Synthesis And Properties Of The Ethyl 2- And 4-pyridylpyruvate Esters.

SYNTHESIS AND PROPERTIES OF THE ETHYL 2- AND 4-PYRIDYLPYRUVATE ESTERS

by

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This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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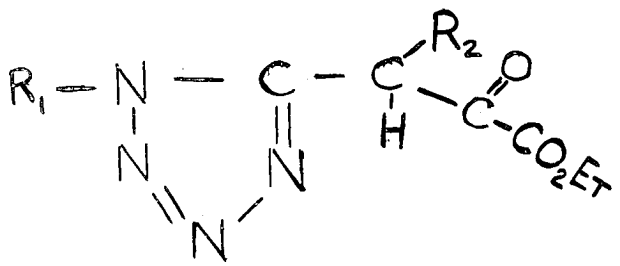
INTRODUCTION

In 1953, Jacobson and Amstutz [1] prepared ethyl 1-phenyl-5-tetrazolylpyruvate (I) and ethyl β-phenyl-1-methyl-5-tetrazolylpyruvate (II) and observed that both esters showed high enol contents in ethanolic solution (93% and 87% respectively), and were surprisingly resistant to decarbonylation.

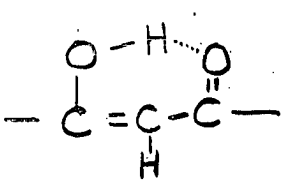


I, $R_1 = \phi, R_2 = H$

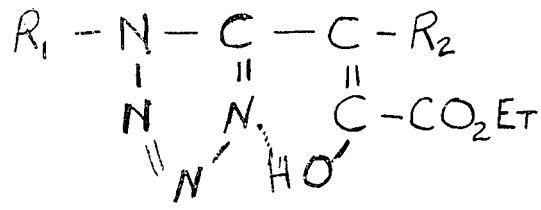
II $R_1 = CH_3, R_2 = \phi$

The behavior of (I) and (II) was particularly striking when compared with that of simple α-dicarbonyl compounds such as biacetyl and methyl pyruvate. The equilibrium enol content of biacetyl has been estimated to be 5.6×10^{-3}% and methyl pyruvate does not form an enol ether on standing for 3 days in an ethereal solution of diazomethane.

It appeared that the behavior of compounds (I) and (II) approached that of β-dicarbonyl compounds where high enol contents were common and considerable evidence available to indicate that the stabilization of the enol forms was due to hydrogen bonded structures.



These workers therefore postulated that the tetrazolylpyruvates existed in a chelated enol structure similar to that generally accepted for β-diketones.



This phenomenon was further explored in this laboratory by Donahue, Stock, and Amstutz (2,3,4). They studied the effect of a variety of β-aryl and β-heteroaryl substituents on the tautomeric behavior of pyruvate esters. Among those compounds studied were the following nitrogen heterocyclic substituted pyruvates:

	Class
Ethyl 2-pyrimidylpyruvate	A
Ethyl 4-pyrimidylpyruvate	A
Ethyl 2-quinolylpyruvate	A
Ethyl 3-pyridazylpyruvate	B
Ethyl 2-pyrazylpyruvate	B
Ethyl 2-quinoxalylpyruvate	B
Ethyl 2-benzoxazolylpyruvate	B
Ethyl 2-benzothiazolylpyruvate	B
Ethyl 4-quinolylpyruvate	C

These workers divided these esters into three classes. Class A comprises those esters in which an heterocyclic nitrogen atom is favorably situated for the formation of a chelated enol structure and which retain their enolic structure in methanol solution.

Class B esters also have an heterocyclic nitrogen atom favorably situated for chelation but methanol solutions of these esters decrease in enol content on aging. The Class C ester is incapable of assuming the chelated enol structure due to the unfavorable location of the nitrogen atom.

Upon comparison of the compounds in classes A and B, it is readily apparent that the structurally simplest compound in this series, ethyl 2-pyridylpyruvate, is missing. Also in Class C, ethyl 4-pyridylpyruvate is not present. The synthesis of ethyl 2-pyridylpyruvate was attempted by several workers in this laboratory and elsewhere [2,3,6,12]. However, none of these attempts were successful.

In view of the desirability of comparing the tautomeric behavior of the pyridyl substituted compounds with that of the other heterocycles already studied, the synthesis of ethyl 2- and 4-pyridylpyruvate was again attempted. It was also hoped that these compounds would serve as intermediates in the preparation of some interesting new pyridine derivatives.

Review of Previous Attempts to Synthesize Ethyl 2-pyridylpyruvate

1. Claisen Condensation

A. Picoline and Potassium Ethoxide

The most convenient method for preparing β-aryl or heteroaryl pyruvate esters is the Claisen ester condensation (8). This involves the condensation of a compound with an active methyl group with diethyl oxalate in the presence of a basic catalyst such as potassium ethoxide. The product is the potassium salt of the pyruvate ester. The salt is then converted to the free ester by treatment with dilute acetic acid. The reaction may be pictured as follows:

$$R\text{-}CH_3 + KOEt \longrightarrow RCH_2{:}K + EtOH$$

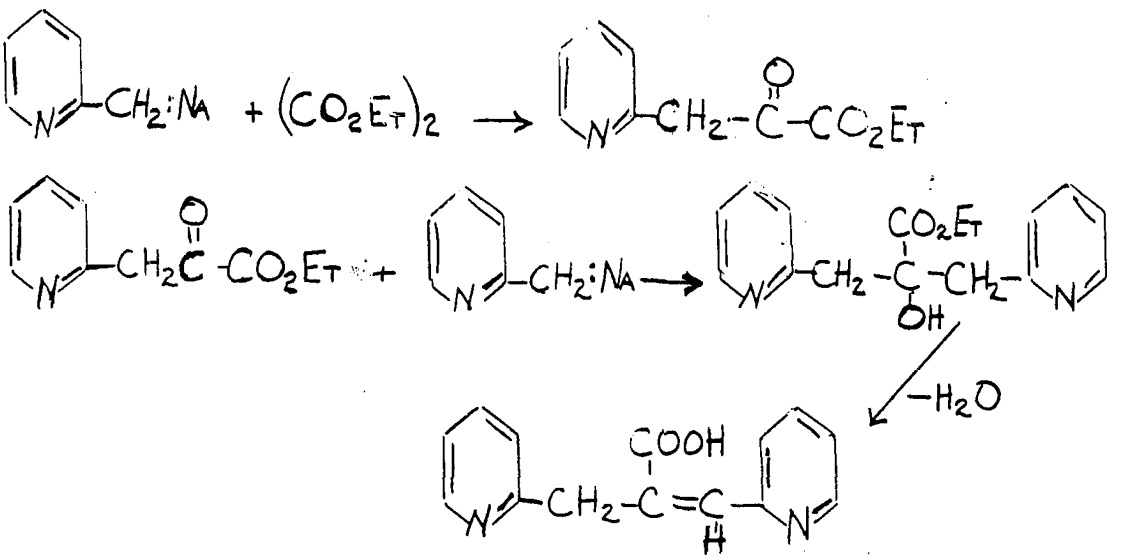
$$RCH_2{:}K + (CO_2Et)_2 \longrightarrow RCH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2Et$$

$$RCH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CO_2Et + KOEt \longrightarrow \left[R\text{-}\underset{H}{C}{=}C\overset{O^{\ominus}}{\overset{|}{-}}CO_2Et\right]K^{\oplus} + EtOH$$

This reaction works satisfactorily for the preparation of all the nitrogen heterocyclic compounds mentioned earlier. However, Adams and co-workers reported that no condensation takes place when 2-picoline is used (5).

B. Picoline and Sodamide (6,7).

Hauser et.al. attempted the same reaction, using sodamide as the base. He prepared 2-picolylsodium in liquid ammonia and then reacted it with diethyl oxalate in ether solution. He obtained condensation, but it was immediately followed by an aldol reaction to give tertiary alcohol which was subsequently dehydrated under the reaction conditions.



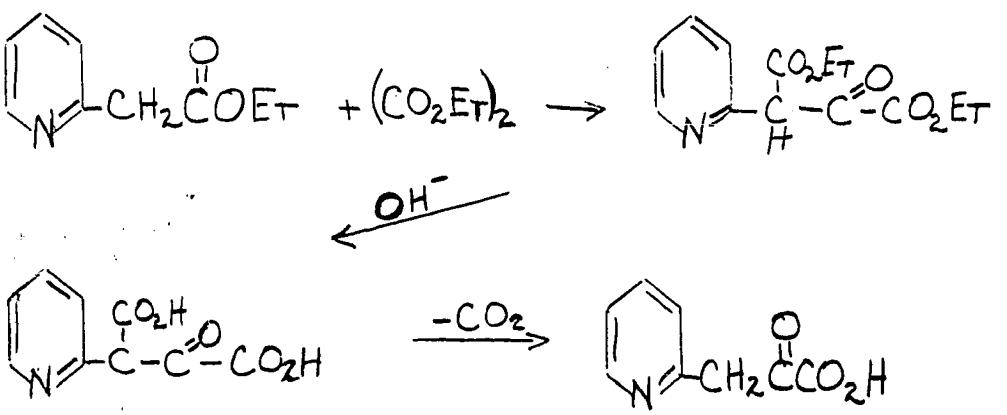
Attempts to stop the reaction at the initial stage failed and led only to the recovery of starting materials.

C. Picoline and Phenyllithium(3,12).

In this laboratory phenyllithium was employed as the base. The preparation of α - picolyllithium was well known (10) and excellent results have been obtained in this general reaction with a variety of esters (11). However, the product obtained was a red tar which could not be characterized.

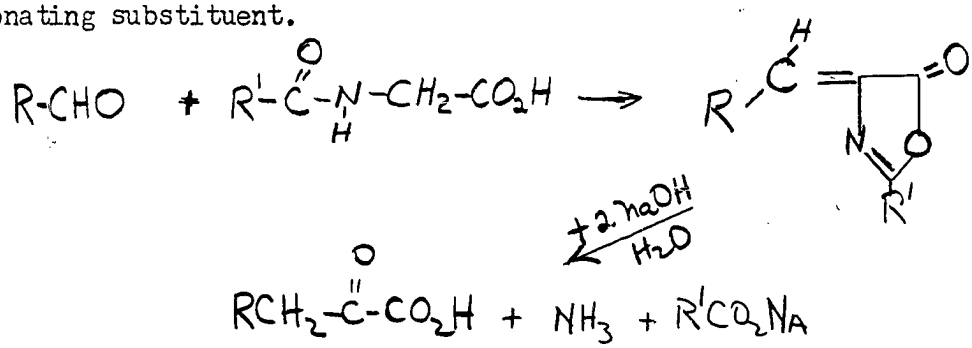
D. Ethyl 2-pyridylacetate and Sodium Ethoxide (12).

In this laboratory, an attempt was made to effect the Claisen ester condensation by reacting ethyl 2-pyridylacetate with diethyl oxalate in the presence of sodium ethoxide. If the reaction were successful, the reaction product would have been saponified and decarboxylated. However, an intractible oil was the condensation product.



2. Azlactone Synthesis (13)

The second general method for the preparation of β-substituted pyruvates is the reaction of an aromatic aldehyde with hippuric acid to form an oxazolinone which is subsequently hydrolysed to yield the desired pyruvic acid. This method is not useful for those compounds in which the β-substituent is an aryl group that is unsubstituted, or bears an electron donating substituent.

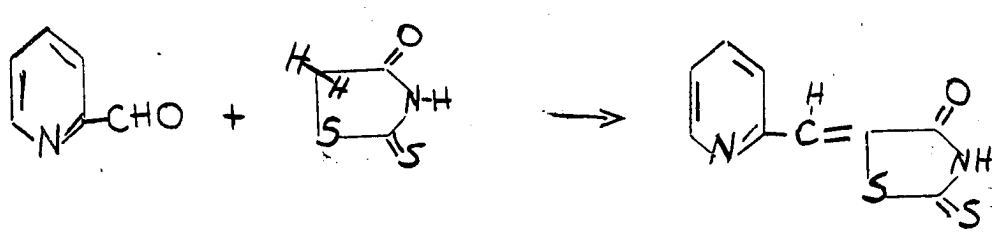


However, it has been reported that 2-pyridine aldehyde does not react with hippuric acid (15).

3. Granacher's Rhodanine Synthesis (16)

In an analogous reaction to the azlactone synthesis, Granacher condensed an aromatic aldehyde with rhodanine and upon hydrolysis, obtained the thiopyruvic acid. After formation of the oxime, the pyruvic acid was obtained by hydrolysis with sulfurous acid (17).

It is interesting that pyridine aldehyde was only recently reacted with rhodanine in good yield (18). However, repeated attempts in this laboratory to hydrolyze the product to the thiopyruvic acid were unsuccessful (19).

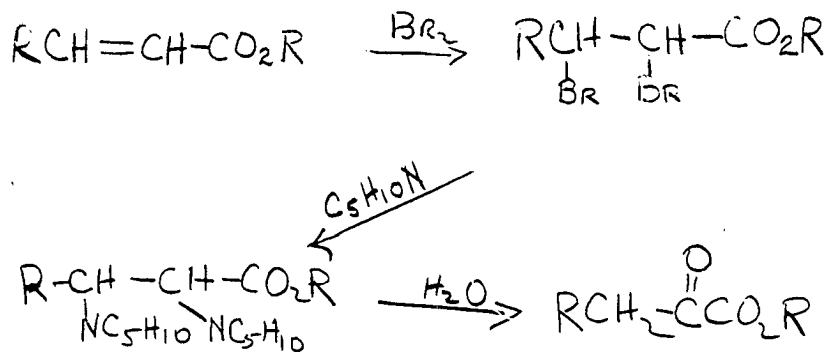


4. Oxidation of 2-Pyridyllactic Acid

An attempt to oxidize 2-pyridyllactic acid to the corresponding pyruvic acid was apparently unsuccessful [1].

5. Moureu's Method [20,21].

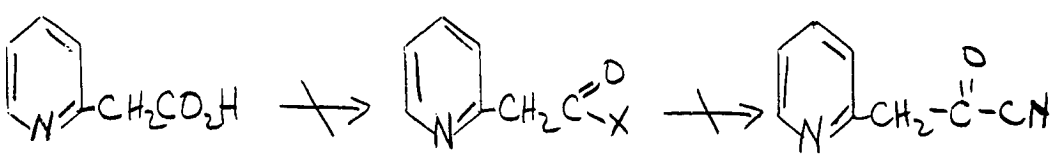
A generally applicable method by Moureu involves the bromination of the ester of the corresponding acrylic acid, then reaction with piperidine, and finally water, as follows:



This method was abandoned by Stock when bromination of the pyridylacrylic acids yielded only the corresponding pyridylacrylic hydrobromides, and not the desired dibromo propionic acids.

6. Pyridylpyruvonitrile [3].

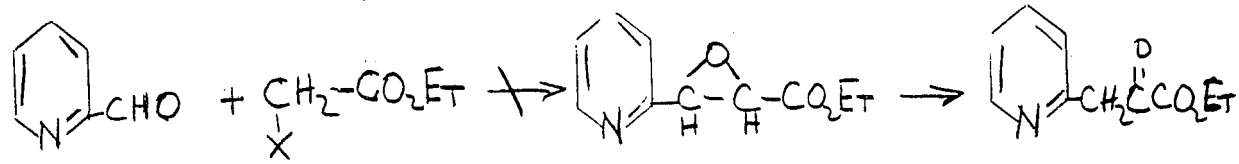
Another method attempted by previous workers was the preparation of pyridylpyruvonitile.



There is no report in the literature of the preparation of 2-pyridylacetyl chloride, and the attempts by previous workers were unsuccessful. Without the desired acid halide, further work was abandoned. In addition, the conversion of acid halides to α-keto nitriles is not a smooth reaction, and difficulties are frequently encountered.

7. Glycidic Ester Rearrangement.

Thermal rearrangement of glycidic esters is another route to the desired product.

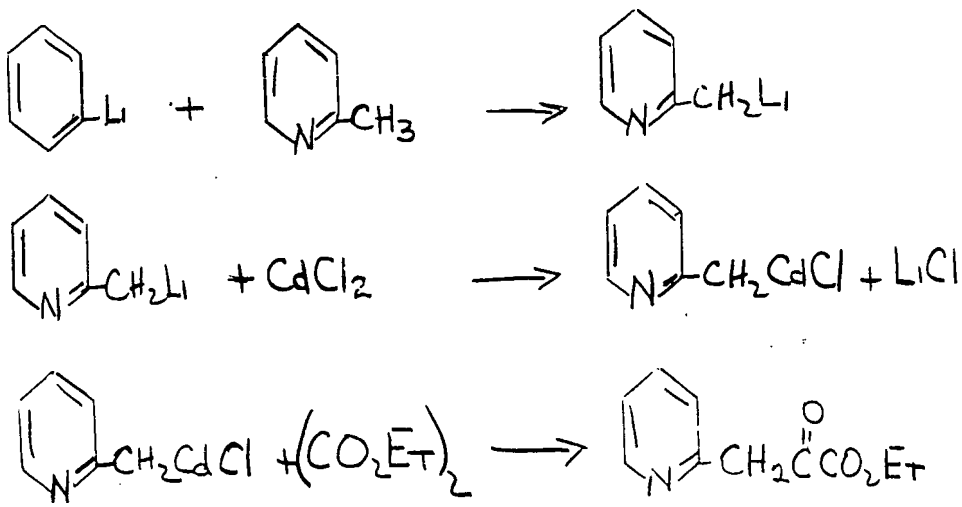


Although some pyridine ketones undergo the Darzens glycidic ester condensation, the reaction with aldehydes was not successful [22].

RESULTS OF INVESTIGATION

Preparation of Ethyl 2-pyridylpyruvate

Ethyl 2-pyridylpyruvate has been prepared in 10% yield by the reaction of 2-picolylcadmium chloride with diethyl oxalate in ether solution at -70° for 5 minutes. The 2-picolylcadmium chloride was prepared in three steps. First, phenyllithium was prepared by reacting bromobenzene with lithium metal. Then 2-picoline was added to the phenyllithium, producing 2-picolyllithium. Finally, cadmium chloride was added to form the 2-picolylcadmium reagent.



Although the reactions of 2-picolyllithium are well known, it is believed that this is the first use of 2-picolylcadmium. The low reaction temperature and addition of the organometallic to the ester were necessary to minimize the formation of tar which always accompanied the product.

The following variations in the reaction conditions failed to improve the yield of desired product or diminish the formation of by-products.

1. excess diethyl oxalate
2. longer reaction time
3. normal addition
4. ethyl oxalyl chloride
5. di-2-picolyl mercury
6. 2-picolyllithium at -70°
7. work up in ammonium chloride

A twofold and fourfold excess of diethyl oxalate was used in successive runs in an attempt to decrease the amount of tar which accompanied the product. There was no difference in yield in either case from the 10% yield of ethyl 2-pyridylpyruvate.

The picolylcadmium diethyl oxalate reaction mixture was maintained at 0° C. for 24 hours instead of the usual 5-10 minutes. Less desired product and more of the byproducts were obtained.

The procedure which led to the synthesis of ethyl 2-pyridylpyruvate involved the addition of the picolylcadmium chloride to the diethyl oxalate. This mode of addition is generally called "reverse addition." An experiment was tried using "normal addition," in which the diethyl oxalate was added to the picolylcadmium. None of the desired product but only intractable tar was present.

Ethyl oxalyl chloride was substituted for the diethyl oxalate and only a trace of ethyl pyridylpyruvate was obtained.

Di-2-picolyl mercury was reacted with both diethyl oxalate and ethyl oxalyl chloride but no product was obtained.

2-Picolyllithium at -70° led to a trace of ethyl 2-pyridylpyruvate with a copious amount of tar.

Ammonium chloride was substitued for dilute hydrochloric acid during the work up. There was no increase in the amount of ethyl 2-pyridylpyruvate obtained.

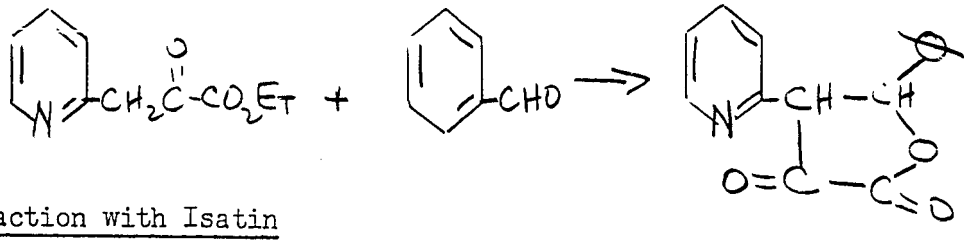
Derivatives of Ethyl 2-pyridylpyruvate

The following derivatives of ethyl 2-pyridylpyruvate were prepared:

		m.p.	
1.	picrate	150-1°	Calc. - C,45.50; H,3.34; N,13.26
			Found - C,45.6; H,3.60; N,13.18
2.	2,4 DNP	141-2°	Calc. - C,51.48; H,4.05; N,18.76
			Found - C,51.55; H,4.20; N,18.86
3.	2,4 DNP·H_2SO_4	168-9°	Calc. - C,40.8; H,3.62; N,14.8
			Found - C,41.35; H,3.88; N,15.15
4.	oxime	120-1°	Calc. - C,57.71; H,5.76; N,13.46
			Found - C,57.22; H,5.84; N,12.90

Reaction with Benzaldehyde

Ethyl 2-pyridylpyruvate reacted with benzaldehyde in the presence of piperidine to produce the lactone.



Reaction with Isatin

Several attempts to employ the Pfitzinger reaction with isatin were unsuccessful. In aqueous sodium hydroxide the pyruvate ester appeared to be destroyed, probably by reverse Claisen condensation, and the isatin was recovered.

When the two reactants were simply heated together in ethanol, no reaction was apparent after 8 hours. Finally, when piperidine was used as a catalyst, some reaction was apparent, but the product was tarry and unidentified.

Reaction with O-aminobenzaldehyde

The Friedlander Synthesis using ethyl 2-pyridylpyruvate and O-aminobenzaldehyde catalyzed with piperidine failed.

Oxidation

Ethyl 2-pyridylpyruvate gave a positive test with Tollens reagent. When placed in aqueous ammoniacal silver oxide, the pyruvate dissolved very slowly with the formation of a silver mirror. The oxidation product was not identified.

Reduction

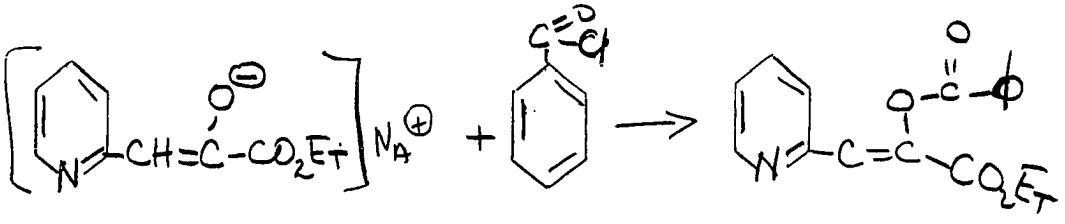
Ethyl 2-pyridylpyruvate was reduced by sodium borohydide in methanol to form 1-(2-pyridyl) 2,3propanediol. The glycol was reacted with 47% HBr but the desired pyrrocoline was not found.

Hydrolysis to Free Acid

Ethyl 2-pyridylpyruvate was hydrolyzed to 2-pyridylpyruvic acid by warm 10% sulfuric acid solution.

Formation of the Enol Benzoate

The pyruvate was reacted with sodium ethoxide to form the sodium enolate. Subsequent treatment with benzoyl chloride yielded the O-benzoyl derivative as a non-fluorescent oil.



Attempted Methylation Reactions

When the sodium salt of the pyruvate ester was reacted with methyl iodide, the reaction product was a dark red oil. Upon treatment with acid, the color changed to a light yellow. It was observed that this was a variable process, the color depending upon the pH of the solution. However, no product could be characterized.

Ethyl 2-pyridylpyruvate did not react with methyl iodide even when heated in a sealed tube at 100° C. for 2 hours.

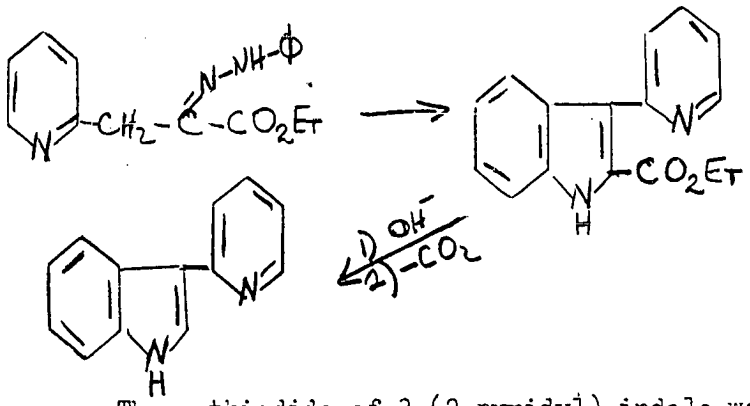
There was no reaction of ethyl 2-pyridylpyruvate with freshly prepared diazomethane in ether solution.

N-Methyl Ethyl 2-Pyridylpyruvate

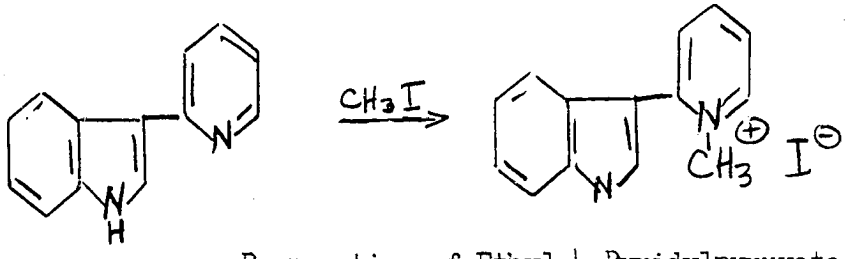
2-Picoline methiodide was reacted with diethyl oxalate and sodium ethoxide to produce N-methyl ethyl 2-pyridylpyruvate.

Fischer Indole Synthesis

The phenylhydrazone of ethyl 2-pyridylpyruvate was prepared as a viscous oil. It underwent the Fischer indole ring closure when heated on a steam bath with polyphosphoric acid. The product, 2-carbethoxy, 3-(2-pyridyl)-indole, was saponified with aqueous sodium hydroxide to the free acid. The acid was conveniently decarboxylated with copper bronze to 3-(2-pyridyl)-indole.

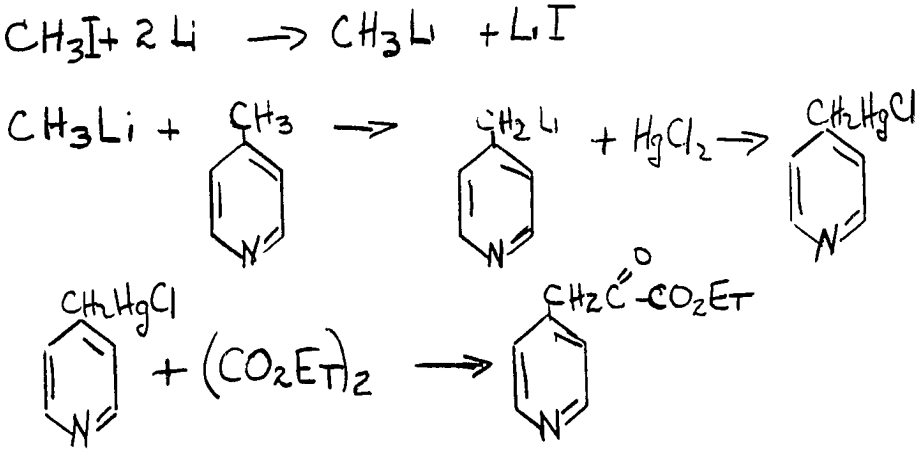


The methiodide of 3-(2-pyridyl)-indole was prepared upon heating with methyl iodide in a sealed tube.



Preparation of Ethyl 4-Pyridylpyruvate

Ethyl 4-pyridylpyruvate was prepared in 10% yield from di-4-picolyl mercury and diethyl oxalate at -70° for ten minutes. The 4-pyridyl mercury reaction mixture was prepared in the following way. First, methyl lithium was prepared from methyl iodide and lithium metal. This reagent was recently shown to be superior to phenyl lithium for metalating 4-picoline (11). The picoline was added and converted to 4-picolyllithium. Finally, mercuric chloride formed the 4-picolyl mercury reagent.



The following reactions were run in attempting to prepare ethyl 4-pyridylpyruvate:

1. 4-picolyllithium in normal and reverse addition
2. 4-picolyllithium at 0 and -70°.
3. Di-4-picolylcadmium at 0 and -70°.
4. Varied amounts of mercuric chloride.

In both normal addition at 0° and reverse addition at -70°, 4-picolyllithium appeared to react only slightly with diethyl oxalate. Reverse addition was tried at 0° with the same result. When di-4-picolylcadmium was used in the same manner that produced ethyl 2-pyridylpyruvate, a small amount of solid which could not be identified was the only product. There was little difference when the reaction was run at 0°. It was also observed that the amount of ethyl 4-pyridylpyruvate produced fell off drastically as the amount of mercuric chloride used was decreased below 0.5 mole per mole of picolyllithium.

Derivatives of Ethyl 4-Pyridylpyruvate

The following derivatives of ethyl 4-pyridylpyruvate were prepared:

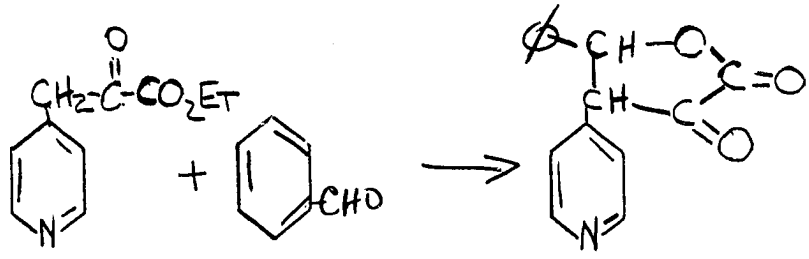
*1) picrate - 164-5° d - Calc. - C,45.50; H,3.34; N,13.26
Found - C,45.80; H,3.73; N,11.81

*2) 2,4,DNP - 139;140° d Calc. - C,57.71; H,5.76; N,13.46
Found - C,57.83; H,5.92; N,13.60

*NOTE - The nitrogen determinations were repeated several times but the results were not reproducible.

Reaction with Benzaldehyde

Ethyl 4-pyridylpyruvate reacted with benzaldehyde when heated in the presence of piperidine to produce a lactone.

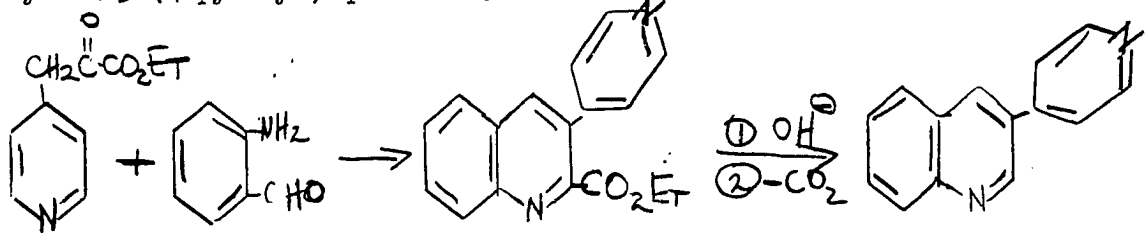


Reaction with Isatin

Several attempts to condense ethyl 4-pyridylpyruvate with isatin in the Pfitzinger reaction failed. The results were the same as in the case of ethyl 2-pyridylpyruvate.

Reaction with O-Aminobenzaldehyde

Ethyl 4-pyridylpyruvate reacted with O-aminobenzaldehyde in the presence of piperidine in a Friedlander synthesis and produced 2-carbethoxy 3-(4-pyridyl)-quinoline. This ester was saponified and decarboxylated to yield 3-(4-pyridyl)-quinoline.



Hydrolysis to the Free Acid

Ethyl 4-pyridylpyruvate was hydrolyzed after warming in 20% sulfuric acid for twenty minutes. The free acid is a light tan powder with a melting point of 232-4°.

Methylation Reactions

Ethyl 4-pyridylpyruvate yielded a crystalline solid with m.p. 199-200° when heated with methyl iodide in a sealed tube at 75°C. for 2 hours. However, a satisfactory analysis was not obtained.

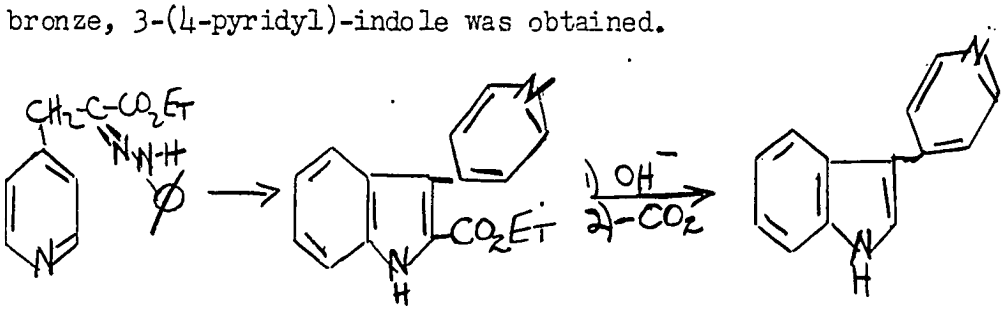
There was no reaction between ethyl 4-pyridylpyruvate and freshly prepared diazomethane in ether solution.

N-Methyl Ethyl 4-Pyridylpyruvate

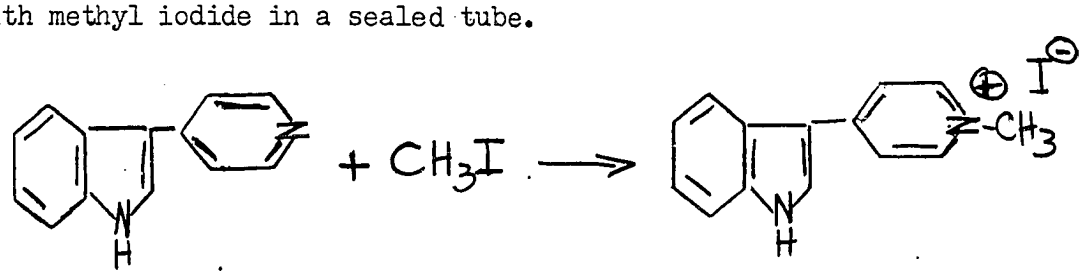
4-Picoline was reacted with diethyl oxalate and sodium ethoxide to yield N-methyl ethyl 4-pyridylpyruvate.

Fischer Indole

The phenyl hydrazone of ethyl 4-pyridylpyruvate was a crystalline compound which melted at 118-119°. It underwent the Fischer indole ring closure upon heating in polyphosphoric acid. The product 2-carbethoxy 3-(4-pyridyl)-indole was saponified with aqueous sodium hydroxide to the free acid. Upon decarboxylation with copper bronze, 3-(4-pyridyl)-indole was obtained.



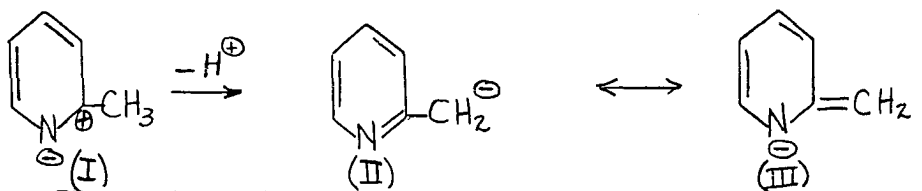
The methiodide of 3-(4-pyridyl)-indole was prepared by heating with methyl iodide in a sealed tube.



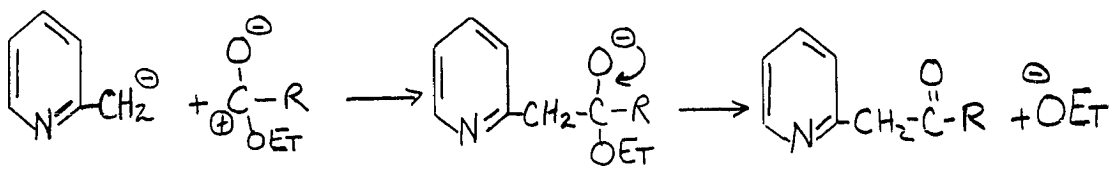
DISCUSSION

Reactivity of Picoline (23)

In terms of modern electronic theory, the reactivity of 2-picoline is attributed to its tendency, in the presence of base, to produce the anion (III) by loss of a proton from one of the contributing structures (I) of the resonance hybrid. The anion is stabilized by resonance with structures (II) and (III) as the major contributors.

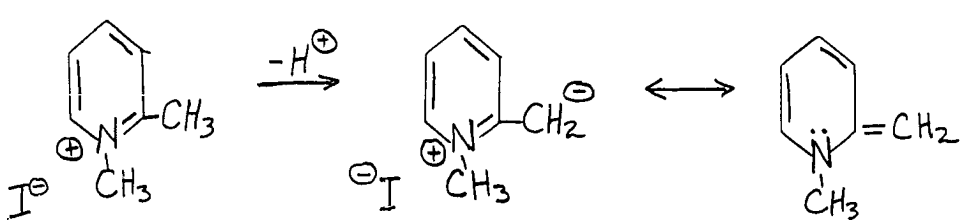


The condensation with an ester can be represented thus:

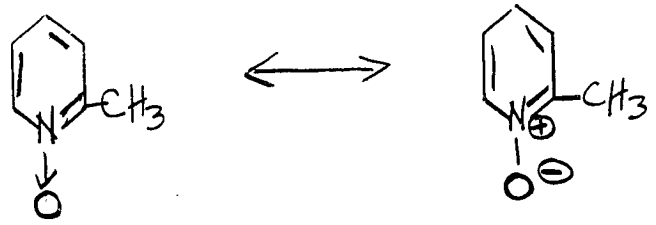


A similar explanation applies to the activity of the methyl group of 4-picoline while the comparative inertness of 3-picoline is related to the instability of the corresponding anion.

In a quaternary salt such as N-methyl picolinium iodide, the tendency of the methyl group to lose a proton in base is enhanced by the positive charge on the nitrogen atom. It has been postulated that the reactive form in condensation with an aldehyde is the methide (24).



As might be expected, the reactivity of the methyl group in 2- and 4-picoline is increased in the N-oxide compounds.

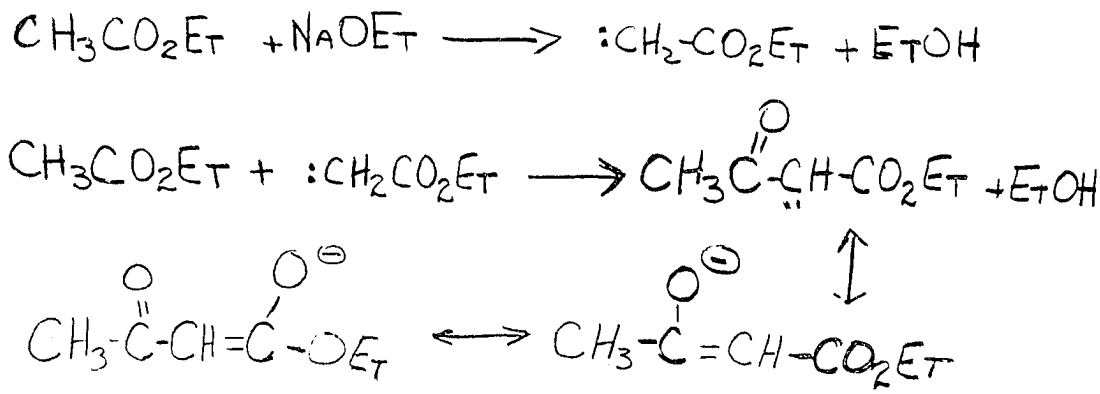


For example, these N-oxides condense readily with diethyl oxalate in the presence of potassium ethoxide, whereas the picolines do not (25).

Reaction with Diethyl Oxalate

In general, the methyl quinolines behave similarly to the picolines and both classes of compounds usually undergo the same reactions. However, quinaldine reacts with diethyl oxalate at ice bath temperatures in the presence of potassium ethoxide for 3-7 days to produce ethyl 2-quinolyl-pyruvate in good yield. Under these conditions, there is no reaction between 2-picoline and diethyl oxalate. It was the failure of picoline in this reaction that made ethyl 2-pyridylpyruvate unavailable to earlier workers and initiated the investigation of other methods of synthesis. In view of the striking difference in reactivity between two compounds of such structural similarity, an explanation is desirable.

The reaction of 2-picoline or quinaldine with diethyl oxalate may be classified as a Claisen ester condensation, the simplest and best known example of which is the self condensation of ethyl acetate in the presence of base.



It is apparent from the reaction sequence above that the first step in the reaction is the loss of a proton from the relatively acidic carbon atom adjacent to the carbethoxyl group.

Subsequently, this carbanion is basic enough to polarize the carbonyl group of another molecule and condense with it. An interesting feature of this reaction is that no further condensation takes place utilizing the reaction product, ethyl acetoacetate. This compound certainly possesses a more acidic carbon atom than ethyl acetate and is, in fact, present as the anion in the basic reaction mixture. The explanation lies in the fact that the ethyl acetoacetate anion is not sufficiently basic to condense with a molecule of ethyl acetate. The resonance hybrid composed of three contributing forms shown above results in a delocalization of the electron pair to such a degree that the rate of this competing reaction is reduced to a negligible one. Although an acidic carbon atom is necessary to form a carbanion, it can not be too weak a base or condensation will not take place.

Let us now consider a compound which would produce a very basic carbanion, for example, ethane. The carbanion produced in this case would be more basic and thereby more reactive than the resonating species produced from ethyl acetate. However, the carbon atoms in ethane are so basic that it is impossible to remove a proton under normal reaction conditions. Therefore it is clear that despite the desirability of a very basic carbanion, sufficient acidity of the carbon atom is necessary for the convenient loss of proton.

These two examples illustrate the amphoteric nature required of compounds in carbanion reactions. This concept affords a simple and consistent explanation of the difference in reactivity between picoline and quinaldine with diethyl oxalate.

In terms of the resonance hybrid, the quinaldyl anion has two more contributing structures than the picolyl anion shown earlier.

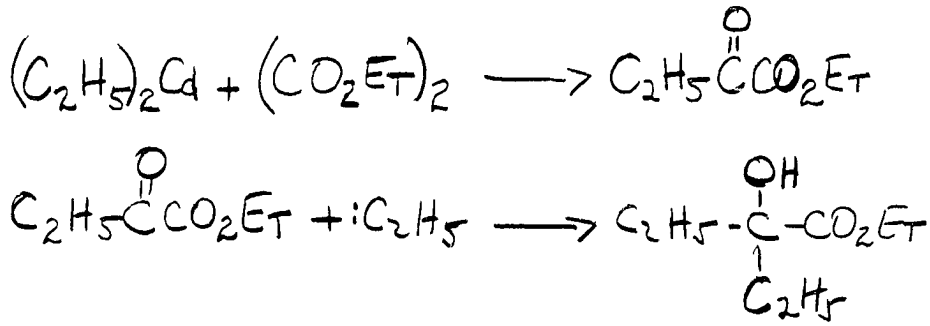
Resonance theory states that the larger number of resonance forms results in a greater distribution of charge and a more stable species. This factor tends to make quinaldine more acidic than picoline. Thus, under the relatively mild reaction conditions the quinaldyl ion is formed and then reacts with diethyl oxalate. On the other hand, 2-picoline, with its more basic methyl group, does not generate a carbanion and no condensation is observed.

Support for this theory is gained by the fact that conversion of 2-picoline to the N-oxide increases the acidity and reaction proceeds smoothly with diethyl oxalate in potassium ethoxide.

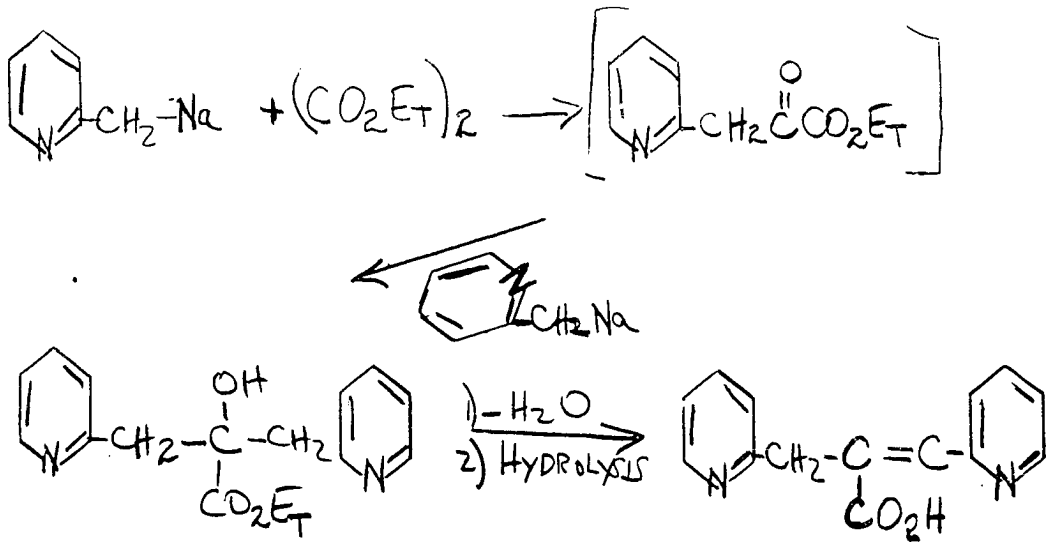
Preparation of Ethyl 2-Pyridylpyruvate

It was necessary for later workers to increase the strength of the base in order to generate the picolyl anion. This led to the use of sodamide and picolyllithium. However, it soon became clear that the anion formed in these systems was too reactive and polycondensation products were obtained.

In the search for a system between these extremes, use was made of Gilman's classic work on the relative reactivity. Organocadmium compounds have long been known to possess a lower order of reactivity then the corresponding lithium or sodium organometallics. They are best known for the preparation of ketones from acid chlorides (27). More recently, they have been reacted successfully with acid anhydrides to yield ketoacids (28). There has been very little published, however, concerning their reaction with esters. In a most interesting paper, Gilman and Nelson reacted diethylcadmium with diethyl oxalate and obtained ethyl α-hydroxy, α-ethyl butyrate in 83% yield (26). When the mono or diacid chloride was used, the same compound was produced, but in lower yields.



It is indeed interesting that Hauser obtained 2-(2-picolyl) pyridylacrylic acid in an analogous fashion when he reacted picolylsodium with diethyl oxalate[6,7].



In that same paper, Gilman suggested that other organocadmium compounds with less reactivity or organomercury compounds might decrease the amount of reaction with the ketone carbonyl of the pyruvate ester, which is undoubtedly an intermediate in the reaction sequence. The first of these ideas has been applied successfully in the preparation of ethyl 2-pyridylpyruvate, and the second resulted in the synthesis of ethyl 4-pyridylpyruvate. The 2-picolyl anion is stabilized by resonance and is certainly more stable and consequently less reactive than a simple alkyl anion. In other words, the picolyl anion is less basic than the ethyl carbanion. Nevertheless, it is apparent from the limited yield of ethyl 2-pyridylpyruvate and the polymeric byproducts formed that 2-picolylcadmium chloride is certainly a very reactive species with diethyl oxalate, even at -70°.

The reacting species, in one case, is identified as 2-picolylcadmium chloride, based on the observation that when one mole of cadmium chloride is added to one mole of 2-picolyllithium, a negative Gilman test with Michler's ketone and iodine in acetic acid, is observed after 3 hours. This reagent produces ethyl-2-pyridylpyruvate in 10% yield when condensed with diethyl oxalate. When 0.5 mole of cadmium chloride per mole of picolyl lithium is employed, a positive Gilman test is observed. This indicates the presence of picolyllithium, because the expected di-2-picolylcadmium would not be expected to give a positive test. Nevertheless, the same yield of ethyl 2-pyridylpyruvate is obtained from this reagent as in the case of 2-picolyl cadmium chloride.

As a general rule, organometallic compounds of the form RMX and RMR show the same reactivity. This generalization applies to the above observations that both picolylcadmium chloride and di-2-picolylcadmium lead to ethyl 2-pyridylpyruvate in the same yield.

Preparation of Ethyl 4-pyridylpyruvate

No report of any previous attempt to prepare ethyl 4-pyridylpyruvate was found. Therefore, as soon as ethyl 2-pyridylpyruvate was synthesized, it was hoped that the same general reaction scheme could be applied, using 4-picoline. The procedure was modified initially by using methyllithium in place of phenyl lithium. Osuch and Levine had reported the necessity of replacing phenyllithium in the acylation of 4-picoline with several esters, in order to reduce interfering addition reactions to the pyridine nucleus.(11)

When 4-picolyllithium was prepared in this way and converted to the cadmium reagent, the desired ethyl 4-pyridylpyruvate was not produced. A small amount of solid which contained inorganic matter was produced, but it could not be characterized. In view of the absence of a large amount of side products, a more reactive system was employed. The 4-pyridylpyruvate was employed directly, but this time there was no reaction product isolated at all. When these reactions failed, attempts employing the "normal addition" were employed. Thereby the diethyl oxalate was added to the 4-picolyllithium, but without success.

Once again reference was made to the work of Gilman and Nelson.[26] These workers had observed that alkyl cadmium reagents prepared from alkyl iodides were less efficient and poor yields resulted. This observation was later confirmed by deBenneville in his work with acid anhydrides.[28] In addition, they had suggested the use of alkyl mercury reagents with diethyl oxalate in order to confine the reaction to the α-dicarbonyl stage.

Thus ethyl 4-pyridylpyruvate was prepared by converting 4-picolyllithium to a 4-picolyl mercury compound with mercuric chloride.

The exact nature of the 4-picolyl mercury compound is not known. One-half mole of mercuric chloride per mole of 4-picolyllithium is employed with the thought of preparing di-4-picolylmercury. However, the Gilman test using Michler's ketone and iodine in acetic acid is positive, even after 24 hours.

Since organomercury compounds would not be expected to show a positive test, it suggests that some 4-picolyllithium remains. When mercuric chloride is added in the ratio of one-fourth mole per mole of picolyllithium, the amount of product is reduced from 10% to 5% yield. If the mole ratio is decreased to one-eighth to one, no ethyl 4-pyridylpyruvate is obtained. These facts suggest that 1) the mercuric chloride combines with 4-picolyllithium to form 4-picolylmercuric chloride and leaves approximately one-half of the picolyllithium unreacted. 2). The solid mercuric chloride reacts incompletely in the heterogenous reaction mixture. Thus, the composition would approach di-4-picolylmercury but some unconverted picolyllithium remains.

In any event, the failure of 4-picolyllithium to produce the product in previous reactions supports the view that a 4-picolyl mercury reagent is the reactive species which leads to the ethyl 4-pyridylpyruvate.

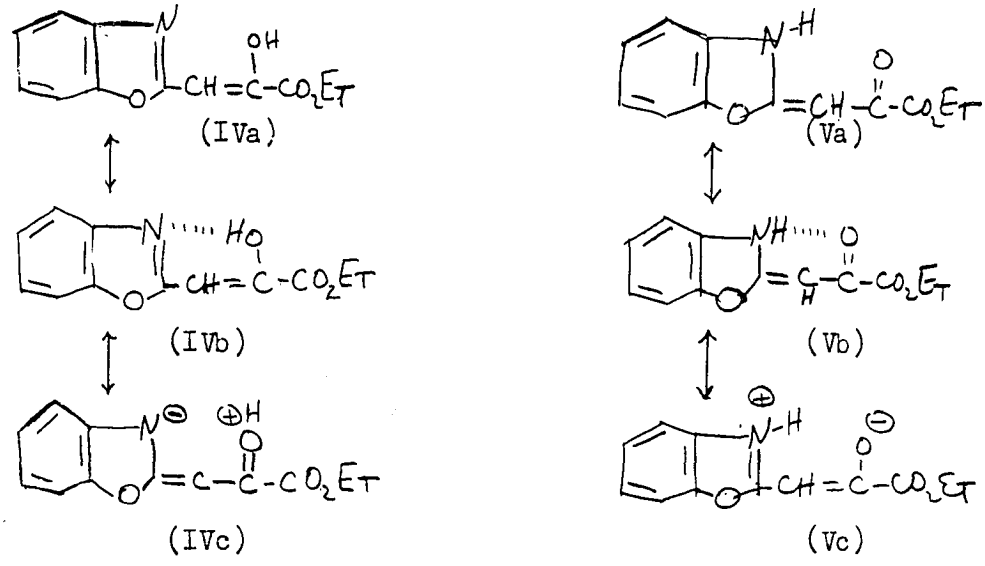
Ethyl 2-Benzoxazolylpyruvate

In order to correlate the behaviour of ethyl 2-pyridylpyruvate and ethyl 4-pyridylpyruvate with the other pyruvate esters previously studied, their properties will be compared to those of ethyl 2-benzoxazolylpyruvate. This compound was chosen because it was previously studied by Stock, and its behaviour is rather well understood (3).

Ethyl 2-benzoxazolylpyruvate is a light yellow crystalline compound melting at 69°. The enol content of a fresh methanolic solution of this ester is 99% and decreases on standing to about 44%. This conclusion was supported by the observation that the absorption maximum attributed to the enol structure decreased on aging. It was conclusively shown that the equilibration process was completely reversible by observing that after the aged solution was evaporated to dryness, the spectrum of the resultant solid was identical with that of the original solution. This ester is therefore classified as belonging to Class B as described by Donahue, Stock, and Amstutz (4). The infrared spectrum of the solid ester (KBr pellet) showed no absorption in the 3 micron region. The solid ester was observed to be fluorescent in the visual range of the spectrum, and wetting depressed the melting point 3 degrees.

This compound reacted readily with ethereal diazomethane yielding N-methyl ethyl 2-benzoxazolylpyruvate.

The electronic absorption spectrum was studied in various solvents and a bathochromic shift was observed in the absorption maximum as the polarity of the solvent increased.



In order for these structures to be capable of independent existence, there must be a real difference in the nature of the O-H and N-H bonds. The hydrogen atom must be bonded to one atom and associated with the other by relatively weak electrostatic forces. Otherwise, if the hydrogen atom occupies the same relative position in either structure then (IVb) and (Vb) are merely canonical forms contributing to a resonance hybrid.

The fact that a nitrogen methylation product was obtained from the diazomethane reaction indicated to Stock that the ester could assume a structure in which the hydrogen atom was attached to nitrogen (V). However, this was not sufficient evidence to prove its existence.

It is believed that some work carried out for this dissertation may offer further corroboration for structure (V). The effects of acid and base on the spectrum of ethyl 2-benzoxazoylylpyruvate in 95% ethanol were determined. (See Table I)

TABLE I

EFFECT OF ACID AND BASE ON THE SPECTRUM

of

ETHYL 2-BENZOXAZOYLYLPYRUVATE

		λ_{max} log ϵ
95%	Ethanol	330 (4.15)
.005N	acid	318 (4.17)
.03N	base	354 (4.27)

The addition of acid produced a hypsochromic shift and base resulted in a bathochromic shift. These results were consistent with structure VI. The addition of acid protonated the enolate oxygen atom and resulted in a weaker auxochrome. On the other hand, the addition of base removed the proton from the nitrogen and produced a more mobile electronic system which absorbed at longer wave lengths.

Structure of Ethyl 2-Pyridylpyruvate

Ethyl 2-pyridylpyruvate is a yellow crystalline compound with a melting point of 82.5-83.5°C. It gives an intense blue-green color when treated with alcoholic ferric chloride solution, a reaction typical of compounds containing an enol group. In addition, the enol content of a 0.005 molar methanolic solution of this compound does not decrease appreciably on standing. After standing for 3 days at 25° C., the enol content decreased from 98% to 92.5%, as measured by the Kurt Meyer (29) technique. (See Table II).

It was also observed that the electronic absorption maxima of an ethanolic solution did not decrease in intensity over this same period of time. (See Table III).

TABLE II

ENOL CONTENT OF ETHYL 2-PYRIDYLPYRUVATE AT 25°C.

Solution Age	% Enol Found
10 min.	99.0
1 hr.	99.3
8 hrs.	98.5
16 hrs.	95.0
1 day	95.2
3 days	92.5

TABLE III

EFFECT OF AGE ON THE ABSORPTION SPECTRUM

of

ETHYL 2-PYRIDYLPYRUVATE IN 95% ETHANOL

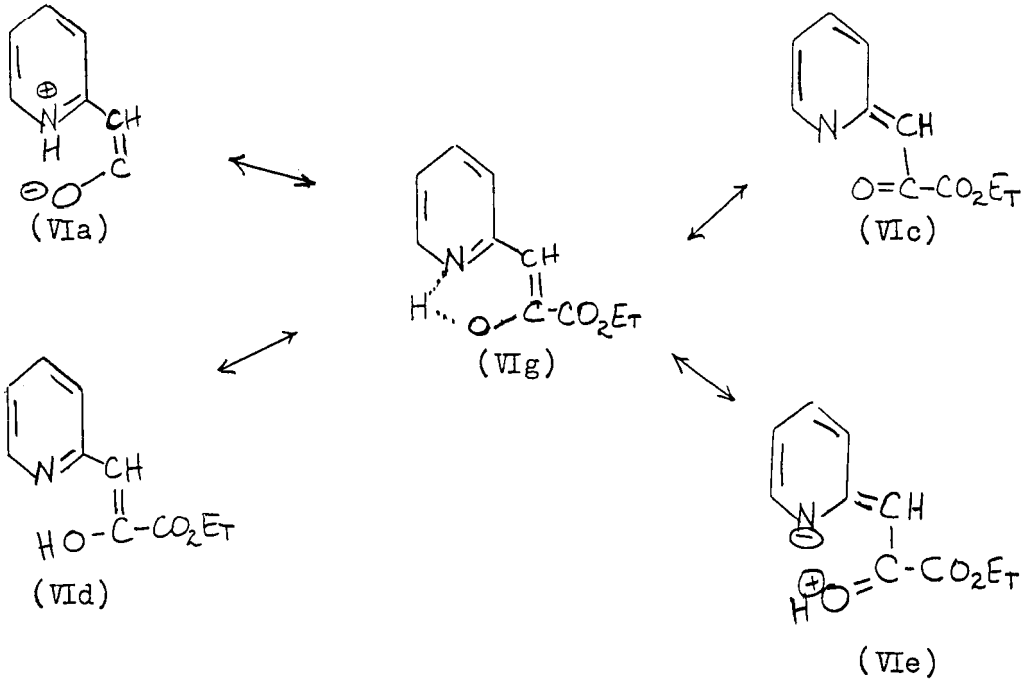
Age of Solution	λ_{max} (log e)		
10 min.	272 (3.90)	315 (4.13)	397 (3.7)
3 days	272 (3.90)	315 (4.13)	397 (3.7)

These results are consistent with Donahue's observation that the ultraviolet spectrum is not as delicate a diagnostic tool as the bromine titration. (2)

Although ethyl 2-pyridylpyruvate is undeniably an enolic compound, it does not react with ethereal diazomethane. Therefore, it can only be assumed that it does not possess an acidic hydrogen atom. The ester shows an intense yellow-green fluorescence in the presence of ultraviolet radiation.

This observation can be explained in terms of an intramolecular O...H...N interaction. It is noteworthy that the O-benzoyl derivative does not fluoresce. In addition, there is no infrared absorption maximum at 2.8-3 microns which would be expected for a compound containing an N-H or O-H group. In a KBr pellet of the ester, there is only a feeble band near 3.4 microns in this area of the spectrum. (See Figure 11) When the infrared spectrum was determined in chloroform solution, a broad feeble band was observed from 3.3 to 4.1 microns. The continued absence of the usual N-H or O-H absorption, even upon dilution, is indicative of intramolecular association. (See Figure 12)

All of these facts suggest that ethyl 2-pyridylpyruvate is a Class A compound in the classification system of Donahue, Stock and Amstutz (4). Its behaviour is thus consistent with a chelated enol structure, as postulated by these workers for the other heterocyclic compounds of this type. The chelated structure is shown below along with the other contributors to the resonance hybrid.



Further evidence for this structure is obtained by observing the effect on the absorption spectrum of adding 0.03 N-hydrochloric acid to 10^{-4} N solution of the ester in 95% ethanol. It is apparent from Table 4 that the maxima are very similar; therefore, the molecular structure is essentially unaffected by mineral acid. This behaviour can be best explained by the chelate structure of the resonance hybrid in which neither the pyridine nitrogen nor the enolic oxygen atom is available for protonation by the added acid (VIb). In all the other canonical forms shown on the previous page, acid would be expected to change the absorption spectrum considerably.

TABLE IV

EFFECT OF ACID AND BASE ON THE ABSORPTION SPECTRUM

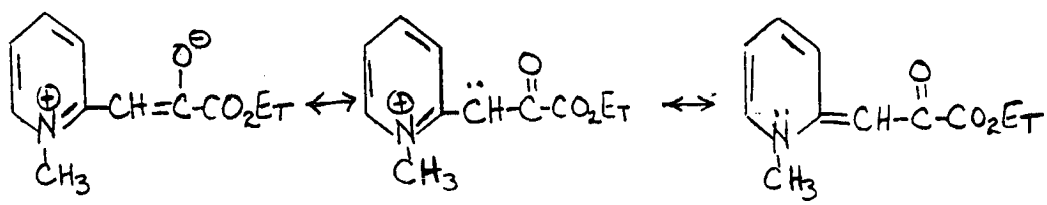
of

ETHYL 2-PYRIDYLPYRUVATE (10^{-4}M)

	λ_{max} logϵ		
95% Ethanol	272 (3.90)	315 (4.13)	397 (3.7)
95% Ethanol -.03N HCl	268 (3.89)	327 (4.09)	395 (3.28)
95% Ethanol -.03N NaOH		355 (4.23)	

The effect of acid and base on the spectrum of ethyl 2-quinolylpyruvate was also studied during the course of this investigation. See Figure 3. This compound behaves very similarly to its pyridyl-analog. The absence of any effect of acid on the spectrum of ethyl 2-quinolylpyruvate seems to indicate a strong bonding of the chelated hydrogen atom between nitrogen and oxygen. The slightly greater effect observed in the case of ethyl 2-pyridylpyruvate particularly, the small bathochromic shift at the 315 millimicron bond may suggest a slightly stronger bond between the oxygen and hydrogen atoms.

Despite repeated efforts to methylate ethyl 2-pyridylpyruvate, neither the O-methyl nor the N-methyl compounds resulted. The N-methyl ethyl 2-pyridylpyruvate was finally obtained by condensing 2-picoline methiodide with diethyl oxalate and sodium ethoxide. This compound is extremely valuable in further confirming the nature of the parent compound.



(VIIa) (VIIb) (VIIc)

Thus compounds (VIIa) and (VIIC) are the methyl analogs of (VIa) and(VIc). The addition of hydrochloric acid to an ethanolic solution of N-methyl ethyl 2-pyridylpyruvate produced a drastic shift in the absorption spectrum by protonating the enolate anion. (See Table V). This contrasting behaviour in acid media further supports the chelate theory and the minor contributions of extreme forms such as (VIa) and (VIc) to the resonance hybrid of ethyl 2-pyridylpyruvate.

TABLE V

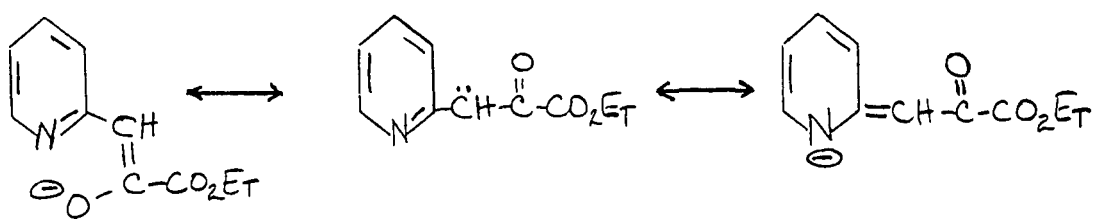
EFFECT OF ACID ON THE SPECTRUM

of

N-METHYL ETHYL 2-PYRIDYLPYRUVATE (10^{-4}N)

		λ mμ(log e)	
95% Ethanol	shoulder 315	325 (3.80)	410 (4.21)
95% Ethanol-.03N HCl		270 (3.78)	335 (3.99)

Considering the slight effect of acid on the chelate structure of ethyl 2-pyridylpyruvate, it would be well to compare it with that of added base. From Table III it is apparent that the spectrum is drastically altered by the addition of 0.03N sodium hydroxide. The loss of the chelated enolic proton in the presence of a strong base undoubtedly produces the resonating anion (VIII).



(VIIIa) (VIIIb) (VIIIc)

The ultraviolet spectrum of the ethyl 2-pyridylpyruvate was determined in a series of solvents of varying polarity. It can be seen in Table VI that a hypsochromic shift occurred as the polarity was increased. Two alternate explanations for such a shift are possible. First, the absorption band may be due to an $N \rightarrow \pi^*$ transition. Such a transition involves the promotion of a non-bonding electron from the nitrogen atom into the π -electron system of the molecule. Alternatively, the absorption may be due to a $\pi \rightarrow \pi^*$ transition, which involves a change in the electron distribution in the π electron system of the molecule. McConnell has pointed out that all $N \rightarrow \pi^*$ bands display hypsochromic shifts as the solvent polarity is increased (30). However, the limiting intensity of such bands is reported to be log e = 3.0. The absorption observed in the present case was considerably more, log e =3.15 to 4.07.

TABLE VI

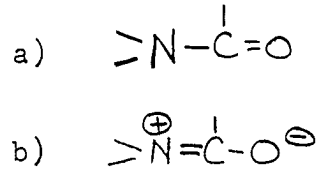
EFFECT OF SOLVENT POLARITY ON THE ABSORPTION SPECTRUM

of

ETHYL 2-PYRIDYLPYRUVATE

Solvent	λ mμ log e		
90% Isooctane - 10% Ethanol	275 (3.96)	317 (4.10)	400 (3.15)
95% Ethanol	272 (3.90)	315 (4.13)	397 (3.70)
90% Water-10% Ethanol		308 (3.90)	386 (4.15)
100% Water		308 (3.78)	385 (4.07)

Thus, the absorption can be attributed to the $\pi \rightarrow \pi^*$ transition. Brooker studied the effect of different solvent polarity on the electronic spectra of the merocyanines and was able to determine whether the molecular structures were weakly, moderately, or strongly polar (31). The merocyanines are unionized dyes and contain the amidic system shown in (IX). For this system there are two plausible extreme structures,



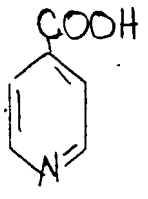
(V)

which are uncharged and dipolar respectively. The basic end of a merocyanine is electron donating in the uncharged form and the other end is electron-attracting, and may be called acidic.

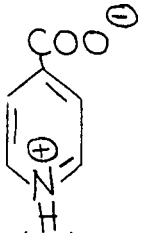
The nitrogen tautomer of ethyl 2-pyridylpyruvate possesses a structure which resembles a merocyanine. (See structures VIa and VIc)

In terms of Brooker's classification, the observed hypsochromic shift with increasing solvent polarity indicates that the ground state is more polar than the excited state and that ethyl 2-pyridylpyruvate is a "strongly polar merocyanine."

It is also apparent from Table VI that the hypsochromic shift is accompanied by an increase in intensity. This observation is contrary to Brooker's finding in that he reported an intensity decrease for the merocyanines. Stock observed that ethyl 2-quinolylpyruvate also behaved differently from the merocyanines and explained it on the basis of the work of Stephenson and Sponer [44]. These workers observed that the absorption intensity of simple monosubstituted pyridines were markedly increased by conversion to their cationic forms. For example, an intensity increase in the case of isonicotinic acid was attributed to conversion of the "neutral" structure (X) to the zwitterion (XI). It is possible therefore, that the pyridyl- and



(X)



(XI)

quinolylpyruvates approach a dipolar form such as (VIa) in highly polar solvents.

Structure of Ethyl 4-Pyridylpyruvate

Ethyl 4-pyridylpyruvate is an orange-yellow powder with a melting point of 138-139°. It gives an intense red-brown color when treated with alcoholic ferric chloride solution, indication the presence of an enol. The enol content at 0 time was determined by adding the solid ester to a methanolic bromine solution. Although the sharp melting point implied a pure compound the enol content of 92% suggests the presence of some of the ketonic tautomer. Unlike the 2-isomer, the enol content of a 0.005 molar methanolic solution of ethyl 4-pyridyl-pyruvate decreased appreciably. It took 10 minutes to dissolve the ester in methanol and by this time the enol content measured approximately 52%. At the end of 3 days the amount of enol present decreased to 33.5%. (See Table 7). At the end of this period the log e of the absorption maximum decreased from 4.04 to 3.88. The solution was evaporated to dryness, redissolved and the spectrum redetermined. The spectrum of the redissolved ester was almost identical with that of the aged solution. Apparently, evaporation did not reverse the process responsible for the disappearance of the enol. (See Figure 5)

TABLE VII

ENOL CONTENT OF ETHYL 4-PYRIDYLPYRUVATE AT 25°C.

Solution Age	% Enol Found
0	92.0
10 minutes	52.0
1 hour	47.3
8 hours	45.0
16 hours	41.9
1 day	39.6
3 days	33.5

In the infrared spectrum no absorption is observed at 2.8-3.0 microns, the region for N-H or O-H groups. However, a strong broad band appears from 3.3-3.8 microns. (See Figure 13) It is suggested that this band is due to the enolic hydroxyl group shifting to longer wave lengths by O-H-N intermolecular association. The breadth of the band supports this view and is very similar to the spectrum of 3-hydroxypyridine recently reported by Heinert and Martell (34). The infrared spectrum in chloroform is very interesting when compared to the previous one in which a potassium bromide pellet was used. In chloroform two sharp peaks are apparent, one at 2.75 and the other at 3.35 microns. The disruption of the associated structure by the solvent resulted in the appearance of the O-H or N-H peak and the C-H peak at their expected wave lengths. (See Figure 14)

In the carbonyl region of the infrared spectrum, there is an apparent doublet evidenced by a shoulder at 5.75 and the primary peak at 5.8 microns. (1740 and 1728 cm.$^{-1}$) This may indicate absorption by a ketone carbonyl in addition to that of the carbethoxyl group. This information is suggestive of a structure such as (XII e) or the presence of the ketonic tautomer having no definite conclusion is possible.

Also in contrast to the 2-isomer, this compound does not fluoresce under ultraviolet radiation. This observation is in harmony with the fact that intramolecular O....H....N interaction can be excluded on steric grounds.

The essential difference between the fluorescing ring structure and the corresponding non-fluorescing associated structure seems to be a certain compactness of the closed structure (32).

This compactness induces a rigidity of the molecule as a whole which is absent in molecules in which parts may vibrate with respect to each other. This asspect of the relationship between molecular structure and fluorescence was emphasized by Lewis and Calvin (33). As a result of the non-rigidity of the structure, low frequency vibrational motions of parts of the molecule occur with respect to each other, increasing the probability of deactivating radiationless transitions.

The high melting point of this compound relative to ethyl 2-pyridyl-pyruvate and the observation that wetting the solid ester depresses its melting point 36° also substantiates an associated structure. (See Table VIII)

TABLE VIII

"WET" AND DRY MELTING POINTS *

of

THE PYRIDYLPYRUVATE ESTERS

Melting Point °C.

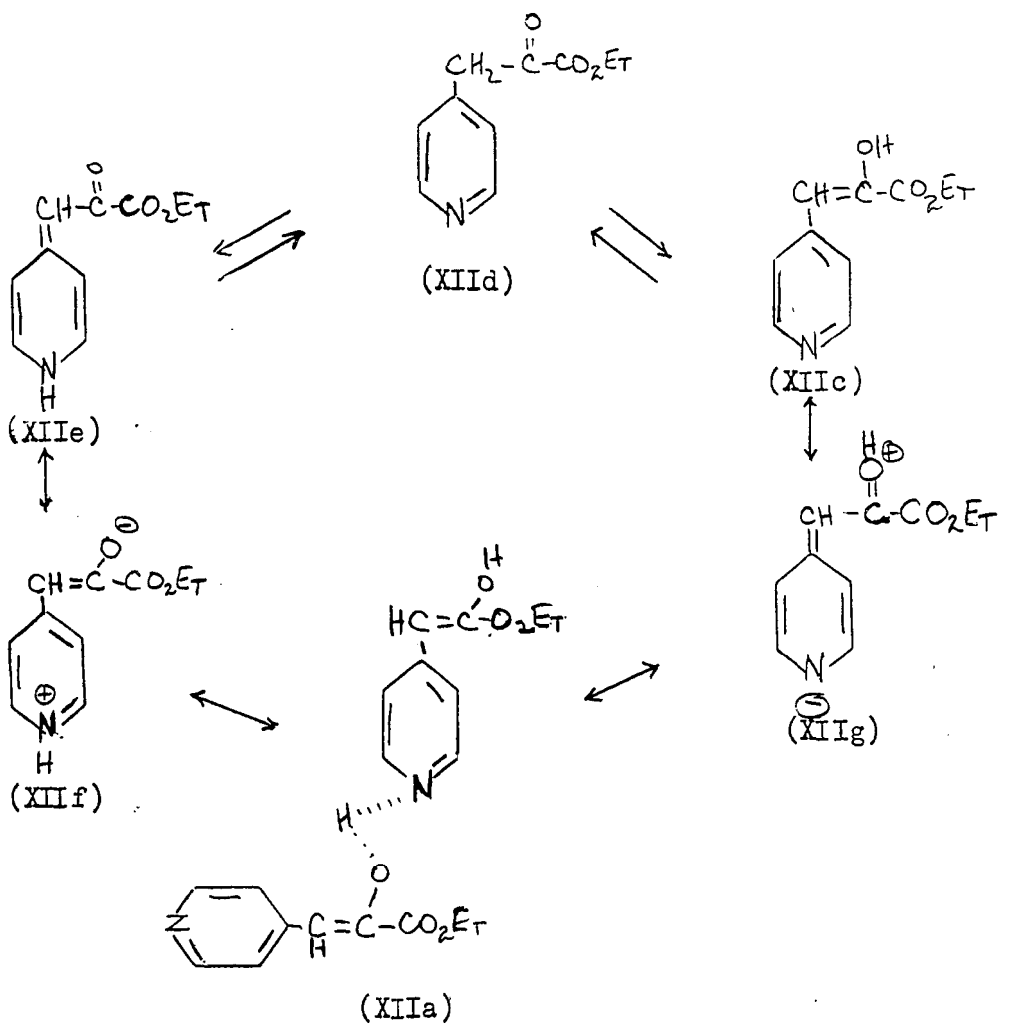
	Dry	Wet	Depression
Ethyl 2-pyridylpyruvate	83.5	79.5	4
Ethyl 4-pyridylpyruvate	139	103	36

*The melting point was taken to be the temperature at which the last crystal disappeared.

The molecular weight of ethyl 4-pyridylpyruvate was determined by the molar freezing point depression of both a camphor and a benzene solution.

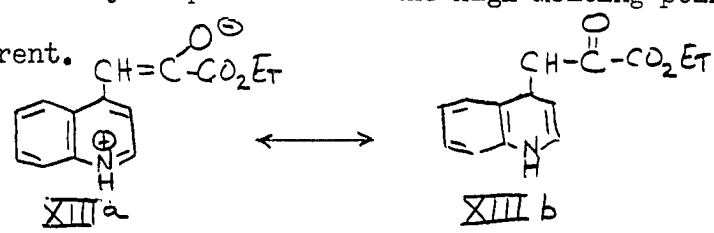
Both methods checked quite closely and indicated a molecular weight of 250 as compared to a calculated value of 193. Both determinations involve solvation of the solid ester by solvent molecules. The results imply that ethyl 4-pyridylpyruvate is associated to some extent, approximately 30%, when in solution. This fact supports the view that the ester is probably even more highly associated in its crystalline form. In contrast to these results, the molecular weight of ethyl 2-pyridylpyruvate was determined to be the theoretical value of 193.

The structure of the solid compound may be pictured by the following resonance structures of both the nitrogen and oxygen tautomers:



Ethyl 4-pyridylpyruvate is a Class C compound, and its properties are very similar to those of the other compound in this class, ethyl 4-quinolylpyruvate.

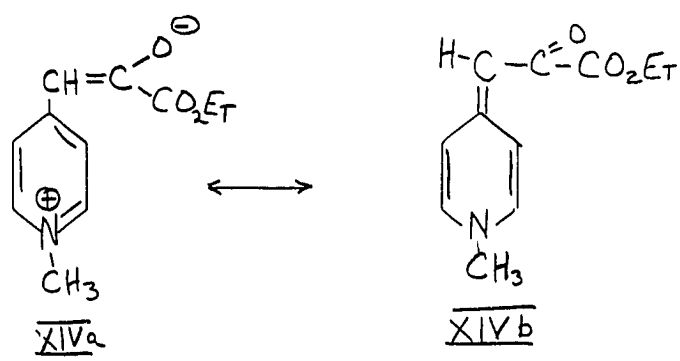
Stock suggested that ethyl 4-quinolylpyruvate might possess the structure (XIII) in order to account for most of the observed properties of the esters (3). If the contribution of the charged form (XIIIa) were large, a satisfactory explanation of the high melting point of the ester would be apparent.



XIIIa ⟷ XIIIb

Unfortunately, the ester failed to react with ethereal diazomethane and further support for this theory was lacking. The corresponding structures (XII f ↔ XII e) could be postulated in an analogous fashion for ethyl 4-pyridylpyruvate. However, this ester also failed to react with an ethereal diazomethane solution.

In order to further investigate the contribution of this structure, the N-methyl ethyl 4-pyridylpyruvate was prepared by means of the Claisen condensation of 4-picoline methiodide and diethyl oxalate. The structure of this compound can only be represented by structure (XIV). Therefore, a comparison of the spectra of ethyl 4-pyridylpyruvate and the N-methyl compound should have been enlightening.



XIVa ⟷ XIVb

The comparison of the spectra is not conclusive however, and a possible explanation is the apparent tautomerism of ethyl 4-pyridyl-pyruvate in alcoholic solution. The rapid decrease in enol content to approximately 50% in only 10 minutes suggests that the spectrum may be a composite of the keto and enol tautomers. The broad band with a maximum of 412 millimicrons in the N-methyl compound would then correspond to the less intense 407 millimicrons band in ethyl 4-pyridyl-pyruvate. It is obvious however, that the spectrum of the latter compound shows absorption at 293 millimicrons which is not present in the N-methyl compound.

In an attempt to further clarify the nature of ethyl 4-pyridyl-pyruvate, the effect of acid and base on the absorption spectrum was observed. From Table IX it can be seen that upon the addition of acid the maximum occurs at much shorter wave lengths. The result is in marked contrast to the slight effect of acid on the 2-isomer.

TABLE IX

EFFECT OF ACID AND BASE ON THE ULTRAVIOLET SPECTRUM

of

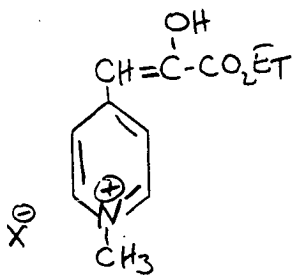
ETHYL 4-PYRIDYLPYRUVATE

	$\lambda_{m\mu}$ log e		
95% Ethanol	293 (4.10)	407	(4.45)
95% Ethanol -.005 N HCl	235 (3.58)	327	(4.19)
95% Ethanol -.03 NaOH	344 (3.56)	355	(4.23)

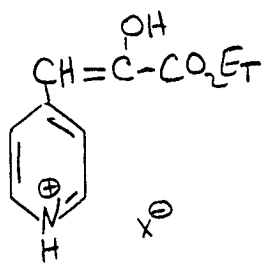
The spectrum of ethyl 4-quinolylpyruvate and the effects of added acid and base were also studied in this work. (See Figure 6) Its behaviour is completely analogous to that of ethyl 4-pyridylpyruvate.

It is apparent from Table X that the effect of acid upon N-methyl ethyl 4-pyridylpyruvate is similar to that of ethyl 4-pyridylpyruvate, and in fact the absorption maxima of both compounds are almost identical in the presence of acid.

This can only be interpreted to mean that in acid media similar species of the two compounds are produced, (XV) and (XVI).



(XV)



(XVI)

The precursor to compound (XVI) could conceivably be either (XII c), (XII f), the ketonic (XII d), or a mixture of these components. Thus, the effect of the acid is the production of a homogenous solution of only one species. This explanation thus could account for the increase in intensity caused by the acid.

TABLE X

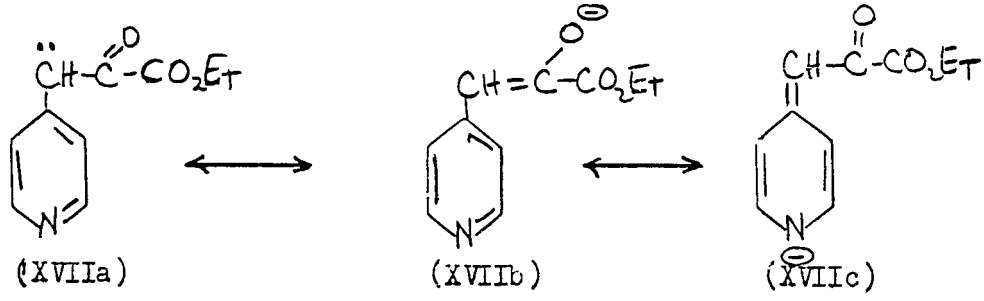
EFFECT OF ACID ON THE ABSORPTION SPECTRUM

of

N-METHYL ETHYL 4-PYRIDYLPYRUVATE

	$\lambda_{m\mu}$ log e	
95% Ethanol	247 (3.81)	412 (4.23)
95% Ethanol -.03 N HCl	235 (3.79)	330 (4.25)

The effect of base on the spectrum of ethyl 4-pyridylpyruvate is very similar to that observed for the 2-isomer. The absorption maximum at 407 millimicrons in the visible spectrum disappears and a maximum is observed at 355 millimicrons in the ultraviolet. It is difficult to say whether the visible band shifted to shorter wave lengths or that the visible peak disappeared due to a change in the structure of the molecule with a concurrent bathochromic shift of the ultraviolet peak. Nevertheless, the resultant anion undoubtedly possesses structure (XVII) which is analogous to that postulated for ethyl 2-pyridylpyruvate in basic solution. (See formula VII).



(XVIIa) (XVIIb) (XVIIc)

The absorption spectra of the 2- and 4-isomer are very similar in basic media, both absorbing at 355 millimicrons.

The spectrum of ethyl 4-pyridylpyruvate was run in various solvent mixtures and the results are recorded in Table XI. As the polarity of the solvent increased, a hypsochromic shift of the absorption maxima took place.

It is important to note that only polar solvents which are capable of associating with the solid ester could dissolve it. The isoöctane-ethanol mixture was obtained by diluting an ethanolic solution with isoöctane.

It is apparent from the data in Table XI that the intensity of the longer wavelength absorption band increased markedly with increasing solvent polarity.

TABLE XI

EFFECT OF SOLVENT POLARITY ON SPECTRUM

of

ETHYL 4-PYRIDYLPYRUVATE

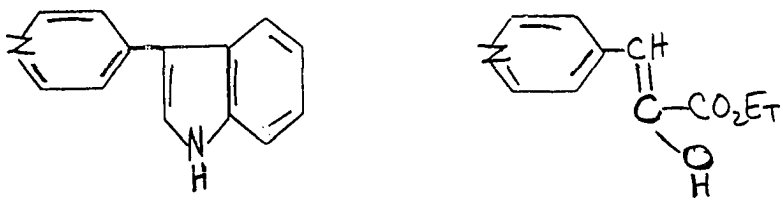
Solvent	λ mμ (ε)	λ mμ (ε)
Chloroform	290 (4.25)	408 (1.95)
90% isooctane-10% ethanol	290 (4.22)	410 (2.70)
95% ethanol-5% water	293 (4.10)	407 (3.45)
90% water-10% ethanol	251 (3.73)	391 (4.14)
water	249 (3.32)	389 (3.96)

Since the high intensity of absorption rules out an $n \rightarrow \pi^*$ transition, a $\pi \rightarrow \pi^*$ transition is responsible for the observed absorption bands. The hypsochromic shift seems to indicate that the ground state is more polar than the excited state and may be classified as a "strongly polar merocyanine" in terms of Brooker's classification. This conclusion is in harmony with the physical properties of this compound, such as the high melting point and large wet melting point depression.

The increase in intensity can be explained on the basis of the work of Stephenson and Sponer mentioned earlier in regard to ethyl 2-pyridylpyruvate (44). Thus, ethyl 4-pyridylpyruvate would approach a dipolar form such as (XII f) in solvents of high polarity.

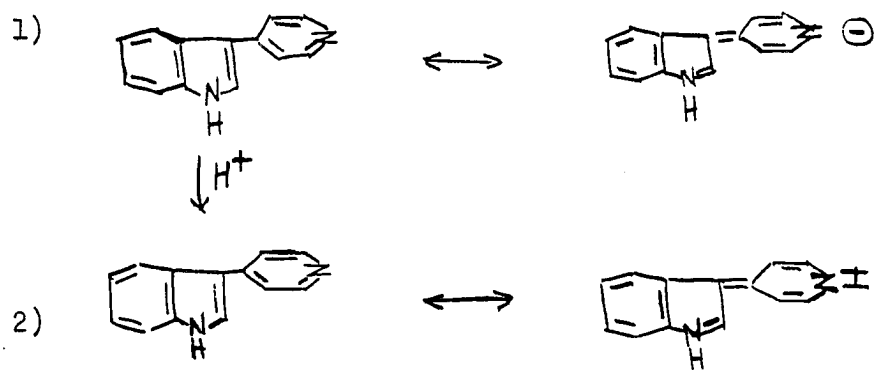
Spectra of the Pyridylindoles

The absorption spectra of the 3-(pyridyl)-indoles are of particular interest because of their similarity to the pyridylpyruvates. It is apparent from the structures whown here that the indole is an enamine



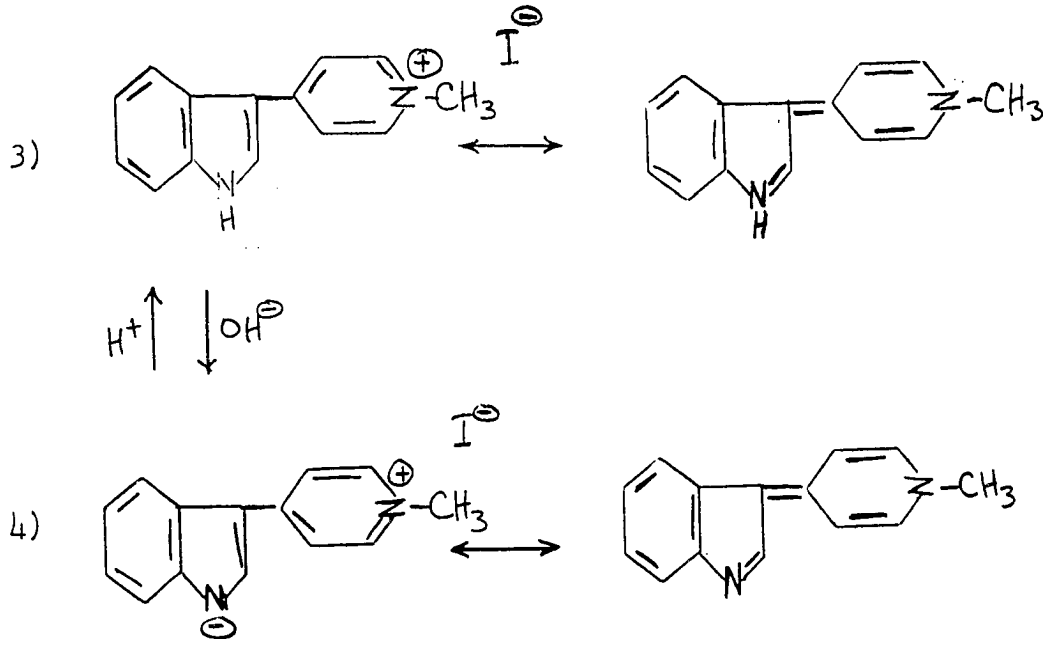
which corresponds to the enolic pyruvate ester. A study of the spectra of these compounds was made with the hope of further elucidating the nature of the pyruvates.

When acid is added to an ethanolic solution of 3-(4)-pyridylindole, a bathochromic shift takes place. (See Figure 17) The pyridine nitrogen is protonated and the transition shown in number 2 is of lower energy than number 1 by virtue of the removal of the negative charge.



The spectrum of the methiodide derivative is very similar to that of the protonated compound, which is to be expected. The addition of base to the methiodide removes the acidic indole proton. (See Figure 18)

A more mobile electronic system is produced which absorbs at longer wave lengths, as shown below in transition 4:



Analogous transitions can be drawn for 3-(2)-pyridylindole which behaves similarly. (See Figures 15 and 16).

It is apparent from this study that protonation of the pyridine nitrogen atom results in a bathochromic shift. It is therefore of interest to compare this behaviour with that of the pyruvate esters in the presence of acid. (See Figures 2 and 4). Ethyl 2-pyridylpyruvate shows a decrease in intensity of the 397 millimicron band and a small bathochromic shift from 315 to 327 millimicrons. Ethyl 4-pyridylpyruvate in acid shows absorption at 327 millimicrons. This value is between the two absorption peaks of 293 and 407 millimicrons in neutral solution. It appears that the spectra of the pyruvates are considerably more complex than thos of the pyridylindoles and no simple comparison is possible.

However, the spectra of the N-methyl pyruvate esters correlate nicely with that of the anhydronium base of the pyridyl indole methiodides. The addition of acid to the anhydronium base is shown on the previous page. (transition 4 → transition 3). In both cases a large hypsochromic shift results from the addition of acid.

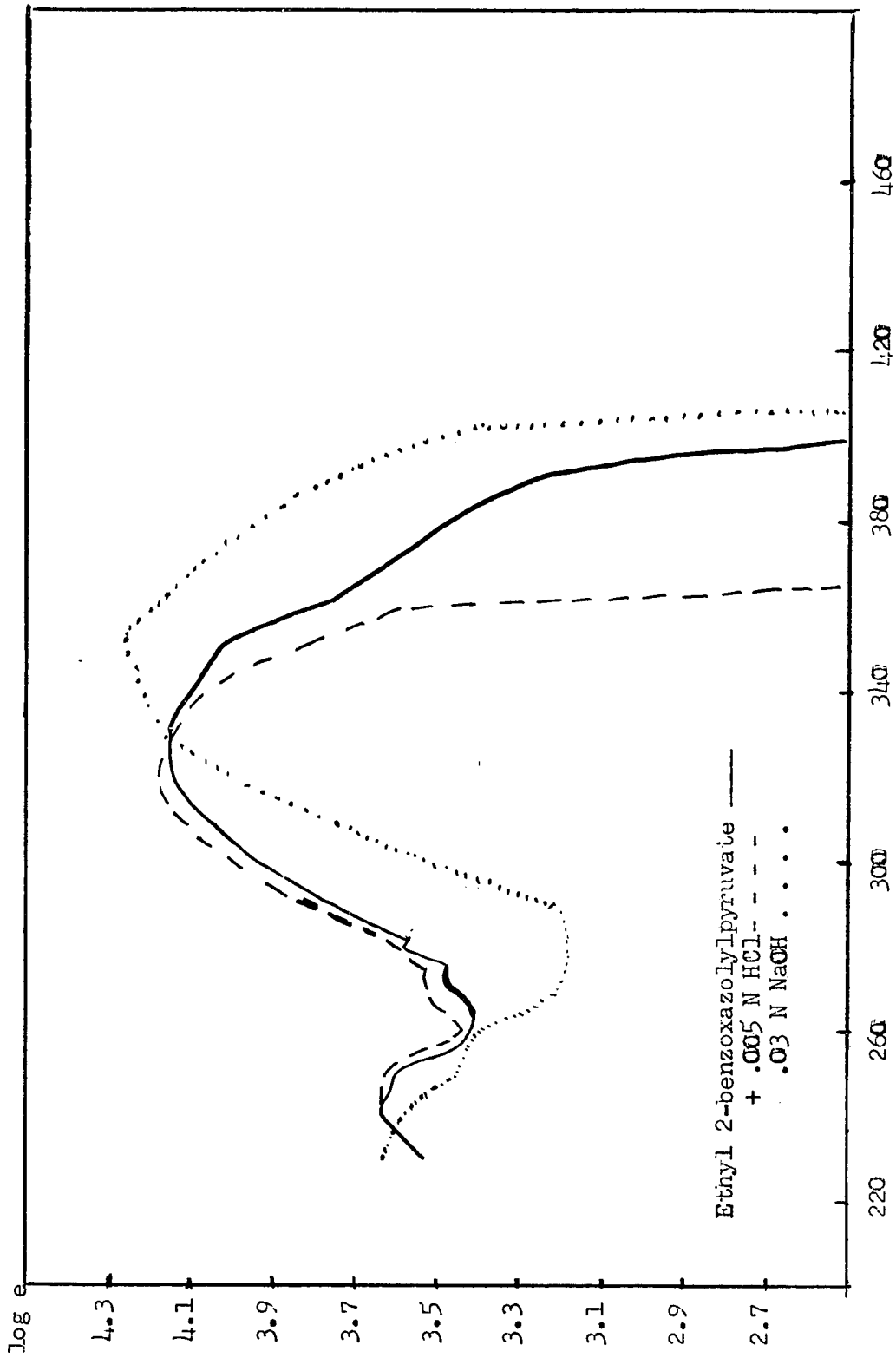


Figure 1

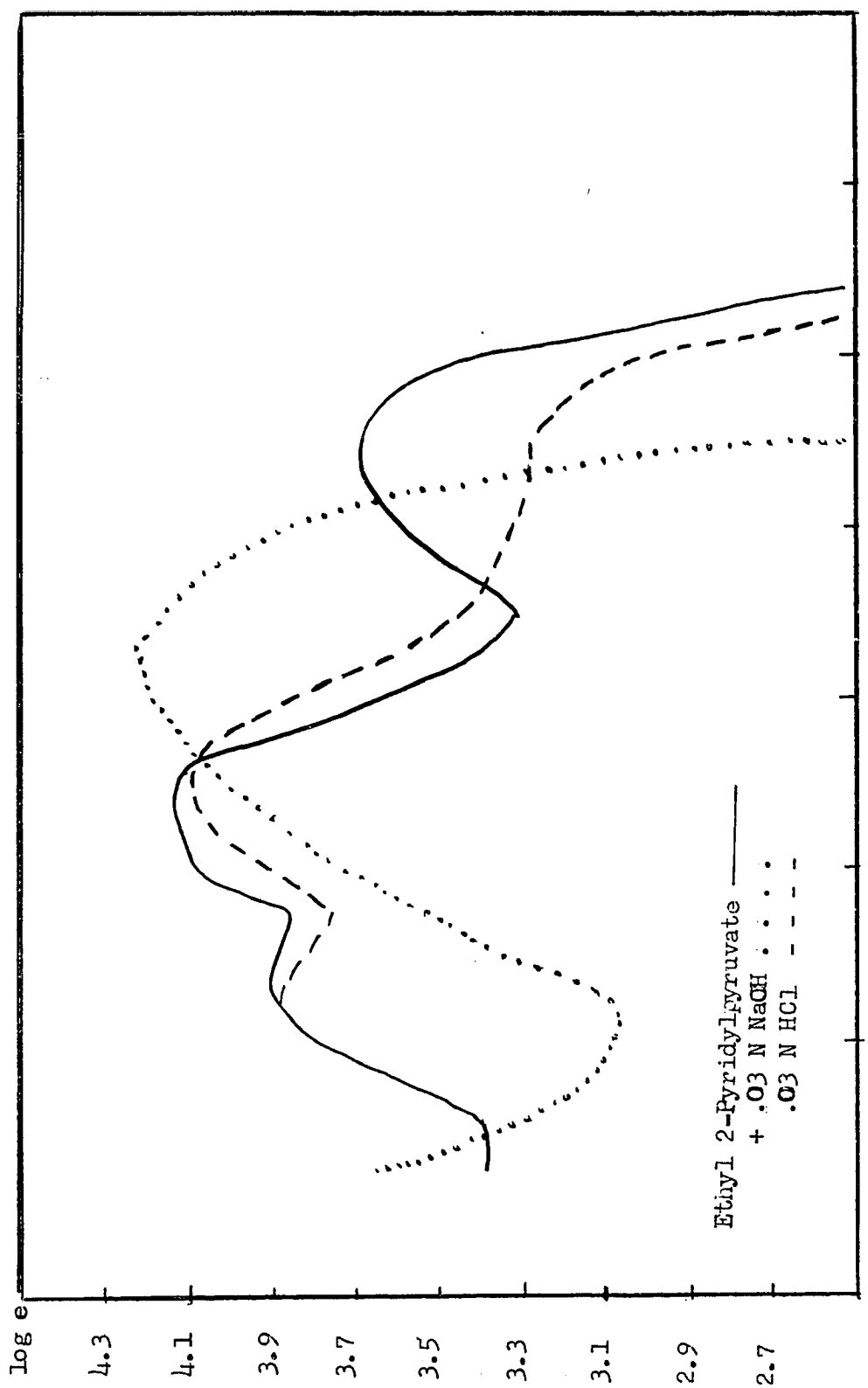


Figure 2

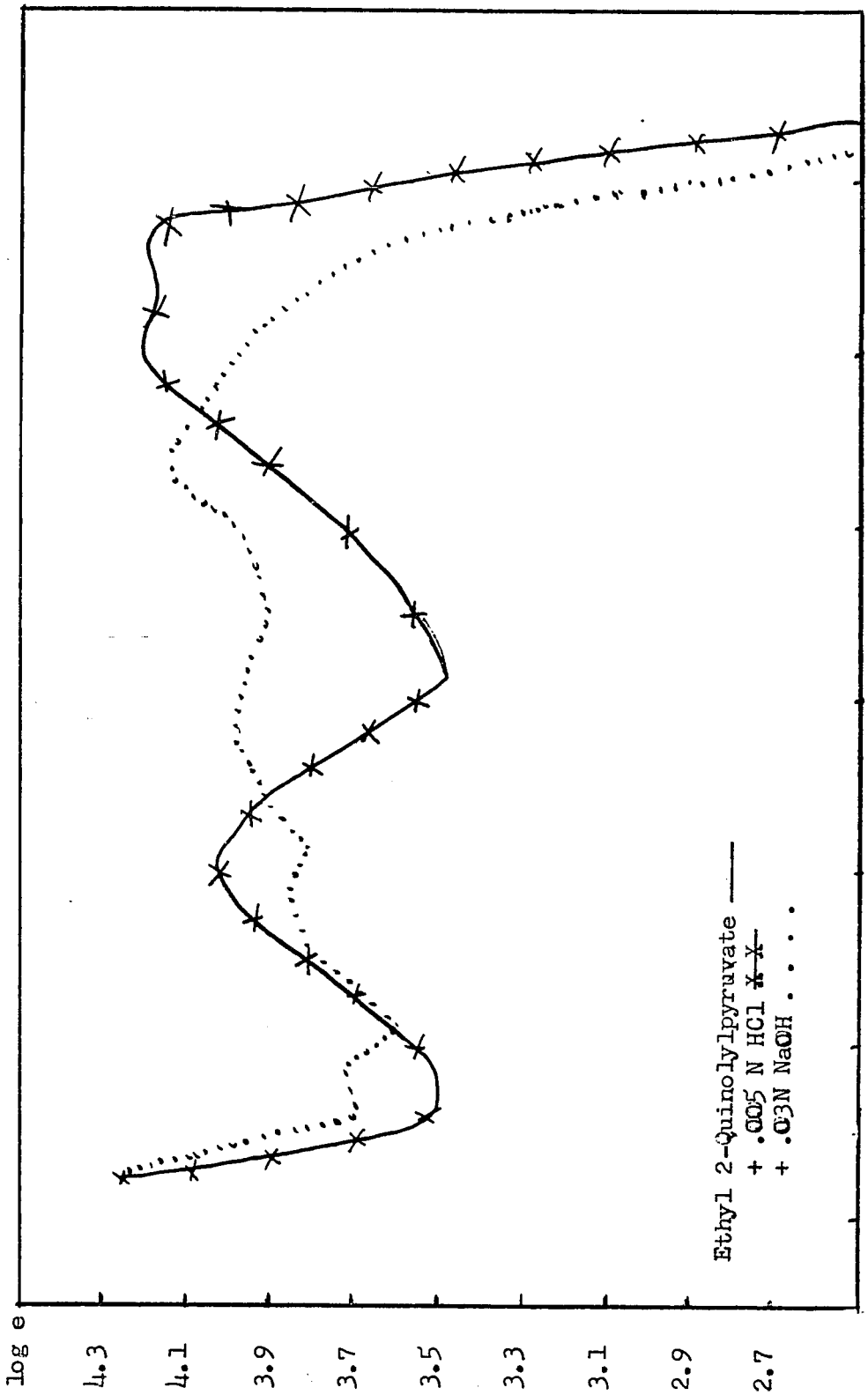


Figure 3

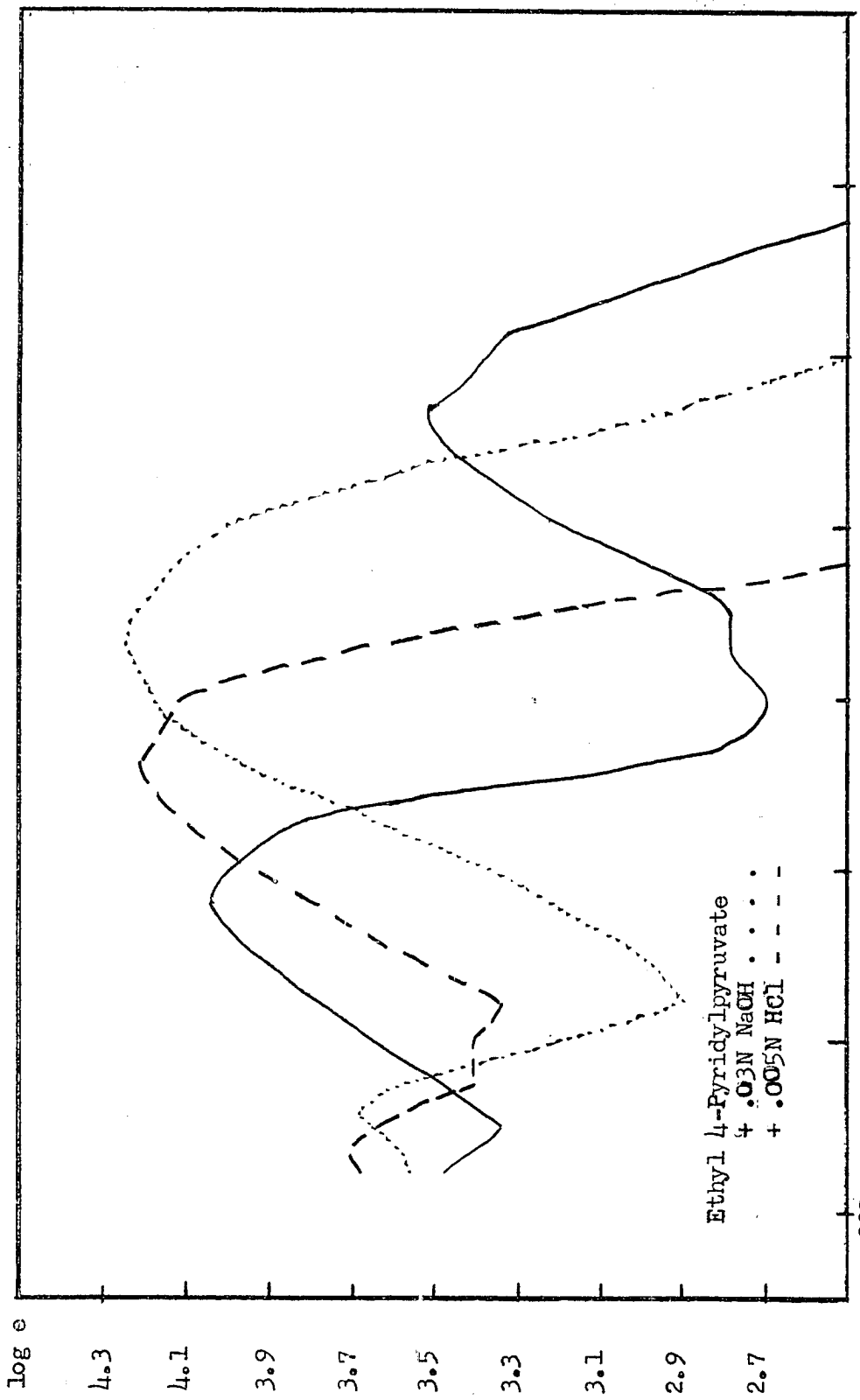


Figure 4

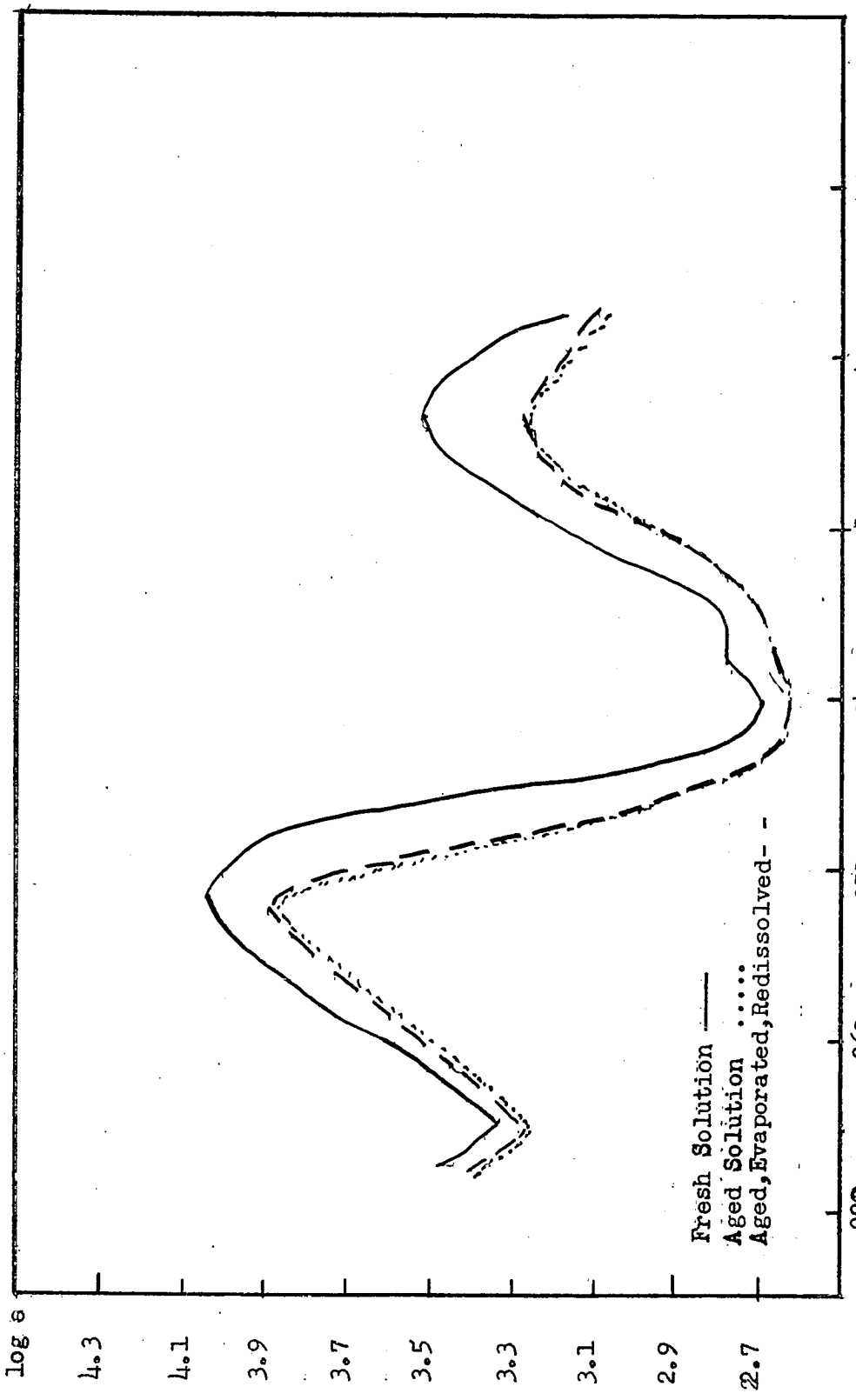


Figure 5

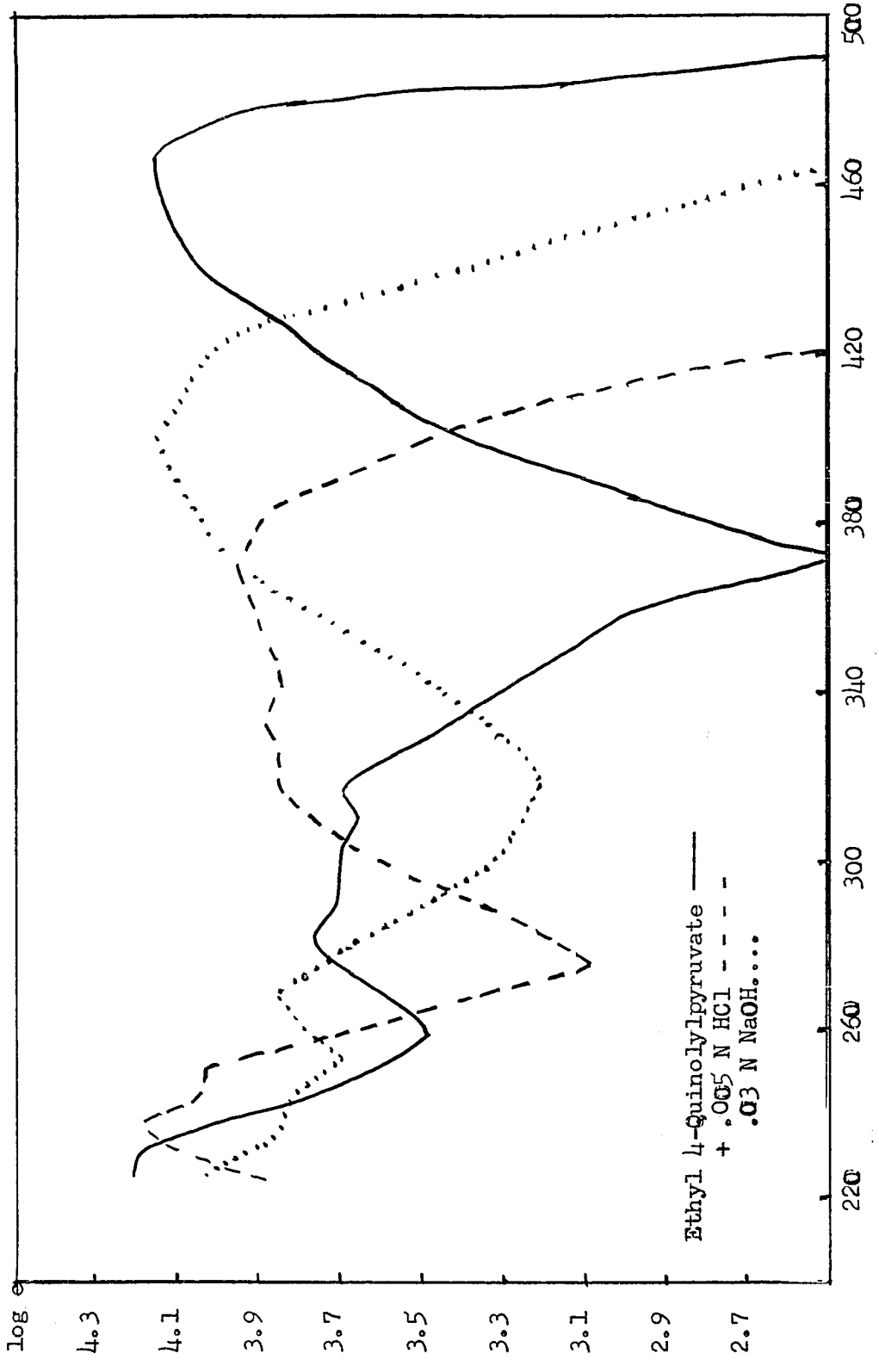


Figure 6

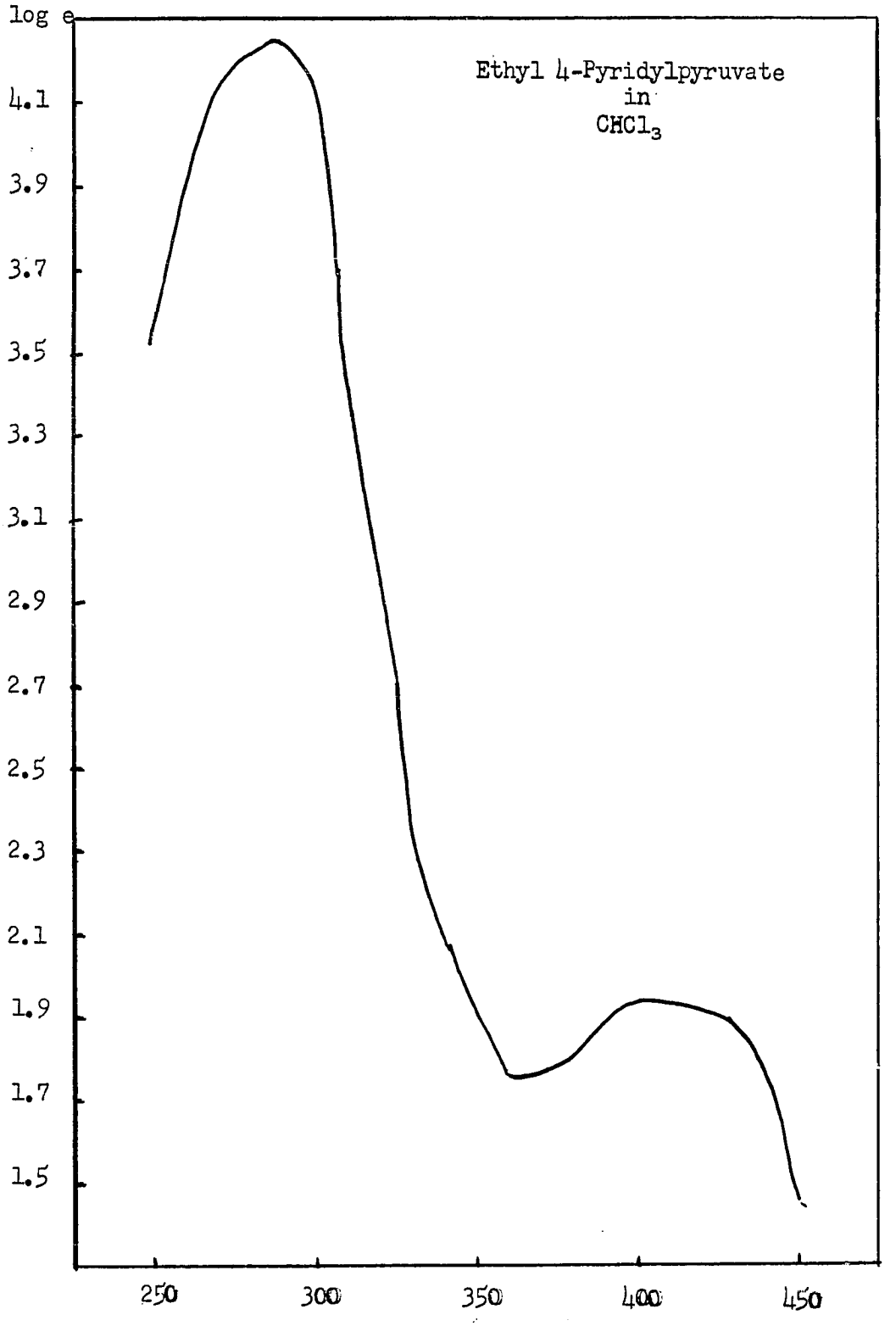


Figure 7

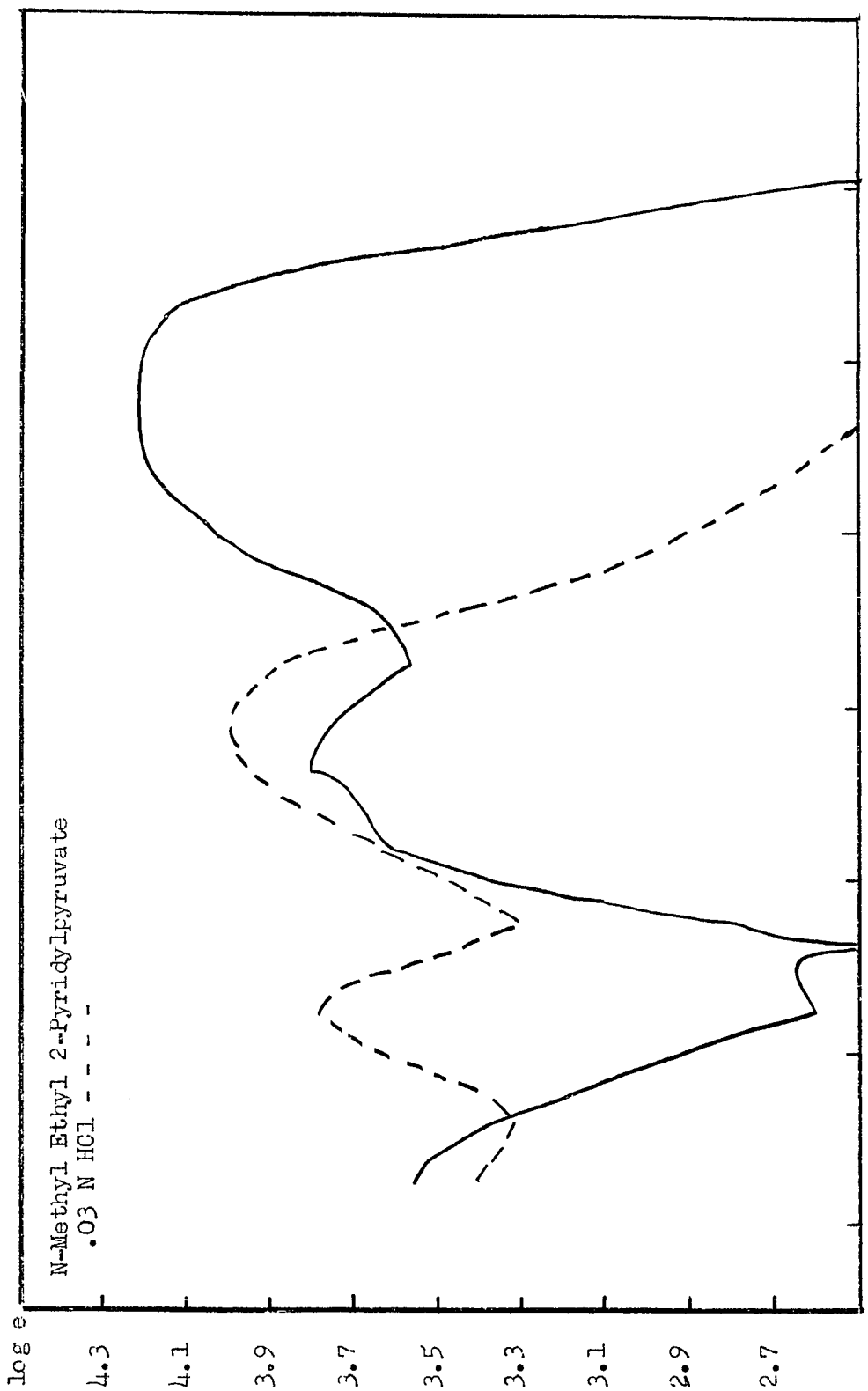


Figure 8

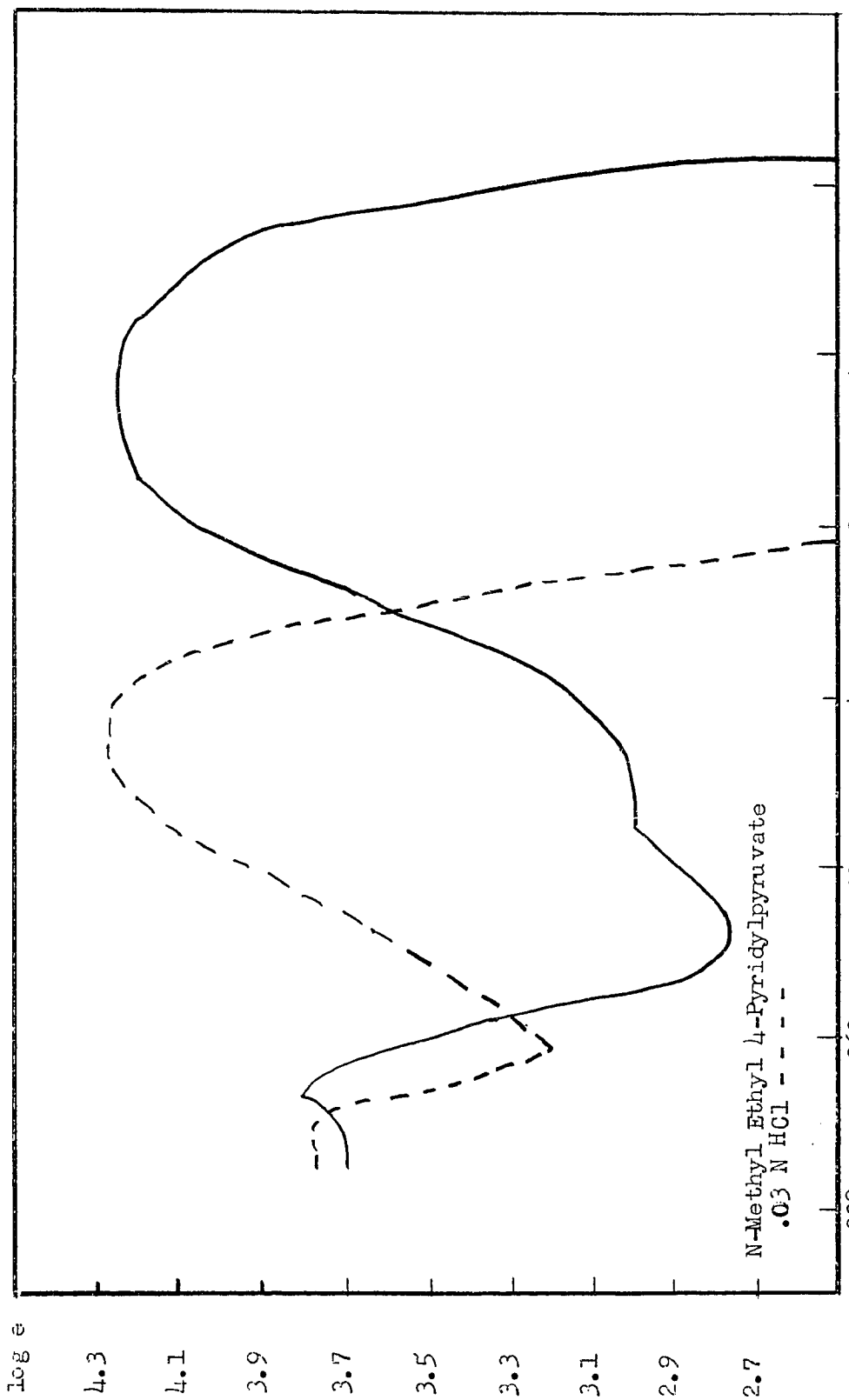


Figure 9

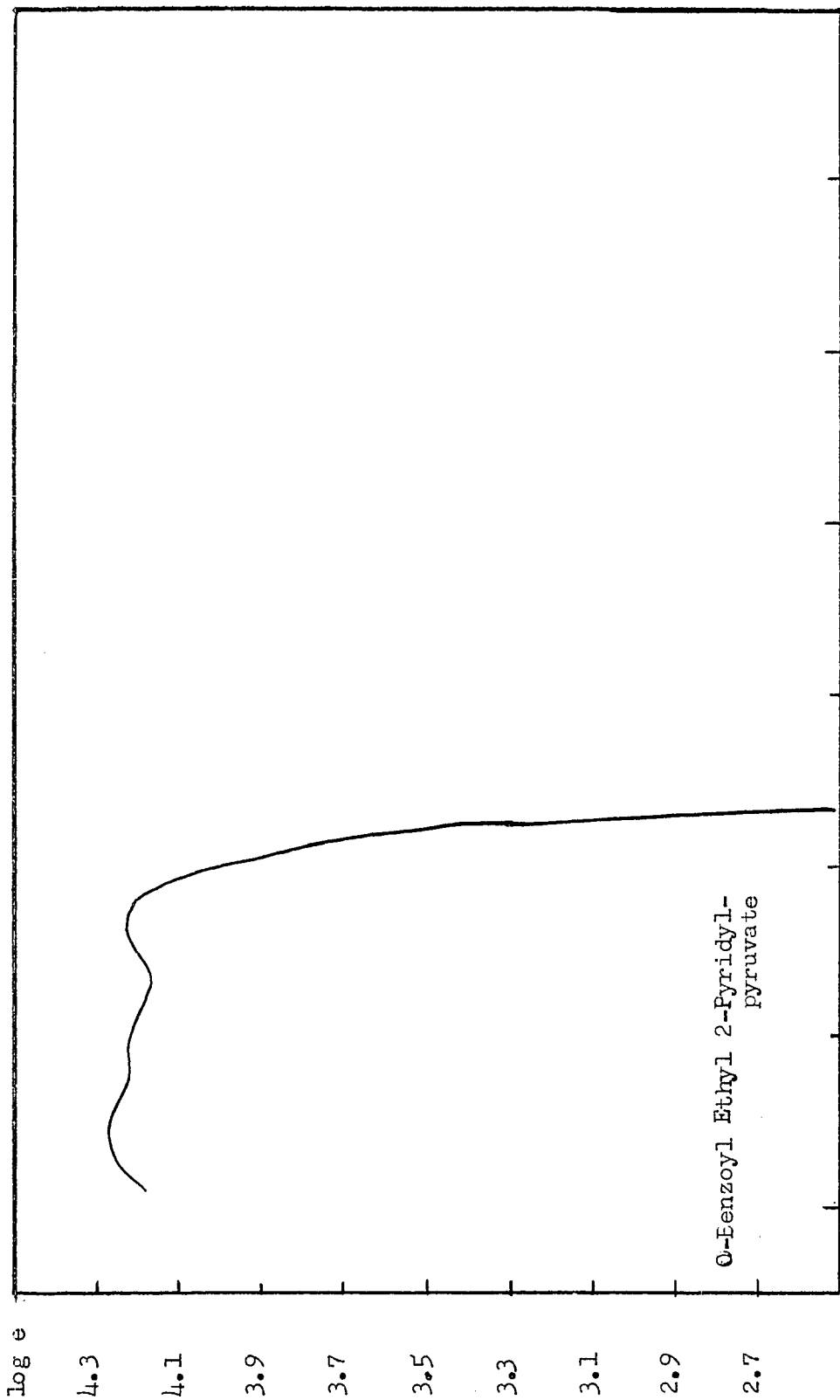


Figure 10

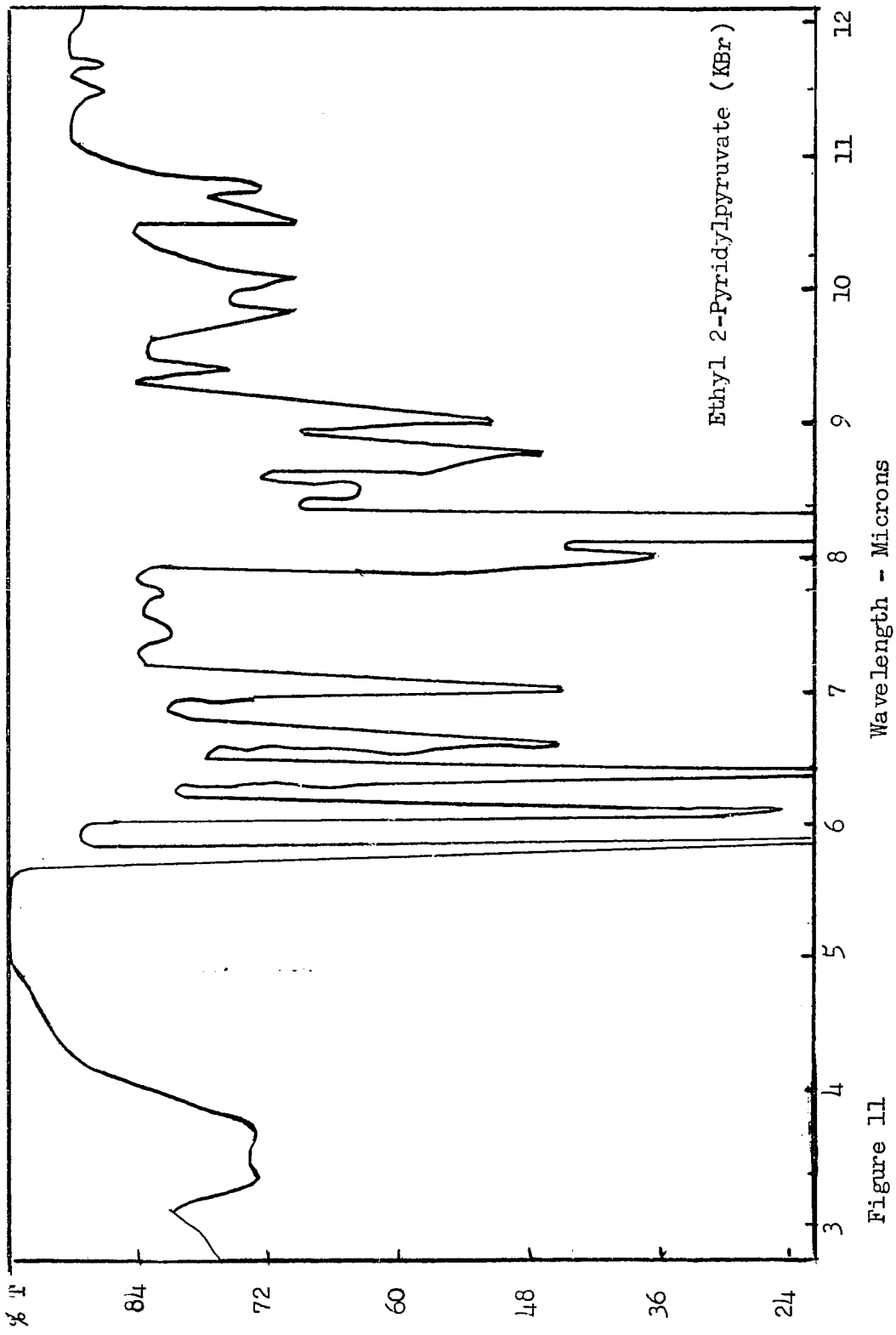


Figure 11

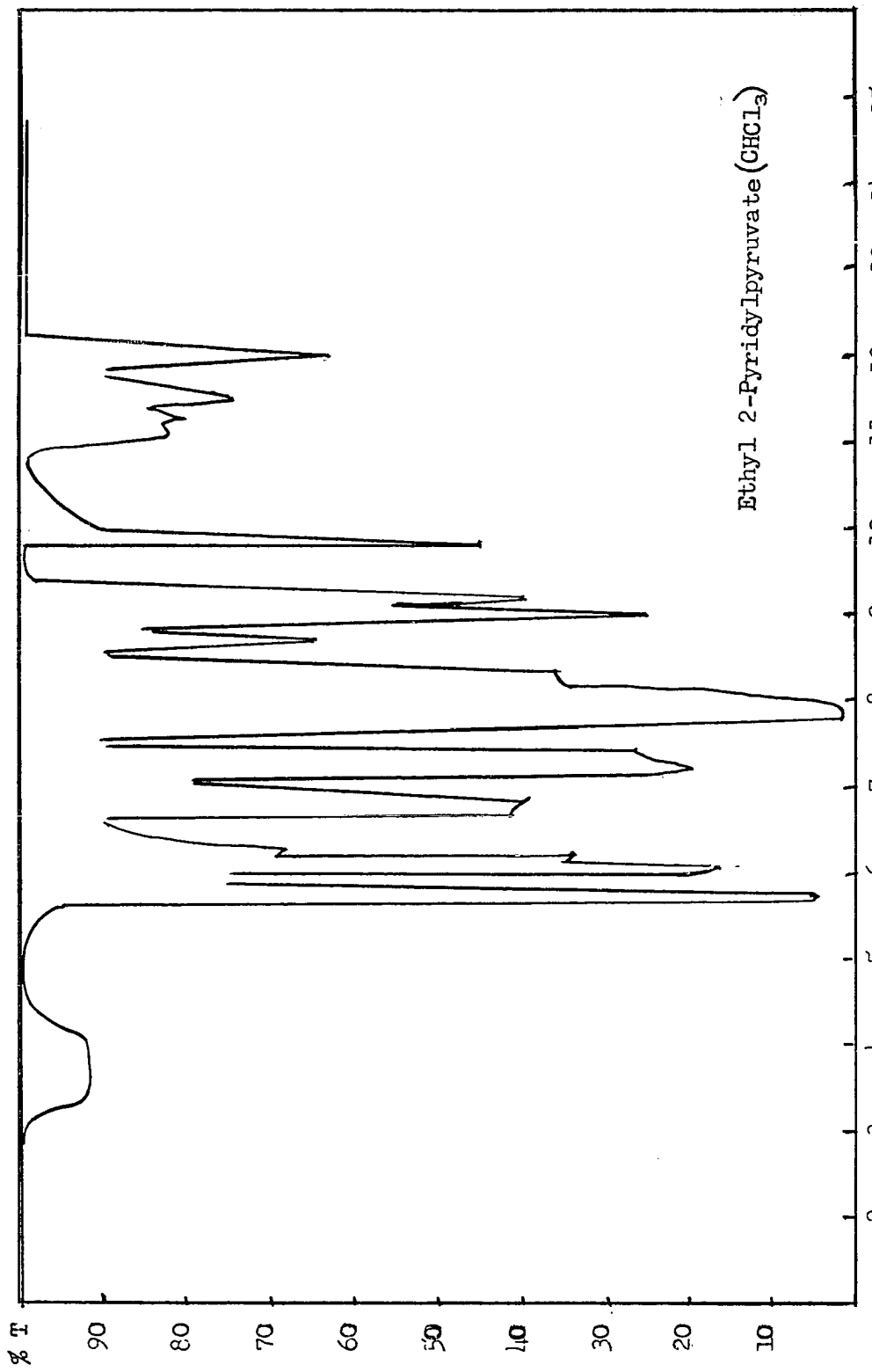


Figure 12

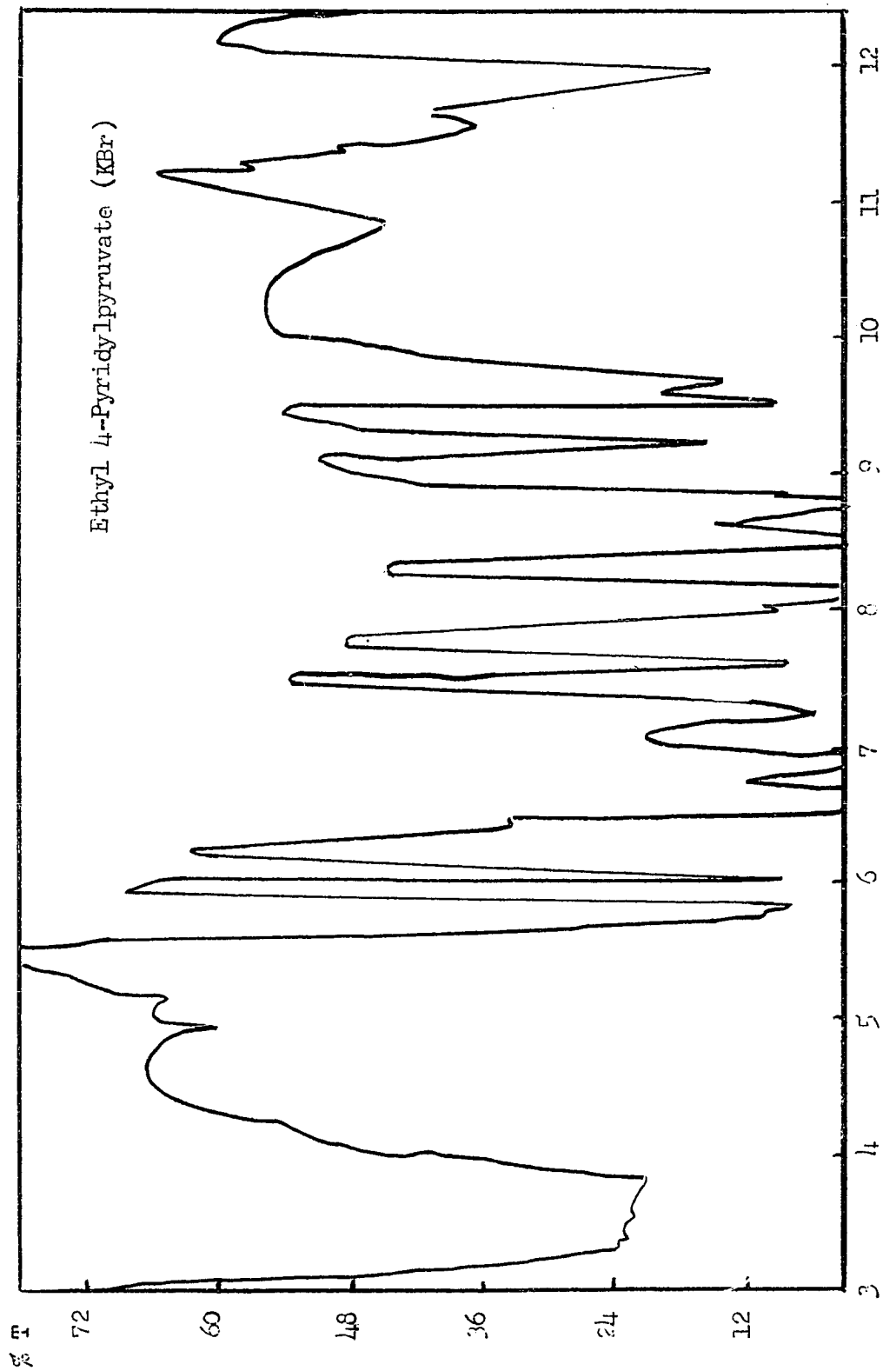


Figure 13

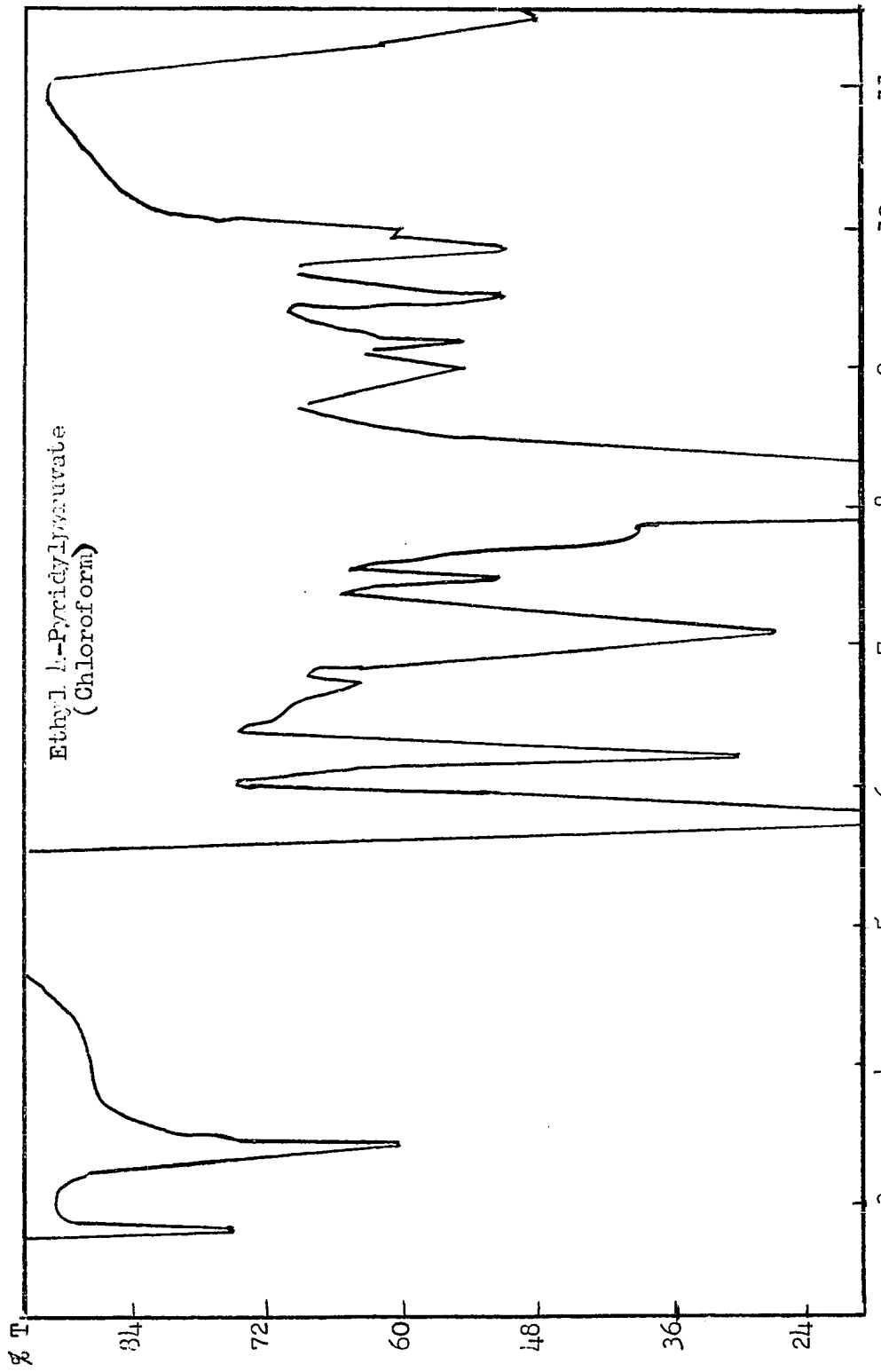


Figure 14

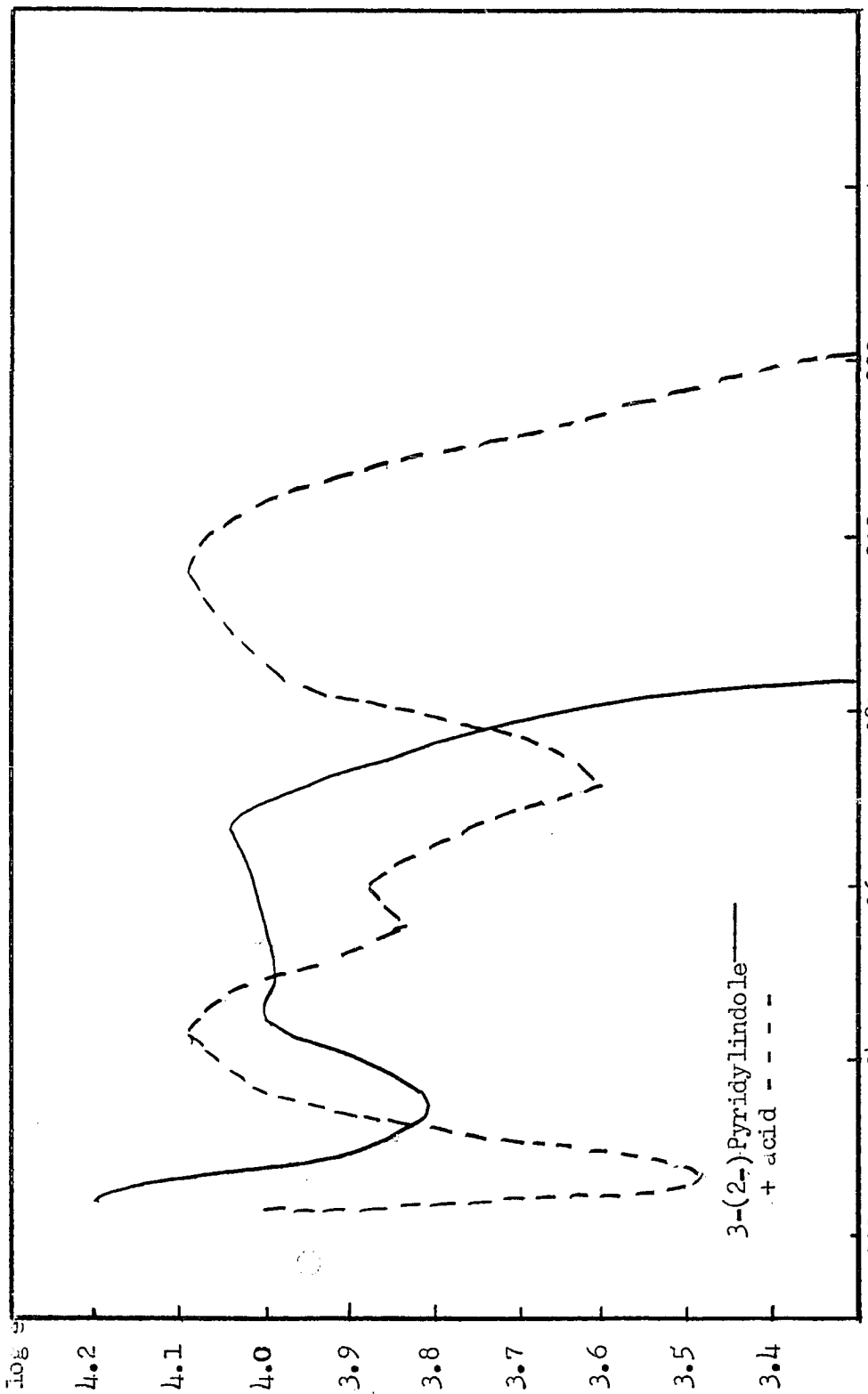


Figure 15

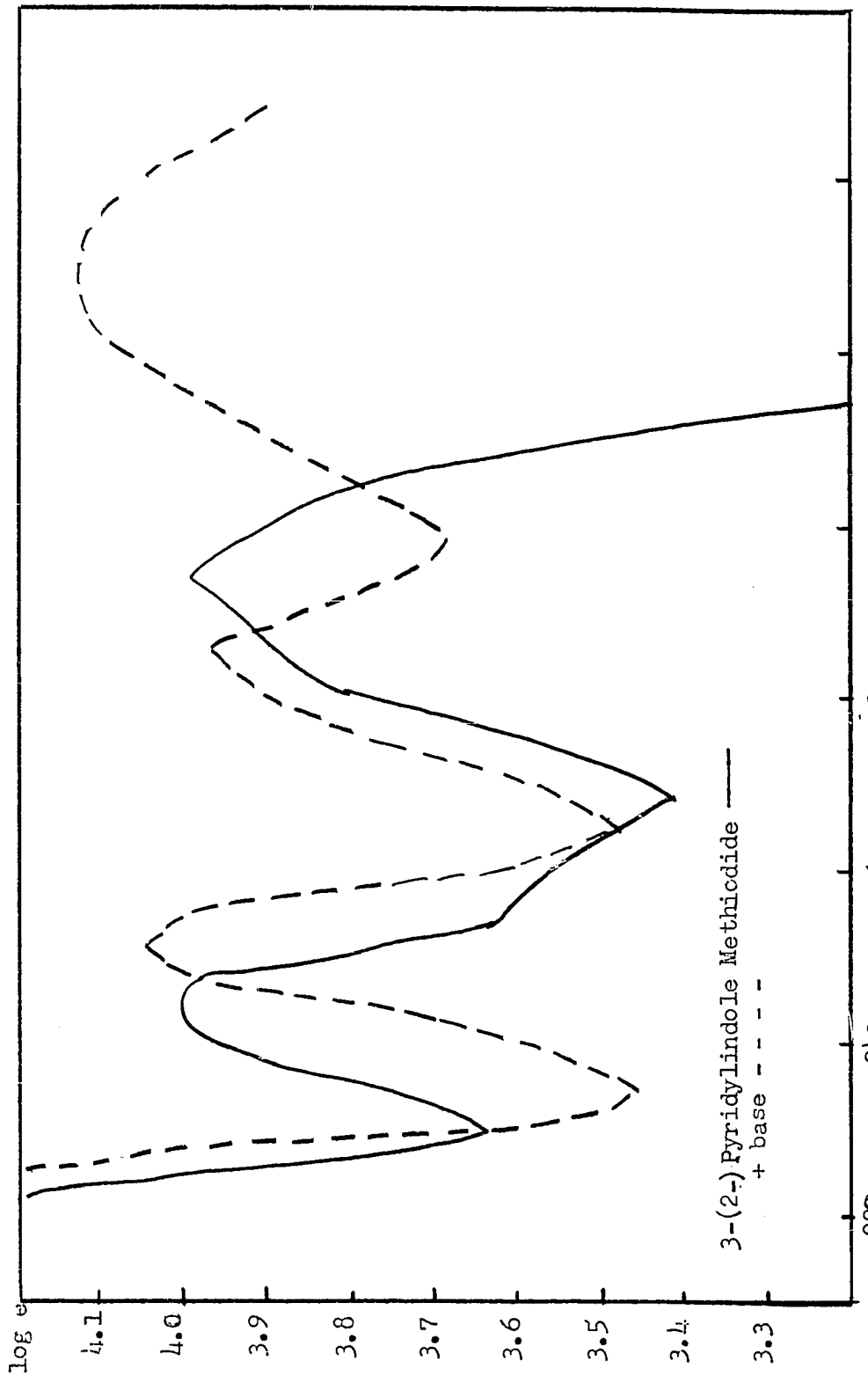


Figure 16

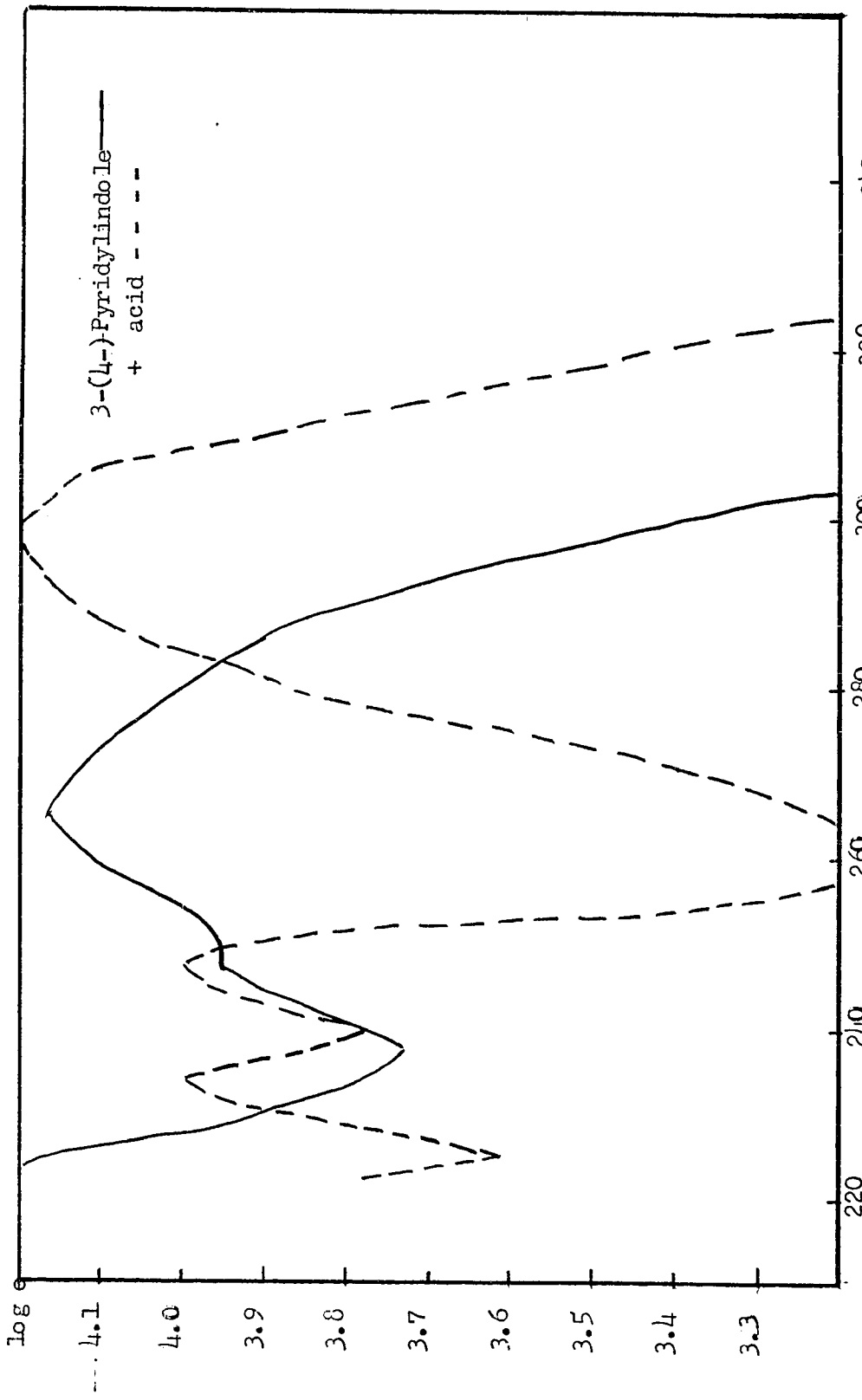


Figure 17

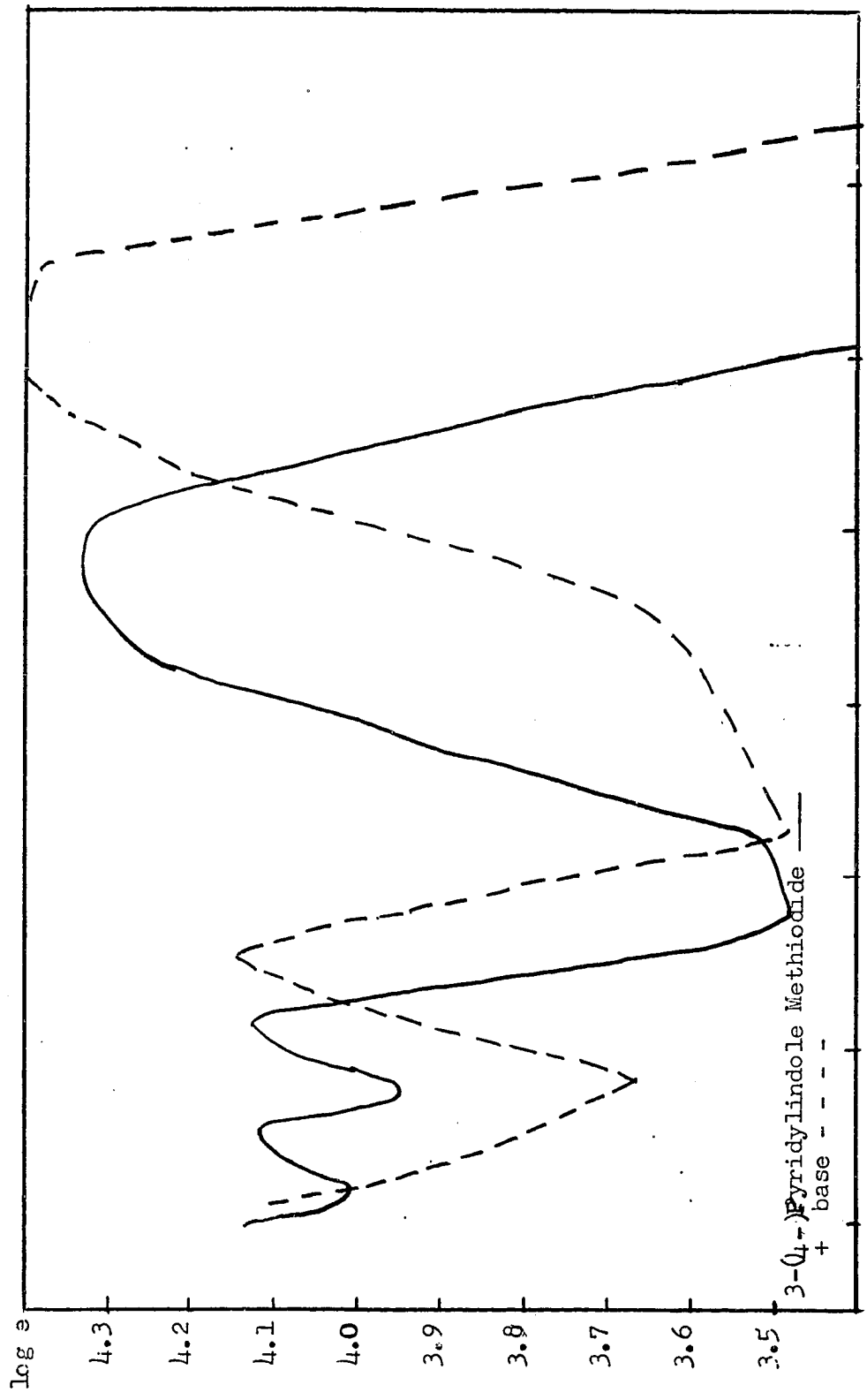


Figure 18

EXPERIMENTAL PROCEDURES

ETHYL 2-PYRIDYLPYRUVATE

1. 2-Picolyllithium

In a 300 ml. round bottom, 3 neck, standard taper flask equipped with a condenser, Hershberg stirrer, and addition funnel, were placed 2.2 g. (0.32 mole) of lithium wire cut into small pieces in 50 ml. of dry ether. Nitrogen passed through a concentrated sulfuric acid trap and then through the reaction flask. Twenty five grams (0.16 mole) of freshly distilled bromobenzene in 50 ml. of dry ether were added dropwise, with stirring. To the 0.16 mole of phenyllithium thus prepared, 7.45 g. (0.08 mole) of α-picoline in 50 ml. of dry ether was added dropwise. After the addition was completed, the reaction mixture was refluxed for 30 minutes. The color of the solution was a deep, blood red. Meanwhile, another three-neck flask of 500 ml. capacity containing 9.76 g. (0.08 mole) of diethyl oxalate in 250 ml. of dry ether was cooled in a dry ice-acetone bath to -70°C. The 2-picolyllithium was added with vigorous stirring to the cold diethyl oxalate solution, with the formation of a copious yellow precipitate. The reaction mixture was added to approximately 6N HCl with stirring. The aqueous solution was extracted repeatedly with ether.

After neutralization with sodium bicarbonate, numerous ether extractions were carried out. The ether extracts were combined and flash distilled until a small volume of ethereal solution remained. The solution was transferred to an evaporating dish, and placed on the steam bath until only a red, tarry residue remained. This was transferred to a filter paper and extracted with 60-70° petroleum ether. Less than .1g. of orange crystals m.p. 82-83° were obtained.

2. Di-2-Picolylcadmium

In a 300 ml. flask, equipped as before, were placed 1.38 g. (0.2 mole) of lithium wire cut into small pieces in 50 ml. of dry ether under a nitrogen atmosphere. Then 15.7 g (0.1 mole) of bromobenzene in 50 ml. of ether were added dropwise with stirring. After the addition was completed, the reaction mixture was heated for 30 minutes. At that point, 9.2 g. (.05 moles) of anhydrous cadmium chloride was added with vigorous stirring. The solution seemed to turn brown, but on settling consisted of a dark red solution, similar to that of picolyllithium, with a dark colored solid suspended in it. The clear solution was displaced from a large amount of residue by nitrogen, and collected in an addition funnel. It was then slowly added to 15 g. (0.1 mole) of diethyl oxalate in 250 ml. of ether at -70°, with vigorous stirring.

There was an immediate precipitation of a thick yellow solid. After five minutes, the whole mixture was added to 6N HCl. A large amount of insoluble tar separated out. The solution was extracted with ether and after neutralization of the aqueous phase with sodium bicarbonate, a copious precipitate was formed. After filtration, air drying, and hot extraction of the solid with 60-70° petroleum ether, 1.8 g. of yellow needles crystallized out of the ligroin solution upon cooling, m.p. 82.5-83.5°. The insoluble residue weighed 4 gms.

Analysis: Calculated - C,62.16%; H,5.74; N,7.25

Found - C,62.35%; H,5.85; N,7.18

Di-2-Picolylcadmium and Excess Diethyl Oxalate

Di-2-picolylcadmium (0.1 mole) was prepared in ether soltuion in the usual fashion. After the addition of 10.5 g. (0.057 mole) of cadmium chloride, the mixture was stirred for forty-five minutes. The 2-picolylcadmium was transferred under nitrogen atmosphere to an addition funnel and then added to 30 g. (0.2 mole) of diethyl oxalate in 250 ml. of dry ether at -70°C. The yellow to green solid which precipitates out was worked up in dilute hydrochloric acid and extracted with ether to remove excess diethyl oxalate. Upon neutralization of the water layer, 9.5 g. of wet crude solid precipitated out. In addition, there was found 7 gms. of red tar which was not soluble in the acid. Extraction of the crude solid with 60-70° petroleum ether yielded 1.8 g. of ethyl 2-pyridylpyruvate and 4.2 g. of residue containing ash.

2-Picolylcadmium (0.1 mole) was prepared as above, and added to 60 g. (0.4 mole) of diethyl oxalate in 250 ml. of ether at -70° C. The usual work up yielded 1 g. of ethyl 2-pyridylpyruvate, 5 g. of acid-soluble tar, and 7.0 g. of insoluble tar. Approximately 40 g. of diethyl oxalate were recovered from the ether layer.

3. Di-2-Picolylmercury

Di-2-Picolyllithium (0.1 mole) was prepared as before. Upon the addition of 13.5 g. (0.05 mole) of dry mercuric chloride, the red color of the solution persisted, perhaps darkening somewhat. There was a positive Gilman test after 20 minutes, and the mixture was added to 0.1 mole of diethyl oxalate in 250 ml. of dry ether at -70°C. After the usual work up in dilute hydrochloric acid and neutralization, 0.5 g. of ethyl 2-pyridylpyruvate and 2 g. of intractable tar was obtained.

4. Di-2-Picolymercury and Ethyl Oxalyl Chloride

As previously, 13.5 g. (0.05 mole) of mercuric chloride were added to 0.1 mole of 2-picolyllithium. After 20 minutes, the mixture was added to 0.1 mole of ethyl oxalyl chloride in 250 ml. of dry ether. After a typical acid work up and neutralization, no solid or tar was found. Extraction of the neutralized aqueous solution gave a red oil which could not be characterized.

Di-2-Picolylcadmium and Ethyl Oxalyl Chloride

In the usual fashion di-2-picolylcadmium (0.5 mole) was prepared, and 45 minutes after the addition of the cadmium chloride, was added to 0.5 mole of ethyl oxalyl chloride in 200 ml. of dry ether at -70°. Solution turned to a light tan color, after acid work up, a tremendous amount of tar was formed and only a trace of ethyl 2-pyridylpyruvate.

2-Picolyllithium and Cadmium Chloride

2-Picolyllithium (0.1 mole) was prepared in the usual way. To that, 9.2 g. (0.1 mole) of cadmium chloride was added with stirring and in five minutes the mixture was added to 15 g. of diethyl oxalate in 200 ml. of dry ether at -70. A great deal of tar was found after neutralization of the acid work up. A trace of ethyl 2-pyridylpyruvate was also found.

2-Picolylcadmium Chloride

By adding 37 g. (0.4 mole) of anhydrous cadmium chloride to 0.2 mole of 2-picolyllithium, 2-picolylcadmium chloride was prepared. After three hours, a negative Gilman test was observed and the reaction mixture was filtered with suction and then added to 30 g. (0.2 mole) of diethyl oxalate in 200 ml. of dry ether at -70°. A thick yellow precipitate was observed and upon work up with dilute hydrochloric acid and sodium bicarbonate, 3.2 g. of ethyl 2-pyridyl-pyruvate was extracted from 10 g. of solid residue with 60-70° petroleium ether.

Normal Addition

Di-2-Picolylcadmium (0.1 mole) in 250 mol. of ether, was prepared as usual and stirred for 13/4 hours, after the addition of the cadmium chloride. At the end of this time, there was still a positive Gilman test. This reaction mixture was then cooled in an ice bath. To it was added 7.5 gram (0.05 mole) of diethyl oxalate in 50 ml. of ether. The solution turned green in color and a granular green precipiate appeared. After acid work up, about 14 gms. of tar were found, but no ethyl 2-pyridylpyruvate.

Di-2-Picolylcadmium and Diethyl Oxalate, Longer Reaction Time.

As described before, 0.1 mole of 2-picolyllithium was prepared in ether solution. Cadmium chloride (0.05 mole) was added and the mixture stirred for 45 minutes. After standing for 5 minutes, the supernatant liquid was added to 0.1 mole diethyl oxalate in 250 ml. of dry ether which had been cooled in a dry ice-acetone bath. A yellow precipitate formed immediately, as usual. The flask was then stoppered and placed in a refrigerator for 24 hours. The reaction mixture was then worked up in a dilute hydrochloric acid in the usual fashion. Approximately 10 gms. of red tar separated from the aqueous acid solution. After the addition of sodium bicarbonate, an orange solid precipitated out. Extraction of the solid with hot 60-70° petroleum ether yielded 0.3 gms. of ethyl 2-pyridylpyruvate and approximately 5 gms. of tarry residue.

Ammonium Chloride Work Up

To diethyl oxalate in ether at -70 was added 0.1 mole of 2-picolylcadmium chloride, and reacted for 5 minutes. After removal of the reaction flask from the cooling bath, an excess of a saturated ammonium chloride solution was added. The aqueous layer was neutralized with sodium bicarbonate, and gave a large amount of precipitate which was largely inorganic matter with no petroleum ether soluble fraction. Extraction of the ether layer with dilute hydrochloric acid and subsequent neutralization yielded 1 gram of ethyl 2- pyridylpyruvate.

ETHYL 4-PYRIDYLPYRUVATE

Di-4-Picolylmercury

In a 300 ml., three necked, round bottom flask with standard taper joints and fitted with a stirrer, addition funnel, and a condenser, were placed 1.38 (0.2 mole) of chopped lithium wire in 50 ml. of dry ether. To this, 14.2 g. (0.1 mole) of methyl iodide in 50 ml. of dry ether was added dropwise, with stirring. After the lithium had completely reacted, 9.3 g. (0.1 mole) of 4-picoline in 50 ml. of ether were added dropwise. The addition completed, the reaction mixture was heated at reflux for thirty minutes. Then 13.5 g. (0.05 mole) of mercuric chloride were added without appreciable change in color of the solution. In subsequent reactions the reaction mixture turned blue black but with no change in yield. This reaction mixture was added to 15 g. (0.1 mole) of diethyl oxalate in 250 ml. of ether at -70° in a dry ice-acetone bath. A thick yellow precipitate formed immediately. The reaction mixture was added to 6N HCl, and the aqueous layer separated and neutralized with sodium bicarbonate. At this point, an orange solid precipitated out. After air drying, the solid was hot extracted with 60-70° petroleum ether. A yellow solid precipitated from the petroleum ether, leaving behind a residue which contained an alkaline ash. The yield was 1.5 g. yellow solid which melted at 138-9°C.

Analysis: Calculated - C,62.16%; H,5.74%; N,7.25%

Found - C,62.40%; H,5.95%; N,7.08%

4-Picolyllithium

4-Picolyllithium (0.1 mole), prepared as on the previous page, was added to 0.1 mole of diethyl oxalate in ether at -70°. There was an immediate color change as usual, with the formation of a yellow precipitate. After a dilute hydrochloric acid work up, no precipitate was formed upon neutralization with sodium bicarbonate. Ether extraction of the aqueous solution yielded only 4-picoline.

Di-4-Picolylcadmium at -70°C.

Di-4-Picolyllithium (0.1 mole) was prepared in the usual way. To this were added 17 g. of anhydrous cadmium chloride, the amount necissary to obtain a negative Gilman test. Upon addition to the ethereal diethyl oxalate solution at -70, a yellow precipitate was formed. After treatment with dilute hydrochloric acid and neutralization with sodium bicarbonate, a very small amount of orange solid, which softened at 139° and melted at 158-159°. It contained inorganic matter and could not be characterized.

4-Picolyllithium and Mercuric Chloride

As before, 0.1 mole of 4-picolyllithium was prepared. To it were added 7 g. (0.025 mole) of mercuric chloride. After 15 minutes, the reaction mixture was added to 15 g. (0.1 mole) of diethyl oxalate in ether at -70°C. After the usual work up and extraction of the crude product, only 0.5 g. of ethyl 4-pyridylpyruvate was obtained.

Di 4-Picolylcadmium at 0°.

In a modification of the other run using 4-picolycadmium, the diethyl oxalate in ether solution was cooled in an ice bath. The di-4-picolylcadmium solution was added by decanting slowly while the di-ethyl oxalate was vigorously stirred.

A yellow precipitate formed which condensed when the reaction flask was removed from the ice bath. The solid was filtered off, and then added to water. A solution with an insoluble sludge was formed. The sludge, on treatment with acetone, gave a yellow precipitate which contained inorganic matter and melted above 200°. The solution was acidified and some orange solid, insoluble in common solvents, and containing inorganic matter was formed.

4-Picolyllithium Using Normal Addition at 0°

From methyllithium and 4-picoline was prepared, in the usual way, 0.1 mole of 4-picolyllithium. This reaction mixture was cooled in an ice bath. Then 7.5 g. (0.5 mole) of diethyl oxalate in 50 ml. of ether was added dropwise, with stirring. Addition took 30 minutes and the color of the reaction mixture turned from dark red to yellow. After 30 minutes it was poured into a mixture of ice and dilute hydrochloric acid, with complete solution. After several ether extractions, the aqueous fraction was neutralized with sodium bicarbonate. There was only a slight turbidity observed in the neutralized solution. It was extracted 6 times with 100 ml. portions of ether. When the ether was removed, a red liquid, weighing 4 gms. and smelling strongly of 4-picoline, was present. The liquid was placed in a vacuum dessicator over sulfuric acid for 24 hours to remove the picoline. The red tar which remained weighed 1.5 g.

4-Picolyllithium Using Normal Additon of Equimolar Quantity of Diethyl Oxalate

The above reaction was repeated with a modification. To 0.1 mole of 4-picolyllithium, cooled in an ice bath, was added 15 g. (0.1 mole) of diethyl oxalate in 50 ml. of ether.

A yellow precipitate formed as usual, and the customary acid work up was used. Upon neutralization, there was no precipitate formed.

DERIVATIVES

Picrate

A solution of 0.1 g. of the pyridine compound in 10 ml. of 95% ethanol was added to 10 ml. of a saturated solution of picric acid in 95% ethanol. The solution was heated to boiling on the steam bath, and slowly cooled. The yellow crystals were filtered and recrystallized from ethanol.

2,4-Dinitrophenylhydrazone

To 0.4 g. of 2,4-dinitrophenylhydrazone in a 25 ml. Erlenmeyer flask was added 2 ml. of concentrated sulfuric acid. Then 3 ml. of water was added dropwise, with swirling until solution was complete. To this warm solution was added 10 ml. of 95% ethanol. A solution of the carbonyl compound of 0.2 g. in 10 ml. of 95% ethanol was prepared. The freshly prepared 2,4-dinitrophenylhydrazone solution was added, and the mixture allowed to stand overnight. The 2,4-dinitrophenylhydrazone was filtered and then recrystallized from 95% ethanol.

Oxime

A mixture of 1 g. of ketone, 1 g. of hydroxylamine hydrochloride, 5 ml. of pyridine, and 5 ml. of absolute ethanol was refluxed for 2 hours on the steam bath.

The residue was titrated thoroughly with 5 ml. of cold water, and the mixture filtered. The oxime was recrystallized from an ethanol water mixture.

Phenylhydrazone

The phenylhydrazone reagent was prepared by dissolving 2 g. of phenylhydrazine hydrochloride in 18 ml. of water, and 3 g. of sodium acetate crystals and one drop of glacial acetic acid were added. Then 1 oz. of the carbonyl compound was dissolved in 10 ml. of ethanol, and water was added until the solution became turbid. The two solutions were combined in a flask, and vigorously shaken until either crystals or a viscous oil separated out.

4-Pyridylpyruvic Acid

For 20 minutes, 1 g. of ethyl 4-pyridylpyruvate in 25 ml. of 20% H_2SO_4 was heated on the steam bath. After cooling in an ice bath, a small amount of dilute ammonium hydroxide was added and a cream colored solid precipitated out. Recrystallization from hot water gave 0.5 g. of light tan powder m.p. 232°C.

Analysis: Calculated - C,58.37%; H,4.27%; N,8.48%

Found - C,58.21%; H,4.41%; N,8.27%

The compound was not fluorescent, but gave a positive test with alcoholic $FeCl_3$.

2-Pyridylpyruvic Acid

For twenty minutes, 1 g. of ethyl 2-pyridylpyruvate in 10 ml. of 10% sulfuric acid was heated on a steam bath. After cooling in an ice bath, the pH was adjusted to 4, and the aqueous solution continuously extracted with ether; about 100 mg. of product was obtained.

Reduction with Sodium Borohydride (36)

In 30 ml. of methanol was reacted 1 g. of ethyl 2-pyridyl-pyruvate with 0.9 g. of sodium borohydride. The reaction was refluxed for 3 hours, after which time the solvent was removed under reduced pressure. The residue was treated with 10 ml. of water, followed by 10 ml. of 40% sodium hydroxide. The resulting solution was extracted with chloroform which yielded 0.3 g. of a yellow oil upon evaporation. There was no color change when an alcoholic solution of this compound was treated with ferric chloride. A picrate derivative had a m.p. 191-2° and Analysis:

Calculated - $C_{14}H_{13}N_4O_8$ N,15.33

Found - N,15.46

Attempted Preparation of Pyrrocoline

A solution of 200 milligrams of the 1-(2-pyridyl) 2,3 propanediol in 5 ml. of 47% of HBr solution was refluxed for 7 hours. The reaction mixture was cooled and sodium carbonate added slowly. When alkaline, it was steam distilled, but none of the product was found. Ether extraction of the steam distillate did not show presence, or organic matter.

Tollens Reagent (37)

The Tollens reagent was prepared by first placing 2 ml. of 5% silver nitrate solution in a clean test tube. To this was added a drop of 10% sodium hydroxide solution and then a very dilute solution of ammonia was added drop by drop with shaking until the precipitate of silver oxide just dissolved.

A very small amount of ethyl 2-pyridylpyruvate was added and slowly dissolved. After about 30 minutes, a silver mirror was deposited on the walls of the test tube.

Reaction of Diazomethane with Ethyl 2-Pyridylpyruvate (38)

To an ethereal solution of diazomethane prepared from 2.06 g. (0.02 mole) of nitrosomethylurea was added 0.48 g. (.0025 mole) of ethyl 2-pyridylpyruvate. No evolution of gas was noticeable. The reaction mixture was allowed to stand for 2 hours; at the end of this time, the ether was evaporated off and the solid recovered. It was recrystallized from petroleum ether. The melting point was identical with that of the starting material.

Reaction of Diazomethane with Ethyl 4-Pyridylpyruvate

When the above procedure was repeated with ethyl 4-pyridylpyruvate, the results were comparable. The ethyl 4-pyridylpyruvate was not soluble in ether and did not appear to change. The melting point of the solid ester verified it to be the same as the starting material.

Reaction of Methyl Iodide

In a sealed tube, 0.5 g. of ethyl 4-pyridylpyruvate was heated with an excess of methyl iodide at 75° for 2 hours. The reaction mixture was washed with ether and then dissolved in hot ethanol. Recrystallization from ethanol-ethyl acetate gave 0.2 g. of yellow solid m.p. 199-200°.

The analysis was unsatisfactory.

Analysis: Calculated for $C_{11}H_{14}NO_3I$- C,39.42; H,4.21

Found- C,42.86; H,4.65

Fischer Indole Synthesis

The phenylhydrazone of ethyl 2-pyridylpyruvate was prepared by the procedure mentioned earlier. The derivative separated out as a yellow oil and was separated from the aqueous phase. The oil was added to a large excess of polyphosphoric acid heated on the steam bath for 30 minutes, during which time considerable darkening of the reaction mixture took place. Water was added and the mixture cooled in an ice bath. The solution was neutralized by the addition of sodium carbonate, yielding a white precipitate. Upon recrystalization from alcohol-water, white crystals were obtained. This compound was heated in 10% aqueous sodium hydroxide on a steam bath for one hour. After neutralization with dilute hydrochloric acid, the free acid was obtained and recrystallized from hot water as a yellow fluorescent crystalline solid, m.p. 263-264°.

Analysis: Calculated for $C_{14}H_{10}N_2O_2$ - C,70.58; H,4.23

Found C,70.86; H,4.59

3-(2-)Pyridylindole

Decarboxylation of 0.2 g. of the acid was done by mixing it with an equal amount of copper bronze and heating it in a vacuum sublimation apparatus, the product collecting on the cold finger. The product was recrystallized from ethanol-water, yielding 0.1 g. of white powder m.p. 150-151°.

Analysis: Calculated for $C_{13}H_{10}N_2$- C,80.38; H,5.19; N,14.43

Found- C,80.60; H,5.45; N,14.18

3-(2-) Pyridylindole Methiodide

The free base was heated with an excess of methyl iodide to 100 C. in a sealed tube for 30 minutes. The crystalline reaction product was washed with ether and dissolved in ethanol and precipitated with ethyl acetate to give light green crystals m.p. 215.6°.

Ethyl 4-pyridylpyruvate phenylhydrazone was prepared by the same general method previously outlined. It precipitated as a crystalline solid m.p. 118-9°.

3-(4-) Pyridylindole Methiodide

One gram of the hydrazone was heated in an excess of polyphosphoric acid for 2 hours at 80-90°. Upon cooling, a yellow-green precipitate m.p. 185-200° was formed. It was collected on a filter paper and then treated with aqueous sodium bicarbonate solution. After considerable frothing, a white precipitate separated out. The white solid was filtered out and then recrystallized from ethanol-water to give 0.5 g. of white crystals, m.p. 210-211° C.

Analysis: Calculated for $C_{16}H_{14}N_2O_2$ - C,72.16; H,5.29;N,10.51

Found - C,71.57; H,5.19;N,10.77

The ester was heated on the steam bath in 10% aqueous sodium hydroxide for one hour. Upon cooling, a precipitate of pearly white crystals formed. When dilute hydrochloric acid was added to pH 4 a yellow fluorescent solid precipitated. Recrystallized from water, m.p. 292-3° d.

Copper bronze powder and 0.2 g. of the acid were mixed and heated in a vacuum sublimation apparatus, the product collecting on the cold finger. The free base was recrystallized from alcohol-water yielding 0.1 g. of white crystals 216.5-217.5° m.p.

Analysis: Calculated for $C_{13}H_{10}N_2$ - C,80.38; H,5.19

Found - C,80.10; H,5.41

The free base was reacted with methyl iodide at 70° for two hours in a sealed tube. The crystalline product was recrystallized from ethanol and ethyl acetate as a golden solid m.p. 250-252°.

Preparation of Potassium Ethyl Oxalate (39)

Until a homogeneous solution was obtained, 100 ml. of water, 100 g. of potassium acetate, and 143 g. of diethy oxalate were agitated on the steam bath. The solution was then heated for 4 hours, followed by concentration in vacuum to 100 ml. Two times the volume of ethanol was added and a sixfold volume of ether precipitated the salts.

Preparation of Ethyl Oxalyl Chloride (40)

Dry ether was used to moisten 50 g. (0.32 mole) of the dry potassium salt and 80 g. of thionyl chloride were added dropwise with ice cooling. The reaction mixture was allowed to come to room temperature and then heated under reflux on the water bath for fifteen hours. The residue was filtered and washed with dry ether. The filtrate plus the washings were distilled through a short column. The ethyl oxalyl chloride was collected from 125-138° with the bulk distilling from 130-132° in 60% yield.

DETERMINATION OF MELTING POINTS

All melting points reported in this work were determined with Anschutz thermometers and are uncorrected.

"Wet" melting points were determined in the following manner: A melting point capillary was filled with the sample to a height of about 2 millimeters. The capillary was then filled with distilled water. Any air bubbles adhering to the sample were removed by gently tapping the capillary. Most of the water was expelled by heating, leaving a column about 1 millimeter in height. The capillary was then resealed as close to the sample as possible. The melting point was determined in the usual way, the entire sealed portion of the capillary being immersed in the bath. The melting point was taken as the temperature at which the last crystal of the sample disappeared.

DETERMINATION OF SPECTRA

Infrared spectra were determined with a Perkin-Elmer Model 21 Infrared Spectrophotometer. Samples weighing approximately 2 milligrams were thoroughly mixed with 500 milligrams of spectroscopic grade potassium bromide. Discs were pressed from 150 milligram portions of the original mixtures. The spectra of the sample discs were then determined using a disc pressed from 300 milligrams of potassium bromide as the reference.

The electronic absorption spectra were determined with a Warren Spectracord . Unless otherwise specified in the text, 95% ethanol was used as the solvent; concentrations of 10^{-3} and 10^{-4} molar were generally used.

Preparation of N-Methyl Ethyl 2-Pyridylpyruvate

A 250 ml. three-neck round-bottom flask was equipped with stirrer, reflux condenser, and addition funnel. Then 20 ml. of absolute alcohol and 1.15 g. of sodium metal (0.05 mole) were added. After the reaction was nearly completed, 100 ml. of dry ether were added. After the sodium had completely reacted, 5.9 g. of 2-picoline methiodide (0.025 mole) were added. The reaction mixture was refluxed for twenty minutes. After cooling with an ice bath, 4 g. of diethyl oxalate (0.025 mole) in 25 milliliters of ether were added slowly with stirring. The reaction mixture was then placed in a refrigerator for three days. The mixture was then filtered and the solid matter dissolved in water. This aqueous solution was repeatedly extracted with chloroform. The chloroform fractions were collected and dried with anhydrous magnesium sulfate. The chloroform was evaporated, leaving two grams of yellow, non-fluorescent crystals. The crystals were recrystallized from an ethyl acetate-ligroin mixture, m.p. 113-114°. This compound formed a 2,4-dinitrophenylhydrazone hydrogen sulfate derivative, m.p. 187-8°.

Analysis for $C_{17}H_{19}N_5O_{10}S$ - Calc. - C,42.06%; H,3.95; N,14.43

Found - C,42.60%; H,4.62; N,14.73

The compound also formed a picrate as yellow crystals m.p. 119-120°.

Analysis for $C_{17}H_{16}N_4O_{10}$: Calculated - C,46.79; H, 3.69
Found - C,46.70; H,4.20

Preparation of N-Methyl Ethyl 4-Pyridylpyruvate

In an identical procedure, 4-picoline methiodide was used. However, only one gram of solid was obtained upon evaporation of the chloroform. Recrystallization from ethyl acetate-ligroin yielded an orange-yellow powder m.p. 113-114° C. The 2,4-dinitrophenylhydrazone hydrogen sulfate melted at 201-2° with decomposition.

Analysis for $C_{17}H_{19}N_5O_{10}S$: Calculated - C,42.06%; H,3.95; N,14.43
Found - C,42.22%; H,4.63; N,13.77

This compound also formed a picrate derivative m.p. 160-161°.

Analysis for $C_{17}H_{16}N_4O_{10}$: Calculated - C,46.79; H,3.69
Found - C,46.65; H,4.19

Preparation of O-Aminobenzaldehyde(41)

A one liter, three necked flask was mounted on a steam bath and fitted with a mechanical stirrer, a reflux condenser, and the third neck was closed with a cork. Then, 175 ml. of water, 105 g. (0.38 mole) of ferrous sulfate heptahydrate, 0.5 ml. of concentrated hydrochloric acid and 6 g. (0.04 mole) of O-nitrobenzaldehyde were introduced in the order given. The stirrer was started and the flask heated by means of the steam bath. When the temperature of the mixture reached 90°, 25 ml. of concentrated ammonium hydroxide was added, and at 2 minute intervals three 10 ml. portions were added. The total reaction was 8-10 minutes.

Immediately after the addition of the last portion of ammonium hydroxide, the reflux condenser and the stirrer were removed and the flask connected to a steam distillation assembly. The mixture was steam distilled as rapidly as possible and two 250 ml. fractions of distillate were collected during a period of 10-13 minutes. The first fraction was saturated with sodium chloride and the solution stirred at 5° until precipitation appeared to be complete. The solid was collected on a Buchner funnel and air-dried. The product weighed 2.7-3.0 g. (57-65%) and melted at 38-39°. The second fraction was saturated with sodium chloride and combined with filtrate remaining from the first fraction. Ether extraction yielded about 0.5 g. of additional product.

Synthesis of 3-(4-Pyridyl)-2-Carbethoxy-Quinoline

To 0.95 g. (0.05 mole) of ethyl 4-pyridylpyruvate was added 0.60 g. (0.05 mole) of o-aminobenzaldehyde and 1 drop of piperidine. The mixture was heated to 145° C. for thirty minutes. Ethanol was added to the red colored melt and it converted it to a red powder. This product was treated with charcoal and recrystallized from alcohol-water to yield white crystals m.p. 127-128°.

Analysis: for $C_{17}H_{14}N_2O_2$

Calculated - C,73.36%; H,5.07; N,10.07

Found - C,73.72%; H,5.65; N,10.75

The ester was hydrolyzed with methanolic sodium hydroxide to the free acid, also as white crystals, m.p. 188-9°.

The acid was decarboxylated with copper bronze in a vacuum sublimation apparatus yielding 3-(4-pyridyl)-quinoline as white crystals, m.p. 127-128°.

Attempted Synthesis of 3-(2-Pyridyl)2-Carbethoxy Quinoline

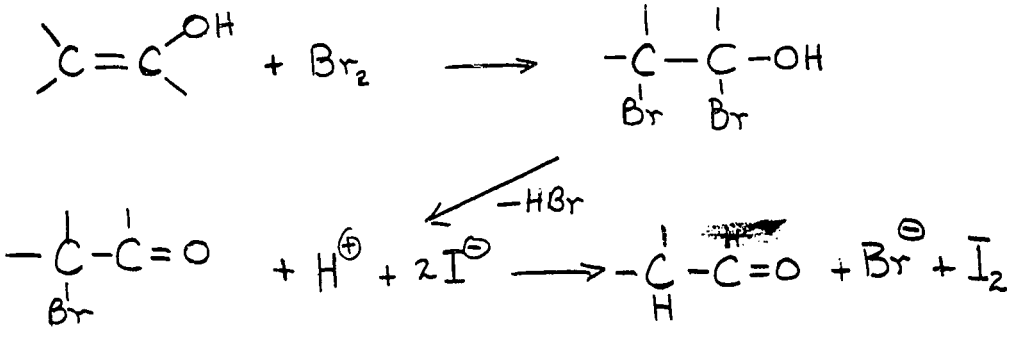
The same reaction was attempted using ethyl 2-pyridylpyruvate. However, on working up the reaction mixture, an interactable brown solid and much of the ethyl 2-pyridylpyruvate were the only products obtained.

Determination of Enol Content

The procedure used in the determination of enols was essentially the same as that described by Meyer and Kappelmeir (29) with the modification of Cooper and Barnes (42). The essential steps are as follows:

1. rapid addition of an excess of alcoholic bromine solution to the enol
2. destruction of the excess bromine with diisobutylene
3. addition of an excess of aqueous potassium iodide solution
4. titration of the liberated iodine with standard sodium thiosulfate

The reactions involved have been formulated by Meyer as follows:



Reagents for Enol Determinations

Methanolic bromine solution was prepared from reagent grade chemicals just prior to its use. The concentration was approximately 0.3 molar.

Practical grade diisobutylene (Eastman) was used.

Aqueous potassium iodide was prepared from 25 grams of reagent grade potassium iodide and 475 ml. of distilled water.

Sodium thiosulfate (.05N) was prepared according to the directions of Kolthoff and Sandell. (43) The solution was standardized against 0.0500 N solution of potassium dichromate.

Starch indicator solution was prepared in a 400 ml. batch according to the directions of Kolthoff and Sandell.

Standard Titration Procedure

Step I An excess of methanolic bromine solution was added to the sample. The sample was assumed to be 100% enolic and a twofold excess was added on this basis. The bromine was added rapidly from a burette with a rapid delivery rate.

Step II Diisobutylene in sufficient amount to destroy all of the bromine added in step I was introduced. The quantity required was estimated by a rough titration of the diisobutylene with bromine solution.

Step III Aqueous potassium iodide solution was added to the sample. One milliliter of the iodide reagent was added for each 5 milliliters of sample solution.

Step IV The sample was allowed to stand at room temperature for thirty minutes.

Step V The liberated iodine was titrated with standard sodium thiosulfate solution, using starch indicator solution to detect the end-point. Just before the end-point was reached, the sample solution was diluted with approximately 25 milliliters of water and the starch indicator solution was introduced.

Step VI A blank titration was run using the same quantities of all the reagents that were used in the titration of the sample. The percent enol was calculated from the following expression:

$$\frac{(\text{ml. of } Na_2S_2O_4 \text{ less blank}) \quad (\text{Normality of } Na_2S_2O_4) \quad (\text{Equivalent weight of enol})}{\text{Sample weight in milligrams}} \times 100$$

The equivalent weight of the enol was half of its molecular weight.

In the titration procedure described above, the following precautions were scrupulously observed. The sample solutions were chilled in a dry ice-acetone bath prior to the addition of the bromine solution. The first two steps were accomplished within twenty seconds and the potassium iodide solution was added immediately after the excess bromine was destroyed.

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VITA

Michael M. Besso, son of Morris and Mollie (Tiller) Besso, was born on March 30, 1930 in Brooklyn, New York. He attended P.S. 104 and graduated from Fort Hamilton High School in 1946.

He then entered Lowell Technological Institute and received the Bachelor of Science Degree in 1950. After graduation, he worked as a textile chemist at the Pinatel Piece Dye Works, Joliette, P.Q. Canada.

In March 1951 he enlisted in the U.S. Army and attended Officer Candidate School at Fort Sill, Oklahoma. As a Second Lieutenant in the artillery, he was assigned to the 3rd Infantry Division in Korea. During this time, he served with the Belgian United Nations Command and was awarded the Croix de Guerre avec Lion en Bronze and the Bronze Star (Merit). Upon discharge from the Army with the rank of First Lieutenant, he was employed by the National Lead Company in November 1953.

After working in both research and technical service, he began graduate study at Lehigh University in 1955 with a followsh.. ..om the National Lead Company. In August of that year he married the former Eva Cikvesvili of New York. He obtained his Master of Science Degree in June 1958 and was blessed with the birth of a son, Marc. The research work completed in the dissertation for the Ph.D Degree was under the continued sponsorship of the National Lead Company.

Recrystallized from benzene, the crystals melted as 105-6° with decomposition. The analysis, however, was not satisfactory.

Analysis: Calculated - C,58.37; H,4.27; N,8.48

Found - C,57.17; H,4.94; N,8.58

Neutralization equivalent

Calculated 165.2

Found 161.0

Reaction with Benzaldehyde

In a small beaker, 0.48 g. (.0025 mole) of ethyl 2-pyridylpyruvate was reacted with .53 g. (.005 mole) of benzaldehyde and 3 drops of pyridine. The reactants were heated on a steam bath, and after 15 minutes, the reaction mixture modified. It was twice washed with ethanol, and then filtered. Recrystallization from ethyl acetate gave 0.3 g. of yellow needles, m.p. 225-6°. The compound was fluorescent under ultraviolet radiation and gave a positive test for an enol with ferric chloride.

Analysis: Calculated for $C_{15}H_{11}NO_3$ - C,71.13; H,4.37; N,5.53

Found - C,71.30; H,4.62; N,5.11

In the same reaction as above, ethyl 4-pyridylpyruvate yielded 0.2 g. of yellow crystals which were recrystallized from ethanol, and melted at 266-7°.

Analysis: Found C,71.36; H,4.55; N,5.51