San Fernando Valley State College

THE REACTIONS OF PYRIDONES WITH UNSATURATED ESTERS

A thesis submitted in partial satisfaction of the requirements for the degree of Master of Science in Chemistry

by

Darryl Edward Thomas

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The thesis of Darryl Edward Thomas is approved:

Committee Chairman

San Fernando Valley State College

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To my wife, Beverly
ACKNOWLEDGMENT

I would like to express my gratitude to Dr. R. A. Silva for allowing me to continue the work he started in 1965 on pyridone chemistry, and for the aid, guidance, and encouragement he gave me to make this thesis possible.
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ABSTRACT

The Reactions of Pyridones with Unsaturated Esters

by

Darryl Edward Thomas

June, 1970

Ethylenic and acetylenic esters have been found to undergo nucleophilic addition with 2-(1H)-pyridone and 4-(1H)-pyridone. With acetylenic monoesters, pyridones yielded predominantly the trans compound. With acetylenic diesters, pyridones yielded predominantly fumarate derivatives. Under the experimental conditions, maleate derivatives were shown to isomerize to fumarate derivatives.

Assumptions in the literature regarding the stereochemistry of products obtained from the nucleophilic addition of pyridone to unsaturated carbon-carbon bonds have been clarified as have some conflicting opinions regarding the stereochemical outcome of additions to acetylenic esters.

Several pmr spectra are reproduced as evidence for the structures postulated and to illustrate the spectral relationships between various compounds.
CHAPTER I
INTRODUCTION

Recently, many studies have been reported on the mechanism and stereochemistry of the addition of nucleophiles to activated carbon-carbon triple bonds.\(^1\) The present work is concerned with the nucleophilic addition of pyridones to unsaturated esters, and so a brief summary of previous work in related areas is included here. A review by Winterfeldt\(^1\) described in some detail the work done prior to 1967. In the reactions of thiols with acetylenes, Truce and co-workers\(^2\) postulated a rule of trans addition. By examining proton magnetic resonance spectra at \(-25^\circ\text{C}\), they found only trans addition products for these reactions. On the other hand, alcohols\(^1\) have been observed to yield trans addition products when the reactions have been catalyzed by alkoxides or tertiary amines, but to yield cis addition products under thermal conditions. In the case of amine additions to activated triple bonds, a variety of products resulted, depending on reaction conditions. Winterfeldt and Pruess\(^3\) found that for secondary amines with acetylenic monoesters, the stereochemical outcome was cis addition (trans configuration). Whereas with acetylenic diesters, amines yielded predominantly (70-90%) cis addition products. Secondary amines yielded more cis product than primary amines, but rapid acid catalyzed isomerization was
shown to occur. The kinetic work performed by Huisgen and co-workers confirmed that the direct, uncatalyzed addition of amines and alcohols proceeded by an intramolecular cyclic proton shift from a primary complex such as I to yield cis addition products. This conclusion was based on the study of the addition of ethyleneimine to dimethyl acetylenedicarboxylate (DMAD). Dolfini's work with amines and aziridines indicated the importance of solvent on the ratio of cis to trans products. However, in a paper on the addition of dialkylamines to ethyl propiolate, Truce reported that the configuration of the product was exclusively trans (cis addition), regardless of the solvent employed. This apparent discrepancy was clarified in a summary by Truce. "Amine additions to ethyl propiolate, owing to transition state linearity of the unsaturated
carbon π system, are nonstereospecific processes (with secondary amine adducts, where immonium type resonance is likely, any cis isomer formed rapidly isomerizes to the more stable trans configuration, in absence of this type of resonance, solvent dependent mixtures of cis and trans isomers are formed; with primary amine adducts, the cis configuration is preferred owing to hydrogen bonding)." McMullen and Sterling\textsuperscript{8} arrived at the same conclusion by studying the configuration of amine-acetylene adducts. They also stated that the cis/trans ratios are not dependent upon either basicity of the amine or polarity of the N-alkyl group. Truce\textsuperscript{7} also stated that the addition of amines to acetylenic esters at -25°C initially gave cis compounds, which isomerized at room temperature to the more stable trans compounds.

Using acetylenedicarboxylic esters to obtain heterocyclic compounds, Henrickson and co-workers\textsuperscript{9} added alpha amino ketones or beta amino-alpha,beta-unsaturated ketones to these esters. In boiling methanol, the first adduct obtained possessed trans stereochemistry. This led these workers to state that "Whenever mobile protons are available, the first product of addition to acetylenedicarboxylic esters is the trans adduct." Other workers\textsuperscript{10} have used Henrickson's method with N-substituted alpha amino ketones to obtain pyrroles, and have assumed that the initial adduct arose through trans addition. They stated "In a proton donating solvent like methanol, the product formed is
predominantly the fumarate derivative, whereas in other aprotic solvents, the pyrrole derivative is obtained."

However, Dolfini\textsuperscript{6} reported that his results, with aziridine and acetylenic esters, seemed contrary to Hendrickson's statement about trans addition. It is apparent that no generalized statement can be made regarding the stereochemistry of nucleophilic addition to acetylenic esters.

Chemically different species (such as amines, alcohols, alpha amino ketones, and thiols) probably involve different mechanisms in reaction with acetylenes or in the case of multi-step mechanisms, different rate constants in the product-determining step. Heindel and co-workers\textsuperscript{11,12} reported that when both an amine and an amide function were present on a single molecule, the product arose exclusively from amine addition.

Earlier studies\textsuperscript{13,14} had established that 2-(1H)-pyridone reacts with DMAD. The present work is concerned with the detailed investigation of the mechanism and scope of this and related reactions.

The chemistry of pyridones had been intensely investigated. One reason for this interest lay in the fact that a tautomeric equilibrium exists and establishment of the position of equilibrium was sought.
Evidence from infrared\textsuperscript{15-17} and ultraviolet spectroscopy,\textsuperscript{16,18} Raman spectroscopy,\textsuperscript{15,16} ionization constants,\textsuperscript{15,19,20} dipole moments,\textsuperscript{20,21} and proton magnetic resonance spectroscopy,\textsuperscript{22-24} established that the equilibrium favored the amide form for these compounds. Thus, 2-pyridone has been described as a type of cyclic amide\textsuperscript{19,22} and 4-pyridone as a vinylogous amide.\textsuperscript{19}

With the finding that 2-pyridones have only about 35\% of the aromaticity of benzene,\textsuperscript{25} various attempts were made to investigate the use of them as dienes. With the exceptions of thermal reactions between pyridones and benzyne\textsuperscript{13,27,28} or maleic anhydride\textsuperscript{34} and the photochemical addition of diphenylacetylene and a 2-pyridone, no other successful additions of the Diels-Alder type to pyridones have been reported to date. The normal mode of reaction of pyridones with acetylenes was found to involve nucleophilic addition.\textsuperscript{30} Previous workers\textsuperscript{13,26} assumed that the nucleophilic addition of 2-pyridone yielded only trans addition products. The present work will present our results on the addition of pyridones to unsaturated esters and our conclusions regarding this and related reactions. Some of the discrepancies in the literature will be discussed in the light of this work.
CHAPTER II
RESULTS

2-(1H)-pyridone

The reaction of 2-pyridone with methyl acrylate produced a product, an oil, in 85% yield. The reagents were dissolved either in dioxane and refluxed for several days, or in dimethylsulfoxide (DMSO) and heated for several hours. In every addition studied in this work, reaction occurred more readily in DMSO than in any other solvent. The oily product was passed through alumina, vacuum distilled, and determined to be methyl 3-(2-pyridon-1-yl) propionate (1).

The structure of the adduct was deduced from the lack of N-H absorbance in ir and pmr spectra. Also, the pmr spectrum clearly revealed two triplets (methylene) and the uv spectrum indicate an unchanged pyridone chromophore.

The reaction of 2-pyridone with dialkyl maleates and fumarates was extremely slow, even at elevated temperatures. Under these conditions, maleate esters isomerize slowly to the more stable fumarate configuration (identified by pmr of the vinylic protons). A small amount of an oily product could be found from both the fumarate and the maleate ester reactions (but only after or during the formation of fumarate esters in the reaction mixture). The oil residue, representing about 8% yield was chromat-
graphed, vacuum distilled and analyzed. The pmr spectrum was compatible with a structure such as dialkyl (ethyl or methyl) 2-(2-pyridon-1-yl) succinate (2).

The acetylenic esters, although simpler in structure, yielded a more complex mixture of products. After the first addition (which can provide cis and trans isomers), an ethylenic ester resulted which could react with still another mole of pyridone.

The reaction of methyl propiolate with 2-pyridone afforded three products. The reaction conditions employed were four days in refluxing dioxane which ensured complete reaction. The major product (66% yield), from apparent cis addition, was trans methyl 3-(2-pyridon-1-yl)acrylate (3). The minor compound, cis methyl 3-(2-pyridon-1-yl)acrylate (4), was isolated by fractional crystallization. Upon further crystallization, a 1:2 adduct could be isolated, methyl 3,3-di(2-pyridon-1-yl)propionate (5).

Cis and trans isomers were distinguished by comparison of the coupling constants and by the relative line positions of various protons in their pmr spectra. For the acrylate compounds, the magnitude of the coupling constants clearly indicated whether the vinyl hydrogens were cis [J around 9 hertz (Hz)] or trans (J around 14 Hz). The cis/trans ratio was obtained by pmr analysis of mixtures after removal of unreacted reagents and solvents by chromatography and evaporation. The reaction of methyl propiolate
with 2-pyridone in dioxane analyzed by the method described above afforded a 28% trans/72% cis (mode of addition) mixture of isomers representing about 80% yield. Table I lists this reaction with various solvents used and the percentage of trans addition isomers in these mixtures.

The reaction of 2-pyridone with DMAD was also investigated. In refluxing dioxane after one day, 65% of the trans addition product could be isolated, dimethyl 2-(2-pyridon-1-yl)fumarate (6), and a few percent of the cis addition product, dimethyl 2-(2-pyridon-1-yl)maleate (7). Both adducts yielded elemental analyses which agree with the formula C_{11}H_{11}NO_{5}. The pmr signal of the vinyl protons in the fumarate ester was further downfield (0.68 ppm) than for the corresponding maleate ester. The uv maximum of the cis isomer (7) was at longer wavelength than that of 2-pyridone, whereas that of the trans isomer (6) was the same. This is attributed to additional conjugation of the pyridone moiety in the cis isomer. In the trans isomer the pyridone moiety is forced out of plane by the neighboring ester group and shows an unchanged pyridone chromophore. The double addition product, dimethyl 2,3-di-(2-pyridon-1-yl)succinate (8) due to its low solubility could usually be isolated either prior to or after purification of the crude reaction mixture. The mass spectrum of this compound showed a parent peak at m/e 332. Table I lists products from this reaction in various
solvents.

Neither excess DMAD, high dilution, nor order of addition of reagents caused any change in the ratio of products. An excess of 2-pyridone appeared to reduce the percent of trans addition product slightly. Since the ratio of isomers did not vary appreciably with solvent, equilibration experiments were performed. When refluxed in dioxane, with or without added pyridone, pure cis isomer (7) was found to isomerize to a mixture containing 85 to 88% of the trans isomer (6). Under similar conditions, the trans isomer (6) was recovered unchanged.

The trans isomer (fumarate configuration) was found to react further with 2-pyridone. In refluxing dioxane for five days, a 1:2 adduct (8) was isolated in about 12% yield.

4-(1H)-pyridone

The reactions of 4-pyridone resembled closely those of 2-pyridone except that 4-pyridone was more reactive and so required less reaction time.

The reaction of 4-pyridone with methyl acrylate was allowed to proceed one day in refluxing dioxane, yielding about 90% of product. The crude reaction mixture, an oil, was passed through Grade I alumina using 2% methanol in methylene chloride and the eluant evaporated to dryness in vacuo. The resulting white solid was recrystallized
from a methanol/methylene chloride solvent mixture. A deliquescent crystalline material of mp 95°-98°C was isolated and characterized as methyl 3-(4-pyridon-1-yl)pro- pionate (9). The pmr spectrum closely resembled that of the 2-pyridone analog (1) except for the pyridone protons. See spectra numbers 1 and 2.

The reaction of 4-pyridone with ethylenic diesters was studied by using dimethyl maleate in DMSO (d6) and by following the course of the reaction within the pmr spectrometer. Upon heating the tube up to 100°C for a considerable time, a small amount of product could be distinguished. Before product could be detected, fumarate protons were visible in the pmr spectrum of the reaction mixture. The product was not isolated for further characterization other than by pmr, which was compatible with a structure such as dimethyl 2-(4-pyridon-1-yl)succinate (10).

Methyl propiolate with 4-pyridone gave two easily isolable compounds after only one hour in refluxing dioxane. The major component, identified by pmr as trans- methyl 3-(4-pyridon-1-yl)acrylate (11) (cis addition product) was quite insoluble and crystallized out easily. The minor component, being very soluble, could be isolated only by repeated crystallization of the mother liquor. It was identified as cis methyl 3-(4-pyridon-1-yl)acrylate (12). No 1:2 addition product was found. The pmr spectra
for both pyridones with methyl propiolate are given (see numbers 3 through 6). Table I also lists products from this reaction in various solvents.

The reaction of 4-pyridone with DMAD gave an oily residue from which cis and trans isomers were identified. Because this reaction was highly exothermic it was run at room temperature. The pyridone was added slowly and the reaction mixture allowed to stand at room temperature overnight. The pmr analysis is given in Table I. No 1:2 addition product could be found. The two identified isomers were not isolated individually, since both decomposed upon attempted vacuum distillation. The two isomers were dimethyl 2-(4-pyridon-1-yl)maleate (13) and dimethyl 2-(4-pyridon-1-yl)fumarate (14). Structure assignments followed from comparison of pmr data with that of the 2-pyridone analogs.

The structures below represent those of the compounds synthesized and identified in this work.
(1) $R_1^1 = H$, $R_2^2 = 2\text{-pyridon-1-yl}$  
(2) $R_1^1 = H$, $R_2^2 = 2\text{-pyridon-1-yl}$ 
(3) $R_1^1 = R_2^2 = 2\text{-pyridon-1-yl}$  
(4) $R_1^1 = R_3^3 = H$, $R_2^2 = \text{COOCH}_3$  
(5) $R_1^1 = H$, $R_2^2 = 4\text{-pyridon-1-yl}$  
(6) $R_3^3 = H$, $R_1^1 = R_2^2 = \text{COOCH}_3$  
(7) $R_2^2 = H$, $R_1^1 = R_3^3 = \text{COOCH}_3$  
(8) $R_1^1 = R_2^2 = 2\text{-pyridon-1-yl}$  
(9) $R_1^1 = H$, $R_2^2 = 4\text{-pyridon-1-yl}$  
(10) $R_1^1 = H$, $R_2^2 = 4\text{-pyridon-1-yl}$  
(11) $R_1^1 = R_2^2 = H$, $R_3^3 = \text{COOCH}_3$  
(12) $R_1^1 = R_3^3 = H$, $R_2^2 = \text{COOCH}_3$  
(13) $R_2^2 = H$, $R_1^1 = R_3^3 = \text{COOCH}_3$  
(14) $R_3^3 = H$, $R_1^1 = R_2^2 = \text{COOCH}_3$
TABLE I

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Reactants

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<td>Methyl propiolate plus 2-pyridone</td>
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<tr>
<td>DMAD plus 2-pyridone</td>
<td>43 83 89 87</td>
</tr>
<tr>
<td>Methyl propiolate plus 4-pyridone</td>
<td>10    --    --       small^a</td>
</tr>
<tr>
<td>DMAD plus 4-pyridone</td>
<td>54^b 75    --       70</td>
</tr>
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a. Insolubility difficulties preclude analysis.

b. At 70°C this value drops to 21%. The reaction was found to come to completion in less than 5 minutes. No change in the initial product ratios was noted even after 30 minutes at 70°C.
CHAPTER III
DISCUSSION

Both 2- and 4-pyridones were studied under as similar conditions as possible, yet some slight differences were found. Both pyridones gave approximately the same product ratios so that the same factors were involved in both reactions. However, 4-pyridone reacted somewhat faster in nucleophilic additions to unsaturated esters than did 2-pyridone.

The reaction medium was changed to observe the effects on the overall reaction. Table I lists the solvents employed. Three of the four solvents (dimethylformamide, t-butyl alcohol, and dioxane) yielded about the same ratio (to within 5%) of cis to trans products, even though they represent a wide range of polarity (one of them is a protic solvent and the other two essentially non-protic). Only in DMSO was there any appreciable change in the product ratio and only in certain instances. Since solvent effects were slight, other observations were needed for proper interpretation of these results.

A study of the products obtained in this work revealed a consistent pattern. With acetylene monocarboxylates, pyridones yielded predominantly trans isomers through cis addition. Yet with acetylene dicarboxylates, pyridones yielded predominantly fumarate derivatives.
through trans addition. Our equilibration studies (by pmr analysis - see spectrum numbers 7 and 8) showed that the fumarate derivatives are thermodynamically more stable than the maleate derivatives. In the absence of evidence to the contrary, it was assumed that trans disubstituted acrylate derivatives such as (3) and (11) are thermodynamically more stable than the cis derivatives, (4) and (12) respectively. Thus our results showed that in the addition of both 2- and 4-pyridones to acetylenic esters, the major product was the thermodynamically more stable isomer.

In earlier work on amines it was found that the second carbonyl group on an acetylenic ester had little effect in determining product ratios. This is in contrast with our results where it was found that under conditions of thermodynamic control, the second carbonyl group strongly affects the configuration of the final products through influencing their relative stabilities. It was not possible to conclude whether the more stable major products were formed faster than the less stable minor products, or whether the major products arose through isomerization of the less stable compounds.

A second major difference between the addition of other nucleophiles to acetylenes and the work described here was the finding that the trans adduct (fumarate configuration) obtained from 2-pyridone and DMAD could be
made to react with a second mole-equivalent of 2-pyridone to yield a 1:2 adduct. Such double additions were not reported in the addition of other nucleophiles. Because of the symmetry of the 1:2 adduct, only three isomeric products are possible, a meso form and an optically active pair of enantiomers (dl mixture). It was decided to attempt to distinguish between the meso form and the dl mixture by pmr analysis alone. This method of analysis had been reported for 1,2-dimethoxy-1,2-diphenylethane, and 2,3-diphenyl-2,3-dicyanobutane.

From one reaction involving DMAD and 2-pyridone, two separate fractions, one oily and the other crystalline were obtained. From these separate fractions, the 1:2 adduct was isolated and analyzed. From the crystalline fraction, clear prisms of the 1:2 adduct were isolated, and the pmr spectrum taken (see spectrum number 9). When no further crystalline 1:2 adduct could be isolated from the oil, extensive evaporation under vacuum finally yielded a solid. After partial solution of the solid, a fine white powder was left behind. Its pmr spectrum exhibited several changes in relative peak intensities when compared to the crystalline 1:2 adduct, and a shift in the positions of the signals attributed to the methine and methoxy protons (see spectrum number 10). It was assumed that the most favorable conformation of the meso isomer and therefore the rotamer which makes the largest
contribution to the pmr signals obtained, places the pyridone rings anti. In this rotamer, the methine proton would be expected to undergo paramagnetic shielding (de-shielding) from both the ester and the pyridone carbonyl groups. In the case of either of the dl isomers, a clear cut decision regarding the relative population of the various rotamers was not possible from the available evidence. However, in only a single one of these rotamers would the methine proton be expected to undergo the same amount of paramagnetic shielding as in the preferred meso rotamer. The methine proton on the other two dl rotamers would be deshielded by either the ester or the pyridone carbonyl, but not by both. Since pmr signals are functions of the population of the various conformations, it was deduced that the chemical shift of the methine proton of the meso isomer must be greater than or equal to that of the dl mixture. Accordingly, the crystalline 1:2 adduct having a pmr signal at 4.5 tau (T) assigned to the methine proton was tentatively assigned the dl configuration, and the minor product having a corresponding pmr signal at 4.21T was tentatively assigned the meso configuration.

It is noteworthy that no 1:2 adducts could be isolated from the reactions involving 4-pyridone. The 1:1 adducts from 4-pyridone were found to be thermally unstable and this may have precluded further reaction with a second mole-equivalent of 4-pyridone.
A reaction mechanism which fits all of the above information is given below for both acetylenic and ethylenic esters.

\[ R' = H, \text{COOR} \]

If \( R' = H \)

If \( R' = \text{COOR} \)

meso and dl
Summary

Pyridones have been shown to react with unsaturated esters to favor the more thermodynamically stable adduct. This result is quite analogous to the work done by Hendrickson\(^9\) on amino ketones. It is evident that the addition of both pyridones and amino ketones to unsaturated esters is similar and that this mode of addition is unlike that of amines.

Work reported previously\(^{13}\) assumes the trans addition of 2-pyridone with hot DMAD. We have shown that the major product is of this configuration, but that some cis addition product is obtained under our experimental conditions. Both chemical and spectral data on these isomers (6) and (7) confirm our assignments.
CHAPTER IV
EXPERIMENTAL

General

All melting points are uncorrected and were determined in a Thomas-Hoover melting point apparatus. The chemical analyses were performed by Schwarzkopf Micro-analytical Labs. Infrared spectra were determined on a Beckman IR-8 Infrared Spectrometer in chlorform solution. Ultraviolet spectra were determined on a Perkin-Elmer Model 202 Spectrometer in absolute ethanol. Proton magnetic resonance spectra were taken on a Hitachi Perkin-Elmer R-20 High Resolution Nuclear Magnetic Resonance Spectrometer. The solvent was CDCl$_3$ with TMS as an internal standard and line positions are expressed as tau values. Coupling constants (J) are reported in hz.

Grade IV-VI alumina (unless otherwise stated) was used for column chromatography. When dioxane was used as solvent, the reaction mixture was refluxed; with dimethyl formamide as solvent, the reaction mixture was kept in the temperature range of 100° to 110° C; with t-butyl alcohol as solvent, the reaction mixture was heated on a steam bath in a sealed tube; with dimethyl sulfoxide (DMSO-d$_6$) as solvent, the reaction was observed directly in the pmr spectrometer.
2-Pyridone and Methyl Acrylate

In a 250 ml round bottom flask were placed 2.84g (33.0 mmoles) (approximately 3 ml) of methyl acrylate, 2.95g (31.0 mmoles) of 2-pyridone and 100 ml dioxane. The system was degassed, flushed with dry nitrogen and heated to reflux. After four days of reflux the solvent was evaporated, leaving an oil. The oil was chromatographed on alumina and eluted with varying proportions of ethyl ether/methylene chloride. The viscous oil obtained in the earlier fractions was vacuum distilled at 135° - 137°C at 1.1 mm Hg. The oil weighed 4.66g representing 85.5% yield of methyl 3-(2-pyridon-1-yl)propionate (1); uv, 229 (w) and 305 μm; ir 1730, 1660, and 1585 cm⁻¹; pmr, 7.15 (triplet 2H, J=6.6, methylene), 6.38 (singlet, 3H, methoxy-carbonyl), 5.91 (triplet, 2H, J=6.6, methylene), 3.98 (double triplet, 1H, J=6.5 and 1.5, ring C-5), 3.66 (pair of double doublets, 1H, J=9.2, 1.5 and 0.8 ring C-3), 2.78 (pair of double doublets, 1H, J=9.2, 6.5 and 2.1, ring C-4), 2.53 (pair of double doublets, 1H, J=6.5, 2.1 and 0.8 ring C-6).


2-Pyridone and Diethyl Fumarate

In a round bottom flask were placed 3.12 g (33.0 mmoles) of 2-pyridone, 3.26g (19.0 mmoles) of diethyl
fumarate, and 100 ml of dimethyl formamide. The solution was refluxed for four days. The solvent was removed (with difficulty) and the residue was chromatographed and analyzed by pmr. The oil contained diethyl fumarate and a product, identified as diethyl 2-(2-pyridon-1-yl)succinate (2); uv, 230 (w) and 306 m\(\mu\); ir, 1730, 1670, and 1590 cm\(^{-1}\); pmr, 2.35-2.60 (multiplets, 2H, 4 and 6 ring H), 3.30-3.90 (multiplets, 2H, 3 and 5 ring H), 4.78 (multiplet, 1H, methine), 5.80 (multiplet, 4H, ester methylenes), 6.70 (multiplet, 2H, methylene), and 8.76 (triplet, 6H, \(J=7.0\), ester methyl). The oily residue represents less than 8% reaction. Vacuum distillation afforded a cleaner oily product, but pmr analysis indicated that this was not a pure compound.

2-Pyridone and Methyl Propiolate

In a 250 ml round bottom flask were placed 3.15g (33.7 mmoles) of 2-pyridone, 3.43g (40.7 mmoles) of methyl propiolate and 100 ml dioxane. The system was heated to reflux under nitrogen and left for four days (reflux temperature initially 104°C, finally 111°C). The light yellow solution was evaporated to dryness, dissolved in methylene chloride and chromatographed on alumina. Crystalization from methanol yielded 4.06g (66%) of the cis addition product: trans methyl 3-(2-pyridon-1-yl)acrylate (3); pale yellow crystals of mp 114°-116°C; uv, 222 (log
fumarate, and 100 ml of dimethyl formamide. The solution was refluxed for four days. The solvent was removed (with difficulty) and the residue was chromatographed and analyzed by pmr. The oil contained diethyl fumarate and a product, identified as diethyl 2-(2-pyridon-1-yl)succinate (2); uv, 230 (w) and 306 m\(\mu\); ir, 1730, 1670, and 1590 cm\(^{-1}\); pmr, 2.35-2.60 (multiplets, 2H, 4 and 6 ring H), 3.30-3.90 (multiplets, 2H, 3 and 5 ring H), 4.78 (multiplet, 1H, methine), 5.80 (multiplet, 4H, ester methylenes), 6.70 (multiplet, 2H, methylene), and 8.76 (triplet, 6H, \(J=7.0\), ester methyl). The oily residue represents less than 8% reaction. Vacuum distillation afforded a cleaner oily product, but pmr analysis indicated that this was not a pure compound.

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$\varepsilon$ 4.150), and 339 (log $\varepsilon$ 3.866) µm; ir, 1710, 1678, and 1600 cm$^{-1}$; pmr, 6.23 (singlet, 3H, methoxycarbonyl), 3.82 (doublet, 1H, J=14.7, vinyl H), 3.76 (overlapping double doublets, 1H, J=6.7 and 1.5, ring C-5), 3.47 (pair of double doublets, 1H, J=9.3, 1.5 and 0.8, ring C-3), 2.69 (pair of double doublets, 1H, J=9.3, 6.7, and 1.9, ring C-4), 2.50 (pair of double doublets, 1H, J=6.7, 1.9, and 0.8, ring C-6), 1.58 (doublet, 1H, J=14.7, vinyl H).

**Anal.** Calculated for C$_9$H$_9$NO$_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.35; H, 5.26; N, 7.86.

The mother liquor was concentrated and the resulting crystals of the above adduct removed. This was repeated several times, and the dried residue was redissolved in acetone. A second product precipitated upon cooling. It was filtered off and washed with ether. Yield: 100 mg (1.5%) of cis methyl 3-(2-pyridon-1-yl)acrylate (4); white crystals, mp 88°-90°C; uv, 205 (w) and 326 µm; ir, 1725, 1670, and 1600 cm$^{-1}$; pmr, 6.30 (singlet, 3H, methoxycarbonyl), 4.18 (doublet, 1H, J=9.8, vinyl H), 3.78 (multiplet, 1H, ring C-5), 3.50 (multiplet, 1H, ring C-3), 2.72 (multiplet, 1H, ring C-4), 2.52 (multiplet, 1H, ring C-6), and 2.72 (doublet, 1H, J=9.8, vinyl H).

**Anal.** Calculated for C$_9$H$_9$NO$_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.38; H, 5.20; N, 7.92.

Sometimes traces of the 1:2 adduct could be isolated from the residue after all crystallizations had been
completed for removal of the cis and trans isomers. It was isolated as a white crystalline material of mp 177°-178°C, methyl 3,3-di-(2-pyridon-1-yl)propionate (5); uv, 229 (w) and 305 μ; ir, 1735, 1662, and 1590 cm⁻¹; pmr, 6.32 (singlet, 3H, methoxycarbonyl), 6.21 (doublet, 2H, J=7.5, methylene), 3.35-3.95 (multiplet, 4H, ring C-3 and C-5), 3.12 (triplet, 1H, J=7.5, methine), 2.50-2.90 (multiplet, 2H, ring C-4), 2.00 (multiplet, 2H, ring C-6).

2-Pyridone and Dimethyl Acetylenedicarboxylate (DMAD)

In a 250 ml round bottom flask were placed 2.48g (26.1 mmoles) of 2-pyridone, 3.65g (25.7 mmoles) of DMAD and 100 ml dioxane. The solution was refluxed overnight. The yellow solution was evaporated to dryness. The residue was taken up in methanol, from which white insoluble crystals were isolated. The melting point was 223°-227°C and the yield was 0.035 (0.57%) of the 1:2 adduct, dimethyl 2,3-(2-pyridon-1-yl)succinate (8); uv, 229 (log ε 4.000) and 300 (log ε 3.908) μ; ir, 1750, 1666, and 1590 cm⁻¹; pmr (dl), 6.22 (singlet, 6H, methoxycarbonyl), 4.45 (broad singlet, 1H, methine), 3.98 (overlapped double doublet, 1H, J=6.7 and 1.6, ring C-5), 3.73 (pair of multiplets, 1H, J=8.6, ring C-3), 2.77 (partially obscured pair of double doublets, 1H, J=6.7 and 2.1, ring C-4), 2.68 (pair of multiplets, 1H, J=6.7, ring C-6); pmr (meso), 6.34 (singlet, 6H, methoxycarbonyl), 4.21
(singlet, 1H, methine), 3.40-3.92 (multiplet, 2H, ring C-5 and C-3), 2.37-2.79 (multiplet, 2H, ring C-4 and C-6).

**Anal. calculated for C_{16}H_{16}N_{2}O_{6} (mixture of meso/dl):**

C, 76.16; H, 6.39; N, 11.10. **Found:** C, 76.02; H, 6.43; N, 10.82.

The residue was again dried, dissolved in methylene chloride, then ether was added. The solution was chromatographed on alumina and eluted with varying proportions of methylene chloride/ether. Evaporation and crystallization of the early yellow fraction yielded 3.98g (65% yield) of the trans 1:1 adduct, dimethyl 2-(2-pyridon-1-yl)fumarate (6); mp 106°-107°C; uv, 213 (log ε 4.096) and 301 (log ε 3.640) μm; ir, 1734, 1672, and 1594 cm⁻¹; pmr, 6.20 and 6.33 (singlets, 6H, methoxycarbonyls), 3.75 (pair of double doublets, 1H, J=7.0, 6.5 and 1.4, ring C-5), 3.48 (pair of double doublets, 1H, J=9.4, 1.4, and 0.9, ring C-3), 2.97 (singlet, 1H, vinyl), 2.83 (pair of double doublets, 1H, J=7.0, 2.1, and 0.9, ring C-6), 2.55 (pair of double doublets, 1H, J=9.4, 6.5, and 2.1, ring C-4).

**Anal. calculated for C_{11}H_{11}NO_{5}:** C, 55.70; H, 4.67; N, 5.90. **Found:** C, 55.59; H, 4.72; N, 5.80.

Subsequent eluent (slightly yellow) was allowed to dry at room temperature. Large, clear prisms were formed after a time. Separation of prisms from the yellow oil was accomplished by the addition of methanol. Recrystallization from methanol (by slow evaporation) yielded 0.266g
(4.3% yield) of the cis 1:1 adduct, dimethyl 2-(2-pyridon-1-yl)maleate (7); mp 114°-116°C; uv, 213 (log ε 4.110) and 324 (log ε 3.709) μ; ir, 1734, 1674, and 1598 cm⁻¹; pmr, 6.13 and 6.17 (singlets, 6H, methoxycarbonyls), 3.67 (pair of double doublets, 1H, J=6.9, 6.2 and 1.3, ring C-5), 3.46 (overlapping pair of double doublets, 1H, J=8.9, 1.3, and 1.1, ring C-3), 3.58 (singlet, 1H, vinyl), 3.65 (pair of multiplets, 1H, J=6.9, ring C-6), 3.30 (pair of double doublets, 1H, J=8.9, 6.2 and 2.0, ring C-4).

Anal. calculated for C₁₁H₁₁NΟ₅: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.70; H, 4.66; N, 5.72.

Fumarate Product (6) and 2-Pyridone

In a round bottom flask were placed 0.236g (2.48 mmole) of 2-pyridone, 0.588g (2.48 mmole) of the fumarate (6) and 10.0 ml dioxane. The solution was refluxed for 115 hours. Evaporation of solvent and recrystallization yielded 0.100 g (12%) of the succinate (8).

Isomerizations of the 1:1 adducts

In a round bottom flask were placed 0.383g (1.60 mmole) of the maleate (7), 0.162g (1.70 mmole) of 2-pyridone, and 50.0 ml dioxane. The system was degassed and refluxed for three days under nitrogen. Solvent was evaporated in vacuo on the steam bath. The residue was dissolved in methylene chloride and chromatographed. The
pmr analysis indicated 85% conversion to the fumarate (6) isomer. Also, the maleate (7) was placed alone in a sealed pmr tube in CDC1₃ solution. After several hours of heating on the steam bath, pmr analysis showed an 88% conversion to the fumarate (7). Identical reactions using the fumarate (6) showed no conversion to the maleate (7) isomer.

4-Pyridone and Methyl Acrylate

In a 250 ml round bottom flask was placed 3.05g (32.2 mmole) of 4-pyridone with 75.0 ml of dioxane. In a dropping funnel was placed 2.87g (33.3 mmole) of methyl acrylate in 25.0 ml of dioxane. The system was degassed and heated to reflux under nitrogen. The acrylate was added and the whole refluxed overnight. The solvent was evaporated and the oil residue was dissolved in methylene chloride and chromatographed on alumina (Grade I). Evaporation of solvent in vacuo from the early fractions yielded a white solid. The solid was recrystallized from methanol/methylene chloride. A deliquescent crystalline material of mp 95°-98°C was obtained in about 70% yield. The product was identified as methyl 3-(4-pyridon-1-yl)-propionate (9); uv, 214 (w) and 266 m\(\lambda\); ir, 1735, 1635, and 1575 cm\(^{-1}\); pmr, 2.44 and 3.65 (doublets, 4H, J=7.8, pyridone ring H's), 5.80 and 7.12 (triplets, 4H, J=6.0, methylene), and 6.28 (singlet, 3H, methoxycarbonyl).
PMR TUBE REACTION. 4-Pyridone and Dimethyl Maleate

In a pmr tube, 0.10g (0.70 mmole) of dimethyl maleate was dissolved in 0.50 ml of DMSO (d₆) and a spectrum was taken. In another pmr tube, 0.06g (0.63 mmole) of 4-pyridone was dissolved in 0.50 ml DMSO (d₆) and a spectrum was taken. The solution from one tube was poured into the other, inverted several times, and then placed in the pmr spectrometer. Usually the pmr spectrum was scanned at different times (with integration) until the reaction was completed. Since no reaction was visible (in this case), the temperature of the probe was raised to 100°C. Fumarate formed from maleate under these conditions as shown by the new proton (vinyllic) signal. After a considerable time a small amount of product was visible, assigned the structure dimethyl 2-(4-pyridon-1-yl)succinate (10); pmr (DMSO-d₆), 2.10 and 3.70 (doublets, 4H, J=8, pyridone ring H's), 4.60 (triplet, 1H, J=7, aliphatic), 6.70 (doublet, 2H, J=7, aliphatic), and 6.25 and/or 6.35 (singlets, 6H, methoxycarbonyl). It was not isolated for characterization other than by pmr in the original reaction tube, hence pmr values are approximate, and the structure assignment is tentative.

4-Pyridone and Methyl Propiolate

In a round bottom flask were placed 3.34g (35.2 mmole) of 4-pyridone and 75.0 ml dioxane (insoluble). In
a dropping funnel was placed 3.08g (36.6 mmole) of methyl propiolate dissolved in 25.0 ml of dioxane. The system was degassed and heated to reflux under nitrogen. The methyl propiolate was added slowly to the pyridone. After refluxing one hour, the reaction was stopped. The solvent was removed and the red residue was dissolved in methanol, treated with charcoal, and filtered. Evaporation of the methanol yielded a white solid and a yellow-colored liquid. Recrystallization of the solid (methanol) gave a compound of mp 220°-223°C, the cis addition product, trans methyl 3-(4-pyridon-1-yl)acrylate (11); uv, 217 (w) and 310 μν; ir, 1727, 1630, and 1600 cm⁻¹; pmr, 2.39 and 3.55 (doublets, 4H, J=8.1, pyridone ring H's), 2.34 and 4.06 (doublets, 2H, J=14.4, vinyl), and 6.18 (singlet, 3H, methoxycarbonyl). After several crystallizations to remove this isomer from the remainder of the residue, another (very soluble) crystalline material was isolated from cold acetone solution. It was identified as cis methyl 3-(4-pyridon-1-yl)acrylate (12); mp 91°-98°C; uv, 214 (w) and 307 μν; ir, 1722, 1630, and 1598 cm⁻¹; pmr, 2.18 and 3.64 (doublets, 4H, J=8.1, pyridone ring H's), 3.15 and 4.30 (doublets, 2H, J=9.8, vinyl), and 6.20 (singlet, 3H, methoxycarbonyl). No 1:2 adduct was found.

4-Pyridone and Dimethyl Acetylenedicarboxylate (DMAD)

In a round bottom flask was placed 3.49g (24.5 mmole)
of DMAD with 35.0 ml of DMF. In a dropping funnel was placed 2.23g (24.0 mmole) of 4-pyridone in 65.0 ml of DMF. The system was degassed, flushed with nitrogen, and cooled. With both reactants around room temperature (approximately 20°C), the pyridone solution was slowly added to the DMAD reagent. After twenty-four hours, the solvent was evaporated (in vacuo on a water bath, temperature below 40°C). The oily residue was chromatographed on alumina and eluted with methylene chloride. Analysis by pmr showed that the early fractions, an oil, consisted of two isomers. Attempted vacuum distillation caused decomposition. The isomers were identified as dimethyl 2-(4-pyridon-1-yl)-fumarate (14); pmr, 2.71 and 3.69 (doublets, 4H, J=5.5, pyridone ring H's), 2.93 (singlet, 1H, vinyl), 6.10 and 6.27 (singlets, 6H, methoxycarbonyls), and dimethyl-2-(4-pyridon-1-yl)maleate (13); pmr, 2.46 and 3.67 (doublets, 4H, J=5.5, pyridone ring H's), 4.67 (singlet, 1H, vinyl), 6.06 and 6.22 (singlets, 6H, methoxycarbonyls). The isomers have yet to be isolated and no 1:2 adduct was observed.
All the pmr spectra were obtained in deuterated chloroform at 34°C unless specified otherwise. The scale of the spectral reproductions is 1 cm = 30 Hz. All values for pmr signals are expressed as tau values. Chemical shifts for multiplets were obtained by first-order analysis only.
BIBLIOGRAPHY

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