# SYNTHESIS OF 2-(2, 5-DICHLORO-PHENYL) TETRAHYDRO-3 METHYL 1-4-H-1, 3 THIOZONE-4-ONE 1, 1-DIOXIDE

# AND

# STUDY OF THE SOMMELET REACTION MECHANISM

by

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I would like to extend my appreciation to Dr. Howard E. Sheffer whose patience, friendship, and guidance have made this work possible. I also wish to thank Mr. Phillip Haines, Mr. Wayne Brantley, and the Schenectady Chemical Company for assistance with NMR spectra and chemical analysis.

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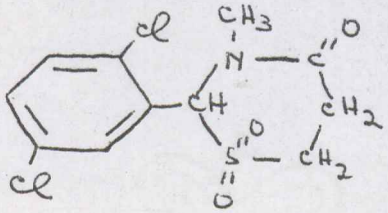
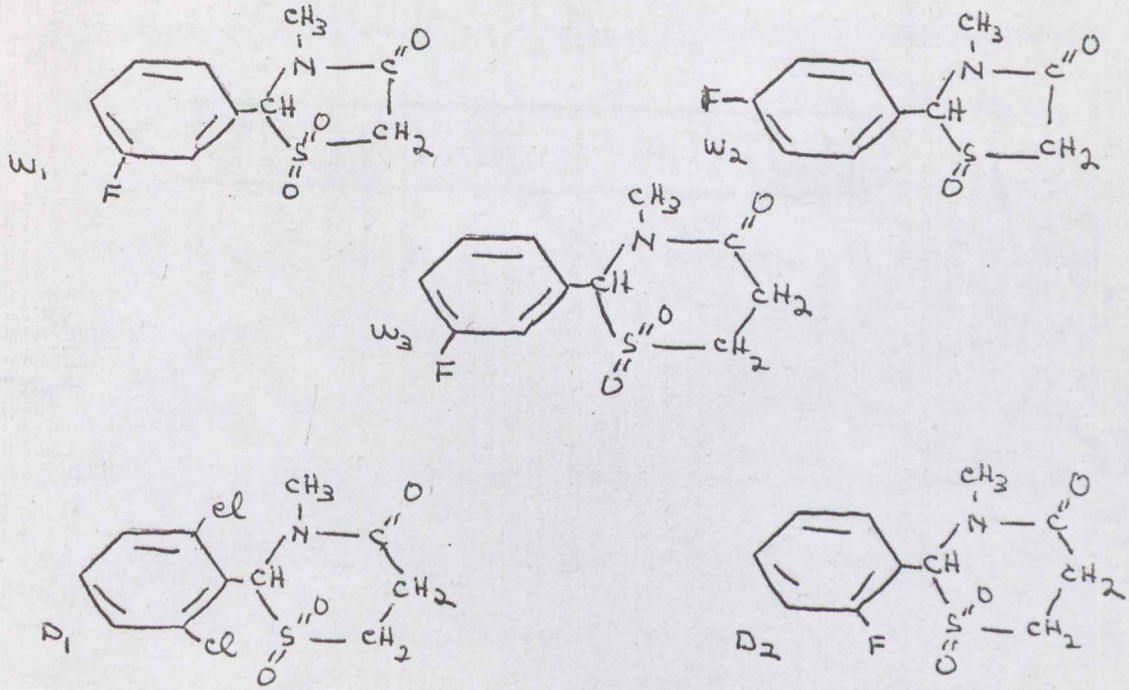
# HISTORICAL BACKGROUND

The text of this thesis deals with two separate, but inter-related problems. The first is the synthesis of 2-(2, 5-Dichloro-phenyl) Tetrahydro-3 methyl 1-4-H-1, 3 Thiozone-4-one 1, 1-Dioxide.



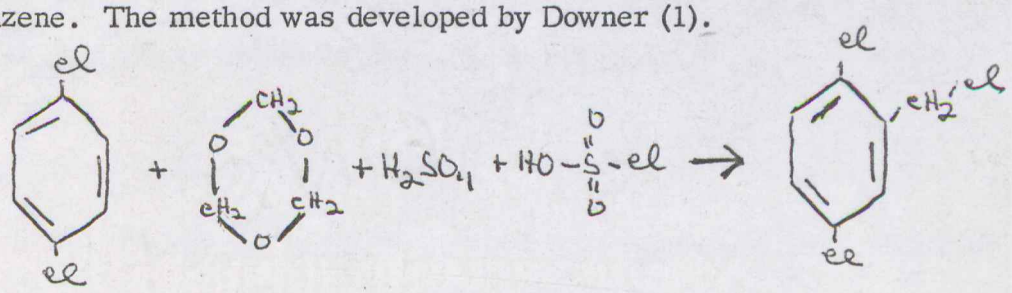
The second is a study of the Sommelet reaction which was employed in the synthesis of the above compound. This project was undertaken to complete the synthesis of a group of analogous compounds which have been synthesized by Wilson and Downer for the Sterling Winthrop Drug Company. The compounds illustrated below have been tested and found to have varying potential as central nervous system depressants.



## SECTION I. EXPERIMENTAL PROCEDURES AND RESULTS

### A. Synthesis of 2, 5-dichlorobenzylchloride

This procedure involves the chloromethylation of paradichlorobenzene. The method was developed by Downer (1).



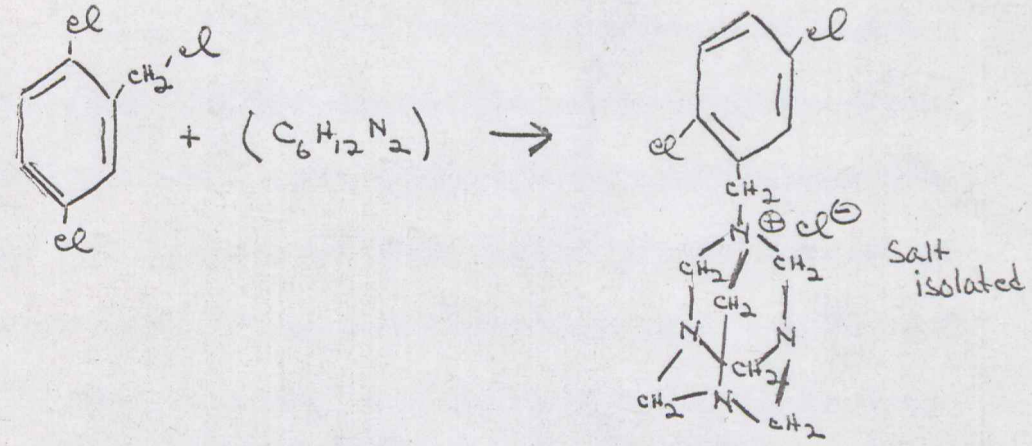
Trioxane (0.187 moles) was dissolved in 0.7 moles of concentrated sulfuric acid which had been cooled to 0-4°C in a one liter three-necked flask. The mixture was stirred constantly while 0.7 moles of chlorosulfonic was added dropwise over a period of two hours. The reaction mixture was maintained between 0-4°C with an ice bath. Paradichlorobenzene (0.5 moles) in solid form was added over a period of fifteen minutes followed by stirring overnight at a low temperature. The reaction mixture was then poured over ice. Two layers appeared with temperatures of 25°C, 20°C and a top water layer at 0°C. The mixture was placed in a separatory funnel in which an emulsion formed. The emulsion was broken with sodium chloride and sodium bicarbonate was added until a neutral solution was obtained. A nuclear magnetic resonance spectrum which was run on this crude reaction product revealed the presence of approximately 60% 2, 5-dichlorobenzylchloride, a small amount of diphenylmethane and large portion of unreacted paradichlorobenzene. Fractional distillation yielded three fractions. The first, a white crystalline material which came over at 87-104°C at 45mm was assumed to be 2, 5-

dichlorobenzene. The second, 145-155°C at 45mm, a clear liquid was shown by NMR to be 2, 5 dichlorobenzylchloride. The third fraction, 190-200°C at 45mm was assumed to be the disubstitution product. The diphenylmethane derivative remained as a residue. The yield of 2, 5-dichlorobenzylchloride was calculated as 23%.

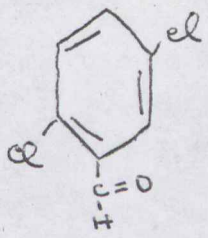
B. Synthesis of 2, 5-dichlorobenzaldehyde

The Sommelet reaction was employed to convert the 2, 5-dichlorobenzylchloride to the corresponding aldehyde. The reaction was conducted in two steps. The first was the formation of the quarternary ammonium salt(a), and the second was the conversion to the aldehyde(b).

a)




b) Salt + $CH_3-\overset{O}{\overset{\|}{C}}-OH$ $\xrightarrow[\text{hydrolysis}\ \text{Oxidation}\ \text{Reduction}]{H_2O}$




The method is analogous to that used by Invkai (2).

(a) 2, 5-dichlorobenzylchloride (0.44 moles) was added to 0.48 moles of hexamethylenetetramine which had been previously dissolved in

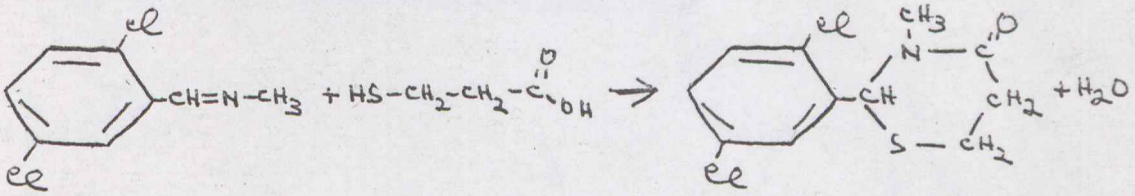
150ml. of warm chloroform. The mixture was refluxed for three hours. The quarternary ammonium salt was then isolated by evaporation of the chloroform (mp 185°C). Recrystallization was attempted in ethanol but abandoned because of excessive loss of product.

(b) To accomplish the second step of the Sommelet reaction, the salt from (a) was placed in a reflux fask and dissolved in 150ml. of 50% acetic acid. The mixture was refluxed for one and a half hours with the separation of a dark yellow oil from the water layer. Isolation of the aldehyde was achieved by separation of the oily layer. This layer was neutralized with a concentrated water solution of sodium bicarbonate. The aldehyde was taken up by the addition of ether leaving the sodium acetate behind in the water layer. Upon evaporation of the separated ether layer, a yellow oily solid appeared. Attempts at recrystallization with cyclohexane failed to yield crystals with a constant melting point. Vacuum distillation produced three fractions, the first, 90-100°C at 1mm, the second 105-100°C at 1mm, and the third 190-200°C at 1mm. The first fraction was not identified; however, NMR showed the second to be 2, 5-dichlorobenzaldehyde in 10% yield, mp. 45°-46°C. The third fraction, which was a white crystalline material with a mp. of 110-112°C, will be considered in more detail in a later section.

C. Synthesis of the Schiff's base Method from Downer (1)

Methylamine was bubbled into a tared flask of benzene until the solution was saturated. The methylamine-benzene solution was then added to a previously prepared mixture of benzene and 0.03 moles of 2, 5-dichlorobenzaldehyde. The solution was then refluxed in a Dean Stark apparatus until the expected 0.54ml of water was evolved. The product desired, 2, 5-dichlorobenzylidine-N-methylamine, was not isolated in this step.

D. Condensation with 3 mercaptopropanoic acid Method from Downer (1)



To the reaction mixture of step C was added 0.03 moles of 3-mercaptopropanoic acid. The solution was again refluxed in a Dean Stark apparatus. The reaction was shut down after twenty-four hours after evolving only 0.3 of the expected 0.7ml of water. During this time, the mixture had become dark red. It was transferred to a separatory funnel and washed as follows:

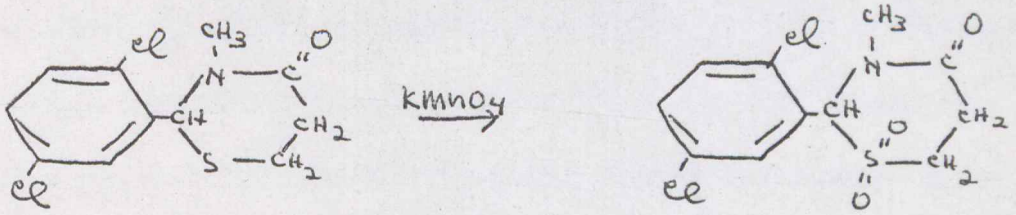
2x with 1:3 $NH_4OH$

2x with 1:5 Hcl

2x with saturated brine

Upon removal of benzene at reduced pressure dark red, light flaky crystals were obtained. Purification of this substance was attempted by recrystallization with an ether/cyclohexane combination. A tan crystalline compound was obtained in this manner but in such small yield that further attempts were abandoned.

E. Proposed oxidation of thio ether

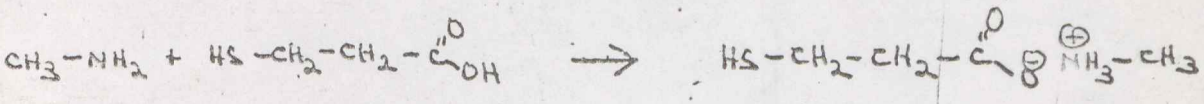



Had the expected product of (d) been isolated, the final step in the synthesis would have been the oxidation of the thio ether to the sulfone with a solution of potassium permanganate (1).

## CONCLUSIONS AND ANALYSIS OF SPECTRA

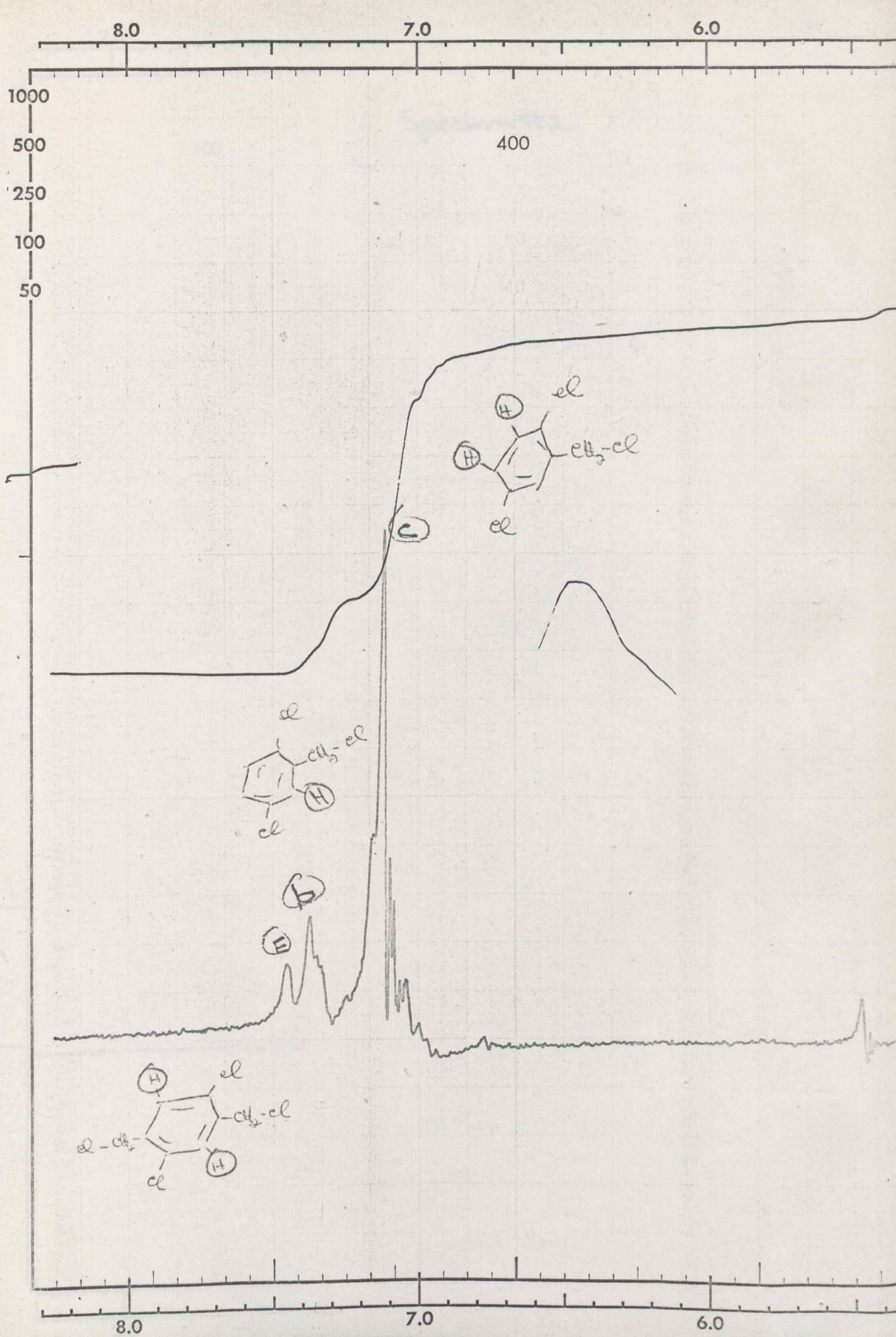
Two major problems were encountered while attempting the synthesis of the desired compound. The first was the extremely low yield obtained from the Sommelet reaction. The possible reasons for this poor yield will be explored more extensively in the following section.

The second problem involved the condensation reaction of 3-mercaptopropanoic acid with 2, 5-dichlorobenzylidine-N-methylamine. The small amount of water evolved indicated that the reaction failed to approach completion. The reason for this may have been that the excess methylamine present in the solution from the previous formation of the Schiff's base may have reacted with the 3-mercaptopropanoic acid to form the salt.



If this was the case, then in order to increase the yield of the conjugation product, the Schiff's base must be isolated and the excess methylamine removed from solution before addition of the 3-mercaptopropanoic acid.

From an examination of a scale model of the condensation product, it is evident that both a large entropy factor and a high degree of steric hindrance from the ortho chlorine must be overcome in order for the reaction to occur.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7.0
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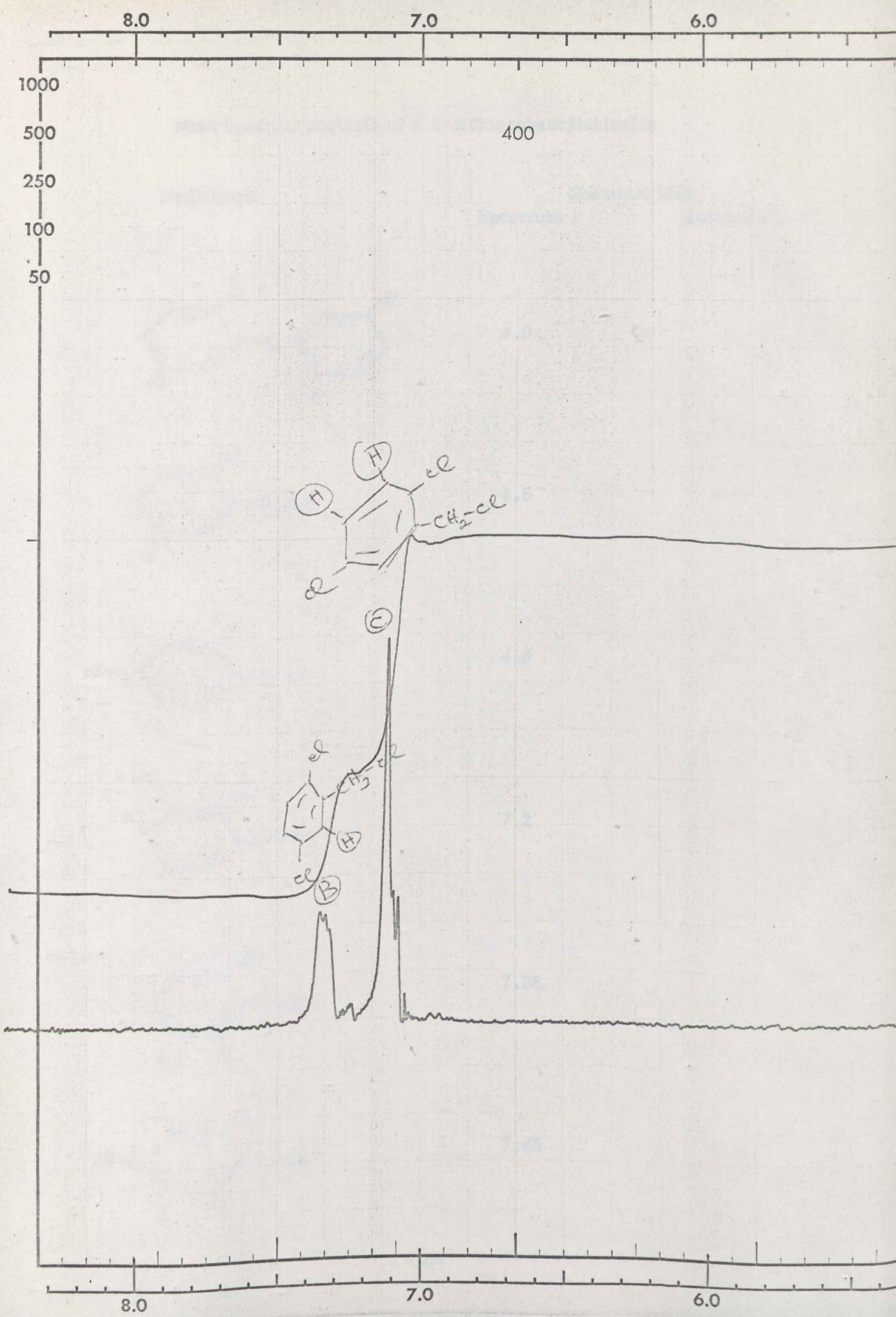
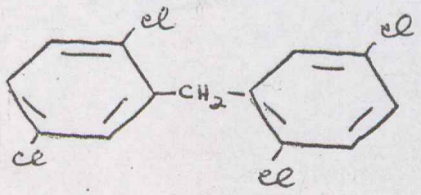
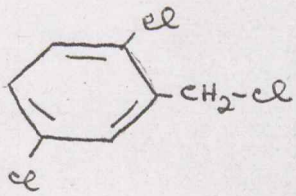
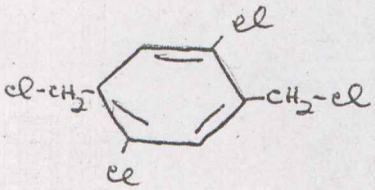
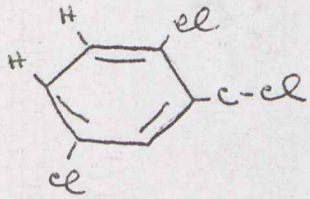
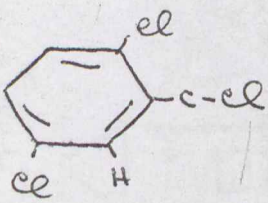
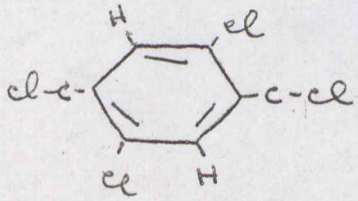
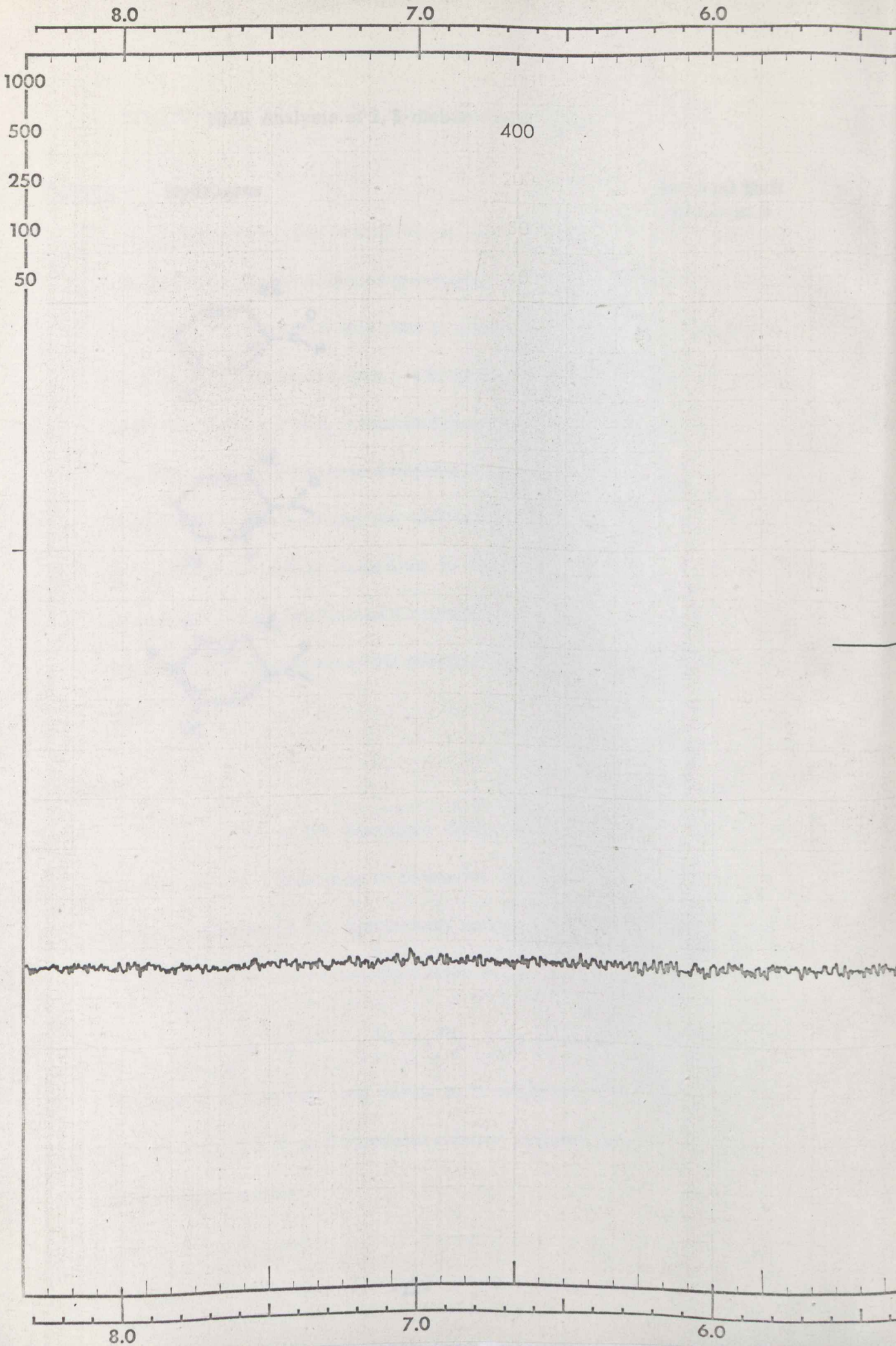
500
250
100
50
400
c
b
a
Cl
H
CH2-Cl


8.0
7.0
6.0
1000
500
250
100
50
400
H
Cl
H
$-CH_2-Cl$
Cl
E
Cl
$CH_2-Cl$
H
Cl
B
8.0
7.0
6.0

NMR Spectral analysis of 2, 5-dichlorobenzylchloride

| Hydrogens | Chemical Shift | |
|---|---|---|
| | Spectrum 1 | Spectrum 2 |
|  | 4.0 | --- |
|  | 4.5 | 4.5 |
|  | 4.6 | --- |
|  | 7.2 | 7.2 |
|  | 7.35 | 7.35 |
|  | 7.45 | 7.45 |


8.0
7.0
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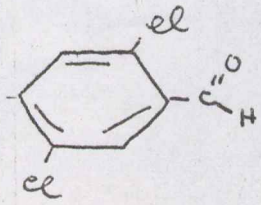
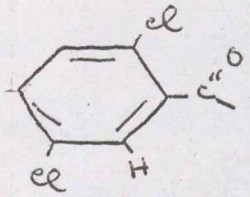
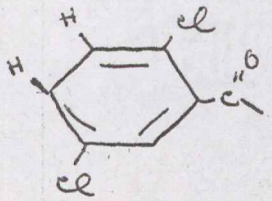
NMR Analysis of 2, 5-dichlorobenzaldehyde

| Hydrogens | Chemical Shift Spectrum 3 |
|---|---|
|  | 10.5 |
|  | 7.8 |
|  | 7.5 |

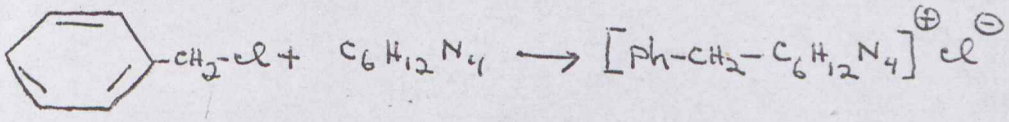
## SECTION II. MECHANISM OF THE SOMMELET REACTION

### Purpose

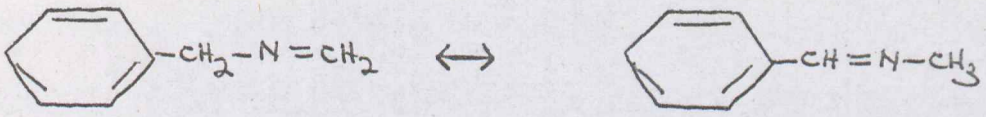
Generally, the Sommelet reaction is employed to convert an arylhalide to the corresponding aldehyde. In the synthesis described in Section I, this reaction was used to convert 2, 5-dichlorobenzylchloride to 2, 5-dichlorobenzyaldehyde. The product was obtained in a disappointingly low yield of 10%. Distillation of the crude reaction production yielded a white crystalline competition product of the aldehyde. It was hoped that by determining the identity of this competition product that some insight would be gained as to the mechanism of the Sommelet reaction. Having determined a probable mechanism, it was thought that appropriate modification of the reaction conditions would lead to a higher yield.

### Literature

A search of the literature first revealed Sommelet's original mechanism (3). According to Sommelet, the first phase of the reaction is the formation of the quarternary ammonium salt by the combination of the arylhalide and hexamethylenetetramine.




Hydrolysis of this salt then yields an N-methylenebenzylamine. In the second step, the N-methylenebenzylamine tautomerizes to the benzylidine N-methylamine.

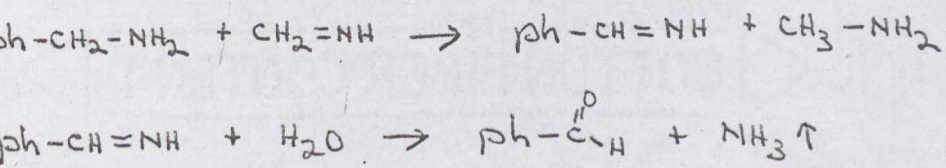


The following hydrolysis of the benzylidine N-methylamine yields the aldehyde and methylamine.

Shoppee, however, in 1929 (3) in his work on tautomerization noted that hydrogen migrations of this type took place only in basic solution in the presence of sodium ethoxide. The pH at which the Sommelet reaction is run is between 3 and 6. Therefore, Sommelet's mechanism must be discounted as improbable.

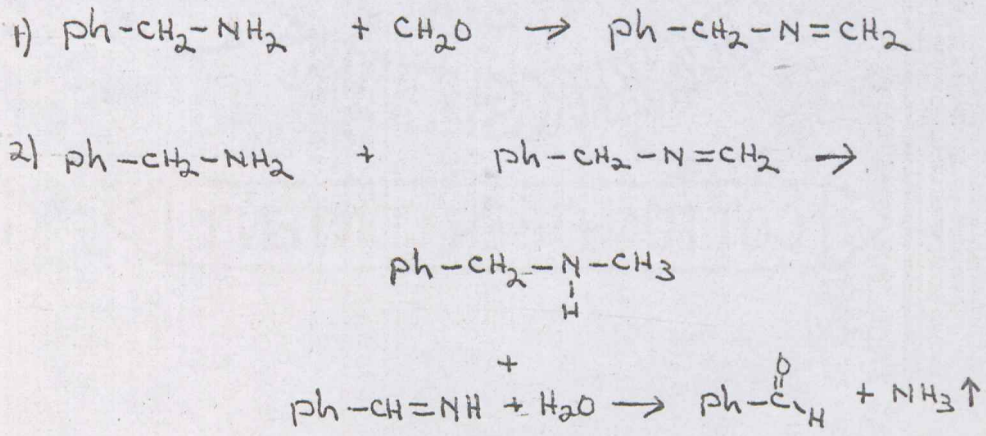
Angyal and Rassack have proposed an alternate mechanism, well documented with experimental evidence which may proceed by two alternate paths (3). They describe the formation of the quarternary salt as Sommelet did. However, they propose the original hydrolysis product to be a benzylamine. The benzylamine may then proceed by either of two routes to the aldehyde.

In this instance, the benzylamine is oxidized by methylimine, a breakdown product of the salt, to a benzylimine. Hydrolysis of the benzylimine yields the aldehyde and ammonia.

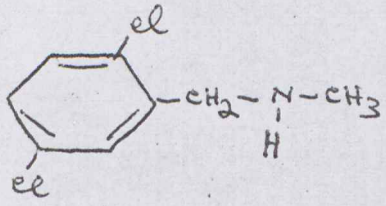


In the second route, the benzylamine is conjugated with formaldehyde from the salt to obtain a N-methylenebenzylamine. The excess

benzylamine present in the reaction mixture is then oxidized by this species to form benzylimine and benzylmethylamine. Hydrolysis of the benzylimine as before yields the aldehyde and ammonia.

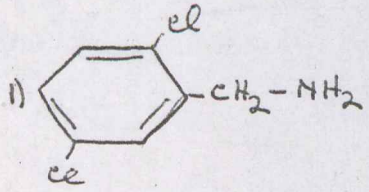


It can be easily seen that the second pathway automatically reduces the yield of aldehyde by diminishing the amount of benzylamine available for conversion to the aldehyde by 50%. If the operation of this mechanism is responsible for the reduced yield of aldehyde in Section I, then the competition product isolated might logically be the reduced form of the N-methylenebenzylamine.

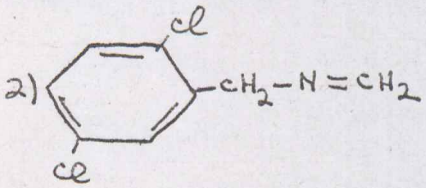


## EXPERIMENTAL PROCEDURES AND RESULTS

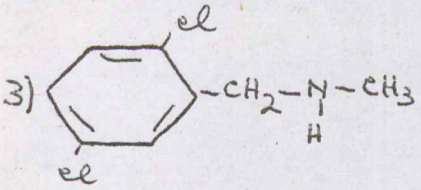
To determine the structure of the competition product, all of the possibilities were considered.



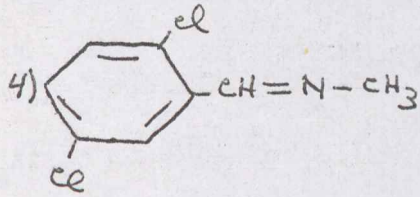
2, 5-dichlorobenzylamine (hydrolysis prod. of salt)



2, 5-dichloro N-methylenebenzylamine (conjugation w/$CH_2O$)



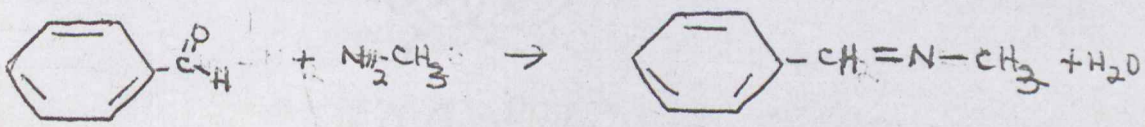
2, 5-dichlorobenzylmethylamine (reduction product of #2)



2, 5-dichlorobenzylidinemethylamine (tautomer of #2)

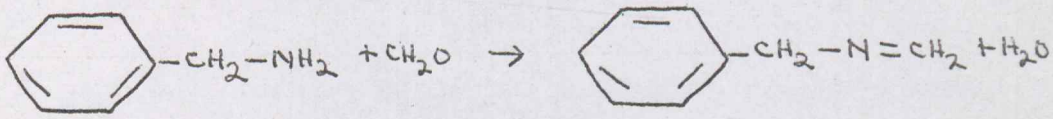
To facilitate interpretation of the NMR Spectrum of the competition product, various compounds with analogous structures to the above possibilities were synthesized. Spectra were run on these compounds and compared with that of the unknown.

A. Synthesis of N-benzylidinemethylamine



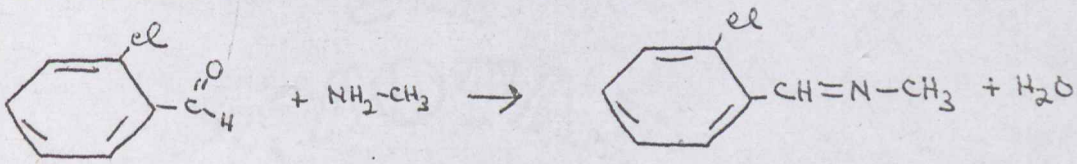
Benzaldehyde (0.20 moles) was mixed with 25ml of ethyl alcohol and cooled in an ice bath. Methylamine was bubbled into the mixture until heat was no longer evolved. Vacuum evaporation of the alcohol yielded a dark brown oil which was distilled at reduced pressure in a nitrogen atmosphere. A clear fraction was obtained at 60°C at 1mm. NMR analysis showed this to be the desired product.

B. Synthesis of N-methylenebenzylamine (4)



Benzylamine (0.05 moles) was mixed with 25ml of 95% ethyl alcohol. To this mixture, 1.4ml of 40% formaldehyde solution was added dropwise. The flask became warm and the reaction mixture turned white upon cooling in an ice bath. Vacuum evaporation of the ethanol followed by reduced pressure distillation in nitrogen obtained an extremely viscous clear liquid. This fraction came over between 150-160°C at 10mm pressure. After a short period the viscous liquid crystallized with a melting point of 36-37°C. The product was identified with NMR.

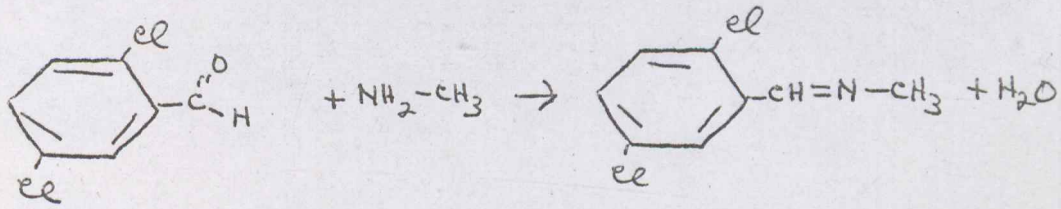
C. Synthesis of Orthochloro N-benzylidinemethylamine



The synthesis of this compound was achieved by mixing orthochlorobenzaldehyde with 25ml of 95% ethyl alcohol. Methylamine was

then bubbled into the cooled solution until heat ceased being evolved. Reduced pressure nitrogen distillation of the crude reaction mixture yielded a fraction between 95-100°C at 7mm. According to NMR analysis, the clear liquid was determined to be the desired product.

D. Synthesis of 2, 5-dichloro N-benzylidinemethylamine



One gram of 2, 5-dichlorobenzaldehyde was dissolved in 5ml of 95% ethyl alcohol and cooled in an ice bath. Methylamine was bubbled into the solution until the flask no longer became warm. The ethanol was removed under vacuum and the crude reaction product distilled in a nitrogen atmosphere at 1mm. NMR showed the liquid fraction collected at 110°C to be 2, 5-dichloro N-benzylidinemethylamine.

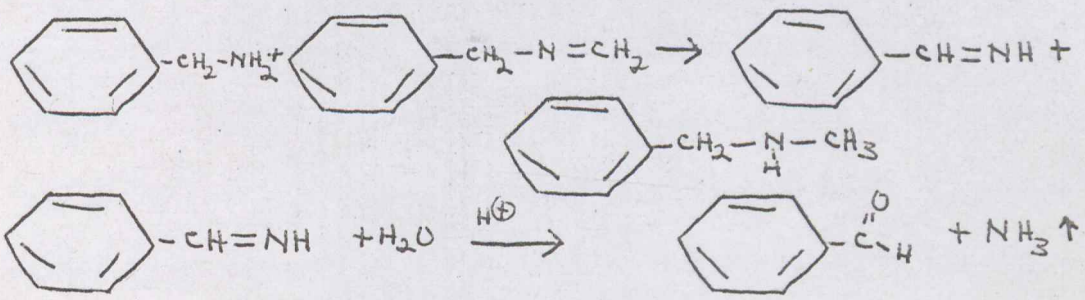
E. Synthesis of N-methylene orthochlorobenzylamine

Orthochlorobenzylamine (11ml) was mixed with 25ml of 95% ethyl alcohol. During the dropwise addition of 7ml of 40% formaldehyde solution, the reaction mixture became warm and when placed in an ice bath, turned white. Vacuum distillation in nitrogen at 1mm, following evaporation of ethanol, yielded a clear viscous liquid. This fraction, which came over at 155°C, did not crystallize. NMR analysis indicated

this to be the desired product.

F. Synthesis of benzaldehyde without hexamethylenetetramine

In order to determine if Angyal and Rassack's second pathway was possible (that an N-methylenebenzylamine could act as an oxidizing agent), the following reaction was run.



N-methylenebenzylamine (2.63 g.) was distilled at reduced pressure into a flask of excess benzylamine. This mixture was promptly added to 50ml of 50% acetic acid and refluxed for one and a half hours. After refluxing, crystals settled out of a yellow mother liquor. Following recrystallization a melting point of 83-85°C was obtained. The mother liquor, which smelled of benzaldehyde, was made acid with Hcl. The aldehyde and acetic acid were taken up in benzene. The solution was then made basic and the aldehyde containing benzene separated. Evaporation of the benzene yielded a light yellow oil. A 2,4-dinotrophenylhydrazine derivative was successfully isolated with a mp of 237°C which agreed with that of benzaldehyde found in the literature (5). A yield of 2.60 gs of the DNP derivative indicated a 31% over-all yield of aldehyde based on 2.63 gs of N-methylenebenzylamine.

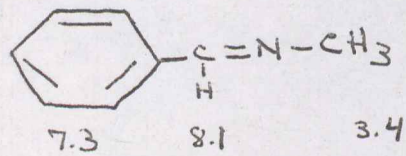
G. Sommelet reaction of 2, 5 dichlorobenzylchloride with molar excess of hexamethylenetetramine

2, 5-dichlorobenzylchloride was prepared as described in Section I A. The quarternary ammonium salt was prepared and isolated from chloroform (Section I B). The salt was then dissolved in 50% acetic acid solution. A 50% molar excess of hexamethylenetetramine was also added to the acetic acid solution and the mixture was refluxed for one and a half hours. During the period of reflux, a dark brown oil was formed at the surface and continued to settle to the bottom of the flask. Following reflux, a dark oil and a light yellow water layer remained. The mixture was placed in a separatory funnel, neutralized with sodium bicarbonate, and extracted with ether. Vacuum distillation of the crude reaction product yielded an oily yellow crystalline material which came over between 180-190$^{o}$C at 1mm. Recrystallization from chloroform produced white crystals with a melting point of 100-102$^{o}$C. An NMR spectrum was taken of this compound.

ANALYSIS OF NUCLEAR MAGNETIC RESONANCE SPECTRA

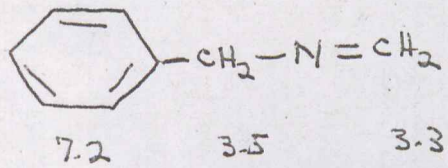
In the following table, the absorption in p.p.m. is indicated adjacent to each hydrogen in the structural representation of the compound.

1) N-benzylidinemethylamine (neat)

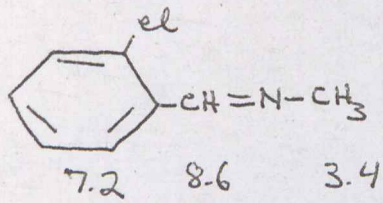



(7.8 due to resonance of imine)

2) N-methylenebenzylamine (DC $Cl_3$)

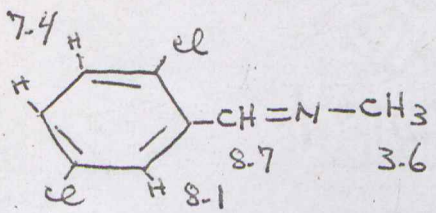



3) Orthochloro N-benzylidinemethylamine (neat)

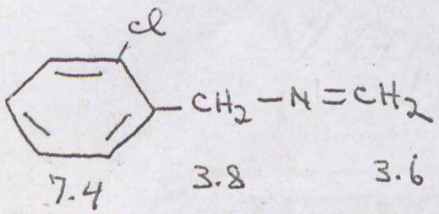



(8.0 due to resonance of imine)

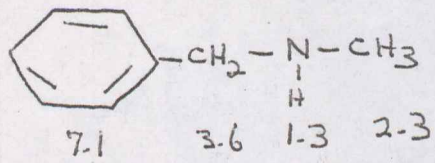
4) 2, 5-dichloro N-benzylidinemethylamine (DC $Cl_3$)



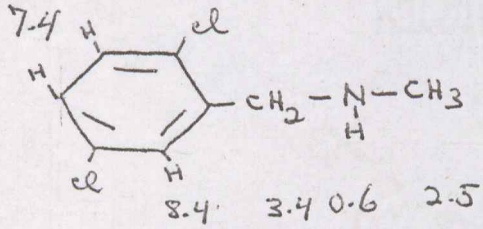

5) N-methylene orthochlorobenzylamine (DC $Cl_3$)



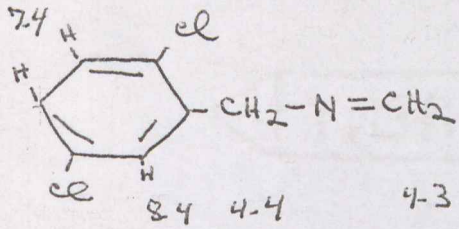
6) Benzylmethylamine (neat) (Eastman Chemical Co.)



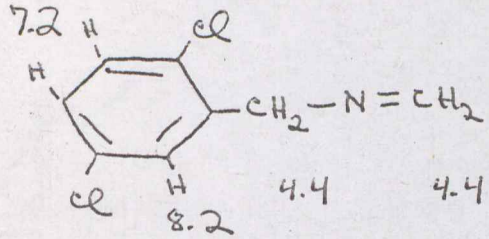

7) Spectrum of competition compound $(D_3C)_2SO$ (Section I B)
2, 5 dichlorobenzylmethylamine

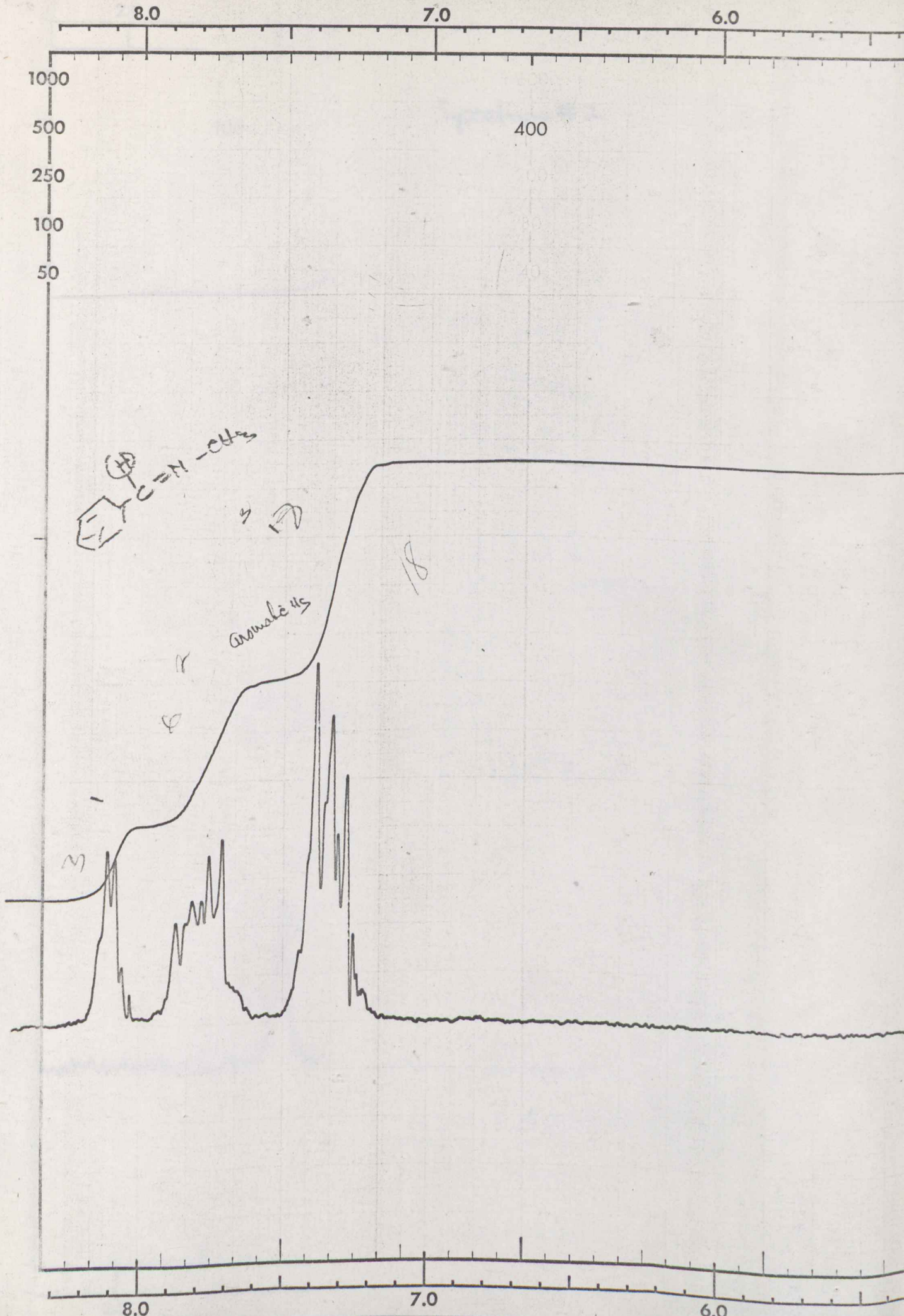



N-methylene 2, 5-dichlorobenzylamine




8) Product of Sommelet reaction (Section II G) ($DCCl_3$)

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7.0
6.0
1000
500
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100
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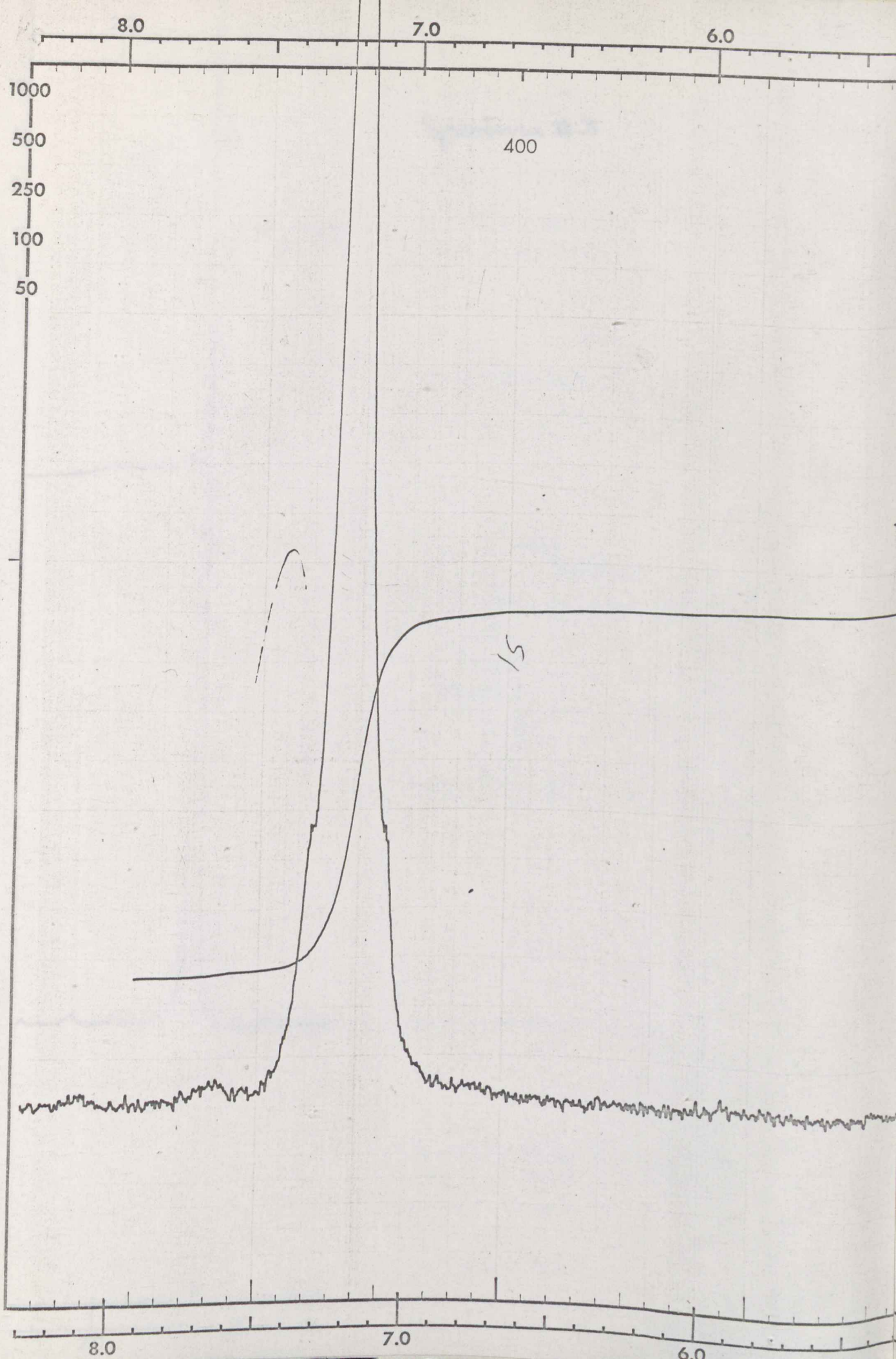
400
C=N-CH3
Aromatic Hs
18
8.0
7.0
6.0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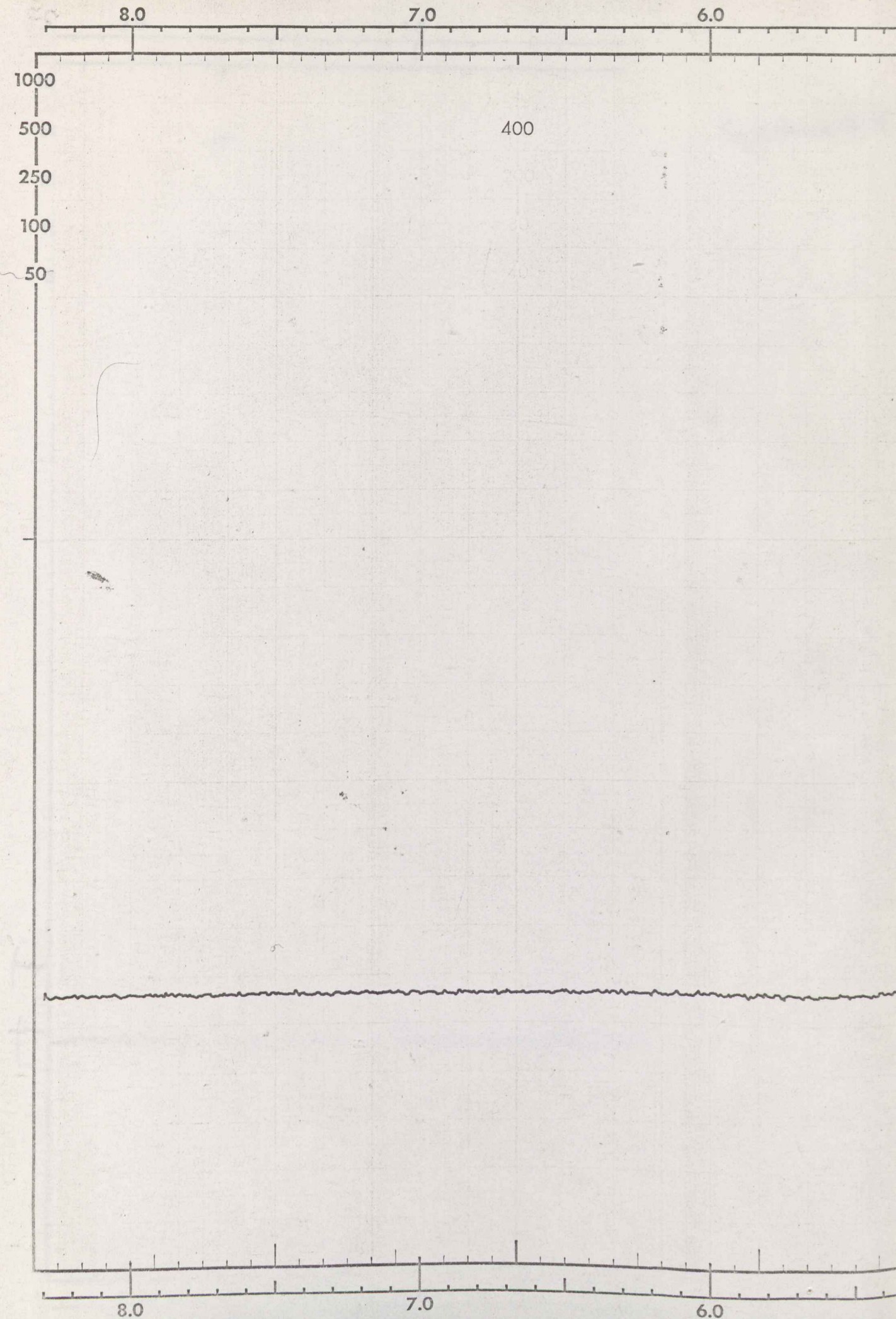
15
8.0
7.0
6.0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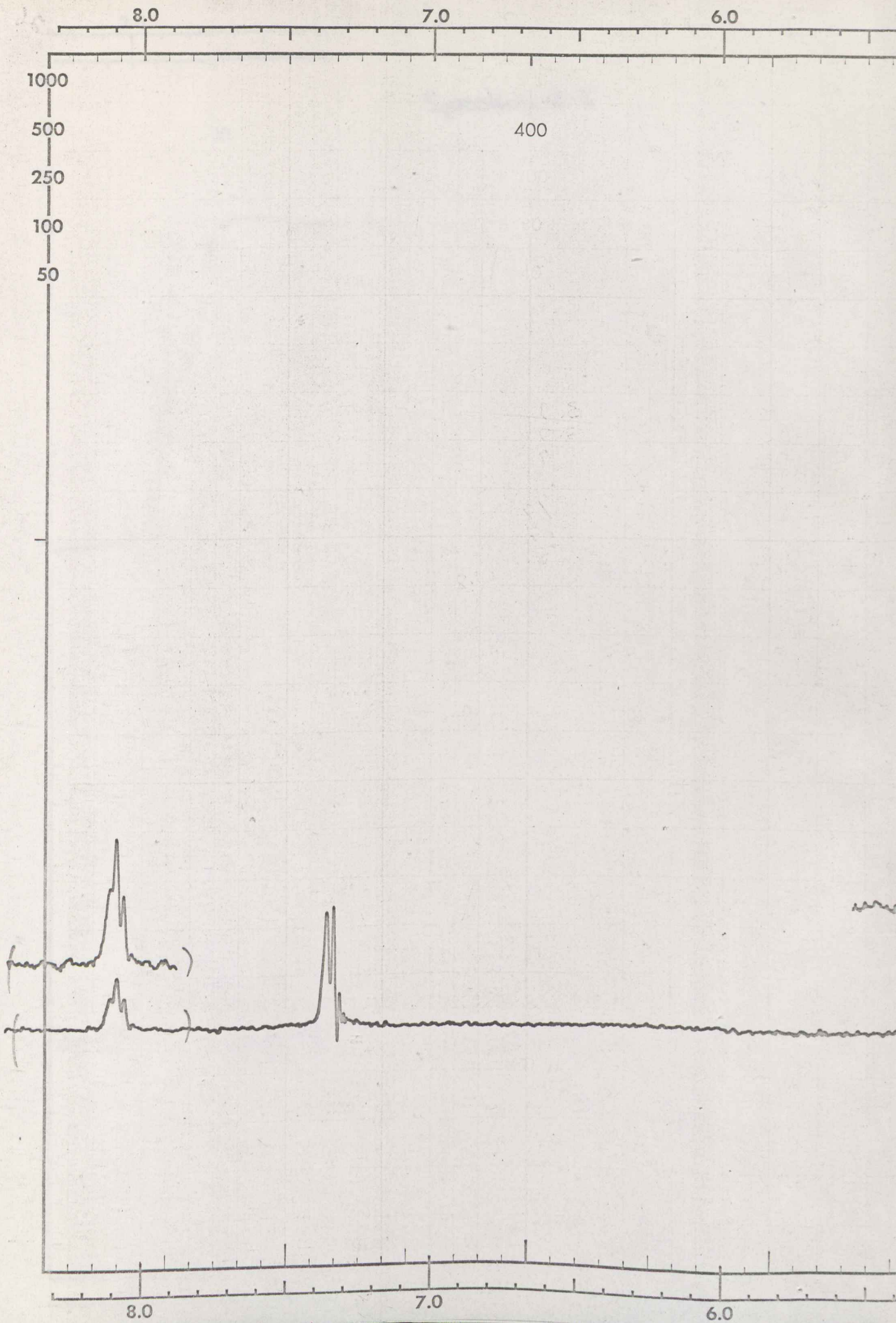
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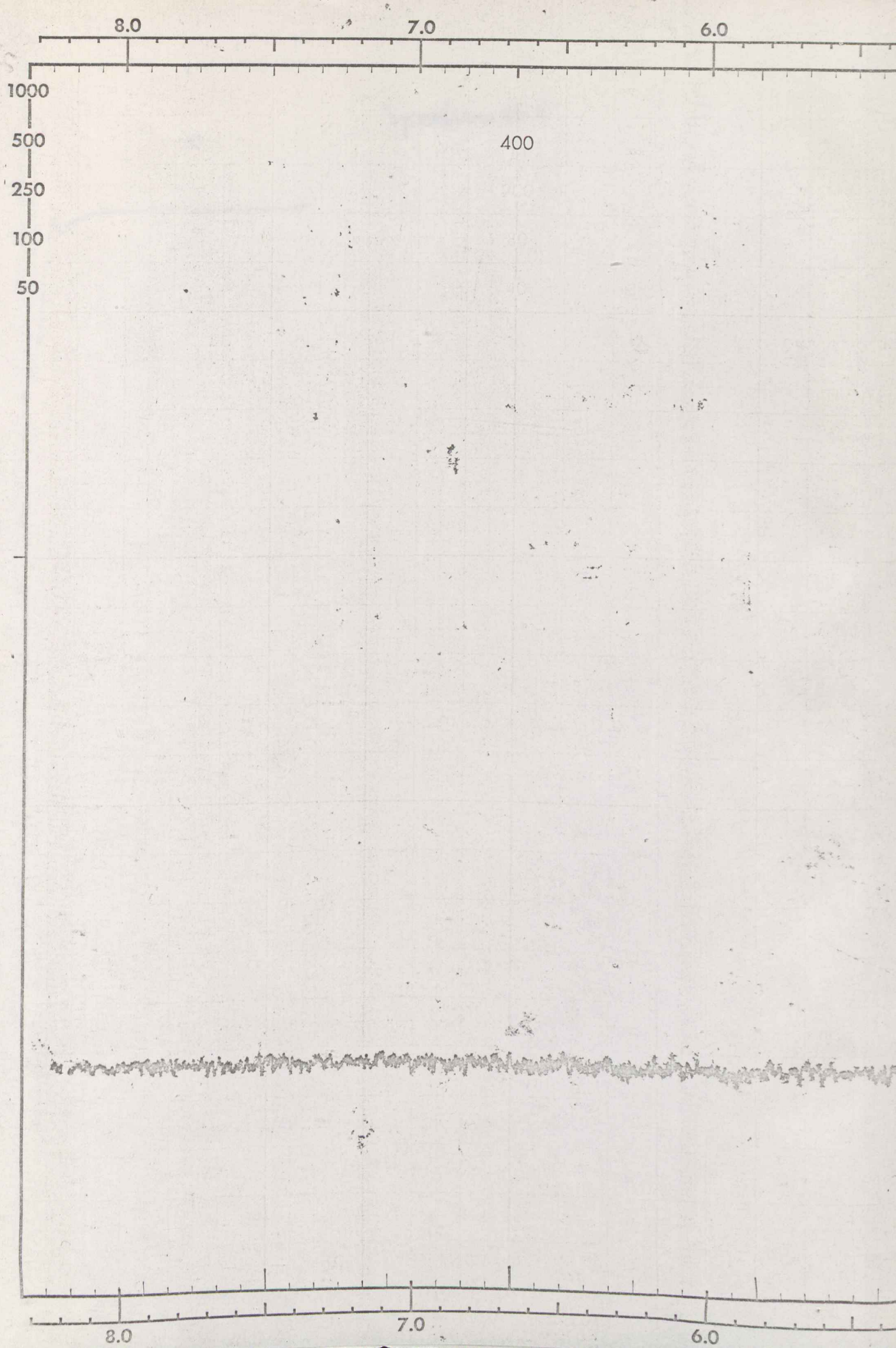
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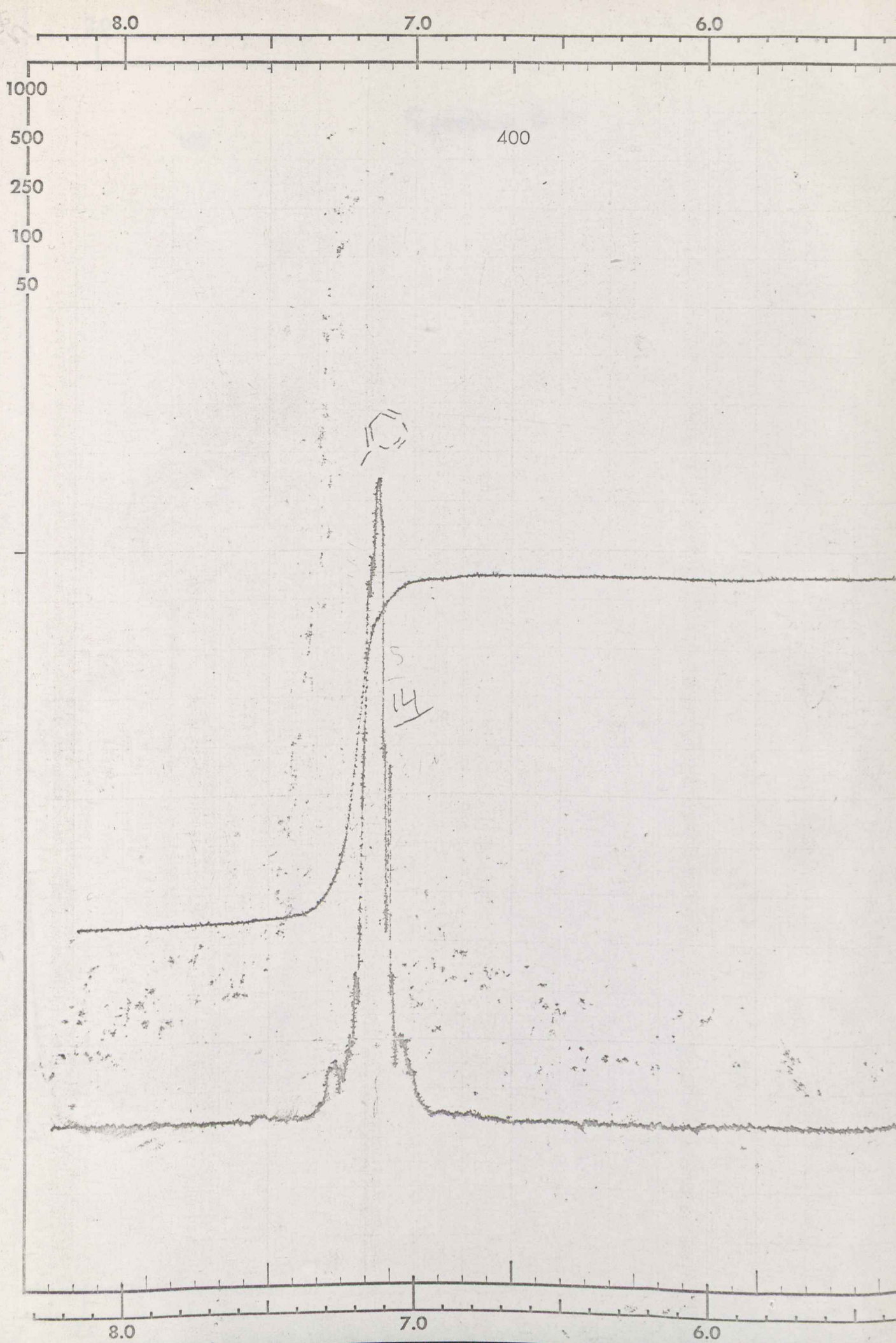
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14
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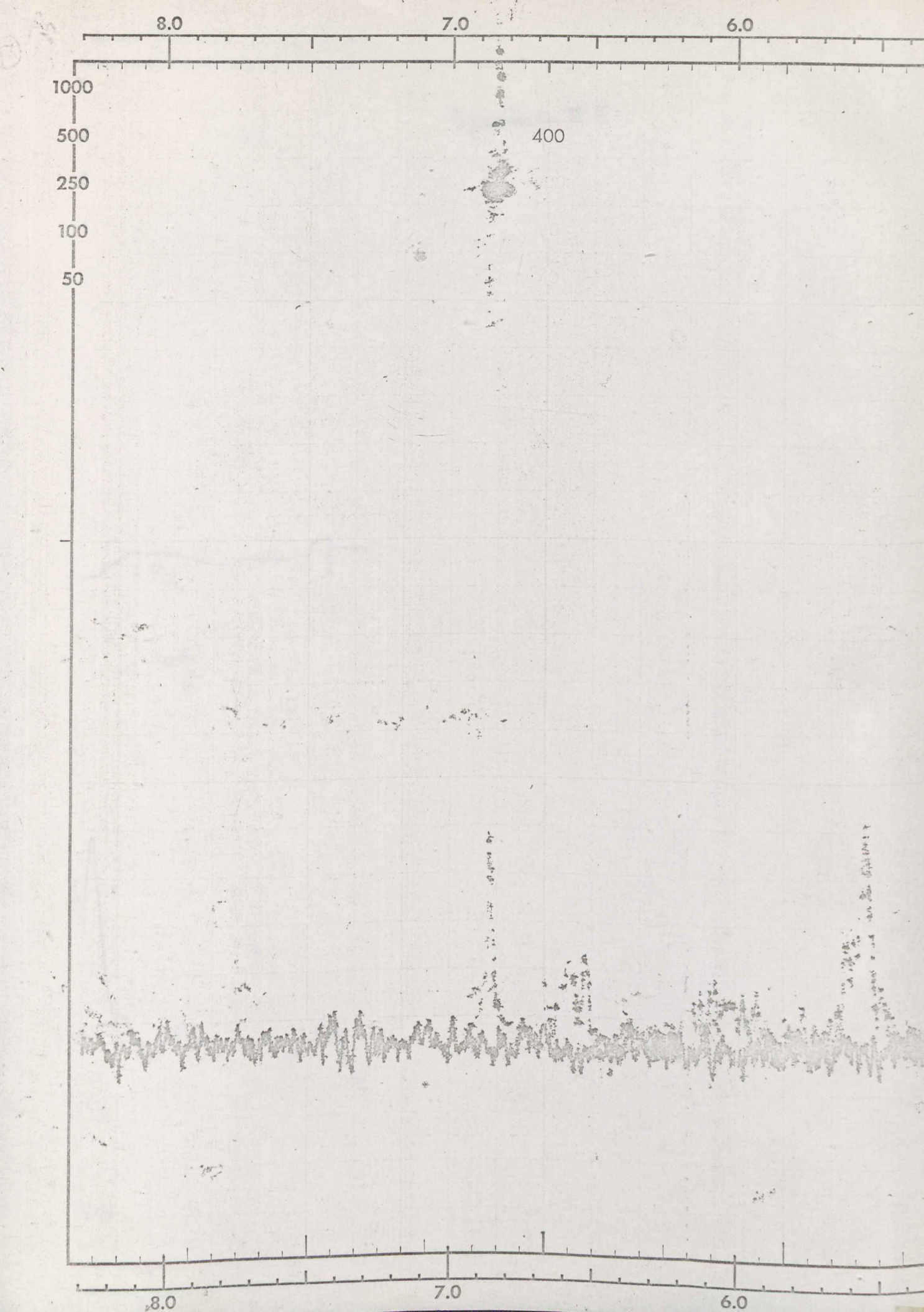
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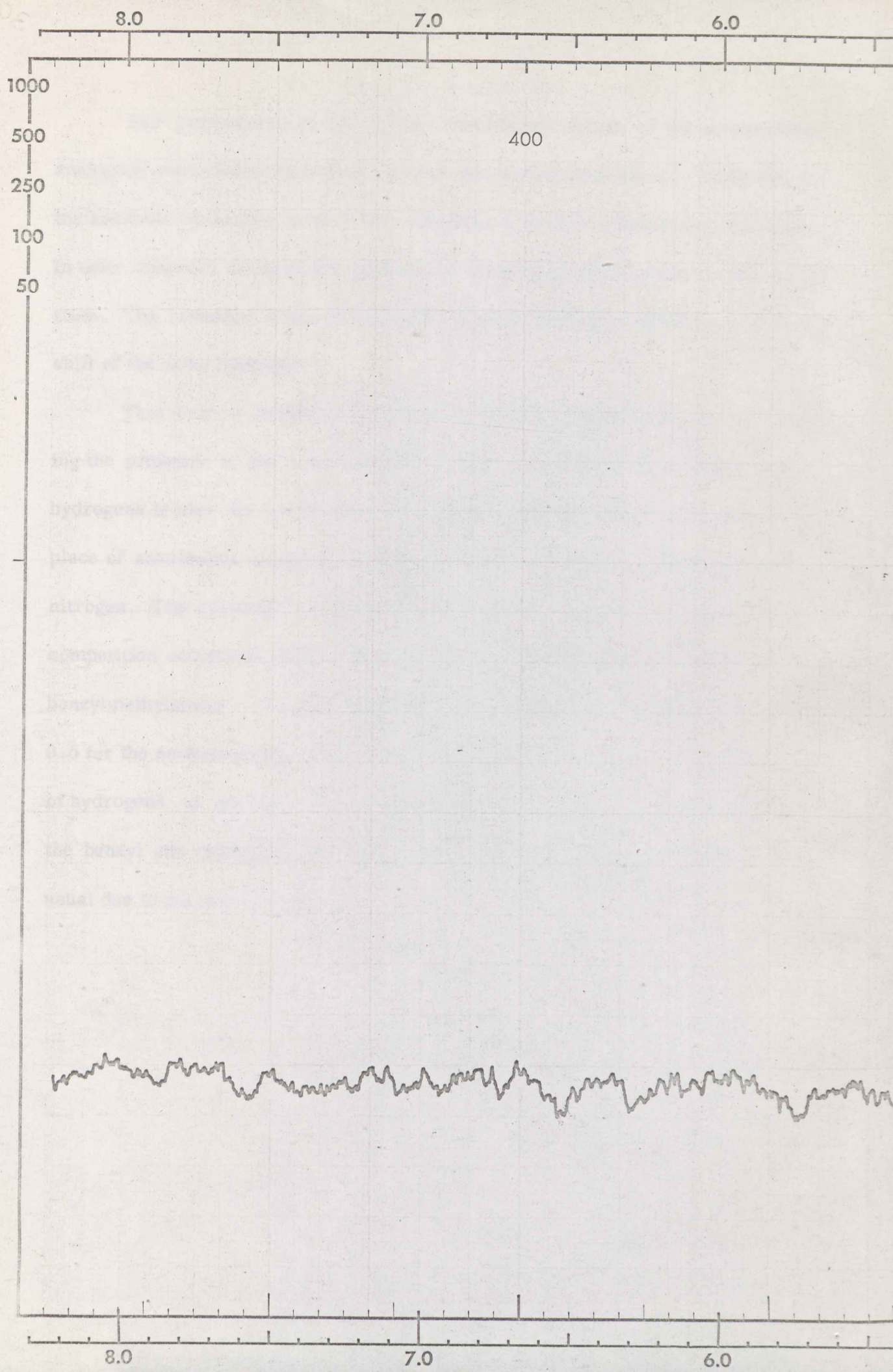
8.0
7.0
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8.0
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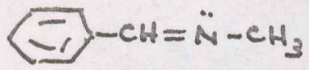
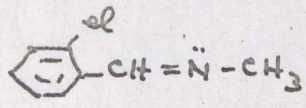
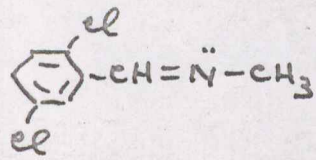
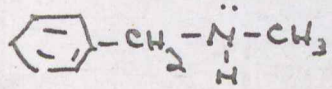
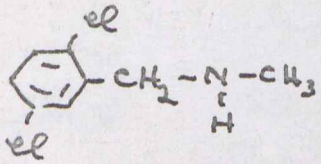
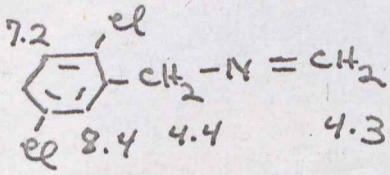
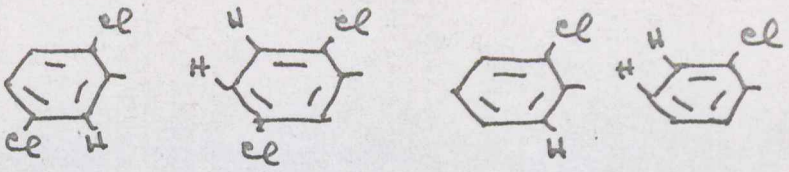
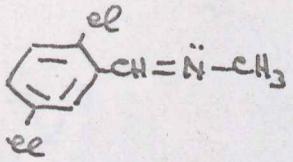
The comparison of the p.p.m. absorbance values of the synthesized analogous compounds illustrates several interesting phenomena. Inspection of the aromatic hydrogens reveals the influence of the 2, 5 disubstituted chlorines. In their absence, all aromatic hydrogens absorb at a single place on the spectrum. The presence of the two chlorine groups, however, causes a downfield shift of the ortho hydrogen.

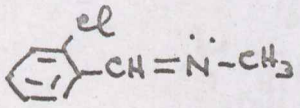
This shift is evident in the spectrum of the competition product indicating the presence of the 2, 5 disubstituted ring. A downfield shift of the benzyl hydrogens is also the result of the two chlorine substituents, while changes in place of absorbance of methyl hydrogens is dependent upon the character of the nitrogen. The presence of absorption at 0.6 p.p.m. in the spectrum of the competition compound gives good indication for the presence of 2, 5-dichlorobenzylmethylamine. The apparent disagreement between the values of 1.3 and 0.6 for the aminohydrogen is not surprising due to the erratic spectral behavior of hydrogens on nitrogen. The double peak at 4.4 p.p.m. is probably due to the benzyl and methylene hydrogens absorbing much further downfield than usual due to the two chlorines.

| | Ph-C(H)=N- | ph-$CH_2$-N | =C-N(H)-C< | =N-$CH_3$ |
|---|---|---|---|---|
|  | 8.1 | | | 3.4 |
|  | 8.6 | | | 3.4 |
|  | 8.7 | | | 3.6 |
|  | — | 3.6 | 1.3 | 2.3 |
|  | | 3.4 | .6 | 2.5 |
|  | 7.2 8.4 | 4.4 | | 4.3 |

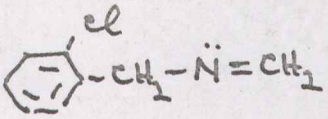




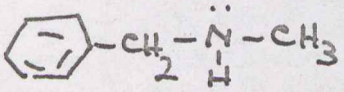
8.1 7.4



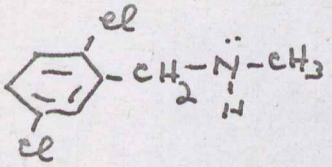
all at 7.1 .



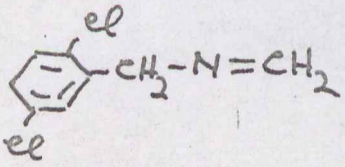
all at 7.2



all at 7.1



8.4 7.4



8.4 7.4

A carbon, hydrogen, nitrogen analysis was run on the competition reaction product of the Sommelet reaction in Section I (mp. 110-112°C). In the table below, the observed values for the determination are listed along with calculated values for a mixture of 40% 2, 5-dichloro-N-methylenebenzylamine, 40% 2, 5-dichloromethylbenzylamine, and 20% 2, 5-dichlorobenzyl chloride.

| | Observed | Calculated |
|---|---|---|
| N | 6.80 | 5.93 |
| C | 47.87 | 49.30 |
| H | 4.00 | 3.92 |
| Other | 41.33 | 40.94 |

## CONCLUSIONS

The successful isolation of benzaldehyde in the absence of hexamethylenetetramine demonstrates the plausibility of Angyal and Rassack's second pathway. As discussed previously, the operation of this mechanism would have the effect of lowering the yield of aldehyde. The NMR analysis of the competition compound produced during the first run of the Sommelet reaction, indicates the presence of two molecular species: 2, 5-dichlorobenzylmethylamine, and N-methylene 2, 5-dichlorobenzylamine. Both species are indicative of the operation of Angyal and Rassack's second pathway. In order to obtain a more favorable yield of aldehyde, it would seem necessary to alter the reaction conditions. The addition of a molar excess of hexamethylenetetramine would shift the equilibrium from the second to the first pathway by increasing the concentration of the oxidative methylimine species.

In the Sommelet reaction of 2, 5-dichlorobenzyl chloride with excess hexamethylenetetramine, a white crystalline compound mp. 100-102°C was isolated. NMR analysis of this compound indicated it to be N-methylene 2, 5-dichlorobenzylamine. The aldehyde, however, could not be isolated.

The reasons for the failure to obtain the aldehyde even in the presence of excess hexamethylenetetramine are unclear. However, it is evident that factors other than the competitive formation of N-methylenebenzylamine and benzylmethylamine are involved. The trouble with using a molar excess of hexamethylenetetramine is that it ties up all available benzylamine as the conjugate with formaldehyde. Thus the formation of the imine is drastically reduced. This was proved when only 2, 5 dichloro-N-methylenebenzylamine

was isolated from the reaction mixture in step G. Another possibility would be that 50% acetic acid is too strong a hydrolytic agent and thus produces an excess of formaldehyde. This excess formaldehyde may conjugate with the benzylamine to initiate the second pathway. If this is the case, the use of a less active solvent such as ethanol might increase the yield of aldehyde.

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