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# The Synthesis of 2, 4, 6, 8 - Tetraoxo - 1, 2, 3, 4, 6, 7, 8, 9 - octahydro-benzo (1, 2-d:-5, 4-d') bis (1, 3) oxazine

Calvin L. Moyer

# The Synthesis of 2,4,6,8-Tetraoxo-1,2,3,4,6,7,8,9-octahydro-benzo(1,2-d:-5,4-d')bis(1,3)oxazine

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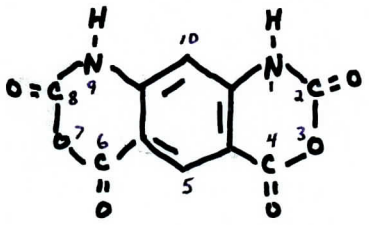
## Introduction

The synthesis and reactions of isatoic anhydride are well known.[1-6] The present investigator has attempted the synthesis of the three ring heterocyclic system containing two dioxo-1,3-oxazine rings.

## Isomers

There are five isomeric tetraoxooctahydrobenzo-bis(1,3)oxazines.



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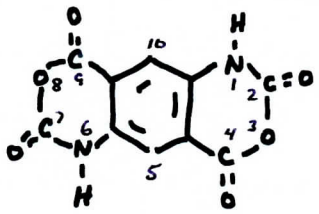

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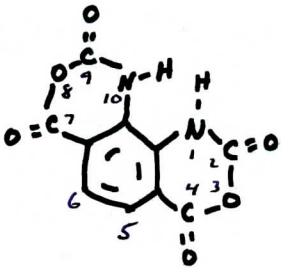

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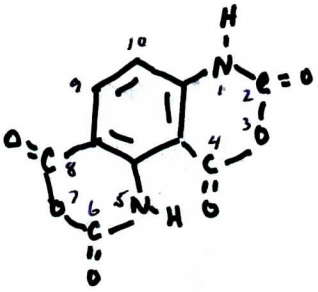

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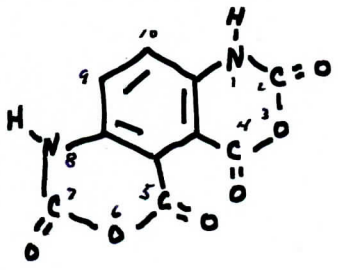


V

Fig 1

Nomenclature

The literature is devoid of these structures with the exception of the 4H,6H-benzo(1,2-d:-5,4-d')bis(1,3)-oxazine.[7] In accordance with this nomenclature, the five isomers above would be named as follows: I 2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydrobenzo(1,2-d:-5,4-d')bis(1,3)oxaxine, II 2,4,7,9-tetraoxo-1,2,3,4,6,7,8,9-octahydrobenzo-(1,2-d:-4,5-d')bis(1,3)oxazine, III 2,4,7,9-tetraoxo-1,2,3,4-7,8 ,9,10-octahydrobenzo(1,2-d:-6,5-d')bis(1,3)oxazine, IV 2-4,6,8-tetraoxo-1,2,3,4,5,6,7,8-octahydrobenzo(1,2-d:-3,4-d')-bis(1,3)oxazine, and V 2,4,5,7-tetraoxo-1,2,3,4,5,6,7,8-octa-hydrobenzo(1,2-d:-4,3-d')bis(1,3)oxazine.

Another system which has been proposed is to divide the isomers into linear and angular anhydrides using the standard o-, m-, and p- to locate the relative positions of the heterocyclic functions.[8] This system gives the following names: I isatoic-m-linearbisanhydride, II isatoic-p-linearbisanhydride, III isatoic-o-angularbisanhydride, IV isatoic-m-angularbisanhydride, and V isatoic-p-angular-bisanhydride. These names can be conveniently abbreviated as IMLB, IPLB, IOAB, IMAB, and IPAB respectively.

Selection of the Problem

Structures III, IV, and V were not chosen for synthesis because of the possibility of steric hindrence. The synthesis of I was chosen rather than II in the hope that if the structure was reactive at two sites as hypothesized, it might undergo interesting reactions with diamines.

Proposed Route

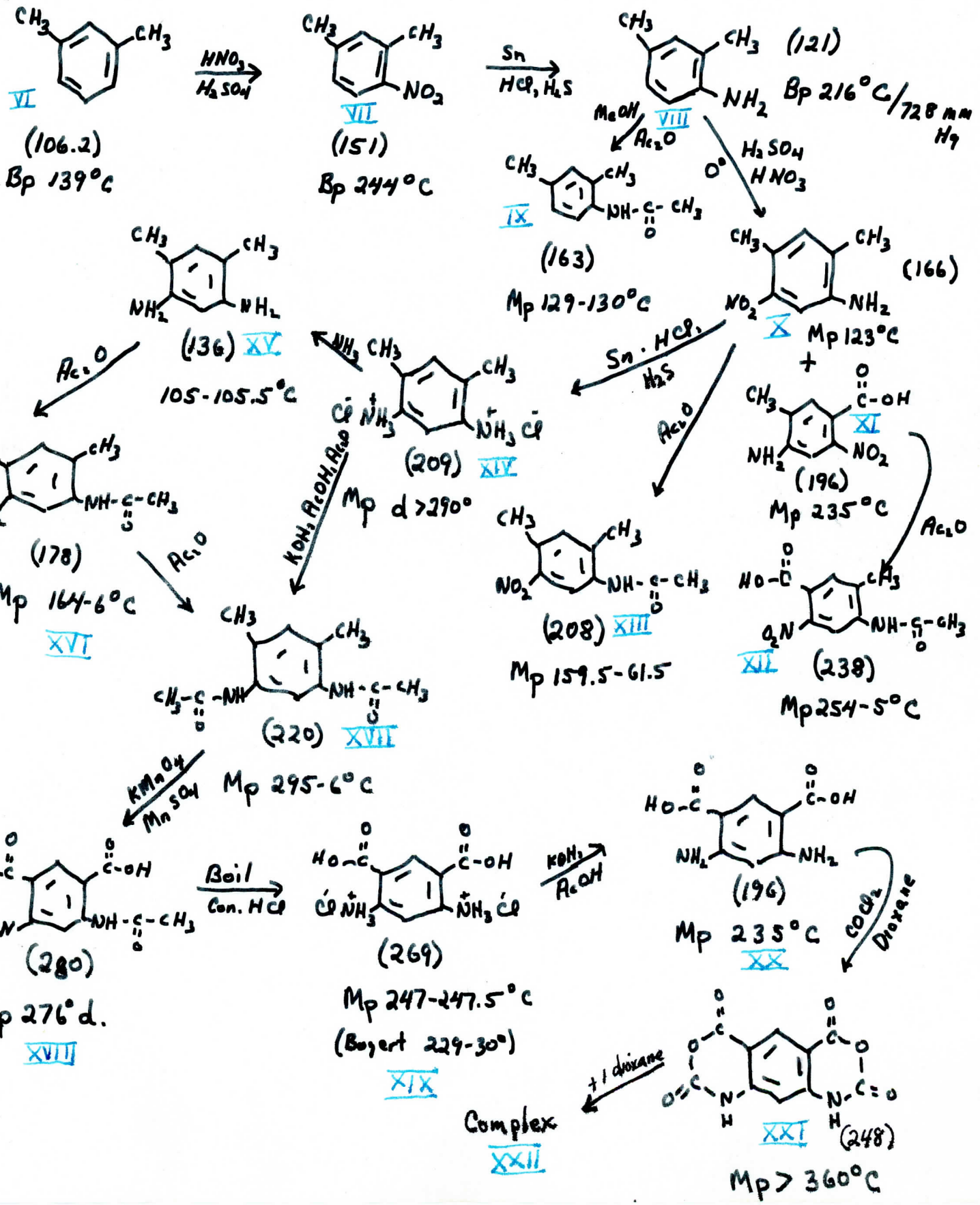
Isatoic anhydride has been prepared in a number of ways. It was first prepared by Friedländer and Wleügel[9] by the action of ethyl chloroformate on anthranil and later by Kolbe[10] by the oxidation of isatin with chromic oxide. Wagner and Fegley[11] prepared isatoic anhydride by passing phosgene through a solution of anthranilic acid in dilute hydrochloric acid. It has also been prepared in good yield from N-bromo- or N-chloro-phthalimide[12] and from phthalic anhydride.[13]

After consideration of the above routes, it was felt that the easiest approch would be to attempt the ring closure of the 4,6-diaminoisophthalic acid with phosgene in dioxane.[14]

Search of the Literature

A search of the literature showed that Bogert[15] and his workers had already synthesized the 4,6-diaminoisophthalic acid in an attempt to obtain quinazoline derivatives.

Theoretical Equations



Outline of the Synthesis

As a starting point, m-xylene may be nitrated to yield 4-nitro-m-xylene (VII) as the major product. Since 4-amino-m-xylene (VIII) is available from Eastman, no attempt is made to reduce 4-nitro-m-xylene to the amine. The nitration of 4-amino-m-xylene at 0°C in concentrated sulfuric acid gives a good yield of 4-amino-6-nitro-m-xylene (X) along with a product which agrees with the data on the toluic acid (XI) described by Bogert.[15] This material is believed to be the salt of the desired compound (X) rather than the toluic acid (XI).

4-Amino-6-nitro-m-xylene is reduced with tin and hydrochloric acid. After removing the tin salts as sulfides, the hydrochloride of 4,6-diamino-m-xylene (XIV) is precipitated by concentrating the mixture. 4,6-diacetamino-m-xylene (XVII) is formed by the direct acetylation of the hydrochloride. 4,6-Diacetamino-m-xylene is then oxidized to 4,6-diacetaminoisophthalic acid with neutral permanganate. Treatment with 5% sodium hydroxide converts 4,6-diacetaminoisophthalic acid (XVIII) to the free amine (XX) which is precipitated with acetic acid.

The two rings are closed through the reaction with phosgene in dioxane[14] forming the desired benzobisoxazine (XXI).

Infra-red spectra are made of all isolated materials. All intermediate compounds are checked against reported literature values.

Experimental

Nitration of m-xylene (VI) to yield 4-nitro-m-xylene (VII)-

m-Xylene (50 ml.), nitric acid (50 ml. conc.), and sulfrric acid (10 ml. conc.) are placed in a 250 ml. round bottom, thick wall flask and the mixture shaken for about ten minutes. Some cooling under cold water may be necessary. The mixture is distilled and the fraction boiling 240-244°C is collected. Yield: 3 ml.

Nitration of 4-amino-m-xylene (VIII) to yield 4-amino-6-nitro-m-xylene (X)-

4-Amino-m-xylene (100 ml.) is dissolved in sulfuric acid (1 Kg. conc.) and the mixture cooled to -5°C in an ice-salt bath. At first the amine sulfate forms as a tan precipitate but it slowly dissolves with stirring. To the stirred mixture at -5°C, a mixture of nitric acid (50 gr. conc.) and sulfuric acid (100 gr. conc.), cooled to 10°C, is added slowly through a dropping funnel at such a rate that the temperature of the reaction mixture does not rise above 0-2°C. On completion of the addition, the reaction is allowed to stand for ten minutes at room temperature then poured over ice (3 l.) in a 3 l. beaker. On standing a precipitate forms which Bogert[15] believed to be the toluic acid (XI). This material is filtered off and treated with sodium hydroxide (5%) to yield 4-amino-6-nitro-m-xylene (X). The filtrate is

neutralized with saturated sodium carbonate solution (about 7-8 l.), the mixture first turning yellow then precipitating orange solids. Enough cold water is added to dissolve any precipitated sodium sulfate and the mixture filtered and washed with water. The crude material is slow drying but it is better to dry it before attempting reduction. A sample of 4-amino-6-nitro-m-xylene (X) recrystallized from methanol gives a mp. 117-120°C. Literature mp. 123°C. Yield: about 70 gr.

Another sample of 4-amino-6-nitro-m-xylene is treated with acetic anhydride and the 4-acetamino-6-nitro-m-xylene (XIII) recrystallixed from water. Mp. 159.5-161.5°C. Literature mp. 160°C.

Reduction of 4-amino-6-nitro-m-xylene (X) to 4,6-diamino-m-xylene (XV)-

The dry crude 4-amino-6-nitro-m-xylene (11 gr.) is placed in a 250 ml. heavy wall, round bottom flask with tin (25 gr.) and mixed well. Hyrochloric acid (50 ml. conc.) is added in 10 ml. portions keeping the materials well mixed. At the end of the addition, the flask is placed on the steambbath for about an hour. It is necessary to add additional tin (10 gr.) and hydrochloric acid (20 ml. conc.) inorder to complete the reduction. The mixture is concentrated to expell some of the excess hydrochloric acid and then diluted to 500 ml. The tin salts are precipitated with hydrogen sulfide and the tin sulfide filtered off.

Hydrochloric acid (50 ml. conc.) is added to the filtrate and it is heated on the steam bath until most of the 4,6-diamino-m-xylene dihydrochloride is precipitated. The crude hydrochloride and what hydrochloric acid remains is dissolved in a small amount of water and neutralized with 10% sodium hydroxide; then acidified with acetic acid. An excess of acetic anhydride (15 ml.) is added and the 4,6-diacetamino-m-xylene (XVII) precipitates on standing. The yield is washed with water and dried. mp. 285-90°C. Literature mp. 295-6°C. Yield: 11.5 gr.

Oxidation of 4,6-diacetamino-m-xylene (XVII) to 4,6-diacetaminoisophthalic acid (XVIII) -

4,6-Diacetamino-m-xylene (4.4 gr.), potassium permanganate (6.4 gr.), manganous sulfate heptahydrate (20 gr.), and water (200 ml.) are placed in a beaker on a low hotplate with stirring. The temperature is slowly raised to 70-80°C and when the pink color has disappeared, additional permanganate (6.4 gr.) is added. When the pink color has again disappeared, the mixture is cooled and made strongly basic with sodium hydroxide (about 100 ml 10%). Allow to stand five minutes and filter. The filtrate is acidified with acetic acid and on standing yields 4,6-diacetaminoisophthalic acid (XVIII). Filter and wash with water. Mp. 275-6°C. Literature 276 d. Yield: 2.3 gr.

Liberation of the free 4,6-diaminoisophthalic acid (XX)-

4,6-Diacetaminoisophthalic acid (XVII) (.2 gr.) is placed in sodium hydroxide (5 ml 5%) and boiled for one half hour. When the mixture is cooled and acidified with acetic acid, a gelatinous material forms which is almost impossible to filter.

Another sample of 4,6-diacetaminoisophthalic acid (XVII) (2 gr.) is placed in hydrochloric acid (30 ml. conc.) and boiled on a hotplate with stirring for one half hour. The mix is cooled, chilled in ice, and the 4,6-diaminoisophthalic acid dihydrochloride (XIX) is filtered off. mp 247.0-47.5°C. Literature mp. 229-30°C. Yield: 1.1 gr.

4,6-Diaminoisophthalic acid dihydrochloride (XIX) (1.1 gr.) is dissolved in water (25 ml.) and made basic with sodium hydroxide (5%). The mix is acidified with acetic acid and the precipitated 4,6-diaminoisophthalic acid (XX) is filtered off, washed with water and dried. Mp. 233-5°C. Literature mp. 235°C. Yield: .7 gr.

Ring closure with phosgene in dioxane-[14]

4,6-Diaminoisophthalic acid (XX) (.7 gr.) is placed in dioxane (25 ml.) and an excess of phosgene passed into the mixture. The reaction turns from white to yellow and a new product precipitates. The reaction mixture is brought to reflux and filtered. A crude

yield (.4 gr. yellow) is obtained in addition to the precipitated product (.15 gr. white) from the dioxane filtrate. A sample of the crude is recrystallized from dioxane and its infra-red spectrum agrees with the spectrum of the crude product and that of the precipitated product. Mp. greater then 360°C.

A sample is sent for analysis. Theoretical for $C_{10}H_4N_2O_6$ : C 48.39 H 1.61 N 11.29.
Found : C 48.93 H 3.65 N 8.54.

After considering the analysis,it is felt that the compound is a complex of one molecule of 2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydrobenzo(1,2-d-5,4-d)bis(1,3)oxazine (XXI) and one molecule of dioxane. Theoretical for $C_{10}H_4N_2O_6 \cdot C_4H_8O_2$ : C 50.1 H 3.64 N 8.34.

A sample of the complex (XXII) (.0217 gr.) is placed in the oven at 110°C for five hours. Theoretical % loss in weight : 26.2 % Found : 26.8 % (loss of .0058 gr.). The infra-red spectra of the dried compound has lost six peaks at 7.96, 8.96, 9,23, 9.57, 11.12 and 11.49 u. Each of these peaks are characteristic of the dioxane spectrum.

A sample of the dried compound is sent for analysis.

C 47.14 % H 1.30 %

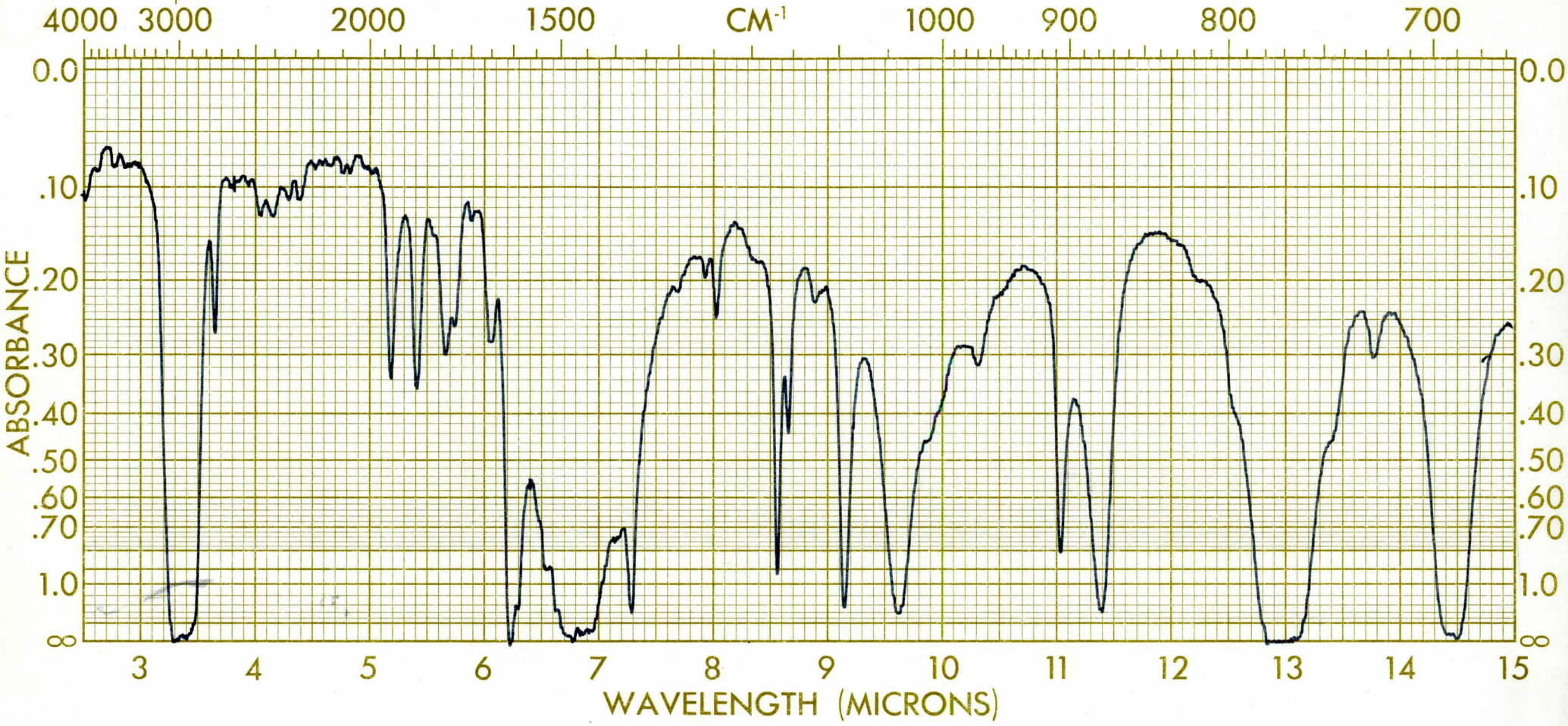
Footnotes

1. Elderfield, Heterocyclic Compounds v.6, 580 (1957)
2. R. H. Clark, J. Org. Chem., 9 55 (1944)
3. R. P. Staiger and E. C. Wagner, J. Org. Chem., 13 347 (1948)
4. R. P. Staiger and E. C. Wagner, J. Org. Chem., 18 1427 (1953)
5. R. P. Staiger and E. B. Miller, J. Org. Chem., 24 1214 (1959)
6. R. P. Staiger, C. L. Moyer and G. R. Pitcher, to be published
7. Ring Index, American Chemical Society
8. System developed by E. B. Miller, Maumee Chemical Company
9. Friedländer and Wleügel, Ber., 16 2227 (1883)
10. Kolbe, J. prakt. Chem., (2) 30, 84, 124, 468 (1884)
11. Wagner and Fegley, Org. Syntheses, 27, 45 (1947)
12. Caronna, Gazz. chim. ital., 71, 189 (1941)
13. Ger. pat. 119,661 (Friedländer) 6 115.
14. Method developed by R. P. Staiger and E. B. Miller
15. Bogert and Kropff, J. Am. Chem. Soc., 31 841 (1909)

Acknowledgment

I would like to thank Drs. R. D. Sturgis and R. P. Staiger for their help and encouragement. Also to the Chemistry Department for the support necessary to carry on the above research, I am grateful.

Infra-red Spectra




| | | | |
|---|---|---|---|
| SPECTRUM NO. 5 | ORIGIN CHM-Honors | LEGEND | REMARKS |
| SAMPLE m-xylene | Bp. 139°C | 1. | |
|  | PURITY Eastman 275 | 2. | |
| VI | PHASE liquid | DATE 10/6/62 Sat. 3:45 pm | |
| MW = 106.17 | THICKNESS .1 mm | OPERATOR Calvin Moyer | |

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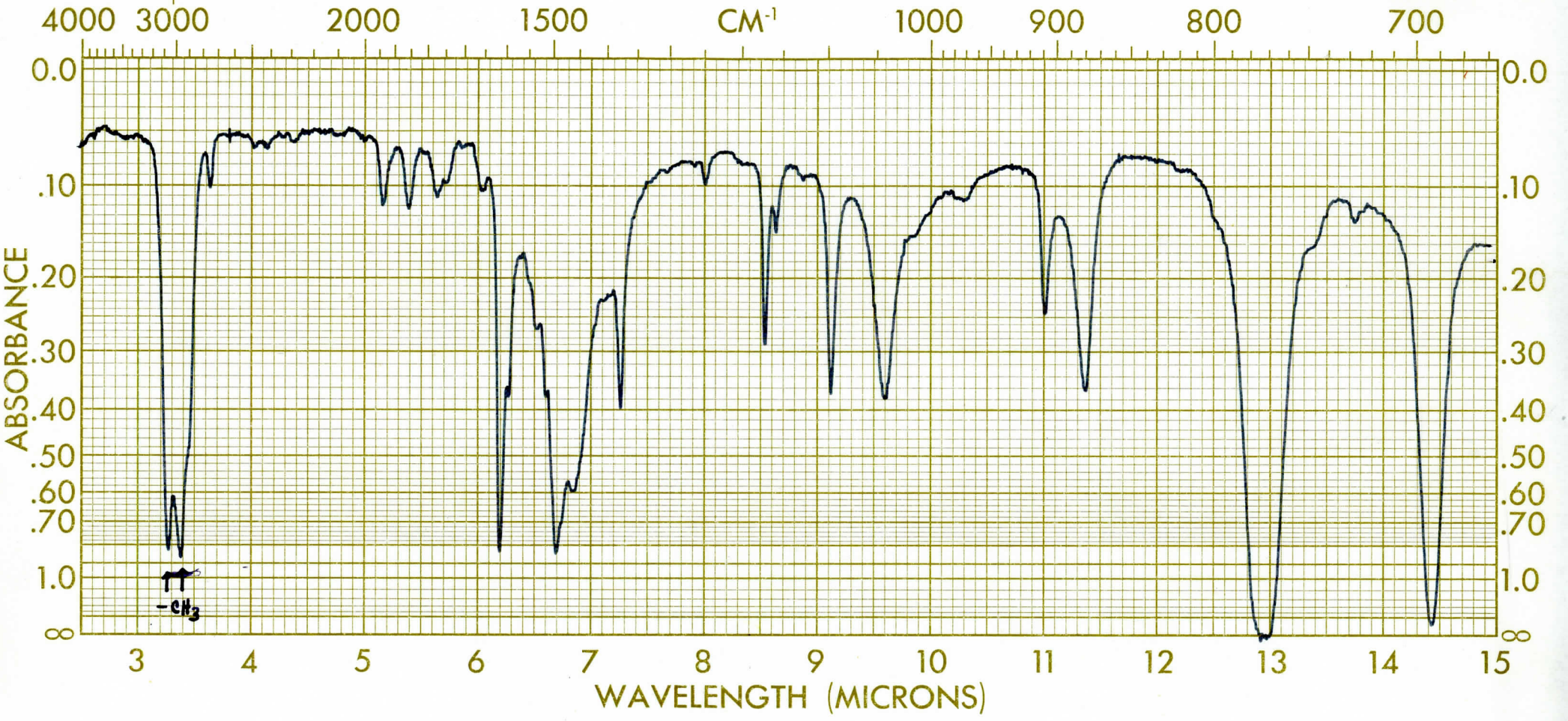


| | | | |
|---|---|---|---|
| SPECTRUM NO. 4 | ORIGIN Calvin Moyer - Honors | LEGEND | REMARKS |
| SAMPLE m-xylene | Eastman 275 | 1. | |
| $H_3C$  $CH_3$ | PURITY Bp. 139°C | 2. | |
| VI | PHASE liquid | DATE 10/6/62 Sat 4:32 pm | |
| MW = 106 | THICKNESS .0269 mm | OPERATOR Calvin Moyer | |

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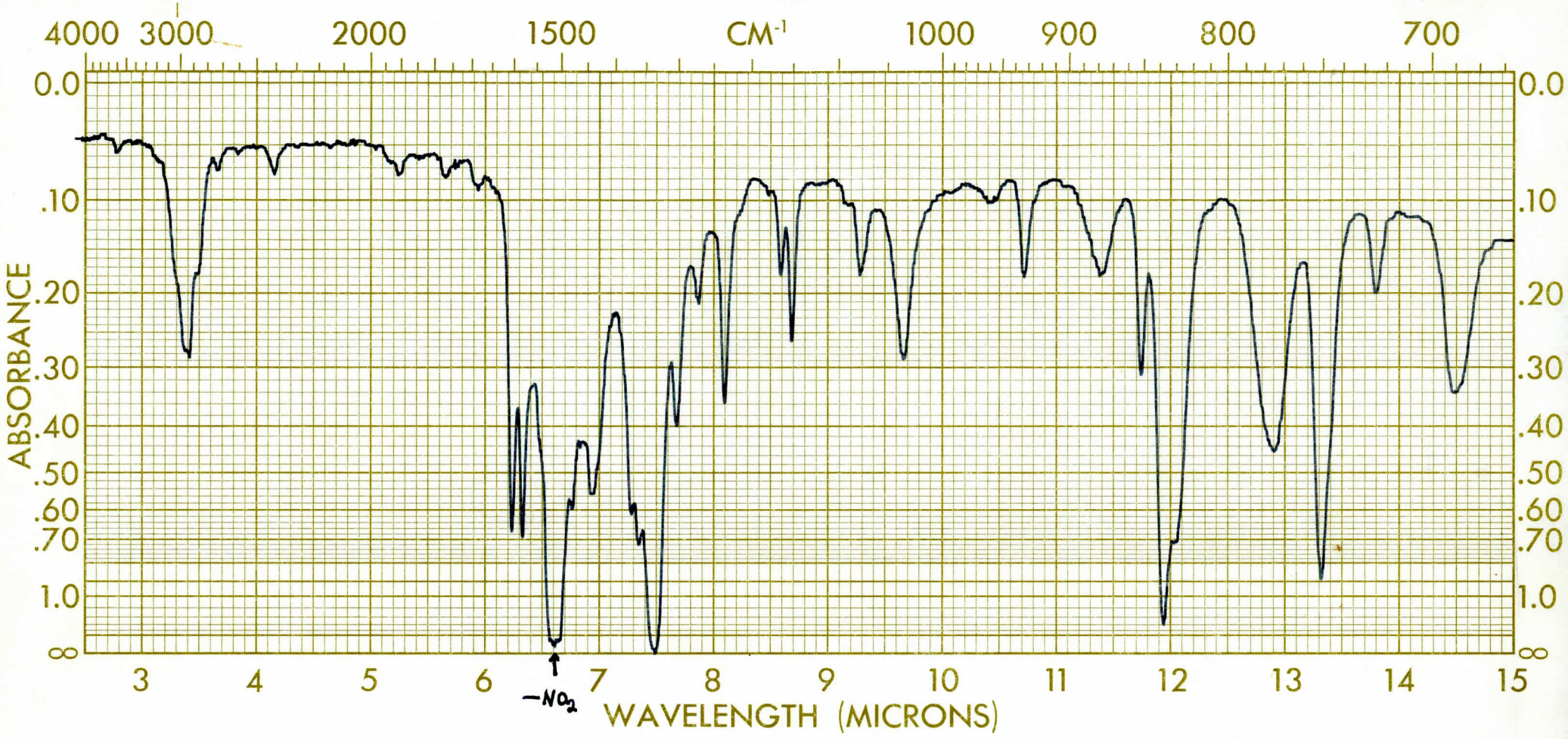


| | | | |
|---|---|---|---|
| SPECTRUM NO. 2 | ORIGIN CLM-H-6 | LEGEND | REMARKS |
| SAMPLE 4-nitro m-Xylene | | 1. | |
|  | PURITY Bp 240-242 | 2. | |
| VII | PHASE liq. | DATE 10/6/62 3 pm | |
| | THICKNESS d. mount Cell | OPERATOR CL Moyer | |

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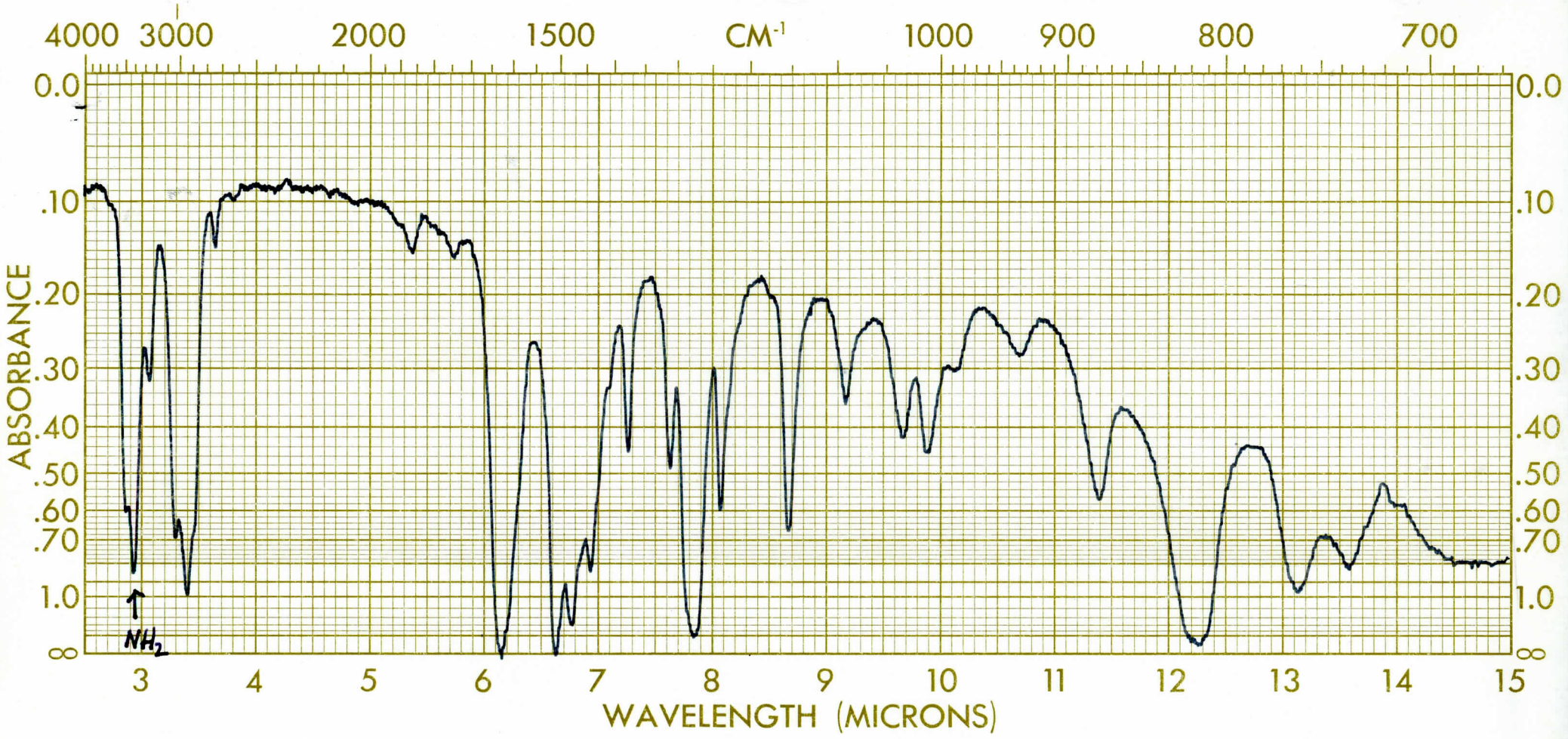


| | | | |
|---|---|---|---|
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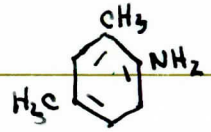
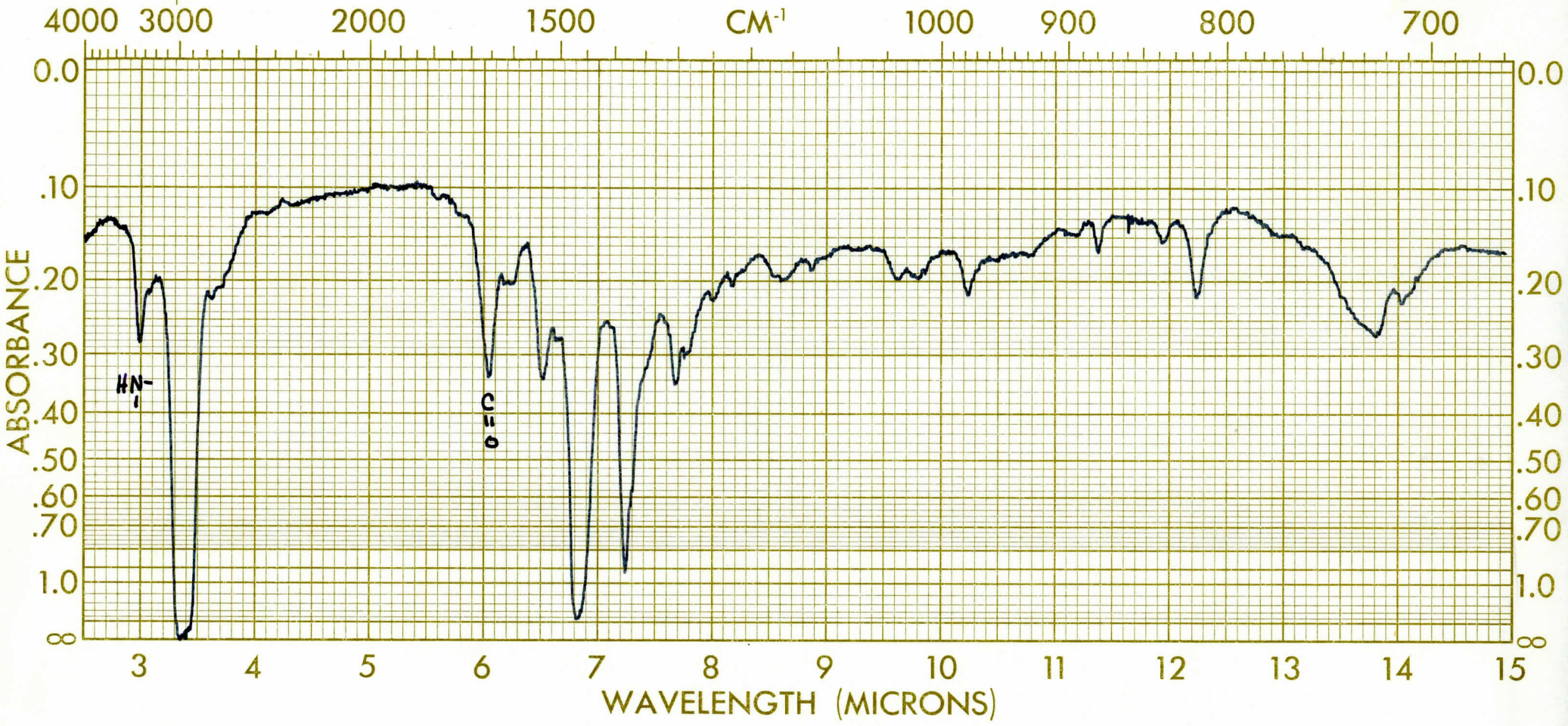
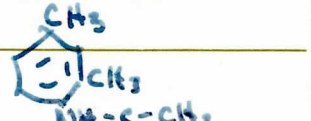
|  | PURITY Tech. | 2. | |
| VIII | PHASE liq | DATE 11/1/62 | |
| | THICKNESS d. Mount Cell | OPERATOR CLMoyer | |

SPECTRUM NO. ____ SAMPLE ____

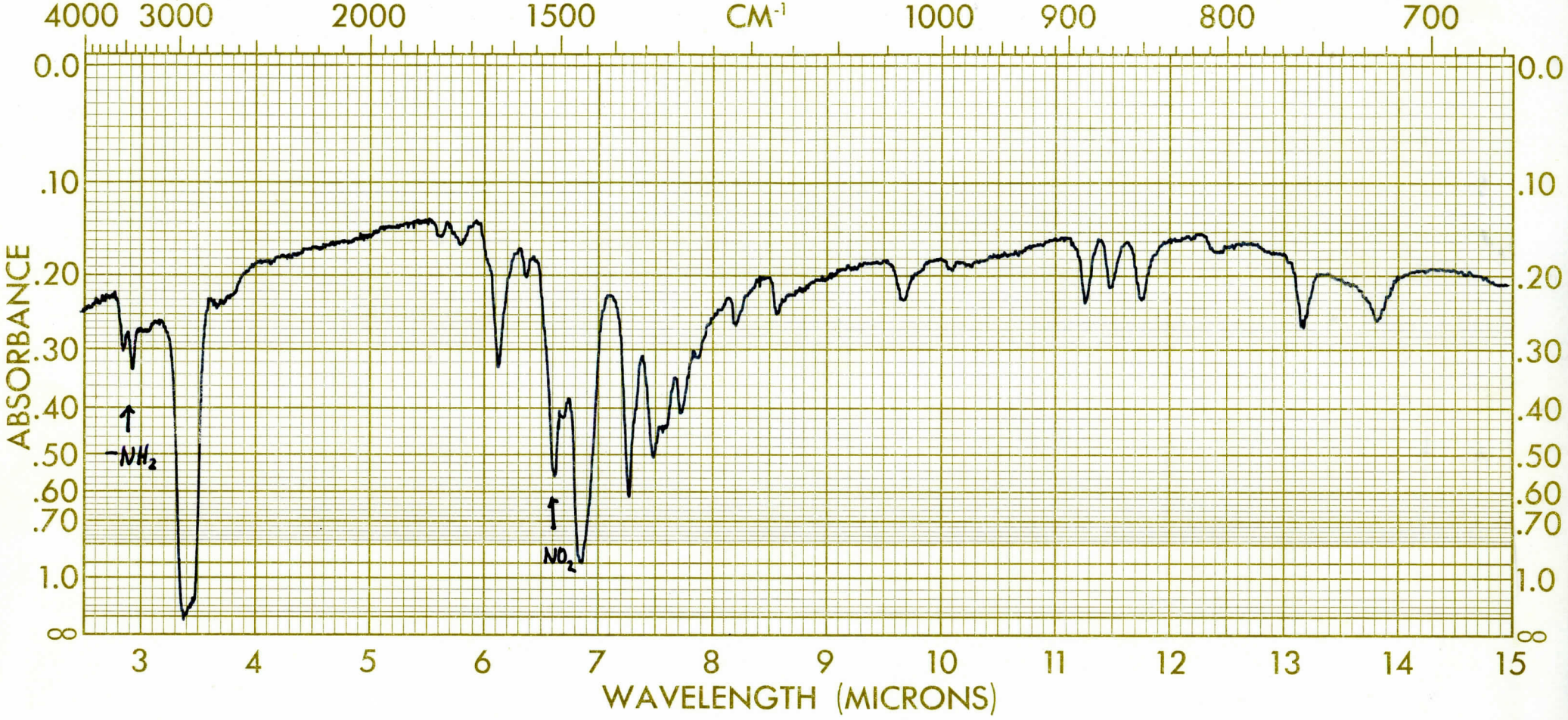


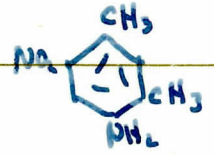

| | | | |
|---|---|---|---|
| SPECTRUM NO. 17 | ORIGIN Mayer Honors - 2 white plates Rx MeOH ~$H_2O$ Mp 125-6°C | LEGEND | REMARKS |
| SAMPLE N-acetyl-2,4-dimethylaniline  | PURITY Lit Mp 129-30°C | 1. | |
| | PHASE Nujol Mull | 2. | |
| IX | THICKNESS demount Cell | DATE 11/8/62 9:15 pm | |
| | | OPERATOR C. L. Mayer | |

SPECTRUM NO. ____ SAMPLE ____

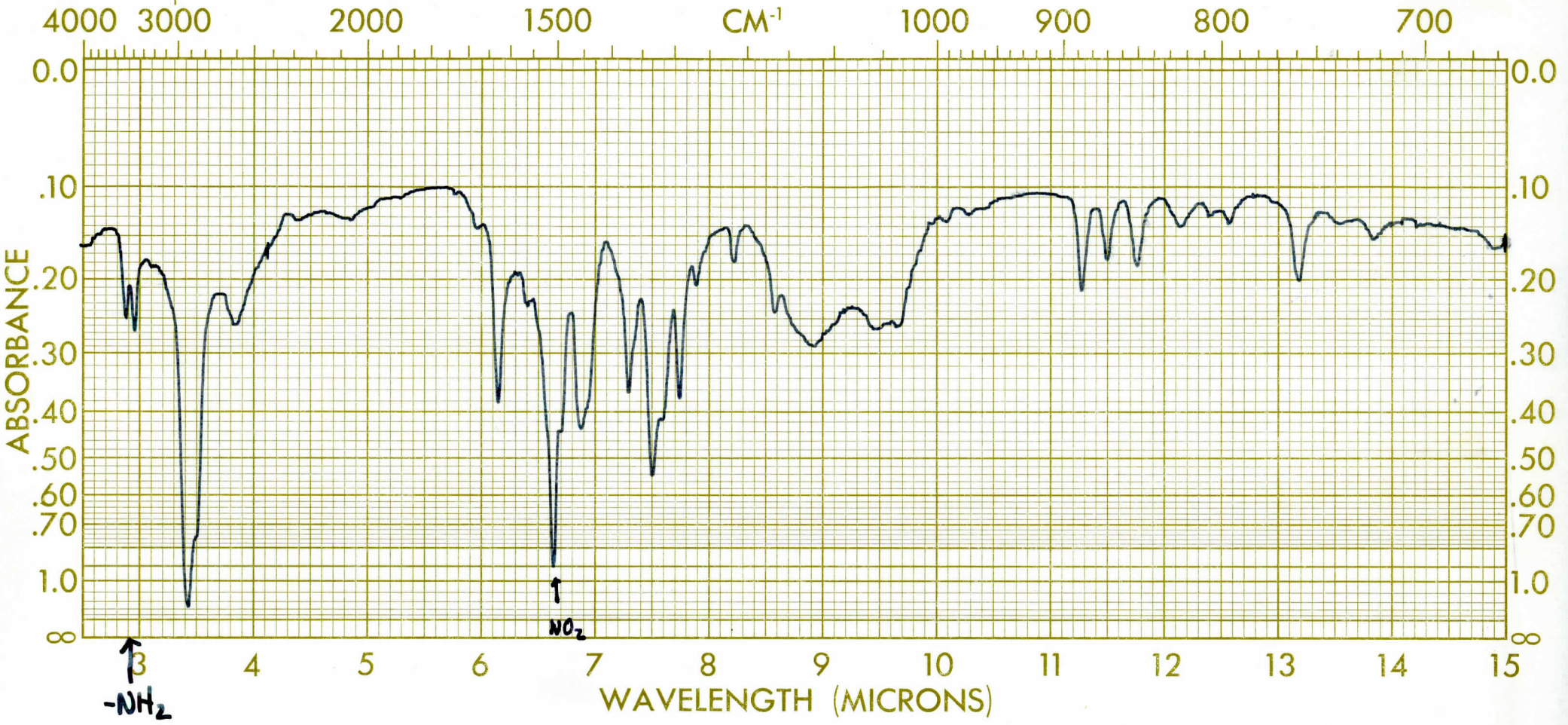


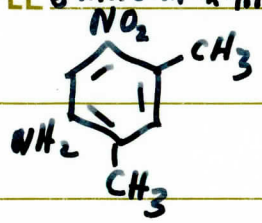
THE PERKIN-ELMER CORPORATION, NORWALK, CONN.



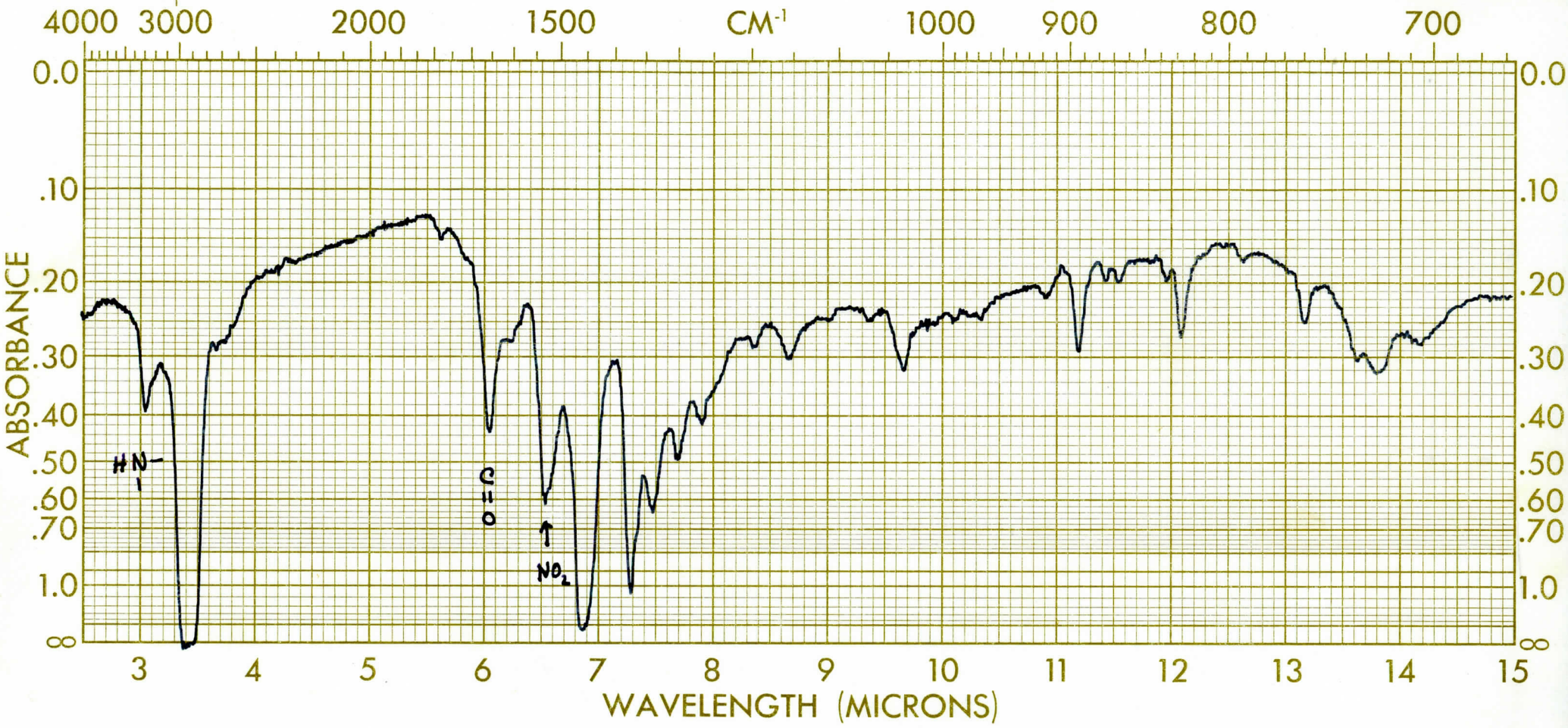

| | | | |
|---|---|---|---|
| SPECTRUM NO. 15 | ORIGIN Moyers Honors-4<br>Red-Orange prisms<br>Rx MeOH 1X<br>Mp 117-120°C | LEGEND | REMARKS |
| SAMPLE 6-nitro-m-4-Xylidine | | 1. | |
|  | PURITY Lit Mp 123°C | 2. | |
| | PHASE Nujol Mull | DATE 11/8/62 @ 45 pm | |
| X | THICKNESS demount Cell | OPERATOR C. L. Moyer | |

SPECTRUM NO. ____ SAMPLE ____




| | | | |
|---|---|---|---|
| SPECTRUM NO. | ORIGIN Moyer Honors Red-Orange Mp 118-123° | LEGEND | REMARKS From the supposed toluic acid with base. |
| SAMPLE 6-nitro-m-Xylidine  | PURITY Lit Mp 123° | 1. | |
| | PHASE Nujol Mull | 2. | |
| | THICKNESS dem cell | DATE 4/20/63 | |
| | | OPERATOR Col Moyer | |

SPECTRUM NO. SAMPLE




| | | | |
|---|---|---|---|
| SPECTRUM NO. 19 | ORIGIN Moyer Honors (5) white needles | LEGEND | REMARKS |
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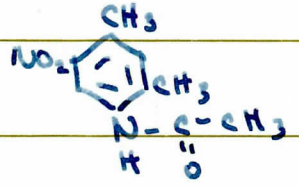
|  | PURITY Mp 159.5-161.5 Lit 160 | 2. | |
| XIII | PHASE Nujol Mull | DATE 11/8/62 8 pm | |
| | THICKNESS demount cell | OPERATOR C.L. Moyer | |

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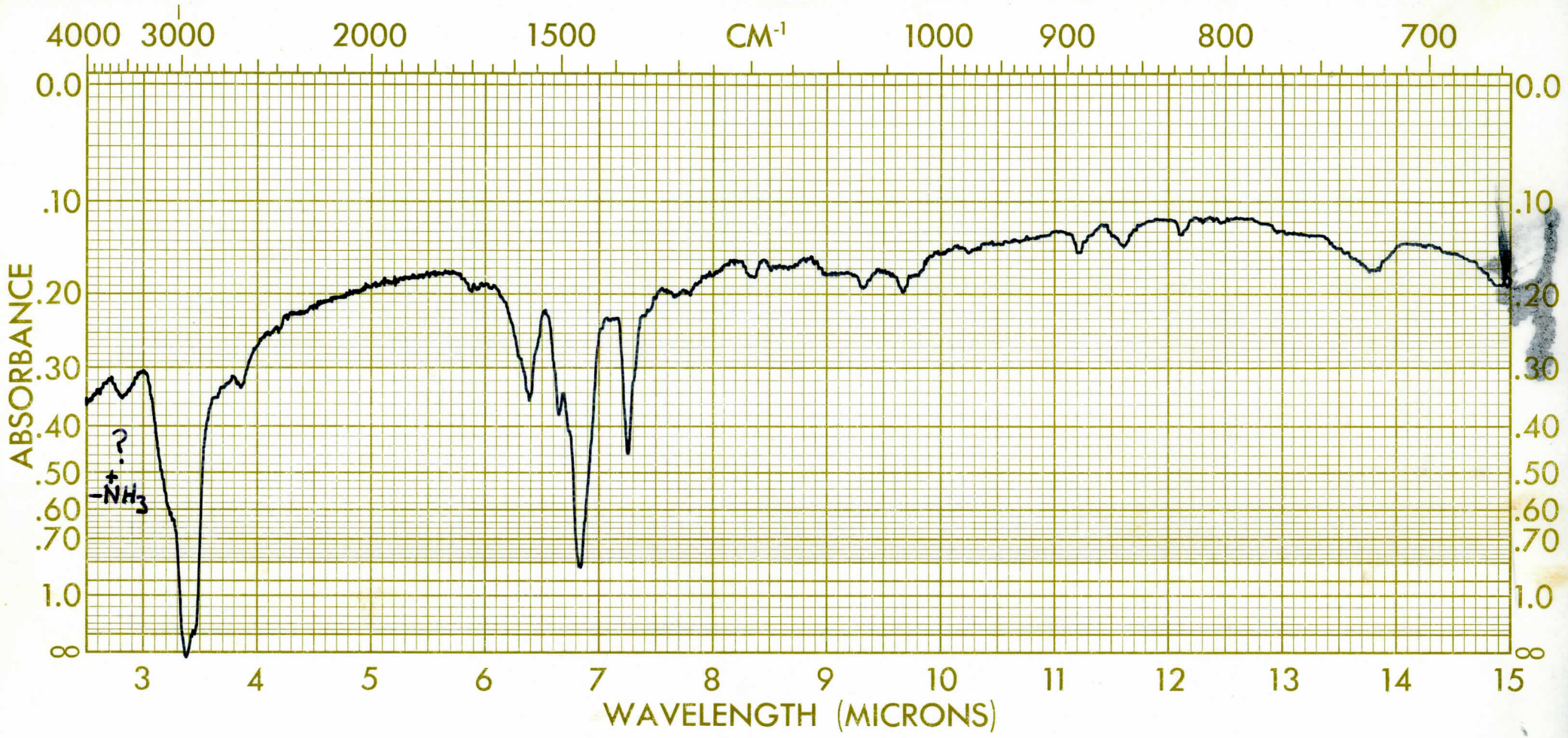
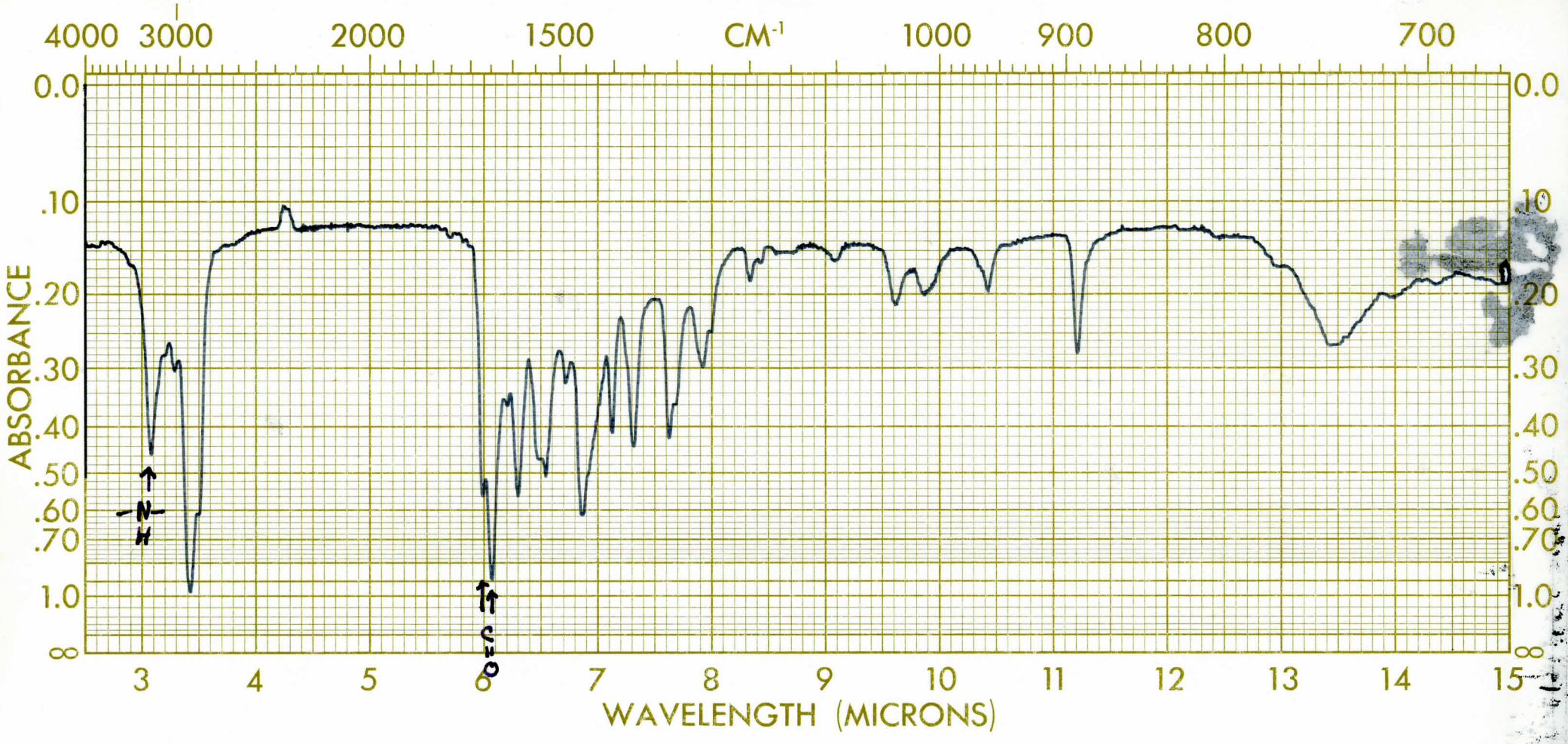
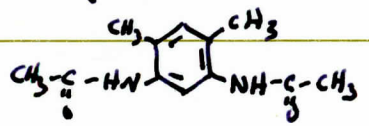


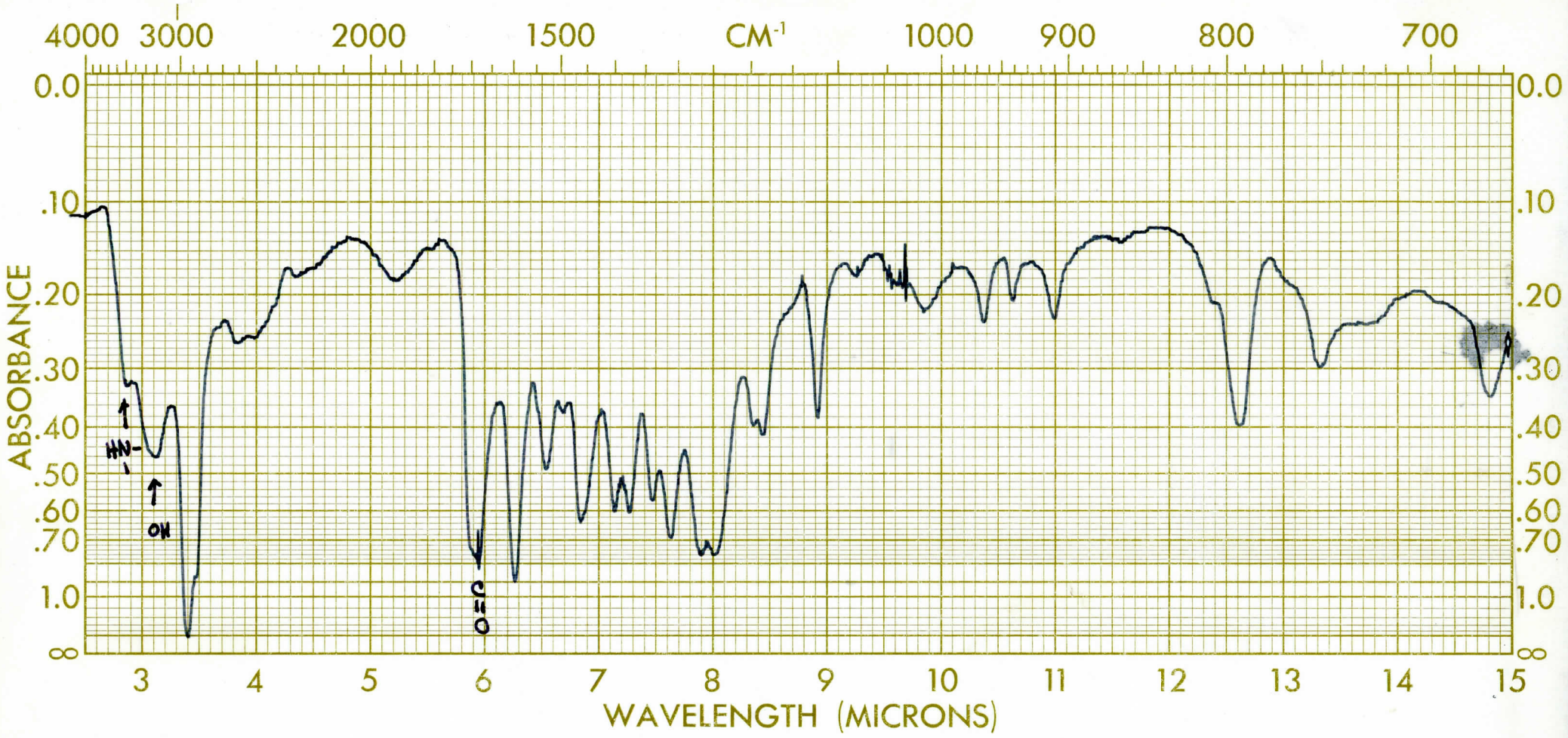

| | | | |
|---|---|---|---|
| SPECTRUM NO. 22 | ORIGIN Moyer Honors #6 Yellow Powder Mp 245-255°C | LEGEND | REMARKS |
| SAMPLE 4,6-diamino m-xylene di HCl | | 1. | May not be the desired product. |
|  | PURITY Crude | 2. | |
| | PHASE Nujol Mull | DATE 2-20-63 2⁰⁰ PM | |
| XIV | THICKNESS Dem Cell | OPERATOR Calvin Moyer | |

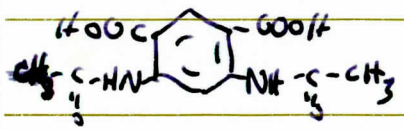
SPECTRUM NO. ____ SAMPLE ____



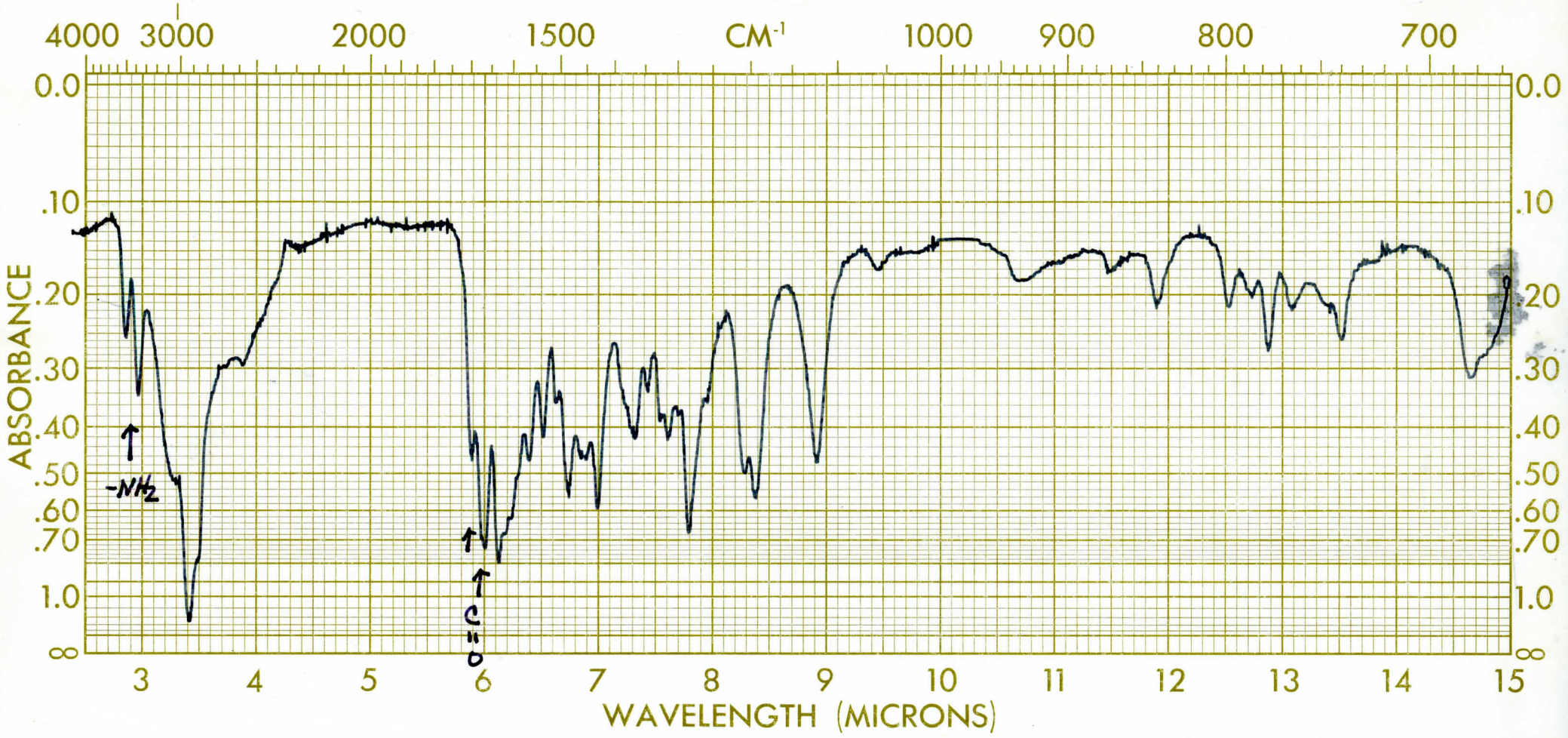

| | | | |
|---|---|---|---|
| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
| SAMPLE 4,6-diacetylamino m-xylene | mp 285-290° C | 1. | |
|  | PURITY | 2. | |
| | PHASE mujol mull | DATE 4/18/63 4⁰⁰ PM | |
| XVII | THICKNESS d.M. Cell | OPERATOR Calvin L. Moyer | |

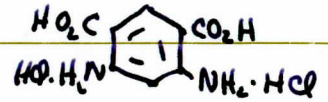
SPECTRUM NO. SAMPLE




| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
|---|---|---|---|
| SAMPLE 4,6-diacetamino isophthalic acid. | Mp. 275-276° d | 1. | |
|  | PURITY | 2. | |
| XVIII | PHASE Nujol Mull | DATE 4/20/63 | |
| | THICKNESS dem. cell | OPERATOR Calvin Moyer | |

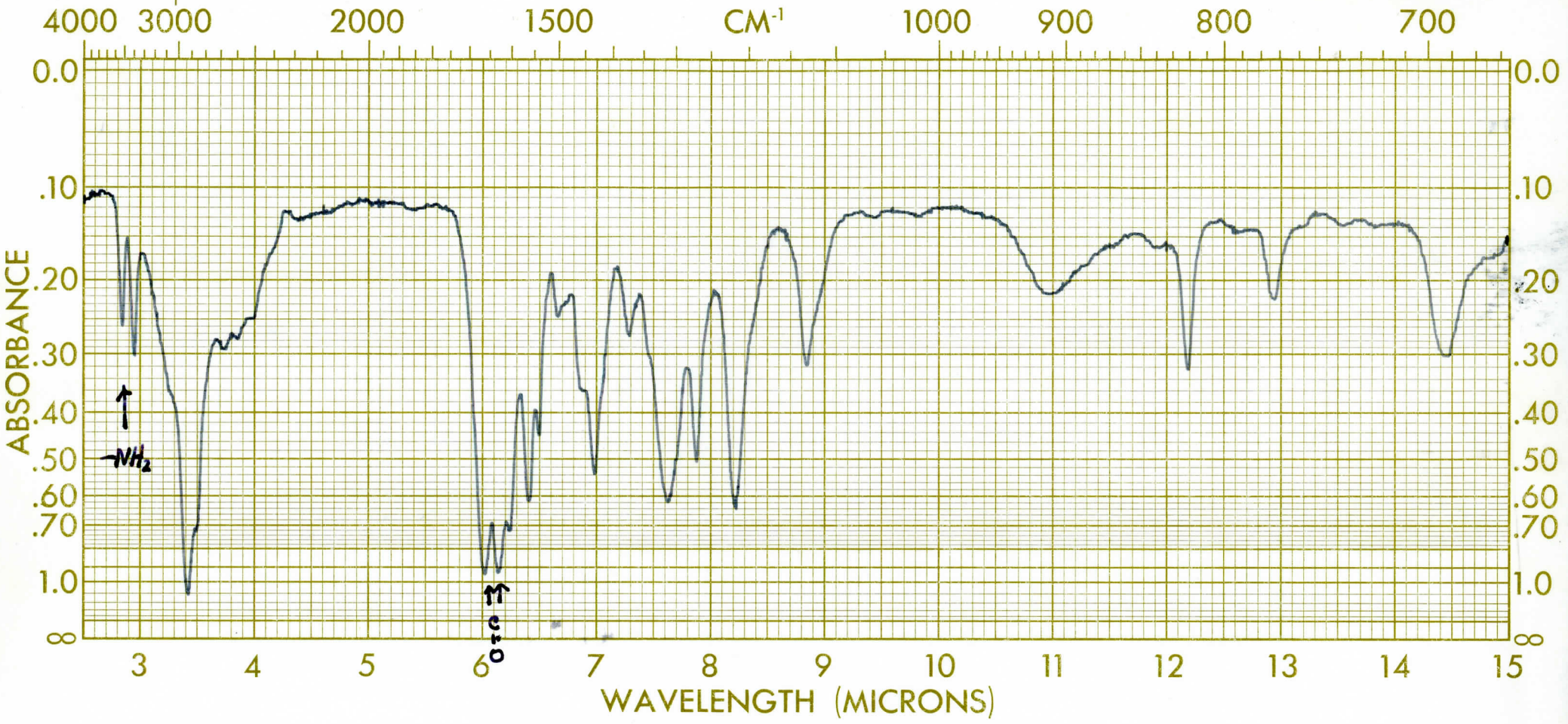
SPECTRUM NO. ____ SAMPLE ____




| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
|---|---|---|---|
| SAMPLE 4,6-diamino iso-phthalic acid dihydrochloride | | 1. | |
|  | PURITY Mp. 247-247.5 | 2. | |
| | PHASE Nujol Mull | DATE 4/20/63 | |
| XIX | THICKNESS dem. cell | OPERATOR Cal Moyer | |



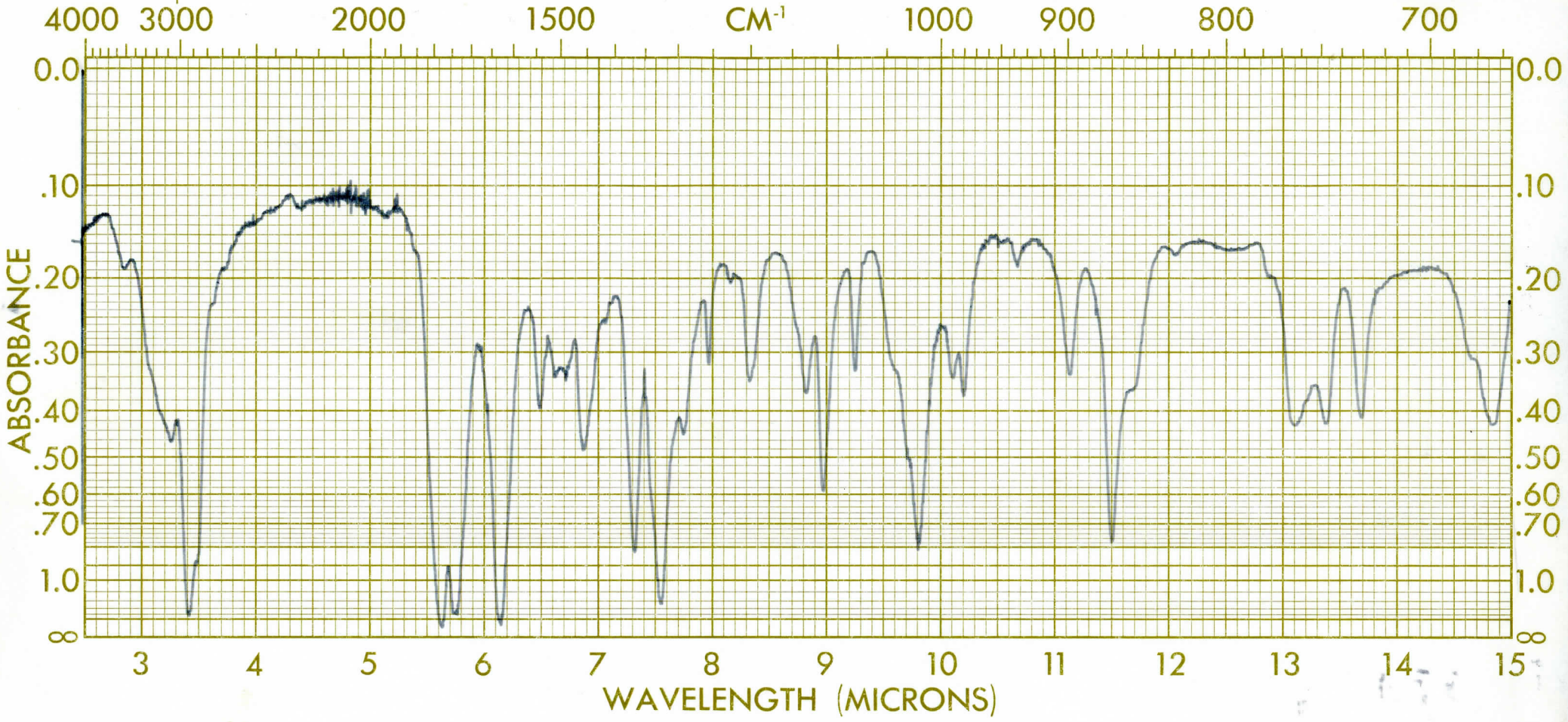
SPECTRUM NO. _____ SAMPLE _____

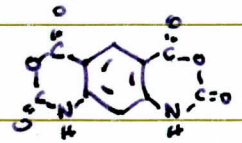



| | | | |
|---|---|---|---|
| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
| SAMPLE 4,6-diamino-isophthalic acid | | 1. | |
|  | PURITY Crude Mp 238-39°C | 2. | |
| XX | PHASE Nujol Mull | DATE 4/20/63 | |
| | THICKNESS demount cell | OPERATOR Calvin L. Moyer | |

SPECTRUM NO. ____ SAMPLE ____

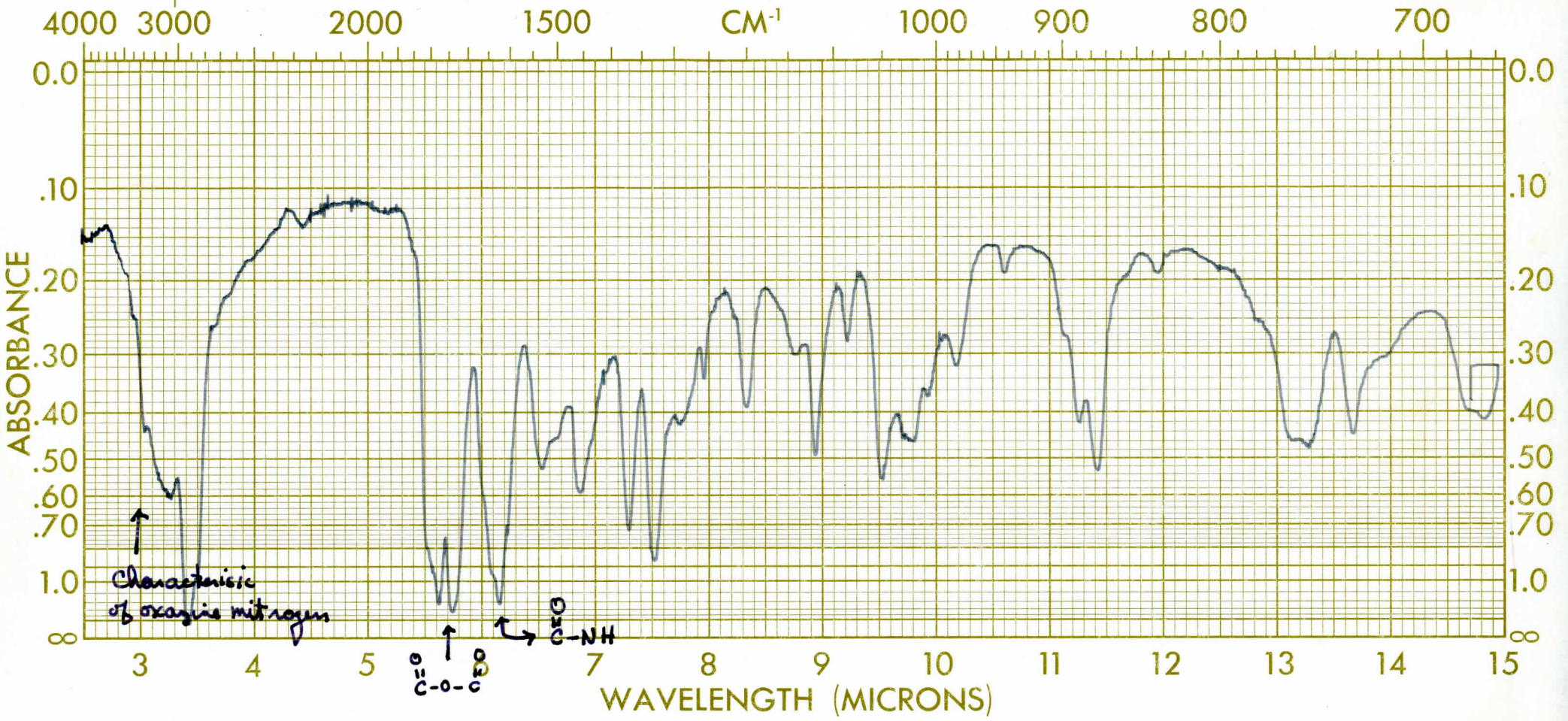
DIA 2x2X

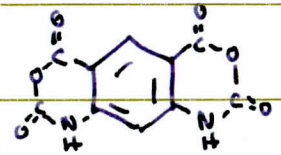



| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
|---|---|---|---|
| SAMPLE 2,4,6,8,-tetra oxo,-1,2,3,4-6,7,8,9-octahydrobenzo [1,2-d-3,4-d]-bis (1,3) oxazine. | Mp > 360 | 1. | Believed to be dioxane |
|  | PURITY Rx from crude Dioxane | 2. | complex |
| XXI | PHASE Nujol Mull | DATE 4/20/63 | |
| | THICKNESS dem. cell | OPERATOR Cal Moyer | |

SPECTRUM NO. SAMPLE

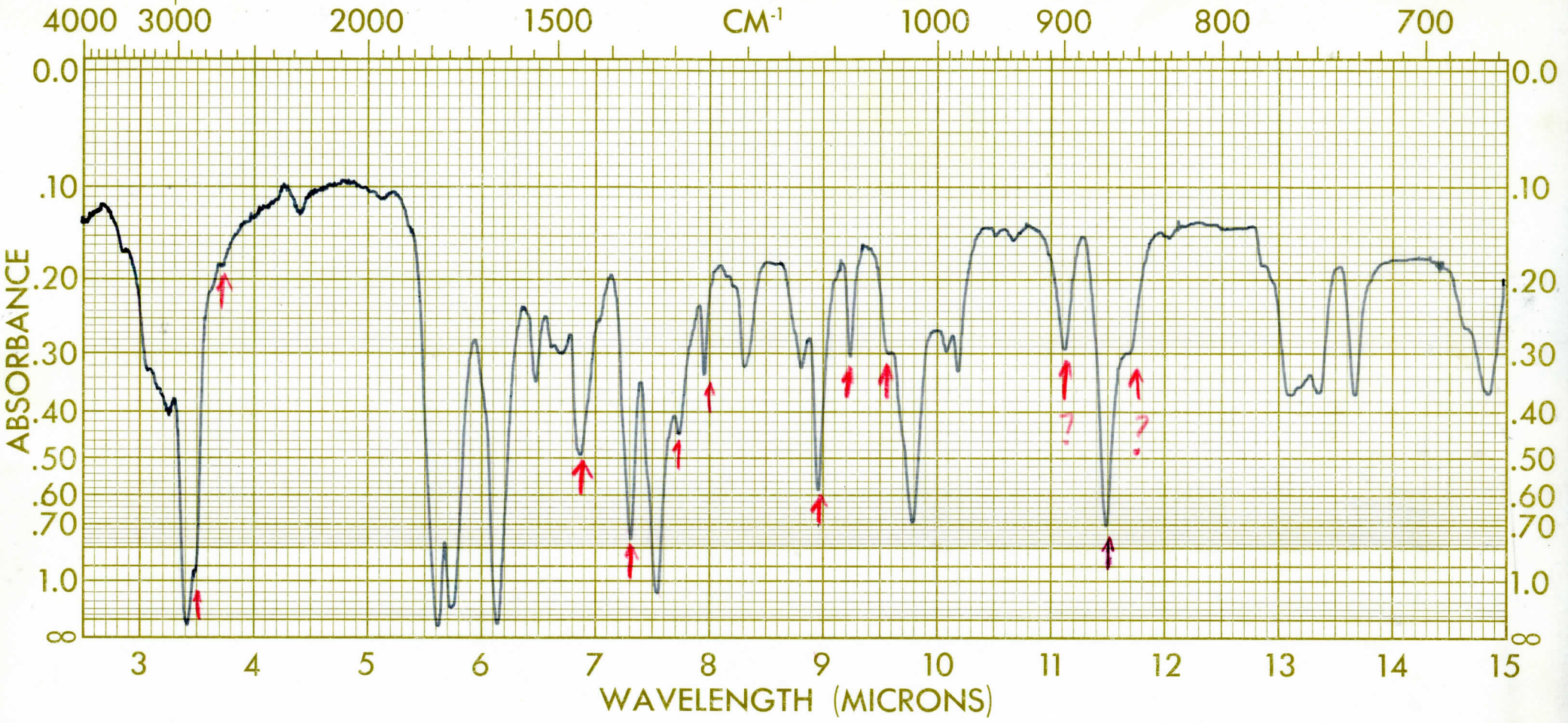
DIA Crude




| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
|---|---|---|---|
| SAMPLE 2,4,6,8-tetraoxo-1,2,3,4,6,7,8,9-octahydrobenzo-(1,2-d:5,4-d') bis(1,3) oxazine | Mp > 360 | 1. | Believed to be dioxane complex. |
|  XXI | PURITY Crude | 2. | |
| | PHASE Nujol Mull | DATE 4/20/63 | |
| | THICKNESS dem. cell | OPERATOR Calvin Moyer | |

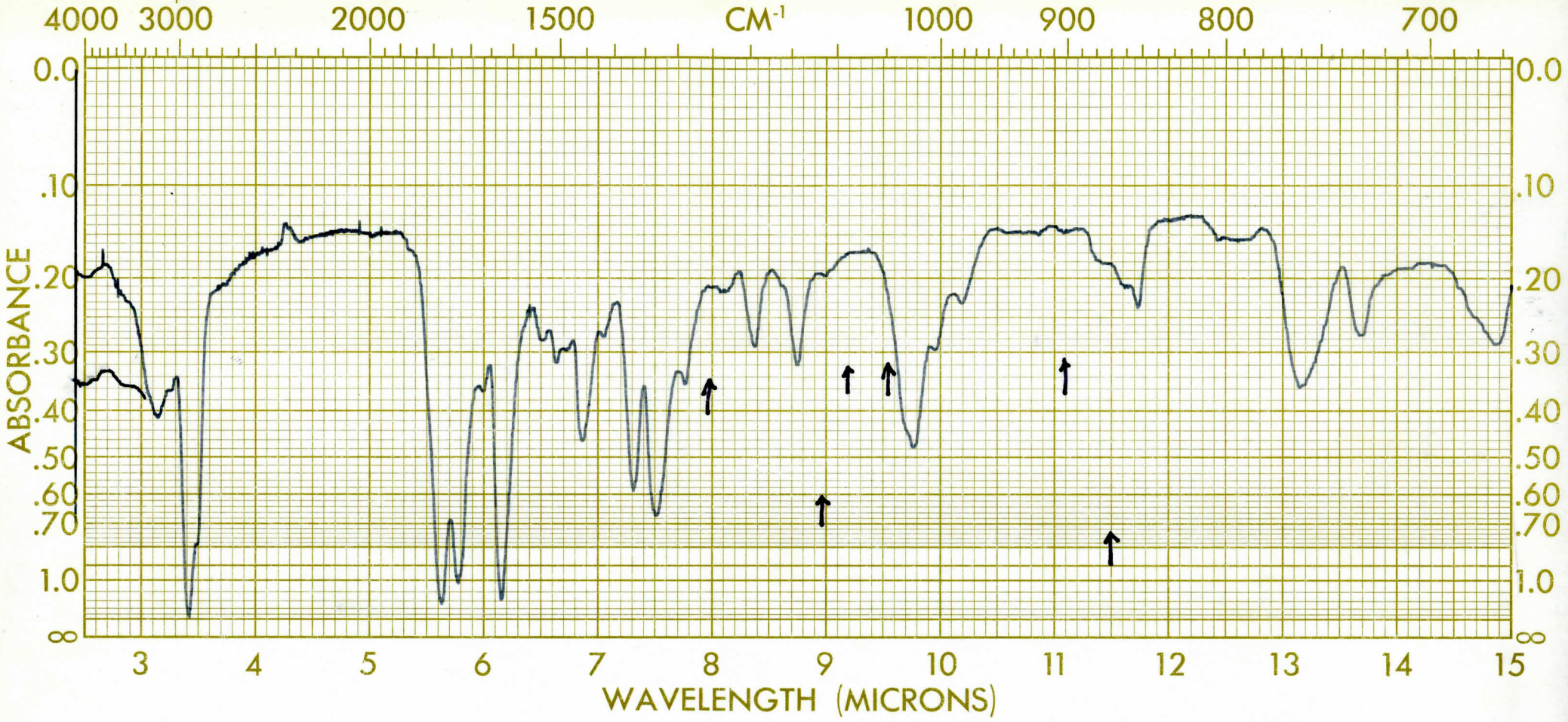
SPECTRUM NO. _____ SAMPLE _____

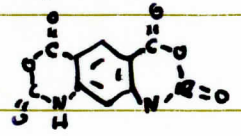
DIA 1X RX




| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
|---|---|---|---|
| SAMPLE 2,4,6,8-tetraoxo-1,3,4-6,7,8,9-octahydrobenzo(1,2-d-5,4-d')bis-(4,7)oxazine | Mp > 360 | 1. | Now believed to |
| | PURITY RX from reaction mix, Dioxane | 2. | be the dioxane complex |
| XXI | PHASE Nujol Mull | DATE 4/20/62 | (XXII) Red arrows indicate |
| | THICKNESS 4cm cell | OPERATOR Calvin Moyer | dioxane peaks |

SPECTRUM NO. SAMPLE




| | | | |
|---|---|---|---|
| SPECTRUM NO. | ORIGIN Moyer Honors | LEGEND | REMARKS |
| SAMPLE 2,4,6,8-tetra oxo 1,2,3,4,5,7,8,9-octahydrobenzo (1,2-d:4,5-d') (1,3) bis oxazine | | 1. | Arrows indicate the |
|  | PURITY Crude decomp. complex | 2. | lossed peaks of the |
| | PHASE Nujol Mull | DATE 4/27/63 12:30 AM | dioxane spectra |
| | THICKNESS 4cm cell | OPERATOR Cal. Moyer | |

SPECTRUM NO. SAMPLE