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## Synthesis of Pyridine Nucleosides by Cycloaddition Reactions and Synthesis and Condensation Reactions of 4-Aryl-2-Oxytetronimides

Glenn L. Heise

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SYNTHESIS OF PYRIDINE NUCLEOSIDES BY CYCLOADDITION REACTIONS AND  
SYNTHESIS AND CONDENSATION REACTIONS OF 4-ARYL-2-OXYTETRONIMIDES

by

Glenn L. Heise

A Thesis  
Submitted to the  
Faculty of The Graduate College  
in partial fulfillment of the  
requirements for the  
Degree of Master of Arts  
Department of Chemistry

Western Michigan University  
Kalamazoo, Michigan  
December 1985

SYNTHESIS OF PYRIDINE NUCLEOSIDES BY CYCLOADDITION REACTIONS AND  
SYNTHESIS AND CONDENSATION REACTIONS OF 4-ARYL-2-OXYTETRONIMIDES

Glenn L. Heise, M.A.

Western Michigan University, 1985

Experiment 1: The reaction of various glutaconaldehyde salts ( $\text{Na}^+$  or  $\text{K}^+$ ) with glycosyl isothiocyanates has resulted in the formation of a novel class of compounds. Relatively mild conditions were utilized for the synthesis which occurs in four steps, and in good yield, starting from glucopentaacetate. These reactions were found to be regiospecific. The unique physical and spectral properties of the model compound 1-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glycopyranosyl)-2-thiono-3-pyridine carboxaldehyde are also discussed.

Experiment 2: Early synthetic methodologies have recently been utilized in the synthesis of 4-aryl-2-oxytetronimides. These compounds have been found to participate in condensation reactions with various substituted o-phenylene diamines. A study of oxidation techniques was also conducted which yielded 4-aryl-2,3-dioxabutyro-1,4-lactones. The physical and spectral properties of these compounds are also discussed.

## ACKNOWLEDGEMENTS

This work is dedicated to my coworkers and committee members of Western Michigan University whose helpful comments and suggestions have helped guide this project to a successful completion.

To my project advisor, respected professor and friend, Dr. Robert E. Harmon, I owe the greatest thanks, his development and keen insight into the unique problems associated with this project have guided it to its successful end.

Support was provided by the Waldo Sangren Scholarship Fund of Western Michigan University.

Lastly I would like to thank my family for their unfailing support of my continued endeavors in the field of chemistry.

Glenn L. Heise

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**SYNTHESIS OF PYRIDINE NUCLEOSIDES BY CYCLOADDITION REACTIONS  
AND SYNTHESIS AND CONDENSATION REACTIONS OF 4-ARYL-2-  
OXYTETRONIMIDES**

*Western Michigan University*

**M.A. 1985**

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## CHAPTER I

### STATEMENT OF THE PROBLEM

This research was undertaken to study:

1. The cycloaddition reactions of glycosylisothiocyanates to both the sodium and potassium salts of glutaconaldehyde to give 1-glycosyl-2-thiono-3-pyridine carboxaldehydes.
2. The various solvent effects and other reaction conditions.
3. The potential synthesis of various silyl derivatives of the potassium glutaconaldehyde salt.
4. The synthesis and condensation reactions of 4-aryl-2-oxy-tetronimides.

## CHAPTER II

### INTRODUCTION

Extensive work has been done in the study of the synthesis and reactions of glycosyl isothiocyanates (1-4). As yet, no one has studied the reactivity of these compounds with the various salts of glutacanaldehyde. The method that we propose is based on the reaction given below in Figure 1.

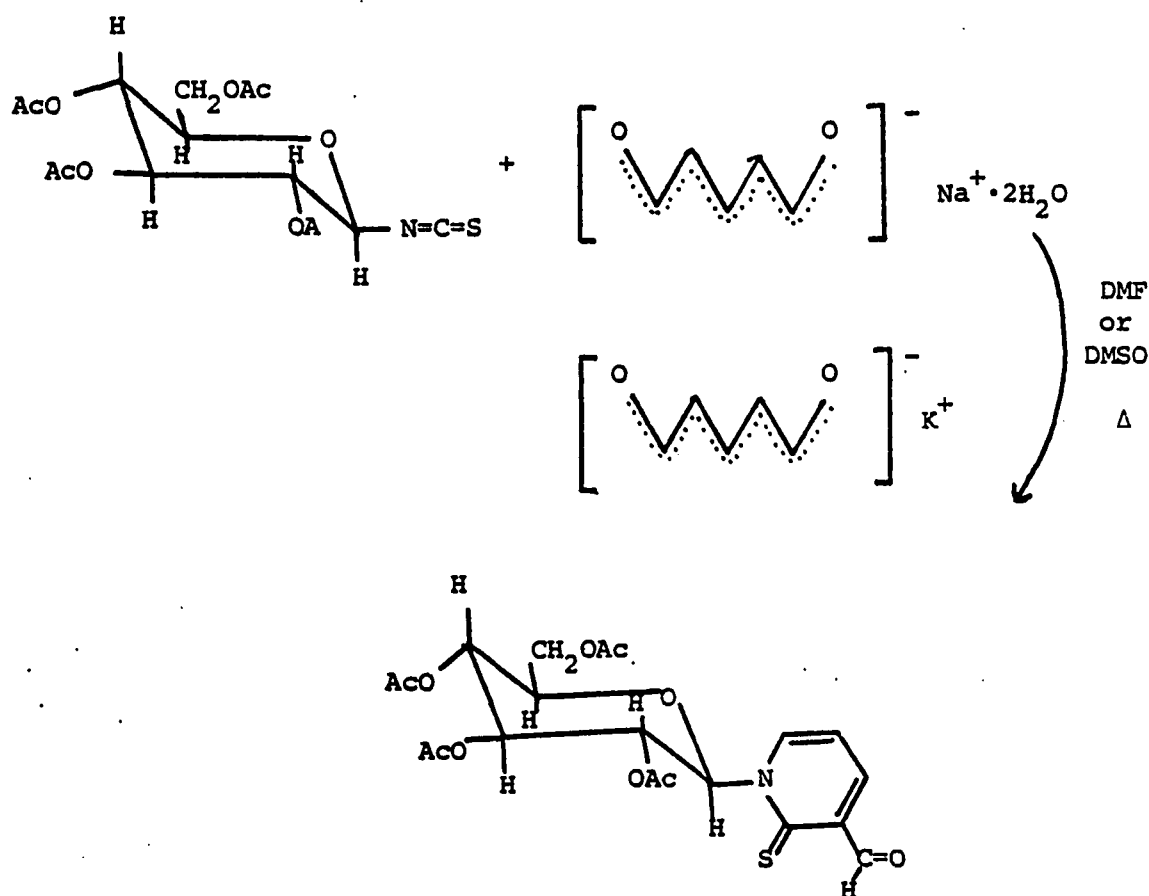


Figure 1. Synthesis of Glycosyl Isothiocyanates.



Reactions utilizing the salts of glutaconaldehyde have been studied by Becher and coworkers using substituted alkyl and aryl isothiocyanates (5-7). This research conducted during 1976-1977 introduced an extensive range of reactions based on the salts of glutaconaldehyde and their resulting reaction products. Their reaction involved the use of one equivalent of the glutaconaldehyde salt (sodium or potassium) with an equivalent amount of either alkyl or aryl isothiocyanate in an aprotic solvent such as DMF or DMSO (Figure 2).

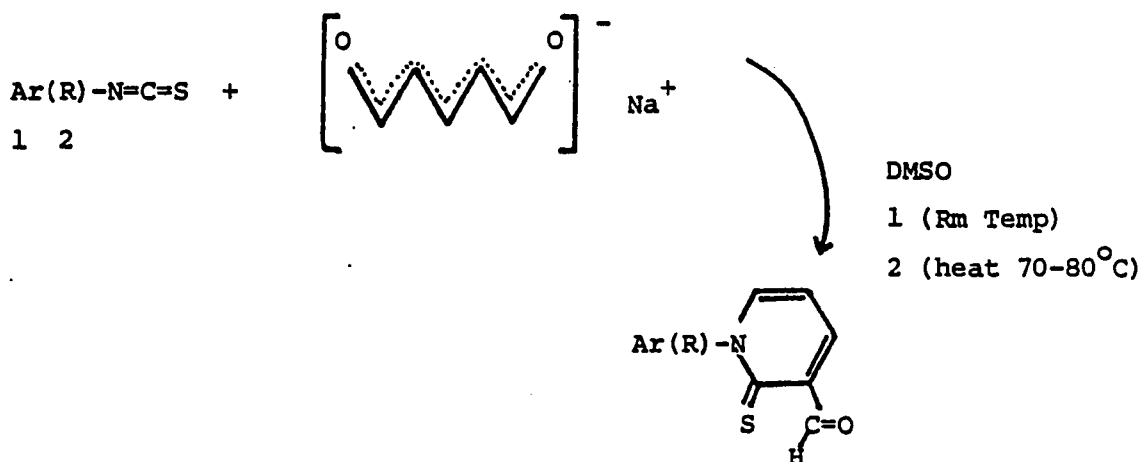


Figure 2. Synthesis of 1-glycosyl-alkyl(aryl)-3-formyl-2(1H)-pyridine-thione.

The reaction mixture must be heated for approximately one hour at 70-80°C in the alkyl series, whereas the reaction readily occurs at room temperature in the aromatic series. Use of aprotic solvents was necessary due to the low solubility of the glutaconaldehyde anion in organic solvents of low polarity. These reactions were found to be regiospecific.

The successful completion of the proposed reaction (Figure 1)

will provide a unique route to 1-substituted-3-pyridine carboxaldehydes and in particular the first synthesis of 1-glycosyl-2-thiono-3-pyridine carboxaldehydes.

## CHAPTER. III

### EXPERIMENT 1

#### Instrumentation

##### General

The compounds synthesized during the course of this investigation were identified by IR, NMR, MS and elemental analysis. IR spectra were run on a Beckman Acculab Spectrophotometer. Proton NMR spectra were recorded using Varian A-60 and a Varian EM 390 spectrophotometers; mass spectra were obtained using a DuPont 41-290B spectrophotometer. TLC analysis were carried out on silica gel plates (Merck, 60, F<sub>254</sub>, precoated, 0.2mm). Melting points were obtained using a Thomas Hoover Uni-melt Capillary Melting Point apparatus, and are uncorrected. <sup>13</sup>C NMR were run on a Varian XL-100F-15FT (3). Microanalysis were carried out by Midwest Microlab, Ltd., Indianapolis, Indiana.

#### Preparations

##### Pyridinium-1-sulfonate

This is a modified procedure of H.H. Sisler and L.F. Audrieth (8).

A solution of 62 g of dry pyridine (dried over solid sodium hydroxide and then redistilled) in 350 mL of dry chloroform, was placed in a triple necked flask fitted with a thermometer, mechanical stirrer,

and a pressure equalizing addition funnel. The flask was cooled in a dry ice isopropyl alcohol bath periodically while 38.5 g (0.33 mol) of chlorosulfonic acid was added slowly to the solution with continuous stirring. The rate of addition was regulated so as to maintain the reaction mixture at 0°C. After stirring (about an hour) the solid pyridinium-1-sulfonate was filtered by suction and washed with four 40 mL portions of ice cold chloroform. The white crystalline product was stored in a dessicator containing silica beads as dessicant under vacuum. The yield was approximately 33 g (62% of theoretical). Product melting point matched that of the literature value.

2-Pentenedial, ion ( $1^-$ ), sodium

This is a modified procedure of J. Becher (9).

In a 500 mL, three-necked, round bottom flask fitted with a thermometer and mechanical stirrer was placed a solution of 42 g (1.05) sodium hydroxide dissolved in 168 mL of water. The solution was cooled to -20°C with stirring using a dry ice isopropyl bath. Once the solution had attained this temperature, 48 g (0.30 mol) of pyridium-1-sulfonate, which had been previously chilled to -20°C, was added in one portion. The mixture was stirred for an additional 20 minutes keeping the temperature below -5°C. At this time, the bath was removed and the stirred reaction mixture was allowed to gradually warm to 20°C over a period of 20 minutes. The dark orange reaction mixture was then raised to 55-60°C (warm water bath) and was then lowered to -5°C after 1 hour. The resulting brown crystals were filtered by suction, and washed with three 100 mL portions of dry

acetone. The yield of crude product amounts to 46-52 g after drying on filter paper overnight or at 50°C (1mm Hg) for 1 hour (see Figure 3).

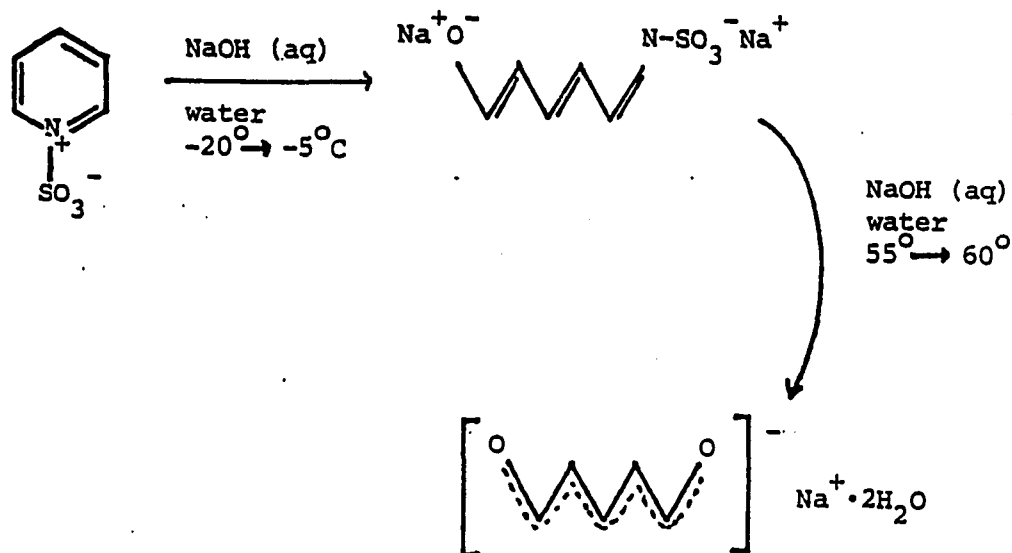


Figure 3. Synthesis of Glutaconaldehyde Sodium Salt.

This crude material was further purified by adding 1 L of methanol to the crude product obtained above in a 2 L triple necked, round bottom flask equipped with mechanical stirrer and refluxed for about 30 minutes, at which time 10 g of Norit decoloring carbon was added carefully. The solution was stirred for an additional 5-10 minutes, and filtered hot through a Celite (R) bed. The resulting red-orange solution was concentrated under vacuum to about 50 mL, and cooled to 0°C. The orange crystals that precipitated were filtered by suction, washed with two 25 mL portions of acetone and dried for 1 hour at 50°C (1mm Hg) yielding 21-27 g (50-58%) of glutaconaldehyde sodium salt dihydrate.

NMR (DMSO- $d_6$ ): 5.07 $\delta$  (d, 2H), 7.03 $\delta$  (t, 1H), 8.58 $\delta$  (d, 2H). IR (KBr)  $cm^{-1}$ : 3320 ( $H_2O$ ), 1723, 1715 (C=O), 1530 (C-O). M.P. > 350°C. Assignments correlate with those given in the literature.

2-Pentenedial, ion (-1), potassium

This compound was prepared by a modification of the procedure of J. Becher (9).

Pyridinium-1-sulfonate (108 g, 0.68 mol) was added to a solution of 155 g (7.8 mol) of potassium hydroxide in 378 mL of water in a 1-L triple necked flask fitted with a thermometer and a mechanical stirrer. The flask was cooled to -20°C with a dry ice isopropyl bath. After one hour the temperature was slowly raised to 20°C over a period of 4 hours. The reaction mixture was then heated at 30-40°C for 30 minutes and then cooled to -5°C. The crude product that precipitated was filtered by suction and washed with three 100 mL portions of acetone and dried in the air to give 120 g of yellow brown crystals. This crude material was purified by adding the entire amount obtained above to 2.5 L of methanol in a 3-L triple necked flask fitted with a reflux condenser and a mechanical stirrer. The material was heated at reflux for 30 minutes at which time 5 g of Norit decolorizing carbon was added (slowly). The solution was filtered through a Celite bed after 5-10 minutes and then concentrated under vacuum to a volume of approximately 100 mL. The pale yellow crystals that result were filtered by suction and washed with two 25 mL portions of acetone. The yield of dried product was 53-57 g (57-62%) (see Figure 4).

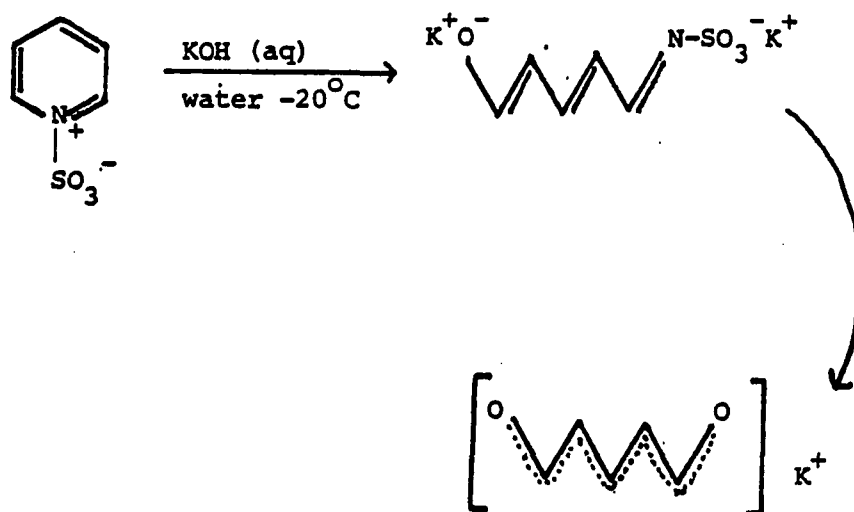


Figure 4. Synthesis of Glutaconaldehyde Potassium Salt.

TLC analysis of both the sodium and potassium glutaconaldehyde salts was run as a purity check. The solvent system used was 2% methanol/methylene chloride. NMR (DMSO- $d_6$ ): 5.07 $\delta$ (d,2H), 7.03 $\delta$ (t,1), 8.58 $\delta$ (d,2H). M.P. >350°C, F.W. 136.55.

#### 2,3,4,6-tetra-O-acetyl- $\alpha$ -glycopyranosyl bromide

This compound was prepared by a modification of the procedure of F. Weygand (10).

B-D-glucose penta acetate, 29.27 g (0.075 mol), was dissolved in 65 mL of acetic anhydride in a 250 mL round bottom triple necked flask fitted with a thermometer, mechanical stirrer, and a pressure equalizing addition funnel. The stirred solution was cooled to 15°C and 9.5 g (0.305 mol) of dry red phosphorus was added. Within a few minutes dropwise addition of 12.5 mL (0.34 mol) of bromine was begun in such a way that the temperature of the mixture was maintained between

15-20°C (periodic cooling in an ice bath may be necessary). After complete addition of the bromine, 12.5 mL of water was added slowly, keeping the temperature below 20°C. The reaction mixture was allowed to stand undisturbed for 1.5 hours and then 75 mL of chloroform was added. Once the unreacted phosphorus had settled, the mixture was filtered through Celite and the residue was washed with a little chloroform. The filtrate was poured into a 2000 mL separatory funnel filled 3/4 full with crushed ice and shaken thoroughly. The chloroform layer was separated and the reaction layer was quickly extracted with 50 mL of chloroform. Washing of the combined chloroform extracts was then quickly carried out with three 75 mL portions of 0°C sodium hydrogen carbonate solution (10% w/w).

The chloroform solution was dried with slight warming over calcium chloride until clear. After addition of a little Norit decolorizing carbon, the solution was allowed to stand 15-20 minutes and was then filtered through Celite. The solution was then concentrated under reduced pressure to a volume of approximately 100 mL. Addition of a little ether and refrigeration overnight yielded crystals which were suction filtered and washed with cold ether. Yield was 25.58 g (83% theoretical), melting point crude 74-77°C. Due to the unstable nature of the 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl bromide it must be stored in a desiccator over diphosphorus pentoxide and potassium hydroxide under vacuum and used within about 12 hours of its initial production. The product may be recrystallized from either ether or diisopropyl ether to obtain pure product, melting point 88-89°C,  $n_D^{20} +198^\circ$  chloroform.



2,3,4,6-tetra-O-acetyl- $\beta$ -D-glycopyranosylisothiocyanate

A modified procedure of the original procedure of E. Fischer (2) was used in the compound preparation.

In a 300 mL round bottom flask equipped with a reflux condenser and magnetic stirrer was placed 30.84 g (.075 mol) of 2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glycopyranosyl bromide dissolved in 200 mL of anhydrous toluene (dried over sodium). The solution was stirred vigorously as 24.89 g (0.15 mol) of AgSCN was added slowly. Upon complete addition of the silver thiocyanate, the mixture was refluxed for one hour. As the reaction proceeded to completion, the solution precipitated yellow silver bromide. After this reflux period, the solution was filtered through a Celite bed and the residue washed with a little toluene. The filtrate was then concentrated under reduced pressure (a vacuum pump was used so as to avoid the necessity of heating the solution to very high temperatures). Once crystals began to form, the solution was refrigerated overnight. The yellowish crystals were obtained in nearly quantitative yield, melting point 100-103°C. The compound was recrystallized from hexane/ ethyl acetate. TLC analysis of purity 2% MeOH/CH<sub>2</sub>Cl<sub>2</sub>. NMR (CDCl<sub>3</sub>): 5.15 (m, 4H), 4.21 (m, 2H), 3.76 (m, 1H), 2.13 (m, 12H). IR (KBr)cm<sup>-1</sup>: 3000-2800 (C-H) , 1750 (C=O), 1450 (CH<sub>2</sub>), 1375(CH<sub>3</sub>).

Trimethyl Silyl Ether of Potassium Glutaconaldehyde Salt

In a 100 mL triple necked flask fitted with a thermometer, N<sub>2</sub> inlet,

and rubber septum, was placed 6.82 g (0.5 mol) of glutaconaldehyde potassium salt in 8.01 mL (0.10 mol) of dry pyridine and 25.00 mL of dimethoxyethane (glyme). The continuously stirred mixture was placed under an atmosphere of nitrogen and cooled to  $-10^{\circ}\text{C}$  in a dry ice/isopropyl alcohol bath. Once this temperature had been attained, 19.04 mL (0.15 mol) of trimethylchlorosilane (TMCS) was injected drop by drop into the mixture. Reaction was immediate, forming an orange-white precipitate. The compound appeared to be stable only at very low temperatures and decomposed readily as temperatures rose (11). IR (neat) (cold)  $\text{cm}^{-1}$ : 3050 (C-H), 2950-2850 (C-H), 2735 (C-H ald), 1672 (C=O), 1130-1040 (C-O).

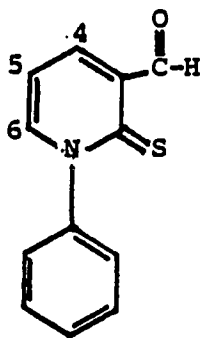
In an attempt to obtain a more stable silyl ether the above reaction was run using diphenylmethylchlorosilane instead of trimethylchlorosilane. The reaction occurred as above with a similar orange-white precipitate forming, again only stable at low temperatures. The direction of these syntheses was to prepare reaction precursors to the target compounds of this work. Further investigation into the nature of these transient compounds needs to be done.

#### 1-Phenyl-3-formyl-2 (1H)-pyridinethione

The sodium or potassium salt of glutaconaldehyde (0.01 mol) and (0.01 mol) phenylisothiocyanate in DMSO (10 mL) or DMF were stirred at room temperature for 1 hour. The dark colored reaction mixture was added to 100 mL of cool water. The resulting precipitate was recrystallized from benzene (% yield 95%), melting point  $180-182^{\circ}\text{C}$  (12). IR (KBr)  $\text{cm}^{-1}$ : 3200-3000 (C-H), 2860 (C-H), 1680 (C=O), 1603

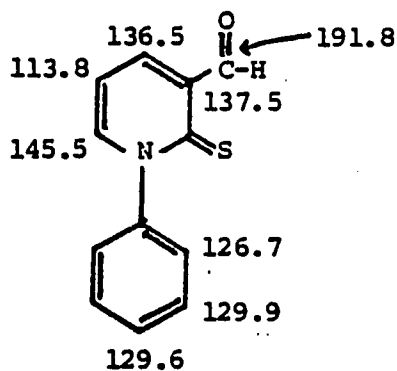
(C=C), 1100 (N-C=S). The prepared compound was confirmed by high correlation of spectral and melting point assignments given in the literature (13). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) assignments 1:

H (4)	H (5)	H (6)	CHO	Other
7.90δ	6.98δ	8.35δ	10.56δ	7.3-7.7 aryl δ



1

<sup>13</sup>C NMR analysis assignments 2, reference data (3).



2

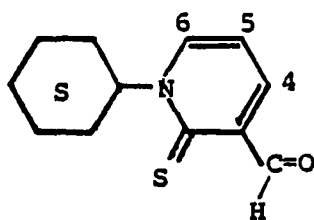
### 1-Cyclohexyl-3-formyl-2 (1H)-pyridinethione 3

The sodium salt of glutacanaldehyde (0.01 mol) and (0.01 mol) of cyclohexylisothiocyanate in DMSO (10 mL) or DMF were heated at 70-80°C for 1 hour. The dark colored reaction mixture was added to 100 mL of

cold water and the resulting solution was continuously extracted with diethyl ether for 20 hours. The extract was dried and concentrated under reduced pressure yielding the product in 98% yield. Product was purified if desired by recrystallization from cyclohexane, melting point 152-154°C, yield 98% of theoretical; preparation of Beecher and coworkers (6). IR (KBr)  $\text{cm}^{-1}$  corrected to polystyrene reference: 2930 (C-H), 2860 (C-H), 1683 (C=O), 1605 (C=C), 1105 (N-C=S). Existence of compound confirmed on basis of correlation of spectral assignments and melting point.

Table 1  
NMR Data Comparison for  
1-Cyclohexyl-3-formyl-2(1H)-pyridinethione

NMR ( $\text{CDCl}_3$ ) <u>3</u> :	H (4)	H (5)	H (6)	CHO
Literature	7.66 $\delta$	6.70 $\delta$	7.88 $\delta$	10.68 $\delta$
Experimental	7.75 $\delta$	6.74 $\delta$	7.88 $\delta$	10.86 $\delta$
Literature	J-4,5	J-5,6	J-4,6	
	6.8 Hz	6.8 Hz	1.5 Hz	



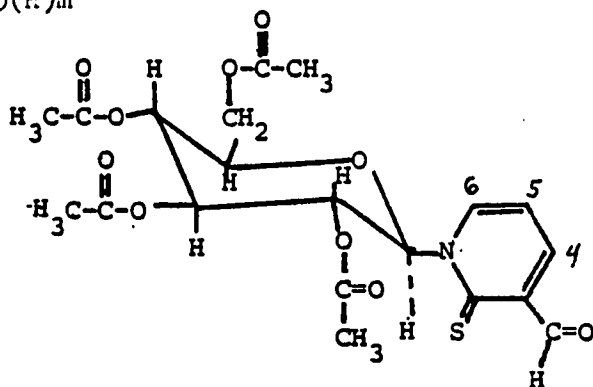
3

1-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glycopyranosyl)-2-thiono-3-pyridine carboxaldehyde

In a 100 mL triple necked flask fitted with a thermometer and vapor condenser was dissolved 2.05 g (0.015 mol) of glutacanaldehyde

potassium salt in 20 mL of DMF. While stirring the solution 3.84 g (0.010 mol) of 2,3,4,6-tetra-*O*-acetyl- $\alpha$ -D-glycopyranosyl-isothiocyanate was added all at once and the solution was gradually heated to 72-74°C. The reaction mixture was stirred continuously for 36 hours while temperature was maintained between 72-74°C. The darkly colored mixture was then poured into 100 mL of cool water. The resulting solution was extracted with diethyl ether for one week in a continuous lighter than water extractor. The extracts were collected every day with a fresh ether charge provided at each collection time. Concentration of the combined ethereal extracts yielded a light yellow solution from which a yellow precipitate of product formed, melting point 117-119°C. IR (neat) (consecutive polystyrene sample run to help fix IR assignments)  $\text{cm}^{-1}$ : 3110 (O-H), 3000-2900 (C-H), 2860 (C-H aliph.), 1750 (C=O) 1682(C=O) 1640 (C=O) 1100 (N-S). NMR ( $\text{CDCl}_3$ ) 4.

H (4)	H (5)	H (6)	CHO
7.78 q	6.78 t	7.96 q	10.76 s
H axials	H		
4H	anomeric	$\text{CH}_2$	$\text{CH}_3$
5.57 1(H)t	7.64 1(H)d	5.23 t	2.10 12(H) multiple singlets
4.25 3(H)m			



Mass spectrum: M (exp.) 469.1042, M (found exact mass) 469.1046 of  $C_{20}H_{23}NO_{10}S$ . Other ions as m/e 331, 169, 140, 109, 97, and 67. Elemental analysis: found C 51.44, H 4.98, N 3.12, S 6.99; calculated C 51.17, H 4.94, N 2.98, and S 6.83. The yield of the compound isolated was 69%.

## CHAPTER IV

### RESULTS AND DISCUSSION

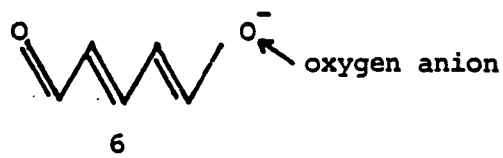
#### Mechanism

The project title "Synthesis of Pyridine Nucleosides by Cycloadition Reactions" suggests a uniqueness to the reaction. This is indeed the case, since reaction products of the type reported by J. Becher and coworkers and now in this work were formerly inaccessible by known procedures. An extensive series of both 1-substituted aromatic and alkyl-3-formyl-2 (1H)-pyridinethiones have been prepared (8); yet, as mentioned in the Introduction, the preparation of glycosyl analogues had not been previously accomplished. In order to be able to make structural comparisons and give spectral assignments to those compounds of the proposed glycosyl series, two reference structures, 1-cyclohexyl-3-formyl-2 (1H)-pyridinethione and 1-phenyl-3-formyl-2 (1H)-pyridinethione, were prepared by literature methods (6).

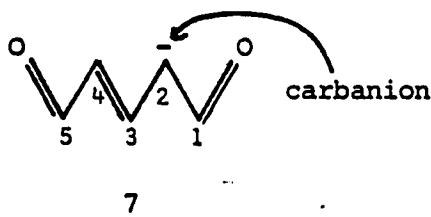
There are many contributing resonance structures to the glutaconaldehyde anion. Among these structures are two (Structures 6 and 7) that are important to explaining the ring closure reactions presented in this work. These resonance structures indicate that the hybrid (or delocalized ion) (5) has two reactive centers.



Resonance structure 6 has the negative charge localized on the oxygen atom. Reactions of the hybrid ion 5 with acid chlorides results in *O*-acylated glutaconaldehyde derivatives (enol esters) as reaction products. Resonance structure 6 may be thought of as being the major



contributing structure in this case. On the other hand, resonance structure 7 with negative charge localized on carbon 2 is the major



contributing structure when the hybrid ion is reacted with substituted isothiocyanates.

1-substituted-3-formyl-2 (1H)-pyridinethiones were the products formed in this case. The literature (5,6) on this subject has further suggested that these reactions may be explained utilizing the principle of hard and soft acids and bases (HSAB). In the hybrid ion 5, carbanion 2 is a softer base than the oxygen anion in structure 6, and can thus react with the soft acid center (thiocarbonyl carbon) of the isothiocyanate.

This HSAB principle was first described by R.G. Pearson in 1973 (14). The HSAB principle is commonly stated as follows: Hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases. The terms hard acids and soft acids can be defined as follows:



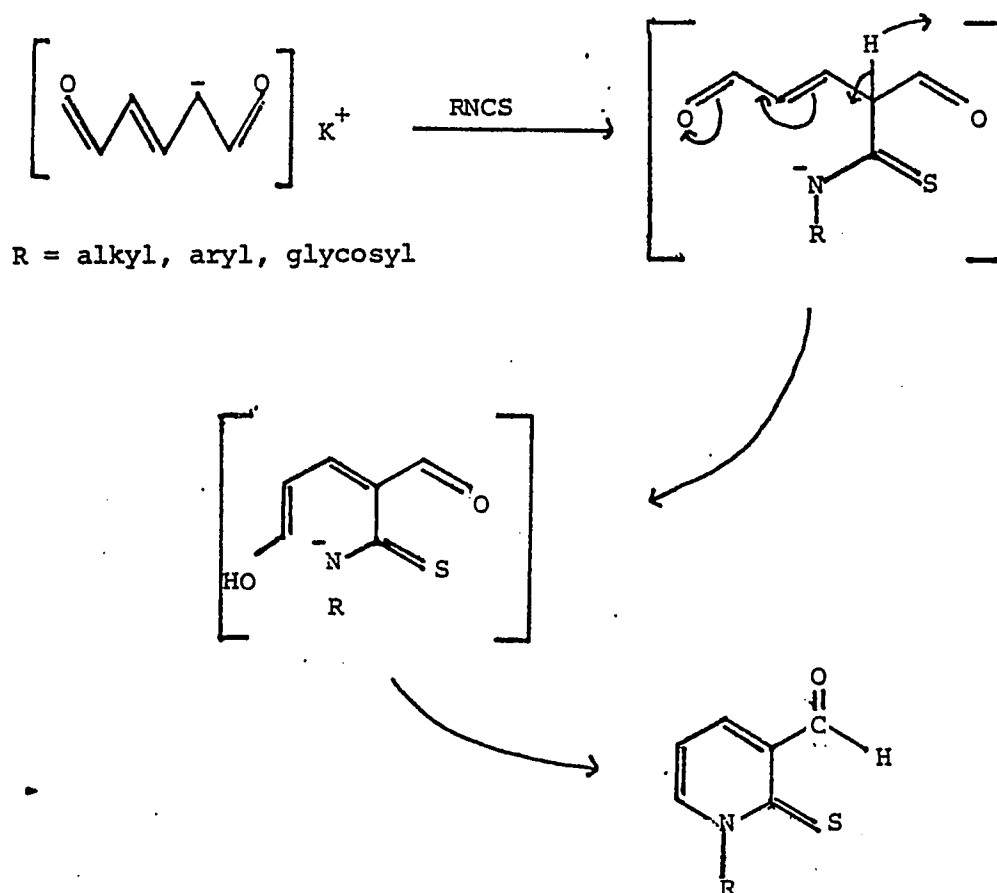


Figure 5. Mechanism of Formation of 1-substituted-3-formyl-2(1H)-pyridinethione.

hard acids are small acceptor atoms that have outer electrons not easily excited and that bear considerable positive charge, soft acids are acceptor atoms of larger size that have easily excited outer electrons, and can bear a much lower positive charge. Similar definitions can be given to hard and soft bases. The course of the reaction under study is also predicted by the fact that only one electrophilic center exists in the isothiocyanate.

#### Preparation of the Pyridine Nucleoside

Early attempts following procedures set forth by J. Becher and coworkers failed to produce the target compounds we were after. Solvent

changes utilizing solvents like acetonitrile, methylene chloride, and dimethoxyethane yielded complex mixtures of products which were not evaluated and identified. Careful thin layer chromatographic analysis of samples taken at selected intervals indicated that much starting material remained unreacted, even after hours of reaction. In an attempt to ease reaction of the attacking nucleophile, the use of phase transfer catalysts and cation complexing agents was tried. A crown ether (18-Crown-6) was used along with tetrabutylammonium bromide phase transfer catalyst in a methylene chloride solvent system. The results of this method were again negative. Although interesting mixtures of what appeared to be primary and secondary amines were formed, further investigation was not begun.

Realizing that perhaps the sheer size and steric effects of the glycosylisothiocyanate may be the problem, a new set of reactions was embarked upon. Increasing the concentration of the nucleophile and returning to the dipolar aprotic solvents (DMF/DMSO) finally yielded positive results. The procedure described in the Experimental section for the synthesis of 1-glycosyl-3-formyl-2 (1H)-pyridinethiones requires heating the reaction mixture for approximately 36 hours before extraction. These conditions are similar to those used in the literature for the preparation of 1-t-butyl-3-formyl-2 (1H)-pyridinethione (13). The low product yields are attributable mainly to the special steric problems (carbon 2 acetyl group interaction with thiocarbonyl group of newly formed ring moiety) that occur in this instance.

The existence of the structure of 1-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glycopyranosyl)-2-thiono-3-pyridine carboxaldehyde was confirmed by

spectrophotometric measurements. The IR data presented in Table 2 below demonstrates the correlations of the functional group assignments among the model compounds and the new compound.

Table 2  
Functional Group Correlations\*

Group or functionality	Structure 1**	Structure 2**	Structure 3**
(C-H) aromatic	3200-3300 $\text{cm}^{-1}$	3100-3200 $\text{cm}^{-1}$	3110 $\text{cm}^{-1}$
(C-H) str.		2930 $\text{cm}^{-1}$	2942 $\text{cm}^{-1}$
(C-H)	---	2860 $\text{cm}^{-1}$	2860 $\text{cm}^{-1}$
			1750
(C=O)	1680 $\text{cm}^{-1}$	1683 $\text{cm}^{-1}$	1682 $\text{cm}^{-1}$
(C=C) vib	1603 $\text{cm}^{-1}$	1605 $\text{cm}^{-1}$	1605 $\text{cm}^{-1}$
(C=C) vib	1500 $\text{cm}^{-1}$	1520 $\text{cm}^{-1}$	1511 $\text{cm}^{-1}$
(N-C=S)	1100 $\text{cm}^{-1}$	1105 $\text{cm}^{-1}$	1100 $\text{cm}^{-1}$
(CH <sub>3</sub> )			1375 $\text{cm}^{-1}$
(CH <sub>2</sub> )		1449 $\text{cm}^{-1}$	1450 $\text{cm}^{-1}$

\* Authors experimental data

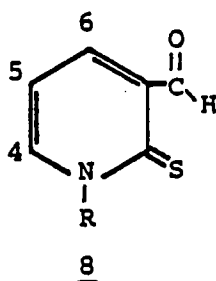
\*\* Structure 1 = 1-phenyl-3-formyl-2 (1H)-pyridinethione

\*\* Structure 2 = 1-cyclohexyl-3-formyl-2 (1H)-pyridinethione

\*\* Structure 3 = 1-(2,3,4,6-tetra-O-acetyl-1-β-D-glucopyranosyl)-2-thiono-3-pyridine carboxaldehyde

Of particular interest in this listing is the -N-C=S functionality. This functionality described as the β band in the literature (12) is comparable to the "Amide I band". Both of these bands have their origin

in the antisymmetrical vibration of the grouping  $\text{N-C=X}$  ( $\text{X} = \text{O}, \text{S}$ ), the main difference being that the stretching of the  $\text{N-C=O}$  grouping has predominantly  $\text{C=O}$  character whereas the stretching of the thioamide group has predominantly  $\text{C=N}$  character. Lastly, the unique position of this band ranging from  $1073 \text{ cm}^{-1}$  to  $1120 \text{ cm}^{-1}$  supports the 3-formyl-2 (1H)-pyridinethione structure 8. The HNMR spectra of structure 8 ring protons give rise to an ABX system which is characteris of



the 3-substituted-2 (1H)-pyridinethione. Table 3 shows the chemical shifts for the model compounds and the new compound. These chemical shifts are quite dependent on concentration and solvent thus the values will vary somewhat from those listed in the literature (7).

Table 3

<sup>1</sup>H NMR Correlations of Ring Protons in ppm ( $\delta$ )

Compound	H (4)	H (5)	H (6)	CHO
1 - Literature	7.90	6.98	8.35	10.56
Experimental	7.92	7.02	8.39	10.73
2 - Literature	7.66	6.70	7.88	10.68
Experimental	7.76	6.75	7.90	10.84
3 - Literature				
Experimental	7.78	7.64	7.96	10.76

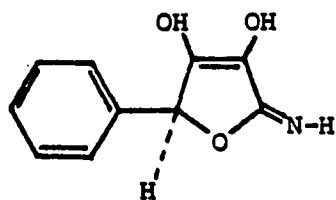
Mass spectra of all compounds prepared were again supportive of their given structures.

One last obstacle that occurred during this investigation requires mentioning at this point. Preparation of crystalline samples can be difficult in many types of experimental organic chemistry; none though can compare with the history of problems that have been and still are encountered in the preparation of crystalline sugar derivatives. The need for an initiating crystal or nucleus goes without further explanation. It is in the production of this first nuclei where the real problem is so evident. Prediction of when the proper arrangement of molecules will come together to form that first nuclei is next to impossible. Factors such as size, shape, temperature, amount of impurities, solvent etc., all have very definitive effects on when crystallization will begin. We experienced difficulty in the crystallization of all but a few of the sugar derivatives prepared. In order to shorten the sometimes lengthy waits associated with the crystallization behavior of these compounds, and compounds like them, it is vigorously recommended that high purity be sought at every step in this type of synthesis work.

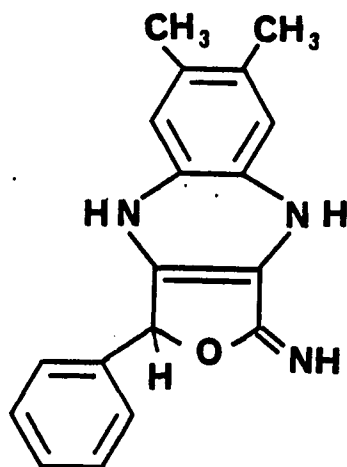
## CHAPTER V

### INTRODUCTION

The synthesis of 4-aryl-2-oxytetronimides (general structure 9) was first accomplished in 1954 by H. Dahn, J.S. Lawendel, E.F. Hoegger, and E. Shenker (15,16). Since that time, little research has been conducted in regards to synthesis of new 4-aryl-2-oxytetronimides, nor in the area of *o*-phenylenediamine condensations. To help fill in this gap in what is known about this class of compounds, we propose to extend the realm of aromatic and heterocyclic aldehydes that can successfully participate in the synthesis of 4-aryl-2-oxytetronimides, and to successfully develop a procedure by which substituted *o*-phenylenediamines may be condensed with 4-aryl-2-oxytetronimides to yield compounds of structure 10.



9



10

There is a mention of a method by which 4-aryl-2-oxytetronimides may be oxidized to 4-aryl-2,3-dioxabutyro-1,4-lactones in the original work. Since the production of a vicinal tricarbonyl compound suggests itself to numerous condensation type reactions, we decided to develop a method by which these compounds could be made, and further investigate their use as synthons to more complex heterocyclics.

## CHAPTER VI

### EXPERIMENT 2

#### Instrumentation

##### General

The compounds synthesized during the course of this investigation were identified by IR, NMR, and MS. IR spectra were run on a Beckman Acculab-8 spectrophotometer. Proton NMR spectra were recorded using a Varian A-60 and a Varian EM 390 spectrophotometer. Mass spectra were obtained using a DuPont 41-290B mass spectrophotometer. Melting points were obtained using a Thomas Hoover Unimelt Capillary Melting Point apparatus, and are uncorrected.

#### Preparations

##### Glyoxal hydrogen sulfite-dihydrate

This compound was prepared by a modified procedure of a procedure of A.R. Ronzio (17).

In a 5000-mL triple necked flask equipped with a mechanical stirrer was placed a solution of  $\text{NaHSO}_3$  and 95% ethanol (previously prepared by adding 312 g of technical sodium hydrogen sulfite in 2.0 L of warm (about 40°C) water, and adding 1.4 L of 95% ethanol). To this continuously stirred solution 249.6 mL of 40% w/w glyoxal was added. The

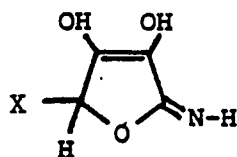


mixture was stirred for 3 hours after the complete addition of the glyoxal. The white addition product that precipitates was suction filtered in an 18 cm Büchner funnel and washed, first with two 150 mL portions of ethanol and then with two 150 mL portions of water. The yield of air dried product was approximately 400 g (90-92% of theoretical). The product was pure enough for most purposes; and was recrystallized by dissolving it in water and adding enough alcohol to make a 40% solution if necessary. The melting point given in the literature (18) of 193-195°C compares with that found experimentally (192-194°C).

#### 4-Aryl-2-oxytetronimides - General Procedure

In a 2000-mL triple necked, round bottom flask fitted with a mechanical stirrer, N<sub>2</sub> inlet tube (extending nearly to the bottom of the flask), and vent tube was placed a solution of 35 g (0.54 mol) of KCN in 1 L of 2N aqueous Na<sub>2</sub>CO<sub>3</sub>. To the continuously stirred solution 87.5 g (0.31 mol) of glyoxal-hydrogen sulfite-dihydrate was added all at once. Nitrogen gas was bubbled into the reaction mixture and 0.24 mol of the aromatic aldehyde in 50 mL of dioxane was quickly added. A colorless precipitate formed in the olive green solution. After about 30 minutes, the reaction mixture was carefully acidified to pH 6 with glacial acetic acid and then allowed to stir for another 3 hours, the resulting precipitate was filtered under suction and washed with 2 or 3 100 mL portions each of water, methanol, and diethyl ether. (See Table 4)

Table 4  
4-Aryl-2-oxytetronimides



X*	Melting Points (°C)		% Yield
	Literature	Experimental	
Phenyl	113-117	157-159	93
3,4-Dimethoxyphenyl	154/161-166	180-182	92
4-Toluy1	153-157	153-157	54
3,4-Dichlorophenyl	185-187	185-187	98
3-Nitrophenyl	181-184	181-183	88
2-Chlorophenyl	183-187	183-186	90
3,4-Methylenedioxy-phenyl	137/195-204	172-174	71
4-Methoxyphenyl	135-136/149-157	135-137	60
4-Chlorophenyl	166-169	149-151	89
2-Pyridyl	190-193	226-229	69
4-Phenylene-bis	250	>250	78
2-Furyl	133*/148-153	138-140	89
2 Napht:hyl	182-186	150-154	69

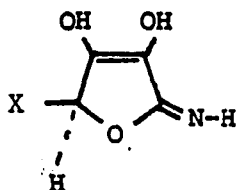
\* Compounds previously prepared in the literature (15,16)

#### o-phenylenediamine adduct - General Procedure

In a 200-mL round bottom flask fitted with reflux condenser, heating mantle, and magnetic stirrer was placed 0.04 mol of the substituted o-phenylenediamine in 100 mL of 95% ethanol. Once the diamine had dissolved 0.04 mol of 4-aryl-2-oxytetronimide was added. The

stirred reaction mixture was heated at reflux temperature for 6-8 hours. The resulting dark colored solution was concentrated under vacuum whereupon crystallization began unusually once the volume of solution had dropped to 60 mL. The compounds were filtered and washed with diethyl ether and air dried. Yields of product were in range of 80-100% of theoretical.

Table 5  
New Compounds Prepared  
4-Aryl-2-oxytetronimides



X	Melting Point ( $^{\circ}$ C)
2,4-Dichlorophenyl	177-179
2-Methoxyphenyl	118-120
9-Anthryl	103-105
5-Indanyl	141-143
3-Methoxyphenyl	150-153
5-Benzoyloxyindole-3-yl	230-233
2-Tolyl	152-153
3-Pyridyl	192-194
3,5-Dimethoxyphenyl	176-178
3,5-Ditertbutyl-4-hydroxyphenyl	188-189
$\beta$ -( $\alpha$ -Methyl) styrenyl	206-208
2-Thiophenyl	163-165

#### 4-Phenyl-2,3-dioxobutyro-1,4-lactones - General Procedure

The compounds were prepared by a modified procedure of a procedure of H.T. Clarke (19).

In a 500-mL triple necked, round bottom flask equipped with a mechanical stirrer, reflux condenser, and inlet tube for introduction of  $O_2$  was placed a mixture of 32.72 g (0.205 mol) of crystalline copper sulfate, 0.625 mol technical pyridine, and 20 mL (1.11 mol) of water. The mixture was heated on a steam bath until the copper sulfate was completely dissolved and then 0.033 mol of 4-aryl-2-oxy-tetronimide was added slowly. The mixture was heated and stirred for 2 hours and became dark green in color. After cooling, the copper sulfate pyridine solution was decanted, the product was washed with water, and heated with 100 mL of 10% HCl. After cooling, the product was filtered and washed with water. Yields range from 50-63% of theoretical.

The melting point for the 4-*o*-chlorophenyl-2,3-diketo-butyrolactone given in the literature (15) (104.5-106.5°C) compares with that found experimentally (104-106°C).

#### Quinoxaline - General Procedure

This is a modified procedure of H.M. Mokhtar and coworkers (20).

In a 100-mL round bottom flask fitted with a reflux condenser, magnetic stirrer, and a heating mantle was placed 0.004 mol of 4-aryl-2,3-dioxobutyrolactone in 20 mL of ethanol with four drops of acetic

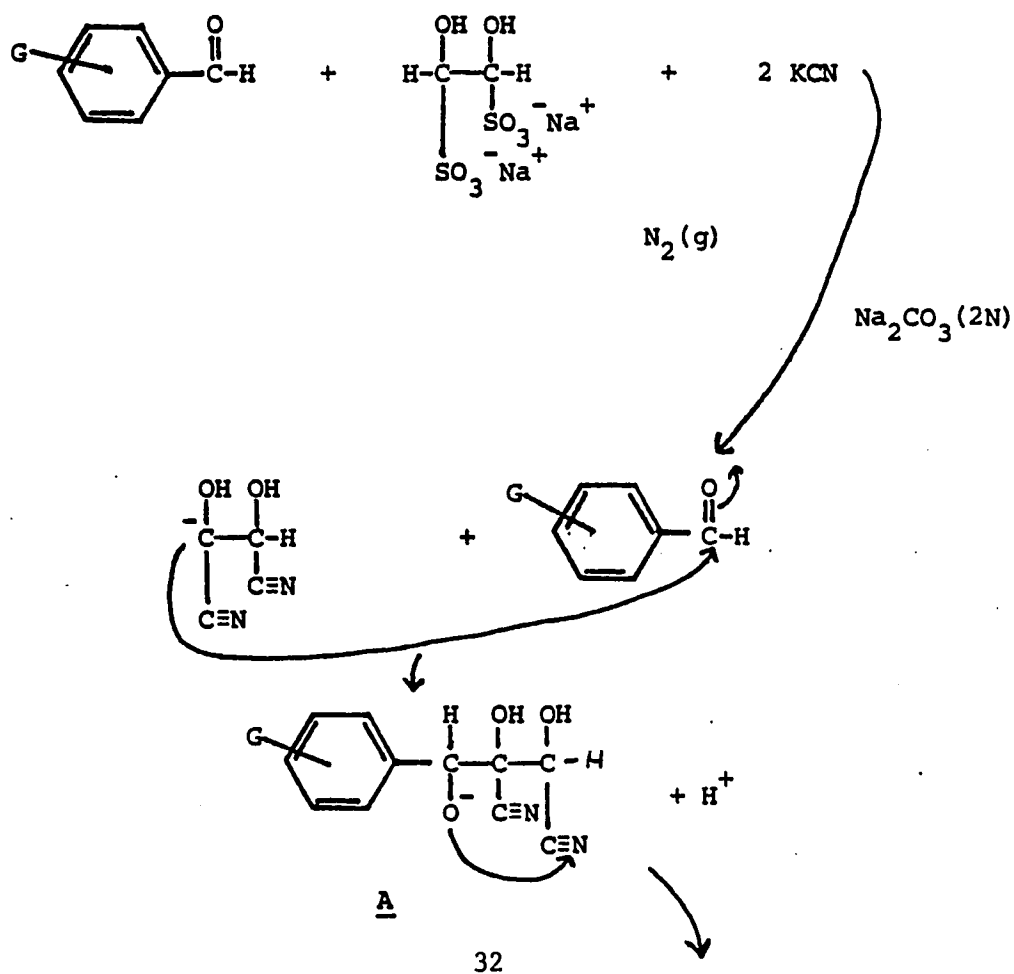
acid. To this stirred solution was added 0.004 mol of *o*-phenylenediamine dissolved in 20 mL of ethanol. The resulting mixture was refluxed for 1 hour. Concentration of the solution yielded the desired product.

# CHAPTER VII

## RESULTS AND DISCUSSION

### Mechanisms

The mechanism by which 4-aryl-2-oxytetronimides are synthesized is thought (by the present author) to proceed via a Benzoin type condensation in which the reaction is specifically catalyzed by cyanide (See Figure 6).



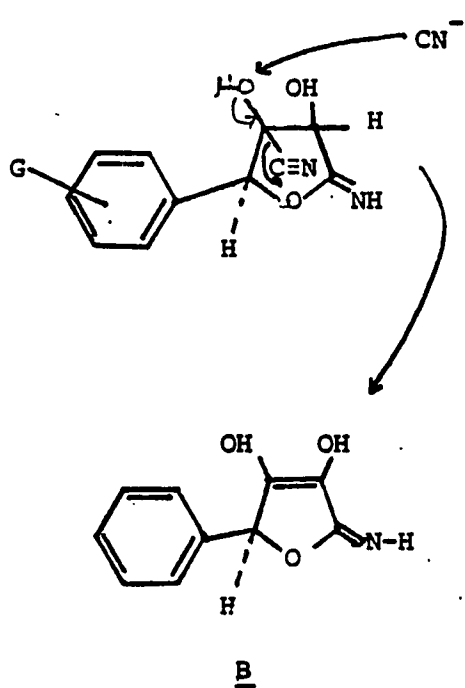


Figure 6. Mechanism of Formation of 4-aryl-2-oxytetronimide.

Cyanide ions, in the initial stages of the reaction, displace the sulfite groups in a molecule of glyoxal bisulfite, along with loss of a proton, to form a cyanohydrin carbanion. The electron deficient carbonyl carbon of the aromatic aldehyde undergoes nucleophilic attack by the cyanohydrin carbanion to yield compound A. Intramolecular cyclization of compound A with loss of a cyanide ion yields the keto form of the 4-aryl-2-oxytetronimide. This form can then enolize to the structure B namely the 4-aryl-2-oxytetronimide first synthesized by H. Dahn and coworkers. Table 5 shows the newly synthesized 4-aryl-2-oxytetronimides.

Examination of the Tables indicates that certain substituent groups and group positions on the ring of aromatic aldehydes prevent their use as precursors to this reaction. For example, 2,6-dichlorobenzaldehyde failed to undergo this reaction. A possible reason could

be steric hinderance. Another example is that of *o*- and *p*-nitro-benzaldehydes whose position allow for through resonance resulting in stabilization of the carbonyl carbon. Or in other words, these groups tend to reduce the polarizability of the carbonyl group, thus deactivating this position to nucleophilic attack.

The  $^1\text{H}$  NMR spectra of 4-aryl-2-oxytetronimides gives rise to characteristic peaks. Aromatic protons range from 7.0-7.6 $\delta$ , imine =N-H proton 5.3-5.7 $\delta$ , hydroxyl protons 7.6-7.8 $\delta$ , and the benzylic proton 2.3-2.5 $\delta$ . In the mass spectra relatively abundant molecular ions were observed. The IR spectra exhibited bands at 3500-3200  $\text{cm}^{-1}$  (OH), 3700-3000  $\text{cm}^{-1}$  (=C-H), 1250-1230  $\text{cm}^{-1}$  (C-O), 1090-1060  $\text{cm}^{-1}$  (C-O), and 1690-1670  $\text{cm}^{-1}$  (C=N-). Example elemental analysis data for 2-Chlorophenyl-2-oxytetronimide is given below.

Calculated    %C 53.23, %H 3.57, %N 6.21, %Cl 15.77

Found            %C 53.47, %H 3.64, %N 6.31, %Cl 15.81

Condensation reactions with the previously discussed 4-aryl-2-oxytetronimides and a select group of substituted *o*-phenylene diamines have been successfully carried out (see Figure 7).

These reactions utilized an equivalent of both the oxytetronimide and the *o*-phenylenediamine compound in a given quantity of refluxing ethanol. The mechanism by which this reaction is thought (author's speculations) to occur is shown in Figure 8.



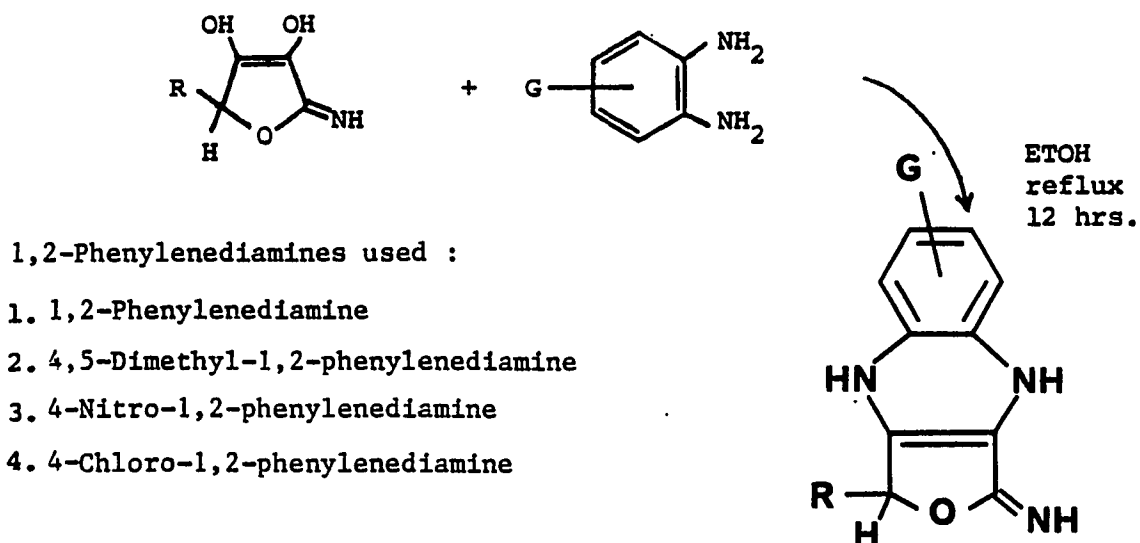


Figure 7. Synthesis of Phenylenediamine Adducts.

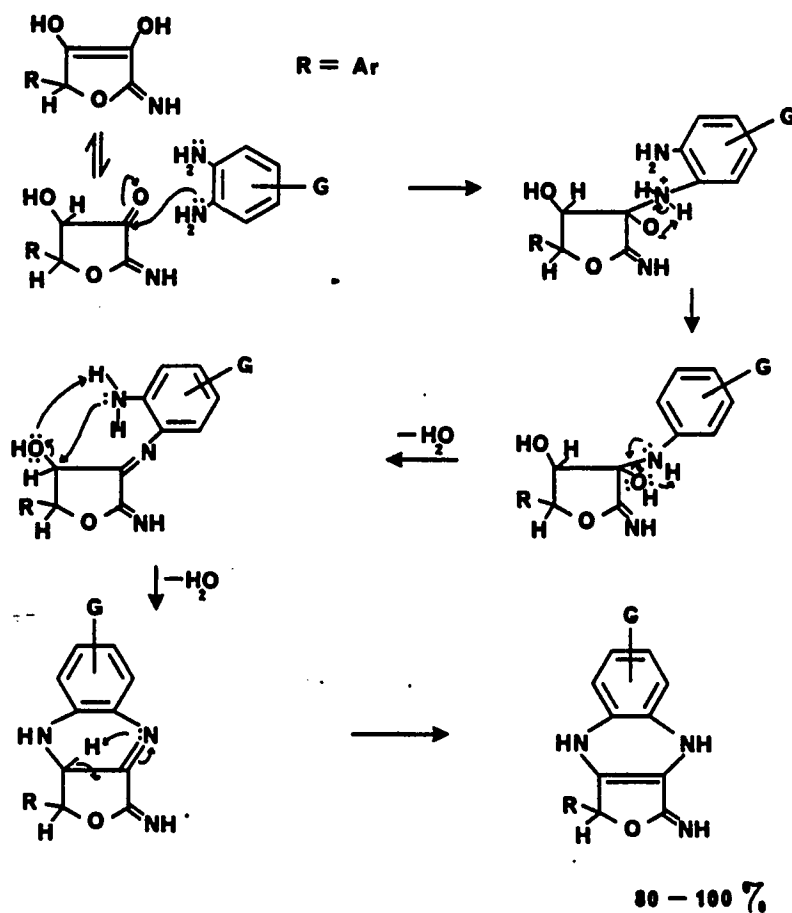
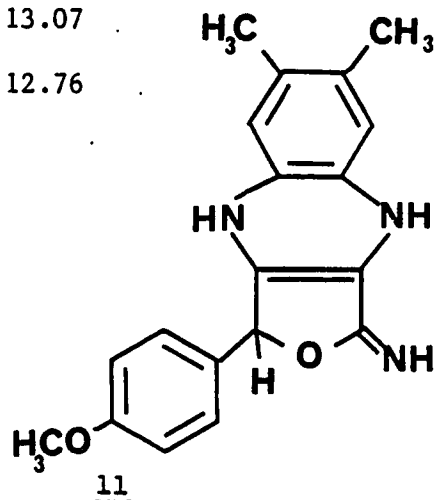


Figure 8. Mechanism of Phenylenediamine Adducts.

The *o*-phenylenediamine adducts exhibited characteristic <sup>1</sup>H NMR peaks and as with the 4-aryl-2-oxytetronimides relatively abundant molecular ions were observed. Table 6 shows some of the melting points observed for each of the substituted *o*-phenylenediamines used in the syntheses. Example elemental analysis data for compound 11 is given below.

Calculated %C 71.01, %H 5.96, %N 13.07

Found %C 70.76, %H 5.86, %N 12.76



A set of reactions eluded to in the original work by H. Dahn and coworkers involves the oxidation of 4-aryl-2-oxytetronimides with nitrite ion or iodine to form 4-aryl-2,3-dioxobutylolactones (See Figure 9).

The yields of the lactones were not given. In order to possibly extend the range of compounds yet to be synthesized, investigation into other methods of oxidation was begun. One method that had reasonable success involved the use of copper sulfate and pyridine as a modified Fehling solution (See Figure 10). Other methods do exist (and have yet to be applied to these compounds) such as the use of a cupric salt in catalytic amounts which can be regenerated in solution.

Table 6  
Melting Points of Substituted *o*-Phenylenediamine Adducts

R	1*	2*	3*	4*
Phenyl	161-162	163-164	196-200	168-170
4-Tolyl	120-123	195-197	197-199	203-205
2-Chlorophenyl		154-156	167-168	176-178
4-Chlorophenyl	207-209	217-220		192-194
3,4-Dichlorophenyl	164-166	164-166	240-242	162-164
3-Nitrophenyl	152-154	166-168	156-158	165-167
4-Methoxyphenyl	158-160	204-206	219-221	184-187
3,4-Dimethoxyphenyl	154-156		178-180	179-181
3,4-Methylenedioxyphenyl	178-181	216-218	129-133/ 234-236	205-207
2-Tolyl		185-187	180-183	173-175
2-Naphtyl			>250	
2-Furyl	155-157			
2-Pyridyl	248-250	234-236	217-220	
4-Pyridyl	207-209	205-207	210-212	
2,4-Dichlorophenyl	176-177	175-177	170-173	>250
2-Methoxyphenyl	175-177	124-126	182-186	200-202
3-Mehtoxyphenyl		165-167	164-166	161-164
9-anthryl		129-131	113-115	
5-Indanyl		198-200	165-168	
5-Benzylloxyindole-3-yl	229-232	229-232	182-185	238-240
3,5-Dimethoxyphenyl	182-184		159-162	
Phenylenēbis	>250	>250	248-250	>250
2,4-Dimethoxyphenyl		218-221	249-251	208-210

1\* = 1,2-Phenylenediamine  
2\* = 4,5-Dimethyl-1,2-phenylenediamine  
3\* = 4-Nitro-1,2-phenylenediamine  
4\* = 4-Chloro-1,2-phenylenediamine

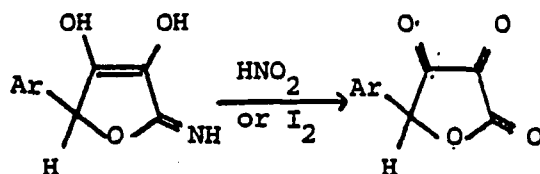


Figure 9. Nitrous Acid Oxidation of 4-aryl-2-oxytetronimide.

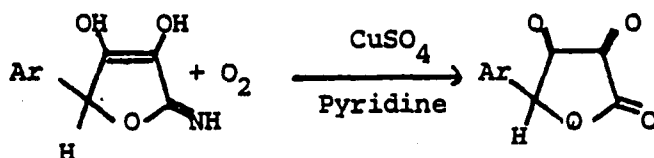


Figure 10. Cupric Sulfate Oxidation of 4-aryl-2-oxytetronimide.

by use of ammonium nitrate (21). This reaction has been successful in 90% to quantitative yields for benzoin and other selected acyloins.

#### Other Reactions

Synthesized 4-aryl-2,3-dioxobutylolactones have been reacted successfully with *o*-phenylenediamines to form Schiff bases 12 and quinoxaline 13 derivatives (13) (See Figure 11).

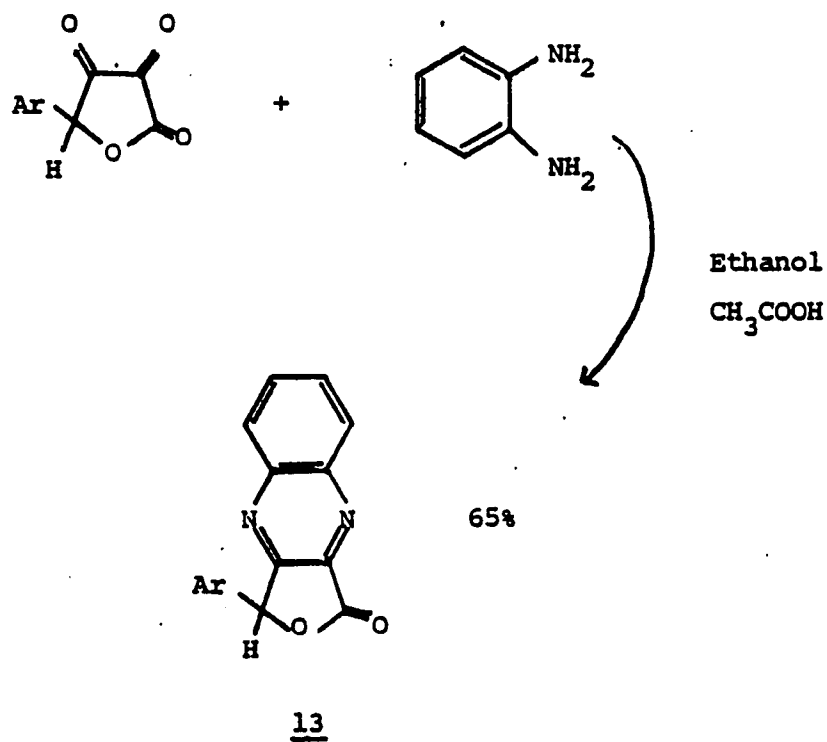
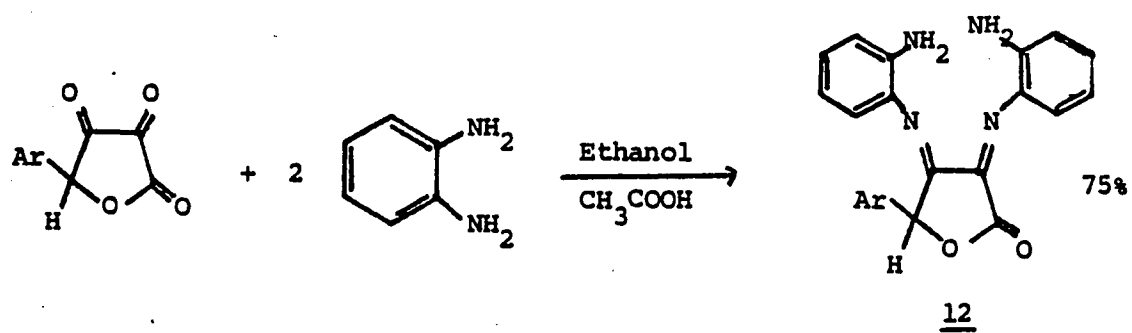


Figure 11. Synthesis of Schiff Bases and Quinoxaline Derivatives.

## CHAPTER VIII

### RECOMMENDATIONS AND CONCLUSIONS

1. Much work has yet to be done in this interesting class of compounds. Investigation into applying this method to other sugars, pentoses in particular, as well as the possible use of the silyl ethers of glutacetaldehyde as synthons to other heterocycles deserves attention.

2. The renewed interest in Vitamin C and its derivatives will undoubtedly spur further investigation into this versatile class of compounds. Investigations into the use of other diamine ring systems which can undergo the demonstrated condensation reactions with the 4-aryl-2-oxytetronimides is just one area that has only just been scratched.

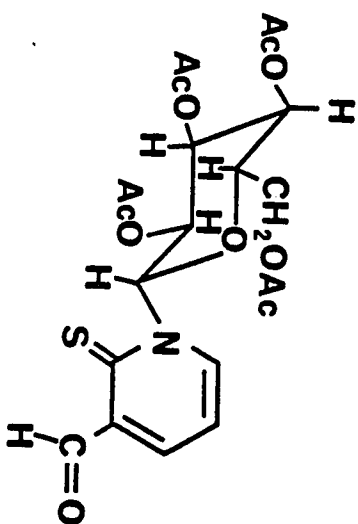
Many of the compounds synthesized during this investigation are currently undergoing anticancer evaluation at the National Cancer Institute. Many have already demonstrated activity in preliminary tests.

#### APPENDIX A

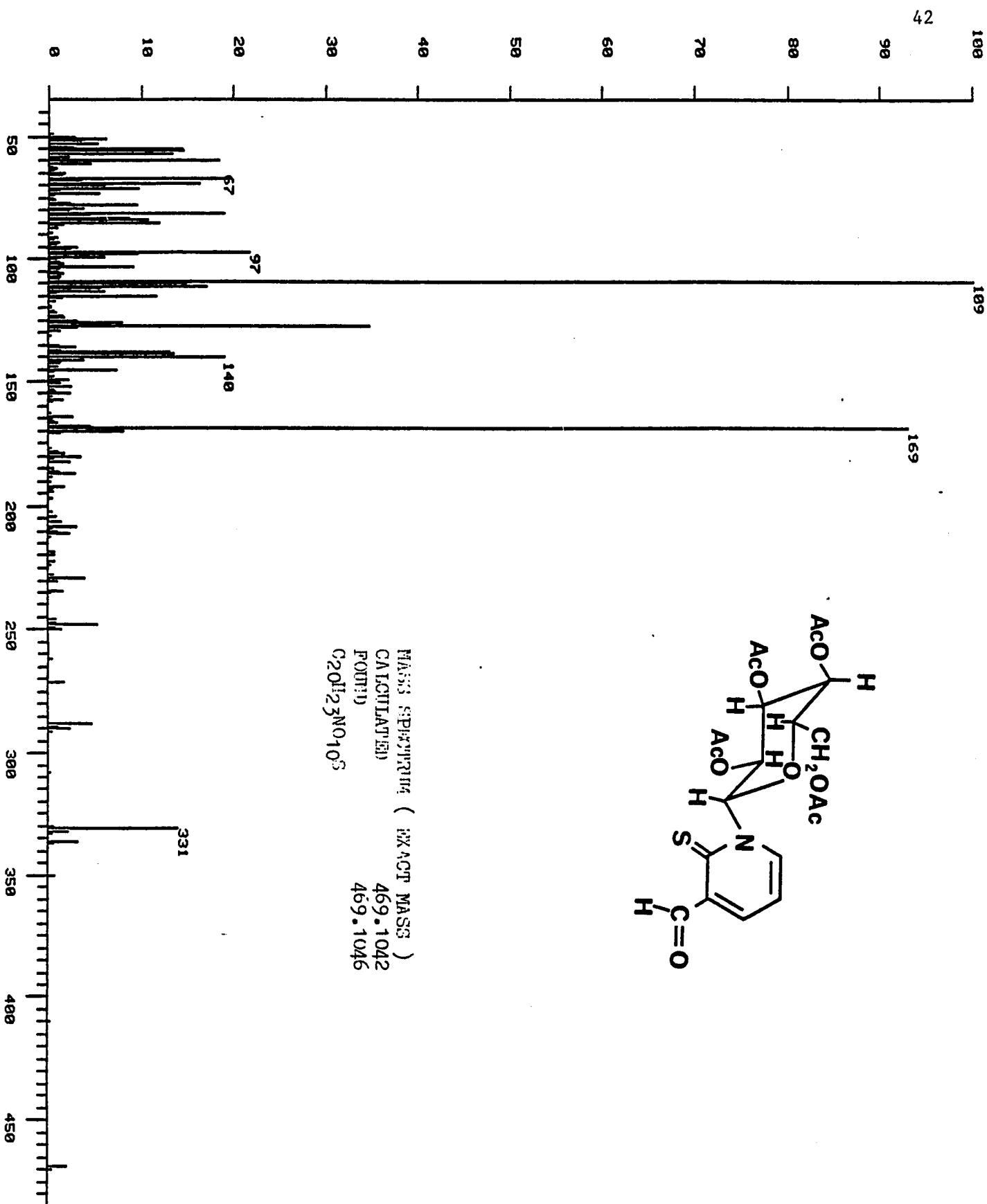
Mass Spectrum 1-2(2,3,4,6-Tetra-O-acetyl-B-D-glycopyransyl)-  
2-thiono-3-pyridine Carboxaldehyde

654.32 (TIC=1175360, 100% = 1385361) E1

I



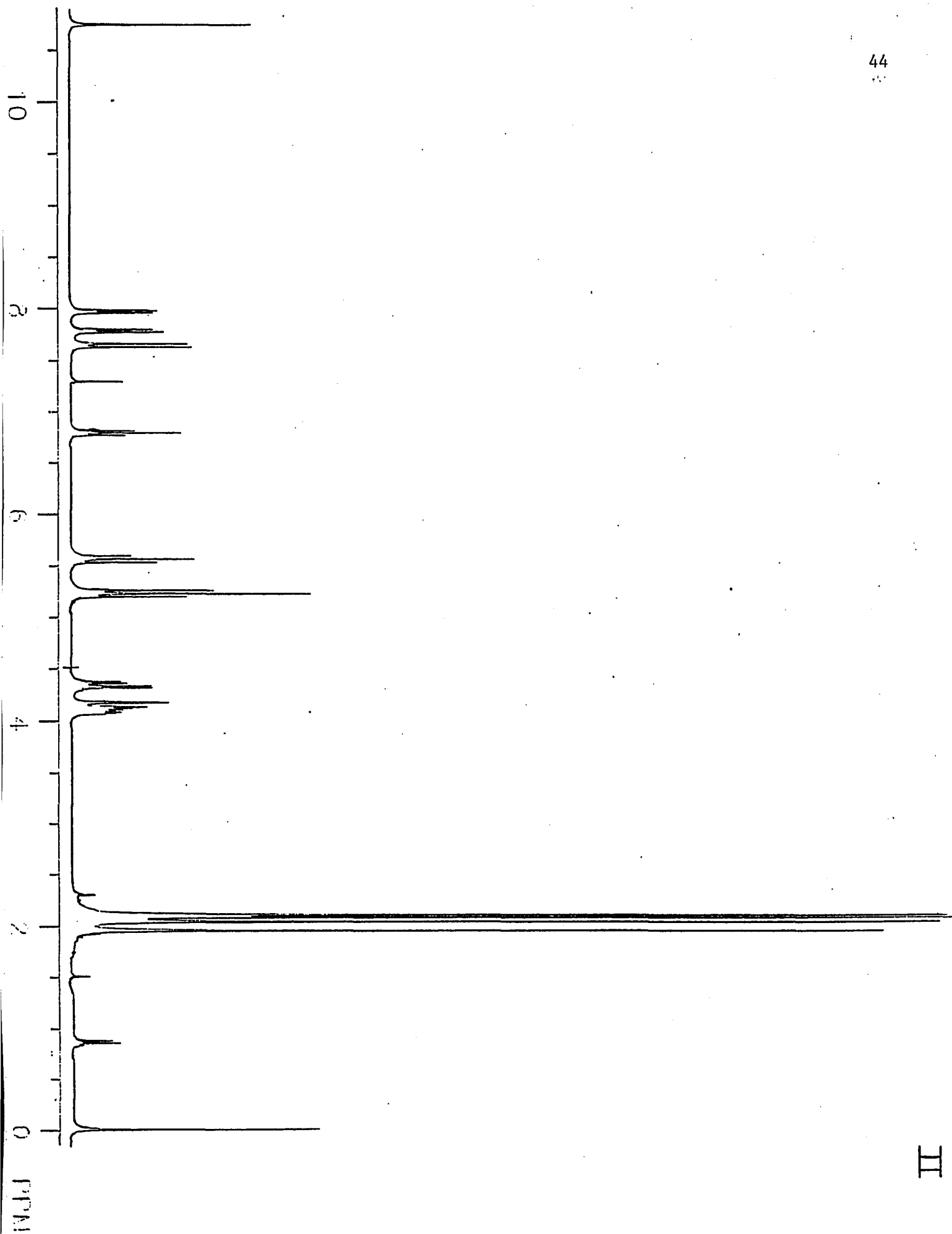
MASS SPECTRUM ( EXACT MASS )  
 CALCULATED 469.1042  
 FOUND 469.1046  
 C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub>





## APPENDIX B

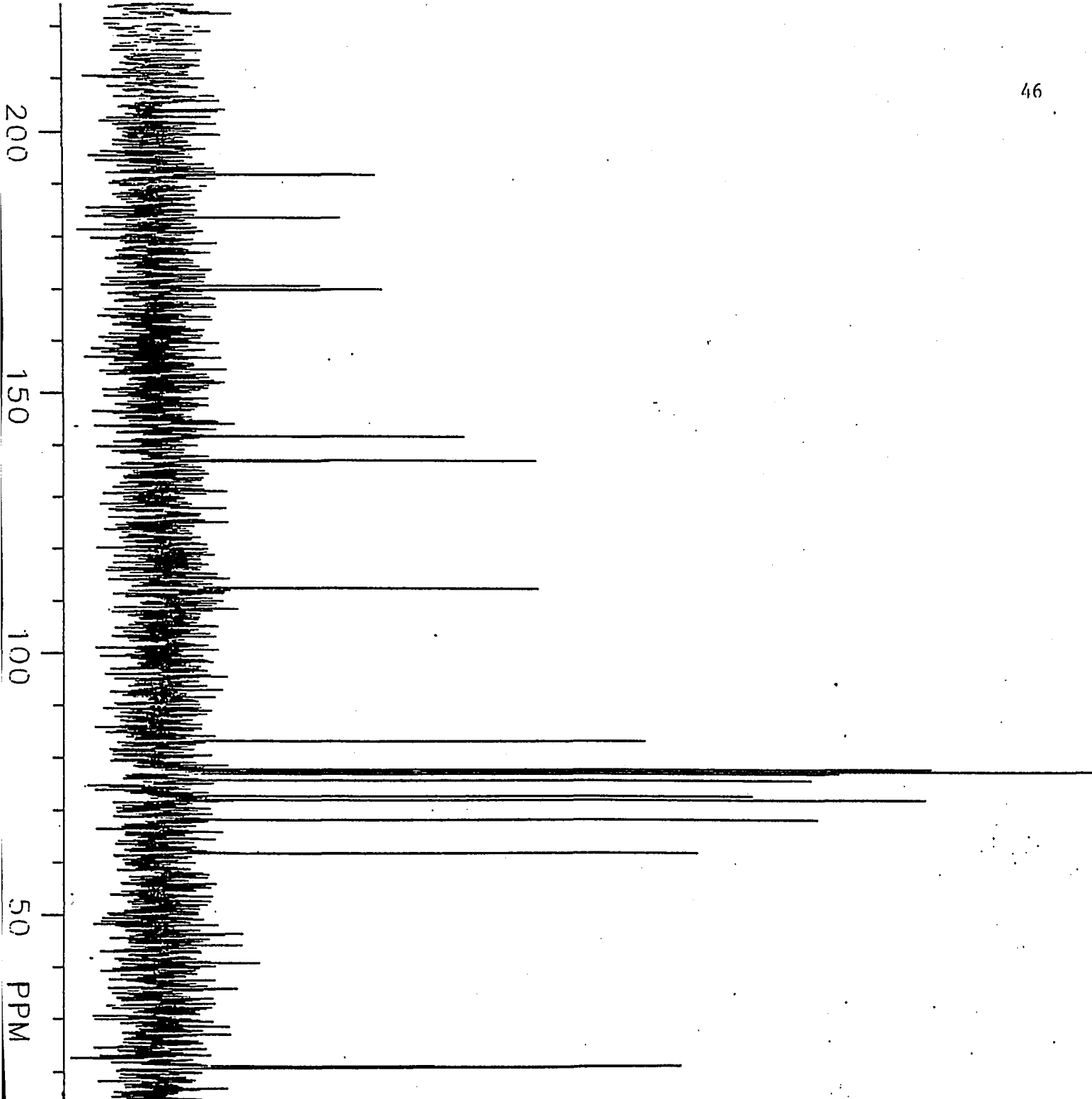
H NMR Spectrum 1-(2,3,4,6-Tetra-D-acetyl-B-D-glycopyransoyl)-  
2-thiono-2-pyridine Carboxaldehyde



II

## APPENDIX C

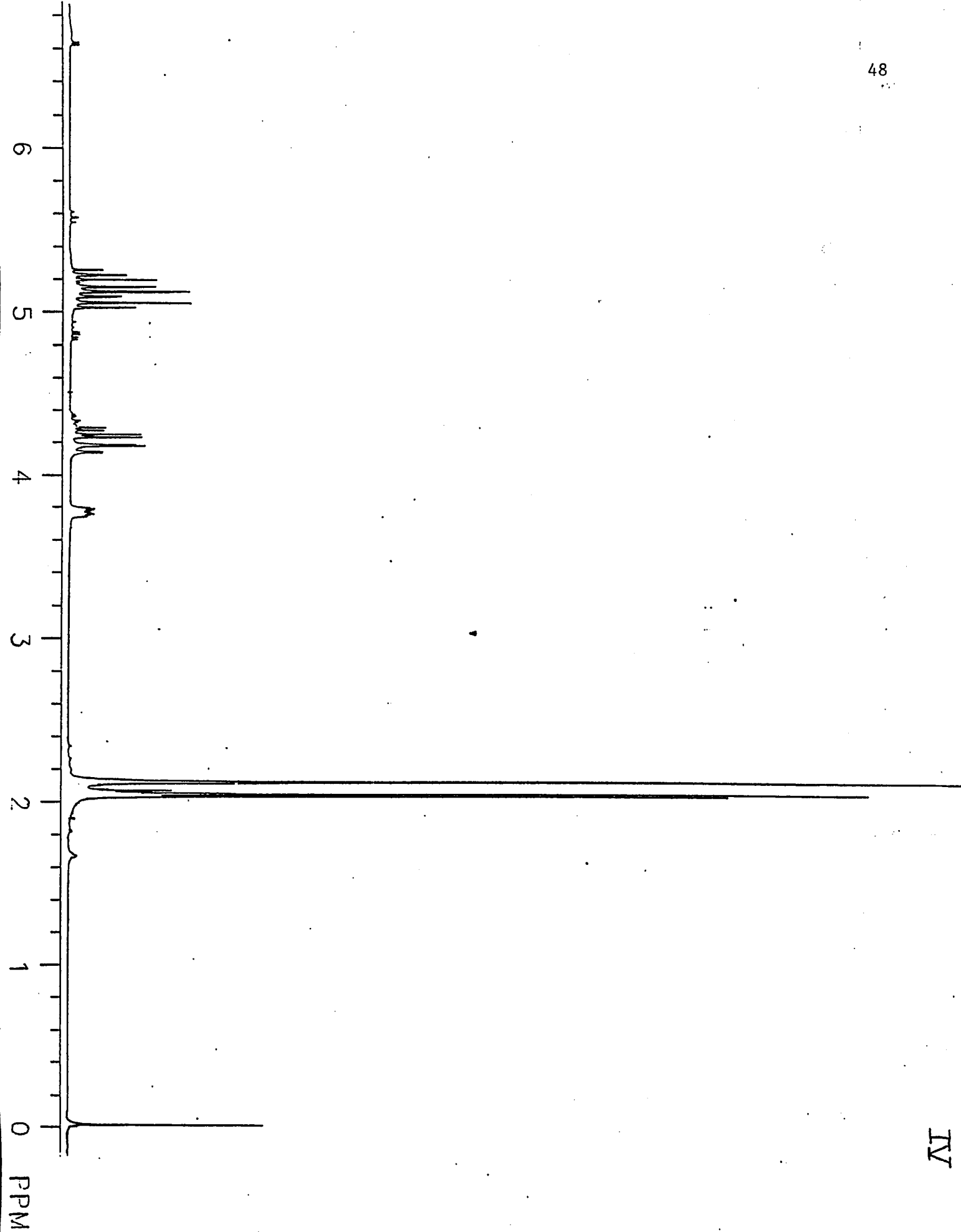
C NMR Spectrum 1-(2,3,4,6-Tetra-O-acetyl-B-D-glycopyransoyl)-  
2-thiono-3-pyridine Carboxaldehyde



H

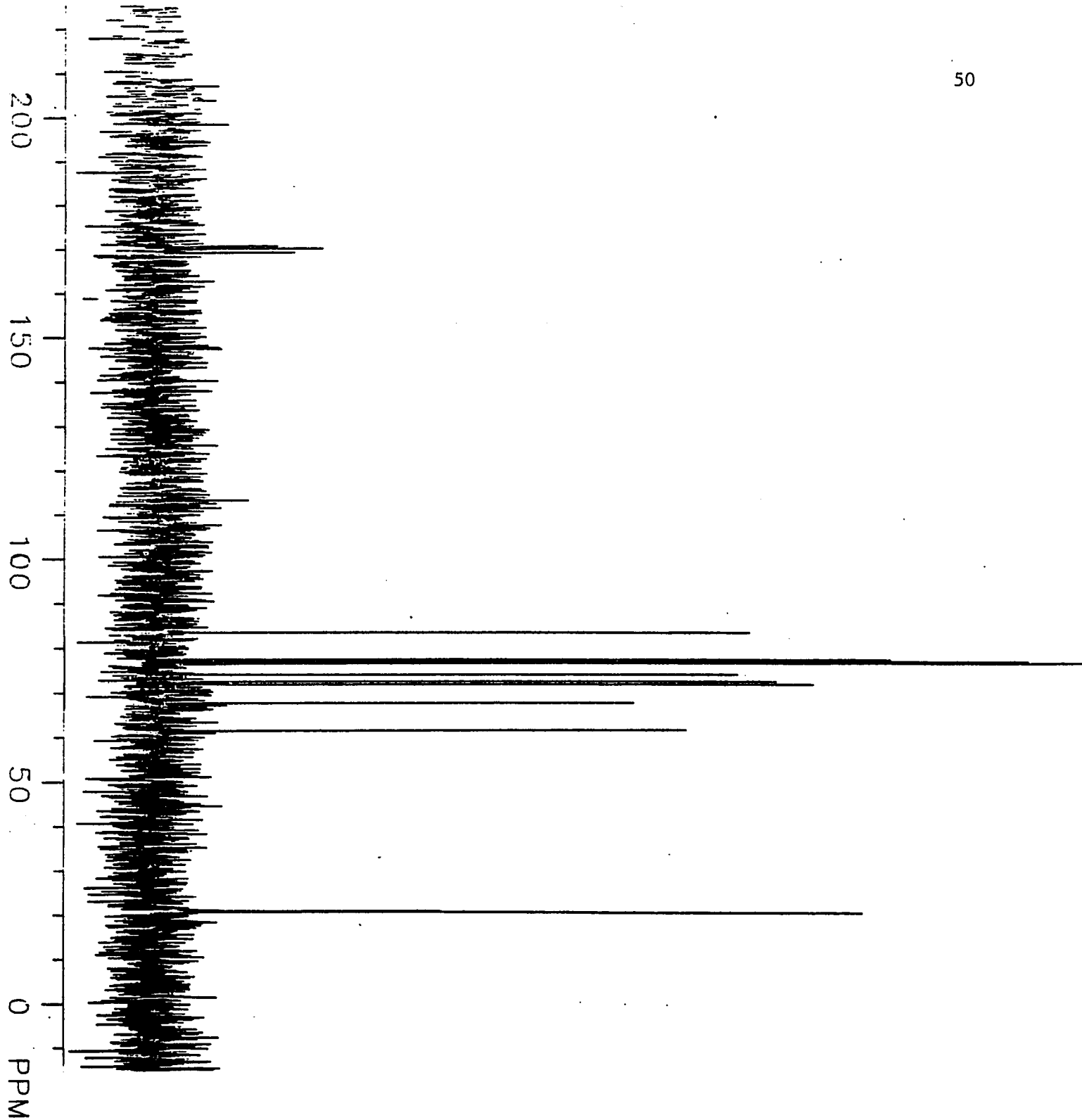
#### APPENDIX D

<sup>1</sup>H NMR Spectrum 2,3,4,6-Tetra-O-acetyl-β-D-glycopyransoyl Isothiocyanate



## APPENDIX E

C NMR Spectrum 2,3,4,6-Tetra-O-acetyl- $\beta$ -D-glycopyransoyl Isothiocyanate



V



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