PREPARATION AND SPECTRA OF m-NITROBENZOATES AND m-AMINOBENZOATES

BY

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ACKNOWLEDGMENT

The author wishes to express his gratitude to Dr. Saul I. Kreps for his counsel and guidance throughout this investigation and for suggesting the problem. He is also grateful to Van Dyk & Company, Inc. who generously supplied the raw materials for this study.

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ABSTRACT

A study of the synthesis of a series of new m-nitrobenzoates, m-aminobenzoates and several derivatives of the latter is presented.

Physical constants and analytical determinations are presented, including the ultraviolet absorption spectra of the compounds prepared.

STATEMENT OF PROBLEM

The purpose of this study was to prepare a series of m-nitro and m-aminobenzoates and their derivatives, and to determine the changes in the ultraviolet absorbtion spectra with changes in molecular structure.

INTRODUCTION

Derivatives of both ortho and para aminobenzoic acids have found use as ultraviolet-absorbing screens, in cosmetics, lacquers and films. Little is known, however, of the corresponding meta aminobenzoates, although these compounds may be prepared rather readily from the corresponding esters of benzoic acid.

This study was undertaken, therefore, to develop practicable methods of synthesis and to determine the ultraviolet absorbing characteristics of a series of m-aminobenzoate esters.

I. m-Nitrobenzoate esters

The literature showed that there are numerous methods of preparing the methyl and ethyl esters of meta-nitrobenzoic acid. The esters have been prepared by the direct esterification of meta-nitrobenzoic acid using gaseous hydrogen chloride as catalyst (1); esterification by the azeotropic method with a sulfuric acid catalyst (2, 3); treatment of ω-trichloro-m-nitroacetophenone with methanol and sodium methoxide (4); esterification by refluxing alcohols with meta-nitrobenzoyl chloride (5); nitration by means of fuming nitric acid to the benzoates (6), and the use of the more satisfactory nitration mixture of concentrated sulfuric acid and concentrated nitric acid (7).

The yields obtained from these various methods ranged from 70 to 90 per cent of theoretical.

II. m-Aminobenzoate esters

The methyl and ethyl esters of meta-aminobenzoic acid have been prepared by esterification (8, 9, 10, 11, 12); and by the reduction of the esters of meta-nitrobenzoic acid with ammonium sulfide (13, 14), electrolytically (15, 16, 17, 18), and with tin and alcoholic hydrochloric acid (19). Although the reducing agent used commercially is generally iron and water in the presence of a little acid (20, 21) the catalytic reduction is by far the most convenient for the laboratory.

There was no detailed information available in the literature pertaining to the derivatives of ethyl-m-aminobenzoates (22, 23, 24); however, most of the methods used to prepare the derivatives of aniline were found applicable to ethyl-m-aminobenzoate (25).

EXPERIMENTAL

The following standard abbreviations are to be found in this section:

b ----------- cell thickness

B.P. ----------- boiling point

c ----------- concentration

cc. ----------- cubic centimeters

ϵ ----------- molar extinction coefficient

$E^{1\%}_{1cm.}$ ----------- specific extinction coefficient

gm. ----------- grams

m.p. ----------- melting point

mm. ----------- millimeters

mμ ----------- millimicrons, wavelength

O.D. ----------- optical density

$n_D^{x°}$ ----------- refractive index at x°

S.G.x°/y° ----------- specific gravity, density of liquid at x° compared to density of water at y°

%T ----------- per cent transmission

The grade of reagent is indicated in the procedure for each compound. Distilled water was used whenever the use of water was required. All temperatures given in this work are in degrees Centigrade.

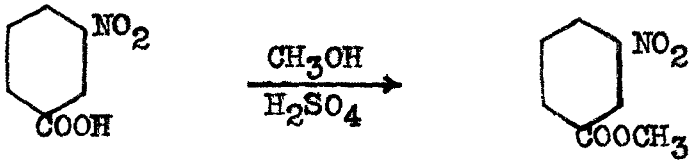
Analytical procedures

For carbon and hydrogen ------------ Pregl method
For nitrogen ------------ Dumas method
For chlorides ------------ Carius method
For melting points ------------ capillary method
For boiling points ------------ micro-boiling point tube method

The micro-quantities used for the carbon, hydrogen and nitrogen determinations were 3 to 5 milligrams; 6 to 10 milligrams of sample were used for the chloride determinations.

EXPERIMENTAL PROCEDURE

I. Methyl-m-Nitrobenzoate



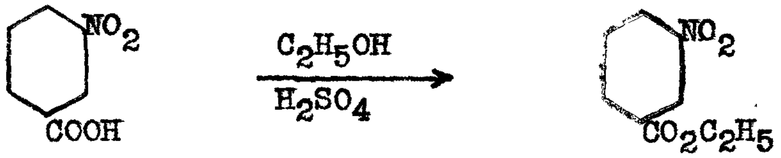
To a 500-cc. three-necked, round-bottomed flask fitted with a condenser, thermometer and addition funnel were added 160 cc. (5.0 mole) of A.C.S. absolute methanol and 167.0 gm. (1.0 mole) of recrystallized, technical grade, m-nitrobenzoic acid (m.p. 141°). By means of the addition funnel, 16.0 cc. of concentrated sulfuric acid (S.G. $\frac{18^\circ}{4^\circ}$ = 1.84) was added slowly over a 10-minute period. The mixture was refluxed for one hour.

The rate of esterification was established by taking a one milliliter aliquot sample from the esterification mixture, at fifteen minute intervals, and titrating the samples with $N/_{10}$ sodium hydroxide. This procedure was continued until two successive samples showed the same titration, indicating that the meta-nitrobenzoic acid was no longer being esterified.

After the esterification was complete, the excess methanol was distilled off and the residue was drowned in two volumes of cracked ice and water. The precipitate was filtered, slurried in water, and 10% sodium bicarbonate solution was added until the slurry was slightly alkaline to litmus paper. The slurry was filtered, washed free of alkali with water, and dried at 40-60°. The crude methyl-m-nitrobenzoate was dissolved in excess methanol; 15.0 gm. of activated carbon, (Darco G-60) was added and the mixture was refluxed for one-half hour. The activated carbon was then filtered, and the filtrate was concentrated to the first sign of crystals and cooled to room temperature. Particularly good crystals were obtained by reheating the filtrate and allowing it to cool slowly without disturbance.

The yield of the crude product, m.p. 76-77.9°, was 160.0 gm. (88.3%); two recrystallizations afforded pure material, m.p. 78.5-79.0°, in yield of 143.6 gm. (79.2%).

II. Ethyl-m-Nitrobenzoate

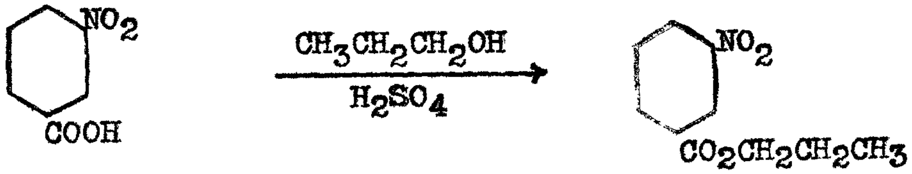


In a 500-cc. three-necked, round-bottomed flask fitted with a Dean-Stark moisture trap, thermometer and addition funnel were added 230.0 cc. (4.98 mole) of 95% ethyl alcohol, 100.0 cc. of A.C.S. benzene and 76.0 gm. (0.45 mole) of recrystallized, technical grade, meta nitrobenzoic acid. By means of the addition funnel, 23.0 cc. of concentrated sulfuric acid was added slowly over a ten-minute period. The mixture was refluxed for an hour and one-half, and the water produced during the esterification was collected in the moisture trap. After the esterification was complete, the excess ethanol was distilled and the residue was thrown into two volumes of cracked ice and water. The precipitate was filtered and slurried in water; 700.0 cc. of 10% sodium bicarbonate solution was added slowly to neutralize the sulfuric acid and any unreacted m-nitrobenzoic acid. The neutralized slurry was filtered, washed with water and air dried.

The crude ethyl-m-nitrobenzoate was dissolved in excess ethanol, 5.0 gm. of activated carbon, was added and the mixture was refluxed for one-half hour. The activated carbon was filtered and the filtrate was concentrated to the first sign of crystals. Particulary good crystals were obtained by reheating the filtrate and allowing it to cool slowly and without disturbance.

The yield of the crude product, m.p. 43.2-46.7° was 80.0 gm. (91.2%); recrystallization afforded pure material, m.p. 47°, in yield of 75.1 gm. (87.6%).

III. n-Propyl-m-Nitrobenzoate



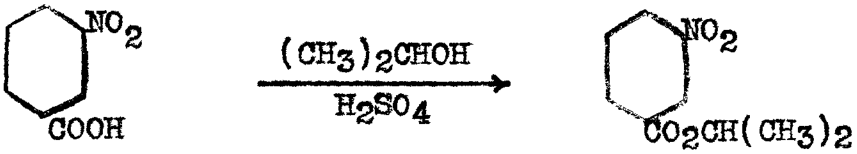
One hundred gm. (0.59 mole) of m-nitrobenzoic acid, 250 cc. (4.1 mole) of U.S.P. n-propanol and 100 cc. of A.C.S. benzene and 25 cc. of sulfuric acid were used in this preparation. The method was similar to that used in the preparation of the ethyl ester (II). After the esterification was complete, the excess propanol was distilled, the residue was cooled to room temperature and extracted with U.S.P. (Merck) ether. The extracts were washed acid and alcohol-free with water, and finally with 10% sodium bicarbonate solution to remove the last traces of sulfuric acid and unreacted m-nitrobenzoic acid. The ether was removed by heating the extracts on a steam bath and the residue was dried over A.C.S. anhydrous potassium carbonate.

Purification of propyl-m-nitrobenzoate was carried out by vacuum distillation using an air condenser and cooling the receiving flask with an ice-water bath. The distillate had a straw-yellow color, and further purification by vacuum distillation, followed by two decolorizations, using activated carbon, did not reduce the color.

The yield of the crude product was 99.5 gm. (80.6%); further purification by distillation afforded pure material, B.P. 194-195°/1mm., $n_D^{25°} = 1.5212$, in yield of 93.9 gm. (76.0%). A micro-boiling point determination, at atmospheric pressure, was made on the pure compound, which was found to be 247° (with decomposition). Calculated for $C_{10}H_{11}O_4N$:

	Theoretical	Actual
C	57.40	57.12
H	5.30	5.27
N	6.69	6.67

IV. Isopropyl-m-Nitrobenzoate



One hundred grams (0.59 mole) of recrystallized, technical grade, m-nitrobenzoic acid, 250 cc. (4.1 mole) of U.S.P. isopropanol, 100 cc. of A.C.S. benzene, and 25 cc. of sulfuric acid were used to prepare this ester. The method was identical with that for n-propyl-m-nitrobenzoate (III). The crude ester distilled at 215-218°/23mm. and solidified upon cooling in the receiving flask.

The dried ester was dissolved in excess isopropanol and 10.0 gm. of activated carbon was added to the solution; the resulting mixture was refluxed for one-half an hour on a steam bath. The decolorized mixture was filtered to remove the activated carbon and the filtrate was concentrated to the first sign of crystals. Particularly good crystals were obtained by reheating the filtrate and allowing it to cool slowly and without disturbanse.

The yield of the crude product, m.p. 137.2-141.9°, was 91.0 gm. (73.5%); one crystallization afforded pure material, m.p. 141.4-142.9°, in yield of 61.8 gm. (50%).

Calculated for $C_{10}H_{11}O_4N$:

	Theoretical	Actual
C	57.40	57.22
H	5.30	5.18
N	6.69	6.73

TABLE I

PREPARATION OF m-NITROBENZOATES

Run No.	Ester	m-Nitro-benzoic Acid	ROH	Time	Yield
I	Methyl	1.0 mole	5.0 mole	1 hr.	79.2%
II	Ethyl	0.45 "	4.98 "	1½ hrs.	81.7%
III	n-Propyl	0.59 "	4.1 "	2¼ "	76.0%
IV	Isopropyl	0.59 "	4.1 "	5 "	50.0%

TABLE I

(con't)

PREPARATION OF m-NITROBENZOATES

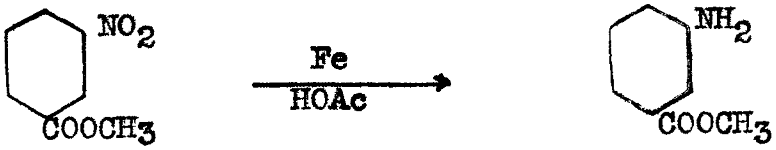
			Physical Constants			Analysis	
Run No.	Ester		Found	Literature		Calc.	Found
I	Methyl	m.p.	78.5-79°	(78-79°) (26)**			
		m.p.		(78.5°) (27)			
II	Ethyl	m.p.	47°	(47°) (26,27)			
III	n-Propyl	B.P.	194-195/1mm.		C	57.40	57.12
		B.P.	*247° (Dec.)		H	5.30	5.27
		$n_D^{25°}$	1.5212		N	6.69	6.67
		S.G. $\frac{25}{25}$	1.191				
IV	Isopropyl	m.p.	141.4-142.9°		C	57.40	57.22
		B.P.	215-218/23mm.		H	5.30	5.18
					N	6.69	6.73

* micro-boiling point at atmospheric pressure

** literature references

V. Reduction of m-Nitrobenzoates using Iron and Acetic Acid Catalyst

Va. Methyl ester



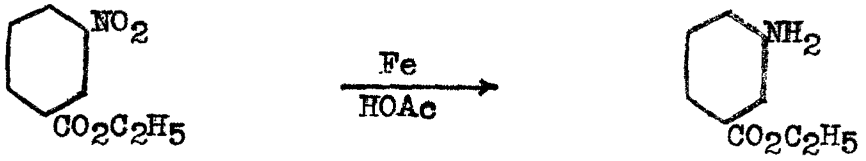
Into a 250 cc. flask fitted with a Hershberg stirrer with a mercury seal (28) and an efficient reflux condenser were placed 40.0 cc. of water, 8.0 cc. of acetic acid and 46.0 gm. (0.26 mole) of methyl-m-nitrobenzoate (I). The mixture was stirred and heated to 75°. Iron powder, 45.0 gm. (0.81 mole) was then added in ten equal parts at intervals of 5 minutes at a rate sufficient to keep the mixture boiling vigorously. After the last addition of iron powder, the reaction mixture was allowed to reflux for an additional hour.

A test for the completion of reduction was then made by putting a drop of the liquid on a piece of filter paper, (the wet ring should be nearly colorless if the reduction is complete). A brownish ring appeared indicating the presence of hydrazo and nitroso compounds. The reduction was continued by refluxing the reaction mixture an additional three hours. The reduced mixture was cooled to 30° and 10.0 gm. of C.P. anhydrous sodium carbonate was added slowly. The alkaline mixture was then poured into a 500 cc. beaker and the flask was rinsed well with 100 cc. of warm toluene. The rinses were added to the beaker and stirred over a steam bath for half an hour in order to extract the amino ester from the iron oxide residues. The mixture was then allowed to settle for 15 minutes, and the toluene was decanted through a large fluted filter paper. The filtrate was cooled in an ice-water bath to crystallize the material which was oily. The extraction was repeated, using methanol, until no more amino ester remained after taking the extracts to dryness.

The amino ester was purified by dissolving it in dry ethyl ether and precipitating the salt by bubbling dry hydrogen chloride gas through the solution. The salt was filtered, and the filter cake washed with cold ether until the washings were colorless. The hydrochloride was dissolved in water and the free amine was precipitated by adding excess sodium carbonate solution (10%). Oily droplets resulted after the sodium carbonate addition. The amine was extracted from the water using ethyl ether, and the resulting ethereal solution was dried over anhydrous sodium sulfate. The ether was evaporated off on a steam bath and the amino ester was placed in an air dryer for two days.

The yield of the crude product was 27.2 gm. (69.2%), purification of the amine by means of hydrogen chloride afforded pure material, m.p. 37.9-38.9° in yield of 23.8 gm. (60.7%).

Vb. Ethyl ester



The reduction of ethyl-m-nitrobenzoate using acetic acid and iron as catalyst was carried out in the same manner as the reduction of methyl-m-nitrobenzoate (Va). The amounts of ester (II), water, iron and acetic acid used were: 50.0 gm. (0.26 mole), 40.0 cc., 45.0 gm. (0.81 mole) and 8.0 cc. respectively. The time required for the reduction was approximately 5 hours. The reduced product was transferred into a 800 cc. beaker after making it alkaline with sodium carbonate. Warm methanol was added to the reaction flask as a rinse. The rinses were then added to the beaker and stirred over a steam bath for half an hour in order to extract the amino ester from the iron oxide residues. The sludge was allowed to settle for 15 minutes, and then decanted through a large fluted filter paper. The filtrate was concentrated to dryness, and the extraction was repeated until no more amino ester remained after concentrating the extracts to dryness.

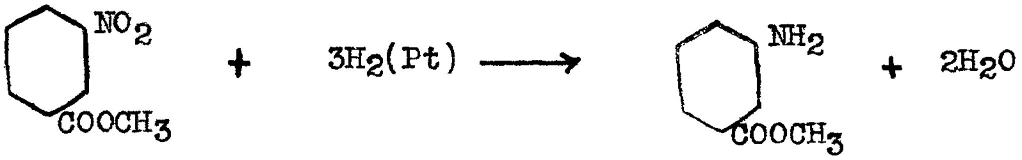
The oily amino ester was purified by dissolving it in dry ethyl ether and precipitating the salt by bubbling dry hydrogen chloride gas through the solution. The salt was filtered and washed with cold portions of ether until the washings were colorless. The hydrochloride was dissolved in water and the free amine was precipitated by adding excess 10% sodium carbonate solution. The liquid amine was then extracted with ether and dried over anhydrous potassium carbonate. The dried ethereal solution was vacuum distilled and the distillate was collected at 156°/10mm. The yield was 29.6 gm. (68.9%).

Purification of the crude amine, by means of hydrogen chloride salt formation and vacuum distillation afforded pure material, B.P. 156°/10mm., in yield of 25.2 gm., (58.6%).

Vc. Ethyl ester

The reduction was repeated a second time to observe the effect of the reverse addition of the reagents: addition of the nitro compound to the reducing mixture. This reverse addition resulted in a slight improvement in yield (62.1%) of pure amine, and an increased rate of reduction (approximately 3 hours).

VI. Reduction of Methyl-m-Nitrobenzoate Using Platinum Oxide Catalyst



A mixture of 18.1 gm. (0.1 mole) of methyl-m-nitrobenzoate (I), 150 cc. of 95% ethyl alcohol and 0.2 gm. of (Baker Platinum) platinum oxide catalyst, suspended in 5.0 cc. of water were charged into a Parr hydrogenation bomb. The air was evacuated from the bomb and the mixture was agitated under a hydrogen pressure of 60 lbs. until the uptake of hydrogen ceased, (about 8 minutes). The temperature ranged from 30 to 35° and the hydrogen uptake was 0.32 moles. The catalyst was removed by filtration and the solvent was evaporated. The residue was dissolved in ether, and the resulting solution was dried over C.P. anhydrous sodium sulfate.

Distillation of the ethereal solution gave a 98.2% yield of the crude methyl-m-aminobenzoate boiling at 152-153°/11mm. The liquid amine crystallized upon cooling for 48 hours in a -20° refrigerator. The oily, reddish, crystals were dissolved in excess ethanol, and five grams of activated carbon was added, and the mixture was refluxed for one hour over a steam bath. The mixture was filtered and the straw-colored filtrate was concentrated until most of the ethanol was removed.

The liquid amine was kept in a -20° refrigerator for three days. The frozen crystals were removed from the refrigerator and placed in an air dryer for two days in order to remove any remaining traces of alcohol.

The yield of the crude product, B.P. 152-153°/11mm., was 14.8 gm. (98.2%); crystallization afforded pure material, m.p. 38.3-39.3°, in yield of 14.6 gm. (96.6%).

VII. Reduction of Ethyl-m-Nitrobenzoate using Platinum Oxide Catalyst

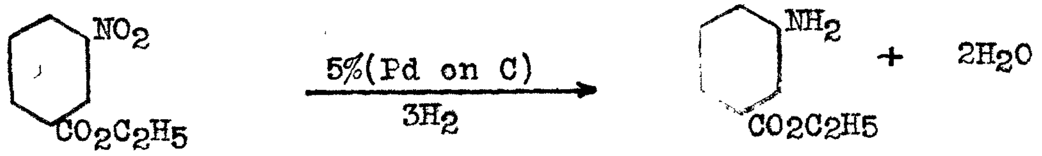
Ethyl-m-aminobenzoate was prepared by the reduction of the corresponding nitro compound, ethyl-m-nitrobenzoate (II). The reduction procedure used was the one already described for compound VI. The amounts used were 19.5 gm. (0.1 mole) of nitro compound, 150 cc. of 95% ethyl alcohol and 0.2 gm. of platinum oxide. The amine boiling at 156°/10mm., was golden-red in color and did not solidify upon cooling.

The yield of the crude amine was 15.9 gm. (96.1%); vacuum distillation afforded pure material, B.P. 156°/10mm., in yield of 15.5 gm. (93.8%). A micro-boiling point determination, at atmospheric pressure, was made on the pure compound and the boiling point was 294° (with decomposition). The refractive index $n_D^{26°}$ = 1.5540, S.G. $\frac{26°}{26°}$ = 1.1310.

VIIa & VIIb. Ethyl ester

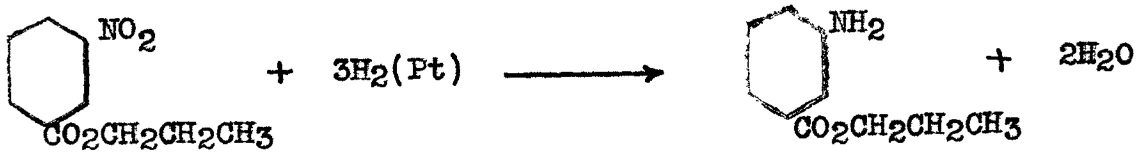
The reduction of ethyl-m-nitrobenzoate was twice repeated (Runs VIIa and VIIb) in order to obtain enough ethyl-m-aminobenzoate for the preparation of the acetamide, benzamide and hydrochloride derivatives.

VIII. Reduction of Ethyl-m-Nitrobenzoate using 5% Palladium on Carbon Catalyst



Ethyl-m-Nitrobenzoate was reduced, isolated and purified as described in Run VI, except that Baker Platinum Co., 5% Palladium on Carbon was used in place of platinum oxide. The yield of the pure compound was 92.8% and the time required to run the reduction was 25 minutes.

IX. Reduction of n-Propyl-m-Nitrobenzoate Using Platinum Oxide Catalyst



The reduction of 20.9 gm. (0.1 mole) of n-propyl-m-nitrobenzoate (III) using 150 cc. of 95% ethyl alcohol and 0.2 gm. (Baker Platinum Co.) platinum oxide was carried out as described for Run VII. The time required for the hydrogen absorption was 15 minutes. The reduced n-propyl-m-aminobenzoate was isolated by filtration of the platinum and evaporation of the ethanol. The residue was dissolved in ether and dry hydrogen chloride gas was bubbled into the ethereal solution. The flocculent precipitate was filtered and washed with several portions of cold ether.

The free base was obtained by treatment of the salt with 10% aqueous sodium carbonate and extraction with ether. The solvent was evaporated and the residue was dried over anhydrous sodium sulfate. The yield of the liquid amine was 17.2 gm. (95.5%). A micro-boiling point determination was made on the pure compound at atmospheric pressure.

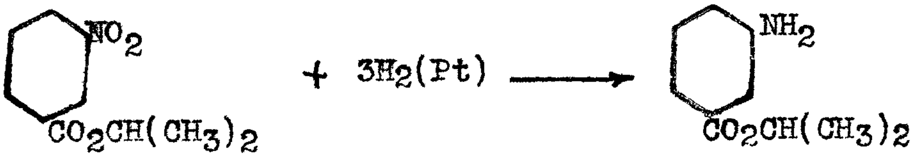
and the B.P. was found to be 283° (Dec.). The refractive index and specific gravity were also determined:

$n_D^{25°} = 1.5467$, S.G. $\frac{25°}{25°} = 1.1029$.

An analysis of the compound showed:

	Calculated	Found
C	67.10	67.23
H	7.30	7.27
N	7.80	7.78

X. Reduction of Isopropyl-m-Nitrobenzoate Using Platinum Oxide Catalyst



One-tenth mole (20.9 gm.) of isopropyl-m-nitrobenzoate (IV), 150 cc. of 95% ethyl alcohol and 0.2 gm. of platinum oxide catalyst were used. The catalyst was filtered and the solvent was evaporated on a steam bath. The organic residue was taken up in ether, dried over sodium sulfate and evaporated on a steam bath. The solid isopropyl-m-aminobenzoate residue was dissolved in excess ethanol and decolorized by adding 5.0 gm. of activated carbon, and refluxing on a steam bath for one-half hour; and then concentrated to the first sign of crystals. The filtrate was reheated and allowed to cool slowly without disturbance.

The yield of the crude product, m.p. 173.1-176.2°, was 17.4 gm. (96.7%), crystallization afforded pure material, m.p. 176-177°, a yield of 16.2 gm. (90.5%).

TABLE II

REDUCTION OF m-NITROBENZOATES

	Ester		Catalyst			
Run No.	Radical	Amount (Mole)	Type	Amount	Time	Yield
Va	Methyl	0.26	Fe-HOAc	0.81 (Mole) Fe	5 hrs.	60.7%
Vb	Ethyl	0.26	Fe-HOAc	0.81 (Mole) Fe	5 hrs.	58.6%
Vc	*Ethyl	0.26	*Fe-HOAc	0.81 (Mole) Fe	3 hrs.	62.1%
VI	Methyl	0.10	Pt.	0.20 gm.	8 min.	96.6%
VII	Ethyl	0.10	Pt.	0.20 gm.	9 min.	93.8%
VIIa	Ethyl	0.50	Pt.	1.0 gm.	95 min.	94.2%
VIIb	Ethyl	0.50	Pt.	1.1 gm.	98 min.	93.1%
VIII	Ethyl	0.10	5% Pd ~~Pt.~~	0.20 gm.	25 min.	92.8%
IX	n-Propyl	0.10	Pt.	0.20 gm.	15 min.	95.5%
X	Isopropyl	0.10	Pt.	0.20 gm.	14 min.	90.5%

* Reverse addition of reagents (page 17)

TABLE II

(con't)

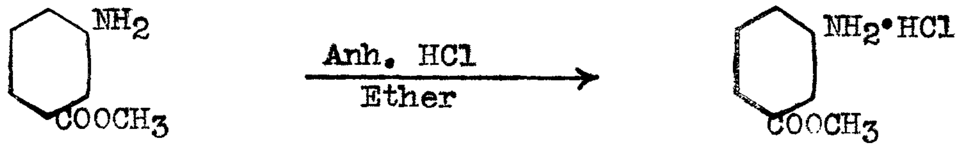
REDUCTION OF m-NITROBENZOATES

		Physical Constants			Analysis		
Run No.	Ester	Found	Literature			Calc.	Found
Va	Methyl	m.p. 37.9-38.9° m.p.	(36,38°) (37°)	(26,29)** (30)			
VI	Methyl	m.p. 38.3-39.3 B.P. 152-153°.11mm.					
Vb,c VIIa,b VIII	Ethyl	B.P. 156°/10mm. B.P.*294° (Dec.) S.G. $\frac{.26°}{26.}$ 1.1310 $\overset{26°}{\text{n.D.}}$ = 1.5540	(294°)	(24,26)			
IX	n-Propyl	B.P. *283° (Dec.) $N_D^{25°}$ = 1.5467 S.G. = 1.1029			C H N	67.10 7.30 7.80	67.23 7.27 7.78
X	Isopropyl	m.p. 176-177°					

* B.P. at atm. pressure

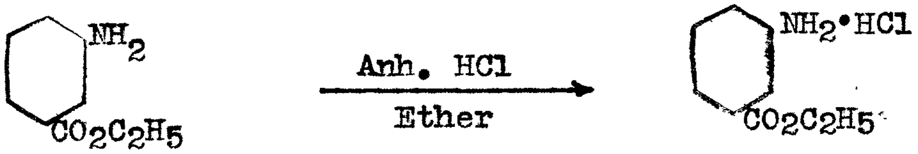
** Literature references

XI. Preparation of Methyl-m-Aminobenzoate Hydrochloride



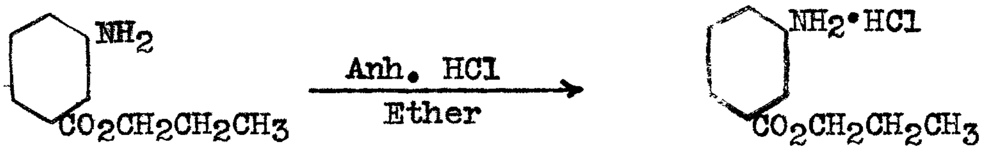
To a 250 cc. suction flask placed in an efficient hood, 7.6 gm. (0.05 mole) of methyl-m-aminobenzoate (VI) was dissolved in 200 cc. of anhydrous ethyl ether. Dry hydrogen chloride gas, prepared by means of a hydrogen chloride generator (31), was bubbled into the ethereal solution, and immediately a flocculent precipitate appeared and settled to the bottom of the flask. As soon as the solution became saturated with hydrogen chloride gas, the precipitate was filtered on a Büchner funnel, and the filtrate was treated with hydrogen chloride gas to completely precipitate the amine. The filter cake was washed with several portions of cold ethyl ether until the washings were colorless. The amine hydrochloride was pressed dry and placed in a dryer for 24 hours. The yield of the amine hydrochloride m.p. 202.1-203.8°, was 9.3 gm. (100%).

XII. Preparation of Ethyl-m-Aminobenzoate Hydrochloride



The procedure used to prepare methyl-m-aminobenzoate hydrochloride (XI) was repeated. The amount of ethyl-m-aminobenzoate (VII) used for the preparation of the hydrochloride was 8.3 gm. (0.05 mole). The yield of the amine hydrochloride m.p. 184.8-188.5°, was 10.1 gm. (100%).

XIII. Preparation of n-Propyl-m-Aminobenzoate Hydrochloride

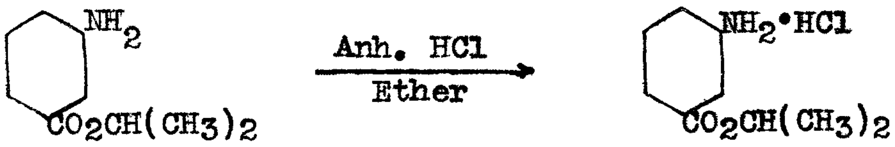


The n-propyl-m-aminobenzoate (IX) used for the amine hydrochloride preparation was 8.9 gm. (0.05 mole). The yield of the amine hydrochloride m.p. 155.1-158.6, was 10.6 gm. (100%).

An analysis of the compound showed:

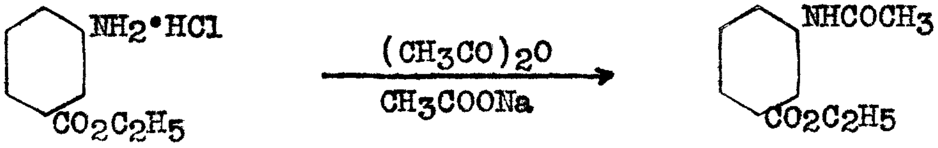
	Theoretical	Actual
C	55.63	55.66
H	6.54	6.43
N	6.49	6.41
Cl	16.43	16.63

XIV. Preparation of Isopropyl-m-Aminobenzoate Hydrochloride



The amount of isopropyl-m-aminobenzoate (X) used for the amine hydrochloride preparation was 8.9 gm. (0.05 mole). The yield of the amine hydrochloride m.p. 283.0-284.0° was 10.6 gm. (100%).

XV. m-Carbethoxy-Acetanilide



To a 500 cc. beaker containing 125 cc. of water were added 4.2 cc. (0.05 mole) of C.P. concentrated hydrochloric acid and 8.3 gm. (0.05 mole) of ethyl-m-aminobenzoate (VIIa). The ethyl-m-aminobenzoate hydrochloride solution was decolorized using 3.0 gm. of activated carbon, and stirring at room temperature for 5 minutes. The mixture was filtered by suction and refiltered through a fresh paper in order to remove the activated carbon completely. To the colorless filtrate was added 6.2 cc. (0.05 mole) of acetic anhydride and also a previously prepared solution of 7.5 gm. (0.05 mole) of C.P. crystalline sodium acetate in 25.0 cc. of water.

The reaction mixture turned milky white as soon as the sodium acetate solution was added to the beaker and then clear oil droplets settled to the bottom of the beaker. Upon stirring the mixture in an ice-water bath for 10 minutes, the clear oily droplets turned into a pure white solid mass. The m-carbethoxy-acetanilide that formed was filtered and washed with 10% sodium bicarbonate solution followed by water. After pressing the filter cake to remove most of the moisture, it was placed in a 40-60° dryer and dried to constant weight.

The yield of the crude product, m.p. 83-84°, was 8.5 gm. (85%). The crude m-carbethoxy-acetanilide was then crystallized from a 30% alcoholic solution and decolorized with activated carbon. After filtering off the activated carbon, the filtrate was concentrated to a saturated solution and was allowed to cool to room temperature. Particularly good crystals were obtained by reheating the filtrate and allowing the filtrate to cool slowly and without disturbance. The crystallization afforded pure material m.p. 83.9-84.9°, in yield of 8.0 gm. (77.0%).

The melting point of m-carbethoxy-acetanilide which was prepared, did not agree with the melting point (110°) given in Shriner and Fuson's Table of Derivatives (24).

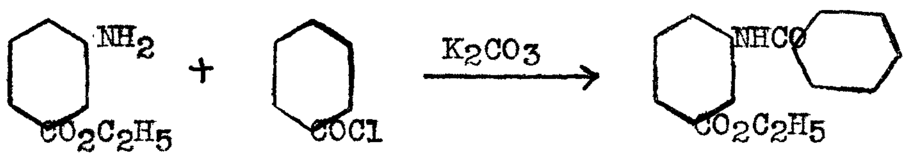
Because of this discrepancy the preparation of m-carbethoxy-acetanilide was repeated. The same procedure described above was used to prepare the acetanilide derivative. The yields obtained were approximately the same, and the crystallized product melted at 84.0-85.0°, reproducing the melting point obtained from the first preparation of m-carbethoxy-acetanilide.

An analysis of m-carbethoxy-acetanilide (m.p. 83.9-84.9°) showed the following:

	Theoretical	Actual
C	63.75	63.52
H	6.32	6.51
N	6.76	6.76

This conclusive determination established that the melting point of m-carbethoxy-acetanilide is 84-85° and not 110° as reported in Shriner and Fuson's *Table of Derivatives* (24).

XVI. m-Carbethoxy-Benzanilide



To a 250 cc. stoppered bottle were added 33.0 gm. (0.2 mole) of ethyl-m-aminobenzoate (VIIa) and 150.0 cc. of anhydrous ethyl ether. The solution was made alkaline by adding 12.0 gm. of finely powdered potassium carbonate. Twenty-eight gm. (0.2 mole) of reagent grade benzoyl chloride was added to the reaction bottle and shaken vigorously (occasionally releasing the pressure) for ten minutes. A heavy white precipitate formed which was filtered and then slurried in a warm 5% sodium carbonate solution. After the mixture was filtered, a halide test was made using silver nitrate. The test proved that halides were present and it was necessary to reslurry the benzamide derivative in warm water for one hour. The filtered and dried product was then recrystallized, using SD-3A alcohol, and activated carbon.

The yield of the crude product, m.p. 108-111°, was 36.3 gm. (67.3%); one crystallization and treatment with activated carbon afforded pure material, m.p. 112-113°, in yield of 28.7 gm. (53.3%).

The melting point of the m-carbethoxy-benzanilide prepared did not agree with the melting point (148°) reported in Shriner and Fuson's Table of Derivatives (24). An analysis of the compound showed the following:

	Theoretical	Actual
C	71.40	70.92
H	5.62	5.49
N	5.21	5.29

Shriner and Fuson (24) reported the following melting points for the acetamide and benzamide derivatives of ethyl-m-aminobenzoate and ethyl-p-aminobenzoate:

	Acetamide	Benzamide
ethyl-m-aminobenzoate	110°	148°
ethyl-p-aminobenzoate	110°	148°

It will be observed that the melting points for both the "para" and the "meta" esters were reported as the same. An error by the translator of the "para" melting points may have been made. A literature search revealed no preparations for the derivatives of the "meta" compounds.

TABLE III

DERIVATIVES OF META-AMINOBENZOATES

Run No.	Ester	Derivative	M.P.	Yield
XI	Methyl	Hydrochloride	*202.1-203.8°	100%
XII	Ethyl	Hydrochloride	*184.8-188.5°	100%
XIII	n-Propyl	Hydrochloride	*155.1-158.6°	100%
XIV	Isopropyl	Hydrochloride	*283.0-284.0°	100%
XV	Ethyl	Acetamide	84.0- 85.0°	77%
XVI	Ethyl	Benzamide	112.0-113.0°	55.3%

* The hydrochlorides all melted with decomposition.

TABLE III

(con't)

DERIVATIVES OF META-AMINOBENZOATES

Run No.	Ester	Derivative		Analysis	
				Calculated	Found
XIII	n-Propyl	Hydrochloride	C	55.63	55.66
			H	6.54	6.43
			O	6.49	6.41
			Cl	16.43	16.63
XV	Ethyl	Acetamide	C	63.75	63.52
			H	6.32	6.51
			O	6.76	6.76
XVI	Ethyl	Benzamide	C	71.40	70.92
			H	5.62	5.49
			O	5.21	5.29

ULTRAVIOLET ABSORBTION SPECTRA
OF COMPOUNDS PREPARED

Ultraviolet absorbtion measurements were made with a Beckman D.U. spectrophotometer equipped with 10 mm. silica cells, using synthetic methanol as the solvent. A sample calculation for determining the molar extinction coefficients is shown on page 40.

FIGURE 1

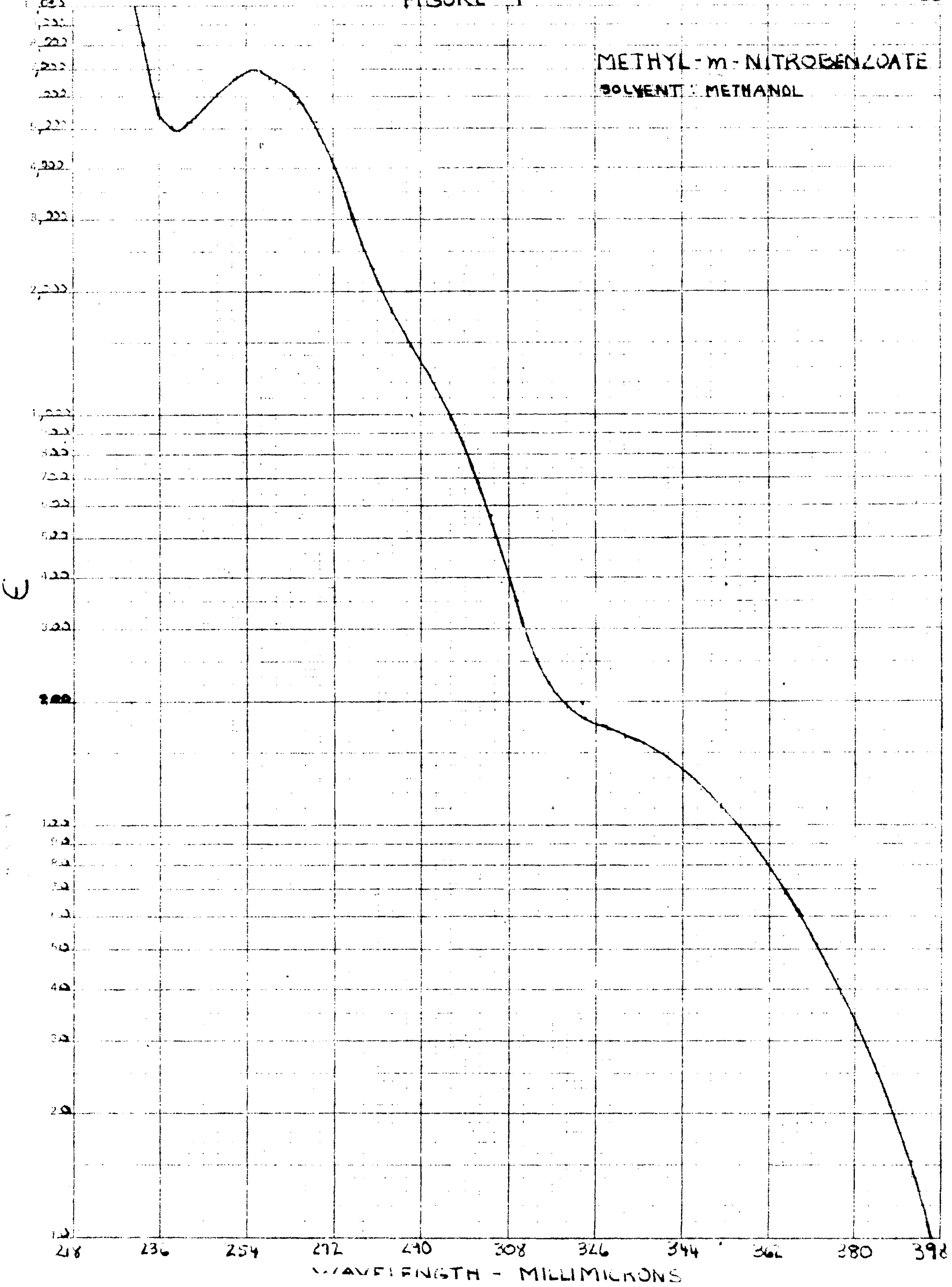

METHYL-m-NITROBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 2

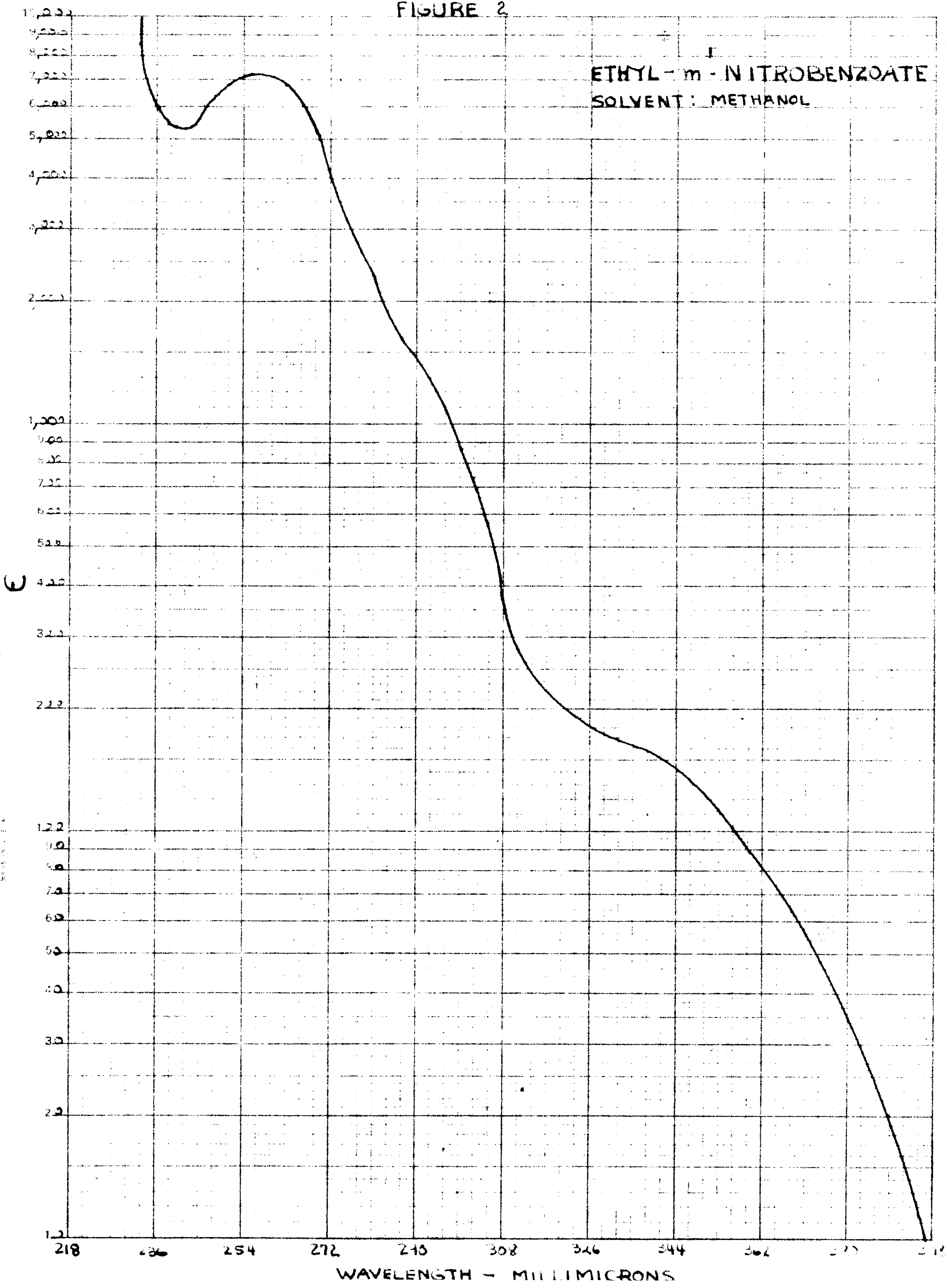

ETHYL - m - NITROBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 3

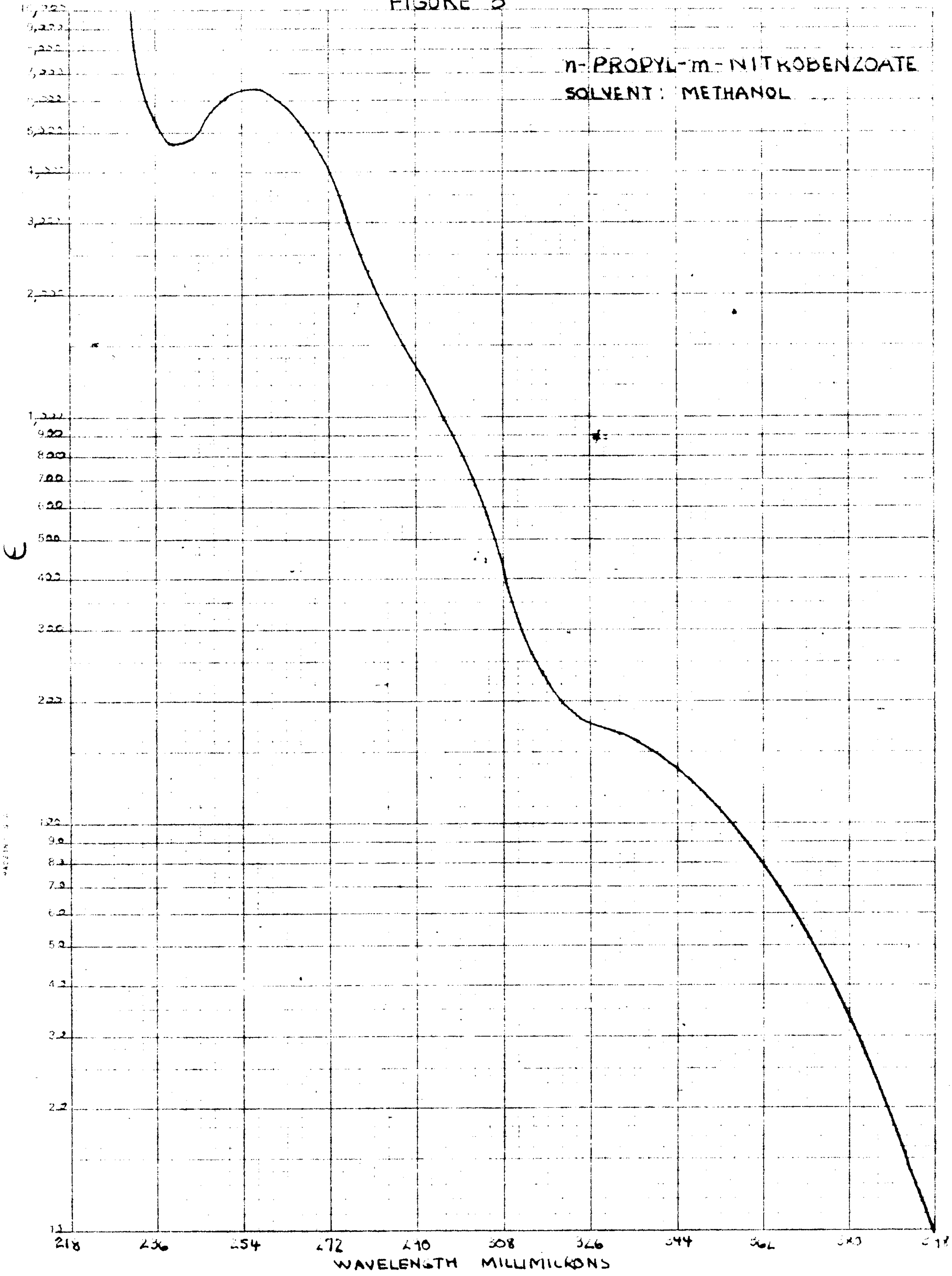

n-PROPYL-m-NITROBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH MILLIMICRONS

FIGURE 4

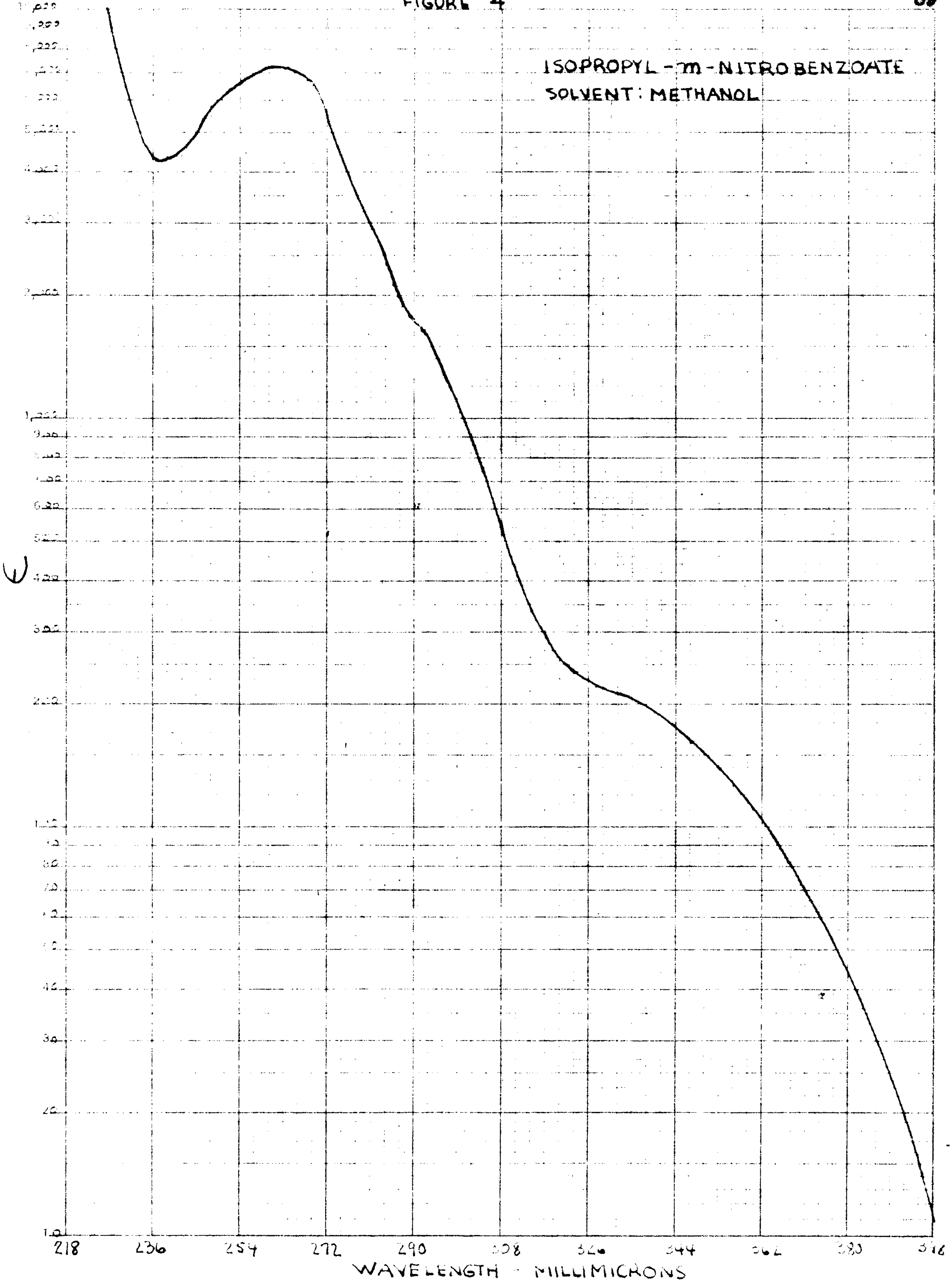

ISOPROPYL-m-NITROBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 5

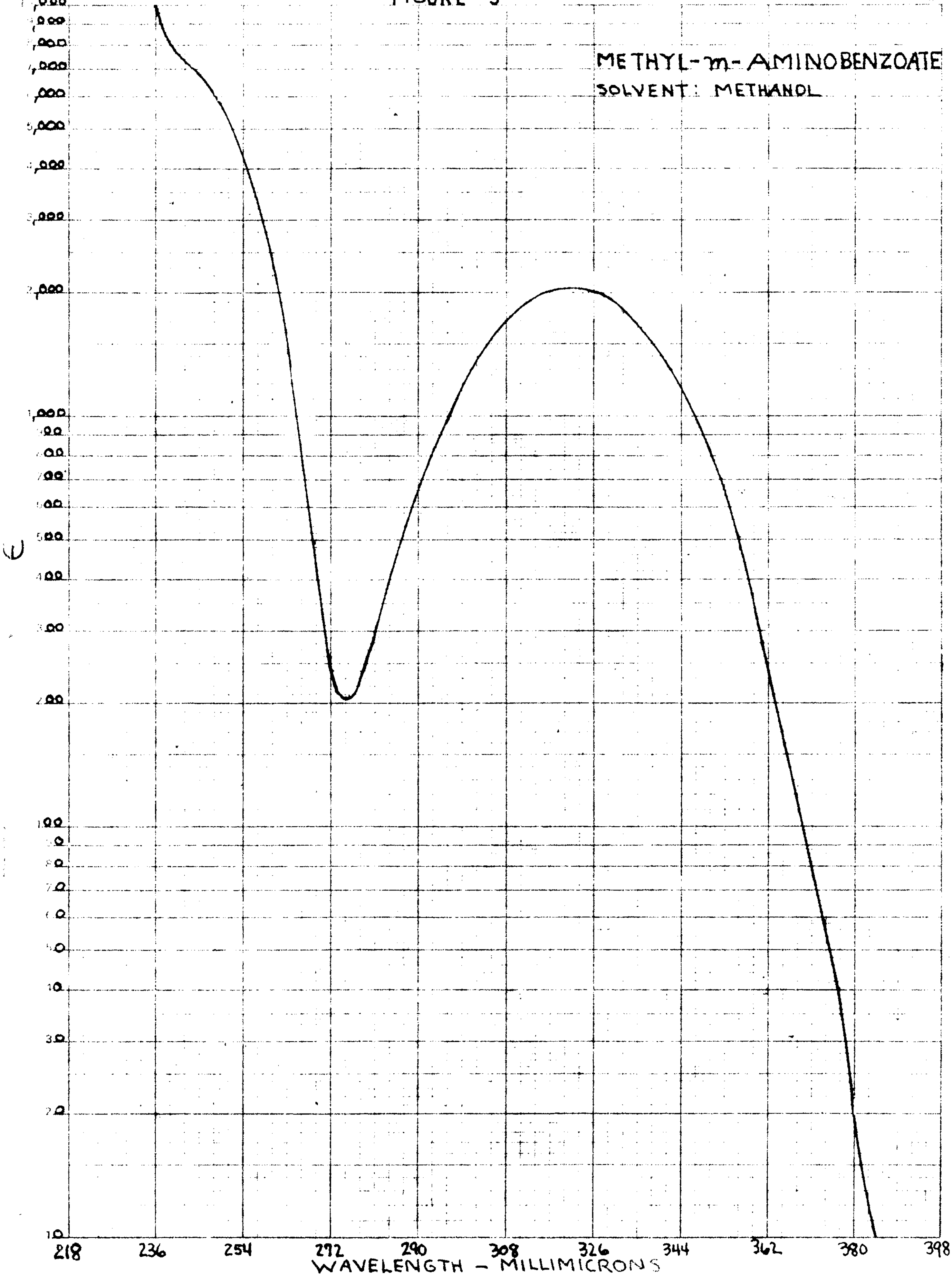

METHYL-m-AMINOBENZOATE
SOLVENT: METHANOL
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
ε
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 6

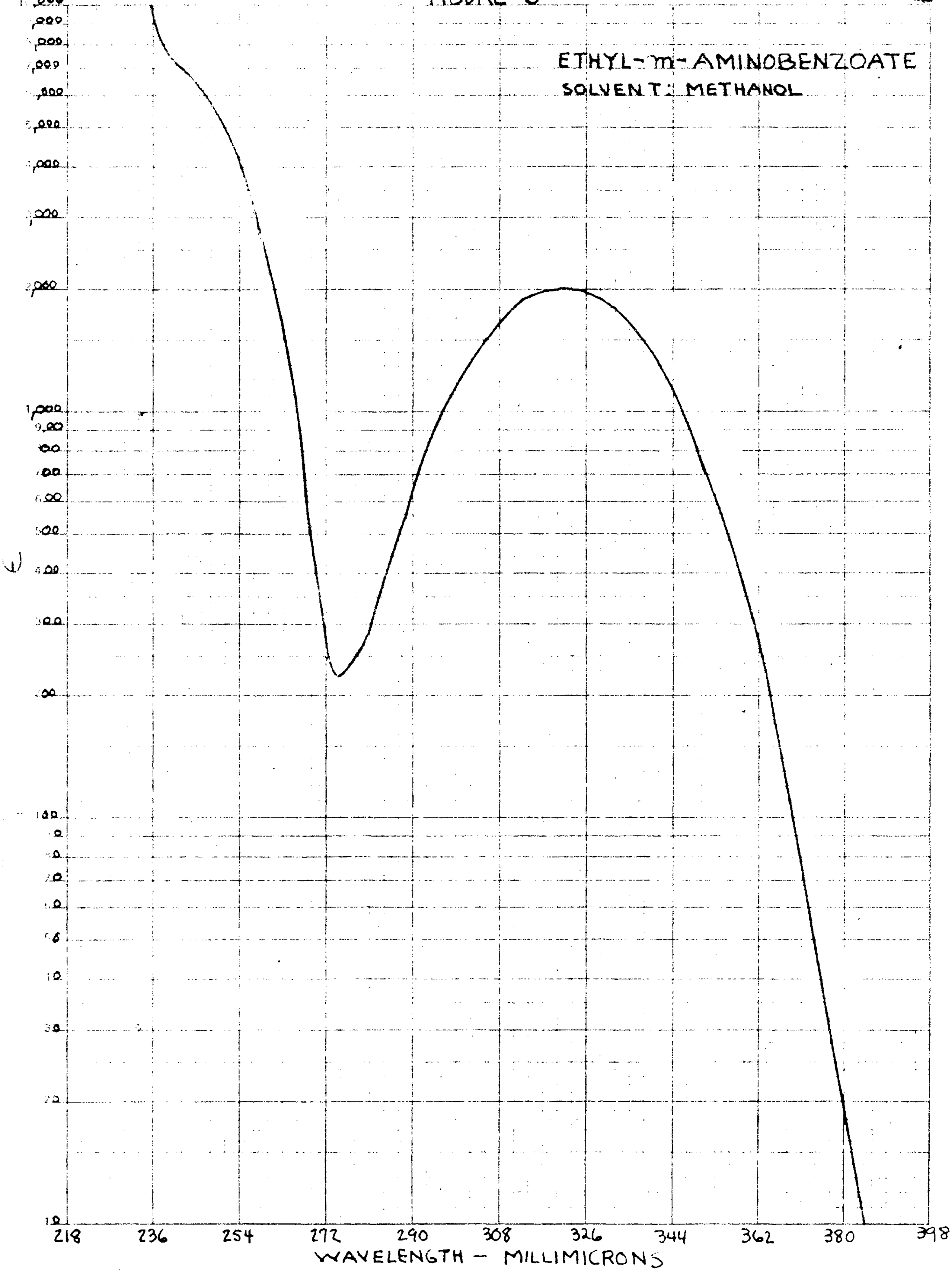

ETHYL-m-AMINOBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 7

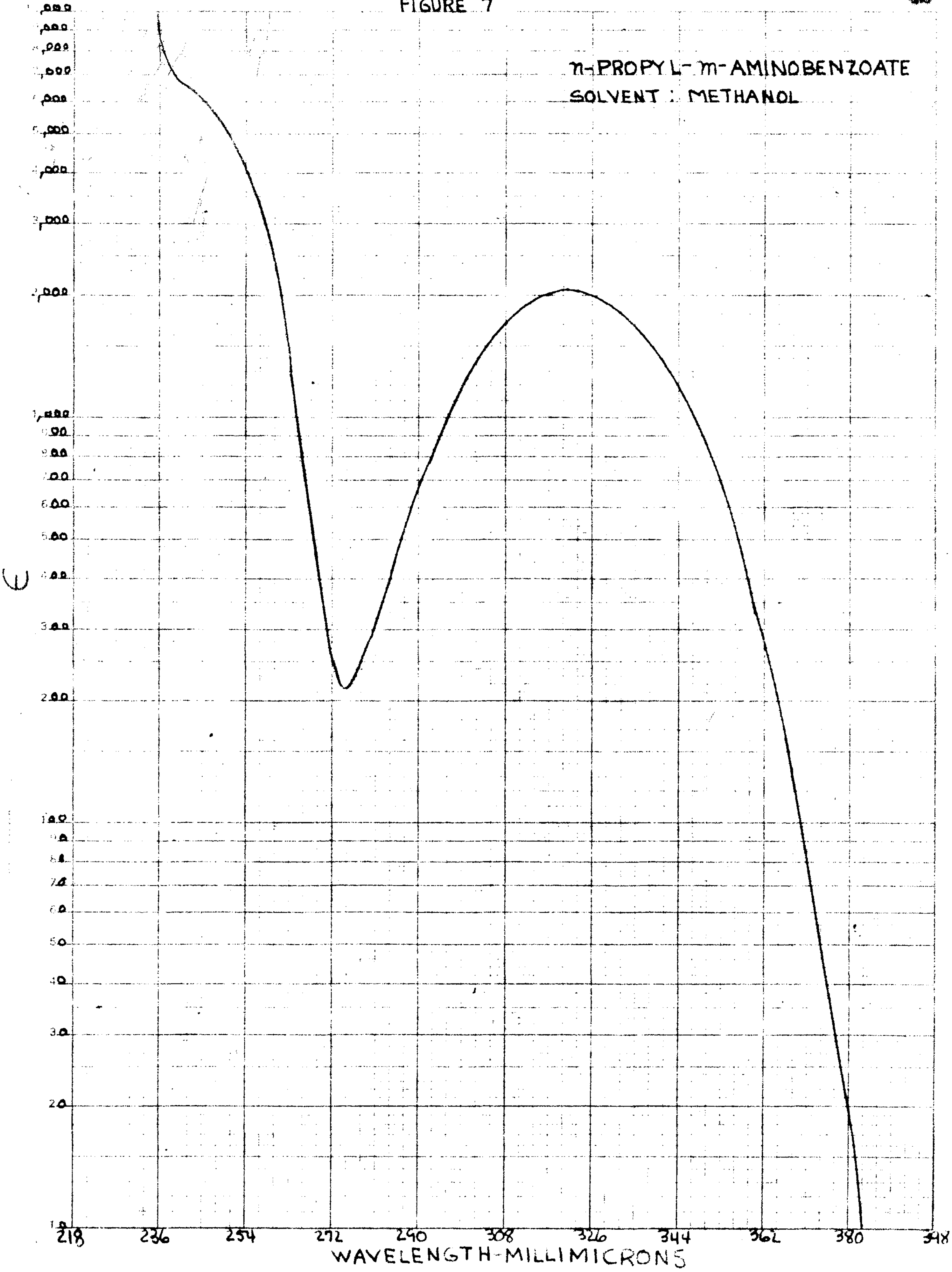

n-PROPYL-m-AMINOBENZOATE
SOLVENT : METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH-MILLIMICRONS

FIGURE 8

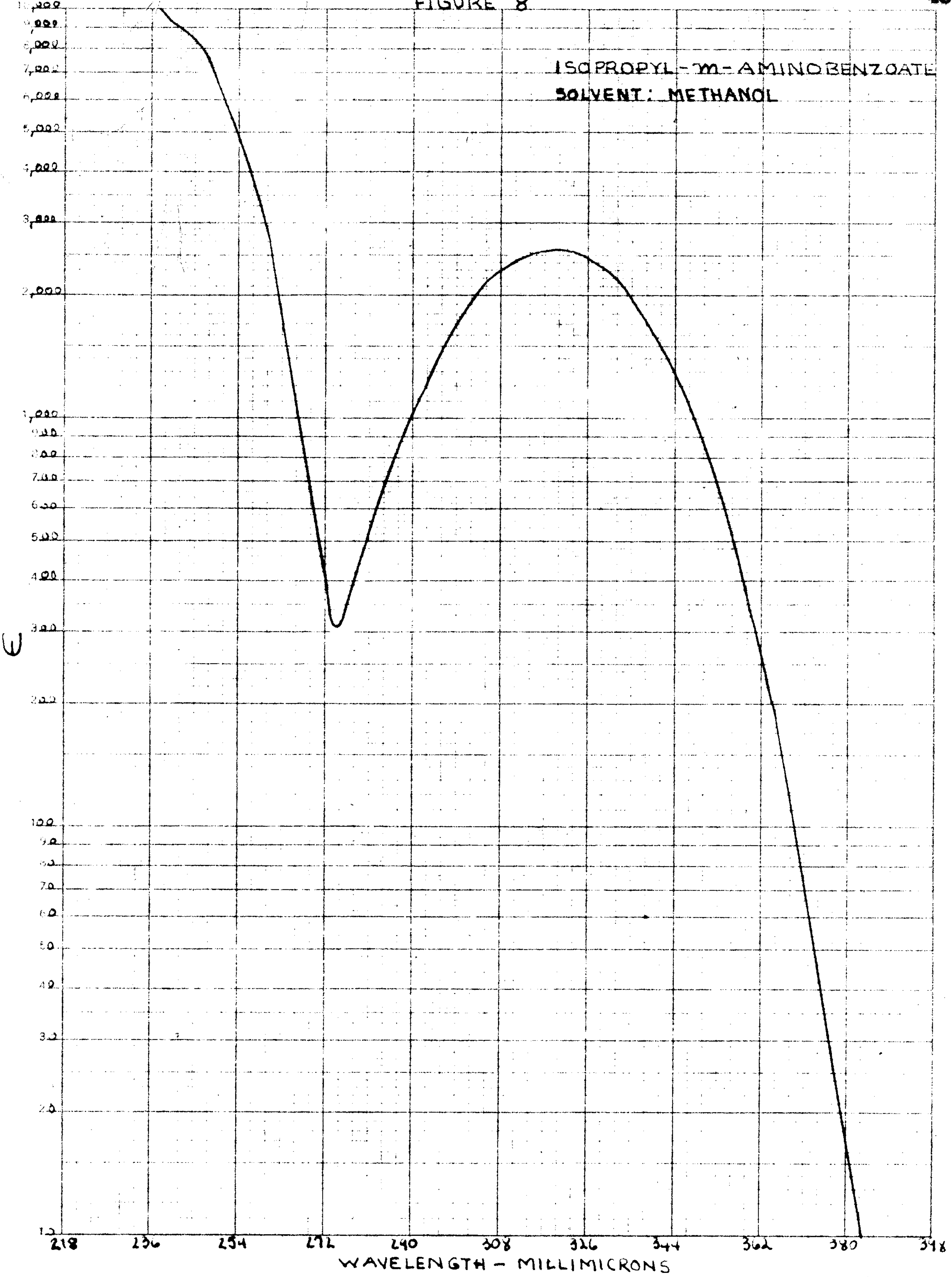

ISOPROPYL-m-AMINOBENZOATE
SOLVENT: METHANOL
ε
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
10
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

FIGURE 9

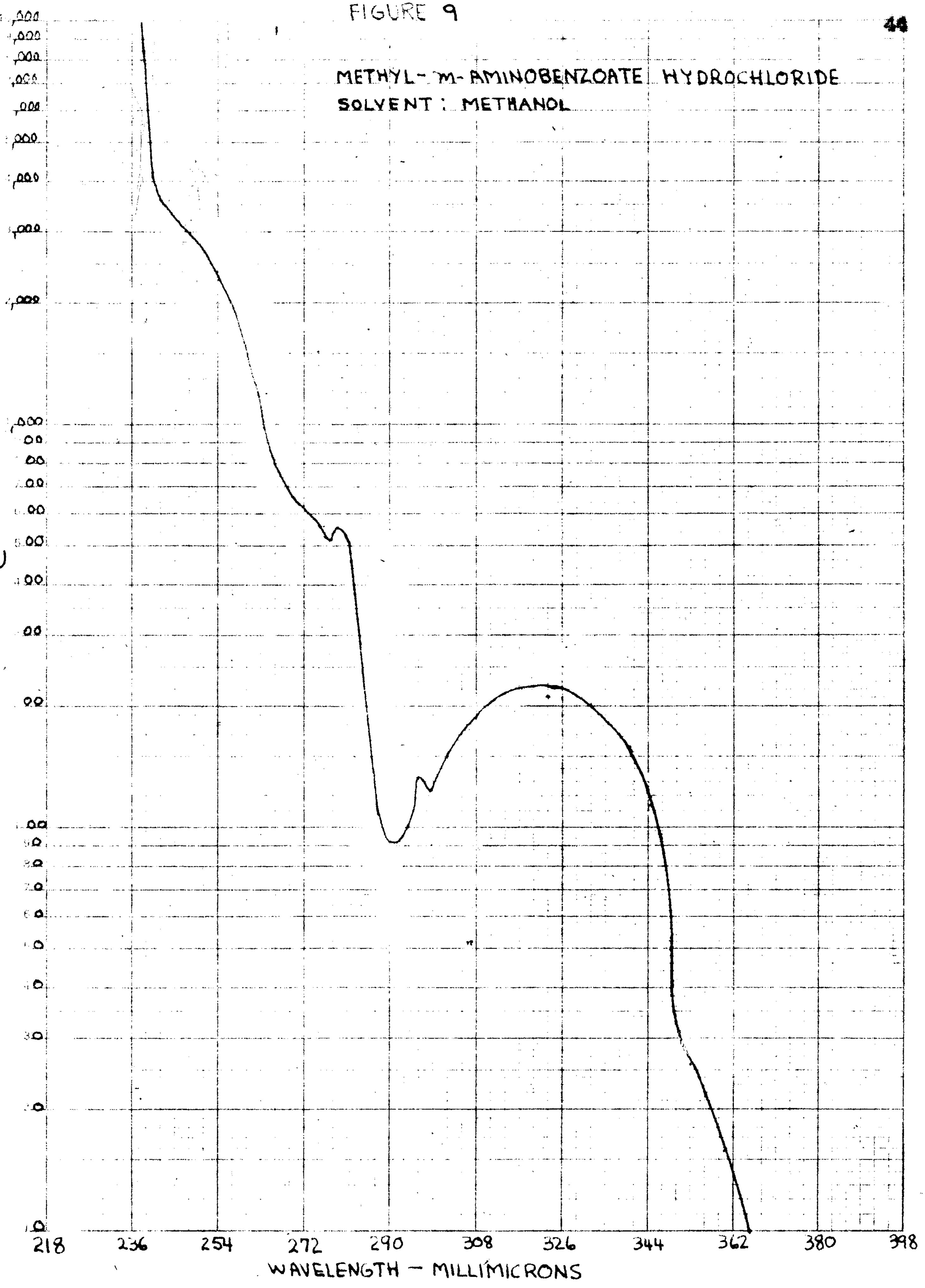
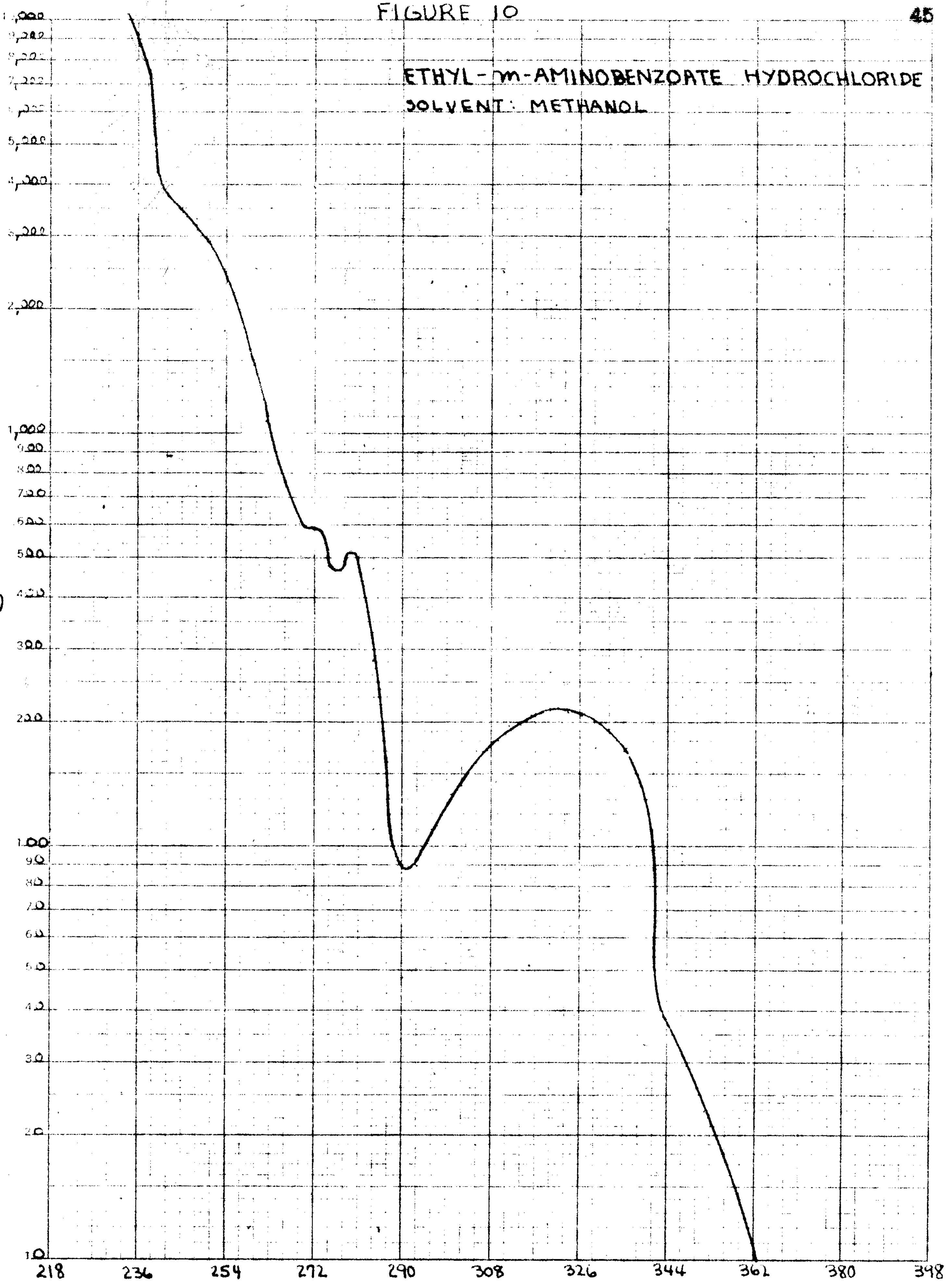

METHYL- m- AMINOBENZOATE HYDROCHLORIDE
SOLVENT : METHANOL
ε
WAVELENGTH — MILLIMICRONS
218
236
254
272
290
308
326
344
362
380
398
1.0
3.0

FIGURE 10



ETHYL-m-AMINOBENZOATE HYDROCHLORIDE
SOLVENT: METHANOL

FIGURE 11

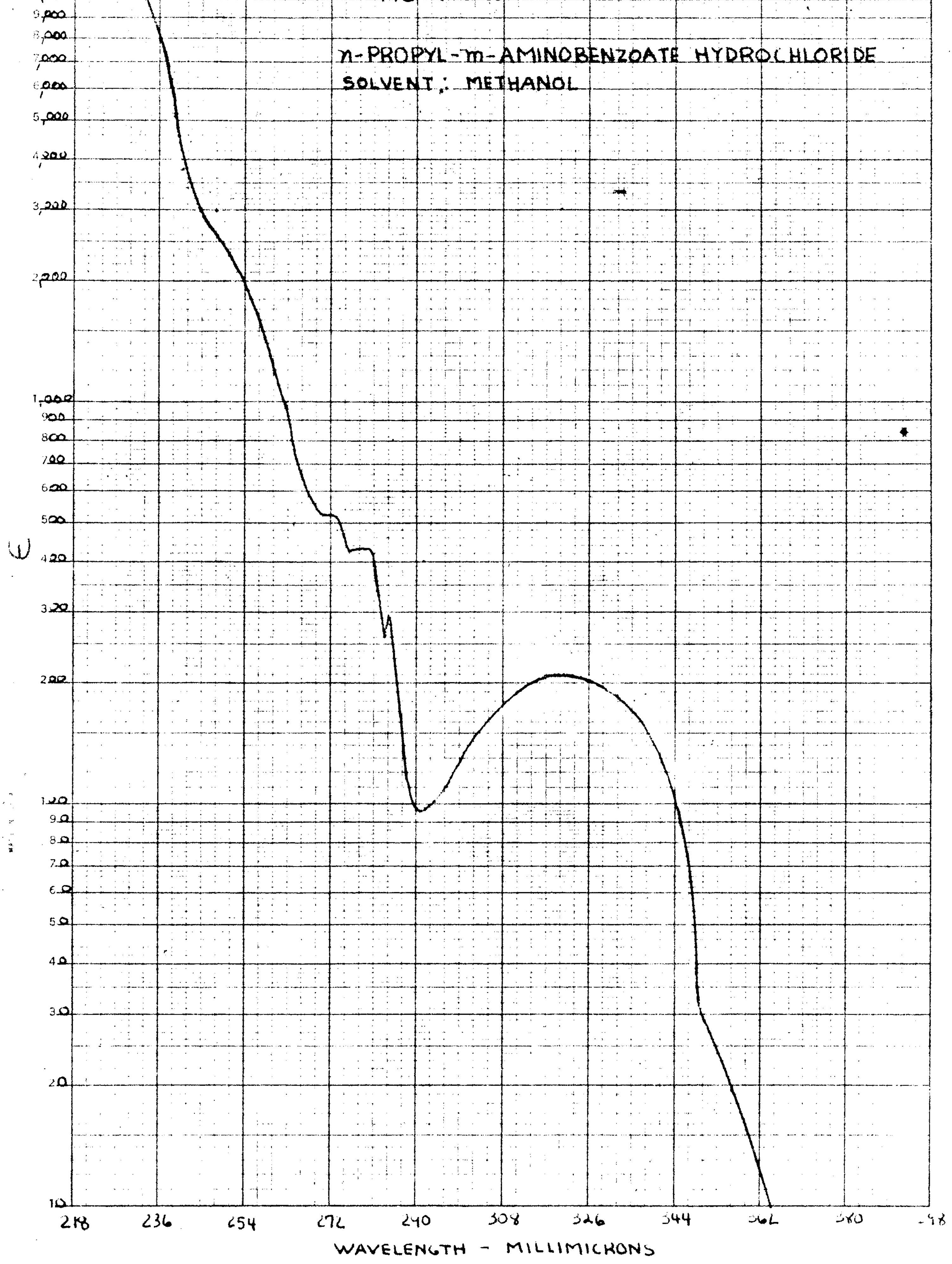

n-PROPYL-m-AMINOBENZOATE HYDROCHLORIDE
SOLVENT: METHANOL

FIGURE 12

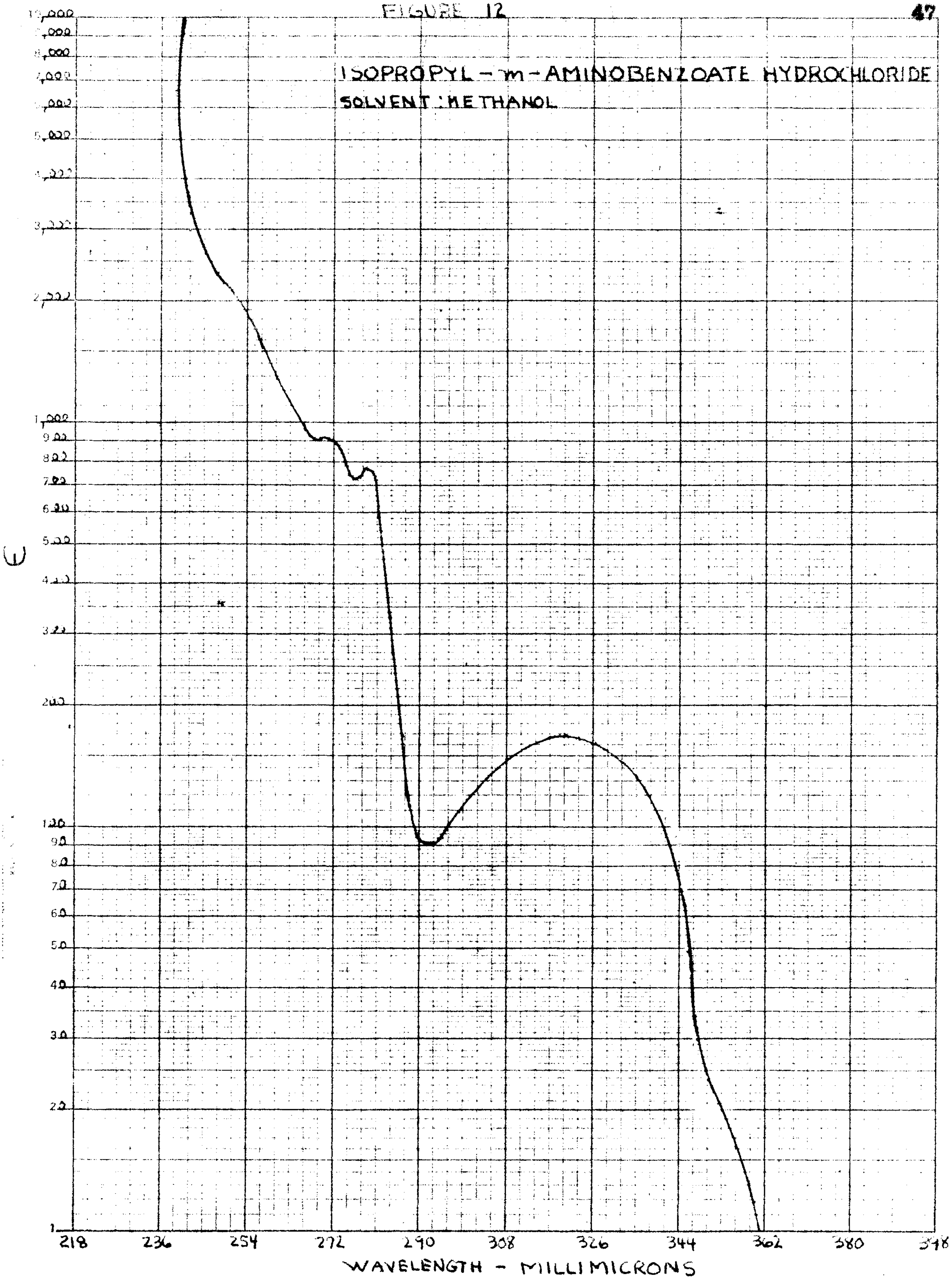

ISOPROPYL - m - AMINOBENZOATE HYDROCHLORIDE
SOLVENT: METHANOL
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
900
800
700
600
500
400
300
200
100
90
80
70
60
50
40
30
20
1
ε
218
236
254
272
290
308
326
344
362
380
398
WAVELENGTH - MILLIMICRONS

TABLE IV

MOLAR EXTINCTION COEFFICIENTS

COMPOUND	MINIMA		MAXIMA	
	mμλ	∈	mμλ	∈
Methyl-m-nitrobenzoate	239	4,949	217.5	23,645
			257	
Ethyl-m-nitrobenzoate	240	5,348	217.5	24,910
			256	7,290
n-Propyl-m-nitrobenzoate	240	4,621	218	22,593
			256	6,458
Isopropyl-m-nitrobenzoate	238	4,238	262	7,493
Methyl-m-aminobenzoate	275	204.2	221	25,177
			322	2,079
Ethyl-m-aminobenzoate	275	222.1	221	23,410
			320	2,011
n-Propyl-m-aminobenzoate	275	215.8	222	22,300
			321	2,059
Isopropyl-m-aminobenzoate	274	309.0	219	36,255
			317	2,622
Methyl-m-aminobenzoate . HCl	277	517.0	222	24,752
	290	91.78	279	555.7
	298	124.6	296	130.2
			320	226.9
Ethyl-m-aminobenzoate . HCl	276	466.9	221	23,436
	291	88.22	279	506.0
			322	216.2
n-Propyl-m-aminobenzoate . HCl	276	411.8	223	20.212
	291	96.06	279	426.2
			319	211.6
Isopropyl-m-aminobenzoate . HCl	269	90.90	221	51,684
	276	724.6	270	920.2
	292	90.79	279	758.2
			319	168.9

SAMPLE CALCULATION FOR DETERMINING THE MOLAR EXTINCTION COEFFICIENT ϵ, OF METHYL-m-AMINOBENZOATE HYDROCHLORIDE

Molecular weight ------------------ 187.66

mμ, wavelength ------------------ 292

%T, transmission ------------------ 62.4

b, cell thickness ------------------ 0.998 cm.

c, concentration ------------------ 0.4136 gm./liter

$$T = \frac{\%T}{100} = 0.624$$

$$\frac{1}{T} = 1.603$$

$$O.D. = \log_{10} \frac{100}{\%T} \text{ or } \log \frac{1}{T} = 0.2049$$

$$E^{1\%}_{1cm.} = \text{specific extinction coefficient} = \frac{O.D.}{b \times c} = \frac{0.2049}{0.4128}$$

$$= 0.4963$$

$$\epsilon = \text{molar extinction coefficient} = E^{1\%}_{1cm.} \times \text{molecular wt.}$$

$$= 0.4963 \times 187.66 = 93.14$$

DISCUSSION

I. Esterification of m-Nitrobenzoic Acid

The esters of meta-nitrobenzoic acid were prepared by the direct esterification method using benzene as the azeogen wherever possible, and sulfuric acid as the catalyst. A large excess of the alcohol was used in each of the esterification mixtures. The ternary distillates formed were condensed into a Dean-Stark trap. The time required to esterify meta-nitrobenzoic acid, using methyl, ethyl, n-propyl, and isopropyl alcohols is shown on page 12, Table I.

It will be observed from the rates shown on Table I that, of the alcohols studied, methanol shows the most rapid rate of esterification. The primary alcohols, ethyl and propyl, have approximately the same rates of esterification, but these are slower than methyl alcohol. The secondary isopropyl alcohol showed the slowest rate of esterification.

II. Reduction of m-Nitrobenzoates

Several methods were employed to reduce the meta-nitrobenzoates to amines: iron, water and acetic acid; platinum oxide and hydrogen; and 5% palladium on carbon and hydrogen.

(a) Chemical Reductions

Iron, water and acetic acid were used in the first attempt to reduce the meta-nitrobenzoates, (hydrochloric acid was not considered because of its hydrolytic effect on the esters). Procedures were varied by adding iron to the nitro compound in water-acetic acid; or the reverse. Both procedures yielded approximately the same amounts of amine (60%); the addition of the nitro compound to the reducing mixture showed a greater rate of reduction (3 hours vs. 5 hours).

(b) Catalytic Reductions

A comparative study was made with platinum oxide and 5% palladium on activated carbon as possible catalysts for the reduction of the meta-nitrobenzoates. Platinum oxide produced the best results: 96.6% yield, and it was used to reduce all four of the m-nitrobenzoates. (See Table II, page 24).

It is well known that the rate of reduction varies directly with the amount of catalyst up to a certain limit. Preliminary experiments in this investigation (17) indicated that 0.2 gm. of catalyst per 0.1 mole of nitro compound in 150 cc. of solvent with hydrogen at 2 to 3 atm. pressure was the critical maximum amount needed for very rapid reduction (8-10 minutes). Larger amounts did not increase the rate of reduction appreciably; small amounts resulted in the expected decrease in reduction rate. However, as little as 0.05 gm. of catalyst could be used and a quantitative reduction still be obtained in about 60 minutes.

III. m-Aminobenzoate Hydrochlorides and Other Derivatives

An attempt was made to prepare the hydrochlorides of the amines and the acetyl, benzoyl, benzal, and benzyl derivatives of ethyl-m-aminobenzoate. The benzal and benzyl derivatives of ethyl-m-aminobenzoate could not be purified readily, and were abandoned.

Both the acetamide and benzamide derivatives of ethyl-m-aminobenzoate, prepared here, gave melting points that disagreed with those reported by Shriner and Fuson (24).

SUMMARY

1. A series of m-nitrobenzoate esters have been prepared. Two compounds, not previously reported are the n-propyl-m-nitrobenzoate and isopropyl-m-nitrobenzoate.
2. Reduction of the nitrobenzoates to corresponding m-aminobenzoates can be accomplished best by catalytic hydrogenation in ethanol solution, using platinum oxide as the catalyst.
3. Chemical reduction with iron and acetic acid gives the best yields of pure amino compound when nitro compound is added to iron-acetic acid mixture, rather than the reverse.
4. Physical constants reported by Shriner and Fuson for m-carbethoxy acetanilide and m-carbethoxy benzanilide were found to be erroneous. Corrected values are given here.
5. Ultraviolet absorption spectra of the compounds synthesized are presented.

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