ENAMINE FORMATION FROM CYCLIC KETONES

by

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ABSTRACT

ENAMINE FORMATION FROM CYCLIC KETONES

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The compound 3,4,5,6,7,8-hexahydro-2(4aH)-naphthalenone (hereafter referred to as octalone) was synthesized by condensation of 2-formylcyclohexanone and diethylaminobutanone methiodide. Conjugate additions of vinyl- and isopropenylmagnesium bromides, respectively, to octalone (catalyzed by Cu^{++}) were carried out. Attempts to purify the conjugate adducts are described.

During the synthesis of octalone an intermediate ketol was isolated and identified as trans-2-decalon-9-ol(i) by infrared and mass spectral studies.

The research initially planned was to study the acid-catalyzed rearrangement of pure vinyl adduct. The vinyl adduct obtained during the conjugate addition of vinyl-bromide to the octalone catalyzed by Cu^{++} was found to be contaminated with the starting material (octalone). It was decided to examine enamines as a possible means of separation of adduct (saturated ketones) from the starting material. Hence this research was undertaken to determine the kinetics of enamine formation, knowledge of which is

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necessary for the separation of products.

In the present study cyclohexanone and octalone were used as model compounds for saturated and α,β-unsaturated cyclic ketones, respectively. The secondary amines used were pyrrolidine, morpholine and piperidine. There is a considerable difference in the rates of enamine formation for the two ketones. The results obtained were rationalized in terms of the steric environments of the ketones.

The rate of formation of cyclohexanone enamines, in the case of morpholine, was found to be about ten times faster than the formation of piperidine enamine. In the case of octalone the rate of formation of morpholine enamine is about thirty times faster than that of piperidine enamine.

The basicity of the secondary amines was also considered in discussion the difference in rates. Rate determinations were successfully achieved using gas chromatographic analysis. The reaction followed second-order kinetics.

ACKNOWLEDGEMENTS

I consider it a great pleasure in expressing my gratitude and thanks to Dr. Leon Rand, Professor and Chairman of the Chemistry Department, for his suggestion of the problem, for his constant help and for the encouragement he gave me throughout the course of this investigation.

I also wish to express my gratitude and thanks to Dr. James A. Reeder for helpful suggestions and many valuable discussions.

Finally, grateful appreciation is extended to Dr. Steven M. Schildcrout for mass spectral analysis and to my friend, Mr. Hemant Vyas, who helped to make part of the figures. Special thanks go out to my parents for the encouragement during the study when it was needed.

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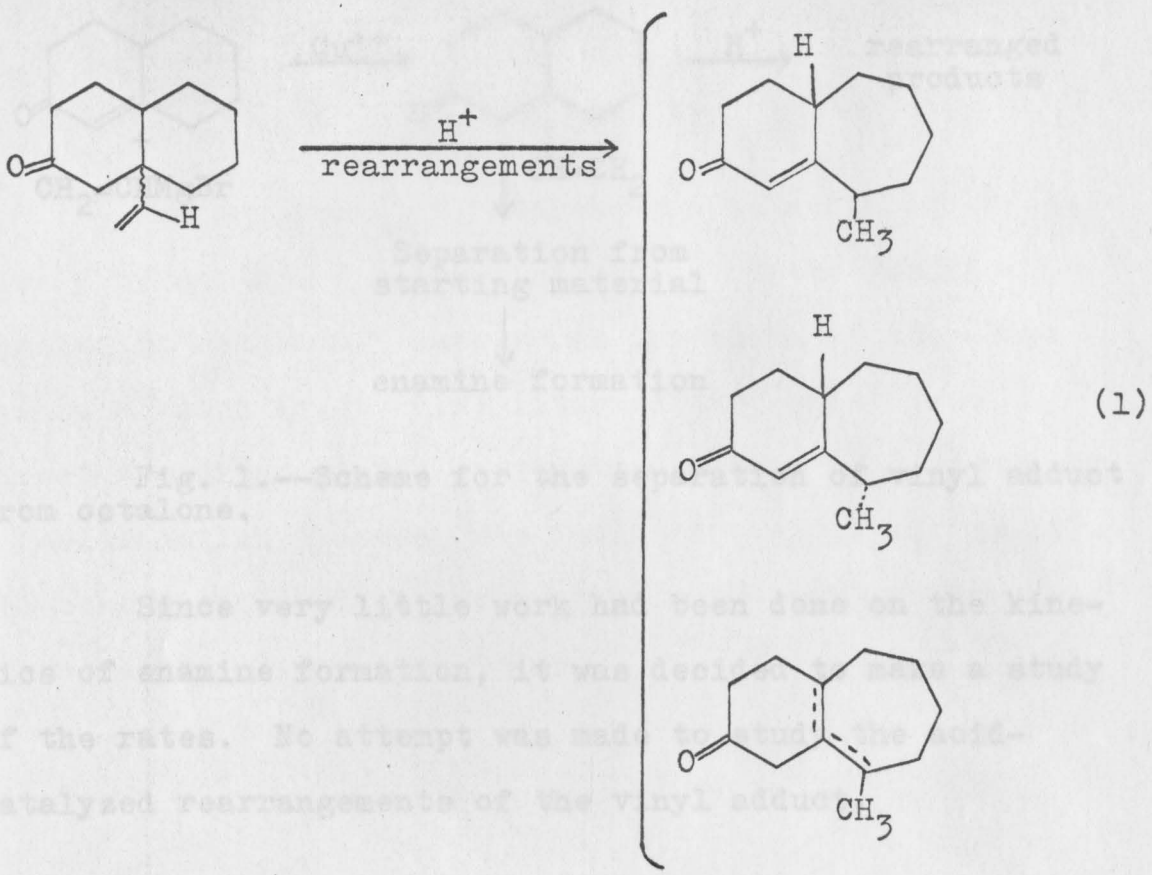
CHAPTER I

INTRODUCTION

Conjugate addition of alkenyl Grignard reagents has only recently been crowned with success. House et al.,[1] reported the simple successful case of conjugate addition of isopropenylmagnesium bromide to cyclohexenone (an α,β-unsaturated ketone) catalyzed by cuprous ion. Previous work on copper-catalyzed 1,4-addition to α,β-unsaturated ketones had been concerned chiefly with alkyl and phenyl Grignard reagents.[2,3] This work was first reported by Birch and Smith[2] and then extensively utilized and investigated by House and Marshal.[3] Steric approach control[2,3] has been shown to be important in deciding the stereochemistry of the product, which is normally cis.

Rand and Rao[4] studied alkenyl Grignard addition to $\Delta^{1,9}$2-octalone and suggested the formation of both cis and trans isomers.

Having this background an attempt was made to study the conjugate addition of vinyl and isopropenylmagnesium bromides to octalone catalyzed by Cu^{++}. Rand and Rao[4] had suggested the possible rearrangement products of vinyl adduct as shown below.



(1)

In the present study enamine formation was used as a means of separation, since purification of vinyl adduct was not possible either by fractional distillation or through column chromatography because of the similar physical behavior (b.p.) of the adduct and the starting material, and also the unstability of the adduct.

The scheme employed to study the rates of enamine formation of vinyl adduct is shown below (Figure 1). However, cyclohexanone was used as the model compound for the pure adduct since it was necessary to obtain the rate of enamine formation of the pure adduct with the secondary amines.

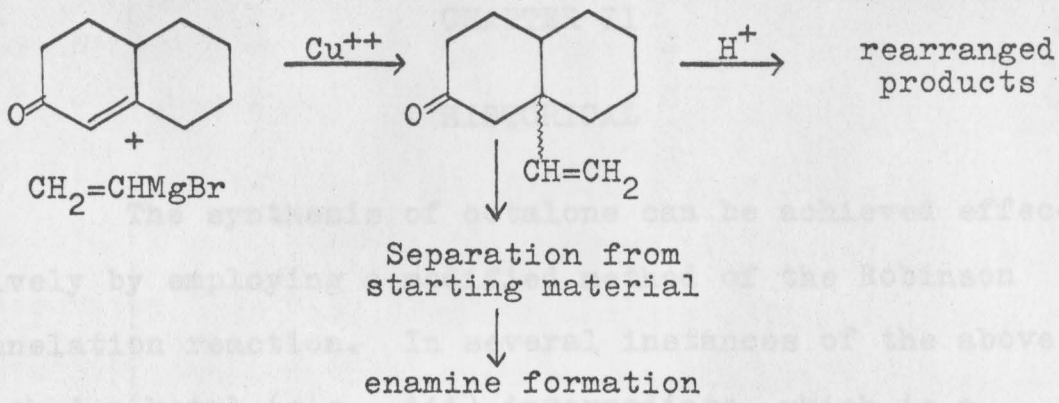


Fig. 1.--Scheme for the separation of vinyl adduct from octalone.

Since very little work had been done on the kinetics of enamine formation, it was decided to make a study of the rates. No attempt was made to study the acid-catalyzed rearrangements of the vinyl adduct.

CHAPTER II

HISTORICAL

The synthesis of octalone can be achieved effectively by employing a modified method of the Robinson annelation reaction. In several instances of the above method a ketol (e.g., iii) intermediate, which is a direct precursor of the unsaturated ketone (ii) formed by a ß-elimination process, was isolated[5] (e.g., iii → ii). The scheme employed in the synthesis of octalone by the above method is depicted below.

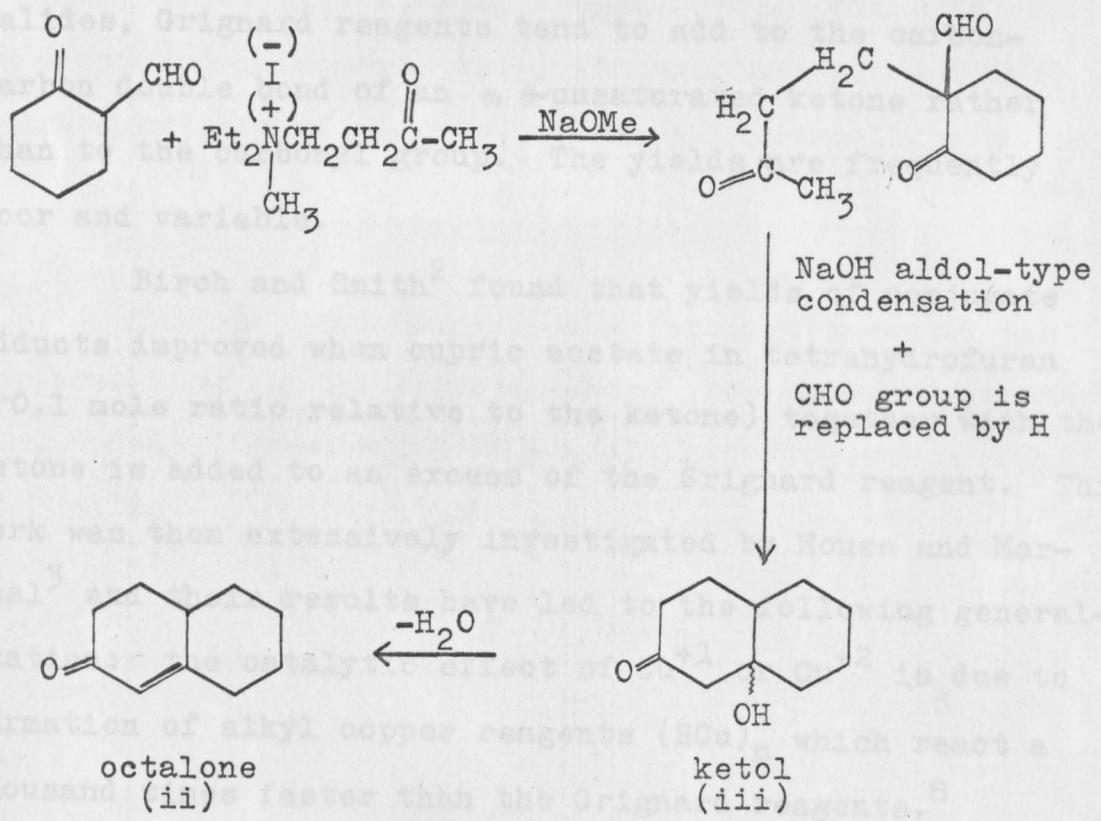


Fig. 2.--Synthesis of octalone

Tsatsos[6] obtained a crystalline product during the synthesis of octalone by the Robinson annelation reaction which involved the condensation of methyl vinyl ketone with cyclohexanone in the presence of triton-B methoxide at 0°. A pure material melting at 147° - 148.5° was separated from this reaction mixture (25% yd). This substance, upon treatment with sodium methoxide, underwent dehydration to produce the octalone. The crystalline product apparently must be the trans ketol (i).

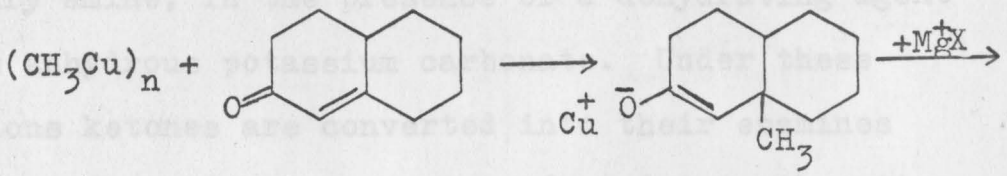
Addition of Grignard Reagents to α,β-Unsaturated Ketones Catalyzed by Copper Salts

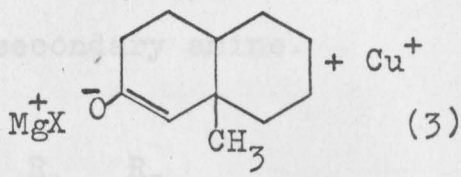
Kharasch[7] observed that, in the presence of cuprous halides, Grignard reagents tend to add to the carbon-carbon double bond of an α, β-unsaturated ketone rather than to the carbonyl group. The yields are frequently poor and variable.

Birch and Smith[2] found that yields of conjugate adducts improved when cupric acetate in tetrahydrofuran (~0.1 mole ratio relative to the ketone) together with the ketone is added to an excess of the Grignard reagent. This work was then extensively investigated by House and Marshal[3] and their results have led to the following generalization: the catalytic effect of Cu^{+1} or Cu^{+2} is due to formation of alkyl copper reagents $(RCu)_n$ which react a thousand times faster than the Grignard reagents.[8]

The formation of the 1,4-adduct is shown below.

$$n CH_3MgX + n Cu^+ \longrightarrow (CH_3Cu)_n + n\overset{+}{M}gX \qquad (2)$$



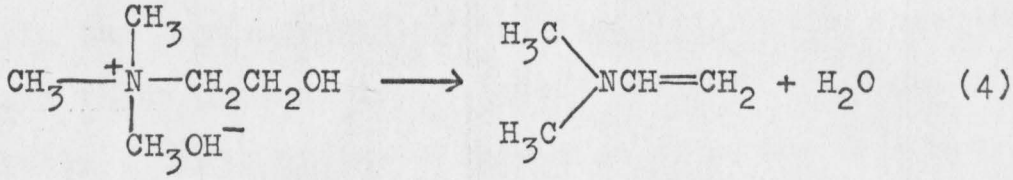


(3)

Steric approach control[2,3] [a steric postulate involving competitive attacks from a favored (unhindered) or an unfavored (hindered) side] is important in deciding stereochemistry of the product which is normally cis.[3]

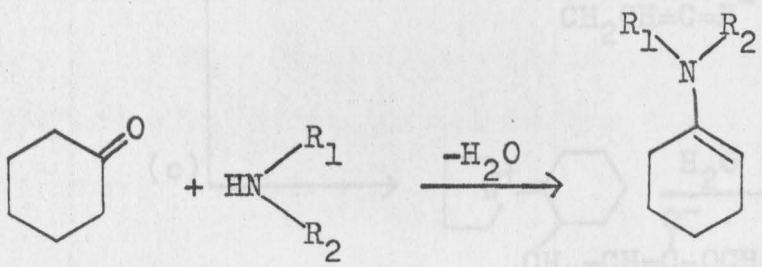
Enamine Formation

The simplest enamine of a carbonyl compound was prepared long ago by Meyer and Hopf[9] who made N,N-dimethyl vinyl amine (the enamine of acetaldehyde) by the pyrolysis of choline.



(4)

The first general method for the synthesis of enamines was provided by Mannich and Davidsen.[10] It involves the reaction of an aldehyde or ketone with a secondary amine, in the presence of a dehydrating agent such as anhydrous potassium carbonate. Under these conditions ketones are converted into their enamines directly while aldehydes are transformed into the nitrogen analog of an acetal, which is then decomposed on distillation to the enamine and a secondary amine.



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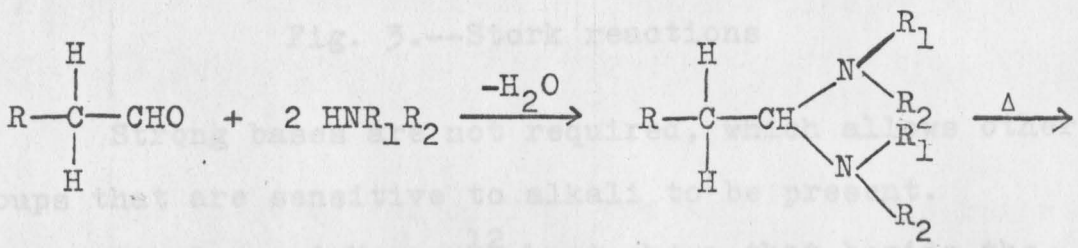

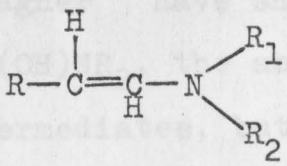

(6)

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The enamines are good nucleophiles and readily undergo alkylation (Stork reaction[11]) and acylation and add to α,β-unsaturated nitriles, ketones, and esters. Hydrolysis regenerates the cyclanone.

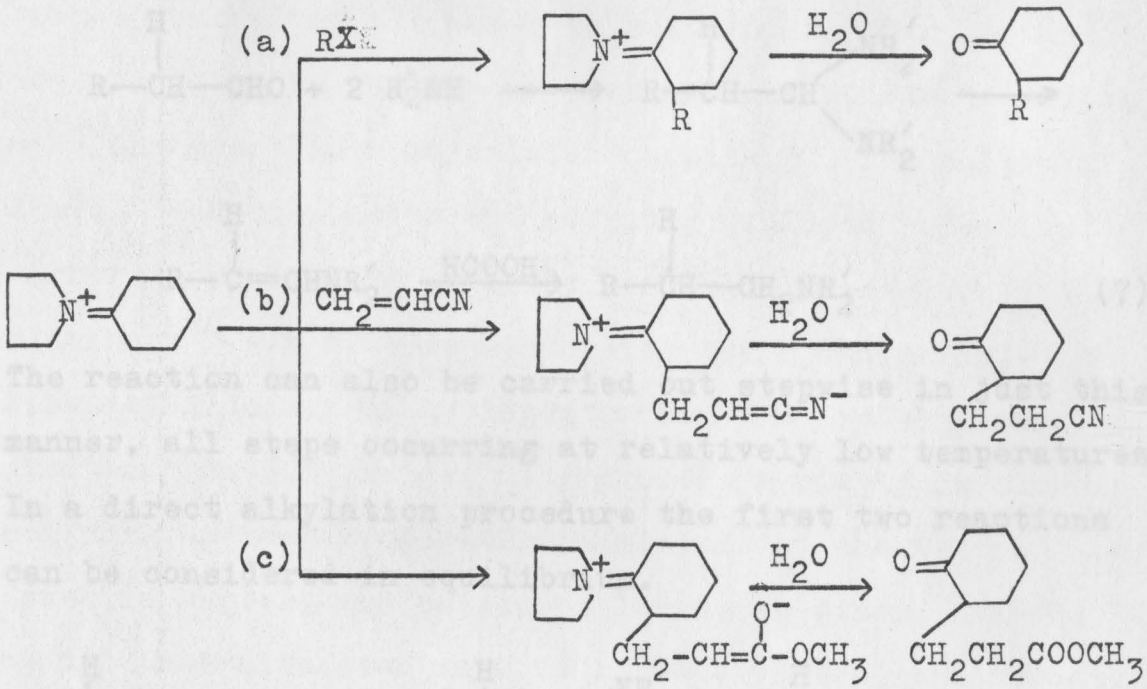
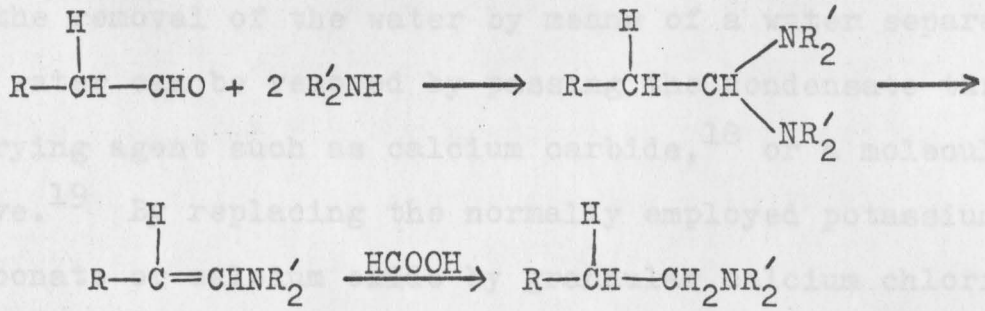


Fig. 3.--Stork reactions

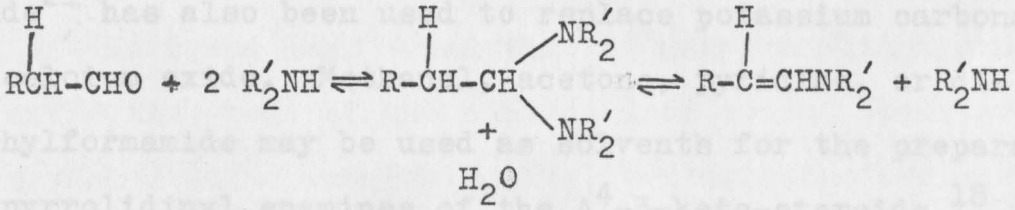
Strong bases are not required, which allows other groups that are sensitive to alkali to be present.

Staples and Wagner[12] have shown that beside the addition product, $RCH(OH)NR_2$, the aminals $RCH(NR_2)_2$ not only are possible intermediates, but that they are more active in the Lenckart-Wallah reaction[12] than the aldehyde and amine taken separately. A great deal of this activity is probably because of the elimination of water as a by-product of the reaction. When an aldehyde bears a hydrogen atom on the α-carbon atom this hydrogen can

become involved in the mechanism of enamine formation and this explains the very mild conditions under which these particular reactions occur.



The reaction can also be carried out stepwise in just this manner, all steps occurring at relatively low temperatures. In a direct alkylation procedure the first two reactions can be considered in equilibrium.



The introduction by Herr and Heyl[13] of the removal of the water produced in the condensation by azeotropic distillation with benzene made possible the preparation of enamines from ketones. This innovation was exploited by Stork and his coworkers[11] for a study of enamines from a variety of cyclic ketones and secondary amines. The benzene may be replaced by toluene or xylene to give a reasonable rate of reaction.[11]

An acid catalyst such as p-toluenesulfonic acid,[14] Dowex-50,[15] montmorillonite catalyst,[16] or even acetic acid[17] may be employed for the normal condensations or when the uncatalyzed reaction is slow. As an alternative to the removal of the water by means of a water separator, the water can be removed by passing the condensate through a drying agent such as calcium carbide,[18] or a molecular sieve.[19] By replacing the normally employed potassium carbonate or calcium oxide by grannular calcium chloride, Blanchard[20] was able to synthesize the N,N-dimethyl- and N,N-diethylamines of cyclopentanone and cyclohexanone in greater than 50% yields. The procedure simply involves stirring at room temperature a mixture of the ketone, the amine in excess, and calcium chloride in ether. Barium oxide[21] has also been used to replace potassium carbonate or calcium oxide. Methanol, acetone, pyridine, or dimethylformamide may be used as solvents for the preparation of pyrrolidinyl enamines of the Δ^4-3-keto-steroids.[18]

Herr and Heyl,[13] from their observations, indicated that C_3 steroidal ketones readily condensed with the secondary amine, pyrrolidine, in such a manner that formation of 3-(N-pyrrolidyl) enamine with the elimination of water appeared to be characteristic of C_3-steroidal ketones. Pyrrolidine, however, failed to react with the C_{17} and C_{20} keto groups of dehydroepiandrosterone and 5-pregnen-3β-ol 20-one, respectively. In the case of progesterone where pyrrolidine did not react readily with the C_3-carbonyl

group, the addition of a catalytic amount of p-toluene sulfonic acid caused the reaction to proceed smoothly.

Mechanisms of Enamine Formation

Heynes[22] has given an excellent review of mechanisms of enamine formation. The overall reaction pathway usually presented for the preparation of an enamine from an aldehyde bearing an α-hydrogen and a secondary amine is given in equations (9) and (10).

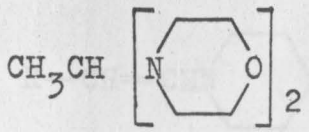
$$R\text{-}\underset{\displaystyle H}{\underset{|}{C}}H\text{-}CHO + 2\ HNR_1R_2 \xrightarrow{-H_2O} R\text{-}CH_2\text{-}CH\text{-}(NR_1R_2)_2 \qquad (9)$$

$$A \xrightarrow{\Delta} R\text{-}HC{=}CHNR_1R_2 + HNR_1R_2 \qquad (10)$$

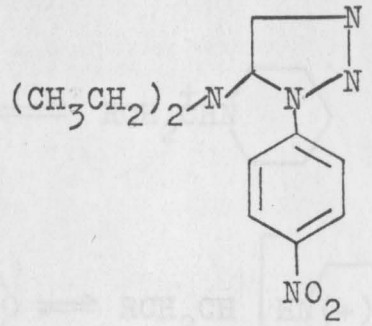
A = aminal

Herr and Heyl[13] found that by using a slight excess of amine the yield of the enamine from two of the steroidal aldehydes studied was 84%. Also, β-fluoroenamines are formed in 60-90% yield from equimolar amounts of the β-fluoroaldehyde and secondary amine.[23] However, neither of these studies was specifically designed to show whether or not aminals were intermediates.

That aminals and enamines are in equilibrium under certain conditions has been demonstrated by Ferruti, Pocar, and Bianchetti.[24]



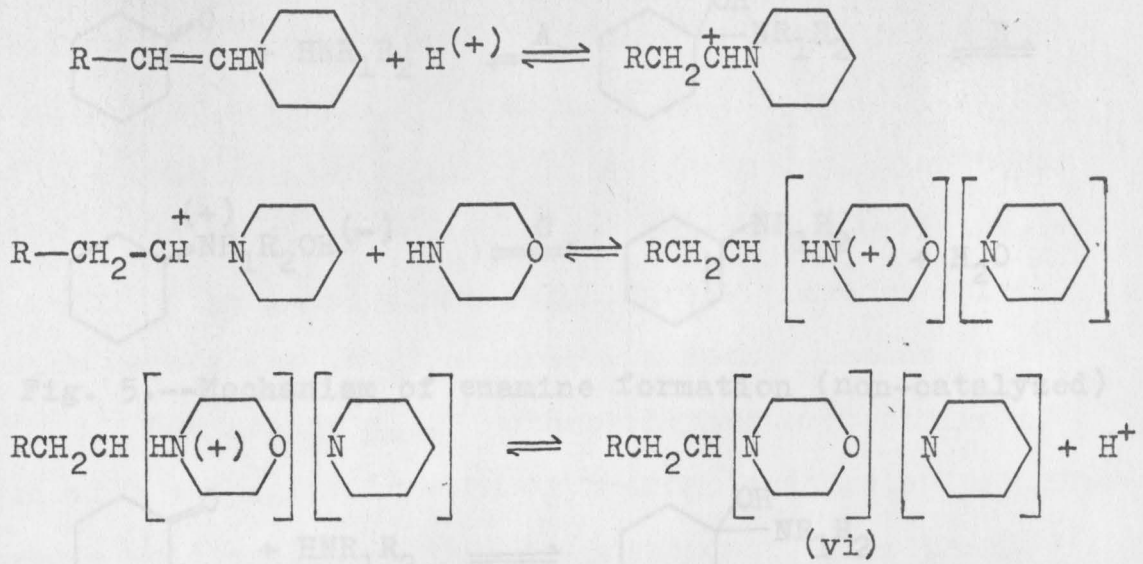
(iv)



(v)

1,1-Di(N-morpholino)ethane (iv) when heated with excess diethylamine for 24 hr. at 60° and then treated with 4-nitrophenyl azide, gave the triazole (v) in 80% yield. These workers contend that for this to occur the aminal (iv) must be in equilibrium with N-vinyl morpholine which is eventually converted to N-vinyl diethyl amine.

Additional evidence that a dynamic equilibrium exists between the enamine and the N-hemiacetal aminal has been presented by Marchese.[25] The piperidine enamine of 2-ethyl hexanol (0.125 mole), morpholine (0.375 mole), and p-toluenesulfonic acid (1.25×10^{-4} mole) diluted with benzene to 500 ml were refluxed for 5 hr. At the end of this time the enamine mixture was analyzed by vapor-phase chromatography, which revealed that exchange of the amino residue had occurred in a ratio of eight morpholine to one piperidine. Marchese[25] proposed a scheme (Figure 4) to account for these results.



(vi)

Fig. 4.--Marchese's scheme

Either the aminal (vi) could break down upon distillation to give the mixture of enamines, or by a series of similar equilibrium steps the piperidine group could be protonated and eventually lost as piperidine.

The intermediacy of an aminal in the formation of enamines is not usually proposed. The only direct evidence for this is the infrared spectra of the reaction mixtures produced when dimethyl or diethyl amine was allowed to react with cyclohexanone or cyclopentanone in ether.[20] The spectra revealed the presence of the enamine double bond (1640 cm^{-1}) prior to distillative workup.

General mechanisms for the non-catalyzed[11, 26] (Figure 5) and acid-catalyzed[25] (Figure 6) reactions have been proposed.

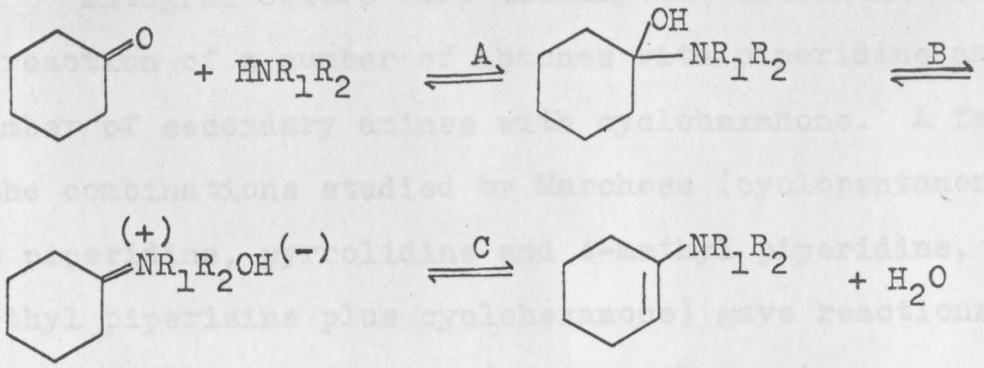


Fig. 5.--Mechanism of enamine formation (non-catalyzed)

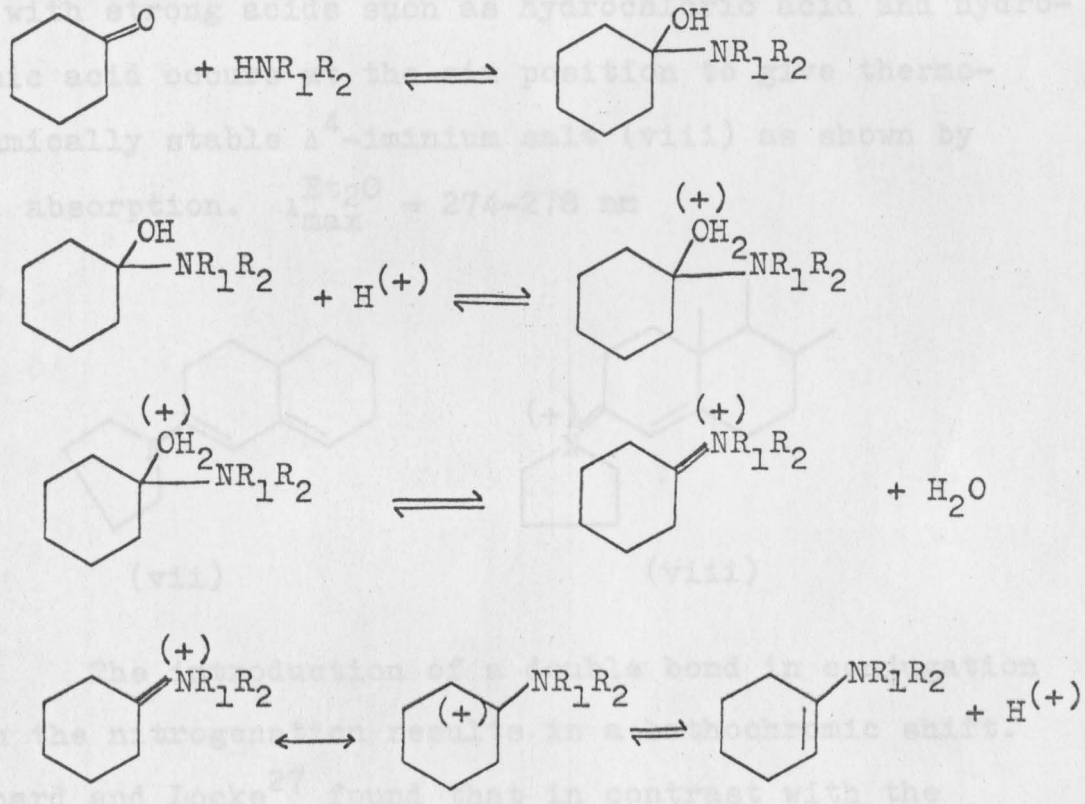
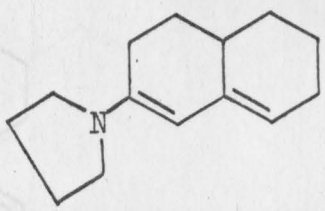


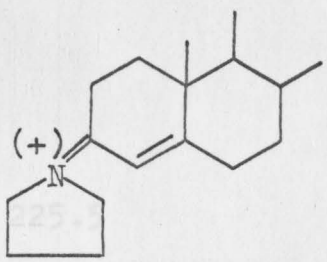
Fig. 6.--Mechanism of enamine formation (acid catalyzed)

Integral orders were usually not obtained[25] for the reaction of a number of ketones with piperidine and a number of secondary amines with cyclohexanone. A few of the combinations studied by Marchese (cyclopentanone plus piperidine, pyrrolidine and 4-methyl piperidine, and 4-methyl piperizine plus cyclohexanone) gave reactions which were close to first order in each reactant.

Johnson et al.,[18] observed that protonation of vii with strong acids such as hydrochloric acid and hydrobromic acid occurs at the six position to give thermodynamically stable Δ^4-iminium salt (viii) as shown by UV absorption. $\lambda_{max}^{Et_2O}$ = 274-278 nm



(vii)



(viii)

The introduction of a double bond in conjugation with the nitrogenation results in a bathochromic shift. Leonard and Locke[27] found that in contrast with the saturated amines (λ_{max} = 215 nm, ε = 3000), the enamines show a maximum at 230±10 nm with a hyperchromic effect on the extinction coefficient (5000-9000). These changes may be ascribed to the overlap between the electron pair on the nitrogen atom and the π electrons on the double bond. The heteroannular dienamines[14, 18] derived from

the α, β-unsaturated ketones show a maximum at 270-280 nm (ε = 19,000-26,000). In Table 1 some examples of U.V. maxima are given.

TABLE 1[a]

UV MAXIMA OF ENAMINES

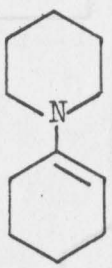
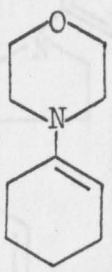
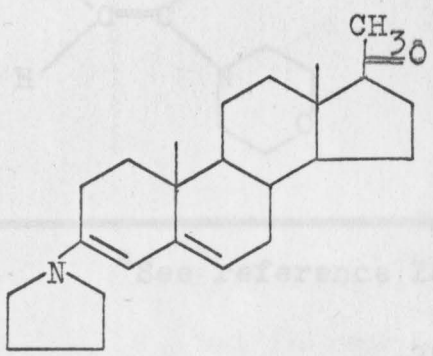
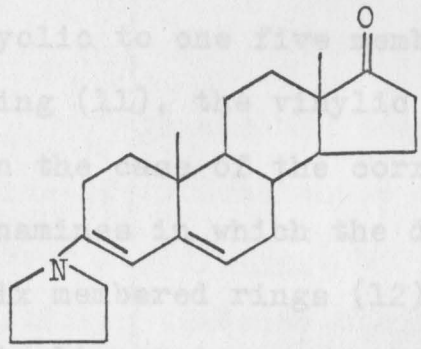
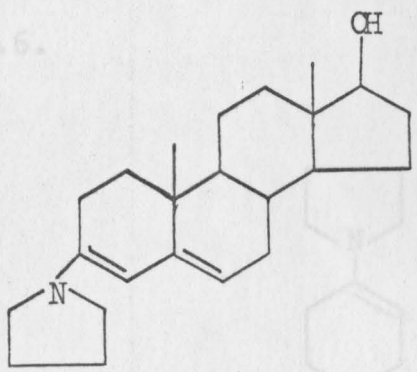
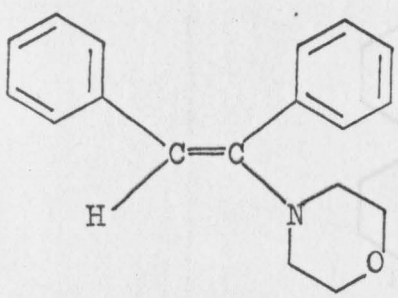
Enamine	λ_{max}, nm	ε_{max}
	224.5	8,300
	225.5	7,900
	281	22,725

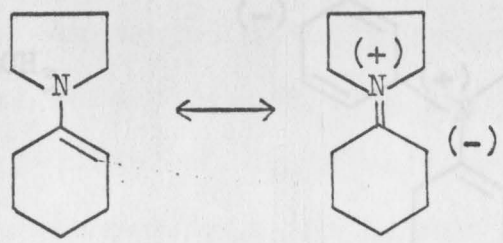
Table 1 (continued)

Enamine	λ_{max}, nm	ε_{max}
	281	23,000
	240	14,600
	320	11,400

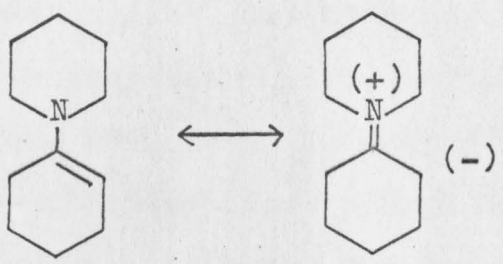
[a]See reference 28.

It was reported[29, 30] that in the NMR spectra of the enamines the position of the vinylic proton is indicative of the degree of overlap between the electron pair on

the nitrogen atom and the double bond. The greater the overlap the higher is the field at which this proton signal appears. For instance, in the case of the pyrrolidine enamine of cyclohexanone in which the double bond is exocyclic to one five membered ring and one six membered ring (11), the vinylic proton appears at δ4.2, whereas in the case of the corresponding morpholine and piperidine enamines in which the double bond is exocyclic to two six membered rings (12)--a less favored situation--the vinylic proton appears at a lower field, i.e., at δ4.5-4.6.

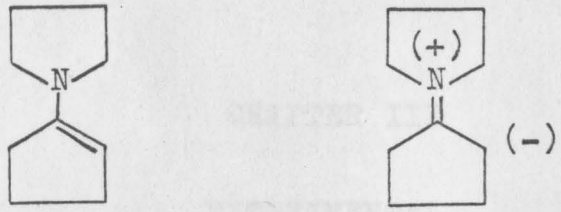


(11)



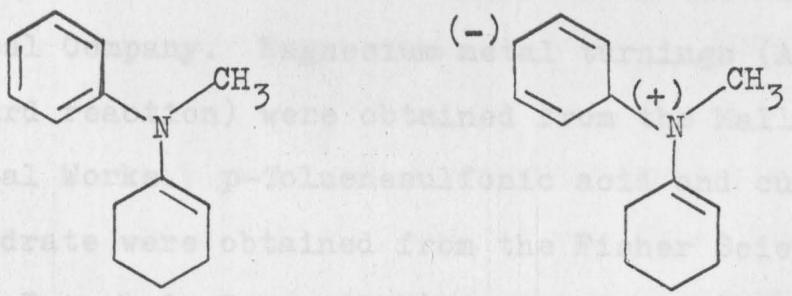
(12)

The pyrrolidine enamine of cyclopentanone in which the double bond is exocyclic to two five membered rings (13) shows the vinylic proton at δ3.9.



(13)

In the NMR spectrum of the N-methyl aniline enamine of cyclohexanone the vinyl proton appears at a much lower field, i.e., at $\delta 5.4$.[30] Here the electron pair on nitrogen tends to conjugate with the phenyl group thus exhibiting a very small degree of overlap with the enamine double bond (14).



(14)

CHAPTER III

EXPERIMENTAL

Materials

Cyclohexanone and ethyl-formate were obtained from Aldrich Chemical Company and were distilled before use. Benzene, n-hexene and toluene were obtained from Fisher Scientific Company. There were stored over sodium ribbon after distillation. Vinyl bromide, 2-bromopropene, 1-diethylaminobutanone were obtained from the Aldrich Chemical Company. Magnesium metal turnings (A.R. for Grignard reaction) were obtained from the Mallinckrodt Chemical Works. p-Toluenesulfonic acid and cupric acetate monohydrate were obtained from the Fisher Scientific Company. Tetrahydrofuran (THF) was obtained from Matheson, Coleman and Bell Company and purified by allowing it to stand overnight from KOH, metallic sodium and lithium-aluminum hydride. Also used were pyrrolidine (Eastman Kodak Company), morpholine (Union Carbide Chemical Company) and piperidine (Allied Chemical Company), each chemically pure grade. Pyrrolidine n_D^{20} 1.4428, lit.[31] n_D^{20} 1.4431; morpholine n_D^{20} 1.4549, lit.[32] 1.4545; piperidine n_D^{20} 1.4532, lit.[33] 1.4534. Diethylaminobutanone methiodide was prepared according to the procedure of Wilds and

Shunk[34] by allowing equal weights of diethylaminobutanone and methyliodide to stand protected from moisture for one half hour at 0° and one half hour at room temperature. Absolute methanol was distilled twice from magnesium methoxide. Perchloric acid was obtained from Allied Chemical Company. NMR spectra were run by Dr. R. C. Phillips with a Varian DA-60 instrument using tetramethyl silane as an internal standard. The carbon-hydrogen analyses were performed by Crobaugh Laboratory, Cleveland, Ohio.

Synthesis of 2-Formylcyclohexanone

The preparation of 2-formylcyclohexanone was based on the method reported by Johnson, Anderson and Shelberg.[35]

Alcohol-free sodium-methoxide was prepared as follows: Sodium (46 g, 2 equiv) was dissolved in dry methanol and most of the methanol was removed under reduced pressure. Benzene (100 ml) was added to the residue and distilled; the last traces were removed under reduced pressure. After cooling, the sodium methoxide was powdered by shaking.

Benzene (600 ml) was added to the powdered sodium methoxide. Ethyl formate (148 g, 2 equiv) was then added. The mixture was stirred for 1 hr and then cooled in ice water. A solution of cyclohexanone (98.15 g, 1 equiv) in benzene (150 ml) was added rapidly with vigorous stirring under a nitrogen atmosphere. A thick yellow precipitate,

which could not be easily stirred, was obtained quickly. The reaction mixture was allowed to stand at room temperature for twenty-four hours. Ice water was added, the aqueous solution was separated and the benzene solution was washed thoroughly with cold dilute NaOH. All of the aqueous solutions were combined, washed once with ether and acidified with 10% sulfuric acid. The resulting oily suspension was saturated with NaCl and extracted thoroughly with ether. The ether solution was washed with water followed by saturated salt solution and dried over anhydrous sodium sulfate. Distillation gave 82 g (65% yd) of 2-formyl cyclohexanone, b.p. 70°-71°/5 torr.

Synthesis of 3,4,5,6,7,8-Hexahydro-2(4aH)-Naphthalenone

This was prepared according to the procedure of Banerjee, Chatterjee and Bhattacharya.[36]

To an ice-cooled, stirred, methanolic solution of sodium methoxide (from 3.3 g Na and 125 ml absolute methanol) was added 2-formyl cyclohexanone (17.0 g) under a nitrogen atmosphere, followed by a methanolic solution of diethylaminobutanone methiodide (prepared from 28 g of diethylaminobutanone, 28 g methyl iodide and 300 ml absolute methanol). The solution was stirred for 1 hour and allowed to stand overnight at room temperature. It was then treated with ice-cold, dilute HCl, saturated with ammonium sulfate and extracted with ether. The ether extract was washed with saturated NaCl, dried ($MgSO_4$) and

the ether removed by distillation. The crude residue left after removal of the solvent was stirred for 1 hour at 20-22° with 1200 ml of 2% NaOH solution under a nitrogen atmosphere. The alkaline solution was thoroughly extracted with ether and the extract dried over anhydrous sodium sulfate. The solvent was removed and the residue on distillation yielded 12.5 g (62.5% yd) of a colorless liquid, b.p. 101-102°/2.8 torr (lit.[37] b.p. 101-102°/2-3 torr). This product showed infrared absorption bands (film) at 1675 (conjugate C=O) and 1615 cm^{-1} (conj C=C). NMR: The NMR spectrum (in $CHCl_3$) of this compound has a peak at δ5.60 (C-1-vinyl proton) with complex absorption in the region δ1.0-3.0 (aliphatic C-H).

The mass spectrum has a parent peak of $\frac{m}{e}$ = 150, as expected for octalone. The results of IR and NMR studies were in agreement with those reported in the literature.[38]

Isolation of Ketol By-Product

The residue (oil) which remained after distillation of octalone was treated with absolute ether. The colorless crystalline solid which remained was filtered and air dried (0.5 g, yd 5%) m.p. 141-144°. The solid, after crystallization twice from ethyl acetate, melted at 146° (m.p. 147-148.5° reported[6]). This was identified as trans-ketol by spectroscopic means.

IR: $\lambda_{max}^{CDCl_3}$ 3570 cm^{-1} (OH), 1700 cm^{-1} (C=O), 966 cm^{-1} (C-O). The parent ion in the mass spectrum was at

97, 69, 55, 43, 41, 39.

71.43; H, 9.60. Found:

um Bromide[4] with the
by Cu^{++}

equipped with a mechan-
was placed Mg turnings
a free-flame under a
min. After the flask
nitrogen flow was
hydrofuran (150 ml)
funnel, followed by
f isopropenyl bromide
d the contents were
as continued until the
hanged to gray. A
g) in 40 ml of tetra-
one hour. The gray
am bath for 15 min by
reacted. The solution
an (200 ml), cooled to
ate (3.0 g) was added
10 g) in 50 ml THF
esulting solution was
ernight at room temp-
hen added to aqueous
) neutralized with

dilute NH_4OH to pH 8 at 0°. The aqueous solution was thoroughly extracted with ether, and the ether extract was filtered, washed with saturated NaCl, dried (Na_2SO_4) and distilled to give a viscous oil (12.0 g), b.p. range 102-106°at 2 torr. The IR spectrum (film) showed bands at 3077 (=C-CH-) 1695, 1718 (C=O), 1634 (C=C) and 899 cm^{-1} ($>C=CH_2$). The adduct was purified by column chromatography. The results of chromatographing 3.0 g of the Grignard addition product on 180 g of basic alumina (Brockmann Activity 1) are tabulated below: (total recovery: 2.61 g)

TABLE 2

CHROMATOGRAPHY OF ISOPROPENYL ADDUCT

Fraction Number	Eluting Solvent	Volume (ml)	Weight of Solute (in g)	Nature of Solute
1	Hexane	200	0.170	Colorless liquid
2	Hexane	200	0.170	Colorless liquid
3	Hexane	200	0.170	Colorless liquid
4	Hexane	200	0.170	Colorless liquid
5	5% Benzene-Hexane	200	0.130	Colorless liquid
6	5% Benzene-Hexane	100	0.130	Colorless liquid

Table 2 (continued)

Fraction Number	Eluting Solvent	Volume (ml)	Weight of Solute (in g)	Nature of Solute
7	10% Benzene-Hexane	300	0.05	Yellow liquid
8	10% Benzene-Hexane	100	0.05	Yellow liquid
9	10% Benzene-Hexane	100	0.05	Yellow liquid
10	10% Benzene-Hexane	200	0.05	Yellow liquid
11	20% Benzene-Hexane	300	0.06	Yellow liquid
12	20% Benzene-Hexane	300	0.06	Yellow liquid
13	30% Benzene-Hexane	300	0.2	Yellow liquid
14	30% Benzene-Hexane	300	0.2	Yellow liquid
15	50% Benzene-Hexane	300	0.150	Yellow liquid
16	50% Benzene-Hexane	300	0.150	Yellow liquid
17	50% Benzene-Hexane	300	0.150	Yellow liquid
18	80% Benzene-Hexane	300	0.220	Yellow liquid
19	80% Benzene-Hexane	300	0.220	Yellow liquid
20	80% Benzene-Hexane	300	0.220	Yellow liquid
21	Benzene	200	0.52	Yellow liquid

Table 2 (continued)

Fraction Number	Eluting Solvent	Volume (ml)	Weight of Solute (in g)	Nature of Solute
22	Benzene	200	0.52	Yellow liquid
23	5% EtOAC-Benzene	300	0.41	Yellow liquid
24	5% EtOAC-Benzene	300	0.34	Yellow liquid
25	5% EtOAC-Benzene	300	0.12	Yellow liquid
26	10% EtOAC-Benzene	300	0.240	Yellow liquid

The infrared and thin-layer characteristics of the various fractions are tabulated below.

TABLE 3

IR AND TLC CHARACTERISTICS OF CHROMATOGRAPHIC FRACTIONS

Fraction Number	IR ($\bar{\nu}$) (Neat)	Thin-layer[a] Chromatography
1 - 6	1695 (>C=O), 1630 (α,β-unsat.)	1 spot (R.F. value 4.2 cm)
7 - 10	3077 (=C-CH) 1695, 1718 (>C=O) 1634 (C=C) 899 (>C=CH_2)	2 spots (R.F. values 4.2 and 3.8 cms)

Table 3 (continued)

Fraction Number	IR ($\bar{\nu}$) (Neat)	Thin-layer[a] Chromatography
11 - 24	3077 (=C-CH), 1718 (C=O), 1634 (C=C), 899 ($>C=CH_2$)	1 spot (R.F. value 3.8 cm)
25	3488 (OH), 3077, 1718, 1634	2 spots (R.F. values 1.9 and 3.8 cms)
26	Not well defined	

[a]The TLC studies were done with silicar, the plates being activated by heating at 120° for 2 hours. They were developed with a 20%-EtOAC-Benzene solvent system.

The IR spectrum of combined fractions from 11-24 was identical with that of the spectrum obtained by isopropenyl adduct by Rand and Rao.[4]

Reaction of Vinyl-magnesium Bromide[4] with the Octalone Catalyzed by Cu^{++}

This reaction was carried out in the same manner as the reaction of isopropenylmagnesium bromide with 5 g of the octalone. The compound was found to decompose in the column (packed with neutral alumina, Brockmann Activity 1) during an attempt to purify it.

In another experiment a two mole excess of vinyl-magnesium bromide was used. This time, a spinning band column (18" x 6 mm id) was used for fractional distillation

but the fractions were found to contain α,β-unsaturated ketone (octalone).

Synthesis of Pyrrolidine Enamine of Octalone

The octalone (1.5 g, 0.01 mole) was dissolved in 50 ml of thiophene-free benzene, and pyrrolidine (2.13 g, 3 mole equivalent) was then added. Stirring was accomplished by means of a magnetic stirrer and the mixture was heated at reflux on a Glas-col mantle. The course of the reaction was followed by noting the amount of water collected in a moisture trap between the reaction flask and the condenser. Reflux was continued until no further separation of water was observed (20 hours), at which point the mixture was concentrated *in vacuo*. Residual oil was used directly to prepare the perchlorate salt.

Preparation of Perchlorate[40]

The aforementioned oil was dissolved in methanol (5 ml); 70% perchloric acid was added dropwise until the mixture was acidic to congo red. It was then left in a refrigerator at 5°C for 6 hours. Pale yellow crystals separated from the solution were filtered, washed with cold methanol and air dried, yield 1.3 g, m.p. 141°-143°. The recrystallized salt (from absolute methanol) melted at 144°. Analysis: Calculated for $C_{14}H_{22}ClNO_4$: C, 55.36; H, 7.25; N, 4.61; Cl, 11.70. Found: C, 55.03; H, 7.27; N, 4.78; Cl, 12.08.

Synthesis of N-(1-Cyclohexenyl)pyrrolidine

This was prepared in a manner similar to that used for the preparation of the pyrrolidine enamine of octalone. It was prepared from 0.01 mole of cyclohexanone, 3 mole equivalent of pyrrolidine and 50 ml of thiophene-free benzene. The mixture was refluxed for 4 hours under a water separator. The enamine was used directly after removal of solvent and excess amine for the preparation of the perchlorate. Addition of 70% perchloric acid to a solution of enamine in methanol gave the salt which crystallized as flakes. This was purified by recrystallization from methanol, m.p. 238-239° (lit.[40] 239-240°).

Synthesis of N-(1-Cyclohexenyl)morpholine

This was prepared according to the procedure of Hünig, et al.,[40] by refluxing a mixture of cyclohexanone (14.7 g, 0.15 mole), morpholine (15.7 g, 0.18 mole), p-toluene sulfonic acid and 30 ml of toluene in a flask fitted with a modified Dean-Stork apparatus and a reflux condenser. The reaction was allowed to proceed until one equivalent of water was collected (5 hours). Most of the toluene was removed at atmospheric pressure and the enamine distilled at 118°-120°/10 torr (lit.[41] 118°-120°/10 torr).

Calibration of Gas Chromatograph

An F and M chromatograph, model 700 was used. The instrument was equipped with a flame ionization detector,

external temperature programming control and Sargent S.R.G. recorder with digital integrator (Vidar model 6300). Helium was used as carrier gas. The flow rate of helium was 40 ml/min. The columns used were 0.317 cm x 182.8 cm with silicone liquid phase NO 10% UC-W98-90-100-S. The column temperature was maintained at 85°C isothermally for 15 min after injection followed by a programmed rise at 10°C/min up to 250°C. The recorder range was 1 mv. The injection port temperature was 250°C and the detector block temperature was 180-210°.

After adjusting the flow-rate and temperature of the inlet column and the detector, the ketones and enamines were run on the gas chromatograph. A retention time for each compound was established as reported in Table 4 and the response factor (R.F. = $(A_e/A_k)/(W_e/W_k)$, where A_e/A_k = ratio of the peak areas of enamine to ketone; W_e/W_k = ratio of the weight of enamine to ketone) for the enamines are given in Table 5.

The cyclic ketones and secondary amines used in the kinetic studies and the experimental conditions for the enamine formation are given in Table 6.

Removal of water formed during the condensation process (except the case of pyrrolidine enamine) was achieved by having an adapter to hold barium oxide (held on a filter paper) between the reaction flask and the condenser.

TABLE 4

RETENTION TIMES OF KNOWN COMPOUNDS

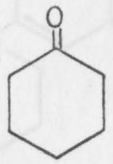
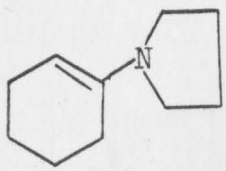
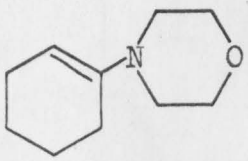
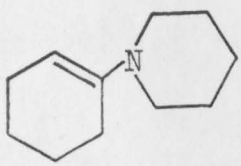
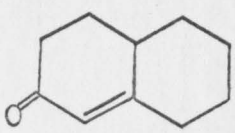
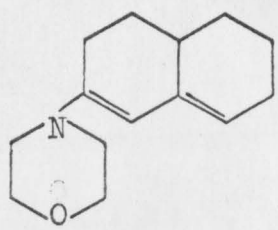
Compounds Run on G.C.	Programmed Temp. (10°C/min)	Retention Time in Min.
	50 - 200	4.0
	50 - 200	10.5
	50 - 200	10.6
	50 - 200	10.6
	85 - 250	7.3
	85 - 250	13.1

Table 4 (continued)

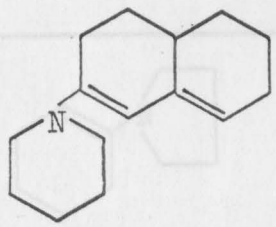
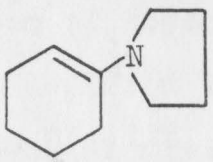
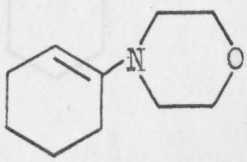
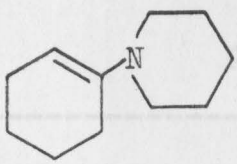
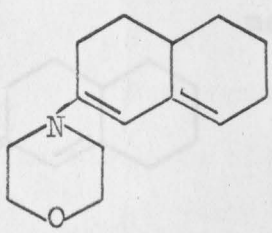
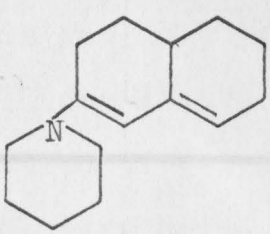
Compounds Run on G.C.	Programmed Temp. (10°C/min)	Retention Time in Min.
	85 - 250	13.0

TABLE 5

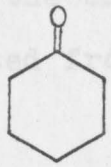
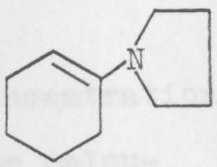
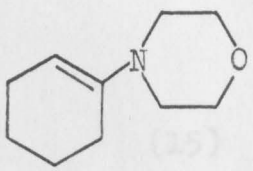
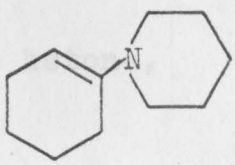
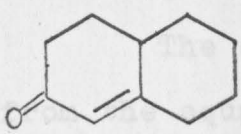
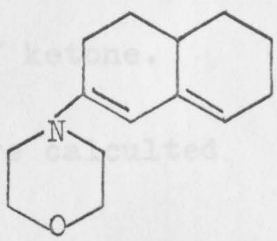
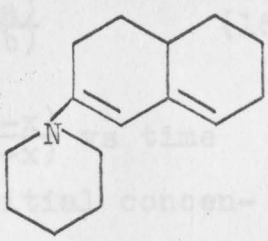
RESPONSE FACTORS

Enamine	W_e [a]	W_k [b]	Response Factor
	0.324	0.324	1.03
	0.324	0.324	1.02
	0.324	0.324	1.02
	0.5	0.5	1.01
	0.5	0.5	1.01

a) W_e = mass of enamine in grams.
b) W_k^e = mass of ketone in grams.

TABLE 6

REACTION CONDITIONS (FOR KINETICS OF ENAMINE FORMATION)

Cyclic Ketone 0.0033 mole	Secondary Amine 0.0099 mole	Solvent (5 ml)	Temp.	Enamine
	pyrrolidine	benzene	24°C	
	morpholine	toluene	110°C	
	piperidine	toluene	110°C	
	morpholine	toluene	110°C	
	piperidine	toluene	110°C	

Kinetic Measurements

The time of mixing was taken as zero time. The formation of enamine during the reaction was followed at known time intervals by running the reaction mixture on the gas chromatograph and measuring the relative peak areas of ketone to enamine.

From the peak areas was obtained the concentration of the enamine (at various intervals). This was calculated from the equation

$$\frac{A_e}{A_k} \text{ R.F.} = \frac{E}{0.6-E} \qquad (15)$$

where A_e/A_k = relative peak areas of enamine to ketone,

R.F. = response factor,

E = molarity of enamine,

0.6 = refers to initial molarity of ketone.

The second-order rate constants were calculted from the equation

$$\log \frac{(a-x)}{(b-x)} = \frac{(a-b)k_2 t}{2.303} + \log \frac{(a)}{(b)} \qquad (16)$$

This was done by plotting a graph of $\log \frac{(a-x)}{(b-x)}$ vs time (t) (see Figures 9 - 13); where a is the initial concentration of ketone and b is the initial concentration of secondary amine. Straight lines were obtained

with slopes equal to $k_2 \frac{(a-b)}{2.303}$.

$$\text{The rate constant } k_2 = \frac{\text{slope} \times 2.303}{a-b} \qquad (17)$$

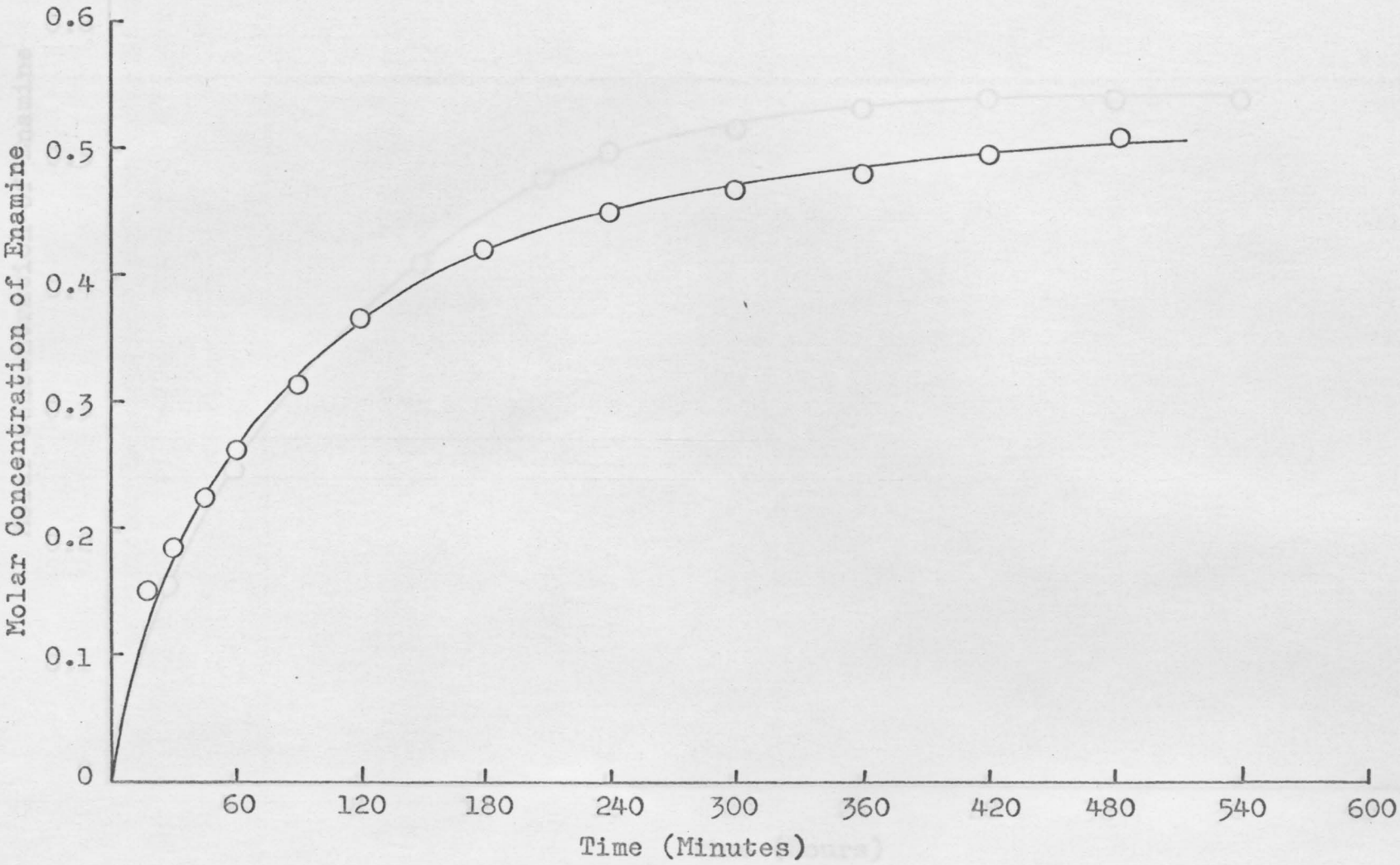


Fig. 7.--Formation of morpholine enamine of cyclohexanone from morpholine and cyclohexanone at 110°.

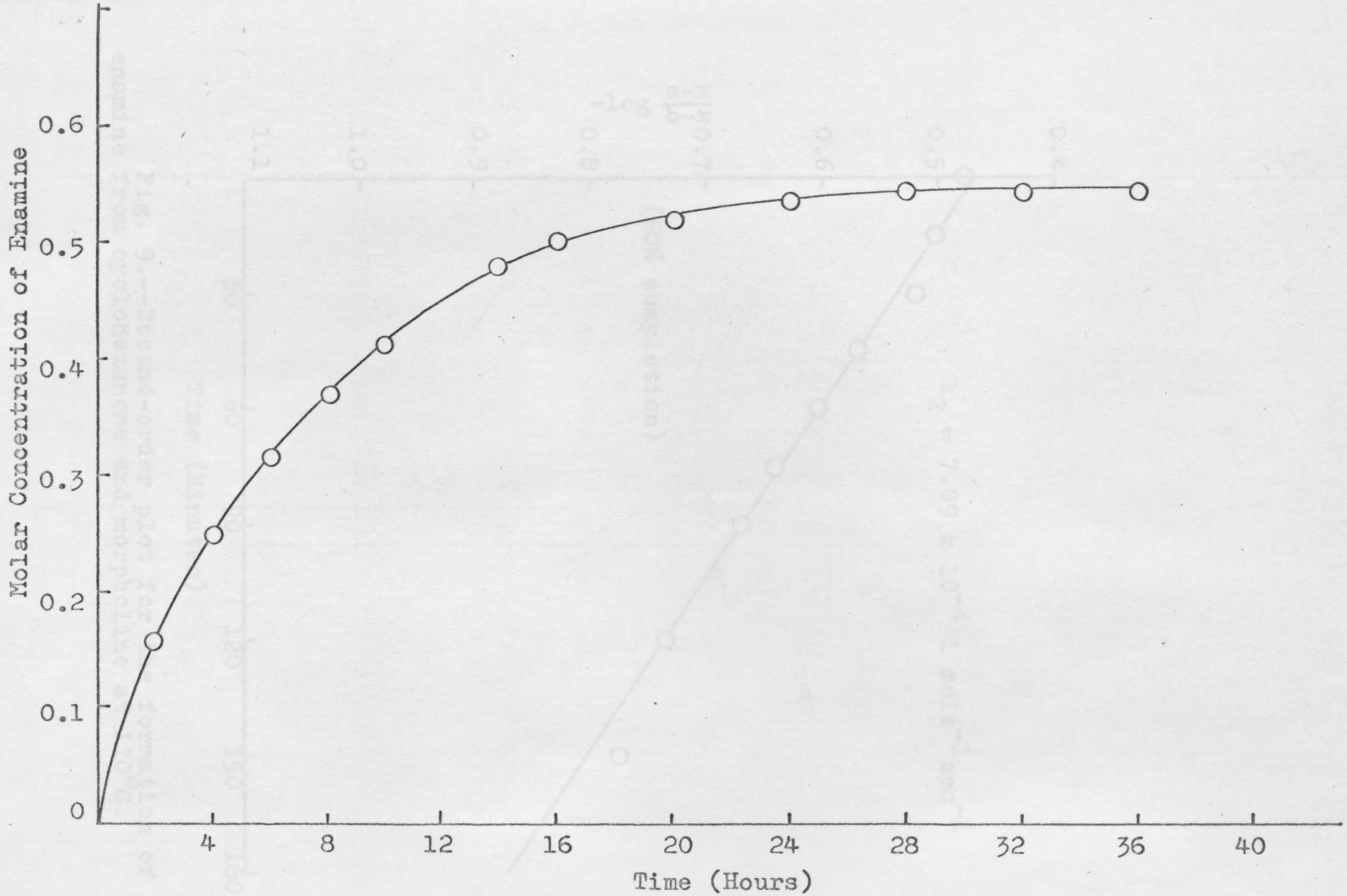


Fig. 8.--Formation of morpholine enamine of octalone from octalone and morpholine at 110°C.

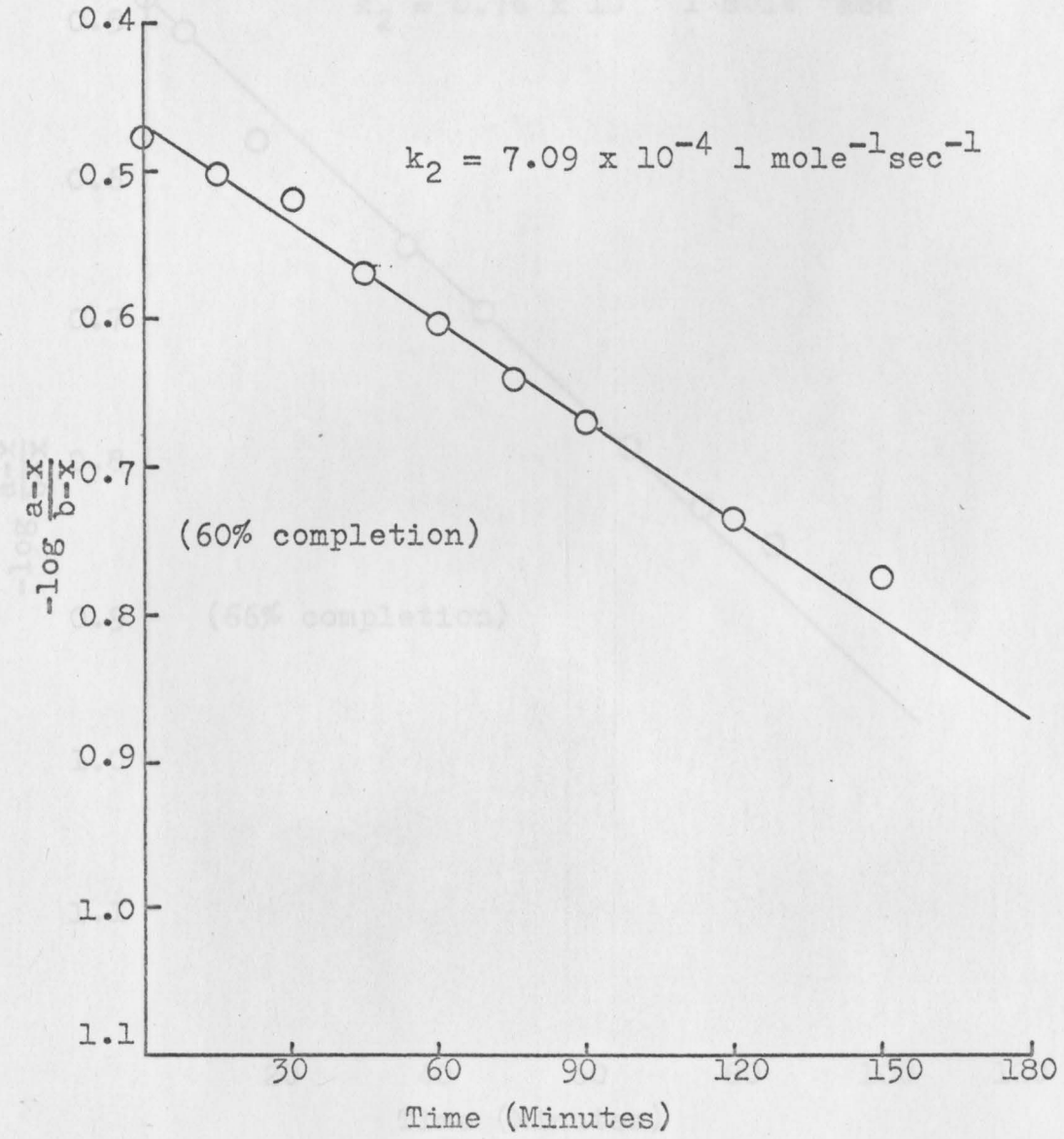


Fig. 9.--Second-order plot for the formation of enamine from cyclohexanone and morpholine at 110°C.

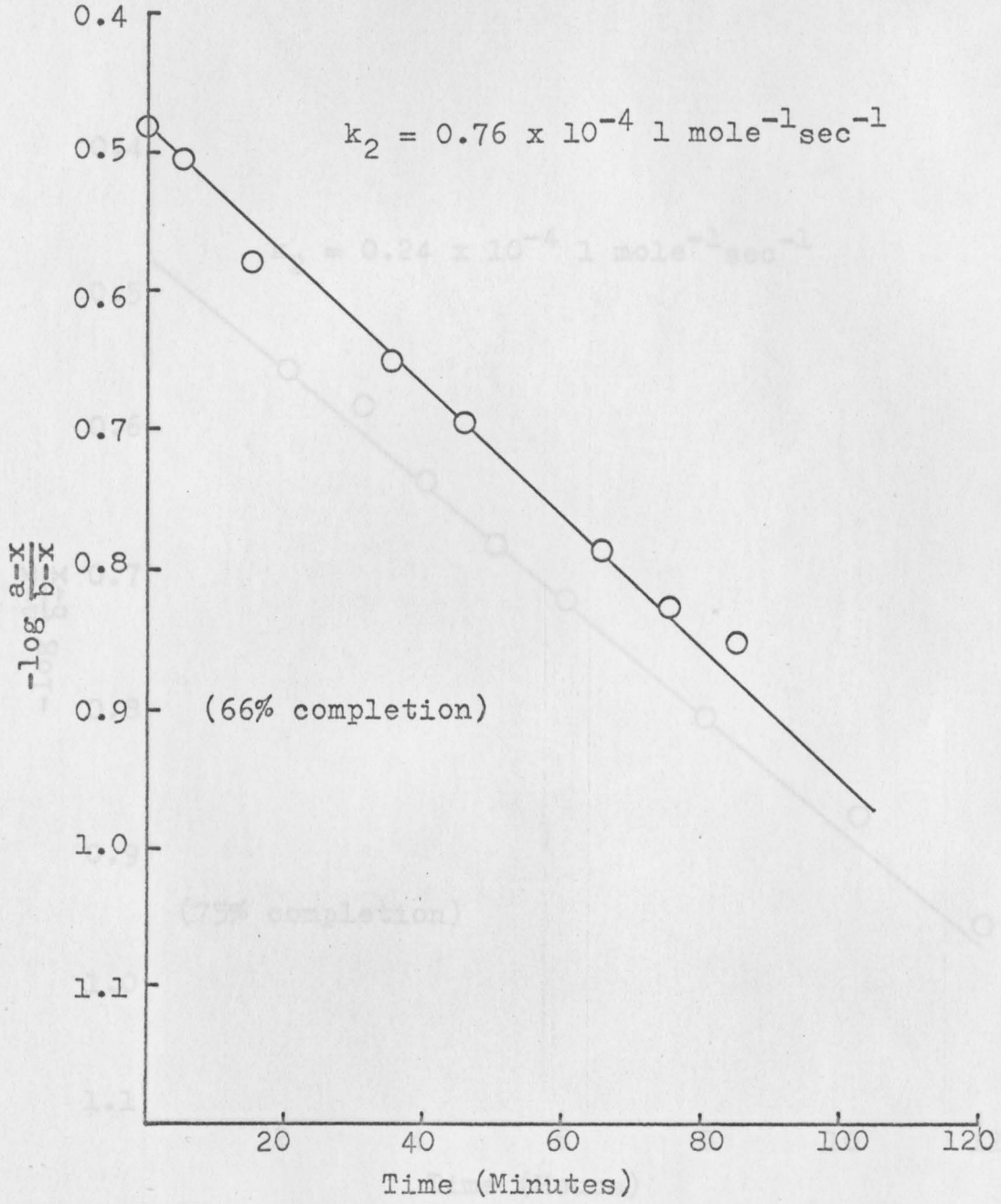


Fig. 10.--Second-order plot for the formation of enamine from cyclohexanone and piperidine at 110°C.

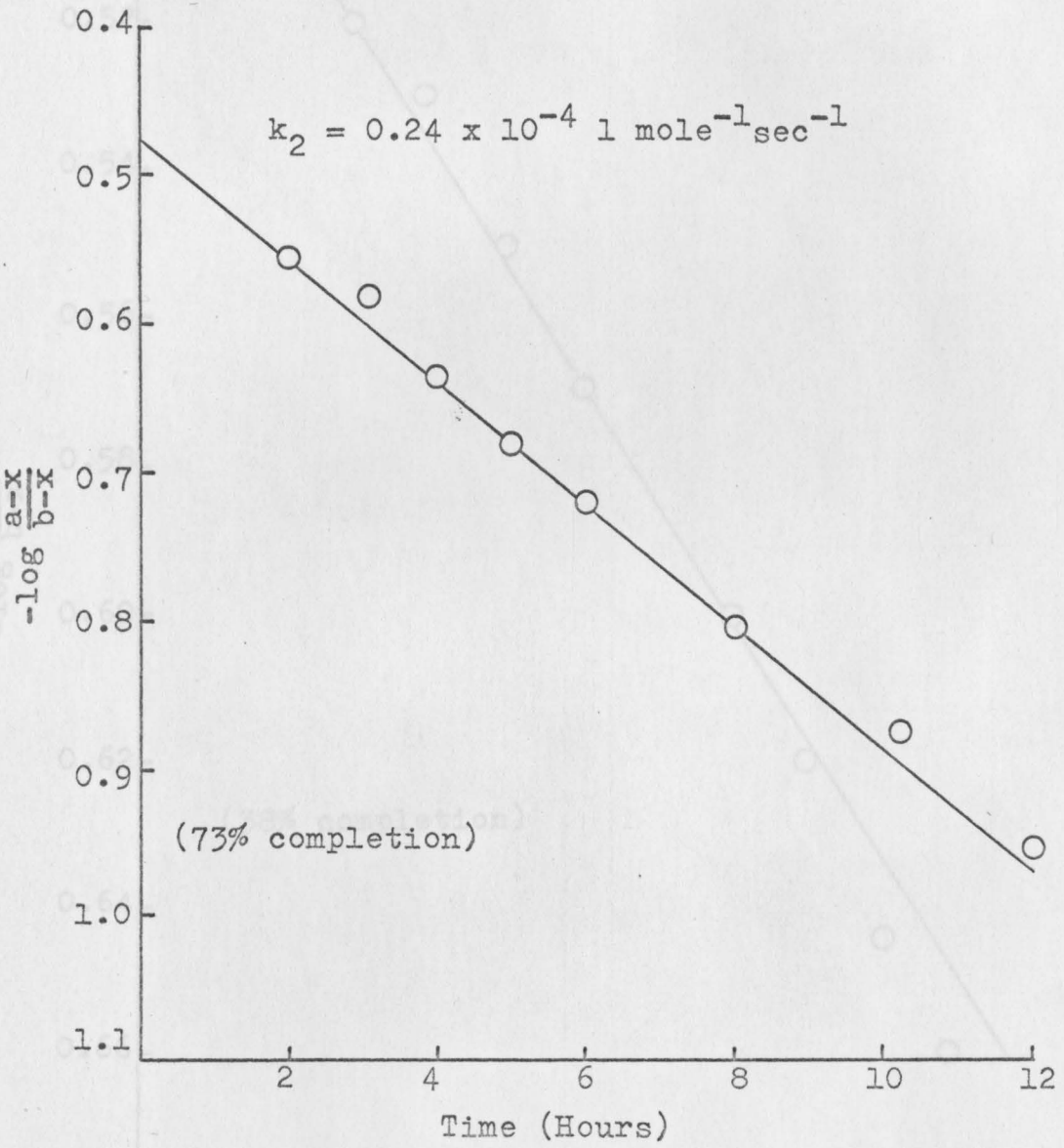


Fig. 11.--Second-order plot for the formation of enamine from octalone and morpholine at 110°C.

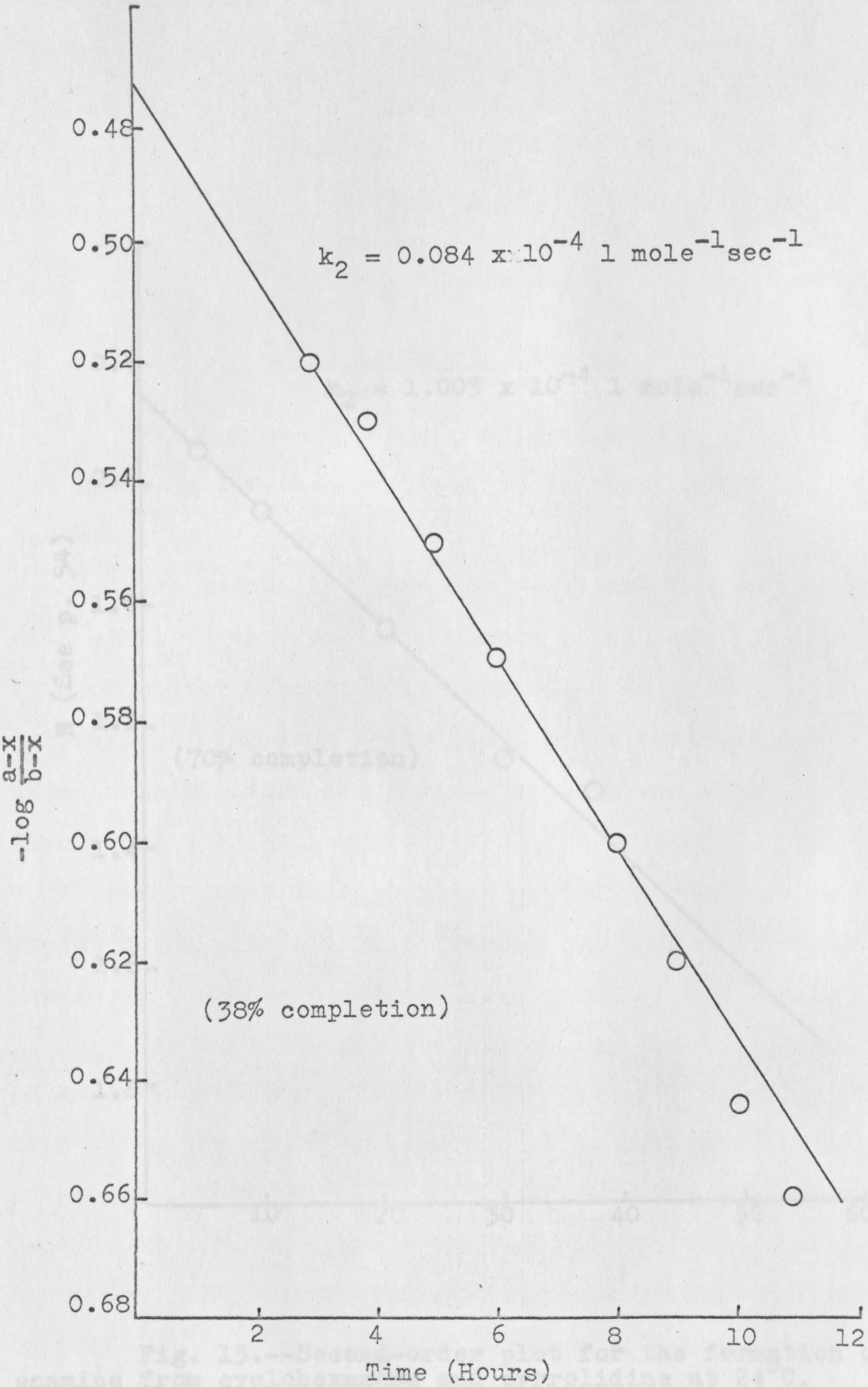


Fig. 12.--Second-order plot for the formation of enamine from piperidine and octalone at 110°C.

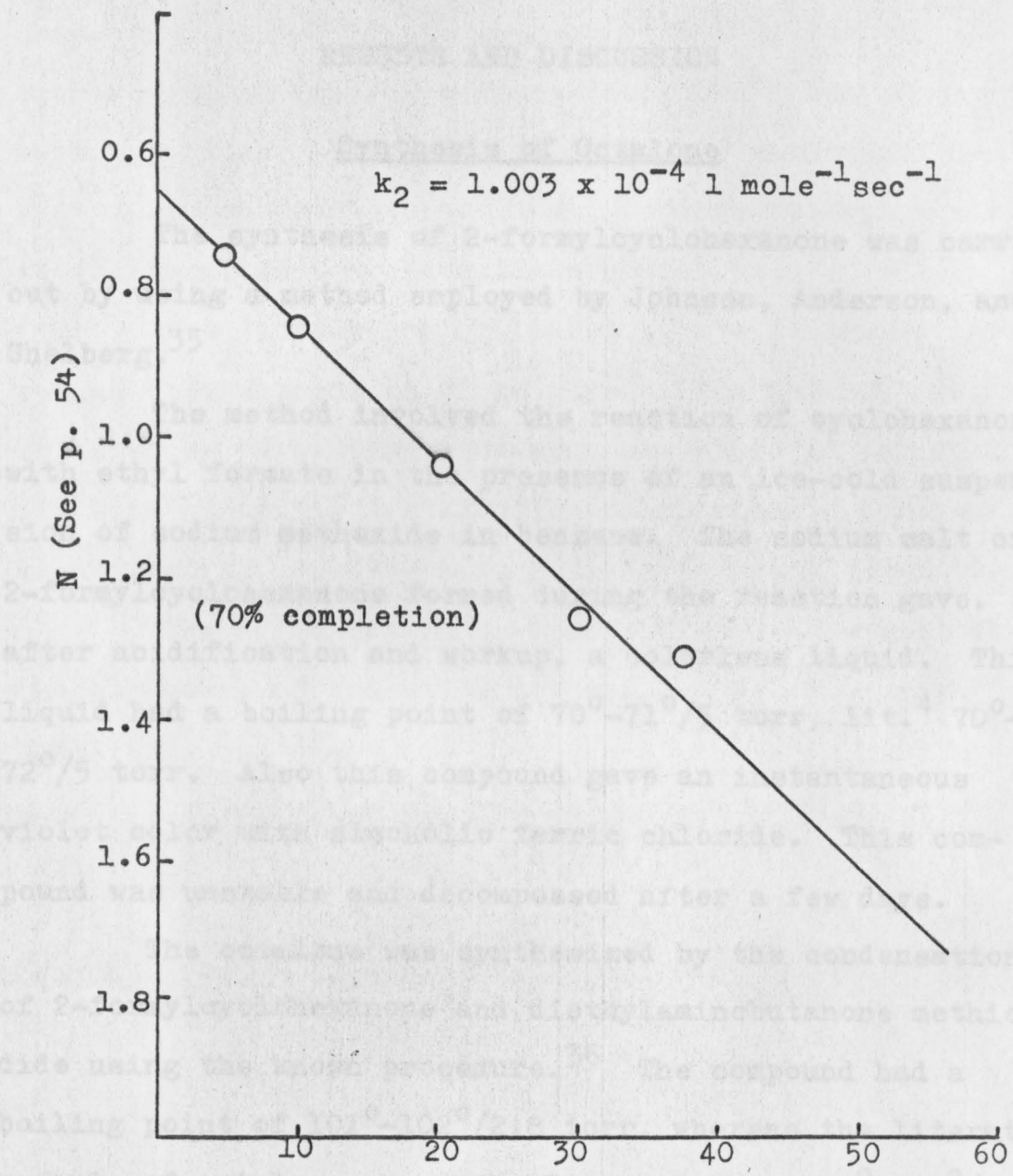


Fig. 13.--Second-order plot for the formation of enamine from cyclohexanone and pyrrolidine at 24°C.

CHAPTER IV

RESULTS AND DISCUSSION

Synthesis of Octalone

The synthesis of 2-formylcyclohexanone was carried out by using a method employed by Johnson, Anderson, and Shelberg.[35]

The method involved the reaction of cyclohexanone with ethyl formate in the presence of an ice-cold suspension of sodium methoxide in benzene. The sodium salt of 2-formylcyclohexanone formed during the reaction gave. after acidification and workup, a colorless liquid. This liquid had a boiling point of 70°-71°/5 torr, lit.[4] 70°-72°/5 torr. Also this compound gave an instantaneous violet color with alcoholic ferric chloride. This compound was unstable and decompossed after a few days.

The octalone was synthesized by the condensation of 2-formylcyclohexanone and diethylaminobutanone methiodide using the known procedure.[36] The compound had a boiling point of 101°-102°/2.8 torr, whereas the literature reports of octalone show a boiling point of 101°-102°/ 2-3 torr. In the present observation the compound (boiling at 101°-102°/2.8 torr) showed a hydroxyl band at 3600 cm^{-1}. The formation of a hydroxylic compound by the same reaction was not reported by the previous studies.[36] However, in

the present study the purification of octalone was effected by repeated fractional distillation. The initial fractions (b.p. 100°-101°/2.8 torr) were free from alcoholic compound as shown by the absence of the OH band in the IR spectrum. The later fractions (b.p. 102°) showed a hydroxyl band. At this stage the exact nature of the hydroxylic compound is not known, and no attempt was made to characterize the alcoholic product formed.

The above reaction led us to the following interesting observation. A white crystalline material was obtained by trituation with absolute ether of the residual oil left after the distillation of octalone. This was identified by spectroscopic studies as trans ketol (i).

The following comparison was used in establishing the structure of the white crystalline solid as trans ketol (i).

TABLE 7

KETOL: A COMPARATIVE STUDY

	Reported[a]	Observed
m.p.	147-148°	147°
IR	3570 (OH) 1700 (C=O) 966 cm^{-1} (C-O) ($\bar{\nu}CHCl_3$)	3570 (OH) 1700 (C=O) 966 cm^{-1} (C-O) ($\bar{\nu}CDCl_3$)
Mass spectrum	Not reported	Parent ion peak $\frac{m}{e}$ 168
Analysis[b] for $C_{10}H_{18}O_2$	Carbon 71.6 Hydrogen 9.6	Carbon 71.61 Hydrogen 10.05

[a] See reference 41.
[b] Calculated for C = 71.39, H = 9.59

In this connection we would like to point out that the formation of trans ketol during the synthesis of octalone by the Robinson annelation reaction was also reported by Johnson and coworkers.[41]

It is hypothesized that during the synthesis of octalone both the cis and trans ketols are formed as intermediate products. The cis product is labile and undergoes facile elimination of a molecule of water to afford octalone. The trans ketol is comparatively more stable and hence does not easily dehydrate to form octalone. This facilitates the isolation of trans ketol from the reaction mixture.

The scheme employed in our present work for the separation of trans ketol is explained as follows.

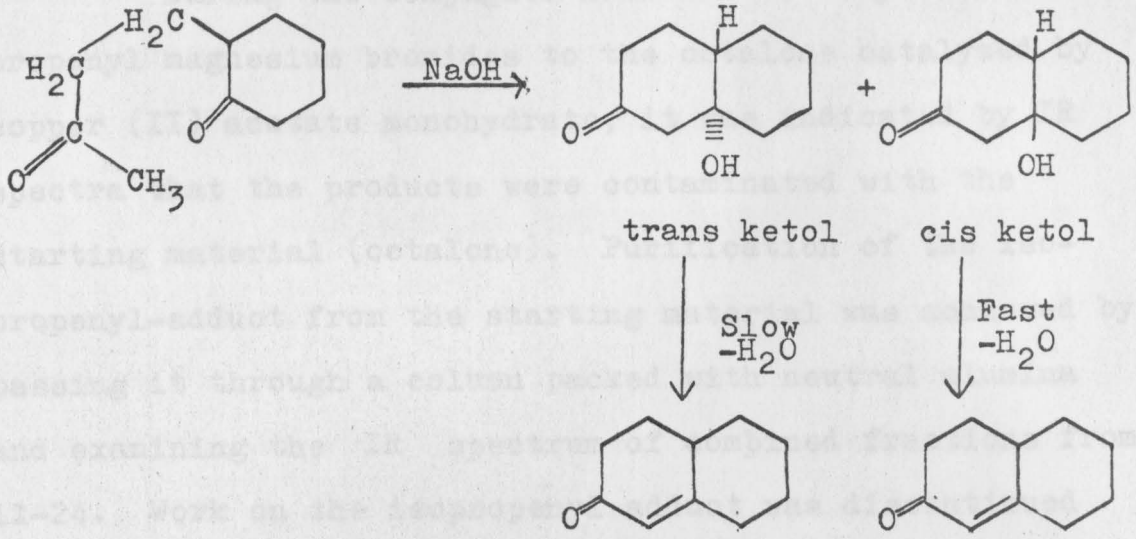
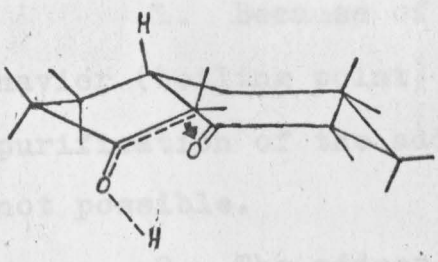


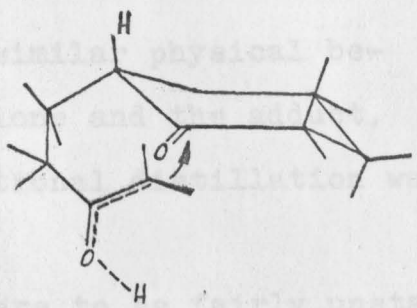
Fig. 14.--Scheme for the separation of trans-ketol

Transition State Leading to trans ketol



(ix)

Transition State Leading to cis ketol



(x)

A comparison of the transition states of the trans and cis ketols as given above demonstrates that the transition state in the case of trans ketol is the more stable and hence the isolation of trans ketol is favored.

Reaction of Vinyl and Isopropenyl Magnesium Bromides with Octalone Catalyzed by Cu^{++}

During the conjugate addition of vinyl and isopropenyl magnesium bromides to the octalone catalyzed by copper (II) acetate monohydrate, it was indicated by IR spectra that the products were contaminated with the starting material (octalone). Purification of the isopropenyl-adduct from the starting material was achieved by passing it through a column packed with neutral alumina and examining the IR spectrum of combined fractions from 11-24. Work on the isopropenyl adduct was discontinued due to the lack of pure isopropenyl bromide needed to prepare the required amount of the adduct for the rearrangement studies.

However, certain difficulties arose in the purification of the vinyl adduct.

1. Because of the nearly similar physical behavior (boiling point) of the octalone and the adduct, purification of the adduct by fractional distillation was not possible.

2. The adduct, which appears to be fairly unstable, was found to decompose when passed through a column packed with neutral alumina so that purification through column chromatography could not be achieved, at least with neutral alumina.

It was decided to try to find a derivative of one of the compounds which would show a sufficient difference

in the rates of formation to allow separation. This was achieved by using enamine formation in which different rates of formation of derivatives was observed. For this cyclohexanone and octalone were used as model compounds for saturated and α,β-unsaturated ketones.

Kinetics of Enamine Formation

No clear picture of the mechanism and order of "enamine formation" is available from the existing literature on the subject. The purpose of the present research was ultimately limited to the investigation of the relative rates of enamine formation of cyclohexanone and octalone with the secondary amines pyrrolidine, morpholine and piperidine, and the determination of the kinetic order of these reactions.

The rate of enamine formation fits the second order expression

$$\frac{d(E)}{dt} = k_2 (C)(A) \qquad (18)$$

where (E) = concentration of enamine,
(C) = concentration of ketone,
(A) = concentration of secondary amine,
k_2 = second-order rate constant.

The closeness of the fit is indicated in Figures 9 - 13 which show the second order plots for the enamine formation of cyclic ketones with secondary amines in

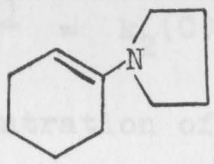
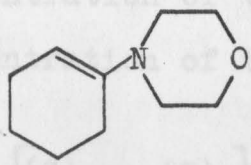
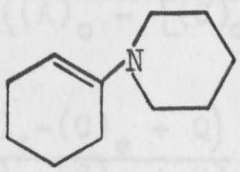
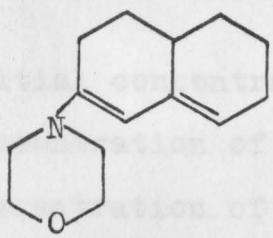
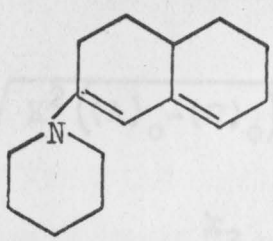
refluxing toluene. The initial concentrations of cyclic ketone and secondary amines, respectively, were 0.6 mole/liter and 1.8 mole/liter. The rate curve is a straight line up to 75% completion. Table 8 shows the values of the rate constants for the cyclic ketones studied for the enamine formation.

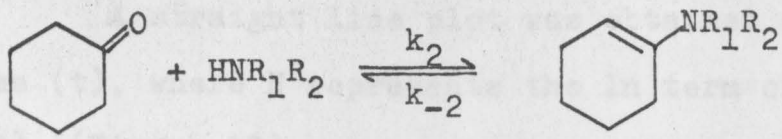
The determination of the rate constants in the case of morpholine and piperidine required that the reaction be carried out at a temperature of about 110°C (refluxing toluene). At this temperature it was possible to remove the water by having an adsorbent (barium oxide) between the reaction flask and the reflux condenser. By removing the water formed, the possibility of a reversible reaction was avoided. It was therefore possible to determine the second order rate constants given in Table 8.

In the case of enamine formation of cyclohexanone with pyrrolidine it was observed that the reaction starts even at room temperature. It was nct possible to remove water as in the above cases. Therefore the water formed reacted with the enamine and the reaction is reversible. Hence only the equilibrium constant could be obtained. If it is assumed that the reverse reaction is second-order, then the second-order rate constant can be calculated from the equilibrium constant[42] as follows.

TABLE 8

VALUES OF SECOND-ORDER RATE CONSTANTS

Temperature	Enamine	$k_2 \times 10^4$ (1 $mole^{-1} sec^{-1}$)
24°C		1.003
110°C		7.09
110°C		0.76
110°C		0.24
110°C		0.084



(19)

$$\frac{d(E)}{dt} = k_2(C)(A) - k_{-2}(E)(H_2O) \qquad (20)$$

where (E) = concentration of the enamine,

(C) = concentration of the ketone,

(A) = concentration of the secondary amine.

$$K = \frac{\left[(C)_o - (C)_e\right]^2}{(C)_e\left((A)_o - \left[(C)_o - (C)_e\right]\right)} = \frac{k_2}{k_{-2}} \qquad (21)$$

$$\ln \frac{\left((C)_o-(C)_e\right)\left((C)_t-(C)_e + Q\right)}{\left((C)_t-(C)_e\right)\left((C)_o-(C)_e + Q\right)} = (k_2-k_{-2})Qt \qquad (22)$$

where $(C)_o$ = initial concentration of ketone,

$(C)_e$ = concentration of ketone at equilibrium,

$(C)_t$ = concentration of ketone at time t,

$(A)_o$ = initial concentration of amine,

K = equilibrium constant.

$$Q = \frac{1}{K-1}\sqrt{K^2\left((A)_o-(C)_o\right)^2 + 4\,(C)_o(A)_oK} \qquad (23)$$

$$K = \frac{k_2}{k_{-2}} \qquad (24)$$

A straight line plot was obtained of N versus time (t), where N represents the ln term of the equation (22), (Figure 13).

$$\text{The slope} = (k_2 - k_{-2})Q \qquad (25)$$

$$k_2 = (K)(k_{-2}) \qquad (26)$$

The absolute values of the second order rate constants are of prime interest in this study (see Table 8).

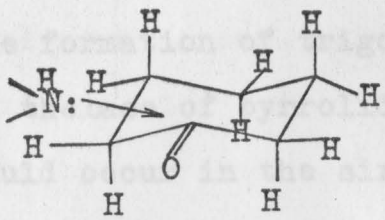
Experiments for determining the second order rate constants for the reactions of pyrrolidine, morpholine, and piperidine with cyclohexanone showed that the reaction rate constant in the case of pyrrolidine is much greater than that of morpholine and that of morpholine is greater than that of piperidine.

When the same compounds were reacted with octalone the same order of reaction rates was observed.

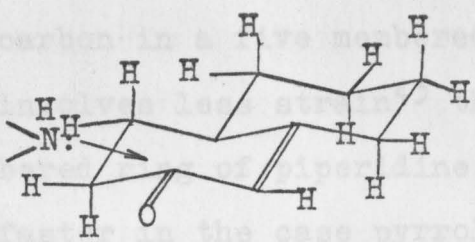
It was also observed that the rate constant in the case of cyclohexanone is greater than that of octalone by about 30 and 10 times respectively for morpholine and piperidine.

Stork *et al.*,[11] conducted experiments with the same secondary amines by using cyclopentanone, cyclohexanone, and cycloheptanone. Their results regarding the order of reactivity of secondary amines coincide with our observation. However, they did not measure the rate constants for the enamine formation and the reaction order.

The observed rates may be explained by considering steric and electronic controls. Octalone has a double bond in the 1,9-position. The secondary amine has a lone pair of electrons on the nitrogen atom. During the reaction the approach of amine moiety towards the carbonyl carbon atom of the octalone is resisted by a repulsive force created due to the presence of π-electron system in the octalone and the lone pair of electrons on the nitrogen atom of the amine. For this reason, the reaction may be slower in the case of octalone.

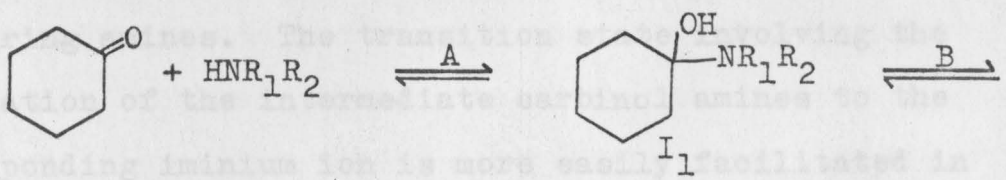


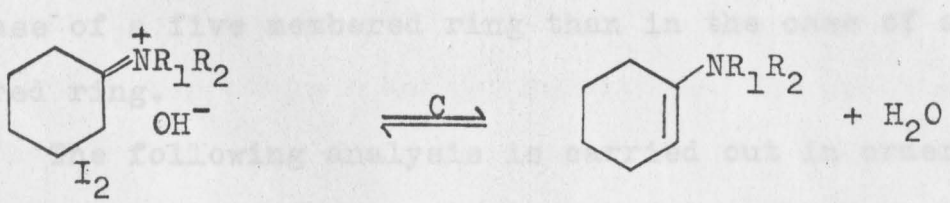
(xi)



(xii)

The mechanism for the enamine formation involves the three equilibrium steps, A, B, C.





The ease of formation of the enamines depends on the basicity and structure of secondary amines as well as the structure of the ketone. This mechanism involves the formation of an iminium ion as the transition state. If this is assumed to be the rate-determining step, we can explain why pyrrolidine reacts faster than morpholine or piperidine.

The difference in reactivity of ketones with secondary amines may be explained similarly. The basicity and steric environment of pyrrolidine and piperidine are quite similar and the difference in their rates may be attributed to the different rates of the dehydration step. The formation of trigonal carbon in a five membered ring in the case of pyrrolidine involves less strain[43] than would occur in the six membered ring of piperidine. Hence the reaction rate is much faster in the case pyrrolodine.

The above observation coincides with those of Stork et al.[11]

In the case of enamine formation from octalone there is a creation of a double bond exocyclic to the heteroring amines. The transition state involving the dehydration of the intermediate carbinol amines to the corresponding iminium ion is more easily facilitated in the case of a five membered ring than in the case of a six membered ring.

The following analysis is carried out in order to provide a better insight as to which of the three steps

contributes in determining the rate constant. One can visualize that the environment of the carbonyl group in both cyclohexanone and octalone is the same and that the attack of the amine moiety is equatorial because of the steric approach control factors. Hence one can predict that the rate-determining step may not be the step A, i.e., aminol formation.

On the other hand, the step B in the reaction involves the formation of an iminium ion and at this stage there is a need to consider the steric factors. From the point of view of steric factors there is considerably more opposition from the axial protons in the case of aminol derived from octalone than in the case of the cyclohexanone aminol. Hence the slow reaction in the case of octalone may be due to the steric factors.

In an experiment conducted with cyclohexanone and octalone for the enamine formation during the present work, it was observed that the reaction followed second-order kinetics. This indicates that one of the steps A, B or C should be the rate-determining step. However, the kinetic measurements cannot show unequivocally whether the formation of carbinol amine or iminium ion or the dehydration step (step C) is a rate-determining step. In order to explain the observed second-order kinetics it was assumed that the steps A and C (forward and reverse) are much faster than step B and the step B is the rate-determining step as shown below.

$$\frac{d(E)}{dt} = k(I_1) \tag{27}$$

$$= k_A k_B (C)(A)$$

$$\text{Since } K_A = \frac{(I_1)}{(C)(A)} \tag{28}$$

$$(I_1) = k_A (C)(A)$$

(E) = concentration of enamine,

(I_1) = carbinol-amine concentration,

(C) = concentration of ketone,

(A) = concentration of secondary amine.

Conclusion

The model compounds employed in this research showed a considerable difference in the rates of enamine formation. These results may be extended to allow the separation of the vinyl adduct from the octalone.

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