THE EFFECT OF CHANGES

IN STRUCTURE OF THE REACTANTS ON THE RATE

OF ENAMINE FORMATION

By

James S. Marchese

APPROVAL SHEET

Title of Thesis: The Effect of Changes in Structure of the
                   Reactants on the Rate of Enamine Formation

Name of Candidate: James Salvatore Marchese
                     Doctor of Philosophy, 1964

Thesis and Abstract Approved: _Ernest F. Pratt_____
                              Ernest F. Pratt
                              Professor
                              Chemistry

Date Approved: _May 9, 1964_

ABSTRACT

Title of Thesis: The Effects of Changes in Structure of the
                   Reactants on the Rate of Enamine Formation.

James Salvatore Marchese, Doctor of Philosophy, 1964.

Thesis Directed by: Professor Ernest F. Pratt.

It has been found that the rate of formation of a wide
variety of enamines can be accurately determined by observ-
ing the rate at which the by-product water collects in a Dean-
Stark trap. On the basis of the results observed upon vari-

$$\bigcirc\!\!=\!O + \bigcirc\!\!NH \quad \xrightarrow{\text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}} \quad \bigcirc\!\!=\!N\bigcirc + H_2O$$
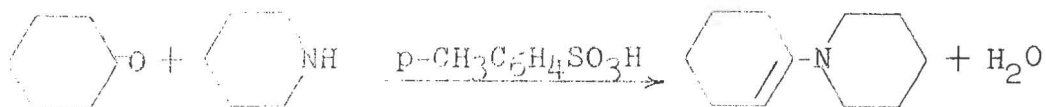
ing the reactant ratio, the catalyst concentration and the
temperature, 0.125 mole of carbonyl compound, 0.375 mole of
amine and 0.001 mole of p-toluenesulfonic acid dissolved in
sufficient benzene to give a total volume of 500 ml. were
employed in the standard procedure. The solution of react-
ants was heated under reflux in an apparatus fitted with a
water trap and frequent readings of time and water volume
were taken until the reaction was complete. Nearly quanti-
tative (98 to 100%) yields of water were ordinarily obtained
and 85 to 100% yields of enamine were usually isolated. As
the structure of the carbonyl component was varied an ex-

tremely wide range of reaction rates was encountered. The
relative reactivity of many of these compounds had not been
determined previously.

It was found that the rate decreased markedly among
cyclic ketones as the ring was expanded from five to six to
seven members and also when the methyl group of methylcylo-
hexanones were shifted from the four to the three to the two
position. Steric effects appear to be responsible for these
rate differences. Somewhat unexpectedly α-tetralone did not
react while β-tetralone reacted smoothly.

Although the literature contains very little information
on the formation of enamines of diketones a number of these
were converted to the mono-enamines very smoothly. The rate
decreased in the sequence, 1,3-cyclohexanedione, dimedone,
acetylacetone, benzoylacetone and 2-acetylcyclopentanone.
Some evidence that ketones having planar structures reacted
faster than those with non-planar structures was found, but
no obvious correlation between degree of enolization and rate
of reaction was observed.

The reaction of acetophenones was much improved when the
reaction temperature was changed from 82° to 112° by using
toluene as a solvent. As the electron attracting ability of
the para substituent was increased in the order, CH_3, H, Cl
and NO_2 the rate consistently increased. Phenylacetone re-
acted smoothly under the standard conditions, but heptanone-2

gave only a 27% yield of water in five days. The importance of steric factors is emphasized by the fact that cyclohexanone gave a 98% yield of water in two hours.

Typical aliphatic aldehydes reacted so rapidly that in order to increase the accuracy of the rate measurements 0.000125 mole of catalyst was used in place of the standard 0.001 mole. The order of decreasing rate was phenylacetaldehyde, n-heptaldehyde, cyclohexylcarboxaldehyde and 2-ethylheptaldehyde. It is apparent that the rate decreasing effect of chain branching at the alpha position diminishes when the branches are joined into a ring. The results for phenylacetaldehyde and phenylacetone indicated that aldehydes react over one thousand times as fast as ketones.

The rate of formation of enamines from cyclohexanone and a variety of amines was also determined under the standard conditions. Shifting a methyl group on the piperidine ring from the four to the three to the two position greatly decreased the rate and pyrrolidine reacted faster than both piperidine and hexamethylene imine. Morpholine and especially N-methylpiperazine reacted much faster than piperidine while n-butylmethylamine reacted most slowly of all the amines mentioned.

In only a few special cases was integral order kinetics obtained. The results can, however, be quite well correlated

with a straightforward mechanism if it is assumed that both
the step in which the amine adds to the carbonyl group and
the step in which this addition product is dehydrated ordin-
arily affect the overall rate.

ACKNOWLEDGMENTS

TABLE OF CONTENTS

TABLE OF CONTENTS - Continued

HISTORICAL

The Preparation and Reactions of Enamines

The term enamine was coined by Wittig[1] to show the analogy between the tautomerism of β-imino ketones

$$\underset{\text{imine}}{R\overset{O}{\overset{\|}{C}}CH_2\overset{NH}{\overset{\|}{C}}CH_3} \rightleftharpoons \underset{\text{enamine}}{R\overset{O}{\overset{\|}{C}}CH=\overset{NH_2}{\overset{|}{C}}CH_3}$$

and keto-enol tautomerism.

$$\underset{\text{ketone}}{R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3} \longrightarrow \underset{\text{enol}}{R\overset{O}{\overset{\|}{C}}CH=\overset{OH}{\overset{|}{C}}CH_3}$$

However, in present day usage the term, enamine signifies any α,β-unsaturated tertiary amine.

$$R_1 - \overset{R_2}{\overset{|}{C}} = \overset{R_3}{\overset{|}{C}} - \overset{R_4}{\overset{|}{N}} - R_5$$
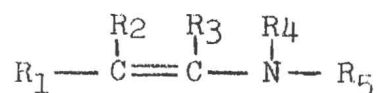
Enamines have been prepared by a number of methods:

a) The condensation of an aldehyde or ketone with a secondary amine[2]

$$\text{(cyclohexanone)}=O + \text{(piperidine)}NH \xrightarrow[\substack{\text{anhyd.}\\ \text{Ca(OH)}_2\\ \text{R.T.}}]{\substack{\text{anhyd.}\\ \text{ether}}} \text{(enamine)}-N + H_2O$$
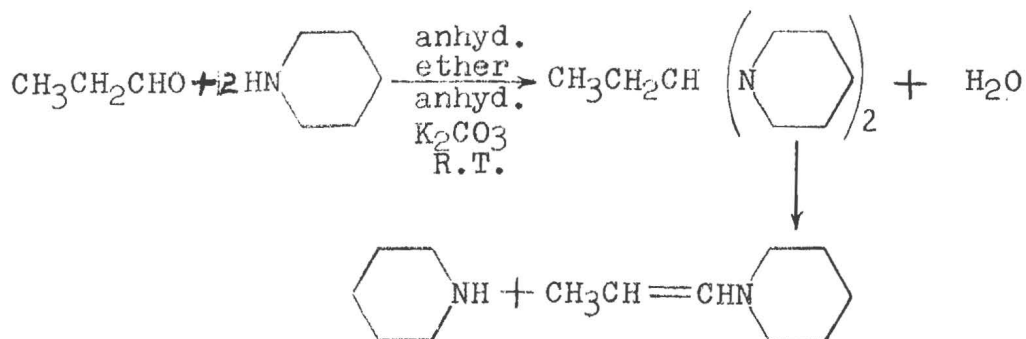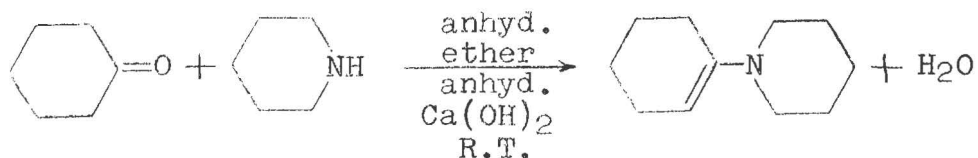
in the presence of a drying agent to take up the water produced. This yields the enamine directly for ketones, though in low yields and the gem-diamine in the case of aldehydes. Distillation of the gem-diamine yields the desired enamine.

b) The acid catalyzed condensation of ketones or aldehydes with secondary amines in benzene, toluene or xylene. In this method the by-product water is azeotropically removed.[3]

$$\text{(steroid ketone, OH)} \xrightarrow[\substack{\text{benzene}\\ \text{P.T.S.}}]{\text{pyrrolidine}} \text{(enamine, OH)} + H_2O$$
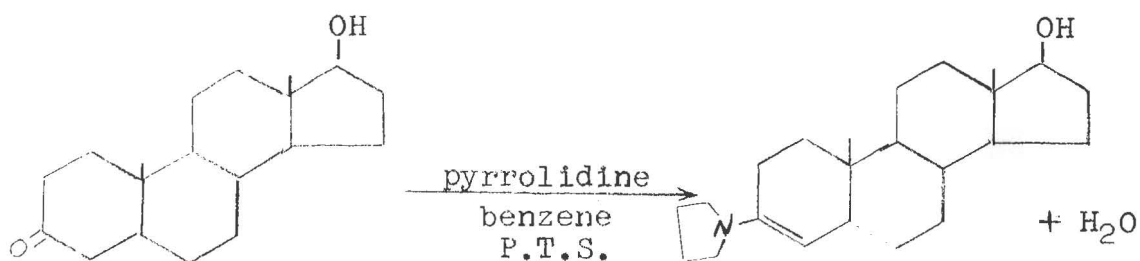
p-Toluenesulfonic acid is the most generally used catalyst but sulfonic acid resins have also found utility.[4] This azeotropic method is the most general and flexible of all those to be discussed.

c) A modification of the preceding method employs a Soxhlet extractor and molecular sieves.[5]

d)   An example of a method of limited utility is the oxidation of a lupin alkaloid, quinolizidine with 5% mercuric acetate[6] in aqueous acetic acid.
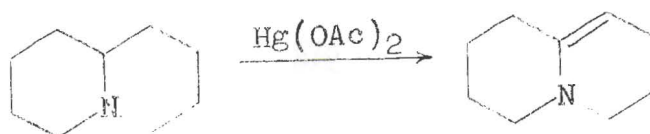
e)   Another specialized method is the reduction[7] of julolidine to Δ^5-tetrahydrojulolidine by lithium in n-propylamine.
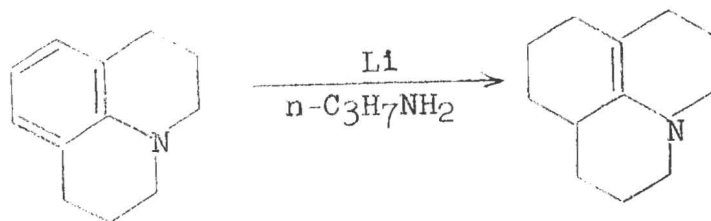
f)   Pyrolysis of choline[8] has been used to prepare dimethylvinyl amine.
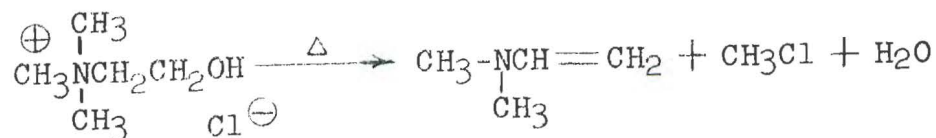
g)   Enamine intermediates have also been detected in metal-ammonia reducing systems.[9]
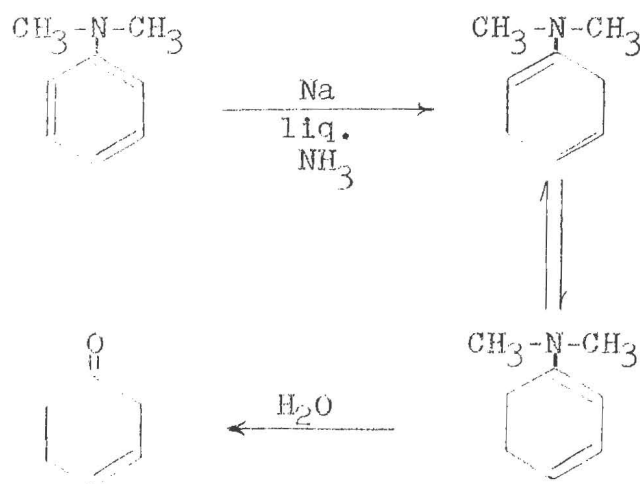
An enamine can be written as a resonance hybrid of two canonical structures, one of which possesses carbanion character and as such is susceptible to electrophilic attack.

It was noted by Collie,[10] as far back as 1884, that ethyl β-aminocrotonate could be alkylated to yield after hydrolysis a substituted ethyl acetoacetate.
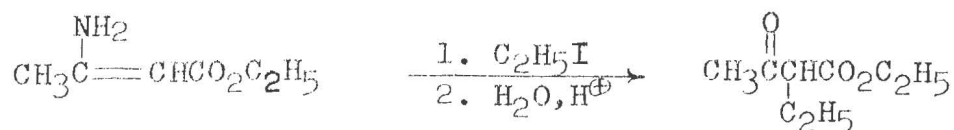
Since, such activated ketones can be conveniently alkylated with alkyl halides and base,[11] it is not surprising that the enamine method has rarely been employed. Mannich,[2,12] in his papers on the preparation of enamines, failed to note their ease of alkylation.

It remained for Stork[13,14] to discover the importance of enamines as valuable synthetic intermediates. He showed that

unactivated ketones such as cyclohexanone could be conveniently converted to a variety of products through their pyrrolidine enamines.
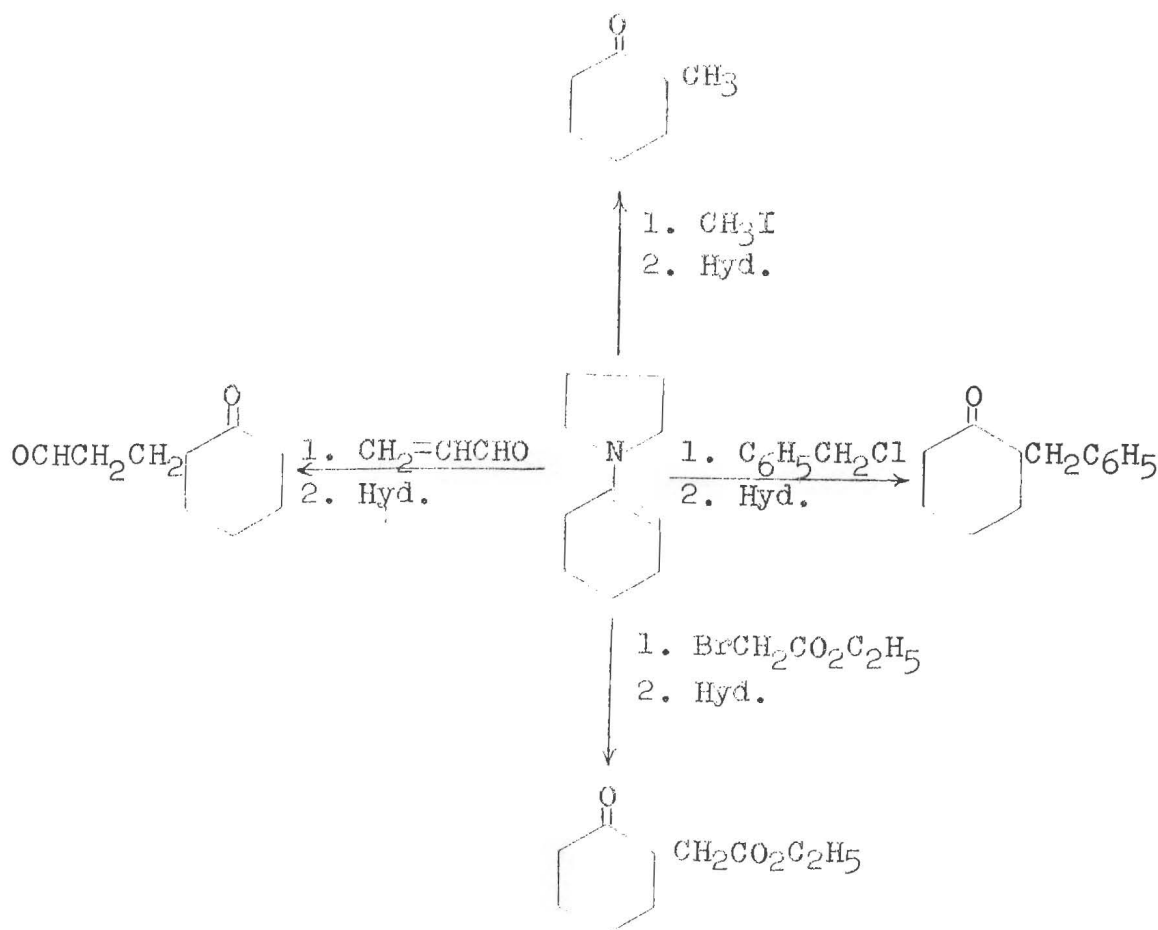
The advantage of Stork's method over previous methods is apparent if the attempted condensation of methyl vinyl ketone with cyclopentanone in the presence of base is considered.[15]
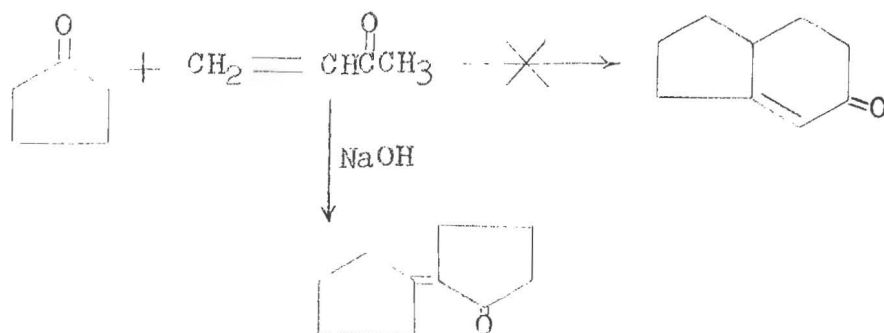
The use of an enamine intermediate yields the desired product.[14]
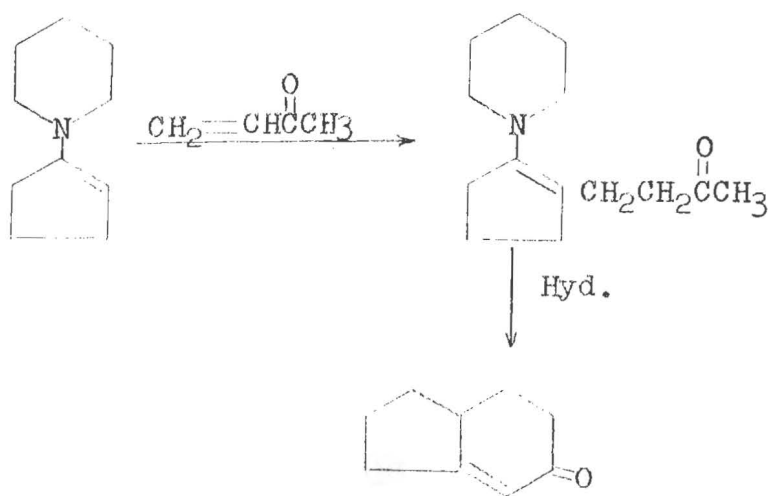
The simplicity of this method is in marked contrast to the complexity of the method previously available.[16]
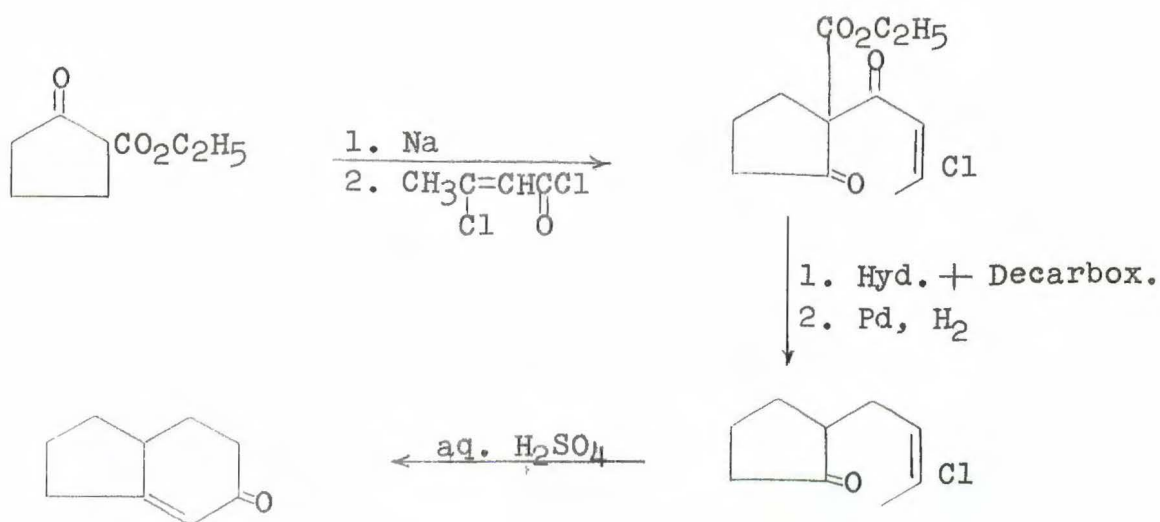
In the case of aldehydes with a methylene group alpha to the carbonyl, the enamine method is about the only way to obtain the desired product since base catalyzed Michael reactions would lead to aldolization. Finally, monoalkylation is obtained, in contrast, to the results obtained in the usual cyanoethylation procedures.
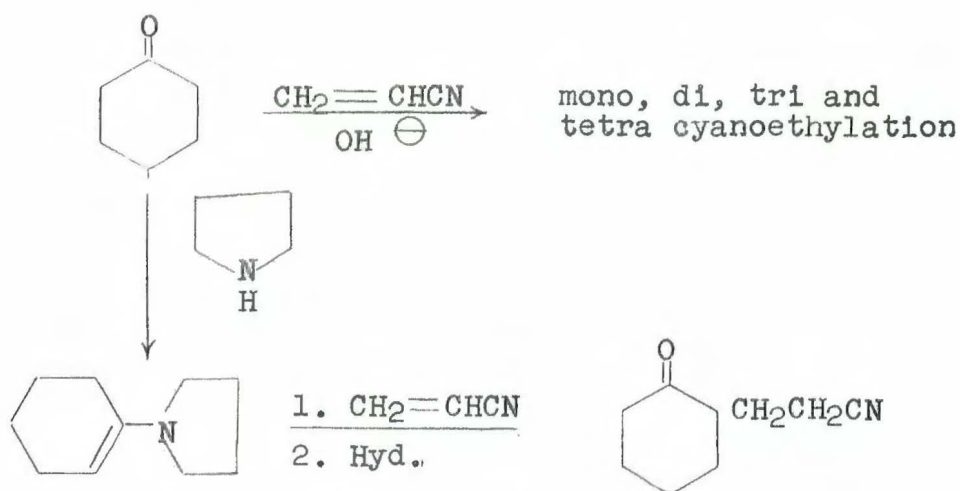
Since Stork's[13] first paper in 1954, the reactions of
enamines have been considerably extended. Kuehne[17] has
shown that a nitrile group can be introduced alpha to a car-
bonyl by treatment of an enamine with cyanogen bromide fol-
lowed by hydrolysis.
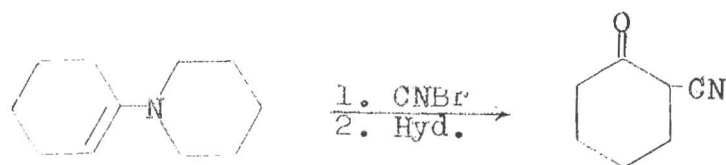
In steroid chemistry, enamines have found use for the
introduction of a fluorine atom[18] onto the A ring of cho-
lestanone.
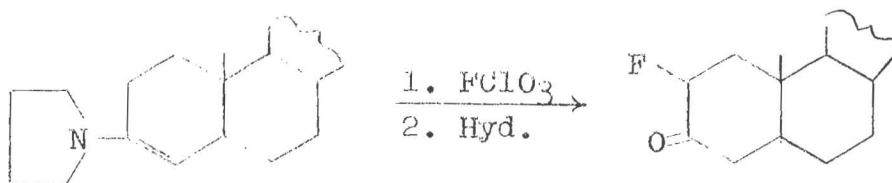
Cyclobutane derivatives have also been obtained from
enamines. Hasek and Martin[19] have reported that ketene
reacts with the dimethylamine enamine of isobutyraldehyde to
yield 3-dimethylamino-2,2-dimethylcyclobutanone.

$$(CH_3)_2C=CHN(CH_3)_2 + CH_2=C=O \xrightarrow[0^\circ]{\text{hexane}}$$
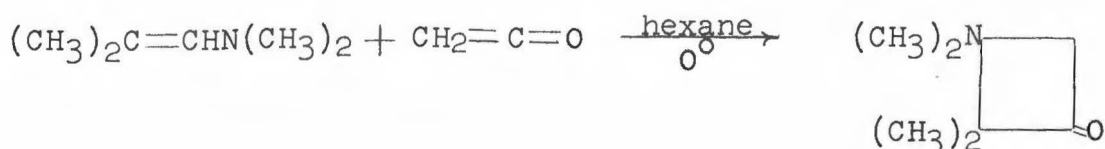
When enamines from α, α-disubstituted aldehydes are reacted with acrylonitrile a neutralization of charges takes place to yield a cyclobutane.[20]
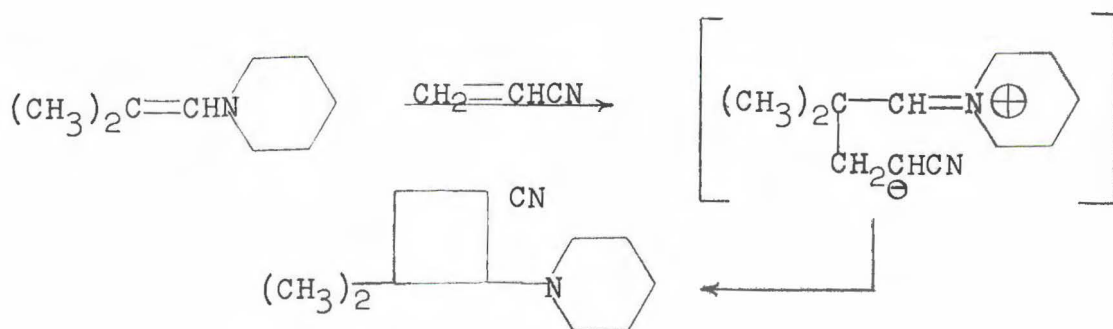
The above results are in contrast to those reported by Berchtold and Harvey[21] who treated 4-N-pyrrolidino-3-penten-2-one with ketene to yield 5-acetyl-4,6-dimethylcoumalin.
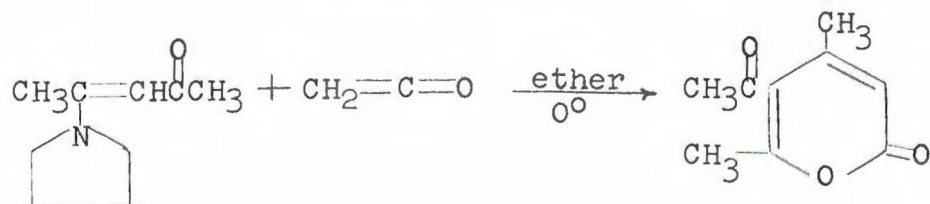
Hünig and coworkers[22] have synthesized long chain acids by means of enamine intermediates.
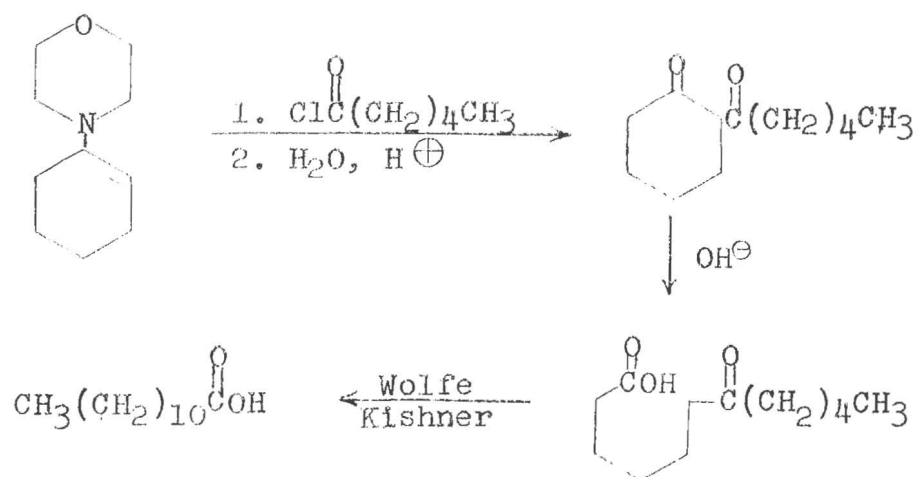
Alkylation[23] of the morpholino enamine of $\Delta^{1,9}$-octalone occurs only at the point indicated.
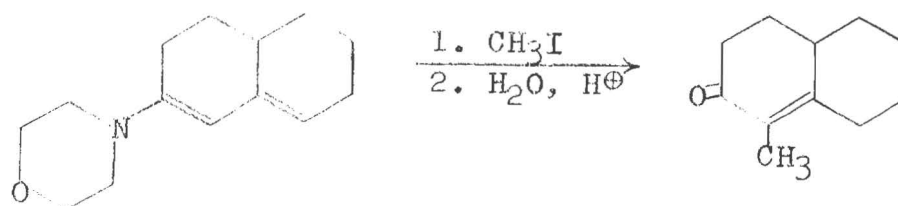
Enamines are believed to be intermediates in the Leuckart-Wallach reaction. de Benneville and Macartney[24] report that reduction of aldehydes proceeds at a lower temperature and under milder conditions when secondary amines are used.

The Relative Reactivity of Aldehydes and Ketones

In the subject investigation one of the major objectives was the determination of the relative reactivity of a number of methyl ketones, cyclic ketones and aldehydes with piperidine to give the corresponding enamines. Only very limited information was found in the literature on the relative reactivity of methyl and cyclic ketones probably because it is difficult to find compounds which will react smoothly and completely with a variety of such ketones. Similarly the literature contains little on the relative reactivity of aliphatic aldehydes. In contrast a number of investigators have studied the relative reactivity of variously substituted benzaldehydes.

The yields obtained in the Perkin reaction have been found to increase with the electron withdrawing ability of the substituent on the benzaldehyde.[25] In Schiff base formation, from para substituted benzaldehydes and aniline, the rate is reported to increase with electron attracting power of the substituent.[26]

In contrast Santerre et al.[27] have reported that any substituent on benzaldehyde decreases its rate of reaction with butylamine. Jencks[28] has reported that the rate of semicarbazone formation for several para substituted benzaldehydes showed no dependence on the substituent.

The azeotropic distillation method has been employed to study the acid catalyzed reaction of various aldehydes and ketones with ethylene glycol in benzene.[29]

$$\text{(cyclohexanone)}=O + HOCH_2CH_2OH \quad \xrightarrow[\text{benzene}]{p\text{-}CH_3C_6H_4SO_3H} \quad \text{(cyclohexanone ethylene ketal)} + H_2O$$
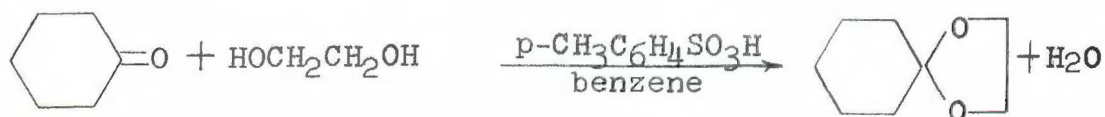
The experimental conditions and procedure were not reported. Only the time for complete reaction was given. It was stated that 2-methylcyclohexanone and cyclohexanone required 1.4 and 1.5 hours, respectively for complete reaction. Heptaldehyde and benzaldehyde required 2.5 hours each for completion of the reaction.

Brown and Ichikawa[30] have investigated the sodium borohydride reduction of the cyclanones, C_5 to C_{18} inclusive. They have found a remarkable dependence of rate upon ring size. This has been attributed to changes in internal strain accompanying the formation of a bond to the ring atom in the rate determining step. They found the following sequence for their most important cyclanones.

$$C_8 > C_6 > C_5 > C_7$$

Brown[31] has stated that the reactivities of aldehydes and ketones could be determined by sodium borohydride reduction. He investigated one aldehyde and three ketones and

placed them in the following order.

$$C_6H_5CHO \ggg \quad CH_3\overset{O}{\overset{\|}{C}}CH_3 > C_6H_5\overset{O}{\overset{\|}{C}}CH_3 > C_6H_5\overset{O}{\overset{\|}{C}}C_6H_5$$
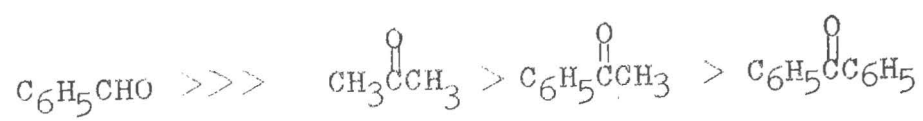
The Relative Reactivity of Amines

Although the literature contains little data on the reactivity of amines, it indicates that the reactivity depends on their basicity, their nucleophilicity and their size and shape.

Although nucleophilicity and basicity are not always identical as will be pointed out in the Discussion, they are identical in Schiff base formation between para substituted anilines and benzaldehyde.[26] A decrease in basicity causes a decrease in rate in the following order.

$$p\text{-}CH_3OC_6H_4NH_2 > p\text{-}CH_3C_6H_4NH_2 > C_6H_5NH_2 > p\text{-}ClC_6H_4NH_2$$
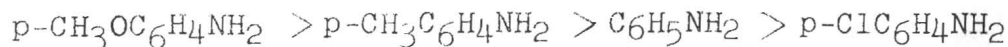
The same order of reactivity has been found for the rate of displacement of chloride ion from 2,4-dinitrochlorobenzene by para substituted anilines in ethanol.[32]

In the displacement reactions of p-nitrohalobenzenes by piperidine and morpholine,[33] piperidine, the stronger base, gives the larger rate constant.

The kinetics of acylation, diazotization and anil formation have been determined for aromatic amines by Poroi-Koshits.[34] He states that the rate of reaction depends both on the basicity and the polarizability of the molecule attacking the amine.

Brown[35] has reported that pyrrolidine is a stronger base than piperidine, since it forms a more stable adduct with

trimethylboron. This is supported by Bruehlman and Verhoek[36] who measured the complexing ability of amines with silver ion. They found that basicity paralleled complexing ability. In contrast, Vosburgh and coworkers[37] found no relationship between basicity and complexing ability with silver ion.

As expected, steric factors may predominate over basic ones. In displacement reactions, dimethylaniline, a stronger base than N-methylaniline, is less active than the latter.[38]

Edwards[39] has attempted to correlate reactivity in terms of basicity and nucleophilicity. He proposed the following equation

$$\log k = \alpha E_n + \beta H.$$

Here α and β are constants dependent on the substrate, E_n, the nucleophilicity parameter is defined in terms of molar refraction and H is the dissociation constant of the base. Good correlation among small inorganic anions was obtained.

DISCUSSION

The Reaction of Cyclohexanone with Piperidine

The distillation method, previously employed in these
laboratories for following reactions which yield water as a
by-product, has been found to be well adapted to the study
of the factors which determine the rate of formation of ena-
mines. Conditions have been developed under which essenti-
ally a quantitative yield of water and about 90% yields of
enamines are obtained from a wide variety of reactants. As
pointed out in the Historical, enamines have recently been
shown to be of considerable value in preparative organic
chemistry.

On the basis of the results from a large number of pre-
liminary experiments the following standard procedure was de-
veloped. A 1000 ml., three necked flask, fitted with a ther-
mometer, a Dean-Stark water collector and a reflux condenser
was employed. A 500 ml. volumetric flask was filled to the
mark with benzene and a volume equal in milliliters to the
weight in grams of the ketone and the amine to be added were
withdrawn. After addition of the amine, the p-toluenesulfonic
acid monohydrate and the benzene to the flask, heating was
started using a hemispherical mantle. After the solution had
come to reflux and any water in the system had been distilled
off, the ketone was added. The course of the reaction was
followed by reading the amount of water collected in the Dean-
Stark trap at suitable intervals. When a number of the ex-

periments were repeated, the $t_{\frac{1}{2}}$ values were readily checked to within about $\pm 3\%$.

Expts. 1 to 10 (Table I) were carried out to determine the effect of varying the catalyst concentration. When the amount of catalyst was increased from 0.000125 mole to 0.0004 mole, Expts. 5 to 10, a consistent increase in rate was observed. Ross[40] in his study of mercaptal formation found that upon increasing the concentration of p-toluene-sulfonic acid, the rate varied approximately with the square of the catalyst concentration. Kamlet[41] in his study of anil formation found that doubling the catalyst concentration, approximately doubled the rate. A plot of log $t_{\frac{1}{2}}$ versus log [HA], for the data for Expts. 7 to 10 was found to give a straight line of slope 1/2. A least mean square calculation yielded a slope of 0.495 with a correlation coefficient of 0.98. Green[42] in his study of the Baeyer condensation also found a slight increase in rate when the catalyst concentration was doubled but had insufficient data to show that the rate depended upon the square root of the catalyst concentration.

This result is consistent with the proposal that the salt formed between p-toluenesulfonic acid and piperidine is only partially dissociated and only the dissociated ion is effective as a catalyst. The undissociated salt may well be ionized but the closeness of the negative ion prevents

the approach of the particle to be attacked by the positive
ion.

$$\left[\left\langle \bigcirc \right\rangle NH_2^{\oplus} \overset{\ominus}{A} \right] \rightleftharpoons \left\langle \bigcirc \right\rangle NH_2^{\oplus} \quad A^{\ominus}$$

associated ions

Let C equal the total concentration of salt which, if disso-
ciation in benzene is slight, can be set equal to the total
concentration of added p-toluenesulfonic acid and let X equal
the concentration of the dissociated positive ion. Then an
equilibrium expression can be written in terms of C and X.

$$K_{diss.} = \frac{X^2}{C}$$

or

$$X = (KC)^{1/2}$$

The results of Expts. 1 to 4 were surprising in that
with an increase in catalyst concentration the rate tended
to remain constant. The curves obtained upon plotting vol-
ume of water versus time were approximately superimposable.

It was found that at high catalyst concentration,
Expts. 1 to 4, the salt formed between the amine and cata-
lyst is not completely soluble. A point of saturation was
reached where the amount of catalyst in solution remained
constant giving rise to a constant rate. The presence of a
colloidal system was demonstrated in Expt. 74 in which 500

ml. of a benzene solution which contained 0.250 mole of piperidine was investigated for the presence of a second phase as successive amounts of p-toluenesulfonic acid monohydrate were added. The addition of 0.002 mole of catalyst showed no Tyndall beam at the reflux temperature but upon slight cooling the beam appeared faintly, then sharply as the solution cooled further. The addition of another 0.002 mole of catalyst, to give a total of 0.004 mole, showed a faint Tyndall beam at the reflux temperature. At 0.016 mole of catalyst, a sharp Tyndall beam was observed at reflux. The catalyst concentration, at which the Tyndall beam first appeared, 0.004 mole, coincides with the concentration at which deviation from the plot of log $t_{\frac{1}{2}}$ versus log $[HA]$ began. On the basis of these results, 0.001 mole of catalyst was selected as the standard.

Expts. 11, 7, and 12 (Table II) were carried out to determine the effect of temperature on the rate. The higher temperature was obtained by using toluene as a solvent, the lower by using a 1:1 by volume mixture of petroleum ether (40° to 50°) and benzene. As expected, an increase in rate was observed with an increase in temperature. The temperature of 82°, obtained using benzene as the solvent, was selected as standard for the experiments which follow.

Expts. 13 to 18 (Table III) were carried out to determine the effect of varying the reactant ratio. In Expt. 15

in which the concentration of cyclohexanone and piperidine
were equal, low yields of water and product were obtained.
It may be that without an excess of amine or ketone the equi-
librium shown cannot be forced completely to the right under
the reaction conditions. It is of interest, that the $t_{\frac{1}{2}}$'s for

the 4/1, 3/1, and 2/1 ratios are almost identical to those
for the 1/4, 1/3, and 1/2 ratios. It appears, therefore,
that an excess of ketone is just as effective as an excess
of amine in displacing the equilibrium and driving the reac-
tion to completion. A ratio of three moles of amine to one
of ketone was selected as the standard for the study of the
effect of changes in structure on the rate of enamine for-
mation.

Table I

Variation of Catalyst Concentration[a]

Expt. No.	P.T.S.,[b] mole	$t_{\frac{1}{2}}$ min.	H_2O, %	Prod., %
1	0.064	92	97	_d
2	0.032	100[c]	93	73
3	0.016	105[c]	98	83
4	0.008	98[c]	88	84
5	0.004	110	92	_d
6	0.002	135	95	_d
7	0.001	215[c]	95	90
8	0.0005	292	96	93
9	0.00025	418	91	85
10	0.000125	554	97	_d

[a]These expts. were carried out with 0.125 mole of cyclohexanone and 0.250 mole of piperidine diluted to 500 ml. with benzene. [b]p-Toluenesulfonic acid. [c]Satisfactory check runs obtained; data given in Experimental. [d]Product not isolated.

Table II

Variation of Temperature[a]

Expt. No.	$t_{\frac{1}{2}}$ min.	H_2O, %	Prod., %	Temp., °C
11	400	102	89	53.0
7	215	95	90	82.0
12	74	98	_b	112.0

[a]These expts. carried out with 0.125 mole of cyclohexanone, 0.250 mole of piperidine and 0.001 mole of catalyst diluted to 500 ml. with benzene-petroleum ether, benzene, and toluene respectively. [b]Product not isolated.

Table III

Variation of Reactant Ratio[a]

Expt. No.	Reactant Ratio[b]	$t_{\frac{1}{2}}$ min.	H_2O, %	Prod., %
13	4/1	101	99	93
14	3/1	124	98	91[c]
7	2/1	215	95	90
15	1/1	547	79	66
16	1/2	161	96	84
17	1/3	121	98	86
18	1/4	80	98	85

[a]These expts. carried out with cyclohexanone, piperidine and 0.001 mole of catalyst diluted to 500 ml. with benzene. [b]Ratio of piperidine to cyclohexanone; unity in the ratio denotes 0.125 mole of piperidine or cyclohexanone. [c]Product not isolated, but this is the average of Expts. 13 and 7.

The Reaction of Piperidine with Cyclic Ketones

The standard procedure developed in the preceding section was employed to determine the relative rates of reaction of a variety of ketones, aldehydes and amines. No quantitative studies of the effects of variations in structure of the reactants on the rate of enamine formation have appeared previously in the literature. In Table IV are listed the results for the cyclic ketones which gave good yields of both water and product.

It is apparent that a wide variety of cyclic ketones react smoothly under these conditions and, therefore, the procedure is of considerable preparative value. The yields of those products which had been made before averaged about 10% higher than the yields previously reported. The plots of water versus time gave smooth curves of constantly decreasing slope of the same general shape; the $t_{\frac{1}{2}}$'s, the time in which a 50% yield of water is evolved, are therefore a valid measure of the relative rates of reaction. The temperature variation for the 5% to 80% portion of a given reaction was in all cases $\pm 0.1^{\circ}$ or less except in Expt. 19 where the variation was $\pm 0.3^{\circ}$. The variation among all experiments of Table IV was $\pm 0.2^{\circ}$ excepting Expt. 19.

Expts. 19 and 14 were carried out to determine the effect of ring size on the rate of enamine formation. Cyclopentanone reacted over three times faster than cyclohexanone

which reacted much faster than cycloheptanone, Expt. 27.
Only a 58% yield of water and a 44% yield of product were
obtained from cycloheptanone in 12 days. This order of re-
activity was also found by Stork and coworkers[43] who used
only a rough qualitative procedure. As was pointed out in
the Historical, Brown[35] has found the opposite order for the
sodium borohydride reduction of these ketones.

The degree of enolization in the pure liquid of cyclo-
hexanone (0.02%) as compared to cyclopentanone (0.0048%) has
been attributed to the fact that a double bond exocyclic to
a cyclohexane ring has a greater tendency to migrate into the
ring than one exocyclic to a cyclopentane ring.[44] In ena-
mines derived from cyclic ketones, there is an endocyclic
double bond.
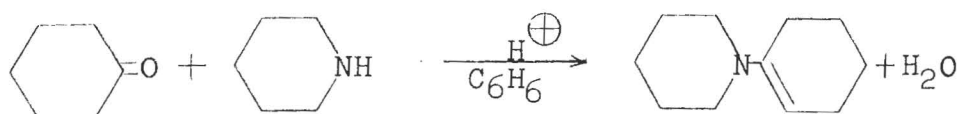
In these two cases the rate of enamine formation is opposite
to the degree of enolization of the ketones. A possible ex-
planation will be discussed under Theoretical Considerations
where relative rates will be interpreted in terms of a pre-
ferred mechanism, insofar as possible.

Introduction of a methyl group onto the cyclohexanone
ring caused a decrease in rate. 2-Methylcyclohexanone, Expt.
28, gave only a 63% yield of water and a 58% yield of product

in three weeks.

3-Methylcyclohexanone, Expt. 21, also gave a slower rate than cyclohexanone, Expt. 14. This can be attributed to steric interaction between the methyl hydrogens and the carbonyl group as is predicted by Newman's Rule.[45] The fact that 3-methylcyclohexanone yields two isomeric enamines does not weaken the above proposal since the rate of water formation is independent of the ultimate position of the double bond. The decrease in rate exhibited by 4-methylcyclohexanone, Expt. 20, as compared to cyclohexanone cannot be readily attributed to steric interactions. A possible explanation would be electron release by the methyl group to the carbonyl group. Roberts and Moreland[46] found large changes in acidity in related saturated ring systems with four carbon atoms between the methyl and carboxyl groups.

$$CO_2H$$

$$CH_3$$
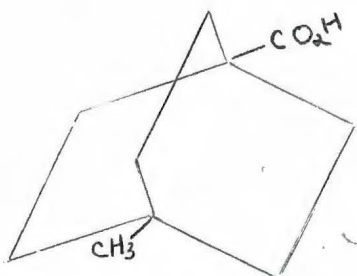
β-Tetralone, Expt. 22, can be considered to be a 3,4-disubstituted cyclohexanone. The rate was much slower than for 3-methylcyclohexanone even though the benzo group is probably electron withdrawing and the product would be stabilized by the fact that it contains a double bond conjugated with the aromatic ring. This slower rate may be due to the greater

rigidity of the substituent in β-tetralone as compared to 3-methylcyclohexanone. In this regard it may be pertinent to note that with α-tetralone, Expt. 29, which can be considered to be a 2,3-disubstituted cyclohexanone, a 0% yield of water was obtained in one day, while with 2-methylcyclohexanone, Expt. 28, water was evolved much faster and a fair yield of product was obtained. A satisfactory explanation of these relative rates is not presently available.

Under the standard procedure, dihydroresorcinol, Expt. 23, and dimedone, Expt. 24, gave good yields of the mono-enamines. Since no excess water was evolved, little if any of the dienamines were formed. Dihydroresorcinol reacted six times as fast as dimedone which indicates great steric hindrance by the gem-dimethyl group. Since both compounds are over 90% enolized[47] in the solid state, enolization probably plays little part in determining the relative rates of reaction

In the case of 2-acetylcyclopentanone, Expt. 26, only the carbonyl group in the ring yielded the enamine under the standard conditions. The infrared spectrum of the enamine indicates that an endocyclic double bond is present. The 2-carbethoxycyclopentanone, Expt. 25, probably reacted faster than the 2-acetylcyclopentanone because the bulky ethyl group is separated from the carbonyl group by the oxygen.[47] The acetyl group of 2-acetylcyclopentanone has there-

fore a larger effective size and decreased the rate of reaction to a greater extent.

It is of interest to compare the results for dihydroresorcinol, Expt. 23, with those for cyclohexanone, Expt. 14. Even though dihydroresorcinol possesses two carbonyl groups, only one of these is readily available for reaction since the compound is over 95% enolized in the solid state and should be even more completely enolized in benzene.[48] A comparison between dihydroresorcinol and cyclohexanone is justified if the reasonable assumption is made that reaction occurs only at the keto group. The greater reactivity of dihydroresorcinol may be due to the fact that its enol form is planar. The ethylenic bond between carbon atoms 2 and 3,
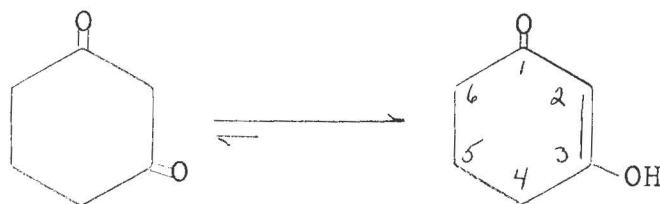
causes atoms 1, 2, 3 and 4 to be coplanar. Since carbon atom 1 is part of the carbonyl group, carbon atom 6 must be coplanar with carbon atoms 1 and 2. This is quite different from cyclohexanone in which only carbon atoms 1, 2 and 6 are coplanar. The planar enolic system (I) would be expected to
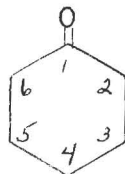
decrease the steric hindrance to attack by the piperidine as compared to either the chair or boat form of cyclohexanone (II and III) which are not planar. If, as seems unlikely,

I   II   III
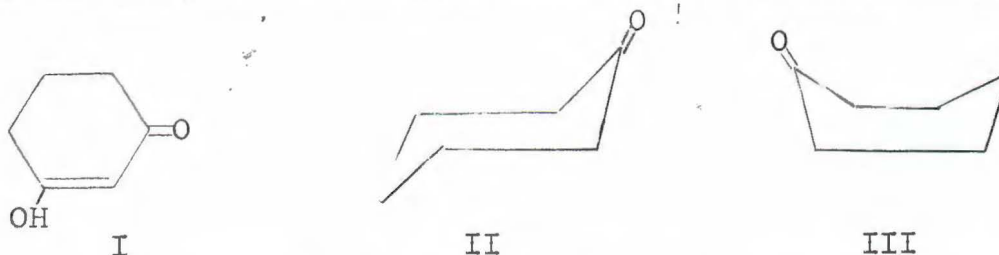
the enolization can be ignored, another possible explanation is that the reaction proceeds through the keto form of dihydroresorcinol and all that is manifested is the statistical factor of the two carbonyl groups. It should be noted that if the reaction proceeds through the enol form of dihydroresorcinol, then enolization is aiding the reaction indirectly by providing a planar substrate for piperidine to attack.

Another pertinent comparison is between cyclopentanone, 2-carbethoxycyclopentanone and 2-acetylcyclopentanone. Aside from any effects due to differences in extent of enolization, substituents adjacent to a carbonyl group slow down the rate.

In the case of 2-carbethoxycyclopentanone and 2-acetyl-cyclopentanone, the 2-substituents are larger than the methyl group on 2-methylcyclohexanone but nevertheless these compounds yielded quantitative yields of water and good yields of product. This re-emphasizes the tendency of cyclopentanone to react more rapidly than cyclohexanone.
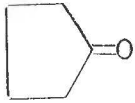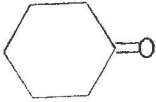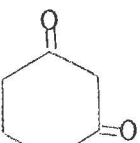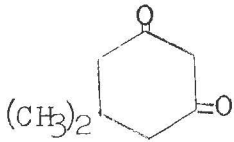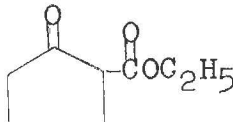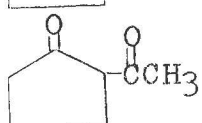
Additional cyclic ketones for which the results are not tabulated because poor yields of water and/or product were obtained are: 1,2-cyclohexanedione, Expt. 30, which gave a 92% yield of water ($t_{\frac{1}{2}}$ was 222 min.) and a 0% yield of product and phloroglucinol, Expt. 31, which gave a 35% yield of water ($t_{\frac{1}{4}}$ was 232 min.) and a 0% yield of product.

1,4-Cyclohexanedione, Expt. 32, gave a 200% yield of water. This indicates that both carbonyl groups reacted. The $t_{\frac{1}{2}}$ was 208 min. and an 87% yield of crude di-enamine was obtained. The product decomposed in a matter of minutes and could not be satisfactorily characterized.

Table IV

Reaction with Cyclic Ketones

Expt. No.	Ketone	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %
	Monoketones			
19		35	101	95
14		124	98	91
20	CH$_3$	136	98	89
21	CH$_3$	177	98	93
22		345	95	71
	Diketones			
23		47	98	68
24	(CH$_3$)$_2$	281	99	81
25	COC$_2$H$_5$	396	98	86
26	CCH$_3$	1320	98	60

Reaction of Piperidine with Methyl Ketones

In Table V are listed the results for the methyl ketones
which reacted smoothly. The yields of water and product are
high except for p-chloroacetophenone and phenylacetone. The
temperature variation for the 5% to 80% portion of a given
reaction was never more than $\pm 0.1^\circ$. The variation among all
the experiments of Table V was $\pm 0.2^\circ$. All the enamines ex-
cept that of acetylacetone, Expt. 36, are new compounds.

It is evident upon comparing the results of Expts. 33,
34 and 35 that phenylacetone, Expt. 33, wherein the bulky
phenyl group is removed from the carbonyl group by the meth-
ylene group reacted faster than either p-chloroacetophenone
or acetophenone even though the phenylacetone reaction was
carried out at a much lower temperature. The results of a
preliminary experiment showed that acetophenone would not
give a good yield of water under the standard conditions.
It was found that by changing the solvent from benzene
(b. p. 82°) to toluene (b. p. 112°) but keeping the reactant
ratio and the amount of catalyst constant, a good yield of
water and product could be obtained.

It can be seen from the results of Expts. 34 and 35 that
electron withdrawing groups increase the rate. Though 83%
and 100% yields of water were obtained from p-methyl and
p-nitroacetophenone, Expts. 39 and 40, the products could not
be isolated. The $t_{\frac{1}{2}}$ values for p-methylacetophenone, aceto-

phenone, p-chloroacetophenone and p-nitroacetophenone were
144 hr., 97.4 hr., 79.2 hr. and 33 hr., respectively. In all
these cases toluene was the solvent and the temperature was
$112° \pm 0.2°$. Thus the order of increasing rate is the order
of increasing ability of the para substituent to attract
electrons.

Acetylacetone, Expt. 36, reacted faster than benzoyl-
acetone, Expt. 38. Acetylacetone is 80% enolized[48] in the
pure liquid and this percentage should be greater in benzene
while benzoylacetone is 99% enolized in the solid state.
Enolization of benzoylacetone takes place so that conjugation
is extended into the ring system.[47] This means that the car-
bonyl group adjacent to the methyl group is more available
for reaction. The reactivity of these compounds can be ra-
tionalized if one considers the enol structures of acetyl-
acetone (IV) and benzoylacetone (V). In both these struc-

$$CH_3-C(=O \cdots H \cdots O)=C-CH_3 \quad (CH)$$

IV

$$CH_3-C(=O \cdots H \cdots O)=C-C_6H_5 \quad (CH)$$
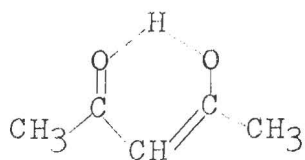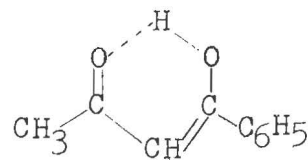
V

tures piperidine probably effectively attacks only the uneno-
lized carbonyl group. The enol forms of the above compounds
(IV and V) are planar[47] and would be expected to possess
some of the rigidity of cyclic compounds due to the hydrogen
bonding. In this sense, they may be considered related to

3-substituted cyclohexanones. The bulkiness of the phenyl group of V even though it is electron withdrawing and might therefore be expected to aid the reaction, decreases the rate relative to the smaller methyl group of IV. Dibenzoyl-methane, Expt. 41, which possesses two bulky phenyl groups gave a 0% yield of water in one day and heptanone-2, Expt. 42, which has no rigidity gave only a 27% yield of water in 5 days. The amyl radical of heptanone-2 could orient itself in any of many ways. This would sterically hinder the attacking piperidine and thus decrease the rate of reaction.

It should be noted that enolization in the case of acetylacetone and benzoylacetone (IV and V) gives rise to two factors which effect the rate in opposing fashions. Enolization in each of these cases gives rise to a planar, more rigid structure which should increase the rate, since there would be less steric hindrance to the approach of the piperidine. At the same time, the methyl and phenyl groups of IV and V, adjacent to the enolized carbonyl groups, are brought into a position, due to ring formation, that may increase the steric interactions. Ethyl acetoacetate, Expt. 37, which contains only 10% enol in benzene, reacts more slowly than acetylacetone which is planar but faster than benzoyl-acetone which although planar has a bulky phenyl group.

The concept that rigidity and planarity arising from enolization increases the rate of reactions apparently has

not been previously noted in the literature. Price and Hammett[49] have reported that oxime formation of simple ketones proceeds through a rigid transition state.

It is of interest to compare the results of Expts. 33 and 38. Both benzoylacetone and phenylacetone possess bulky groups which give rise to steric hindrance but benzoylacetone because of its high degree of enolization gives rise to a more rigid structure and therefore might be expected to react faster. Dihydroresorcinol, Expt. 23, probably reacted faster than acetylacetone, Expt. 36, because the carbonyl groups are tied back into a ring system.

A comparison between ethyl acetoacetate, Expt. 37 and 2-carbethoxycyclopentanone, Expt. 25, shows that tieing back the ketonic carbonyl group into the cyclopentanone ring increased the rate of reaction. 2-Carbethoxycyclopentanone is 4.5% enolized while ethyl acetoacetate is 7.5% enolized.[48] This small difference in enolization does not seem to explain the difference in rate.

Additional methyl ketones which did not give good yields of water and product were diacetyl, Expt. 43, which gave a 100% yield of water ($t_{\frac{1}{2}}$ was 98 min.) and a 0% yield of product; and acetonylacetone, Expt. 44, which gave only a 93% yield of water ($t_{\frac{1}{2}}$ was 88 hrs.) and a 0% yield of product.

3-Methyl-2,4-pentanedione, Expt. 45, gave a 52% yield of water ($t_{\frac{1}{4}}$ was 32.5 hrs.) and a 0% yield of product. This

result is consistent with the proposal that the methyl group decreases the amount of enolization because it decreases the stability of a planar hydrogen bonded ring.[48]

4-Piperidino-3-pentene-2-one, Expt. 46, the enamine of acetylacetone, gave a 0% yield of water and a 0% yield of product even though the solvent was o-xylene (b. p. 140°). This may be due to steric hindrance by the bulky piperidino group or it may be due to contribution by the canonical form VI, which decreases the sp^2 character of the carbon oxygen

$$CH_3-\overset{\oplus}{\underset{}{C}}-CH=\overset{O\ominus}{\underset{}{C}}-CH_3$$
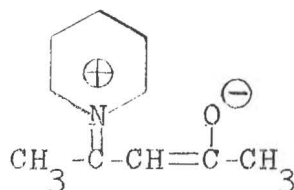
VI

bond.

Acetoacetanilide, Expt. 47, gave a 100% yield of water; $t_{\frac{1}{2}}$ was 37 min. The product obtained did not give a typical enamine reaction nor a satisfactory elemental analysis. On the basis of the anomalous $t_{\frac{1}{2}}$ value it can be assumed that the product was not an enamine. o-Chloroacetoacetanilide, Expt. 48, gave an 80% yield of water ($t_{\frac{1}{2}}$ was 272 min.) and a 0% yield of product.

Table V

Reaction with Methyl Ketones

Expt. No.	Ketone	$t_{\frac{1}{2}}$, hr.	H_2O, %	Prod., %
	Monoketones			
33	$CH_3\overset{O}{\overset{\|}{C}}CH_2C_6H_5$	29.7	80	72
34	$CH_3\overset{O}{\overset{\|}{C}}C_6H_4Cl\text{-}p$[a]	79.2	80	67
35	$CH_3\overset{O}{\overset{\|}{C}}C_6H_5$[a]	97.4	99	83
	Diketones			
36	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_3$	10.7	101	87
37	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OC_2H_5$	13.0	100	86
38	$CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}C_6H_5$	19.0	100	99

[a]These expts. were carried out in refluxing toluene (b.p. 112°) in place of benzene (b.p. 82°.)

The Reaction of Piperidine with Various Aldehydes

Preliminary studies showed that aldehydes reacted very quickly under the standard conditions described above. It was desirable, therefore, to redetermine the optimum catalyst concentration and reactant ratio. 2-Ethylhexaldehyde was selected as a model aldehyde for these studies.

In Tables VI and VII are listed the results obtained upon varying the catalyst concentration and reactant ratio. No exact mathematical relationship between $t_{\frac{1}{2}}$ and catalyst concentration is apparent among the results of Expts. 49, 50 and 51. On the basis of these results 0.000125 mole of catalyst was selected as standard.

Expts. 50, 52 and 53, Table VII, were carried out to determine the effect of varying the reactant ratio. An excess of carbonyl compound increased the rate much more than an equivalent excess of amine. Excess amine actually decreased the rate probably because of increased deactivation of the catalyst. This was contrary to the results observed for cyclohexanone, Table III, where a given excess of ketone or piperidine was found to increase the rate approximately the same amount. Here the reaction proceeded smoothly even at a one to one ratio of reactants. This suggests that the equilibrium shown lies farther to the right for 2-ethylhexaldehyde than for cyclohexanone or is more easily shifted to the right by removal of the by-product water by distillation

$$CH_3(CH_2)_3\underset{\underset{C_2H_5}{|}}{C}HCHO + HN\bigcirc \rightleftharpoons CH_3(CH_2)_3\underset{\underset{C_2H_5}{|}}{C}H\overset{OH}{C}H-N\bigcirc$$
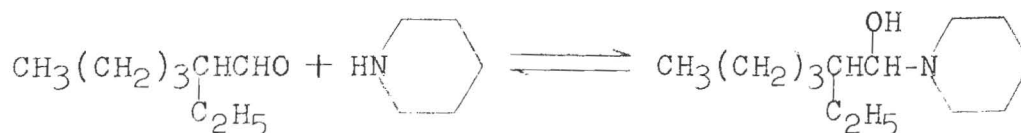
On the basis of these results a ratio of three moles of amine to one of aldehyde was chosen as standard. Thus the standard conditions for aldehydes were the same as those for ketones except, 0.000125 mole instead of 0.001 mole of catalyst was used. In all the cases tabulated, the reactions proceeded smoothly to give good yields of water and product. Generally, the yields of product obtained from these aldehydes by the distillation method for this reaction were about 20% greater than by the Mannich method.[2] The temperature variation for the 15% to 80% portion of a given reaction was not more than $\pm 0.1^\circ$ among all experiments of Tables VI, VII and VIII.

The $t_{\frac{1}{2}}$ value for Expt. 50 compared to that for Expt. 55 shows that branching alpha to a carbonyl group greatly slows down the rate. If, however, the branched chain is tied back, as in cyclohexanecarboxaldehyde, Expt. 56, the decrease in rate is much less. Steric hindrance reasonably explains these results. Since the rates for phenylacetaldehyde, Expt. 54, and heptaldehyde are so high the differences may not be large enough to be of great significance.

It should be noted that aldehydes, even those with

alpha substituents, react much more readily than ketones. The rate sequence is a reasonable result of increasing steric

$$CH_3(CH_2)_5CHO > CH_3(CH_2)_3\underset{\underset{C_2H_5}{|}}{C}HCHO > CH_3(CH_2)_4\overset{O}{\overset{\|}{C}}CH_3$$
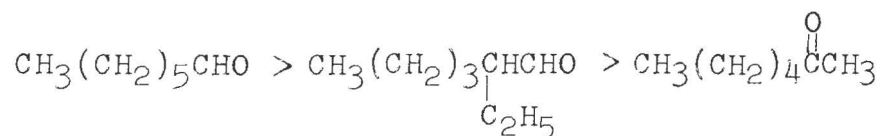
hindrance as the point of branching approaches the carbonyl group. In agreement with this, phenylacetaldehyde, Expt. 54, reacted much faster than phenylacetone, Expt. 33, Table V.

Additional aldehydes which were reacted with piperidine under the standard conditions but which did not give a good yield of product were 3-phenylpropionaldehyde, Expt. 57, which gave a 100% yield of water and a 0% yield of product and isovaleraldehyde, Expt. 58, which gave a 100% yield of water and a 0% yield of product.

Table VI

Variation of Catalyst Concentration[a]

Expt. No.	P.T.S.[b] mole	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %
49	0.00025	28	100	91
50	0.000125	48	100	91
51	0.0000625	63	101	89

[a]These expts. carried out with 0.125 mole of 2-ethylhexaldehyde and 0.375 mole of piperidine diluted to 500 ml. with benzene. [b]p-Toluenesulfonic acid.

Table VII

Variation of Reactant Ratio[a]

Expt. No.	Reactant[b] Ratio	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %
50	3/1	48	100	91
52	1/1	35.5	99	92
53	1/3	8.5	99	93

[a]These expts. carried out with 2-ethylhexaldehyde, piperidine and 0.000125 mole of catalyst diluted to 500 ml. with benzene. [b]Ratio of piperidine to 2-ethylhexaldehyde; unity in the ratio denotes 0.125 mole of aldehyde or piperidine.

Table VIII

Reaction with Aldehydes

Expt. No.	Aldehyde	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %
54	$C_6H_5CH_2CHO$	2.8	99	88
55	$CH_3(CH_2)_5CHO$	3.6	99	92
56	$\overline{CH_2(CH_2)_4CH}-CHO$	12.0	98	90
50	$CH_3(CH_2)_3CHCHO$ $\quad\quad\quad\quad C_2H_5$	48.0	100	91

The Reaction of Cyclohexanone with Various
Amines and Mercaptans

The standard procedure developed for methyl and cyclic ketones, Tables IV and V, was employed to determine the relative rates of reaction of a variety of amines with cyclohexanone. In Table IX are listed the results for amines which gave good yields of both water and product. The temperature variation among all experiments listed in Table IX was $\pm 0.2°$ for the 10% to 80% portion of a given reaction except for Expt. 59 where the variation was $\pm 0.4°$. It is apparent that a wide variety of cyclic secondary amines react smoothly under these conditions.

The results of Expts. 59, 60 and 14 showed that the rate of reaction was sensitive to changes in the ring size of the amine. Pyrrolidine and hexamethylene imine which have an odd number of carbon atoms in the ring reacted faster than piperidine which has an even number of carbon atoms in the ring.

The basicities of the amines used in Expts. 59, 60, and 14 are essentially identical;[50] also Fischer-Hirschfelder-Taylor models indicated that the steric environments about the nitrogen atom of each ring system due to the hydrogen atoms on the methylene groups adjacent to the nitrogen atom were similar; it would therefore seem that the rate of reaction was not dependent on these factors. A possible explana-

tion for the above results will be considered in the next section.

It is of interest that pyrrolidine which has a five membered ring reacted faster than any other amine, while cyclopentanone, which also has a five membered ring reacted faster than any other ketone. It should be noted however, that cyclohexanone reacted faster than cycloheptanone while hexamethylene imine reacted faster than piperidine.

It is apparent that substituents on the piperidine ring had the expected results. 3-Methylpiperidine, Expt. 62, reacted faster than 2-methylpiperidine, which gave only a 33% yield of water in four weeks, but slower than 4-methylpiperidine, Expt. 61. These results are similar to those obtained for the methylcyclohexanones where the rate decreased as the methyl group was brought closer to the point of reaction.

Replacement of the carbon at the four position of piperidine with oxygen or nitrogen, as in morpholine, Expt. 64, and N-methylpiperazine, Expt. 63, caused a large increase in rate even though morpholine and possibly N-methylpiperazine are weaker bases than piperidine. Hall[50] has observed that piperazine (pk_a 9.81) is a weaker base than piperidine (pk_a 11.2). He has also found that N-methylpiperidine (pk_a 10.4) and N-methylmorpholine (pk_a 7.41) are weaker bases than piperidine and morpholine (pk_a 8.36). It is reasonable,

therefore, to assume that the imine nitrogen of N-methyl-
piperazine is less basic than the nitrogen of piperidine. A
possible explanation for these results will be considered in
a later section.

N-Methyl-N-butylamine, Expt. 65, wherein the two groups
on the nitrogen are not joined into a ring reacted slowest
of all the amines for which results are tabulated. Dibutyl-
amine, Expt. 68, which has bulkier groups gave only a 41%
yield of water in 6 days, while N-methylaniline, Expt. 69,
which also has bulky groups gave only a 20% yield of water
in 4 days.

Several experiments were done to compare mercaptans and
alcohols with amines. Thiophenol, Expt. 67, reacted very
much more slowly than octyl mercaptan, Expt. 66. This is

$$RSH + O=\!\!\!\left\langle\bigcirc\right\rangle \longrightarrow RS\!\!-\!\!\left\langle\bigcirc\right\rangle + H_2O$$

probably due to the unavailability of the unshared electrons
of the sulfur atom due to resonance with the phenyl ring.
In contrast n-butanol, Expt. 70, gave only 63% yield of water.

Table IX

Reaction with Various Amines and Mercaptans

Expt. No.	Amine or Mercaptan	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %

Pyrrolidine and its Homologs

59		5.5	101	85
60		58.0	99	94
14		124.0	98	91

Methyl Piperidines
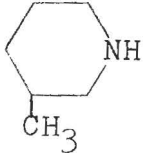
| 61 | | 120.0 | 99 | 91 |
| 62 | | 165.0 | 99 | 87 |

Table IX (continued)

Expt. No.	Amine or Mercaptan	$t_{\frac{1}{2}}$, min.	H_2O, %	Prod., %
	Other Amines			
63	CH$_3$N⌬NH	6.5	101	83
64	O⌬NH	46.5	101	87
65	$CH_3NHC_4H_9$	277.0	95	88
	Mercaptans			
66	$CH_3(CH_2)_6CH_2SH$	8.8	101	86
67	C_6H_5SH	197.0	101	85

Theoretical Considerations

One of the objectives of this investigation, in addition to the study of the factors which determine the rate of enamine formation was to correlate the results insofar as possible with a mechanism for the reaction.

It is pertinent at this point to reconsider two mechanisms for the addition of neutral molecules to carbonyl compounds. In Fig. I is presented a mechanism for Schiff base formation which has been proposed recently by Kamlet.[41] It is believed that the carbonyl group of benzaldehyde is activated through hydrogen bonding in a fast equilibrium. The rate controlling step, step 2, is the attack of the aniline. This mechanism is consistent with the second order kinetics observed.

In an alternate mechanism,[26] consistent with the observed kinetics, benzaldehyde and aniline interact rapidly and reversibly to give an intermediate, VI. The intermediate,

$$\underset{\text{VI}}{\overset{\displaystyle \overset{\text{OH}}{|}}{C_6H_5CHNHC_6H_5}} \qquad\qquad \underset{\text{VII}}{\overset{\displaystyle \overset{\oplus OH_2}{|}}{C_6H_5CHNHC_6H_5}}$$
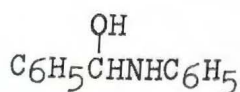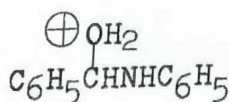
VI, is then protonated in a fast equilibrium with the catalyst to give VII. The loss of water from VII is rate determining. It should be noted that para substituents on the benzaldehyde that are electron withdrawing should aid the

addition, step 2, (Fig. I) of aniline to benzaldehyde. Those that are electron releasing should aid the dehydration, step 3. Kamlet[41] found that electron withdrawing groups on the aldehyde increased the rate. This is consistent with the proposal that step 2 is rate determining.

Santerre[27] and coworkers have found a maximum in the $\rho\sigma$ plot at benzaldehyde itself for the reaction between benzaldehydes and butylamine. These workers explain this on the basis that there are two rate controlling steps, the addition and the dehydration. These findings are also supported by Jencks[28] in his study of semicarbazone formation of p-substituted benzaldehydes.

In Fig. II is presented a mechanism for mercaptal formation which has been proposed by Champaigne. The only major difference between the mechanism presented in Fig. II and that of Fig. I is the further reaction of the dehydrated intermediate to give a bis compound.

The above may be briefly summarized as follows: a) Additions of neutral molecules to carbonyl compounds are usually first order in each reactant. b) The addition or dehydration step may be rate controlling. A generalized mechanism for enamine formation which is consistent with the mechanisms given in Figs. I and II is presented in Fig. III. The mechanism of enamine formation has been considered only to a very limited extent in the literature.

Figure I

$$\text{C}_6\text{H}_5\text{-C(H)=O} + \text{HA} \xrightleftharpoons{\text{fast}} \text{C}_6\text{H}_5\text{-C(H)=O}\cdots\text{HA} \quad (1)$$

$$\text{C}_6\text{H}_5\text{-C(H)=O}\cdots\text{HA} + \text{H}_2\text{N-C}_6\text{H}_5 \xrightarrow{\text{slow}} \quad (2)$$

$$\quad (3)$$

$$\quad (4)$$

$$\quad (5)$$

$$\quad (6)$$

Figure II

$$C_6H_5CHO + RSH \rightleftharpoons C_6H_5\underset{\underset{OH}{|}}{C}HSR \qquad (1)$$

$$C_6H_5\underset{\underset{OH}{|}}{C}HSR + H^{\oplus} \xrightarrow{\text{fast}} C_6H_5\underset{\underset{\oplus OH_2}{|}}{C}HSR \qquad (2)$$

$$C_6H_5\underset{\underset{\oplus OH_2}{|}}{C}HSR \rightleftharpoons C_6H_5\overset{\oplus}{C}HSR + H_2O \qquad (3)$$

$$C_6H_5\overset{\oplus}{C}HSR + RSH \rightleftharpoons C_6H_5\underset{\underset{H}{|}}{\overset{\oplus}{C}}H(SR)_2 \qquad (4)$$

$$C_6H_5\underset{\underset{H}{|}}{\overset{\oplus}{C}}H(SR)_2 \rightleftharpoons C_6H_5CH(SR)_2 + H^{\oplus} \qquad (5)$$
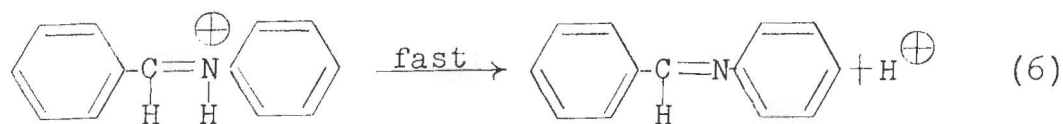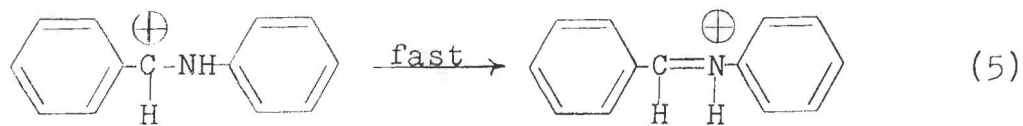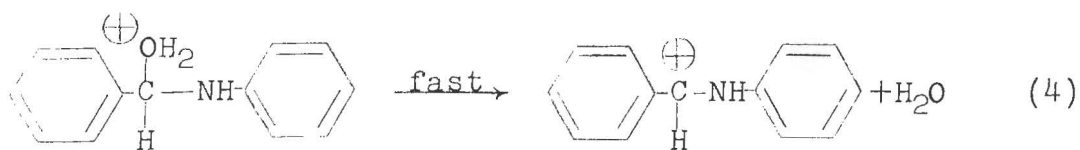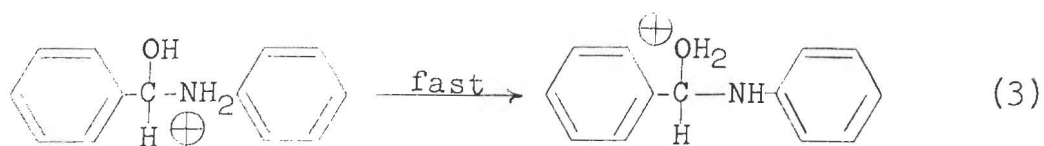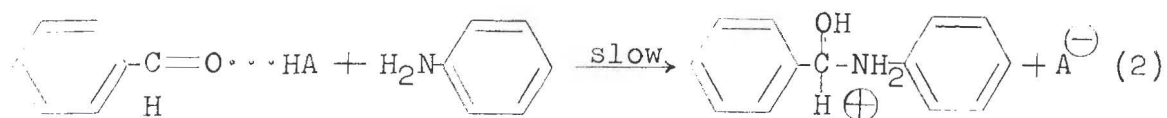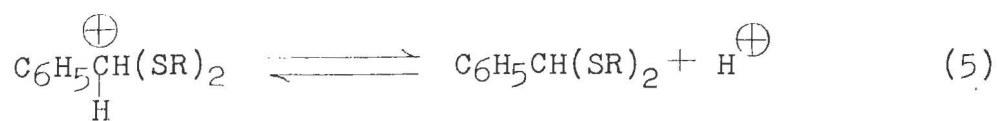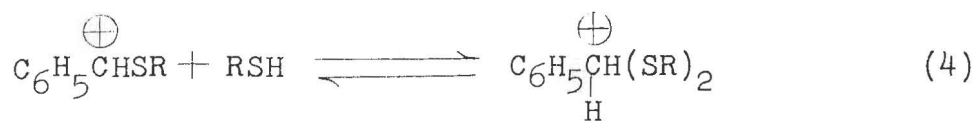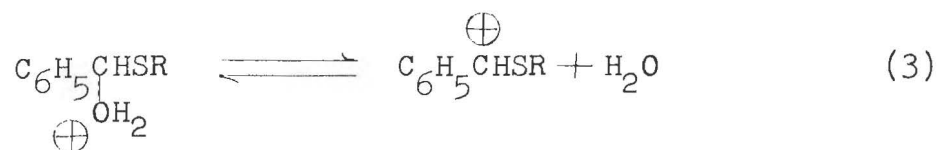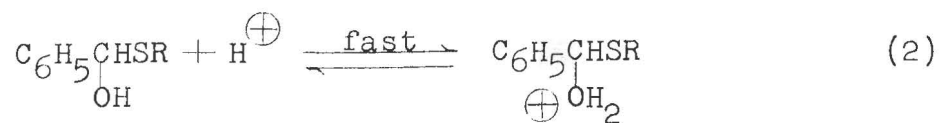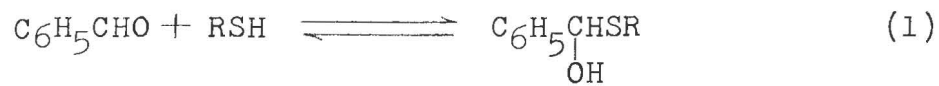
Figure III

Ketones

(1)

(2)

(3)

(4)

(5)
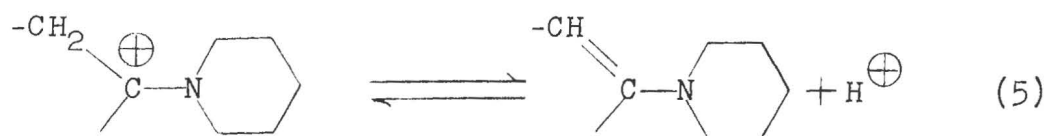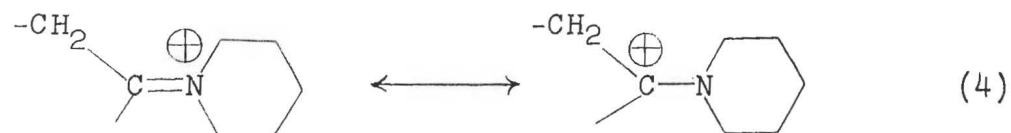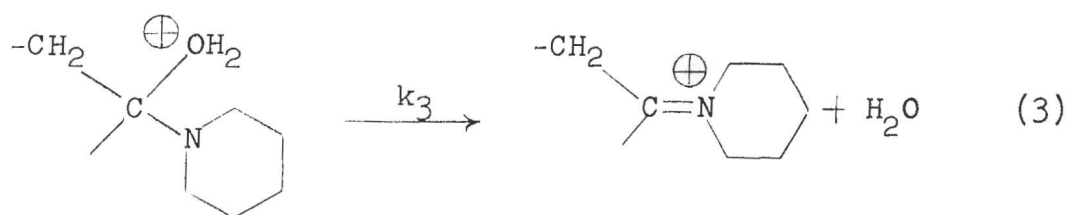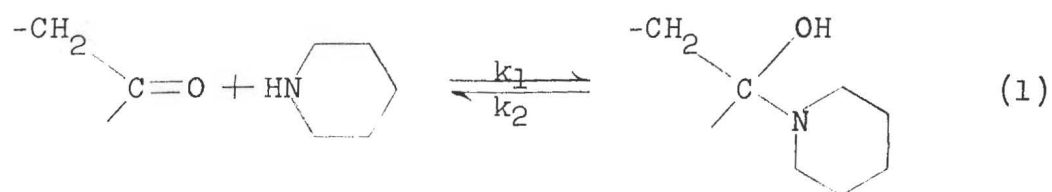
It was proposed by Brown[31] that for the sodium borohydride reduction of cyclic ketones the addition of the hydride ion to the carbonyl group was rate determining. This corresponds to step 1 of Fig. III. The addition of the hydride ion converted the sp^2 carbonyl carbon to a sp^3 carbon. This would result in internal strain and tend to increase steric interaction between the oxygen and certain of the hydrogen atoms. The least strain would be introduced into the cyclohexanone ring which reacted faster than cyclopentanone. The greatest interaction and strain would be introduced into the cycloheptanone ring which reacted the slowest.

The results found in this study are not inconsistent with those observed by Brown[31] if certain factors are considered. Brown,[31] in the reduction reaction, only measured the rate of addition. No dehydration took place. In this study, as in most carbonyl group reactions a loss of water occurred. It is reasonable to assume that the rate of addition of piperidine to the cyclic ketones is in the order $C_6 > C_5 > C_7$ for step 1 of Fig. III, but the rate of dehydration is in the order $C_7 > C_5 > C_6$ for step 3 of Fig. III. This order for dehydration is reasonable if one considers that addition to cycloheptanone would yield the greatest interactions between oxygen and the hydrogen atoms and the dehydration should therefore be most sterically accelerated in this case. A balance between rate of addition and dehydra-

tion, steps 1 and 3 could give the observed order of
$C_5 > C_6 > C_7$. It is pertinent to note that the addition of
piperidine to cycloheptanone is extremely slow and the equi-
librium of step 1 lies far to the left.

It was observed that pyrrolidine reacted faster than
hexamethyleneimine which reacted faster than piperidine.
These results lend support to step 3 as the rate controlling
step in which there is participation by the unshared pair of
electrons on the nitrogen atom. The concerted push of these
electrons results in an elemination of a molecule of water
and the conversion of an sp^3 nitrogen to an sp^2 nitrogen.
The amines with five and seven membered rings, pyrrolidine
and hexamethylene imine, release their internal strain in this
manner and react faster than piperidine which has less strain.[31]

The enhancement of the rate by the introduction of oxy-
gen or nitrogen into the amine ring as in morpholine and
N-methylpiperazine is probably due to a field effect, which
produces a greater push by the unshared electron pair, step
3, Fig. III. This type of interaction has been observed by
Leonard[51] in the infrared spectra of cyclic ketones. He
found that nitrogen had a greater effect than oxygen which
supports the results found in this investigation.

For most of those reactions listed in Table X, it is
difficult to state with any certainty which step is rate
controlling, the addition or the dehydration. It is very

probable that with reactants so varied in structure, the rate controlling step or steps is not the same in all cases and the steps themselves may even be different.

Since under the conditions used with the acetophenones, Expts. 34, 35, 39, and 40, discussed above, electron with-drawing groups in the para position increased the rate. It appears that here the addition step rather than the dehydration step chiefly controlled the rate.

The reaction of aldehydes, in contrast to ketones, with piperidine is always assumed to proceed through a bis-amine intermediate which on distillation yields the desired enamine and piperidine. If this is the case, reaction between excess aldehyde and piperidine should result in less than the theoretical amount of water and enamine. The results for the Experiments 52 and 53, Table VII, in which the reactant ratio was varied show that essentially quantitative yields of both water and enamine are obtained even with excess aldehyde. Consideration of steps 1 and 2 of Fig. IV indicates that the bis-amine can be protonated and give rise to a series of equilibria. If piperidine in step 1, Fig. IV, is replaced by another amine such as morpholine an intermediate, VIII, would result. On distillation, VIII could give either the piperidino or morpholino enamine, equivalent quantities of each and/or different amounts of each. Clear cut evidence of the smooth formation of bis-amine was obtained when the reaction of benz-

Figure IV

Aldehydes

$$(1)$$

$$(2)$$
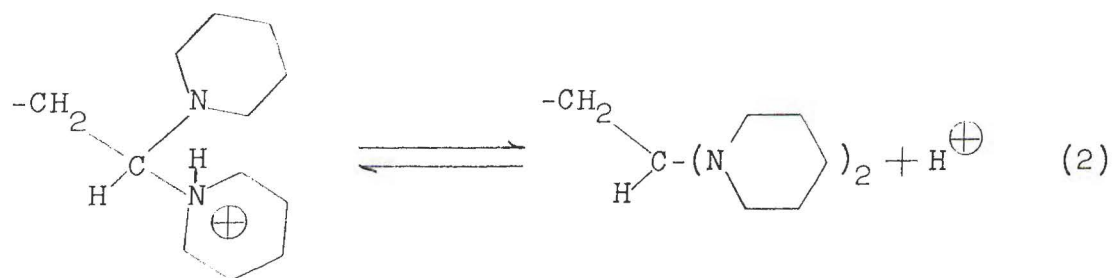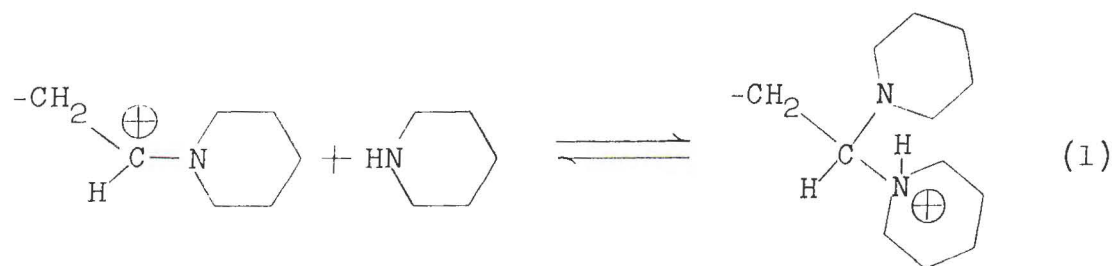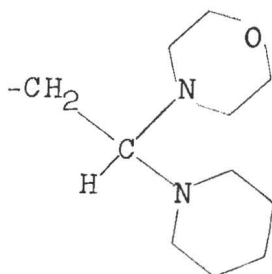
VIII

aldehyde and piperidine was carried out under the standard
conditions for aldehyde, Expt. 71. A 67% yield of the bis-
amine was isolated and the reaction was exactly first order
in each reactant (see Experimental.)

Transenamination was effected, Expt. 72, by refluxing
0.125 mole of the piperidino enamine of 2-ethylhexaldehyde,
0.375 mole of morpholine and 0.000125 mole of catalyst di-
luted to 500 ml. with benzene. The results of vapor phase
chromatography of the product showed that exchange of the
amine residue had occurred in a ratio of 8 morpholine to 1
piperidine. Repitition of this experiment with 0.125 mole
of the morpholino enamine, Expt. 73, and 0.375 mole of piper-
idine showed that the morpholino enamine was produced in a
5.3 to 1 excess. This indicates the greater stability of
the morpholino enamine over that of the piperidine. Also,
the fact that exchange occurs makes steps 1 and 2, Fig. IV,
seem reasonable. Further it explains why with an excess of

aldehyde, theoretical quantities of water and enamine are obtained.

It should be noted that enamines in general are not stable to atmospheric moisture and hydrolyze to the parent carbonyl compound and amine. In only one case, dimedone was the enamine found to be stable.

The perchlorates of enamines are quite stable compared to the enamines themselves but slowly decompose over a length of time. Most products were identified by elemental analysis of the perchlorates or by titration of the enamines themselves with standard hydrochloric acid to a bromphenol blue end point.

The infrared spectra of the enamine perchlorates gave some indications that protonation occurs on the α-carbon in

$$-\overset{|}{\underset{H}{C}} = \overset{|}{\underset{H}{C}} - \overset{|}{N} - \quad \xrightarrow{\ \ H\ \ } \quad -\overset{H}{\underset{H}{\overset{|}{C}}} - \overset{\oplus}{\underset{H}{\overset{|}{C}}} = \overset{\oplus}{N} -$$
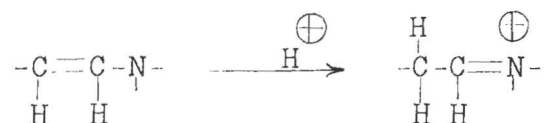
preference to the nitrogen atom. This selectivity also exists in enamines derived from β-diketones.

Integral order kinetics was ordinarily not obtained for the experiments of Table I through IX. In a few special cases, summarized in Table X, however, the reaction was quite close to first order in each reactant. Here possibly either the addition of the amine to the carbonyl group, step 1, Fig. III, or the dehydration, step 3, Fig. III, was probably rate

controlling while in the other cases both steps may have influenced the rate.

The reaction rate constants given in Table X where calculated from the expression

$$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)} = kt$$

where b is the concentration of amine, a the concentration of carbonyl compound and x is the amount of water produced in time, t. Since equilibrium conditions were not immediately obtained, an accurate determination of $t_{0\%}$ was not possible. For this reason, calculation of all rate constants was based upon $t_{10\%}$, the time at which the reaction was 10% complete.

Table X

Experiments Yielding Second Order Kinetics

$$k \times 10^3 \text{ l. mole}^{-1} \text{ min.}^{-1}$$

Reactant	Expt. No.	15%	20%	25%	30%	35%	40%	45%	50%	55%	60%	Avge. Dev.
Cyclopentanone	19	33.0	34.9	34.1	34.7	34.9	34.0	33.9	32.1	33.5	--	0.6
1,3-Cyclohexanedione	23	25.3	25.3	25.3	25.9	26.2	25.7	25.0	23.66	-- -	--	0.5
Acetylacetone	36	1.73	1.73	1.75	1.76	1.78	1.74	1.69	1.69	1.69	1.69	0.3
Ethyl Acetoacetate	37	1.26	1.32	1.34	1.35	1.34	1.36	1.35	1.35	1.39	1.40	0.03
2-Ethylhexaldehyde	50	1.76	1.74	1.68	1.79	1.74	1.76	1.77	1.77	1.79	- -	0.03
Phenylacetaldehyde	54	41.8	40.9	40.5	40.7	40.3	40.1	39.9	39.9	40.1	-- -	0.5
Pyrrolidine	59	253.0	238.0	235.0	234.0	231.0	232.0	233.0	245.0	242.0	-- -	6.0
4-Methylpiperidine	61	98.3	99.5	97.5	97.7	97.2	96.0	94.7	94.7	96.2	95.6	1.7
N-Methylpiperazine	63	17.4	18.0	17.6	17.5	17.2	17.4	17.4	17.8	-- -	-- -	0.2

EXPERIMENTAL

General Considerations[*]

The thiophene free benzene was distilled before use. The first and last 15% were discarded.

All of the compounds in Table XI were purified by standard techniques of crystallization or distillation until their physical constants agreed closely with the literature values; they also exhibited a high degree of purity according to the results of vapor phase chromatography. The vapor phase chromatograph used in this work was an F and M Scientific Co. Chromatograph Model 300.

The reactions were conducted in a 1 l. round bottomed flask with three standard tapered necks. One side neck was fitted with a modified Dean-Stark water separator surmounted by a West condenser while the other side neck was fitted with a thermometer well which contained silicone oil; a calibrated thermometer was placed in the well. The center neck was fitted with a glass stopper. All joints were lightly greased and the apparatus was always assembled with the joints properly matched. The same Variac, mantle and thermometer, were used with each set-up.

The flask was rinsed with acetone, scrubbed with detergent and water, scrubbed again with scouring powder and

---

[*]The author wishes to thank Dr. Franz J. Kasler for the microanalysis reported in this thesis.

water, dried and then filled with chromic acid cleaning so-
lution and placed on a steam bath for at least 10 hours.
After pouring out the cleaning solution, the flask was rinsed
ten times with warm water after the disappearance of the
last trace of color of the cleaning solution.

The water separator and condenser were scrubbed with
detergent and water, twice with scouring powder and water,
again with detergent and water. The trap was then rinsed
with cold water until completely free from traces of soap
and scouring agent. The openings of the water separator
were closed with aluminum foil. The condenser was scrubbed
as described for the water separator and the ends were cov-
ered with aluminum foil until the apparatus was assembled.
The flask, water separator and condenser were washed within
one hour of the beginning of the experiment, thus they were
still wet when the solution began to reflux.

Preparation of the solvent was accomplished by filling
a 500 ml. volumetric flask with benzene. A volume of sol-
vent equal in ml. to the weight, in grams, of the catalyst,
the amine, and the carbonyl compound under investigation was
withdrawn by means of a graduated pipet. Three-eighths of a
mole of amine and 0.001 mole of p-toluenesulfonic acid mono-
hydrate were introduced into the flask and the remainder of
the solvent was poured into the reaction flask. The glass-
ware used for liquid transfers was allowed to drain for one

minute.

The water separator was filled with solvent and about 1.0 ml. of water. A few boiling chips were introduced into the reaction mixture and it was refluxed for approximately two hours by means of a hemispherical heating mantle which was controlled by a Variac. One-eight of a mole of carbonyl compound was weighed into a short vial. "Zero" time was taken when the vial and its contents were dropped into the flask. After the vial was dropped in, the flask was swirled to insure thorough mixing of the reactants. Numerous readings of water volume, time and temperature were taken. The reaction was allowed to proceed for a period of time equal to 10 to 15 times the time for 50% of the water to be evolved. The $t_{\frac{1}{2}}$ values were read from plots of water volume versus time. This standard procedure was used in all cases unless otherwise noted.

Once the reaction was stopped, the reaction flask was connected to a water aspirator and the benzene was evaporated at reduced pressure. The residue was transferred to a 250 ml. one neck, round bottomed flask with three 10 ml. portions of ether. The flask was fitted with a three inch Claisen column and condenser. The ether was distilled at atmospheric pressure. The pressure was then reduced and the enamine distilled.

The enamines of most ketones were converted to their

respective perchlorates by means of the following procedure: 0.01 mole of the enamine was dissolved in 25 ml. of ether and cooled in an ice bath. A solution of 10 ml. of absolute alcohol and 10 ml. of 70% perchloric acid was added dropwise to the ether solution until congo red paper turned blue. The white, solid perchlorate was collected by filtration and recrystallized from a mixture of ether and acetone.

In the case of enamines of aldehydes and some ketones which did not yield perchlorates, the enamines were analyzed by titration with standard hydrochloric acid by the following procedure: Approximately one gram of enamine was dissolved in a solution consisting of 25 ml. of acetone and 25 ml. of distilled water; 5 drops of 1% bromphenol blue indicator were added and the enamine solution was then titrated with standard 0.1445 N hydrochloric acid.

Table XI

Physical Constants of Reactants

Compound	Observed[a]	Literature[b]	Purity, %[c]
Cyclic Ketones			
Cyclohexanone	n_D^{20} 1.4500	n_D^{20} 1.4509	100
Cyclopentanone	n_D^{20} 1.4370	n_D^{20} 1.4366	100
4-Methylcyclohexanone	n_D^{20} 1.4458	n_D^{20} 1.4458	100
3-Methylcyclohexanone	n_D^{20} 1.4431	n_D^{20} 1.4430	100
α-Tetralone	b.p. 136-137°(18mm)	b.p. 136°(16mm)	100
1,3-Cyclohexanedione	m.p. 105-106°	m.p. 105-106°	---
Dimedone	m.p. 146.6-146.9°	m.p. 144-144.5°	---
2-Carbethoxycyclopentanone	n_D^{20} 1.4522	n_D^{20} 1.4519	99
2-Acetylcyclopentanone	n_D^{20} 1.4882	--	98
Cycloheptanone	n_D^{20} 1.4612	n_D^{20} 1.4608	100
2-Methylcyclohexanone	n_D^{20} 1.4480	n_D^{20} 1.4482	100
β-Tetralone	b.p. 91-91.5°(2mm)	m.p. 68.5-69.0°	100
1,2-Cyclohexanedione	m.p. 35-36°	m.p. 34°	---
Phloroglucinol	m.p. 208-212°	m.p. 209-219°	---
1,4-Cyclohexanedione	m.p. 77.5-78.5°	m.p. 77-78°	---

Table XI (continued)

Compound	Observed[a]	Literature[b]	Purity, %[c]
	Methyl Ketones		
Phenylacetone	n_D^{20} 1.5170	n_D^{20} 1.5168	99
p-Chloroacetophenone	b.p. 100-101°(6mm)	b.p. 99°(7mm)	100
Acetophenone	$n_D^{18.8}$ 1.5338	$n_D^{18.8}$ 1.5338	100
Acetylacetone	n_D^{19} 1.4540	n_D^{17} 1.4541	100
Ethylacetoacetate	n_D^{20} 1.4197	n_D^{20} 1.4198	99.5
Benzoylacetone	m.p. 60-61°	m.p. 60-61°	--
p-Methylacetophenone	n_D^{20} 1.5337	n_D^{20} 1.5335	95
p-Nitroacetophenone	m.p. 78.9-79.1°	m.p. 80-81°	--
Dibenzoylmethane	m.p. 77.8-78.4°	m.p. 78°(72-73)	--
Heptanone-2	n_D^{20} 1.4084	n_D^{20} 1.4083	100
Diacetyl	n_D^{20} 1.3942	$n_D^{18.5}$ 1.3933	100
Acetonylacetone	n_D^{20} 1.4230	n_D^{20} 1.4232	100
Acetoacetanilide	m.p. 84.3-84.9°	m.p. 85°	--
o-Chloroacetoacetanilide	m.p. 107-108°	m.p. 107°	--

Table XI (continued)

Compound	Observed[a]	Literature[b]	Purity, %[c]
Aldehydes			
Phenylacetaldehyde	n_D^{20} 1.5256	$n_D^{19.6}$ 1.5255	100
Heptaldehyde	n_D^{20} 1.4120	$n_D^{19.9}$ 1.4125	100
Cyclohexanecarboxaldehyde	n_D^{19} 1.4496	n_D^{19} 1.4495	100
2-Ethylhexaldehyde	n_D^{20} 1.4160	n_D^{20} 1.4160	100
3-Phenylpropionaldehyde	n_D^{17} 1.5242	$n_D^{17.5}$ 1.5280	100
i-Valeraldehyde	n_D^{20} 1.3905	n_D^{20} 1.3902	100
Benzaldehyde	$n_D^{18.5}$ 1.5460	n_D^{20} 1.5450	100
Amines and Mercaptans			
Piperidine	n_D^{20} 1.4530	n_D^{20} 1.4530	100
Morpholine	n_D^{20} 1.4545	n_D^{20} 1.4545	100
Hexamethyleneimine	n_D^{23} 1.4116	$n_D^{23.3}$ 1.4132	98.5
Pyrrolidine	n_D^{15} 1.4271	n_D^{15} 1.4270	100
2-Methylpiperidine	n_D^{20} 1.4466	n_D^{20} 1.4464	100
3-Methylpiperidine	n_D^{24} 1.4465	$n_D^{24.3}$ 1.4463	99
4-Methylpiperidine	n_D^{20} 1.4370	$n_D^{21.6}$ 1.4378	100
N-Methylaniline	n_D^{20} 1.5705	$n_D^{21.2}$ 1.5702	100

Table XI (continued)

Compound	Observed[a]	Literature[b]	Purity, %[c]
Amines and Mercaptans (continued)			
N-Methyl-N-butylamine	n_D^{20} 1.4015	$n_D^{18.3}$ 1.4018	100
Dibutylamine	n_D^{20} 1.4095	n_D^{20} 1.4097	100
N-Methylpiperazine	b.p. 135°(760)	b.p. 133-136°(760)	99
n-Octylmercaptan	n_D^{25} 1.4516	n_D^{25} 1.4519	100
Phenylmercaptan	n_D^{25} 1.5859	$n_D^{23.2}$ 1.5861	100
Other Compounds			
Benzene	n_D^{25} 1.4985	n_D^{25} 1.4985	100
Toluene	n_D^{20} 1.4968	n_D^{20} 1.4969	100
p-Toluenesulfonic Acid Monohydrate	m.p. 105-106°	m.p. 106°	---

[a] m.p. or n_D^{o}C   [b] Physical constants obtained from standard handbooks

[c] Determined by vapor phase chromatography

The Reaction of Cyclohexanone with Piperidine

Expt. 1. The experiment numbers throughout this section correspond to the numbers given in the Discussion.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
10	0.220	85	1.090
15	0.380	105	1.185
20	0.460	125	1.260
25	0.550	155	1.350
35	0.690	200	1.450
45	0.810	250	1.550
55	0.910	300	1.655
65	0.975	360	1.735
75	1.035	Final	2.170

The product was not isolated.

Expt. 2.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.165	135	1.235
9	0.280	180	1.340
14	0.390	250	1.450
21	0.510	310	1.520
30	0.635	380	1.595
38	0.735	440	1.670
55	0.875	500	1.745
76	1.000	630	1.820
105	1.130	Final	2.090

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 75° (80 mm.) after which the main fraction of 15.00g. was obtained at 130-131° (27 mm.)

Expt. 2A.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.180	130	1.305
10	0.320	160	1.400
15	0.450	190	1.500
20	0.550	280	1.610
30	0.690	340	1.680
40	0.800	400	1.740
50	0.900	520	1.830
70	1.025	640	1.900
90	1.150	Final	2.020

This is a duplicate of Expt. 2. The product was not isolated.

Expt. 3.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
6	0.160	130	1.210
9	0.260	170	1.325
15	0.385	210	1.415
20	0.460	280	1.525
30	0.600	380	1.660
40	0.720	680	1.820
55	0.860	845	1.870
75	0.995	1760	1.960
100	1.110	Final	2.190

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 63° (110 mm.) after which the main fraction was obtained at 80-81° (3 mm.)

Expt. 3A

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
6	0.160	100	1.110
10	0.265	130	1.240
15	0.380	165	1.360
20	0.470	210	1.465
25	0.560	280	1.545
35	0.670	345	1.620
45	0.775	440	1.720
55	0.870	640	1.820
80	0.990	Final	2.175

This is a duplicate of Expt. 3. The product was not isolated.

Expt. 4

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.105	125	1.225
10	0.245	175	1.395
15	0.385	235	1.520
25	0.515	315	1.625
35	0.655	400	1.725
45	0.745	505	1.800
55	0.830	810	1.875
75	0.965	1520	1.935
95	1.115	Final	1.985

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of fore-run was obtained at 63-78°(140 mm.) after which the main fraction of 17.34g. was obtained at 132-133°(26 mm.)

Expt. 4A.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
6	0.120	90	1.055
10	0.230	120	1.165
15	0.350	160	1.310
20	0.430	215	1.435
25	0.515	285	1.580
35	0.625	390	1.690
45	0.730	510	1.760
55	0.820	645	1.815
70	0.930	Final	2.010

This is a duplicate of Expt. 4. The product was not isolated.

Expt. 5.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
6	0.135	104	1.100
13	0.270	127	1.200
21	0.400	155	1.300
28	0.500	185	1.400
36	0.600	225	1.500
46	0.700	300	1.620
57	0.800	370	1.700
70	0.900	440	1.795
86	1.000	Final	2.100

The product was not isolated.

74

Expt. 6.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.105	140	1.120
15	0.245	180	1.250
25	0.405	220	1.370
40	0.525	270	1.475
50	0.615	360	1.595
60	0.710	430	1.710
70	0.795	520	1.765
90	0.915	1582	2.015
110	1.015	Final	2.115

The product was not isolated.

Expt. 7.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
15	0.100	240	1.135
25	0.200	300	1.280
35	0.300	360	1.380
55	0.425	440	1.495
65	0.500	540	1.600
85	0.610	725	1.705
115	0.770	1449	1.925
145	0.900	1899	2.000
185	1.000	Final	2.125

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount of
forerun was obtained at 65-80° (90 mm.) after which the main
fraction of 18.46 g. was obtained at 134-136° (29 mm.)

Expt. 7A.

Time, min.	H$_2$O, ml.	Time, min.	H$_2$O, ml.
15	0.150	271	1.275
28	0.275	300	1.330
42	0.400	385	1.480
60	0.525	465	1.585
82	0.650	645	1.710
107	0.775	750	1.795
137	0.900	1440	1.965
173	1.025	2160	2.095
216	1.150	Final	2.115

This is a duplicate of Expt. 7. The product was not isolated.

Expt. 8.

Time, min.	H$_2$O, ml.	Time, min.	H$_2$O, ml.
10	0.085	270	1.100
30	0.195	310	1.180
50	0.310	350	1.265
70	0.460	430	1.370
90	0.550	495	1.475
115	0.630	605	1.570
145	0.755	735	1.675
175	0.865	1305	1.920
210	0.970	Final	2.150

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 37° (30 mm.) after which the main fraction of 19.30 g. was obtained at 135-136° (28 mm.)

Expt. 8A.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		240	1.005
10	0.070	280	1.115
20	0.145	360	1.250
40	0.270	440	1.370
60	0.390	510	1.470
80	0.490	665	1.570
110	0.580	800	1.675
125	0.665	1448	1.880
165	0.790	Final	2.175
185	0.870		

This is a duplicate of Expt. 8. The product was not isolated.

Expt. 9.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		330	0.995
10	0.030	430	1.125
30	0.150	555	1.300
50	0.230	655	1.400
70	0.330	795	1.500
90	0.400	865	1.560
110	0.495	1470	1.800
150	0.580	1830	1.900
195	0.700	Final	2.025
255	0.850		

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 55° (25 mm.) after which the main fraction of 17.55 g. was obtained at 133° (25 mm.)

Expt. 10.

Time, min.	H₂O, ml.	Time, min.	H₂O, ml.
20	0.095	655	1.170
60	0.210	715	1.270
90	0.320	845	1.360
150	0.470	1447	1.660
210	0.570	1687	1.770
270	0.690	1897	1.840
355	0.840	2917	1.970
415	0.950	3557	2.070
475	1.045	Final	2.170

The product was not isolated.

Expt. 11.

Time, min.	H₂O, ml.	Time, min.	H₂O, ml.
15	0.055	300	0.925
30	0.150	385	1.085
45	0.235	420	1.155
75	0.630	495	1.255
105	0.460	585	1.355
140	0.555	650	1.435
160	0.645	850	1.535
200	0.745	1845	2.025
270	0.870	Final	2.275

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 49° (140 mm.) after which the main fraction of 18.55 g. was obtained at 134-135° (27 mm.)

Expt. 10.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
20	0.095	655	1.170
60	0.210	715	1.270
90	0.320	845	1.360
150	0.470	1447	1.660
210	0.570	1687	1.770
270	0.690	1897	1.840
355	0.840	2917	1.970
415	0.950	3557	2.070
475	1.045	Final	2.170

The product was not isolated.

Expt. 11.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
15	0.055	300	0.925
30	0.150	385	1.085
45	0.235	420	1.155
75	0.630	495	1.255
105	0.460	585	1.355
140	0.555	650	1.435
160	0.645	850	1.535
200	0.745	1845	2.025
270	0.870	Final	2.275

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 49° (140 mm.) after which the main fraction of 18.55 g. was obtained at 134-135° (27 mm.)

Expt. 12.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.155	60	1.095
10	0.300	70	1.190
15	0.445	90	1.300
20	0.545	110	1.440
25	0.605	140	1.590
30	0.725	170	1.690
35	0.795	220	1.800
40	0.890	380	2.025
50	0.990	Final	2.195

The product was not isolated.

Expt. 13.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
10	0.135	85	1.030
15	0.230	105	1.150
20	0.325	125	1.255
25	0.405	145	1.360
35	0.530	175	1.490
45	0.640	215	1.610
55	0.750	275	1.740
60	0.810	315	1.830
75	0.935	Final	2.230

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 66° (120 mm.) after which the main fraction of 19.75 g. was obtained at 133-135° (26 mm.); the perchlorate which was prepared by the procedure given previously melted at 212-213° (dec.). Anal. Calcd. for $C_{11}H_{20}ClNO_4$: C, 47.99; H, 7.91. Found: C, 48.21; H, 8.11.

Expt. <u>14</u>.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
9	0.150	155	1.270
18	0.270	190	1.400
28	0.400	220	1.500
37	0.500	259	1.600
49	0.625	310	1.700
66	0.775	335	1.750
83	0.900	365	1.790
104	1.025	395	1.805
128	1.150	Final	2.200

The product was not isolated.

Expt. <u>15</u>.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
10	0.070	340	0.940
20	0.140	440	1.040
40	0.240	605	1.165
60	0.330	805	1.270
100	0.470	1480	1.400
140	0.580	2260	1.520
180	0.670	3580	1.630
205	0.715	5050	1.670
265	0.840	Final	1.770

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 50-63° (26 mm.) after which the main fraction of 13.55 g. was obtained at 133-135° (25 mm.).

Expt. 16.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
10	0.120	130	1.020
15	0.220	180	1.145
25	0.320	200	1.215
35	0.420	285	1.420
40	0.495	345	1.535
50	0.600	405	1.625
70	0.715	465	1.715
90	0.820	540	1.815
110	0.915	Final	2.160

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 50-75° (35 mm.) after which the
main fraction of 17.35 g. was obtained at 140-141° (35 mm.).

Expt. 17.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
10	0.105	105	1.010
15	0.190	125	1.135
25	0.335	155	1.240
30	0.400	175	1.305
35	0.480	200	1.400
45	0.580	230	1.500
55	0.695	260	1.590
75	0.810	290	1.635
85	0.900	Final	2.200

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 67° (120 mm.) after which the
main fraction of 17.95 g. was obtained at 136-137° (27 mm.).

Expt. 18.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.080	61	0.950
11	0.240	71	1.040
16	0.340	84	1.110
21	0.440	100	1.240
26	0.540	115	1.335
31	0.625	130	1.425
36	0.660	160	1.540
41	0.740	190	1.640
51	0.840	Final	2.220

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 63-65° (27 mm.) after which the main fraction of 17.81 g. was obtained at 134-136° (27 mm.).

The Reaction of Piperidine with Cyclic Ketones

Expt. 19.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.190	41	1.225
8	0.320	50	1.355
11	0.460	60	1.495
14	0.595	70	1.590
17	0.690	80	1.670
20	0.790	95	1.780
26	0.920	110	1.855
29	1.000	185	2.090
35	1.120	Final	2.275

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 36-39° (27 mm.) after which the
main fraction of 18.95 g. was obtained at 118-119.5° (26 mm.);
the perchlorate which was prepared by the procedure given
previously melted at 220-221° (dec.). Anal. Calcd. for
$C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21. Found: C, 48.00; H, 7.25.

Expt. 20.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.060	95	0.925
15	0.170	123	1.065
20	0.260	145	1.160
30	0.365	160	1.200
40	0.495	175	1.285
51	0.585	205	1.460
60	0.665	235	1.560
72	0.765	485	1.795
85	0.855	Final	2.200

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount of
forerun was obtained at 85° (27 mm.) after which the main
fraction of 17.88 g. was obtained at 138-140° (27 mm.); the
perchlorate which was prepared by the procedure given
previously melted at 210-212° (dec.). <u>Anal</u>. Calcd. for
$C_{12}H_{22}ClNO_4$: C, 51.52; H, 7.93. Found: C, 51.75; H, 8.01.

Expt. 21.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		140	0.995
10	0.080	175	1.105
20	0.200	205	1.200
30	0.300	325	1.500
40	0.400	360	1.590
50	0.495	405	1.640
70	0.600	520	1.735
80	0.690	580	1.800
100	0.800	Final	2.200
120	0.895		

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 69-75° (27 mm.) after which the
main fraction of 20.08 g. was obtained at 141-142° (27 mm.);
the perchlorate which was prepared by the procedure given
previously melted at 205-207° (dec.). <u>Anal</u>. Calcd. for
$C_{12}H_{22}ClNO_4$: C, 51.52; H, 7.93. Found: C, 51.69; H, 7.89.

Here, as well as in Expt. 28, the enamine is doubtlessly
a mixture of the two isomers; but the perchlorate is a single
compound.

Expt. 22.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
30	0.130	285	1.010
60	0.250	345	1.130
90	0.390	405	1.230
120	0.505	465	1.330
150	0.615	525	1.450
195	0.750	660	1.605
240	0.865	Final	2.130

The residue obtained according to the standard proce-
dure was recrystallized from Skelly B to yield 16.93 g. of
solid melting at 33-35°. The perchlorate which was prepared
by the procedure given previously melted at 196-197° but was
not stable. The enamine was titrated with standard 0.1445N
hydrochloric acid. Eqt. wt. Calcd. 219. Found: 216, 217.

Expt. 23.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.115	55	1.220
10	0.305	65	1.315
15	0.475	75	1.415
20	0.615	95	1.535
25	0.735	110	1.615
30	0.835	125	1.665
35	0.945	135	1.715
40	1.025	150	1.740
45	1.115	Final	2.200

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount

of forerun was obtained at 75° (1 mm.) after which the main fraction of 14.30 g. was obtained at 168-170° (1 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 268. Found: 269, 270.

Expt. 24.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
15	0.085	220	0.995
30	0.190	235	1.020
45	0.290	320	1.220
60	0.350	365	1.320
85	0.480	405	1.400
105	0.555	465	1.460
145	0.725	495	1.520
165	0.810	630	1.645
195	0.905	Final	2.225

The residue obtained according to the standard procedure was recrystallized from ether-benzene to yield 20.93 g. of yellow-white needles melting at 90.4-91.9°. The perchlorate prepared by procedure given previously melted at 198.5-200.1° (dec.). Anal. Calcd. for $C_{13}H_{22}ClNO_5$: C, 50.73; H, 7.21. Found: C, 50.79; H, 7.40.

Expt. 25.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		356	1.045
21	0.100	397	1.120
47	0.200	427	1.190
83	0.335	499	1.280
120	0.490	552	1.330
152	0.590	1148	1.720
180	0.675	1477	1.780
212	0.740	Final	2.220
242	0.815		

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 74-76° (0.3 mm.) after which the
main fraction of 12.97 g. was obtained at 105-107° (0.3 mm.).
The enamine was titrated with standard 0.1445N hydrochloric
acid. Eqt. wt. Calcd: 227. Found: 228, 230.

Expt. 26.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		1192	1.050
60	0.110	1454	1.140
120	0.220	1835	1.245
180	0.320	2700	1.360
240	0.415	3162	1.520
360	0.520	3280	1.620
461	0.630	Final	2.220
574	0.725		

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained 39-40° (0.5 mm.) after which the

main fraction of 21.19 g. was obtained at 114-116° (0.3 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 193. Found: 189, 190.

Expt. 27.

After 12 days, 1.305 ml. of water was obtained. The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 85-90° (26 mm.) after which the main fraction of 9.83 g. was obtained at 143-144° (26 mm.); the perchlorate which was prepared by the procedure given previously melted at 195-197° (dec.). Anal. Calcd. for $C_{12}H_{22}ClNO_4$: C, 51.52; H, 7.93. Found: C, 51.45; H, 7.87.

Expt. 28.

After three weeks, 1.410 ml. was obtained. The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 78-85° (33 mm.); the perchlorate which was prepared by the procedure given previously melted at 222-223° (dec.). Anal. Calcd. for $C_{12}H_{22}ClNO_4$: C, 51.52; H, 7.93. Found: C, 51.56; H, 7.99.

Expt. 29.

α-Tetralone yielded only 0.050 ml. of water after 24
hours of refluxing. The reaction mixture was discarded.

Expt. 30.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
4	0.095	92	0.620
8	0.170	140	0.775
12	0.250	195	0.870
24	0.330	290	1.150
36	0.395	450	1.270
42	0.445	515	1.340
60	0.490	575	1.370
67	0.520	1140	1.705
78	0.570	Final	2.060

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. The material
charred and polymerized at a bath temperature of 250° and a
pressure of 0.2 mm.

Expt. 31.

Phloroglucinol yielded 0.900 ml. of water in 11 days.
Attempts to distill the residue obtained according to the
standard procedure under reduced pressure resulted in char-
ring.

Expt. 32.

Time, min.	H$_2$O, ml.	Time, min.	H$_2$O, ml.
15	0.220	175	2.025
30	0.485	207	2.220
40	0.610	235	2.400
55	0.815	265	2.560
70	1.020	333	2.910
95	1.185	383	3.100
115	1.440	443	3.305
135	1.655	513	3.495
155	1.840	Final	4.540

The residue obtained according to the standard procedure was recrystallized from benzene to yield 21.65 g. of yellow-brown needles melting at 79-82°. Attempts to further purify the material from ether or benzene resulted in tarry residues.

The Reaction of Piperidine with Methyl Ketones

Expt. 33.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
15	0.040	600	0.540
90	0.090	660	0.595
115	0.160	870	0.705
175	0.210	1050	0.805
225	0.260	1440	0.990
250	0.300	1825	1.115
350	0.385	1955	1.185
465	0.445	2295	1.275
525	0.505	Final	1.795

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. A small amount
of forerun was obtained at 30-32° (0.2 mm.) after which the
main fraction of 17.39 g. was obtained at 95° (0.2 mm.); the
perchlorate prepared by the method given previously melted
at 124-125°. Anal. Calcd. for $C_{14}H_{20}ClNO_4$: C, 55.72;
H, 6.68. Found: C, 55.91; H, 6.94.

Expt. 34.

Time, hr.	H_2O, ml.	Time, hr.	H_2O, ml.
3	0.110	65	0.570
6	0.160	70	0.600
20	0.195	78	0.695
44	0.310	102	0.910
48	0.400	126	1.310
54	0.470	Final	1.795

The residue obtained according to the standard procedure was distilled at reduced pressure. A small amount of forerun was obtained at 95-100° (10 mm.) after which the main fraction of 18.57 g. was obtained at 135-137° (0.2 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 222. Found: 219, 220.

Expt. 35.

Time, hr.	H_2O, ml.	Time, hr.	H_2O. ml.
		73.0	0.980
1.0	0.075	93.6	1.110
7.0	0.195	110.4	1.175
12.0	0.270	128.9	1.290
20.0	0.400	152.9	1.375
25.0	0.470	163.9	1.400
28.0	0.500	573.0	1.600
35.6	0.595	602.0	1.640
45.0	0.700	Final	2.220
53.7	0.800		

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 70° (100 mm.) after which the main fraction of 19.47 g. was obtained at 90-92° (0.2 mm.); the perchlorate obtained by the procedure given previously melted at 129-130° (dec.). Anal. Calcd. for $C_{13}H_{18}ClNO_4$: C, 54.26; H, 6.31. Found: C, 54.00; H, 6.07.

Expt. 36.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		510	0.955
15	0.040	575	1.040
30	0.095	660	1.140
85	0.205	835	1.320
130	0.305	1010	1.465
190	0.430	1255	1.525
240	0.530	1315	1.575
310	0.680	1450	1.630
385	0.790	Final	2.275
455	0.885		

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 65-67° (70 mm.) after which the main fraction of 18.00 g. was obtained at 112-114° (1 mm.); the perchlorate prepared according to the procedure given previously melted at 164.5-165°. Anal. Calcd. for $C_{10}H_{18}ClNO_5$: C, 44.86; H, 6.78. Found: C, 45.14; H, 7.04.

Expt. 37.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		620	0.960
15	0.030	775	1.105
35	0.085	890	1.220
65	0.150	1195	1.475
125	0.270	1320	1.550
155	0.300	1455	1.625
230	0.425	1560	1.685
305	0.555	1875	1.800
425	0.700	Final	2.240
485	0.790		

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 35-40° (1 mm.) after which the main fraction of 21.18 g. was obtained at 110-112° (1 mm.); the perchlorate prepared by the method given previously melted at 80.6-81.0°. <u>Anal</u>. Calcd. for $C_{11}H_{20}ClNO_6$: C, 44.37; H, 6.77. Found: C, 44.57; H, 7.01.

Expt. <u>38</u>.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
		900	0.995
60	0.085	1080	1.085
120	0.175	1380	1.245
210	0.300	1500	1.315
300	0.410	1988	1.510
390	0.515	2820	1.615
420	0.610	3840	1.695
510	0.700	4660	1.750
600	0.775	Final	2.250
720	0.850		

The residue obtained according to the standard procedure was recrystallized from ether-benzene to yield 21.67 g. of solid melting at 97-98°. The perchlorate prepared by the method given previously melted at 162-163° (dec.). <u>Anal</u>. Calcd. for $C_{15}H_{20}ClNO_5$: C, 54.63; H, 6.11. Found: C, 54.68; H, 6.35.

Expt. 39.

Time, hr.	H_2O, ml.	Time, hr.	H_2O, ml.
		85.5	0.925
5.0	0.100	97.0	0.980
10.5	0.170	110.7	1.040
15.0	0.220	122.4	1.105
24.0	0.310	136.5	1.150
36.5	0.460	144.5	1.205
48.0	0.560	157.0	1.250
58.5	0.630	207.0	1.410
63.5	0.740	Final	1.900
74.5	0.830		

The residue obtained according to the standard procedure charred and polymerized on distillation.

Expt. 40.

Time, hr.	H_2O, ml.	Time, hr.	H_2O, ml.
			0.905
0.5	0.050	24.0	1.065
1.0	0.100	29.0	1.150
2.0	0.170	33.0	1.210
4.0	0.265	37.0	1.330
6.0	0.350	44.0	1.390
9.0	0.470	48.0	1.505
12.0	0.565	54.0	1.655
16.0	0.680	60.7	2.240
20.0	0.780	Final	

The residue obtained according to the standard procedure charred and polymerized on distillation.

Expt. 41.

The standard experiment with dibenzoylmethane yielded

no water after refluxing for 4 days.

Expt. 42.

Heptanone-2 yielded 0.605 ml. of water after reacting 5 days. The small amount of residue obtained according to the standard procedure did not yield an identifiable fraction on distillation.

Expt. 43.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.080	85	1.060
10	0.170	105	1.145
15	0.295	143	1.245
20	0.420	163	1.280
25	0.550	250	1.440
35	0.680	370	1.550
41	0.770	490	1.650
50	0.860	610	1.720
65	0.965	Final	2.210

The residue obtained by the standard procedure was a black, intractable tan which could not be distilled.

Expt. 44.

Acetonylacetone yielded 2.100 ml. of water after refluxing for 22 days. No identifiable product could be obtained on distillation.

Expt. 45.

3-Methyl-2,4-pentanedione yielded 1.170 ml. of water after refluxing for 6 days. No identifiable product could be obtained on distillation.

Expt. 46.

4-Piperidino-3-pentene-2-one on refluxing with piperi-dine in o-xylene for 2 days did not yield any water.

Expt. 47.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
7	0.320	32	1.040
15	0.585	35	1.090
18	0.670	39	1.150
20	0.740	58	1.440
23	0.820	89	1.730
26	0.900	130	1.910
29	0.950	Final	2.205

The residue obtained according to the standard proce-dure was recrystallized from benzene and 8.77 g. of yellow-white solid which melted at 162-167° was obtained. Recrys-tallization from benzene yielded white solid which melted at 169-170°. Anal. Calcd. for $C_{15}H_{20}N_2O$: C, 73.76; H, 8.21; N, 11.47. Found: C, 70.41; H, 7.94; N, 13.49.

Expt. 48.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
11	0.105	158	0.910
25	0.215	194	1.040
40	0.320	261	1.170
50	0.390	294	1.260
61	0.460	319	1.315
75	0.540	382	1.390
90	0.620	464	1.510
111	0.720	623	1.630
135	0.820	Final	1.840

The residue obtained by the standard procedure was a
viscous, red liquid which contained some yellow solid. The
residue was dissolved in benzene but attempts to obtain
crystals from the solution were unsuccessful.

The Reaction of Piperidine with Various Aldehydes

Expt. 49.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
2	0.090	23	0.955
4	0.220	26	1.040
6	0.300	29	1.140
8	0.420	32	1.240
10	0.470	35	1.325
12	0.560	39	1.430
14	0.640	42	1.505
17	0.740	45	1.570
20	0.860	Final	2.240

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. The pressure was
reduced to 97 mm. with the bath temperature at 120° to de-
compose the bis-amine. After 1 hr. the pressure was lowered
to 16 mm. and 20.99 g. of enamine distilled at 116-117° with
a minimum of foaming.

Expt. 50.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.130	47	1.090
9	0.230	53	1.200
14	0.370	59	1.290
18	0.470	66	1.410
22	0.560	74	1.525
25	0.630	81	1.625
28	0.700	88	1.725
31	0.780	103	1.833
35	0.880	Final	2.260

The residue obtained according to the standard procedure was distilled at reduced pressure. The pressure was reduced to 100 mm. with the bath temperature at 150° to decompose the bis-amine. Ater 1 hr. the pressure was lowered to 20 mm. and the enamine distilled at 175-176° with a minimum of foaming; yield 24.09 g. The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 196. Found: 195, 197.

Expt. 51.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.100	54	0.980
9	0.230	59	1.060
13	0.330	64	1.150
18	0.420	77	1.300
23	0.530	85	1.380
28	0.600	92	1.460
33	0.680	100	1.540
38	0.760	125	1.700
43	0.900	Final	2.250

The residue obtained according to the standard procedure was distilled under reduced pressure. The pressure was reduced to 100 mm. with the bath temperature at 150° to decompose the bis-amine. After 1 hr. the pressure was lowered to 20 mm. and 21.69 g. of enamine distilled at 130-132° with a minimum of foaming.

Expt. 52.

Time, min.	H$_2$O, ml.	Time, min.	H$_2$O, ml.
4	0.090	37	1.150
6	0.180	41	1.250
8	0.265	46	1.340
12	0.420	51	1.400
15	0.520	57	1.500
18	0.605	65	1.580
21	0.700	71	1.660
24	0.780	79	1.740
28	0.930	Final	2.220

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. The pressure was
reduced to 100 mm. with the bath temperature at 150° to de-
compose the bis-amine. After 1 hr. the pressure was lowered
to 20 mm. and 21.89 g. of enamine distilled at 123-124° with
a minimum of foaming.

Expt. 53.

Time, min.	H$_2$O, ml.	Time, min.	H$_2$O, ml.
1.0	0.120	8.5	1.020
3.0	0.300	9.5	1.120
3.8	0.395	11.3	1.330
4.3	0.440	12.3	1.420
4.8	0.520	13.3	1.500
5.3	0.590	14.3	1.560
6.0	0.700	16.0	1.690
6.8	0.820	18.5	1.800
7.5	0.920	Final	2.240

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. The pressure was

reduced to 100 mm. with the bath temperature at 150° to de-
compose the bis-amine. After 1 hr. the pressure was lowered
to 16 mm. and 19.70 g. of enamine distilled at 117-118° with
a minimum of foaming.

Expt. 54.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
0.3	0.140	3.0	1.190
0.5	0.300	3.3	1.270
0.8	0.430	4.0	1.400
1.0	0.520	4.5	1.500
1.3	0.650	5.0	1.600
1.7	0.770	5.5	1.670
2.0	0.890	6.0	1.725
2.3	0.995	6.5	1.815
2.7	1.100	Final	2.240

The residue obtained according to the standard proce-
dure was distilled under reduced pressure. The pressure was
reduced to 100 mm. with the bath temperature at 143° to de-
compose the bis-amine. After 1 hr. the pressure was lowered
to 0.3 mm. and 18.17 g. of enamine distilled with a minimum
of foaming. This enamine has been reported previously.[2]

Expt. 55.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
0.4	0.100	3.0	1.020
0.7	0.270	3.5	1.100
1.0	0.350	4.0	1.195
1.3	0.460	4.5	1.290

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
1.5	0.520	5.0	1.390
1.8	0.620	5.7	1.490
2.0	0.700	6.3	1.580
2.5	0.800	7.7	1.720
2.8	0.900	Final	2.230

The residue obtained according to the standard procedure was distilled under reduced pressure. The pressure was reduced to 100 mm. with the bath temperature at 150° to decompose the bis-amine. After 1 hr. the pressure was reduced to 2 mm. and 21.60 g. of enamine distilled at 140-142° with a minimum of foaming. This enamine has been previously reported.[24]

Expt. 56.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
1.0	0.050	10.0	0.990
2.0	0.110	11.0	1.080
3.0	0.260	13.0	1.200
4.0	0.370	15.0	1.350
5.0	0.460	17.0	1.480
6.0	0.600	19.0	1.570
7.0	0.690	21.5	1.700
8.0	0.790	24.0	1.770
9.0	0.880	Final	2.200

The residue obtained according to the standard procedure was distilled under reduced pressure. The pressure was reduced to 100 mm. with the bath temperature at 165° to decompose the bis-amine. After 1 hr. the pressure was reduced

to 14 mm. and 20.20 g. of enamine distilled at 115 116°
(n_D^{13} 1.5074) with a minimum of foaming. The enamine was
titrated with standard 0.1445N hydrochloric acid. Eqt. wt.
Calcd: 179. Found: 179, 181.

Expt. 57.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
0.3	0.100	3.3	1.185
0.7	0.205	4.0	1.305
1.0	0.405	4.7	1.405
1.2	0.505	5.0	1.505
1.5	0.605	5.5	1.600
1.8	0.705	6.5	1.715
2.3	0.845	7.0	1.790
2.7	0.975	7.5	1.865
3.0	1.095	Final	2.225

The residue obtained according to the standard proce-
dure turned dark and could not be distilled.

Expt. 58.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
0.3	0.100	2.5	0.890
0.5	0.200	2.8	0.940
0.8	0.320	3.3	1.050
1.0	0.400	3.7	1.130
1.3	0.500	4.0	1.200
1.5	0.600	5.0	1.340
1.8	0.680	6.0	1.450
2.0	0.730	7.0	1.530
2.3	0.800	Final	2.200

During the isolation of the residue, water was sucked into the flask destroying the product.

The Reaction of Cyclohexanone with Various
Amines and Mercaptans

Expt. 59.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
1.0	0.170	6.0	1.270
1.2	0.270	7.0	1.370
1.5	0.350	8.3	1.520
2.0	0.470	9.0	1.570
2.5	0.570	10.0	1.670
2.8	0.670	11.0	1.750
3.3	0.770	12.0	1.790
4.3	0.970	14.0	1.890
5.0	1.090	Final	2.270

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 57° (28 mm.) after which the main fraction of 16.90 g. was obtained at 120-121° (23 mm.). This enamine has been reported previously.[14]

Expt. 60.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
4	0.095	55	1.110
6	0.245	70	1.190
9	0.365	73	1.270
13	0.470	93	1.395
18	0.605	100	1.465
23	0.720	123	1.570
29	0.820	184	1.680
35	0.890	211	1.790
44	0.990	Final	2.270

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 76° (85 mm.) after which the main fraction of 20.96 g. was obtained at 139-141° (21 mm.). This enamine was reported previously.[14]

Expt. 61.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
12	0.095	117	1.075
18	0.195	123	1.150
28	0.300	144	1.280
35	0.400	163	1.380
58	0.630	211	1.500
67	0.730	255	1.600
82	0.880	343	1.800
100	0.985	Final	2.220

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 50° (25 mm.) after which the main fraction of 20.43 g. (n_D^{25} 1.5036) was obtained at 127° (16 mm.). Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 12.12. Found: C, 80.31; H, 12.00.

Expt. 62.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.030	141	1.000
15	0.100	165	1.130
20	0.190	190	1.220
30	0.275	227	1.340
57	0.500	254	1.410
73	0.660	294	1.470
93	0.790	337	1.590
113	0.890	Final	2.230

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 62° (125 mm.) after which the main fraction of 18.34 g. (n_D^{25} 1.5027) was obtained at 126-127° (15 mm.). Anal. Calcd. for $C_{12}H_{21}N$: C, 80.38; H, 12.12. Found: C, 80.10; H, 11.85.

Expt. 63.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
1.0	0.200	6	1.090
1.5	0.300	7	1.200
2.0	0.410	8	1.300
2.5	0.510	9	1.400
3.0	0.610	10	1.490
3.5	0.730	12	1.620
4.0	0.800	13	1.700
4.5	0.850	16	1.820
5.0	0.940	Final	2.280

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount

of forerun was obtained at 105° (14 mm.) after which the main fraction of 17.20 g. was obtained at 120-123° (0.3 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 180. Found: 177, 176.

Expt. 64.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
5	0.150	50	1.165
9	0.290	58	1.205
14	0.490	69	1.350
18	0.620	85	1.470
23	0.745	101	1.570
28	0.840	126	1.750
33	0.940	146	1.820
42	1.060	Final	2.260

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 62-65° (30 mm.) after which the main fraction of 19.31 g. (n_D^{25} 1.5066) was obtained at 129-130° (22 mm.). This enamine has been reported previously.[22]

Expt. 65.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
7	0.120	140	0.890
14	0.220	179	0.985
22	0.320	204	1.045
39	0.455	237	1.100
49	0.520	277	1.130

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
63	0.610	301	1.180
80	0.685	810	1.540
107	0.800	Final	2.140

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 75° (87 mm.) after which a main fraction of 17.30 g. was obtained at 105° (16 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 156. Found: 154, 153.

Expt. 66.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
2.0	0.175	8.5	1.105
2.8	0.305	9.3	1.195
3.3	0.405	10.0	1.270
4.0	0.515	11.0	1.375
4.8	0.635	12.0	1.445
5.5	0.730	13.0	1.545
6.3	0.845	14.0	1.605
7.0	0.925	15.0	1.685
7.8	1.010	Final	2.265

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 55° (2.5 mm.) after which the main fraction of 22.57 g. was obtained at 120-122 (1.5 mm.). Anal. Calcd. for $C_{14}H_{28}S$: C, 74.77; H, 11.58. Found: C, 74.57; H, 11.69.

Expt. 67.

Time, min.	H_2O, ml.	Time, min.	H_2O, ml.
32	0.120	197	1.120
46	0.240	224	1.210
69	0.340	248	1.340
93	0.460	254	1.440
106	0.575	261	1.540
121	0.710	269	1.590
144	0.840	274	1.640
166	0.940	Final	2.260

The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 65-68° (25 mm.) after which the main fraction of 31.32 g. was obtained at 93° (1.5 mm.). This was redistilled and 20.18 g. of material was obtained at 101-103° (1.5 mm.). Anal. for $C_{12}H_{14}S$: C, 75.78; H, 7.42. Found: C, 75.57; H, 7.31.

Expt. 68.

Dibutylamine yielded 1.040 ml. of water after reacting with cyclohexanone for six days. The residue obtained according to the standard procedure was distilled under reduced pressure. A small amount of forerun was obtained at 110° (130 mm.) after which the main fraction of 10.70 g. was obtained at 134-136° (11 mm.). The enamine was titrated with standard 0.1445N hydrochloric acid. Eqt. wt. Calcd: 213. Found: 212, 211.

Expt. 69.

N-Methylaniline yielded 0.440 ml. of water after react-
ing with cyclohexanone for 4 days. A small amount of residue
was obtained by the standard procedure. The residue did not
yield any pure product.

Expt. 70.

n-Butanol yielded 1.400 ml. of water after reacting
with cyclohexanone for 5 days. The residue obtained accord-
ing to the standard procedure was distilled under reduced
pressure. A small amount of forerun was obtained at 43-45°
(15 mm.) after which the main fraction of 10.20 g. (n_D^{20} 1.4480)
was obtained at 101-103 (11 mm.).

Theoretical Considerations

Expt. 71.

Time, min.	H_2O, %	$k \times 10^3$	Time, min.	H_2O, %	$k \times 10^3$
9.0	15.0	4.45	31.0	50.0	4.45
11.3	20.0	4.18	36.0	55.0	4.53
13.8	25.0	4.22	41.5	60.0	4.53
16.5	30.0	4.36	48.5	65.0	4.53
19.5	35.0	4.30	57.5	70.0	4.53
23.0	40.0	4.32	68.5	75.0	4.53
27.0	45.0	4.45	83.0	80.0	4.53
31.0	50.0	4.45	Final	100.0	- --

$$t_{10\%} = 6.8 \text{ min.}$$

The white solid remaining after evaporation of the solvent was recrystallized from ether to yield 24.32 g. of white needles melting at 81.4-82.1°, reported 82°.

Expt. 72.

Transenamination was effected by refluxing the solution described above for five hours. The residue obtained by the standard procedure was distilled at reduced pressure. The distillate was vapor phase chromatographed on a 6 foot decyl phthalate column at 175°. A comparison of peak areas showed that exchange had occurred in a ratio of 8 morpholine to 1 piperidine.

Expt. <u>73</u>.

Transenamination was effected by refluxing the solution described above for five hours. The residue obtained by the standard procedure was distilled at reduced pressure. The distillate was vapor phase chromatographed on a 6 foot decyl phthalate column at 175°. A comparison of peak areas showed that exchange had occurred in a ratio of 5.3 morpholine to 1 piperidine.

Expt. <u>74</u>.

The formation of the Tyndall beam as described above was observed when the flask was illuminated with a small projector in a darkened room.

BIBLIOGRAPHY

1. G. Wittig and H. Blumenthal, Ber., 60, 1085 (1927).

2. C. Mannich and H. Davidsen, Ber., 69, 2106 (1936).

3. F. E. Heyl and M. E. Herr, J. Am. Chem. Soc., 75, 1918 (1953).

4. S. Hünig, E. Benzing and E. Lucke, Chem. Ber., 90, 2833 (1957).

5. Private Communication, Merck, Sharpe, & Dohme Company.

6. N. J. Leonard, A. S. Hay, R. Fulmer, and V. Gash, J. Am. Chem. Soc., 77, 439 (1955).

7. N. J. Leonard, C. K. Steinhardt and C. Lee, J. Org. Chem., 27, 4027 (1962).

8. K. H. Meyer and H. Hopf, Ber., 54, 2277 (1921).

9. B. B. Millward, j. chem. soc., 26 (1960).

10. J. N. Collie, Ann., 226, 316 (1884).

11. R. Robinson, j. chem. soc., 109, 1038 (1916).

12. C. Mannich and H. Davidsen, Ber., 69, 2112 (1936).

13. G. Stork, R. Terrell and J. Szmuszkovicz, J. Am. Chem. Soc., 76, 2029 (1954).

14. G. Stork and H. Landesman, J. Am. Chem. Soc., 78, 5128 (1956).

15. E. D. Gergmann, Bull. soc. chim., 290 (1957).

16. V. Prelog and M. Zimmerman, Helv. Chim. Acta, 32, 2360 (1949).

17. M. E. Kuehne, J. Am. Chem. Soc., 81, 5400 (1959).

18. R. Gabbard and E. Jensen, J. Org. Chem., 23, 1406 (1958).

19. R. H. Hasek and J. C. Martin, J. Org. Chem, 26, 4775 (1961).

20. K. C. Brannock, A. Bell, R. D. Burpitt and C. A. Kelly, J. Org. Chem., 26, 625 (1961)

21. G. Berchtold, G. Harvey and G. E. Wilson, Jr., J. Org. Chem., 26, 4776 (1961).

22. S. Hünig and E. Luche, Chem. Ber., 92, 652 (1959).

23. G. Stork and G. Birnbaum, Tetra. Letters, No. 10, 313 (1961).

24. P. L. de Benneville and J. H. Macartney, J. Am. Chem. Soc, 72, 3073 (1950).

25. E. E. Royal, "Advanced Organic Chemistry," p. 774, New York, Prentice-Hall, Inc., 1954.

26. E. F. Pratt and M. Kamlet, J. Am. Chem. Soc., 28, 1366 (1963).

27. G. M. Santerre, C. Hansrote and T. Crowell, J. Am. Chem. Soc., 80, 1254 (1958).

28. W. Jencks, J. Am. Chem. Soc., 81, 475 (1959).

29. M. Sulzbacher, E. Bergmann and E. R. Pariser, J. Am. Chem. Soc., 70, 2827 (1948).

30. H. C. Brown and K. Ichikawa, Tetrahedron, 1, 221 (1957).

31. H. C. Brown, O. H. Wheeler and K. Ichikawa, Tetrahedron, 1, 214 (1957).

32. J. F. Bunnett and R. E. Zahler, Chem. Rev., 49, 273 (1951).

33. J. F. Bunnett and G. T. Davis, J. Am. Chem. Soc., 76, 2011 (1954).

34. A. Poroi-Koshits, J. Soc. Dyers Colourists, 68, 4464 (1952). C. A. 47:10980

35. H. C. Brown and M. Gerstein, J. Am. Chem. Soc., 72, 2926 (1950).

36. R. J. Bruehlman and F. H. Verhoek, J. Am. Chem. Soc., 70, 1402 (1948).

37. W. C. Vosburgh and S. A. Cogswell, J. Am. Chem. Soc., 65, 2412 (1943).

38. G. Salomon and A. J. Ultee, Jr., Rec. trav. chim., 69, 95 (1950).

39. J. O. Edwards, J. Am. Chem. Soc., 78, 1819 (1956).

40. J. Ross, Ph.D. Thesis, University of Maryland, 1957

41. M. Kamlet, Ph.D. Thesis, University of Maryland, 1954.

42. L. Green, Ph.D. Thesis, University of Maryland, 1948

43. G. Stork, J. Am. Chem. Soc., 85, 272 (1963).

44. G. Schwarzenbach, Helv. Chim. Acta, 23, 1191 (1940).

45. M. Newman, J. Am. Chem. Soc., 72, 4783 (1950).

46. J. D. Roberts and W. Moreland, J. Am. Chem. Soc., 75, 2167 (1953).

47. E. Gould, "Mechanism and Structure in Organic Chemistry," p. 376, New York, Henry Holt and Company, 1959.

48. K. Meyer, Ber., 45, 2843 (1912).

49. F. Price and L. Hammett, J. Am. Chem. Soc., 63, 2387 (1941).

50. J. Hall, J. Phys, Chem., 60, 64 (1956).

51. N. J. Leonard, J. Am. Chem. Soc., 82, 4675 (1960).