# THE STRUCTURE AND THE ABSOLUTE CONFIGURATION OF ANISOMYCIN, THE REACTION OF BENZENEDIAZONIUM-2-CARBOXYLATE AND 3-PYRROLINE, AND THE PREPARATION AND NUCLEAR MAGNETIC RESONANCE STUDIES OF SUBSTITUTED α-FLUOROTOLUENES

by

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# PART [A]

## THE STRUCTURE AND THE ABSOLUTE CONFIGURATION OF ANISOMYCIN

## ABSTRACT [A]

The antibiotic anisomycin ( A-I ) has been isolated and its structure has been elucidated as 2-p-methoxyphenylmethyl-3-acetoxy-4-hydroxypyrrolidine. However, the absolute configuration of the antibiotic was still unknown. In order to determine this, work was carried out in this laboratory to stereospecifically prepare compounds that could be correlated to the natural antibiotic or its derivatives. In one approach, L-tyrosine was converted stereospecifically to N-benzoyl-2-(p-methoxybenzyl)-3-hydroxy-4-cyanopyrrolidine ( A-XXXV ) which has the absolute stereochemistry 2S, 3S, 4S and a specific rotation $[\alpha]_D^{20}$ +97°. Anisomycin was also converted to N-benzoyl-2-(p-methoxybenzyl)-3-hydroxy-4-cyanopyrrolidine ( A-XXXX ) which has an infrared spectrum superimposable to that of A-XXXV and a specific rotation $[\alpha]_D^{20}$ -110°. Thus the absolute configuration of the three asymmetric centres in A-XXXX are 2R, 3R, 4R and hence anisomycin should have the absolute stereochemistry 2R, 3S, 4S as depicted in A-III.

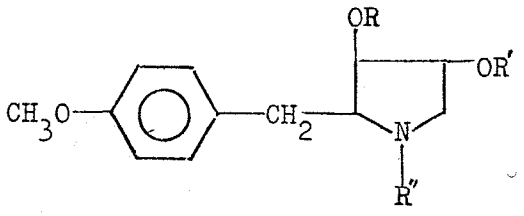
# INTRODUCTION [A]

In 1954 B. A. Sobin and F. W. Tanner Jr.[A-1] isolated a monobasic antibiotic anisomycin from cultures of various species of Streptomyces. It has been shown to have a widespread high degree of activity against certain pathogenic protozoa[A-1,A-2], notably Trichomonas vaginalis and Endamoeba histolytica. It has been found to be effective in the treatment of amoebic dysentery and has been used for that purpose[A-3]. In 1966, Grollman found, in the study of the ipecac alkaloids, that these alkaloids block the aminoacyl-sRNA transfer reaction in protein biosynthesis[A-4]. In 1967, he found that anisomycin effects a similar inhibition[A-5]. On the basis of these results and common structural features between the ipecac alkaloids and anisomycin, Grollman has formulated a structural basis for the inhibition of protein synthesis.

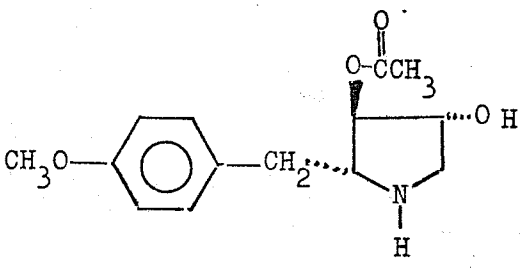
In 1954, Tanner found that titration data and analysis are in agreement with the molecular formula $C_{14}H_{19}NO_2$ for anisomycin ( A-I )[A-1]. Further chemical studies[A-6] indicated that A-I possesses a methoxyl group, an acetyl group and two active hydrogens. The basicity of A-I ( $pK_a$ 7.9 from the titration of A-I ) indicates that the nitrogen must be present as an amine. The infrared spectrum of A-I indicates the presence of a hydroxyl group ( 2.82 $\mu$ ), an ester group ( 5.78 and 8.05 $\mu$ ) and an aromatic ring ( 6.22 $\mu$ ). The ester group was determined as an acetoxy group since either acidic or basic hydrolysis of A-I yielded acetic acid and deacetylanisomycin ( A-IV ). The presence of an aromatic ring system was further substantiated by the ultraviolet spectrum of A-I ( $\lambda_{max}$ 224 and 277 m$\mu$ ) which is very similar to that of p-anisyl alcohol. This aromatic ring was identified as p-methoxyphenyl group by oxidative degradation of A-I to anisic acid by means of potassium

permanganate. Since A-I does not absorb hydrogen in the presence of platinum catalysts, the presence of a double bond is highly unlikely. The molecular formula requires then the presence of a second ring in the molecule. The nature of this second ring was shown to be pyrrolidine since after zinc dust distillation of A-I a pyrrolic material was obtained, which gave positive tests with pyrrole reagents — such as concentrated hydrochloric acid and p-dimethylaminobenzaldehyde in methanol — and whose infrared spectrum was virtually identical with that of the synthetic 2-anisylpyrrole. The positions of the p-methoxyphenyl group and the hydroxyl group were established by a series of reactions and degradations on deacetylanisomycin ( A-IV ) and O-methyl-anisomycin ( A-V ) as follows. Treatment of A-IV with methyl iodide in the presence of base provided N-methyl-deacetylanisomycin methiodide ( A-IX ). Reaction of A-IX with strong caustic solution resulted in a Hofmann elimination reaction to provide 1-(p-methoxyphenyl)-3,4-dihydroxy-5-dimethyl-amino-1-pentene ( A-XI ). Both hydroxyl groups were still present in the molecule since treatment of A-XI with acetic anhydride and pyridine gave the corresponding diacetyl compound ( A-XIII ). The ultraviolet spectrum of A-XI ( peak at 262 and shoulders at 292 and 303 m$\mu$) were quite similar to those reported for anethole[A-7], indicating that the double bond is in conjugation with the p-methoxyphenyl ring. Then the location of the p-methoxyphenyl group was established as at C-2 of the pyrrolidine ring. N-acetylanisomycin ( A-VI ) was obtained as crystalline precipitates after dissolving A-I in acetic anhydride. Reaction of A-VI with methyl iodide in the presence of silver oxide provided O-methyl-N-acetylanisomycin ( A-VII ) as indicated by the disappearance of hydroxyl absorption in the infrared spectrum and by methoxyl analysis of A-VII. Basic hydrolysis of A-VII removed the acetyl groups to give A-V. A-V was subjected to a similar series of reactions as

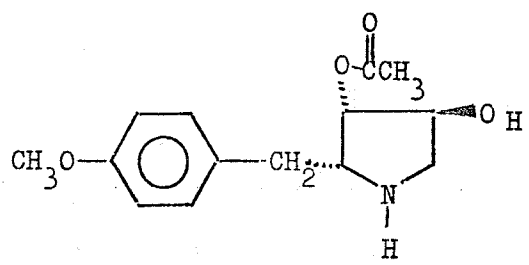
A-IV to give first A-X and then A-XII. The position of the hydroxyl group was obtained by the mild oxidation of A-XII — an allylic alcohol — with manganese dioxide. The resulting ketone ( A-XIV ) was shown to be α,β-unsaturated by its infrared spectrum ( 5.93 μ ). The ultraviolet spectrum of A-XIV ( $\lambda_{max}$ 331 mμ ) was similar to that of 1-p-methoxyphenyl-5-dimethylamino-1-penten-3-one hydrochloride ( $\lambda_{max}$ 323 mμ )[A-8] indicating conjugation of the carbonyl with the double bond and the p-methoxyphenyl ring. Thus the position of the hydroxyl group is at C-4 of the pyrrolidine ring. A-XI suggested that the acetoxy group is located at C-3 of the pyrrolidine ring. However, there is an alternative possibility that A-XI can be produced from a benzylic alcohol via an allylic rearrangement as shown in equation (A-1). Nevertheless, this possibility was eliminated by the work done earlier in mass spectrometry. One would expect facile cleavage at the benzylic carbon atom[A-9]. If a hydroxyl group were present at the benzylic position an ion of m/e 137 should result. Such a peak was not found, but instead there was a peak at m/e 121 assignable to the p-methoxybenzyl ion or more properly the methoxytropylium ion[A-10]. Thus the gross structural features of anisomycin are best accomodated by the formula A-I.



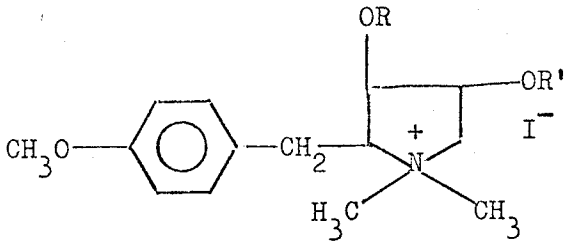
A-I R=$COCH_3$; R′,R″=H
A-IV R,R′,R″=H
A-V R,R″=H; R′=$CH_3$
A-VI R,R″=$COCH_3$; R′=H
A-VII R,R″=$COCH_3$; R′=$CH_3$
A-VIII R,R″=H; R′=$COCH_3$



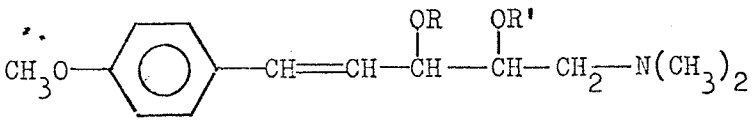
A-II



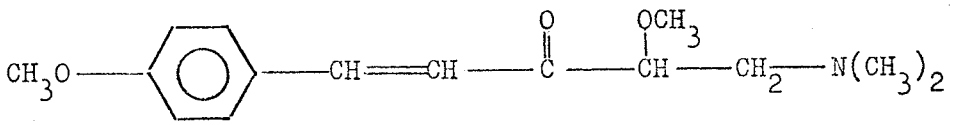
A-III



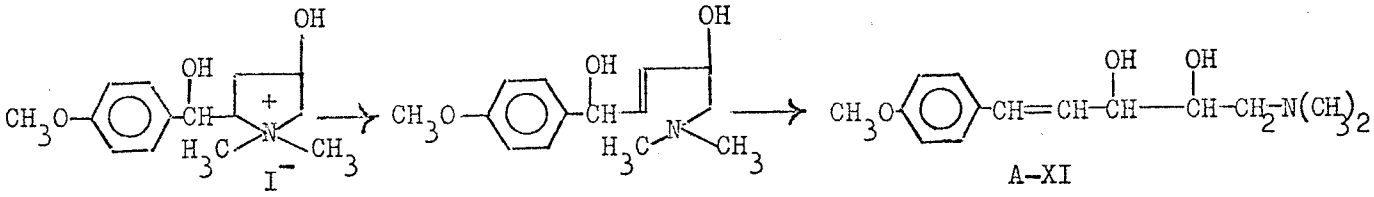
A-IX R,R'=H
A-X R=H; R'=$CH_3$



A-XI R,R'=H
A-XII R=H; R'=$CH_3$
A-XIII R,R'=$COCH_3$



A-XIV



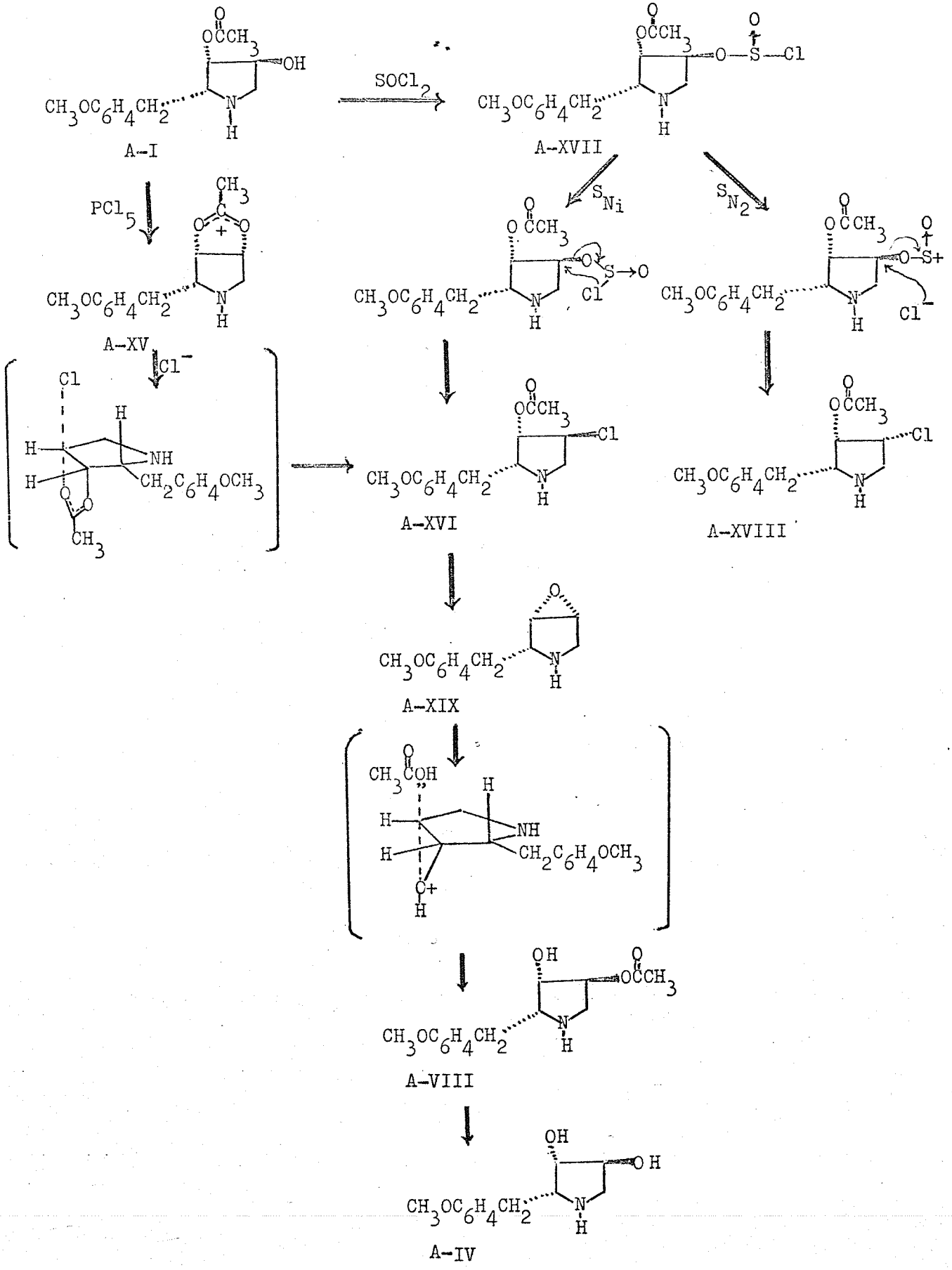
A-XI

.....(A-1)

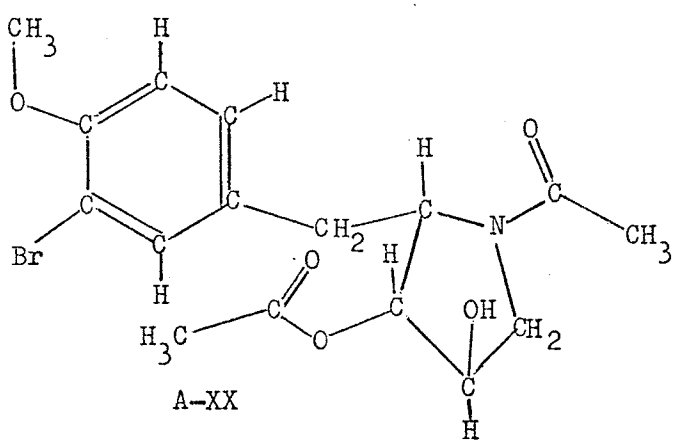
In order to establish the relative stereochemical relationships of the substituents on A-I, a complex series of transformations of the hydroxyl and acetoxy group was undertaken as follows. Reaction of A-I with phosphorus pentachloride produced A-XVI while reaction of A-I with thionyl chloride gave a crystalline chlorosulfite ( A-XVII ) which decomposed on heating to a mixture of A-XVI and A-XVIII. Both A-XVI and A-XVIII contain chlorine and an acetoxy group. However, on treatment with alcoholic potassium hydroxide only A-XVI gave a rapid formation of the epoxide ( A-XIX ) but A-XVIII remained unchanged. Therefore, the chlorine atom in A-XVI is trans to the acetoxy group. Formation of A-XIX from A-XVI gave further proof that anisomycin has a glycol-like structure. The mechanisms for the formation of A-XVI and A-XVIII throw light on the relative configuration of the acetoxy and hydroxyl groups with respect to each other. The thermal decomposition

of the chlorosulfite ( A-XVII ) must involve both $S_{N_2}$ and $S_{N_i}$ mechanisms to obtain inversion as well as retention of configuration. Phosphorus halides are known to react with alcohols by first forming a phosphorus ester. These esters are usually displaced with the inversion of configuration at carbon by a halide ion acting as a nucleophile[A-11,A-12]. However, if a neighbouring group is present which can act as a nucleophile, it can frequently intercede and replace the halide ion as the nucleophile[A-13—A-15]. If this reaction of A-I with phosphorus pentachloride involves neighbouring-group participation of the acetoxy function at C-3 to form a stable bridged carbonium ion ( A-XV ) it will allow retention of configuration in producing A-XVI. The intermediacy of A-XV in the formation of A-XVI and the relative configuration of the latter can be visuallized by analogy to the trans opening of the epoxide ( A-XIX ) with acetic acid giving primarily A-VIII, which on hydrolysis with sodium hydroxide solution gave A-IV and then should have the same configuration as A-I. Thus the formation of A-VI from A-XIX[A-6] then indicates that the acetoxy group is trans to the hydroxyl group in anisomycin. It is unfortunate that J. J. Beereboom and coworkers drew the wrong conclusion for the configuration of the substituent at C-2 from their result of the opening of A-XIX. They argued that it must be steric hindrance at the C-3 atom due to the p-methoxyphenylmethyl substituent at C-2 inhibiting the nucleophilic attack at C-3 and therefore the p-methoxyphenylmethyl group must be trans to the epoxide ring in A-XIX as well as the acetoxy group in anisomycin as shown in A-II. In 1967, J. P. Schaefer and P. J. Wheatley[A-16,A-17] carried out a three-dimensional X-ray diffraction analysis of N-acetylbromo-anisomycin ( A-XX ). The structure of the latter compound was determined as a substituted pyrrolidine in which the p-methoxy-m-bromobenzyl moiety on the 2 position is cis to the 3-acetoxy group which is, in turn, trans

SCHEME (A-i)



to the 4-hydroxyl function. The stucture of anisomycin was then revised to that as shown in A-III.



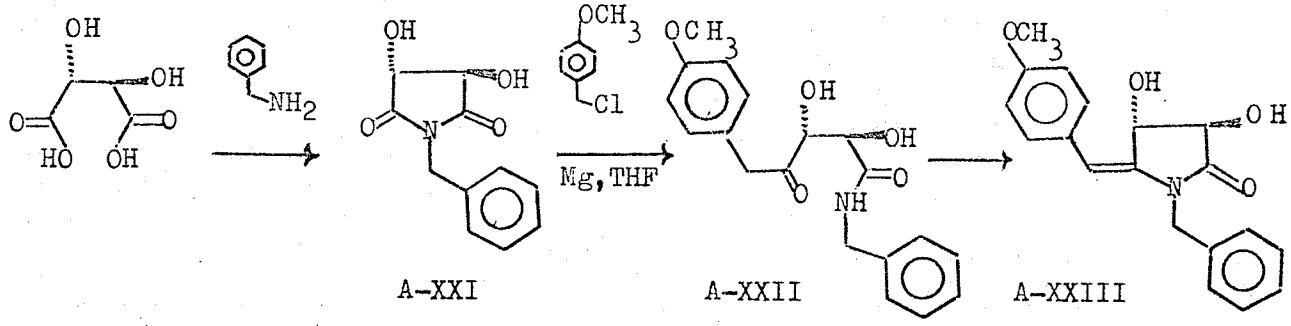
A-XX

Schaefer and Wheatley then explained the opening of the bridged carbonium ion ( A-XV ) and the epoxide ( A-XIX ) as controlled by the energy of the transition state. It is possible that if the nucleophile attacks at C-3, in the transition state, the hydrogen atom at C-3 may come quite close to the p-methoxyphenylmethyl group at C-2 and hence increase the energy of the system. This will not happen when the nucleophile attacks at C-4 and hence has the lowest transition state energy for the ring opening. Scheme (A-i) summarizes the reactions.

Since the X-ray study only showed the relative configuration of anisomycin and the absolute configuration of the antibiotic was still unknown, it was our interest to stereospecifically prepare compounds that could be correlated to the natural antibiotic or its derivatives and hence to determine the absolute configuration of anisomycin.

## RESULTS AND DISCUSSION [A]

In one of our approaches to synthesize anisomycin, 2R 3R (+)-tartaric acid was refluxed with benzyl amine in xylene solution to give N-benzyl tartarimide ( A-XXI )[A-18]. A solution of A-XXI in anhydrous tetrahydrofuran was added to the Grignard reagent of anisyl chloride and the mixture was stirred at 40°C. in an oil bath. After the decomposition of the excess Grignard reagent, the keto-amide ( A-XXII ) was isolated. The recyclization of the heterocyclic ring was unsuccessful by simple sublimation or by refluxing in a high boiling solvent such as dimethylformamide, but was achieved by heating a solution of A-XXII in absolute ethanol -- under nitrogen ( 50 psi ), at 138°C. for seven hours -- to form the unsaturated lactam ( A-XXIII ) as shown in equation (A-2). At first, it was not sure if the keto group in A-XXII will enolize and hence may epimerize the α hydroxyl group. The formation of A-XXIII then showed the reactivity of the benzylic hydrogens and hence even if A-XXII did enolize, the hydrogen involved would be the benzylic one.

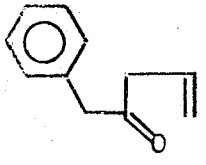



A-XXI A-XXII A-XXIII

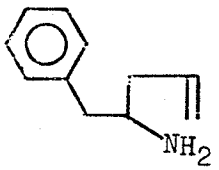
.....(A-2)

In fact, enolization did not occur even in 4-keto-5-phenyl-1-pentene ( A-XXIV ), a similar but much simpler compound isolated in the model reaction of another approach to prepare anisomycin. As a model reaction in that approach, a solution of benzyl cyanide in anhydrous ether was added to and then refluxed with allyl magnesium bromide. A-XXIV was isolated after

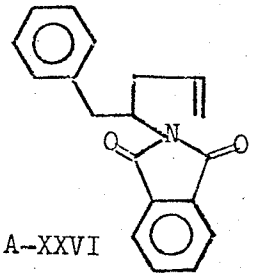
the decomposition of a small portion of the reaction mixture. The infrared spectrum of A-XXIV showed definitely a non-conjugated ketone ( 5.84 $\mu$) and a non-conjugated double bond ( 6.10 $\mu$). The remaining reaction mixture which was then free of excess benzyl cyanide as shown by the infrared spectrum of the decomposed portion, was treated and refluxed with lithium aluminium hydride. After the decomposition of the excess lithium aluminium hydride, 4-amino-5-phenyl-1-pentene ( A-XXV ) was isolated. The phthalimide ( A-XXVI ) was prepared by the action of phthalic anhydride on A-XXV in refluxing toluene, while on warming A-XXV at 60°C. in acetic anhydride and pyridine N-acetylation occurred to give A-XXVII. In attempting to modify the olefin function in A-XXVI and A-XXVII to some other functions that are useful for the cyclization of the two side chains into a heterocyclic ring, A-XXVI and A-XXVII were subjected to the action of various reagents: a) 90% hydrogen peroxide in acetic acid at 40°C.[A-19], b) silver iodobenzoate in anhydrous benzene[A-20,A-21], c) powdered potassium permanganate in ice-cold acetone and piperidine[A-22,A-23], and d) osmium tetroxide in pyridine and anhydrous benzene[A-24]. However, only one of the above reactions, namely the action of osmium tetroxide gave the corresponding diol A-XXVIII. Apparently, unexpected reactions occur due to the reactivity of the benzylic hydrogens. Hence this approach was abandoned.



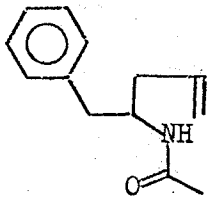
A-XXIV



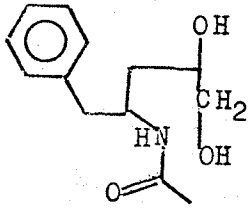

A-XXV




A-XXVI



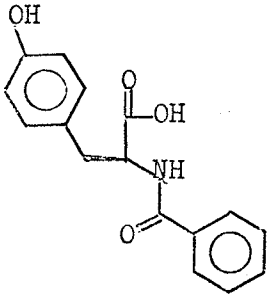

A-XXVII



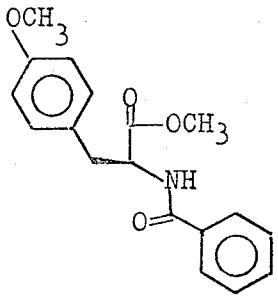

A-XXVIII

In another approach[A-25], S (-)-tyrosine was treated with benzoyl chloride

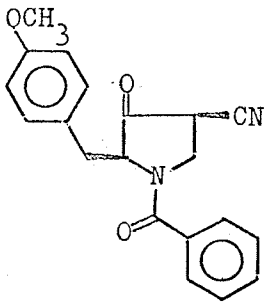
in chloroform solution followed by hydrolysis with methanolic potassium carbonate solution to give the N-benzoyl carboxylic acid ( A-XXIX ). Methylation of A-XXIX with methyl iodide in absolute methanol and potassium carbonate solution gave the ester ( A-XXX ). Condensation of A-XXX with acrylonitrile in anhydrous ether solution containing sodium hydride gave an acidic product. The infrared spectrum of the latter showed the presence of a five-membered ring ketone and a cyano group. All efforts to crystallize the amorphous acidic product were unsuccessful. It was assumed that this product was a mixture of the ketonitriles ( A-XXXI and A-XXXII ). Sodium borohydride reduction of the acidic ketonitriles in absolute methanol gave a neutral amorphous product. The infrared spectrum showed the presence of hydroxyl and cyano groups.



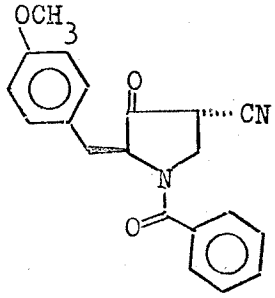
A-XXIX



A-XXX



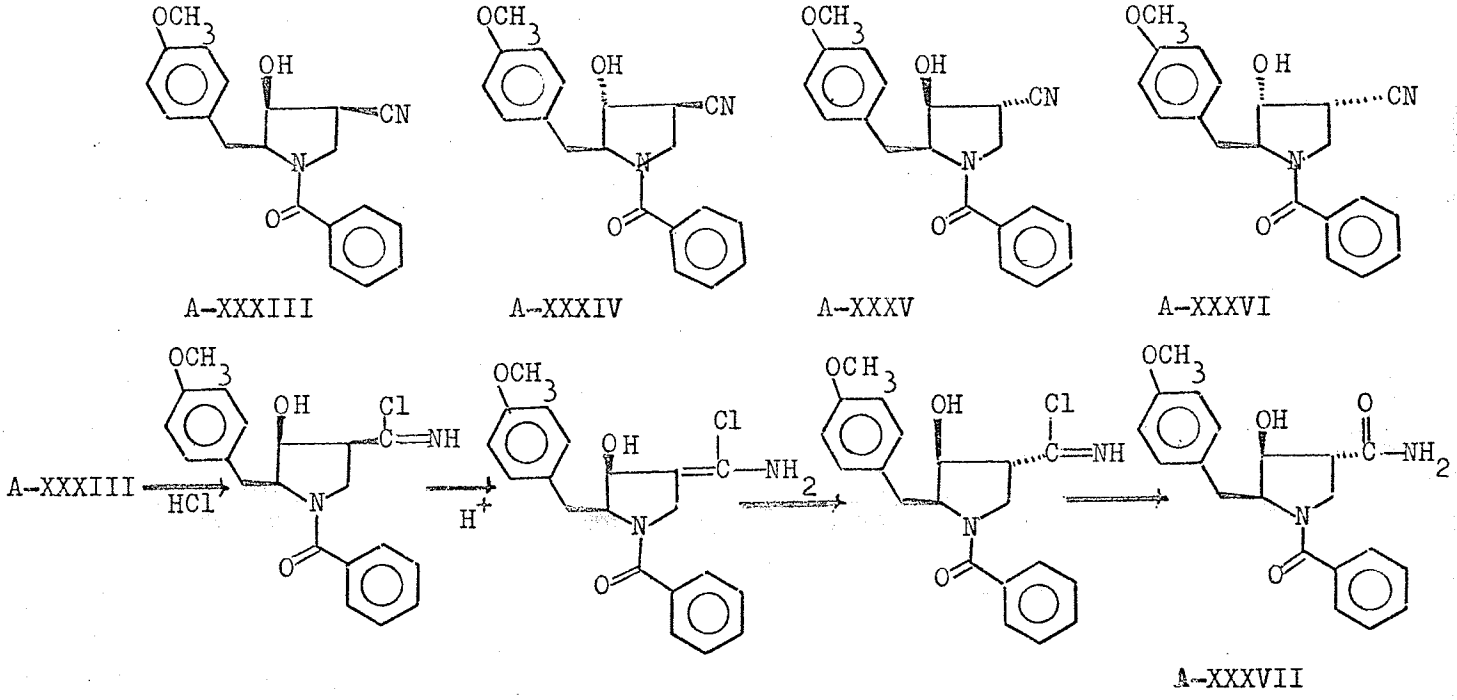
A-XXXI



A-XXXII

Sodium borohydride reduction of the ketonitriles ( A-XXXI and A-XXXII ) could give four hydroxynitriles ( A-XXXIII, A-XXXIV, A-XXXV and A-XXXVI ). However, due to the steric effect of the p-methoxy-phenylmethyl group at C-2 of the pyrrolidine ring, the borohydride complex should come mainly from the α side of the pyrrolidine ring to give A-XXXIII, as the major product from A-XXXI, and A-XXXV, as the major product from A-XXXII. Separation of the reduction product by thin layer chromatography ( neutral alumina ) showed two major bands after four developments. These two fractions gave extremely similar infrared and mass spectra. One could be easily crystallized while the other remained as an amorphous solid, possibly due to the presence of small

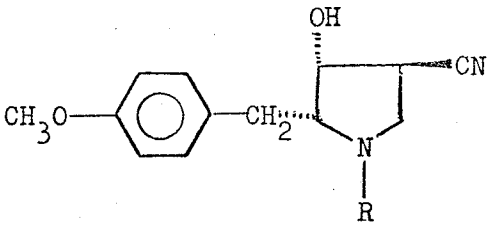
amounts of other isomers. Hydrolysis of the crystalline and amorphous hydroxynitriles with concentrated hydrochloric acid led to an identical hydroxycarboxamide. This shows that the hydroxycarboxamide should be assigned the structure A-XXVII, having the more stable configuration of the two possible structures. The conversion of A-XXXIII to A-XXXVII can then be interpreted as shown in equation (A-3).




.....(A-3)

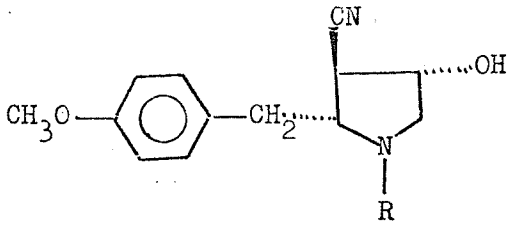
The crystalline synthetic hydroxynitrile was assigned the structure A-XXXV ( with the hydroxyl group trans to the cyano group ) after it was successfully correlated with its enantiomer ( A-XXXX ) which was obtained from the epoxide ( A-XIX ) of anisomycin as follows. Action of sodium cyanide on A-XIX in aqueous t-butanol gave two basic hydroxynitriles ( A-XXXVIII and A-XXXIX ) which could not be separated by thin layer chromatography or fractional recrystallization. This mixture was then converted into the corresponding benzoyl derivatives ( A-XXXX and A-XXXXI ) after reaction with benzoyl chloride

and pyridine in chloroform. This product could then be separared by thin layer chromatogrphy into two fractions. Both fractions showed the presence of hydroxyl, cyano and N-benzoyl groups in their infrared spectra. One fraction was easily crystallized while the other remained an amorphous solid. The crystalline fraction had an infrared spectrum superimposable with that of A-XXXV and an optical rotation of $-110^{\circ}$ as compared to $+97^{\circ}$ for A-XXXV. Thus, the crystalline fraction could be represented by the structure A-XXXX ( with the hydroxyl group at C-3 of the pyrrolidine ring ) and the amorphous fraction could then be assigned the structure A-XXXXI. Since A-XXXV was prepared from S (-)-tyrosine, the absolute configuration of A-XXXV should be 2S, 3S, 4S and then the absolute configuration of A-XXXX should be 2R, 3R, 4R. Thus, anisomycin should have the absolute stereochemistry 2R, 3S, 4S as depicted in A-III.




A-XXXVIII R=H

A-XXXX R=-C(=O)-Ph




A-XXXIX R=H

A-XXXXI R=-C(=O)-Ph

# EXPERIMENTAL [A]

## A-i PREPARATION OF 4-KETO-5-PHENYL-1-PENTENE ( A-XXIV ) AND 4-AMINO-5-PHENYL-1-PENTENE ( A-XXV )

Magnesium ( 2.9 g. ) in anhydrous ether ( 200 ml. ) was stirred vigorously. Then a solution of allyl bromide ( 8.4 g. ) in anhydrous ether ( 100 ml. ) was added first one third of its volume to start the reaction and then at such a rate that the reaction mixture refluxed without external heating. After the completion of the addition, the mixture was stirred for half of an hour and then refluxed for five minutes. A solution of benzyl cyanide ( 1.9 g. ) in anhydrous ether ( 50 ml. ) was then added dropwise. The resulting mixture was refluxed for thirty-six hours. A small portion ( 2 ml. ) of this reaction intermediate was pipetted out and hydrolysed by stirring with ice water ( 20 ml. ) for fifteen minutes. The hydrolysate was then extracted with ether ( 3 x 25 ml. ). The ether extract was then washed successively with 5% hydrochloric acid solution ( 25 ml. ) and 5% sodium hydroxide solution ( 25 ml. ) before being dried ( magnesium sulphate ) and concentrated under vacuum to give A-XXIV ( 100 mg. ).

Infrared spectrum number A-1.

The remaining reaction intermediate, which was free of excess benzyl cyanide as shown by the infrared spectrum of the decomposed portion, was treated and refluxed overnight with lithium aluminium hydride ( 1.4 g. ). The reaction product was allowed to cool and the ether layer was decanted into a beaker ( 1 l. ). The residue was extracted with more anhydrous ether ( 5 x 25 ml. ). The ether solution and extracts were combined, and the remaining lithium aluminium hydride in the ether solution was decomposed by dropwise addition of ethyl alcohol. Sodium chloride ( 10 g. ) and water

( 400 ml. ) were then added. This mixture was well stirred and then filtered through a thick layer of sand. The ether layer of the filtrate was separated and the aqueous layer of the filtrate was extracted with ether ( 5 x 25 ml. ). The ether layer and extracts were combined and then washed successively with 5% hydrochloric acid solution ( 50 ml. ) and 5% sodium hydroxide solution ( 50 ml. ) before being dried ( magnesium sulphate ) and concentrated under vacuum to give A-XXV ( 1.7 g. ).

Infrared spectrum number A-2.

Nuclear magnetic resonance spectrum number A-1.

A-ii PREPARATION OF 4-PHTHALIMINO-5-PHENYL-1-PENTENE ( A-XXVI )

A-XXV ( 800 mg. ) was refluxed overnight with phthalic anhydride in toluene ( 50 ml. ) inside a flask fitted with a water separator and condenser. The toluene was distilled off and ether was added. The ether solution was extracted with 5% sodium hydroxide solution ( 3 x 25 ml. ) before being dried and concentrated. Chromatography of the residue ( neutral alumina ) gave an oil ( A-XXVI, 500 mg. ).

Infrared spectrum number A-3.

Nuclear magnetic resonance spectrum number A-2.

A-iii PREPARATION OF 4-(ACETYLAMINO)-5-PHENYL-1-PENTENE ( A-XXVII )

A-XXV ( 800 mg. ) was heated overnight with acetic anhydride ( 3.2 g. ) and pyridine ( 800 mg. ) at 60°C. in an oil bath. The excess acetic anhydride was distilled off at reduced pressure to give A-XXVII ( 1.0 g. ).

Infrared spectrum number A-4.

A-iv PREPARATION OF N-BENZOYL-O-METHYL-L-TYROSINE METHYL ESTER ( A-XXX )

L-tyrosine ( 10 g. ), benzoyl chloride ( 34 g. ) and pyridine ( 8 g. ), in a chloroform ( 100 ml. ) solution, were heated at 70°C. in an oil bath under anhydrous condition for fifteen hours. The chloroform solution was evaporated under reduced pressure to give a heavy oil. Aqueous methanolic potassium carbonate solution ( 150 ml., 10% ) was added to the oily residue. The solution was stirred at room temperature for two hours. After acidification with concentrated hydrochloric acid, the solution was extracted with chloroform ( 5 x 100 ml. ) and dried over magnesium sulphate. The chloroform solution was then concentrated under reduced pressure. The residue was washed with ether ( 200 ml. ). The insoluble material was separated and dried under reduced pressure. Methyl iodide ( 35 ml. ) was added to the residue together with absolute methanol ( 100 ml. ) and anhydrous potassium carbonate ( 7 g. ). After stirring for twenty-four hours at room temperature, the solution was evaporated under reduced pressure to a slurry. The slurry was diluted with water and the aqueous solution was exhaustively extracted with chloroform. The extract, dried over magnesium sulphate, was evaporated to dryness giving a yellow oily residue. Chromatography of the residue ( neutral alumina ) gave the crystalline ester A-XXX ( 6.5 g. ) which was recrystallized from ether.

Melting point: 88—89°C..

| Analysis | C | H | N |
|---|---|---|---|
| Calculated for $C_{18}H_{18}O_4N$: | 69.01 | 6.07 | 4.44 |
| Found: | 67.94 | 6.27 | 4.74 |

Infrared spectrum number A-5.

Nuclear magnetic resonance spectrum number A-3.

A-v CONDENSATION OF THE ESTER ( A-XXX ) WITH ACRYLONITRILE

Sodium hydride ( 1.5 g. ) in mineral oil suspension was added to a solution of A-XXX ( 3.0 g. ) in anhydrous ether ( 200 ml. ). The solution was refluxed under anhydrous conditions with stirring for half of an hour. Anhydrous acrylonitrile ( 4 ml. ) was injected into the solution and the resulting solution was then refluxed for forty-eight hours with vigorous stirring. The excess sodium hydride was decomposed by dropping methanol into the reaction mixture cooled in an ice bath. The solution was then extracted with water ( 50 ml. ). The aqueous solution was then extracted with chloroform ( 2 x 30 ml. ). The aqueous solution was strongly acidified with concentrated hydrochloric acid. Exhaustive extraction of the cloudy acidic solution with chloroform gave a light-yellow foam ( 2.3 g. ). Chromatography ( silica gel ) gave a white amorphous solid ( 1.8 g. ).

| Analysis | C | H | N |
|---|---|---|---|
| Calculated for $C_{20}H_{18}O_3N_2$: | 71.85 | 5.39 | 8.38 |
| Found: | 72.27 | 5.02 | 7.81 |

Infrared spectrum number A-6.

Nuclear magnetic resonance spectrum number A-4.

A-vi SODIUM BOROHYDRIDE REDUCTION OF THE KETONITRILES ( A-XXXI AND A-XXXII )

The amorphous solid ( 2.2 g. ) obtained in experimental A-v was dissolved in absolute methanol ( 100 ml. ). Sodium borohydride pellets ( 8 g. ) were added to the solution over a period of three hours. After stirring the solution at room temperature for twelve hours, the solution was concentrated to a slurry under reduced pressure. The slurry was diluted with water and extracted with chloroform. Dried over magnesium sulphate and evaporated to dryness, the extract gave an amorphous solid ( 1.8 g. ) which was then separated into

two components by thin layer chromatography ( neutral alumina ). The less polar component was recrystallized from methanol and ether.

Melting point: 156—158°C..

$[\alpha]_D^{20}$: +97° ( $CHCl_3$ ).

| Analysis | C | H | N |
|---|---|---|---|
| Calaulated for $C_{20}H_{20}O_3N_2$: | 71.43 | 5.96 | 8.33 |
| Found: | 71.69 | 6.18 | 8.20 |

Infrared spectrum number A-7.

Nuclear magnetic resonance spectrum number A-5.

A-vii HYDROLYSIS OF THE CRYSTALLINE HYDROXYNITRILE ( A-XXXV )

Concentrated hydrochloric acid ( 3 ml. ) was added to A-XXXV ( 230 mg. ). The solution was stirred at room temperature for three hours. Water ( 15 ml. ) was added and a white precipitate appeared. The solution was extracted exhaustively with chloroform. The chloroform solution was dried ( magnesium sulphate ) and concentrated to give the crystalline amide ( A-XXXVII, 168 mg. ) which was recrystallized from methanol and ether.

Melting point: 175—176°C..

| Analysis | C | H | N |
|---|---|---|---|
| Calculated for $C_{20}H_{22}O_4N_2$: | 67.80 | 6.22 | 7.91 |
| Found: | 68.00 | 6.19 | 7.81 |

Infrared spectrum number A-8.

A-viii PREPARATION OF THE HYDROXYNITRILE ( A-XXXX ) FROM THE EXPOXIDE ( A-XIX )

A-XIX$^{A-6}$ ( 608 mg. ) was refluxed with sodium cyanide ( 4 g. ) in a solution of t-butanol ( 40 ml. ) and water ( 10 ml. ) for sixty hours under nitrogen. The solution was concentrated under reduced pressure and then diluted

with water. Exhaustive extraction with chloroform gave a yellow oil ( 580 mg. ). Chromatography ( neutral alumina ) of the oily residue gave a mixture of A-XXXVIII and A-XXXIX ( 210 mg. ). Recrystallization from methanol and ether gave white crystals (170 mg. ).

Melting point: 120---124°C..

Infrared spectrum number A-9.

The white crystals ( 170 mg. ) were then dissolved in anhydrous chloroform ( 10 ml. ). Benzoyl chloride ( 300 mg. ) and pyridine ( 5 drops ) were added to the solution. After stirring for half of an hour, the chloroform solution was concentrated to an oily residue. Separation of the residue by thin layer chromatography ( silica gel ) gave the hydroxynitrile ( A-XXXX ) which was purified by recrystallization from ether and methanol.

Melting point: 156---158°C..

$[\alpha]_D^{20}$: -110° ( $CHCl_3$ ).

| Analysis | C | H | N |
|---|---|---|---|
| Calculated for $C_{20}H_{20}O_3N_2$: | 71.43 | 5.96 | 8.33 |
| Found: | 71.55 | 5.97 | 8.42 |

Infrared spectrum number A-10.

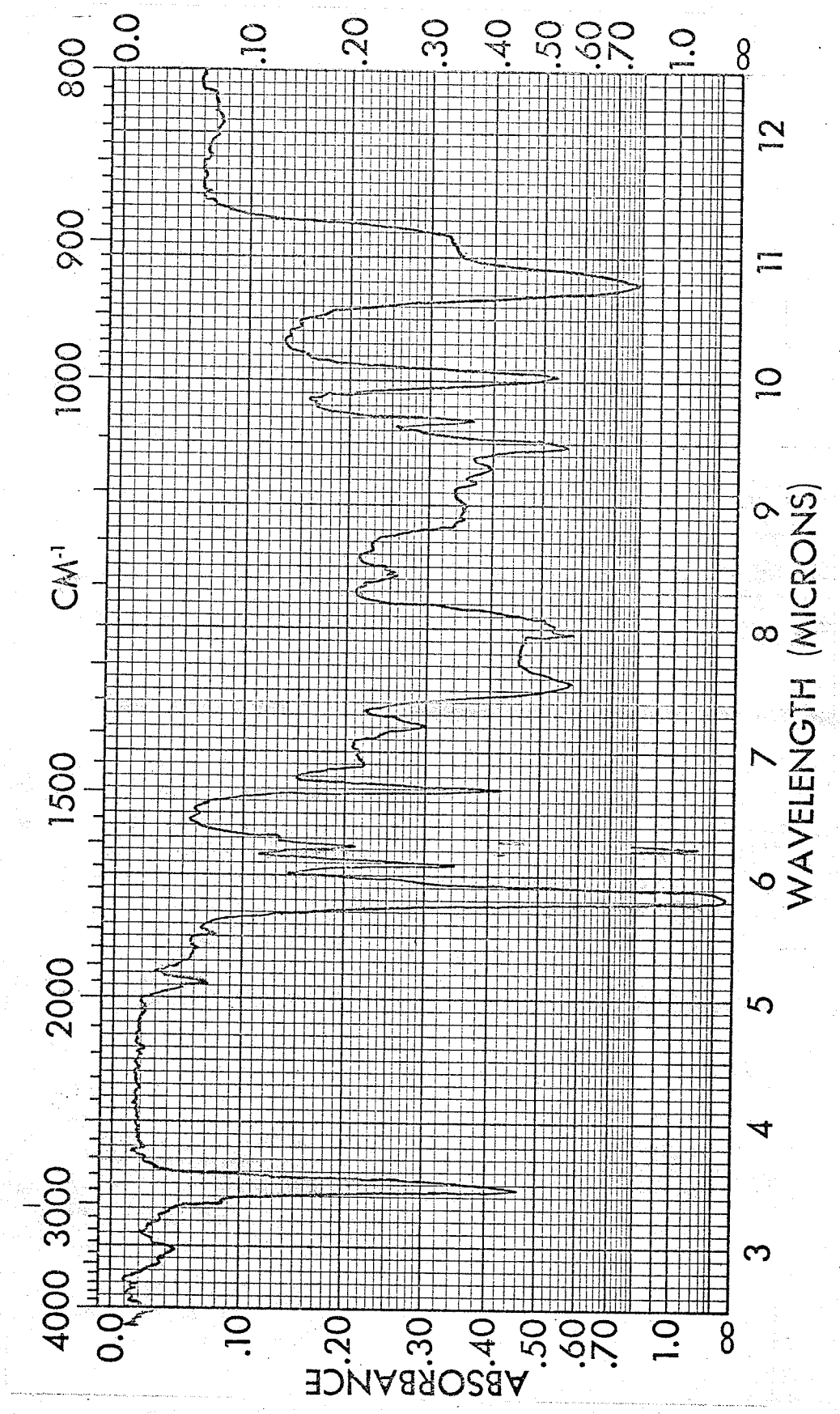



FIGURE I. Infrared spectrum number A-1.

4-keto-5-phenyl-1-pentene ( $CH_2Cl_2$ ).

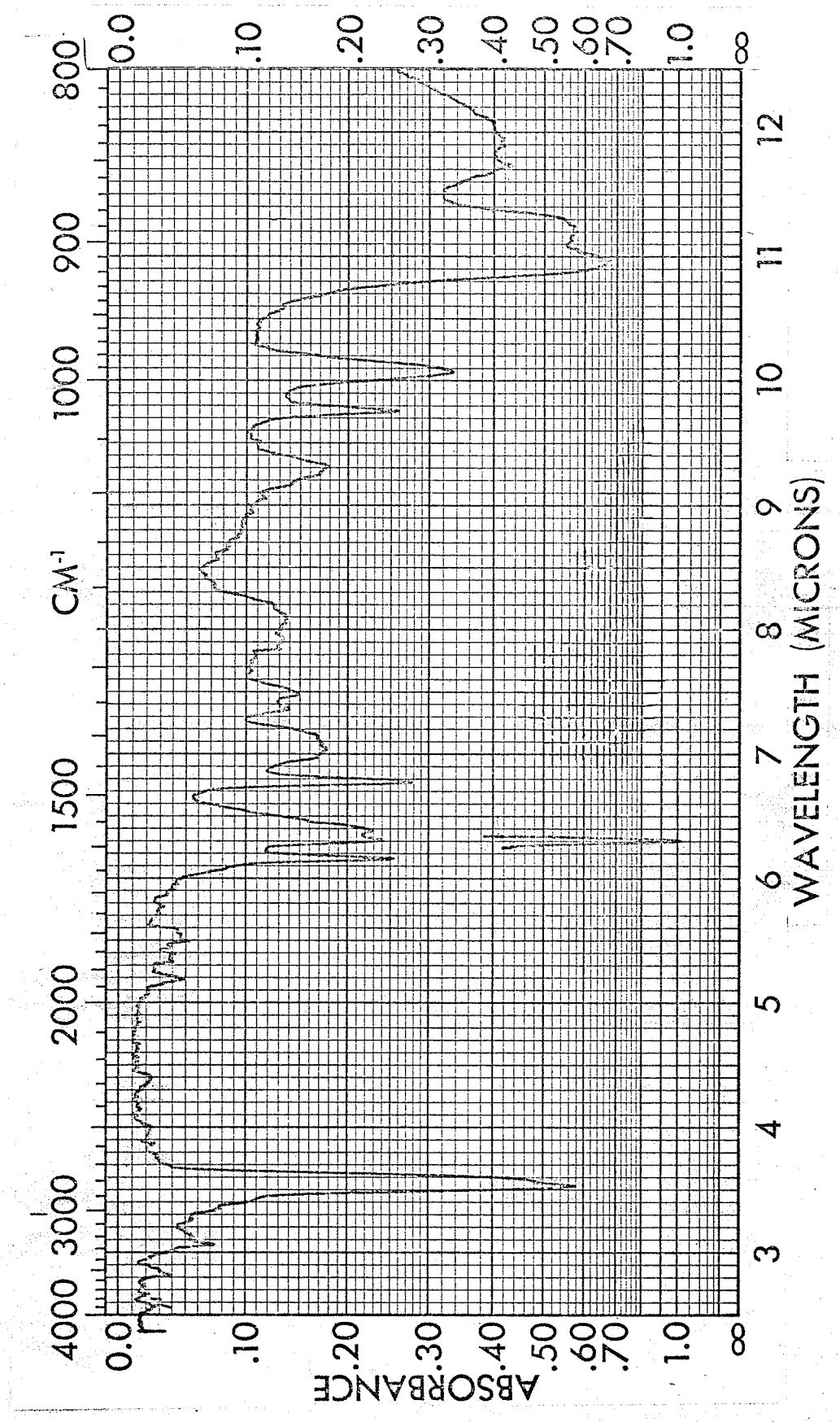



FIGURE II. Infrared spectrum number A-2.

4-amino-5-phenyl-1-pentene ( $CH_2Cl_2$ ).

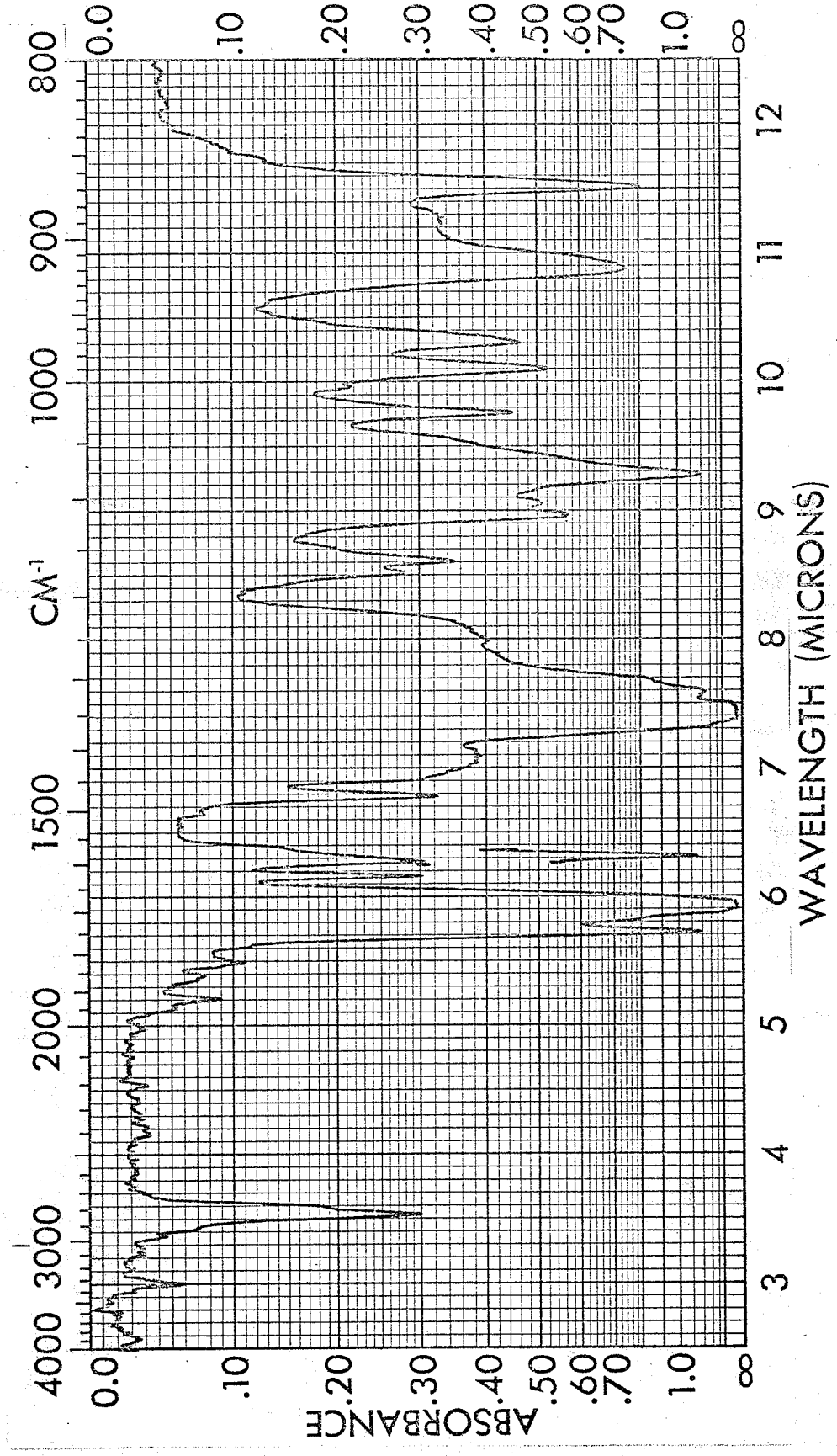



FIGURE III. Infrared spectrum number A-3.

4-phthalimino-5-phenyl-1-pentene ( $CH_2Cl_2$ ).

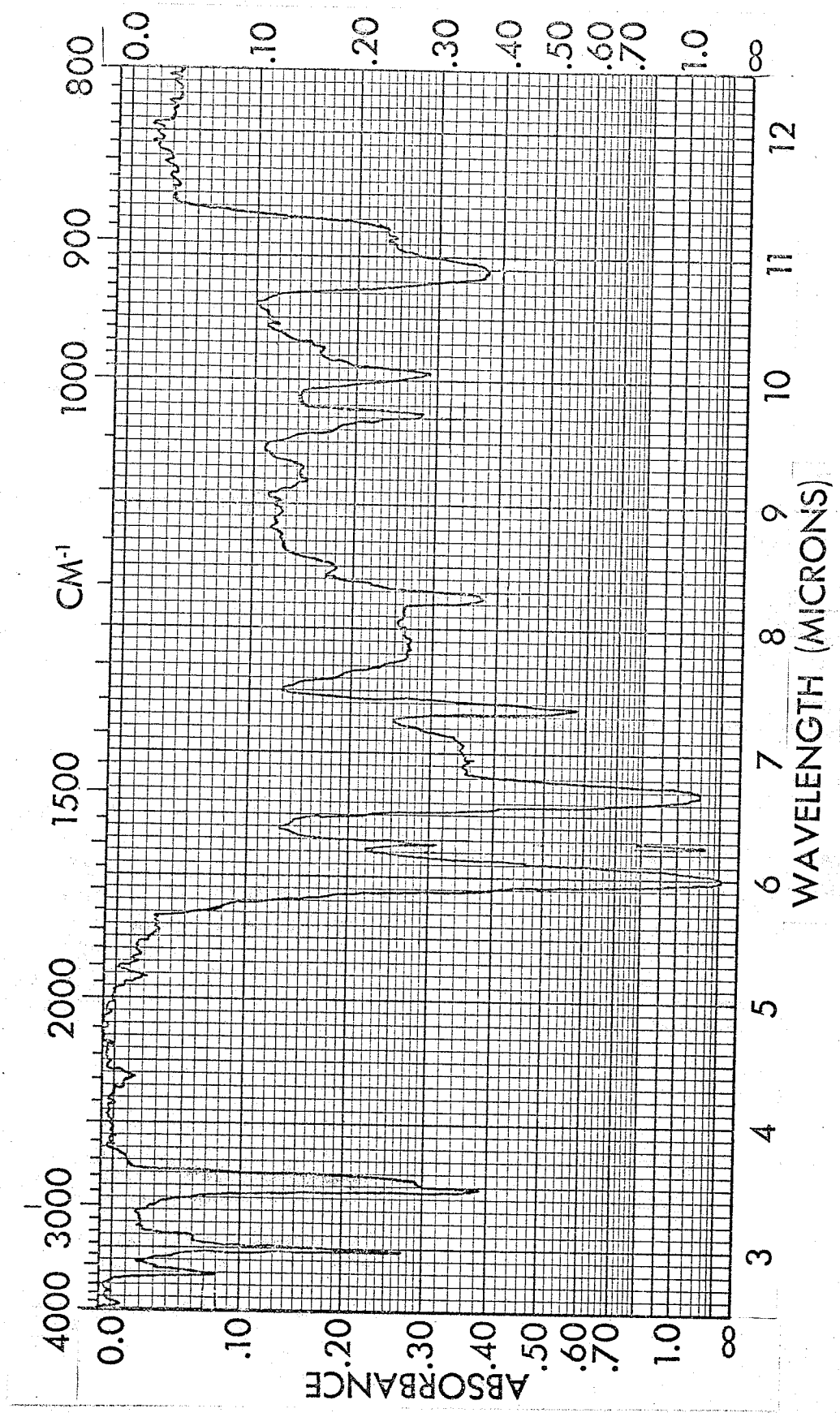



FIGURE IV. Infrared spectrum number A-4.

4-(acetylamino)-5-phenyl-1-pentene ( $CH_2Cl_2$ ).

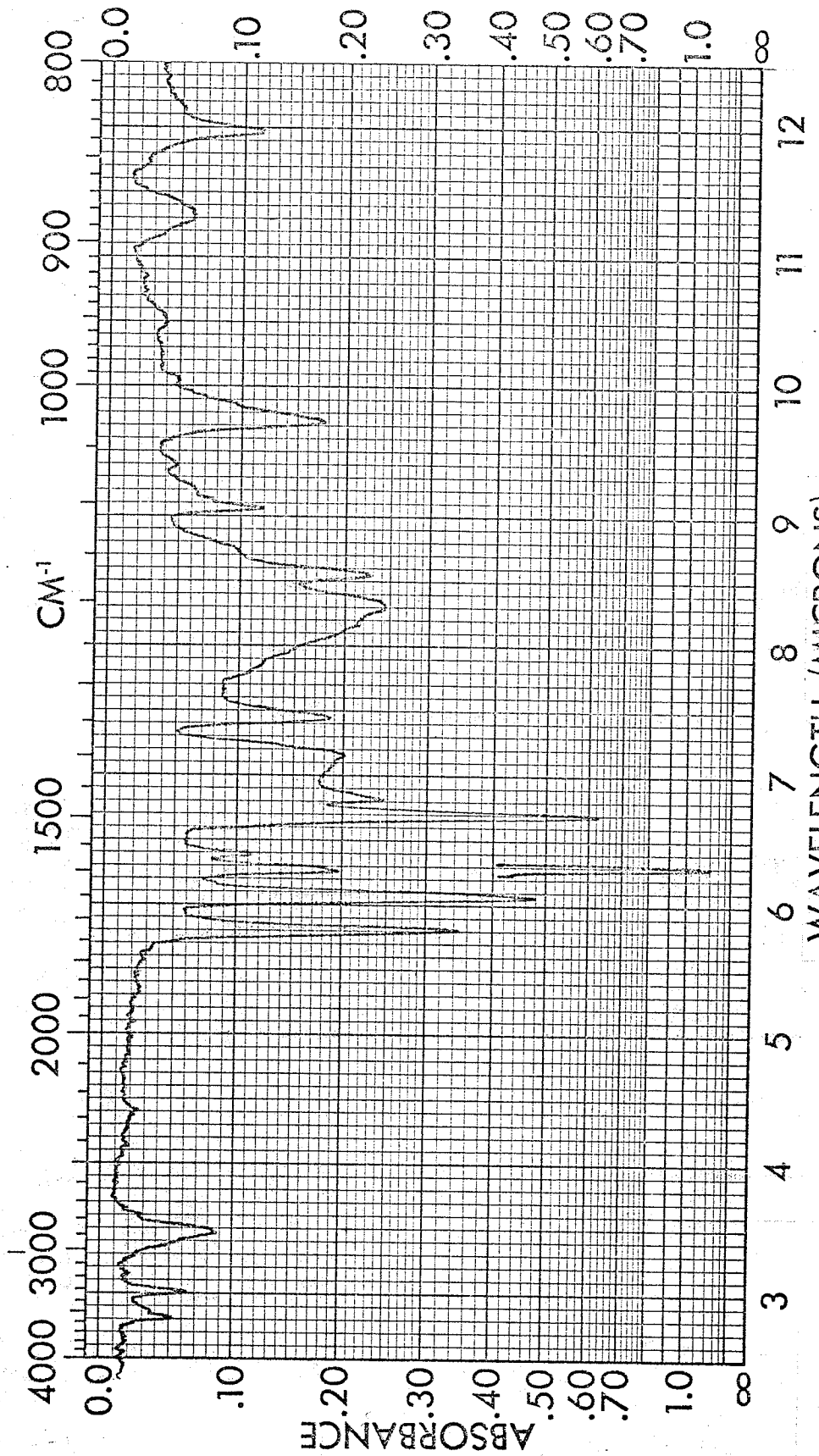



FIGURE V. Infrared spectrum number A-5.

N-benzoyl-O-methyl-L-tyrosine methyl ester ( $CH_2Cl_2$ ).

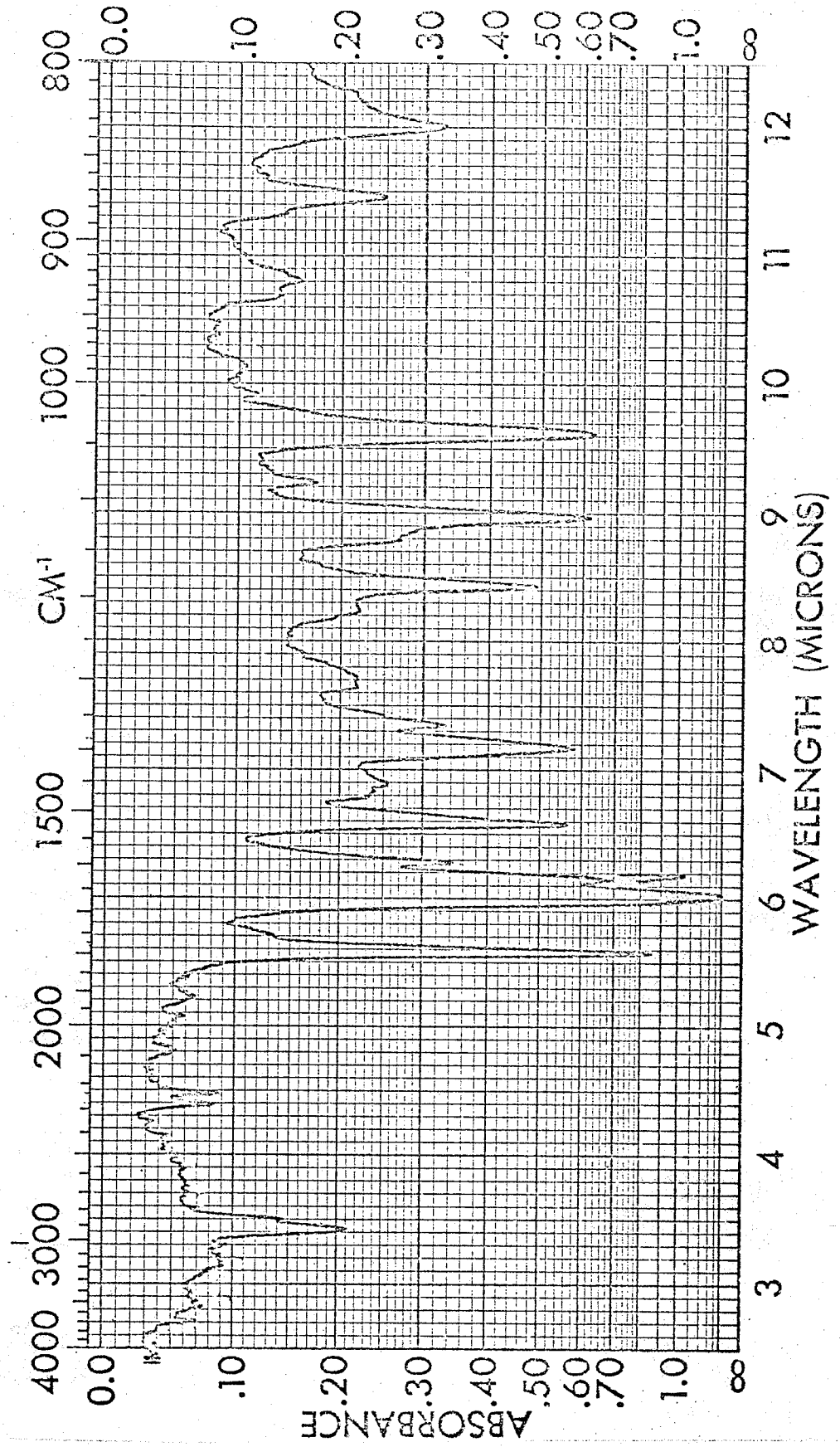



FIGURE VI. Infrared spectrum number A-6.

Ketonitriles — A-XXXI and A-XXXII — ( $CH_2Cl_2$ ).

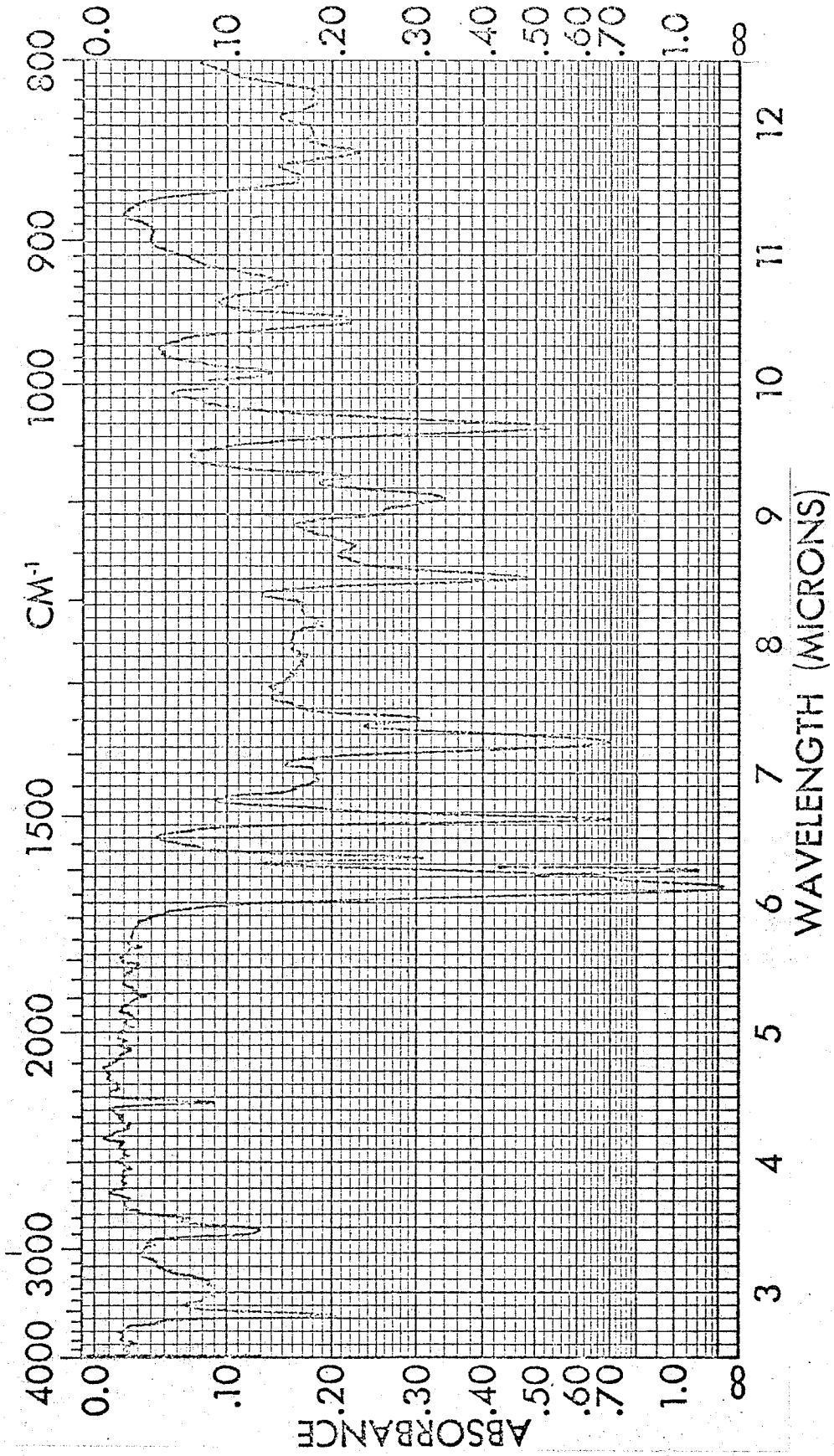



FIGURE VII. Infrared spectrum number A-7.

Hydroxynitrile — A-XXXV — ( $CH_2Cl_2$ ).

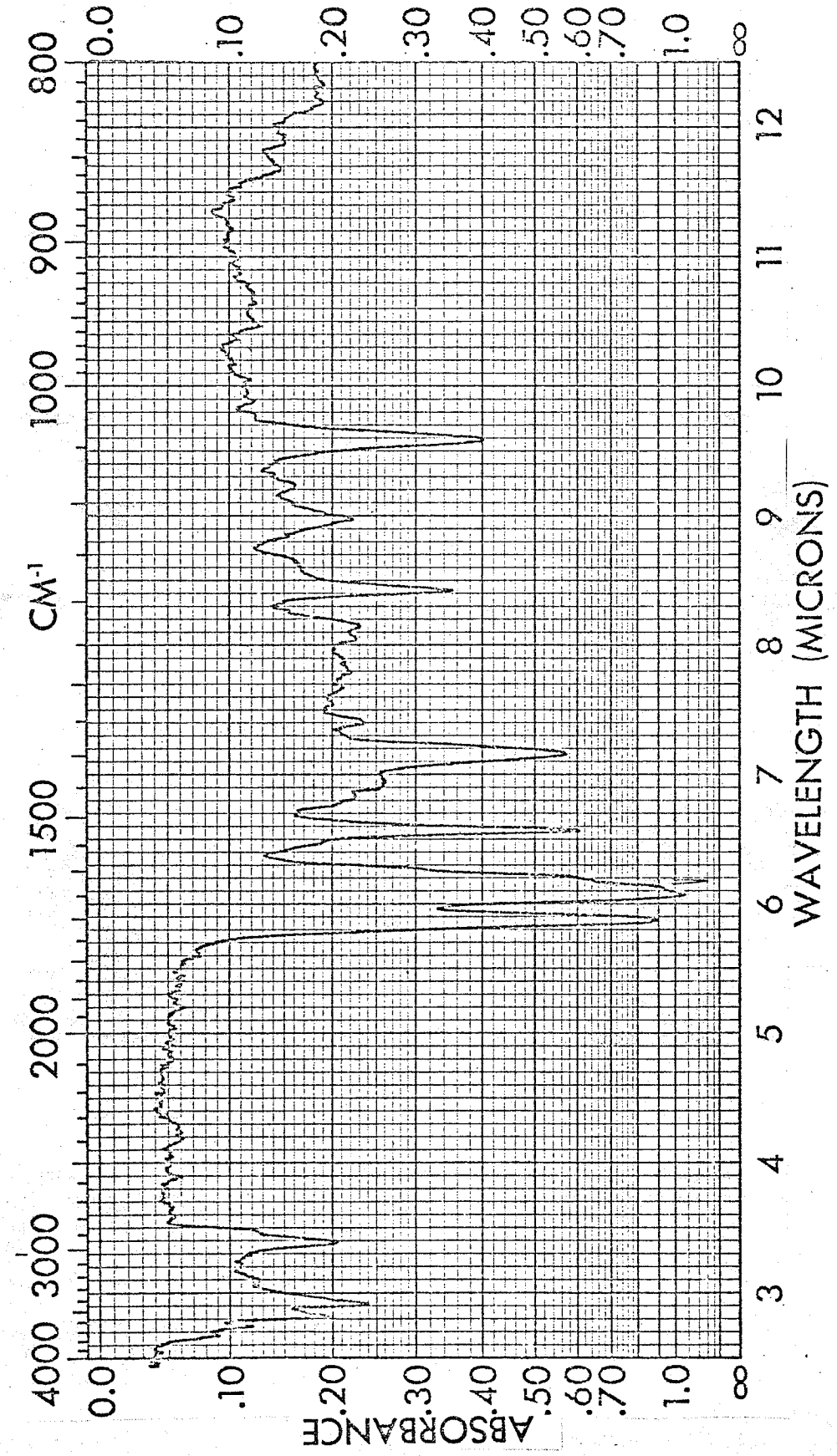



FIGURE VIII. Infrared spectrum number A-8.

Hydroxycarboxamide — A-XXXVII — ( $CH_2Cl_2$ ).

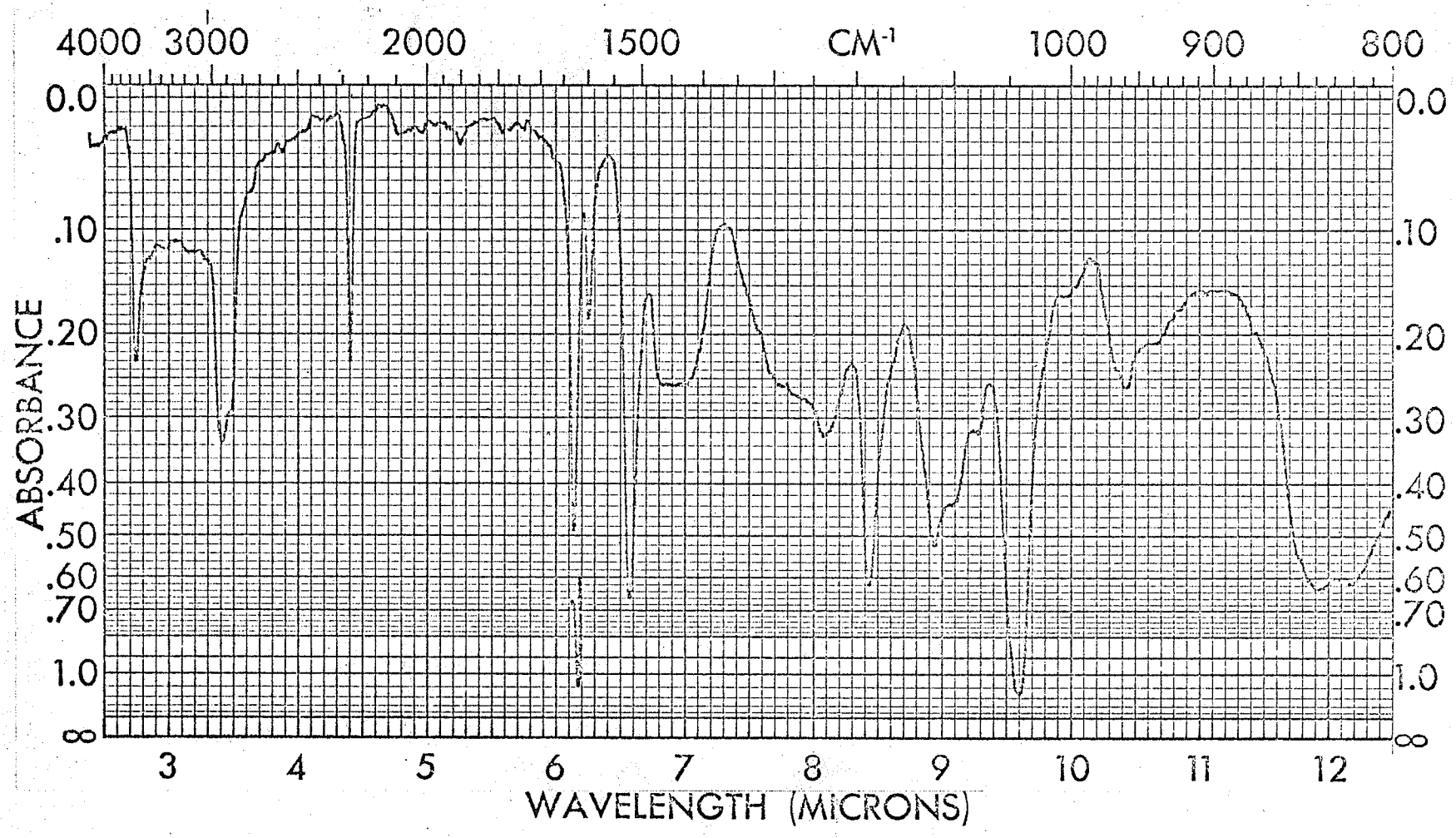



FIGURE IX. Infrared spectrum number A-9.

Basic hydroxynitriles — A-XXXVIII and A-XXXIX — ( $CH_2Cl_2$ ).

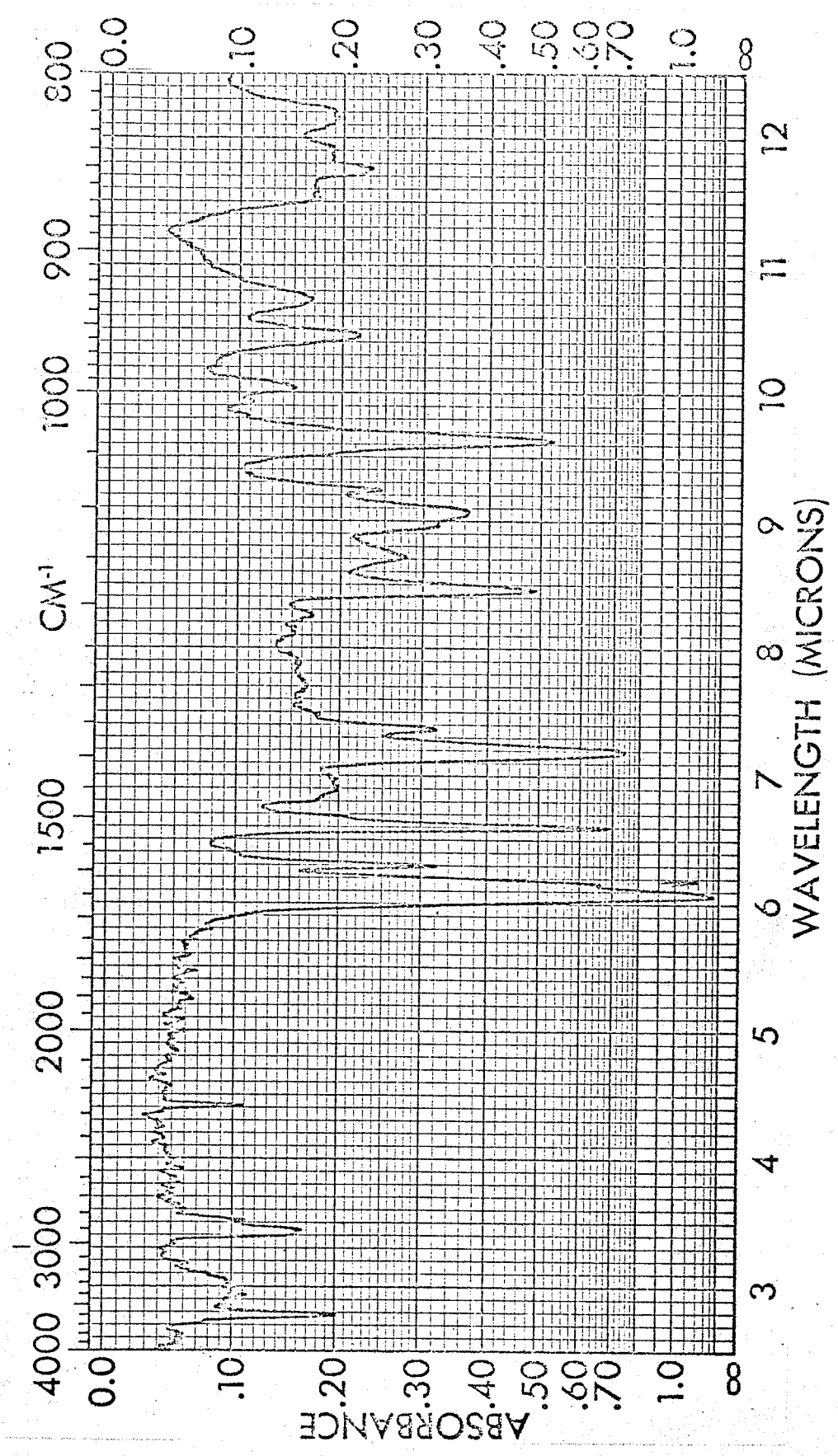



FIGURE X. Infrared spectrum number A-10.

Hydroxynitrile — A-XXXX — ( $CH_2Cl_2$ ).

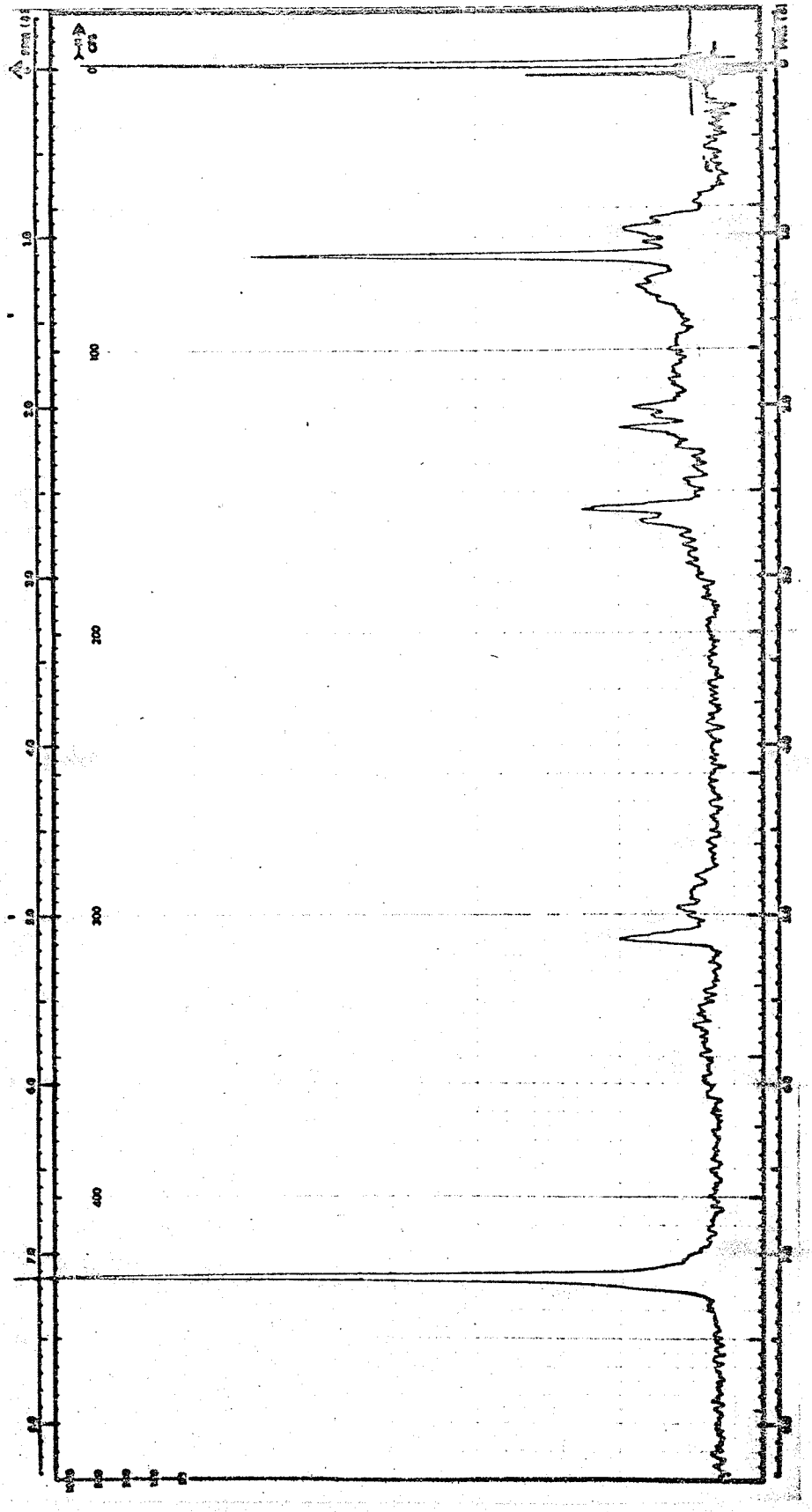


FIGURE XI. Nuclear magnetic resonance spectrum number A-1.

4-amino-5-phenyl-1-pentene ( $CDCl_3$ ).

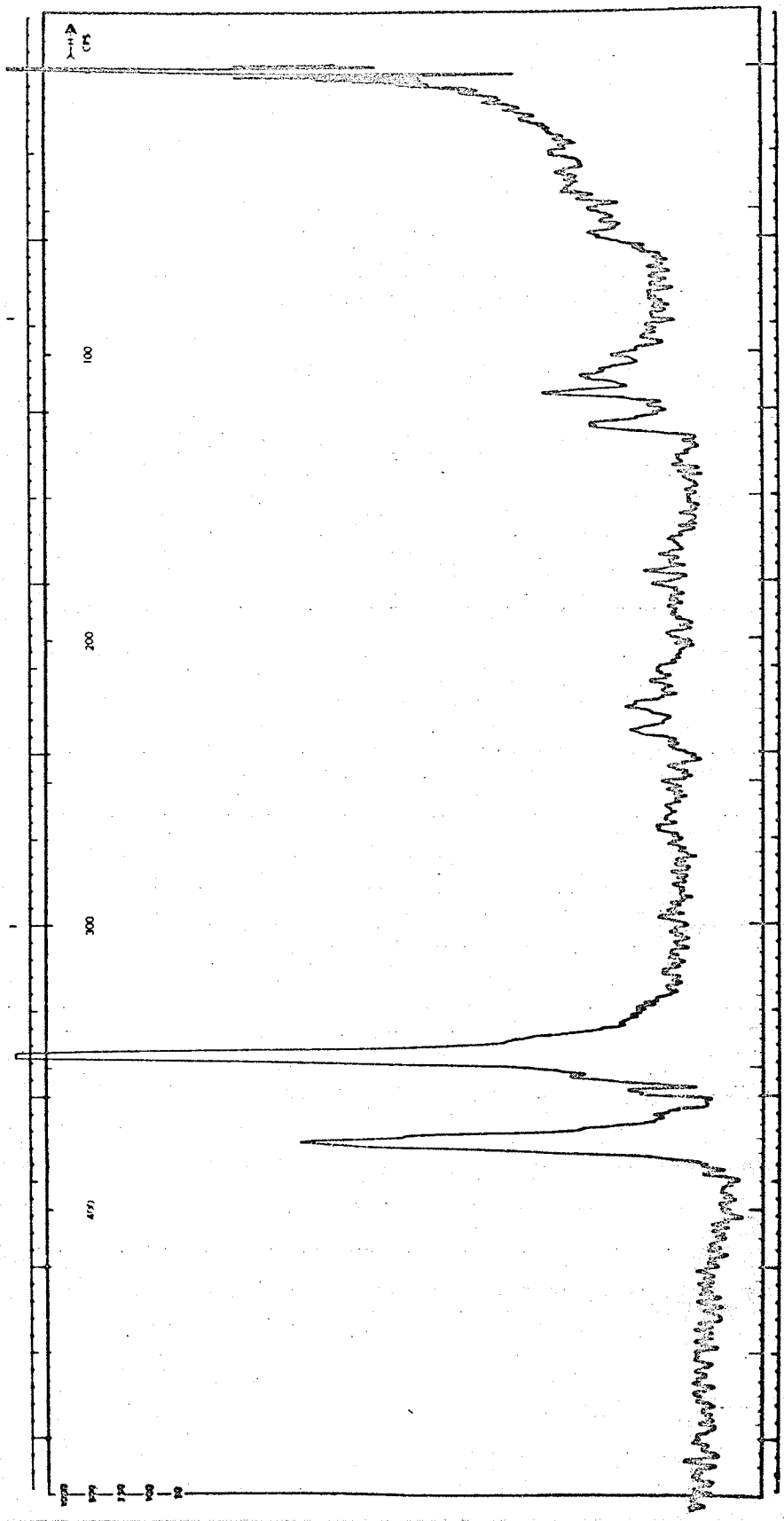


FIGURE XII. Nuclear magnetic resonance spectrum number A-2.

4-phthalimino-5-phenyl-1-pentene ( $CDCl_3$ ).

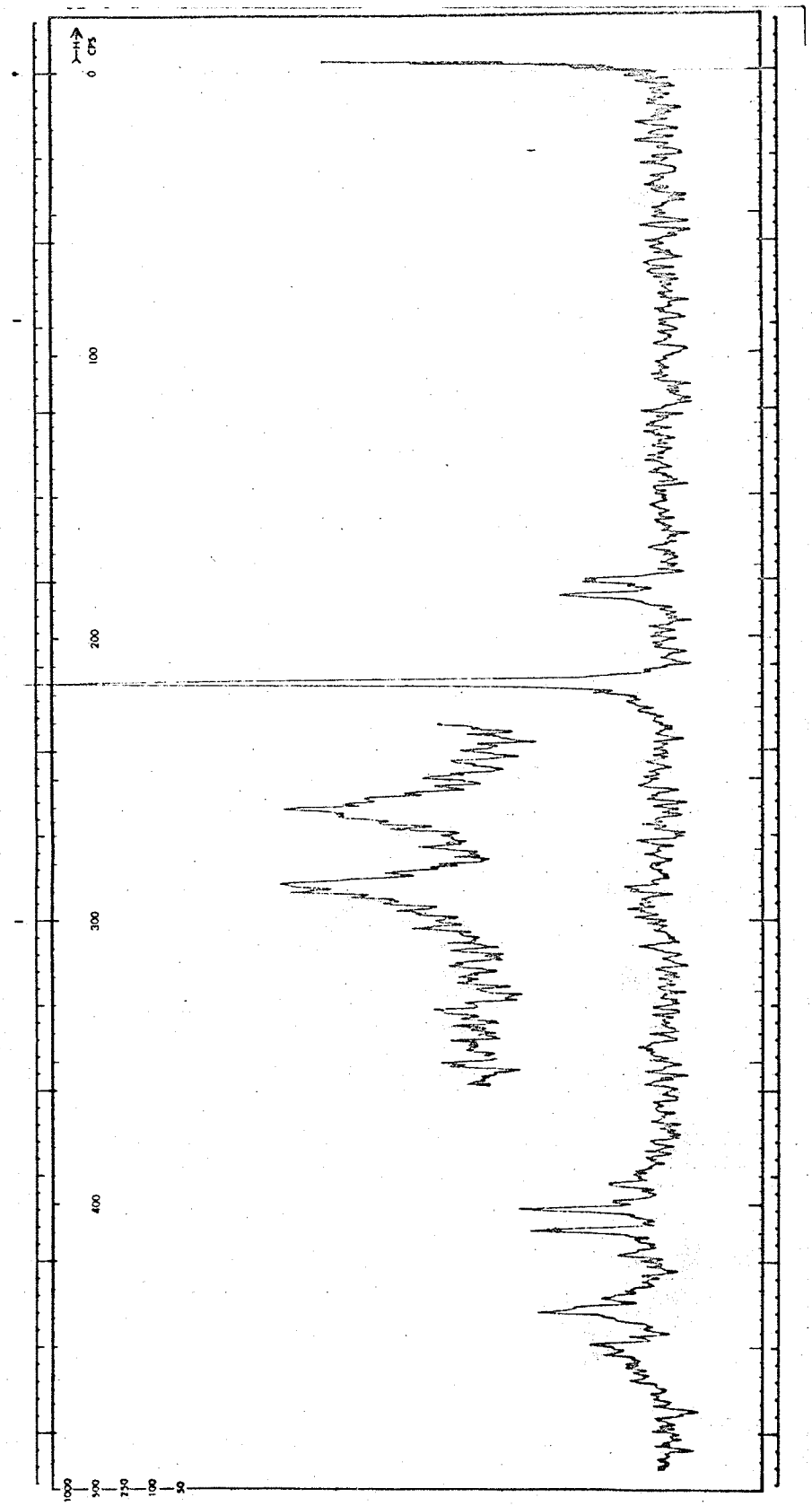



FIGURE XIII. Nuclear magnetic resonance spectrum number A-3.

N-benzoyl-O-methyl-L-tyrosine methyl ester ( $CDCl_3$ ).

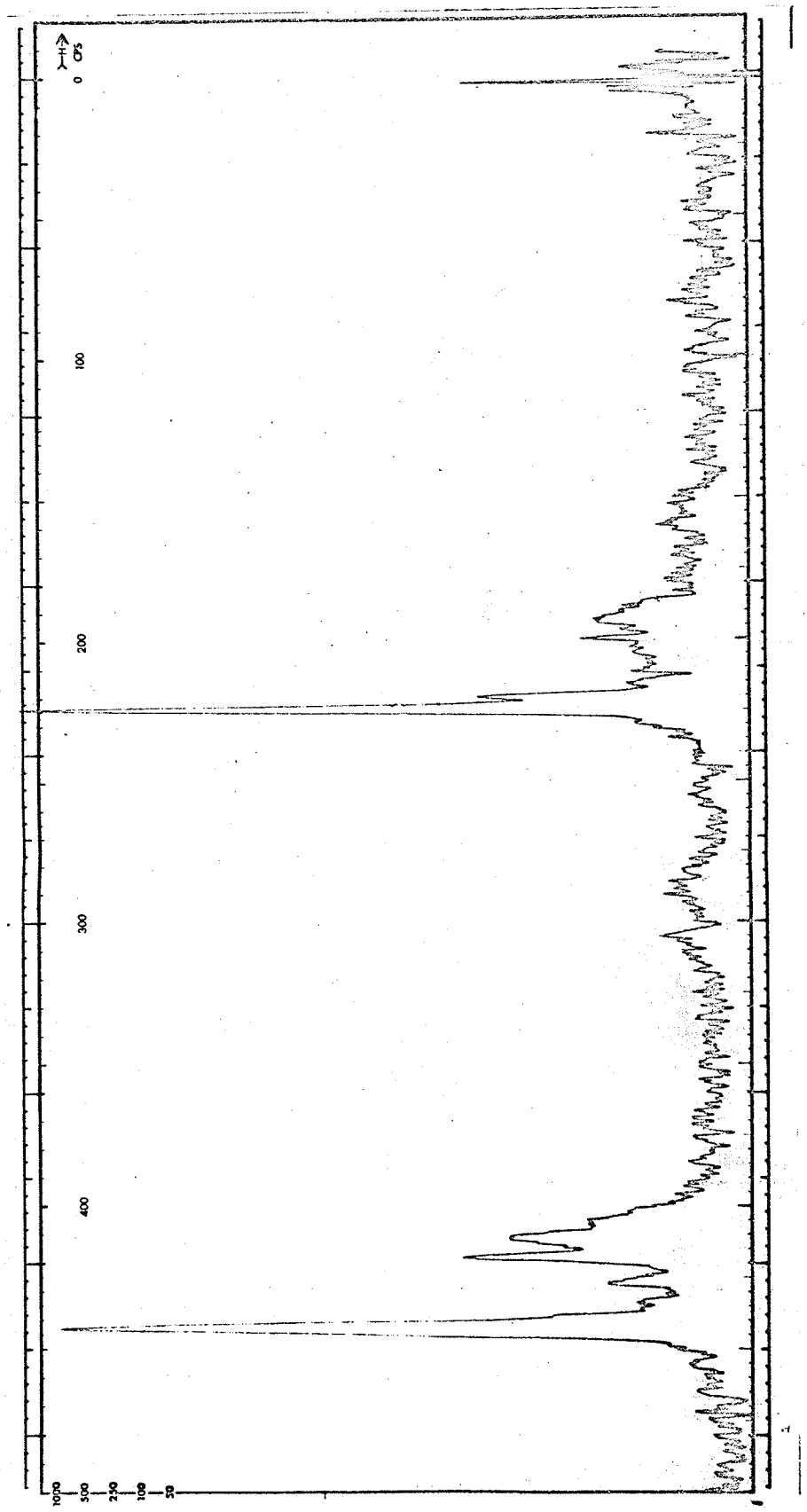



FIGURE XIV. Nuclear magnetic resonance spectrum number A-4.

Ketonitriles — A-XXXI and A-XXXII — ( $CDCl_3$ ).

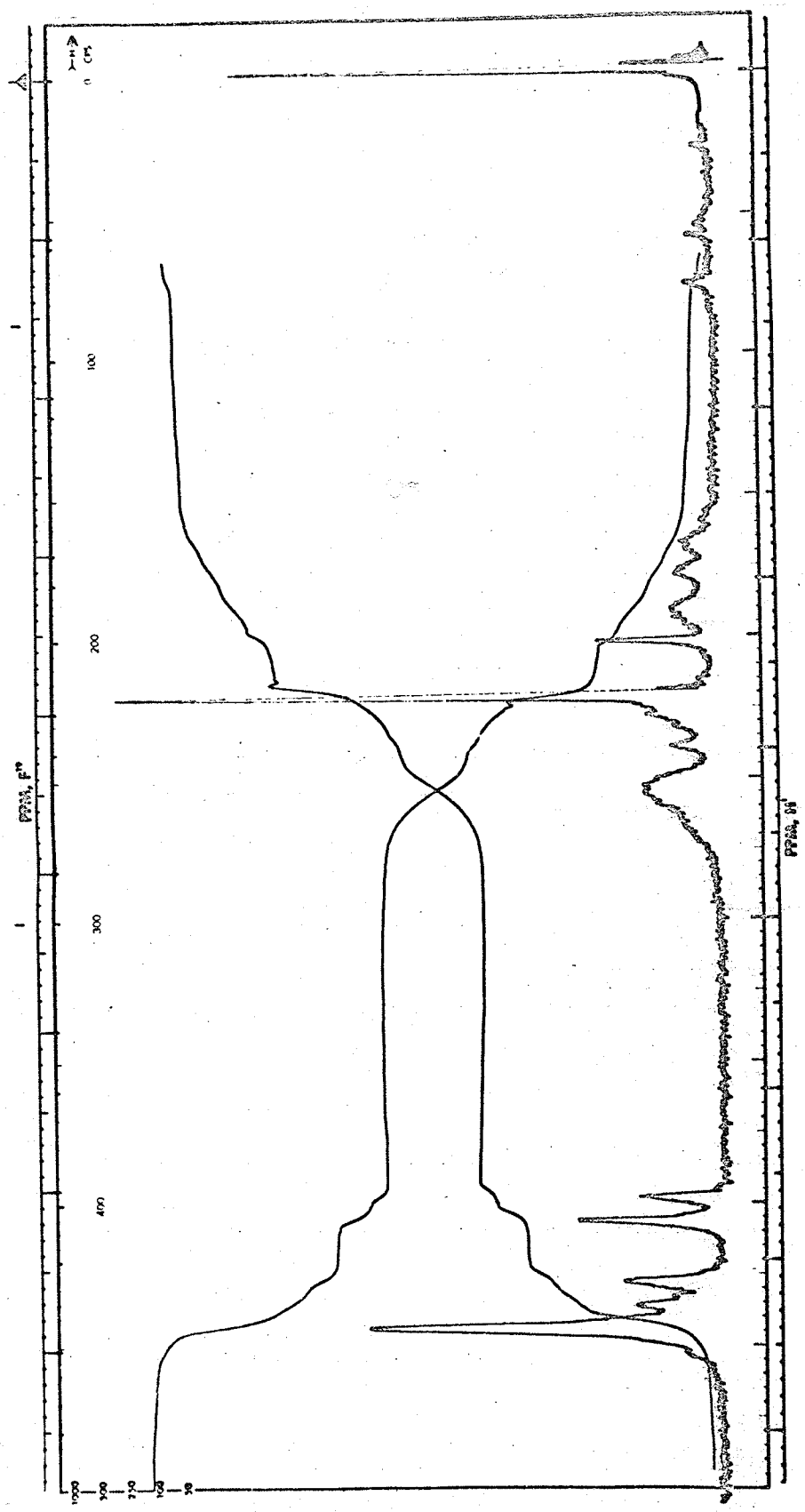


FIGURE XV. Nuclear magnetic resonance spectrum number A-5.

Hydroxynitrile — A-XXXV — ( $CDCl_3$ ).

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# PART [B]

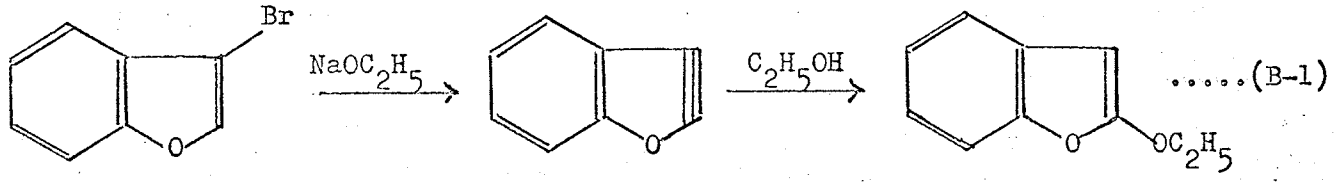
## THE REACTION OF BENZENEDIAZONIUM-2-CARBOXYLATE AND 3-PYRROLINE

## ABSTRACT [B]

It is well known that on heating, various ortho-substituted benzoic acids will either decarboxylate or generate 1,2-dehydrobenzene ( benzyne ) if the ortho-substituent is a good leaving group -- for instance, a diazotized amino group. It is also known that on certain occasions, 1,2-dehydrobenzene may serve as an oxidizing agent. The oxidizing power of 1,2-dehydrobenzene has not however been directly demonstrated. o-(N-diaza-3-pyrrolino)benzoic acid was prepared by condensing benzene-diazonium-2-carboxylate with 3-pyrroline. It was observed that the pyrolysis of the former compound at its melting point ( 140°C. ) -- under nitrogen atmosphere -- gave 1-phenyl-3-pyrroline, benzoic acid and pyrrole which may involve 1,2-dehydrobenzene as an intermediate. The formation of benzoic acid indicates a reduction while the formation of pyrrole shows an oxidation.

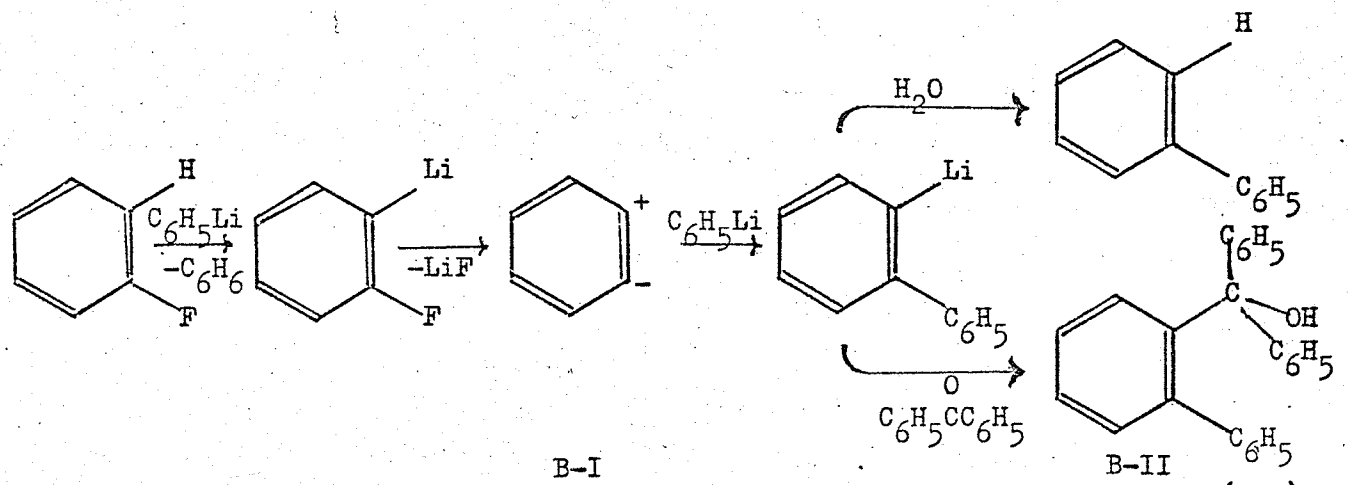
# INTRODUCTION [B]

Dehydroaromatic intermediates ( arynes ) had been proposed, ad hoc, as early as 1902 by R. Stoermer and B. Kahlert[B-1] who explained the rearrangement as shown in equation (B-1).



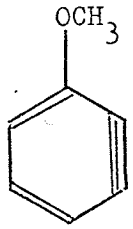

.....(B-1)

In 1942 G. Wittig[B-2] then advanced the hypothesis — although in its primitive form only — with experimental evidence. He discovered that the products from the reaction of phenyllithium with fluorobenzene depend on the subsequent treatment of the reaction mixture. When water was added, biphenyl was the product; when benzophenone was added, however, o-biphenyl-diphenylcarbinol ( B-II ) was obtained. He also claimed that 2- and 3-methoxybiphenyl were formed from the reactions of 2- and 3-fluoroanisole respectively[B-3]. On the basis of this, he proposed that the intermediate ( B-I ) is permanently polarized as shown in equation (B-2).



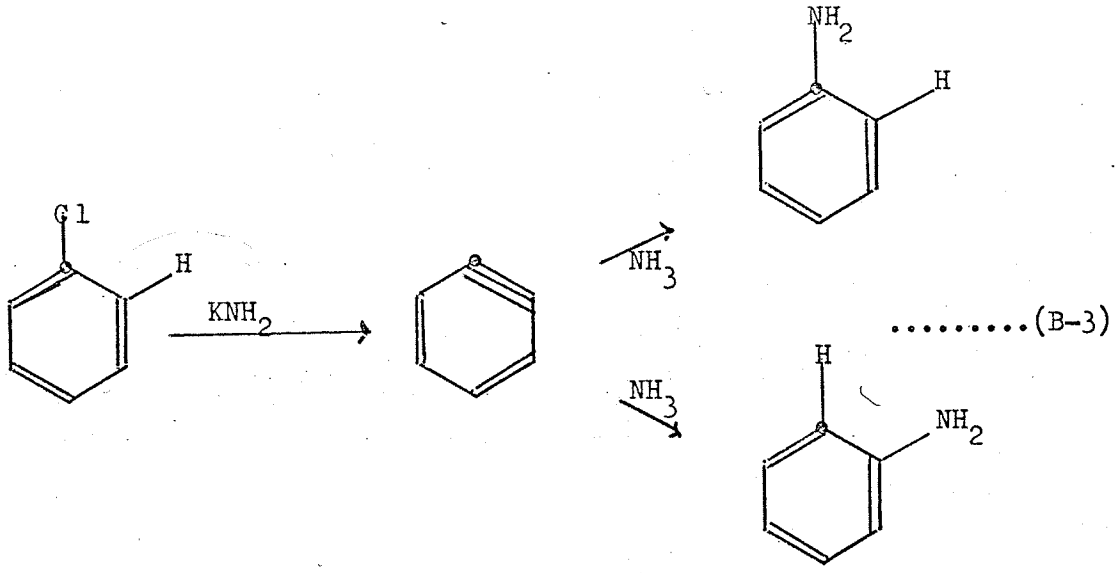

.....(B-2)

However, both reactions mentioned above gave the same product -- 3-methoxybiphenyl -- as later R. Huisgen and H. Rist demonstrated[B-4], attesting to a common intermediate -- 2,3-dehydroanisole ( 3-methoxybenzyne, B-III ).



B-III

In 1953 J. D. Roberts[B-5] showed that chlorobenzene-(1-$^{14}$C) gives nearly equal amounts of aniline-(1-$^{14}$C) and aniline-(2-$^{14}$C) from the reaction with potassium amide in liquid ammonia. He suggested the mechanism as shown in equation (B-3).

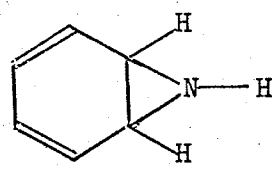



.....(B-3)

The slight difference from a 1:1 product ratio was of the magnitude and direction expected of a $^{12}$C/$^{14}$C isotope effect. An alternative interpretation, that independent "rearrangement" and "non-rearrangement" mechanisms

were accidentally matched in rate, was minimized by showing that iodobenzene-(1-$^{14}$C) gives the same ratio of the two anilines[B-6]. It is very unlikely that the change from chlorine to iodine would affect the rate of two independent reactions equally.

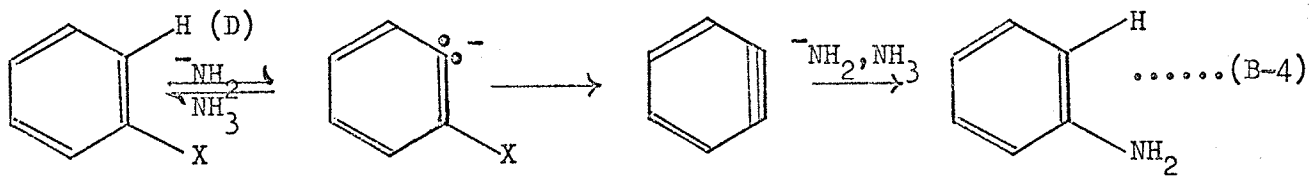
The implication that ortho hydrogens are intimately involved, as in Roberts' proposal, was supported by the fact that halobenzenes lacking ortho hydrogen — for example 2-bromo-3-methylanisole[B-7] — are unreactive with sodium amide in ammonia, and was confirmed by hydrogen isotope experiments[B-6]. When the reaction of a mixture of ordinary bromobenzene and bromobenzene-(2-D)with potassium amide was interrupted, the recovered bromobenzene was richer in deuterium than the original mixture. This shows that molecules with ortho deuterium react slower than ordinary bromobenzene. From the precise deuterium analyses and yields of halide ions, the rate $k_H/k_D$ was reckoned to be 5.5, a magnitude characteristic of C-H bond breaking in the rate determining step. The hydrogen-isotope results then excluded the possibillity of such species as B-IV.




B-IV

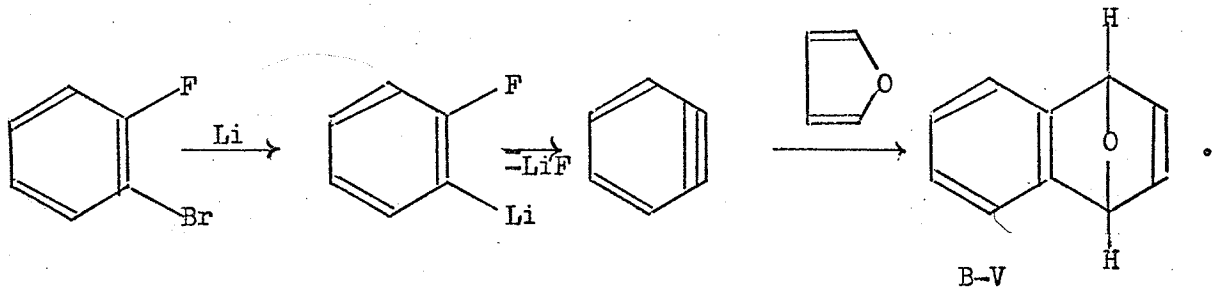
The hypothesis of competing "rearrangement" and "non-rearrangement" reactions was decisively disproven by the demonstration[B-8] that iodobenzene-(1-$^{14}$C-2,4,6-D$_3$) gives the same — 47:53 — ratio of aniline-(1-$^{14}$C) to aniline-(2-$^{14}$C) as does iodobenzene-(1-$^{14}$C). On that hypothesis the "non-rearrangement" reaction, a direct displacement of iodine by an amide ion, should have been insensitive to the change from protium to deuterium in

the ortho position while the "rearrangement" reaction should have been fully responsible for the retardation caused by ortho-deuteration; the proportion of aniline-(1-$^{14}$C) should therefore have increased sharply. Equation (B-4) then generalized the reaction mechanism:




.....(B-4)

This dehydroaromatic intermediate hypothesis has been supported also by trapping the intermediate — for instance, 1,2-dehydrobenzene — with dienes. Wittig[B-9] showed that o-bromofluorobenzene reacts with lithium metal in furan solution to form naphthalene-1,4-endoxide ( B-V ) in 76% yield. The probable course of the reaction can be as that shown in equation (B-5).

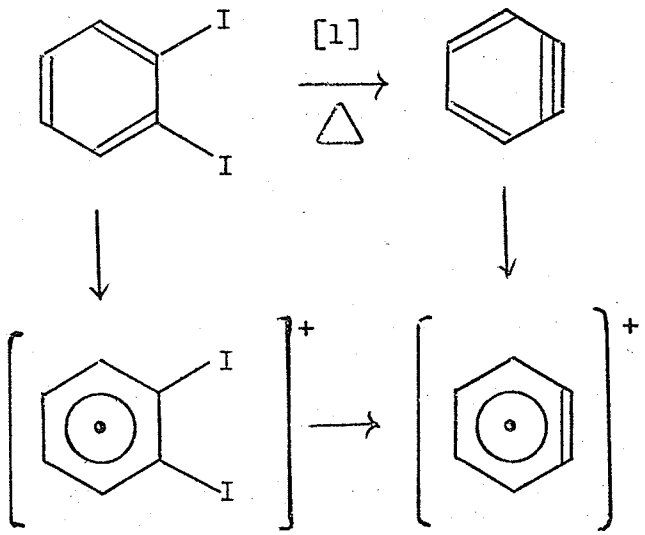



..(B-5)

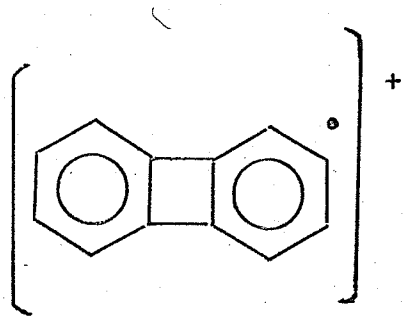
Lastly, evidence in gas phase reactions also indicates the presence of dehydroaromatic intermediate. By the flash photolysis technique, it was noted that the formation of biphenylene lagged a few microseconds behind the activating flash, and that in the interval another species with a different spectrum could be detected. Furthermore, biphenylene has been obtained from both bis-2-iodophenylmercury and phthaloyl peroxide[B-10] or from both o-iodophenylmercuric iodide and benzenediazonium-2-carboxylate[B-11]

or from fluoro-, chloro-, bromo-, and iodobenzene as well as from phenylacetylene and benzene[B-12]. In each set of reactions comparable conditions were applied, hence the conclusion can be drawn that the reactive intermediate is the largest molecular unit common to all these precursors, namely $C_6H_4$. Physical evidence for the existence of 1,2-dehydrobenzene in the gas phase can be obtained by means of mass spectrometry. A species of m/e = 76 has been detected during the thermolysis of o-diiodobenzene in the gas phase[B-13]. This could be the 1,2-dehydrobenzene ion ( B-VI ). The appearance potential of B-VI is 9.75 V., a value significiantly higher than that of 9.45 V. required to ionize m- and p-diiodobenzene to the open chain species of m/e = 76. Moreover a peak at m/e = 152 attributed to B-VII appears only with o-diiodobenzene as thermolysis substrate. Thus route [1] which incorporates 1,2-dehydrobenzene as an intermediate is the most likely route as shown in scheme (B-i). Even closer insight has been obtained by means of time-resolved mass spectrometry[B-14,B-15] as well as time-resolved ultra violet absorption spectroscopy[B-15,B-16] to detect 1,2-dehydrobenzene directly.

SCHEME (B-i)

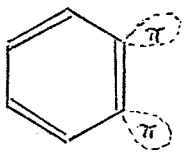



B-VI

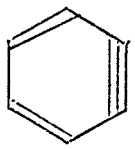


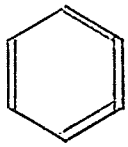

B-VII

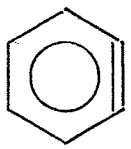
From Roberts' experiments and mass spectrometric data a symmetrical intermediate of molecular formula $C_6H_4$ obviously would be the correct one. However, more than one structural formula can be used to depict this intermediate --- 1,2-dehydrobenzene ( B-VIII --- B-XI ).

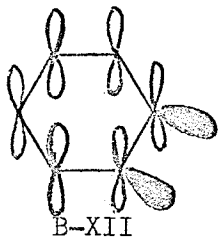


B-VIII


B-IX


B-X


B-XI


B-XII

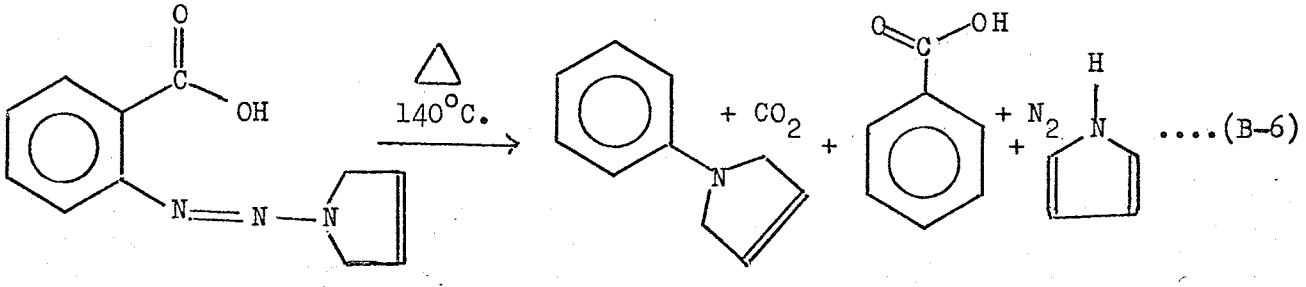
1,2-dehydrobenzene can be imagined as being produced by the removal of two adjacent hydrogen atoms from benzene. Then one electron from each of the C-H bonds participating in this homolytic cleavage is left on each carbon atom. Thus, in order to choose the most appropiate formula the nature of the bond formed from these two electrons has to be considered.

Formula B-VIII[B-4] implies that there are two $\pi$-orbitals arranged at an angle of $60^{\circ}$. This can be visualized as that the two electrons are left in the carbon orbitals which have nearly trigonal $sp^2$ hybridization. These two $sp^2$-orbitals are orthogonal to the $\pi$ molecular orbitals of the benzene ring, as depicted in B-XII. Unless the system departs from planarity the overlapping of and hence the interaction between these sets of orbitals will be only weak. Since this sidewise overlap does not form a strong bond, it is in excellent accord with the high chemical reactivity of 1,2-dehydrobenzene. R. Huisgen, W. Mack and L. Mobius[B-18] have shown that phenyllithium is a more active nucleophile than lithium piperidine in reactions with dehydroaromatic intermediates, but the ratio $k_{LiPh}/k_{LiNC_5H_{10}}$ varies, as follows: 1,2-dehydrobenzene 4.4 ; 1,2-dehydronaphthalene ( 1,2-naphthalyne ) 5.8 ; 9,10-dehydrophenanthrene ( 9,10-phenanthryne ) 12.8. The greater

selectivity of 9,10-dehydrophenanthrene implies that it is a more stable compound, more able to wait for the strong nucleophile to come along, less obliged to react with the first one it encounters. Bond length measurements in the parent hydrocarbons tells that carbon atoms 9 and 10 of phenanthrene are closer than 1 and 2 of naphthalene which in turn are closer than any two adjacent carbons of benzene. Closer spacing should cause better sidewise overlap of the $sp^2$-orbitals and therefor a stronger "third" bond. Since B-XII retains the normal benzene geometry and aromatic resonance, and it does have a weak bond in the orthogonal plane, 1,2-dehydrobenzene can be depicted better by formulae B-IX[B-2,B-4,B-5] and B-X. Unfortunately B-X is rarely explicitely mentioned in the literature. Then the use of formula B-IX alone induces the reader to neglect B-X and visually implies the presence of a triple bond in 1,2-dehydrobenzene. A fully triple bond is definitely absent. It is however conceivable that some sort of compromise is reached, each part of the ring yielding its usual geometrical preference to some extent. Though this view has been advanced in certain quarters[B-6,B-20] this proposal is not currently in favour. In order to give the best picture and circumvent so many difficulties encountered with B-VIII -- B-X, formula B-XI[B-21] will be used from hereon although this opposes a recommendation not to use circle and double bond signs within one and the same formula[B-22]. Using this formula the nomenclature can also be rectified. 1,3-Cyclohexadien-5-yne is the one used in Chemical Abstracts. Its only merit is that of systematic clarity, otherwise it is gravely misleading for chemists who are used to connecting chemical behaviour with structures and their names. The term "benzyne" or its generic name "aryne" enjoy wide popularity. However, the term "benzyne" is somewhat misleading as is formula B-IX since it also suggests the presence of a formal triple bond. The name "1,2-dehydrobenzene"

may therefore be taken as a good compromise between the all too rigid statements expressed by systematic names and the unusual electronic and geometrical state of the true reactive intermediate; also it has no misleading connotation since it is indeterminate with respect to the nature of the extra bond. In order to be absolutely precise the notation 1,2-dehydrobenzene is required. However since such species as 1,3- and 1,4-dehydrobenzene[B-23,B-24] are very uncommon, the simplification -- dehydrobenzene instead of 1,2-dehydrobenzene -- will be used from hereon.

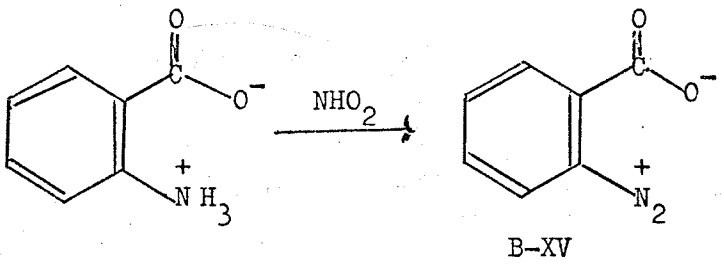
Other than the historical generation of dehydrobenzene from the ortho halo-phenyl anion with halide as leaving group, now it is known that the formation of dehydrobenzene can be achieved from other ortho-anionized benzene derivatives with varios leaving groups such as phenoxide[B-25], α-naphthoxide, β-naphthoxide[B-26], other anions, triethylamine[B-27], diphenyl sulphide[B-28] and nitrogen[B-29], as well as by cleavage of heterocyclic system such as 1,2,3-benzothiadiazole-1,1-dioxide[B-30]. It was our interest to investigate the pyrolysis of o-(N-diaza-3-pyrrolino)benzoic acid ( B-XIII ) to see if dehydrobenzene would be generated. It was observed that at its melting point ( 140°C. ) -- under nitrogen atmosphere -- B-XIII gave 1-phenyl-3-pyrroline ( B-XIV ), benzoic acid and pyrrole as shown in equation (B-6). Possibly this may involve dehydrobenzene as an intermediate.




B-XIII B-XIV

## RESULTS AND DISCUSSION [B]

In 1960 M. Stiles[B-31] succeeded in preparing dehydrobenzene in the absence of metal cations, halide ions and strong bases. He prepared benzene-diazonium-2-carboxylate ( B-XV ), the zwitterionic diazonium salt, which is stable ( although explosive ) and can be isolated, from anthranilic acid as shown in equation (B-7). It decomposes on heating in furan to form B-V and in a benzene solution of anthracene to form triptycene. These reactions imply that B-XV loses carbon dioxide and nitrogen to form the same intermediate, dehydrobenzene, as derived historically from organo-metallic compounds, and constitutes a very easy approach to dehydrobenzene under extremely mild conditions. The synthesis of B-XV as well as the modes of decomposition of B-XV have been improved meanwhile. It is now extremely convenient and safe to generate B-XV in situ by diazotation of anthranilic acid with organic nitriles[B-32].



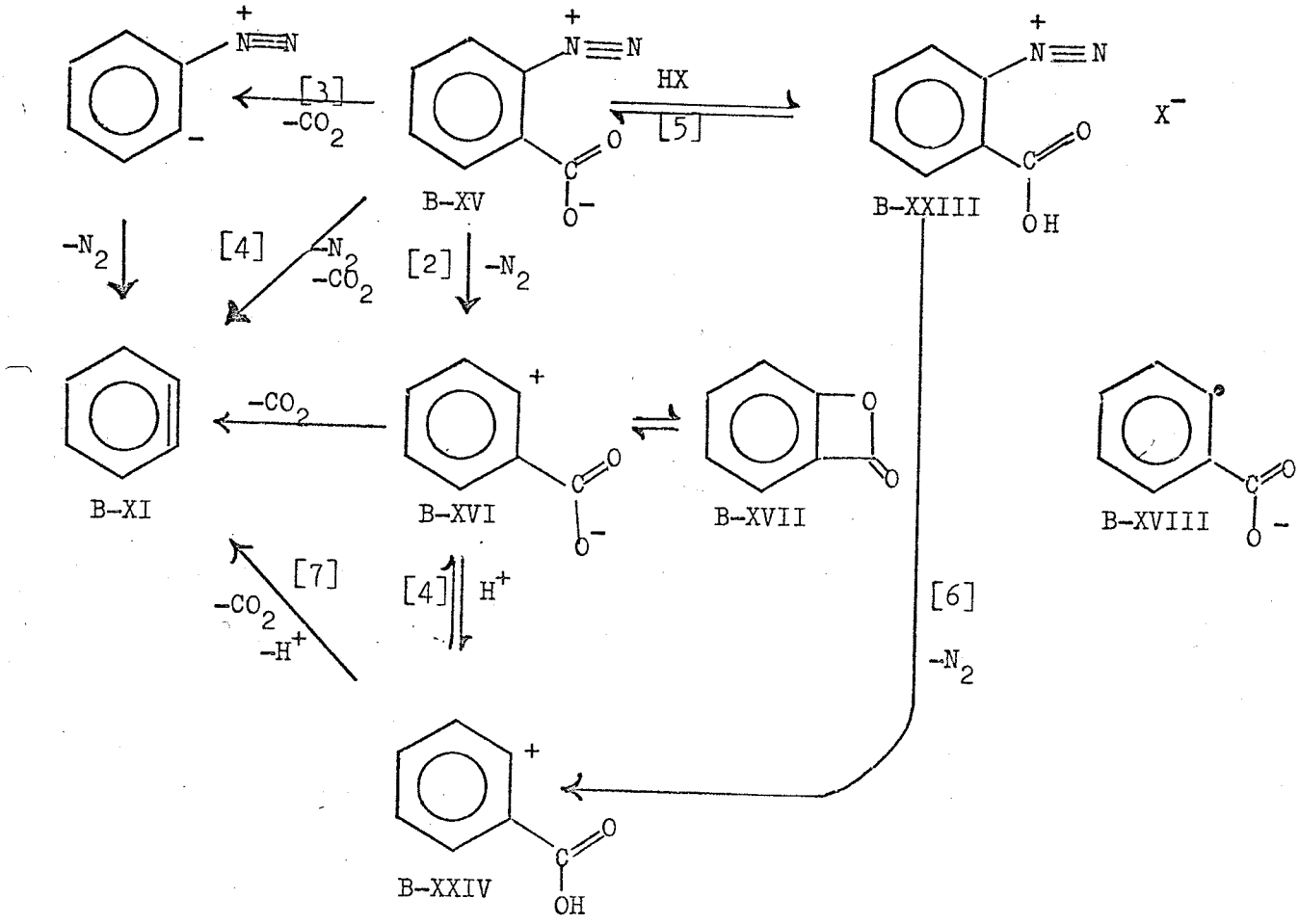

B-XV

.....(B-7)

B-XV is fortunately insoluble in most organic solvents. Its rate of decomposition is therefore of zero order because the concentration of dissolved B-XV remains constant in a saturated solution. Hence the rate depends strongly on the solution properties of the solvent. The decomposition is much faster in t-butanol at 60°C. than in benzene at the same temperature[B-33]. The mechanism of the decomposition of B-XV is ambiguous. Two stepwise mechanisms [2] and [3], and a concerted mechanism [4] are

conceivable as shown in scheme (B-ii).

SCHEME (B-ii)

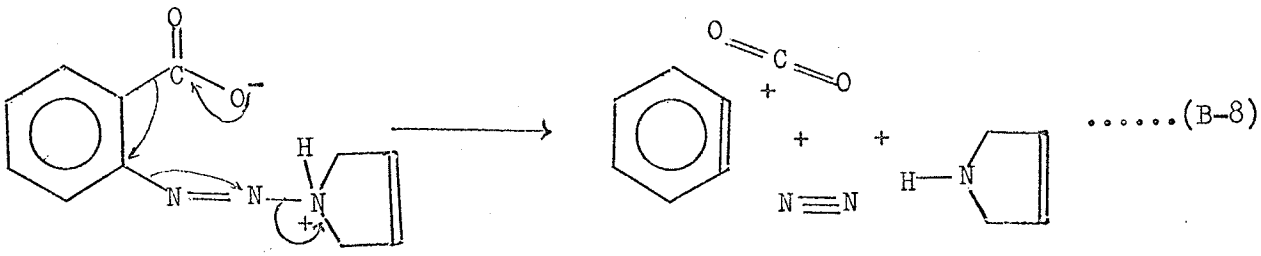



In 1,2-dichoroethane in the presence of anthracene, the ratio of nitrogen to carbon dioxide evolved is unity. This ratio is increased in the absence of suitable substrates for dehydrobenzene, suggesting some reaction of dehydrobenzene with carbon dioxide. The ratio is also strongly dependent upon the solvent used: it varies from 1.7 in benzene through 3.0 in t-butanol to infinity in water[B-31,B-33]. This indicates the occurrence of reaction [2] — though not necessarily as the only reaction — leading

to B-XVI which may be diverted in nucleophilic solvent, for example in water to salicylic acid[B-31,B-34,B-35]. There is some further evidence for the intermediacy of B-XVI: in the aqueous decomposition of B-XV labelled with $^{18}O$ 10% of the salicylic acid formed contains $^{18}O$ in the phenolic position. This part probably arises via B-VII, of which B-VI must be the direct precursor. Decomposition of B-XV in carbon tetrachloride leads to predominant loss of nitrogen, but after subsquent processing in water substantial amounts of salicylic acid were obtained. This probably arose via B-XVII. The decomposition of B-XV is further complicated by the formation of benzoic acid which might arise via B-XVIII by hydrogen abstraction. However, it is more likely that it is formed from B-XVI by hydride transfer from the solvent[B-36,B-37]. Furthermore, in 1965, F. M. Logullo found that it is the sole reaction product in dimethylformamide under certain conditions[B-38]. It is our interest to investigate the pyrolysis of o-(N-diaza-3-pyrrolino)benzoic acid ( B-XIII ), obtained from the condensation of B-XV with 3-pyrroline, to see if it undergoes more or less the same route as the thermal decomposition of B-XV and generates dehydrobenzene.

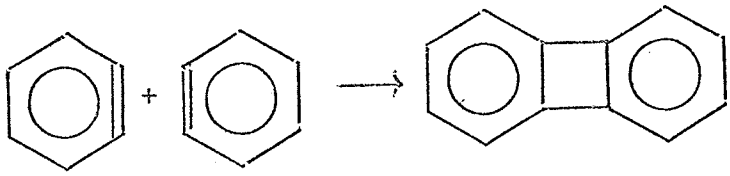
B-XIII was prepared in 40% yield by adding 3-pyrroline very slowly to a benzene solution containing solid B-XV[B-33] at 60°C. in an oil bath. The crystalline product ( B-XIII ) was filtered and purified by recrystallization. It is well known that heating various ortho-substituted benzoic acids will often lead to decarboxylation[B-39,B-40]. Since the diazo linkage in B-XIII is quite labile to thermal decomposition -- though this should be to a lesser extent than that of B-XV -- thermal decomposition of B-XIII might lead to the generation of dehydrobenzene in a concerted mechanism as shown in equation (B-8). If this is true it will be expected that the stationary

concentrations of dehydrobenzene and 3-pyrroline are more or less the same, and that the active sites are the multiple bonds and the nucleophilic nitrogen atom.



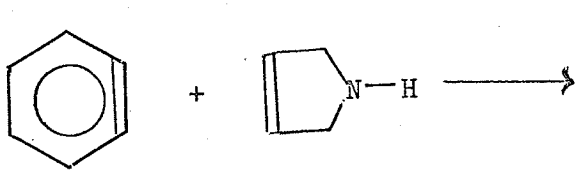
B-XIII B-XI .....(B-8)

Hence the dimerization of dehydrobenzene to biphenylene might be possible as shown in equation (B-9).



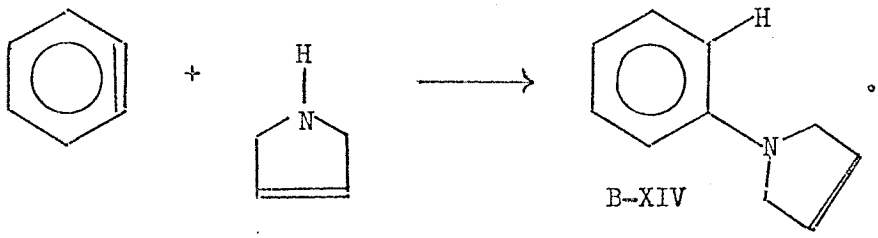
.....(B-9)

The cycloaddition of dehydrobenzene to 3-pyrroline leading to a four-membered ring might be expected as shown in equation (B-10).



.....(B-10)

It is known that dehydrobenzene is able to undergo cycloaddition to a nucleophilic reagent, and hence dehydrobenzene might add to 3-pyrroline to produce 1-phenyl-3-pyrroline ( B-XIV ) as shown in equation (B-11).

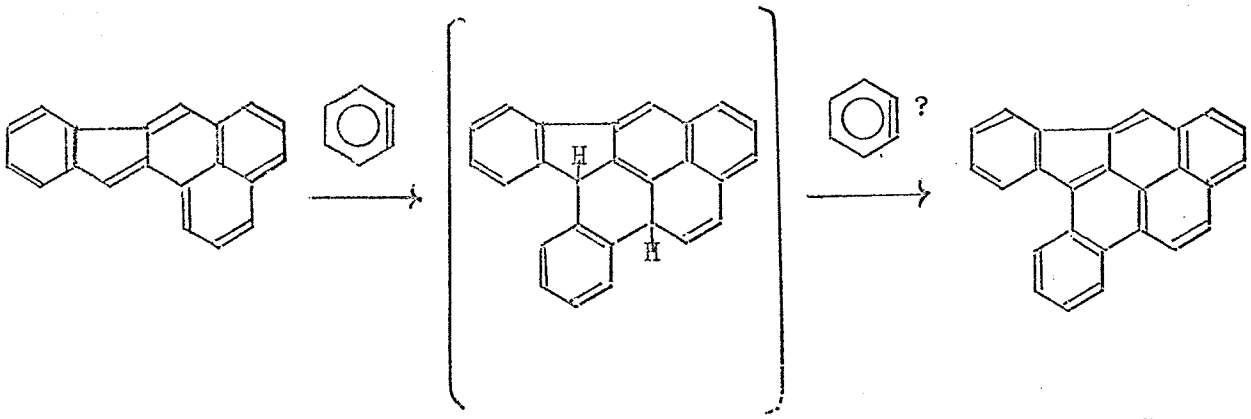



B-XIV .....(B-11)

Experimentally, when B-XIII was heated under nitrogen to its melting point ( 140°C. ) instantaneous decomposition took place. The sublimed products were collected. The presence of pyrrole was identified by comparing the retention time of the product with that of an authentic sample. The brown residue was subjected to further heating at 120°C. under vacuum. The sublimed materials were combined and then separated by thin layer chromography ( silica gel ). Two crystalline compounds were isolated and identified as 1-phenyl-3-pyrroline ( B-XIV ) and benzoic acid by comparison with authentic samples[B-41]. Hence only one out of the several compounds that are expected, namely B-XIV, was isolated. The formation of B-XIV can be explained, as before, by the pyrolysis of B-XIII to dehydrobenzene and 3-pyrroline which is followed by the addition of 3-pyrroline to dehydrobenzene. However, oxidation and reduction must be involved in the formation of pyrrole and benzoic acid.

It is known that dehydrobenzene on certain occasions will serve as an oxidizing agent. S. Wawzonek and J. H. Wagenknecht, in 1963, reported the polarographic reduction of dehydrobenzene to benzene[B-42]. In 1960 T. M. Aitken and D. F. Reid[B-43] obtained an aromatic dehydrogenated adduct ( B-XXI ) by refluxing indeno(2,1-a)perinaphthene, o-benzofluorobenzene and magnesium in tetrahydrofuran as shown in equation (B-12). This may be the result of a purely thermal elimination of hydrogen atoms from the nearly aromatic adduct ( B-XX ). Alternatively, two hydrogen atoms may be removed by the

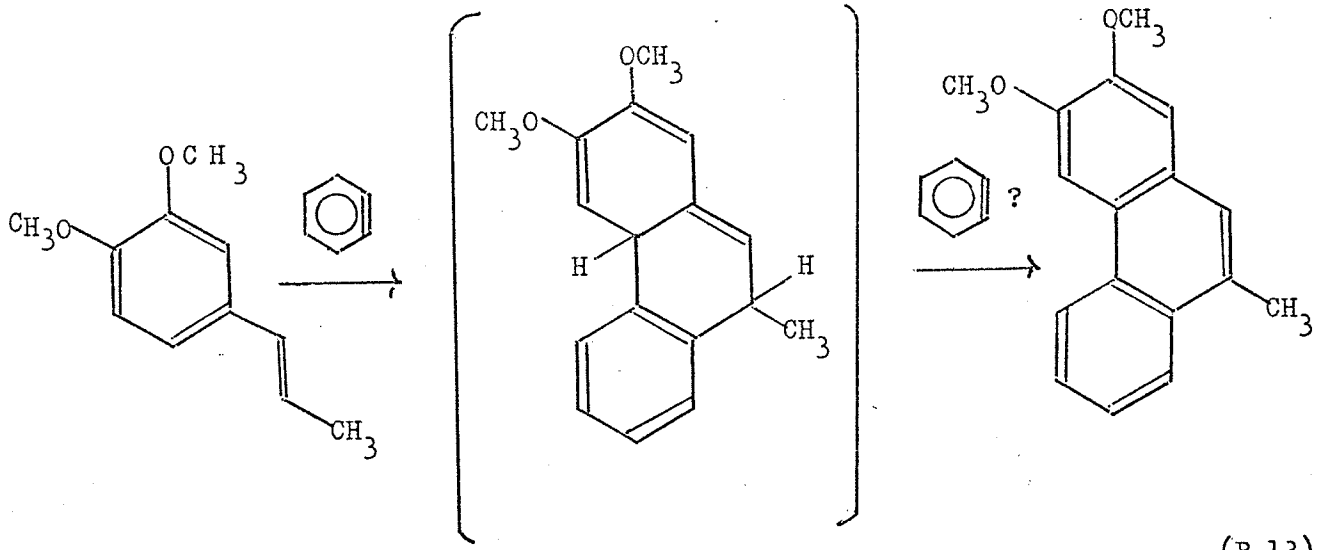
excess of dehydrobenzene serving as a hydrogen acceptor and giving benzene. The latter alternative is favoured because the conditions are too mild to allow spontaneous thermal dehydrogenation of B-XX.



B-XIX B-XX B-XXI

.....(B-12)

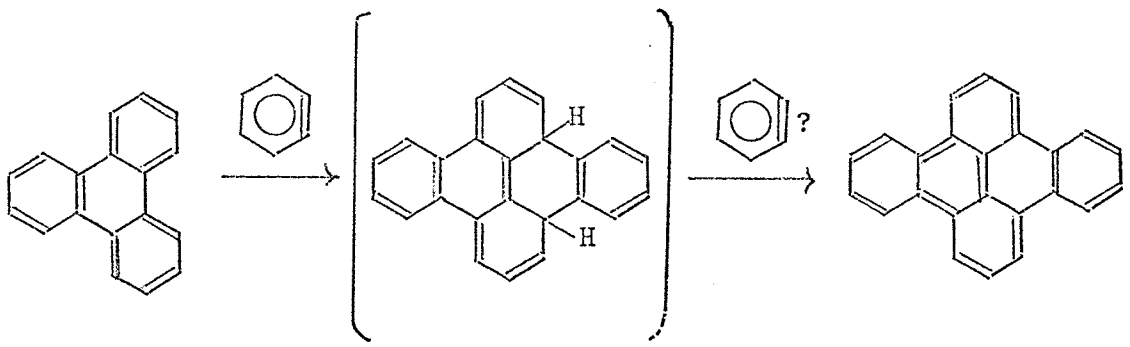
In the addition of dehydrobenzene to the styrene type of compounds — for example, to isoeugenole as shown in equation (B-13) — again low yields of dehydrogenated adducts were obtained under mild conditions[B-19,B-44,B-45].



.....(B-13)

Similarly, interaction of dehydrobenzene with triphenylene gives rise to dibenzo(e,l)pyrene, a reaction involving dehydrogenation of the intermediate ( B-XXII ), possibly with dehydrobenzene as hydrogen acceptor

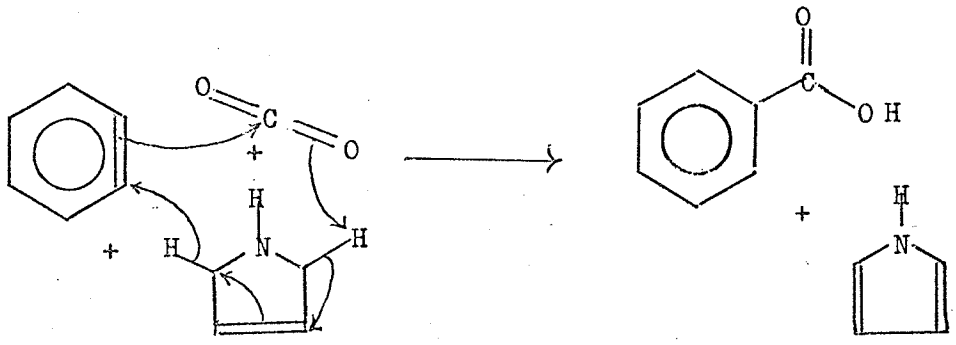
as shown in equation (B-14)[B-17].



B-XXII

.....(B-14)

In our case, however, since there was no benzene isolated, dehydrobenzene alone cannot be the hydrogen acceptor. It is possible that an interesting and unusual concerted oxidation and reduction occurs among three molecules of the decomposition intermediates of B-XIII, namely carbon dioxide, dehydrobenzene and 3-pyrroline as shown in equation (B-15). However, the presence of other possible mechanisms leading to the formation of benzoic acid and pyrrole should not be neglected.

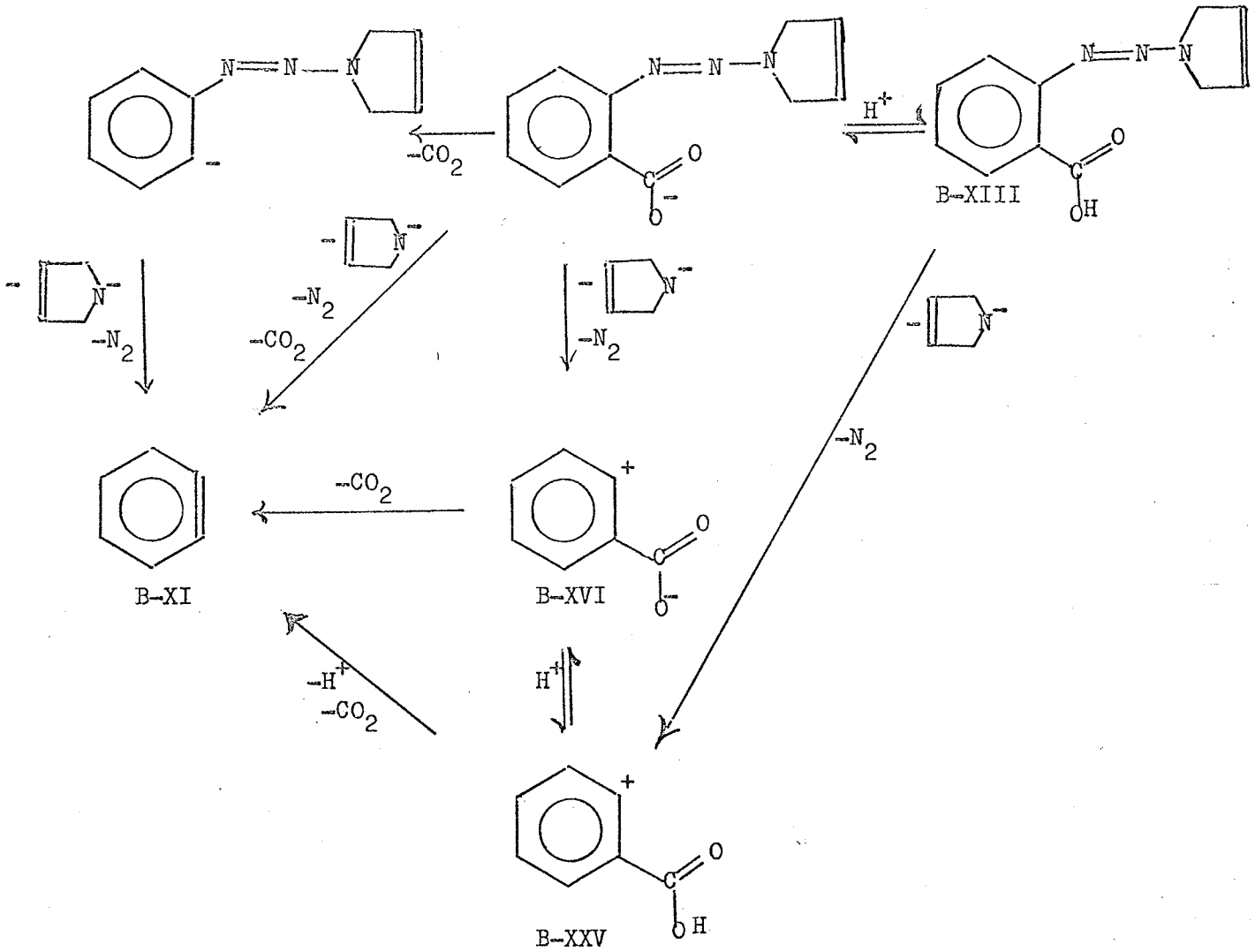


.....(B-15)

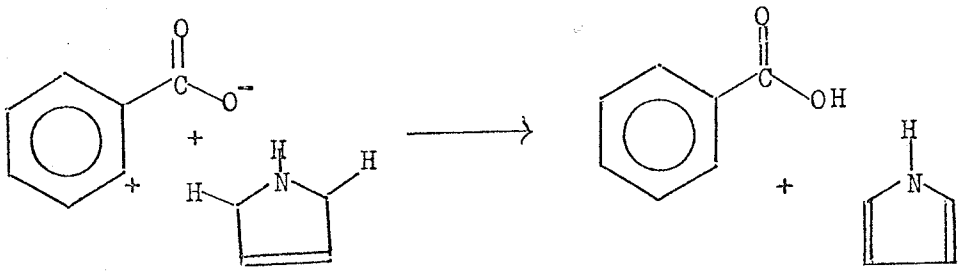
First, B-XIII may undergo the same mechanisms as B-XXIII ( acidified B-XV ), which also get several conceivable mechanisms as shown in scheme (B-ii). It is difficult to decide, whether B-XXIII

decomposes to dehydrobenzene via the steps [6] and [7] with B-XXIV as an intermediate, whereby a detour via B-XXIV to B-XVI is also conceivable or wherther B-XV and B-XVI mark the stages for the decomposition of B-XXIII. With analogy to the possible pathways for the thermal decomposition of B-XXIII, the pathways as shown in scheme (B-iii) may then be that of B-XIII.

SCHEME (B-iii)

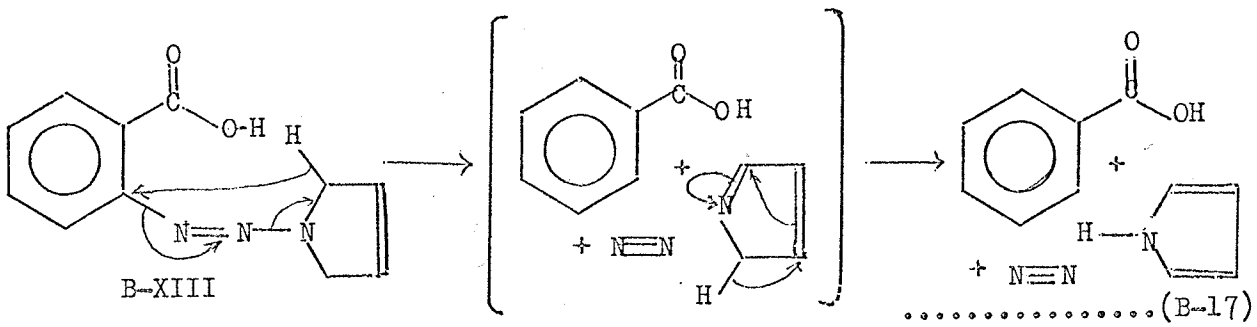



If the intermediacy of B-XVI is true, the formation of pyrrole and benzoic acid can be explained as that B-XVI abstracts one hydride and one proton from 3-pyrroline as shown in equation (B-16).



.....(B-16)

Lastly, the possibility of the concerted oxidation and reduction within the molecule of B-XIII can be outlined as shown in equation (B-17).



B-XIII

.....(B-17)

Further work has to and will be done in order to investigate which mechanism is the correct one.

# EXPERIMENTAL [B]

## B-i PREPARATION OF BENZENEDIAZONIUM-2-CARBOXYLATE ( B-XV )[B-32]

(NOTE: All diazonium halides and diazonium-carboxylates are explosive when heated rapidly or scraped against a hard surface.)

A solution of anthranilic acid ( 2.74 g. ) in absolute ethanol ( 30 ml. ) was cooled to 0°C. in an ice bath and then treated with concentrated hydrochloric acid ( 2 ml. ). Ice-cold isoamyl nitrite ( 5 ml. ) was added dropwise to the stirred solution over a period of approximately 10 minutes. A light orange solution was obtained. On addition of anhydrous ether ( 30 ml. ) the diazonium salt precipitated. The precipitate was collected in a funnel and was washed with anhydrous ether ( 3 x 5 ml. ). The funnel containing the precipitate was then transferred to a clean filter flask, and the smallest convenient volume ( about 5 to 10 ml. ) of cold water was then added to the funnel to dissolve the diazonium salt. The aqueous solution was then stirred at 0°C. with silver oxide powder ( 3 g. ) for 2 hours. After removal of the solid by filtration, the solution was poured into a mixture of absolute ethanol ( 100 ml. ) and anhydrous ether ( 50 ml. ), previously cooled to 0°C.. Additional anhydrous ether was added until the diazonium-carboxylate began to crystallize. After 10 to 20 minutes standing at 0°C., the product was collected, washed with cold anhydrous ether ( 5 ml. ), and stored in a dessicator ( dried with indicating drierite ) inside the refrigerator. The yield was 50% ( 1.5 g. ).

## B-ii PREPARATION OF o-(N-DIAZA-3-PYRROLINO)BENZOIC ACID ( B-XIII )

3-pyrroline ( 1.5 g. ) was added very slowly to a benzene ( 70 ml. ) solution of benzenediazonium-2-carboxylate ( 3 g. ). The solution was warmed at 60°C. in an oil bath for 1 hour. Half of the benzene was then removed

under reduced pressure and the remaining solution was cooled in an ice bath. Crystalline needles separated and were recrystallized by warming in benzene to 60°C. with subsequent cooling to give a 40% yield ( 1.4 g. ).

Melting point: 138—140°C. ( decomposed ).

| Analysis | C | H | N |
|---|---|---|---|
| Calculated for $C_{11}H_{11}O_2N_3$: | 60.90 | 5.07 | 19.35 |
| Found: | 62.02 | 5.04 | 18.74 |

Ultraviolet spectrum number B-1.

Infrared spectrum number B-1.

Nuclear magnetic resonance spectrum number B-1.

B-iii PYROLYSIS OF o-(N-DIAZA-3-PYRROLINO)BENZOIC ACID ( B-XIII )

o-(N-diaza-3-pyrrolino)benzoic acid ( 400 mg. ) was heated under nitrogen in a flask ( 50 ml. ) fitted with a condenser in an oil bath. Decomposition took place immediately when the temperature of the oil bath reached 140°C.. The condenser was washed with ether and part of the ether solution was injected into a Varian Aerograph (1520) (SE-30). The presence of pyrrole was identified by comparing the retention time of the product with that of an authentic sample. The residue of the pyrolysis was heated at 120°C. under vacuum. The sublimed material was combined with the ether solution. Evaporation of the ether solution to dryness followed by thin layer chromatography ( silica gel ) gave benzoic acid ( 11 mg. ) and 1-phenyl-3-pyrroline ( 30 mg. ) identical with authentic samples[B-41].

| Melting point: | benzoic acid | 1-phenyl-3-pyrroline |
|---|---|---|
| Product: | 121°C. | 97—98°C. |
| Authentic sample: | 121°C. | 100.5°C. |
| Mixture: | — | 97—98°C. |

| Infrared spectrum number: | benzoic acid | 1-phenyl-3-pyrroline |
|---|---|---|
| Product: | B-2 | B-4 . |
| Authentic sample: | B-3 | B-5 |

Nuclear magnetic resonance spectrum number B-2 ( 1-phenyl-3-pyrroline ).

B-iv PREPARATION OF 1-PHENYL-3-PYRROLINE ( B-XIV )[B-41]

A solution of thionyl chloride ( 12.5 ml. ) in chloroform ( 20 ml. ) was added dropwise, over a period of one hour, to a cooled ( ice-salt mixture ) stirred solution of cis-2-butene-1,4-diol ( 5.4 ml. ) and pyridine ( 1.0 ml. ) in chloroform ( 5 ml. ). The mixture was stirred overnight at room temperature and distilled through a 10-cm. Vigreux column under water pump vacuum. The fraction boiling at 84°C. ( 75 mm. ) was collected and amounted to 83% ( 6.3 g. ) yield of cis-1,4-dichlor-2-butene. A solution of cis-1,4-dichloro-2-butene ( 6.3 g. ) in anhydrous benzene ( 4 ml. ) was added slowly to a stirred solution of aniline ( 27.9 ml. ) in anhydrous benzene ( 30 ml. ) cooled in an ice bath. The mixture was allowed to stand for three days. The precipitate ( aniline hydrochloride ) was filtered off. The filtrate was distilled under water pump vacuum ( 75 mm. ) to remove benzene and then under oil valve pump vacuum ( 0.5 mm. ) to remove aniline. The white solid collected inside the condenser was combined with the still-pot residue, recrystallized from methanol twice and amounted to 60% yield ( 4.4 g. ) of 1-phenyl-3-pyrroline.

Melting point: 100.5°C..

Infrared spectrum number B-5.

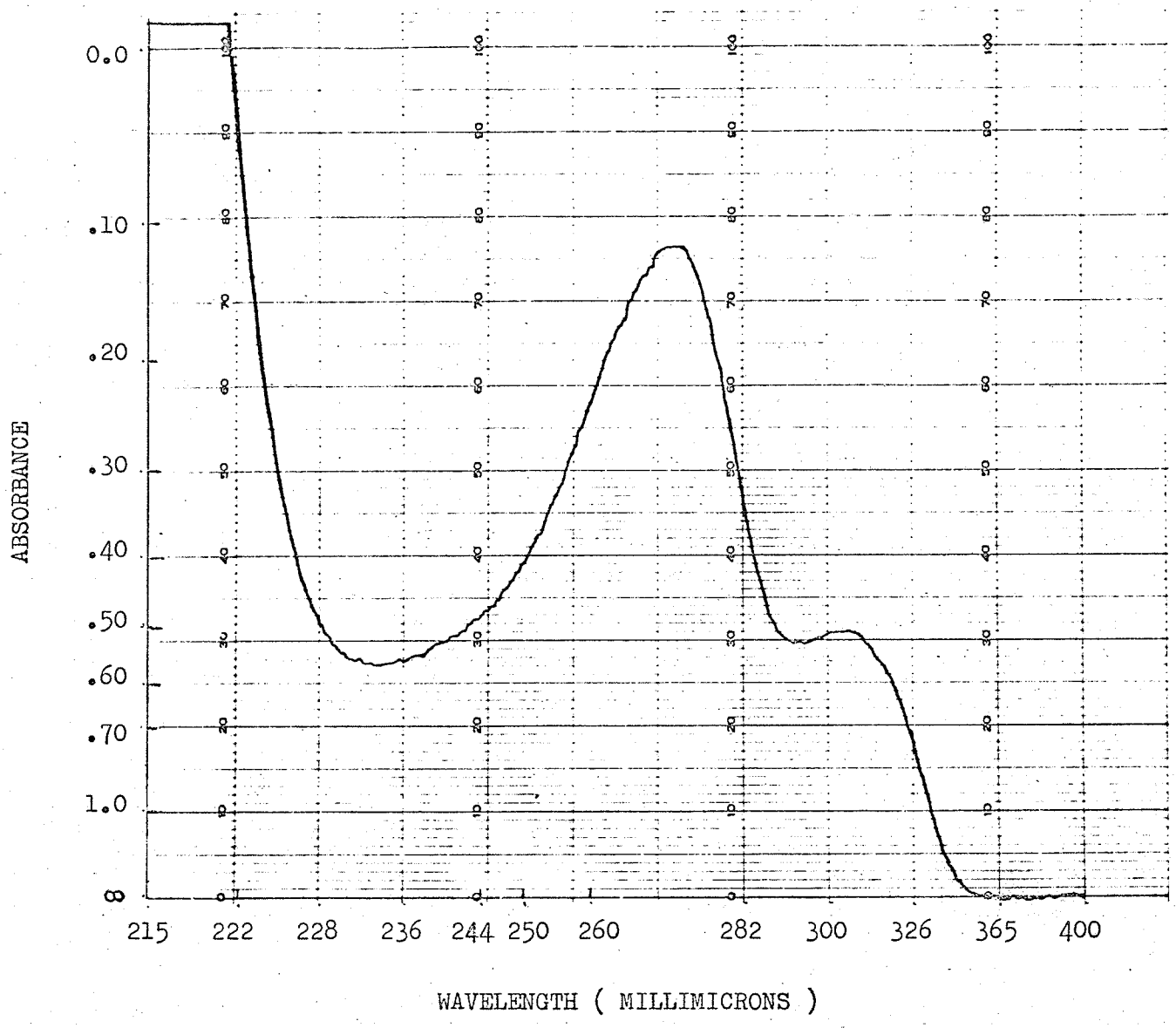



FIGURE XVI. Ultraviolet spectrum number B-1.

o-(N-diaza-3-pyrrolino)benzoic acid ( 2N HCl ).

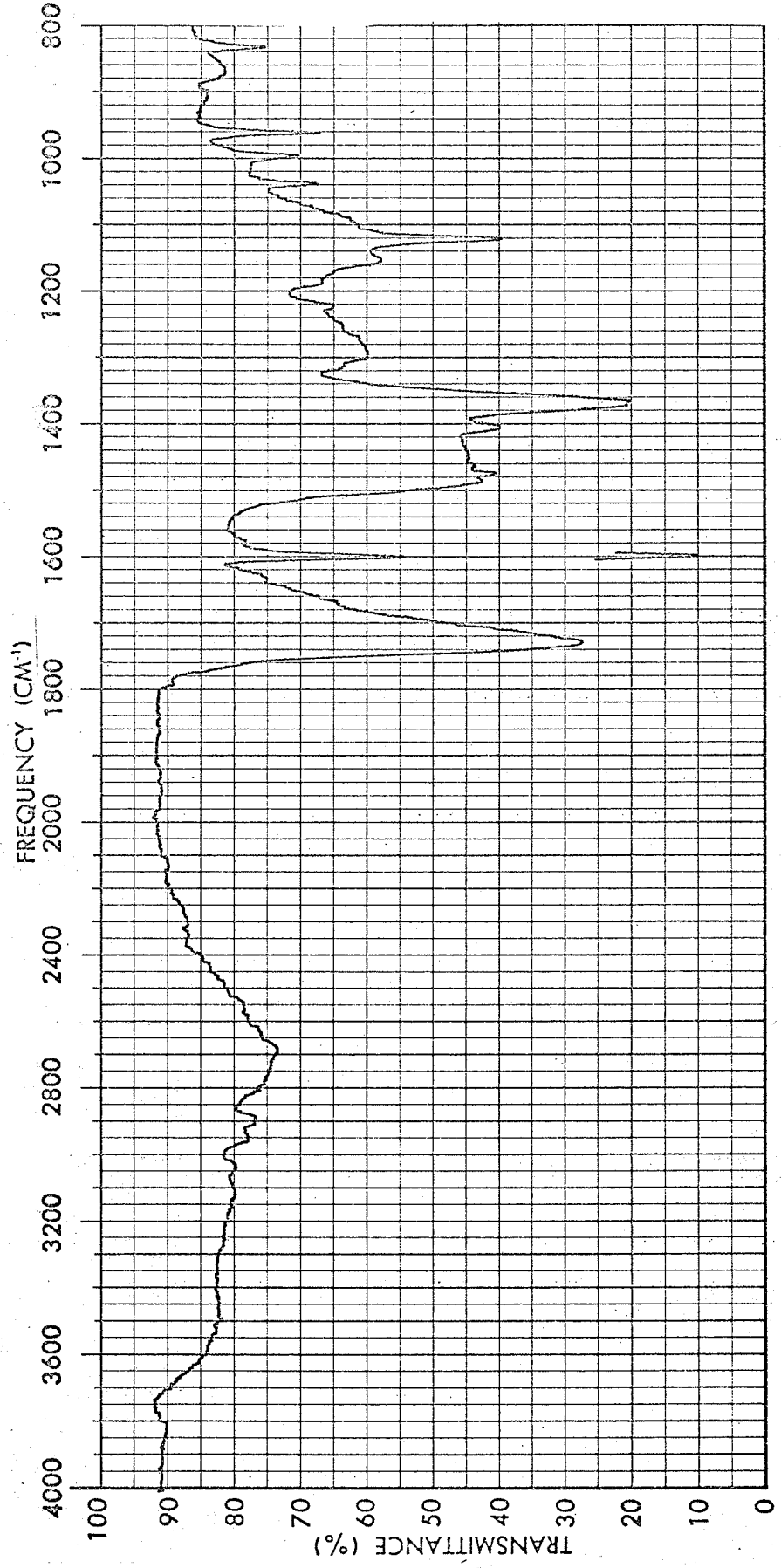



FIGURE XVII. Infrared spectrum number B-1.

o-(N-diaza-3-pyrrolino)benzoic acid ( $CH_2Cl_2$ ).

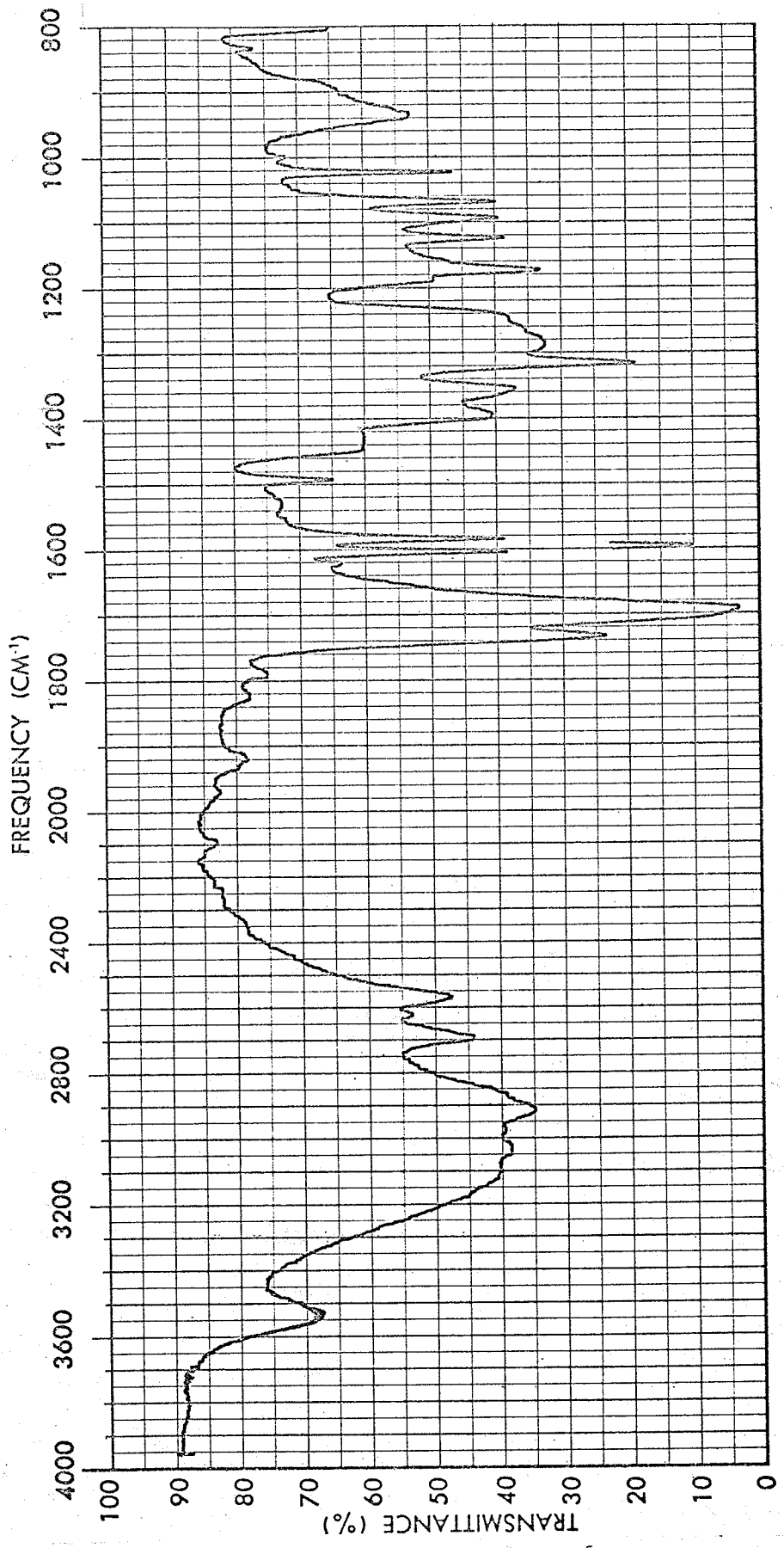



FIGURE XVIII. Infrared spectrum number B-2.

Benzoic acid ( product, $CH_2Cl_2$ ).

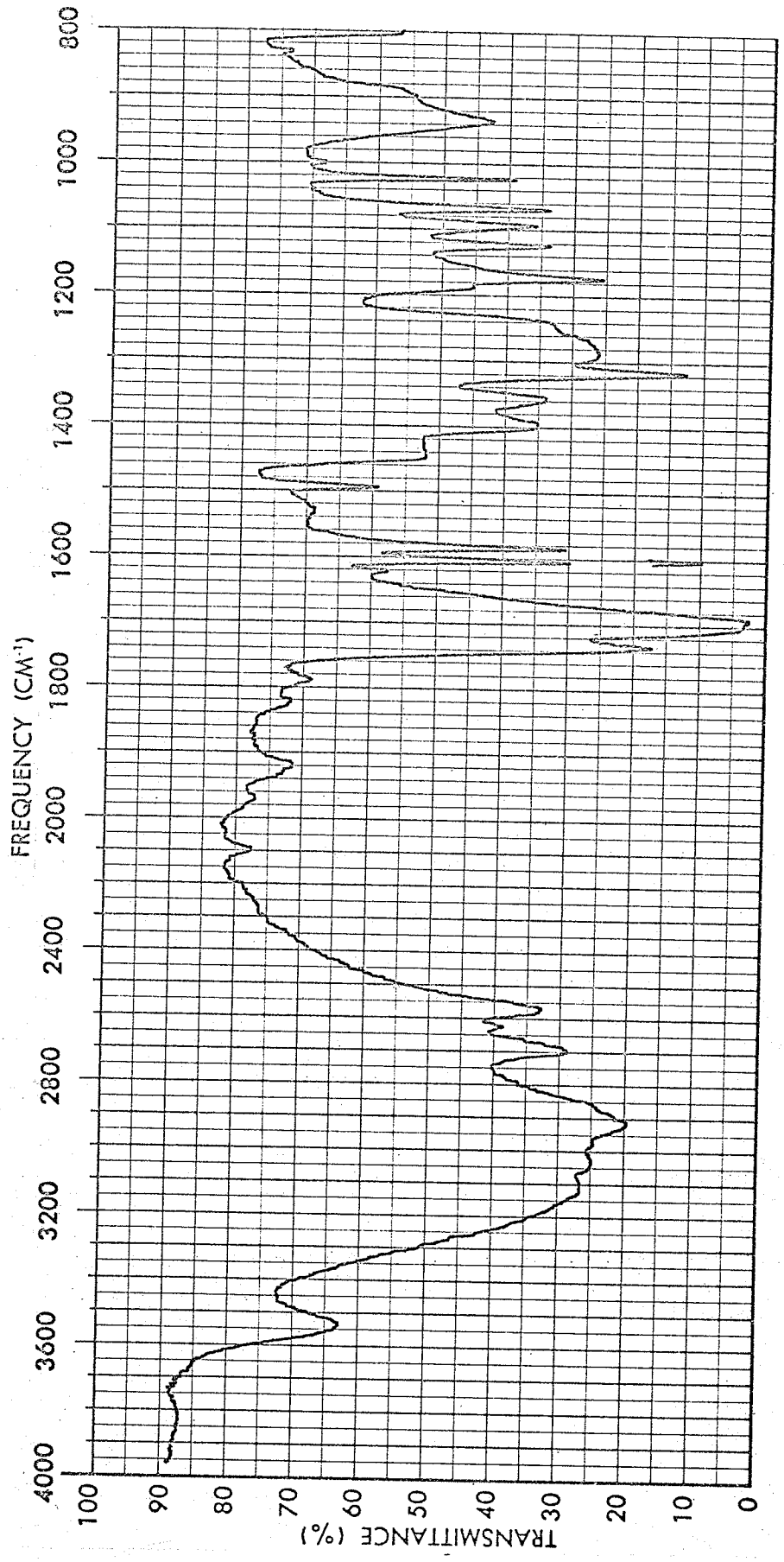



FIGURE XIX. Infrared spectrum number B-3.

Benzoic acid ( authentic sample, $CH_2Cl_2$ ).

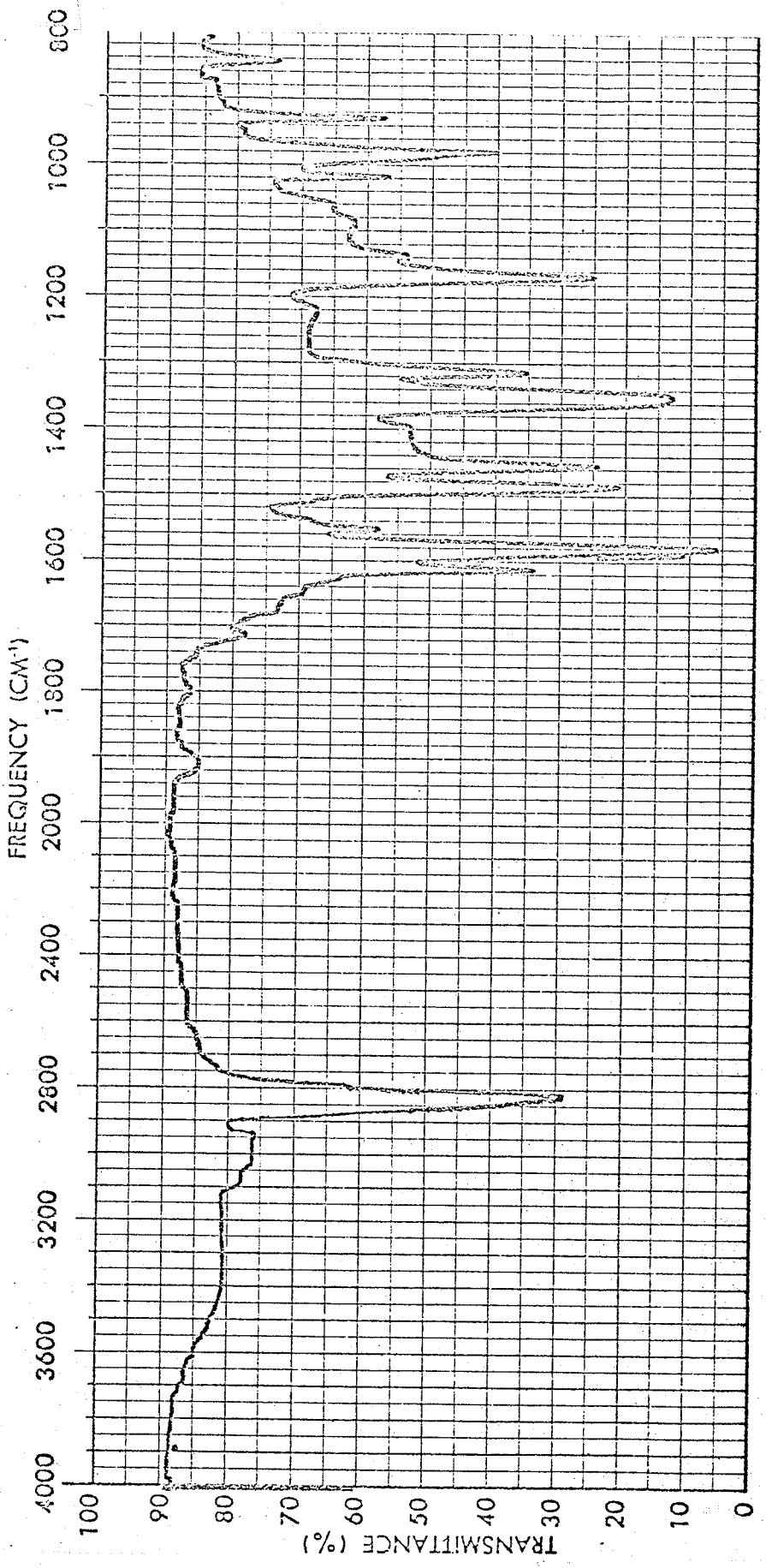



FIGURE XX. Infrared spectrum number B-4.

1-phenyl-3-pyrroline ( product, $CH_2Cl_2$ ).

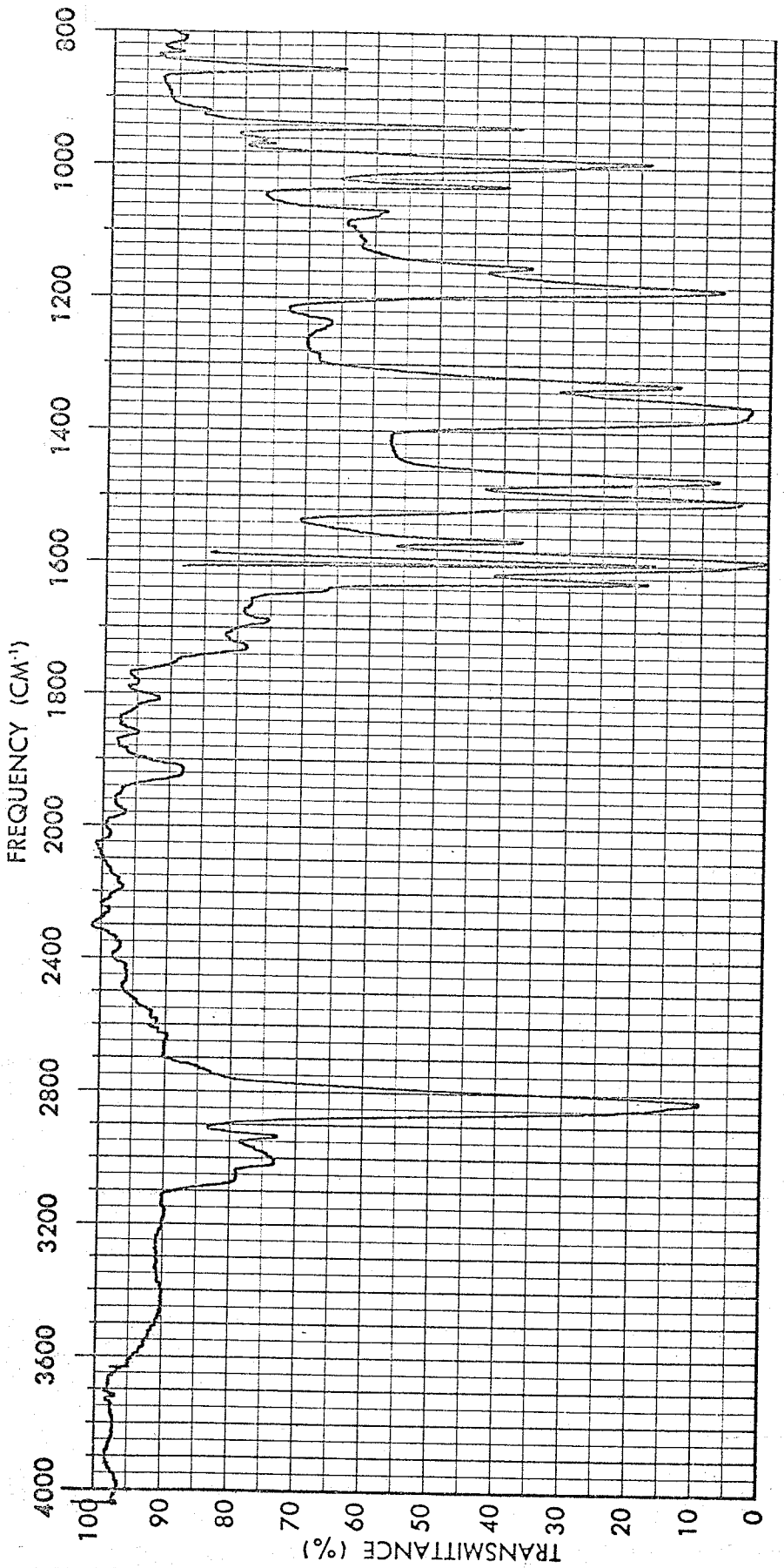



FIGURE XXI. Infrared spectrum number B-5.

1-phenyl-3-pyrroline ( authentic sample, $CH_2Cl_2$ ).

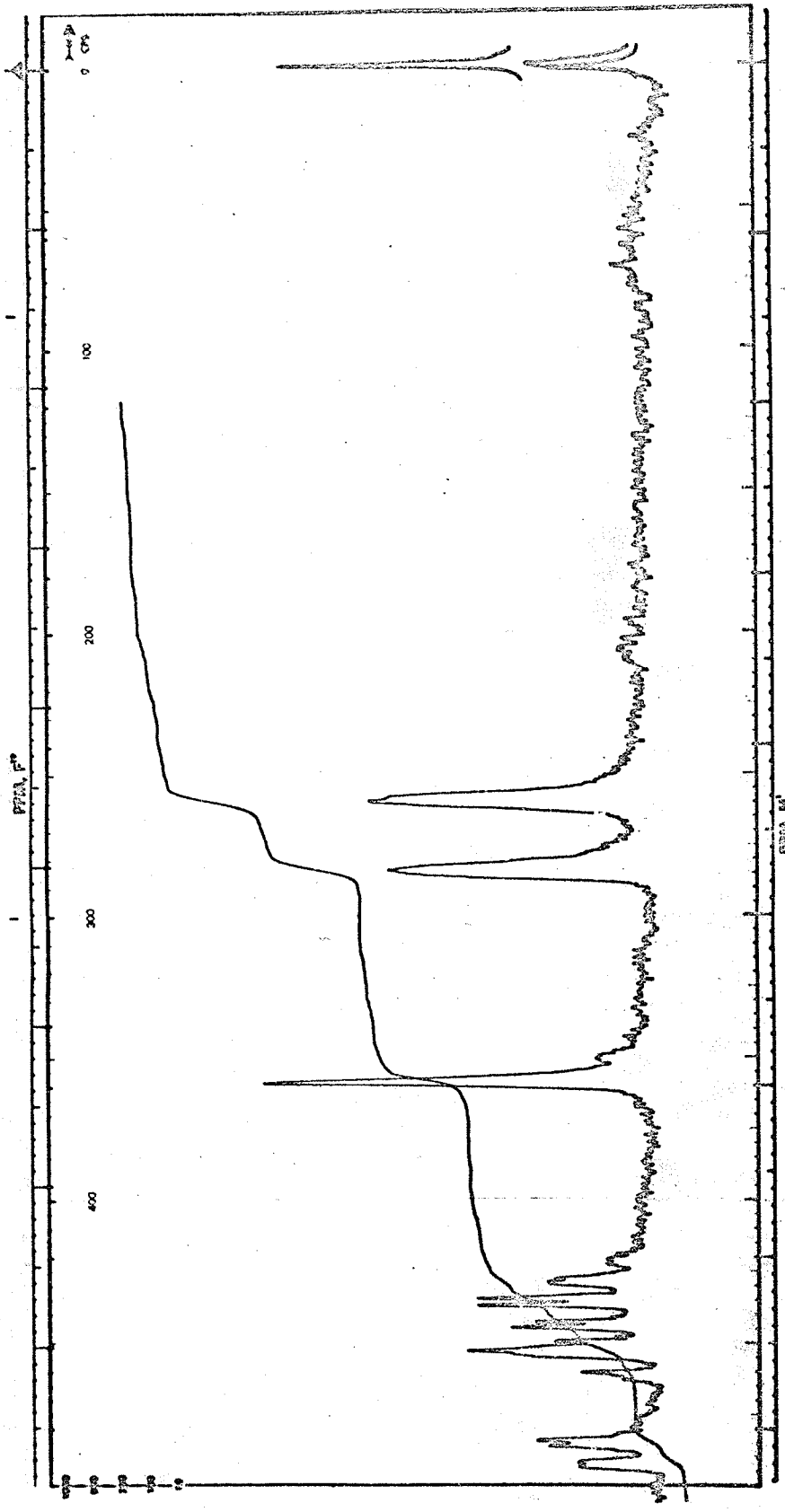


FIGURE XXII. Nuclear magnetic resonance spectrum number B-1.

o-(N-diaza-3-pyrrolino)benzoic acid ( $CDCl_3$ ).

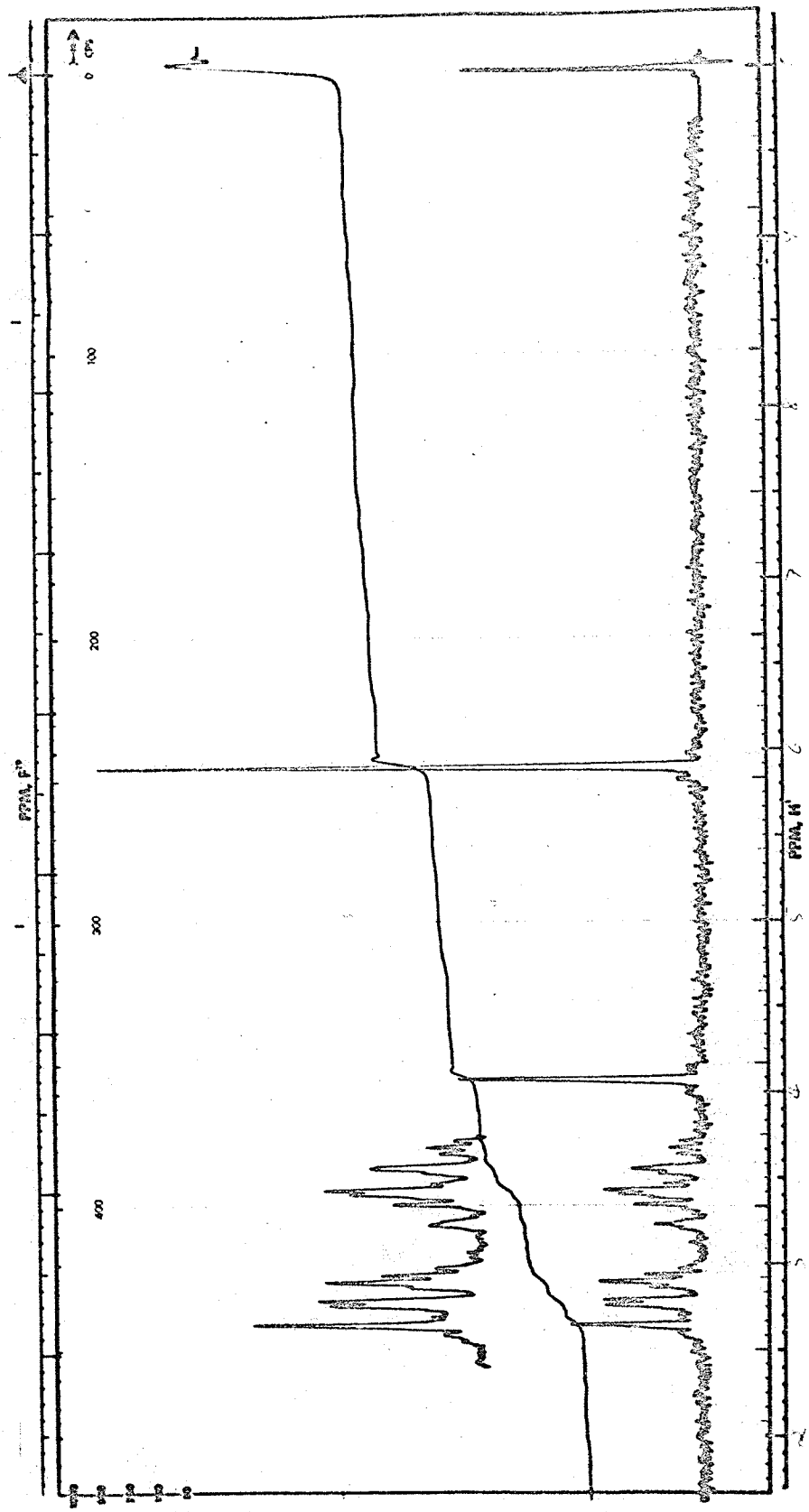


FIGURE XXIII. Nuclear magnetic resonance spectrum number B-2.

1-phenyl-3-pyrroline ( product, $CDCl_3$ ).

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# PART [C]

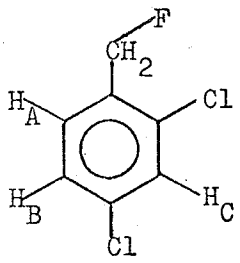
# THE PREPARATION AND NUCLEAR MAGNETIC RESONANCE STUDIES OF SUBSTITUTED α-FLUOROTOLUENES

## ABSTRACT [C]

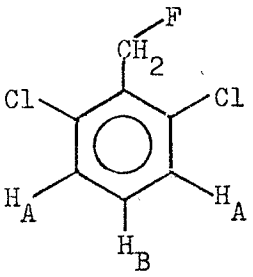
α-fluoro-2,4-dichlorotoluene and α-fluoro-2,6-dichlorotoluene were prepared from α,2,4-trichlorotoluene and α-bromo-2,6-dichlorotolune respectively by thermal decomposition of the corresponding quaternary ammonium fluorides formed by treatment of the respective halides with first 66% triethylamine in absolute ethanol, then excess powdered silver oxide and lastly 20% hydrofluoric acid. The nuclear magnetic resonance spectrum of α-fluoro-2,4-dichlorotoluene ( a $ABCR_2X$ spectrum ) is too complicated and full analysis requires more work to be done in the future. Because of the symmetry of the molecule, the nuclear magnetic resonance spectrum of α-fluoro-2,6-dichlorotoluene ( a $A_2BR_2X$ spectrum ) is less complicated. Since the spin-spin coupling constant between the fluorine nucleus and methylene protons ( a geminal coupling ) is positive, the spin-spin coupling constant between the fluorine nucleus and the meta ring proton ( $H_A$ ) is determined as positive while that between the fluorine nucleus and the para ring proton ( $H_B$ ) is determined as negative.

# INTRODUCTION [C]

Even though the chemistry of organic fluorine compounds grew in leaps and bounds in the past few decades, the corresponding chlorides, bromides and iodides are still more familiar than the organic fluorides themselves. Hence, although α,2,4-trichlorotoluene and α-bromo-2,6-dichlorotoluene are commercially available, the preparation of the respective substituted α-fluorotoluenes ( C-I and C-II ) were not yet reported.




C-I




C-II

Since $F^{19}$ has a spin 1/2 nucleus, in this sense, the nuclear magnetic resonance spectrum of the organic fluoride is more interesting than those of other corresponding halides. The signs and magnitudes of the long-range coupling constants between ring protons and methyl protons in substituted toluenes are in qualitative agreement with a theory based on $\sigma$-$\pi$ interactions[C-1 — C-6]. In 1967, D. J. Blears, S. S. Danyluk and T. Schaefer[C-7] determined the signs of spin-spin coupling constants between the methyl protons and fluorine nuclei in ortho, meta, and para fluorotoluene derivatives by double-resonance techniques. ( The signs of $J_o^{F,CH_3}$, $J_m^{F,CH_3}$, $J_p^{F,CH_3}$ were related to $J_o^{H,H}$ — which is positive — in substituted benzenes[C-8]. ) $J_o^{F,CH_3}$ and $J_p^{F,CH_3}$ are positive while $J_m^{F,CH_3}$ is negative[C-9 — C-18]. This sign sequence is opposite to that of the corresponding methyl proton-ring proton couplings and is the consequence of a positive hyperfine coupling constant associated with the C-F bond. This result implies that the double-bond character of the C-F

bond entails an additional $\sigma-\pi$ interaction overshadowing that expected by analogy with the C-H bond. It was our interest to prepare the substituted α-fluorotoluenes mentioned before, and investigate the spin-spin couplings between the α-fluorine nuclei and the ring protons.

## RESULTS AND DISCUSSIONS [C]

Fluorination by halogen exchange[C-32] is by far the most widely used way of synthesizing organic fluorine compounds, in both the laboratory and industry. This may be achieved by treatment with any of several inorganic fluorides. The most important ones are hydrogen fluoride, potassium fluoride, mercurous fluoride, mercuric difluoride, silver fluoride, antimony trifluoride, sodium fluoride and thallous fluoride. The choice of the reagent is based on the reactivity and hence the ease of the replacement of the halogen to be displaced. Generally, iodine is displaced more easily than bromine and bromine again more easily than chlorine. The ease of the displacement of the same halogens depends on its position in the molecule. Displacement of halogen atoms is easy in reactive halogen derivatives such as sulphohalides, acid halides, α-halocarbonyl compounds, α-haloacids or esters, allylic halides, benzylic halides, and aromatic halogen derivatives with nitro groups in ortho- or para- positions to the halogen atom. Sulphohalides, phosphohalides, acid halides, and α-haloketones, acids and their derivatives are usually treated with potassium fluoride[C-19 — C-21] in order to accomplish the halogen exchange reaction. Allylic fluoride has been obtained by gentle heating of a mixture of allyl chloride and silver fluoride[C-22]. For introducing fluorine atoms into the side chain of the benzene homologs, various reagents have been used. The easiest to prepare are the derivatives with fluorine atoms on the carbon adjacent to the ring ( that is, in the α-position ). Vigorous reactions are obtained for polyhalides of the types $ArCX_2R$, and $ArCX_3$. Benzotrichloride reacts with antimony trifluoride so rapidly that control of the reaction is difficult[C-23]. Benzotrifluoride is obtained in yields of about 60%, the remainder being lost through decomposition. The intermediate chlorofluorides

$C_6H_5CCl_2F$ and $C_6H_5CClF_2$, are seldom found and then only in small amounts. The action of benzal chloride with antimony trifluoride is even more difficult to control, but benzal fluoride still can be obtained in 40% yield by skillful manipulation[C-24]. Heating benzyl bromide with potassium fluoride[C-25] or thallous fluoride[C-26] affords benzyl fluoride. Better results are obtained by treatment of benzyl bromide with mercuric fluoride[C-27] or by thermal decomposition of trimethylbenzylammonium fluoride[C-28]. Yields up to 60% are obtained in both instances. However our attempts to prepare the corresponding α-fluoro derivatives ( C-I and C-II ) from α,2,4-trichlorotoluene as well as α-bromo-2,6-dichlorotoluene by halogen exchange were unsuccessful. This fact suggested that the α-halogen atoms were not sufficiently reactive. When α-bromo-2,6-dichlorotoluene was refluxed under nitrogen with sodium fluoride in absolute t-butanol, no reaction occurred. When α-bromo-2,6-dichlorotoluene was heated under nitrogen with a mixture of antimony trifluoride and antimony dichlorotrifluoride at 100°C. in an oil bath, there was again no reaction. When α-bromo-2,6-dichlorotoluene was refluxed under nitrogen with sodium fluoride in anhydrous dimethyl sulphoxide, the main product was the corresponding aldehyde while there was also a mysterous minor product that does not give a fluorine nuclear magnetic resonance spectrum but give a proton nuclear magnetic resonance spectrum showing the aromatic ring protons as well as two proton-singlets separated by 114.9 ± 0.1 c/s. Apparently, dimethyl sulphoxide behaved as an oxidizing agent. At this point, the unreactivity of α-bromo-2,6-dichlorotoluene suggested the possibility of steric hindrance. Hence, α,2,4-trichlorotoluene was subjected to the action of a mixture of antimony trifluoride and antimony dichlorotrifluoride at 100°C. in an oil bath. Again, there was no reaction.

Since the direct halogen exchange was unsuccessful, other indirect

methods were then studied. α-hydroxy-2,6-dichlorotoluene could be obtained in quantitative yield by refluxing α-bromo-2,6-dichlorotoluene in a basic aqueous solution in acetone. The treatment of the alcohol inside a polyethylene bottle with anhydrous hydrogen fluoride at $0^{o}C$. ( cooled in an ice bath ) gave a pinkish-white solid which was insoluble in most organic solvents. Very likely, the water produced during the reaction combined with the excess hydrogen fluoride to form a concentrated acid solution, which might catalyse the polymerization of the fluoride formed. Acid catalysis has been demonstrated for the solvolysis in aqueous acetone of benzyl fluoride[C-29] and in aqeous ethanol of benzyl fluoride and substituted benzyl fluorides[C-30]. C. K. Ingold and E. H. Ingold[C-28] found that when benzyl fluoride is left in contact with either concentrated hydrofluoric acid or concentrated sulphuric acid, benzyl fluoride readily loses hydrogen fluoride. The product is an opaque white glass. It is sparingly soluble in alcohol and moderately easily soluble in benzene; but it could neither be distilled nor crystallized. It contained not more than a trace of fluorine, and analysis indicated the empirical composition $C_6H_7$ although the molecular weight is undoubtably high. Apparently, the pinkish-white solid obtained from the treatment of α-hydroxy-2,6-dichlorotoluene with anhydrous hydrogen fluoride is a result of the same type of polymerization as discussed above.

In their study of the decomposition of quaternary ammonium salts, W. Hanhard and C. K. Ingold[C-31] have shown that under structural conditions antagonistic to the formation of an olefin the alkyl radical most tolerant to a positive charge is ejected and subsequently combined with the anion of the salt. Thus the distillation of a quaternary ammonium fluorides such as a substituted benzyltriethylammonium fluoride, containing only the substituted benzyl and ethyl groups, should yield a predominant proportion of the substituted

benzyl fluoride ( that is, substituted α-fluorotoluene ). The quaternary ammonium salts of α,2,4-trichlorotoluene and α-bromo-2,6-dichlorotoluene were prepared by heating overnight with a 66% solution of triethylamine in absolute ethanol at 50°C. in an oil bath under anhydrous conditions. Here, the insufficiency in reactivity of the α-halogen atoms was again shown by the fact that neither reaction was exothermic as in the case of benzyl chloride. The aqueous solution of each quaternary ammonium salt was treated with excess powdered silver oxide. The solid was separated by filtration, and the filtrate was neutralized with 20% hydrofluoric acid and concentrated to half of its original volume. The thermal decomposition of the final solution under a water-pump vacuum ( 20 mm. ) gave a mixture of the corresponding substituted α-fluorotoluene, the starting material, and the substituted benzyldiethylamine. Very likely, the conversion of each quaternary ammonium halide to the quaternary ammonium hydroxide by the treatment of silver oxide was incomplete, and some original halide ions were still present in the final solution before the thermal decomposition. Chromatography ( silica gel ) of each mixture separated out the corresponding substituted benzyldiethylamine. α-fluoro-2,4-dichlorotoluene ( C-I ) was purified further by fractional distillation under an oil-valve-pump vacuum ( 0.5 mm. ) while α-fluoro-2,6-dichlorotoluene ( C-II ) was purified further by rechromatography ( silica gel ). The nuclear magnetic resonance spectrum of α-fluoro-2,4-dichlorotoluene ( a $ABCR_2X$ spectrum ) is too complicated. So far, only the following is known:

$$\nu_F = -12272 \text{ c/s.} \quad ( \delta_F = -217.6 \text{ ppm.} )$$

$$\nu_{CH_2} = 307.0 \text{ c/s.} \quad ( \delta_{CH_2} = 5.12 \text{ ppm.} )$$

$$J_{F,CH_2} = 47.0 \pm 0.2 \text{ c/s.} \quad ( \text{positive} )$$

( The proton shifts are given in cycles per second at 60.0 Mc/sec. to the low field of internal tetramethylsilane while the fluorine shifts are

given in cycles per second at 56.4 Mc/sec. to the high field of external trichlorofluoromethane. )

Because of the symmetry of the molecule, the nuclear magnetic resonance spectrum of α-fluoro-2,6-dichlorotoluene ( a $A_2BR_2X$ spectrum ) is less complicated. The following summarizes the analysis obtained so far:

$\nu_F$ = -11959 c/s. ( $\delta_F$ = -212.0 ppm. )

$\nu_{CH_2}$ = 323.4 c/s. ( $\delta_{CH_2}$ = 5.39 ppm. )

$J_{F,CH_2}$ = 47.5 ± 0.2 c/s. ( positive )

$\nu_{H_A}$ = 401.4 c/s. ( $\delta_{H_A}$ = 6.69 ppm. )

$\nu_{H_B}$ = 415.6 c/s. ( $\delta_{H_B}$ = 6.93 ppm. )

$J_{F,H_A}$ = + 1.25 ± 0.04 c/s.

$J_{F,H_B}$ = - 2.43 ± 0.02 c/s.

$J_{H_A,H_B}$ = + 8.14 ± 0.05 c/s.

$|J_{H_A,CH_2}|$ = 0.16 ± 0.02 c/s.

$|J_{H_B,CH_2}|$ = 0.34 ± 0.04 c/s.

Other information from the the analysis of the nuclear magnetic resonance spectrum of α-fluoro-2,4-dichlorotoluene requires more work to be done in the future.

# EXPERIMENTAL [C]

## C-i PREPARATION OF α-FLUORO-2,4-DICHLOROTÓLUENE

α,2,4-trichlorotoluene ( 12.8 g. ), triethylamine ( 5.2 g. ) and absolute ethanol ( 5 ml. ) were mixed and stirred overnight at 50°C. in an oil bath under anhydrous conditions. The mixture was allowed to cool and then anhydrous ether ( 100 ml. ) was added to precipitate the 2,4-dichlorobenzyltriethyl-ammonium chloride. The supernant was decanted through a filtering crucible, and the precipitate was stirred with more anhydrous ether ( 2 x 50 ml. ). The precipitate was then dissolved in water ( 50 ml. ). The solution was stirred with a suspension of powdered silver oxide ( 10 g. ) for one hour and then filtered. This process was repeated twice more. The final filtrate was neutralized with 20% hydrofluoric acid ( approximately 4 ml. ) and concentrated on an steam bath to half of its original volume. The resulting solution was distilled under a water-pump vacuum ( 20 mm. ) from a flask, equipped with a heating mantle, through a condenser into a flask cooled below 0°C. ( ice-salt mixture ). α-fluoro-2,4-dichlorotoluene and other impurities were collected as oil droplets. The distillate was exhaustively extracted with ether ( 5 x 40 ml. ). The ether extracts were combined, dried ( sodium sulphate ), and concentrated into an oil. Chromatography ( silica gel ) of the residue gave a mixture of α,2,4-trichlorotoluene and α-fluoro-2,4-dichlorotoluene ( 1.0 g. ). Fractional distillation under an oil-valve-pump vacuum ( 0.5 mm. ) gave a more volatile liquid ( 40—60°C., 500 mg. ), which is richer in the fluoro compound as shown by the nuclear magnetic resonance spectrum. Redistillation of this volatile liquid yielded another liquid ( 42—46°C., 300 mg. ) which is mostly α-fluoro-2,4-dichlorotoluene ( with some α,2,4-trichlorotoluene, amounting to 1% to 2% as estimated from

the proton resonance spectrum ).

Infrared spectrum number C-1.

Nuclear magnetic resonance spectrum numbers C-1 to C-5.

C-ii PREPARATION OF α-FLUORO-2,6-DICHLOROTOLUENE

α-bromo-2,6-dichlorotoluene ( 10 g. ), triethylamine ( 5 g. ), and absolute ethanol ( 5 ml. ) were mixed and stirred overnight at 50°C. in an oil bath under anhydrous conditions. The mixture was allowed to cool and then anhydrous ether ( 100 ml. ) was added to break up the cake formed. The supernant was decanted through a filtering crucible and the precipitate was stirred with more anhydrous ether ( 2 x 50 ml. ). The precipitate was then dissolved in water ( 50 ml. ). The solution was stirred with a suspension of powdered silver oxide ( 10 g. ) for one hour and then filtered. This process was repeated twice more. The final filtrate was neutralized with 20% hydrofluoric acid ( approximately 4 ml. ) and concentrated on an steam bath to half of its original volume. The resulting solution was distilled under a water-pump vacuum ( 20 mm. ) from a flask, equipped with a heating mantle, through a condenser into a flask cooled below 0°C. ( ice-salt mixture ). α-fluor-2,6-dichlorotoluene and other impurities were collected as a white solid. The distillate was then exhaustively extracted with ether ( 5 x 40 ml. ). The ether extracts were combined, dried ( sodium sulphate ), and concentrated into a foam ( 2.2 g. ). Chromatography ( silica gel ) of the residue gave a mixture of α-bromo-2,6-dichlorotoluene and α-fluoro-2,6-dichlorotoluene ( 1.2 g. ). Rechromatography ( silica gel ) separated out α-fluoro-2,6-dichlorotoluene as white needles ( 700 mg. ).

Melting point: 58—59°C..

Infrared spectrum number C-2.

Nuclear magnetic resonance spectrum numbers C-6 to C-10.

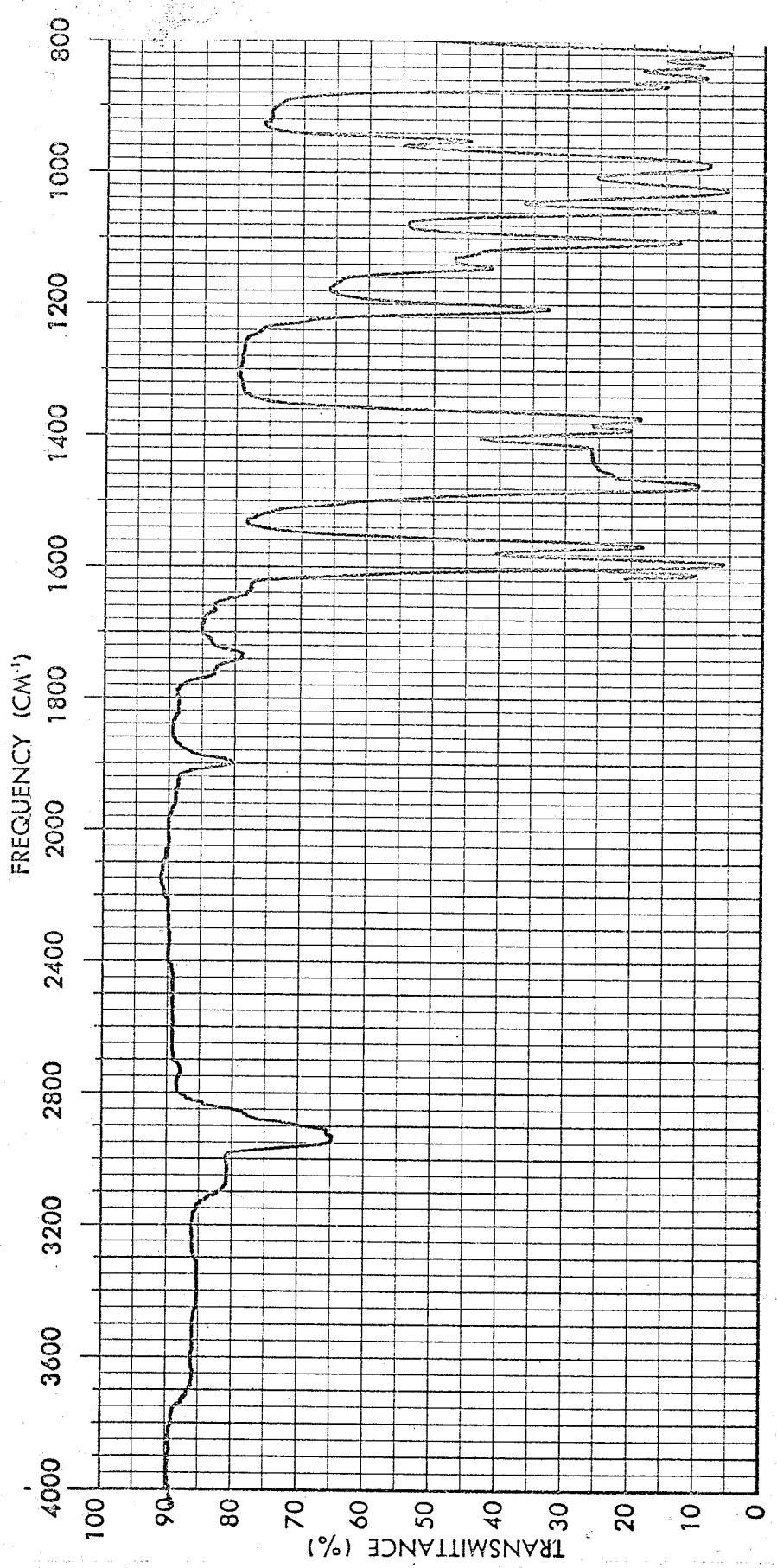



FIGURE XXIV. Infrared spectrum number C-1.

α-fluoro-2,4-dichlorotoluene ( $CH_2Cl_2$ ).

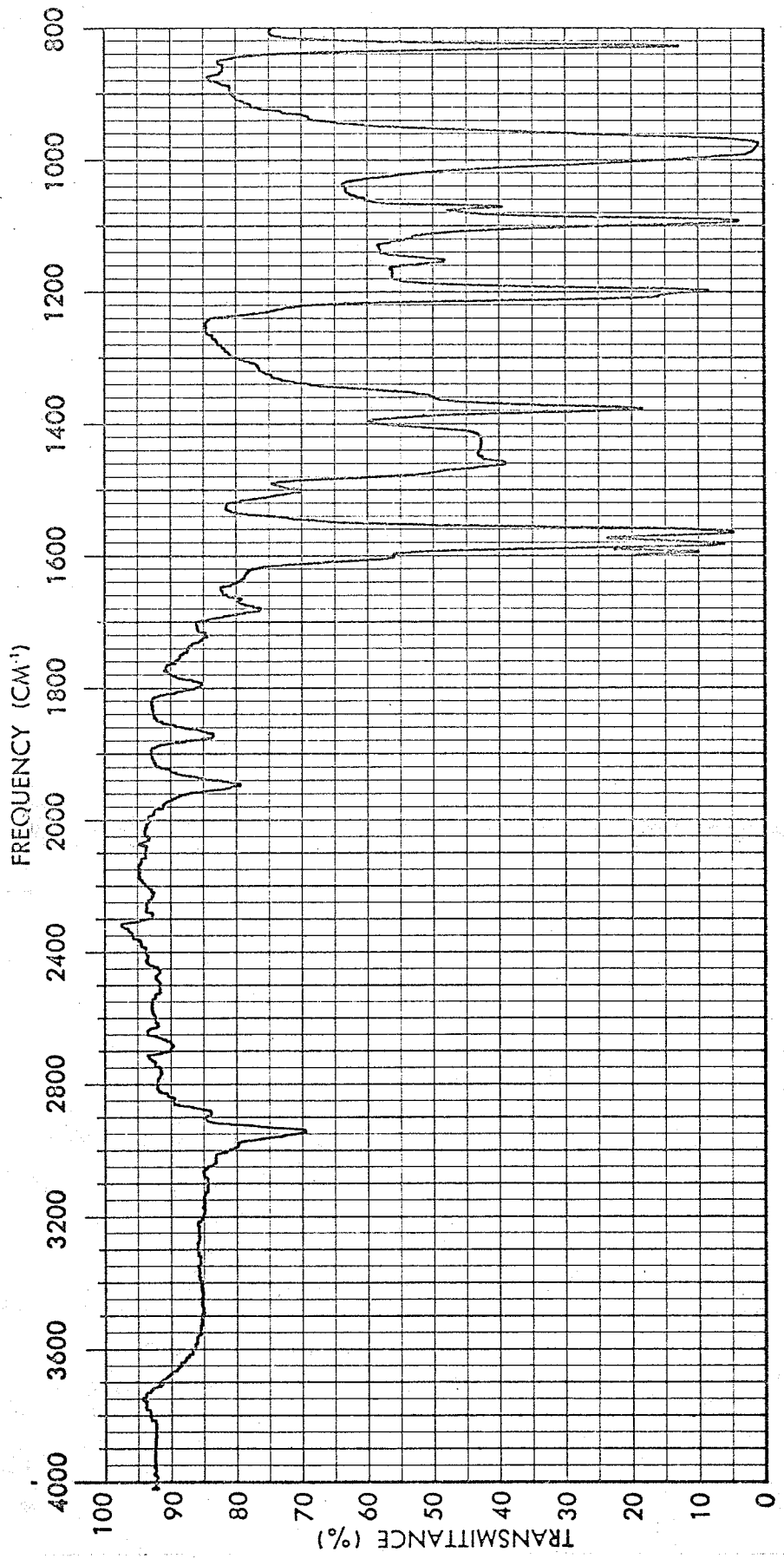



FIGURE XXV. Infrared spectrum number C-2.

α-fluoro-2,6-dichlorotoluene ( $CH_2Cl_2$ ).

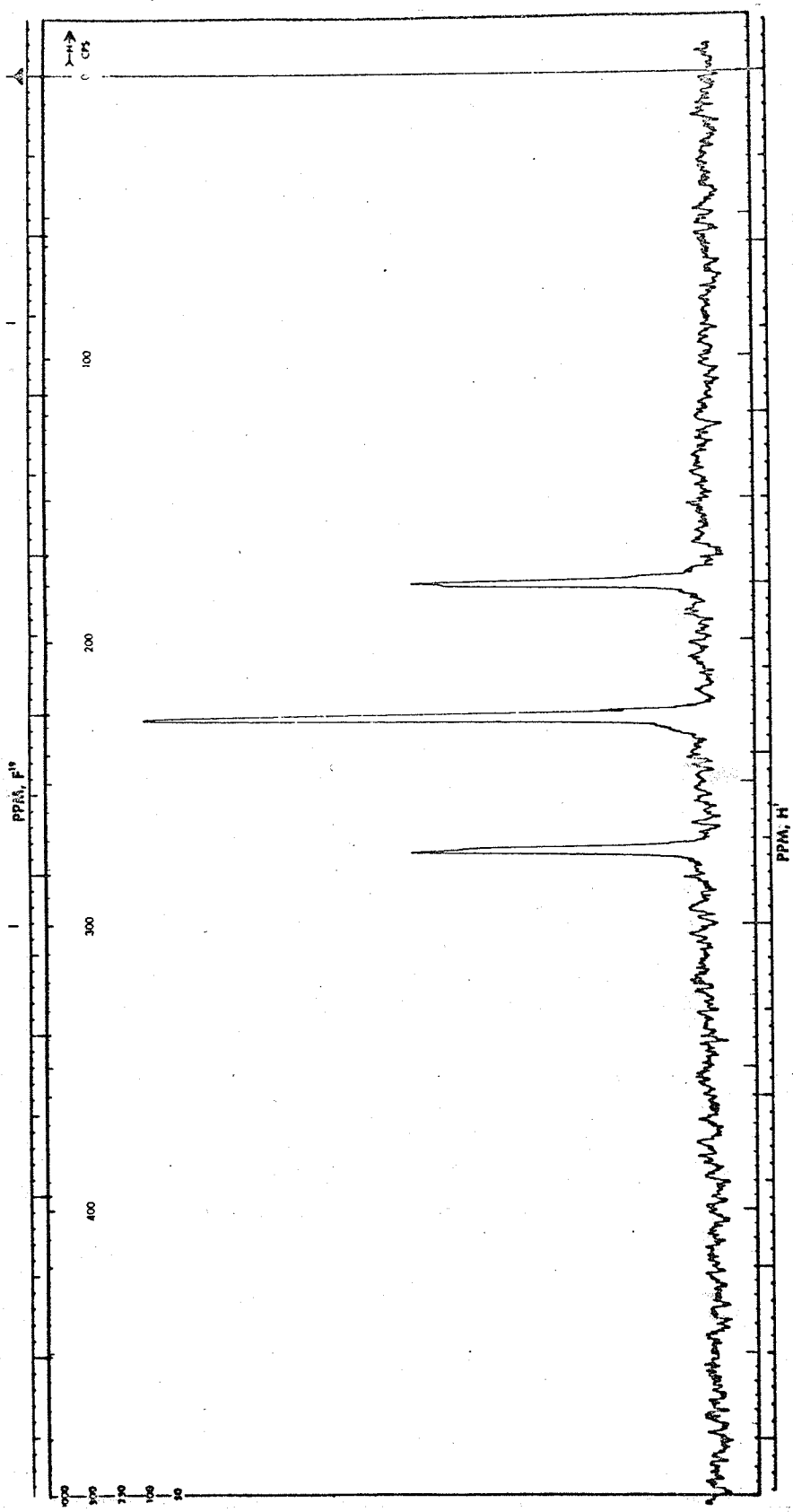



FIGURE XXVI. Nuclear magnetic resonance spectrum number C-1.

α-fluoro-2,4-dichlorotoluene ( sweep width 500 c/s, offset -12500 c/s, $F^{19}$, $C_6D_6$ ).

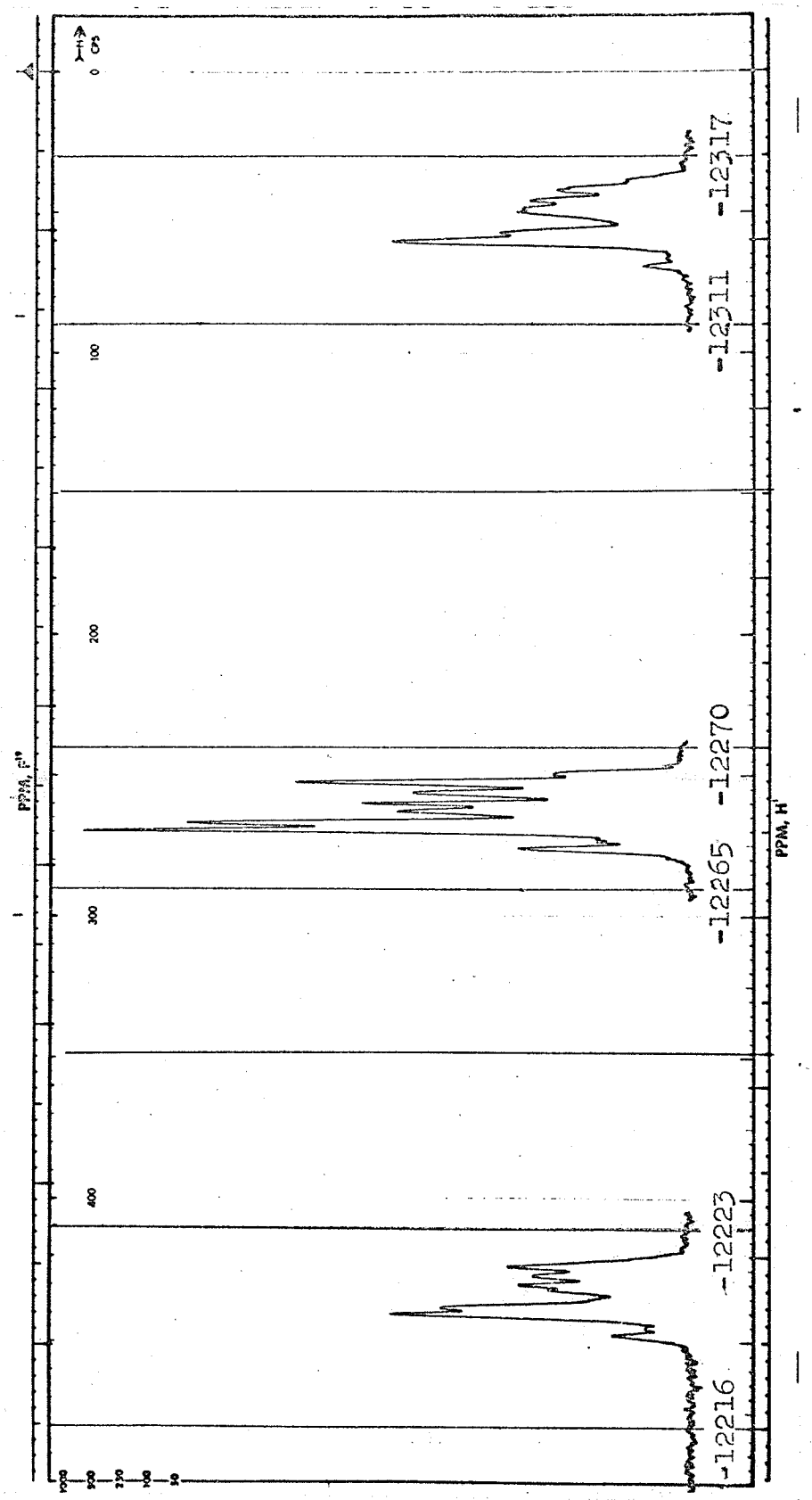



FIGURE XXVII. Nuclear magnetic resonance spectrum number C-2.

α-fluoro-2,4-dichlorotoluene ( $F^{19}$, $C_6D_6$ ).

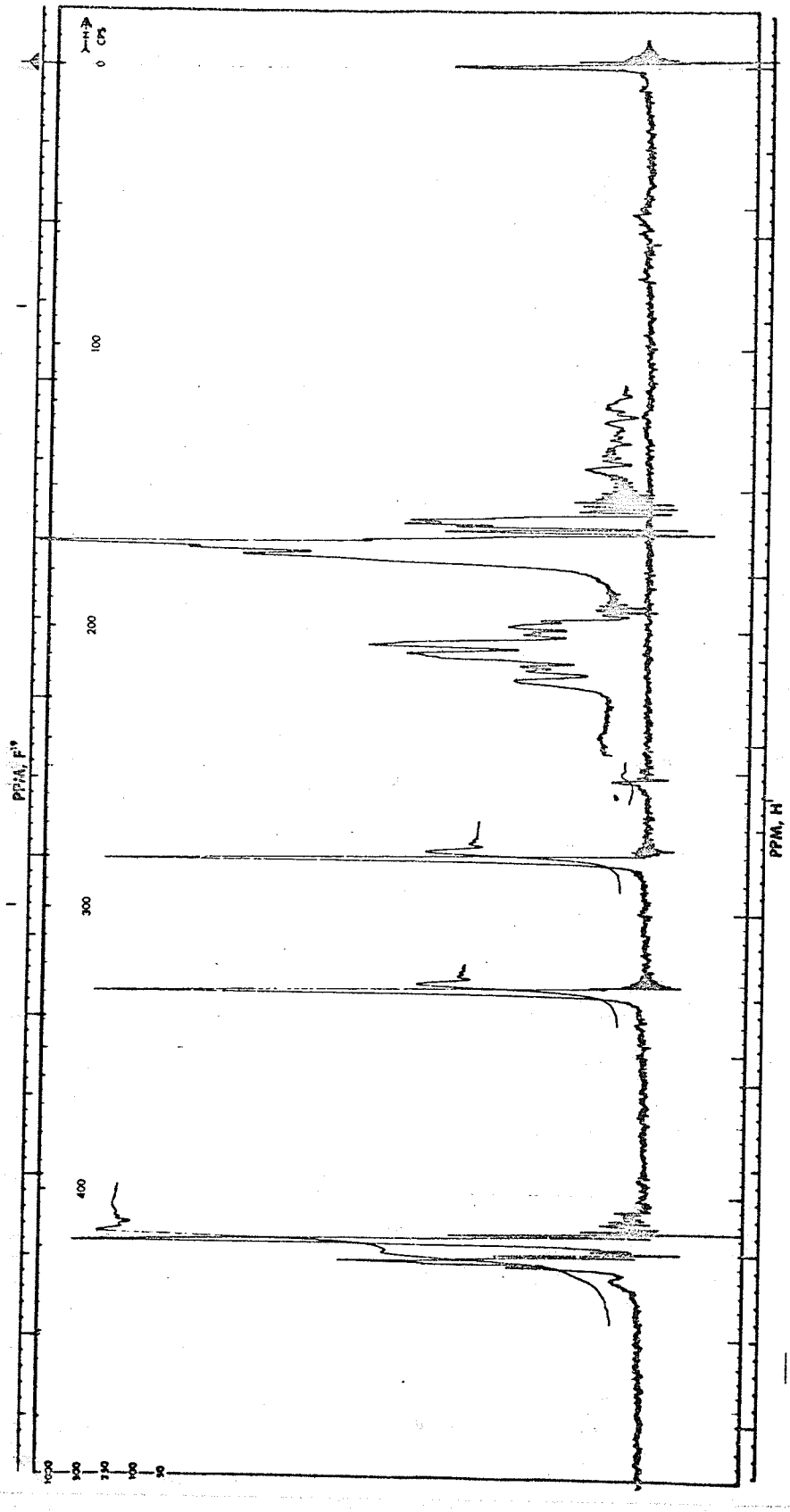



FIGURE XXVIII. Nuclear magnetic resonance spectrum number C-3.

α-fluoro-2,4-dichlorotoluene ( sweep width 500 c/s, $H^1$, $C_6D_6$ ).

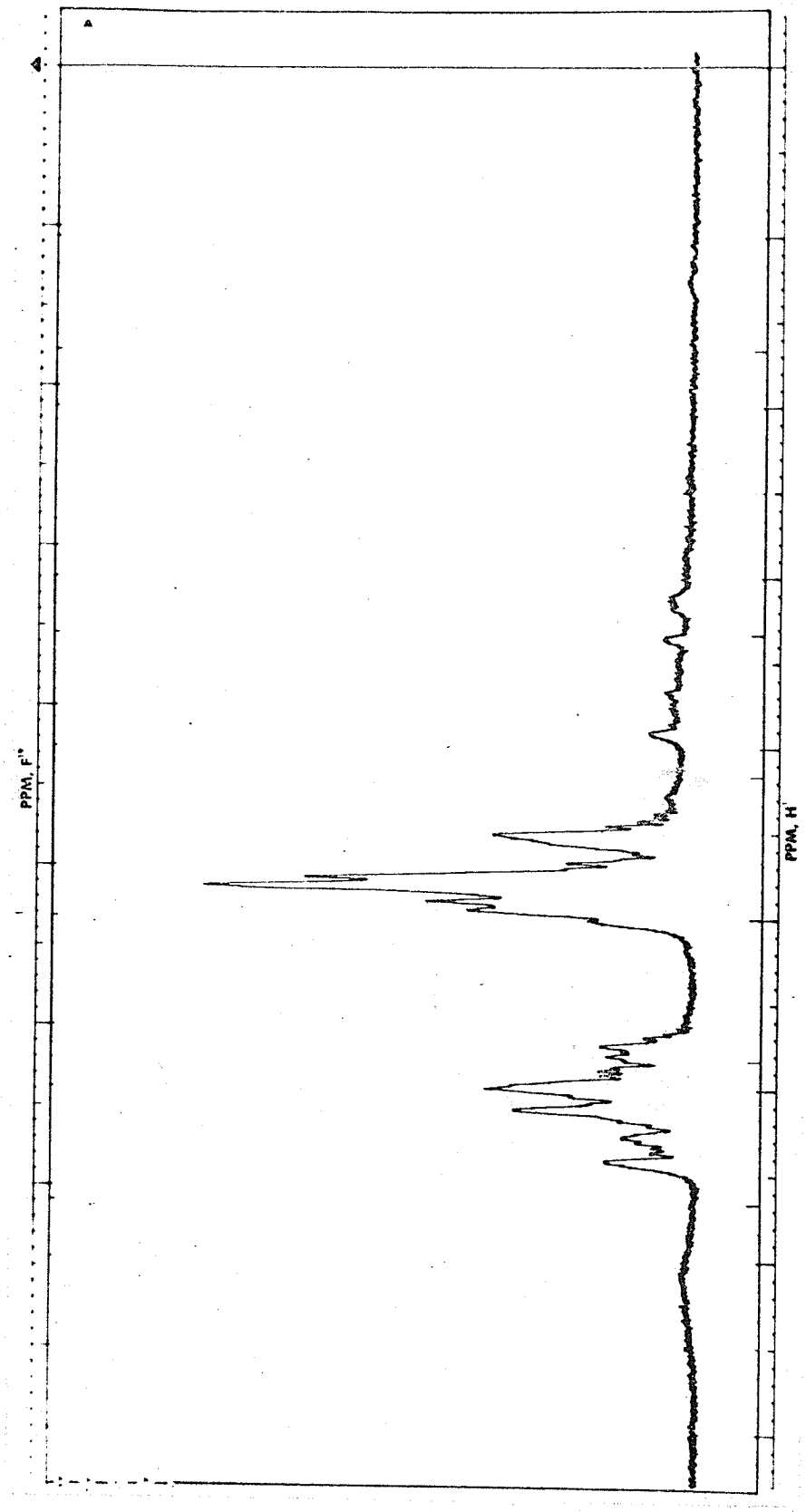



FIGURE XXIX. Nuclear magnetic resonance spectrum number C-4.

α-fluoro-2,4-dichlorotoluene ( sweep width 50 c/s, offset 390 c/s, $H^1$, $C_6D_6$ ).

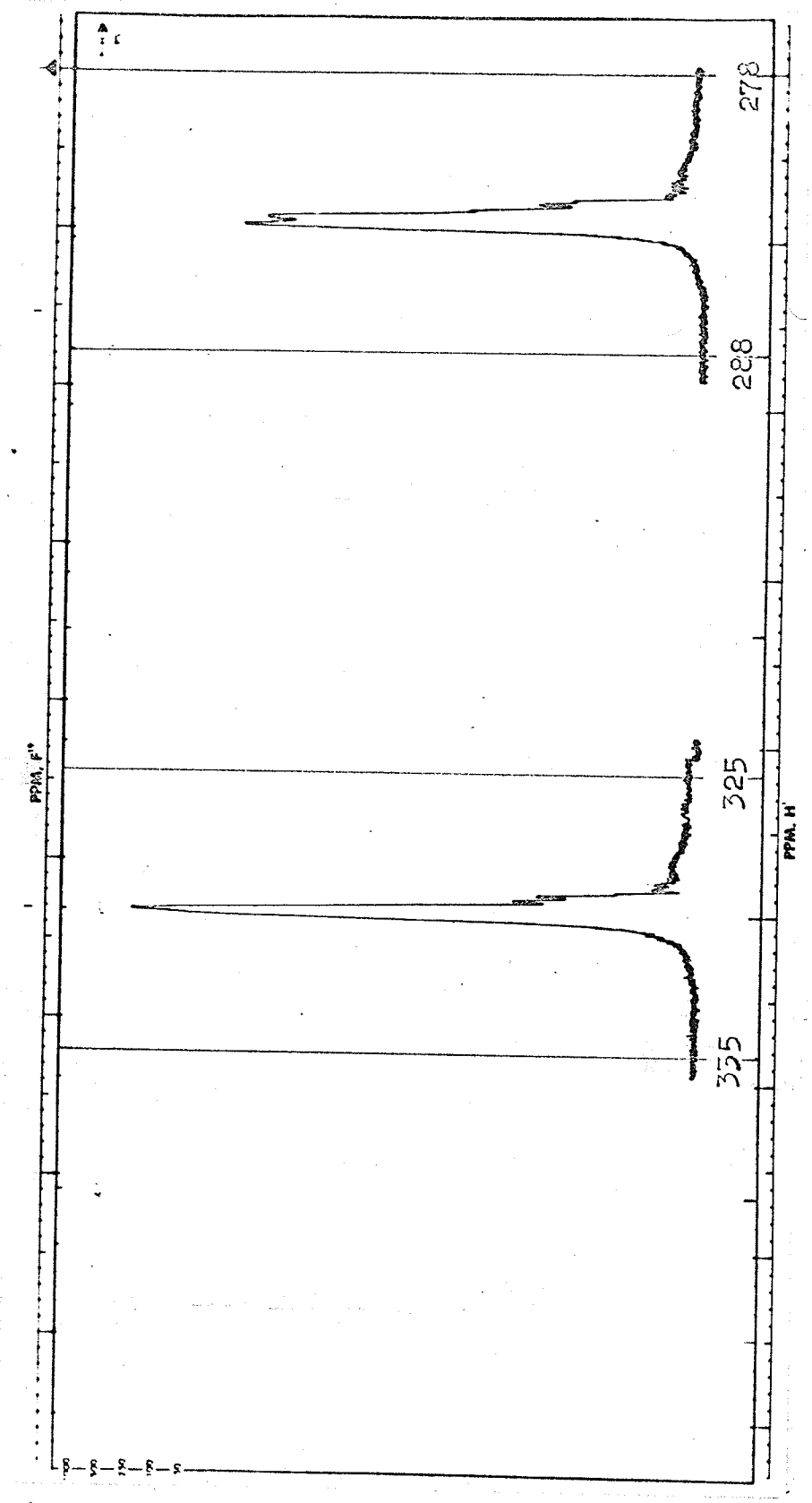



FIGURE XXX. Nuclear magnetic resonance spectrum number C-5.

α-fluoro-2,4-dichlorotoluene ( $H^1$, $C_6D_6$ ).

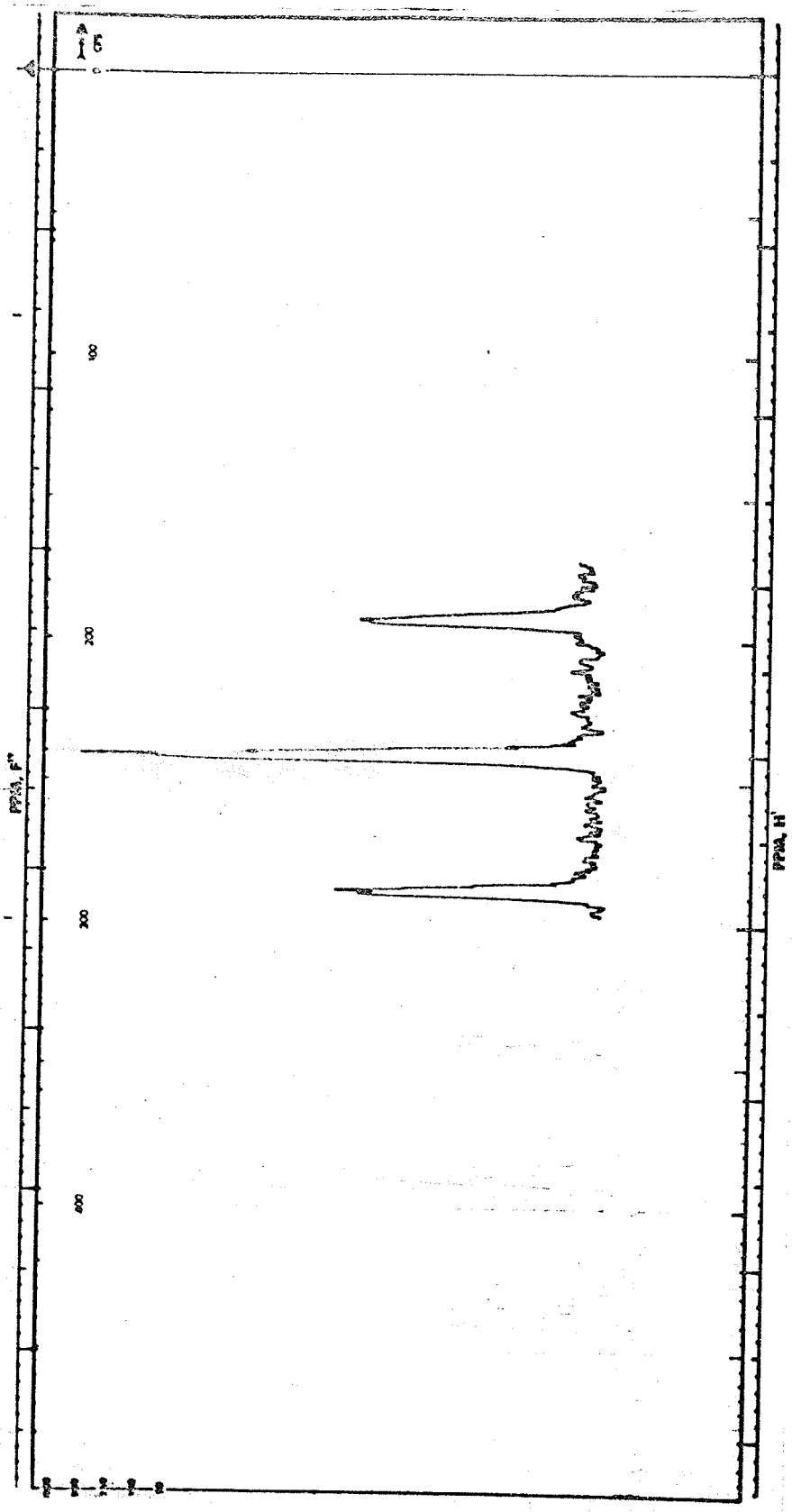


FIGURE XXXI. Nuclear magnetic resonance spectrum number C-6.

α-fluoro-2,6-dichlorotoluene ( sweep width 500 c/s, offset -12200 c/s, $F^{19}$, $C_6D_6$ ).

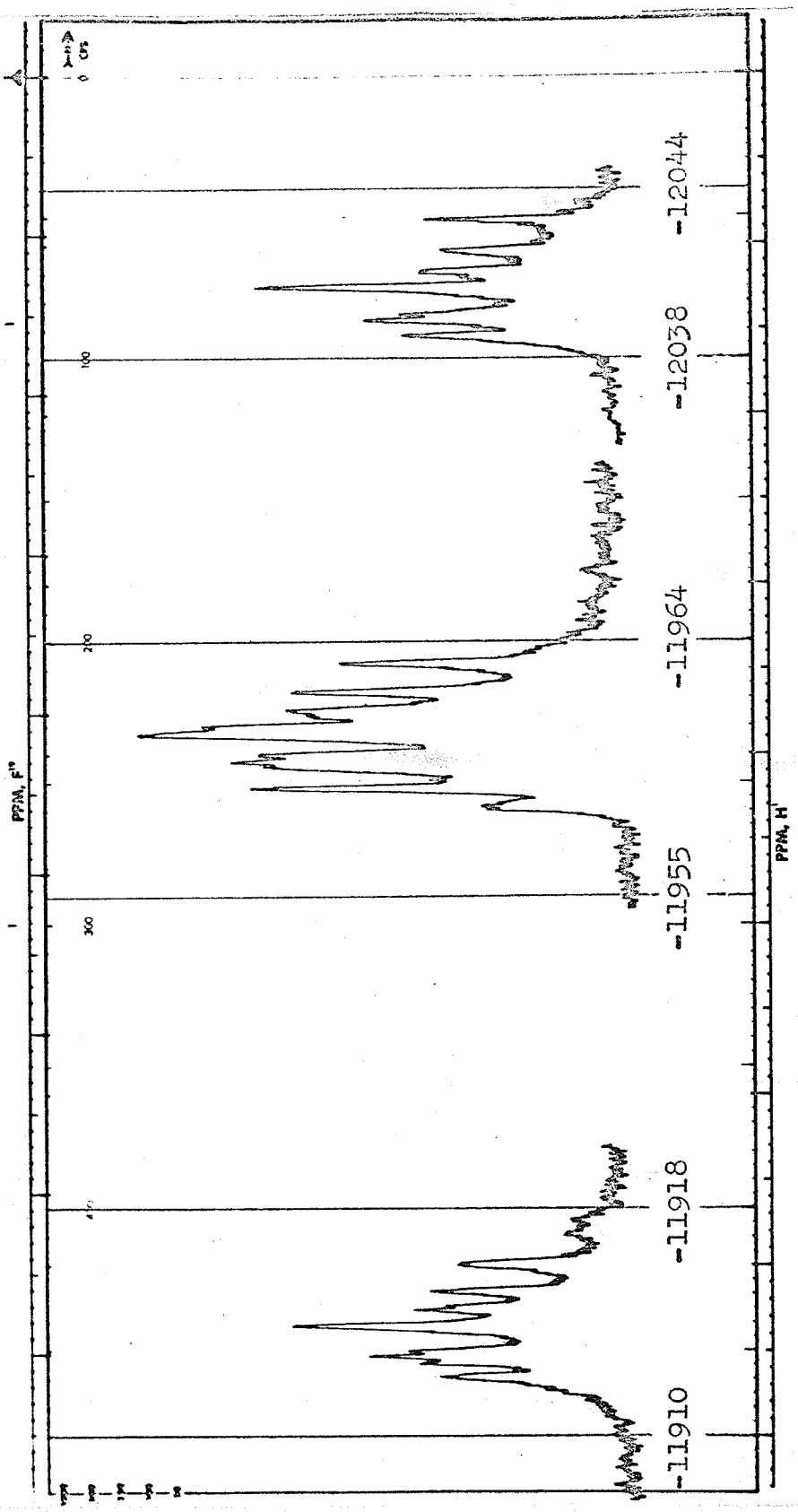



FIGURE XXXII. Nuclear magnetic resonance spectrum number C-7.

α-fluoro-2,6-dichlorotoluene ( $F^{19}$, $C_6D_6$ ).

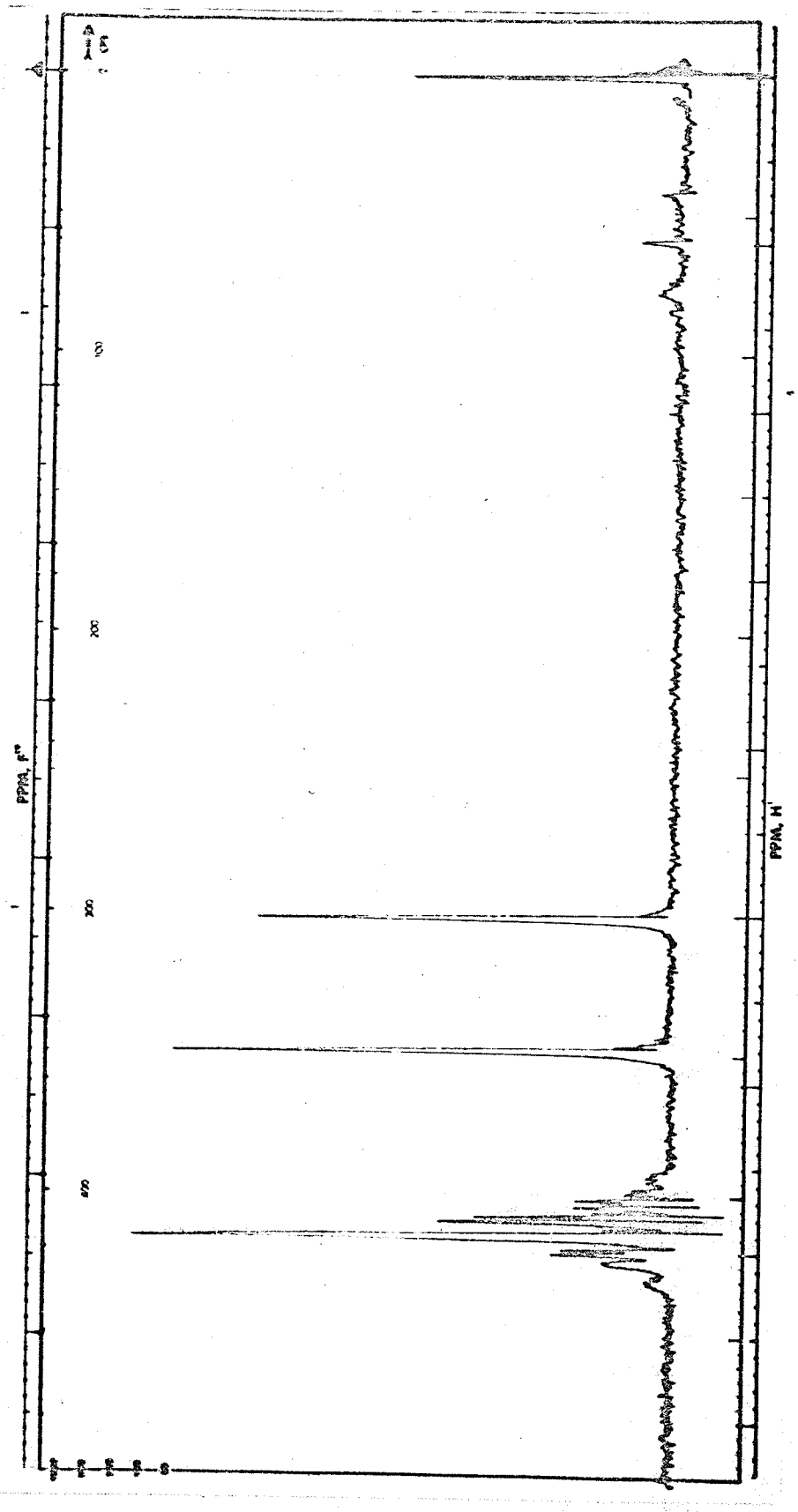



FIGURE XXXIII. Nuclear magnetic resonance spectrum number C-8.

α-fluoro-2,6-dichlorotoluene ( sweep width 500 c/s, $H^1$, $C_6D_6$ ).

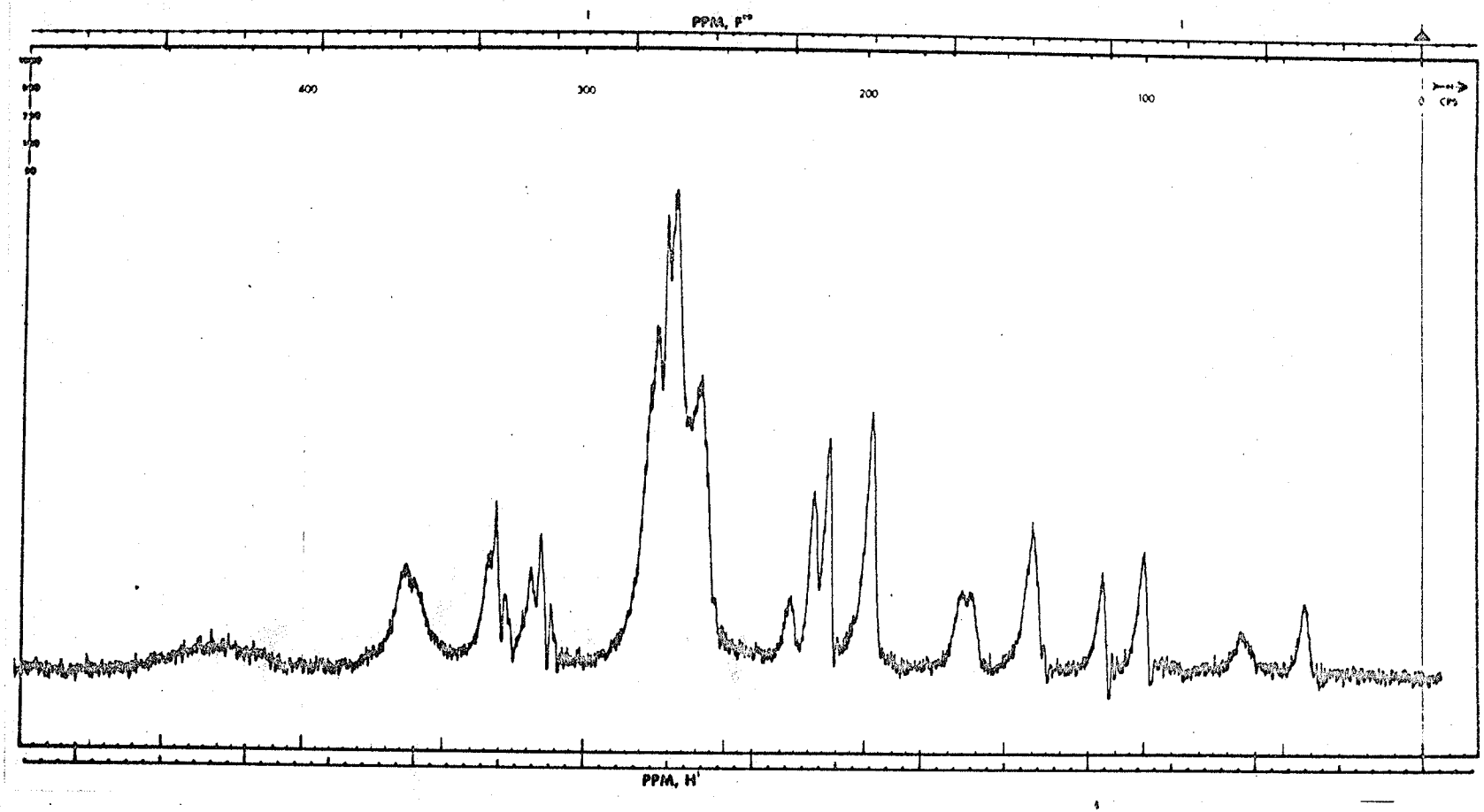



FIGURE XXXIV. Nuclear magnetic resonance spectrum number C-9.

α-fluoro-2,6-dichlorotoluene ( sweep width 50 c/s, offset 390 c/s, $H^1$, $C_6D_6$ ).

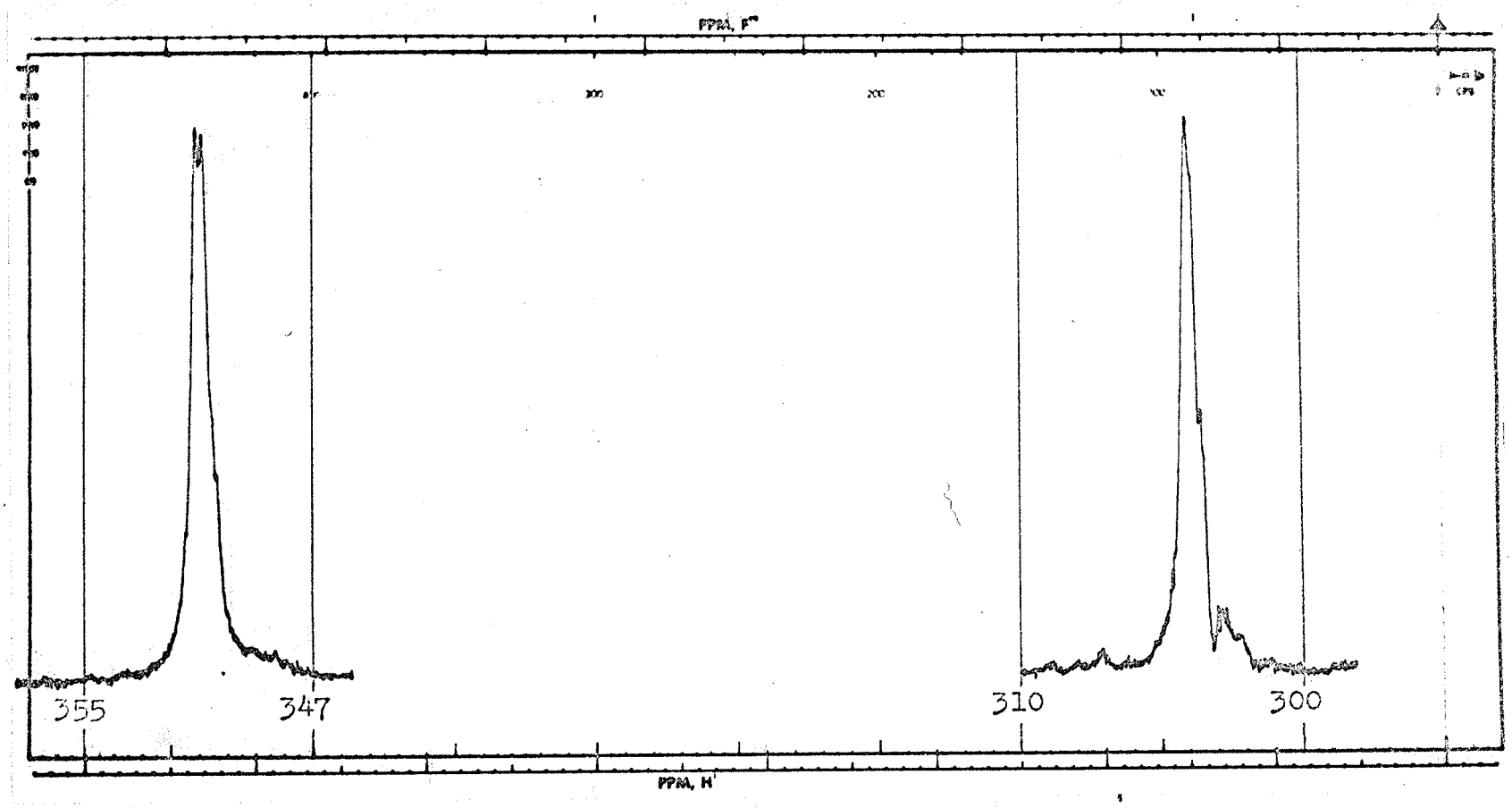



FIGURE XXXV. Nuclear magnetic resonance spectrum number C-10.

α-fluoro-2,6-dichlorotoluene ( $H^1$, $C_6D_6$ ).

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