Sec. 2. Removal of Protecting Groups.—The conditions for removal of the tert-butyl ester group were studied using the tert-butyl esters of the tert-butoxyamino acids. Two drops of sample was treated with 3 drops of reagent. After an allotted time the reaction was stopped by the addition of an excess of pyridine. The results determined by chromatography of the reaction mixture either by Whatman No. 1 paper using the solvent system 1-butanol-acetic acid-water, 4:1:5, (BAW), or on silica gel plates (this is using the solvent system see-butyl alcohol-acetic acid-water, 8:1:3 (BAM).

Ex. A. Removal of tert-Butyl Groups from H-ser(O-t-Bu)-O-t-Bu(DL).—Using ninhydrin in butanol as the detecting reagent, the RF values in the BAW system were: H-ser-OH (DL), 0.17; H-ser-O-t-Bu (DL), 0.70; H-ser-O-t-Bu OH (DL), 0.72; H-ser(O-t-Bu)-O-t-Bu(DL) 0.89. Since the second and third compounds could not be satisfactorily separated, the BAM system was used. The results are shown in Table III.

<table>
<thead>
<tr>
<th>Product from H-ser(O-t-Bu)-O-t-Bu(DL), Rf Values (BAW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment at 25°</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Standards</td>
</tr>
<tr>
<td>HBr/HOAc (5 min.)</td>
</tr>
<tr>
<td>HI (57%) (5 min.)</td>
</tr>
<tr>
<td>HCl/CHCl (5 min.)</td>
</tr>
<tr>
<td>HBr/HOAc (30 min.)</td>
</tr>
<tr>
<td>HCl/CHCl (30 min.)</td>
</tr>
</tbody>
</table>

Thus, the best method of removing both protecting groups appears to be hydrogen bromide in acetic acid for a 30-minute period.

Ex. B. Removal of tert-Butyl Groups from H-cy(S-t-Bu)-O-t-Bu(L) (XX).—The RF values in the BAW system for the ester-thioether and related compounds were: H-cy(S-t-Bu)-OH (L), 0.05; H-cy(S-t-Bu)-O-t-Bu (L), 0.89. The ester-thioether was treated, as described in ex. A, with perchloric acid (70%) and hydrogen chloride in chloroform, and @-toluenesulfonic acid. All reagents were removed both tert-butyl groups. The BAW system was used, the spots being detected with ninhydrin; RF 0.03 for tyrosine and 0.04 for H-tyr(O-t-Bu)-O-t-Bu(L).

Acknowledgment.—The authors wish to thank Mr. L. Brancome and his staff for the analyses and Mr. W. Fulmor and his staff for spectra and optical rotations.

[CONTRIBUTION FROM THE CHASDLD LABORATORIES OF COLUMBIA UNIVERSITY, NEW YORK 27, N. Y.]

The Enamine Alklyation and Acylation of Carbonyl Compounds

By GILBERT STORK, A. BRIZZOLARA, H. LANDESMAN, J. SZMUSZKOVICZ AND R. TERRELL

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The enamine alkylation and acylation of carbonyl compounds is discussed with regard to the preparation of enamines, their alkylation with electrophilic olefins, their alkylation with alkyl halides and finally their acylation or alkylation can be achieved.

Introduction

In 1954, we introduced a new and relatively general synthetic method for the acylation and alkylation of carbonyl compounds. In the ensuing years the usefulness of the new reaction has been abundantly demonstrated by work in this laboratory and elsewhere, and well over ninety papers have appeared since our initial publications. A progress report on our own further work in this field has also been given. Our interest in devising new methods for the formation of the carbon–carbon bond stems from the fact that there is a relative scarcity of reactions that will accomplish this fundamental synthetic operation. In fact, a high proportion of the carbon–carbon-forming reactions of interest in complex syntheses belong to two categories: the addition of a carbonan to a carbonyl group (aldol, Grignard, metal acetylide reactions, etc.; cf. A) and the reaction of the enolate derived from a carbonyl group with an electrophilic carbon (aldol, Claisen and related reactions, Michael reaction, alkylation of metal enolates, etc.; cf. B).

\[ \text{O} + \text{C} \rightarrow \text{O}^- \text{C} \]

Reactions of type B, although of considerable synthetic importance, suffer from a number of serious limitations which we will illustrate using the alkylation of enolates and the related Michael reaction. Two major difficulties are: (1) the necessity, particularly in the case of alkylation, of using a strong base (e.g., amide ion, triphenylmethyl ion, t-alkoxides) to transform the carbonyl compound into its anion; (2) the proton transfer reaction between the alkylated ketone formed initially and the unreacted enolate ion. The first problem is illustrated by, e.g., the self-condensation of cyclopentanone by bases under conditions of the

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(2) G. Stork and H. Landesman, ibid., 78, 5128 (1956).
Claisen or Michael condensation,\(^8\) the transformation of 4-hydroxycyclohexanone benzoate into cyclopropane derivatives with t-butoxide\(^6\) and, of course, the well-known self-condensation of acetaldehyde and its mono-substituted derivatives even with mild bases. The second problem may be illustrated by a typical example: Attempted monoalkylation of 6-methoxy-\(\beta\)-tetralone with one equivalent of methyl iodide in the presence of strong bases leads to almost no mono-methyl compound: a mixture of 6-methoxy-1,1-di-methyl-\(\beta\)-tetralone and recovered starting material is obtained instead.\(^7\) While this is perhaps an extreme case, this experience is very general and is a result of the rapid equilibration of enolates via proton transfers which take place under the usual alkylation conditions. The same difficulty is of course encountered in Michael addition reactions. Among many examples, one may cite the reaction of acrilonitrile with cyclohexanone in the presence of a variety of bases which leads to a mixture of the mono-, di-, tri- and tetracyanoethylated ketones.\(^8\)

It occurred to us that a new method for the alkylation and acylation of ketones and aldehydes might emerge from the very interesting possibility that the enamines derived from an ordinary ketone or aldehyde might react with an electrophilic reagent (symbolized here by \(\text{"R+"}\)) to some extent on carbon as well as on nitrogen. The carbon alkylation product would of course be hydrolyzed by water to an alkylated ketone or aldehyde.\(^9\) It is remarkable that the possibility of the occurrence of this reaction had not been explored until our publication in spite of the fact that the necessary enamines of ketones and aldehydes had been prepared by a simple procedure, almost twenty years previously, by Mannich and Davidsen.\(^10\) This may well be due to the fact that apparently exclusive N-alkylation had been recorded with a number of vinylamines. For instance, reaction with methyl iodide converts neostrychnine\(^11\) (I) and the simpler dimethyldihydroprydine\(^12\) II into their respective N-methyldihydrosiders. Similarly, the pyrrolidine enamine of testosterone (III) has been shown to give very largely the "expected" N-methyldihydroidine.\(^13\)

As is now well known,\(^14\) we have found that the enamines of ketones (and of aldehydes in some cases) generally lead to predominant carbon alkylation and acylation. Since no base or other catalyst is needed for these reactions, the first of the two difficulties with the direct alkylation of carbonyl compounds is avoided. At the same time monoalkylation or acylation is easily carried out, and the enamine alkylation or acylation is not beset by the second problem (poly-alkylation). There is a further difference with base-catalyzed alkylations and Michael additions which we will mention before taking up the various reactions in detail: an unsymmetrically substituted ketone such as 2-methylcyclohexanone reacts with an alkyl halide in the presence of a strong base, or acrylonitrile and other electrophilic olefins to give, in general, the product in which the newly introduced group appears as 2-methylcyclohexanone (cf. IV \(\rightarrow\) V, VI).\(^15\) The enamines derived from such ketones, however, normally lead to substitution on the less substituted carbon (cf. IV \(\rightarrow\) VII, VIII). Finally, it is possible to alkylate, especially with electrophilic olefins, but also with allyl and benzyl halides, mono- and disubstituted acetaldehydes. As we have mentioned above, the formation of a mixture of the mono-, di-, tri- and tetracyanoethylated ketones.\(^8\)

\[\text{CH}_3C\text{C}CH_2\text{CO}_2\text{Et} \rightarrow \text{CH}_3C\text{C}CH_2\text{CO}_2\text{Et} \rightarrow \text{CH}_3C\text{C}CH_2\text{CO}_2\text{Et} \rightarrow \text{CH}_3C\text{C}CH_2\text{CO}_2\text{Et} \rightarrow \text{CH}_3C\text{C}CH_2\text{CO}_2\text{Et} \]

presence of mild bases and its monoalkylation can usually be effected without difficulty. The two problems we have mentioned in connection with the alkylation of unactivated carbonyl compounds are thus not normally present with \(\beta\)-ketoesters and it is perhaps not surprising that Collie's procedure for the alkylation of acetoacetic ester (cf. R. Robinson, J. Chem. Soc., 109, 1038 (1916)) has only rarely been used (see, however, G. Böglina and M. C. Whiting, ibid., 3032 (1933)).

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As long ago as 1883, Collie noted (Ann., 285, 316 (1883)) that ethyl iodide reacts with ethyl 2-aminoacetocetate to produce, after hydrolysis, ethylacetocacetic ester. Acetoacetic ester can be alkylated readily in the presence of mild bases and its monoalkylation can usually be effected without difficulty. The two problems we have mentioned in connection with the alkylation of unactivated carbonyl compounds are thus not normally present with \(\beta\)-ketoesters and it is perhaps not surprising that Collie's procedure for the alkylation of acetoacetic ester (cf. R. Robinson, J. Chem. Soc., 109, 1038 (1916)) has only rarely been used (see, however, G. Böglina and M. C. Whiting, ibid., 3032 (1933)).

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mer cannot be alkylated under the usual base-catalyzed
conditions because of their rapid self condensation.

We will now direct our discussion to (i) The Prepara-
tion of Enamines, (ii) The Enamine Alkylation of
Carbonyl Compounds with Electrophilic Olefins, (iii)
The Enamine Alkylation of Carbonyl Compounds with
Alkyl Halides, (iv) The Enamine Acylation of Car-
bonyl Compounds.

I. The Preparation of Enamines

The simplest enamine of a carbonyl compound was
prepared long ago by Meyer and Hopf who made
\[
\text{CH}_2\text{N}^+\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{NCH} = \text{CH}_2
\]
N,N-dimethylyvinylamine (the enamine of acetald-
hyde) by pyrolysis of choline. This is obviously not a
general method and it remained for Mannich and
Davidsen\(^\text{19}\) to provide the synthesis which with some
modification of details is still the one used today: reac-
tion of an aldehyde or ketone with a secondary amine,
in the presence of a dehydrating agent such as an-
dehydros potassium carbonate. Under these conditions
ketones are converted into their enamines directly
while aldehydes are transformed into the nitrogen
analog of an acetal which is then decomposed, on dis-
tillation, to enamine and secondary amine. Removal
of water by azotropic distillation with benzene is a
more efficient alternative for the preparation of
enamines from most ketones as well as from disub-
stituted acetalddehydes.\(^\text{17}\)

In our work the practice has been to use azotropic
distillation with benzene, toluene, or xylene, depending
on the rate of the reaction, for cyclic ketones and
disubstituted acetones. The Mannich procedure is
the preferred one for monosubstituted acetalddehydes.
There are two cases for which neither method is satis-
factory: monosubstituted acetones, which often (but
not always; \textit{cf}. ref. 45) give self-condensation products;
and ketones which are too hindered or otherwise un-
reactive to give an appreciable rate of water formation
even at the boiling point of xylene. The amines found
most generally useful are pyrrolidine (reactions of
ketone enamines with alkyl halides and electrophilic
olefins), morpholine (acylation reactions, electrophilic
olefins with ketone and aldehyde enamines) and piper-
dine (electrophilic olefins with aldehyde enamines).
The differences between the behavior of enamines made
from these various amines will be elaborated on in the
appropriate section of this paper.

Rate of Formation of Enamines.—The rate is affec-
ted, not unexpectedly, by two factors: the basicity
and steric environment of the secondary amino group
and the nature and environment of the carbonyl group.
Of the secondary amines used, pyrrolidine gives a
higher reaction rate than the more weakly basic mor-
pholine,\(^\text{18}\) while cyclic amines generally produce
enamines faster than open-chain ones. This is of
course what would be expected, but the fact that pyr-
rolidine reacts faster than piperidine may deserve con-

ment. The basicity and steric environment of the
two bases are closely similar\(^\text{19}\) and the differences in rate
are probably to be ascribed to the different rates of the
dehydration steps: The transition state with pyrroli-
dine involves making a trigonal carbon in a five-mem-
bered ring and the faster rate of solvolysis of methyl-
cyclopentyl chloride than that of the corresponding
cyclohexyl compound\(^\text{19}\) correlates with the faster forma-
tion of an enamine from pyrrolidine than from piperi-
dine. The effect of the ring size in the case of cyclic
ketones is also notable: cyclopentanone reacts most
rapidly, followed by cyclohexanone which is faster than
the seven- and higher-membered ketones. If the rate
of formation of enamines were solely a reflection of the
rate of formation of the intermediate carbinolamines,
cyclohexanone would form its enamine faster than
cyclopentanone. If, on the other hand, the rate of de-
hydratation of the carbinolamine were the controlling
factor, then the seven-membered ring would be faster than
the six. Since neither of these orders corresponds
to the experimental one, the over-all rate is evidently
not solely ascribable to any single one of the reversible
steps A, B and C involved in the formation of the
enamine.

The last step in the formation of an enamine is shown
as a reversible step, and in fact simply adding water
to an enamine will normally suffice to hydrolyze it to
the corresponding carbonyl compound. This is quite
unlike the behavior of enol ethers, which are stable in
water, and is a reflection of the basicity of enamines
toward water. Direct measurement in water is ob-
viously impossible, but measurement in chloroform
solution shows that enamines, \textit{in that solvent}, are about
10 to 30 times weaker bases than the secondary amines
from which they are formed.\(^\text{20}\) In any case, the actual
basicity is amply to give an appreciable rate of proton
addition from water and hence hydrolysis to the more
stable carbonyl compound. It is evident that all reac-
tions with enamines must be conducted with rigorous
exclusion of moisture, but on the other hand this ex-
treme ease of hydrolysis makes the regeneration of an

\(^{16}\) K. H. Meyer and H. Hopf, \textit{Ber.}, 54, 2777 (1921); \textit{cf}. J. v. Braun and
G. Kirchbaum, ibid., 53, 2261 (1920).
\(^{18}\) Pyrrolidine has \(K = 1.3 \times 10^{-3}\), morpholine has \(K = 2.44 \times 10^{-4}\)
and piperidine has \(K = 1.6 \times 10^{-4}\).
alpha-alkylated or acetylated substance feasible under conditions sufficiently mild to be compatible with groups such as esters, nitriles, beta-diketones, beta-keto esters, etc., whether present ab initio in the carbonyl compound or newly introduced via the alkylating agent.

Spectral Properties of Enamines.—The ultraviolet and infrared spectra of enamines have been discussed previously in the literature. The enamines derived from ketones and aldehydes, with which we are concerned here, have a maximum in the ultraviolet around 230 ± 10 nm (ε 5,000–8,000) and the double bond stretching in the infrared shows up as a strong band at about 6.07 ± 0.5 μ (1630–1660 cm⁻¹). In the nuclear magnetic resonance spectrum in benzene solution we have observed that the vinyl hydrogen appears normally as a multiplet (triplet in the case of cyclohexanone and similar compounds) centered at τ = 5.58. This position is very little affected by small changes in the basicity of the amine and is the same for the pyrrolidine or the morpholine enamine; in the case of the enamine derived from N-methylaniline and cyclohexanone, the vinyl hydrogen is moved to around τ = 4.6, but much of the effect probably is due to the anisotropy of the aromatic ring attached to nitrogen.

Structure of the Enamines from Unsymmetrical Ketones.—The less substituted enamine is formed from unsymmetrical ketones such as 2-alkylcyclohexanones. The integrated intensity of the triplet centered at 5.58 τ in the pyrrolidine enamine of 2-methylcyclohexanone corresponds essentially to one proton. Even 2-phenylcyclohexanone has been shown to give the less substituted enamine, on the basis of its ultraviolet spectrum. This result is of intrinsic interest since, in contrast, the more stable enol, enol ether, or enol acetate is normally the more substituted one. It is, of course, also of considerable practical interest since it means that reaction on carbon of enamines of this type will lead, as we have already pointed out earlier in this paper, to the introduction of a group on the alpha-carbon in systems such as IV and IVa which would normally lead (e.g., in base-catalyzed alklylation reactions) to further alpha-substitution.

One reason for this greater stability of the less substituted enamine is probably that the trivacency of nitrogen causes one of the alkyl groups of the nitrogen base to interfere with the alpha-substituent (cf. IX) if overlap is to be maintained between the nitrogen unshared electrons and the double bond. This repulsion can be decreased by moving the substituent out of the plane, as in X.

II. The Enamine Alkylation of Carbonyl Compounds with Electrophilic Olefins

Enamines of ketones and aldehydes can react with electrophilic olefins to give high yields of monoalkylated carbonyl compounds.

As we have pointed out in our preliminary communication on the subject, this type of reaction is especially successful because competition from N-alkylation is inconsequential: the criterion formed by addition on nitrogen can readily regenerate the two components and N-alkylation is thus reversible. On the other hand, there exists a simple path for proton transfer leading to a neutral molecule in the case of C-alkylation. This is illustrated using acrylonitrile as the electrophilic olefin and cyclopentanone as the ketone.

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22 The effect of increased electron density on the carbon bearing the vinyl hydrogen is shown by the shift to higher field compared to the corresponding hydrogen in cyclohexane (δ = 1.32).
advantages of this method of alkylation. In the first place, no catalyst is needed for the addition reaction; this means that base-catalyzed polymerization (of the α,β-unsaturated ketone, nitrile, ester, etc.) is not normally a factor to contend with, in contrast to the situation with the usual base-catalyzed reactions of the Michael type. This means further that the carbonyl compound itself is not subject to aldol condensations which often preclude the use of base catalysis; in the case of cyclopentanone, for instance, the direct condensation with methyl vinyl ketone and base leads mainly to cyclopentylidene-cyclopentanone. The formation of the desired indanone XII by the enamine procedure is easily achieved and may be contrasted with the previously available method outlined in XIII → XII.

\[
\text{XIII} \xrightarrow{\text{OH}^-} \text{XII}
\]

In the case of aldehydes with a methylene group α- to the carbonyl, the enamine method is about the only way to achieve the desired reaction since base-catalyzed Michael reactions would lead to aldolization. Finally, monoalkylation is easily achieved in contrast to the results obtained, for instance, in the usual cyanoethylation procedures

\[
\text{XIV, } 80\%
\]

This considerably greater rate of the first alkylation step than of further alkylation is remarkable and is responsible for the successful monoalkylation of enamines since in the reactions under discussion in this section the product is itself an alkylatable enamine (cf. XI). The transition state for C-alkylation necessitates the coplanarity of the starred atoms in XV and the resulting interference between the hydrogens on the methylene α- to the nitrogen atom and R is obviously greater when R is alkyl (the monoalkylated product) than when R is H (in the starting material): hence the higher energy of the transition state for the second alkylation. This factor is of course absent with the usual enolate ions.

A further point of difference with base-catalyzed Michael addition is illustrated with 2-methylcyclohexanone: cf. IV → VIII vs. IV → VI. This is, of course, the result to be expected from the structure, which we have considered earlier in this paper, of the enamines from 2-alkyl ketones.

The general conditions most useful for the alkylations under discussion consist in refluxing a mixture of the enamine and an equimolar quantity of the reactive olefin for about five hours in a solvent such as dioxane, acetonitrile, benzene or absolute ethanol. Decomposition to the ketone is then effected, except in the case of the vinyl ketone reaction products of pyrrolidine enamines, by simple heating with water. Representative examples are shown here and, together with additional ones, are described in detail in the Experimental section of this paper.

\[
\text{XV}
\]

The reaction products from vinyl ketones and pyrrolidine enamines are not decomposed merely by heating with water. The products are enamines of a,β-unsaturated ketones and these are considerably more stable to hydrolysis than enamines of saturated
carboxyl compounds. Decomposition is effected in these cases by the use of a hot mixture of acetic acid, sodium acetate and water.\(^\text{[13]}\) We can illustrate the course of the reaction with the pyrrolidine enamine of cyclohexanone and methyl vinyl ketone. If the reaction is conducted in toluene, direct distillation of the reaction mixture before hydrolysis leads to a high yield of the pyrrolidine enamine of \(\Delta^1\)-3-2-octalone (XXV). With the less reactive morpholine enamine, on the other hand, the reaction stops at the stage of the initial alkylation product and simple refluxing with aqueous base leads directly to the octalone.

**Effect of Solvent and of the Amine Used in Enamine Formation.**—In general, any convenient secondary amine which forms enamines readily may be used. As expected, the pyrrolidine enamines are the most reactive and piperidine or morpholine enamines considerably less. This point is discussed in greater detail in connection with alkylations with alkyl halides (cf. section III). For instance, in the reaction of enamines of aldehydes with \(\alpha,\beta\)-unsaturated ketones the less reactive piperidine enamines are preferable to the pyrrolidine derivatives.

We have just discussed in the previous section the difference in the course of the reaction of vinyl ketones with the pyrrolidine and morpholine enamines of carboxyl compounds. A particularly illuminating case, which shows also the effect of the solvent polarity, is that of the reaction of cyclohexanone enamines with acrylonitrile or ethyl acrylate. With the pyrrolidine enamine, monoalkylation is easily achieved in benzene or dioxane to give XXVI or XXVIII in 80\% yield even with an excess of alkylating agent. Changing the solvent to ethanol leads, with 3 equivalents of acrylonitrile or ethyl acrylate, to the symmetrical dialkylated products XXIX or XXX in 70\% yield. On the other hand, even in alcohol, it is difficult to go further than monoalkylation with the morpholine enamine. The effect of the solvent is again shown in the case of the morpholine enamine of diethyl ketone: in benzene, after 15 hours refluxing, the yield of the carbethoxyethylated ketone XXII is only 15\%, whereas a 60\% yield is obtained in ethanol.

We have already indicated that the reaction with electrophilic olefins is quite general. We would only like to draw attention to two special cases: the reaction with the enamines from \(\beta\)-decalone and those derived from aldehydes.

In the case of \(\text{trans-}\beta\)-decalone, the pyrrolidine enamine, reacts with methyl vinyl ketone, to give, after hydrolysis, a 60\% yield of the cyclic ketones which were shown (by conversion to phenanthrene and anthracone) to consist of 10\% XXXI and 90\% XXXII. With cis-\(\beta\)-decalone, the product obtained in the same yield consisted of 40\% XXXIV and 60\% XXXV.

This result shows that in trans 2-decalone there is qualitatively the same advantage to the \(\Delta^1\)-olefin as in the case of the steroid A/B trans system but that the difference in energy between the two positions possible for the double bond is somewhat lower, as would be expected from the absence of the angular methyl group between the two rings.\(^\text{[24]}\) In the cis series the result is of considerable interest since it is well-known that the A/B cis system of the steroids leads to a lower energy for the double bond position corresponding to that of XXXIII.\(^\text{[25]}\) In the simple cis-\(\beta\)-decalone there appears to be practically no difference in the energy of the two possible olefins.

Turning now to the reactions of aldehyde enamines with \(\alpha,\beta\)-unsaturated ketones, it appears that these take place well only with vinyl ketones in which the double bond is unsubstituted.\(^\text{[26]}\) The method is thus general for the synthesis of 4-substituted cyclohexenones and for 2,4-disubstituted \(\Delta^1\)-cyclohexenones. It is worth noting that the last mentioned cyclohexenones are not the same as would be produced by the Birch reduction\(^\text{[27]}\) of 2,4-dialkyl derivatives and the method is thus complementary to the Birch reduction in such cases. For instance, the enamine of propionaldehyde reacts with ethyl vinyl ketone to give, after aqueous acid treatment of the intermediate, 2,4-dimethyl-\(\Delta^1\)-cyclohexenone (XXXVI) in 69\% yield. The preparation of this compound by other methods is in contrast both laborious and unsatisfactory.\(^\text{[28]}\)

Although we have chosen to represent the addition of vinyl ketones as a typical electrophilic olefin reaction

\[\text{XXXVII} \rightarrow \text{XXXVIII} \rightarrow \text{XXXIX} \rightarrow \text{XXX} \rightarrow \text{XX} \rightarrow \text{XXI} \rightarrow \text{XXII} \rightarrow \text{XXIII} \rightarrow \text{XXIV} \rightarrow \text{XXV} \]

The effect of the solvent is easily rationalized: the transition state for alkylation involves considerable charge separation and its energy should be appreciably lower in ethanol than in benzene or dioxane.

\[\text{XXXVII} \rightarrow \text{XXXVIII} \rightarrow \text{XXXIX} \rightarrow \text{XXX} \rightarrow \text{XX} \rightarrow \text{XXI} \rightarrow \text{XXII} \rightarrow \text{XXIII} \rightarrow \text{XXIV} \rightarrow \text{XXV} \]

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In the case of \(\text{trans-}\beta\)-decalone, the pyrrolidine enamine, reacts with methyl vinyl ketone, to give, after hydrolysis, a 60\% yield of the cyclic ketones which were shown (by conversion to phenanthrene and anthracone) to consist of 10\% XXXI and 90\% XXXII. With cis-\(\beta\)-decalone, the product obtained in the same yield consisted of 40\% XXXIV and 60\% XXXV.

This result shows that in trans 2-decalone there is qualitatively the same advantage to the \(\Delta^1\)-olefin as in the case of the steroid A/B trans system but that the difference in energy between the two positions possible for the double bond is somewhat lower, as would be expected from the absence of the angular methyl group between the two rings.\(^\text{[24]}\) In the cis series the result is of considerable interest since it is well-known that the A/B cis system of the steroids leads to a lower energy for the double bond position corresponding to that of XXXIII.\(^\text{[25]}\) In the simple cis-\(\beta\)-decalone there appears to be practically no difference in the energy of the two possible olefins.

Turning now to the reactions of aldehyde enamines with \(\alpha,\beta\)-unsaturated ketones, it appears that these take place well only with vinyl ketones in which the double bond is unsubstituted.\(^\text{[26]}\) The method is thus general for the synthesis of 4-substituted cyclohexenones and for 2,4-disubstituted \(\Delta^1\)-cyclohexenones. It is worth noting that the last mentioned cyclohexenones are not the same as would be produced by the Birch reduction\(^\text{[27]}\) of 2,4-dialkyl derivatives and the method is thus complementary to the Birch reduction in such cases. For instance, the enamine of propionaldehyde reacts with ethyl vinyl ketone to give, after aqueous acid treatment of the intermediate, 2,4-dimethyl-\(\Delta^1\)-cyclohexenone (XXXVI) in 69\% yield. The preparation of this compound by other methods is in contrast both laborious and unsatisfactory.\(^\text{[28]}\)

Although we have chosen to represent the addition of vinyl ketones as a typical electrophilic olefin reaction

\[\text{XXXVII} \rightarrow \text{XXXVIII} \rightarrow \text{XXXIX} \rightarrow \text{XXX} \rightarrow \text{XX} \rightarrow \text{XXI} \rightarrow \text{XXII} \rightarrow \text{XXIII} \rightarrow \text{XXIV} \rightarrow \text{XXV} \]

The effect of the solvent is easily rationalized: the transition state for alkylation involves considerable charge separation and its energy should be appreciably lower in ethanol than in benzene or dioxane.

\[\text{XXXVII} \rightarrow \text{XXXVIII} \rightarrow \text{XXXIX} \rightarrow \text{XXX} \rightarrow \text{XX} \rightarrow \text{XXI} \rightarrow \text{XXII} \rightarrow \text{XXIII} \rightarrow \text{XXIV} \rightarrow \text{XXV} \]
with an enamine, it is of course conceivable, by analogy with the reaction with enol ethers,\(^\text{(33)}\) that the reactions are 4-center reactions of the Diels-Alder type. Indeed Opitz\(^\text{(34)}\) has represented in this manner the addition of aldehyde enamines to \(\alpha,\beta\)-unsaturated aldehydes. Since the dihydropyrans from such a reaction would be in equilibrium with the open enamines, as would the products of direct addition to cyclobutane derivatives, it is not possible to decide at this time the true sequence of events leading to any one of these final structures. In the absence of further data we see no reason to abandon the usual enamine alkylation mechanism (path a).

\[
\text{RCH} = \text{CHNR}_2 + \overset{\text{b}}{\text{O}} \rightarrow \overset{\text{c}}{\text{RCH} = \text{CHXR'}} + \overset{\text{d}}{\text{RCH} = \text{CHXR'}}
\]

Whatever the structure of the intermediate (dihydropyran, enamine or aminoacylcyclobutane) from the addition of an \(\alpha,\beta\)-unsaturated carbonyl compound to an aldehyde enamine, they are all irreversibly converted on treatment with acid to the desired \(\delta\)-ketoaldehydes. Thus, although, as we have mentioned, the cyclobutane derivatives can sometimes be isolated from the reaction of an \(\alpha,\alpha\)-dialkylated aldehyde enamine and an electrophilic olefin, acid hydrolysis and cyclization still gives the desired cyclohexenone (4,4-dialkylated in this case). For instance, although base-catalyzed addition of methyl vinyl ketone to the aldehyde ester XXXVII was unsuccessful, the addition to the pyrrolidine enamine proceeded readily to give after acid treatment the desired cyclohexenone XXXVIII.

Brief mention should finally be made of the results obtained in the alkylation of ketone enamines with \(\alpha,\beta\)-unsaturated aldehydes. The reaction with aldehyde enamines is normal, the final product after hydrolysis being a substituted glutaraldehyde.\(^\text{(35)}\) On the other hand, the reaction of \(\alpha,\beta\)-unsaturated aldehydes with ketone enamines leads, as we have previously reported,\(^\text{(35)}\) to bicyclic aminoketones which are formally the product of an internal Mannich reaction of the expected aldehydeketone and the secondary amine used to form the enamine. For example, with the pyrrolidine enamine of cyclohexanone and acrolein in benzene the product isolated is XXXIX.

\[
\overset{\text{O}}{\text{O}} \rightarrow \overset{\text{N}}{\text{N}} \rightarrow \overset{\text{XXXIX}}{\text{XXXIX}}
\]

We only mention this reaction here for the sake of completeness. It is, as we have shown, of considerable interest in connection with the synthesis of medium size rings\(^\text{(36)}\) and we will discuss it in detail in another paper.

### III. The Enamine Alkylation of Carbonyl Compounds with Alkyl Halides

Simple unactivated primary alkyl bromides or iodides give only a fair yield of 2-alkyl ketones by the enamine method with the exception of \(\beta\)-tetralone derivatives which are thus monoaalkylated in very high yield. We have found that the alkylation with alkyl halides gives good yields with strongly electrophilic halides such as allyl halides, benzyl halides, propargyl halides, \(\alpha\)-halo ethers, \(\alpha\)-haloketones, esters and nitriles. Since these are the very substances which would often not be compatible with the conventional sequence involving transformation of a ketone into a \(\beta\)-keto ester followed by alkylation, acid hydrolysis and decarboxylation, the enamine–alkyl halide reaction has turned out to be very valuable in such cases. A few examples will be given here:

\[
\overset{\text{XLIII}}{\text{XLIII}} \rightarrow \overset{\text{XL}}{\text{XL}}
\]

\[
\overset{\text{XLIV}}{\text{XLIV}} \rightarrow \overset{\text{XLII}}{\text{XLII}} \rightarrow \overset{\text{XL}}{\text{XL}}
\]

\[
\overset{\text{XLV}}{\text{XLV}}
\]

---


Details will be found in the Experimental section, but in general these reactions are carried out by refluxing the required pyrrolidine enamine in benzene or acetonitrile (the former is especially useful with α-halo carbonyl compounds, the latter with allyl and related halides) with a slight excess of the halide for three or four hours, followed by addition of water and stirring at room temperature for fifteen minutes. Yields of 50 to 75% are usually obtained.

Pyrrolidine enamines have been found most generally useful in alkylation with allyl halides. One would of course expect the rate of the reaction to be higher with pyrrolidine than with morpholine on the basis of the difference in the strengths of the parent bases since electron removal from nitrogen is involved in the transition state for the alkylation reactions. That this is not the whole story is shown by the fact that pyrrolidine enamines give considerably higher yields than the piperidine derivatives. We have ascribed this to the greater ease of formation of a trigonal carbon in a five-membered ring than in a six-membered one (compare the relative rates of solvolysis of 1-methylecycloalkyl chlorides). Since the transition state for C-alkylation (but not for N-alkylation) involves forming a trigonal atom in the amine portion of the molecule (cf. XV) one would expect (and one observes) the most favorable ratio of C to N alkylation to be obtained with the cyclic five- and seven-membered amines. We have generally used the readily available pyrrolidine for alkylation with allyl halides.

Many alkylation of this type have been carried out since our introduction of this reaction, and a great variety of substances are thus made readily available. For example, the diketones derived from α-haloketones can be cyclized to cyclopentenones, the product from the pyrrolidine enamine of cyclohexanone and bromoacetate ester has been transformed into thioctic acid, the ketonitrile from cyclohexanone enamine and chloroacetone has been used to make hydroindole derivaties.

α,β-Unsaturated ketones have not been studied extensively. We have shown that methylation of the pyrrolidine enamine of Δ4,10-octalone-2 leads to the 1-methyl compound XLVII rather than the a priori possible γ-alkylated product. This alkylation of an α,β-unsaturated ketone, when it proceeds on carbon, is a possible solution to the problem of the monoalkylation of α,β-unsaturated carbonyl compounds with which dialkylation by the usual base-alkyl halide method is sometimes even more of a complication than with saturated ketones. The high yields obtained in the monoalkylation of ketones of the β-tetralone type have already been mentioned. The alkylation of a β-tetralone is formally related to that of an α,β-unsaturated ketone in the sense that the enamine is here also a conjugated enamine.

The usefulness of the enamine alkylation method over direct alkylation in the case of enones has been noted by Julia, et al., who obtained 46% yield of the keto ester L in the alkylation of the pyrrolidine enamine of...
XLIX, while direct base-catalyzed alkylation led to only 24% of the desired substance which was used in an ingenious synthesis of chrysanthemumcarboxylic acid.

Again, alkylation of the unsaturated ketone LI by the enamine method was stated to be superior to direct alkylation:

Hunig and his co-workers have subsequently made two valuable contributions to this enamine synthesis. They showed that the less reactive morpholine enamine carry a 3-@-substituent. Substituents can, of course, also be present in the acid chloride chain.


(50) The cyclopentanone and cyclohexanone rings can obviously be substituted to produce acids with substituents at various places along the chain. Unsymmetrically substituted ketones will, however, lead to mixtures unless they carry a 2-substituent. Substituents can, of course, also be present in the acid chloride chain.


In some cases, acylation can be carried out also with anhydrides. For instance, the mixed anhydride of formic and acetic acid converts the pyrrolidine enamine of cyclohexanone to 2-hydroxymethylenecyclohexanone in 50% yield. Similarly, acetic anhydride gives a 42% yield of \( \text{p-keto ester LXVIII} \) in 54% yield.

\[
\begin{align*}
\text{CHOH} & \quad \text{N} \\
\text{O} & \quad \text{COCH}_3 \\
\text{O} & \quad \text{S-C-NHR} \\
\text{O} & \quad \text{S-C-NR} \\
\end{align*}
\]

\( \beta\text{-Keto esters} \) can also be made in certain cases by the enamine acylation method (see LIII). In these cases the triethylamine method is not successful. Acylation is effected by heating ethyl chlorocarbonate with two equivalents of the morpholine enamine in benzene solution and then decomposing the \( \text{p-keto ester} \) by stirring for 15-30 minutes at room temperature with 10% hydrochloric acid. Under these conditions, cyclohexanone gives 2-carbethoxycyclohexanone in 62% yield while 4-methylcyclohexanone, cyclopentanone and cycloheptanone give the corresponding \( \beta\text{-ketoesters} \) in 65, 76 and 46% yields, respectively. The case of cyclopentanone is of some interest since the usual decarbonylation of glyoxylates to \( \beta\text{-keto esters} \) is not applicable in this case.\(^{64}\) Acyclic ketones may also be used: dipropyl ketone gave the \( \beta\text{-keto ester} \) \( \text{LXVIII} \) in 54% yield.

\[
\begin{align*}
\text{CO} & \quad \text{Et} \\
\end{align*}
\]

**Conclusion. Remaining Problems**

We have shown in the preceding discussion that the enamine alkylation of ketones and aldehydes is a general and very useful method for the alkylation of these carbonyl compounds with electrophilic olefins. It is also of considerable generality with acyl halides and similar substances. On the other hand, the alkylation reaction with alkyl halides is limited in scope to the use of the strongly electrophilic halides and (mostly cyclic) ketones. Aldehydes give poor yields, even with this type of halide and, for practical purposes, only alkyl halides give serviceable yields, usually in large part via a Claisen rearrangement involving the formation (except of course with unsubstituted allyl halides) of mixtures of rearranged and unarranged products. It remains to be determined whether, even with cyclic ketone enamines, the first step is direct carbon alkylation or involves reversible quaternary salt formation. It is interesting in connection with the latter possibility that those halides which give satisfactory yield might be those expected to be most easily removed from nitrogen by reaction with halide ion, thus regenerating the starting materials for eventual C-alkylation. Further study will be required to elucidate this point.

In any event, it is clear that another method is needed for the monoalkylation of ketones (cyclic and acyclic) and also of aldehydes with ordinary primary and secondary halides. Such a method has now been developed in this Laboratory and will be the subject of future communications.

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**Experimental**

**Preparation of Enamines. A. Cyclic Ketones.**—The most generally useful method consists in heating one equivalent of ketone with 1.5-2 equivalents of pyrrolidine or morpholine using about 900 ml. of benzene per mole of ketone. Refluxing under a water separator is continued until no further separation of water is observed. This usually takes from 5 to 8 hours with cyclopentanones and cyclohexanones. Medium size rings (7,8,9) require the use of toluene and longer refluxing periods (ca. 24 hours). In some cases when water separation is especially slow some p-toluene sulfonic acid may be added to the mixture. In this instance the enamine can be used directly after removal of solvent and excess amine. It should be remembered that enamines are unstable but may be kept in the refrigerator under nitrogen. Some specific examples of enamine preparations and properties are presented here.

- **Cyclopentanone:** pyrrolidine enamine (80-90% yield) b.p. 88-92° (15 mm.) (reported \( \text{b.p.} \) 97-98° (20 mm.).) (Calcd. for \( \text{C}_7\text{H}_8\text{N} \): C, 79.77; H, 11.02; N, 9.21. Found: C, 79.89; H, 10.89; N, 10.16.)
- **morpholine enamine (80-90% yield) b.p. 104-106° (12 mm.), reported \( \text{b.p.} \) 97° (7.5 mm.).

- **Cyclohexanone:** pyrrolidine enamine (85-90% yield) b.p. 105-107° (15 mm.), reported \( \text{b.p.} \) 115-117° (20 mm.). (Calcd. for \( \text{C}_6\text{H}_{11}\text{N} \): C, 79.40; H, 11.34; N, 9.26. Found: C, 79.69; H, 11.38; N, 9.00.)
- **morpholine enamine (85%) b.p. 104-106° (12 mm.), reported \( \text{b.p.} \) 117-120° (20 mm.). (Calcd. for \( \text{C}_6\text{H}_{11}\text{N} \): C, 79.78; H, 10.25; N, 8.97. Found: C, 79.16; H, 10.16; N, 8.62.)
- **hexamethylene imine enamine (85%) after 40 hours refluxing in toluene: b.p. 122-128° (8 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{12}\text{N} \): C, 80.37; H, 11.81; N, 7.81. Found: C, 80.29; H, 11.50; N, 7.85.)
- **morpholine enamine (98%) after 40 hours refluxing in benzene with some \( \text{p-toluene sulfonic acid; b.p.} \) 142-148° (14 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{12}\text{N} \): C, 80.76; H, 11.69; N, 7.62. Found: C, 81.13; H, 11.26; N, 7.50.)
- **eptamethylene imine enamine (72%) after 100 hours refluxing in toluene with 2.0 g. of \( \text{p-toluene sulfonic acid per mole; b.p.} \) 148-153° (12 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{12}\text{N} \): C, 81.53; H, 9.15; N, 7.45. Found: C, 83.61; H, 8.45; N, 7.48.; camphidine enamine (63%) after 24 hours reflux in toluene with \( \text{p-toluene sulfonic acid; b.p.} \) 101-110° (0.4 mm.). (Calcd. for \( \text{C}_{12}\text{H}_{12}\text{N} \): C, 82.33; H, 11.69; N, 6.00. Found: C, 81.94; H, 11.62; N, 6.35.)
- **2-Methylcyclopentanone:** pyrrolidine enamine (77%) after 48 hours refluxing in benzene: b.p. 112-114° (15 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{12}\text{N} \): C, 79.90; H, 11.38; N, 8.47. Found: C, 79.84; H, 11.50; N, 8.78.)
- **3-Methylcyclohexanone:** morpholine enamine (86%) after 35 hours refluxing in toluene: b.p. 124-127° (15 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{14}\text{NO} \): C, 72.86; H, 10.56; N, 7.73. Found: C, 72.75; H, 10.89; N, 7.53.) This is undoubtedly a mixture of double bond isomers.
- **2-Methylcyclohexanone:** morpholine enamine (75% after 25 hours refluxing in toluene: b.p. 108-110° (17 mm.). (Calcd. for \( \text{C}_{10}\text{H}_{14}\text{NO} \): C, 72.86; H, 10.56; N, 7.73. Found: C, 72.72; H, 10.90; N, 7.53.)
- **4-Methoxyacetoacetic acid:** morpholine enamine (78%) after 48 hours refluxing in toluene with \( \text{p-toluene sulfonic acid; b.p.} \) 130-135° (10 mm.). (Calcd. for \( \text{C}_{11}\text{H}_{12}\text{NO} \): C, 76.05; H, 7.91; N, 7.10. Found: C, 76.22; H, 8.26; N, 7.10.)
- **Cyclohexanone:** morpholine enamine (82%) after 48 hours refluxing in toluene with \( \text{p-toluene sulfonic acid; b.p.} \) 133-135°.


**Enamine Alkylation and Acylation of Carbonyls**

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(17 mm.) (Calcd. for C₈H₈N₂O: C, 72.88; H, 10.56; N, 7.33. Found: C, 73.00; H, 10.56; N, 7.80.)

2-Tetralone: pyrrolidine enamine (98%) after refuxing under nitrogen with 4 g. of tetralone in 100 ml. of benzene for 3 hours. This enamine was obtained crystalline on removal of the solvent: m.p. 72-74°. Recrystallization from petroleum ether gave m.p. 81-82° (Calcd. for C₁₇H₂₃N₂O: C, 84.40; H, 8.45; N, 7.04. Found: C, 84.37; H, 8.60; N, 7.03.)

A. Aliphatic Ketones.—As mentioned in the Discussion, simple monosubstituted acetones (and acetone itself) are usually satisfactorily converted into enamines by the existing methods. Others can be used but often react sluggishly. The use of molecular sieves as drying agent may be generally preferable with those ketones that readily form hydrates.

Diethyl Ketone.—Pyrrolidine enamine was obtained in only 22% yield after 175 hours refluxing with benzene and p-toluene-sulfonic acid. However, in the presence of 20 g. of Lindie No. 4 a molecular sieve contained in an extraction thimble through which the condensed vapor passed before returning to the flask a mixture of 20 g. of diethyl ketone and 40 g. of pyrrolidine gave a 51% yield of ethyl 4-piperidino-3-cyclohexyl-2-butanone, b.p. 62-67° (8 mm.) (Calcd. for C₁₉H₂₃NO: C, 77.66; H, 12.32; N, 10.07. Found: C, 77.38; H, 12.27; N, 9.85.).

**Morpholine enamine** was prepared in the same manner with molecular sieves and a small amount of p-toulene-sulfonic acid. After 250 hours reflux (1) the enamine was obtained in only 7% yield. Undoubtedly, the use of molecular sieves would be advantageous here also: b.p. 102-106° (12 mm.) (Calcd. for C₁₇H₂₃N₂O: C, 72.06; H, 11.55; N, 7.64. Found: C, 72.06; H, 11.64; N, 7.84.).

Aldehydes.—Enamines of aldehydes were made by the procedure of Mannich and Davidsen except that with disubstituted acetaldehydes, the water separator method can be used to advantage (cf. example 11-10 below). For instance, the piperidine enamine of isovaleraldehyde was prepared by adding dropwise over an hour, to an ice-cold stirred mixture of 25 g. of piperidine and 6.0 g. of anhydrous potassium carbonate, 10.75 g. of isovaleraldehyde. After stirring at room temperature for 2 hours, the mixture was filtered, the flask was washed with ether which was then added to the original filtrate and distillation gave 14.15 g. (74%), b.p. 83.5-85° (18 mm.); reported b.p. 74-75° (12 mm.). The 2,4-dialkyl-2,6-dinitrophenylhydrazone crystallized from methanol as orange needles, m.p. 87-88°.

**Diethyl Ketone.**—Morpholine enamine was prepared by the usual benzene azotrop method in the presence of p-toluene-sulfonic acid. After 250 hours reflux (1) the enamine was obtained in only 7% yield. Undoubtedly, the use of molecular sieves would be advantageous here also: b.p. 102-106° (12 mm.) (Calcd. for C₁₇H₂₃N₂O: C, 72.06; H, 11.55; N, 7.64. Found: C, 72.06; H, 11.64; N, 7.84.).

**Aldehydes.**—Enamines of aldehydes were made by the procedure of Mannich and Davidsen except that with disubstituted acetaldehydes, the water separator method can be used to advantage (cf. example 11-10 below). For instance, the piperidine enamine of isovaleraldehyde was prepared by adding dropwise over an hour, to an ice-cold stirred mixture of 25 g. of piperidine and 6.0 g. of anhydrous potassium carbonate, 10.75 g. of isovaleraldehyde. After stirring at room temperature for 2 hours, the mixture was filtered, the flask was washed with ether which was then added to the original filtrate and distillation gave 14.15 g. (74%), b.p. 83.5-85° (18 mm.); reported b.p. 74-75° (12 mm.). The 2,4-dialkyl-2,6-dinitrophenylhydrazone crystallized from methanol as orange needles, m.p. 87-88°.

**D.**

**Acrylic Acids.**—The reaction was carried out as with the cyclohexyl compound (example 4 above). The 2-(2-cyanoethyl)-cyclohexanone (XVII) thus obtained in 67% yield had b.p. 144-147° (13 mm.). The 2,4-dinitrophenylhydrazone formed fine orange needles from chloroform-methanol; m.p. 93-96°.

**E.**

**Cyclopentanone with Acrylonitrile.**—The reaction was carried out as with the cyclohexyl compound (example 4 above). The 2-(2-cyanoethyl)-cyclopentanone (XVII) thus obtained in 67% yield had b.p. 144-147° (13 mm.). The 2,4-dinitrophenylhydrazone formed fine orange needles from chloroform-methanol; m.p. 93-96°.

**F.**

**Acrylic Acids.**—The reaction was carried out as with the cyclohexyl compound (example 4 above). The 2-(2-cyanoethyl)-cyclopentanone (XVII) thus obtained in 67% yield had b.p. 144-147° (13 mm.). The 2,4-dinitrophenylhydrazone formed fine orange needles from chloroform-methanol; m.p. 93-96°.

**G.**

**Acrylic Acids.**—The reaction was carried out as with the cyclohexyl compound (example 4 above). The 2-(2-cyanoethyl)-cyclopentanone (XVII) thus obtained in 67% yield had b.p. 144-147° (13 mm.). The 2,4-dinitrophenylhydrazone formed fine orange needles from chloroform-methanol; m.p. 93-96°.

**H.**

**Cyclohexanone with Acrylonitrile.**—The reaction was carried out as with the cyclohexyl compound (example 4 above). The 2-(2-cyanoethyl)-cyclohexanone (XVII) thus obtained in 67% yield had b.p. 144-147° (13 mm.). The 2,4-dinitrophenylhydrazone formed fine orange needles from chloroform-methanol; m.p. 93-96°.
The semicarbazone, from dilute ethanol, had m.p. 163–164°.

**Analyt.** Calcd. for C_{17}H_{17}O_{4}N: C, 59.44; H, 8.16; N, 25.22. Found: C, 59.78; H, 8.46; N, 25.12.

A solution of 15.0 g. (1 mole) of the morpholine enamine of diethyl ketone in 100 ml. of absolute ethanol kept under nitrogen was added dropwise with stirring 10.0 g. (0.1 mole) of ethyl acrylate. The solution was allowed to stand overnight, and an additional hour after the addition of 25 ml. of water. Addition of water, extraction, washing with 10% hydrochloric acid, drying and distillation gave 9.7 g. (67.7%) of ethyl 3-keto-4-methylenanthate (XXII), b.p. 108–109° (0.5 mm.).

**Anal.** Calcd. for C_{17}H_{17}O_{4}N: C, 59.54; H, 8.92. Found: C, 59.86; H, 6.02; 16.19 μ (which was 75% α, β) from the ultraviolet intensity (\textit{λ}_{max} 238 mm., ε 12,900).

**Alkylation.** 1. Butyraldehyde Enamine and Methyl Acrylate.---To a solution of 130 g. (1 mole) of the butyraldehyde enamine and piperidine, in 750 ml. of acetic acid, 10% hydrochloric acid, and 12.5 g. of methyl acrylate in 250 ml. of water. The mixture was then refluxed for 15 hours, and an additional hour after the addition of 25 ml. of water. Separation of the layers, extraction of the aqueous layer with benzene and washing the combined extracts with 10% hydrochloric acid, and then aqueous sodium bicarbonate gave, after removal of the benzene at atmospheric pressure and distillation, 31.6 g. (71%) of octalone XXVI, b.p. 135–138° (15 mm.).

The infrared showed the usual α, β, γ mixture (\textit{λ}_{max} 5.86, 6.02, 16.19 μ) which was 75% α, β, γ from the ultraviolet intensity (\textit{λ}_{max} 238 mm., ε 12,900).

**Alkylation** 2. Heptaldehyde Enamine and Acrylonitrile.---As we have mentioned in the discussion there is no good method for the formation of enamines of monosubstituted acetones. A possible—but not too satisfactory—method for circumventing this difficulty is illustrated here in the synthesis of the N-methyl-N-cyclohexyl enamine of methyl amyl ketone. A benzene solution of 60 g. of the Schiff base from methyl amyl ketone and cyclohexanamine in 500 ml. of dry benzene was treated dropwise with 50 g. of methyl iodide. After the solution had been allowed to stand with occasional shaking for 2 hours, 30 g. of dry diethylamine was added dropwise with mechanical stirring. The heavy precipitate of diethylamine hydrofide was filtered off after 2 hours further stirring at room temperature. Benzene was then added and fractionation, after filtering off a further precipitate of the benzene was then refluxed for 3 hours. The benzene was then distilled off, and the solution was heated cautiously to the boiling point and 6.1 g. of methyl acrylate in 250 ml. of toluene. After addition was complete, the solution was refluxed for 1.5 hours and the solvent was removed by distillation at water-pump pressure. Fractionation then gave 10.2 g. (67%) of the pyrrolidine enamine of δ-2-octalone (XXVII), b.p. 150–150° (0.3 mm.).

**Anal.** Calcd. for C_{12}H_{12}O_{4}N: C, 55.36; H, 8.14; 16.25 μ and boiling point were identical with those of authentic enamine made in 85% yield from the δ-2-octalone-2 mixture and pyrrolidine by the usual procedure, using toluene.

The semicarbazone prepared and recrystallized from alcohol had m.p. 93–94°.

**Analyt.** Calcd. for C_{13}H_{15}O_{4}N: C, 60.74; H, 8.82. Found: C, 60.83; H, 8.13.

**2. Heptaldehyde Enamine and Acrylonitrile.**—Reaction of the enamine of heptaldehyde with acrylonitrile was carried out as described for the case of cyclohexanone (example A-4): 2-cyanoethylheptaldehyde was obtained in 46% yield as a liquid, b.p. 140–145° (12–13 mm.).

The mixture was stirred at room temperature for 5 hours and refluxed for 36 hours. Addition of 60 ml. of acetic acid in 400 ml. of water and 8 hours was followed by extraction after saturation with salt. Further workup as usual gave 106 g. (67%) of methyl 4-formylhexanenitracil (XXXII), b.p. 95–98° (10 mm.).

**Anal.** Calcd. for C_{14}H_{12}O_{4}N: C, 60.47; H, 8.92. Found: C, 60.35; H, 8.13.

**2-Heptanone and Acrylonitrile.**---A solution of 15.5 g. (0.1 mole) of 2-heptanone and methyl acrylate in 250 ml. of absolute ethanol kept under nitrogen was added 8.4 g. (0.1 mole) of methyl isopropenyl ketone in 100 ml. of absolute ethanol. The solution was then refluxed for 15 hours and the solvent was removed by distillation at water-pump pressure. Fractionation then gave 11.8 g. (65%) of the pyrrolidine enamine of δ-2-octalone (XXV), b.p. 146–150° (0.5 mm.). The infrared showed the characteristic absorption band of the benzene in the νCH=CH bending vibration at 6.14 mm., in 4970 yield.

**Anal.** Calcd. for C_{13}H_{12}O_{4}N: C, 55.32; H, 6.00; N, 20.10. Found: C, 55.81; H, 5.98; N, 20.22.
isomers, became partially crystalline. From chromatography on neutral alumina it was possible to elute with ether a crystal-
line benzene, m.p. 112-118°; this was recrystallized from a
small quantity of carbon tetrachloride and melted unsharply at 116-118°. It was obviously still a mixture of benzoate and
phenanthrene and was analyzed by comparison of its infrared spectrum with that of the pure compound, using the peaks in the 11-14 μ region (carbon disulfide solution) for analysis. The same
per cent composition was obtained. After recrystallization before chromatography because the impurity did not absorb in
the 11-14 μ region. The results are accurate to within ±5%.

7. Cyclonaphthalene Enamine and Ethyl Acetatecrilate.—A solution of 15.1 g. of the pyrroline enamine in 65 ml. of
diisoxane was allowed to stand at room temperature for 14 hours after addition of 14 g. of ethyl acetate. Hydrolysis with
water and acetic acid-water buffer left a solid residue which dissolved in 50 ml. of acetic acid in 4 hours and usual work up gave 10.6 g. (75% of ethyl 2,8-di-
decalone-4-carboxylate (XVIII), b.p. 142-144° (0.4 mm.). This solidified on standing in the refrigerator and had m.p. 58-59°. Recrystallization ether raised the melting

8. 2-Methylcyclohexanone Enamine and Methyl Vinyl Ketone.—The reaction was carried out as described under ex-
ample II-2, of the pyrroline enamine of 2-methylcyclohexanone and 4 g. of methyl vinyl ketone. The 8-methyl-α,ω-
dodecylenc (XXI) obtained in 45% yield had b.p. 102-104° (2 mm.), b.p. 102° (2 mm.). The 2,4-dinitrophenylhydrazone
resulted upon neutral alumina it was possible to elute with ether a crystal nearly free of impurities. The 2,4-dinitrophenylhydrazone recrystallized from ethyl acetate had m.p. 169-170° (reported6
m.p. 172°) and depressed strongly the m.p. of the isomeric di-
water and extracted with ether. Distillation gave 6.50 g.

9. Methyl Vinyl Ketone.66—To 8 g. of the pyrroline enamine of diethyl ketone, stirred under nitrogen at room temperature, was added 1.90 g. of methyl vinyl ketone (1 equiv.). After 16 hours at room temperature the enamine absorption in the infrared had disappeared. Addition of 15% hydrochloric acid, then 10
g. of water and 440 ml. of methanol. The mixture was poured into
water and extracted with ether. Distillation gave 6.50 g.

10. Cyclicpentone Enamine and Methyl Vinyl Ketone.—In the same manner described under example II-2, a solution of 13.7 g. of the pyrroline enamine of cyclopentanone in 65 ml. of
diisoxane was allowed to react with 7 g. of methyl vinyl ketone. On distillation after hydrolysis, 5.7 g. (427,) of 5,6,7,8-
dinitrophenylhydrazone, m.p. 169-170° (reported6
m.p. 172°) and depressed strongly the m.p. of the isomeric di-
water and extracted with ether. Distillation gave 6.50 g.

11. trans-2-Decalone Enamine and Methyl Vinyl Ketone.—The pyrroline enamine of trans-2-decalone was prepared by
refluxing a mixture of 5.0 g. of trans-2-decalone, 3.50 g. of pyr-
roline and 50 ml. of benzene for 20 hours under a water sepa-
ator. Removal of the benzene and distillation gave 5.50 g. of
enamine, b.p. 102-105° (0.2 mm.). To a stirred solution of
5.5 g. of the pyrroline enamine in 125 ml. of dry benzene was
added 1.90 g. of methyl vinyl ketone (1 equiv.). After refluxing
under nitrogen for 12 hours, hydrolysis was effected by refluxing for an additional 7 g. of methyl vinyl ketone. On distillation after hydrolysis, 5.7 g. (427,) of 5,6,7,8-
dinitrophenylhydrazone, m.p. 169-170° (reported6
m.p. 172°) and depressed strongly the m.p. of the isomeric di-
water and extracted with ether. Distillation gave 6.50 g.

12. cis-2-Decalone Enamine and Methyl Vinyl Ketone.66—The morpholine enamine was prepared in the manner de-
scribed under example II-2, of cis-2-decalone, 5.6 g. of methyl vinyl ketone and 100 ml. of toluene. After 16 hours under a water separator and distillation, 11.7 g. of enamine (80%) was obtained, b.p. 110-115° (0.35 mm.). The enamine thus obtained was dissolved in 100 ml. of dry benzene and methyl vinyl ketone (3.72 g.) was added drop-
wise over half an hour and the solution was then refluxed under nitrogen for 10 hours. Further treatment as described in the preceding example gave 9.34 g. (67) of diketone, b.p. 118-119° (0.3 mm.). This was cyclized by refluxing for 4 hours under nitrogen with a mixture of 17.6 g. of potassium hydroxide, 10 ml.
of water and 440 ml. of methanol. The mixture was poured into
water and extracted with ether. Distillation gave 6.50 g.

13. Diethyl Ketone Enamine and Methyl Vinyl Ketone.—To 8 g. of the pyrroline enamine of diethyl ketone, stirred under nitrogen at room temperature, was added 1.90 g. of methyl vinyl ketone (1 equiv.). After 16 hours at room tem-
perature the enamine absorption in the infrared had disappeared. Addition of 15% hydrochloric acid, then 10 g. of water and 440 ml. of methanol. The mixture was poured into
water and extracted with ether. Distillation gave 6.50 g.

14. Isovaleraldehyde Enamine and Methyl Vinyl Ketone.66—To 10 g. of ice-cold piperidine enamine of isovaleraldehyde under nitrogen was added with stirring, over 45 minutes, 4.8 g. of
methyl vinyl ketone. After 24 hours at room temperature, the mixture was treated with 125 ml. of 15% hydrochloric acid and
stirred under nitrogen for 30 hours at room temperature, fol-
lowed by heating half an hour on the steam-bath. The oil which separated was extracted with ether, and after washing with dilute hydrochloric acid, then with water, drying and distilling, gave 4.0 g. (50%), 2,5,6-trimethyl-2-cyclo-
hexanone (XXIV), b.p. 105-106° (15 mm.), reported69 b.p. 53-56° (0.4 mm.). This was in the preceding example by degradation to enamine and purified by preparative chloroform extraction from the original tricyclic ketone mixture to have been 3 parts of
XXV and 2 parts of XXXIV.

15. Propionaldehyde Enamine and Ethyl Vinyl Ketone.66—In the same manner as described above, reaction of 11.4 g. of
the piperidine enamine of propionaldehyde was treated with 7.05 g. of ethyl vinyl ketone. Further hydrolysis and work-up as before gave 7.00 g. of methyl vinyl ketone (86%). The enamine (XXXV), b.p. 70-72° (20 mm.) (reported68 b.p. 95° (35 mm.)). The infrared spectrum was identical with that of an authentic sample.32 The red 2,4-dinitrophenylhydroxylamine had m.p. 185-187° (re-
ported69 m.p. 183-184°).

16. Enamine of Methyl 4-Formylhexanoate and Methyl Vinyl Ketone.66—A solution of 7.1 g. (0.1 mole) of pyrroline and 15 g. of methyl 4-formylhexanoate in 400 ml. of benzene was refluxed for 1 hour under a water separator and then was added to 150 ml. of a solution of 2,5,6-trimethyl-2-cyclo-
hexenone (XXXI) at room temperature, was added dropwise 4.1 g. of methyl vinyl ketone (0.13 mole) of methyl vinyl ketone (1 equiv.). After 2 days at room tem-
perature the enamine absorption in the infrared had disappeared. Addition of 15% hydrochloric acid, then 10 g. of water
and 440 ml. of methanol. The mixture was poured into
water and extracted with ether. Distillation gave 6.50 g.

(67) This experiment was carried out by J. Fujah.
Alylation with Alkyl Halides

Many alkylations are recorded in detail in the literature. A few examples from our own work are listed here.

Propargyl Bromide on the Enamine of the Ethylene Glycol Monoketal of 1,4-Cyclohexanediol.

The enamine was prepared by refluxing a solution of 5 g. of pyrrolidine and 10 g. of 1,4-dioxaspiro[4,5]decan-8-one in 100 ml. of dry methanol under nitrogen, for 7 hours. Most of the methanol was removed and the residue distilled to give 10 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.). This was used directly for alkylation with propargyl bromide. To a solution of 10 g. of the ethylene glycol monoketal of 1,4-cyclohexanediol in 25 ml. of dry benzene, under nitrogen, was added 11 g. of propargyl bromide. The solution was refluxed for 4 hours and, after addition of 10 ml. of water, was further refluxing for half an hour. The resulting solution was cooled and extracted with ether. The ether solution was dried with sodium carbonate, filtered and distilled to give 6.7 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

Acetylation of Enamines to D-Ketones and D-Keto Esters

Acetylation of 2-Methylcyclohexanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of anhydrous ether was treated with 15 g. of acetic anhydride. After removal of most of the acetoxydine ether, the residue was stirred with 100 ml. of water, and the mixture was refluxed for half an hour. The resulting solution was cooled and extracted with ether. The ether solution was dried with sodium carbonate, filtered and distilled to give 2.9 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

Acetylation of 2-Butanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry benzene was slowly added to 100 ml. of dry acetic anhydride. The mixture was stirred at room temperature for 1 hour. After removal of most of the acetoxydine ether, the residue was stirred with 100 ml. of water, and the mixture was refluxed for half an hour. The resulting solution was cooled and extracted with ether. The ether solution was dried with sodium carbonate, filtered and distilled to give 2.2 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

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Acetylation of 2-Butanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry benzene was slowly added to 100 ml. of dry acetic anhydride. The mixture was stirred at room temperature for 1 hour. After removal of most of the acetoxydine ether, extraction of the aqueous layer with ether and drying with sodium carbonate, filtered and distilled to give 2.2 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

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Acetylation of 2-Butanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry benzene was slowly added to 100 ml. of dry acetic anhydride. The mixture was stirred at room temperature for 1 hour. After removal of most of the acetoxydine ether, extraction of the aqueous layer with ether and drying with sodium carbonate, filtered and distilled to give 2.2 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

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Acetylation of 2-Methylcyclohexanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of anhydrous ether was treated with 15 g. of acetic anhydride. After removal of most of the acetoxydine ether, extraction of the aqueous layer with ether and drying with sodium carbonate, filtered and distilled to give 2.9 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).

Acetylation of 2-Butanone. A solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry benzene was slowly added to 100 ml. of dry acetic anhydride. The mixture was stirred at room temperature for 1 hour. After removal of most of the acetoxydine ether, extraction of the aqueous layer with ether and drying with sodium carbonate, filtered and distilled to give 2.2 g. of colorless liquid, b.p. 120° (0.1-0.15 mm.).
Some of the solvent was removed under water-pump vacuum and the mixture was poured into 200 ml. of water and extracted with chloroform several times. The extraction of the organic layer was made with 10% hydrochloric acid and extracted with chloroform, and the solution was stirred rapidly. After stirring and refluxing for 10–15 hours the mixture was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with diethyl ether. The ether extracts were discarded. The solution was refluxed with vigorous stirring for 4–6 hours. The layers were then separated, the aqueous layer was extracted with benzene, and the combined organic layers were subjected to distillation at atmospheric pressure, leaving 25.0 ml. of water, made strongly acid with concentrated sulfuric acid, and extracted with benzene. The benzene was removed by distillation at atmospheric pressure, leaving 3.7 g. of an oily solid, which, on crystallization from n-pentane, gave 2.04 g. of product. The infrared spectrum was identical with that of an authentic sample of 2-carbethoxy-4-methylcyclohexanone.

6-Ketotetracosenic acid (LXII, R = CH(CH2)6CH3) was prepared from 2-propylcyclopentanone in 75% yield by the method described above as white crystals, m.p. 67.0–67.5° (reported m.p. 65.5°) [1].


7-Ketomyristic acid (LVII, R = CH(CH2)11CH3) was prepared in a similar manner from 2-propylcyclohexanone, in 65% yield, as white crystals, m.p. 67.0–67.5° [2].


7-Ketopentadecane-1,15-dioic acid (LVIII, n = 7) was prepared by refluxing with vigorous stirring for 4–6 hours. The solution was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with chloroform. The chloroform was added under nitrogen while the aqueous hydrochloric acid solution was being stirred rapidly. After refluxing for 20 hours the mixture was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with benzene. The benzene was removed by distillation at atmospheric pressure, leaving 3.7 g. of an oily solid, which, on crystallization from n-pentane, gave 2.04 g. of product, m.p. 64–65°, on crystallization from n-pentane.

Ketopentadecane-1,15-dioic acid (LVIII, n = 7) was prepared in 95% yield by refluxing with vigorous stirring for 4–6 hours, the solution was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with benzene. The benzene was removed by distillation at atmospheric pressure, leaving 3.7 g. of an oily solid, which, on crystallization from n-pentane, gave 2.04 g. of product, m.p. 64–65°, on crystallization from n-pentane.

Cyclohexanone and Caprylyl Chloride.—To a solution of 28.0 g. (0.17 mole) of the morpholine enamine of cyclohexanone in 150 ml. of dry benzene, capryloyl chloride (13.0 g., 0.066 mole) was added under nitrogen while the enamine solution was stirred rapidly. After stirring and refluxing for 20 hours, the mixture was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with chloroform. The chloroform was added under nitrogen while the aqueous hydrochloric acid solution was being stirred rapidly. After refluxing for 20 hours the mixture was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The combined filtrate and washings were returned to the reaction flask, 50 ml. of water and extracted with benzene. The benzene was removed by distillation at atmospheric pressure, leaving 3.7 g. of an oily solid, which, on crystallization from n-pentane, gave 2.04 g. of product, m.p. 64–65°, on crystallization from n-pentane.

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2-Carbethoxy cyclohexane.—In a similar manner, 33.5 g. (0.18 mole) of the morpholine enamine of cyclohexanone and 11.0 g. (0.122 mole) of ethyl chloroformate in 150 ml. of dry benzene gave 7.53 g. (46%) of 2-ketoester, b.p. 110-125° (16 mm.), reported3 b.p. 125-126° (12 mm.); phenylpyrazolone, m.p. 210-214° (reported2 m.p. 210°).

2-Carbethoxypentane-3.—In a similar manner, 25.0 g. (0.16 mole) of the morpholine enamine of diethyl ketone and 9.0 g. (0.083 mole) of ethyl chloroformate in 150 ml. of dry benzene gave 4.6 g. (37%) of 3-keto ester, b.p. 87-92° (12 mm.). The phenylpyrazolone was prepared from the carbethoxy ketone by reaction with phenylhydrazine; m.p. 109-110.5° (reported2 112.5°).

3-Carbethoxyheptane-4 (LVIII).—In a similar manner, 25.0 g. (0.138 mole) of the morpholine enamine of dipropyl ketone and 9.0 g. (0.083 mole) of ethyl chloroformate in 150 ml. of dry benzene gave 6.7 g. (53.3%) of 4-keto ester, b.p. 105-106° (16 mm.) (reported4 b.p. 88-90° (12 mm.).)

2-Carbethoxy cyclohexane by Reaction in the Presence of Diethylamine.—The morpholine enamine of cyclohexanone (16.7 g., 0.19 mole) and diethylamine (16.4 g., 0.11 mole) were dissolved in 100 ml. of chloroform and, while the system was kept under a nitrogen atmosphere, ethyl chloroformate (12.0 g., 0.11 mole) was added and the mixture was refluxed for 7 hours. The soln was then transferred to a separatory funnel and 3 ml. of concentrated hydrochloric acid in 35 ml. of water was added. The mixture was shaken at intervals over a period of 15-30 minutes. The layers were then separated, and the chloroform solution was washed successively with two 25-ml. portions of 10% hydrochloric acid and four 25-ml. portions of water. These wash solutions and the original hydrochloric acid solution were combined and extracted with three 50-ml. volumes of benzene. The benzene extracts and chloroform solution were combined and dried over anhydrous sodium carbonate. After filtration from drying agent (which was washed with dry benzene) solvent was removed from the filtrate by atmospheric pressure distillation. Fractionation of the residue through a short-path column gave 9.47 g. (56%) of product, b.p. 100-110° (10 mm.). The infrared spectrum of this compound was identical with that of authentic 2-carbethoxy cyclohexanone.

Under the same conditions but with one equivalent of triethylamine instead of diethylamine no 3-keto ester could be obtained.

Studies in Organic Peroxides. XXIX. The Structure of Peroxides Derived from 2,4-Pentanediene and Hydrogen Peroxide

BY NICHOLAS A. MILAS, ORVILLE L. MAGELI, ALEKSANDAR GOLUBOVIĆ, ROLF W. ARNDT, and JESSIE C. J. HO

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2,4-Pentanediene (II) reacts at 0° with one mole of hydrogen peroxide to form 3,5-dimethyl-3,5-dihydroxy-1,2-peroxycyclopentane (IV) or 3,5-dimethyl-3,5-dihydroxy-1,2-dioxolane. When the same reaction is carried out with two moles of hydrogen peroxide (V), 3,5-dimethyl-3-hydroxy-5-hydroperoxy-1,2-peroxycyclopentane (VI) is formed. With three moles of hydrogen peroxide in dilute acid solutions, II yields 3,5-dimethyl-3,5-dihydroperoxy-1,2-peroxycyclopentane (V). Peroxide V can be converted either in dilute aqueous acid solution or in anhydrous ether with phosphorus pentoxide to the bicyclic peroxide VII. Peroxide VI forms readily a crystalline bis-p-nitrobenzoate. The infrared spectra of all peroxides in this group have been measured by the mill method and in dimethoxyethane. The ultraviolet spectra of peroxides IV and V in dilute solution show considerable dissociation to their original components. The dissociation of peroxide IV in dilute ether and chloroform solutions is a nonmolecular reaction. The n.m.r. spectra of all peroxides in this group were measured in CDCl3, CD3OD and D2O solutions. It has been found that the undisassociated peroxide IV exists in solution as a 2:3 mixture of cis and trans isomers, although in the solid state it may exist as a single isomer which is equilibrated in solution to the 2:3 mixture. Peroxides V and VI exist only as the trans isomers while by reason of its symmetry the bicyclic peroxide VII exists only in the cis configuration.

In previous publications6,b,c we have described several organic peroxides derived from the reaction of simple aliphatic monoketones and hydrogen peroxide. The present communication deals with the structure and composition of peroxides derived from the preparation of hydrogen peroxide and 2,4-pentanediene. When diketene II was allowed to react at 0° with one mole of 50% hydrogen peroxide, a crystalline peroxide was formed in the course of 4 hr. ± 5 min. in yields of 90-92.5%. The analytical data for this peroxide support either structure III or IV. However, infrared spectra taken by the mill method6 in Nujol or 10% in dimethylformamide6 failed to show a carbonyl band; we are therefore in favor of structure IV. Moreover, the n.m.r. spectra show also no evidence for the presence of peroxide III. The strong infrared bands near 1080 and 1160 cm. -1, respectively, may be attributed to 1,3-dioxol, while the region 1150-1080 cm. -1 also been attributed to ketals6 in which two oxygen atoms are attached to the same carbon atom, as in the case of the peroxides described in this paper.

In spite of its stability at room temperature, when peroxide IV was heated in a long tube at the b.p. of acetic acid and at a pressure of about 2 mm., it appeared to dissociate to its original components which recombined in the cold part of the tube to form a crystalline peroxide of much less purity, and a liquid which was collected in a trap immersed in Dry Ice-acetone mixture. The liquid showed the presence of both free hydrogen peroxide (silver foil test) and 2,4-pentanediene.

The hydroxyhydroperoxyperoxide V was obtained either by adding one mole of hydrogen peroxide to the dihydroperoxyperoxide IV or by adding directly two moles of hydrogen peroxide to 2,4-pentanediene. This peroxide had essentially the same infrared spectrum as peroxide IV except in the hydroxyl region, 3230-3430 cm. -1, where it showed a doublet due perhaps to the difference in the structure of the two groups attached to carbon atoms 3 and 5. Similarly, the dihydroperoxyperoxide VI was obtained either by adding one mole