# A STUDY OF STERIC EFFECTS IN THE REACTIONS OF ARYL ESTERS WITH ARYL GRIGNARD REAGENTS

Thesis for the Degree of M. S.
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Arthur John Pastor

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A THESIS

Submitted to the College of Science and Arts of Michigan
State University of Agriculture and Applied Science
in partial fulfillment of the requirements
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Department of Chemistry

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# ABSTRACT

A study of steric effects in the reactions of aryl esters with aryl Grignard reagents has been made by conducting two series of block experiments. In one series phenylmagnesium bromide, _o_-methylphenylmagnesium bromide, _o_-ethylphenylmagnesium bromide and _o_-isopropylphenylmagnesium bromide were each reacted with the phenyl esters of benzoic acid, _o_-methylbenzoic acid, _o_-ethylbenzoic acid and _o_-isopropylbenzoic acid. In the second series the same Grignard reagents were reacted with the _o_-cresyl esters of the above benzoic acids.

Infrared absorption spectrophotometry was used to analyze the reaction mixtures for ketones and tertiary alcohols. The infrared method was checked by determination of ketones by oxime formation, determination of tertiary alcohols by formation of the 3,5-dinitrobenzoates, and by determination of unreacted ester by hydrolysis and titration of the acid salts.

Results of this study indicate that alkyl groups in any of the three steric areas, i.e., the acyl portion of the ester, the aryloxy portion of the ester and the Grignard reagent, hinder the reaction of Grignard reagent with ester. Substitution in the ortho position of the Grignard reagent was shown to cause the greatest hindrance. As would be expected the degree of hindrance was shown to increase as the size of the alkyl group increased. The formation of the initial complex between Grignard reagent and ester was shown not to be appreciably affected by steric factors of the order of magnitude employed in this study. The reaction by which alcohol is formed was shown to be markedly influenced by steric factors in the aryloxy portion of the ester. Evidence was obtained to show that the alcohol is formed by a direct reaction of the initial complex formed with Grignard reagent.

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# INTRODUCTION

## Statement of Problem

The problem of steric effects of alkyl groups in the addition of Grignard reagents to esters has been widely studied (1-8). However, a review of the literature reveals no systematic comparison of effects of alkyl substitution in the three possible steric areas, i.e. the acyl portion of the ester, the alcohol portion of the ester, and the Grignard reagent. The purpose of this investigation was to study the steric effects of ortho substituted methyl, ethyl, and isopropyl groups in the reactions of aryl Grignard reagents with a series of substituted phenyl and o-cresyl benzoates. It was desired to establish in which of the three possible positions mentioned alkyl substitution exhibited the most pronounced steric hindrance. It was also desired to establish if the greater decrease in reactivity took place in the intermediate ketone form or in the parent ester, and if possible to establish more information concerning the mechanism of the reactions. A third purpose of this work was to compare the relative effects of the methyl, ethyl, and isopropyl groups on reactivity and to establish if the steric effects were additive if the alkyl substituents were in more than one of the possible positions.

In order to study the steric effects of these alkyl groups in the three positions, the phenyl and o-cresyl esters of benzoic acid, 2-methylbenzoic acid, 2-ethylbenzoic, and 2-isopropylbenzoic acid were prepared. These esters were chosen to avoid possible side reactions due to enolization. The phenyl esters were each reacted with the Grignard reagents from bromobenzene, 1-bromo-2-methylbenzene, 1-bromo-2-ethylbenzene, and 1-bromo-2-isopropylbenzene. Each of the o-cresyl esters were reacted with two Grignard reagents to correlate the results obtained with the phenyl esters and to establish the effect of ortho methyl substitution on the phenyl portion of the ester. The effects of these groups were determined by comparing the relative yields of diaryl ketones and triaryl tertiary alcohols in a series of reactions performed under the same conditions. The diaryl ketones and triaryl tertiary alcohols were determined quantitatively by infrared absorption methods.

The reactions were all performed in refluxing toluene with constant reaction times. The initial ratio of Grignard reagent to ester was 1:1 in all instances, and the initial concentration of reagents was maintained approximately constant for all reactions studied. To avoid possible undesirable side reactions, iodine and other activators were not employed in the preparation of the Grignard reagents; the Grignard reagents were filtered prior to use to remove unreacted magnesium. The order of addition of reagents was in reverse to the accepted method, i.e. the Grignard reagents were added to the ester dissolved in toluene to avoid favoring the formation of tertiary alcohol.

## Historical

The effects of steric hindrance on Grignard reactions regarding both normal addition and side reactions have been studied by several investigators. Fuson and co-workers (1) studied the reaction of alkyl and aryl Grignard reagents with alkyl and aryl mesitoates; the reactions did not produce any of the expected tertiary alcohol. The products of the reactions of the Grignard reagents and the alkyl mesitoates were mesitoic acid and the alkyl halide of the alkyl group of the ester. The reactions with the aryl mesitoates and the alkyl Grignard reagents produced a ketone and the phenol of the aryl group of the ester.

In the case of the reaction of aryl mesitoates with aryl Grignard reagents the expected ketone was not obtained, but one in which ortho substitution by a second mole of Grignard reagent had taken place. R. T. Arnold, H. Bank, and R. Liggett (2) also investigated the effects of substitution in the ortho position of the acyl portion of allyl benzoates. These workers studied the reactions of phenylmagnesium bromide with allyl benzoate, allyl o-toluate, and allyl mesitoate in ethyl ether. They found that the yields of the expected triphenylcarbinol in the cases of allyl benzoate and allyl o-toluate were, respectively, 86% and 68%, indicating that the single ortho group did not greatly interfere with normal Grignard addition. However, with the allyl mesitoate no ketone nor triphenyl alcohol were formed; but instead, mesitoic acid and allyl benzene were the products. These same investigators studied the effect of methyl substitution on the reactivity of allyl alkyl esters. In the reaction of phenylmagnesium bromide with allyl trimethyl acetate a high yield of t-butyldiphenyl carbinol was experienced. The reaction of o-methylphenylmagnesium bromide with ethyl o-toluate was studied by Boyd and Hatt (3). They found that no tri-o-tolylcarbinol was produced. The diaryl ketone and the pinacol of the diaryl ketone were isolated. The pinacol formation was attributed to the presence of excess magnesium in the reaction mixture.

Kohler and Baltzly (4) studied the steric effects of methyl substitution upon the addition and enolization reactions of Grignard reactions with ketones. In comparing the results obtained in reactions of acetomesitylene, dimesityl ketone, and dimesityl diketone with ethylmagnesium bromide, they concluded that the ortho groups affect only those reactions which involve direct addition to the carbonyl and in no way promote the competing enolization reaction. Their work was confirmed in the studies of Smith and Guss (5) who found that the di-*o*-alkyl substituted ketones underwent complete enolization in reacting with methylmagnesium bromide.

The effect of steric hindrance as introduced by the reacting Grignard was noted by Hauser and co-workers (6) in their study of competitive reactions of esters with alkyl Grignard reagents, and by Whitmore and George in their study of Grignard reactions with alkyl ketones. Hauser found that as the complexity of the Grignard reagent increased from ethyl to isopropyl to tert-butyl to mesityl magnesium bromide, the degree of normal addition decreased rapidly and condensation reactions were experienced. Whitmore and George found that the degree of addition of the Grignard reagent to diisopropyl ketone was greatly decreased as the Grignard reagent employed changed from methylmagnesium bromide to isobutylmagnesium bromide.

In discussing the problem of steric hindrance in Grignard reactions with esters, Kharasch and Reinmuth (8) concluded that the ability to form ketones when the intermediate is reasonably soluble is primarily the function of the Grignard reagent, the branched chain alkylmagnesium halides displaying a marked tendency toward ketone formation. They also postulated that when the intermediate is of limited solubility in the reaction media, the primary product in ester reactions is a ketone. No literature references of the effects of methyl substitution in the ortho position of the phenyl portion of the ester were encountered.

# EXPERIMENTAL

Basic chemicals employed in this investigation were: bromobenzene, 1-bromo-2-methylbenzene, 1-bromo-2-ethylbenzene, 1-bromo-2-isopropylbenzene, o-cresol, phenol, benzoyl chloride and o-toluic acid. Compounds prepared and isolated were o-ethylbenzoic acid, o-ethylbenzoyl chloride, o-tolyl chloride, o-isopropylbenzoic acid, o-isopropylbenzoyl chloride; and the phenyl and o-cresyl esters of benzoic acid, o-toluic acid o-ethylbenzoic acid, and o-isopropylbenzoic acid. The compounds synthesized and not previously reported in the literature were the phenyl and o-cresyl esters of o-ethylbenzoic acid and o-isopropylbenzoic acid and the o-cresyl ester of o-toluic acid.

Each of the phenyl esters were reacted with the Grignard reagents prepared from the above bromo substituted benzene compounds. Each o-cresyl ester was only reacted with two Grignard reagents prepared from the bromo substituted benzene compounds. The amount of ketone and tertiary alcohol produced in each reaction was determined by infrared analysis. In order to correlate infrared analysis, a portion of the ketones were also determined by reaction with hydroxylamine hydrochloride in pyridine. A portion of the reaction mixtures were also treated with 3,5-dinitrobenzoyl chloride to determine the tertiary alcohol content. A determination of the unreacted ester was affected by hydrolyzing the ester with sodium hydroxide and titrating the benzoic acid sodium salt.

## PURIFICATION AND PREPARATION OF REAGENTS

### Purification of Starting Reagents

The bromobenzene, 1-bromo-2-ethylbenzene, and 1-bromo-2-isopropylbenzene were supplied by The Dow Chemical Company as technical grade materials. The 1-bromo-2-methylbenzene employed was obtained from Eastman Kodak Company. These compounds were each purified by fractional distillation. The bromobenzene and 1-bromo-2-methylbenzene were distilled at atmospheric pressure, while the 1-bromo-2-ethylbenzene and 1-bromo-2-isopropyl-benzene were distilled at 30 mm Hg. pressure. In each instance a two-foot adiabatic Vigreux column equipped with a Corad Fractionating condenser was employed. All fractions were collected at a reflux ratio of 30:1.

In the purification of these liquids, the fractionating column was allowed to attain equilibrium at infinite reflux for a minimum of three hours prior to collecting any distillate. In the case of bromobenzene, 1-bromo-2-methylbenzene and 1-bromo-2-ethylbenzene the first condensate representing approximately 10% of initial amount was collected at the expected boiling point of the compounds. However, these first fractions were discarded and the desired product was collected at a reflux ratio of 30:1 after the column again attained equilibrium.

In the purification of the 1-bromo-2-isopropylbenzene, two initial fractions were discarded. The technical grade material was reported to contain 16% 1-bromo-4-ethylbenzene and 6% 1-bromo-4-isopropylbenzene. The first fraction was collected in the temperature range of 103.6 to 106°C. The second fraction representing 10% of the total

## TABLE I

## COMPARISON OF OBSERVED PHYSICAL PROPERTIES OF PURIFIED REAGENTS TO ACCEPTED LITERATURE VALUES*

| Reagent | Index of Refraction, 25°C. | | Boiling Point, 20 mm Hg | |
|---|---|---|---|---|
| | Observed | Literature | Observed | Literature |
| Bromobenzene | 1.5572 | 1.5571 | 62°C | 61.7°C |
| 1-Bromo-2-methyl-benzene | 1.5538 | 1.5541 | 82.5°C | 82.3°C |
| 1-Bromo-2-ethyl-benzene | 1.5462 | 1.5462 | 96°C | 97.6°C |
| 1-Bromo-2-isopropyl-benzene | 1.5390 | 1.5385 | 107°C | 107.13°C |

*R. R. Dreisbach, Physical Properties of Chemical Compounds, A.C.S., Washington, D. C., 1955.

1-bromo-2-isopropylbenzene was collected in the temperature range of 106 to 107°C.

The observed boiling points and refractive indexes of the purified materials are compared to the literature values in Table I. Each of these compounds was employed in the synthesis of its respective Grignard reagent, which in turn was reacted with the phenyl and o-cresyl esters. The 1-bromo-2-ethylbenzene and the 1-bromo-2-isopropylbenzene were also employed in the synthesis of 2-ethylbenzoyl chloride and 2-isopropylbenzoyl chloride, respectively.

The o-cresol was Eastman Kodak technical grade material. This was purified by distillation at 30 mm Hg pressure employing a Claisen distillation head on a 1 liter flask. Distillate boiling at 97-98°C was collected and retained. Literature value for boiling point of pure o-cresol is 97.4°C at 30 mm Hg pressure (9). Purified o-cresol was employed in the synthesis of the o-cresol esters of benzoic acid, o-methylbenzoic acid, o-ethylbenzoic acid, and 2-isopropylbenzoic acid.

## SYNTHESIS OF ACID CHLORIDES

Preparation of 2-methylbenzoyl chloride -- One hundred grams of 2-methylbenzoic acid (0.73 mole), Eastman Kodak, was reacted with 139 grams of thionyl chloride (1.17 moles), Eastman Kodak, according to the procedure employed by Zuffanti (10). The 2-methylbenzoic acid was placed in a 500 ml round-bottomed, ground jointed flask equipped with a Claisen distillation head. The side arm of the Claisen head was cork stoppered and the flask inclined at approximately 30 degrees to avoid any retention of condensate in the side arm. After addition of thionyl chloride, a condenser with drying tube was attached and the system gently refluxed for 6.5 hours. The reaction was considered complete when no further evolution of hydrogen chloride and sulfur dioxide was evidenced.

The apparatus was then rearranged to permit normal distillation and unreacted thionyl chloride distilled off at atmospheric pressure, temperature range 75-85°C. A second fraction which was collected at 108 to 113°C at 30 mm Hg pressure was discarded. Ninety-two and five-tenths grams of product were collected at 113°C at 30 mm Hg pressure. The yield was 81.9% of theoretical.

Preparation of 2-ethyl benzoyl chloride -- Seven grams of 1-bromo-2-ethylbenzene was added with 100 ml. of sodium dried ethyl ether to 16.03 gms (0.66 gm. atom) of 99.9% magnesium, Mallinckrodt Grignard Reagent Grade, in a three neck, 1 liter, round bottomed flask, equipped with stirring motor, condenser, and separatory funnel. A crystal of iodine was added to initiate the reaction. After initiation, 115 gms of 1-bromo-2-ethylbenzene dissolved in 450 ml of sodium dried ethyl ether was added to the reaction dropwise over a period of 1 hour. The reaction mixture was gently refluxed for an additional hour to insure complete reaction of the magnesium, and then allowed to cool to room temperature.

The prepared Grignard reagent was then transferred with dry nitrogen pressure onto 800 gms of finely divided solid carbon dioxide in a 5 liter beaker. The system was vigorously stirred during the addition. Unreacted carbon dioxide was allowed to evaporate and the mixture was treated with 350 ml of 10% hydrochloric acid solution containing crushed ice. The mixture was then transferred to a 1 liter separatory funnel and the aqueous phase discarded. Four hundred ml of 10% sodium hydroxide solution was added to the ether solution and the mixture was shaken for 3 minutes. Following separation, the aqueous phase was transferred to a second separatory funnel containing 500 ml of C. P. chloroform and 200 ml of 1.5% hydrochloric acid in water solution. After separation from the water phase, the chloroform solution was evaporated. The yield of crude 2-ethylbenzoic acid melting at 62-64°C was 84.7%. Literature value for melting point is 65°C (11).

The 2-ethylbenzoic acid was converted to 2-ethylbenzoyl chloride by the same procedure employed in the synthesis of 1-methylbenzoyl chloride. Seventy-six and four-tenths grams of the crude acid (0.5 mole) was reacted with 95 grams thionyl chloride (0.8 mole) for a period of 3.5 hours. The reaction mixture was distilled at 300 mm Hg pressure. Approximately 10% of the total product was discarded in the initial fraction. The yield of acid chloride collected at a constant boiling point of 120°C at 30 mm Hg was 84.6% based on the weight of acid employed; 71.8% based on the initial starting material, 1-bromo-2-ethylbenzene.

Preparation of 2-isopropylbenzoyl chloride -- The acid chloride of 2-isopropylbenzoic acid was prepared in the exact manner employed in the synthesis of 2-ethylbenzoyl chloride. One hundred and ten grams of previously purified 1-bromo-2-isopropylbenzene (0.55 mole) was reacted for 3 hours with 13.4 grams of 99.9% pure magnesium (0.55 gram atoms) in a total of 550 ml anhydrous ethyl ether. In addition to employing a crystal of iodine to initiate the reaction, two drops of 1-bromo-2-methylbenzene were added. The resulting Grignard reagent was transferred by nitrogen pressure onto 1000 grams of finely divided solid carbon dioxide. The yield of crude 2-isopropylbenzoic acid was 84.2%. It was initially a dark amber liquid which solidified after prolonged storage. The observed melting point was 53 to 55°C.

Sixty-four and nine-tenths grams of crude 2-isopropylbenzoic acid (0.4 mole) was reacted with 76 g thionyl chloride (0.64 mole) for 6.5 hours. After discarding the initial 10% fraction, 61.6 grams of 2-isopropylbenzoyl chloride were collected over a boiling range of 127 to 128°C at 30 mm Hg pressure. The yield of acid chloride was 93.5% based upon the amount of 2-isopropylbenzoic acid; 77.7% based upon the initial amount of 1-bromo-2-isopropylbenzene.

## SYNTHESIS OF ESTERS

Phenol and o-cresol esters of benzoic, 2-methylbenzoic, 2-ethylbenzoic, and 2-isopropylbenzoic acids were prepared from the corresponding acid chlorides according to the method recommended by Hickenbottom (12). In each instance an equivalent molecular weight of the acid chloride was added to the phenol, Eastman Kodak Reagent Grade, or purified o-cresol dissolved in five times its weight of pyridine, Merck & Company Reagent Grade, at 0°C. The reactions were performed in 500 ml Iodine flasks to facilitate vigorous agitation. After standing for 12 hours and attaining a temperature of approximately 25°C, 100 ml of U.S.P. chloroform was added and the mixture was extracted with four equivalent volumes of 1.5% hydrochloric acid, two volumes of 3% sodium carbonate, and two volumes of distilled water. Following removal of the chloroform, the products were purified by deposition from a methyl alcohol solution of 0°C. Precipitation from the methyl alcohol solution was induced by the addition of a small amount of distilled water. Samples of esters not listed previously in the literature were submitted for carbon and hydrogen analysis.

Phenyl benzoate -- One-half mole phenol was caused to react with 0.5 mole benzoyl chloride, Eastman Kodak, melting point -0.5° to 0.5°C. Yield of purified crystals melting at 69-70°C was 94.4 gm., 95.2% theoretical. The melting point of phenyl benzoate is 70°C.

o-Cresyl benzoate -- One-half mole each of o-cresol and benzoyl chloride yielded 99.85 gm of ester, 94.1% yield. Refractive index of colorless liquid at 25°C was 1.5680.

Phenyl o-methylbenzoate -- Four-tenths mole each of phenol and o-methylbenzoyl chloride yielded 69.6 gms, 84.1% theoretical. Refractive index of light yellow liquid at 25°C was 1.5695.

o-Cresyl o-methylbenzoate -- Two-tenths mole each of o-cresol and o-methylbenzoyl chloride yielded 30.9 gms ester, 69.78% theoretical. Refractive index at 25°C of light yellow liquid was 1.5657. Carbon-hydrogen analysis revealed 79.46% and 6.34%, respectively; theoretical is C, 79.62% and H, 6.18%.

Phenyl o-ethylbenzoate -- Three-tenths mole each of phenol and o-ethylbenzoyl chloride yielded 57.9 gms ester, 91.4% theoretical. Refractive index at 25°C of amber liquid was 1.5678. Carbon-hydrogen analysis showed C, 79.13% and H, 6.33%; theoretical is C, 79.62% and H, 6.18%.

o-Cresyl o-ethylbenzoate -- Fifteen hundredths mole each of o-cresol and o-ethylbenzoyl chloride yielded 30.5 gms. ester, 90.5% theoretical. Refractive index at 25°C of amber liquid was 1.5593. Carbon-hydrogen analysis showed C, 79.72% and H, 6.72%; theoretical is C, 79.97% and H, 6.71%.

Phenyl o-isopropylbenzoate -- Two-tenths mole each of phenol and o-isopropylbenzoyl chloride yielded 45.9 gms ester, 97.1% theoretical. Refractive index at 25°C of dark amber liquid 1.5551. Carbon-hydrogen analysis showed C, 79.90% and H, 6.83%; theoretical is C, 79.97% and H, 6.71%.

o-Cresyl o-isopropylbenzoate -- One-tenth mole each of o-cresol and o-isopropylbenzoyl chloride yielded 20.8 gms ester, 74.2% theoretical. Refractive index at 25°C of dark amber liquid was 1.5514. Carbon-hydrogen analysis showed C, 79.60% and H, 7.14%; theoretical is C, 80.28% and H, 7.13%.

# REACTION OF GRIGNARD REAGENTS WITH ESTERS

The Grignard reagents prepared from the above bromobenzenes were each reacted with all of the prepared phenyl esters. The effect of the methyl-substituent in the ortho position of the phenyl portion of the esters was studied in the reaction of phenylmagnesium bromide with o-cresyl benzoate and o-cresyl o-isopropylbenzoate, o-methyl-phenylmagnesium bromide with o-cresyl o-methylbenzoate and o-cresyl o-ethylbenzoate, o-ethylphenylmagnesium bromide with o-cresyl o-methylbenzoate and o-cresyl o-ethylbenzoate, and o-isopropyl-phenylmagnesium bromide with o-cresyl benzoate and o-cresyl o-isopropylbenzoate.

In each reaction studied, freshly prepared 25 ml of Grignard reagent in ethyl ether was added to an equal molar amount of ester dissolved in toluene. Grignard reagent concentrations were determined by titration to a methyl orange end-point with 0.2N hydrochloric acid. Initial ester concentrations were 0.025 mole per 100 ml in order to provide nearly equal concentrations in all reactions. Each reaction was allowed to proceed exactly 1 hour and was terminated by addition of a hydrochloric acid solution. Following extraction with sodium carbonate solutions and distilled water to insure complete removal of the liberated phenol or o-cresol, the solutions were azeotropically dried and diluted to standard volumes. Concentrations of ketones and tertiary alcohols were determined by infrared analysis. A typical reaction is exemplified by the reaction of phenylmagnesium bromide with phenyl o-isopropylbenzoate given below.

### Reaction of Phenylmagnesium Bromide with Phenyl o-Isopropylbenzoate --

Preparation and analysis of Grignard Reagent: Fifteen and seven-tenths grams of purified bromobenzene (0.1 mole) was reacted with 2.43 gms of 99 .9% magnesium turnings (0.1 gram atom) in 100 ml of sodium dried ethyl ether. The bromobenzene in ethyl ether was added over a period of one hour to the magnesium; heat was applied for an additional one hour to maintain gentle reflux. No iodine was employed as an activator to avoid subsequent side reactions upon addition to the ester. The phenylmagnesium bromide solution was filtered through a 1 inch pad of Pyrex wool to remove unreacted magnesium. Twenty-five milliliters was transferred into a 125 ml separatory funnel and 2 ml was pipetted into 25 ml of distilled water. The water layer was then titrated with 0.2N hydrochloric acid to the methyl orange end-point. Ten and eight-tenths milliliters of acid were required to attain an end-point. Calculation of mole fraction of phenyl magnesium bromide per 25 milliter was performed by the following equation:

$$\begin{array}{l} \text{Moles of Grignard reagent} \\ \text{per 25 milliliter} \end{array} = \frac{0.2 \text{ x ml of acid}}{2 \text{ x } 1000} \text{ x } 25$$

$$= 0.027 \text{ mole.}$$

One hundred and eight milliliters of phenyl 2-isopropyl-benzoate in toluene solutions at a concentration of 0.025 mole of ester per 100 ml was placed in a 250 ml three neck flask. The flask was equipped with a motor driven Teflon stirrer and a Dean-Stark condensation trap with condenser. The separatory funnel containing the Grignard reagent was attached to the third joint. The Grignard reagent was added in five approximately equal portions over a period of five minutes. Agitation was initiated prior to the addition of the phenylmagnesium bromide. The temperature was raised to 110°C over the next 10 minute interval and removal of ethyl ether was facilitated by means of the Dean-Stark condensation trap. A deep red coloration was formed in the reaction mixture as the ethyl ether was removed. After maintaining the temperature at 110°C for one additional hour, the reaction was quenched by addition of 100 ml of 10% hydrochloric acid solution.

The mixture was transferred to a 250 ml separatory funnel and extracted with two 100 ml portions of 10% sodium carbonate solution and two 100 ml portions of distilled water. Seventy-five milliliters of toluene was added and the toluene solution placed in a 500 ml flask equipped with a Claisen distillation head. The water in solution was removed by azeotropic distillation with the excess toluene and the solution concentrated to approximately 50 ml. After cooling to 20°C, the solution was diluted to 125 ml with sodium dried toluene. The resulting solution was a light amber color. Yield of ketone and percent ketone converted to tertiary alcohol were determined in infrared analysis and were found to be 33.88% and 38.35%, respectively.

The concentrations of reagents employed in all reactions are presented in Table II.

## TABLE II

## MOLE FRACTIONS OF REAGENTS AND VOLUME OF TOLUENE EMPLOYED IN REACTIONS OF GRIGNARD REAGENTS WITH ESTERS

| Reaction | Mole Fraction Reagents | Milliliters Toluene |
|---|---|---|
| Phenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 0.0271 | 133.5 |
| 2) Phenyl *o*-methylbenzoate | 0.0271 | 133.5 |
| 3) Phenyl *o*-ethylbenzoate | 0.0299 | 145 |
| 4) Phenyl *o*-isopropylbenzoate | 0.0271 | 133.5 |
| 5) *o*-Cresyl benzoate | 0.0299 | 145 |
| 6) *o*-Cresyl 2-isopropylbenzoate | 0.0299 | 145 |
| 2-Methylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 0.031 | 149 |
| 2) Phenyl *o*-methylbenzoate | 0.0265 | 131 |
| 3) Phenyl *o*-ethylbenzoate | 0.0265 | 131 |
| 4) Phenyl *o*-isopropylbenzoate | 0.0265 | 131 |
| 5) *o*-Cresyl *o*-methylbenzoate | 0.0234 | 119 |
| 6) *o*-Cresyl *o*-ethylbenzoate | 0.0234 | 119 |
| 2-Ethylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 0.0254 | 126.5 |
| 2) Phenyl *o*-methylbenzoate | 0.0254 | 126.5 |
| 3) Phenyl *o*-ethylbenzoate | 0.026 | 129 |
| 4) Phenyl *o*-isopropylbenzoate | 0.0313 | 150 |
| 5) *o*-Cresyl *o*-methylbenzoate | 0.0313 | 150 |
| 6) *o*-Cresyl *o*-ethylbenzoate | 0.0313 | 150 |
| *o*-Isopropylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 0.0264 | 130.5 |
| 2) Phenyl *o*-methylbenzoate | 0.0264 | 130.5 |
| 3) Phenyl *o*-ethylbenzoate | 0.0265 | 131 |
| 4) Phenyl *o*-isopropylbenzoate | 0.0274 | 135 |
| 5) *o*-Cresylbenzoate | 0.0274 | 135 |
| 6) *o*-Cresyl *o*-isopropylbenzoate | 0.0274 | 135 |

## METHODS OF ANALYSIS

Concentrations of diaryl ketone and triaryl tertiary alcohols produced in the above reactions were determined by infrared analysis using a Perkin-Elmer Model 21 Double Beam Infrared Spectrophotometer. Employing benzophenone as a standard, a molar extinction coefficient of 360 was obtained. Since the maximum absorption of all diaryl ketones obtained in this study appeared at 6 microns, this molar extinction coefficient was employed for all ketone determinations. The validity of this treatment has been discussed by Bellamy (14). The determination of the triaryl tertiary alcohols required the use of a calibration graph obtained with triphenylcarbinol. An attempt to correlate infrared analysis with precipitation methods of analysis was made employing hydroxylamine hydrochloride determinations of three ketones and 3,5-dinitrobenzoyl chloride determinations of three alcohols. Analysis of unreacted ester was affected by hydrolyzing the ester with sodium hydroxide and titrating the acid salt.

### Determination of Ketone Concentrations

Infrared Method -- The molar extinction coefficient of benzophenone was determined by measuring the absorptions of four solutions of the ketone in sodium dried C. P. toluene. Solution concentrations in grams per liter were 25, 12.5, 5, and 1. Absorptions were determined with a Double Beam Perkin-Elmer Infrared Spectrophotometer Model 21. Sodium chloride solution cells of 0.05 cm thicknesses were employed in the sample and in the reference positions of the instrument. Sodium dried

C. P. toluene was placed in the reference cell. Extinction coefficients were calculated by the following equation:

$$e = -\frac{M}{cd} \log \frac{I}{I_0}$$

e = Molar extinction coefficient

M = Molecular weight of ketone

c = Concentration of ketone in grams per liter

d = Thickness of cell in centimeters

I = Intensity of light transmitted

$I_0$= Intensity of light at zero absorption.

The values of the molar extinction coefficients obtained with the standard benzophenone solutions are presented in Table III. At concentrations of 1 to 5 grams per liter, the molar extinction coefficient is approximately a constant 360 at 6.0 microns. This value differs from the extinction coefficient of 404 found by Cross and Rolfe at 6.09 microns (13). In subsequent analysis of ketones, it was found that the area of maximum absorption was constant for all diaryl ketones prepared in this study. Therefore, the experimentally determined extinction coefficient for benzophenone was employed in all calculations. This decision was made on the basis of the findings of Bellamy (14) which indicated that the extinction coefficient of similar compounds remains constant provided there is no change in area of maximum absorption.

To determine the effect of the triaryl tertiary alcohols and aryl esters upon the maximum absorption peak of benzophenone, the infrared

## TABLE III

## INFRARED MOLAR EXTINCTION COEFFICIENTS FOR BENZOPHENONE IN TOLUENE AT 6.0 MICRONS

| Concentration Benzophenone in grams/liter | Molar Extinction Coefficient x 36.44 |
|---|---|
| 25 | 14.07 |
| 12.5 | 12.27 |
| 5 | 10.19 |
| 3 | 10.10 |
| 1 | 10.07 |

spectrograph of a toluene solution containing 16.66 grams per liter benzophenone, 8.33 grams per liter triphenylcarbinol, and 6.66 grams per liter *o*-cresyl benzoate was studied. The spectrographs of triphenylcarbinol and *o*-cresyl benzoate were also studied individually. Neither the tertiary alcohol nor the ester exhibited absorptions in the 5.9 to 6.1 micron range. The *o*-cresyl benzoate exhibited a sharp absorption at 5.75 microns, and the triphenylcarbinol absorbed at 2.80 microns.

A sample calculation of the ketone concentration is exemplified employing the data obtained in the analysis of the reaction mixture of *o*-ethylphenylmagnesium bromide with phenyl *o*-ethylbenzoate diluted to 500 ml.

Reaction: 0.026 mole ester
0.026 mole Grignard reagent

Infrared absorption: I = 47.8

Concentration of ketone in grams per liter

$$= -\frac{M}{360 \times 0.05} \log \frac{I}{I_0}$$

$$= -\frac{238.31}{18} \log 0.478$$

$$= 13.24 \times 0.321$$

$$= 4.25 \text{ grams per liter}$$

Total number of grams per 500 ml is 2.13

Theoretical yield of ketone:

Molecular weight of ketone = 238.31

238.31 x 0.026 = 6.20 grams

Percent yield:

(2.13 ÷ 6.2)100 = 34.4%

The results of all infrared ketone determinations are incorporated with infrared determinations of alcohol concentrations in Table V.

*Hydroxylamine Hydrochloride Method* -- In an effort to correlate the results obtained by infrared analysis the oximes of the ketones produced in the reactions of *o*-ethylphenylmagnesium bromide phenyl, with phenyl *o*-ethylbenzoate, *o*-methylphenylmagnesium bromide with phenyl *o*-methylbenzoate, and *o*-isopropylphenylmagnesium bromide with phenyl *o*-isopropylbenzoate were prepared by the method outlined by Byrant and Smith (15). A 25 ml aliquot of the reaction mixture in 125 ml toluene solution was placed in a Citrate of Magnesia bottle with 30 ml 0.5 N hydroxylamine hydrochloride in 80% ethanol and 100 ml of a 20% pyridine in ethanol solution containing 0.2% bromophenol blue indicator. The samples and a blank containing only toluene with the reagents were heated in a water bath at 95°C for 4 hours. After cooling to room temperature, the samples were titrated with 0.36 N potassium hydroxide in methanol and 0.20 N hydrochloric acid in methanol to the color of the blank sample. In addition to the unknown samples, one known to contain 1.05 gms of benzophenone was analyzed. An example of the method of calculation is shown with the known benzophenone sample.

Milliliters 0.36 N KOH = 16.77
Milliliters 0.20 N HCl = 0.27

$$\text{grams of benzophenone} = [(16.77 \times 0.36) - (0.27 \times 0.20)]\ 0.1822$$

$$= 1.09$$

Percent error:

$$[(1.09 - 1.05) \div 1.04]\ 100 = +\ 3.5\%$$

Analysis indicated: 2.0 grams ketone, 32.3% yield, in reaction of o-ethylphenylmagnesium bromide with phenyl o-ethylbenzoate; 2.55 grams ketone, 46.6% yield, in reaction of o-methylphenylmagnesium bromide with phenyl o-methylbenzoate; and 1.20 grams, 16.6% yield, in reaction of o-isopropylphenylmagnesium bromide with phenyl o-isopropylbenzoate. These results compare, respectively, to 34.4%, 49.5%, and 21.8% obtained by infrared analysis.

## DETERMINATION OF ALCOHOL CONCENTRATIONS

Infrared Method -- Infrared analysis of solutions of triphenyl carbinol of varying concentrations from 2.5 to 25 grams per liter indicated that a constant molar extinction coefficient was not exhibited in this range. Therefore a ~~the~~ calibration graph, ~~Figure 1,~~ was made, plotting percent absorption against concentration of benzophenone. Data employed in plotting this graph was obtained employing 0.05 centimeter solution cells and is presented in Table IV.

The series of triaryl tertiary alcohols analyzed all exhibited absorption at 2.8 microns. Therefore it was assumed, as in the case of the ketone determinations, that all alcohol concentrations could be determined from the same graph. Results of these determinations are presented in Table V.

3,5-Dinitrobenzoyl Chloride Method -- To correlate the infrared analysis of alcohol concentrations, 3,5-dinitrobenzoyl chloride derivatives were prepared of the alcohols formed in the reactions of phenylmagnesium bromide with phenyl benzoate, phenyl-o-methylbenzoate, and

## TABLE IV

## ABSORPTION OF TRIPHENYLCARBINOL IN TOLUENE AT 2.80 MICRONS WITH 0.05 CM. NaCl SOLUTION CELL

| Triphenylcarbinol Concentration grams liter | Percent Absorption |
|---|---|
| 18.75 | 33.57 |
| 12.50 | 22.14 |
| 10.0 | 18.57 |
| 6.25 | 11.78 |
| 5.0 | 6.79 |
| 2.5 | 1.43 |

# TABLE V

## INFRARED DETERMINATION OF DIPHENYL KETONES AND TRIPHENYL TERTIARY ALCOHOLS IN REACTIONS OF GRIGNARD REAGENTS WITH ESTERS

| Reaction | Ketone (grams) | Tertiary Alcohol (grams) |
|---|---|---|
| Phenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 0.21 | 2.01 |
| 2) Phenyl *o*-methylbenzoate | 0.98 | 1.38 |
| 3) Phenyl *o*-ethylbenzoate | 1.28 | 1.48 |
| 4) Phenyl *o*-isopropylbenzoate | 1.27 | 1.07 |
| 5) *o*-Cresyl benzoate | 0.22 | 3.05 |
| 6) *o*-Cresyl *o*-isopropylbenzoate | 0.80 | 1.33 |
| 2-Methylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 1.54 | 0.72 |
| 2) Phenyl *o*-methylbenzoate | 2.71 | 0.47 |
| 3) Phenyl *o*-ethylbenzoate | 2.68 | 0.50 |
| 4) Phenyl *o*-isopropylbenzoate | 2.16 | 0.60 |
| 5) *o*-Cresyl 2-methylbenzoate | 2.15 | 0.56 |
| 6) *o*-Cresyl 2-ethylbenzoate | 1.82 | 0.66 |
| 2-Ethylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 1.79 | 0.60 |
| 2) Phenyl *o*-methylbenzoate | 1.70 | 0.70 |
| 3) Phenyl *o*-ethylbenzoate | 2.13 | 0.62 |
| 4) Phenyl *o*-isopropylbenzoate | 2.90 | 0.62 |
| 5) *o*-Cresyl 2-methylbenzoate | 2.71 | 0.64 |
| 6) *o*-Cresyl 2-ethylbenzoate | 2.65 | 0.74 |
| 2-Isopropylphenylmagnesium Bromide | | |
| 1) Phenyl benzoate | 1.99 | 0.52 |
| 2) Phenyl *o*-methylbenzoate | 2.47 | 0.56 |
| 3) Phenyl *o*-ethylbenzoate | 1.67 | 0.40 |
| 4) Phenyl *o*-isopropylbenzoate | 1.59 | 0.57 |
| 5) *o*-Cresylbenzoate | 1.50 | 0.66 |
| 6) *o*-Cresyl 2-isopropylbenzoate | 1.16 | 0.70 |

phenyl o-ethylbenzoate. As a control reaction, a solution known to contain 0.500 grams triphenylcarbinol in 25 ml toluene was also analyzed by this method. For the unknown concentrations, a 25 ml aliquot of the reaction mixtures in 125 ml was dissolved in 25 ml C. P. pyridine, Eastman Kodak, and cooled to 0°C in 125 ml Iodine flasks. One gram of 3,5-dinitrobenzoyl chloride was added to each sample and the mixtures were allowed to stand for 6 days. Samples were then washed with four equal volumes of 5% hydrochloric acid, five equal volumes of 10% sodium carbonate, and two volumes of distilled water. The samples were then evaporated down to approximately 5 ml, and 50 ml of a 50% toluene 50% methyl alcohol solution added. This solution was cooled to 0°C. for 4 hours and then filtered through weighed filter papers. The filtrate were evaporated to approximately 50% and chilled to 0°C for 4 hours. In no instance was there evidence of crystallization in the filtrates. The method of calculation of weight of alcohol is exemplified with the known concentration of triphenylcarbinol.

Molecular weight of triphenyl carbinol = 260.32

Molecular weight of 3,5 dinitrobenzoic acid ester of triphenyl carbinol = 454.42

Gravimetric factor $= \frac{260.32}{454.42} = 0.5729$

Weight of ester = 0.2417 grams

Weight of alcohol = 0.2417 x 0.5729

= 0.1385 grams

Percent yield = 100 [0.139 ÷ 0.500]

= 27.7%

Analysis of samples indicated 0.527 grams alcohol in reaction of phenylmagnesium bromide with phenyl benzoate, 0.373 grams alcohol in the reaction with phenyl o-methylbenzoate, and 0.387 grams alcohol in the reaction with phenyl o-ethylbenzoate. These results compare, respectively, with 2.01 grams, 1.38 grams and 1.48 grams alcohol as determined by infrared analysis.

It is interesting to note that the gravimetric determination of the known sample of triphenylcarbinol was approximately one-fourth of the actual amount present. If the gravimetric determinations obtained with the unknown samples are each multiplied by 4, they are, respectively, 2.11 gm., 1.49 gm., and 1.55 gm., closely correlating with the infrared determinations.

## Determination of Unreacted Ester

The amount of unreacted ester was determined by hydrolysis in six of the reactions studied. Hydrolysis was accomplished by refluxing 20 ml of the ester in toluene with 25 ml of 0.22 N sodium hydroxide in 90% ethylene glycol 10% water solution for 24 hours. Fifty milliliters of ethanol was added and the mixture was titrated with 0.196 N hydrochloric acid in ethanol to a pH of 9.75 employing a Beckman Model G pH Meter equipped with glass and calomel electrodes. The equivalence point was determined by plotting pH curves of the standard sodium hydroxide solution and the sodium hydroxide solution containing 1 milliequivalent of phenol. In this manner the difference in titration of the blank and unknown samples was a measure of the milliequivalents of aryl acid and hence, the original ester.

The reactions in which the unreacted ester was determined are presented in Table VI. The method of calculation is exemplified in the analysis of the o-cresyl benzoate in the toluene solution obtained in the reaction of the ester with phenylmagnesium bromide.

Ml. of toluene solution of ester = 20
at 0.030 mole/250 ml.
Ml. of 0.22 N NaOH in Ethylene glycol = 25
Ml. of 0.196 N HCl in Ethanol = 20.92
Meq. ester = (25 x 0.22) - (20.91 x 0.196)
present in solution
= 5.50 - 4.09
= 1.41

Percent ester reacted.

$$\frac{2.39-1.41}{2.39} \times 100 = 41.2\% \text{ ester reacted}$$

## TABLE VI

## EXTENT OF ESTER REACTION WITH ARYL GRIGNARD REAGENTS AS DETERMINED BY HYDROLYSIS AND AMOUNT OF KETONE FORMED

| Reaction | Percent Ester Reacted | |
|---|---|---|
| | Determined by Hydrolysis | Determined by Ketone Formed |
| Phenyl *o*-ethyl benzoate with phenylmagnesium bromide | 35.6 | 37.5 |
| Phenyl *o*-ethylbenzoate with *o*-methylphenylmagnesium bromide | 49.5 | 51.0 |
| Phenyl *o*-isopropylbenzoate with *o*-methylphenylmagnesium bromide | 58.3 | 60.1 |
| *o*-Cresyl benzoate with phenylmagnesium bromide | 51.2 | 43.1 |
| *o*-Cresyl *o*-methylbenzoate with *o*-ethylphenylmagnesium bromide | 52.4 | 44.7 |
| *o*-Cresyl *o*-isopropylbenzoate with phenylmagnesium bromide | 39.3 | 26.6 |

# RESULTS

The results of this study are assembled in four tables according to the Grignard reagent employed. The data are presented on the basis of: 1) the total yield of ketone complex,* calculated from the actual yield of ketone plus the weight of ketone or ketone complex consumed in the formation of tertiary alcohol; 2) the percent of the total ketone complex which was converted to alcohol during the reaction and 3) the percent of Grignard reagent reacting to give ketone and alcohol. On the basis of these comparisons, the results indicate that the over-all reactivity of the esters, based on percent Grignard reagent reacted, decreases with increased size of the alkyl substituent on the Grignard reagent. The results also indicate that the ketone or ketone complex is more reactive toward phenylmagnesium bromide than is the ester, that the electron donating ability of the alkyl group is probably more important in the Grignard reagent than in the ester, that steric hindrance is slightly less important in the ester than in the Grignard reagent. Finally, the results indicate that the o-cresyl esters are less reactive than the corresponding phenyl esters and that the percent of ketone complex reacting to give tertiary alcohol is higher with the o-cresyl esters than with the phenyl esters.

---

*The ketone complex is considered to be the intermediate resulting when one molecule of a Grignard reagent reacts with one molecule of an ester. This complex may decompose to the ketone or it may react with more Grignard reagent to form a tertiary alcohol.

## The Phenylmagnesium Bromide Series

The results of the reactions of phenylmagnesium bromide with the phenyl esters of the four benzoic acids, benzoic, methylbenzoic, ethylbenzoic and isopropyl-benzoic, and the o-cresyl esters of benzoic and isopropylbenzoic acid are presented in Table VII. With both the phenyl and o-cresyl esters the over-all reactivity, based upon the amount of Grignard reagent reacted, decreased with the introduction of an alkyl substituent on the acyl portion of the ester. With the phenyl esters of o-methyl and o-ethyl benzoic acid there was only a slight difference in the over-all reactivity and in the amount of ketone converted to alcohol. A more significant decrease was experienced with phenyl 2-isopropylbenzoate. These results indicate that the introduction of an alkyl substituent in the acyl portion of the ester results in decreased reactivity of both the ester and the resulting ketone intermediate. The results also indicate that the most marked decrease of reactivity takes place in the ketone complex since the greatest decrease in the amounts of complex converted to alcohol occurs in descending from phenyl benzoate to phenyl 2-methylbenzoate and from phenyl 2-ethylbenzoate to phenyl 2-isopropylbenzoate. In the case of phenyl benzoate, the resulting ketone complex was sufficiently more reactive than the ester to result in a lower yield of total ketone as compared to the other phenyl esters. Table VII indicates that o-cresyl benzoate is considerably more reactive than phenyl benzoate but that o-cresyl o-isopropylbenzoate is somewhat less reactive than the corresponding phenyl ester. Significantly, however, the percents of ketone complex

## TABLE VII

## PERCENT KETONE COMPLEX FORMED, PERCENT KETONE COMPLEX CONVERTED TO ALCOHOL AND PERCENT GRIGNARD REAGENT REACTING IN THE REACTIONS OF PHENYLMAGNESIUM BROMIDE WITH ARYL ESTERS

| Ester | Percent Ketone Complex Formed | Percent Ketone Complex Converted to Alcohol | Percent Grignard Reacting |
|---|---|---|---|
| Phenyl benzoate | 32.79 | 87.04 | 62.96 |
| Phenyl o-methylbenzoate | 37.01 | 50.05 | 55.55 |
| Phenyl o-ethylbenzoate | 37.52 | 45.72 | 54.67 |
| Phenyl o-isopropylbenzoate | 33.88 | 38.35 | 48.15 |
| o-Cresyl benzoate | 43.12 | 90.85 | 80.27 |
| o-Cresyl isopropylbenzoate | 26.64 | 55.08 | 40.23 |

converted to alcohol is greater for both o-cresyl benzoate and o-cresyl o-isopropylbenzoate than for the corresponding phenyl esters. This indicates that the ketone complex somehow controls the reaction which produces alcohol.

## The o-Methylphenylmagnesium Bromide Series

Table VIII presents the results obtained in the reactions of 2-methylphenylmagnesium bromide with the same four phenyl esters and the o-cresyl esters of 2-methylbenzoic acid and 2-ethylbenzoic acid. In this series the amount of Grignard reagent reacted and the total amount of ketone formed both decreased as the size of the alkyl substituent increased, the more significant change taking place between the 2-ethylbenzoate and 2-isopropylbenzoate. In contrast to the previous series, the reactivity of the ketone complex increased.

These results suggest that decomposition of the ketone complex is especially sensitive to steric hindrance but that, as the hindrance increases, the complex becomes slightly more reactive. This is possibly due to a loosening of the bonds of the complex which would enhance reaction with any reagent which could break through the steric barrier. In addition, the o-methyl group of the Grignard reagent apparently increases the ease with which the ketone complex forms. The total ketone complex formed is increased from 8 to 17 percent in this series.

The over-all yield of ketone and percent Grignard reagent reacted are less for the o-cresyl esters of this series than for the phenyl esters. The percent of ketone complex converted to alcohol is

## TABLE VIII

## PERCENT KETONE COMPLEX FORMED, PERCENT KETONE COMPLEX CONVERTED TO ALCOHOL AND PERCENT GRIGNARD REAGENT REACTING IN THE REACTIONS OF o-METHYLPHENYLMAGNESIUM BROMIDE WITH ARYL ESTERS

| Ester | Percent Ketone Complex Formed | Percent Ketone Complex Converted to Alcohol | Percent Grignard Reacting |
|---|---|---|---|
| Phenyl benzoate | 33.38 | 21.14 | 41.94 |
| Phenyl o-methylbenzoate | 55.39 | 10.79 | 60.38 |
| Phenyl o-ethyl benzoate | 51.01 | 11.68 | 56.60 |
| Phenyl o-isopropylbenzoate | 41.52 | 16.72 | 49.06 |
| o-Cresyl o-methylbenzoate | 51.63 | 15.31 | 59.82 |
| o-Cresyl o-ethylbenzoate | 43.62 | 20.44 | 51.28 |

considerably greater for the o-cresyl compounds than for the corresponding phenyl esters. Both of these observations confirm the trend noted in the previous series, i.e. that the o-cresyl esters are less reactive than their phenyl analogues but that the o-cresyl moiety is involved in the reactions which produce alcohol.

## The o-Ethylphenylmagnesium Bromide Series

The results of the reactions of the four phenyl esters and the o-cresyl esters of o-methylbenzoic acid and o-ethylbenzoic acid with o-ethylphenylmagnesium bromide are presented in Table IX. The over-all reactivity and the total ketone complex formed increases slightly as the size of the o-substituent in the acyl portion of the ester increases. There is, however, a decrease in reactivity in this series compared to the previous series. This decrease is greatest with the o-methyl and o-ethylbenzoates. The percent of ketone complex reacting to form alcohol is observed to decrease as the size of the o-substituent on the acyl portion of the ester increases. This parallels the results obtained with phenylmagnesium bromide.

The results obtained with the ortho-cresyl esters are similar to those obtained in the previous series. The amount of ketone converted to alcohol increases with increasing size of the alkyl substituent; however, these values do not increase in comparison to the corresponding phenyl esters of the series.

## The o-Isopropylphenylmagnesium Bromide Series

The results obtained in the reactions of the four phenyl esters and

## TABLE IX

## PERCENT KETONE COMPLEX FORMED, PERCENT KETONE COMPLEX CONVERTED TO ALCOHOL AND PERCENT GRIGNARD REAGENT REACTING IN THE REACTIONS OF o-ETHYLPHENYLMAGNESIUM BROMIDE WITH ARYL ESTERS

| Ester | Percent Ketone Complex Formed | Percent Ketone Complex Converted to Alcohol | Percent Grignard Reacting |
|---|---|---|---|
| Phenyl benzoate | 41.01 | 18.22 | 48.48 |
| Phenyl o-methylbenzoate | 38.25 | 21.79 | 46.51 |
| Phenyl o-ethylbenzoate | 41.13 | 16.86 | 47.24 |
| Phenyl o-isopropylbenzoate | 42.33 | 13.05 | 47.85 |
| o-Cresyl o-methylbenzoate | 44.67 | 13.82 | 50.84 |
| o-Cresyl o-ethylbenzoate | 42.42 | 16.20 | 49.29 |

the o-cresyl esters of benzoic acid and o-isopropylbenzoic acid with o-isopropylphenylmagnesium bromide closely resemble those obtained in the o-methylphenylmagnesium bromide series. The results of this series are presented in Table X. Both the percent Grignard reagent reacted and the total ketone complex formed decrease with increasing size of the alkyl substituent on the ester. This decrease is greatest between the reactions of phenyl o-methylbenzoate and phenyl o-ethyl benzoate.

As the size of the alkyl substituent of the ester increases the percent of ketone complex reacting to form alcohol also increases. A similar trend appears when o-methylphenylmagnesium bromide is used. The results with the o-cresyl esters indicate again the lower reactivity of these esters compared with the corresponding phenyl esters. The percent ketone complex reacting to form alcohol is much higher for the o-cresyl esters than for the phenyl compounds supporting the trend of the first and second series.

## TABLE X

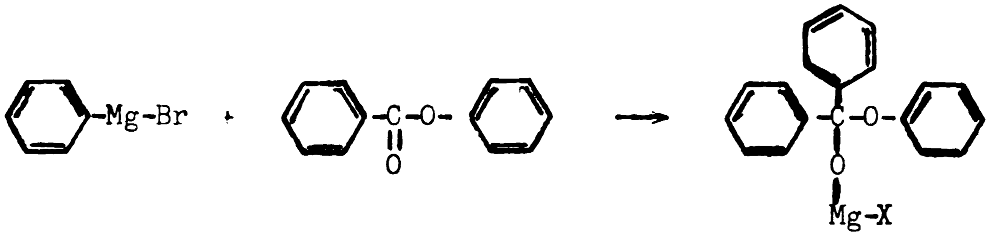
## PERCENT KETONE COMPLEX FORMED, PERCENT KETONE COMPLEX CONVERTED TO ALCOHOL AND PERCENT GRIGNARD REAGENT REACTING IN THE REACTIONS OF o-isoPROPYLPHENYLMAGNESIUM BROMIDE WITH ARYL ESTERS

| Ester | Percent Ketone Complex Formed | Percent Ketone Complex Converted to Alcohol | Percent Grignard Reacting |
|---|---|---|---|
| Phenyl benzoate | 39.49 | 14.55 | 44.23 |
| Phenyl o-methylbenzoate | 45.29 | 13.10 | 51.21 |
| Phenyl o-ethylbenzoate | 29.15 | 14.26 | 33.30 |
| Phenyl o-isopropylbenzoate | 27.18 | 19.85 | 32.57 |
| o-Cresyl benzoate | 31.46 | 22.28 | 38.39 |
| o-Cresyl o-isopropylbenzoate | 22.51 | 29.39 | 29.25 |

# DISCUSSION

The results of this work may be conveniently summarized under three headings, i.e. the effect of steric factors on 1) the formation of the ketone complex, 2) the reaction of this complex to produce the alcohol and 3) the total amount of Grignard reagent reacting.

The formation of the ketone complex, which can be simply represented by the reaction:



is apparently only slightly affected by steric factors of the order of magnitude employed in this work. This can be visualized clearly by reference to Table XI which assembles the yields of ketone complex obtained from the block of experiments reported in this study. Only when o-isopropylphenylmagnesium bromide is employed does the yield of complex decrease appreciably. The activating effect of the o-methyl group of o-tolylmagnesium bromide is, however, quite apparent.

The stability of this complex, which has long been a topic of speculation, is apparently great enough that the rate of formation of alcohol is controlled by it. Until now, the question of alcohol formation has centered about two questions: 1) does the complex decompose to ketone and the ketone then react with more Grignard reagent to give alcohol or 2) does the Grignard reagent react directly with the

## TABLE XI

## PERCENT OF KETONE COMPLEX FORMED WITH PHENYL ARYL ESTERS AND ARYL GRIGNARD REAGENTS

| Grignard Reagent* | Ester* | | | |
|---|---|---|---|---|
| | o-Hydrogen | o-Methyl | o-Ethyl | o-Isopropyl |
| o-Hydrogen | 32.79 | 37.01 | 37.52 | 33.88 |
| o-Methyl | 33.38 | 55.39 | 51.01 | 41.52 |
| o-Ethyl | 41.01 | 38.25 | 41.13 | 42.33 |
| o-Isopropyl | 39.49 | 45.29 | 29.15 | 27.18 |

*Yields are reported in percent of the theoretical quantity of ketone complex.

complex? The results of this work strongly suggest that the latter interpretation is correct. This is based on the following reasoning: A comparison of the yields of alcohol from reactions of o-cresyl or phenyl esters indicates that the o-cresyl compounds give higher yields than the corresponding phenyl esters. This can only mean that the formation of alcohol is dependent on the aryloxy portion of the ester. Since this group is not present in the ketone, it seems reasonable to propose that the ketone complex is sufficiently stable so that either the Grignard must react with it or with the ketone which is formed only after the slow decomposition of this complex. In either case the complex will control the reaction.

The fact that the o-cresyl esters increase the alcohol yield is also significant. If the o-methyl group acts sterically it will tend to loosen the complex and possibly hasten its decomposition to ketone. This favors the picture of Grignard reaction with the ketone. If the o-methyl group acts electrically its election donating properties will increase the basicity of oxygen atoms in the complex and will favor the picture of Grignard reaction with the complex.

A possible clarification of this picture can be seen by examining the values obtained for percent of ketone complex going to alcohol. These values are arranged in block pattern in Table XII. Here the striking steric effect produced by changing the Grignard reagent from the phenyl to the o-alkyl compounds strongly suggests that the Grignard reagent is reacting with the complex rather than with the ketone since the latter type of reaction is not expected to be so profoundly affected by such a change.

## TABLE XII

## PERCENT OF KETONE COMPLEX REACTING TO FORM ALCOHOL IN REACTIONS OF ARYL GRIGNARD REAGENTS WITH PHENYL ARYL ESTERS

| Grignard Reagent | Ester | | | |
|---|---|---|---|---|
| | o-Hydrogen | o-Methyl | o-Ethyl | o-Isopropyl |
| o-Hydrogen | 87.04 | 50.05 | 45.72 | 38.35 |
| o-Methyl | 21.14 | 10.79 | 11.68 | 16.72 |
| o-Ethyl | 18.22 | 21.79 | 16.86 | 13.05 |
| o-Isopropyl | 14.55 | 13.10 | 14.26 | 19.85 |

An examination of the block pattern (Table XIII) of the values obtained for the total Grignard reagent reacting with phenyl esters presents some interesting correlations. The diagonal values extending from upper right to lower left may be viewed as follows: the two values at the ends of the diagonal illustrate the interaction of an o-hydrogen and an o-isopropyl group. The greater reactivity is obtained when the o-isopropyl group is in the ester rather than in the Grignard reagent. The remaining two diagonal values illustrate the interactions of o-methyl and o-ethyl groups. Here, the greater reactivity is obtained when the ethyl group is in the ester rather than in the Grignard reagent.

Reading along the diagonal extending from upper left to lower right indicates the relative magnitude of steric interaction between two o-hydrogen atoms, two o-methyl, two o-ethyl and two o-isopropyl groups respectively. The electrical properties of the o-methyl group are apparently not great enough to overcome its steric factor in this reaction. This is shown by the fact that the o-methyl interaction gives slightly less reactivity than the o-hydrogen interaction. If electrical factors predominate, a greater reactivity would be expected.

Finally a comparison of these diagonal relations with the corresponding values obtained from the o-cresyl esters indicates the same trends as those noted above but with lower reactivities for the o-cresyl compounds. This latter summary (Table XIV) best exemplifies the interplay among the three types of steric factors in the reaction under study.

## TABLE XIII

## PERCENT OF GRIGNARD REAGENT REACTING IN REACTIONS OF ARYL GRIGNARD REAGENTS WITH PHENYL ARYL ESTERS

| Grignard Reagent | Ester | | | |
|---|---|---|---|---|
| | *o*-Hydrogen | *o*-Methyl | *o*-Ethyl | *o*-Isopropyl |
| *o*-Hydrogen | 62.96 | 55.55 | 54.67 | 48.15 |
| *o*-Methyl | 41.94 | 60.38 | 56.60 | 49.06 |
| *o*-Ethyl | 48.48 | 46.51 | 47.24 | 47.85 |
| *o*-Isopropyl | 44.23 | 51.21 | 33.30 | 32.59 |

## TABLE XIV

## PERCENT OF GRIGNARD REAGENT REACTING IN REACTIONS OF ARYL GRIGNARD REAGENTS WITH PHENYL AND o-CRESYL ESTERS

| Grignard Reagent | Ester | | | |
|---|---|---|---|---|
| | o-Hydrogen | o-Methyl | o-Ethyl | o-Isopropyl |
| o-Hydrogen | 62.96<br>80.27 | | | 48.15<br>40.23 |
| o-Methyl | | 60.38<br>59.82 | 56.60<br>51.28 | |
| o-Ethyl | | 46.51<br>50.85 | 47.24<br>49.29 | |
| o-Isopropyl | 44.23<br>38.39 | | | 32.57<br>29.25 |

Note: Values in the upper portion of the square refer to phenyl esters; values in the lower portion refer to o-cresyl esters.

# CONCLUSIONS

1. Results of this work indicate that bulky groups in any of the three steric areas, i.e. the acyl portion of the ester, the aryloxy portion of the ester and the Grignard reagent, hinder the reaction of the Grignard reagent with ester.

2. The degree of hindrance has been shown to increase with the increased size of the o-substituent as anticipated.

3. Substitution in the ortho position of the Grignard reagent has been shown to cause the greatest hindrance.

4. Formation of the initial complex between Grignard and ester has been shown to be not appreciably affected by steric factors of the order of magnitude employed in this study.

5. The reaction by which alcohol is formed has been shown to be markedly influenced by steric factors in the aryloxy portion of the ester.

6. Evidence to show that the alcohol is formed by a direct reaction of the initial complex with Grignard reagent is presented.

# BIBLIOGRAPHY

(1) R. C. Fuson, E. M. Bottorff, and S. B. Speck, J. Am. Chem. Soc., 64, 1450-1453 (1942).

(2) R. T. Arnold, H. Blank, R. Liggett, J. Am. Chem. Soc., 63, 3444-3446 (1941).

(3) D. R. Boyd and H. H. Hatt, J. Chem. Soc., 80, 898-910 (1927).

(4) E. P. Kohler and R. Baltzly, J. Am. Chem. Soc., 54, 4015-26 (1932).

(5) L. Smith and C. Guss, J. Am. Chem. Soc., 59, 804-805 (1937).

(6) C. R. Hauser, P. Saperstein and J. C. Shivers, J. Am. Chem. Soc., 70, 606-608 (1948).

(7) F. C. Whitmore and R. S. George, J. Am. Chem. Soc., 64, 1239-1240 (1942).

(8) M. S. Kharasch and O. Reinmuth, Grignard Reactions of Nonmetallic Substances, New York, Prentice-Hall, 1954, pp. 549-688.

(9) R. R. Dreisbach, Physical Properties of Chemical Compounds, A.C.S. June 1955, Washington, D. C.

(10) Saverio Zuffanti, J. Chem. Education, 25 481 (1948).

(11) M. Crawford and F. H. C. Stewart, J. Chem. Soc., 4443-7 (1952).

(12) W. J. Hickinbottom, Reactions of Organic Compounds, Longmans, Green and Co., New York, 1948, pp. 258-261.

(13) J. Cross and W. Rolfe, Trans Faraday Soc., 47 354 (1951).

(14) L. Bellamy, The Infra-Red Spectra of Complex Molecules, London and New York, John Wiley & Sons, 1954, pp. 129-136.

(15) W. M. D. Bryant and D. M. Smith, J. Am. Chem. Soc., 57 57-61 (1935).

# APPENDIX

Figure I

Infrared Spectrograph of
Reaction Products of
0.0274 mole o-Isopropylphenylmagnesium
Bromide
0.0274 mole Phenyl o-Isopropylbenzoate

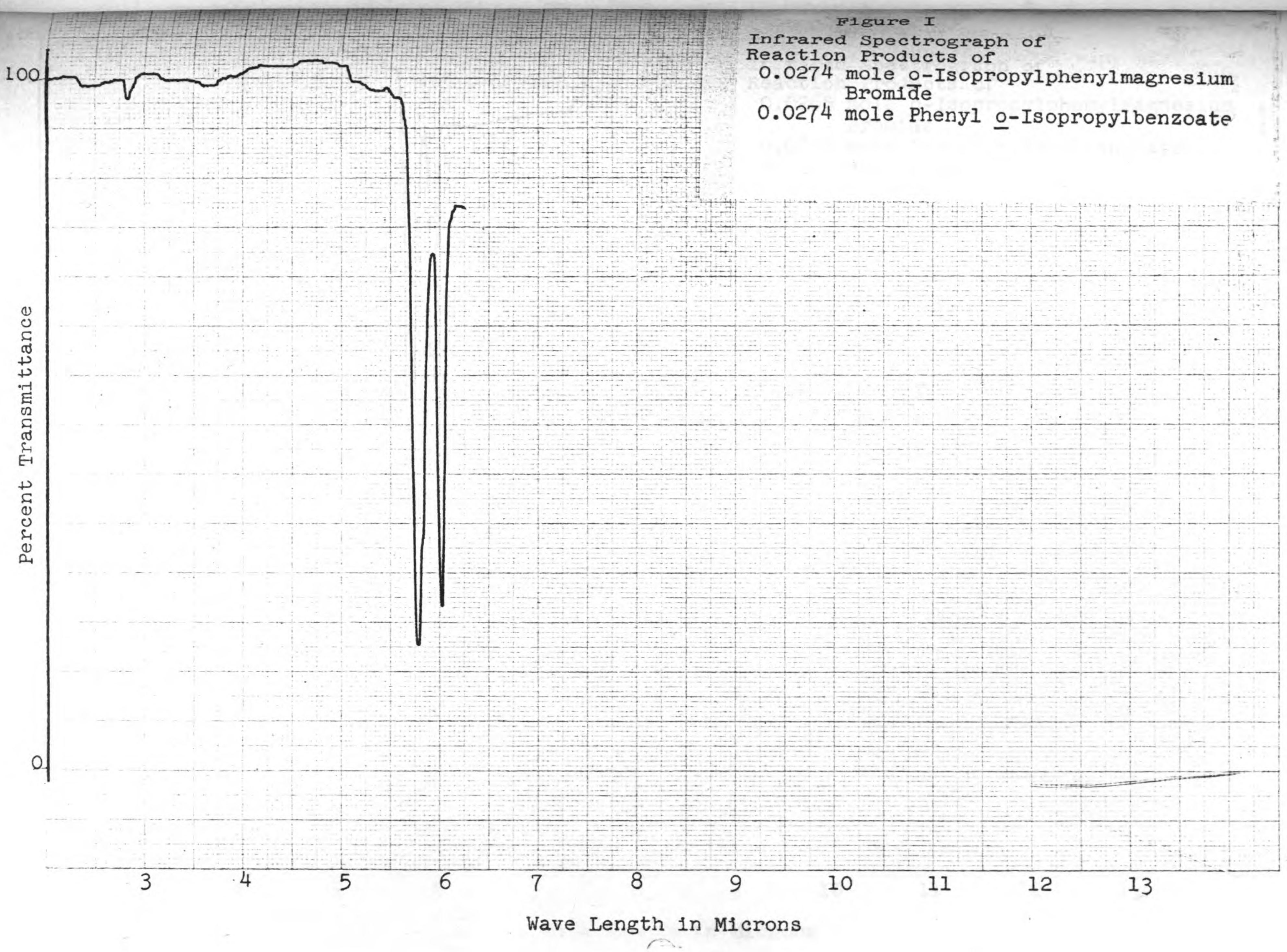


Figure II

Infrared Spectrograph of
Reaction Products of
0.0265 mole o-Isopropylphenylmagnesium
Bromide
0.0265 mole Phenyl *o*-Ethylbenzoate
in 500 ml. Toluene

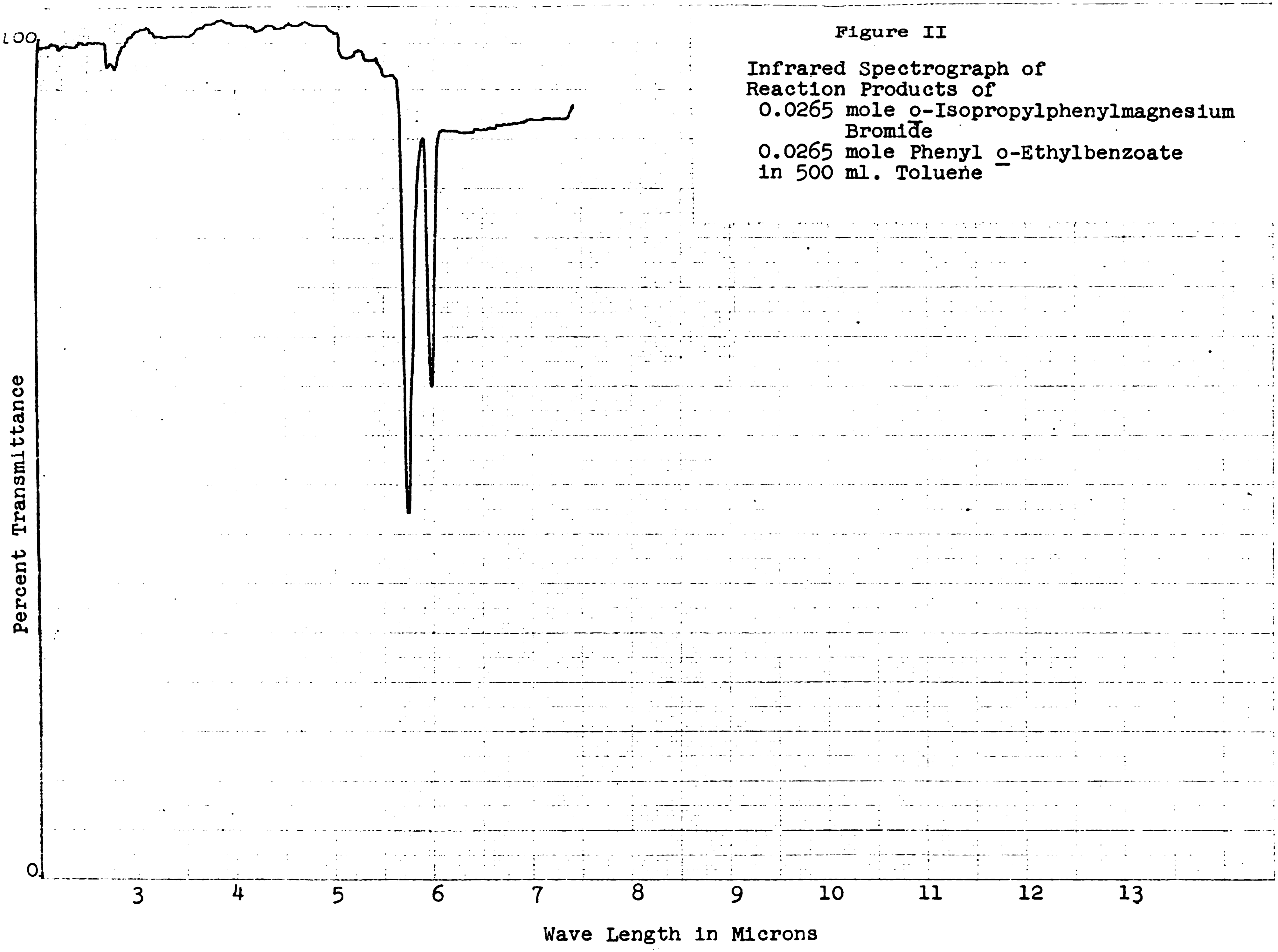


Figure III

Infrared Spectrograph of
Reaction Products of
0.0274 mole o-Isopropylphenylmagnesium
Bromide
0.0274 mole o-Cresyl o-Isopropylbenzoate
in 250 ml. Toluene

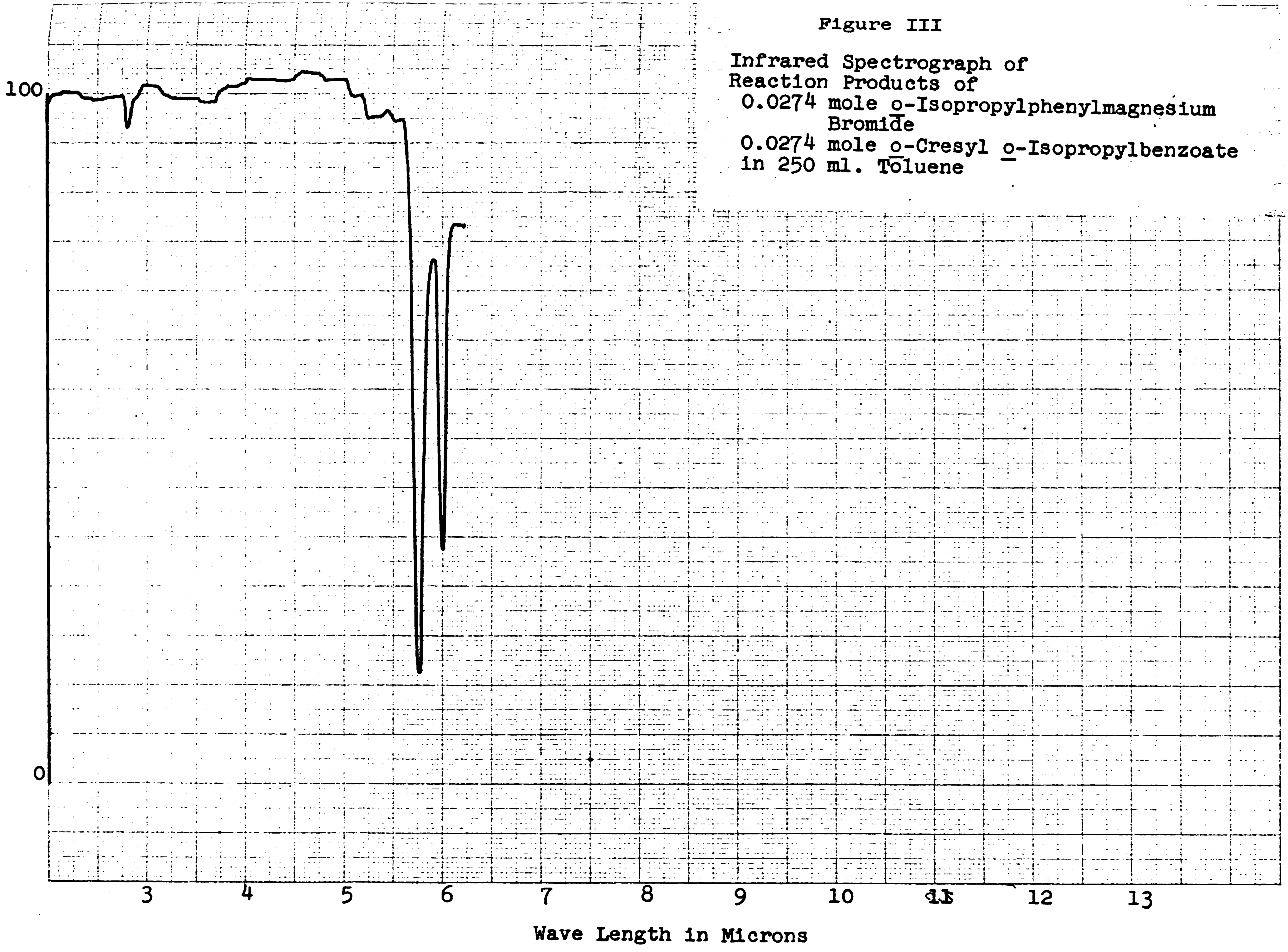


Figure IV

Infrared Spectrograph of
Reaction Products of
0.0313 mole o-Ethylphenylmagnesium
Bromide
0.0313 mole o-Cresyl o-Ethylbenzoate

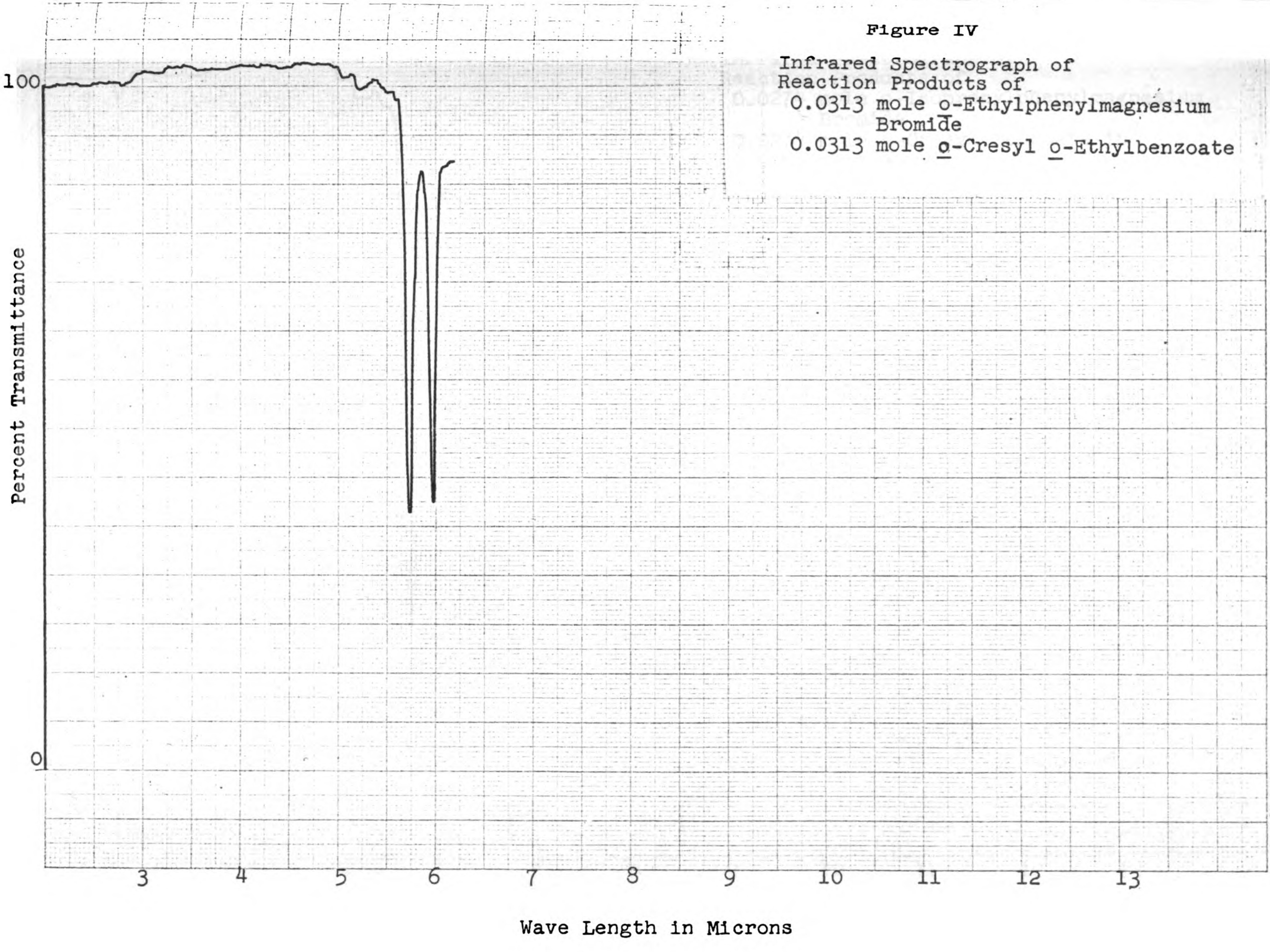
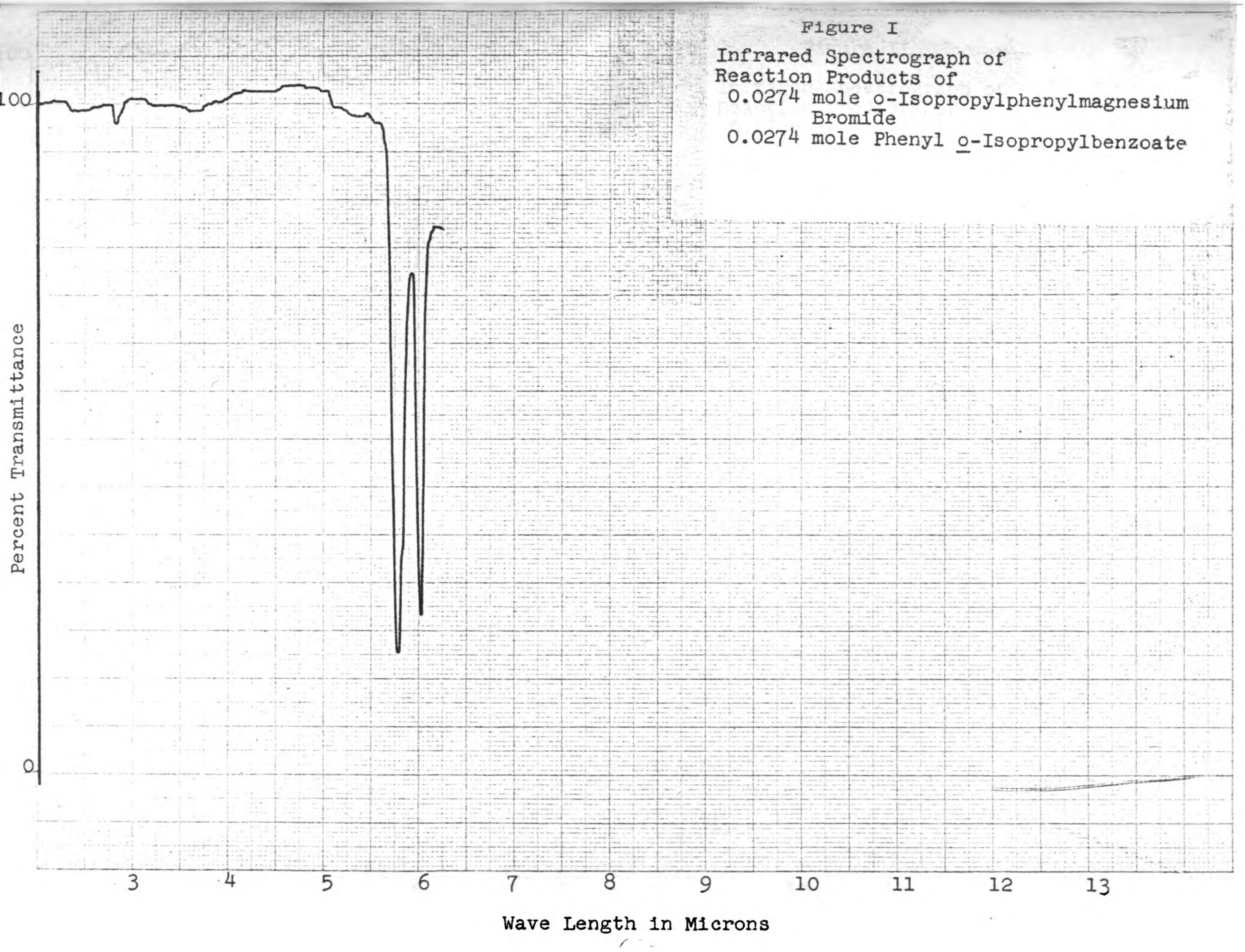


Figure I

Infrared Spectrograph of
Reaction Products of
0.0274 mole o-Isopropylphenylmagnesium Bromide
0.0274 mole Phenyl o-Isopropylbenzoate



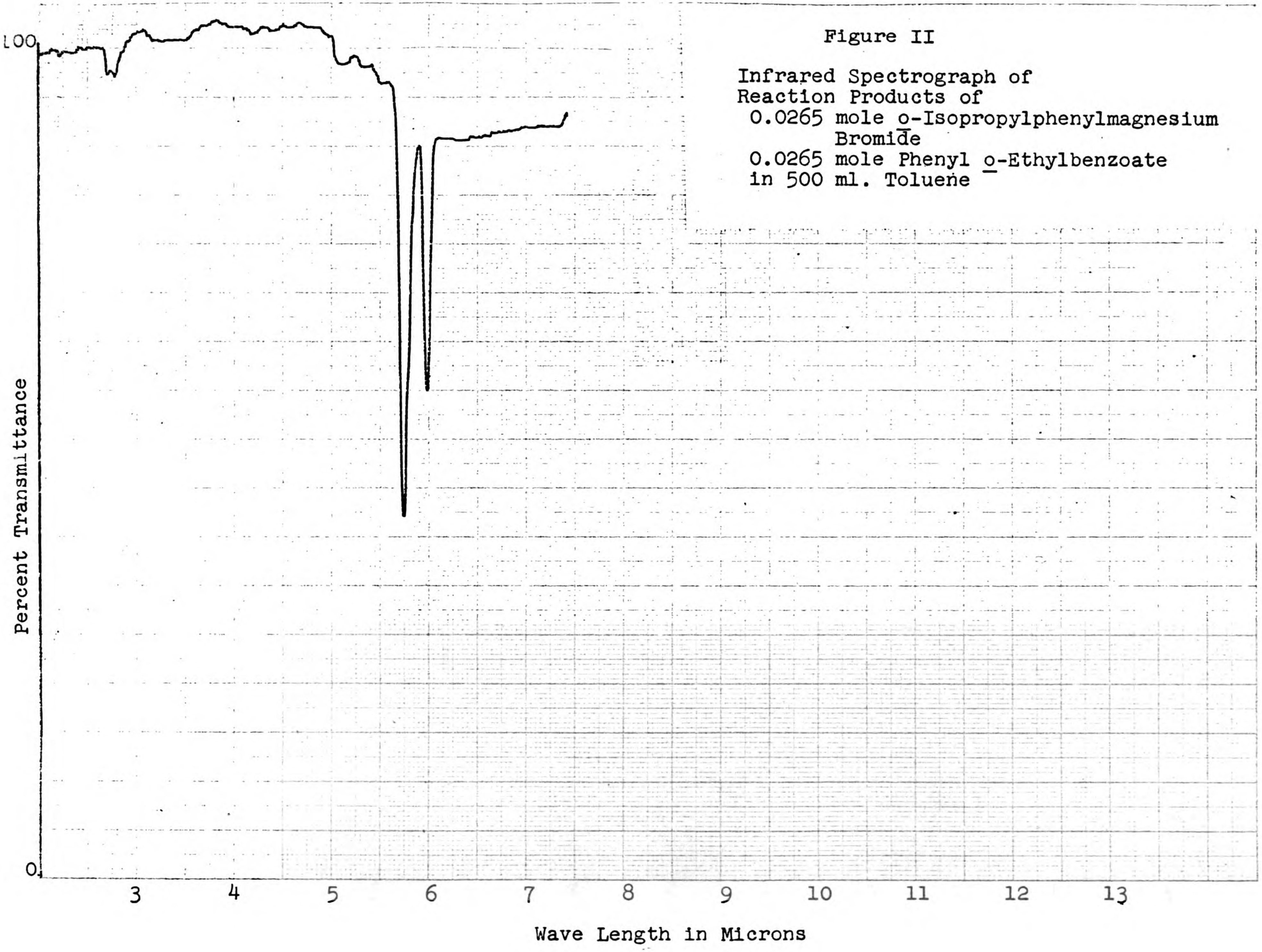


Figure II

Infrared Spectrograph of
Reaction Products of
0.0265 mole o-Isopropylphenylmagnesium
Bromide
0.0265 mole Phenyl o-Ethylbenzoate
in 500 ml. Toluene

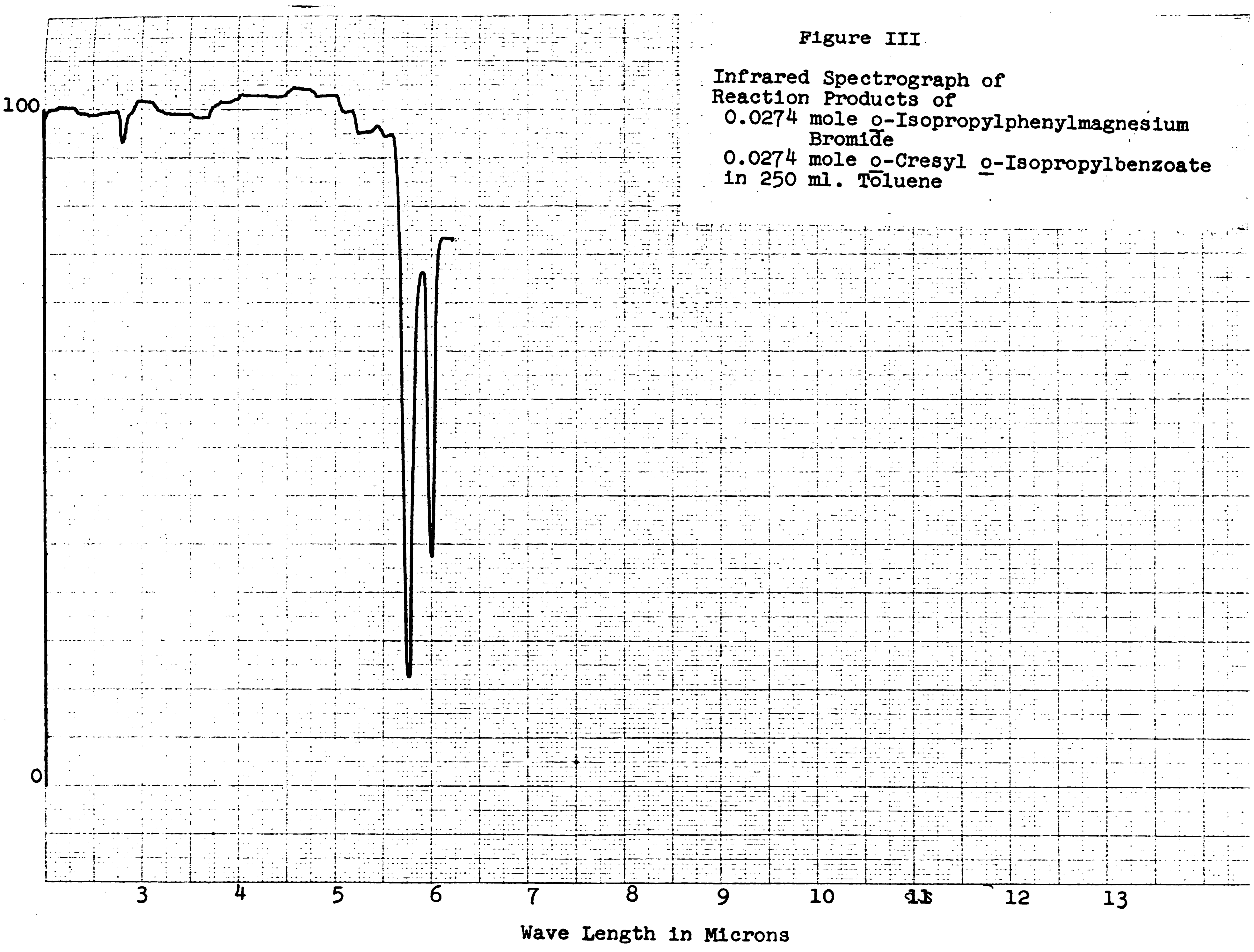
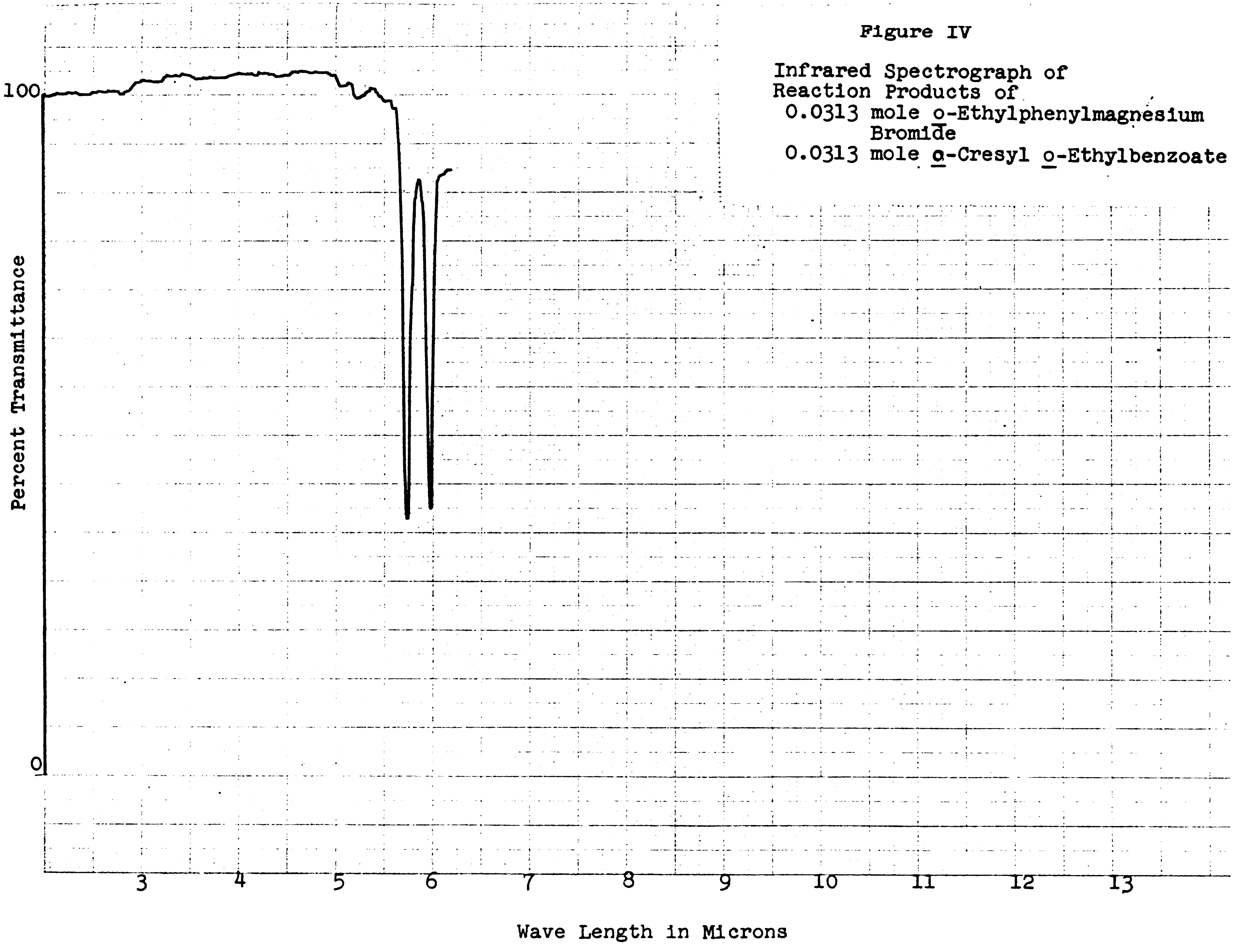


Figure III

Infrared Spectrograph of
Reaction Products of
0.0274 mole o-Isopropylphenylmagnesium
Bromide
0.0274 mole o-Cresyl o-Isopropylbenzoate
in 250 ml. Toluene

Figure IV

Infrared Spectrograph of
Reaction Products of
0.0313 mole o-Ethylphenylmagnesium
Bromide
0.0313 mole o-Cresyl o-Ethylbenzoate



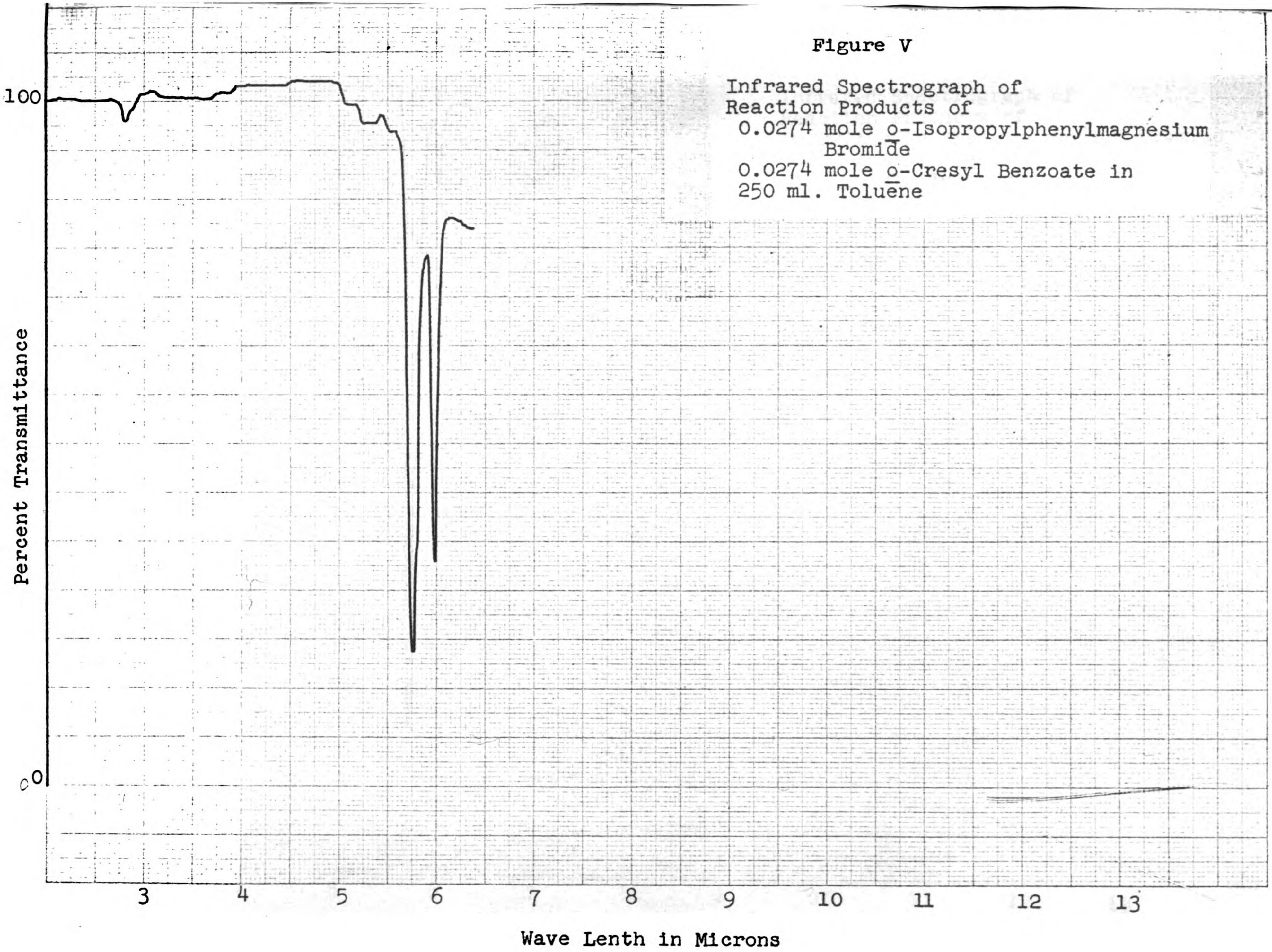


**Figure V**

Infrared Spectrograph of
Reaction Products of
0.0274 mole o-Isopropylphenylmagnesium
Bromide
0.0274 mole o-Cresyl Benzoate in
250 ml. Toluene

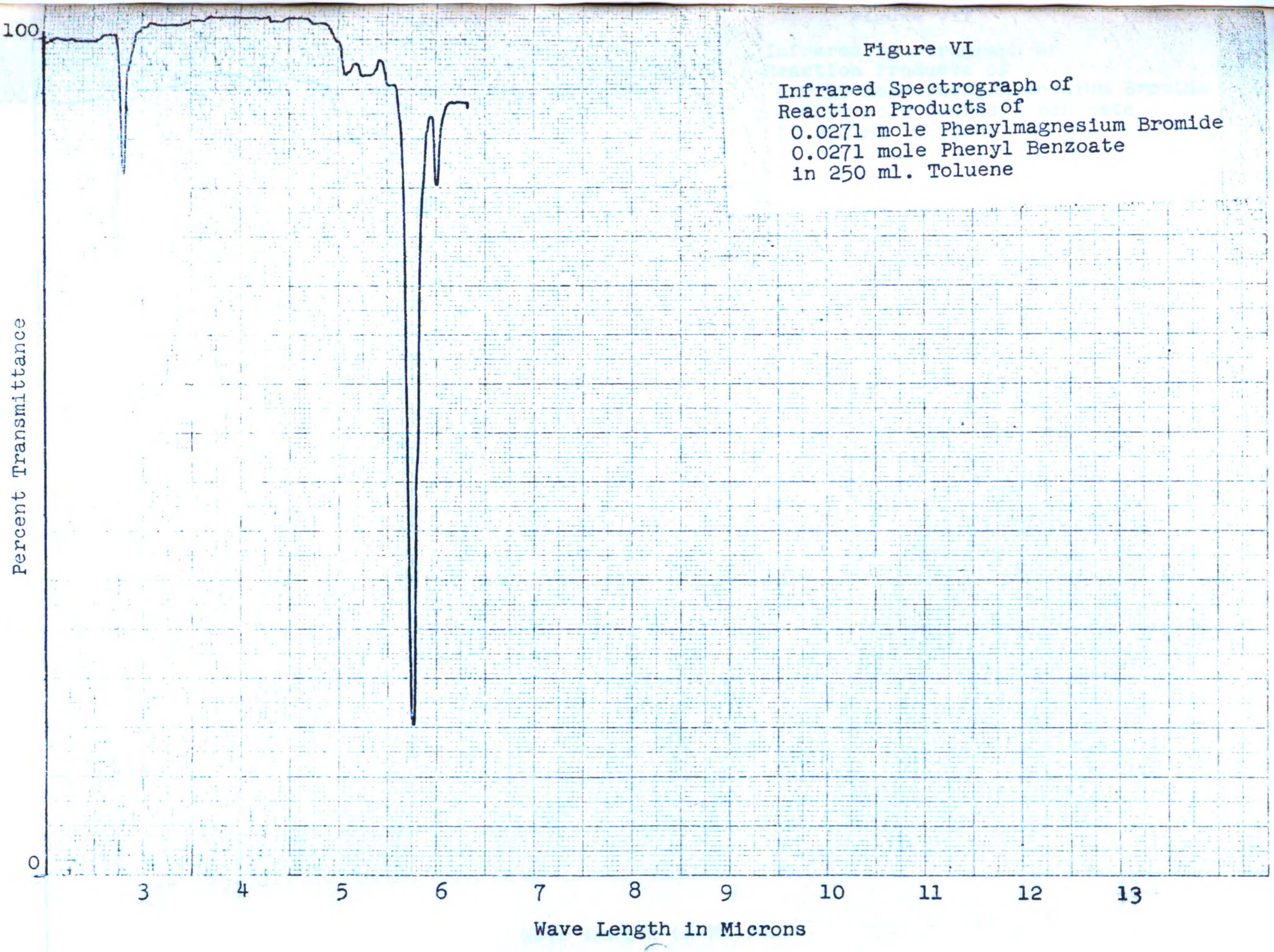
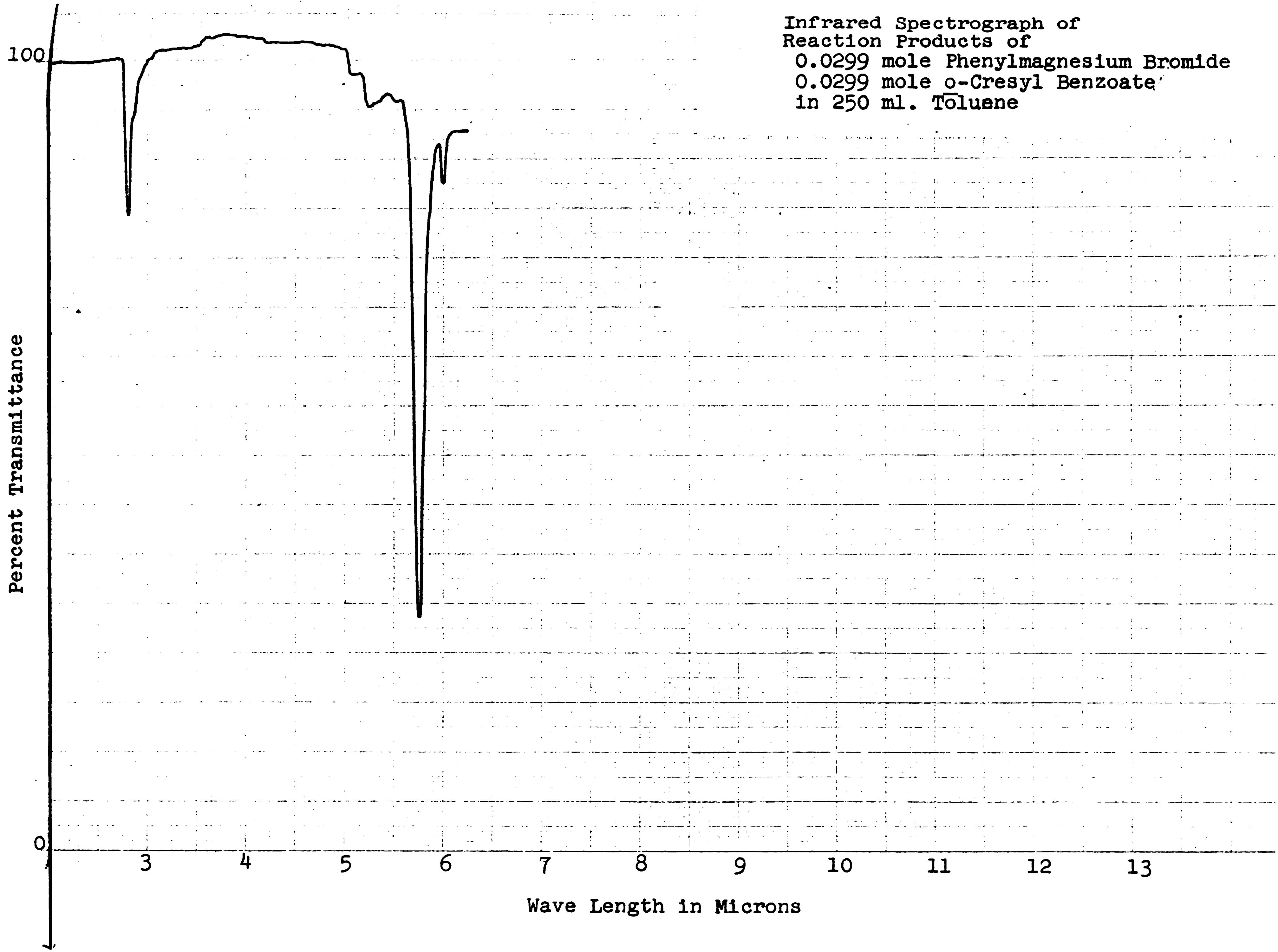


Figure VI

Infrared Spectrograph of
Reaction Products of
0.0271 mole Phenylmagnesium Bromide
0.0271 mole Phenyl Benzoate
in 250 ml. Toluene

Figure VII

Infrared Spectrograph of
Reaction Products of
0.0299 mole Phenylmagnesium Bromide
0.0299 mole o-Cresyl Benzoate
in 250 ml. Toluene



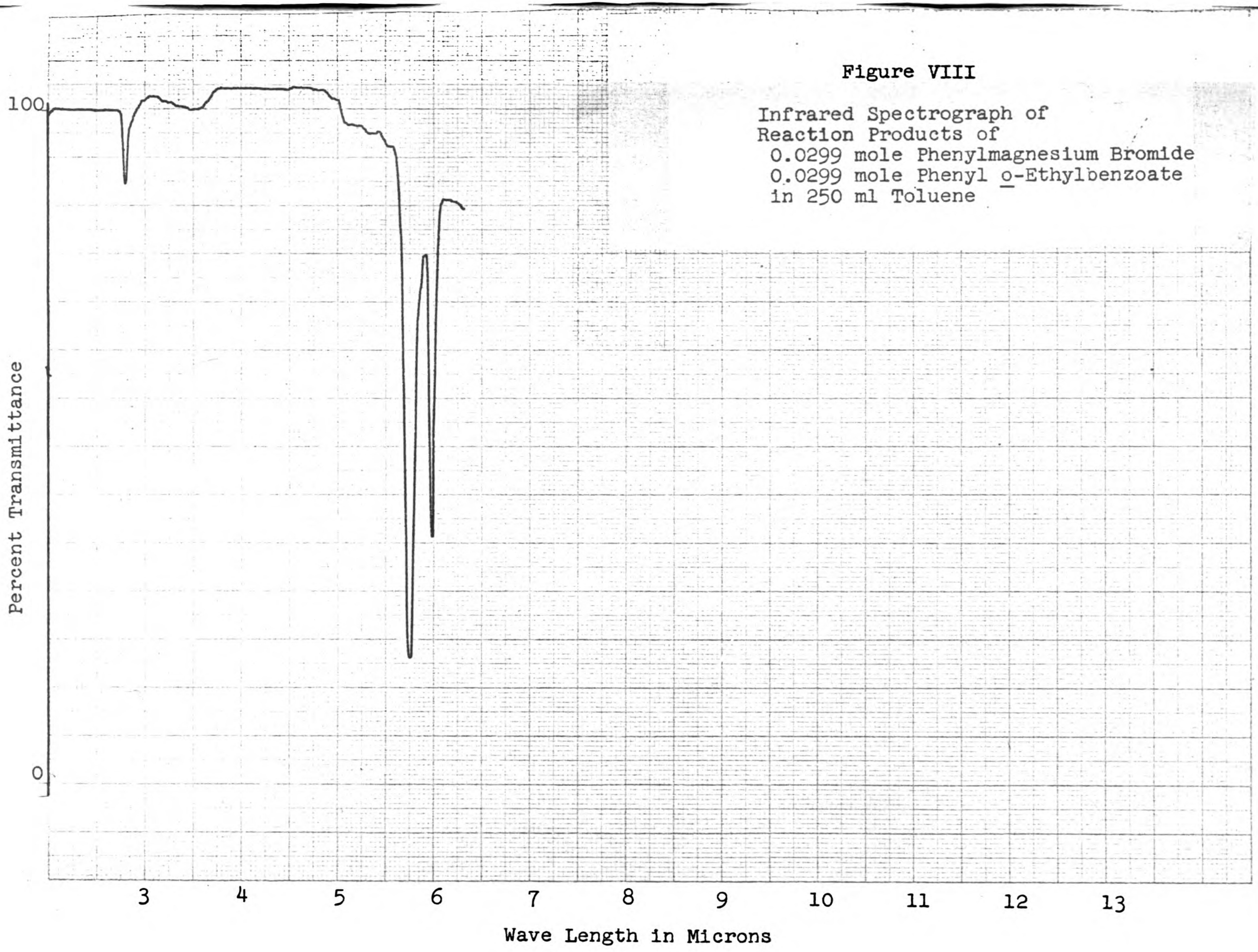


**Figure VIII**

Infrared Spectrograph of
Reaction Products of
0.0299 mole Phenylmagnesium Bromide
0.0299 mole Phenyl o-Ethylbenzoate
in 250 ml Toluene

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