1964

Ring-opening addition reactions of 11-disubstituted cyclopropanes with amines

Halvor Holt Westberg

The University of Montana

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RING-OPENING ADDITION REACTIONS OF 1,1-DISUBSTITUTED CYCLOPROPANES WITH AMINES

by

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B.A. Montana State University, 1963

Presented in partial fulfillment of the requirements for the degree of Master of Science

MONTANA STATE UNIVERSITY

1964

Approved by:

Chairman, Board of Examiners

Dean, Graduate School

AUG 17 1964
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ACKNOWLEDGMENT

I want to extend my sincerest thanks to my very worthy advisor, Dr. Stewart, who has spent many hours of his time guiding the work reported in this investigation. His help has provided much of the support necessary to achieve this present goal; and through association with him, I have gained the desire to continue on to more advanced levels in the field of chemistry.

Grateful acknowledgment is made to the Research Committee, Montana State University, for financial help in the form of a summer research assistantship during the completion of this work, and to the Petroleum Research Fund of the American Chemical Society, whose research grant to Dr. Stewart has supplied funds for chemicals used and for the necessary microanalyses.

I would also like very much to thank my wife, Sandy, for her patience throughout this past year and especially for her help in the preparation of this paper.
INTRODUCTION

It is well known that many physical and chemical properties of cyclopropanes resemble those of olefins much more closely than those of saturated hydrocarbons or unstrained alicyclic hydrocarbons. This implies that the cyclopropane ring must possess a degree of unsaturation similar to that of olefins. Such a resemblance provides a valuable asset to the investigator involved with cyclopropane chemistry since it allows a comparison with the thoroughly investigated and well-established reactions of olefins.

Within the field of organic chemistry, the classical criterion of unsaturation is the ability to undergo addition reactions. This is exemplified by the addition reactions of simple olefins. The double bond of the alkene in this case acts as a nucleophilic center which readily combines with electrophilic reagents. If simple cyclopropanes are unsaturated in the sense of alkenes, they should also exhibit this tendency toward addition of electrophiles rather than the substitution reactions characteristic of alkanes. It has been shown by many investigators that the unsubstituted cyclopropane ring does indeed display a nucleophilic character and reacts with electrophilic reagents such as halogens, hydrogen halides and strong acids by ring opening and addition. These reactions are generally somewhat slower than those for olefins but are exactly analogous to the corresponding reactions of alkenes in respect to the type of product and influence of substituents on ease of reaction and direction of unsymmetrical addition. Thus, electron-donating groups enhance, while electronegative groups diminish the additive reactivities.

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of both alkenes and cyclopropanes toward electrophilic reagents by inductomeric or electromeric electron shifts toward or away from the nucleophilic center. This suggests a second phenomenon characteristic of unsaturation; the ability of a site of unsaturation to conjugate with other functional groups within the molecule. Observation of certain of the molecules physico-chemical properties is the way this criterion is most commonly detected. Absorption of energy by a molecule that is conjugated throughout is characteristically at longer wavelengths than that of a molecule which possesses no chain of conjugation but has the same functional groups. This is reflected in the spectroscopic properties of the respective molecules. Thus, one finds that a molecule such as 1,3,5 hexatriene (CH\(_2\)-CH=CH=CH=CH\(_2\)) absorbs at a longer wavelength than 1,5 hexadiene (CH\(_2\)-CH=CH\(_2\)CH=CH=CH\(_2\)).

When a cyclopropane ring is conjugated with an ethylenic double bond or a carbonyl group, the absorption in the ultraviolet region is more intense and at a longer wavelength than would be predicted on the basis of considering the two groups as separate entities.\(^1\) Raman spectra\(^2\) also verify the fact that compounds containing a cyclopropane ring resemble more closely the olefins than paraffins.

It is now believed that unsaturation within a molecule is a property due to loosely held electrons; in an olefin, for example, these are the electrons comprising the pi bond. The cyclopropane ring, then, must also have loosely bound electrons associated with it. The famous Strain Theory of Baeyer has most commonly been cited to explain this phenomenon. It holds that the higher reactivity of cyclopropane compared to alkanes is due to strain created by compressing
the C-C bond angles to 60 degrees, as is required in cyclopropane, from the preferred angle of 109 degrees. This brings valence electrons closer together and creates repulsions between them due to the association of like charges. However, within the last few years, much of the old idea of strain has been translated in terms of hybridization. D. Peters has presented work which indicates that both from localized and delocalized molecular orbital theory the C-C bonds in the cyclopropane ring are formed from hybrid atomic orbitals which are very close to pure 2p atomic orbitals. His calculations indicate that these bonds possess from 0-4 percent s character. He proposes a picture as follows:

The dotted lines represent the 60 degree angles, while the solid lines represent the actual line of overlap of bonding orbitals. Peters assigns a value between 21 and 25 degrees to \( \angle \). From this illustration, it is evident that there is neither the sideways overlap of orbitals characteristic of pi bonds nor the endwise overlap characteristic of sigma bonds but rather an intermediate combination between these two extremes. Hence, the so-called "banana bonds" of cyclopropane are understandable.

With the increased amount of p character in the C-C bonds, there must be a corresponding decrease elsewhere. Therefore, the C-H bonds must contain less p character and more s character. In other words, carbon valencies toward hydrogen are nearly \( sp^2 \) in type. This is verified in

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two ways. The first is bond angle measurements of the H-C-H angle. Electron-diffraction measurements\textsuperscript{4} show that this angle is $118^\circ \pm 2^\circ$. This is almost the same as that found in ethylene and indicates that the carbon valencies toward hydrogen are indeed close to the $sp^2$ hybrid type characteristic of ethylenic carbon atoms. The second justification comes from dipole moment studies of cyclopropylchloride. The dipole moment of this compound is less than isopropylchloride or cyclopentylchloride.\textsuperscript{5} From strained ring theory, just the reverse would be predicted since electrons in the ring of former must be considered to be weakly bound and therefore partially polarizable. Also the polarizable matter is concentrated more nearly in line with the original dipole. This low dipole moment is best rationalized on the basis that chlorine is attached to a trigonal carbon. A trigonal carbon has a higher electronegativity in its $sp^2$ valencies than has a tetrahedral carbon atom in its $sp^3$ hybrid state. This, coupled with some delocalization of the chlorine lone-pair electrons, accounts for the lower dipole moment of vinyl and phenyl chlorides as compared to the corresponding paraffinic chlorides and can be likewise set forth to explain the cyclopropylchloride case.

The quenching cross-section of cyclopropane for cadmium resonance radiation also indicates loosely held electrons.\textsuperscript{6} The cross-section greatly increases if weakly bound electrons are present. The value for cyclopropane is midway between olefins and paraffins.

The foregoing discussion of background evidence and theory leaves little doubt that the cyclopropane ring possesses a high degree of "unsaturation."
The electronic character of the double bond in an alkene can be changed from an electron-rich site to a more positively charged character by placing an electron withdrawing group on one of the carbons connected by the double bond. The double bond now acts as an electrophilic center and reacts readily with nucleophilic reagents such as amines, alcohols and mercaptans. This is well exemplified by the cyanoethylation reactions of acrylonitrile or the addition reactions of ethyl acrylate with nucleophiles. Considering the latter, one can account for the change in character from nucleophilic to electrophilic by proposing electromeric shifts of the following nature:

\[
\text{CH}_2=\text{CH}-\text{C}^\equiv\text{O}^+\quad\longleftrightarrow\quad \text{CH}-\text{CH}=\text{C}^\equiv\text{O}^+\ 
\]

The ionic resonance structure on the right becomes of importance under influence of the nucleophile with attack by the latter being on the carbon associated with the positive charge. The typical sequence of steps in the reaction of ethylacrylate and a nucleophilic reagent, \(R-Z\), might then be as follows:

\[
\begin{align*}
\text{CH}_2=\text{CH}-\text{C}^\equiv\text{O}^- & \quad + \quad R^+Z^- \rightarrow \text{CH}_2=\text{CH}-\text{C}^\equiv\text{O}^- \\
\text{CH}_2=\text{CH}-\text{C}^\equiv\text{O}^- & \quad + \quad R^+ \rightarrow \text{CH}_2=\text{CH}-\text{C}^\equiv\text{O}^-
\end{align*}
\]

By continuing the analogy between olefins and cyclopropanes, it is not possible to establish a well-defined nucleophilic center in a...
cyclopropane ring conjugated with an unsaturated electronegative group. Therefore, it is not unreasonable to expect that the compound ethyl 1-cyclopropanecarboxylate (\(-\text{CO}_2\text{Et}\)) might exhibit behavior analogous to that of ethyl acrylate by acting as an electrophilic site and reacting with nucleophiles. If such be the case, the following indicated polarized resonance form might contribute significantly at the time of reaction:

\[
\text{\begin{align*}
\text{C}_{\text{=C}} & \quad \text{CH}_2 \quad \text{CH}_2 \\
\text{O} & \quad \text{+} \\
\text{O} & \quad \text{C}_{\text{=C}} \quad \text{OC}_2\text{H}_5 \\
\text{O} & \quad \text{OC}_2\text{H}_5
\end{align*}}
\]

Nucleophilic attack could then occur at the most positive position, this being one of the two equivalent carbon atoms of the ring which are located \(\beta\)-relative to the carbon atom substituted by the ester group.

There is justification for postulating a contribution in the overall electronic distribution due to an ionic structure such as appears in the last illustration. This comes from quantum mechanical studies which indicate that intense absorption in the ultraviolet region by cyclopropanes is due to electronic transitions from a neutral ground state to ionic excited states.\(^7\)

The question then arises whether cyclopropanes substituted with electron-withdrawing groups will, in fact, exhibit behavior similar to olefins when treated with a nucleophile. This presents an interesting and, for the most part, unexplored area of chemical research.

While one finds common reference to cyclopropane ring openings by electrophiles, nucleophilic ring cleavage reactions are relatively
rare. The earliest, and most commonly cited example, is that reported by Bone and Perkin\textsuperscript{8} in 1895. This involved the base-catalyzed ring-opening of diethyl 1,1-cyclopropanedicarboxylate by attack of ethyl sodiomalonate to give tetraethyl 1,1,4,4-butanetetracarboxylate.

\[
\begin{align*}
\text{CO}_2\text{C}_2\text{H}_5 + \text{Na}^+ \text{CH(CO}_2\text{C}_2\text{H}_5)_2 \rightarrow (\text{C}_2\text{H}_5\text{O}_2\text{C})_2\text{CHCH}_2\text{CH}_2\text{CH(CO}_2\text{C}_2\text{H}_5)_2
\end{align*}
\]

The mechanism in this case is presumed to involve nucleophilic attack by the malonate ion at one of the indicated \(\beta\)-ring carbons to give an open-chain anion with negative charge in the \(\alpha\)-position,

\[
(\text{C}_2\text{H}_5\text{C}_2\text{C})_2\text{CHCH}_2\text{CH}_2\text{C}(\text{CO}_2\text{C}_2\text{H}_5)_2^-
\]

Hydrogen exchange then occurs between this anion and a molecule of malonic ester to give the observed product. This reaction is quite reminiscent of the well-known Michael reaction where an \(\alpha\)-unsaturated ester is involved. Here, also, the nucleophile becomes attached to the \(\beta\)-position relative to the carbonyl carbon.

Kohler and Conant\textsuperscript{9} initiated an investigation in 1917 in the expectation that their results would be of assistance in explaining the phenomenon of the structures formed from addition reactions of \(\alpha\)-unsaturated compounds as well as those of cyclopropane derivatives. The compounds they employed are represented by the general formula \(\text{C}_6\text{H}_5\text{COC}_6\text{H}_5\). Their results establish that it is possible to open the cyclopropane ring in at least three different positions depending on the attacking reagent and reaction conditions employed. Anhydrous bases such as sodium amide, ammonia and amines

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caused ring cleavage between the carbons substituted with the phenyl group and ester groups. They feel the facts obtained justify the conclusion that there is no fundamental difference between corresponding derivatives of ethylene and cyclopropane.

The next investigation to be reported was conducted by Kierstead, Linstead and Weedon\textsuperscript{10} in 1952. They found that the ring structure of 

\[ \text{CH}_2 = \text{CH} - \bigtriangleup - (\text{CO}_2\text{C}_2\text{H}_5)_2 \]

could be changed by addition of ethyl sodiomalonate.

\[
\begin{align*}
\text{CH}_2 = \text{CH} - \text{CH} - \text{C} - (\text{CO}_2\text{C}_2\text{H}_5)_2 + \text{Na}^+ \text{CH}_2 \text{CO}_2\text{C}_2\text{H}_5 & \rightarrow \text{CH}_2 = \text{CH} - \text{CH} - \text{CH}\text{CO}_2\text{C}_2\text{H}_5 \\
& \text{CH}_2 - \text{CH}(\text{CO}_2\text{Et})_2
\end{align*}
\]

The reaction didn't give the expected tetraester, \( \text{CH}_2 = \text{CH} - \text{CH} - \text{CH}(\text{CO}_2\text{Et})_2 \), but rather that shown. Presumably, the observed product results from a condensation of diethyl malonate with the vinyl cyclopropyl ester followed by elimination of the elements of ethyl carbonate. A small amount of \((\text{Et}_2\text{O}_2\text{C})_2\text{CHCH}_2\text{CH} = \text{CHCH}_2\text{CH}(\text{CO}_2\text{Et})_2\) was also isolated from the above reaction which led the investigators to believe that conjugation exists between the double bond and the three-carbon ring since this product is formed by 1,6-addition at opposite ends of the system.

More recently, two additional groups of chemists have presented evidence in favor of ring cleavage of cyclopropanes by nucleophiles. Truce and Lindy\textsuperscript{11} found that methyl cyclopropylketone, when reacted with sodium benzenethiolate, gave \( \gamma - (\text{phenylmercapto}) \) propyl methyl ketone.

\[
\begin{align*}
\bigtriangleup - \text{C} - \text{CH}_3 - \text{HS} \rightarrow \text{Na} & \rightarrow \bigtriangleup - \text{S} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{C} - \text{CH}_3
\end{align*}
\]
Their main interest was in opening the ring of cyclopropyl sulfones; however, this proved unsuccessful, and they postulated their failure was due to a lower tendency toward protonation on the part of the sulfone group compared to carbonyls. This results from the lower stabilizing effect by a sulfone group on the incipient $\alpha$-carbanion.

Diethyl 1,1,2,2-tetracyanocyclopropane-3,3-dicarboxylate when treated with ammonia in anhydrous ether resulted in ring cleavage as reported by T. H. Regan in 1962. Based on spectral and chemical evidence, he assigned an open-chain structure, postulated to be ammonium 1,1,3,3-tetracyano-2-carbethoxypropinide.

These few examples just cited, which encompass roughly a period of sixty-five years, give a summary of the literature in which base-catalyzed nucleophilic addition reactions involving cleavage of the cyclopropane ring are concerned.

Undoubtedly, there have been other attempts to cleave the cyclopropane ring which have been unsuccessful and therefore, have not been reported in the literature. One such known example involves the work of I. L. Klundt. His attempted opening of the ring of cyclopropane carbonitrile by nucleophilic addition could, under no conditions, be achieved. Experimental conditions employed included both high and low temperature, changes in molar ratios of reactants and numerous catalysts, but no simple addition product could be isolated.

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DISCUSSION

The material which has been presented in the preceding brief
historical discussion points out the fact that very little work has
been done which would indicate what to expect from the combination
of a nucleophile with 1,1-disubstituted cyclopropane compounds.
Consequently, it has been the purpose of this present investigation
to attempt to cleave the ring of certain 1,1-disubstituted cyclopropanes
by addition of amines. Both primary and secondary amines have been
employed as the nucleophile, and their effects on the following five
1,1-disubstituted cyclopropanes have been studied:

\[
\begin{array}{c}
\text{diethyl 1,1-cyclopropanedicarboxylate} \\
\text{cyclopropane-1,1-dicarboxamide} \\
\text{ethyl 1-cyanocyclopropane-1-carboxylate} \\
\text{1-cyanocyclopropane-1-carboxamide} \\
\text{cyclopropane-1,1-dicarbonitrile}
\end{array}
\]

Since no work of this exact nature has been previously reported, any
positive results obtained will provide a new and better understanding
of this area of cyclopropane chemistry.
A major obstacle encountered during this investigation was the preparation of the desired 1,1-disubstituted cyclopropane compounds, mentioned previously, in pure form and in reasonably good yields. Accordingly, the first portion of this discussion will contain a summary of the synthetic methods used to prepare these cyclopropane derivatives.

Diethyl 1,1-cyclopropanedicarboxylate was initially prepared by Perkin. His procedure followed the course of an acetoacetic or malonic ester condensation. In these esters, the methylene group is unusually reactive and can combine with a base such as sodium ethoxide to form a sodium salt by abstraction of one of the pseudo acidic hydrogens attached in the methylene group. The sodium salt thus formed can then be combined with a polymethylene halide to give the corresponding cyclic structure. Consequently, preparation of the cyclopropane diester requires a sequence of steps as follows:

\[
\begin{align*}
\text{CO}_2\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\text{Et}\text{CH}_2 & \quad \text{Et}\text{CH}_2 \\
\text{NaOEt} & \quad \text{NaOEt} \\
\rightarrow & \quad \rightarrow \\
\text{Na}^+\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 & \quad \text{Na}^+\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \\
\text{BrCH}_2\text{CH}_2\text{Br} & \quad \text{BrCH}_2\text{CH}_2\text{Br} \\
\rightarrow & \quad \rightarrow \\
\text{Na}^+\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 & \quad \text{Na}^+\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \\
\text{CO}_2\text{C}_2\text{H}_5 & \quad \text{CO}_2\text{C}_2\text{H}_5 \\
\end{align*}
\]

Perkin reported a yield of 27-29 percent from this method.

Since the initial work by Perkin in 1885, only one report appears in the literature which attempts to improve on Perkin's procedure. This contribution was from Dox and Yoder, with their method entailing...
a similar route but providing an improved yield of about 40 percent. Their investigation was published in 1921; and since that time, literature references dealing with this cyclopropane compound refer mainly to its physical and spectral properties, in which case the investigators only required a small amount of the material and were, therefore, probably unconcerned with the low yield.

A 40 percent yield, in many cases, is acceptable if the method employed is such that it can be easily duplicated when more material is desired. The process required to prepare this compound, however, is quite tedious in that there are stringent restrictions on the order of addition of reactants and temperature control. There are numerous ways in which one can combine these three reactants; however, success has been achieved only when the sodium ethoxide is dissolved in absolute alcohol, transferred to a dropping funnel and admitted dropwise to a mixture of diethylmalonate and ethylene bromide as described by Dox and Yoder.

With the hope of obtaining a better yield, several other experimental runs have been made which differ in order of addition of the three starting materials as well as thermal conditions. All have been failures since little or no diethyl 1,1-cyclopropanedicarboxylate could be isolated. Attempts which have employed sodium hydride as the base with dimethylformamide (DMF) as the solvent have also proven to be unsuccessful. Both absolute alcohol and DMF were employed in another unsuccessful attempt. The sodiomalonate salt was first prepared in absolute ethanol, followed by separation from the solvent by filtration. It was then dissolved in DMF and the ethylene bromide added. Again, none of the desired diester was obtained. These numerous
failures left no alternative but to use the method as established by Perkin and amended by Dox and Yoder.

There proved to be still another difficulty which was not apparent at first but became increasingly so as the investigation progressed. This resulted from the inability to separate the desired product, diethyl 1,1-cyclopropanedicarboxylate, from unreacted diethyl malonate by distillation. The boiling points have been reported as 215°C and 206°C respectively at 760 mm pressure; the closeness of which accounts for this inability to effect significant changes in the composition of this mixture through distillation. Theoretically, it should be possible to separate the two on the basis of acidity, diethyl malonate possessing a pair of pseudo acidic hydrogens while the cyclopropane analog lacks this acidity. Therefore, the attempt was made to form the sodiomalonate salt in a nonpolar medium from which it would precipitate and could be separated by filtration. However, attempts at this separation met with no success. Initially, attention was brought to the presence of the impurity of diethyl malonate by the formation of a solid product from reactions involving the cyclopropane diester with primary amines. This solid was shown to be the diamide of malonic acid formed by attack of the primary amine involved on the two ester groups of diethyl malonate.

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The cyclopropane diester proved less reactive and remained unaffected on periods of short heating with the primary amine. This process then provided a means of separating the two.

In summary, then, the preparation of pure diethyl 1,1-cyclopropane-dicarboxylate has been achieved by condensing diethyl malonate with ethylene bromide in the presence of sodium ethoxide followed by combining the product from this reaction with butylamine. After a short period of heating, the impurity is removed by filtration and a final distillation gives the pure cyclopropane diester.

Cyclopropane-1,1-dicarboxamide is prepared by amidization of diethyl 1,1-cyclopropanedicarboxylate with aqueous ammonia.

\[ \text{CO}_2\text{C}_2\text{H}_5 + \text{NH}_3 \xrightarrow{\text{H}_2\text{O}} \text{CONH}_2 \]

Dox and Yoder have reported a yield of 84 percent from this reaction. This is contrary to the results from the present investigation, since at no time has this product been obtained in yields of more than 50 percent. The substitution of ethereal ammonia for aqueous ammonia proved to be no more successful.

Ethyl 1-cyanocyclopropane-1-carboxylate was also prepared originally by Perkin, first being reported in 1899. The procedure follows the same principle as for the diester; however, this time employing ethyl cyanoacetate rather than diethyl malonate.
Since Perkin's time, several investigators have attempted to improve his method; however, only slight alterations to the original procedure have been advanced. Recorded yields have been somewhat higher than those for the diester, with Perkin reporting yields above 50 percent and various others reporting yields as high as 80 percent. Yields obtained in this present investigation have been in this higher category.

A similar problem of contamination by unreacted starting material, ethyl cyanoacetate, has been encountered in this preparation; and as with the diester, it is best removed chemically by the action of a primary amine on the mixture. Subsequent filtration then takes away the solid amide (CN—CH₂—CO₂H) formed by attack of the amine on the ester group of ethyl cyanoacetate. Again, loss of the cyclopropane compound by amidization is minimal.

Again, it would be desirable to establish a method of preparing ethyl 1-cyanocyclopropane-1-carboxylate which would afford pure product and eliminate the necessity for the purification step making use of the primary amine. A method has been devised which does give a much more pure product. However, to date, this procedure has the
disadvantage of providing poorer yields. It involves the same starting materials as Perkin's method but differs in thermal condition and order used for combination of the three reactants. The exact procedure is described in detail in the experimental section of this paper.

The corresponding amide, 1-cyanocyclopropane-1-carboxamide, has been prepared by amidizing ethyl 1-cyanocyclopropane-1-carboxylate with aqueous ammonia. Yields once more have not exceeded 50 percent.

The other cyclopropane compound of interest in this investigation, cyclopropane-1,1-dicarbonitrile, is previously unreported. It was considered likely that this compound could be obtained by known methods of reacting either 1-cyanocyclopropane-1-carboxamide or cyclopropane-1,1-dicarboxamide with a dehydrating agent such as phosphorus pentoxide, phosphorus pentachloride or thionyl chloride. Both of these approaches were successful in the preparation of this compound. However, because of the more favorable conditions and better yields obtained in the preparation of ethyl 1-cyanocyclopropane-1-carboxylate, this compound has been employed exclusively as the starting point in the dinitrile preparation. The stepwise procedure, then, is as follows:

\[
\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{CO}_2\text{C}_2\text{H}_5 & + \text{NH}_3 \xrightarrow{\text{H}_2\text{O}} \text{CN} & \text{CONH}_2 \\
\text{CN} & \quad \text{CN} \\
\text{CONH}_2 & + \text{P}_2\text{O}_5 \xrightarrow{} \text{CN} & \text{CN}
\end{align*}
\]

Phosphorus pentoxide proved to be the only dehydrating agent of the three mentioned above that gave the desired product. Yields obtained
from this dehydration step have been poor with the maximum yield obtained being 45 percent.

With the route to cyclopropane-1,1-dicarbonitrile just described leaving much to be desired from the standpoint of yield, other methods of preparation were sought. The most obvious choice would be a one-step process involving the condensation of malononitrile with ethylene bromide in the presence of a base. This is basically the same as that employed for the cyclopropane diester and cyanoester and would, if successful, form the desired compound directly.

\[
\text{NaH} / \text{N} \text{C} \text{N} \quad \text{CH}^\text{CN} \quad - \quad \text{H BrCH}^\text{CH}^\text{Br} \quad \longrightarrow \quad \triangle \text{CN} \quad \text{or} \quad \text{NaOEt}
\]

Several experiments involving various reaction conditions have been carried out, but unfortunately no cyclopropane-1,1-dicarbonitrile could be obtained from this type of reaction.

Experimental work directed at determining the possibility of ring opening of 1,1-disubstituted cyclopropanes by nucleophilic addition was initiated by studying the reaction of cyclopropane-1,1-dicarbonitrile (\(\triangle-(\text{CN})_2\)) with the secondary amine piperidine. This was considered a logical starting point since it was felt that the two nitrile groups connected to one carbon would cause sufficient electron withdrawal from the ring to create the necessary electrophilic character within the system. As indicated earlier, Klundt\(^{13}\) had determined that cyclopropanecarbonitrile (\(\triangle-\text{CN}\)) would not react with secondary amines. The single nitrile group apparently did not give sufficient electron
withdrawal from the ring so that amines could attack it, at least under the reaction conditions used.

A spontaneous reaction resulted from mixing piperidine with the dinitrile in benzene, as evidenced by evolution of heat and separation of a colored layer. Removal of the solvent, after having washed the crude product with water, resulted in the formation of a viscous oil which could not be recrystallized nor distilled without decomposition. It proved possible to isolate a product by converting the crude reaction product to a hydrochloride. However, analysis of this hydrochloride did not correspond with calculated values for the simple mono-addition compound expected from the reaction indicated:

\[
\begin{align*}
\text{CN} & \quad \text{CN} \\
\text{NH} & \quad \rightarrow \\
\text{N} & \quad \text{CH}_2\text{CH}_2\text{CN} \\
\text{HCl} & \quad \text{Hydrochloride}
\end{align*}
\]

An infrared spectrum of this hydrochloride showed no nitrile absorption peak at 4.5 and hence, it is evident that, while ring opening might have occurred, attack by the amine must in some way have affected both of the nitrile groups. This was an unexpected type of reaction since amines do not add to simple nitriles; however, there is evidence in the literature to support a nitrile group reaction of this nature if a strong electron-withdrawing group is located adjacent to the nitrile group. Such is exemplified by the reaction of trifluoroacetonitrile with secondary amines to produce amidines:

\[
\text{F}_3\text{C-CN} + \text{R}_2\text{NH} \rightarrow \text{F}_3\text{C-CN^+R}_2\text{NH}
\]

The electron-withdrawing effect of the \(-\text{CF}_3\) group enhances the electrophilic character of the \(-\text{CN}\) carbon involved in the resonance
hybrid which allows this type of reaction to take place. Cyanogen will also exhibit this same type of behavior when combined with an amine. It was believed then that the unidentified product might be a diamidine (\[
\begin{array}{c}
\text{C} = \text{NH} \\
\text{NR}_2
\end{array}
\]). However, this hypothesis was not validated by elemental analysis nor infrared spectroscopy. The \(-C=\text{N}-\) absorption peak between 1600 and 1650 cm\(^{-1}\), which is prominent in amidines was entirely absent from the spectrum of this hydrochloride. Furthermore, amidines are easily hydrolyzed to the corresponding amides, a reaction which this unknown product did not undergo.

As another hypothetical approach, it was considered possible that one or both of the nitrile groups had been entirely replaced by amine functions. The basis for this postulate was the reported reaction of tetracyanoethylene with amines.\(^{18}\) It has been demonstrated that this compound will undergo replacement of a nitrile group when treated with an amine.

\[
\text{NC} = \text{C} = \text{CN} + \text{R}_2\text{NH} \rightarrow \text{NC} = \text{C} = \text{CN} \quad \text{NR}_2
\]

Again, however, elemental analysis data of the unknown compound did not indicate that this type of replacement reaction had occurred.

Returning once again to the similarities between olefins and cyclopropanes, it can be seen that a reasonable analogy can be drawn between cyclopropane-1,1-dicarbonitrile and methylene malononitrile (\(\text{CH}_2 = \text{C} = \text{CN}\)). Unfortunately, however, the literature contains no information on the reactions of this compound with anhydrous amines nor are there any reports of their effect on malononitrile, which

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might provide a clue as to the identity of the unknown product. A final rationalization, then, is that the inability to establish a structure consistent with analysis may likely be due to polymer formation in the product.

The experimental work with cyclopropane-1,1-dicarbonitrile made it apparent that if work along those lines originally proposed was to be continued it would be necessary to make use of other 1,1-disubstituted cyclopropanes in which preferential attack of nucleophiles could not occur at the substituent groups. Hence, work was shifted to investigate the effects of amines on diethyl 1,1-cyclopropanedicarboxylate (\( \triangle CO_2C_2H_5 \)). When this diester was treated with piperidine both in the presence and absence of a solvent and refluxed for twenty hours, a product was obtained which could be distilled. It was basic and formed derivatives characteristic of tertiary amines, which indicated that the desired open-chain compound had been formed by addition of piperidine and fission of the cyclopropane ring:

\[
\begin{align*}
\triangle CO_2C_2H_5 + \text{N} & \rightarrow N-\text{CH}_2\text{CH}_2\text{CH}(CO_2C_2H_5)_2 \\
\end{align*}
\]

Maximum yield of the product was obtained when no solvent was used and a 2 to 1 ratio of amine to diester was employed. Table I shows the effects of varying certain of the reaction conditions.
TABLE I

<table>
<thead>
<tr>
<th>Mole Ratio</th>
<th>Solvent</th>
<th>Length of Time Refluxed, 78°C (hours)</th>
<th>Percentage Yield of Open-chain Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amine - Diester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 1</td>
<td>Abs. Alcohol</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>1 1</td>
<td>Abs. Alcohol</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>2 1</td>
<td>Benzene</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>2 1</td>
<td>Benzene</td>
<td>72</td>
<td>52</td>
</tr>
<tr>
<td>2 1</td>
<td>Toluene</td>
<td>20(^b)</td>
<td>35</td>
</tr>
<tr>
<td>2 1</td>
<td>---</td>
<td>20(^c)</td>
<td>73</td>
</tr>
</tbody>
</table>

a. Based on total amount of ester used, these values are necessarily lower than the actual value for conversion based on pure diethyl 1,1-cyclopropanedicarboxylate since the total amount of ester used contained approximately 20 percent diethylmalonate.

b. 106°C
c. 102°C

The formula indicated for product I shows the piperidine group attached to a $\beta$-carbon with respect to substitution by the ester groups. This indicates that initial attack should be by the nucleophile, either the piperidine molecule or piperidide ion, at the more positive position, this being the $\beta$-position as postulated earlier. Although it is conceivable that an isomer with the addition just reversed ($\text{CH}_3\text{CH}_2\text{C} = \text{CO}_2\text{C}_2\text{H}_5$) could result, no such compound has been isolated from this reaction. The structure I, diethyl $\beta$-piperidinoethyl-malonate, is a known compound and the boiling point and refractive index of our compound were in close agreement with reported values.\(^{19}\)

Proof of structure for this open-chain product was accomplished by preparing it by the unequivocal route described in the literature.\(^{19}\)
This method involved the condensation of $\beta$-piperidinoethyl chloride with the sodium salt of diethylmalonate:

\[
\begin{align*}
\text{N-CH}_2\text{CH}_2\text{Cl} + \text{Na}^+\text{CH}2\text{CH(CO}_2\text{C}_2\text{H}_5)^- & \rightarrow \text{N-CH}_2\text{CH}_2\text{CH(CO}_2\text{C}_2\text{H}_5)^- + \text{Na}^+\text{Cl}^- \\
\end{align*}
\]

Comparison of boiling points, refractive indices and infrared spectra for the product from these two reactions indicate a common product. Furthermore, both of these compounds have been converted to the corresponding solid diamides, \(\text{N-CH}_2\text{CH}_2\text{CH(CON}\text{H}_2)^-\), II, with methanolic ammonia; and a mixed melting point determination with the amides showed no depression.

At first glance, it would appear that verification of ring cleavage could be achieved much more simply by means of infrared spectroscopy. The literature contains numerous studies which provide data concerned with characterizing the cyclopropane ring structure by its absorption in this region of the spectra. A survey of these references indicates that in over three hundred derivatives of cyclopropane tested, all had a peak near 9.7 \(\mu\). Other reports indicate moderately strong bands near 10.3 and 11.7 \(\mu\). Unfortunately, however, it has become apparent that analysis by this spectral method is not possible in the present case. The difficulty arises from the fact that absorption peaks mentioned previously as characteristic of the cyclopropane ring appear also in open-chain alkyl substituted malonates. For instance, a spectrum of diethyl ethylmalonate (\(\text{CH}_3\text{CH}_2\text{CH(CO}_2\text{Et})_2\)) shows a strong absorption close to 9.7 \(\mu\) and also one near the 10.3 and 11.7 \(\mu\) values. Since this latter group structure is an integral part of the products from the reaction of diethyl 1,1-cyclopropanedicarboxylate
with amines, it is apparently impossible to establish by this method whether or not cleavage of the ring has occurred. This contention was supported on a general basis by Horst Weitkamp, et. al., who stated that, "An identification of the cyclopropane structure exclusively by infrared spectroscopy is presently not possible."

A spectrogram has also been obtained for diethyl B-piperidino-ethylmalonate in the near-infrared region (1.0-3.0 μ). R. F. Goddu has put together a spectra-structure correlation chart for this region which indicates absorption peaks for cyclopropanes at 1.37, 1.67 and 2.22 μ. The scan for the product mentioned above shows no absorption at either of the first two locations, which probably indicates absence of a three-membered ring structure. This latter statement is qualified with the word "probably" since near-infrared analysis is a new field and as yet the investigation of specific structures such as those of small-ring compounds has been very limited.

When diethylamine was used as the nucleophile, the ring of diethyl cyclopropane-1,1-dicarboxylate was cleaved in a manner identical to that shown with piperidine:

\[
\begin{align*}
\text{CO}_2\text{C}_2\text{H}_5 + (\text{C}_2\text{H}_5)_2\text{NH} &\rightarrow (\text{C}_2\text{H}_5)_2\text{NCH}_2\text{CH}_2\text{CH(}\text{CO}_2\text{C}_2\text{H}_5)_2 \\
&\text{IIII}
\end{align*}
\]

III

The boiling point and refractive index for III agree very closely with those reported in the literature for diethyl B-diethylamino-ethylmalonate as prepared by the unequivocal route described earlier for the piperidine analog. Elementary analysis also confirmed the product indicated above.
After having experienced the success just described with diethyl 1,1-cyclopropanedicarboxylate, a similar study was next directed toward reactions of secondary amines and cyclopropane 1,1-dicarboxamide. This compound was treated with piperidine in the presence of absolute ethanol and refluxed for the same period of time as was used with the diester. However, with this diamide no product could be obtained after twenty hours of heating, and it was found necessary to keep the reactants at 78°C for a much longer time in order to acquire significant amounts of product. Maximum yields were obtained only after one hundred hours of heating. The product from this reaction has also been proven to be non-cyclic in character and once again was formed by nucleophilic attack at a β-position of the cyclopropane ring accompanied by ring fission and protonation at the α-position to give β-piperidinoethylmalonamide:

\[
\begin{align*}
\text{CONH}_2 + \text{NH} & \rightarrow \text{CH}_2\text{CH}_2\text{CH(CONH)}_2
\end{align*}
\]

Structural proof for this product was simply a matter of showing that it was the same as the diamide (II) prepared by either of the two methods previously described through the diester. A mixed melting point determination with the two showed no depression; hence verifying that the ring of cyclopropane-1,1-dicarboxamide was cleaved by nucleophilic addition.

Ethyl 1-cyanocyclopropane-1-carboxylate (\(\text{CO}_2\text{C}_2\text{H}_5\)) and 1-cyanocyclopropane-1-carboxamide (\(\text{CONH}_2\)) when treated with secondary amines accorded the same type of product structures as those formed by the cyclopropane diester and the diamide. Under no conditions was the nitrile group in either of these compounds found to be affected by the
amine, nor were polymeric products obtained as was the case with
cyclopropane-1,1-dicarbonitrile. With the cyanoester, as with the
diester, optimum yields were obtained when no solvent was used, and
when the amine was present in a molar amount twice that of the
cyclopropane compound. The product obtained using piperidine as the
nucleophile was then ethyl 2-cyano 2-(β-piperidinoethyl) acetate;

\[
\text{This compound is previously unreported; hence, there are no recorded}
\text{physical properties to which it could be compared. By analogy to the}
\text{structure proof employed for the diester, it appeared likely that a}
\text{similar route should be possible for unambiguous synthesis of compound}
\text{IV; the only difference being in the sodio-organic salt used. Consequently,}
\text{β-piperidinoethylchloride was combined with the sodium salt of ethyl}
\text{cyanocarbonate;}
\]

\[
\text{Analysis for the product obtained agreed with the structure indicated.}
\text{A comparison of the infrared spectra of this compound and that of IV}
\text{confirmed that the two were the same, thus establishing, once again,}
\text{that ring opening had taken place, and in the manner illustrated.}
\]

As stated before, it proved to be impossible to establish the
presence or absence of the cyclopropane ring structure by infrared
spectroscopy; however, a spectrum of this type is useful in that it
indicates whether or not the nitrile group has remained unaffected.

The presence of the nitrile group in IV is manifested by a weak
absorption peak at 4.5 μ. The weakness of this band is explained by the following quote from Bellamy,22 "The introduction of an oxygenated group into the molecule results in a 'quenching' of the C=O absorption intensity to a remarkable extent, and its effect is greater when the oxygen-containing group is attached to the same carbon atom as the nitrile."

The reaction of 1-cyanocyclopropane-1-carboxamide with piperidine also results in an open-chain product as indicated:

\[
\begin{align*}
\text{CN} & \quad \text{CONH}_2 \\
+ & \\
\text{N-H} & \quad \text{CN} \\
\rightarrow & \\
\text{N-CH}_2\text{CH}_2\text{CH}_2\text{CONH}_2
\end{align*}
\]

The cyclopropane ring in this amide is considerably more susceptible to cleavage than that in the diamide as displayed by formation of good yields of 2-cyano 2-(β-piperidinoethyl) acetamide in one-fourth the time required to get comparable results with cyclopropane-1,1-dicarboxamide. Heating for twenty-four hours gave the optimum yield of the aforementioned product. Near infrared analysis also indicated an open-chain structure since no absorption was found in the regions assigned to bonds characteristic of the cyclopropane ring structure. Unequivocal proof of structure V was achieved by amidizing the appropriate ester

\[
\begin{align*}
\text{N-CH}_2\text{CH}_2\text{CH}_2\text{CONH}_2 & \quad \text{CN} \\
\rightarrow & \\
\text{N-CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5
\end{align*}
\]

then demonstrating that product V from the cyclopropane reaction and this amide were the same. A mixed melting point determination with the two showed no depression.

The reactions involving the latter four cyclopropanes just described were carried out either without a solvent or in the presence of either
absolute ethanol or benzene. Aside from percentage yield, the same products were formed irrespective of solvent conditions. A quite different situation was encountered when dimethylformamide (DMF) was employed as the solvent medium. Diethyl 1,1-cyclopropanedicarboxylate, when heated with piperidine in the presence of DMF, resulted in two products not previously described. Both were liquids formed by exchange reactions between the amine group in the amide structure of DMF and the ethoxy groups in the ester. The product previously described as resulting from the combination of piperidine and diethyl 1,1-cyclopropanedicarboxylate was presumably first formed followed by the exchange mentioned above:

![Chemical structures]

These structures were assigned on the basis of elemental analysis and their spectral and chemical properties. The infrared spectrum of both exhibits an amide I band at 6.05 μ, and a carboxyl band at 5.75 μ is evident in the one presumed to contain the ester group. The two products exhibited chemical properties generally ascribed to tertiary amines, since VI was converted to a quaternary salt with iodomethane and VII was transformed to a hydrochloride. Furthermore, neither was soluble in water but both were miscible with dilute acid.
Results from reactions employing amines and the cyclopropane diamide, cyanoester and cyanoamide in DMF were inconclusive, and therefore, it was not possible to assign structures to products from these reactions.

It can be noted that reactions discussed thus far have concerned only secondary amines as the nucleophilic reagents. Many difficulties were encountered in isolating products from reactions employing primary amines. As mentioned before, reactions of cyclopropane compounds having substituent ester groups with primary amines led to the discovery of marked contamination of the cyclopropanes by the respective parent esters, diethyl malonate and ethyl cyanoacetate. These latter esters reacted preferentially with the primary amines to form low melting amides which were very difficult to separate from other reaction products. In fact, it was found necessary to remove these undesired esters first before products could be obtained that resulted from the action of the primary amine on diethyl 1,1-cyclopropanedicarboxylate or ethyl 1-cyanocyclopropane-1-carboxylate. Even after removal of these unwanted contaminants, products were much more unmanageable than in reactions employing piperidine as the nucleophile. The difficulty stemmed from the fact that most were oils that could not be crystallized and could be distilled only under conditions of high temperature and low pressure. From reactions involving cyclopropane-1,1-dicarboxamide and 1-cyanocyclopropane-1-carboxamide, only the unreacted amides were obtained plus a small amount of unworkable oil.

Most of the work involving primary amines has made use of the cyclopropane diester, with the assumption that if the ring in this
compound could be opened, that in the cyanoester could also be opened. Thus, diethyl 1,1-cyclopropanedicarboxylate was combined with several primary amines under varying conditions of temperature, catalysis, and solvent media. Experiments involving iso-butylamine have provided the most tangible results, and therefore, will be discussed first. This amine was initially combined with the diester under conditions similar to those utilized with the secondary amines. The two compounds were mixed in a two to one ratio of amine to diester with no solvent present and refluxed for twenty hours. Distillation of the crude product resulted in the recovery of approximately fifty percent of the starting diester plus a slight amount of a higher boiling fraction. This latter material is assumed to be the amide formed by attack of the iso-butylamine on one of the ester groups of diethyl 1,1-cyclopropanedicarboxylate.

\[
\text{CO}_2\text{C}_2\text{H}_5 + \text{i-C}_4\text{H}_9\text{NH}_2 \rightarrow \begin{array} {c} \text{CO}_2\text{C}_2\text{H}_5 \end{array} \begin{array} {c} \text{C-NH(i-C}_4\text{H}_9) \end{array}
\]

VIII

This assignment of structure is based on elemental and spectral analysis. The infrared spectrum shows two carbonyl absorptions, one for the ester (\(5.85 \mu\)) and one for the amide (\(6.02 \mu\)) function, together with an amide II band at \(6.50 \mu\), all of which give justification for postulating the structure indicated above. By keeping reaction conditions the same, but adding a few drops of Triton B (benzyltrimethyl ammonium hydroxide) as a catalyst, no new product was obtained and the only consequence was a higher yield of VIII.

Much more difficulty was encountered in isolating products from reactions employing cyclohexylamine as the nucleophile. These products
were consistently oils from which products could be separated only by distillation under very low pressure. None of the compounds were basic enough to be extracted from the oil with dilute acid, which indicated that the reaction which took place must have, once again, involved amidization of one or more ester groups rather than opening of the cyclopropane ring by addition, since in the latter case a basic compound would be expected. Finally, from this reaction of cyclohexylamine with the cyclopropane diester, two products were isolated for which a monoamide and di-amide structure have been tentatively assigned:

\[
\begin{align*}
\text{(CONHR)}_2 + \text{C}_x \text{H}_y \text{O}_z & \quad \text{R} = \text{Cyclohexyl} \\
\text{R} = \text{Cyclohexyl} & \quad \text{CO}_2 \text{C}_x \text{H}_y
\end{align*}
\]

The failure to cleave the cyclopropane ring by either iso-butylamine or cyclohexylamine under conditions comparable to those in which ring opening did occur with secondary amines led to the conclusion that this desired ring-opening addition would require more severe conditions. In order to avoid the amidization reaction, conditions were changed to favor higher temperatures and the presence of absolute ethanol. It was felt these conditions should hinder amidization since reactions of this nature are usually exothermic and hence, would be favored by low temperatures. Also, according to Le Chatelier's principle, an excess of ethanol should favor the ester.

Accordingly, n-butylamine, which gave the same results as iso-butylamine and cyclohexylamine under the conditions just discussed, was treated with diethyl 1,1-cyclopropanedicarboxylate in the presence of absolute alcohol. These reactants were subjected to temperatures of 150° for a period of twenty hours. Isolation of products by distillation
once again gave only unreacted starting diester and the type of amides already described as formed by attack of the primary amine on the ester groups. Catalysis by Triton B had no apparent effect on these reactions run at 150°.

The failure of these 1,1-disubstituted cyclopropanes to undergo ring-opening addition reactions with primary amines as compared to the successful additions with secondary amines can best be ascribed to the difference in basicity or nucleophilic strength of the two classes of amines. It is felt that further work, perhaps with stronger basic catalysts, should result in the development of conditions whereby these reactions could be successfully performed.
EXPERIMENTAL

**Diethyl 1,1-cyclopropanedicarboxylate.**—A. Most successful preparations followed the method described by Dox and Yoder\(^{15}\) and resulted in yields of 40-50 percent. The highest yield was obtained when the product was collected by distillation at reduced pressure; however, in this case it was more highly contaminated with unreacted diethyl malonate. B.p. 111-115\(^\circ\) (20 mm.), 201-203\(^\circ\) (690 mm.), \(n^\circ_{D} 1.4315\), \[lit.\(^{15}\) b.p. 214-216\(^\circ\) (748 mm.)\]. A new method of purification was developed to remove the last of the diethyl malonate. The impure cyclopropane diester containing some diethyl malonate was mixed with an amount of n-butylamine estimated to provide a slight molar excess over the amount of diethyl malonate believed to be present. This mixture was then heated at reflux temperature for a period of 2 hr., followed by thorough cooling. A solid precipitated at this point and was separated by filtration. The filtrate was then distilled to give the purified diethyl 1,1-cyclopropanedicarboxylate, b.p. 120-125\(^\circ\) (22 mm.), \(n^\circ_{D} 1.4350\).

The solid, \(\text{CH}_2(\text{CONC}_9\text{H}_4)_2\), formed by reaction of the diethyl malonate impurity, was recrystallized from ethyl acetate, m.p. 131-133\(^\circ\), \[lit.\(^{24}\) m.p. 130\(^\circ\).\]

**Anal.** Calcd. for \(\text{C}_{11}\text{H}_{20}\text{O}_2\cdot\text{N}_2\): C, 61.63; H, 10.37

Found: C, 61.34; H, 10.25

**B.** The following procedure describes an unsuccessful attempt to improve the yield in the preparation of this compound: The apparatus

\(^{a}\text{Carbon, hydrogen and nitrogen analyses were done by Galbraith Laboratories, Inc., Knoxville, Tennessee.}\)
used in this experiment consisted of a three-necked flask equipped with dropping funnel, argon inlet, reflux condenser and magnetic stirrer. A sodium ethoxide solution was prepared in an argon atmosphere by dissolving 14.3 g. (0.622 mole) of sodium in 180 ml. of absolute ethanol. This mixture was then heated to boiling, followed by the dropwise addition of 49.6 g. (0.310 mole) of diethyl malonate with continuous stirring. When addition was complete, the flask was maintained at 80°C for 30 min. Upon cooling, a white solid precipitated which was assumed to be principally the disodium salt of diethyl malonate. This was removed by filtration and washed with petroleum ether. After air drying for 10 min., the solid material was returned to the original flask and dissolved in 100 ml. of dimethylformamide. The flask was then heated to 90°C and 56.4 g. (0.310 mole) of ethylene bromide was added dropwise with stirring. This mixture was maintained at 90°C with stirring for 15 hr. Cooling resulted in the separation of a small amount of solid which was removed by filtration. DMF was distilled from the filtrate under reduced pressure followed by distillation of the remaining crude product, b.p. range between 90°C and 120°C (20 mm.). A second distillation of this fraction did not give a distinct boiling point and the refractive indices of both an initial and a final cut were well below that of the desired product.

Ethyl 1-cyanocyclopropane-1-carboxylate.--Two methods proved successful for the synthesis of this compound, both involving modifications of the reaction of ethyl cyanoacetate with ethylene bromide in the presence of sodium ethoxide: A. This method essentially followed the procedure set forth by Jones and Scott. The title compound was obtained in 80% yields, b.p. 115-118°C (15 mm.), nD 1.4339, [lit. b.p. 212-216°C (760 mm.)]. The same purification procedure was employed as
described for the diester. The solid amide, \((\text{CNCH}_2\text{CONHC}_4\text{H}_9)\), formed by reaction of the ethyl cyanoacetate impurity with n-butylamine, was recrystallized from \(\text{CCl}_4\), m.p. 70-71°, \([\text{lit. m.p. 73°}]\). The purified cyanoester distilled at 110° (10 mm.), \(n^{20}D 1.4380\).

B. The apparatus employed in this experiment was the same as that used in section B, page 32: A solution of sodium ethoxide was prepared by dissolving 14.3 g. (0.622 mole) of sodium in 200 ml. of absolute ethanol in an argon atmosphere. When solution was complete, the flask was heated to 80°C and 33.9 g. (0.300 mole) of ethyl cyanoacetate was added dropwise with continuous stirring. A white solid, assumed to be the sodium salt of ethyl cyanoacetate, separated and, after the flask had been cooled, was removed by filtration. This salt was washed with petroleum ether, after which it dried rapidly and then was placed in a vessel capable of being attached by a Gooch rubber connector to one neck of a three-necked flask. In the original three-necked flask was placed 56.4 g. (0.300 mole) of ethylene bromide and 100 ml. of absolute ethanol. This flask was then heated to 80°C and the solid isolated previously was added in small increments, accompanied by stirring. When addition was complete, heating and stirring were continued for 4 hr. After cooling of the flask, sodium bromide was filtered off and most of the alcohol was removed by distillation. At this point a small amount of water was added to dissolve the solid which had separated. The mixture was then extracted with ether, and the ether layer was washed twice with water and dried over anhydrous calcium chloride. The ether was stripped at reduced pressure and distillation of the remaining crude product gave 18.1 g. (43.5%) of product boiling between 95° and 100° (5 mm.), \(n^{20}D 1.4343\).
Cyclopropane-1,1-dicarboxamide. — A mixture of 18.5 g. (0.100 mole) of diethyl 1,1-cyclopropanedicarboxylate in 120 ml. of conc. aqueous ammonia was shaken for 48 hr., and then was allowed to stand for an additional 12 hr. At this point 3.0 g. of the desired amide was separated by filtration. The mother liquor was then subjected to two successive stages of evaporation to half its volume, followed by cooling and filtration of any solid formed. This treatment gave an additional 2.5 g. of the cyclopropane diamide. Hence, a total of 5.5 g. (43%) of the desired product was obtained which was best recrystallized from water, m.p. 194-195°, \([\text{lit.}^5 \text{ m.p. 192-194}^\circ]\).

1-Cyanocyclopropane-1-carboxamide. — A solution of 62.2 g. (0.447 mole) of ethyl 1-cyanocyclopropane-1-carboxylate and 250 ml. of conc. aqueous ammonia was shaken for 5 hr. and then was allowed to stand for an additional 24 hr. Filtration of the mixture gave 10.5 g. of the desired solid product. Evaporation of the filtrate to half its original volume, followed by cooling and filtration, resulted in isolation of 10 g. more of the cyanoamide; the total yield then being 20.5 g. (41%). Recrystallization from water gave a purified product, m.p. 158-160°, \([\text{lit.}^6 \text{ m.p. 160}^\circ]\).

Cyclopropane-1,1-dicarbonitrile. A. By dehydration of 1-cyanocyclopropane-1-carboxamide. — 1-Cyanocyclopropane-1-carboxamide, 7.0 g. (0.064 mole), was thoroughly mixed with 11.4 g. (0.080 mole) of phosphorus pentoxide and heated in a vacuum distillation apparatus. A reaction began when the temperature reached 155° (10 mm.) and 3.0 g. of crude product distilled between 160 and 210°. Extreme swelling of the reactants occurred which necessitated the discontinuation of heating at this latter temperature. Redistillation of the crude product gave 2.0 g. (34%) of the dinitrile with
b.p. 90° (10 mm.), n\textsuperscript{20}D 1.4491.

Anal. Calcd. for C\textsubscript{6}H\textsubscript{4}N\textsubscript{2}: C, 65.20; H, 4.37

Found: C, 65.42; H, 4.46

B. Attempted preparation of cyclopropane-1,1-dicarbonitrile by direct condensation in the presence of sodium ethoxide and absolute alcohol.—A solution of sodium ethoxide was prepared under an argon atmosphere by dissolving 12.6 g. (0.548 mole) of sodium in 225 ml. of absolute ethanol and was immediately transferred to a dropping funnel. Into a three-necked flask equipped with the dropping funnel, a mechanical stirrer, reflux condenser and argon inlet was placed 50.8 g. (0.270 mole) of ethylene bromide and 18 g. (0.270 mole) of malononitrile. The flask was then heated to 80° followed by the dropwise addition of the sodium ethoxide solution with stirring under an argon atmosphere. After heating for 4 hr., most of the alcohol was removed by distillation. The residue that remained was somewhat basic and was neutralized with conc. hydrochloric acid. This was followed by the addition of a small amount of water and an attempted extraction of the desired product with ether. Only a negligible amount of material remained after the ether was stripped under reduced pressure.

Reaction of cyclopropane-1,1-dicarbonitrile with piperidine.

In a small Erlenmeyer flask was placed 5.6 g. (0.061 mole) of cyclopropane-1,1-dicarbonitrile, 15.5 g. (0.183 mole) of piperidine and 40 ml. of benzene. The flask was flushed with argon, tightly sealed and allowed to stand at room temperature for 4 hr., during which time a colored layer separated. Water was added and the organic layer was separated, washed with water and dried over anhydrous calcium chloride.
Upon removal of the benzene by distillation, an oil remained which could not be recrystallized or distilled. However, it was converted to a hydrochloride by dissolving approximately 3 ml. of the material in ether and passing into it dry hydrogen chloride gas. The solid which separated was recrystallized from absolute ethanol, m.p. 189-190°. A carbon and hydrogen analysis was obtained for this compound which disagreed with the values calculated for any product formed by the single addition of piperidine to cyclopropane-1,1-dicarbonitrile.

Reaction of diethyl 1,1-cyclopropanedicarboxylate with secondary amines: A. With piperidine.--Diethyl 1,1-cyclopropanedicarboxylate was heated at reflux temperature with piperidine both with and without a solvent and in varying molar ratios, usually for a period of 20 hr. (Infra. Table I, p. 21). Temperatures naturally were dependent on the solvent employed. After removal of the solvent by distillation, the residue was distilled under reduced pressure. The product, diethyl \( \beta \)-piperidinoethylmalonate, was collected between 123-125° (0.5 mm.), \( n^{20}D 1.4595 \) [lit. 19 b.p. 128-132° (1.6 mm.), \( n^{20}D 1.4625 \)].

B. With piperidine in DMF.--A mixture of 4.2 g. (0.023 mole) of diethyl 1,1-cyclopropanedicarboxylate, 3.9 g. (0.046 mole) of piperidine and 15 ml. of DMF was placed in a flask equipped with a reflux condenser and heated at 147°C for 20 hr. Following the distillation of DMF under reduced pressure, two higher boiling fractions were collected: (1) assumed to be \( \text{C}_n\text{H}_{26}\text{N}_2\text{O}_3 \) b.p. 72-73° (1 mm.), \( n^{20}D 1.4777 \). Anal. Calcd. for \( \text{C}_n\text{H}_{26}\text{N}_2\text{O}_3 \): C, 62.18; H, 9.71; Found: C, 61.93; H, 9.78

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(2) assumed to be $\text{N}-\text{CH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$ – b.p. 178-182° (1 mm.), n$^\text{D}$ 1.4872.

**Anal. Calcd. for C$_{14}$H$_{27}$N$_3$O$_2$:** C, 62.40; H, 10.12

**Found:** C, 63.17; H, 9.80

C. With diethylamine. – Into a flask equipped with a water condenser was placed 4.2 g. (0.023 mole) of diethyl 1,1-cyclopropanedicarboxylate, 1.5 g. (0.023 mole) of diethylamine and 15 ml. of absolute ethanol. The mixture was heated at reflux temperature for 72 hr. After the solvent was removed by distillation at atmospheric pressure, further distillation gave a crude product boiling between 90-105° (0.4 mm.). Redistillation gave 1.7 g. (29%) of colorless liquid, diethyl $\beta$-diethylaminoethylmalonate, b.p. 101° (0.3 mm.), n$^\text{D}$ 1.4391 [lit.$^\text{19}$ b.p. 128-130° (4 mm.) n$^\text{D}$ 1.4385].

**Conversion of diethyl $\beta$-piperidinoethylmalonate to the corresponding diamide.** – This procedure follows the general method described by Russell$^\text{26}$ for amidization of malonic esters. A solution of 5.0 g. (0.018 mole) of the ester in 25 ml. of methanol was added to a solution prepared by saturating 50 ml. of methanol with ammonia at 0°C. A solution of sodium methoxide, prepared from approximately 0.1 g. sodium, was then added and the mixture was allowed to stand at room temperature for 72 hr. Very few crystals formed during this period but cooling caused the immediate separation of 1.0 g. of product. Evaporation of the mother liquor gave an additional 1.5 g. of solid. The 2.5 g. (64%) of $\beta$-piperidinoethylmalonamide thus obtained was recrystallized from absolute alcohol, m.p. 194-195° (dec.). This compound has not been previously reported in the literature.

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Reaction of $\beta$-piperidinoethylchloride with diethyl malonate.

This procedure essentially follows that set forth by H. Goldhahn.\textsuperscript{19} The apparatus consisted of a three-necked flask equipped with dropping funnel, stirrer and reflux condenser. A solution of sodium ethoxide was prepared in an argon atmosphere by adding 0.65 g. (0.028 mole) of sodium to 25 ml. of absolute ethanol. When the flask had cooled to room temperature, 4.5 g. (0.028 mole) of diethyl malonate was added dropwise with stirring followed immediately by the dropwise addition of 4.2 g. (0.026 mole) of $\beta$-piperidinoethylchloride. The mixture was then heated to 80$^\circ$C and maintained at that temperature with stirring for 3 hr. After cooling, a small amount of water was added, followed by extraction of the product with ether and washing of the ether solution twice with water. The ether extract was then dried over anhydrous magnesium sulfate. After the ether was stripped under reduced pressure, 2.0 g. (28\%) of diethyl $\beta$-piperidinoethylmalonate was collected by distillation between 135-140$^\circ$ (2 mm.), $n^{\text{D}}_20 1.4555$ \text{[lit.}\textsuperscript{19} b.p. 128-132$^\circ$ (1.6 mm.), $n^{\text{D}}_20 1.4625$].

Reaction of cyclopropane-1,1-dicarboxamide with piperidine.

In a flask equipped with a reflux condenser was placed 20 ml. of absolute alcohol, 3.0 g. (0.023 mole) of cyclopropane-1,1-dicarboxamide, and 4.0 g. (0.047 mole) of piperidine. The flask was heated on a steam bath for 100 hr., following which the product mixture was cooled and filtered. A crude yield of 2.2 g. (45\%) of solid $\beta$-piperidinoethylmalonamide was separated and recrystallized from absolute alcohol, m.p. 194-196$^\circ$.

Reaction of ethyl 1-cyanocyclopropane-1-carboxylate with piperidine.

This reaction has been run either in absolute ethanol or without a solvent.

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**Anal.** Calcd. for $\text{C}_{10}\text{H}_{19}\text{N}_3\text{O}_2$: C, 56.30; H, 9.00

Found: C, 56.36; H, 9.01
Either equimolar ratios or a 2-1 ratio of reactants favoring the amine were employed and the mixtures were heated at reflux temperature for a period of 20 hr. Distillation under reduced pressure gave the product, ethyl 2-cyano 2-\(\beta\)-piperidinoethyl) acetate, as a colorless liquid, b.p. 124-126° (1 mm.), \(n^{25}_D\) 1.4643. Yields varied somewhat with the exact conditions used but never exceeded 25%.

Reactions of piperidinoethyle chloride with ethyl cyanoacetate.
The apparatus used consisted of a three-necked flask equipped with stirrer, dropping funnel, reflux condenser and argon inlet. A solution of sodium ethoxide was prepared in an argon atmosphere by adding 0.5 g. (0.022 mole) of sodium to 25 ml. of absolute ethanol. When the solution had cooled, 2.8 g. (0.025 mole) of ethyl cyanoacetate was added dropwise with stirring followed immediately by the dropwise addition of 3.2 g. (0.022 mole) of \(\beta\)-piperidinoethyl chloride. The mixture was heated at reflux temperature for 2 hr., followed by removal of most of the alcohol under slightly reduced pressure. Sufficient water was added to dissolve the solid present, and the desired product was then extracted with ether, water washed and dried over anhydrous calcium chloride. Ether was removed under reduced pressure and the remaining residue was distilled to give 1.5 g. (30%) of ethyl 2-cyano 2-\(\beta\)-piperidinoethyl) acetate, b.p. 138° (2 mm.), \(n^{20}_D\) 1.4637.

**Anal. Calcd. for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\): C, 64.24; H, 9.00**

**Found: C, 64.29; H, 9.21**

Conversion of ethyl 2-cyano 2-\(\beta\)-piperidinoethyl) acetate to the corresponding amide.--A mixture of 3.0 g. (0.014 mole) of ethyl 2-cyano 2-\(\beta\)-piperidinoethyl) acetate and 10 ml. of conc. aqueous ammonia was shaken constantly for 15 min. Since there was no apparent reaction, an

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additional 10 ml. of the aqueous ammonia was added, followed by shaking for an additional 10 min. A solid precipitated during this latter period of agitation and was separated by filtration. After recrystallization from ethyl acetate, 1.0 g. (37%) of the previously unreported amide, 2-cyano 2-((B-piperidinoethyl) acetamide, was obtained, m.p. 128-130°.

Anal. Calcd. for C_{10}H_{17}N_{3}O: C, 61.49; H, 8.79

Found: C, 61.25; H, 8.61

Reaction of 1-cyanocyclopropane-1-carboxamide with piperidine.—
A mixture of 4.2 g. (0.038 mole) of 1-cyanocyclopropane-1-carboxamide, 6.5 g. (0.076 mole) of piperidine and 30 ml. of absolute ethanol was placed in a flask equipped with a reflux condenser and heated on the steam bath for 24 hr. After removal of most of the alcohol, a white solid precipitated, which on recrystallization from ethyl acetate gave 3.6 g. (49%) of 2-cyano 2-((B-piperidinoethyl) acetamide, m.p. 126-128°.

Reaction of diethyl 1,1-cyclopropanedicarboxylate with primary amines: A. At reflux temperature of solvent or amine.—Several reactions were carried out in this general category, the procedure being to combine the amine and diester in a 1:1 or 2:1 molar ratio followed by a heating period of from 6-50 hr. In several runs a catalyst of either sodium methoxide or Triton B was added. No products could be extracted with dilute acid, hence, it was necessary to isolate them by vacuum distillation. These products, which have been obtained in yields of less than 20%, have all proven to be amides containing an unopened cyclopropane ring which are characterized as follows:
(1) Product with n-butylamine — assumed to be \( \text{C}=\text{NH(N-(Bu)} \), 
\( \text{b.p. 115-120}^\circ (1 \text{ mm.}), \) \( n_{D}^{24} 1.4588 \).

**Anal.** Calcd. for \( C_{11}H_{19}NO_{3} \): C, 61.93; H, 9.00; N, 6.57

Found: C, 60.42; H, 8.93; N, 6.31

(2) Product with i-butylamine — assumed to be \( \text{C}=\text{NH(i-Bu)} \), 
\( \text{b.p. 105-108}^\circ (1 \text{ mm.}), \) \( n_{D}^{27} 1.4572 \).

**Anal.** Calcd. for \( C_{11}H_{19}NO_{3} \): C, 61.93; H, 9.00

Found: C, 61.90; H, 9.05

(3) With cyclohexylamine two amide products were obtained:

(a) mono-amide — assumed to be \( \text{C}=\text{NH(C}_{6}\text{H}_{11}) \), 
\( \text{b.p. 165-172}^\circ (1 \text{ mm.}), \) \( n_{D}^{24} 1.4944 \).

**Anal.** Calcd. for \( C_{13}H_{21}NO_{3} \): C, 65.23; H, 8.86

Found: C, 65.11; H, 8.96

(b) di-amide — assumed to be \( \text{C}=\text{NH(C}_{6}\text{H}_{11}) \), 
\( \text{m.p. 130-132}^\circ \) (recrystd. from 3:1 water-ethanol).

**Anal.** Calcd. for \( C_{17}H_{28}N_{2}O_{2} \): C, 69.80; H, 9.67

Found: C, 69.76; H, 9.46

B. Reactions carried out at \( 150^\circ \).—The reactants were mixed in exactly the same manner as described in part A, but in this case, they were sealed in a large test tube and placed in a bomb where the temperature was maintained at \( 150^\circ \) for 20 hr. Under these conditions, however, n-butylamine was the only nucleophile employed. Results from reactions run at this temperature are identical with those described for n-butylamine in the preceding section.
SUMMARY

a. Attempts were made to improve established methods of preparing diethyl 1,1-cyclopropanedicarboxylate and ethyl 1-cyanocyclopropane-1-carboxylate from the standpoint of yield and purity of product. A method was found to improve the purity of these esters, but no success was achieved in gaining larger yields.

b. Cyclopropane-1,1-dicarbonitrile was prepared by the dehydration of 1-cyanocyclopropane-1-carboxamide with phosphorus pentoxide.

c. The feasibility of opening the ring of certain 1,1-disubstituted cyclopropanes by the nucleophilic addition of an amine has been investigated. It was found that the cyclopropane ring in four of the five compounds used could be cleaved by addition of secondary amines. However, all attempts to open the ring of these compounds using a primary amine as the nucleophile were unsuccessful.
BIBLIOGRAPHY


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