml/kg) using 0.25% aqueous agar as the vehicle. Observed symptomatology was:

100 mg/kg intraperitoneally: +5-30 min possible miosis; +10-30 min somewhat more passive to head-tap challenge; +15-30 min slight decrease in respiratory rate with little to no change in respiratory depth; +15-60 min slight exopthalmos and somewhat tearful to body-grasp challenge; by +24 hrs loss of 18 grams of body weight (no sign of diarrhea so due to dehydration); no other symptoms; surviving.

316 mg/kg intraperitoneally: +10 min some decrease in spontaneous motor activity accompanied by decrease in respiratory rate; no other definite symptomatology; surviving.

1000 mg/kg intraperitoneally: +5-60 min decrease in spontaneous motor activity (definite from +30-60 min); +15 min some analgesia and tendency for loss of hind-leg grip strength; +15-60 min reversible palpebral ptosis (maximal from +30-60 min) accompanied by definite passive responses to head-tap and body-grasp challenges; +60-120 min definite micturition; by +24 hrs loss of 11 grams of body weight (no sign of diarrhea so due to dehydration); no other symptoms; surviving.

Summary: Some dose-response patterns of equivocal to low-order central nervous system depression (sedation) accompanied by dehydration diuresis in the dosage range of 100-1000 mg/kg intraperitoneally. For a compound to have feasible commercial therapeutic potential, it should produce significant dose-related phenomena at doses below 100 mg/kg. For comparison purposes, alpha-chloralose (Light Chemical) was also screened:

100 mg/kg intraperitoneally, alpha-Chloralose: +5 min fearful reaction to head-tap and body-grasp challenges coupled with increased startle sensitivity, reversing by +10 min to profoundly passive reaction to each of these parameters, which reaction persisted through death; by +10 min onset of decreased spontaneous motor activity, decreased respiratory rate, ataxia, back plasticity, loss of fore- and hind-leg grip strength, loss of righting reflex, and onset of miosis -- each increasing in degree until death: +15 min decrease in respiratory depth and loss of corneal reflex plus 1.9°F drop in body temperature; death of respiratory arrest by +60 min; on necropsy: intestines motile and hyperemic, heart beating in rhythm, prompt blood clotting, body organs grossly normal.

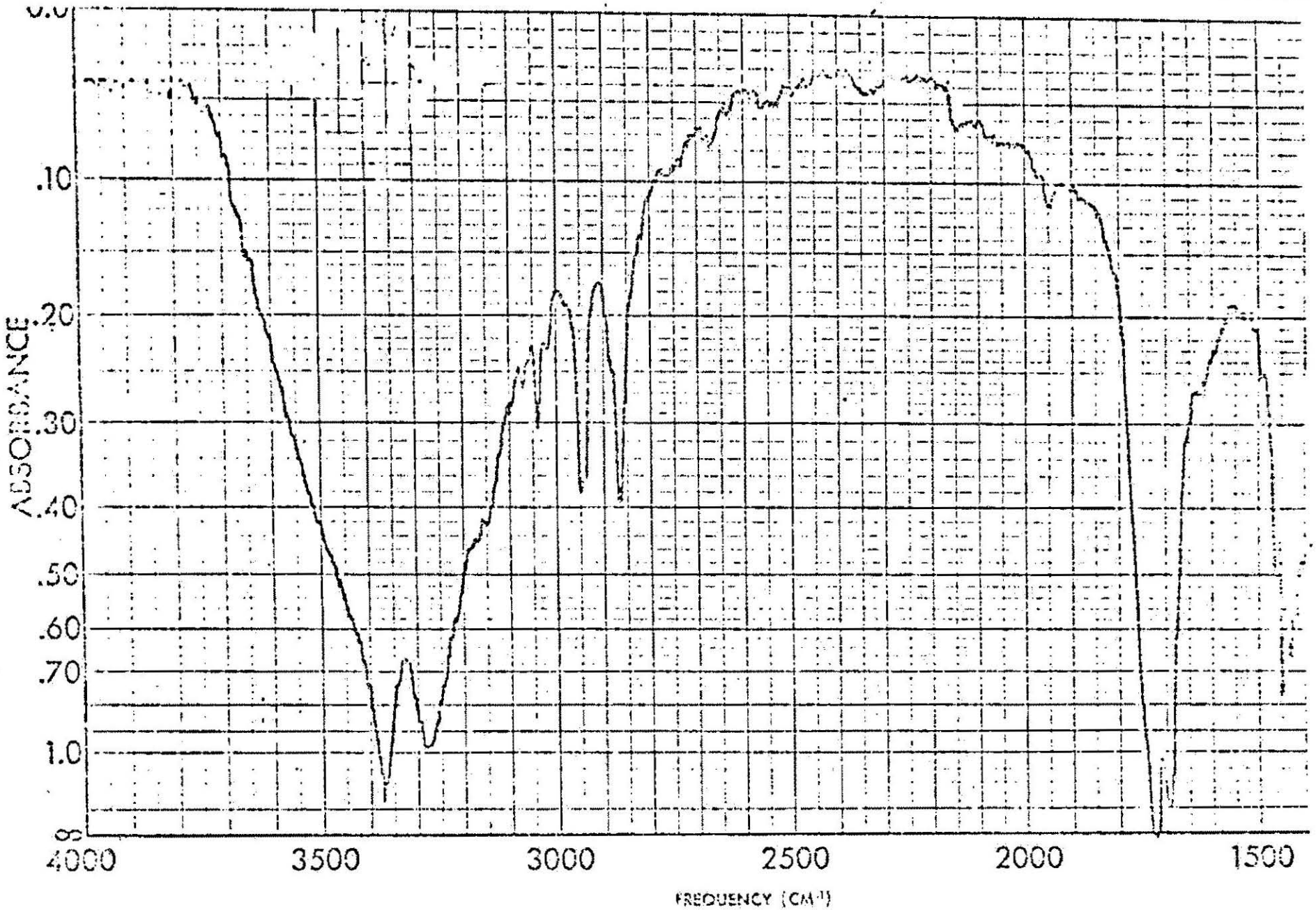
Relative to RB-14-C:MP214, alpha-chloralose appears interesting -- 100 mg/kg appears to be an overdose, but nevertheless useful anesthetic potential (without significant autonomic nervous system involvement) is quite apparent.

RB-14-C:MP214 has no useful pharmacologic activity although at massive doses there is some sedative/diuretic potential.

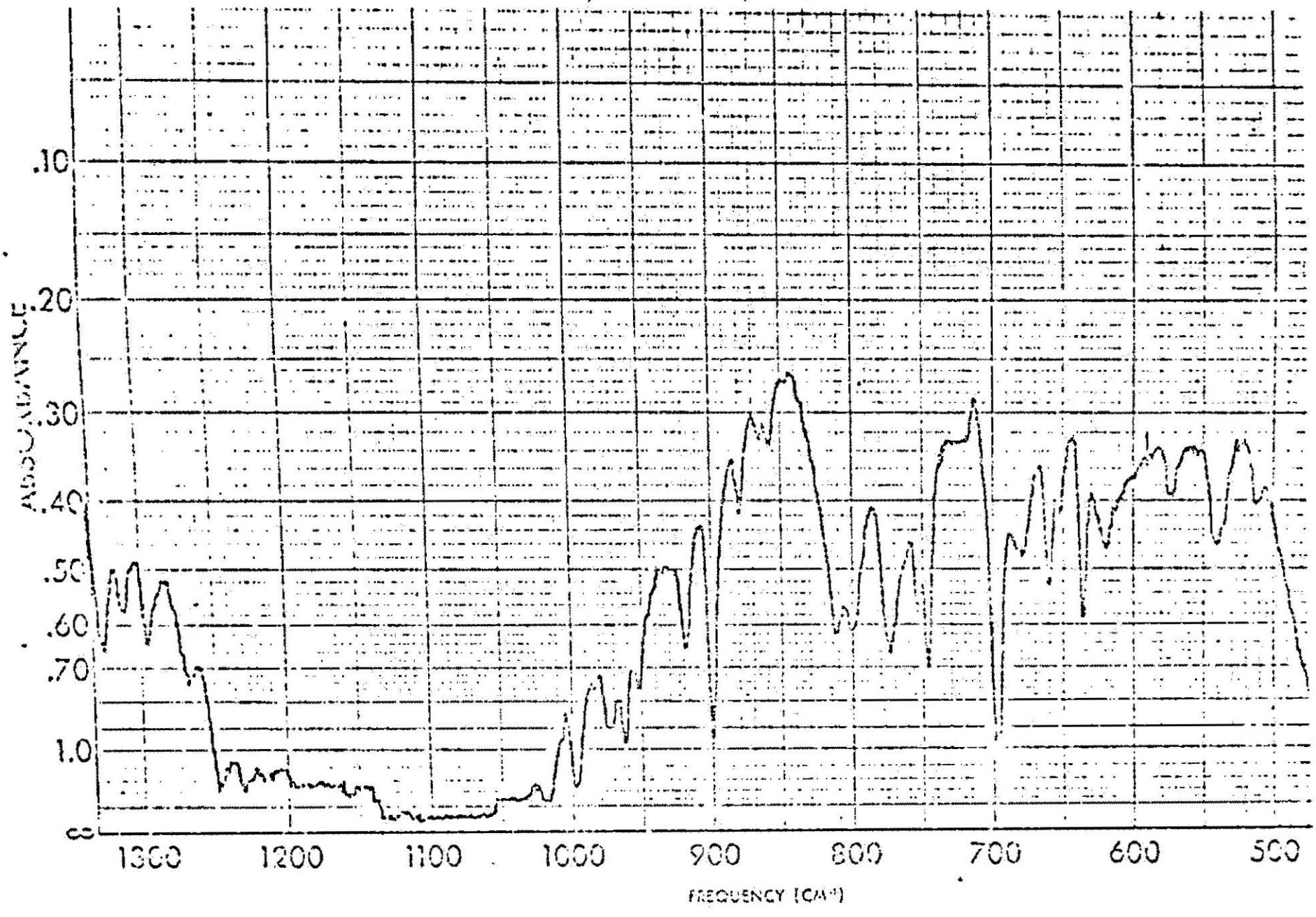
Reference: (1) Malone, M.H. and Robichaud, R.C., Lloydia, 25:320(1962).

Investigators: Ron C. Cooke, John E. Taylor, and Dr. Marvin H. Malone

Marvin Malone



4,6-O-Benzylidene-D-allopyranosido-[2,3:4',5']-2'-oxazolidinone (3).



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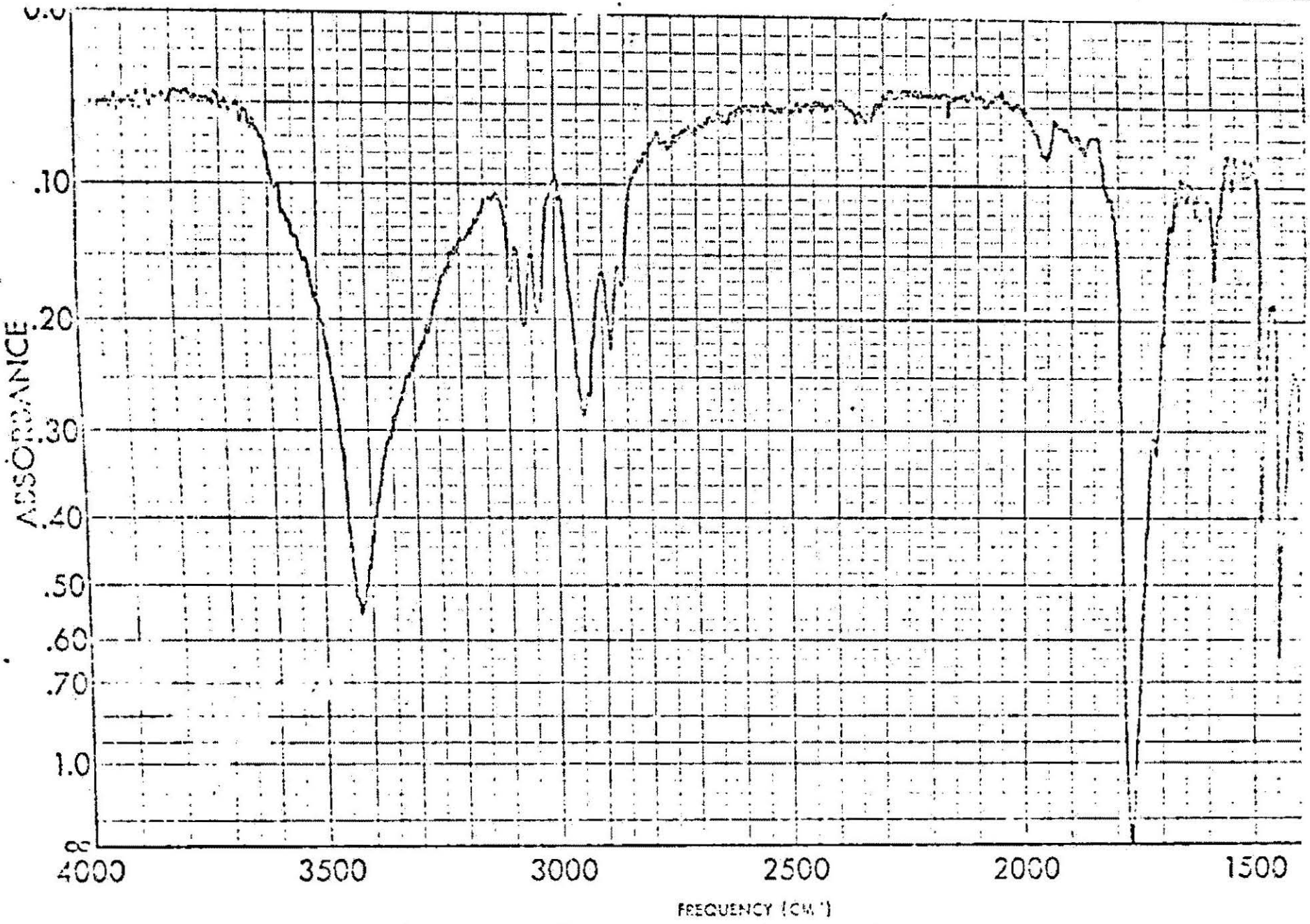
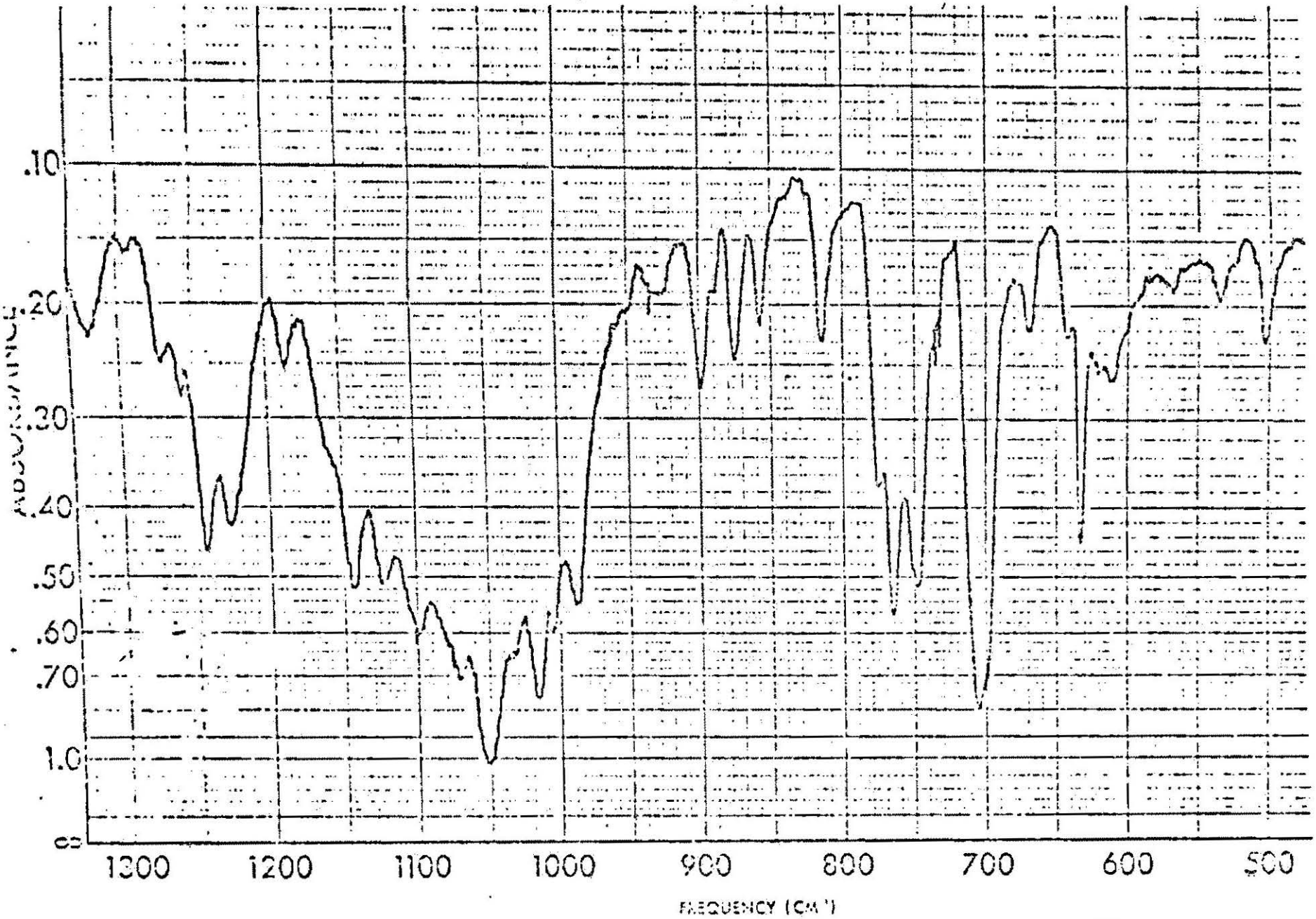


Benzyl 2-bromoxy-6-O-triphenyl-β-D-allopyranoside[2,3:4',5']-2'-oxazolidinone (5).



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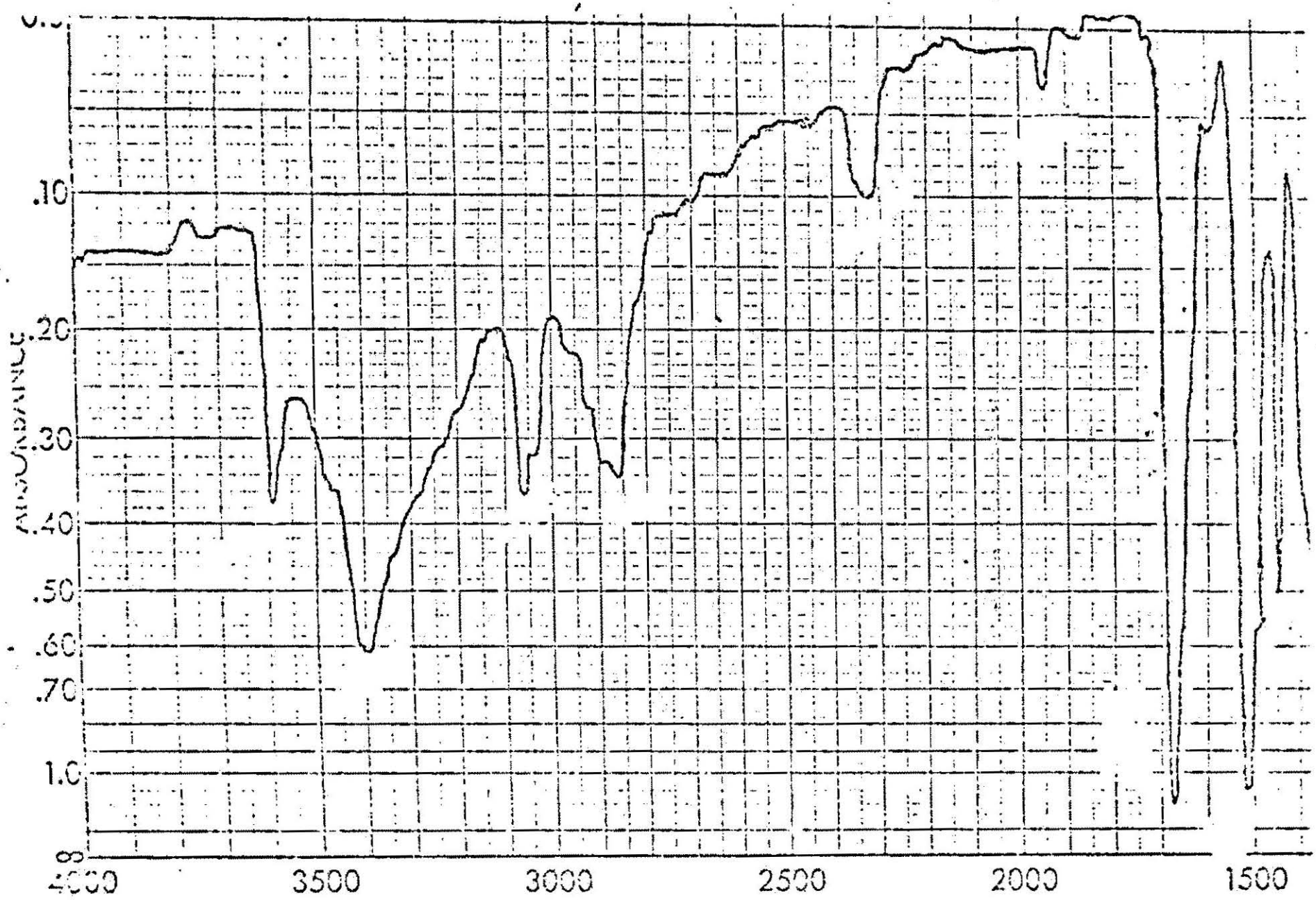

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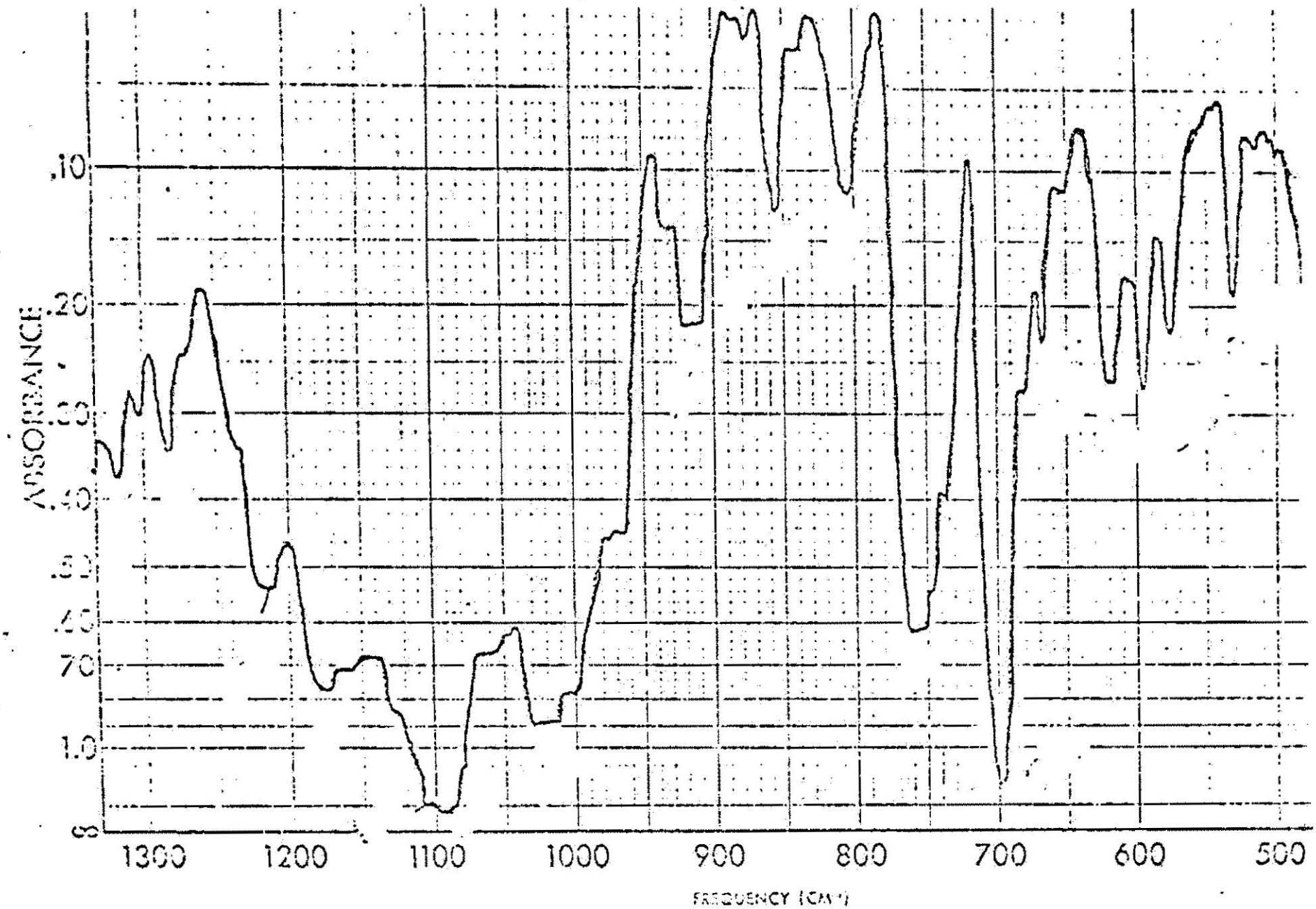

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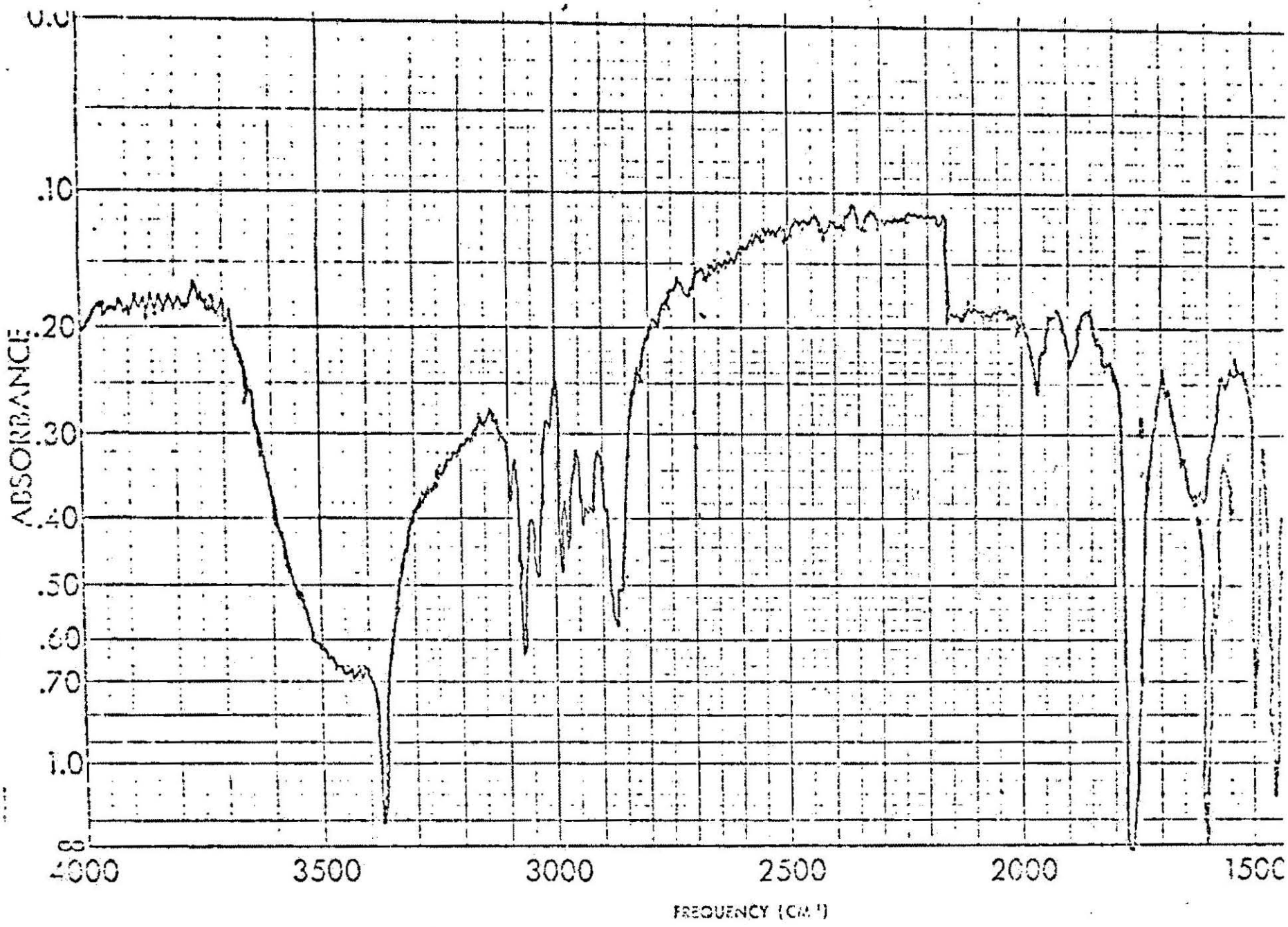
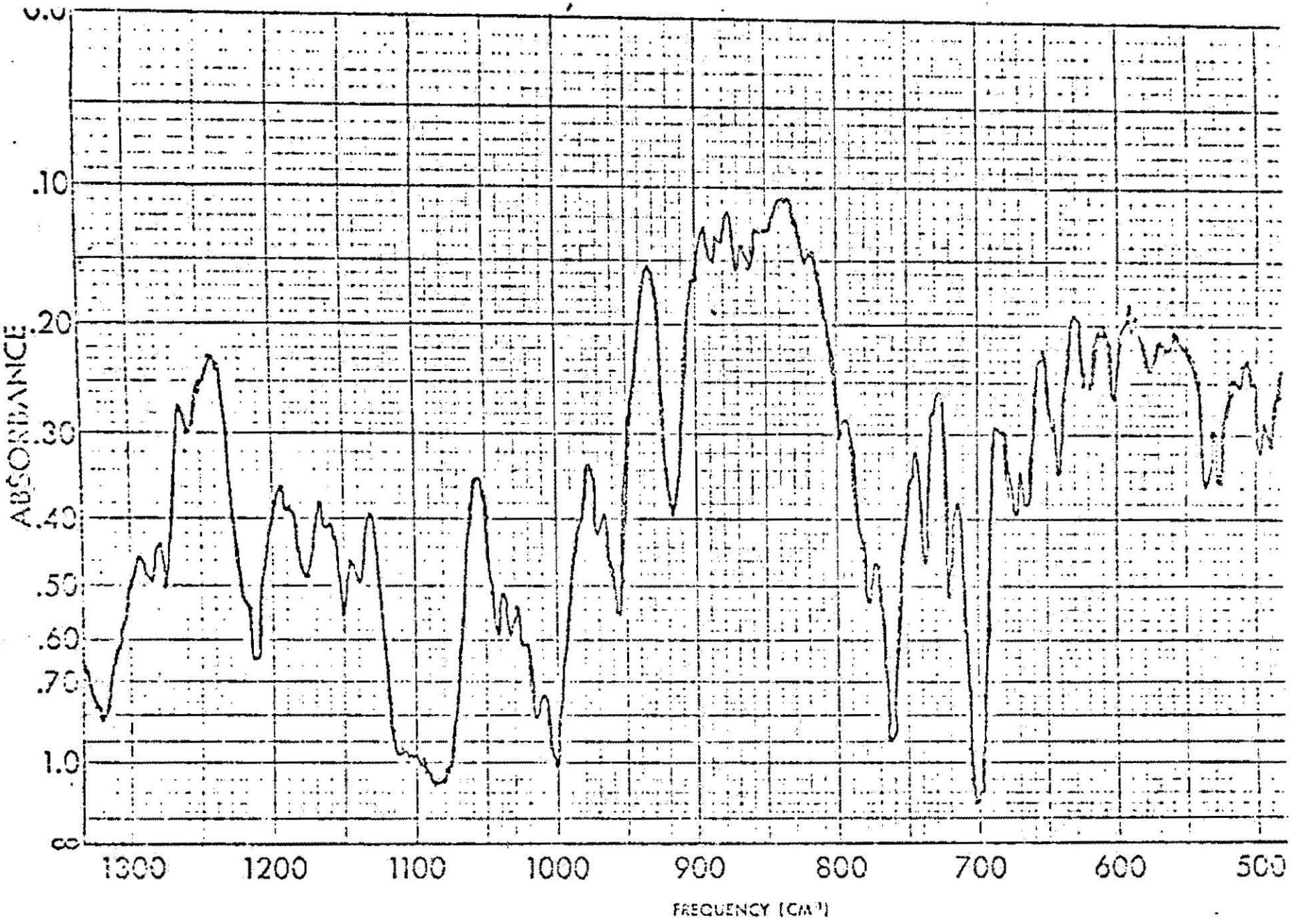


Benzyl 4,6-O-benzylidene-β-D-allopyranoside[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (6).



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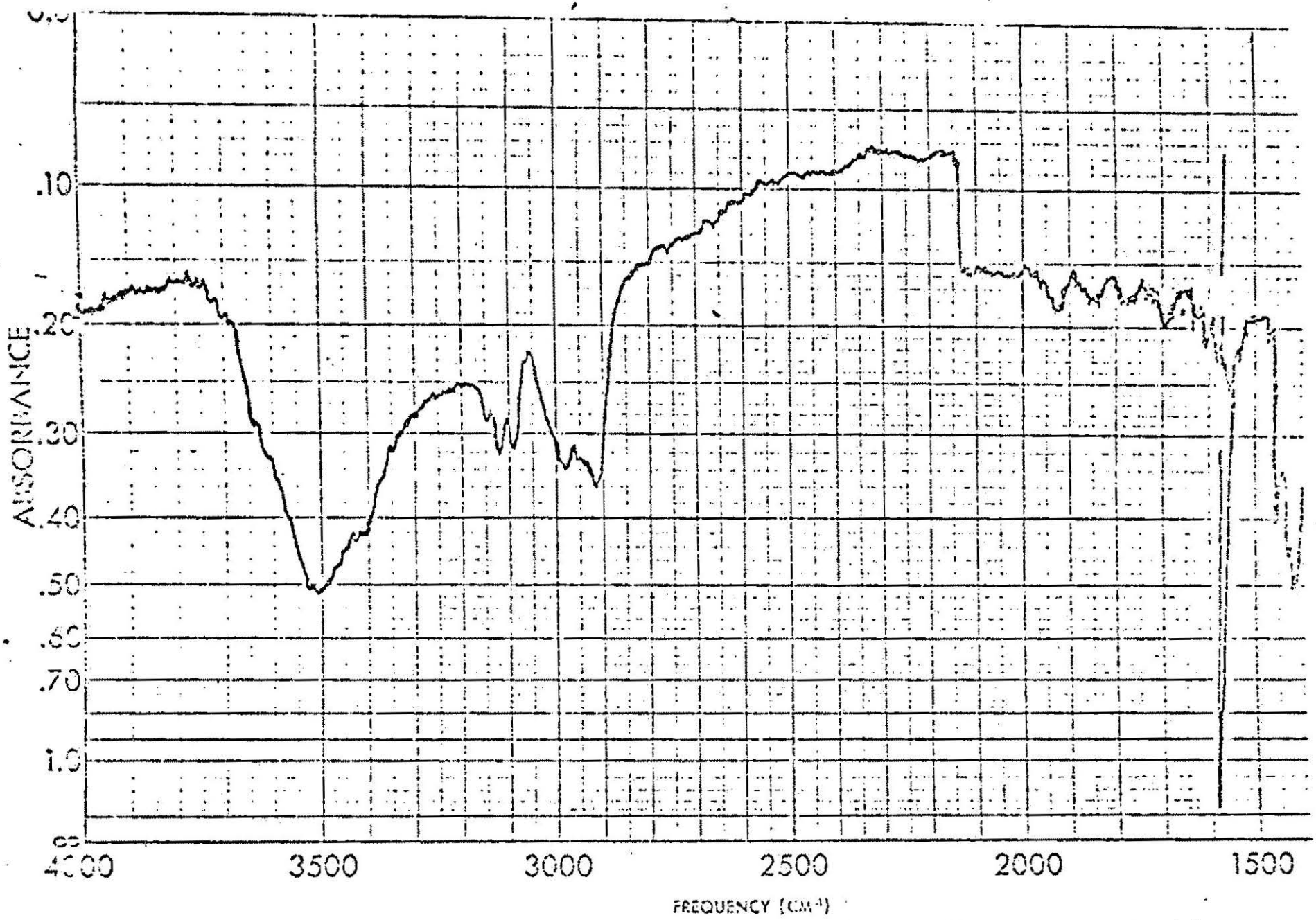
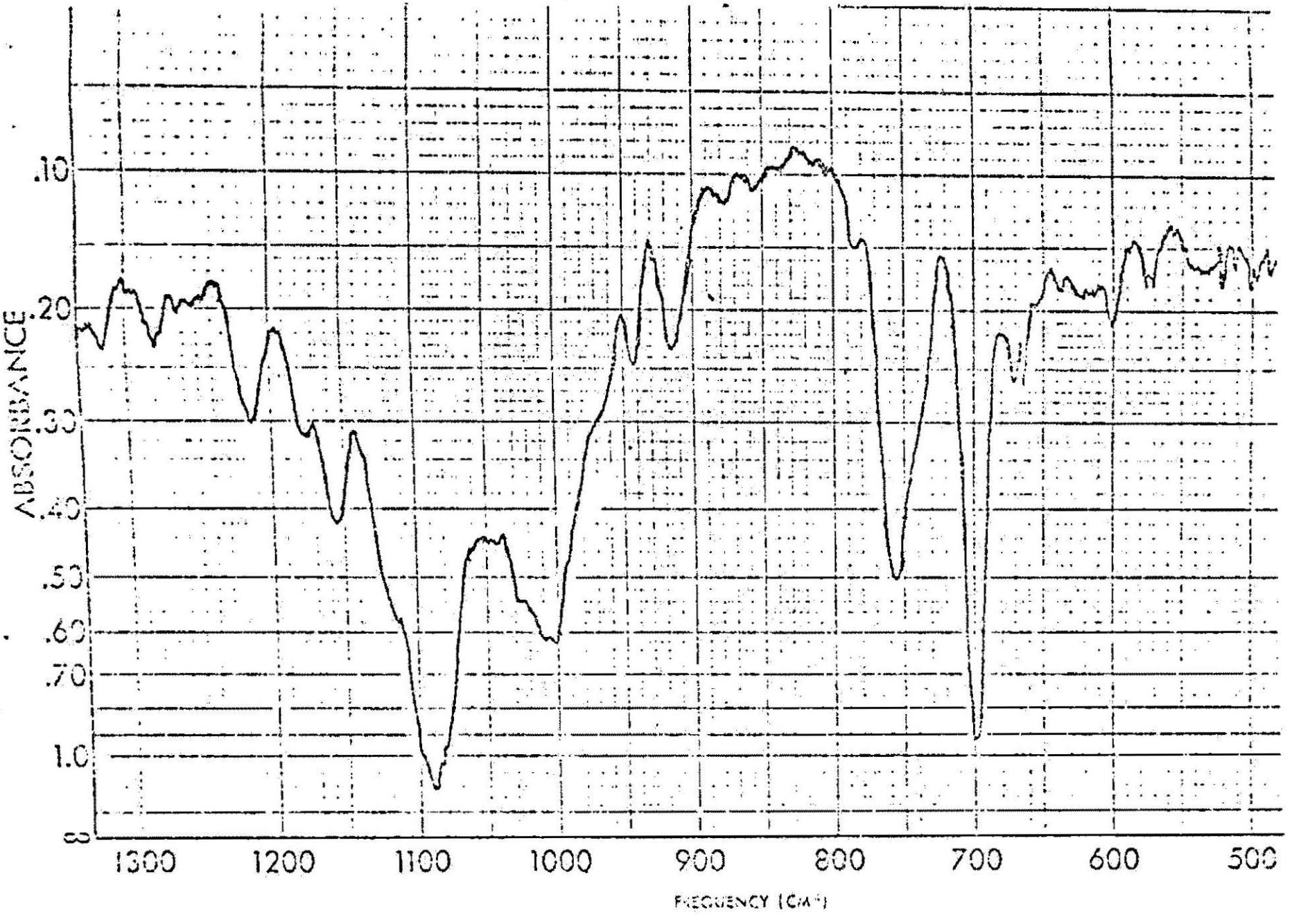
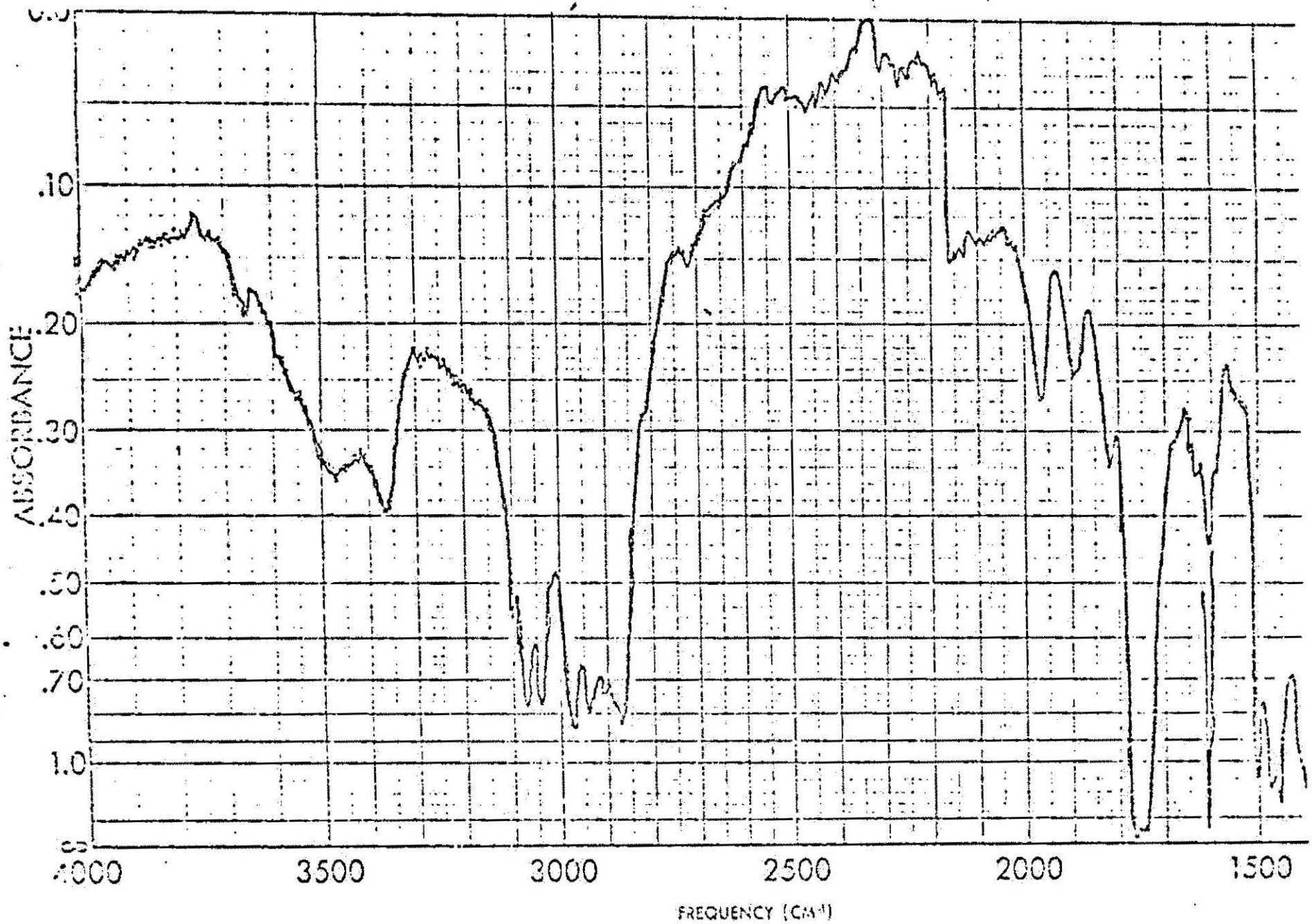


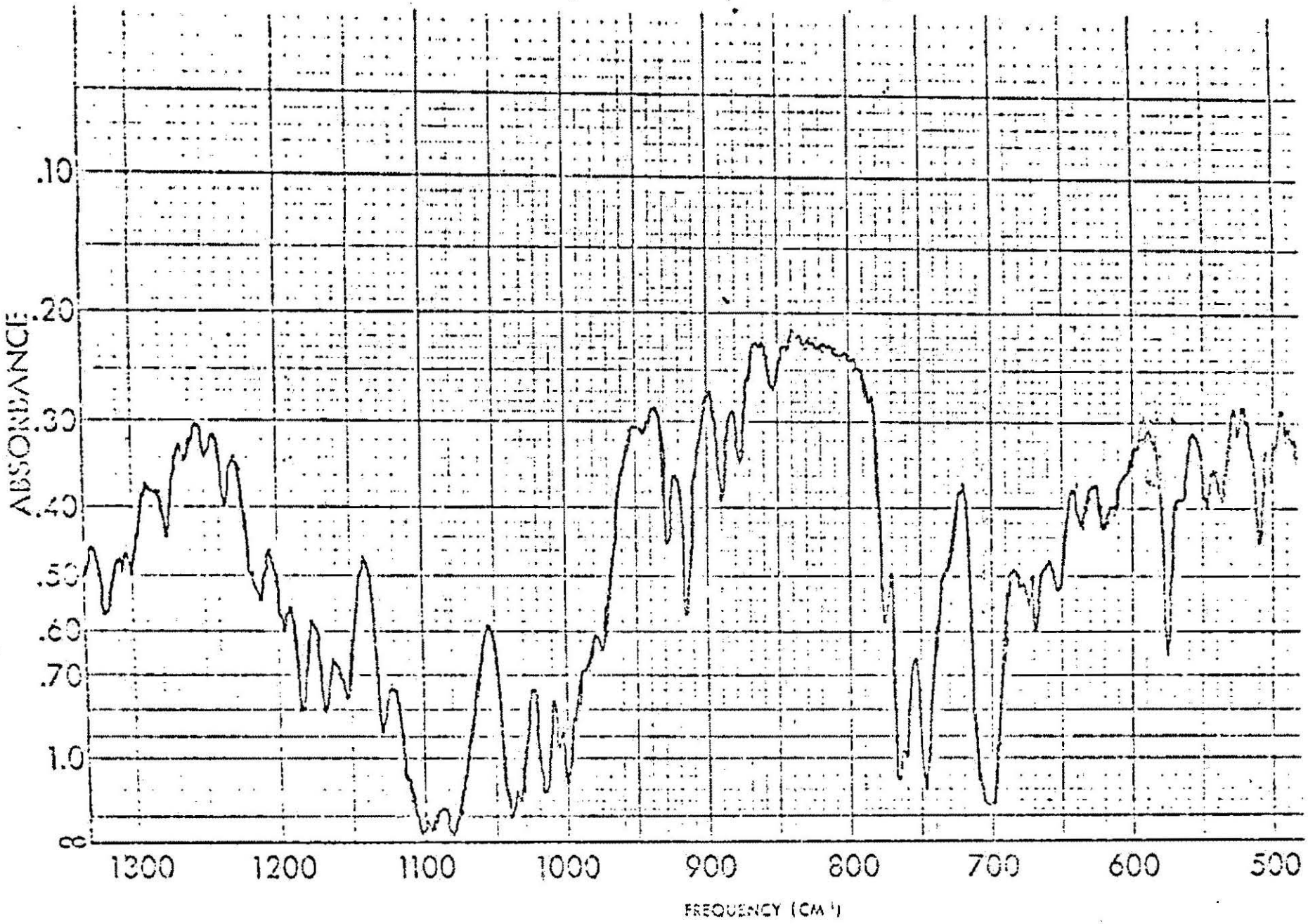
Benzyl 4,6-O-benzylidene-2-[(1,1 diphenyl-2-hydroxyethyl)amino]-2-deoxy-β-D-allopyranoside (9).



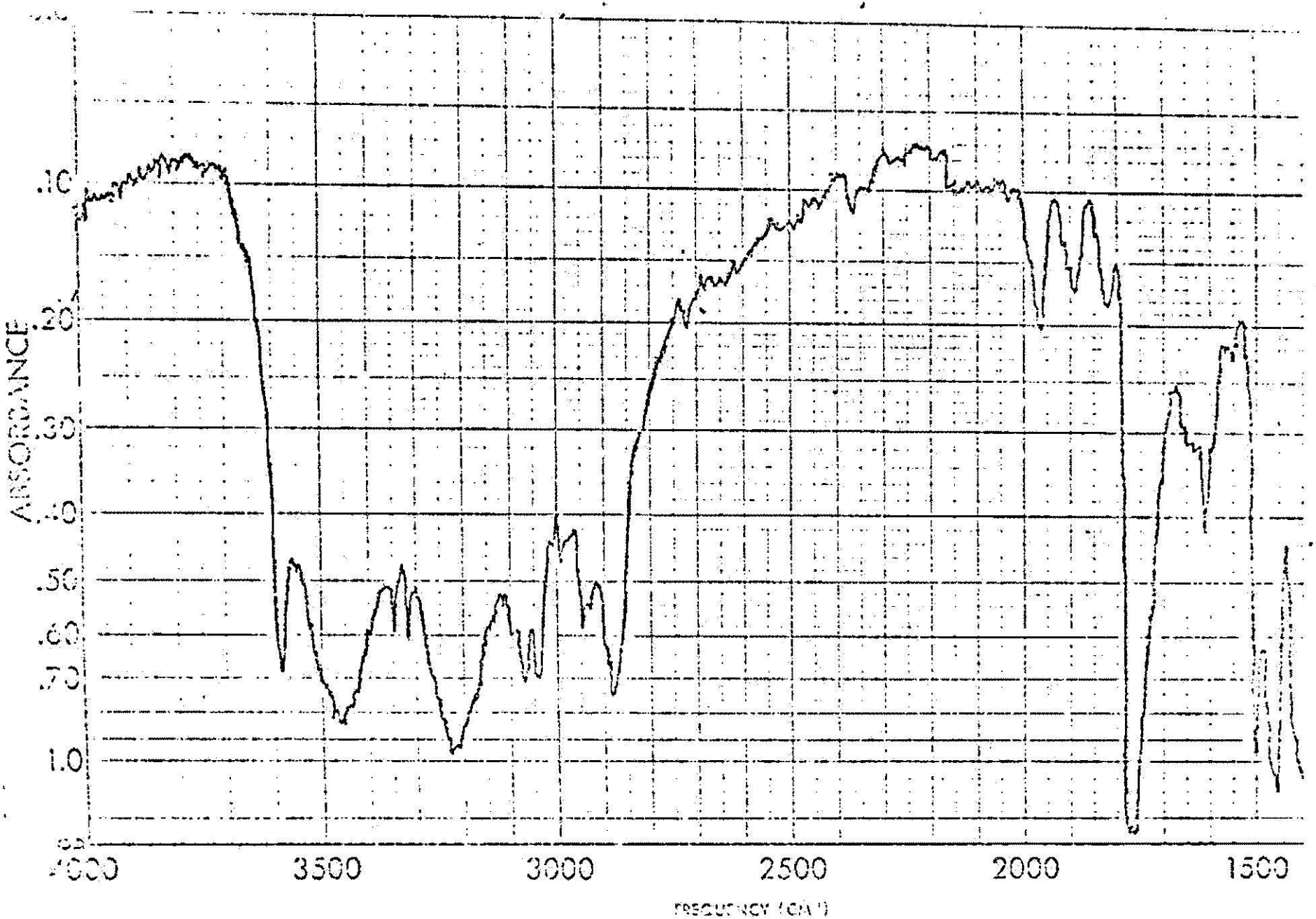
Benzyl 4,6-O-benzylidene-2-[(1,1 diphenyl-2-hydroxyethyl)amino]-3-deoxy-β-D-allopyranoside (9).



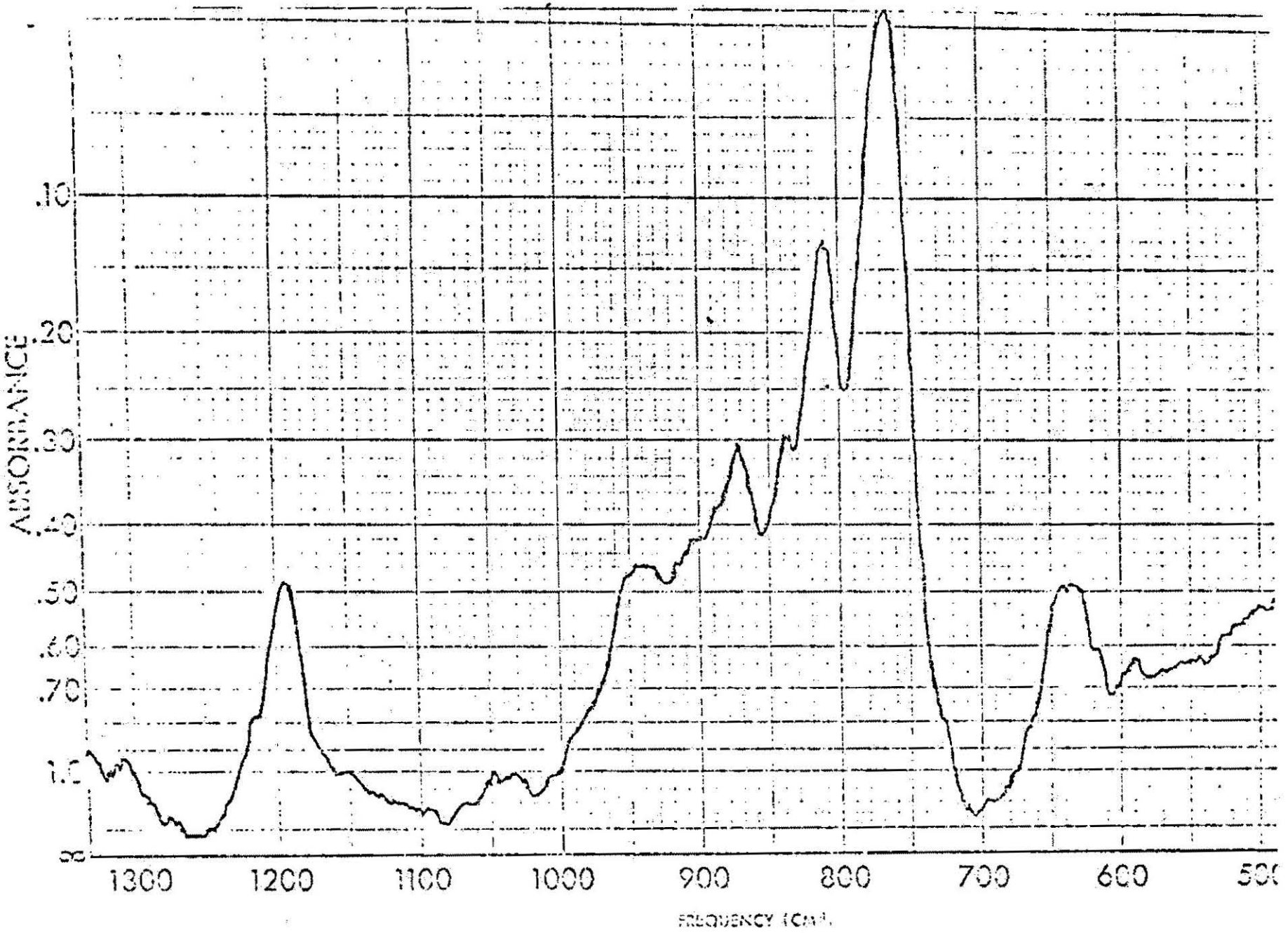
Benzyl 4,6-O-benzylidene-3-O-acetyl-2[(1,1-Diphenyl-2-acetoxyethyl)amino]-2-deoxy-β-D-allopyranoside (10).



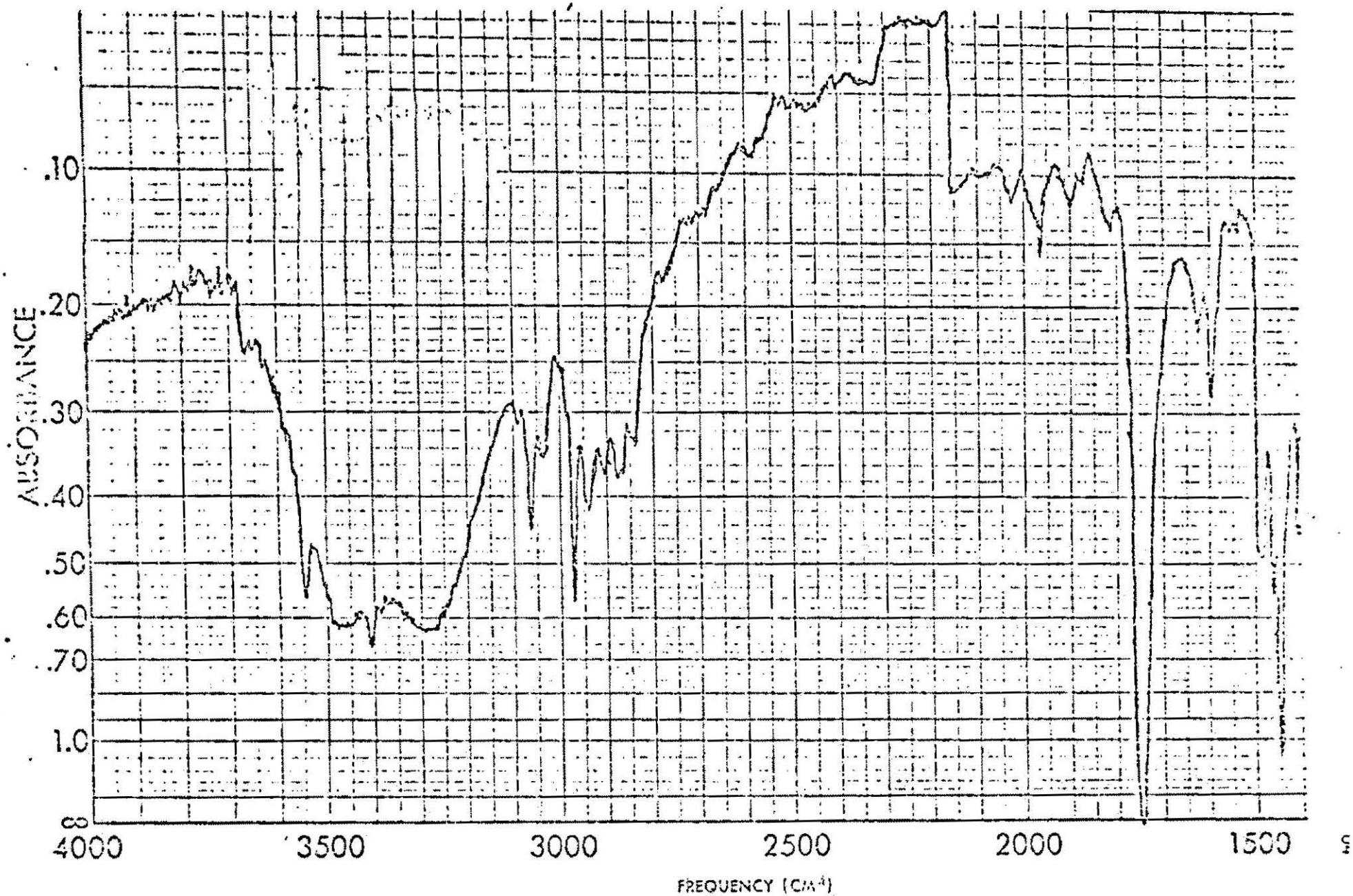
Benzyl 4,6-O-benzylidene-3-O-acetyl-2[(1,1-diphenyl-2-acetoxyethyl)amino]-2-deoxy-β-D-allopyranoside (10).



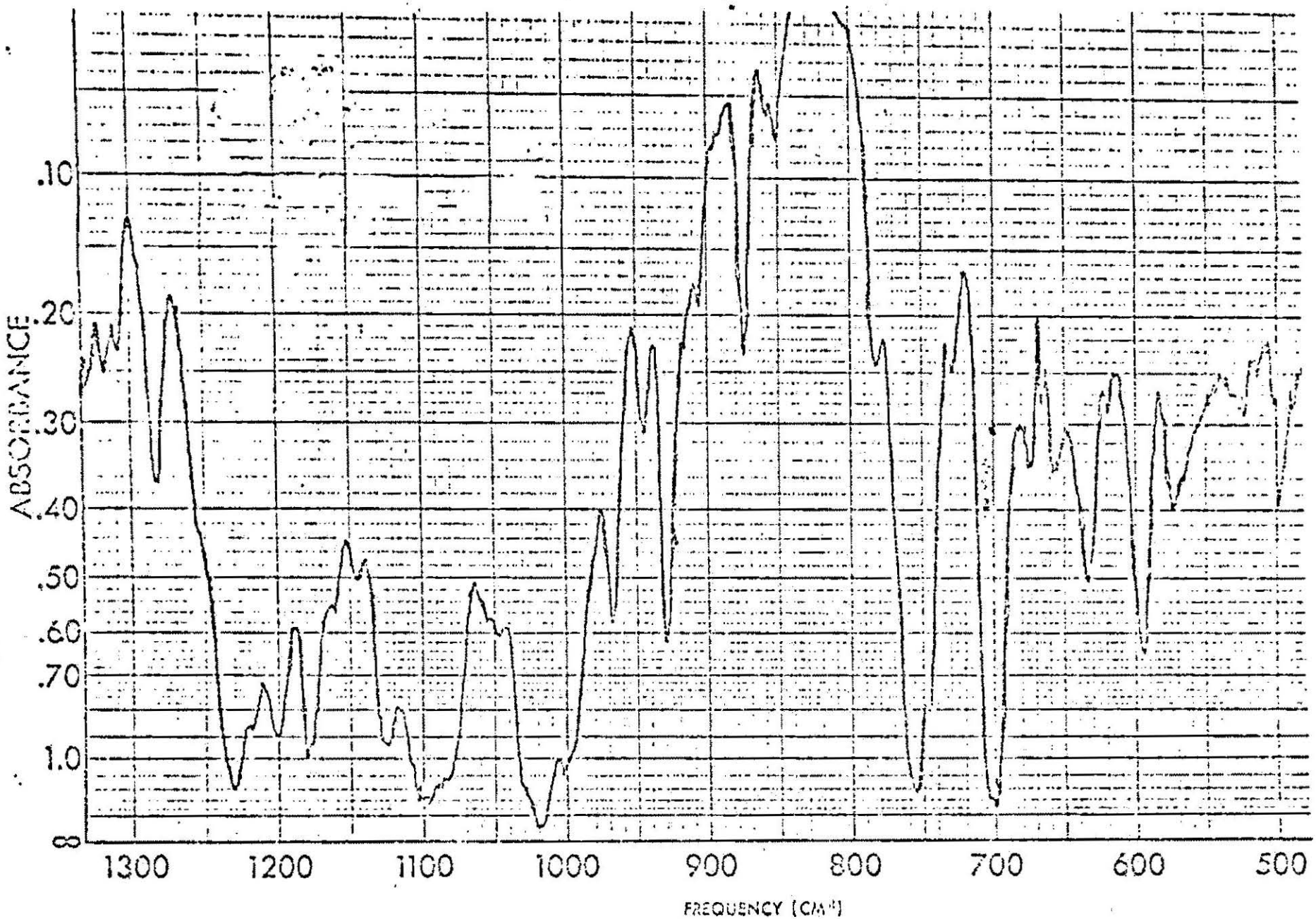
Benzyl 4,6-O-benzylidene-2-[(carboxyliphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11).



Benzyl 4,6-O-benzylidene-2-[(carboxydiphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11).



4,6-O-Benzylidene-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (14).



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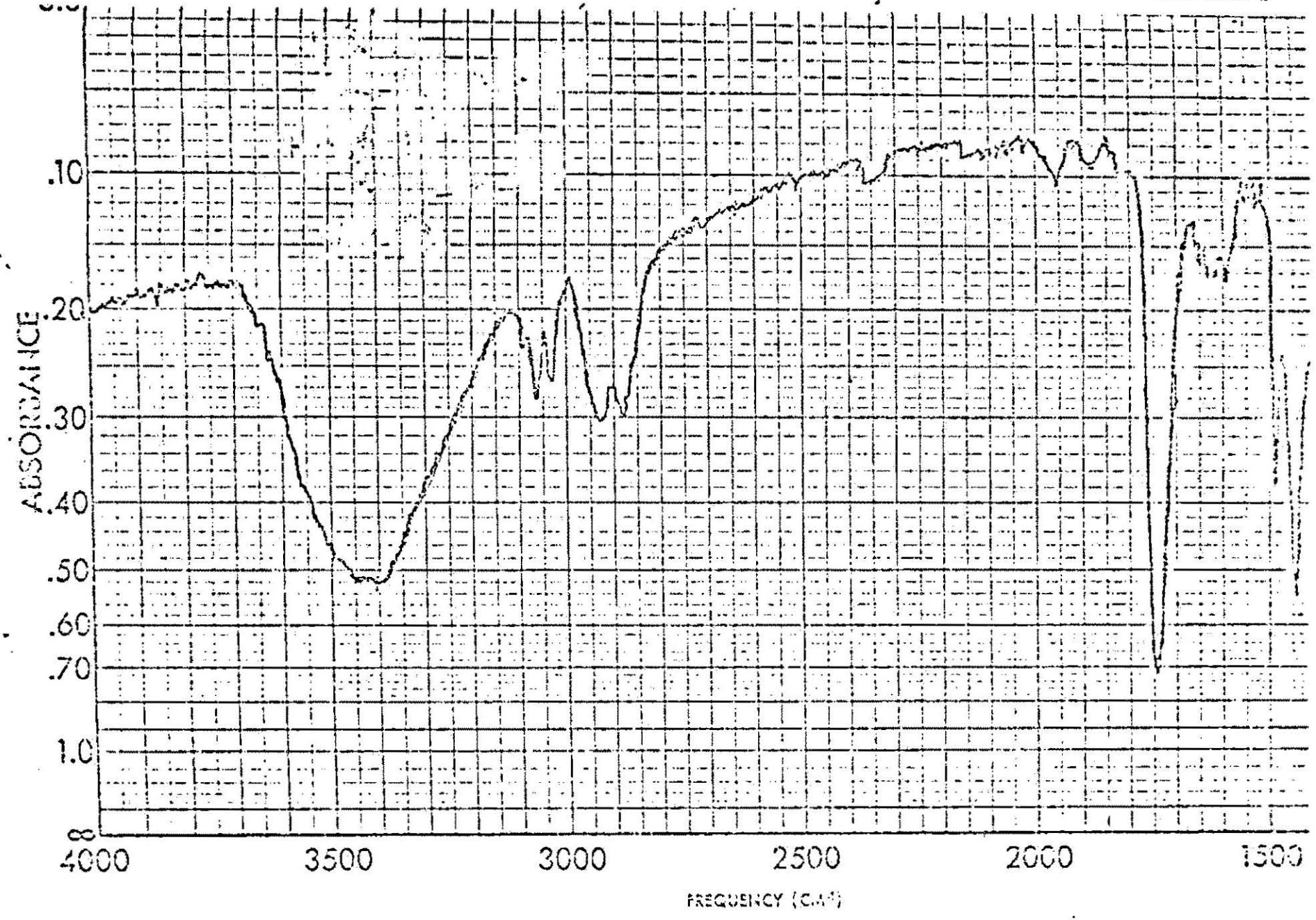

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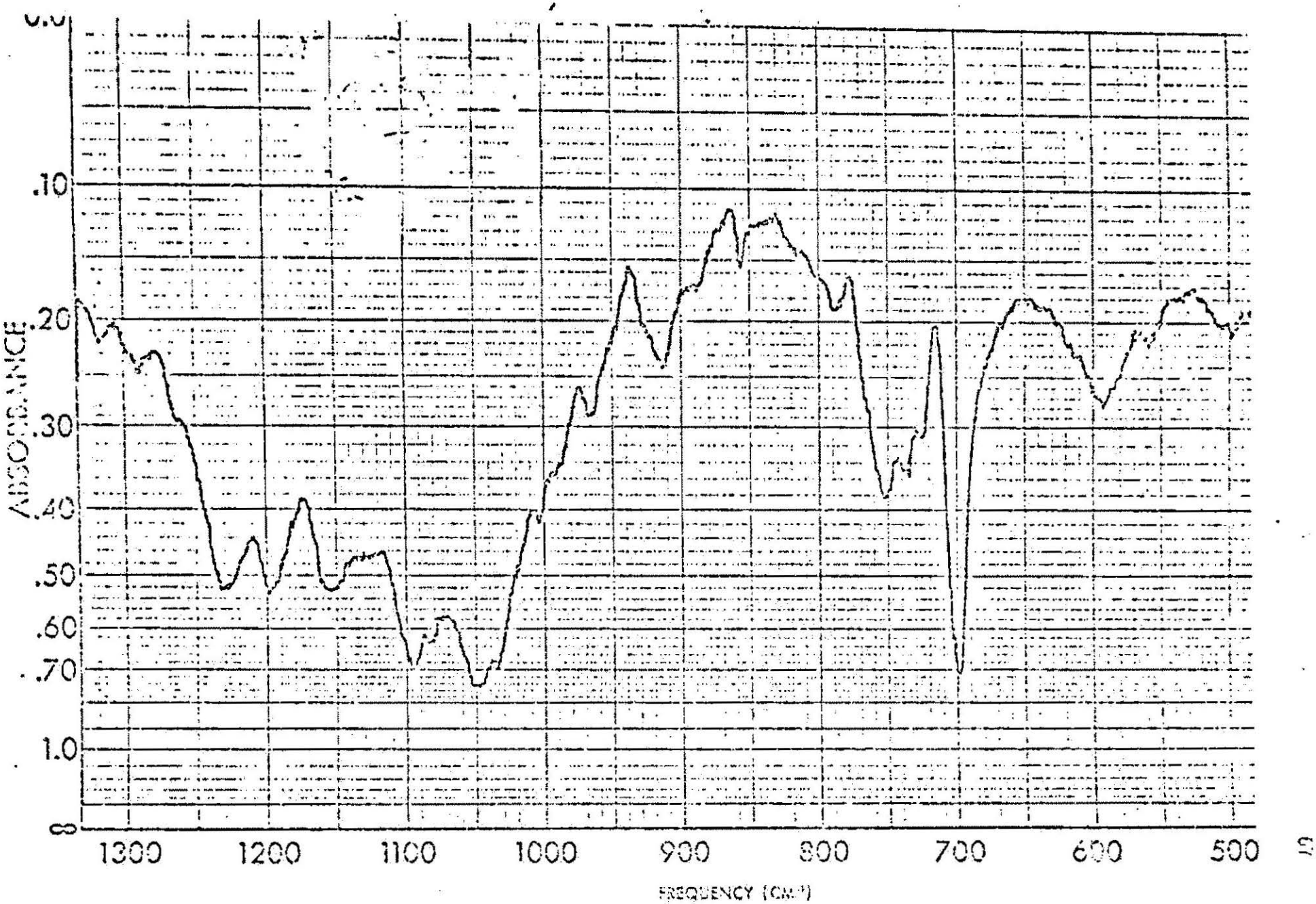

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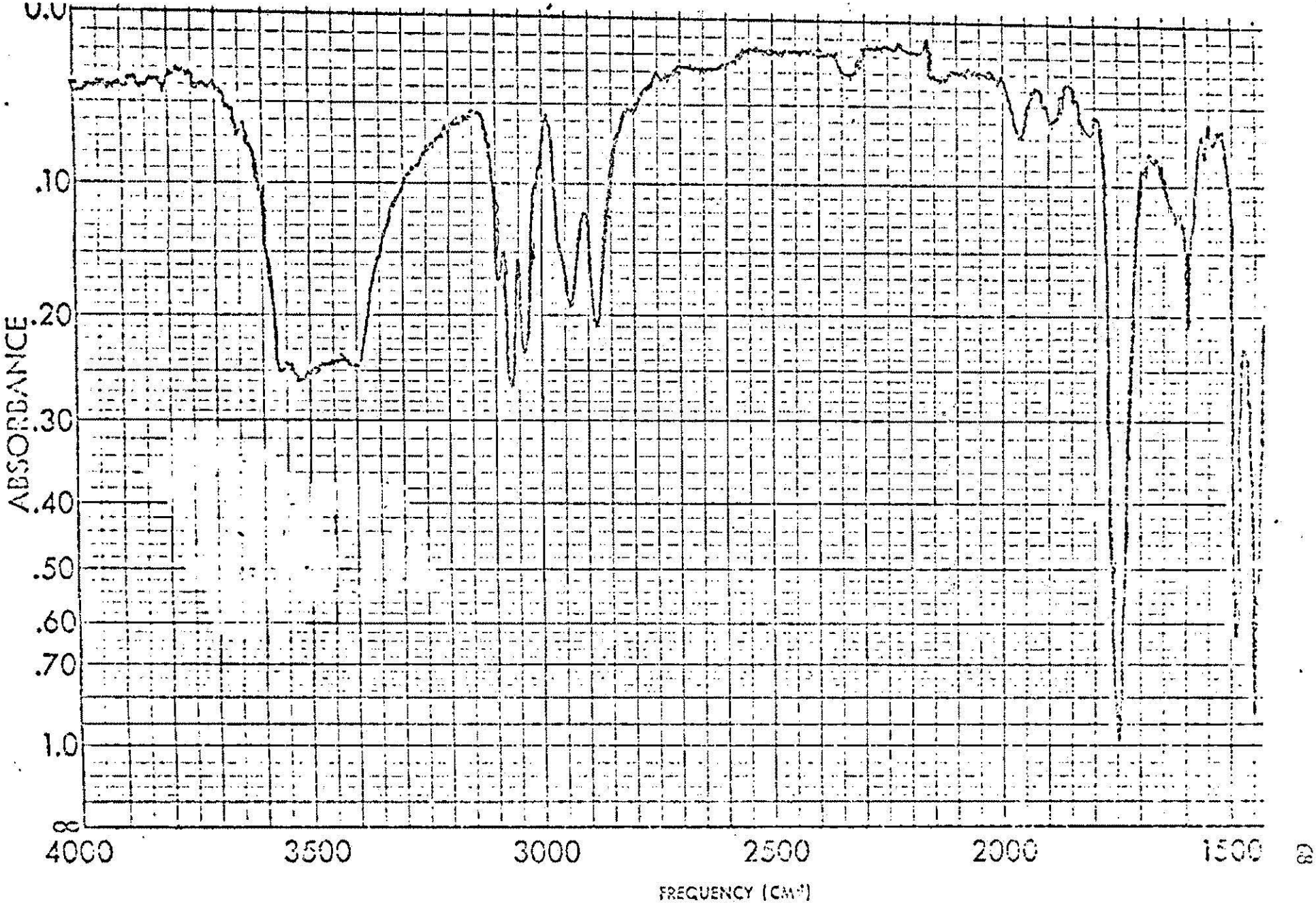
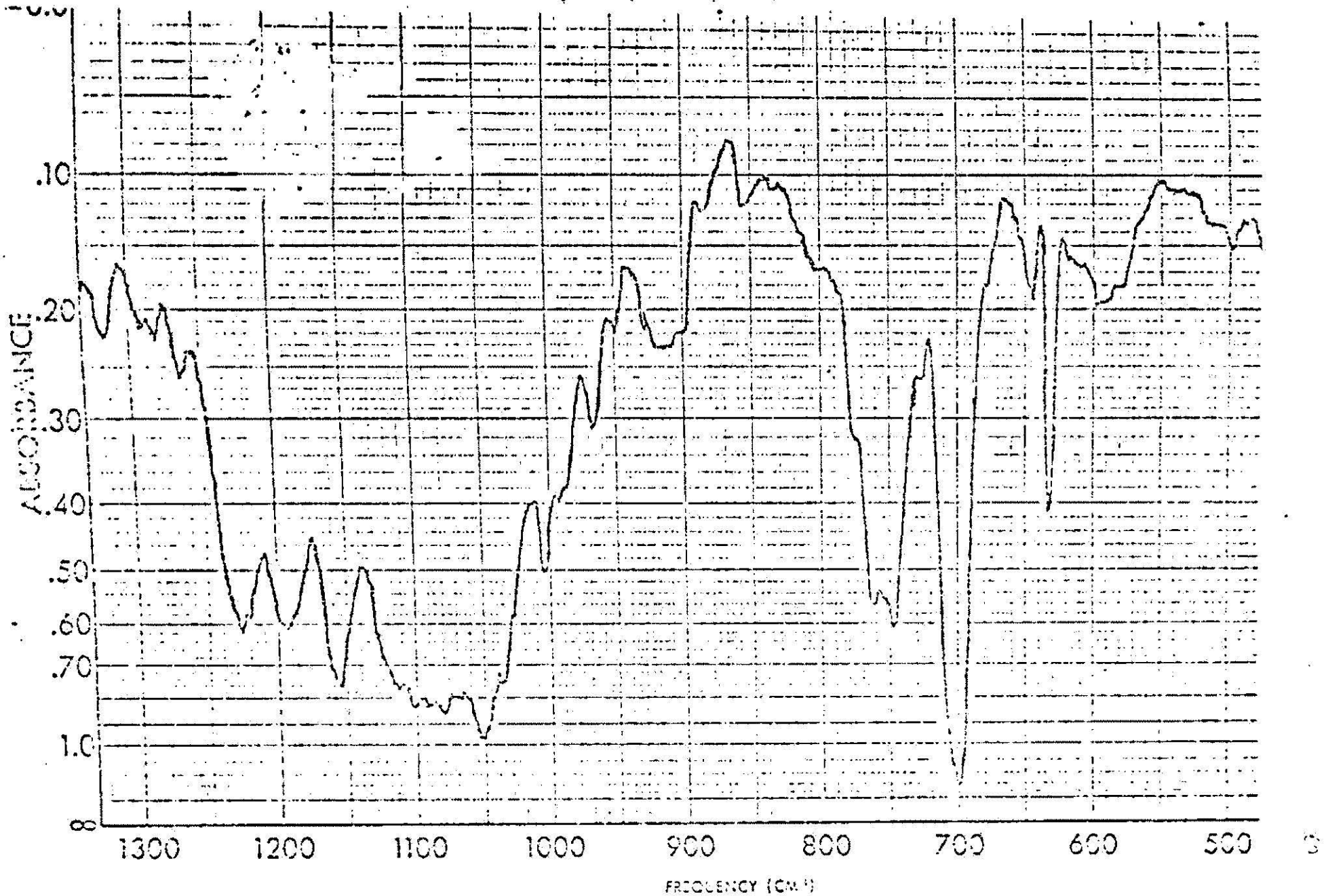


Benzyl-6-O-(triphenylmethyl)-β-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (16).



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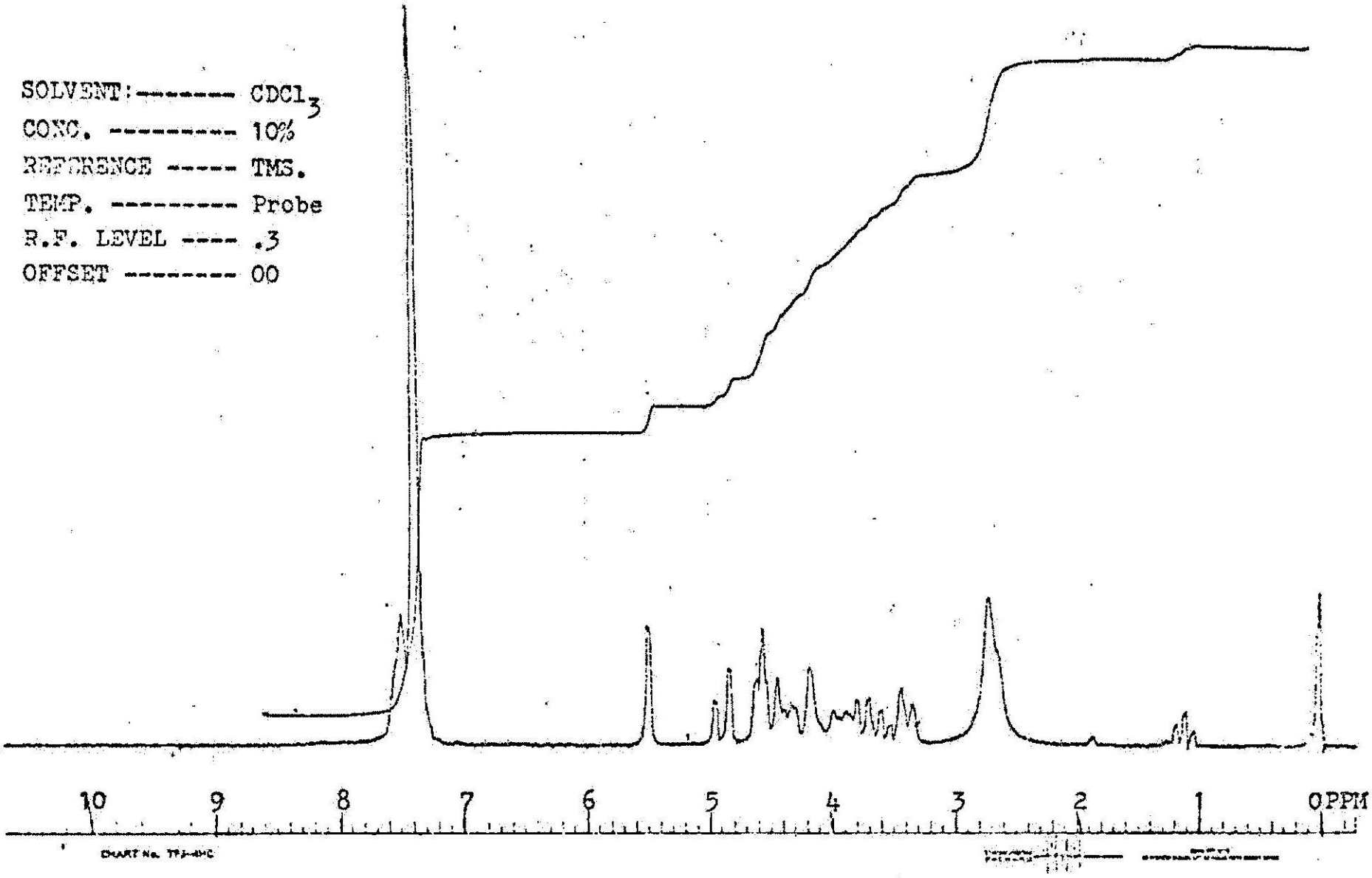
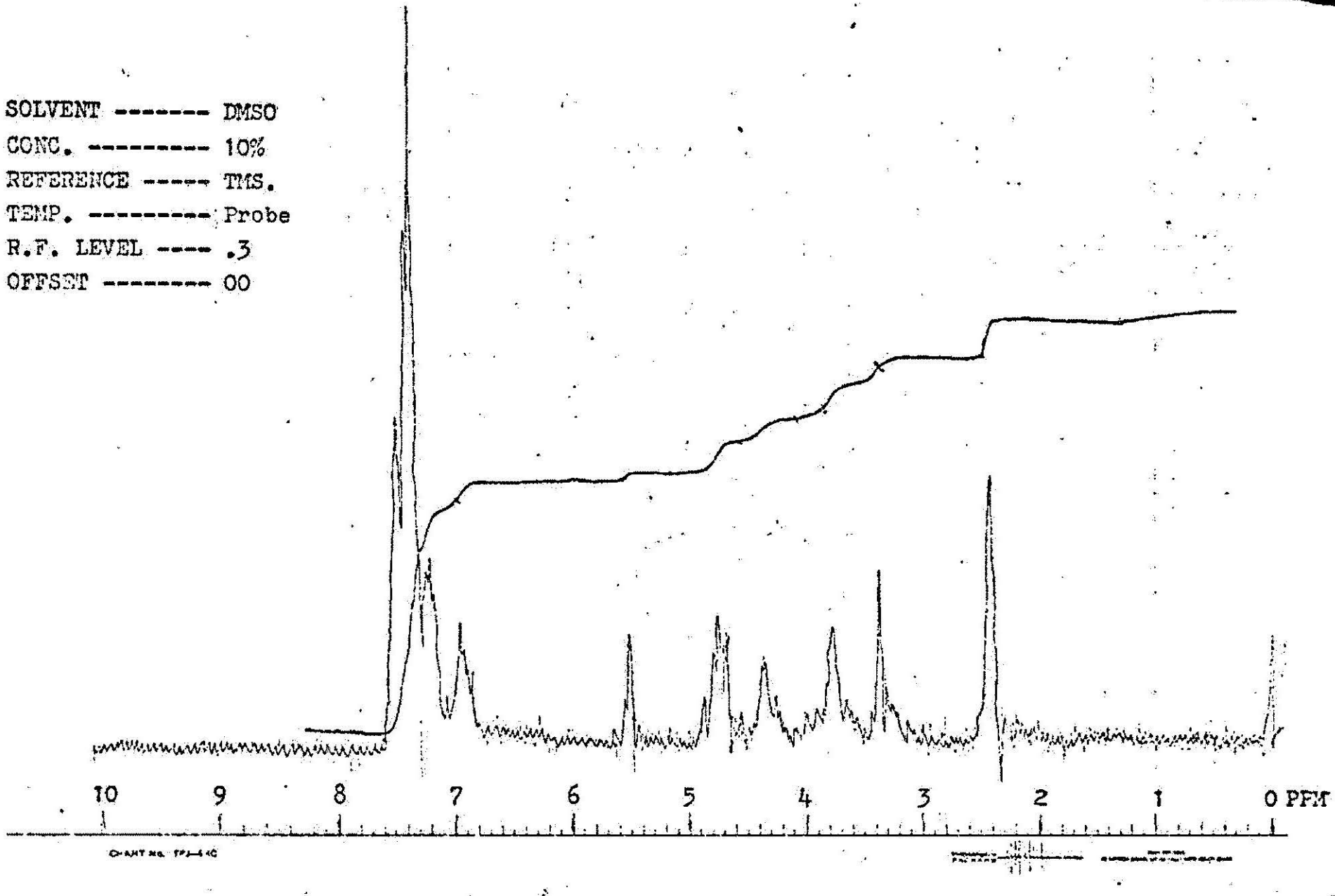


Benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (1).



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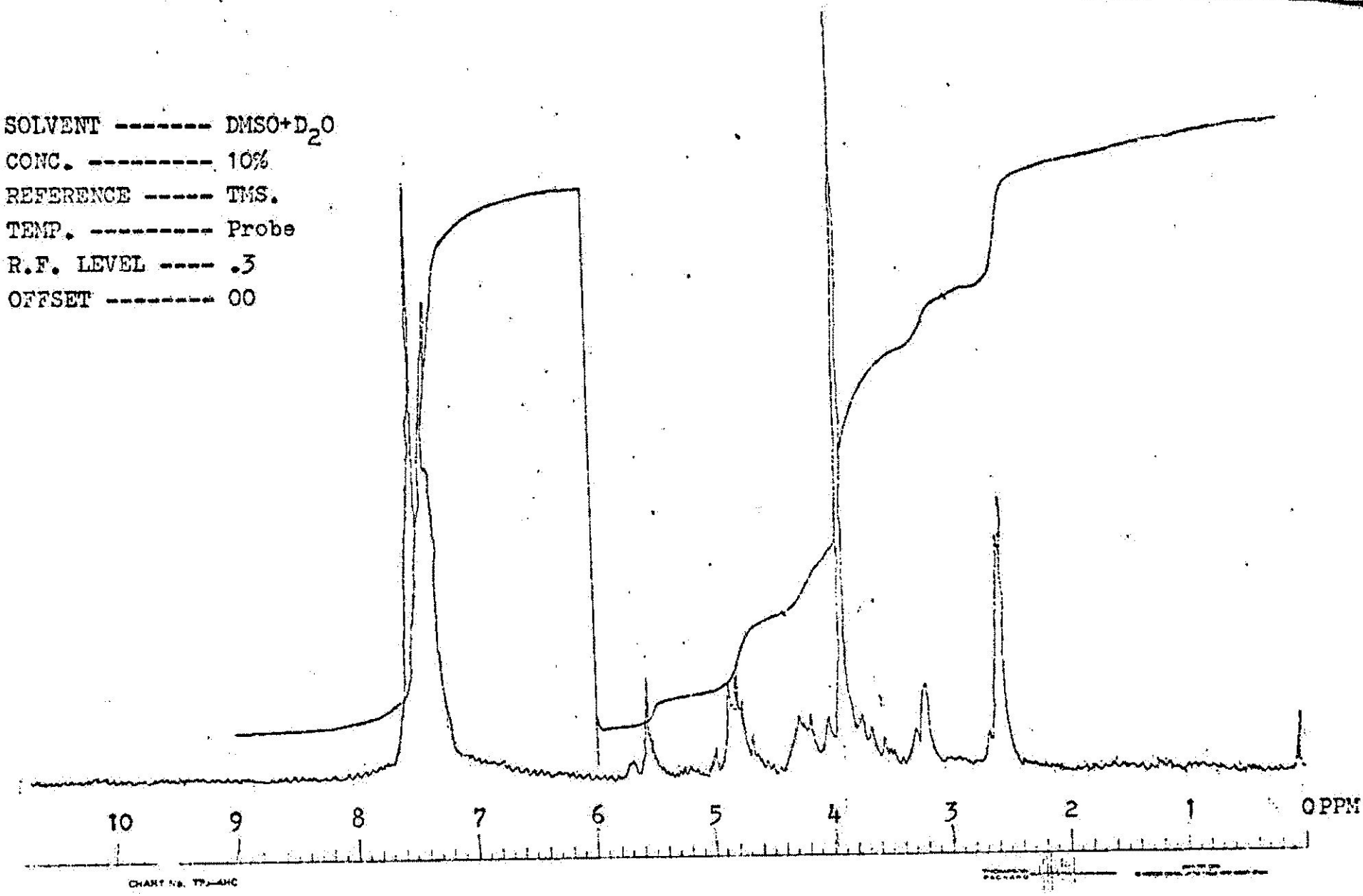
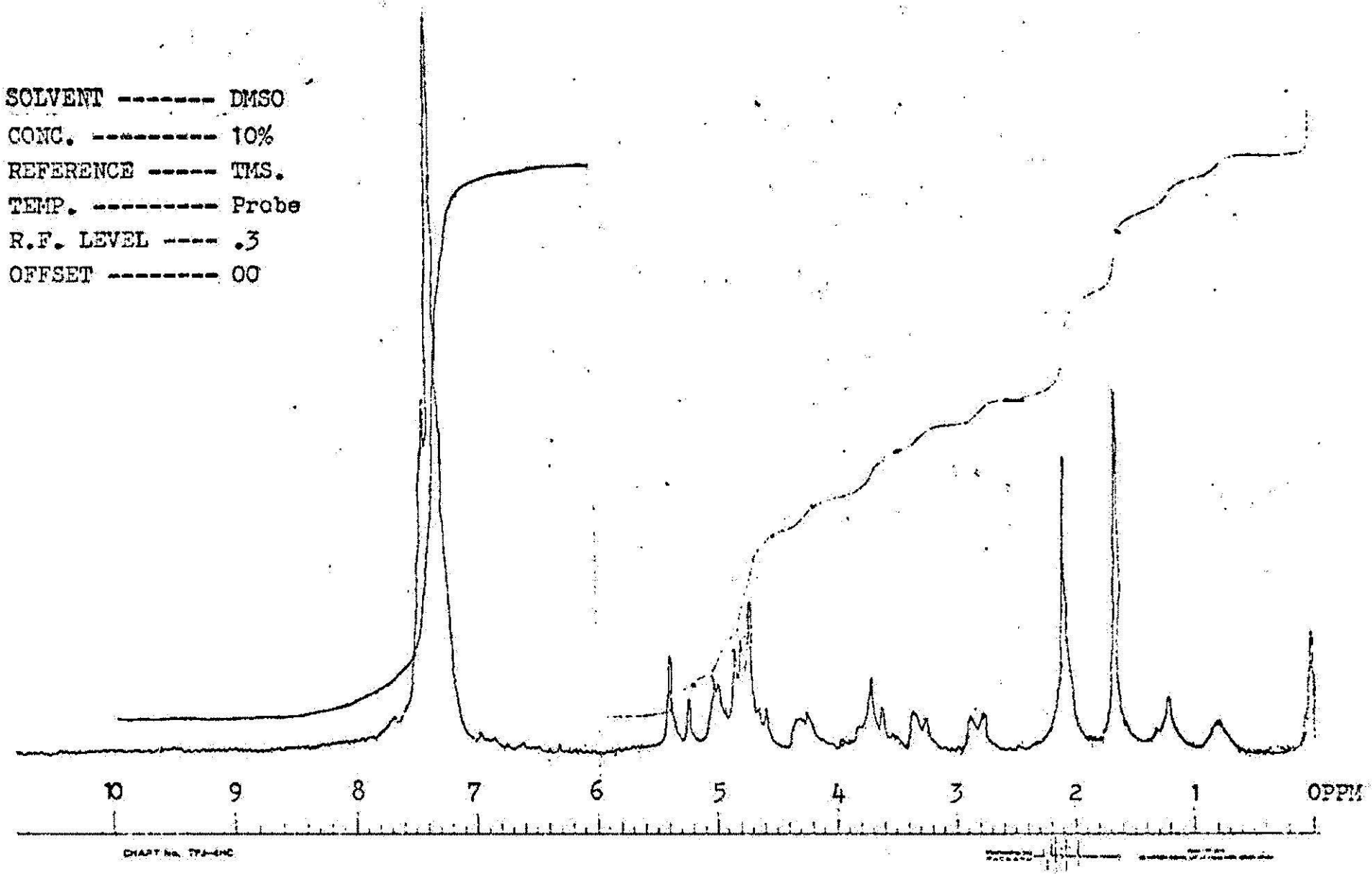
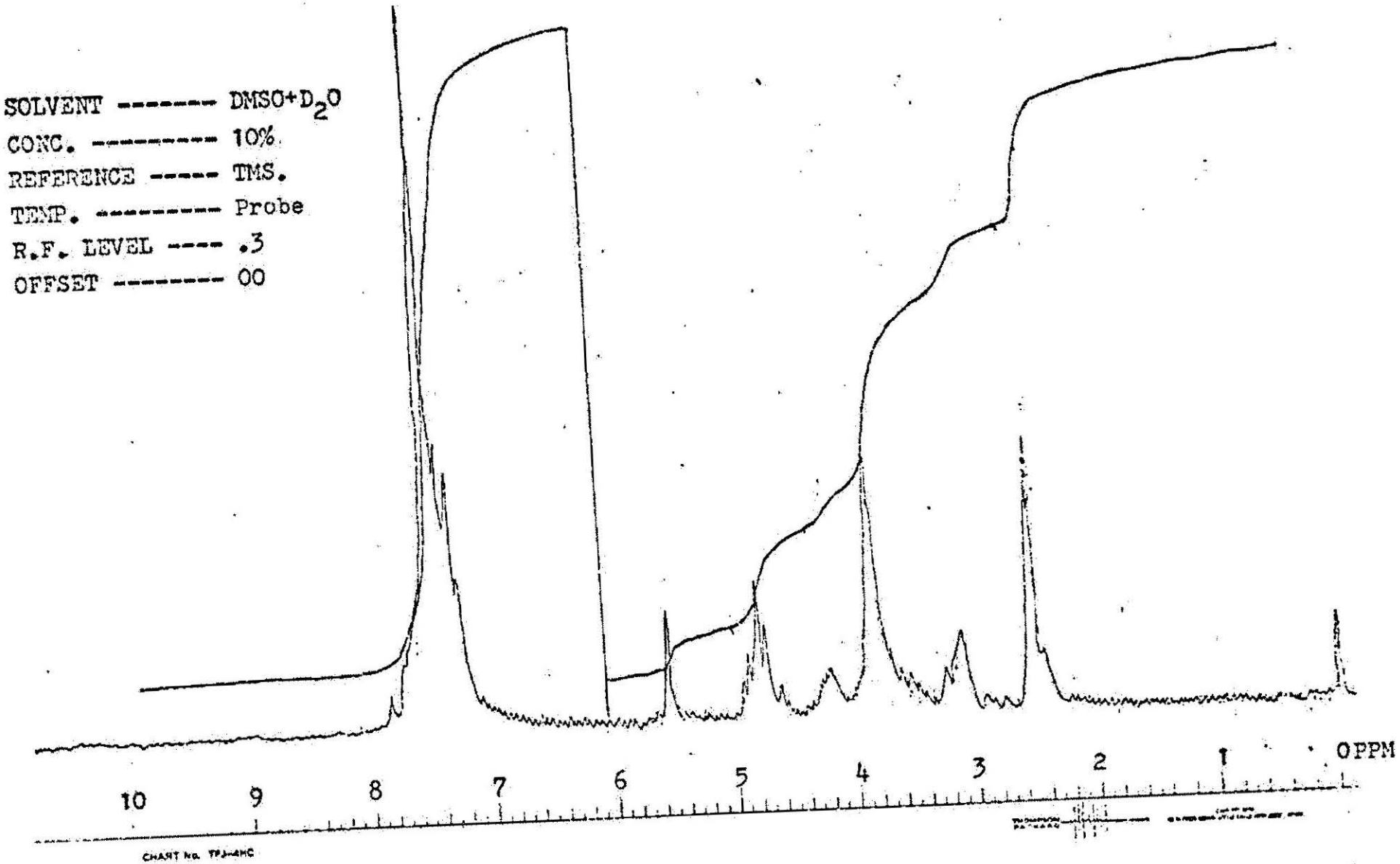


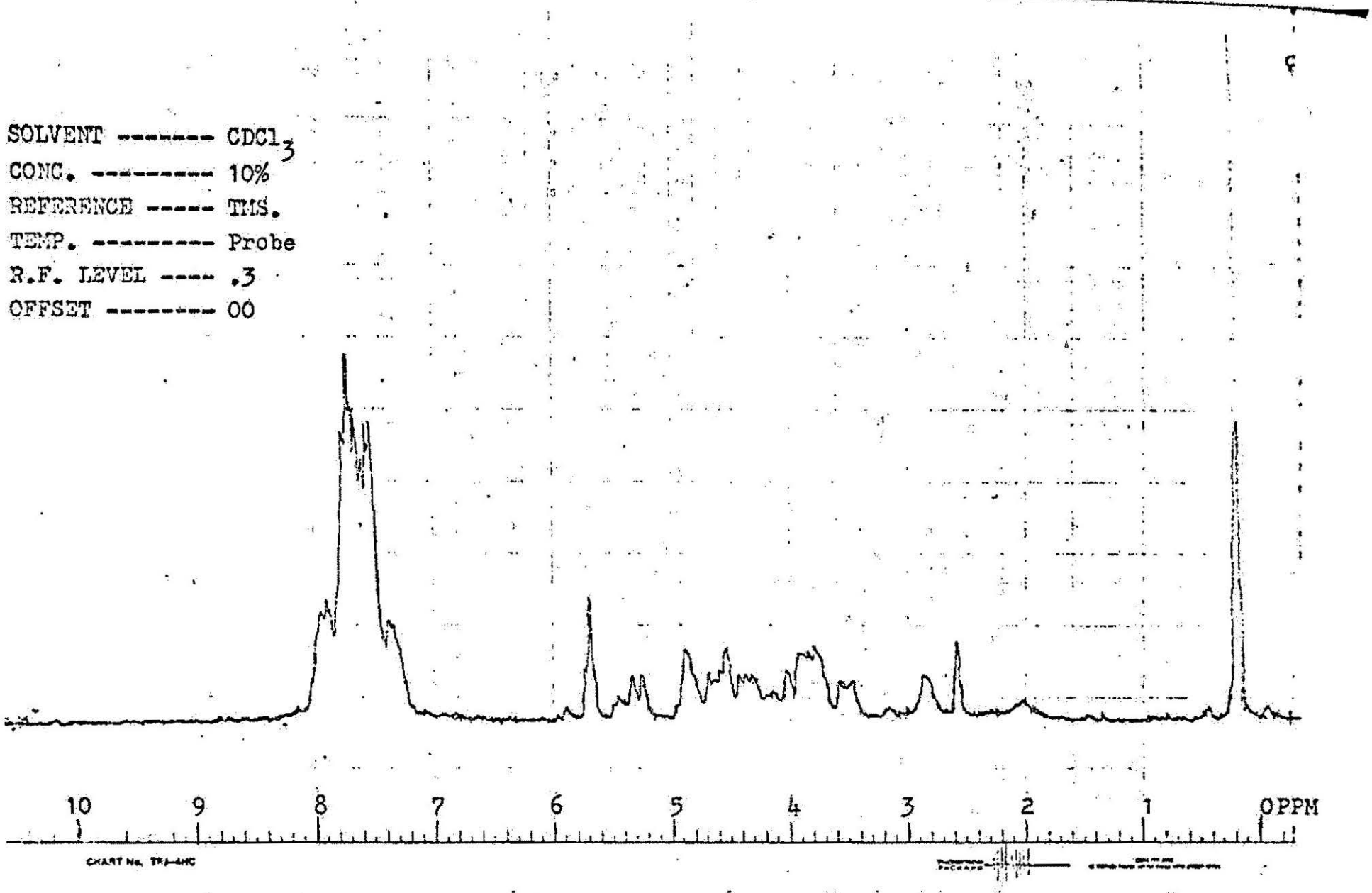
Benzyl 4,6-O-benzylidene-2-[(1,1 diphenyl-2-hydroxyethyl)amino]-2-deoxy-β-D-allopyranoside (9).



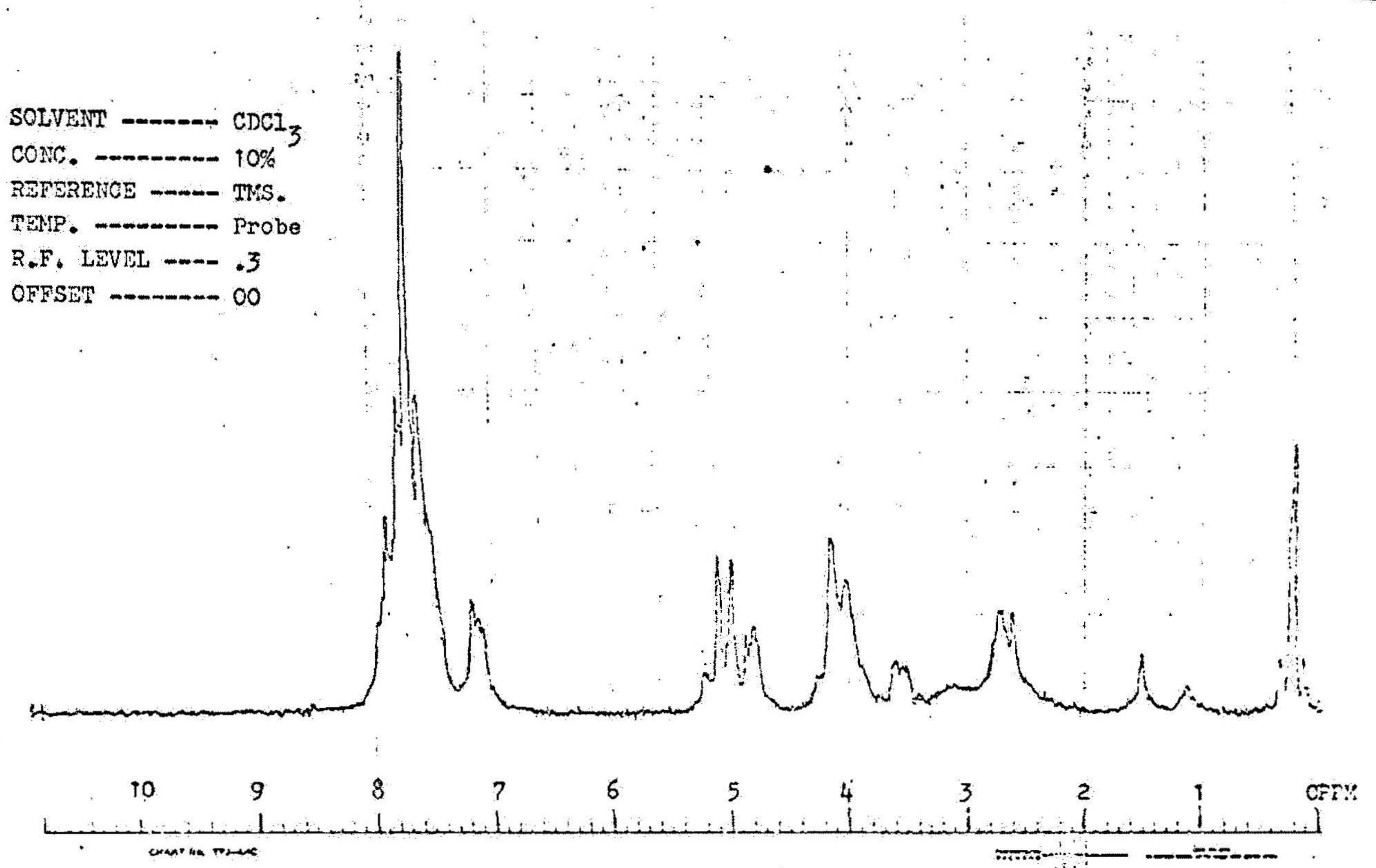
Benzyl 4,6-O-benzylidene-3-O-acetyl-2[(1,1-diphenyl-2-acetoxyethyl)amino]-2-deoxy-β-D-allopyranoside (10).



Benzyl 4,6-O-benzylidene-2-[(carboxydiphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11).

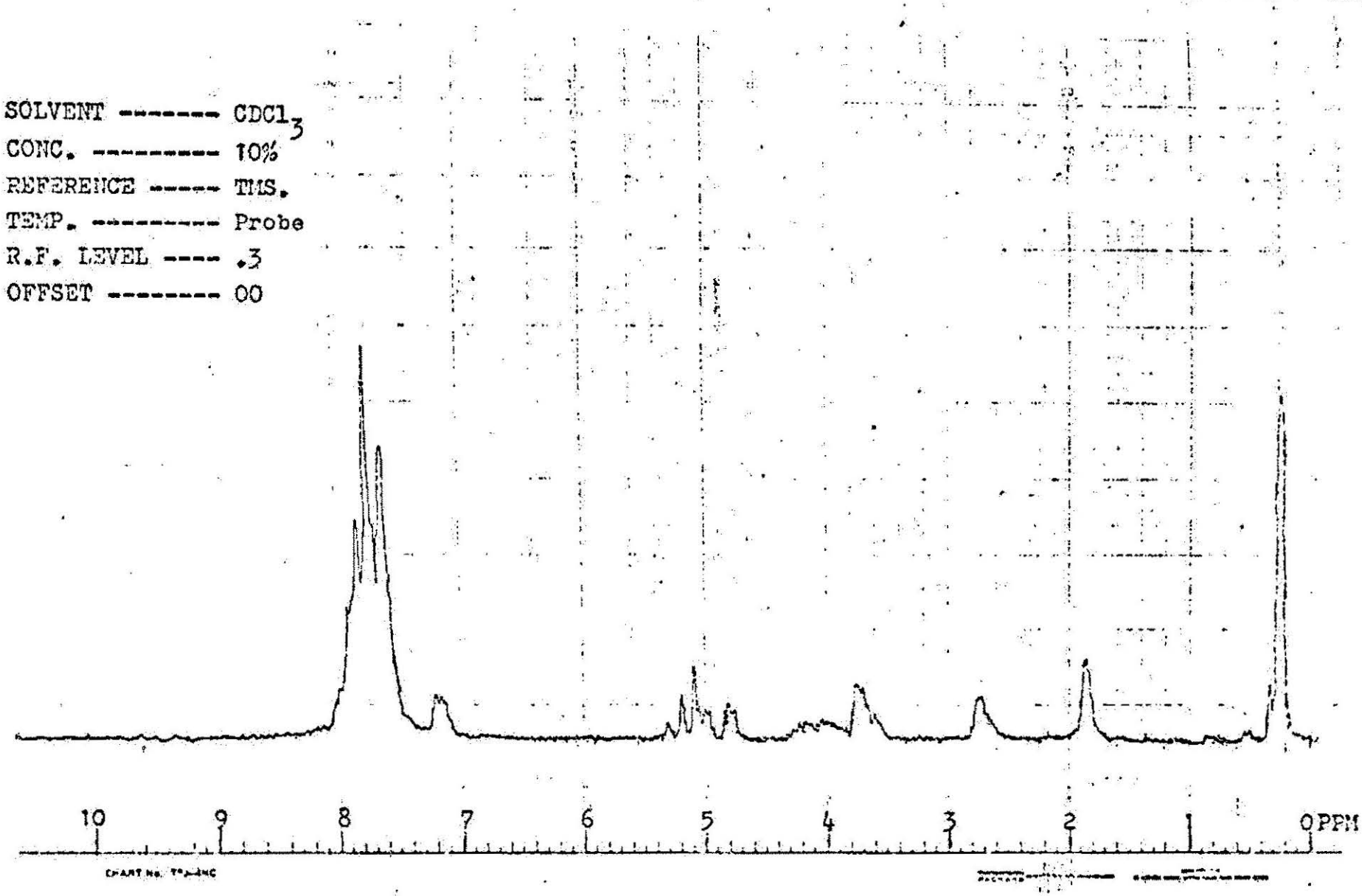


4,6-O-Benzylidene-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (14).



[illegible] β -D-[illegible][2,3:5',6']-3',3'-[illegible]-2'-[illegible] (25).

SOLVENT ------- $CDCl_3$
CONC. --------- 10%
REFERENCE ----- TMS.
TEMP. --------- Probe
R.F. LEVEL ---- .3
OFFSET -------- 00



2-O-acetyl-6-O-(triphenylmethyl)-α-D-allofuranosido[2,3:5',6']-3',3'-dimethyl-2'-oxepanone (1%).

SOLVENT ---------- $CDCl_3$

CONC. ---------- 15%

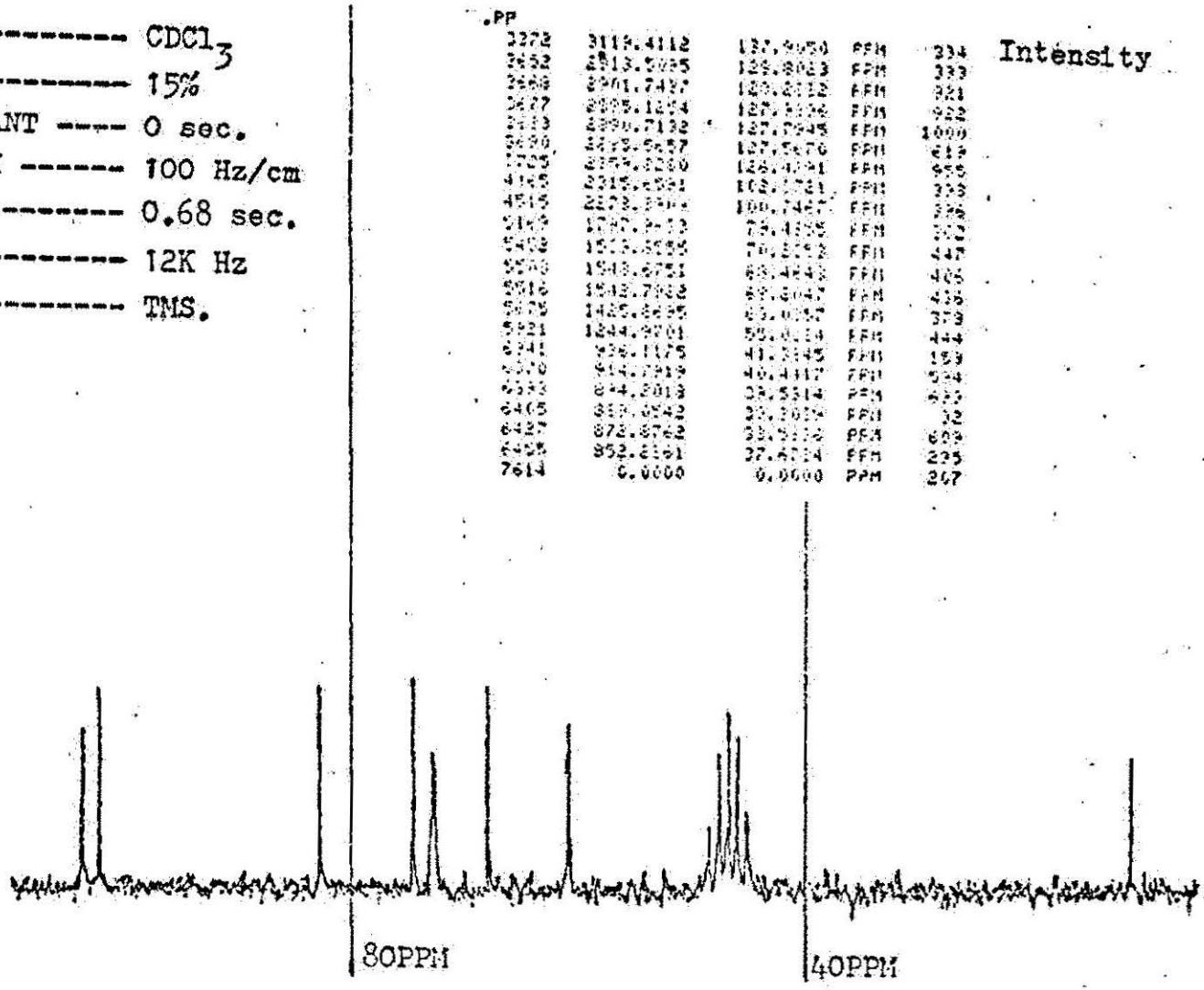
TIME CONSTANT ---- 0 sec.

SWEEP WIDTH ------ 100 Hz/cm

SWEEP TIME ------- 0.68 sec.

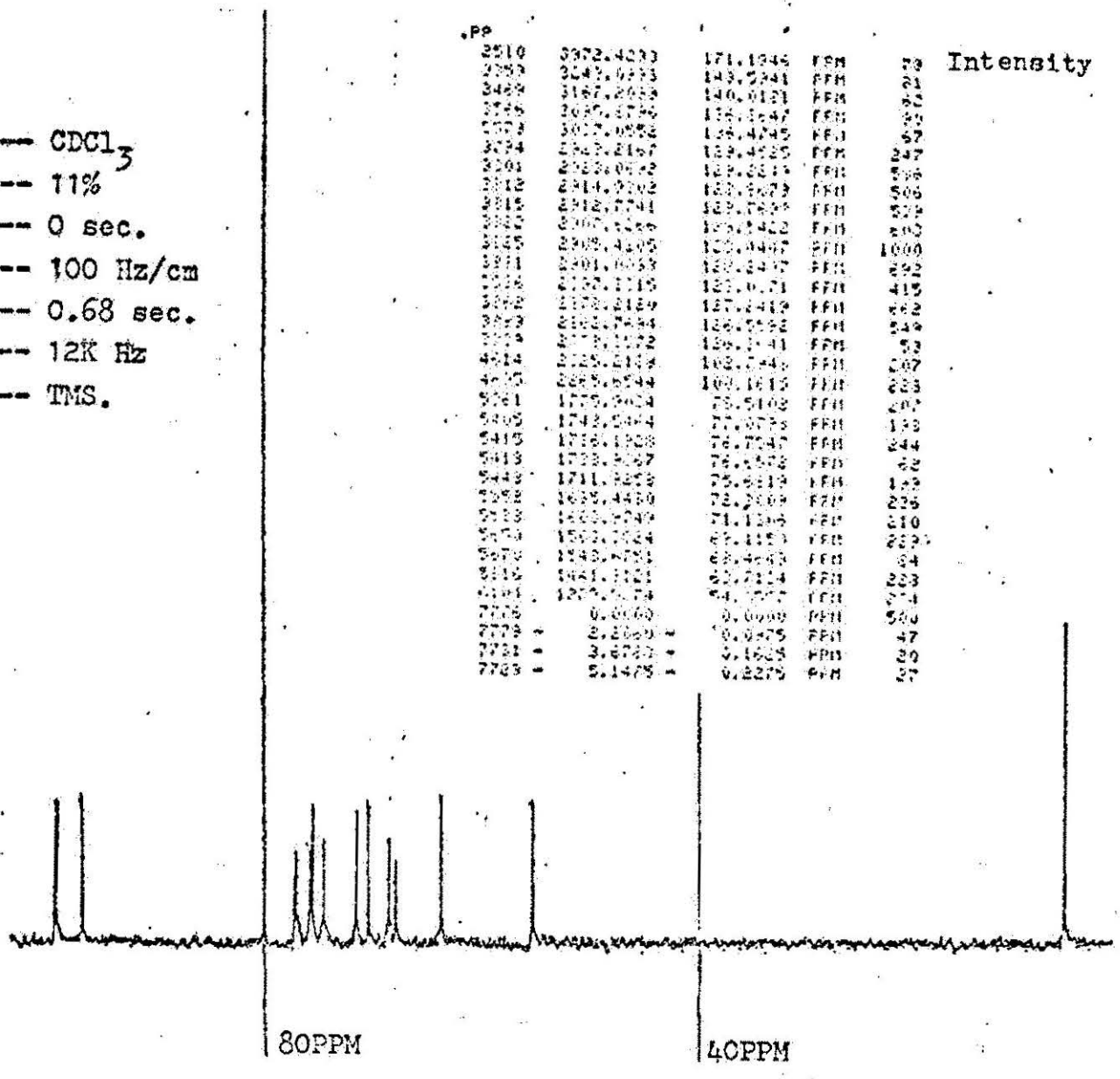
OFFSET ----------- 12K Hz

REFERENCE -------- TMS.



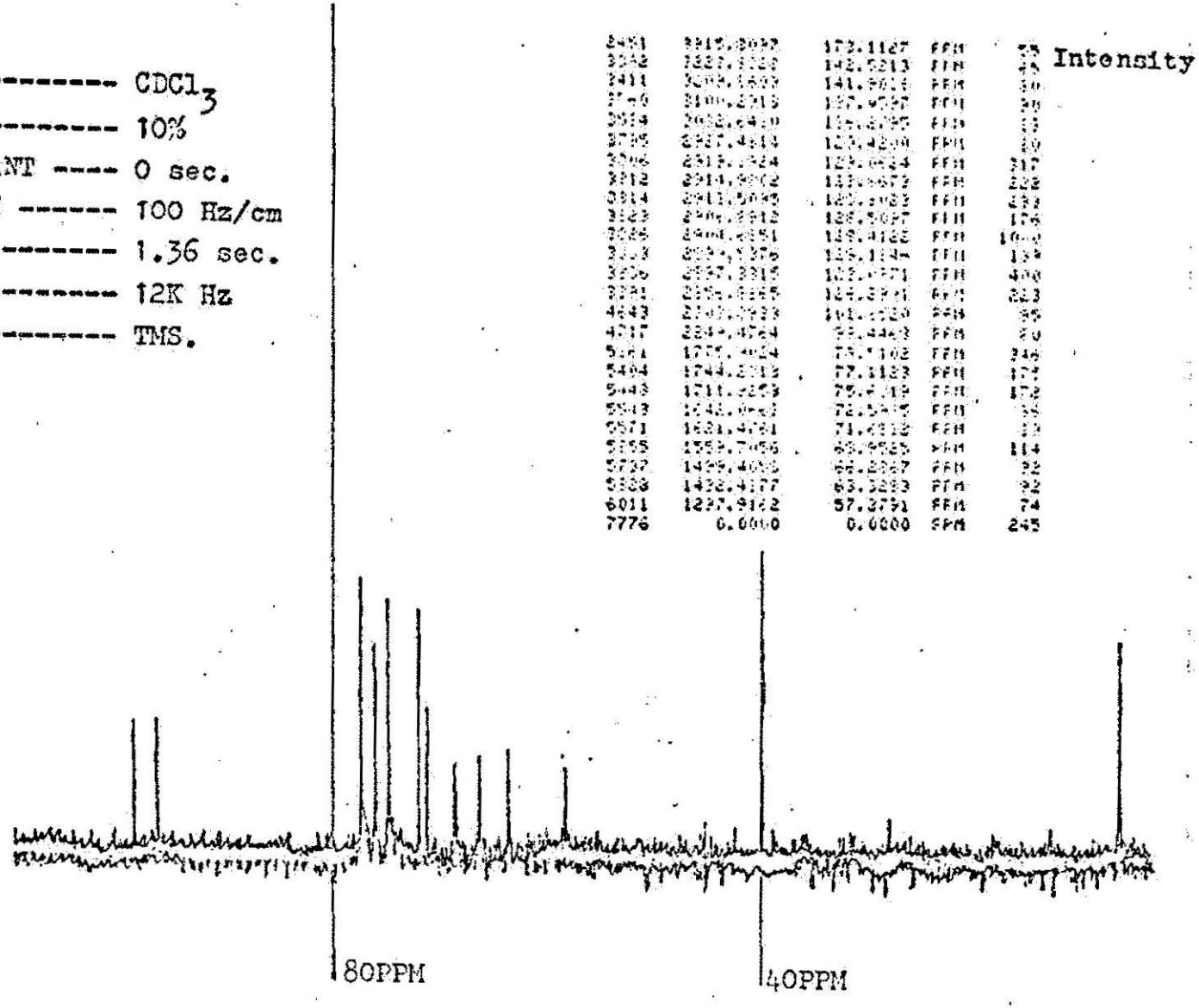
Benzyl 2-amino-4,6-O-benzylidene-2-deoxy-β-D-allopyranoside (1).

SOLVENT ---------- $CDCl_3$
CONC. ---------- 11%
TIME CONSTANT ---- 0 sec.
SWEEP WIDTH ------ 100 Hz/cm
SWEEP TIME ------- 0.68 sec.
OFFSET ----------- 12K Hz
REFERENCE -------- TMS.



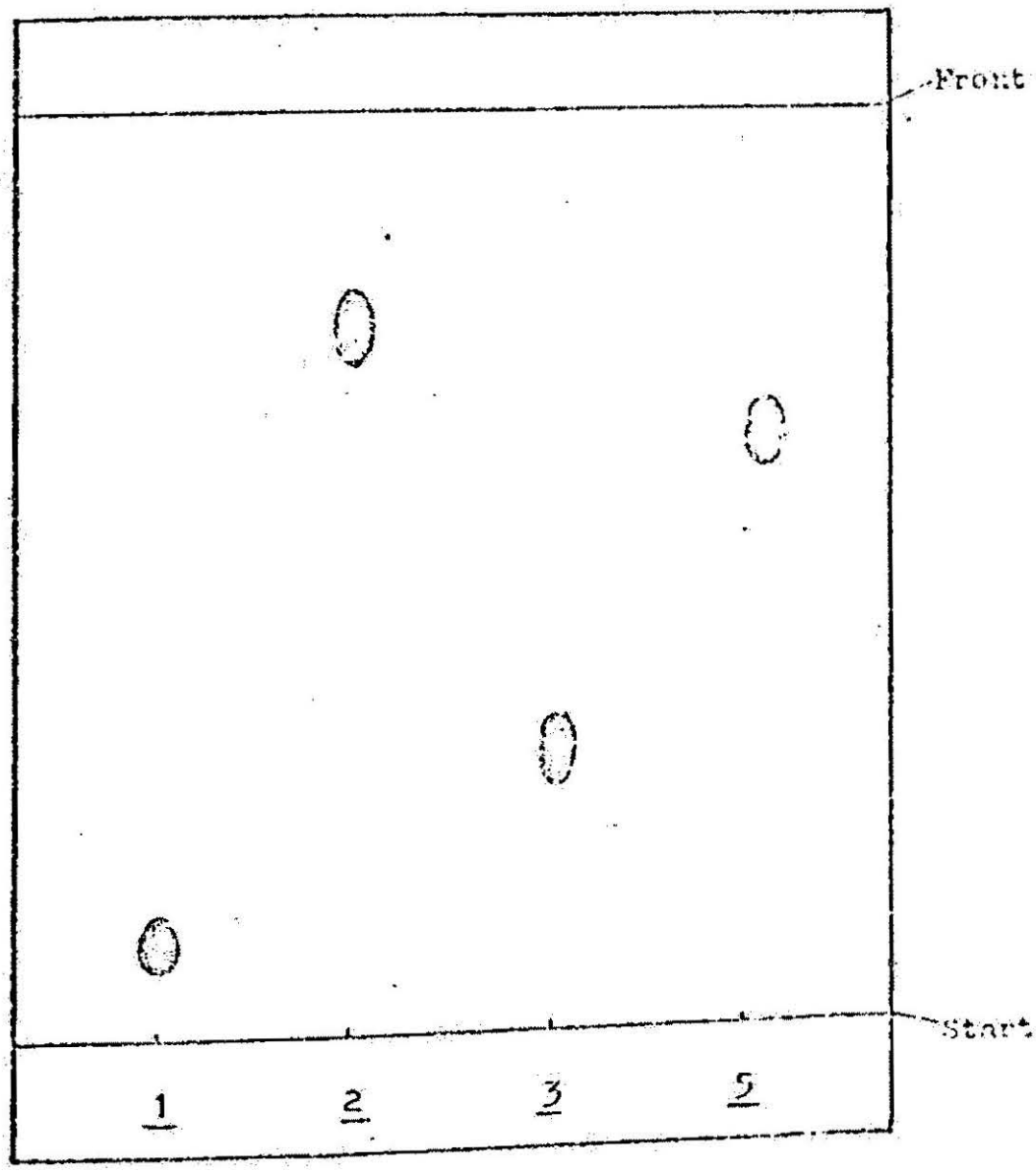
Benzyl 4,6-O-benzylidene-β-D-allopyranosido[2,3:5',6']-3',3'-diphenyl-2'-morpholinone (8).

SOLVENT ---------- $CDCl_3$
CONC. ---------- 10%
TIME CONSTANT ---- 0 sec.
SWEEP WIDTH ------ 100 Hz/cm
SWEEP TIME ------- 1.36 sec.
OFFSET ----------- 12K Hz
REFERENCE -------- TMS.



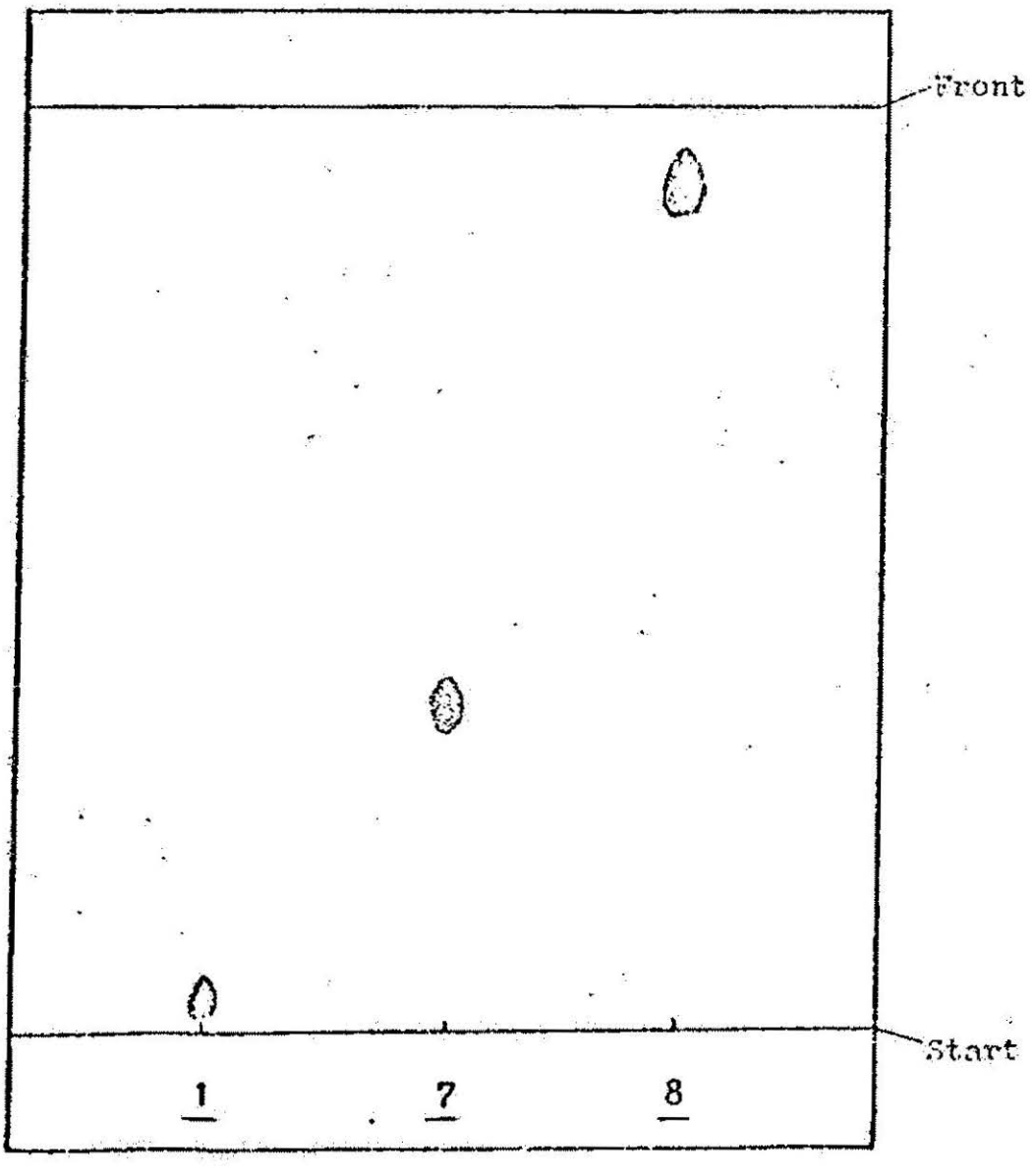
Benzyl 4,6-O-benzylidene-2-[(carboxydiphenylmethyl)amino]-2-deoxy-β-D-allopyranoside (11).

Thin-layer Chromatographic Comparison
of Compounds in Figure 2.1.



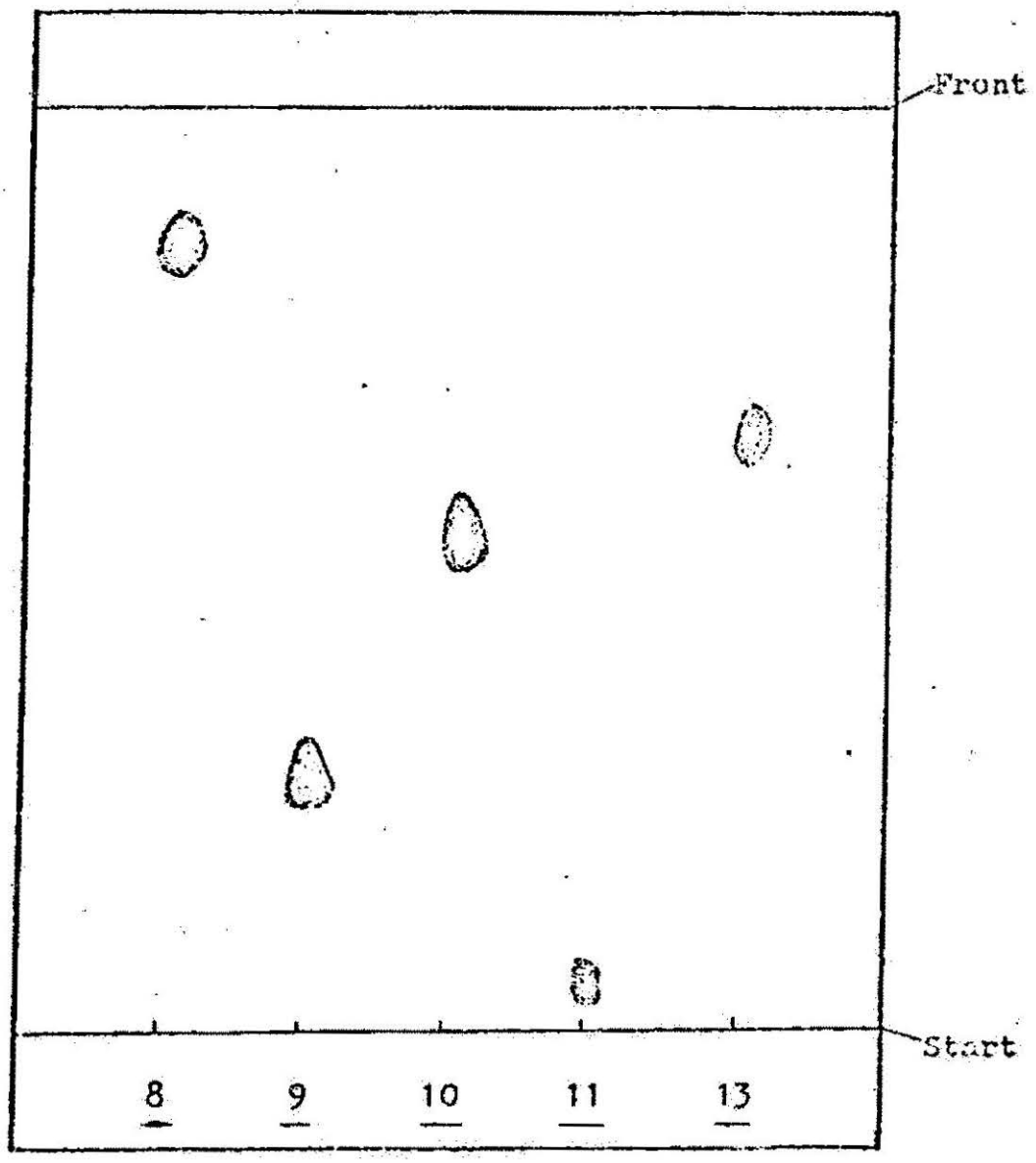
Solvent: methanol (3%) in chloroform

Thin-layer Chromatographic Comparison
of Compounds in Figure 2.2.



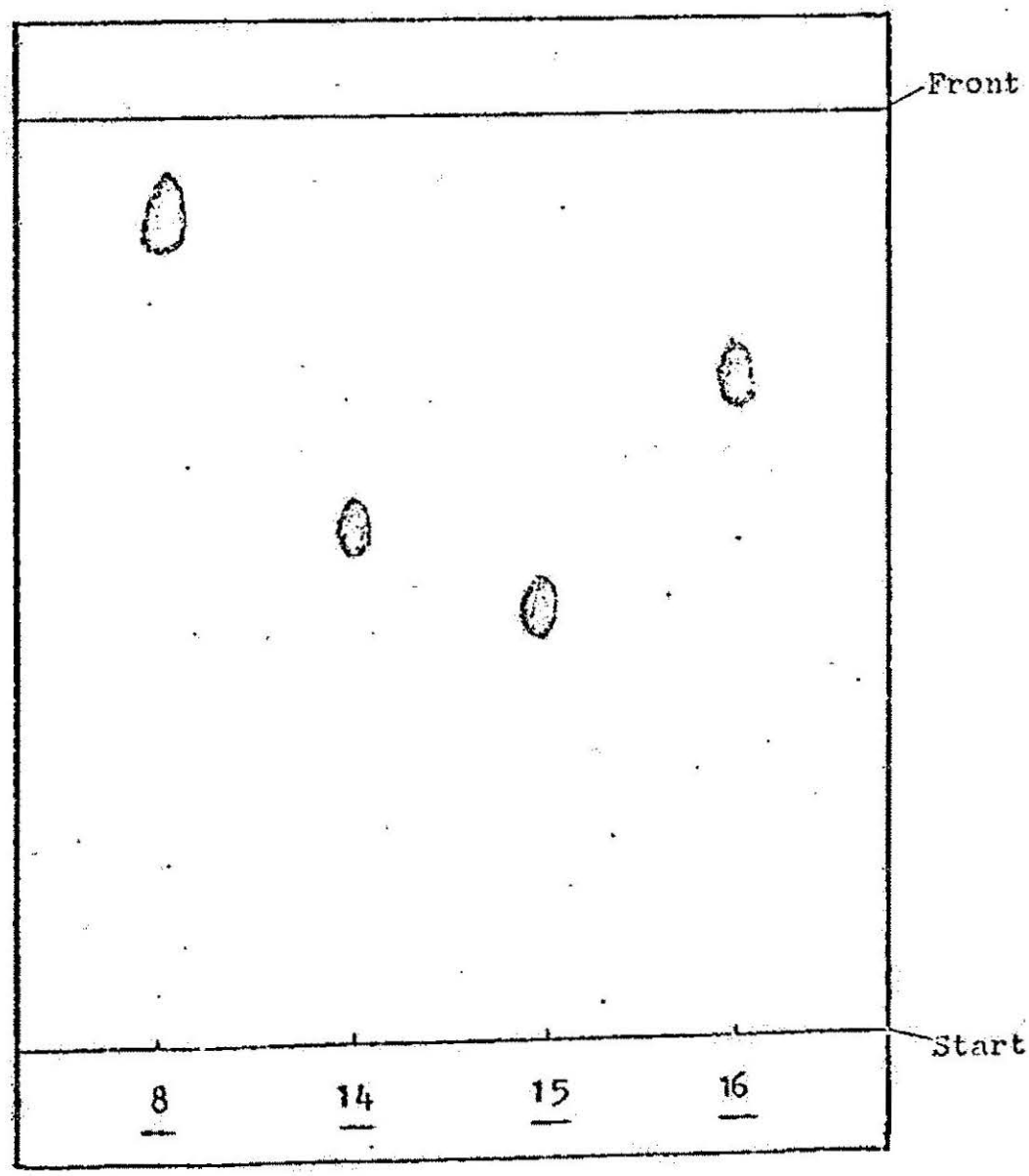
Solvent: chloroform

Thin-layer Chromatographic Comparison
of Compounds in Figure 2.5.



Solvent: chloroform

Thin-layer Chromatographic Comparison
of Compounds in Figure 2.6.



Solvent: chloroform