Sec. 2. Removal of Protecting Groups.—The conditions for removal of the *tert*-butyl ether 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 on Whatman No. 1 paper using the solvent system 1-butanol–acetic acid–water, 4:1:5, (BAW), or on silica gel plates (thin layer) using the solvent system *sec*-butyl alcohol–3% ammonia, 3:1 (BAM).

Ex. A. Removal of *tert*-Butyl Groups from H·ser(*O*-*t*-Bu)·-*O*-*t*-Bu(DL) (III).—Using ninhydrin in butanol as the detecting reagent, the R_f 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 III

PRODUCTS FROM H·ser·(O-*t*-Bu)·O-*t*-Bu(DL), R_f VALUES (BAM)

Treatment at 25°	H·ser·OH	H·ser(O-*t*-Bu)·OH	H·ser·O-*t*-Bu	H·ser(O-*t*-Bu)·O-*t*-Bu
Standards	0.04	0.17	0.48	0.60
HBr/HOAc (5 min.)	.02	.16	.48	.60
HI (57%) (5 min.)	.05	.19	.46	.62
HCl/$CHCl_3$ (5 min.)	.04	.16	.44	.59
HBr/HOAc (30 min.)	.04			
HCl/$CHCl_3$ (30 min.)	.03	.17	.53	.68

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 R_f values in the BAW system for the ester-thioether and related compounds were: H·cySH·OH(L), 0.06; H·cy(S-*t*-Bu)·OH(L), 0.78; 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%), hydriodic acid (57%), hydriodic acid in acetic acid, and trifluoroacetic acid (TFA). The chromatograms were treated with ninhydrin, then Feigl reagent,[91] the latter reagent showing the presence of a free SH- group. Although all of the reagents except TFA yielded free cysteine, none of the reactions went to completion. The latter reagent gave a product with an R_f value of 0.70 which was positive to Feigl reagent. This has been tentatively identified as H·cySH·O-*t*-Bu(L), since a spot which was ninhydrin positive with the same R_f value was found in the starting base (ex. XX).

The R_f values of the cysteine derivatives in BAM were determined as: H·cySH·OH(L), 0.05 H·cy(S-*t*-Bu)·OH(L), 0.19; H·cy(S-*t*-Bu)·O-*t*-Bu(L), 0.72; H·cySH·O-*t*-Bu, 0.62. Pure compounds were used, except the last value was tentatively determined from a very weak ninhydrin-positive spot which appeared in the distillate of the original preparation. This was eliminated if the base was initially purified as the hydrochloride salt. In addition to the previous reagents, three additional ones were tested: hydrogen chloride in chloroform, hydrogen bromide in nitromethane and perchloric acid (70%) dissolved in glacial acetic acid. A second perchloric acid treatment was continued for an hour.

Development of color on the chromatograms by ninhydrin as well as subsequent treatment with chlorine and potassium iodide–tolidine reagent[92] indicated that no reaction had gone to completion. However, perchloric acid treatment for an hour gave the best results with H·cySH·OH(L) forming, and only one ninhydrin-positive spot remaining. This corresponded to H·cy-(S-*t*-Bu)·OH(L). An unidentified spot (tolidine positive) remained with an R_f of 0.39.

Ex. C. Removal of *tert*-Butyl Groups from H·tyr(O-*t*-Bu)-·O-*t*-Bu(L) (II).—The ester-ether was treated as previously described with hydrogen bromide in acetic acid, hydrobromic acid (40%), hydrogen chloride in chloroform, and *p*-toluenesulfonic acid. All reagents removed both *tert*-butyl groups. The BAW system was used, the spots being detected with ninhydrin; R_f 0.59 for tyrosine and 0.94 for H·tyr(O-*t*-Bu)·O-*t*-Bu(L).

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

(91) Fritz Feigl, "Qualitative Analysis of Spot Tests," 2nd English Ed., Nordeman Pub. Co., Inc., New York, N. Y., 1939, pp. 195 and 291.

(92) F. Reindel and A. Hoppe, *Ber.*, **87**, 1103 (1954).

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

The Enamine Alkylation and Acylation of Carbonyl Compounds

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

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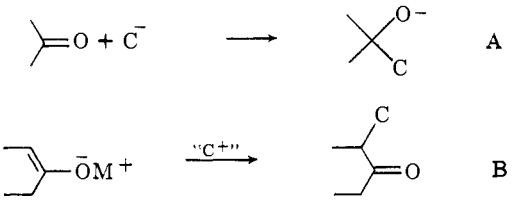
The enamine alkylation and acylation of carbonyl compounds is discussed with regard to the preparation of enamines, their alkylation with electrophilic olefins, their alkylation with alkyl halides and finally their acylation with acid chlorides. This new synthetic method is remarkable by its mildness and by the ease with which monoalkylation or acylation can be achieved.

Introduction

In 1954, we introduced a new and relatively general synthetic method for the acylation and alkylation of carbonyl compounds.[1,2] 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.[3] A progress report on our own further work in this field has also been given.[4] 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 carbanion 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).



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, triphenylmethide 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

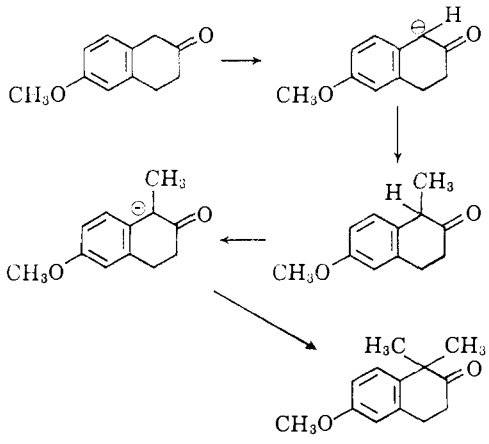
(1) G. Stork, R. Terrell and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **76**, 2029 (1954).

(2) G. Stork and H. Landesman, *ibid.*, **78**, 5128 (1956).

(3) The literature on enamines is reviewed in a chapter by J. Szmuszkovicz in a forthcoming volume of "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y.

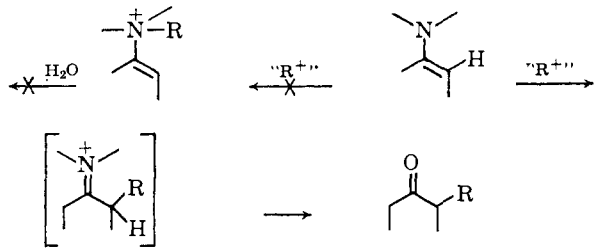
(4) XVIth National Organic Symposium Abstracts, Seattle, Wash., June, 1959, pp. 44 ff.

Claisen or Michael condensation,[5] 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 monosubstituted derivatives even with mild bases. The second problem may be illustrated by a typical example: Attempted monoalkylation of 6-methoxy-β-tetralone with one equivalent of methyl iodide in the presence of strong bases leads to almost no monomethyl compound: a mixture of 6-methoxy-1,1-dimethyl-β-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

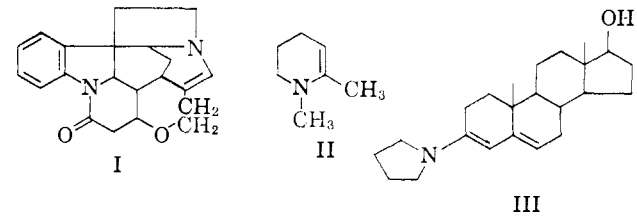


cite the reaction of acrylonitrile with cyclohexanone in the presence of a variety of bases which leads to a mixture of the mono-, di-, tri- and tetracyanoethylated ketones.[8]

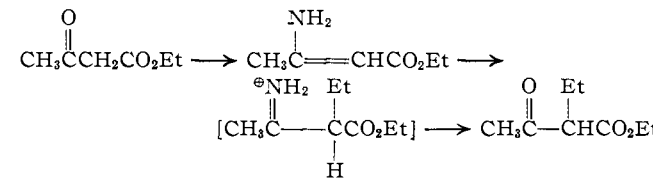
It occurred to us that a new method for the alkylation and acylation of ketones and aldehydes might energe from the very interesting possibility that the enamines derived *from an ordinary ketone or aldehyde* might react with an electrophilic reagent (symbolized here by "R⁺") to some extent on carbon 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 dimethyltetrahydropyridine[12] II into their respective N-methiodides. Similarly, the pyrrolidine enamine of testosterone (III) has been shown to give very largely the "expected" N-methiodide.[1,13]



As is by 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 (polyalkylation). 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 with acrylonitrile and other electrophilic olefins to give, in general, the product in which the newly introduced group appears on the more substituted carbon (*cf.* IV → V, VI).[15] The enamines derived from such ketones, however, normally lead to substitution on the *less* substituted carbon (*cf.* IV → 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 for-



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 β-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. Eglinton and M. C. Whiting, *ibid.*, 3052 (1953).

(5) *Cf. inter alia:* (a) V. Prelog and O. Metzler, *Helv. Chim. Acta*, **30**, 878 (1947); (b) J. H. Burkhalter and P. Kurath, *J. Org. Chem.*, **24**, 990 (1959). (c) The "condensation product" of cyclopentanone and methyl vinyl ketone described by E. D. Bergmann, *et al.* (*Bull. soc. chim. France*, 290 (1957)) as the indenone XII is obviously (*cf.* ultraviolet spectrum) 2-cyclopentylidenecyclopentanone, the self-condensation product of cyclopentanone.

(6) P. Yates and C. D. Anderson, *J. Am. Chem. Soc.*, **80**, 1264 (1958).

(7) J. Rundquist, Ph.D. Thesis, Harvard University, 1951.

(8) *Cf.* H. A. Bruson in "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 101; H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, **64**, 2850 (1942).

(9) As long ago as 1883, Collie noted (*Ann.*, **226**, 316 (1883)) that ethyl iodide reacts with ethyl β-aminocrotonate to produce, after hydrolysis, α-ethylacetoacetic ester. Acetoacetic ester can be alkylated readily in the

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

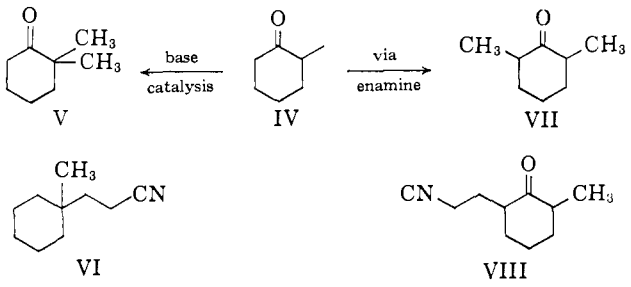
(11) O. Achmatowicz, G. R. Clemo, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 787 (1932).

(12) A. Lipp, *Ann.*, **289**, 216 (1896).

(13) J. L. Johnson, M. E. Herr, J. C. Babcock, A. E. Fonken, J. E. Stafford and F. W. Heyl, *J. Am. Chem. Soc.*, **78**, 430 (1956).

(14) So well known in fact that the method has often been used without reference of any kind to its source. *Cf.* (a) L. Velluz, *et al.*, *Tetrahedron Letters*, **No. 3**, 127 (1961); (b) E. Demole and M. Stoll, *Helv. Chim. Acta*, **45**, 692 (1962); (c) E. Demole and M. Winter, *ibid.*, **45**, 1256 (1962); (d) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes and C. D. Slater, *J. Am. Chem. Soc.*, **84**, 2611 (1962).

(15) *Cf. inter alia:* J. M. Conia, *Bull. soc. chim. France*, 533 (1950); R. Frank and R. C. Pierle, *J. Am. Chem. Soc.*, **73**, 724 (1951).

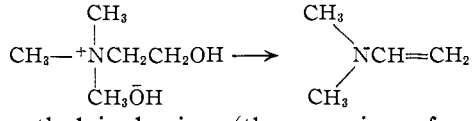


mer cannot be alkylated under the usual base-catalyzed conditions because of their rapid self condensation.

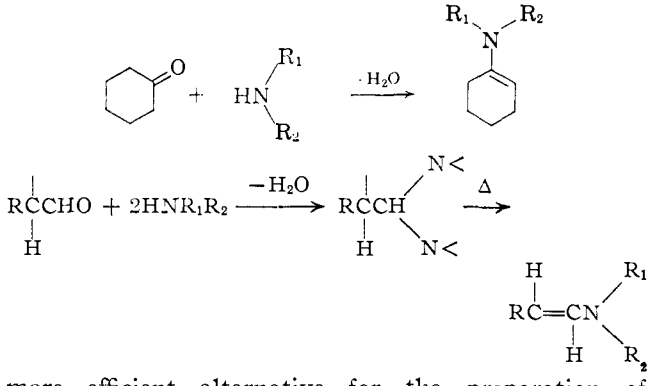
We will now direct our discussion to (I) The Preparation of Enamines, (II) The Enamine Alkylation of Carbonyl Compounds with Electrophilic Olefins, (III) The Enamine Alkylation of Carbonyl Compounds with Alkyl Halides, (IV) The Enamine Acylation of Carbonyl Compounds.

I. The Preparation of Enamines

The simplest enamine of a carbonyl compound was prepared long ago by Meyer and Hopf[16] who made



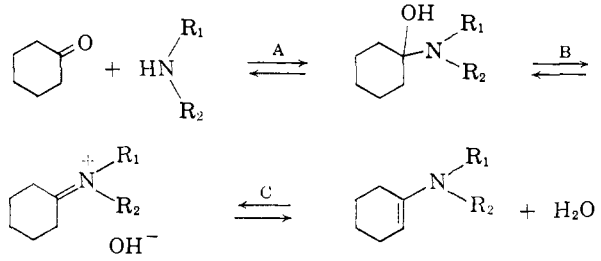
N,N-dimethylvinylamine (the enamine of acetaldehyde) by pyrolysis of choline. This is obviously not a general method and it remained for Mannich and Davidsen[10] to provide the synthesis which with some modification of details is still the one used today: reaction of an aldehyde or ketone with a secondary amine, in the presence of a dehydrating agent such as anhydrous potassium carbonate. Under these conditions ketones are converted into their enamines directly while aldehydes are transformed into the nitrogen analog of an acetal which is then decomposed, on distillation, to enamine and secondary amine. Removal of water by azeotropic distillation with benzene is a



more efficient alternative for the preparation of enamines from most ketones as well as from disubstituted acetaldehydes.[17]

In our work the practice has been to use azeotropic 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 acetaldehydes. There are two cases for which neither method is satisfactory: monosubstituted acetones, which often (but not always; *cf.* ref. 45) give self-condensation products; and ketones which are too hindered or otherwise unreactive 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 piperidine (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 affected, 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 morpholine,[18] while cyclic amines generally produce enamines faster than open-chain ones. This is of course what would be expected, but the fact that pyrrolidine reacts faster than piperidine may deserve comment. The basicity and steric environment of the two bases are closely similar[18] and the differences in rate are probably to be ascribed to the different rates of the dehydration steps: The transition state with pyrrolidine involves making a trigonal carbon in a five-membered ring and the faster rate of solvolysis of methylcyclopentyl chloride than that of the corresponding cyclohexyl compound[19] correlates with the faster formation of an enamine from pyrrolidine than from piperidine. 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 dehydration 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 obviously impossible, but measurement in chloroform solution shows that enamines, *in that solvent*, are about 10 to 30 times weaker bases than the *secondary* amines from which they are formed.[20] In any case, the actual basicity is ample to give an appreciable rate of proton addition from water and hence hydrolysis to the more stable carbonyl compound. It is evident that all reactions with enamines must be conducted with rigorous exclusion of moisture, but on the other hand this extreme ease of hydrolysis makes the regeneration of an

(16) K. H. Meyer and H. Hopf, *Ber.*, **54**, 2277 (1921); *cf.* J. v. Braun and G. Kirschbaum, *ibid.*, **52**, 2261 (1920).

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

(18) Pyrrolidine has $K = 1.3 \times 10^{-3}$, morpholine has $K = 2.44 \times 10^{-6}$ and piperidine has $K = 1.6 \times 10^{-3}$.

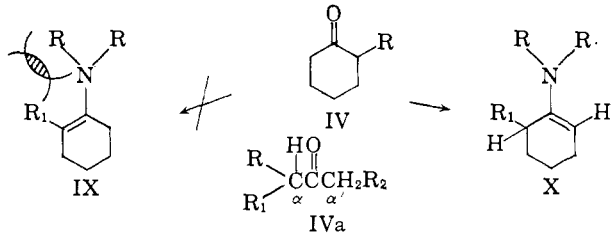
(19) *Cf.* H. C. Brown, *J. Chem. Soc.*, 1248 (1956).

(20) *Cf.* W. Lendle, Dissertation, Marburg, 1959.

α-alkylated or acy ated substance feasible under conditions sufficiently mild to be compatible with groups such as esters, nitriles, β-diketones, β-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 mμ (ϵ 5,000–8,000) and the double bond stretching in the infrared shows up as a strong band at about 6.07 ± 0.05 μ (1630–1660 cm.$^{-1}$).[21] 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 $\tau = 5.58$.[22] This position is very little affected by small changes in the basicity of the amine and is the same with 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 $\tau = 4.6$, 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[23] 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.[24] 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 α'-carbon in systems such as IV and IVa which would normally lead (*e.g.*, in base-catalyzed alkylation reactions) to further α-substitution.



One reason for this greater stability of the less substituted enamine is probably that the trivalency of nitrogen causes one of the alkyl groups of the nitrogen base to interfere with the α-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.[2]

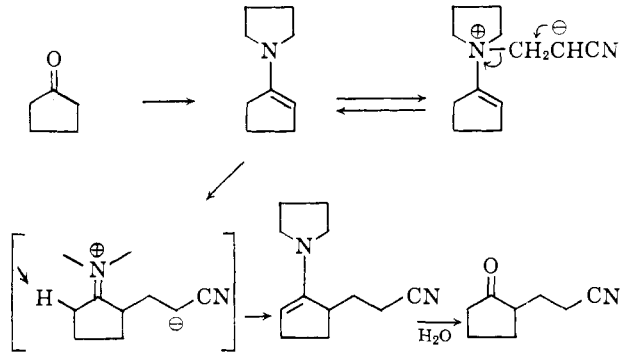
(21) *Cf. inter alia:* (a) G. Opitz, H. Hellman and H. W. Schubert, *Ann.*, **623**, 112 (1959); (b) E. Benzing, *Angew. Chem.*, **71**, 521 (1959); N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

(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 cyclohexene ($\tau = 4.43$).

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

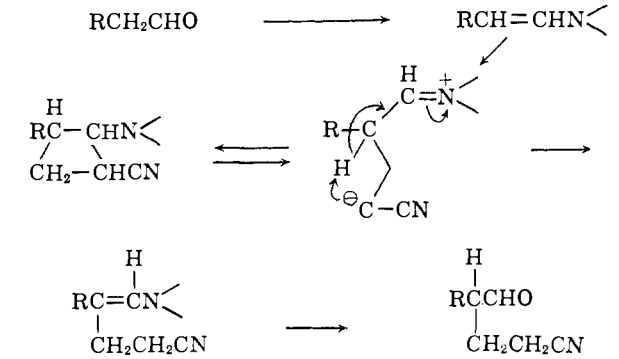
(24) *Cf.* E. J. Eisenbraun, J. Osiecki and C. Djerassi, *ibid.*, **80**, 1261 (1958).

As we have pointed out in our preliminary communication on the subject,[2] this type of reaction is especially successful because competition from N-alkylation is inconsequential: the zwitterion 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

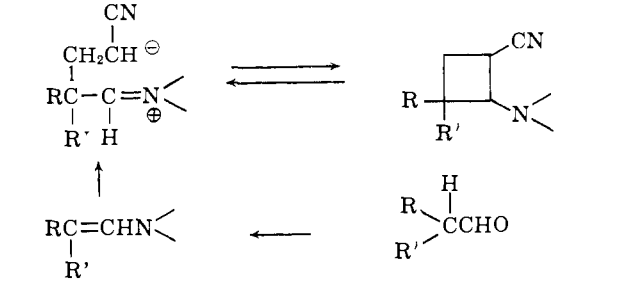


XI

It is interesting that the enamine which results from the reaction (*cf.* XI) is that which derives from transfer of the proton marked by an arrow (possibly *via* an intramolecular 6-membered transition state) thus leading to the more stable, less substituted, enamine. In the case of aldehydes the possibility of such a proton transfer *via* a six-membered ring is unavailable and the formation of a stable neutral alkylated enamine can only result from the intervention of a 4-membered transition state (or from intermolecular reactions).



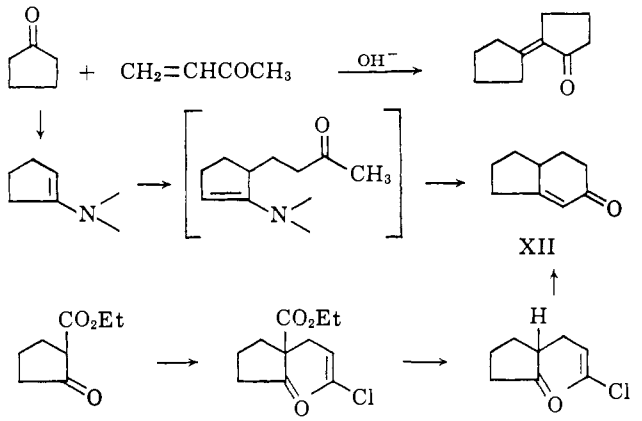
The molecule can also become neutral by *addition* of the anion to the >C=N$^+$<: In a number of cases it is possible to isolate the cyclobutane derivative formed by direct neutralization of the charges. This is of course especially true when the aldehyde enamine adduct cannot become neutral by proton transfer, *e.g.* with α,α-disubstituted aldehydes[25]



Before we turn to experimental conditions and results, we would like to emphasize a number of important

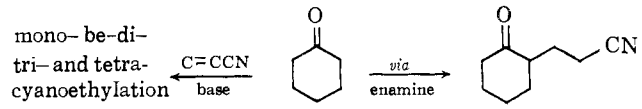
(25) *Cf.* K. C. Brannock, A. Bell, R. D. Burpitt and C. A. Kelley, *J. Org. Chem.*, **26**, 625 (1961).

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.[5c] The formation of the desired indanone XII by the enamine procedure is easily achieved and may be contrasted with the previously available method[26] outlined in XIII → XII.



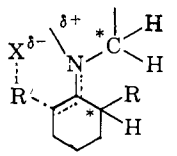
XIII

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



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



XV

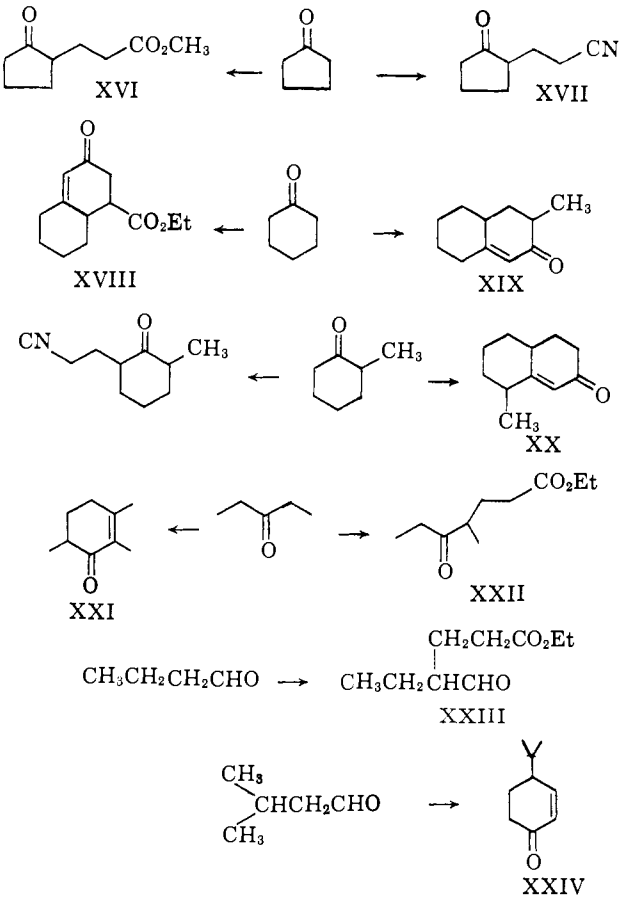
methylene α- to the nitrogen atom and R is obviously greater when R is alkyl (the monoalkylated product) than when R is H (in the starting material): hence the higher energy of the transition state for the second alkylation.[4,27] This factor is of course absent with the usual enolate ions.

(26) V. Prelog and M. Zimmermann, *Helv. Chim. Acta*, **32**, 2360 (1949).

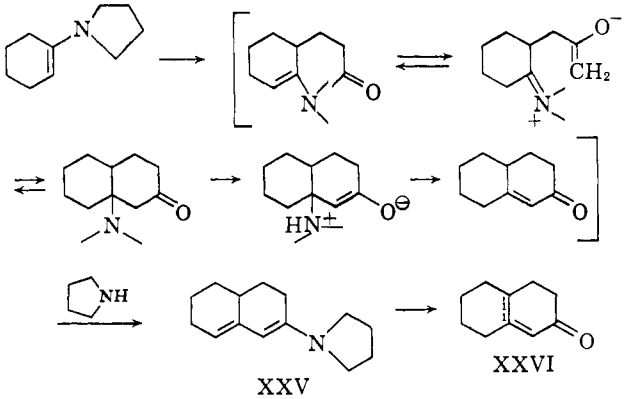
(27) H. Landesman, Ph.D. Thesis, Columbia, 1956; *cf.* W. R. N. Williamson, *Tetrahedron*, **3**, 314 (1958).

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.



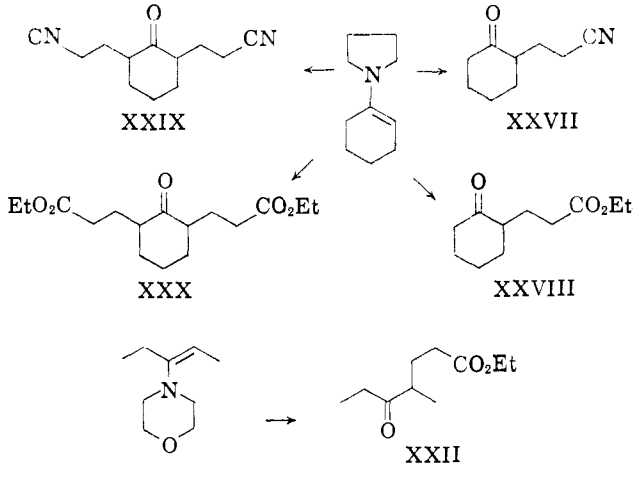
The reaction products from vinyl ketones and *pyrrolidine* enamines are not decomposed merely by heating with water. The products are enamines of α,β-unsaturated ketones and these are considerably more stable to hydrolysis than enamines of saturated



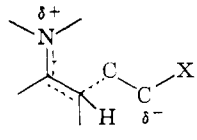
carbonyl compounds. Decomposition is effected in these cases by the use of a hot mixture of acetic acid, sodium acetate and water.[13] We can illustrate the course of the reaction with the pyrrolidine enamine of cyclohexanone and methyl vinyl ketone. If the reaction is conducted in toluene, direct distillation of the reaction mixture before hydrolysis leads to a high yield of the pyrrolidine enamine of $\Delta^{1,10}$-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 α,β-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 carbonyl 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 XXVII 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.



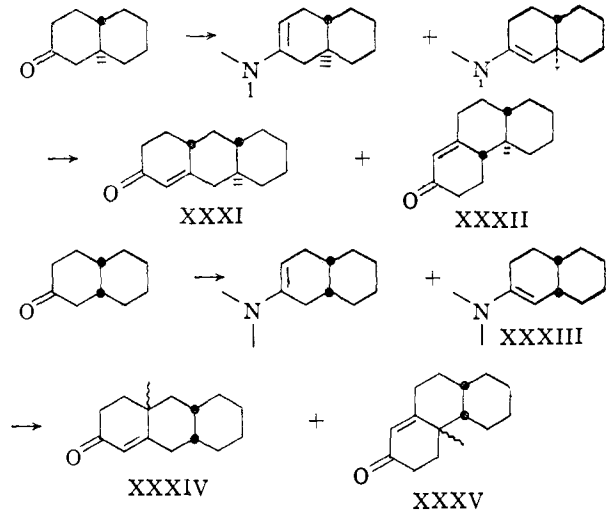
The effect of the solvent is easily rationalized: the transition state for alkylation involves considerable charge separation and its energy should be appreciably lower in ethanol than in benzene or dioxane.



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 β-decalone and those derived from aldehydes.

In the case of *trans*-β-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 anthracene) to consist of 10% XXXII and 90% XXXI. With *cis*-β-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 Δ^2-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.[28] 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.[29] In the simple *cis*-β-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 α,β-unsaturated ketones, it appears that these take place well only with vinyl ketones in which the double bond is unsubstituted.[30] The method is thus general for the synthesis of 4-substituted cyclohexenones and for 2,4-disubstituted Δ^2-cyclohexenones. It is worth noting that the last mentioned cyclohexenones are not the same as would be produced by the Birch reduction[31] of 2,4-dialkylanisoles 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-Δ^2-cyclohexenone (XXXVI) in 69% yield. The preparation of this compound by other methods is in contrast both laborious and unsatisfactory.[32]

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

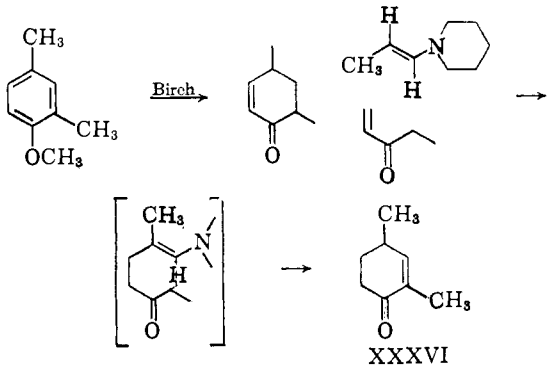
(28) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962); B. Berkoz, E. P. Chavez and C. Djerassi, *ibid.*, 1323 (1962).

(29) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954).

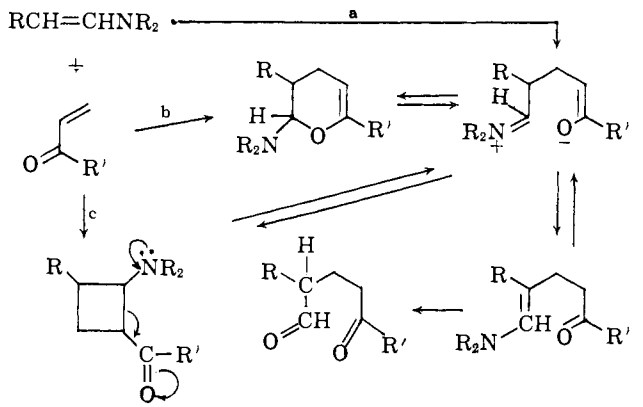
(30) In contrast to enamines derived from ketones, enamines from aldehydes with an α-methylene group self-condense readily (*cf.* C. Mannich and E. Kniss, *Ber.*, **74**, 1629 (1941)). Only with α,β-unsaturated ketones with an unsubstituted vinyl group is the alkylation reaction fast enough to compete successfully with this duplication process.

(31) *Cf.* A. J. Birch and H. Smith, *Quart. Rev.*, **12**, 17 (1958).

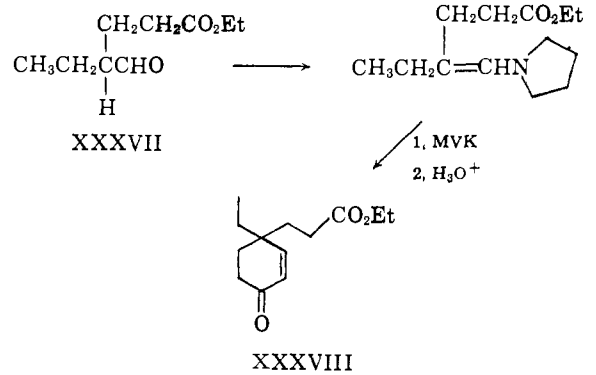
(32) Unpublished experiments by Dr. Y. W. Chang in this Laboratory; see also ref. 70.



with an enamine, it is of course conceivable, by analogy with the reaction with enol ethers,[33] that the reactions are 4-center reactions of the Diels–Alder type. Indeed Opitz[34] has represented in this manner the addition of aldehyde enamines to α,β-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).

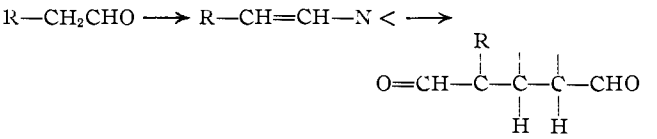


Whatever the structure of the intermediate (dihydropyran, enamine or aminoacylcyclobutane) from the addition of an α,β-unsaturated carbonyl compound to an aldehyde enamine, they are all irreversibly converted on treatment with acid to the desired δ-ketoaldehydes. Thus, although, as we have mentioned, the cyclobutane derivatives can sometimes be isolated from the reaction of an α,α-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

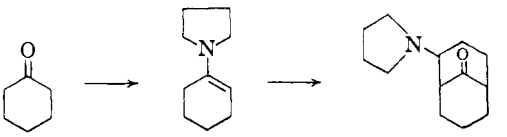


methyl vinyl ketone to the aldehydo ester XXXVII was unsuccessful, the addition to the pyrrolidine enamine proceeded readily to give after acid treatment the desired cyclohexenone XXXVIII.

Brief mention should finally be made of the results obtained in the alkylation of *ketone* enamines with α,β-unsaturated aldehydes. The reaction with *aldehyde* enamines is normal, the final product after hydrolysis being a substituted glutaraldehyde.[34] On the other



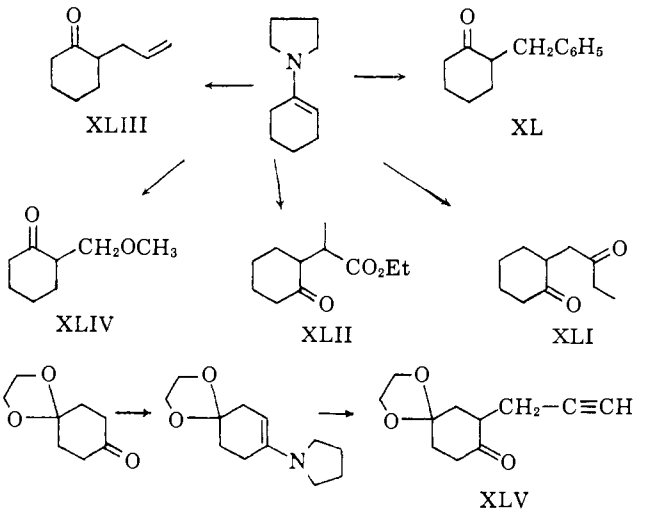
hand, the reaction of α,β-unsaturated aldehydes with *ketone* enamines leads, as we have previously reported,[35] to bicyclic aminoketones which are formally the product of an internal Mannich reaction of the expected aldehydoketone and the secondary amine used to form the enamine. For example, with the pyrrolidine enamine of cyclohexanone and acrolein in benzene the product isolated is XXXIX.



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[35] 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 β-tetralone derivatives which are thus monoalkylated 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, α-halo ethers, α-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 β-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:



(33) R. I. Longley and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).

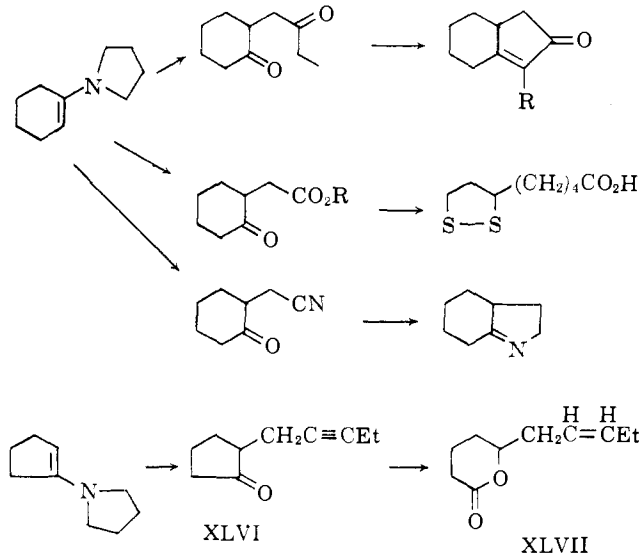
(34) G. Opitz and I. Loschmann, *Angew. Chem.*, **72**, 523 (1960).

(35) G. Stork and H. Landesman, *J. Am. Chem. Soc.*, **78**, 5129 (1956).

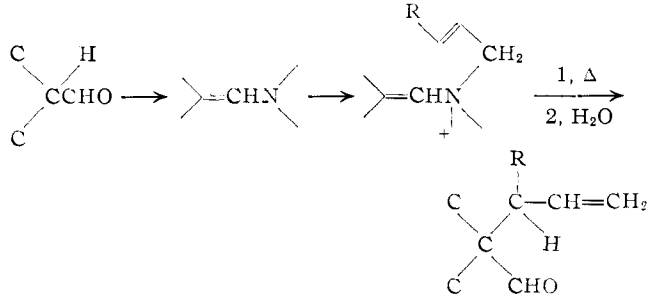
Details will be found in the Experimental section, but in general these reactions are carried out by refluxing the required pyrrolidine enamine in benzene or acetonitrile (the former is especially useful with α-halo carbonyl compounds,[36] the latter with allyl and related halides) with a slight excess 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 alkylations with alkyl 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-methylcycloalkyl chlorides).[19] 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.[37] We have generally used the readily available pyrrolidine for alkylations with alkyl halides.

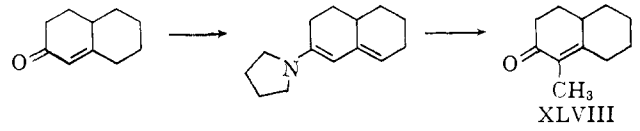
Many alkylations of this type have been carried out since our introduction of this reaction, and a great variety of substances are thus made readily available. For example. the diketones derived from α-haloketones can be cyclized to cyclopentenones,[36] the product from the pyrrolidine enamine of cyclohexanone and bromoacetic ester has been transformed into thioctic acid,[38] the ketonitrile from cyclohexanone enamine and chloroacetonitrile has been used to make hydroindole derivatives,[39] methylation of the pyrrolidine enamine from 6-isopropyl-2-tetralone provides the starting material for the total synthesis of *dl*-dehydroabietic acid,[40] and we may finally mention the recent synthesis of the lactone XLVII, one of the constituents of the essential oil of jasmine from XLVI obtained *via* enamine alkylation of cyclopentanone.[14c]



Aldehydes can generally be alkylated *via* their enamines with the same strongly electrophilic reagent which we have just discussed, as recent work[41] has shown. Yields are good only, however, with *allyl halides* while the simple alkyl halides appear to give almost entirely N-quaternary salts.[41b,c] Allyl halides themselves lead to C-alkylation usually *via* an initial quaternary salt which then undergoes Claisen rearrangement with the usual structural inversion.[42]

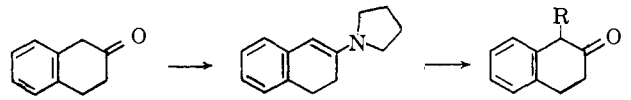


α,β-Unsaturated ketones have not been studied extensively. We have shown[43] that methylation of the pyrrolidine enamine of $\Delta^{1,10}$-octalone-2 leads to the 1-methyl compound XLVIII rather than the *a priori*



XLVIII

possible γ-alkylated product. This alkylation of an α,β-unsaturated ketone, when it proceeds on carbon,[44] 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.*[45], who obtained 46% yield of the keto ester L in the alkylation of the pyrrolidine enamine of

(36) H. E. Baumgarten, P. L. Creger and C. E. Villars, *J. Am. Chem. Soc.*, **80**, 6609 (1958).

(37) The energy of the transition state for *N-alkylation* might be expected to parallel the rates of formation of a tetrahedral reaction product from a ketone, as for example in hydride reduction. The lower rate of such a reaction with cyclopentanone and cycloheptanone than with cyclohexanone (*cf.* H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957)) argues also for the preferred use of pyrrolidine or hexamethylene imine in the C-alkylation reactions. Further progress in that direction (*e.g.*, by the use of heptamethylene imine) is blocked by the increased interference of the α-methylene of these larger amines with the alkylatable carbon atom. This cuts down the yields of C-alkylated products.

(38) A. Segre, R. Viterbo and G. Parisi, *J. Am. Chem. Soc.*, **79**, 3503 (1957).

(39) V. Boekelheide, M. Müller, J. Jack, T. T. Grossnickle and M. Chang, *ibid.*, **81**, 3955 (1959).

(40) G. Stork and J. W. Schulenberg, *ibid.*, **84**, 284 (1962).

(41) (a) G. Opitz and H. Mildenberger, *Angew. Chem.*, **72**, 169 (1960); (b) E. Elkik, *Bull. soc. chim. France*, 972 (1960); (c) compare G. Opitz, *Angew. Chem.*, **73**, 437 (1961), and G. Opitz and H. Mildenberger, *Ann.*, **649**, 26 (1961).

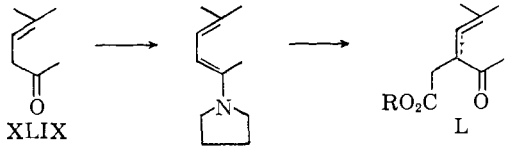
(42) K. C. Brannock and R. C. Burpitt, *J. Org. Chem.*, **26**, 3576 (1961); G. Opitz, H. Hellmann, H. Mildenberger and H. Suhr, *Ann.*, **649**, 36 (1961); G. Opitz, *ibid.*, **650**, 122 (1961).

(43) G. Stork and G. Birnbaum, *Tetrahedron Letters*, **No. 10**, 313 (1961).

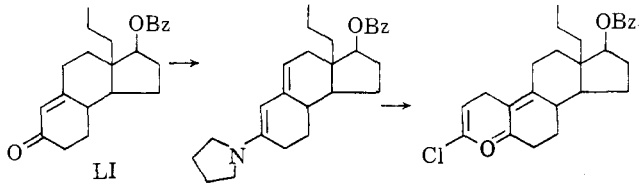
(44) See, however, the N-alkylation of cholestenone pyrrolidine enamine (refs. 1 and 13). This greater difficulty of C-alkylation is presumably due to steric interference by the axial C-10 methyl group.

(45) M. Julia, S. Julia and C. Jeanmart, *Compt. rend.*, **251**, 249 (1960)

XLIX, while direct base-catalyzed alkylation led to only 24% of the desired substance which was used in an ingenious synthesis of chrysanthemumcarboxylic acid.



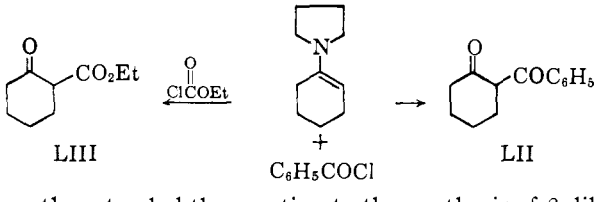
Again, alkylation of the unsaturated ketone LI by the enamine method was stated[14a] to be superior to direct alkylation:



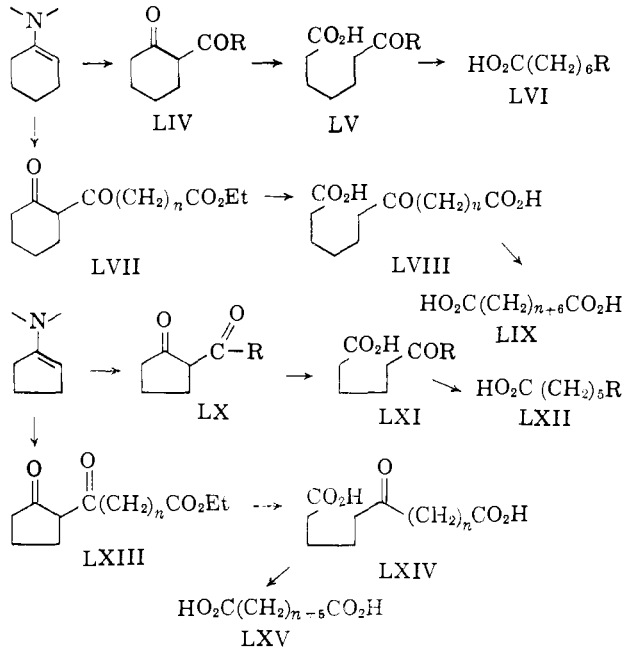
Before we leave the subject of the alkylation of enamines with alkyl halides it should be mentioned that the reaction has recently been shown by Kuehne[46] to be applicable to certain activated aryl halides. These reactions are, however, really reactions with electrophilic olefins since they involve an addition–elimination mechanism.

IV. The Enamine Acylation of Carbonyl Compounds

We reported in our original communication[1] that enamines could be used for the synthesis of β-diketones by reaction with acid chlorides, followed by aqueous acid hydrolysis. The two examples mentioned were the reaction of the pyrrolidine enamine of cyclohexanone with benzoyl chloride to give 2-benzoylcyclohexanone (LII) and with ethyl chlorocarbonate to form 2-carbethoxycyclohexanone (LIII). We subsequently extended the reaction to the synthesis of β-diketones from aliphatic acid chlorides (*cf.* LIV, LVII) and also from the half-ester acid chlorides of dibasic acids.[47] These β-diketones can be cleaved by base to ketoacids[48] which in turn may be reduced by the Wolff–Kishner procedure to saturated mono- or dicarboxylic acids with a chain six carbon atoms longer than the starting acid chloride (*cf.* LVI, LIX). Similarly, the β-diketones from the acylation of cyclopentanone lead to acids with five carbon atoms more in the chain than the initial acid chloride (*cf.* LXII, LXV).[49]



Hünig and his co-workers[50] have subsequently made two valuable contributions to this β-diketone synthesis. They showed that the less reactive morpholine enamines give better results than the pyrrolidine enamines in these reactions, and that the extra mole of enamine which we used to take up the hydrogen chloride liberated in the reaction could be avoided, in most cases, by substituting a mole of triethylamine.



One specific example for our conditions for the β-diketone and acid synthesis will suffice here (further illustrations are in the Experimental section): The morpholine enamine of cyclohexanone (2 equiv.) on heating in dioxane solution with one equivalent of the half-ester acid chloride from azelaic acid, after filtration of the precipitated cyclohexanone enamine hydrochloride and hydrolysis of the acylated enamine by heating for three hours on the steam-bath with 10% hydrochloric acid, gives the β-diketone LVII (n = 7) in 65% yield. Refluxing overnight with 20% methanolic potassium hydroxide then gives 7-ketopentadecane-1,15-dioic acid, m.p. 105.5–107°. The latter on Wolff–Kishner reduction leads to the known 1,15-pentadecanedioic acid (LIX, n = 7) in 70% yield based on the β-diketone.

It is worth noting that the use of the half-ester-acid chloride of azelaic acid can be obviated by using the acid chloride of oleic acid. The β-diketone obtained by the above procedure from the morpholine enamine of cyclohexanone was an oil and was cleaved with potassium hydroxide to 7-keto-15-tetracosenoic acid, obtained as a solid with a broad melting range (54–64°), possibly because of the inhomogeneity of the starting oleic acid. Oxidation of the unsaturated acid by the method of Lemieux[51] gave, in 66% yield, the same 7-ketopentadecanedioic acid, m.p. 105–107°, obtained above from azelaic acid.

Related acylation reactions which have been described since our initial publication include the synthesis of β-ketonitriles by Kuehne[23] from *pyrrolidine* enamines and cyanogen chloride, the acylation of enamines with isocyanates and isothiocyanates[52] to form β-keto amides, and the acylation with diketene to form chromane derivatives.[53]

(46) M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).

(47) This extension was first reported at the New York Meeting of the American Association for the Advancement of Science on December 29, 1956; *cf. Science*, **124**, 1040 (1956). The method is much to be preferred to other acylation methods (compare C. R. Hauser, F. W. Swamer and J. T. Adams in "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter III.

(48) *Cf.* C. R. Hauser, F. W. Swamer and B. I. Ringler, *J. Am. Chem. Soc.*, **79**, 4023 (1948).

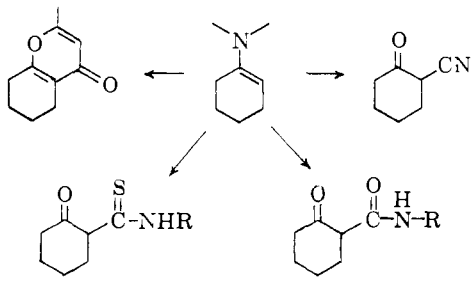
(49) The cyclopentanone and cyclohexanone rings can obviously be substituted to produce acids with substituents at various places along the chain. Unsymmetrically substituted ketones will, however, lead to mixtures unless they carry a 2-substituent. Substituents can, of course, also be present in the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

(50) *Cf. inter alia*, S. Hünig and E. Lücke, *Chem. Ber.*, **92**, 652 (1959); S. Hünig and W. Lendle, *ibid.*, **93**, 913 (1960); also S. Yurugi, M. Numata and T. Fushimi, *J. Pharm. Soc. Japan*, **80**, 1165 (1960).

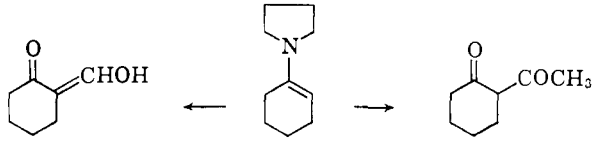
(51) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(52) G. Berchtold, *J. Org. Chem.*, **26**, 3043 (1961); S. Hünig, K. Hübner and E. Benzing, *Chem. Ber.*, **95**, 926 (1962); S. Hünig and K. Hübner, *ibid.*, **95**, 937 (1962); R. Fusco, G. Bianchetti and S. Rossi, *Gazz. chim. ital.*, **91**, 825 (1961).

(53) B. B. Millward, *J. Chem. Soc.*, **26** (1960); S. Hunig, E. Benzing and K. Hübner, *Chem. Ber.*, **94**, 486 (1961).



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 2-acetylcyclohexanone with the pyrrolidine enamine of cyclohexanone.



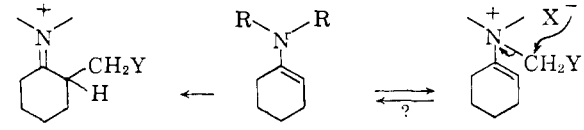
LXVII LXVI

β-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 β-keto ester enamine 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 β-ketoesters in 65, 76 and 46% yields, respectively. The case of cyclopentanone is of some interest since the usual decarbonylation of glyoxylates to β-keto esters is not applicable in this case.[54] Acyclic ketones may also be used: dipropyl ketone gave the β-keto ester LXVIII in 54% yield.

LXVIII

Conclusion. Remaining Problems

We have shown in the preceding discussion that the enamine alkylation of ketones and aldehydes[1,2] 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 allyl 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 unrearranged 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.



Y = CO_2R, C=C, etc.

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.

Acknowledgment.—This work was supported in part by grants from the National Science Foundation and the Petroleum Research Fund of the American Chemical Society.

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 300 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*-toluenesulfonic acid may be added to the mixture. In many instances 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[55a] b.p. 97–98° (20 mm.)) (Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02; N, 10.21. Found: C, 78.98; H, 10.89; N, 10.16); **morpholine enamine** (80–90% yield) b.p. 104–106° (12 mm.), reported[55b] b.p. 97° (7.5 mm.).

Cyclohexanone: pyrrolidine enamine (85–90% yield) b.p. 105–107° (13 mm.), reported[55a] b.p. 115–117° (20 mm.) (Calcd. for $C_{10}H_{17}N$.; 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[55c] b.p. 117–120° (20 mm.)[55c] (Calcd. for $C_{10}H_{17}NO$: C, 71.78; H, 10.25; N, 8.37. Found: C, 71.86; H, 10.16; N, 8.62.); **hexamethylene imine enamine** (85%) after 40 hours refluxing in toluene; b.p. 122–126° (8 mm.) (Calcd. for $C_{12}H_{21}N$: C, 80.37; H, 11.81; N, 7.81. Found: C, 80.20; H, 11.61; N, 7.85.); **heptamethyleneimine enamine** (58%) after 40 hours refluxing in toluene with some *p*-toluenesulfonic acid; b.p. 142–148° (14 mm.) (Calcd. for $C_{13}H_{23}N$: C, 80.76; H, 11.99; N, 7.25. Found: C, 81.12; H, 12.26; N, 6.93); **N-methylaniline enamine** (72%) after 100 hours refluxing in toluene with 2.0 g. of *p*-toluenesulfonic acid per mole; b.p. 148–153° (12 mm.) (Calcd. for $C_{13}H_{17}N$: C, 83.38; H, 9.15; N, 7.48. Found: C, 83.61; H, 9.45; N, 7.45.); **camphidine enamine** (63%) after 24 hours reflux in toluene with *p*-toluenesulfonic acid; b.p. 104–116° (0.4 mm.) (Calcd. for $C_{16}H_{17}N$: C, 82.33; H, 11.66; N, 6.00. Found: C, 81.96; H, 11.52; N, 6.35).

2-Methylcyclohexanone: pyrrolidine enamine (77%) after 48 hours refluxing in benzene; b.p. 112–114° (15 mm.) (Calcd. for $C_{11}H_{19}N$: C, 79.90; H, 11.58; N, 8.47. Found: C, 79.84; H, 11.56; N, 8.78).

3-Methylcyclohexanone: morpholine enamine (86%) after 35 hours refluxing in toluene; b.p. 124–127° (15 mm.) (Calcd. for $C_{11}H_{19}NO$: C, 72.86; H, 10.56; N, 7.73. Found: C, 72.75; H, 10.60; N, 7.53). This is undoubtedly a mixture of double bond isomers.

4-Methylcyclohexanone: morpholine enamine (75%) after 25 hours in toluene; b.p. 138–140° (17 mm.) (Calcd. for $C_{11}H_{19}O$: C, 72.86; H, 10.56; N, 7.73. Found: C, 72.72; H, 10.32; N, 7.58).

4-Methoxycyclohexanone: morpholine enamine (79%) after 12 hours in toluene; b.p. 159–163° (15 mm.) (Calcd. for $C_{11}H_{19}NO_2$: C, 66.95; H, 9.71; N, 7.10. Found: C, 67.22; H, 9.83; N, 7.19).

Cycloheptanone: morpholine enamine (82%) after 48 hours refluxing in toluene with *p*-toluenesulfonic acid; b.p. 133–135°

(54) *Cf.* R. Mayer, *Chem. Ber.*, **88**, 1861 (1955).

(55) (a) R. Terrell, Ph.D. Thesis, Columbia, 1954; (b) E. D. Bergmann and R. Ikan, *J. Am. Chem. Soc.*, **78**, 1485 (1956); (c) S. Hünig, E. Benzing and S. Lücke, *Chem. Ber.*, **90**, 2833 (1957).

(17 mm.) (Calcd. for $C_{11}H_{19}NO$: C, 72.86; H, 10.56; N, 7.73. Found: C, 73.07; H, 19.59; N, 7.80).

2-Tetralone: pyrrolidine enamine (93%) after refluxing under nitrogen a solution of 5 g. of 2-tetralone with 4 g. of pyrrolidine 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 $C_{14}H_{17}N$: C, 84.40; H, 8.45; N, 7.04. Found: C, 84.37; H, 8.60; N, 7.03).

B. Aliphatic Ketones.—As mentioned in the Discussion, simple monosubstituted acetones (and acetone itself) are not 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 to other methods with those ketones.

Diethyl Ketone.—Pyrrolidine enamine was obtained in only 22% yield after 175 hours refluxing with benzene and *p*-toluenesulfonic acid. However, in the presence of 20 g. of Linde No. 4A molecular sieves 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 after 40 hours refluxing 51% yield of the pyrrolidine enamine, b.p. 62–67° (8 mm.) (Calcd. for $C_9H_{17}N$: C, 77.66; H, 12.32; N, 10.07. Found: C, 77.39; H, 12.27; N, 9.85.). Morpholine enamine was prepared in the same manner with molecular sieves and a small amount of *p*-toluenesulfonic acid and obtained in 49% yield after 44 hours refluxing; b.p. 77–78° (9 mm) (Calcd. for $C_9H_{17}NO$: C, 69.65; H, 11.05; N, 9.03. Found: C, 69.69; H, 11.23; N, 9.29).

Dipropyl Ketone.—Morpholine enamine was prepared by the usual benzene azeotrope method in the presence of *p*-toluenesulfonic acid. After 250 hours reflux (!) the enamine was obtained in 65% yield. Undoubtedly, the use of molecular sieves would be advantageous here also; b.p. 102–106° (12 mm.) (Calcd. for $C_{11}H_{21}NO$: C, 72.06; H, 11.55; N, 7.64. Found: C, 72.06; H, 11.64; N, 7.84).

C. 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 II-16 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 an additional 2 hours, the solution 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[21a] b.p. 74–75° (12 mm.). The distillation was accompanied by much foaming which could be controlled by adding 1 ml. of silicone oil to the distillation flask.

Alkylation of Enamines with Electrophilic Olefins

I. α,β-Unsaturated Esters and Nitriles. **A. With Cyclohexanone. 1. Ethyl Acrylate.**—The pyrrolidine enamine was prepared from 2 moles of cyclohexanone and 10% excess of pyrrolidine in 800 ml. of benzene under the usual conditions. Removal of benzene and excess pyrrolidine left the crude enamine which was dissolved in 755 ml. of dry dioxane. Addition of 332 ml. (3 moles) of ethyl acrylate and refluxing for 3 hours was followed by addition of 100 ml. of water and a further hour of refluxing. Removal of solvent and extraction with ether, washing with dilute hydrochloric acid, etc. gave on distillation ethyl 3-(2-oxocyclohexyl)-propionate (XXVIII) in 80% yield, b.p. 98° (0.7 mm.); reported[56] b.p. 115–120° (1.5 mm.).

2. Ethyl Crotonate.—A solution of 15.1 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry dimethylformamide was refluxed for 36 hours with 18 g. of ethyl crotonate and refluxing was continued for another hour after the addition of 10 ml. of water. The mixture was then poured into 500 ml. of water and extracted several times with ether. The combined extracts were washed with 5% hydrochloric acid and then 5% sodium bicarbonate. Drying and distillation gave 11 g. (56%) of ethyl 3-(2-oxocyclohexyl)-butyrate as a colorless oil, b.p. 165–170° (18 mm.).

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.93; H, 9.44.

3. Methyl Methacrylate.—A solution of 15.1 g. of the pyrrolidine enamine of cyclohexanone was treated with 18 g. of methyl methacrylate in dimethylformamide solution, as in the preceding example. The methyl 2-methyl-3-(2-oxocyclohexyl)-propionate was obtained as a colorless oil, b.p. 148–150° (18 mm.). The yield was 16.6 g. (80%).

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.02; H, 9.02.

4. Acrylonitrile.—The reaction of the pyrrolidine enamine of cyclohexanone (13.5 g.) and acrylonitrile (6 g.), carried out as in example 1 but with 12 hours refluxing in 50 ml. of dioxane, gave 80% yield of 2-β-cyanoethylcyclohexanone (XXVII), b.p. 141–145° (10 mm.) (reported[8] b.p. 138–142° (10 mm.)); 2,4-dinitrophenylhydrazone m.p. 154.5–156° (from methanol–chloroform).

Anal. Calcd. for $C_{15}H_{17}N_5O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 54.48; H, 5.00; N, 20.86.

5. 2,6-Dialkylation with Ethyl Acrylate.—The crude pyrrolidine enamine (1 mole), prepared as in example 1, was refluxed for 4 hours in 350 ml. of absolute ethanol with 300 g. (3 moles) of freshly distilled ethyl acrylate. Water (75 ml.) was then added and refluxing was continued for an additional hour. The solvent was then removed under reduced pressure and the residual liquid was taken up in ether (1.5 l.) washed with 4 × 150 ml. of 10% hydrochloric acid, followed by washing with water (3 × 50 ml.) and drying over sodium sulfate. Evaporation and distillation gave 208 g. (70%) of diethyl cyclohexanone-2,6-dipropionate (XXX), b.p. 160–168° (0.8 mm.). Hydrolysis with 20% potassium hydroxide solution gave after acidification the known cyclohexanone-2,6-dipropionic acid, m.p. 142–143° (reported[57] m.p. 145°). The mixed m.p. with an authentic sample[58] was undepressed.

6. 2,6-Dialkylation with Acrylonitrile.—Alkylation of the pyrrolidine enamine of cyclohexanone with 3 equivalents of acrylonitrile by the procedure described in the example above gave 2,6-dicyanoethylcyclohexanone (XXIX), b.p. 178–180° (0.4 mm.).

Anal. Calcd. for $C_{12}H_{16}ON_2$: C, 70.55; H, 7.90. Found: C, 70.76; H, 8.14.

Hydrolysis produced the same diacid, m.p. 145–146°, described above.

B. With Other Ketones. 1. Methyl Acrylate and Cyclopentanone.—The reaction was carried out by refluxing a solution of 9.1 g. of cyclopentanone pyrrolidine enamine and 11 g. of methyl acrylate in 25 ml. of dioxane for 3.5 hours. Addition of 5 ml. of water and refluxing for another 30 minutes, followed by removal of most of the solvent under reduced pressure and work up as usual, gave 6.8 g. (60%) of methyl 3-(2-oxocyclopentyl)-propionate (XVI) b.p. 127–130° (11 mm.). The 2,4-dinitrophenylhydrazone crystallized from methanol as orange needles, m.p. 87–88°.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.42; H, 5.18; N, 15.99. Found: C, 51.59; H, 5.00; N, 16.12.

2. Acrylonitrile and Cyclopentanone.—This 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. 166–167°.

Anal. Calcd. for $C_{14}H_{15}N_5O_4$: C, 52.99; H, 4.77; N, 22.07. Found: C, 53.10; H, 4.79; N, 21.90.

3. 2-Methylcyclohexanone with Acrylonitrile.—A solution of 16.5 g. (0.1 mole) of the pyrrolidine enamine of 2-methylcyclohexanone in 100 ml. of absolute ethanol was refluxed for 4 hours with 6.2 g. (0.17 mole) of acrylonitrile. Hydrolysis and work up as usual gave 55% yield of 2-(2-cyanoethyl)-6-methylcyclohexanone (VIII), b.p. 132–133° (2 mm.).

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.69; H, 9.15. Found: C, 72.81; H, 8.94.

The compound in CCl_4 gave the typical doublet for the methyl group at *ca.* $\tau = 9$ in the n.m.r., showing that it has the 2,6- rather than the 2,2-disubstituted structure. The 2,4-dinitrophenylhydrazone had m.p. 151–152° (from chloroform–methanol).

Anal. Calcd. for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55. Found: C, 55.90; H, 5.57.

4. Cycloheptanone with Acrylonitrile.—The pyrrolidine enamine from 2.24 g. of cycloheptanone was prepared in the usual way and the crude product was refluxed in 25 ml. of benzene with 1.72 g. of freshly distilled acrylonitrile for 22 hours. Addition of 25 ml. of water and further refluxing for one hour was followed by ether extraction, washing with dilute sulfuric acid and drying. Distillation then gave 1 g. of recovered cycloheptanone, b.p. 55–60° (10 mm.), and 1.1 g. of 2-(2-cyanoethyl)-cycloheptanone, b.p. 140–145° (10 mm.), 60% yield based on unrecovered cycloheptanone. Subsequent experience with aliphatic ketones makes it likely that the yield would be better in ethanol.

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 73 02; H, 9.26; N, 8.32.

The 2,4-dinitrophenylhydrazone from ethanol–chloroform had m.p. 114–116°.

Anal. Calcd. for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55; N, 20.28. Found: C, 55.60; H, 5.61; N, 20.31.

(56) D. K. Banerjee, S. Chatterjee and S. P. Bhattacharya, *J. Am. Chem. Soc.*, **77**, 408 (1955).

(57) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937).

(58) Kindly supplied by Professor N. J. Leonard.

The semicarbazone, from dilute ethanol, had m.p. 163–164°.

Anal. Calcd. for $C_{11}H_{18}N_4O$: C, 59.44; H, 8.16; N, 25.22. Found: C, 59.76; H, 8.46; N, 25.12.

5. Diethyl Ketone with Ethyl Acrylate.—To a solution of 15.5 g. (0.1 mole) of the morpholine enamine of diethyl ketone in 100 ml. of absolute ethanol kept under nitrogen was added dropwise 10.0 g. (0.1 mole) of ethyl acrylate. The solution was refluxed for 15 hours 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. (55%) of ethyl 3-keto-4-methylenanthate (XXII), b.p. 108–109° (10 mm.). The 2,4-dinitrophenylhydrazone formed yellow crystals, m.p. 73.0–74.4°.

Anal. Calcd. for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05. Found: C, 52.73; H, 5.98.

6. 2-Heptanone 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 cyclohexylamine 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 hydriodide was filtered off after 2 hours further standing at room temperature. Removal of most of the benzene and fractionation, after filtering off a further precipitate of the salt, gave the N-methyl-N-cyclohexyl enamine, b.p. 105–107° (2.5 mm.), in 49% yield.

A solution of 10.4 g. (0.05 mole) of the above enamine in 100 ml. of dioxane was refluxed for 12 hours with 5.3 g. (0.1 mole) of acrylonitrile. Heating with water etc. as usual then gave 4.2 g. (50%) of 3-(2-cyanoethyl)-heptanone-2, b.p. 160–170° (20 mm.). The semicarbazone prepared and recrystallized from alcohol had m.p. 93–94°.

Anal. Calcd. for $C_{11}H_{20}ON_4$: C, 59.54; H, 8.92. Found: C, 59.16; H, 9.10.

C. With Aldehydes. 1. Butyraldehyde Enamine and Methyl Acrylate.[59]—To a solution of 139 g. (1 mole) of the enamine from butyraldehyde and piperidine, in 750 ml. of acetonitrile cooled to below 5°, was added during half of an hour a solution of 107 g. (25% excess) of methyl acrylate in 250 ml. of acetonitrile. 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 refluxing for 8 hours was followed by extraction after saturation with salt. Further workup as usual gave 106 g. (67%) of methyl 4-formylhexanoate (XXIII), b.p. 95–98° (10 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.73; H, 8.15.

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 49% yield as a liquid, b.p. 140–148° (12–13 mm.). The 2,4-dinitrophenylhydrazone crystallized from methanol as fine orange-yellow needles, m.p. 92–94°.

Anal. Calcd. for $C_{16}H_{21}N_5O_4$: C, 55.32; H, 6.09; N, 20.16. Found: C, 55.61; H, 5.99; N, 20.22.

II. Alkylation of Enamines with α,β-Unsaturated Ketones.

1. Cyclohexanone Morpholine Enamine and Methyl Vinyl Ketone.—To a solution of 150 g. of the morpholine enamine of cyclohexanone in 140 ml. of benzene was added dropwise with stirring 5 g. of methyl vinyl ketone. After addition was complete, the solution was heated cautiously to the boiling point and then refluxed 3 hours. The benzene was then distilled off, aqueous methanol (1:1) was added and the mixture was refluxed overnight. The methanol was largely removed by distillation, and after addition of 400 ml. of water the mixture was extracted with ether (2 × 300 ml.). After drying over magnesium sulfate, distillation gave 90 g. (67%) of the $\Delta^{1,9}$–$\Delta^{9,10}$-octalone mixture, b.p. 66° (0.05 mm.) (reported[60] b.p. 101–102° (2 mm.)); 2,4-dinitrophenylhydrazone m.p. 168–170° from ethyl acetate, undepressed with an authentic sample,[60] m.p. 168°. The ultraviolet spectrum shows the octalone mixture (XXVI) to be 72% α,β- and 28% β,γ-isomer; λ_{max}^{EtOH} 239 mμ, ε 12,300.[61]

The pure α,β-isomer may be obtained by the following procedure: A solution of 75 g. of octalone in 200 ml. of hexane was cooled in a Dry Ice–acetone mixture. The pure $\Delta^{1,9}$-octalone crystallizes and is obtained free of the β,γ-isomer by removing the solvent with suction through a fritted glass filter. The material so obtained is a liquid at room temperature. It has b.p. 68–69° (0.1 mm.) and is essentially pure $\Delta^{1,9}$-octalone as shown by the absence of saturated carbonyl in the infrared and by the intensity of the maximum in the ultraviolet: λ_{max}^{EtOH} 239 mμ, ε 17,400. For most purposes the mixture gives the same reactions as the pure isomer.

2. Cyclohexanone Pyrrolidine Enamine and Methyl Vinyl Ketone.—The main difference between this and the preceding experiment is that under the conditions of the alkylation reaction the more reactive pyrrolidine forms the enamine of the product. Since it is the enamine of an α,β-unsaturated ketone it must be decomposed by the use of a sodium acetate–aqueous acetic acid buffer.[13] To a solution of 45.3 g. of the pyrrolidine enamine of cyclohexanone in 200 ml. of benzene was added, under nitrogen, 21.0 g. of methyl vinyl ketone. The mixture was then refluxed for 24 hours. A buffer solution made up of 25 ml. of acetic acid, 25 ml. of water and 12.5 g. of sodium acetate was then added and refluxing was continued for 4 hours. 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–β,γ-mixture ($\lambda_{max}^{CHCl_3}$ 5.86, 6.02, 6.19 μ) which was 75% α,β from the ultraviolet intensity (λ_{max}^{EtOH} 238 mμ, ε 12,900).

3. Direct Formation of $\Delta^{1,9}$-Octalone Pyrrolidine Enamine from Cyclohexanone Enamine and Methyl Vinyl Ketone.—Since in some circumstances the enamine of octalone (or related substances) may be required for further work rather than the α,β-unsaturated ketone itself, it is of interest that it may be isolated in good yield by carrying out the addition to the *pyrrolidine* enamine in toluene and omitting the hydrolysis step: Methyl vinyl ketone (18.6 g., 0.27 mole) was added dropwise with stirring to a solution of 40.0 g. (0.27 mole) of the pyrrolidine enamine of cyclohexanone in 250 ml. of toluene. After addition was complete the solution was refluxed for 15 hours and the solvent was removed by distillation at water-pump pressure. Fractionation then gave 35.9 g. (67%) of the pyrrolidine enamine of $\Delta^{1,9}$-octalone-2 (XXV), b.p. 146–150° (0.3 mm.). The infrared spectrum ($\lambda_{max}^{CCl_4}$ 6.14, 6.25 μ) and boiling point were identical with that of authentic enamine made in 85% yield from the $\Delta^{1,9}$-$\Delta^{9,10}$-octalone-2 mixture and pyrrolidine by the usual azeotrope method, using toluene.

4. Cyclohexanone Enamine and Ethyl Vinyl Ketone.—To a solution of 15.1 g. (0.1 mole) of the pyrrolidine enamine of cyclohexanone in 100 ml. of dry dioxane was added 8.4 g. (0.1 mole) of ethyl vinyl ketone. Immediate heat evolution took place and the mixture was allowed to stand at room temperature for 3 hours. A mixture of 10 ml. of acetic acid, 20 ml. of water and 5 g. of sodium acetate was then added and the solution was heated on the steam-bath for 45 minutes. Addition of water, extraction with ether, etc., gave 11.8 g. (65%), b.p. 125–128° (1 mm.). This appeared to be the uncyclized 1-(2-oxocyclohexyl)-pentanone-3 as it showed a split carbonyl band at 5.94 μ. The substance was cyclized in 82% yield by the method of Shunk and Wilds[62] to 1-methyl-$\Delta^{1,9}$-octalone-2, b.p. 150–155° (18 mm.), reported[63] b.p. 140–145° (17 mm.). The infrared of this compound was identical with that of an authentic sample made from ethyl vinyl ketone and hydroxymethylenecyclohexanone.

5. Cyclohexanone Enamine and Methyl Isopropenyl Ketone.—A solution of 15.1 g. (0.1 mole) of cyclohexanone pyrrolidine enamine and 8.4 g. (0.1 mole) of methyl isopropenyl ketone in 75 ml. of dioxane was refluxed for 12 hours. Further work-up as described under example 2 above gave 10.8 g. (66%) of 3-methyl-$\Delta^{1,9}$-octalone-2 (XIX), b.p. 100–105° (0.5 mm.), reported[64] b.p. 132–134° (13 mm.). The semicarbazone prepared and recrystallized from ethanol had m.p. 201–202° (reported[64] m.p. 202°).

6. 4-Hydroxycyclohexanone Benzoate Enamine and Methyl Vinyl Ketone.—A solution of 109 g. of 4-hydroxycyclohexanone benzoate, m.p. 64–65°, and 55 g. of pyrrolidine in 800 ml. of benzene was transformed as usual into the enamine (about 3 hours). The benzene and excess pyrrolidine were removed, finally under vacuum. Dry benzene (500 ml.) was then added followed by 48 g. of freshly distilled methyl vinyl ketone, added dropwise during 15 minutes. The solution was then refluxed for 3 hours, most of the benzene was removed *in vacuo* and hydrolysis was then effected by refluxing for 5 hours with a solution of anhydrous sodium acetate (75 g.), acetic acid (150 ml.) and methanol (150 ml.) in water (150 ml.). Removal of most of the methanol under vacuum, addition of water and extraction with ether, followed by the usual washing and drying gave on distillation from an oil-jacketed flask 87 g. (64%) of 6-hydroxy-$\Delta^{1,9}$-2-octalone benzoate as a thick oil, b.p. 200–220° (0.1 mm.). On standing, the benzoate, which is a mixture of diastereo-

(59) This experiment was performed by Dr. J. Dolfini.

(60) R. Robinson, E. C. du Feu and F. J. McQuillin, *J. Chem. Soc.*, 53 (1937).

(61) *Cf.* D. J. Baisted and J. S. Whitehurst, *ibid.*, 4089 (1961).

(62) C. H. Shunk and A. L. Wilds, *J. Am. Chem. Soc.*, **71**, 3946 (1949).

(63) Y. Kawase, *Bull. Chem. Soc. Japan*, **31**, 336 (1958).

(64) J. Colonge, *Bull. soc. chim. France*, 1106 (1954).

isomers, became partially crystalline. From chromatography on neutral alumina it was possible to elute with ether a crystalline benzoate, m.p. 112–118°; this was recrystallized from a small quantity of carbon tetrachloride and melted unsharply at 116–120°. It was obviously still a mixture of benzoate epimers; $\lambda_{max}^{CHCl_3}$ 5.92, 6.15 μ, λ_{max}^{EtOH} 233 mμ (27,000).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.53; H, 6.91.

7. Cyclohexanone Enamine and Ethyl Acetylacrylate.—A solution of 15.1 g. of the pyrrolidine enamine in 65 ml. of dioxane was allowed to stand at room temperature for 14 hours after addition of 14 g. of ethyl acetylacrylate. Hydrolysis with the usual sodium acetate–acetic acid–water buffer by boiling for 4 hours and usual work up gave 16.6 g. (75%) of ethyl $\Delta^{1,9}$-2-octalone-4-carboxylate (XVIII), b.p. 142–144° (0.4 mm.). This solidified on standing in the refrigerator and had m.p. 50–52°. Recrystallization from petroleum ether raised the melting point to 54–55°; λ_{max}^{EtOH} 238 mμ ϵ 13,900; $\lambda_{max}^{CCl_4}$ 5.82, 6.15 μ.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.45; H, 8.37.

The 2,4-dinitrophenylhydrazone recrystallized from ethanol as red plates, m.p. 160–162°.

Anal. Calcd. for $C_{19}H_{22}O_6N_4$: C, 56.71; H, 5.51; N, 13.92. Found: C, 56.93; H, 5.60; N, 13.81.

8. 2-Methylcyclohexanone Enamine and Methyl Vinyl Ketone.—The reaction was carried out as described under example 2, from 8 g. of the pyrrolidine enamine of 2-methylcyclohexanone and 4 g. of methyl vinyl ketone. The 8-methyl-$\Delta^{1,9}$-2-octalone[60] (XX) obtained in 45% yield had b.p. 102–104° (2 mm.), reported b.p. 102° (2 mm.). The 2,4-dinitrophenylhydrazone recrystallized from ethyl acetate had m.p. 169–170° (reported[60] m.p. 172°) and depressed strongly the m.p. of the isomeric dinitrophenylhydrazone, m.p. 169°, of 10-methyl-$\Delta^{1,9}$-octalone.[65]

9. Ethyl 2-Oxocyclohexanepropionate Enamine and Methyl Vinyl Ketone.—The enamine of 2-carbethoxyethylcyclohexanone and pyrrolidine can be made conveniently by omitting the hydrolysis step in the addition, described earlier (I-A-1), of ethyl acrylate to the pyrrolidine enamine of cyclohexanone. It had b.p. 127–137° (0.4 mm.); $\lambda_{max}^{CCl_4}$ 5.85, 6.17 μ. A solution of 18.0 g. of the above enamine in 60 ml. of dry dioxane was treated dropwise with 5.5 g. (10% excess) of methyl vinyl ketone Following the addition, the solution was refluxed for 15 hours. Hydrolysis by refluxing 4 hours with a solution of 5 g. of sodium acetate in 10 ml. of water and 10 ml. of acetic acid and work-up as usual gave 10.94 g. (61%) of 8-(2-carbethoxyethyl)-$\Delta^{1,9}$-2-octalone, b.p. 146–157° (0.35 mm.); $\lambda_{max}^{CCl_4}$ 5.82, 6.01 μ. The 2,4-dinitrophenylhydrazone, dark red crystals from ethanol–chloroform, had m.p. 129.5–130.5°.

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09. Found: C, 58.82; H, 6.31.

10. Cyclopentanone Enamine and Methyl Vinyl Ketone.—In the same manner described under example II-2, a solution of 13.7 g. of the pyrrolidine enamine of cyclopentanone in 65 ml. of dry dioxane was allowed to react with 7 g. of methyl vinyl ketone. On distillation after hydrolysis, 5.7 g. (42%) of 5,6,7,8-tetrahydroindanone-5 (XII), b.p. 80–81° (0.4 mm.), was obtained (reported[26] b.p. 107–112° (12 mm.)), λ_{max}^{EtOH} 233 mμ (12,700). The semicarbazone, recrystallized from 1-butanol melted at 214–219° (reported[26] m.p. 220°).

11. *trans*-2-Decalone Enamine and Methyl Vinyl Ketone.[66]—The pyrrolidine enamine of *trans*-2-decalone was prepared by refluxing a mixture of 5.0 g. of *trans*-2-decalone, 3.50 g. of pyrrolidine and 50 ml. of benzene for 20 hours under a water separator. 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 pyrrolidine 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 4 hours with 10 g. of sodium acetate in 20 ml. of acetic acid and 20 ml. of water. Separation of layers, washing, etc., gave 3.26 g. (60%) of the mixture of tricyclic ketones, b.p. 113–120° (0.25 mm.). This was shown to consist of 1 part of XXXII and 9 parts of XXXI by the following degradation: The unsaturated ketone mixture (1.0 g.) was hydrogenated in the presence of 200 mg. of platinum oxide in 40 ml. of acetic acid. After the theoretical 2 moles of hydrogen had been absorbed, the catalyst was removed and the acetic acid was distilled off under vacuum. Addition of 10 ml. of acetic anhydride and 2.0 g. of sodium acetate to the residual oil was followed by heating on the steam-bath for 12 hours. Addition of aqueous bicarbonate to destroy the excess acetic anhydride and extraction with ether gave the oily acetate which was dehydrogenated by heating with 200 mg. of 30% palladium-on-charcoal for 1 hour at 250–260° and 6 hours at 330–340°. Hot chloroform was added to the mixture and the catalyst was filtered off. Removal of the solvent left a solid residue weighing 0.52–0.54 g. Some paraffinic impurity was removed (0.16–0.18 g.) with hexane by chromatography on alumina and the second fraction—a mixture of anthracene and phenanthrene—was analyzed by comparison of its infrared spectrum with that of various reference mixtures of phenanthrene and anthracene, using the peaks in the 11–14 μ region (carbon disulfide solution) for analysis. The same percentage composition was obtained directly from the crude mixture before chromatography because the impurity did not absorb in the 11–14 μ region. The results are accurate to within ±5%.

12. *cis*-2-Decalone Enamine and Methyl Vinyl Ketone.[66]—The morpholine enamine was prepared in this case from 10 g. of *cis*-2-decalone, 8.6 g. of morpholine and 100 ml. of toluene. After 16 hours of reflux 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 dropwise over half an hour and the solution was then refluxed under nitrogen for 16 hours. Further treatment as described in the preceding example gave 9.34 g. of diketone, b.p. 118–135° (0.3 mm.). This was cyclized by refluxing for 4 hours under nitrogen with a mixture of 17.5 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. (60%) of tricyclic ketone mixture, b.p. 131–134° (0.4 mm.). This was analyzed as in the preceding example by degradation to a mixture of phenanthrene and anthracene. This showed the original tricyclic ketone mixture to have been 3 parts of XXXV and 2 parts of XXXIV.

13. Diethyl Ketone Enamine and Methyl Vinyl Ketone.[67]—To 8 g. of the pyrrolidine enamine of diethyl ketone, stirred under nitrogen at room temperature, was added dropwise 4.1 g. of methyl vinyl ketone (1 equiv.). After 2 days at room temperature the enamine absorption in the infrared had disappeared. Addition of 100 ml. of ice-cold 15% hydrochloric acid and keeping at room temperature for 48 hours, followed by extraction with ether, washing with dilute hydrochloric, then with water, drying and distilling, gave 4.0 g. (50%) of 2,3,6-trimethyl-2-cyclohexenone (XXI), b.p. 101–103° (24 mm.) (reported[68] b.p. 88–90° (12 mm.)), λ_{max}^{EtOH} 243 mμ; 2,4-dinitrophenylhydrazone, m.p. 187–188° (from chloroform–ethanol).

Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.63; H, 5.67; N, 17.41.

14. Isovaleraldehyde Enamine and Methyl Vinyl Ketone.[67]—To 10 g. of ice-cold piperidine enamine of isovaleraldehyde under nitrogen was added with stirring, over 45 minutes, 4.6 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, followed 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 water and drying, distillation gave 6.3 g. (74%) of 4-isopropylcyclohexenone (XXIV), b.p. 103–104° (15 mm.), reported[69] b.p. 53–56° (0.4 mm.)). The 2,4-dinitrophenylhydrazone had m.p. 137.5–139° (reported[69] m.p. 135–136°).

15. Propionaldehyde Enamine and Ethyl Vinyl Ketone.[67]—In the same manner as described above, reaction of 11.4 g. of the piperidine enamine of propionaldehyde was treated with 7.63 g. of ethyl vinyl ketone. Further hydrolysis and work-up as before gave 7.90 g. of 2,4-dimethyl-2-cyclohexenone (XXXVI), b.p. 70–72° (20 mm.) (reported[32] b.p. 95° (35 mm.)). The infrared spectrum was identical with that of an authentic sample.[32] The red 2,4-dinitrophenylhydrazone had m.p. 185–187° (reported[70] m.p. 183–184°).

16. Enamine of Methyl 4-Formylhexanoate and Methyl Vinyl Ketone.[59]—A solution of 7.1 g. (0.1 mole) of pyrrolidine and 15 g. of methyl 4-formylhexanoate in 400 ml. of benzene was refluxed for 1 hour under a water separator. After concentration the reaction to 150 ml., a solution of 8.8 g. (0.13 mole) of methyl vinyl ketone in 10 ml. of benzene was added dropwise, with stirring under a nitrogen atmosphere at room temperature, over *ca.* 20 minutes. The mixture was kept at room temperature for 1 hour and refluxed for 17 hours. Acetic acid (6.0 g.) was added and refluxing was continued for 4 hours. The solution was then cooled, washed with water, 5% hydrochloric acid, dried and distilled to give 10.0 g. (48%) of 4-ethyl-4-(2-carbomethoxyethyl)-2-cyclohexenone (XXXVIII), b.p. 118–122° (0.25 mm.); $\lambda_{max}^{CHCl_3}$ 5.78 6.00 μ; λ_{max}^{EtOH} 226 mμ ϵ, 12,300. Redistillation gave an analytical sample, b.p. 105° (0.05 mm.).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.73; H, 8.41.

(65) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957)

(66) This experiment was performed by J. J. Pappas.

(67) This experiment was carried out by J. Pugach.

(68) R. N. Lacey, *J. Chem. Soc.*, 1639 (1960).

(69) M. D. Soffer and M. A. Jevnik, *J. Am. Chem. Soc.*, **77**, 1003 (1955).

(70) A. J. Birch, *J. Chem. Soc.*, 1642 (1947).

Alkylation with Alkyl Halides

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

Pyrrolidine Enamines of Cyclohexanones. 1. Allyl Bromide.[71]—To a solution of 125 g. of the pyrrolidine enamine of cyclohexanone in one liter of acetonitrile was added dropwise 120 g. of allyl bromide. After completion of the addition, the solution was refluxed for 13 hours under nitrogen. After removal of most of the acetonitrile the residue was diluted with 600 ml. of water and heated on the steam-bath for 20 minutes. The resulting solution was cooled and extracted with ether. The ether extract was dried, concentrated and distilled under reduced pressure to give 2-allylcyclohexanone (XLIII) in 66% yield, b.p. 100–105° (18–20 mm.); reported[72] b.p. 94° (16 mm.).

2. Benzyl Chloride.—To a solution of 5 g. of the pyrrolidine enamine of cyclohexanone in 25 ml. of dioxane was added 6 g. of benzyl chloride and the mixture was refluxed for 12 hours. At the end of that time, 5 ml. of water was added and refluxing was continued for another 3 hours. Removal of solvent under reduced pressure, extraction with ether and washing with 5% hydrochloric acid, 5% sodium carbonate, water and finally drying and distillation gave 3.3 g. (55%) of 2-benzylcyclohexanone (XL), b.p. 165–167° (18 mm.), reported[73] b.p. 165–166° at 18 mm. This was further characterized by its oxime, m.p. 125.5–126.5° from methanol (reported[73] m.p. 126–127°), and by its semicarbazone, m.p. 165.2–165.4° from methanol (reported[73] m.p. 166–167°). The residue from the distillation crystallized on trituration with petroleum ether to give, after recrystallization from methanol, 0.5 g. (5.4%) of colorless, shiny plates, m.p. 122–123°, of 2,6-dibenzylcyclohexanone (reported[74] m.p. 122°) semicarbazone, from methanol, m.p. 192.5–193.5° (reported[74] m.p. 190°). When the reaction was carried out in benzene, the yield of 2-benzylcyclohexanone was only 30%; in methanol it was 40%. The piperidine enamine in dioxane gave 26% yield.

3. Methyl α-Bromopropionate.—To a solution of 5 g. of cyclohexanone pyrrolidine enamine in 50 ml. of dry methanol was added 6.7 g. (1 equiv.) of ethyl α-bromopropionate. The solution was refluxed for 10 hours and, after addition of 10 ml. of water, refluxing was continued for another hour. Addition of water (100 ml.) and extraction with ether then gave, after drying and distillation, a 44% yield of methyl 2-(2-oxocyclohexyl)-propionate (XLII), b.p. 130–131° (10 mm.). The semicarbazone was prepared and recrystallized from ethanol; m.p. 204–205°.

Anal. Calcd. for $C_{11}H_{19}O_3N_3$: C, 54.75; H, 7.94; N, 17.42. Found: C, 55.16; H, 7.92; N, 17.40.

4. Propargyl Bromide on the Enamine of the Ethylene Glycol Monoketal of 1,4-Cyclohexanedione.[71]—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[75] in 100 ml. of dry benzene under a water separator, under nitrogen, for 7 hours. Most of the benzene was removed and the residue was distilled to give 10 g. of the pyrrolidine enamine as a colorless liquid, b.p. 110–120° (0.1–0.15 mm.). This was used directly for alkylation with propargyl bromide: To a solution of 10 g. of the above enamine in 100 ml. of dry acetonitrile was added dropwise 8 g. of propargyl bromide. The solution was refluxed for 16 hours under nitrogen. After removal of most of the acetonitrile the residue was stirred with 100 ml. of 10% potassium hydroxide solution at room temperature for 24 hours. Extraction with ether, drying and distillation gave 50% yield of the desired propargyl ketone XLV, b.p. 110–125° (0.1–0.15 mm.). This crystallized on standing, but because of its instability it was analyzed and characterized as its semicarbazone, m.p. 198–200°, which was prepared and recrystallized from a mixture of ethanol and water.

Anal. Calcd. for $C_{12}H_{17}O_3N_2$: C, 57.35; H, 6.82; N, 16.72. Found: C, 57.20; H, 6.89; N, 16.74.

5. 1-Bromo-2-butanone.—To a solution of 10 g. of the pyrrolidine enamine of cyclohexanone in 30 ml. of dry benzene was added 11 g. of 1-bromo-2-butanone in 30 ml. of benzene. The solution was refluxed for 3 hours and, after the addition of 20 ml. of water, refluxing was continued for a further 2 hours. Extraction with ether, drying and distillation gave 6.2 g. of 2-(2-ketobutyl)-cyclohexanone (XLI), b.p. 128–131° (9 mm.). The infrared showed λ_{max} at *ca.* 1700 cm.$^{-1}$. The γ-diketone was cyclized by refluxing with 50 ml. of methanol containing 300 mg. of sodium methoxide for 1 hour. Acidification with 2 *N* hydrochloric acid and extraction with ether gave a crude product which had λ_{max} *ca.* 1685 and 1630 cm.$^{-1}$ typical of a cyclopentenone, while gas chromatography showed the product to be essentially one component. Distillation gave 3.5 g. of 1-methyl-$\Delta^{1,8}$-tetrahydro-2-indanone, b.p. (mainly) 119–121° (9 mm.). This gave a red 2,4-dinitrophenylhydrazone, m.p. 197–199° (reported[76] b.p. 74–81° (1 mm.); 2,4-dinitrophenylhydrazone, m.p. 195.2–196°).

With the isomeric (secondary) bromide 3-bromo-2-butanone no clean product could be obtained.

6. *n*-Butyl Iodide.—A solution of 7.55 g. of the pyrrolidine enamine of cyclohexanone was refluxed for 19 hours in 50 ml. of toluene with 19.4 g. of *n*-butyl iodide. Addition of 10 ml. of water and further refluxing for half an hour was followed by addition of 10 ml. of 10% sulfuric acid and ether extraction of the aqueous solution, following separation of the toluene layer. The combined extracts were washed with 5% aqueous sodium thiosulfate, dried over magnesium sulfate and distilled to give recovered cyclohexanone and 2-butylcyclohexanone, b.p. 90–95° (13 mm.); 2,4-dinitrophenylhydrazone (from 95% ethanol) m.p. 112.5–113.5° (reported[77] b.p. 93–94° (11 mm.); 2,4-dinitrophenylhydrazone m.p. 110–111°). The actual conversion to 2-butylcyclohexanone was determined by vapor phase chromatography of the total mixture obtained from the alkylation reaction on 20% silicone on fire-brick at 190° under 8 lb. helium. The conversion was 44% and the yield based on unrecovered cyclohexanone was 57%. Butyl bromide gave lower yields.

7. Methyl Iodide.—Under the same conditions as described above for butyl iodide, but with benzene as solvent, methyl iodide gave 44% conversion to 2-methylcyclohexanone (63% yield based on unrecovered cyclohexanone). In methanol the yield was around 35%. Piperidine, morpholine, hexamethylene imine and heptamethylene imine enamines gave lower yields in either benzene or methanol, the yields being lowest with piperidine and heptamethylene imine. In the methylation reactions a small amount (5–10%) of 2,6-dimethylcyclohexanone could be demonstrated by vapor phase chromatography. It is interesting that the **N-methylaniline enamine** of cyclohexanone with methyliodide under the same conditions as above (toluene solvent) gave 42.4% conversion or 69% yield based on unrecovered cyclohexanone. There was no 2,6-dimethylcyclohexanone in this case. The long time required (see above) for the preparation of the enamine of cyclohexanone with the weakly basic N-methylaniline is a drawback, however.

8. Chloromethyl Ether.—A solution of 19.3 g. of the pyrrolidine enamine of cyclohexanone in 100 ml. of anhydrous ether was treated with 12 g. of chloromethyl ether. Heat evolution was moderated by intermittent cooling with ice. After standing at room temperature for 12 hours, addition of water and extraction, followed by drying and distillation, gave 6.0 g. (33%) of 2-methoxymethylcyclohexanone (XLIV), b.p. 92–94° (12 mm.). The semicarbazone, prepared and recrystallized from ethanol, had m.p. 160–161°.

Anal. Calcd. for $C_{14}H_{20}ON_2$: C, 52.17; H, 5.63. Found: C, 51.81; H, 5.79.

Alkylation of β-Tetralones.—We have previously described[10] the alkylation of 6-isopropyl-2-tetralone pyrrolidine enamine with methyl iodide. We will describe here the alkylation of the parent substance.

Methyl Iodide on the Pyrrolidine Enamine of 2-Tetralone.—The crude pyrrolidine enamine from 10 g. of β-tetralone and 7 g. of pyrrolidine was refluxed for 10 hours with 20 ml. of methyl iodide in 50 ml. of dioxane. Addition of 25 ml. of water and 1 ml. of acetic acid and further heating for 4 hours, followed by removal of most of the solvent under reduced pressure and work-up as usual, gave 9 g. (81%) of 1-methyl-2-tetralone, b.p. 138–142° (20 mm.), reported[78] b.p. 137–138° (18 mm.). The infrared spectrum of the distillate was identical with that of an authentic sample.[78]

III. Acylation of Enamines to β-Diketones and β-Keto Esters

1. Cyclohexanone Enamine and Acetic Anhydride.—A solution of 10 g. of the pyrrolidine enamine of cyclohexanone in 25 ml. of dioxane was allowed to stand at room temperature for 12 hours after addition of 8 g. of acetic anhydride. Addition of 5 ml. of water was followed by refluxing for half an hour. Removal of solvent under reduced pressure, extraction with ether, washing with 5% hydrochloric acid and finally with water, drying and distillation gave 3.9 g. (42%) of 2-acetylcyclohexanone (LXVI), b.p. 97–104° (12–14 mm.) (reported[79] b.p. 106–108° (14 mm.)).

2. Cyclohexanone and Mixed Anhydride of Formic and Acetic Acid.—To a solution of 20 g. of the pyrrolidine enamine of cyclohexanone in 50 ml. of dry dioxane, cooled in an ice–salt-bath, was added dropwise with rapid stirring 19.4 g. of the mixed anhydride of formic and acetic acid.[80] After 1 hour, 10 ml. of water was added and the solution was stirred for another hour.

(71) This experiment was performed by S. Malhotra.

(72) R. Cornubert, *Compt. rend.*, **158**, 1901 (1914).

(73) M. Tiffeneau and M. Porcher, *Bull. soc. chim. France*, **31**, 331 (1931).

(74) R. Cornubert, *ibid.*, **2**, 195 (1935).

(75) D. Prins, *Helv. Chim. Acta*, 1021 (1957).

(76) *Cf.* J. A. Hartman, *J. Org. Chem.*, **22**, 466 (1957). This experiment was carried out by Dr. Michael Rosenberger.

(77) B. B. Elsner and H. E. Strauss, *J. Chem. Soc.*, 588 (1957).

(78) J. Cornforth, R. Cornforth and R. Robinson, *ibid.*, 689 (1942).

(79) G. Vavon and J. M. Conia, *Compt. rend.*, **233**, 876 (1951).

(80) C. D. Hurd and A. S. Roe, *J. Am. Chem. Soc.*, **61**, 3355 (1939).

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. Extraction of the organic layer with 10% sodium hydroxide solution, acidification of the aqueous basic extract with 10% hydrochloric acid and extraction with chloroform gave after drying and distillation 7.6 g. (49%) of hydroxymethylenecyclohexanone (LXVII), b.p. 80–85° (13 mm.), reported[81] b.p. 80° (12 mm.). The infrared spectrum was identical with that of an authentic sample.

3. Cyclohexanone and Caprylyl Chloride.—To a solution of 25.0 g. (0.15 mole) of the morpholine enamine of cyclohexanone in 150 ml. of dry dioxane, caprylyl chloride (12.2 g., 0.075 mole) was added under nitrogen while the enamine 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 10% aqueous hydrochloric acid was added, and the solution was refluxed for 2–3 hours. After removal of most of the solvent by distillation at reduced pressure, the residue was diluted with 25–50 ml. of water and extracted with ether. The combined extracts were washed with 5% potassium bicarbonate and dried over magnesium sulfate. After removal of solvent, distillation of the residue gave 12.6 g. (75% based on acid chloride) of 2-caprylylcyclohexanone (LIV, R = $CH_3(CH_2)_6$–), b.p. 110–120° (0.5 mm.).

When the enamine was prepared from pyrrolidine, the yield of 2-caprylylcyclohexanone was 50%.

4. Cyclopentanone and Caprylyl Chloride.—2-Caprylylcyclopentanone (LX, R = $CH_3(CH_2)_6$–) was prepared in 54% yield from cyclopentanone morpholine enamine and caprylyl chloride by the same general method described above, as an oil, b.p. 108–116° (0.4 mm.).

5. Cyclohexanone and Caproyl Chloride.—To a solution of 28.0 g. (0.17 mole) of the morpholine enamine of cyclohexanone in 150 ml. of dry benzene, caproyl chloride (13.0 g., 0.096 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, 60 ml. of 10% aqueous hydrochloric acid added, and the mixture was refluxed with vigorous stirring for 4–6 hours. The layers were then separated, the aqueous layer was extracted with benzene, the benzene solutions were combined, and most of the solvent was removed by distillation at atmospheric pressure. The residue was fractionated, giving 11.41 g. of 2-caproylcyclohexanone (LIV, R = $CH_3(CH_2)_4$–), b.p. 132–155° (0.25 mm.). An additional 1.5 g. of product was obtained by boiling the residue with 20 ml. of dioxane and 10 ml. of 10% aqueous hydrochloric acid for 3 hours; total yield, 65–70%.

6. Cyclohexanone and 8-Carbethoxyoctanoyl Chloride.—In a similar manner, 14.5 g. (0.09 mole) of the morpholine enamine of cyclohexanone and 10.0 g. (0.043 mole) of the half-chloride ethyl ester of azelaic acid in 100 ml. of dry dioxane gave 8.0 g. (63%) of 2-(8-carbethoxyoctanoyl)-cyclohexanone (LVII, n = 7), b.p. 160–175° (0.4 mm.).

7. Cyclohexanone and Oleic Acid Chloride.—To a solution of 8.2 g. (0.05 mole) of the morpholine enamine of cyclohexanone in 50 ml. of dry benzene, oleic acid chloride (8.14 g., 0.03 mole) was added under nitrogen while the enamine solution was being stirred rapidly. After stirring and refluxing for 15–20 hours, the mixture was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry diethyl ether. The filtrate and washings were returned to the reaction flask, 10 ml. of 10% aqueous hydrochloride acid was added, and the mixture was refluxed with vigorous stirring for 4–6 hours. The layers were then separated, the aqueous layer was extracted once with benzene, and the benzene solutions were combined. After removal of solvent by distillation at atmospheric pressure, the residue was distilled from an oil-jacketed flask giving 4.5 g. (52%) of 2-oleylcyclohexanone as an oil, b.p. 180–205° (0.5 mm.). The yield was 64% using 1 equiv. of enamine and 1 equiv. of triethylamine in chloroform solution.

Cleavage of Acyl Cyclanones. 7-Ketododecanoic Acid (LV, R = $CH_3(CH_2)_4$–).—A solution of 3.0 g. (0.015 mole) of 2-caproylcyclohexanone and 4.0 g. of 85% potassium hydroxide in 15.0 g. of methanol was refluxed for 20 hours. The mixture was then diluted with 50 ml. of water and extracted with diethyl ether. The ether extracts were discarded. The solution was made strongly acid with concentrated sulfuric acid and extracted with benzene. Distillation of the benzene left 2.75 g. of a yellow solid, which, on recrystallization from n-pentane, gave 2.04 g. (63%) of white crystals, m.p. 56.5–57°.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.37. Found: C, 67.45; H, 10.27.

(81) Pl. A. Plattner, P. Treadwell and C. Scholz, *Helv. Chim. Acta*, **28**, 771 (1945).

6-Ketotridecanoic acid (LXI, R = $CH_3(CH_2)_6$–) was prepared from 2-caprylylcyclopentanone in 75% yield by the method described above as white crystals, m.p. 67.0–67.5° (reported[82] m.p. 68°).

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.39; H, 10.64.

7-Ketomyristic acid (LV, R = $CH_3(CH_2)_6$–) was prepared in a similar manner from 2-caprylylcyclohexanone, in 65% yield, as white crystals, m.p. 67.0–67.5°.

Anal. Calcd. for $C_{14}H_{26}O_3$: C, 69.38; H, 10.82. Found: C, 69.55; H, 10.84.

7-Ketopentadecane-1,15-dioic acid (LVIII, n = 7) was prepared from 2-(8-carbethoxyoctanoyl)-cyclohexanone in 65% yield by the method described above, as white crystals, m.p. 105.5–107°.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.05; H, 9.15.

Compound LVIII was also prepared by oxidation of 7-keto-15-tetracosenoic acid (see following) according to the method of Lemieux and von Rudloff,[51] in 66% yield, as a white solid, m.p. 105–107°, which gave no depression in mixed melting point with the authentic 7-ketopentadecane-1,15-dioic acid described above.

7-Keto-15-tetracosenoic Acid.—A solution of 3.62 g. (0.01 mole) of 2-oleylcyclohexanone and 5.0 g. of 85% potassium hydroxide in 15 g. of methyl alcohol and 10 g. of dioxane was refluxed for 20 hours. The solution was then diluted with 50 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 gave 2.0 g. (53%) of white crystals, m.p. 54–64°, on crystallization from n-pentane.

Anal. Calcd. for $C_{24}H_{44}O_3$: C, 75.73; H, 11.65. Found: C, 75.43; H, 11.51.

Reduction of Keto-acids. Myristic acid (LVI, R = $CH_3(CH_2)_6$–) was prepared in 80% yield by reduction of 7-keto-myristic acid according to the method of Huang-Minlon[83]; white crystals, m.p. 57–58°, after recrystallization from n-pentane (reported[84] m.p. 58°).

Pentadecane-1,15-dioic acid (LIX, n = 7) was prepared in 95% yield by reduction of 7-ketopentadecane-1,15-dioic acid, according to the method of Huang-Minlon,[83] as white crystals, m.p. 112.5–113.5° after recrystallization from n-pentane (reported[85] m.p. 114.6–114.8°).

β-Keto Esters. 2-Carbethoxycyclohexanone (LIII).—To a solution of 20.0 g. (0.12 mole) of the morpholine enamine of cyclohexanone in 100 ml. of dry benzene, ethyl chloroformate (7.2 g., 0.066 mole) was added under nitrogen while the enamine solution was being stirred rapidly. After refluxing for about 10 hours, the solution was cooled and filtered with suction, the precipitate of enamine hydrochloride being washed with dry ether. The combined filtrate and washings were returned to the reaction flask, 22 ml. of 10% aqueous hydrochloride acid was added, and the mixture was stirred vigorously for 15–30 minutes. The layers were separated, the aqueous layer was extracted with benzene, and the combined organic layers were distilled at atmospheric pressure to remove solvent. Fractionation of the residue gave 6.2 g. (62%) of β-keto ester, b.p. 112–115° (10 mm.), reported[86] b.p. 111–112° (14 mm.). The infrared spectrum was identical with that of an authentic sample. The 2,4-dinitrophenylhydrazone had m.p. 154.5–156° (reported[87] m.p. 156°).

2-Carbethoxy-4-methylcyclohexanone was prepared in a similar manner from 33.6 g. (0.186 mole) of the morpholine enamine of 4-methylcyclohexanone and 11.0 g. (0.102 mole) of ethyl chloroformate in 80 ml. of dry benzene, giving 10.83 g. (65%) of a product, b.p. 121–126° (20 mm.), reported[88] b.p. 117–120° (14–15 mm.), the infrared spectrum of which was identical with that of an authentic sample of 2-carbethoxy-4-methylcyclohexanone.

2-Carbethoxycyclopentanone.—In a similar manner, 28.4 g. (0.19 mole) of the morpholine enamine of cyclopentanone and 11.5 g. (0.11 mole) of ethyl chloroformate in 115 ml. of dry benzene gave 10.9 g. (75.5%) of β-keto ester as an oil, b.p. 99–104° (15 mm.), reported[89] b.p. 102° (11 mm.). The infrared spectrum was identical with that of an authentic sample; semicarbazone, from 35% ethanol–water, m.p. 139–140° (reported[90] m.p. 143°).

(82) J. Plesek, *Chem. Listy*, **49**, 1840 (1955).
(83) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).
(84) P. A. Levene and C. J. West, *J. Biol. Chem.*, **18**, 463 (1914).
(85) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926).
(86) F. M. Jaeger and J. A. van Dijk, *Proc. Acad. Sci. Amsterdam*, **39**, 384 (1936).
(87) H. Ruhkopf, *Ber.*, **72**, 1978 (1939).
(88) B. R. T. Keene and K. Schofield, *J. Chem. Soc.*, 3181 (1957).
(89) R. P. Linstead and E. M. Meade, *ibid.*, 935 (1934).
(90) M. L. Bouveault, *Bull. soc. chim. France*, **21**, 1019 (1899).

2-Carbethoxycycloheptanone.—In a similar manner, 33.5 g. (0.18 mole) of the morpholine enamine of cycloheptanone and 11.0 g. (0.102 mole) of ethyl chloroformate in 150 ml. of dry benzene gave 7.35 g. (46%) of β-ketoester, b.p. 110–125° (10 mm.), reported[91] b.p. 125–126° (12 mm.); phenylpyrazolone, m.p. 210–214° (reported[92] m.p. 210°).

2-Carbethoxypentanone-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 β-keto ester, b.p. 87–97° (12 mm.). The phenylpyrazolone was prepared from the carbethoxy ketone by reaction with phenylhydrazine; m.p. 109–110.5° (reported[93] 112.5°).

3-Carbethoxyheptanone-4 (LXVIII).—In a similar manner, 25.0 g. (0.136 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 β-keto ester, b.p. 105–106° (15 mm.) (reported[94] b.p. 88–90° (12 mm.)).

(91) V. Prelog and W. Hinden, *Helv. Chim. Acta*, **27**, 1854 (1944).
(92) W. Dieckmann, *Ber.*, **55**, 2470 (1922).
(93) O. Emmerling and L. Kristeller, *ibid.*, **39**, 2452 (1906).
(94) J. C. Shivers, M. L. Dillon and C. R. Hauser, *J. Am. Chem. Soc.*, **69**, 119 (1947).

2-Carbethoxycyclohexanone by Reaction in the Presence of Diethylaniline.—The morpholine enamine of cyclohexanone (16.7 g., 0.10 mole) and diethylaniline (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 solution 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-carbethoxycyclohexanone.

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

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

Studies in Organic Peroxides. XXIX. The Structure of Peroxides Derived from 2,4-Pentanedione and Hydrogen Peroxide[1]

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2,4-Pentanedione (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, 3,5-dimethyl-3-hydroxy-5-hydroperoxy-1,2-peroxycyclopentane (V) is formed. With three moles of hydrogen peroxide in dilute acid solutions, II yields 3,5-dimethyl-3,5-dihydroperoxy-1,2-peroxycyclopentane (VI). 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 mull 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 monomolecular reaction. The n.m.r. spectra of all peroxides in this group were measured in $CDCl_3$, CD_3OD and D_2O solutions. It has been found that the undissociated 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 publications[5a,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 preparation and structure of peroxides derived from the reaction of hydrogen peroxide and 2,4-pentanedione. When diketone 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%. The analytical data for this peroxide support either structure III or IV. However, infrared spectra taken by the mull method[6] in Nujol or 10% in dimethoxyethane[7] 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-diols,[8] while the region 1150–1080 cm.$^{-1}$ has also been attributed to ketals[9] 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 acetone 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-pentanedione.

The hydroxyhydroperoxyperoxide V was obtained either by adding one mole of hydrogen peroxide to the dihydroxyperoxide IV or by adding directly two moles of hydrogen peroxide to 2,4-pentanedione. 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

(1) Since our original manuscript was submitted Jan. 19, 1961, a paper appeared on the same subject by A. Rieche and C. Bischoff, *Chem. Ber.*, **95**, 77 (1962).
(2) Lucidol Division of Wallace and Tiernan, Inc.
(3) Postdoctoral Research Associate.
(4) Research Assistant.
(5) N. A. Milas and A. Golubović, *J. Am. Chem. Soc.*, **81**, (a) 3361; (b) 5824; (c) 6461 (1959).
(6) J. P. Wibaut and Th. J. De Boer, *Rec. trav. chim.*, **78**, 183 (1959).
(7) Dimethoxyethane was the only suitable solvent for infrared measurement of this peroxide in the hydroxyl and carbonyl regions.
(8) E. Nagai, S. Kuribayashi, M. Shiraki and M. Ukita, *J. Polymer. Sci.*, **35**, 295 (1959).
(9) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 116.