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The Synthesis and Reactions of 6-Carboxy Isatoic Anhydride

Jacqueline I. Kroschwitz

The Synthesis and Reactions of 6-Carboxy Isatoic Anhydride

by Jacqueline I. Kroschwitz

This paper is submitted to the faculty of Ursinus College in partial fulfillment of the requirements for departmental honors in chemistry.

Approved by:

Roger P. Staiger

Submitted by:

Jacqueline I. Kroschwitz

April 30, 1964

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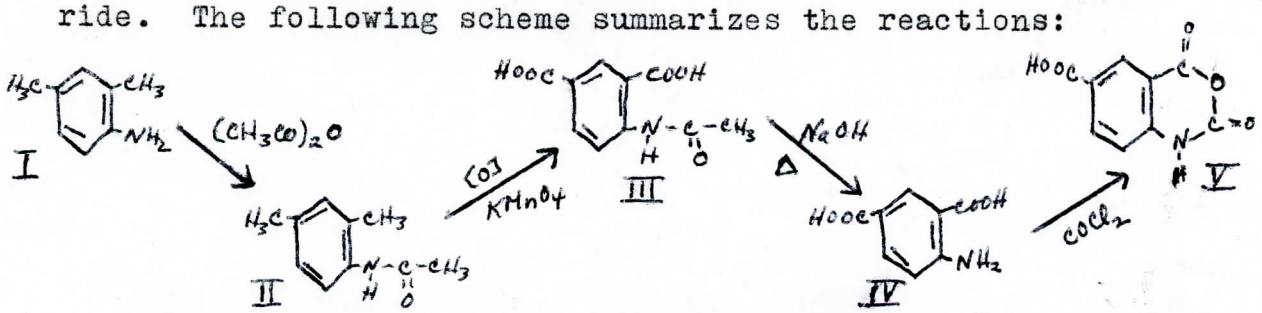
Introduction

The object of this research project was the preparation and characterization of 6-carboxy isatoic anhydride and the study of the reactions of this compound, leading to the synthesis of a series of compounds of new composition.

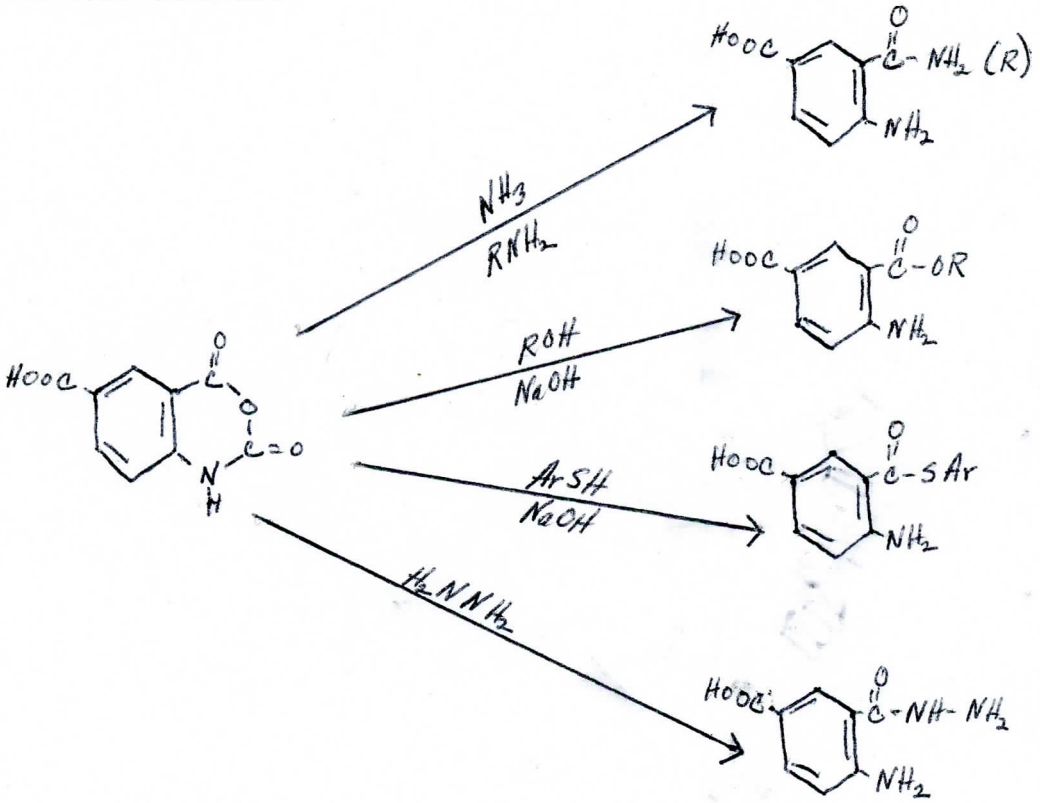
The path of synthesis chosen was the acetylation of 2,4 dimethyl aniline, oxidation to 4-acetamino isophthalic acid, and hydrolysis of the 4-acetamino isophthalic acid to form 4-amino isophthalic acid. Ring closure was effected with phosgene to yield the desired 6-carboxy isatoic anhydride. The following scheme summarizes the reactions:



The preparation of 4-amino isophthalic acid[1] has been reported in the literature, but it is not commercially available. 2,4 Dimethyl aniline was chosen as the starting material because of its availability and inexpensiveness.

Since 6-carboxy isatoic anhydride had previously been prepared in limited quantity,[2] it was decided to establish its identity absolutely by the preparation and analysis of its derivatives. 6-carboxy isatoic anhydride undergoes ring cleavage when attacked by various nucleophiles in a manner analagous to that of the unsubstituted isatoic anhydride.[3] 6-carboxy isatoic anhydride reacts with ammonia and with aliphatic and aromatic amines to form

2-amino-5-carboxy benzamides; with alcohols to form 2-amino-5-carboxy benzoates; with thio phenols to form 2-amino-5-carboxy thio benzoates; and with hydrazine to form 2-amino-5-carboxy benzhydrazides as outlined in the following reaction scheme:



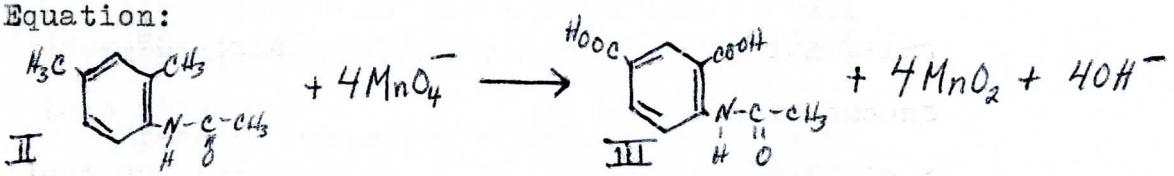
These products are compounds of new composition and are characterized for physical properties and confirmed by analysis. Infra red spectra are available for each chemical entity.

Synthesis of 6-Carboxy Isatoic Anhydride

Preparation of 4-acetamino isophthalic acid

4-acetamino isophthalic acid was prepared according to the buffered permanganate oxidation process described by Bogert and Kropff[4] with modifications intended to increase the meager yields predicted. The buffer used is magnesium sulfate heptahydrate which precipitates as magnesium hydroxide, keeping the mixture nearly neutral, though on the alkaline side. The reaction described is for small quantities (5 grams of acetylated amine suspended in 100 ml of water). However, it was found that increasing the amount of acetylated amine while maintaining the same volume of water tends to increase the oxidizing power of the potassium permanganate. For this reason, and also to obtain workable amounts of product, 50 grams of acetylated amine was used in the initial reaction mix.

Equation:



Experimental: 2,4 dimethyl aniline is acetylated with excess acetic anhydride to form 4-acetamino m-xylene. 50 grams of 4-acetamino m-xylene, 62 grams of potassium permanganate, and 100 grams of magnesium sulfate heptahydrate are suspended in 150 ml of water in a 2-l. beaker. This mix is heated on a low hot plate until the vigorous oxidation reaction begins. It is then removed from the

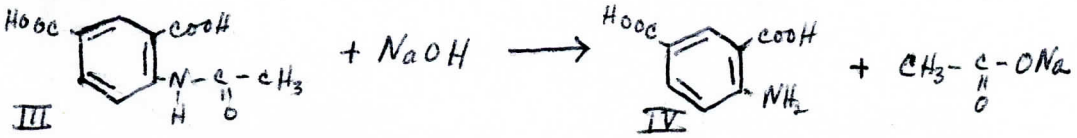
heat, the heat of reaction itself maintaining a temperature of 75-80°C for ten minutes. When the reaction subsides, the sides of the beaker are sparingly washed down with water from a wash bottle, the reaction mix is stirred well, and a second 62 grams of potassium permanganate is added. The mix is heated again until oxidation starts and then removed from heat until the reaction subsides. Then again the beaker sides are washed down and the mix heated with occasional stirring until the pink color is completely dissipated and the sludge is smooth and brown. When no trace of pink remains, the mix is cooled to 0-5°C. Twenty per cent potassium hydroxide is added until the sludge is strongly basic to indicator. The sludge is stirred vigorously and well. The filter paper in a large (30 cm) Buchner funnel is saturated with 20% potassium hydroxide and the sludge is filtered thereon. The initial filtrate is removed and saved. The sludge is washed twice with approximately 300 ml of 10% potassium hydroxide, the filtrate being removed and saved after each washing. During the washings, the sludge is stirred in the Buchner. The sludge is removed from the funnel, mixed with water and 20% potassium hydroxide, stirred vigorously, and then filtered. Thus are attained four portions of filtrate. The filtrate contains magnesium hydroxide which is colloidal and which was drawn through the filter paper by suction. Therefore, the filtrate is gravity filtered

to eliminate the magnesium hydroxide. This final filtrate is acidified with acetic acid and allowed to stand overnight to insure complete precipitation. The fine, white precipitate is suction filtered and dried. The yield is a white powder and is 19.4 grams or 28% of the theoretical. The filtrate is saved and made strongly acidic with concentrated hydrochloric acid. 8.8 grams additional yield results, bringing the percentage yield to 41% of the theoretical. Recrystallization is not necessary before proceeding to the next step, but it can be accomplished with ethanol. Decomposition by heat prohibits the obtaining of a sharp melting point. The value given in the literature is 295-6°C.[5] Infra red spectrum of 4-acetamino isophthalic acid: Exp. #548 Step I (3) 4/22/64.

Preparation of 4-amino isophthalic acid

This is a simple basic hydrolysis procedure to liberate the free amine.

Equation:



III IV

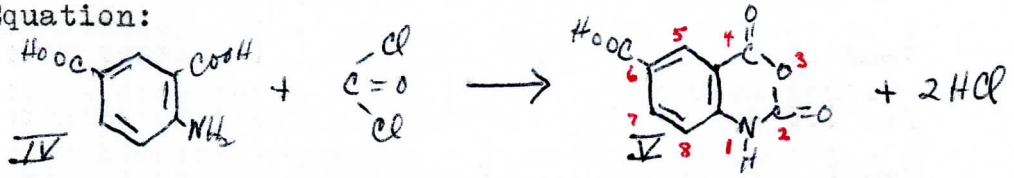
Experimental: 28.2 grams of crude 4-acetamino isophthalic acid are dissolved in 100 ml of 5% sodium hydroxide. The solution is boiled gently for one-half hour. It is then cooled and acidified with acetic acid. The solution is allowed to stand overnight in order to insure complete

precipitation. The precipitate is suction filtered and dried. The yield is a yellow powder and is 22.4 grams or 98% of the theoretical. Once again recrystallization is not necessary before proceeding to the next step, but ethanol will accomplish this. The material melts at 335-6°C. The value cited in the literature is 336-7°C.[6] Infra red spectrum of 4-amino isophthalic acid: Exp. #548 Step II (3) 4/22/64.

Synthesis of 6-Carboxy Isatoic Anhydride

6-carboxy isatoic anhydride was prepared according to a procedure[7] for ring closure with phosgene in dioxane as the solvent.

Equation:

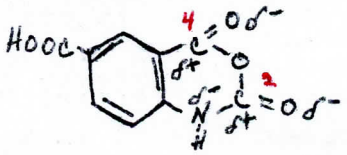


Experimental: 10 ml of dioxane is added to each gram of 10 grams of 4-amino isophthalic acid in a 500 ml Erlenmeyer flask. The flask is set on a scale so that a known weight of phosgene can be bubbled through the solution through suitable safety equipment. Two moles of phosgene for each mole of 4-amino isophthalic acid present are bubbled through (i. e. 11 grams phosgene to 10 grams acid). The reaction mix is then refluxed gently with frequent stirring for one-half hour. After the mixture has cooled, it is poured into ice and water and the beige-

colored precipitate is filtered off. The yield is 6 grams, or 52% of the theoretical. When recrystallized from dioxane, 6-carboxy isatoic anhydride is a white powder which melts over 350°C. The analysis of the compound is as follows: theoretical carbon 52.17%, hydrogen 2.42%; found[8] carbon 52.04%, hydrogen 2.69%. Infra red spectrum of 6-carboxy isatoic anhydride: Exp. #548 Step III (3) 4/16/64.

Reactions of 6-Carboxy Isatoic Anhydride

In 6-carboxy isatoic anhydride the carbonyl oxygen atoms withdraw electrons from both the number two and the number four carbon atoms. However, the high electron density of the nitrogen atom partially compensates for the positive character of the number two carbon atom. Therefore, the likely candidate for nucleophilic attack is the number four carbon atom, and this is indeed the case.



Common nucleophilic agents attack the number four carbon atom attaching their particular characteristic functional group with the evolution of carbon dioxide.

Though 6-carboxy isatoic anhydride undergoes ring cleavage through reactions similar to those effective on its unsubstituted parent compound, these reactions are not as easily carried out and generally require much more vigorous conditions. Also, occasionally the carboxy group creates special solubility problems not encountered with the unsubstituted isatoic anhydride. The carboxy group also presents the problem of salt formation accompanying the ring cleaving reaction.

Synthesis of 2-Amino-5-Carboxy Phenyl Thio Benzoate

Experimental: Ten ml. of dioxane are added to one gram of 6-carboxy isatoic anhydride in a 50 ml round bottom flask.

Five ml. of thio phenol and a chip of sodium hydroxide, as a catalyst for the reaction, are added and the mixture is refluxed for one-half hour. The solution is cooled and upon standing a jelly-like precipitate separates. To obtain a crystalline form the precipitate is recrystallized from methanol. The solution must be cooled slowly at room temperature, not in ice.

2-amino-5-carboxy phenyl thio benzoate is a yellow solid when recrystallized from methanol using decolorizing charcoal, and has a melting point of 257-8°C. The analysis for this compound is as follows: theoretical carbon 61.52%, hydrogen 4.06%; found carbon 61.37%, hydrogen 4.05%. Infra red spectrum: Exp. #548B (3) 4/16/64.

Synthesis of 2-Amino-5-Carboxy Benzamide

Experimental: One gram of 6-carboxy isatoic anhydride is mixed with 10 ml of water. Dropwise addition of a 50% solution of ammonium hydroxide in water produces an orange solution. This solution is heated and the evolution of carbon dioxide is noted. The solution is cooled and acidified with acetic acid. A light brown precipitate separates and is filtered and dried. This product is recrystallized from a 50% water-ethanol solution.

2-amino-5-carboxy benzamide when recrystallized with charcoal is an off-white powder which melts at 268-9°C. The analysis of this product is as follows: theoretical carbon 53.33%, hydrogen 4.44%; found carbon 53.22%, hydrogen

4.59%. Infra red spectrum: Exp. #548C (4) 4/15/64.

Synthesis of 2-Amino-5-Carboxy Benzanilide

Experimental: Ten ml of dioxane are added to one gram of 6-carboxy isatoic anhydride in a 50 ml round bottom flask. 0.9 ml of aniline, representing a two to one molar ratio of aniline to 6-carboxy isatoic anhydride, is added. The reaction mixture is refluxed for 3/4 hour. Upon evaporating a very small volume of the solvent, a yellow precipitate separates. This product is recrystallized from dioxane.

2-amino-5-carboxy benzanilide when recrystallized from dioxane using charcoal is an off-white powder which melts at 248-9°C. The analysis is as follows: theoretical carbon 65.63%, hydrogen 4.72%; found carbon 65.50%, hydrogen 4.90%. Infra red spectrum: Exp. #548D (2) 4/16/64.

Synthesis of 2-Amino-5-Carboxy Benzhydrazide

Experimental: One gram of 6-carboxy isatoic anhydride is suspended in 10 ml of water. A one to one solution of hydrazine in water is added dropwise until the solution is slightly basic. A considerable evolution of carbon dioxide is noted. When the mixture is heated, an orange solution is formed. During the fifteen minutes of heating, enough hydrazine solution is added to keep the reaction mixture basic. The solution is cooled and acidified with 30% acetic acid. A tan precipitate forms and is filtered. Methanol is used for recrystallization.

2-amino-5-carboxy benzhydrazide is a fluffy off-white solid when recrystallized using charcoal. It fuses at 278-9°C. The analysis is as follows: theoretical carbon 49.23%, hydrogen 4.65%; found carbon 49.20%, hydrogen 4.80%. Infra red spectrum: Exp. #548E (2) 4/16/64.

Synthesis of 2-Amino-5-Carboxy Methyl Benzoate

Experimental: One gram of crude 6-carboxy isatoic anhydride is suspended in 10 ml of methanol, and chip of sodium hydroxide is added as a catalyst. This mixture is refluxed for five hours. Most of the starting material goes into the yellow solution. The solution is gravity filtered and the filtrate is partially evaporated until a yellowish precipitate forms. The crude product is recrystallized from a 1-1 methanol-water solution.

Recrystallized 2-amino-5-carboxy methyl benzoate is a white, sweet-smelling solid which melts at 216-8°C. The analysis is as follows: theoretical carbon 55.38%, hydrogen 4.65%; found carbon 55.18%, hydrogen 4.53%. Infra red spectrum: Exp. #548A (3) 4/28/64.

Summary

1. 6-Carboxy isatoic anhydride is prepared by acetylation of 2,4 dimethyl aniline, oxidation of the methyl groups to form 4-acetamino isophthalic acid, hydrolysis of this to form 4-amino isophthalic acid, and subsequent ring closure with phosgene to form the desired product.

2. 6-Carboxy isatoic anhydride is attacked by common nucleophiles as is unsubstituted isatoic anhydride, but the 6-carboxy isatoic anhydride is less reactive than its unsubstituted parent.

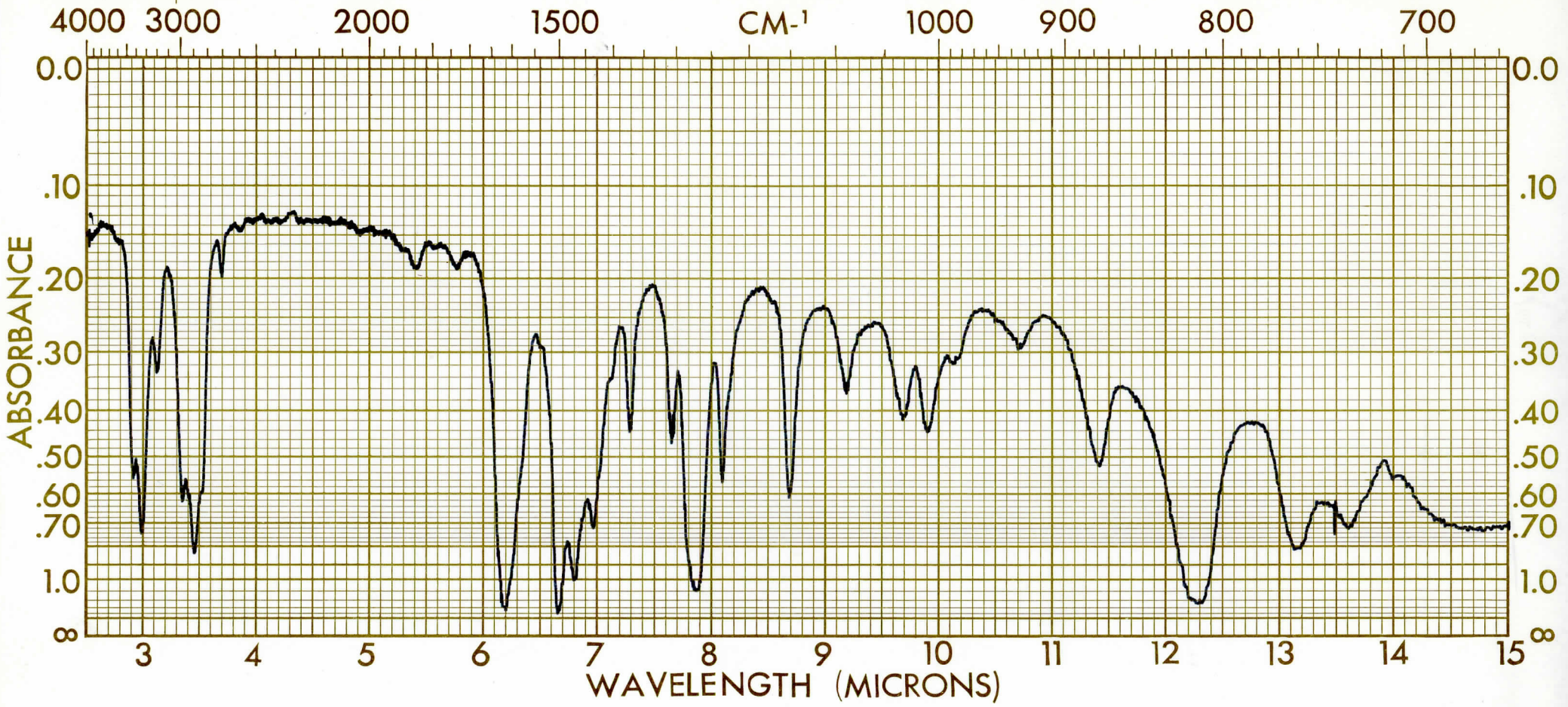
3. Five compounds of new composition are characterized.

Footnotes

1. Beilsteins Handbuch der Organische Chemie, XIV, 555.
2. Unpublished works of Calvin L. Moyer, Exp. #548, 4/22/63.
3. Roger P. Staiger and Emery B. Miller, Journal of Organic Chemistry, XXIV, 1214, (1959).
4. Bogert and Kropff, "On Some Amino and Nitroamino Derivatives of Benzoic, Metatoluic, and Metaphthalic Acids," Journal of the American Chemical Society, July, 1909, 841.
5. Heilbron, Dictionary of Organic Compounds, I, 101.
6. ibid.
7. Unpublished works of Roger P. Staiger, Exp. #487.
8. Moyer, op. cit.

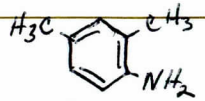
Acknowledgment

The author gratefully acknowledges the assistance of the entire Chemistry Department and especially of Dr. Staiger in the preparation of this paper.



SPECTRUM NO. #2

SAMPLE 2,4 Dimethyl Aniline



I

ORIGIN Exp #548 Step I

PURITY Distilled B.p. 203

PHASE Liquid

THICKNESS Demount. Cell

LEGEND

1.

2.

DATE 4-22-64

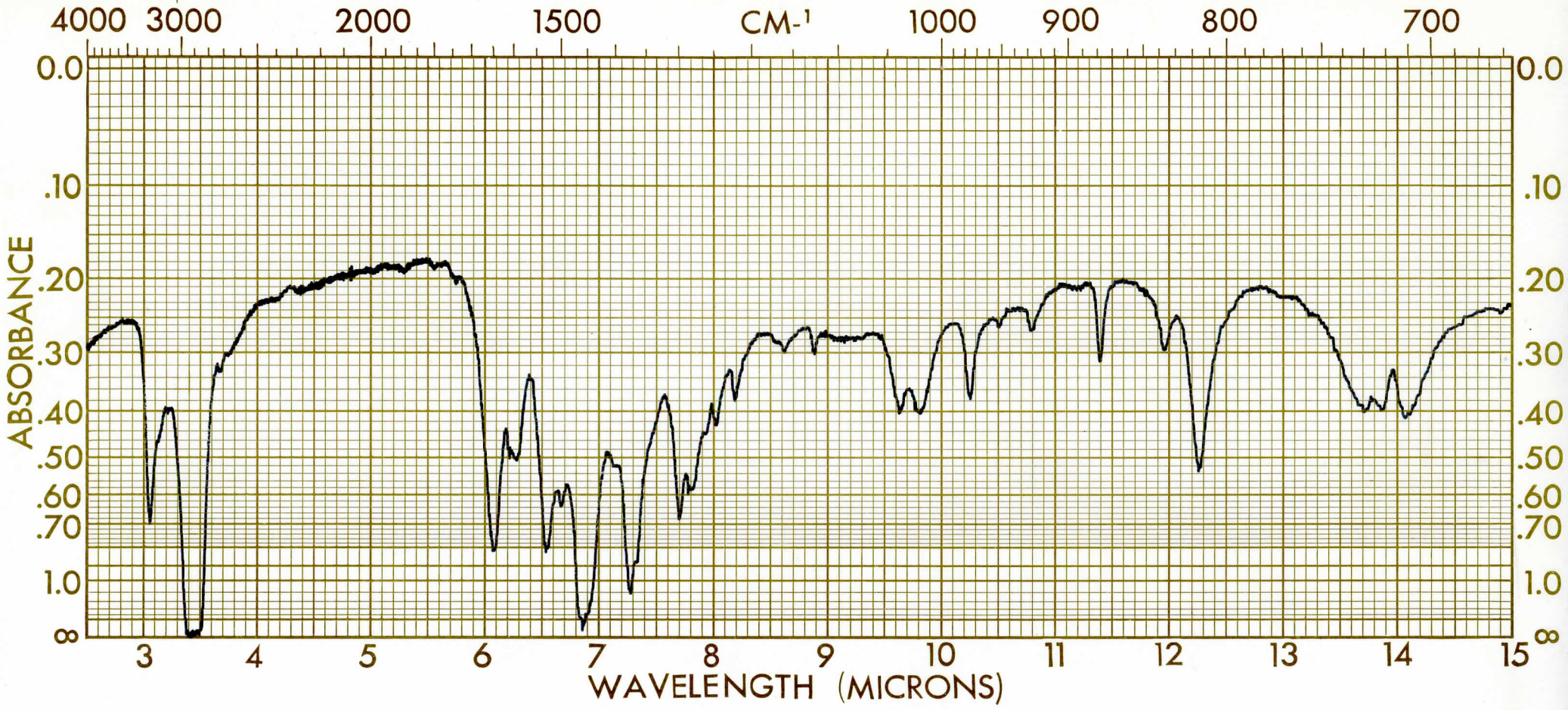
OPERATOR J.I.K.

REMARKS

Double peak at 2.8-3.0 is characteristic of the free amine functional group.

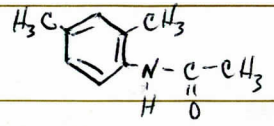
SPECTRUM NO.

SAMPLE



SPECTRUM NO. #2

SAMPLE 4-Acetamino m-Xylene



II

ORIGIN Exp #548 Step I

RX - MeOH

PURITY M.p. 122

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

DATE 4-22-64

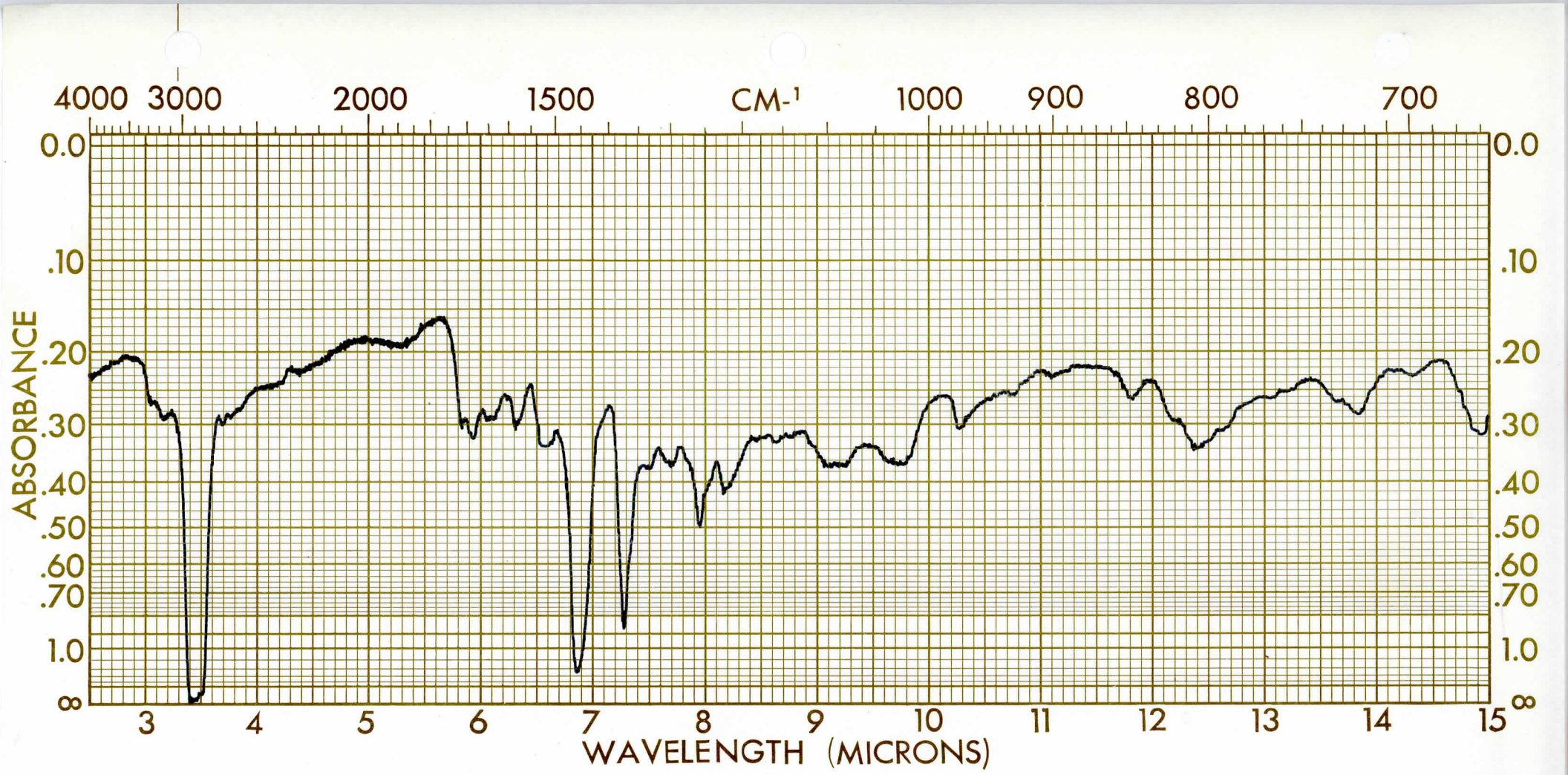
OPERATOR J.I.K.

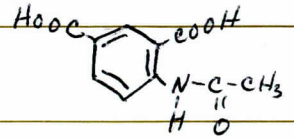
REMARKS

Disappearance of amine peak indicates amide formation.

SPECTRUM NO.

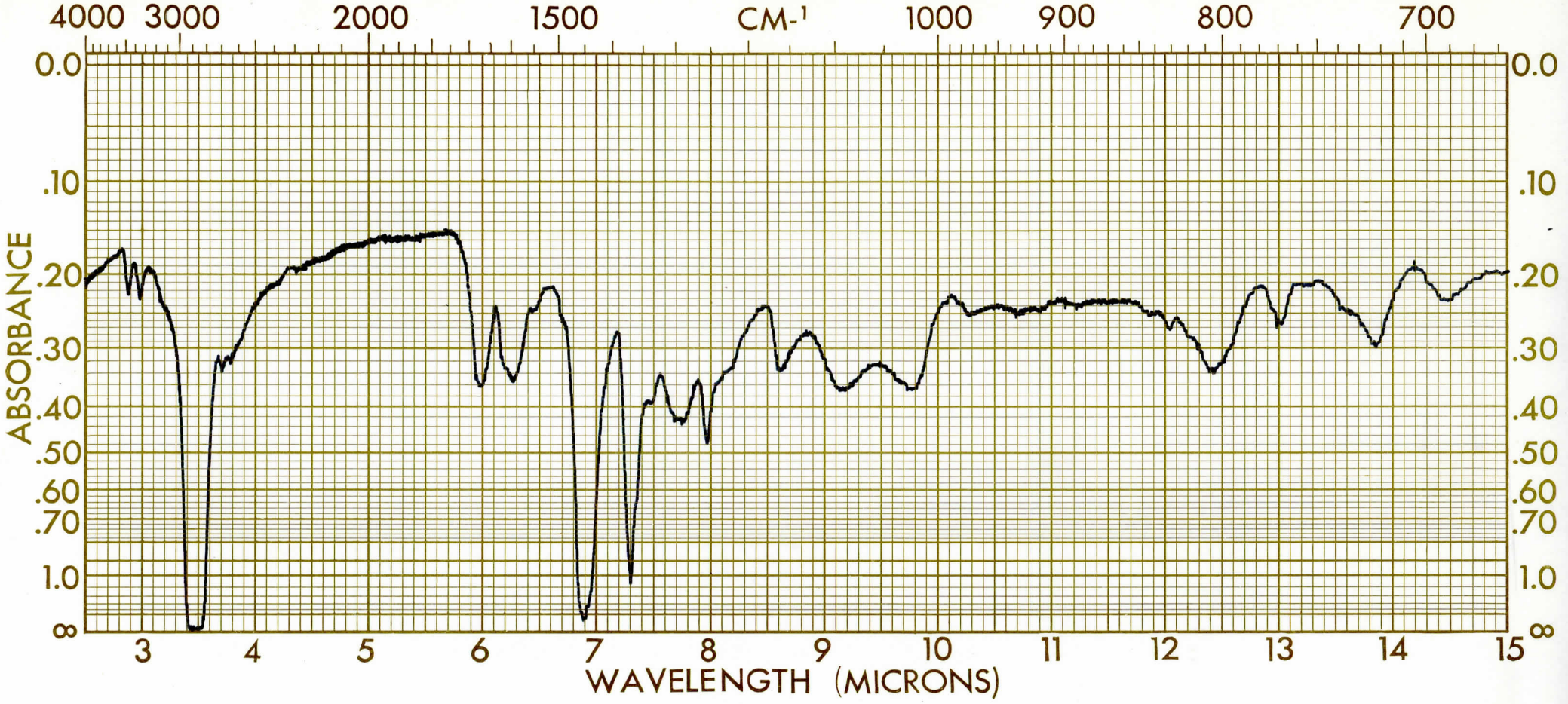
SAMPLE



SPECTRUM NO. #3	ORIGIN Exp. #548 Step I	LEGEND	REMARKS
SAMPLE 4- Acetamino Isophthalic Acid	RX - EtOH	1.	Amine peak obscured by acetyl group.
	PURITY M.p. - Decomposes	2.	
III	PHASE Nujol Mull	DATE 4-22-64	
	THICKNESS Demount. Cell	OPERATOR J.I.K.	

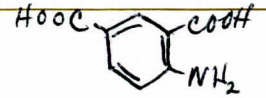
SPECTRUM NO. ____ SAMPLE ____

THE PERKIN-ELMER CORPORATION, NORWALK, CONN.



SPECTRUM NO. #3

SAMPLE 4-Amino Isophthalic Acid



IV

ORIGIN Exp #548 Step II

RX - EtOH

PURITY M.p - 335-6

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

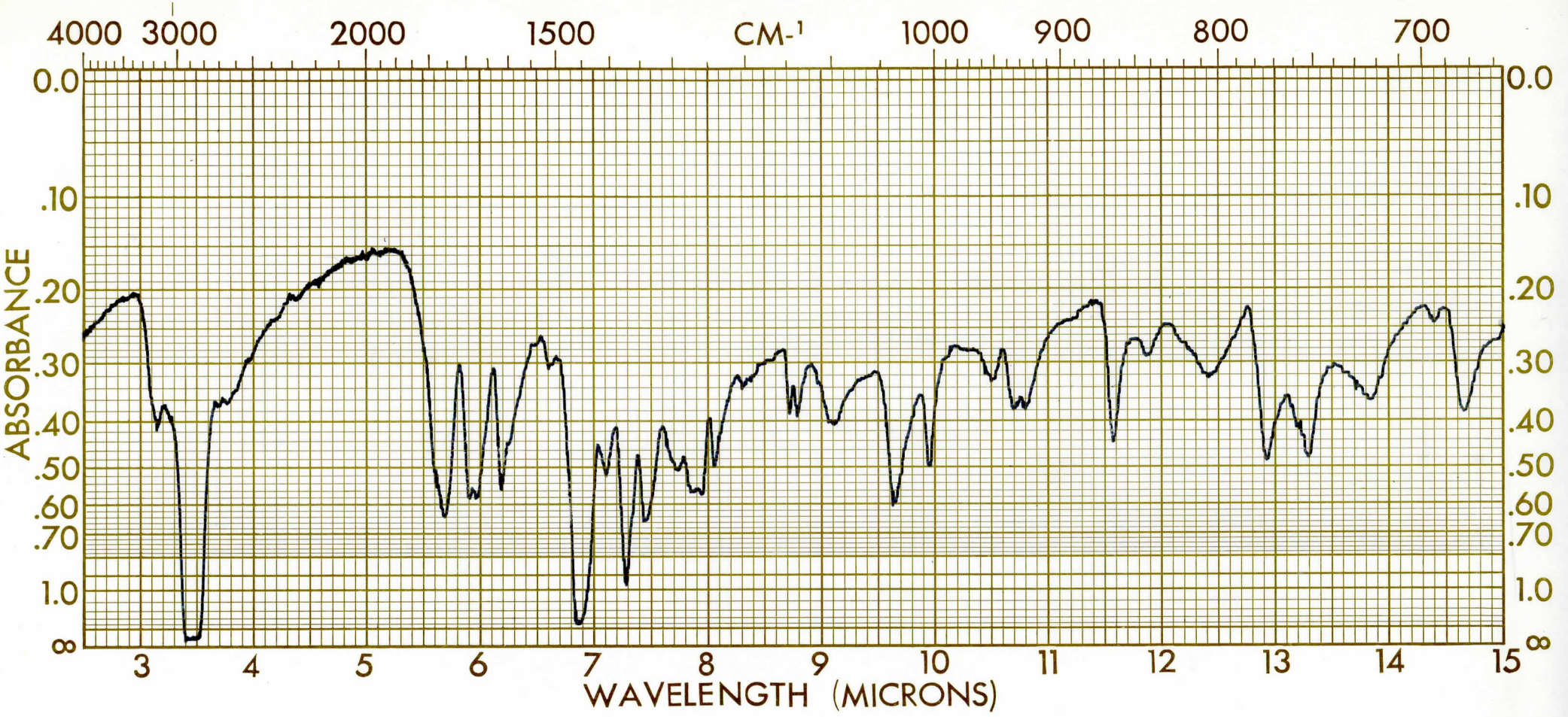
DATE 4-22-64

OPERATOR J.I.K.

REMARKS

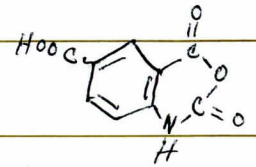
Double amine peak 2.9-3.0 indicates liberation of free amine.

SPECTRUM NO.
SAMPLE



SPECTRUM NO. #3

SAMPLE 6- Carboxy- Isatoic Anhydride



V

ORIGIN Exp #548 Step III

RX - 2X - Dioxane

PURITY White M.p. > 350

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

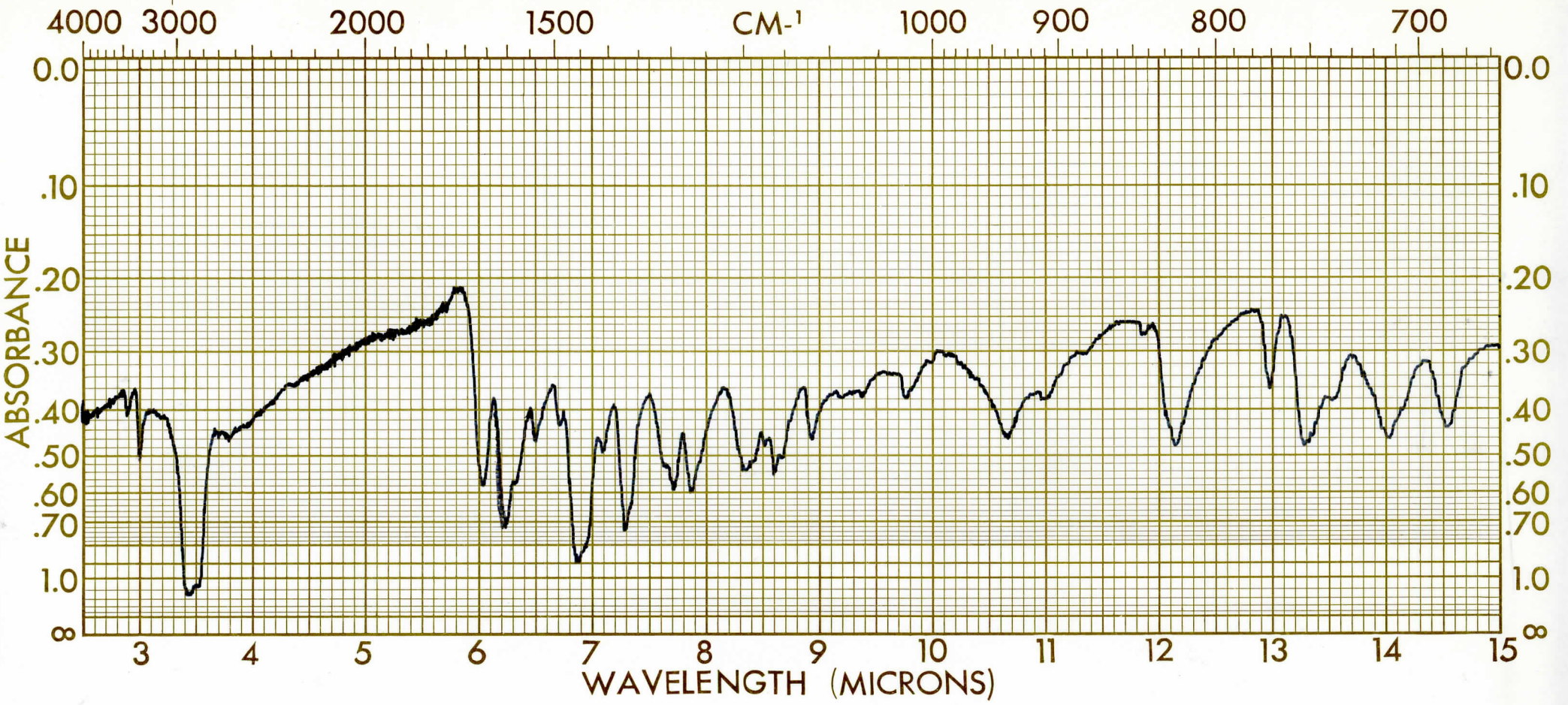
DATE 4-16-64

OPERATOR J. I. K.

REMARKS

Loss of the amine peak at 2.9 - 3.0 and appearance of strong C=O peak at 5.69 indicates desired compound.

SPECTRUM NO. SAMPLE



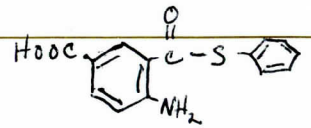
SPECTRUM NO. #3

ORIGIN Exp #548B

LEGEND

REMARKS Reappearance of free amine peak at 2.9-3.0 indicates ring cleavage.

SAMPLE 2-Amino-5-Carboxy Phenyl Thio Benzoate



PURITY RX -3X- MeOH Yellow M.p. 257-58

PHASE Nujol Mull

THICKNESS Demount. Cell

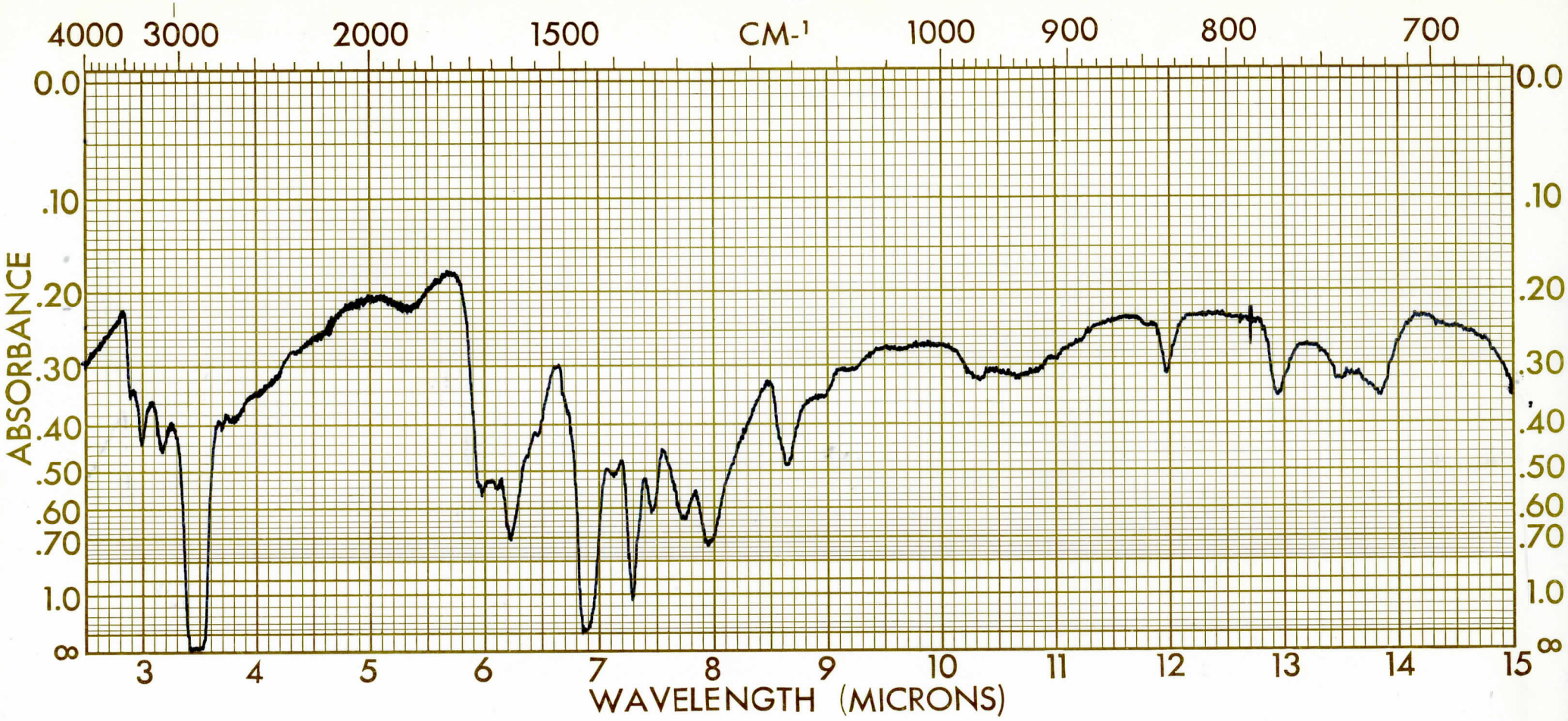
1.

2.

DATE 4-16-64

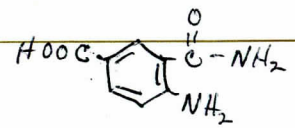
OPERATOR J.I.K.

SPECTRUM NO.
SAMPLE



SPECTRUM NO. #4

SAMPLE 2-Amino-5-Carboxy Benzamide



ORIGIN Exp. #548C

PURITY Rx - 3X - H_2O - EtOH off white M.p. 268-69

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

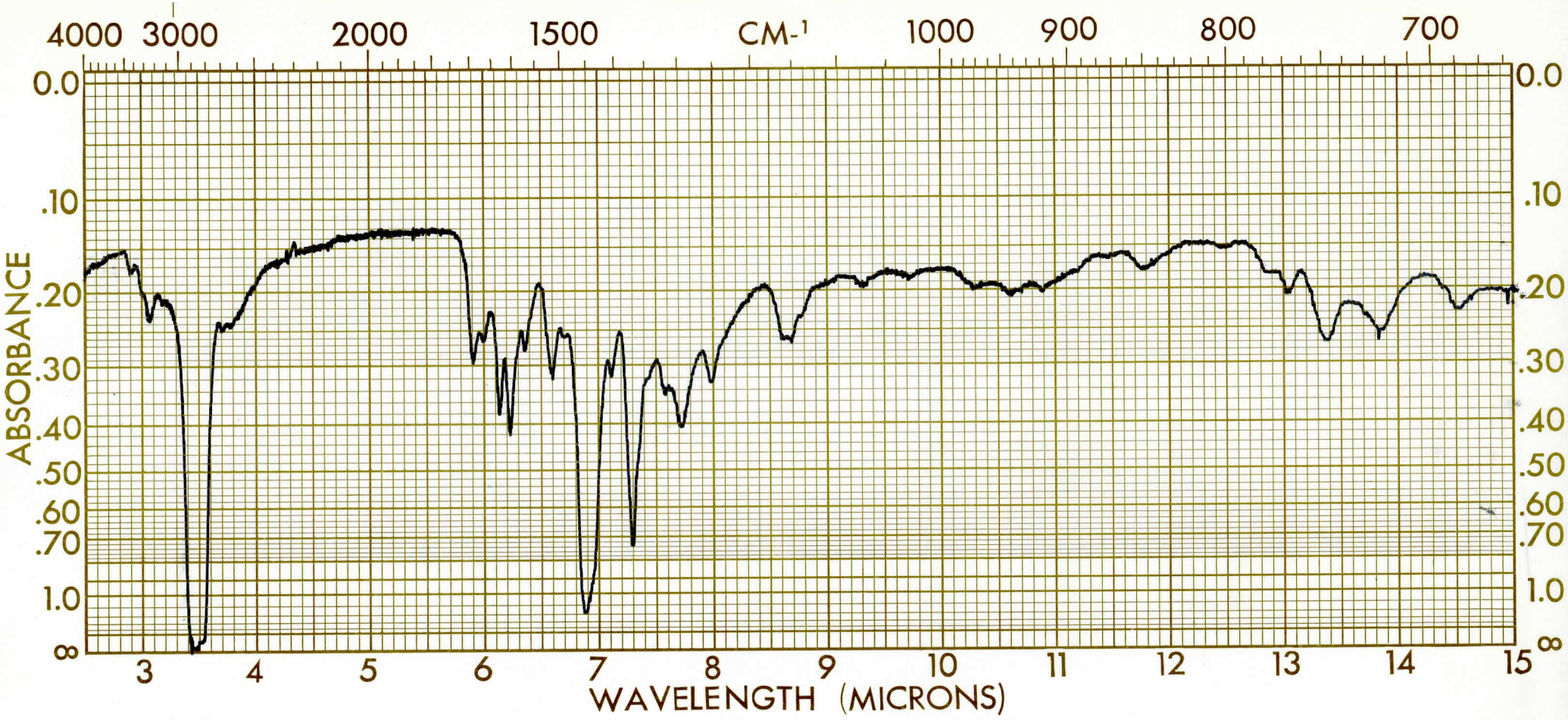
DATE 4-15-64

OPERATOR J.I.K.

REMARKS

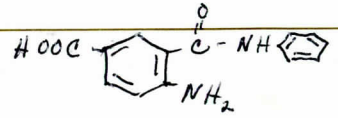
Reappearance of free amine peak at 2.9-3.0 indicates ring cleavage.

SPECTRUM NO. SAMPLE



SPECTRUM NO. # 2

SAMPLE 2-Amino-5-Carboxy Benzanilide



ORIGIN Exp. # 548D

PURITY RX - 3 X - MeOH Off white M.p 248-49

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

DATE 4-16-64

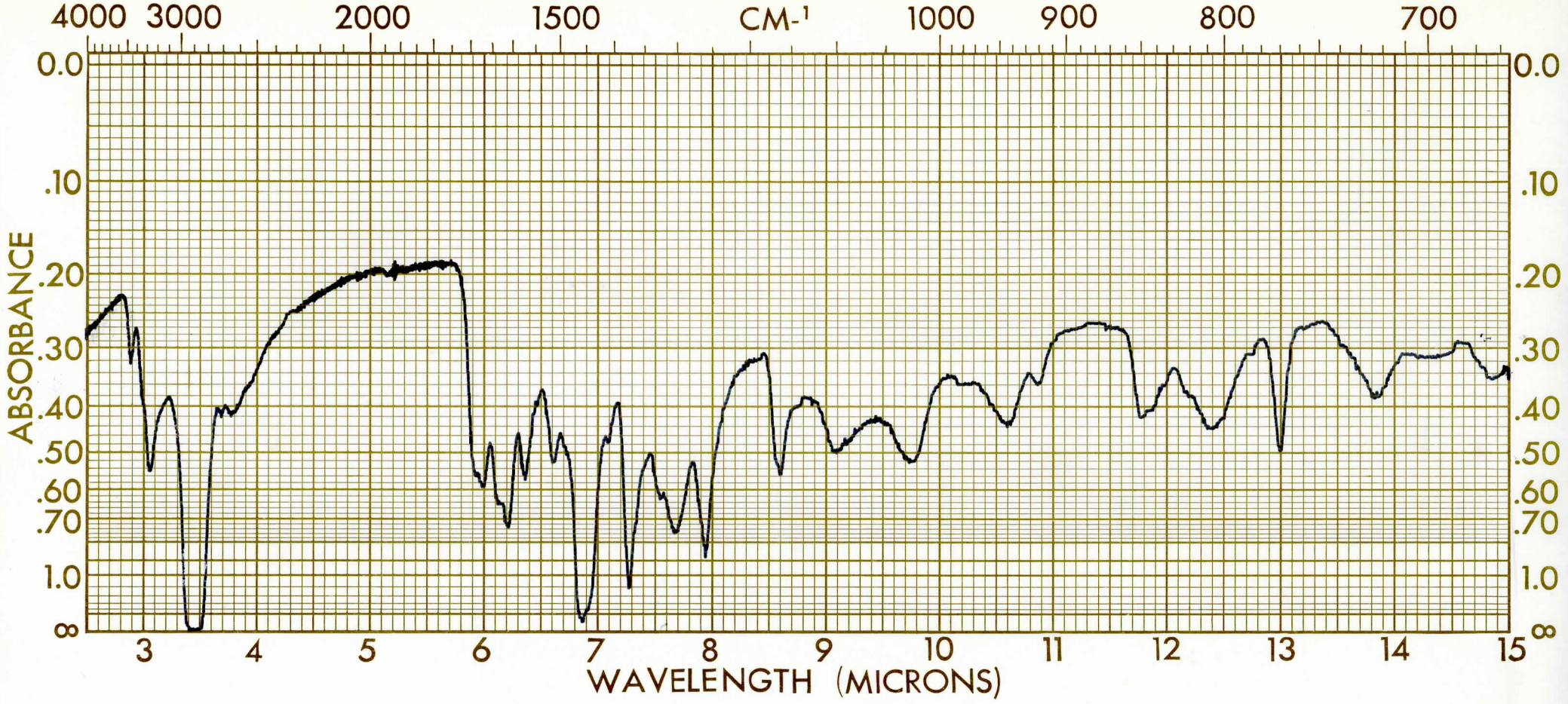
OPERATOR J.I.K.

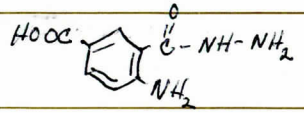
REMARKS

Reappearance of free amine peak at 2.9-3.0 indicates ring cleavage.

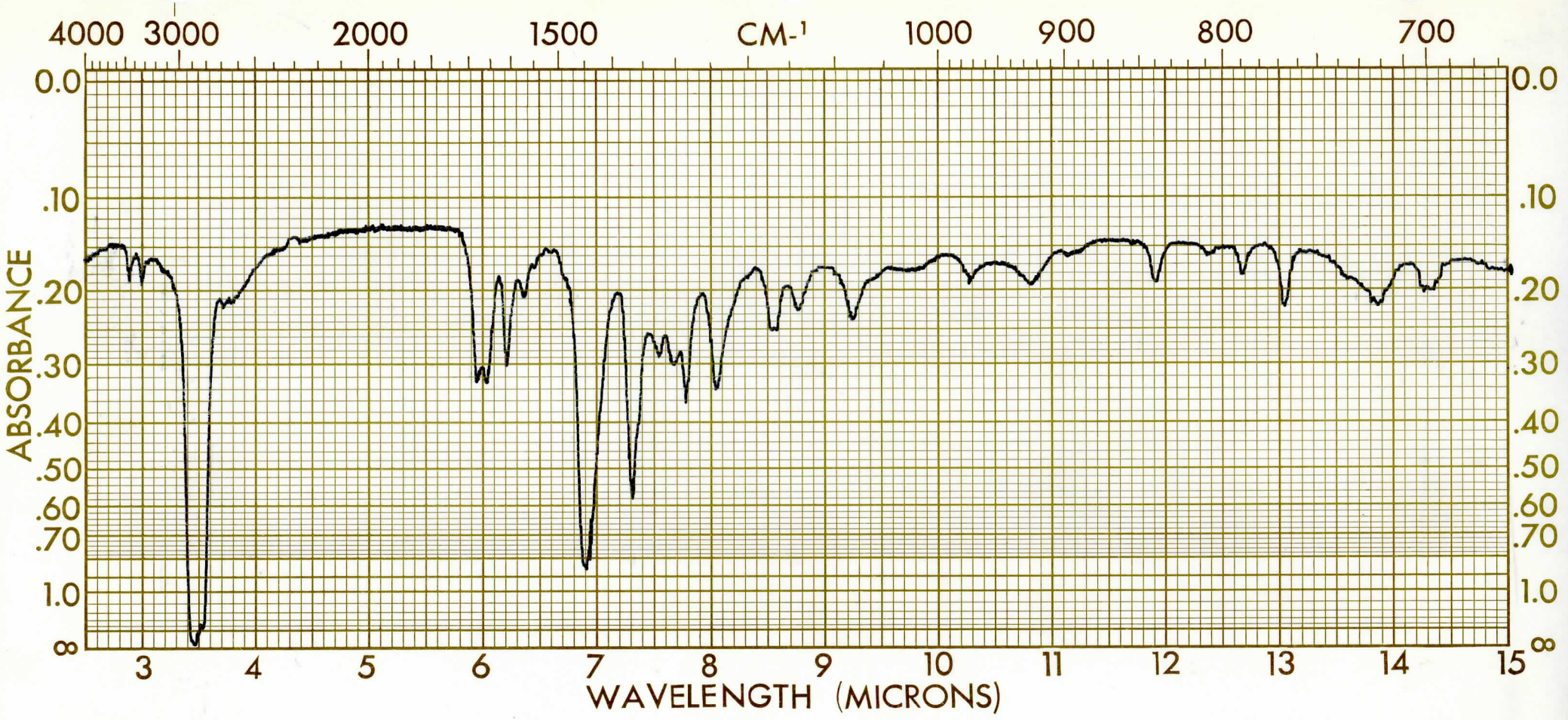
SPECTRUM NO.

SAMPLE



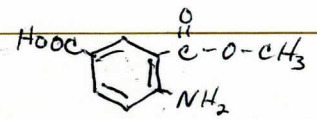
SPECTRUM NO. #2	ORIGIN Exp # 548E	LEGEND	REMARKS
SAMPLE 2-Amino-5-Carboxy Benzhydrazide		1.	Reappearance of free amine peak at 2.9-3.0 indicates ring cleavage.
	PURITY RX - 3X - MeOH Off-white Fuses 278-79	2.	
	PHASE Nujol Mull	DATE 4-16-64	
	THICKNESS Demount. Cell	OPERATOR J.I.K.	

SPECTRUM NO. ____ SAMPLE ____



SPECTRUM NO. # 3

SAMPLE 2-Amino-5-Carboxy Methyl Benzoate



ORIGIN Exp. #548A

PURITY RX -2X- 4,0- MeOH White M.p 216-8

PHASE Nujol Mull

THICKNESS Demount. Cell

LEGEND

1.

2.

DATE 4-28-64

OPERATOR J.I.K.

REMARKS

Reappearance of free amine peak at 2.9-3.0 indicates ring cleavage.

SPECTRUM NO. ____
SAMPLE ____

HARRY W. GALBRAITH, PH.D.
PRESIDENT

SIDNEY GAIL RAKES
VICE-PRESIDENT

VELMA M. RUSSELL
SEC.-TREASURER

GALBRAITH
Laboratories, Inc.

QUANTITATIVE ORGANIC MICROANALYSES

P. O. Box 4187 KNOXVILLE, TENNESSEE 37921 PHONE 525-0317
D. D. AREA CODE 615

Dr. Roger P. Staiger
Department of Chemistry
Pfahler Hall
Ursinus College
Collegeville, Pennsylvania

April 24, 1964

Received: April 22nd

Dear Dr. Staiger:

Analysis of your compounds gave the following results:

Your #,	My #,	% C,	% H,
548A	J-8082	31.21	2.60
548B	J-8083	61.37	4.05
548C	J-8084	53.22	4.59
548D	J-8085	65.50	4.90
548E	J-8086	49.20	4.80

This is confirming our telegram of April 24th.

Sincerely yours,

Harry W. Galbraith

Harry W. Galbraith

HWG:np

HARRY W. GALBRAITH, PH.D.
PRESIDENT

SIDNEY GAIL RAKES
VICE-PRESIDENT

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QUANTITATIVE ORGANIC MICROANALYSES

P. O. Box 4187 KNOXVILLE, TENNESSEE 37921 PHONE 525-0317
D. D. AREA CODE 615

Dr. Roger P. Staiger
Pfahler Hall
Ursinus College
Collegeville, Pennsylvania

May 6, 1964

Received: May 5th

Dear Dr. Staiger:

Analysis of your compound gave the following results:

Your #,	My #,	% C,	% H,
548A-2	J-8744	55.18	4.53

Sincerely yours,

Harry W. Galbraith

Harry W. Galbraith

HWG:kj