1-ALKOXYVINYL ESTERS

AS SYNTHETIC INTERMEDIATES

by

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ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. D. Cohen, for his valuable guidance, Professor H.D. Springall for the provision of laboratory facilities, and the University of Keele for financial support.

All the experimental work reported in this thesis was carried out by the author, under the supervision of Dr. D. Cohen.

ABSTRACT

The chemistry and properties of 1-alkoxyvinyl esters and of cyclopropanones are reviewed.

A number of 1-ethoxyvinyl esters have been isolated, both for their intrinsic interest and also because of their value as synthetic intermediates.

Phthaloyl and 4-nitrophthaloyl derivatives of amino-acid esters have been prepared by reaction of phthalic acid or 4-nitrophthalic acid with ethoxyacetylene (without isolation of the corresponding di-1-ethoxyvinyl esters), in the presence of the corresponding amino-acid ester hydrochloride. Reaction of maleic acid and succinic acid with ethoxyacetylene under the same conditions, however, has yielded only the corresponding maleamic or succinamic acid.

1-Ethoxy-2-ethoxycarbonylcyclopropyl carboxylates (2-ethoxycarbonylcyclopropanone acylals) have been prepared by the thermal decomposition of ethyl diazoacetate, catalysed by anhydrous copper sulphate, in the presence of an excess of the corresponding 1-ethoxyvinyl ester. When 1-ethoxyvinyl thiolacetate was used in this reaction, however, the product was a nitrogen containing compound, to which a pyrazoline structure has been tentatively assigned.

Experiments with 1-ethoxyvinyl esters, methylene di-iodide and zinc-copper couple yielded products which could not be successfully purified

Conversion of the 2-ethoxycarbonylcyclopropanone acylals to 2-ethoxycarbonylcyclopropanone was attempted using a variety of conditions. However, in every case, only products arising from ring cleavage reactions were obtained. An interesting boron trifluoride-catalysed rearrangment to the corresponding acyl (or aroyl) succinic acid ester was observed.

CONTENTS

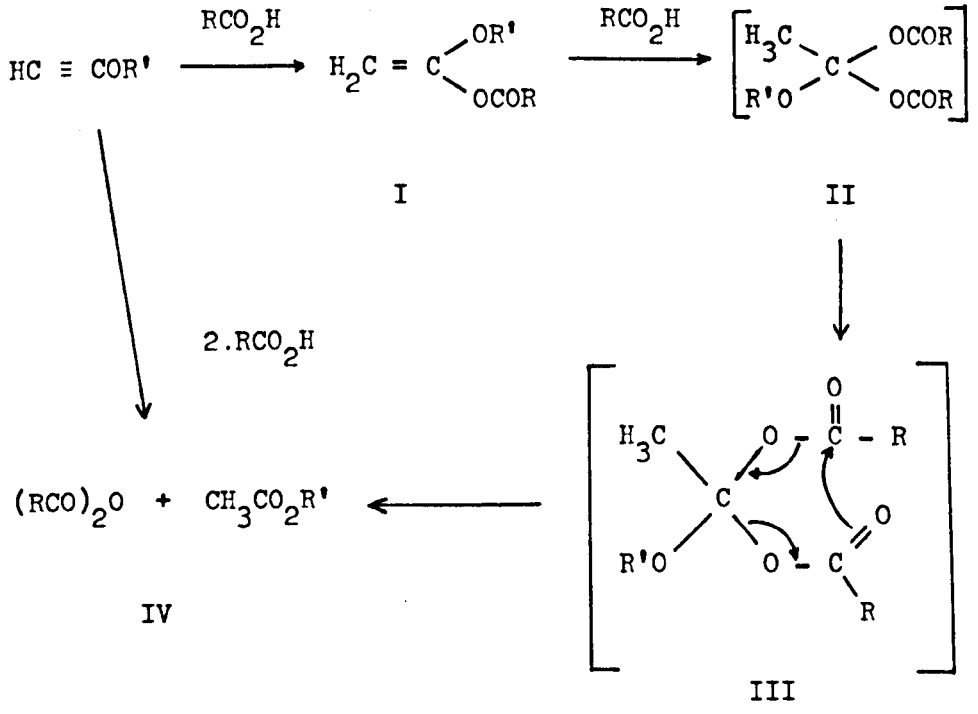
PART I

I. 1-ALKOXYVINYL ESTERS

A. Introduction and Preparation of 1-Alkoxyvinyl Esters.

The reaction of ethoxyacetylene with hydroxylic acids was first studied by Arens,[1,2] in 1950, and then by Eglinton, Jones and co-workers,[3] in 1954. It was found that when two moles of acid were reacted with one mole of ethoxyacetylene at, or below, room temperature, the corresponding anhydride was formed in high yield; the only other product being ethyl acetate. The reaction was carried out with a large number of carboxylic acids and also successfully applied to the syntheses of toluene-p-sulphonic anhydride and diethylpyrophosphate from the corresponding acids.

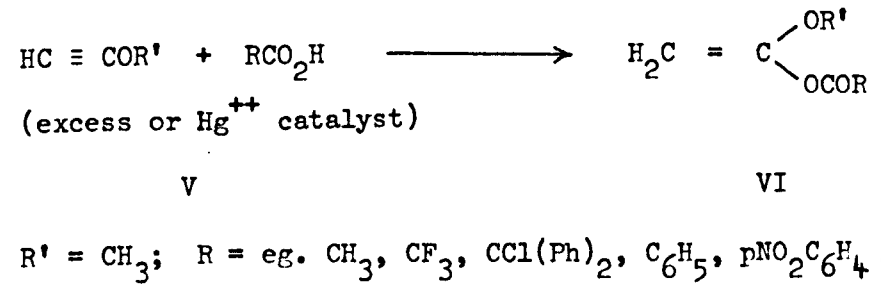
Arens postulated that the reaction proceeded by way of an intermediate 1-alkoxyvinyl ester (I) formed by addition of one mole of acid to one mole of ethoxyacetylene. This was then converted, by reaction with a second mole of acid, into the unstable intermediate 1-alkoxyethylidene diester (II) which decomposed, via the six-membered cyclic transition state (III), to give the corresponding anhydride (IV) and an acetic acid ester (Scheme 1).



Scheme 1

Early attempts to isolate the intermediate 1-alkoxyvinyl ester (I) in the case of the reaction of acetic acid with ethoxyacetylene were unsuccessful when either an equimolar amount,[3] or an excess[1] of ethoxyacetylene were used. However, the 1-ethoxyvinyl esters of trichloroacetic acid and dichloroacetic acid were prepared by addition of the acid to ethoxyacetylene (the reverse addition procedure to that used for anhydride preparation), although monochloroacetic acid was converted to its anhydride under these conditions.[4]

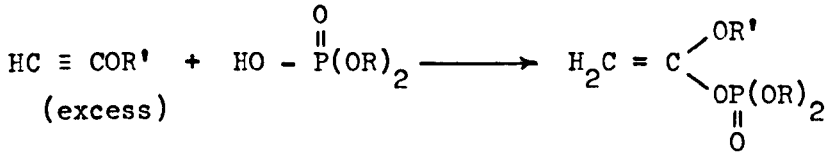
More recently Wasserman has reported general methods for the preparation of 1-alkoxyvinyl esters.[5] Using either an excess of methoxyacetylene (V, R' = CH_3) or employing the known catalytic effect of mercuric ions on reactions involving additions to the acetylenic linkage, Wasserman synthesized a variety of 1-methoxyvinyl esters (VI, R' = CH_3) (Scheme 2). The actual excess of methoxyacetylene used varied from a slight excess with trifluoroacetic acid to a near fifty-fold excess with acetic acid: the unreacted methoxyacetylene, however, could easily be recovered by distillation. For large scale preparations



Scheme 2

a mercuric salt as catalyst is particularly useful. The method used was to treat the acid (1 mole) with methoxyacetylene (2 to 3 moles) in dilute methylene dichloride (ca. 0.1 molar in acid) in the presence of a mercuric salt (0.02 mole), preferably the salt of the acid used. Under these conditions only very small amounts of the corresponding anhydrides were formed and the yields of 1-methoxyvinyl esters, obtained after removing the catalyst and any anhydride by distillation or crystallisation, ranged from 66 - 98%.

Using this technique, 1-alkoxyvinyl esters of hydroxylic acids, other than carboxylic acids, have been prepared. The formation of the 1-alkoxyvinyl phosphates (VII, R' = C_2H_5; R = C_6H_5, $C_6H_5 \cdot CH_2$, p-NO_2-C_6H_5) has been demonstrated by spectral analysis and by chemical reaction, and in two cases (VII, R' = C_2H_5; R = C_6H_5, $C_6H_5 \cdot CH_2$) analytical samples were obtained.[6,7] (Scheme 3)

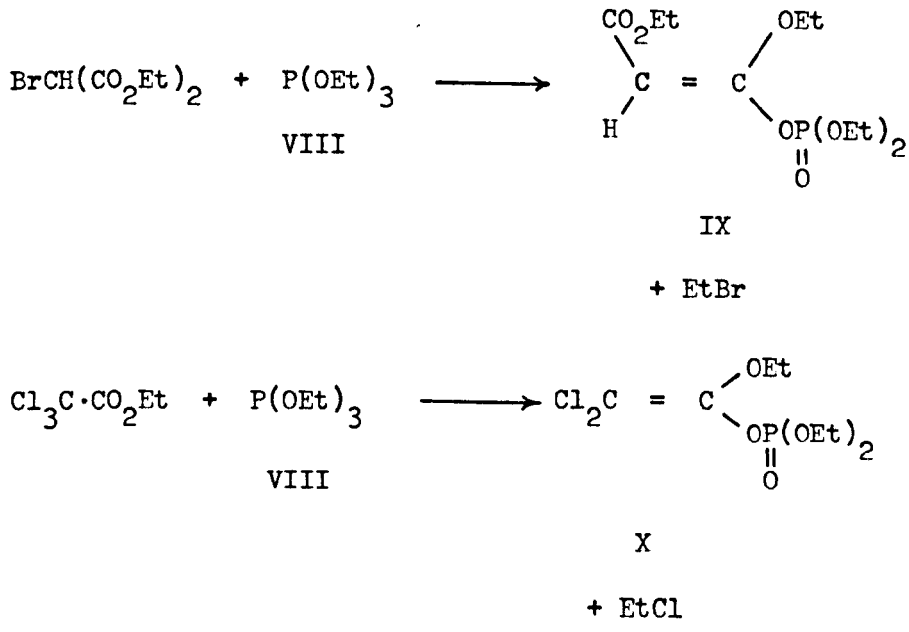


VII

R' = C_2H_5; R = C_6H_5, $C_6H_5CH_2$, $pNO_2 \cdot C_6H_4$.

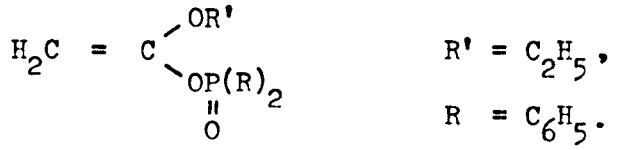
Scheme 3

Cramer[8,9] has reported the preparation of similar systems (IX, X) using the Perkow reaction between triesters of phosphorous acid and α-halo esters. In this way the compound (IX) was prepared from diethyl α-bromomalonate and triethyl phosphite (VIII);[8,9] and the compound (X) was prepared from trichloroacetic acid and triethyl phosphite.[9] (Scheme 4)



Scheme 4

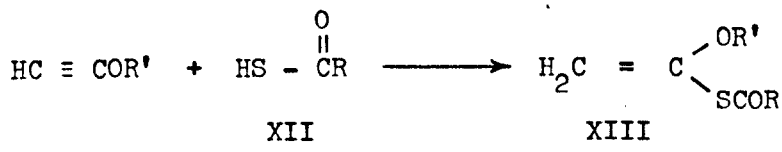
1-Ethoxyvinyl diphenylphosphinate (XI, R' = C_2H_5; R = C_6H_5) has also been prepared and characterised: the preparation and some properties of this compound are examined in the Experimental Discussion Section.



XI

Thiolacetic acid (XII, R = CH_3) and thiolbenzoic acid (XII, R = C_6H_5) when reacted with ethoxyacetylene have yielded the corresponding

1-alkoxyvinyl thiolesters (XIII, R = CH_3, C_6H_5, R' = C_2H_5).[10] (Scheme 5) The reproducibility of these reactions is in some doubt, however, as the

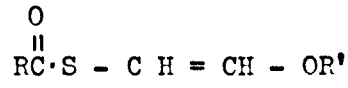


XII XIII

R = CH_3, C_6H_5; R' = C_2H_5

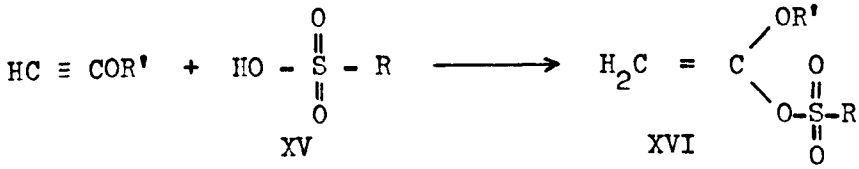
Scheme 5

anti-Markownikoff addition product (2-alkoxyvinyl ester; XIV; R = CH_3, C_6H_5; R' = C_2H_5) is also formed in some cases, and may even be the major product. (Work on this subject is treated fully in the Experimental Discussion Section).



XIV

Sulphonic acids (XV) have been reacted with ethoxyacetylene to yield anhydrides without the isolation of the intermediate 1-ethoxyvinyl esters (XVI, R' = C_2H_5).[2,3] Banks[11] has shown, by infrared spectral analysis and by chemical reaction with nucleophiles, that the 1-alkoxyvinyl esters (XVI, R = CH_3, C_6H_5; R' = C_2H_5) are formed when the sulphonic acids (XV, R = CH_3, C_6H_5) are reacted with an excess of ethoxyacetylene; although they proved to be too unstable for satisfactory analyses to be obtained. (Scheme 6)

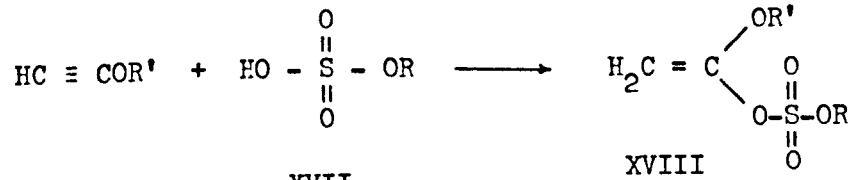


XV XVI

$R = CH_3$, C_6H_5; $R' = C_2H_5$.

Scheme 6

Similarly, evidence has been obtained showing that 1-alkoxyvinyl esters (XVIII, $R = CH_2C_6H_5$, CH_2CH_2CN; $R' = C_2H_5$) are formed in the reactions of the sulphuric acids (XVII, $R = CH_2C_6H_5$, CH_2CH_2CN) with an excess of ethoxyacetylene.[12] (Scheme 7)



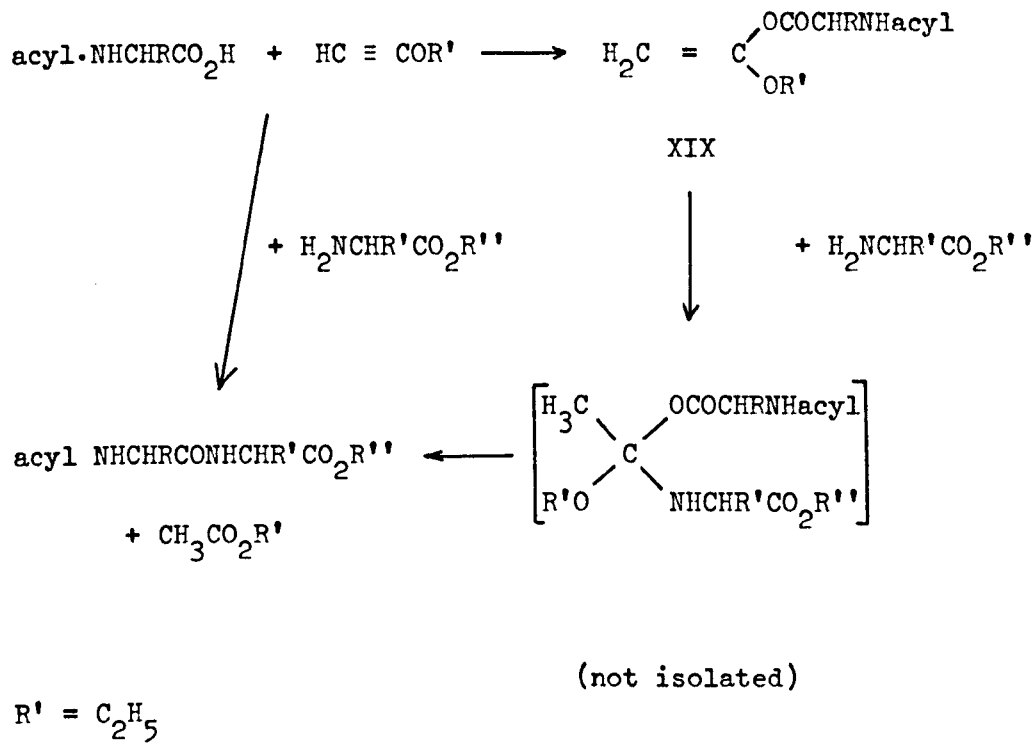
XVII XVIII

$R = C_6H_5CH_2$, $CNCH_2CH_2$; $R' = C_2H_5$.

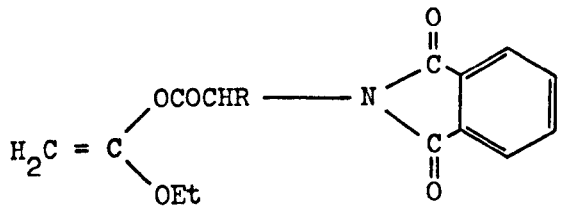
Scheme 7

Ethoxyacetylene has been used to form peptide links without isolation of reaction intermediates by reaction of an N-protected amino-acid with an amino-acid ester, in the presence of ethoxyacetylene.[13,14,15] A suggested mechanistic path for the reaction is <u>via</u> the intermediate 1-alkoxyvinyl ester (XIX, $R' = C_2H_5$). (Scheme 8)[14] When the N-protecting group is phthaloyl, the 1-alkoxyvinyl ester can be prepared easily, without the use of mercuric ion catalyst, but in the case of the benzyloxycarbonyl

protecting group, mercuric ion catalysis is necessary and the products are often contaminated with chemically bound mercury.[17]



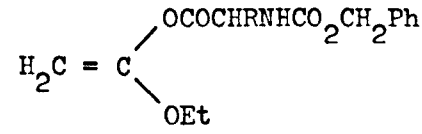
Scheme 8



R = H[16,17]

R = CH_3 (L and DL), $C_6H_5CH_2$ (L and DL)[17]

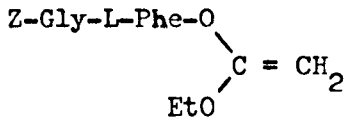
XX



R = H[17]

XXI

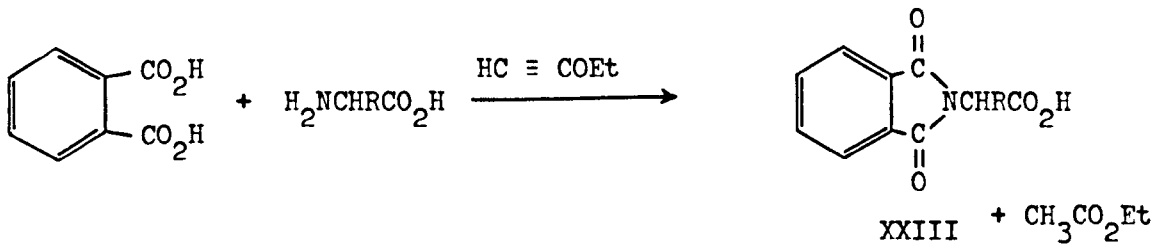
In one case,[18] the 1-ethoxyvinyl ester of a benzyloxycarbonyl protected dipeptide (XXII) has been prepared.



Z = $PhCH_2O_2C$

XXII

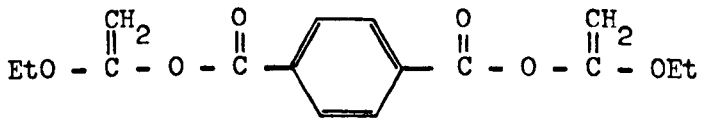
Phthalic acid (or its 4-nitro derivative) has been allowed to react with ethoxyacetylene in the presence of a number of amino-acids (or esters) to give the corresponding N-phthaloylamino-acids (XXIII) (or esters) in good yield, and under mild conditions.[19] (Scheme 9)



XXIII + CH_3CO_2Et

Scheme 9

This reaction can be formulated as proceeding through an intermediate di-1-ethoxyvinyl ester of the dicarboxylic acid but attempts to isolate this diester failed in the case of phthalic acid, although the di-1-ethoxyvinyl ester of terephthalic acid (XXIV) has been prepared.[19] (This topic is dealt with more fully in the Experimental Discussion Section).



XXIV

B. Properties of 1-Alkoxyvinyl Esters.

Physical and Chemical Properties:

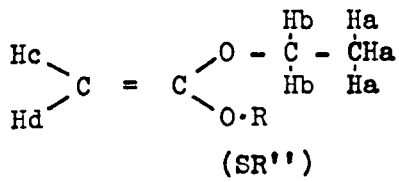
In general, 1-alkoxyvinyl esters are liquids, distillable under reduced pressure, or crystalline solids of fairly low melting point. They are thermally relatively stable, except that some esters, particularly those of keto-carboxylic acids, undergo a facile thermal rearrangement (see next section on "Rearrangements"). Although stable to atmospheric oxygen, 1-alkoxyvinyl esters are hydrolysed at differing rates by contact with moist air: esters of the phosphoric, phosphinic, sulphonic and sulphuric acid series being hydrolysed very rapidly whereas solid esters such as di-1-ethoxyvinyl terephthalate are relatively resistant to such hydrolysis. Rapid hydrolysis of all esters occurs in aqueous acid or alkaline solution.

Spectral Properties:

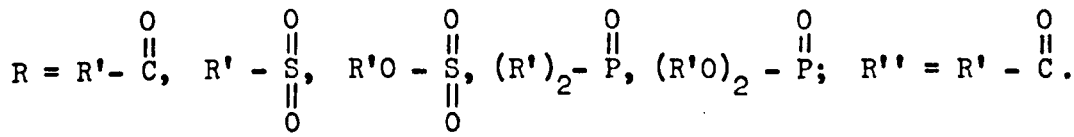
Typical members of the class are colourless, e.g. 1-methoxyvinyl acetate which shows no absorption in the Ultra-Violet spectrum at longer wavelengths than 210 mμ (with an ε greater than 200).[5]

The proton magnetic resonance spectrum of 1-ethoxyvinyl esters (XXV) shows a triplet for the methyl protons (Ha) of the ethoxy group, centred at about 8.7τ ($J \sim 7$ c.p.s.); a quartet for the methylene protons (Hb) of the ethoxy group, centred at about 6.1τ ($J \sim 7$ c.p.s.); and superimposed on the methylene quartet, are the absorptions of the

vinyl protons (Hc, Hd) which appear as an unsplit peak in some cases (e.g. the 1-ethoxyvinyl esters of some aliphatic carboxylic acids) but with a more complex splitting pattern in other cases. (See Experimental Discussion Section). (These results are for solution of approximately 10% in deuterochloroform using T.M.S. as internal standard).

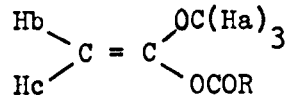


(SR'')



XXV

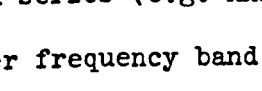
Wasserman and co-workers[20] have examined the p.m.r. spectra of a number of 1-methoxyvinyl esters (XXVI, R = CH_3, C_6H_5, CF_3) and report that the methoxy protons (Ha) absorb at about 5.4τ and the vinyl protons (Hb and Hc) appear as a typical AB quadruplet with the main peaks at about 5.25τ and 5.35τ with a coupling constant (J) of about 4 c.p.s. (These spectra were recorded in dilute carbon tetrachloride solution with reference to a benzene capillary. In order to transform these results into τ values the absorption of benzene has been taken as 2.60τ).



R = CH_3, C_6H_5, CF_3

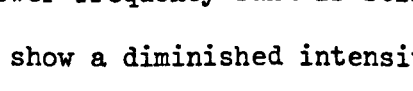
XXVI

The most useful single spectral characteristic of this class of compound is the infrared absorption. All the 1-alkoxyvinyl esters, studied to date, show two bands in the 1650 - 1780 cm^{-1} (6.06 - 5.62μ) region of the infrared; one below and one above 1700 cm^{-1}. The relative intensity of these two bands varies with the acid from which the ester is derived. The esters of carboxylic acids (e.g. XXVII), show two intense bands in this region, the upper frequency band being slightly more intense. This is also true of the thiolic esters (e.g. XXVIII) except that the lower frequency band is slightly more intense, in this case. In the phosphorus acid series (e.g. XXIX) the lower frequency band is still intense but the upper frequency band tends to show a diminished intensity, particularly in the case of 1-ethoxyvinyl diphenylphosphinate which shows a weak band in the upper-frequency region.



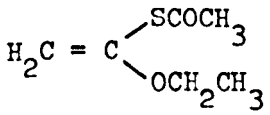
(1783 cm^{-1}, 1680 cm^{-1})

XXVII

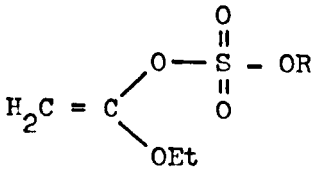


(1742 cm^{-1}, 1680 cm^{-1})

XXIX



(1720 cm^{-1}, 1680 cm^{-1})



(1725 cm^{-1}, 1650 cm^{-1})

XXVIII

The lower frequency absorption (1680 - 1650 cm^{-1}) can be assigned to the carbon-carbon stretching frequency of the ($H_2C = C\leq$) bond; and in the case of the carboxylic esters and the thiolic esters the upper frequency absorption (1780 - 1720 cm^{-1}) may be assigned to the carbon-oxygen stretching frequency of the ($\geq C=O$) bond. However, in the other cases the upper frequency absorption remains unassigned. In 1-substituted vinyl acetates[21] and keten acetals[22] the band characteristic of $\geq C=CH_2$ stretching appears at approximately 1670 cm^{-1} (6.0μ).

The variation in intensity of the lower frequency band ($\geq C=CH_2$), during reactions of 1-alkoxyvinyl esters, has been used both qualitatively and quantitatively in studies of these reactions.

C. Reactions of 1-Alkoxyvinyl Esters.

(i) With Nucleophiles:

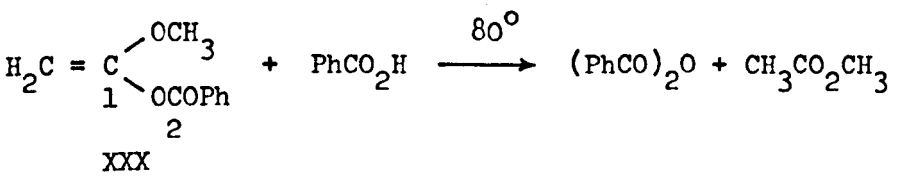
1-Alkoxyvinyl esters are very susceptible to nucleophilic attack and this has been utilised in many synthetic routes involving these esters as isolated or non-isolated intermediates. They can act as acylating,

phosphorylating, phosphinylating, sulphonating, sulphating agents, reacting with acids, alcohols, amines, etc., to yield the corresponding anhydride, ester, or amide. Synthetically these reactions have been widely used in the fields of nucleotide, co-enzyme and peptide chemistry. Reaction with a nucleophile, particularly a primary amine, has also been frequently employed as a means of preparing derivatives for the characterisation of some of the more unstable 1-alkoxyvinyl esters.

The reaction of an alkoxyacetylene with a hydroxylic acid to yield the corresponding anhydride (or pyrophosphate) has been mentioned previously. This reaction was postulated as proceeding *via* an intermediate 1-alkoxyvinyl ester and a number of these compounds have subsequently been isolated and found to react readily with one mole of hydroxylic acid to produce a symmetrical or unsymmetrical anhydride (or pyrophosphate).

Wasserman[23] has studied the mechanism of this reaction using 1-methoxyvinyl benzoate (XXX) and O^{18} labelled benzoic acid. The alternative pathways for the conversion of 1-methoxyvinyl benzoate to benzoic anhydride, considered by Wasserman, are shown in Scheme 10. Path A proceeds by nucleophilic attack at C_1 followed by decomposition of the intermediate 1-alkoxyethylidene diester (XXXI) *via* a cyclic intramolecular transition state: this mechanism was also postulated by Arens.[4] In path B, direct intermolecular acylation occurs similar to that postulated for the formation of anhydrides from the reaction of acids with

carbodiimides.[24] If benzoic acid, labelled with O^{18}, is used in this reaction then path A would result in an equal distribution of the excess O^{18} between benzoic anhydride and methyl acetate; whereas path B would yield methyl acetate containing none of the excess O^{18}. The results shown (Scheme 10) are those expected exclusively for anhydride formation by path A. Experiments were also performed, which ruled out the possibility of complete exchange of the benzoyloxy groups of 1-methoxyvinyl benzoate and labelled benzoic acid occurring.



XXX

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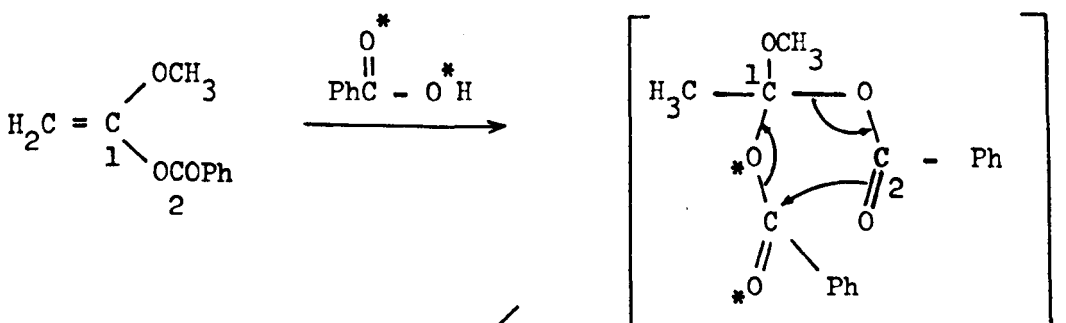
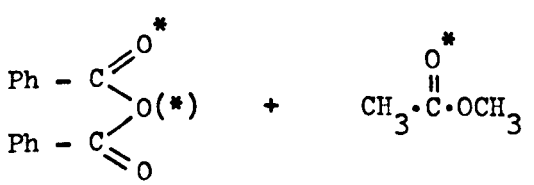
Path A (attack at C_1)



XXXI

(not isolated)



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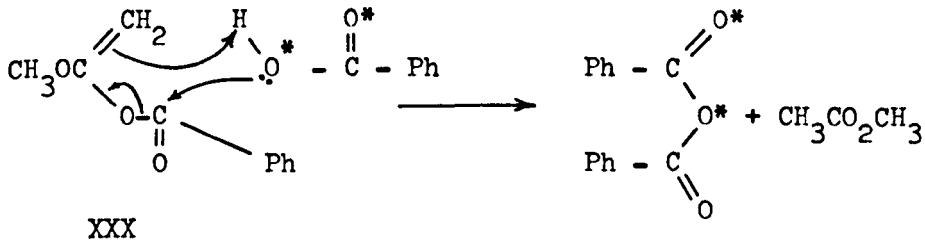
Path B (attack at C_2)



XXX

Excess O^{18} in $PhCO_2H$ (atom %) - 1.06

	Calc. for Path A	Calc. for Path B	Found
Anhydride	0.53	0.71	0.53
Ester Carbonyl	0.53	0.00	0.52

Scheme 10

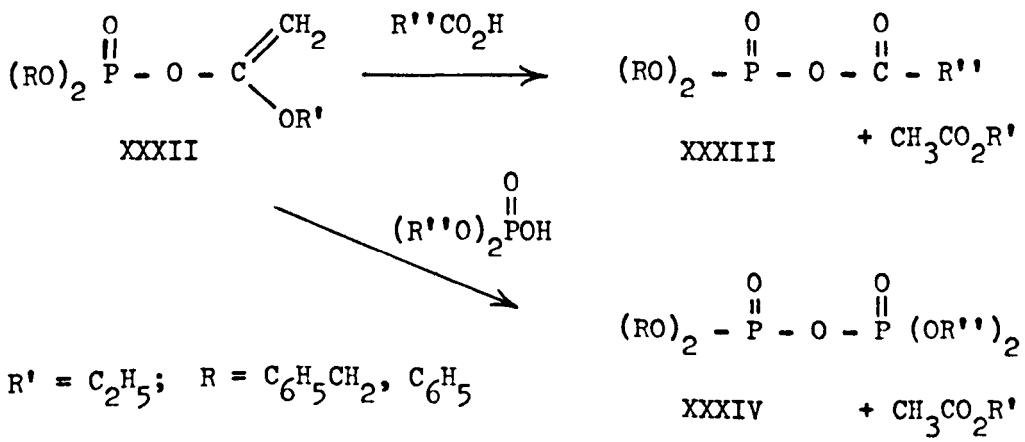
The kinetics of the reaction of 1-ethoxyvinyl esters with carboxylic acids in non-aqueous solvents has been studied by Zwanenburg and Drenth.[47a] They concluded that, in a number of pre-equilibria, a solvation complex is formed between a molecule of 1-ethoxyvinyl ester and two, three, or four molecules of carboxylic acid. These pre-equilibria are followed by the rate determining step in which a proton is transferred to the substrate giving an ion-pair as intermediate. The products are formed from this ion-pair. The reaction was followed, kinetically, by titrating the 1-ethoxyvinyl ester with alcoholic iodine solution in a medium buffered at pH 6.8 (since 1-ethoxyvinyl esters are easily hydrated in acidic solution).[47a]

The same workers have also studied the kinetics of the reaction of 1-ethoxy-1-alkynes with carboxylic acids in non-aqueous solvents and

concluded that proton transfer occurs in the rate determining step in which an ion-pair is formed.[47b]

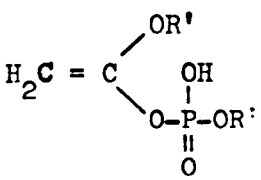
The reaction of 1-alkoxyvinyl esters with a hydroxylic acid represents a good synthetic route to symmetrical and unsymmetrical anhydrides, and is of particular synthetic use in the fields of nucleotide and coenzyme chemistry. Requiring only mild conditions, the reaction gives good yields of anhydrides with an alkyl acetate as the only other product.

The phosphorylating properties of the 1-ethoxyvinyl esters of dibenzyl- and diphenylphosphoric acids have been exploited in the formation of internucleotide linkages. Wasserman and Cohen[6,7] reacted the esters, XXXII, ($R' = C_2H_5$; $R = C_6H_5.CH_2$, C_6H_5) with carboxylic acids to form mixed anhydrides of the type XXXIII or with phosphoric acids to form pyrophosphates (XXXIV) (Scheme 11). The presence of XXXIII was shown by its infrared spectrum and by its reaction with cyclohexylamine to produce the expected products, N-cyclohexylbenzamide and cyclohexyl ammonium dibenzylphosphate.



Scheme 11

In the co-enzyme field XXXII (R = $C_6H_5CH_2$) has been allowed to react with the pyridinium salt of uridine-5' monophosphate (UMP) to yield uridine-5' diphosphate (UDP).[7] This technique was extended to the direct activation of nucleotides, such as the preparation of 1-alkoxyvinyl esters of the type XXXV (R' = C_2H_5, R = Adenosine-5'). This could not be isolated but, in methanol solution, a methyl ester was obtained which proved to be identical with the monomethyl ester of AMP which had previously been prepared by another route.[6,7]



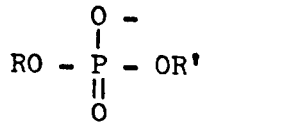
R' = C_2H_5

R = Adenosine-5'

not isolated

XXXV

Internucleotide linkages have been successfully formed using this technique by reacting 3'acetyl thymidine-5' phosphoric acid as the pyridinium salt with excess of ethoxyacetylene and one mole of 5-trityl thymidine.[7] The detritylated and deacylated product was isolated and shown to be the dinucleotide phosphate (XXXVI, R = thymidine-3'; R' = thymidine-5').



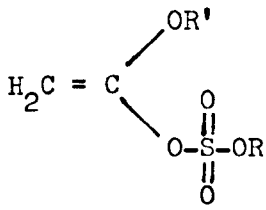
R = thymidine-3'

R' = thymidine-5'

XXXVI

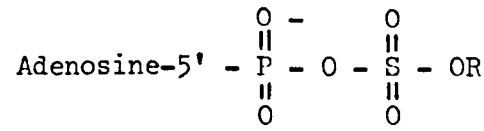
Flavin adenine dinucleotide (FAD) has been prepared in yields of 10 - 15% by reaction of (XXXV, R' = C_2H_5, R = Adenosine-5') with riboflavin 5'-monophosphate.[7] The excess of ethoxyacetylene can be removed before the addition of the riboflavin phosphate, thus keeping to a minimum the formation of the cyclic 4',5' riboflavin phosphate which is the major product of the dicyclohexylcarbodiimide route to FAD.

Banks and Cohen[12] have applied a similar technique to the preparation of adenosine-5' sulphatophosphate, important biosynthetically as an analogue of "active sulphate". Benzyl hydrogen sulphate as the pyridinium salt, and 2-cyanoethyl sulphate as the barium salt were each allowed to react with ethoxyacetylene. The corresponding 1-ethoxyvinyl ester (XXXVII, R = $C_6H_5CH_2$, $CNCH_2CH_2$; R' = C_2H_5) was obtained, as shown by examination of the infrared spectrum, and this was allowed to react, without purification, with pyridinium 5'-adenylate to yield adenosine-5' sulphatophosphate (XXXVIII, R = H), after removal of protecting groups.



R = $C_6H_5CH_2$, $CNCH_2CH_2$; R' = C_2H_5

XXXVII



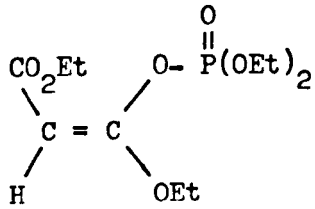
R = $C_6H_5CH_2$, $CNCH_2CH_2$

XXXVIII

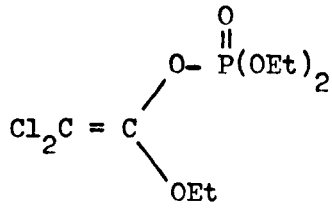
Cramer[8,9,25] during his studies on enol phosphates, prepared the keten acylals XXXIX (from triethyl phosphite and diethyl

bromomalonate)[8,9] and XL (from triethylphosphite and ethyl trichloroacetate).[9,25] These compounds, like the analogous 1-alkoxyvinyl phosphates (XXXII), are powerful phosphorylating agents, reacting easily with hydroxylic acids to give high yields of the corresponding mixed anhydrides, which are mentioned in the Patent Literature as being useful insecticides and petroleum additives.[49]

Reaction of XXXIX with adenosine-5' monophosphate results in the formation of the diethyl ester of adenosine-5' diphosphate.

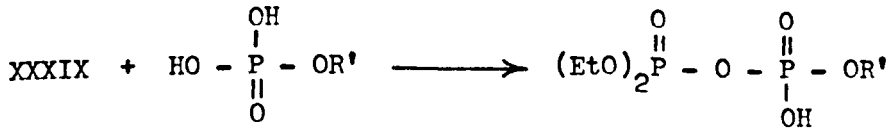


XXXIX



XL

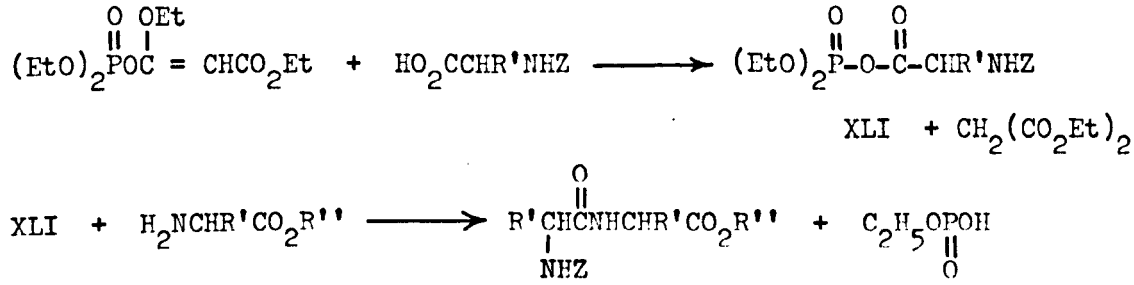
When nucleotides, such as thymidine-3' phosphate or adenosine-3' phosphate are condensed with XXXIX, the diethyl thymidyl and adenyl pyrophosphates formed initially can undergo further reaction to form oligonucleotides.[29] The reaction of (XXXIX) with monoesters of phosphoric acid enables unsymmetrical triesters of pyrophosphoric acid to be synthesized (Scheme 12).[30]



+ malonic ester

Scheme 12

Keten acylals have also been used to initiate peptide synthesis, which by analogy with the enzymatic synthesis,[26,27] involve formation of mixed anhydrides between phosphoric acid and various amino-acids.[28] Thus XXXIX readily reacted with N-protected amino-acids, giving the mixed anhydrides (XLI) which, without isolation, yielded dipeptide derivatives (XLII) in high yields on subsequent aminolysis with esters or salts of other amino-acids (XLIII) (Scheme 13).



Z = benzyloxycarbonyl

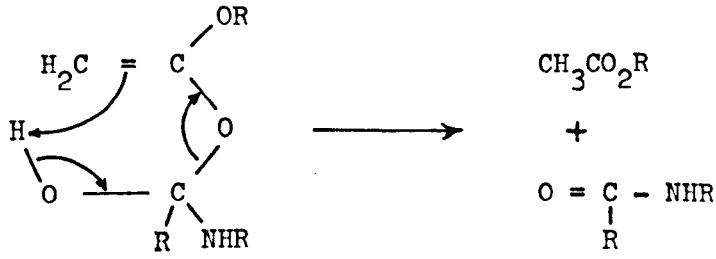
Scheme 13

N-Benzyloxycarbonylglycylglycine and N-benzyloxycarbonylglycyl-D,L-phenylalamine, for example, were synthesized in yields of 82 and 61% by this method, using the corresponding amino-acid derivatives.[28]

1-Alkoxyvinyl esters react easily, and often exothermically with many organic bases. Thus amines are converted to the corresponding amides and alcohols to the corresponding esters. Weak bases, such as

β-naphthylamine and p-nitrobenzyl alcohol are acylated less readily and in fact some 1-alkoxyvinyl esters can be crystallised from alcohol.

Wasserman[5] postulated the reaction of acylation of bases as occurring by initial addition of base to the carbonyl carbon atom of the 1-alkoxyvinyl ester, the subsequent decomposition proceeding with an inter- or intramolecular proton transfer (Scheme 14).

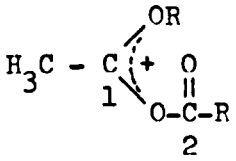


Scheme 14

This reaction has been successfully applied to all types of 1-alkoxyvinyl ester and a number of unstable esters, for example the 1-alkoxyvinyl esters of sulphonic and phosphoric acids have been reacted with ammonia or a primary amine, such as benzylamine or aniline, to yield the corresponding crystalline sulphonamide[11] or phosphoramidate.[6,7]

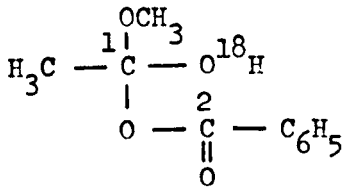
Acid-catalyzed acylations also occur. Strong acids, such as hydrochloric acid, are acylated almost instantaneously to give the corresponding acid chloride, and weaker acids such as 2,4-dinitrophenol are also acylated, although more slowly. Such acylations are thought to

proceed by initial protonation of the 1-alkoxyvinyl ester to form the ion (XLIV) which may be attacked by a nucleophile at either of the positively charged carbon atoms C_1 or C_2.

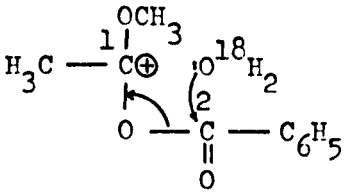


XLIV

An investigation of this mechanism has been carried out by Wasserman[5] using O^{18} labelling techniques. 1-Methoxyvinyl benzoate was hydrolysed with dilute (0.1 N) hydrochloric acid in excess O^{18} labelled water and the benzoic acid which was recovered was found to contain less than 10% of the excess O^{18} originally present in the water. Of the alternative modes of nucleophilic attack on the ion XLIV, XLV would lead to benzoic acid containing little of the excess O^{18} present in the water whereas XLVI would yield benzoic acid containing all of the label.



XLV



XLVI

Thus the mechanism of acid-catalyzed ~~acylation~~ hydrolysis of 1-alkoxyvinyl esters is that of initial protonation, followed by nucleophilic attack on the 1-vinyl carbon atom (C_1) with subsequent cleavage to give a molecule

of benzoic acid.

Presumably the small amount of O^{18} label found in the benzoic acid is caused by acid catalysed exchange after the benzoic acid is formed. Because of this possibility it would perhaps have been better to examine the ethylacetate formed for O^{18} label.

1-Alkoxyvinyl esters have been used in peptide synthesis both as isolated and non-isolated intermediates. Arens[31] used methoxyacetylene to convert mixtures of acids and amines into amides (Scheme 15) and later[13,14,17] extended this to the syntheses of peptides using a benzyloxycarbonyl N-protected amino-acid and an amino-acid ester hydrochloride or peptide ester hydrochloride (Scheme 16).

$$R\,CO_2H + H_2NR' + HC \equiv C{\cdot}OCH_3 \longrightarrow RCONHR + CH_3CO_2CH_3$$

Scheme 15

$$ZNHCHRCO_2H + HCl{\cdot}H_2NCHR'CO_2C_2H_5 + H\,C{\equiv}C\,OEt$$

$$\downarrow$$

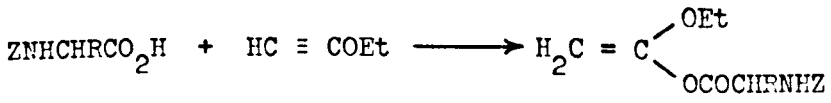
$$ZNHCHRCOHNCHR'CO_2Et + CH_3CO_2Et + HCl$$

Z = benzyloxycarbonyl

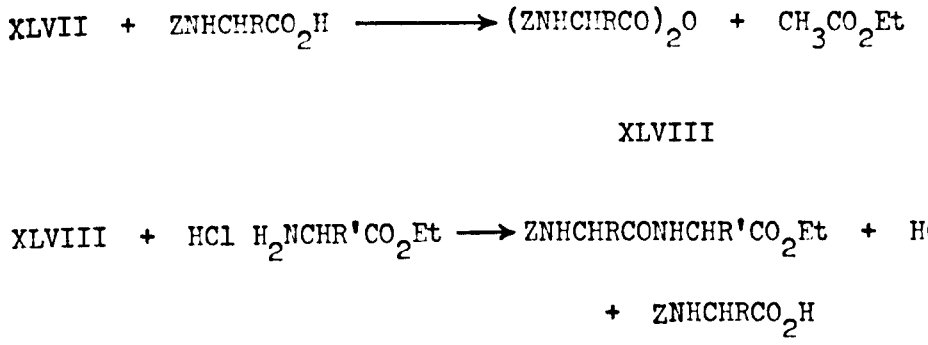
Scheme 16

The syntheses were carried out in one of three ways:-[14] (a) by

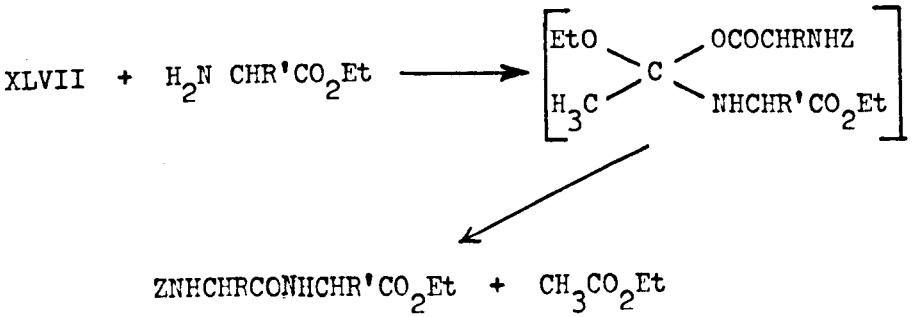
warming the components together in the absence of a solvent, the amino-component being added always as the hydrochloride; (b) by working in boiling, moist, ethyl acetate (0.5% water) and using the amino-component as the hydrochloride or hydrobromide; (c) by working with the free amino-component in boiling moist ethyl acetate (0.5% water). Method (a) was found to be very quick but not to give the best yields; (b) was found to be suitable for dipeptides and sometimes tripeptides; and (c) was found to be the most suitable for higher peptides. The synthesis was found to be accompanied by little or no racemization. Two possible mechanisms have been proposed for this reaction: both involve a 1-alkoxy-vinyl ester as intermediate. In one mechanism the 1-alkoxyvinyl ester of th N-protected amino-acid (XLVII) is assumed to react with one mole of acid to form the anhydride (XLVIII), a well known reaction in the chemistry of 1-alkoxyvinyl carboxylates. The anhydride then reacts further to yield the peptide and amino-acid starting material (Scheme 17). The alternative mechanism envisages direct interaction of the free amino-component with (XLVII) according to (Scheme 18), again a reaction with a counterpart in the chemistry of 1-alkoxyvinyl carboxylates.



XLVII



Scheme 17



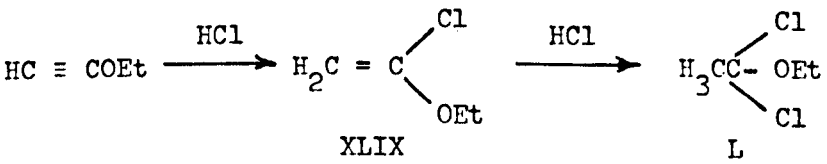
Z = benzyloxycarbonyl

Scheme 18

Anhydrides of the type (XLVIII) have been prepared[17] and used to prepare peptides, but since the yields are, in general, lower than in the reaction of the amino- and acid-components with ethoxyacetylene, Scheme 18 would seem to be the favoured mechanism. A number of

1-alkoxyvinyl esters (XLVII) have been isolated, although this is difficult in cases other than those involving N-phthaloyl amino-acids.[17] On reaction with amino-acid esters (or hydrochlorides) the corresponding peptide is obtained.[17]

When the hydrochloride of the amino-component is used in this reaction another possible mechanism must also be considered since although much of the hydrogen chloride liberated in the reaction escapes through the reflux condenser some of it might react with the excess of ethoxyacetylene present according to Scheme 19.



Scheme 19

Arens[32] has isolated ethyl α-chlorovinyl ether (XLIX) and α,α-dichlorodiethyl ether (L) from the reaction of hydrogen chloride with ethoxyacetylene. When either of these compounds is refluxed with an acylamino-acid and an amino-acid ester hydrochloride a peptide is formed in good yield.[32] (Scheme 20)

$$AcNHCHRCO_2H \;+\; HCl\cdot H_2NCHR'CO_2Et \;+\; H_2C = C(Cl)OEt$$

LI — LII

$$AcNHCHRCONHCHRCO_2Et \;+\; CH_3CO_2Et \;+\; 2HCl$$

LIII

OR. $$LI + LII + CH_3C(Cl)_2OEt \longrightarrow LIII + CH_3CO_2Et + 3HCl$$

Ac = benzyloxycarbonyl or phthaloyl

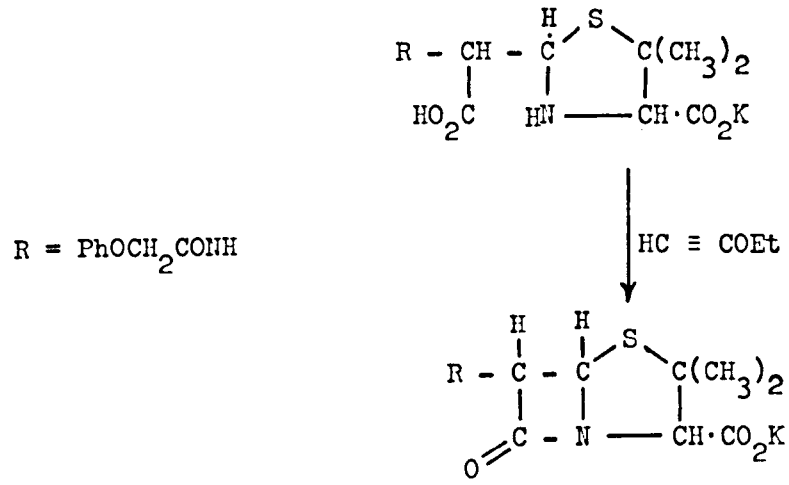
Scheme 20

The most probable intermediates in this reaction are acyl amino-acid chlorides.

Thus it is unlikely that any single mechanistic path can be written for the reaction of an amino-acid and an amino-acid ester with an alkoxyacetylene under all conditions.

The special advantage of this method of peptide synthesis is the easy removal of the excess of the reagent and its transformation product, ethyl acetate.

According to Sheehan,[15] ethoxyacetylene can be used for closure of the four-membered ß-lactam ring of penicillin, but dicyclohexyl-carbodiimide gives better results (Scheme 21).



Scheme 21

There have been recent reports of an analogous use of ynamines (LIV), in the synthesis of peptides.[33,34] However considerable racemization has been found to occur by this route.[34]

$$RC \equiv CNR'_2$$

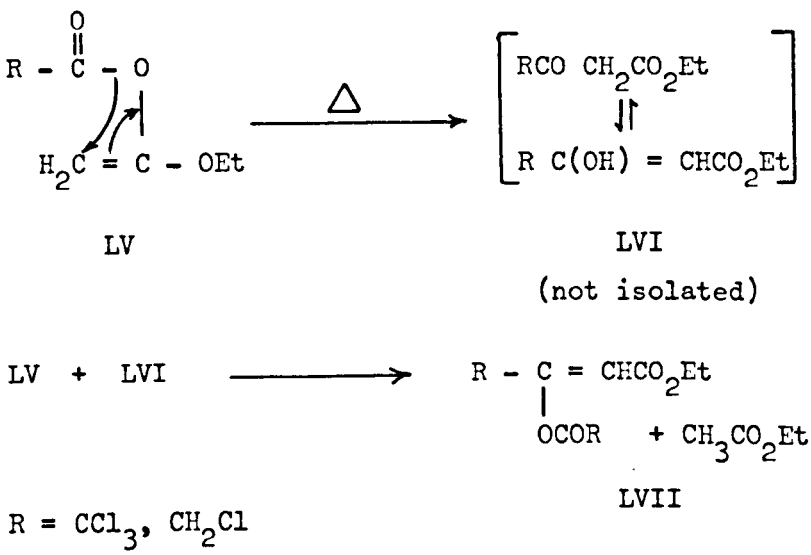
LIV

(ii) Rearrangements of some 1-alkoxyvinyl esters:

Zwanenburg[37] has made a detailed study of the thermal decomposition of 1-ethoxyvinyl esters following the preliminary work of Arens[4] on the thermal decomposition of 1-ethoxyvinyl trichloroacetate.

1-Ethoxyvinyl esters of carboxylic acids containing strongly electron withdrawing groups (LV, R = CCl_3, CH_2Cl) were found to undergo rearrangement when heated to a temperature of about 150°, to yield the

compound LVII (R = CCl_3, CH_2Cl) (Scheme 22).

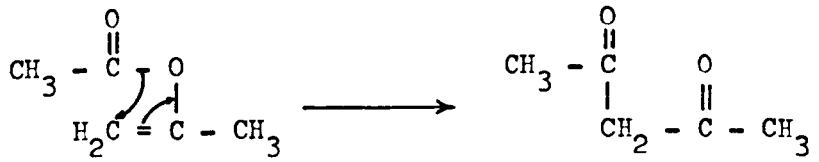


Scheme 22

The reaction was formulated as occurring by a four-centre rearrangement of LV into the β-keto ester LVI which is not isolated but which is acylated in the tautomeric enol form by a further molecule of LV to yield the compound LVII.

This is analogous to the reported rearrangement of isopropenyl acetate in the vapour phase, in the absence of a catalyst, at 400 - 450°.[35] Under these conditions a good yield of acetylacetone is obtained and use of homologues of isopropenyl acetate provides a general route to 1,3 diketones. The by-products (keten, acetone, methylacetylene, acetic acid, etc.) and mechanism of this reaction have been studied[36] and the rearrangement postulated (Scheme 23) is formally the same as the conversion of LV to LVI. In this case, of course, since isopropenyl acetate is not an efficient

acylating agent, the isolated product is the 1,3 diketone.

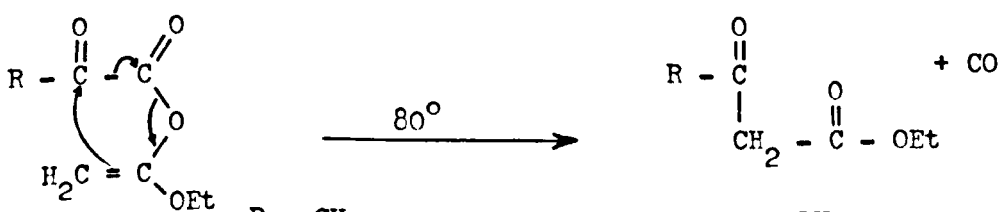


Scheme 23

It would seem preferable to formulate these rearrangements as a nucleophilic attack by the π electrons of the vinyl group on the carbonyl carbon atom followed by cleavage of the adjacent carbon-oxygen bond (LVIII).

LVIII

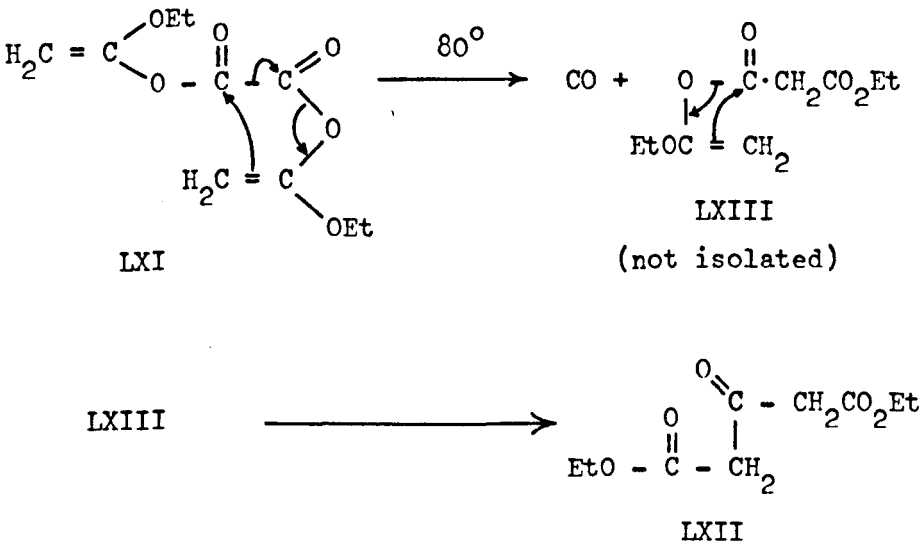
Banks, Cohen and Springall[38] followed this work with some studies on the thermal rearrangement of the 1-ethoxyvinyl esters of the α-keto acid, pyruvic acid, and the dicarboxylic acid, oxalic acid. 1-Ethoxyvinyl pyruvate (LIX) was found to rearrange to the β-keto ester, ethyl acetoacetate (LX), at 80°, with the evolution of the theoretical quantity of carbon monoxide. A five-centre reaction path was postulated (Scheme 24). No products arising from the acylation of (LX) were found.[38]



LIX

Scheme 24

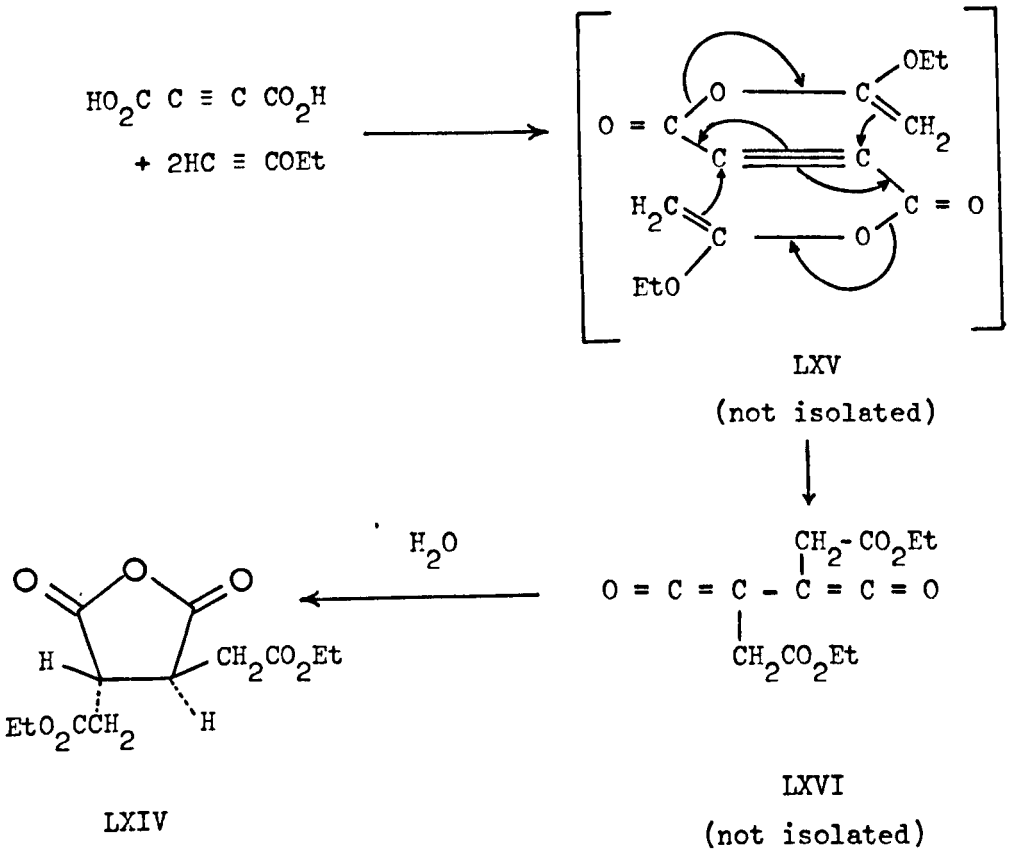
Similarly the di-1-ethoxyvinyl ester of oxalic acid (LXI) was found to rearrange easily at 80° to diethyl acetonedicarboxylate (LXII), with the evolution of carbon monoxide.[38] Again a five-centre rearrangement was assumed to yield the intermediate (LXIII), which is not isolated, but which is assumed to undergo a four-centre rearrangement, of the type proposed by Zwanenburg,[37] to yield the isolated product (LXII) (Scheme 25). The reaction is considered to proceed by direct rearrangement of the transition state (LXIII), without the need of passing through the ground state of (LXIII), since the four-centre rearrangement does not normally occur at such a low temperature.[37]



Scheme 25

Arens[41] reacted ethoxyacetylene with acetylene dicarboxylic acid (butynedioic acid) in an attempt to prepare the polymeric anhydride. Instead, the product LXIV was isolated, and its formation was rationalised by assuming the formation of the di-1-ethoxyvinyl ester, LXV, which

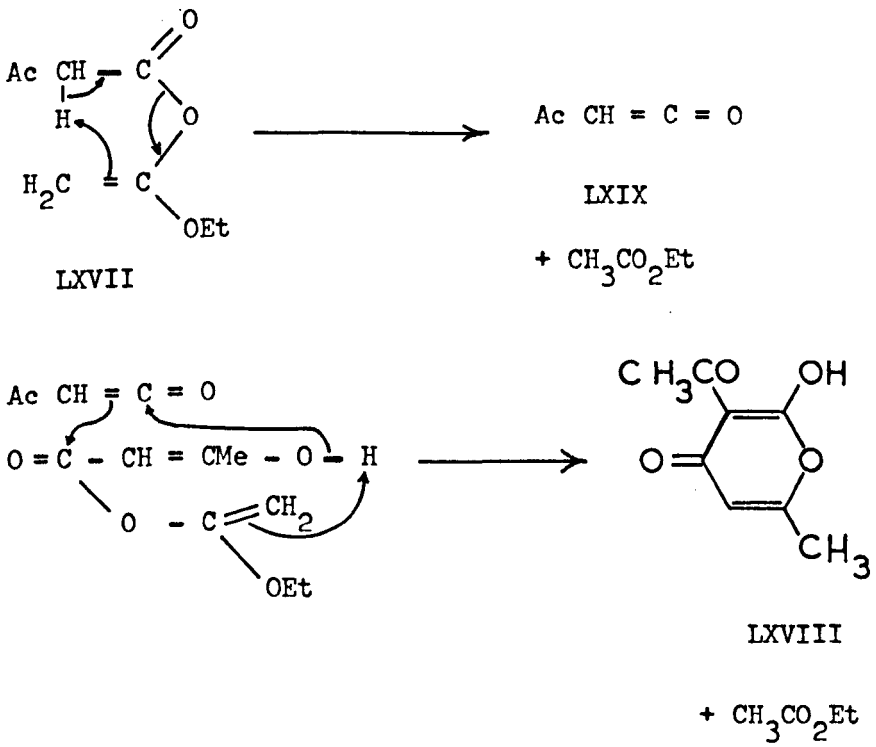
rearranges to the bis keten (LXVI): neither of these products is isolated, instead LXVI reacts with water in the solvent to yield the final product (LXIV) (Scheme 26).



Scheme 26

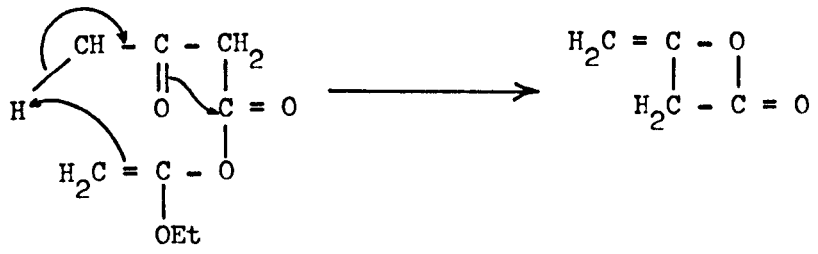
The 1-ethoxyvinyl esters of the β-keto acid, acetoacetic acid, and the γ-keto acid laevulinic acid have been prepared by Cohen and Pattenden.[39] 1-Ethoxyvinyl acetoacetate (LXVII) was prepared at a low temperature, and characterised by its infrared spectrum, but on warming

to room temperature it spontaneously rearranged to 3-acetyl-2-hydroxy-6-methyl-4-pyrone (LXVIII) (dehydroacetic acid). The formation of this product has been explained by postulating an intramolecular elimination of ethyl acetate to produce an intermediate acyl keten which could react further, either with a second acyl keten molecule or with a molecule of the 1-ethoxyvinyl ester to yield the γ-pyrone after elimination of a second molecule of ethyl acetate (Scheme 27).[39]



Scheme 27

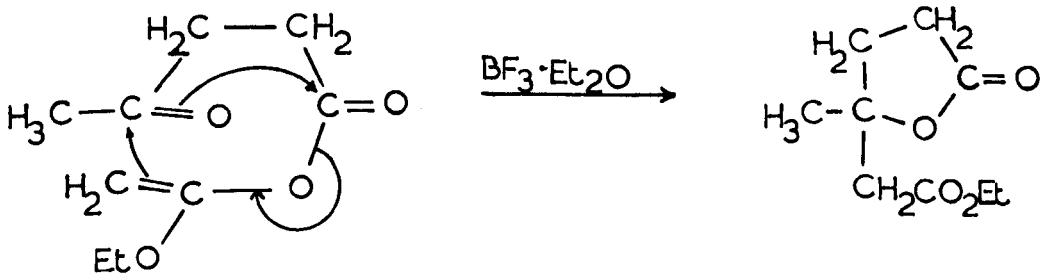
Alternatively the reaction could proceed via the formation of keten dimer (LXX) which is known to form dehydroacetic acid on treatment with sodium acetate and acetic anhydride.[39] (Scheme 28)



LXVII LXX

Scheme 28

The 1-ethoxyvinyl ester of laevulinic acid (LXXI), although thermally quite stable (distillable at 102°, 1 mm.) reacts exothermically when catalyzed by boron trifluoride-etherate to yield the γ-lactone ester (LXXII).[39] (Scheme 29).

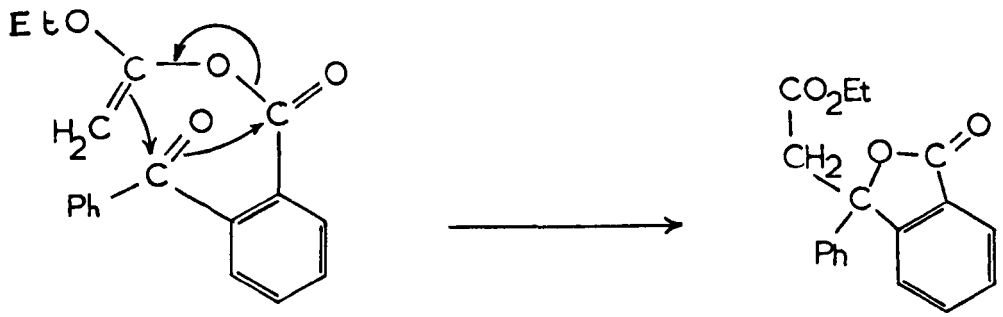


LXXI LXXII

Scheme 29

This reaction path is the same as that proposed by Newman and Courduvelis[40] for the rearrangement of 1-ethoxyvinyl-2-benzoyl benzoate (LXXIII) to ethyl 3-phenylphthalide-3-acetate (LXXIV) (Scheme 30): this

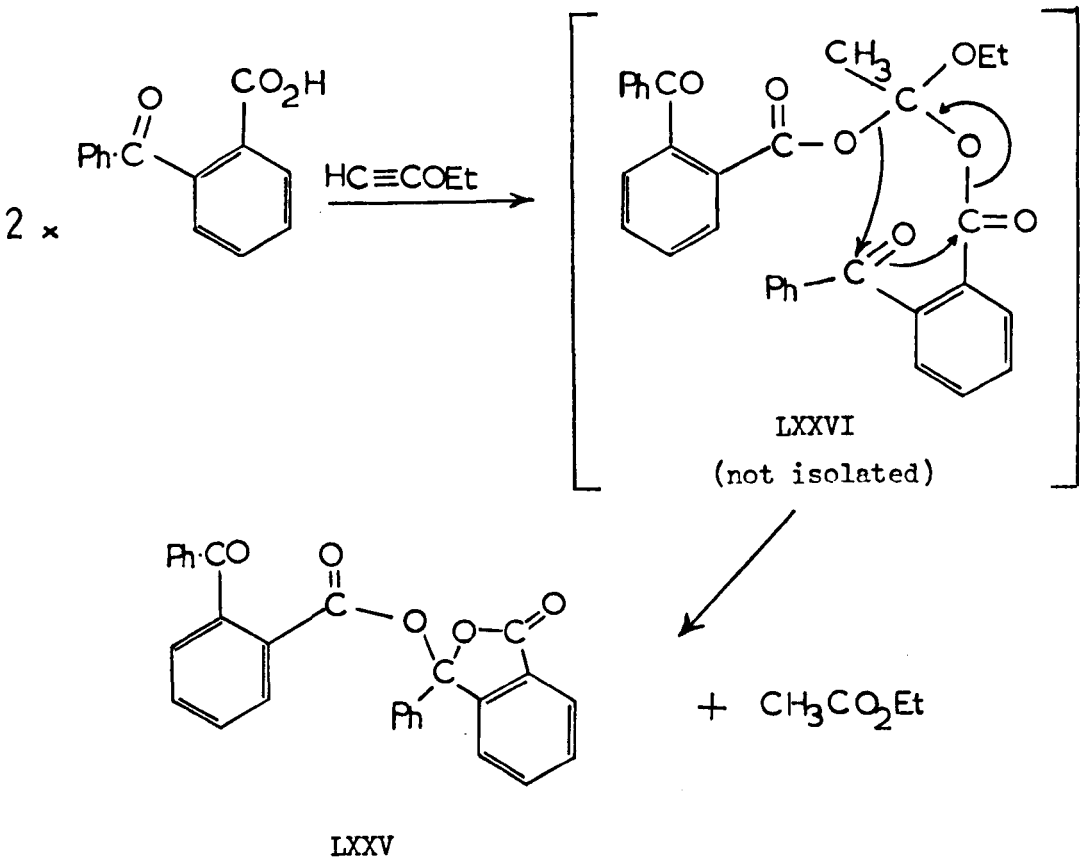
rearrangement occurs by heating or prolonged standing at room temperature in the absence of moisture.



LXXIII LXXIV

Scheme 30

The mechanism of this type of intramolecular rearrangement has been classified as a [3.2.1] bicyclic path and a number of other examples recorded.[40] Of particular interest, here, is the reaction of 2-benzoylbenzoic acid with ethoxyacetylene to yield LXXV. The initial stage of the reaction has been formulated as addition of two molecules of the acid to give the intermediate LXXVI, which is not isolated, but decomposes via a [3.2.1] bicyclic path to give LXXV, with loss of a molecule of ethyl acetate (Scheme 31).



LXXV

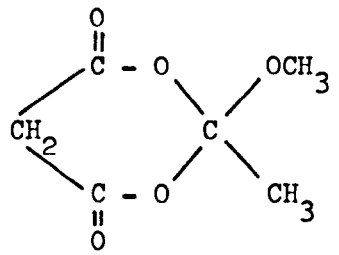
Scheme 31

The intermediate diester (LXXVI) is presumably not formed directly but via the corresponding 1-ethoxyvinyl ester. This is supported by the observation that LXXIII is converted to LXXV on exposure to moisture for a time.[40]

The 1-ethoxyvinyl esters of cinnamic and crotonic acids, both colourless, distillable liquids, have been found to be resistant to rearrangement either by thermal means or by boron trifluoride catalysis: the corresponding anhydrides are the only products.[42] 1-Ethoxyvinyl acrylate was found to be less stable, slowly polymerizing at room temperature without intramolecular rearrangement while 1-ethoxyvinyl propiolate proved

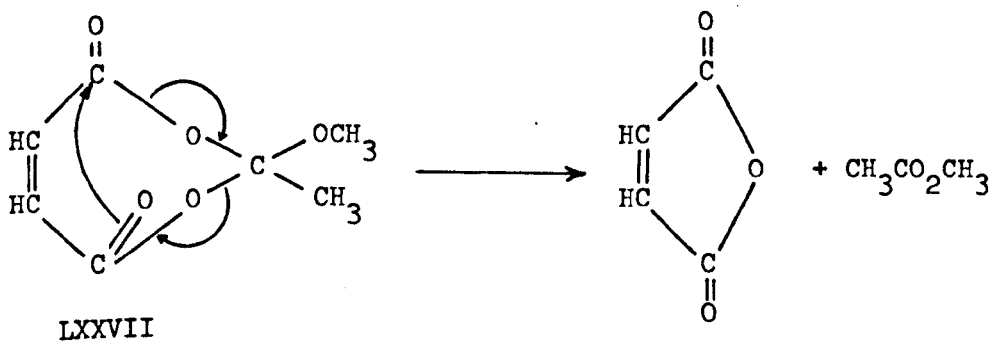
to be spontaneously explosive.[42]

Eglinton, Jones and co-workers,[3] in their studies on the reactions of carboxylic acids with methoxyacetylene obtained a compound from the reaction of malonic acid and methoxyacetylene, to which they tentatively assigned the structure (LXXVI).



LXXVI

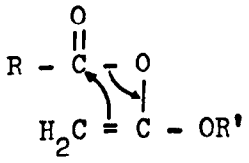
In the case of maleic acid, the intramolecular anhydride was the product formed and they proposed that, by analogy with LXXVI, an intermediate LXXVII is formed which decomposes by a [3.2.1] bicyclic path to the anhydride (Scheme 32). However this work was carried out before 1-alkoxyvinyl esters had been proved to be intermediates in these reactions,[5] and it seems much more probable, from this viewpoint, and also from steric considerations, that the reaction proceeds through an intermediate mono- or di-1-alkoxyvinyl ester of maleic acid. (See Experimental Discussion Section).



LXXVII

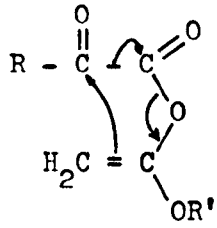
Scheme 32

Studies on rearrangements of 1-alkoxyvinyl esters seem to suggest that these intramolecular rearrangements proceed by one of two possible mechanisms. One involves initial nucleophilic attack by the π electron system of the vinyl group on a carbonyl carbon atom, followed by cleavage of a bond adjacent to this carbon atom: the other proceeds by the intermediate formation of a keten derivative. Examples of rearrangements of the first type are the rearrangements of:- 1-alkoxyvinyl esters of carboxylic acids having strongly electronegative groups (LV); 1-alkoxyvinyl esters of α-keto acids (LIX) and di-1-alkoxyvinyl esters of 1,2 dicarboxylic acids (LXI); and 1-alkoxyvinyl esters of γ-keto acids (LXXI, LXXIII). The second category includes the rearrangement of 1-alkoxyvinyl esters of β-keto acids (LXVII) and, possibly, the intermediate stages of the reaction of butynedioic acid with ethoxyacetylene (Scheme 26).



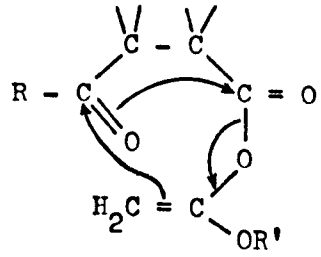
R = CCl_3, CH_2Cl;
R' = C_2H_5

LV



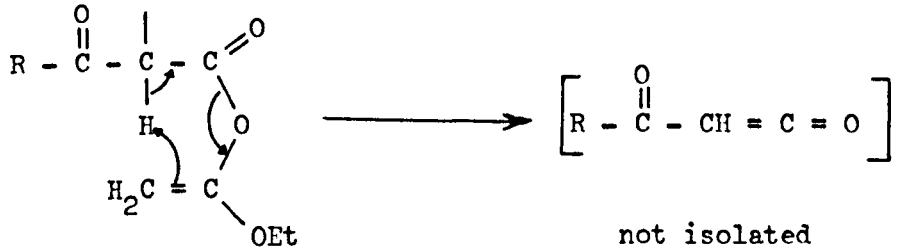
R = CH_3, ($H_2C = C(OEt)-O-$) (1-ethoxyvinyl laevulinate)
R' = C_2H_5

LIX, LXI



(1-ethoxyvinyl 2-benzoyl benzoate)

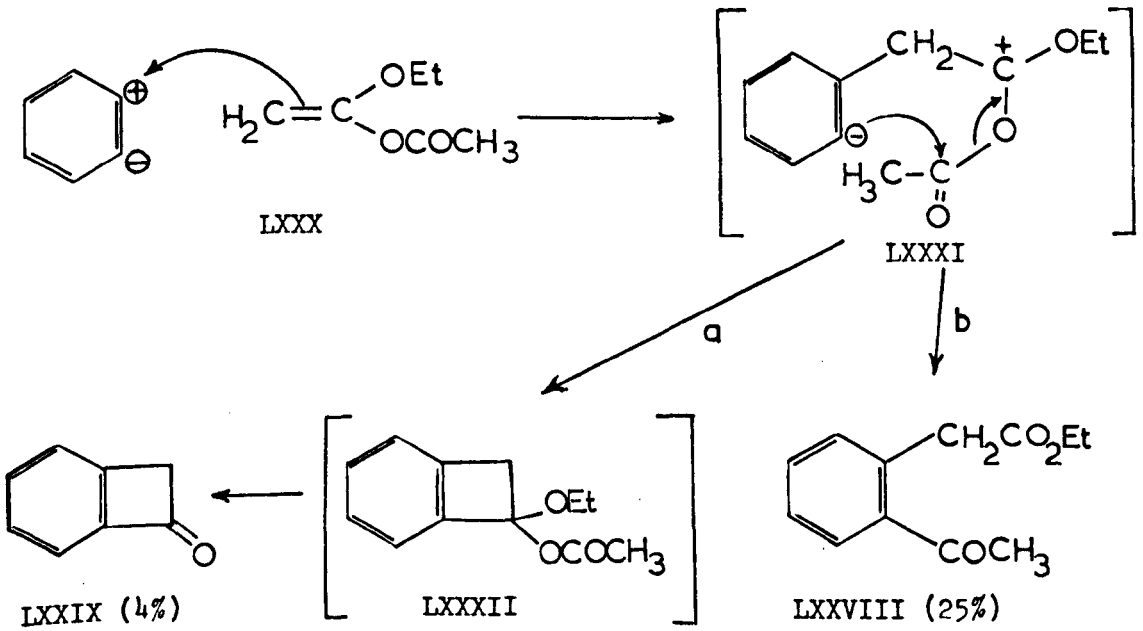
LXXI, LXXIII



LXVII

(iii) Reaction of 1-alkoxyvinyl esters with benzyne:

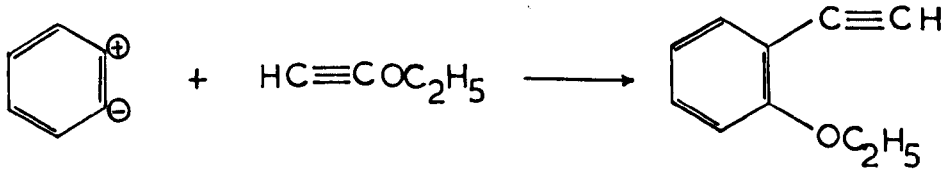
The reaction of 1-ethoxyvinyl acetate with benzyne, generated by the thermal decomposition of benzenediazonium-2-carboxylate, yields mainly the ethyl ester of o-acetylphenylacetic acid (LXXVIII) rather than the expected benzocyclobutenone (LXXIX) (Scheme 33).[43]



Scheme 33

This ortho disubstitution of the aromatic ring appears to involve benzyne acting as an electrophilic agent and forming an intermediate such as LXXXI. Collapse of LXXXI to the four-membered ring (Scheme 33, path a) or intramolecular acylation (Scheme 33, path b) represent alternate reaction paths. Benzocyclobutenone (LXXIX) which presumably arises by hydrolysis of the acylal, LXXXII, was recovered in 4% yield and LXXVIII in 25% yield.[43]

A similar ortho disubstitution occurs in the reaction of benzyne with ethoxyacetylene when a 37% yield of 2-ethoxyphenylacetylene (LXXXIII) is obtained (Scheme 34).[44]



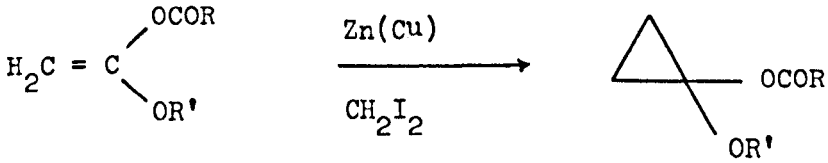
LXXXIII

Scheme 34

In this case no products resulting from a 1,2-cycloaddition reaction were reported.[44]

(iv) Formation of Cyclopropanone Acylals:

Wasserman and Clagett[45,46] have prepared cyclopropanone acylals (LXXXIV) by reacting 1-ethoxyvinyl esters with methylene di-iodide and a zinc/copper couple in the presence of 1,2 dimethoxyethane.[45] (Scheme 35)



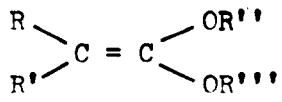
$R' = C_2H_5$; $R = CH_3$, C_6H_5

Scheme 35

They have studied the reactions of these compounds with acidic and basic reagents and with Grignard reagents.[45,46] (See: "Cyclopropanones" Section and Experimental Discussion Section).

D. Related Compounds: Keten Acetals.

Keten Acetals (LXXXV) have, in general, been prepared from the corresponding α-bromo acetals by dehydrohalogenation; or by the action of sodium on α-bromo orthoesters; or by the pyrolysis of orthoesters. Their chemistry has been reviewed by McElvain.[49]



LXXXV

For the purposes of comparison with 1-alkoxyvinyl carboxylates, keten diethylacetal (LXXXV; $R = R' = H$; $R'' = R''' = C_2H_5$) is a suitable member of this class of compound.

Keten diethylacetal reacts with a variety of nucleophiles. Water and ethyl alcohol react vigorously with the acetal to yield ethyl acetate and ethyl orthoacetate, respectively. The formation of the former compound probably, and the latter compound obviously, involves addition across the carbon to carbon double bond of keten acetal.[49,50] (Scheme 36)

$$H_2C = C(OEt)_2 + HOH \longrightarrow CH_3CO_2Et + EtOH$$
$$H_2C = C(OEt)_2 + EtOH \longrightarrow CH_3C(OEt)_3$$

Scheme 36

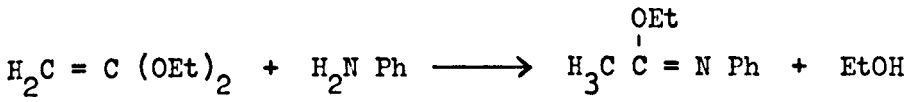
The halogen hydracids, carboxylic acids and phenol appear to add to keten acetal in a similar manner. The reaction takes place at room temperature with the liberation of considerable heat. The addition product LXXXVI, however, is unstable and decomposes into ethyl acetate and C_2H_5X (X is -Br, RCOO-, or C_6H_5O-) (Scheme 37). In the case of the phenol reaction, a small amount of LXXXVI decomposes into phenyl acetate and diethyl ether.[49,50]

$$H_2C = C\begin{matrix}OEt\\OEt\end{matrix} \xrightarrow{HX} H_3C - C\begin{matrix}OEt\\OEt\\X\end{matrix} \longrightarrow CH_3CO_2Et + C_2H_5X$$

LXXXVI

Scheme 37

Aniline reacts quite readily with keten acetal at 25°. The main reaction product is ethyl N-phenyl iminoacetate (LXXXVII) which is obtained in an 81% yield.[49,50] (Scheme 38)

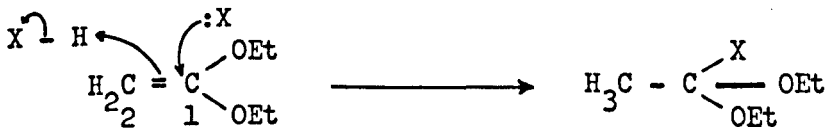


LXXXVII

Scheme 38

N-Ethylaniline reacts similarly, although more slowly, whereas piperidine and ammonia show no reaction at room temperature although reactions do occur at 100°.

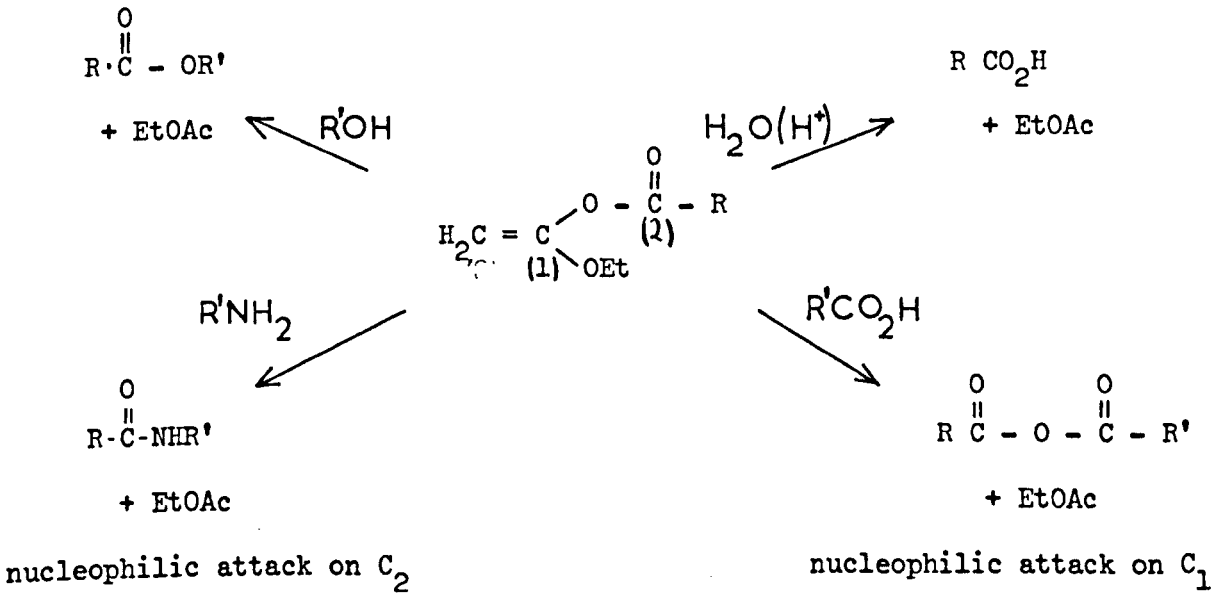
The reactions of keten acetals with the nucleophilic reagents, considered above, would seem to have a common reaction path. This may be formulated as nucleophilic attack at the 1-vinyl carbon atom, C_1, and protonation at the 2-vinyl carbon atom, C_2, to give the compound LXXXVIII. (Scheme 39)



LXXXVIII

Scheme 39

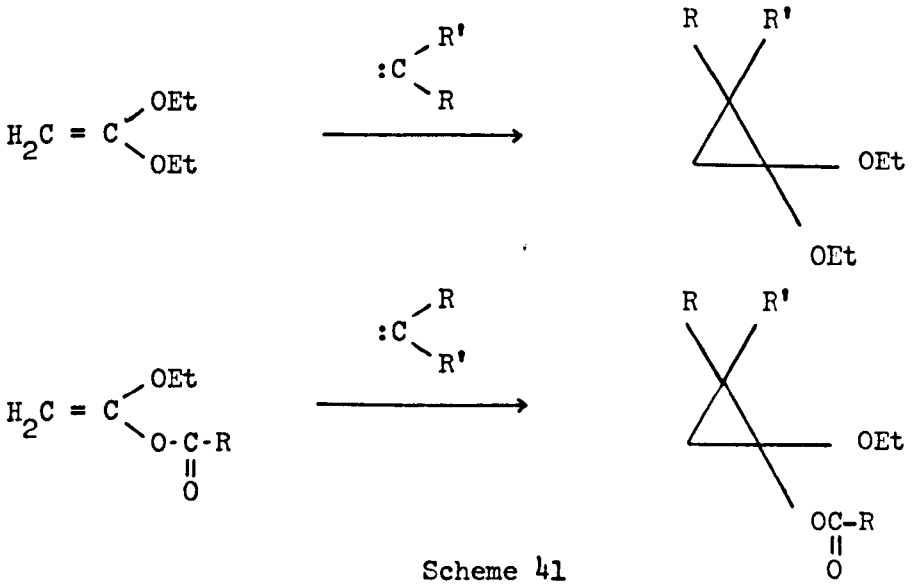
This contrasts with the reactions of 1-alkoxyvinyl carboxylates with similar reagents since in this case there are two electrophilic centres - the 1-vinyl carbon atom, C_1, and the carbonyl carbon atom, C_2. In basic media initial attack is preferentially on C_2, while in acid media after initial protonation attack on C_1 takes place.[5,23] (e.g. Scheme 40).



Scheme 40

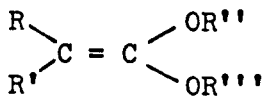
Similarities between keten acetals and 1-alkoxyvinyl carboxylates are evident, however, in their 1,2-cycloaddition reactions with carbenes and similar intermediates to form cyclopropanone acetals[51,52] and acylals.[45,46] (Scheme 41). Only the double bond is involved in these reactions. (See

Experimental Discussion).



Scheme 41

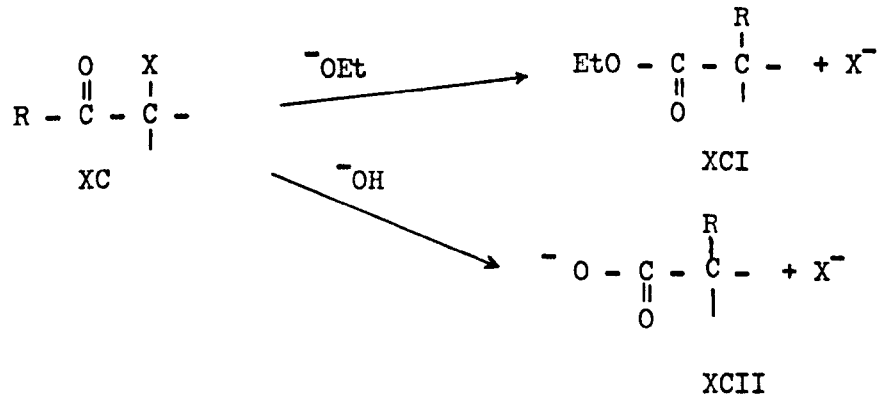
Pattenden[42] has shown that the unsymmetrical keten acetals, LXXXV (R = R' = H; R'' = Et; R''' = 2,4-dinitrophenyl, or 2,4,5-trichlorophenyl, or 2,4,6-tribromophenyl) are formed by reaction of the corresponding phenol with an excess of ethoxyacetylene. They proved to be too unstable to be analysed, although in one case (LXXXV, R''' = 2,4,6-tribromophenyl) the compound could be distilled under reduced pressure, and they were characterised from spectral evidence and by their reactions with amines.



LXXXV

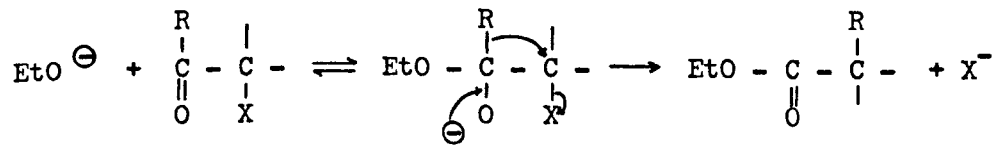
II. CYCLOPROPANONES

In the Favorskii rearrangement, an α-halo ketone (XC) is transformed to an ester (XCI), using alkoxide, or to a carboxylate salt (XCII), using hydroxide (Scheme 42). The reaction has been reviewed by Kende.[53]



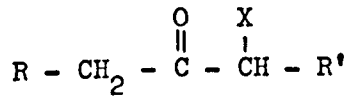
Scheme 42

One of the early mechanisms proposed for this rearrangement was analogous to the benzilic acid rearrangement: the basic anion attacks the carbonyl group "pushing" substituent R to the adjacent carbon where it, in turn, displaces halide. (Scheme 43)

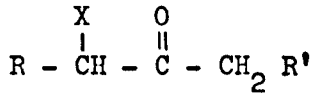


Scheme 43

This mechanism would predict different products for the Favorskii rearrangement of the two α-halo ketones XCIII and XCIV, but, in fact, ketones of this type have been found to yield the same product. Thus, a symmetrical intermediate must be involved in the reaction.

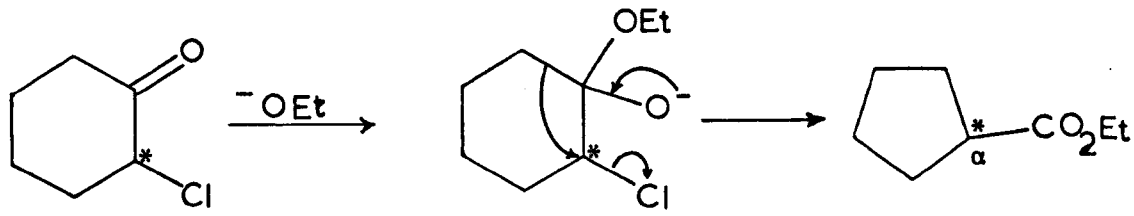


XCIII



XCIV

Loftfield[54] has studied the mechanism of the rearrangement of 2-chlorocyclohexanone with ethoxide. Using a sample of this ketone, labelled with C^{14} at the chlorinated carbon (XCV), he found that the isolated ester contained half of the labelled carbon at C_α and the other half at C_β. This is in contrast to the predicted result of a benzilic-type rearrangement when <u>all</u> of the labelled carbon would be present at the α-position of the resultant ester. (Scheme 44)

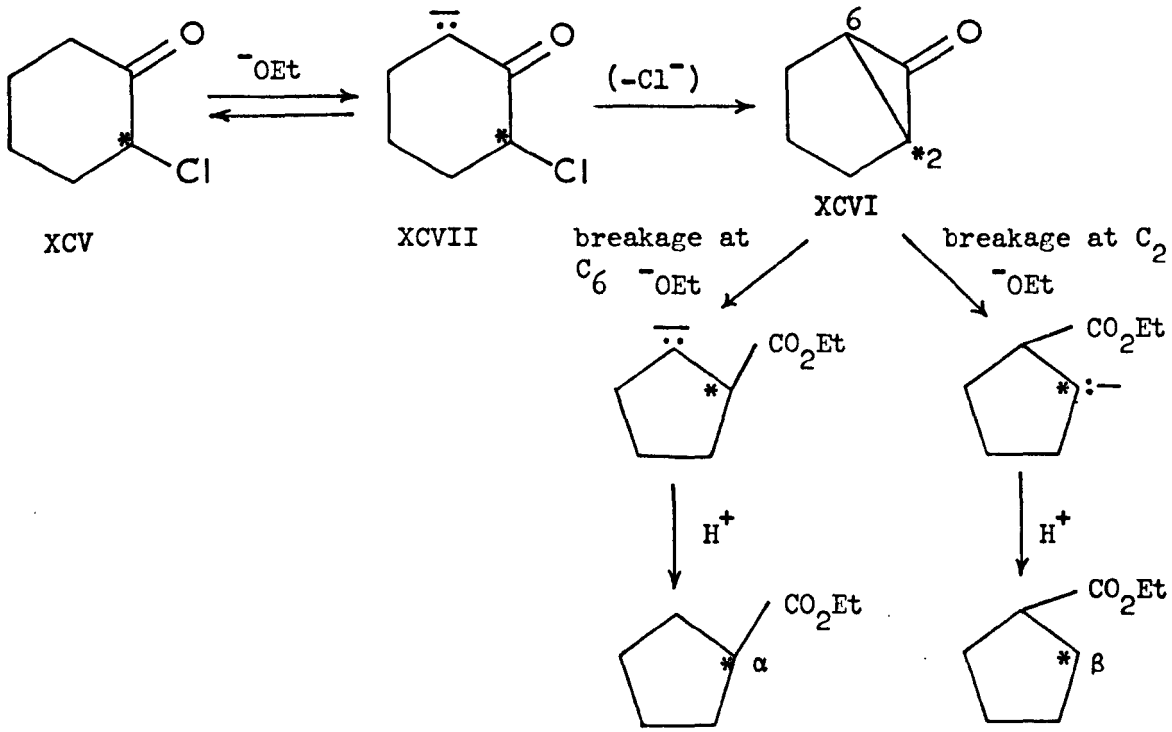


XCV

Scheme 44

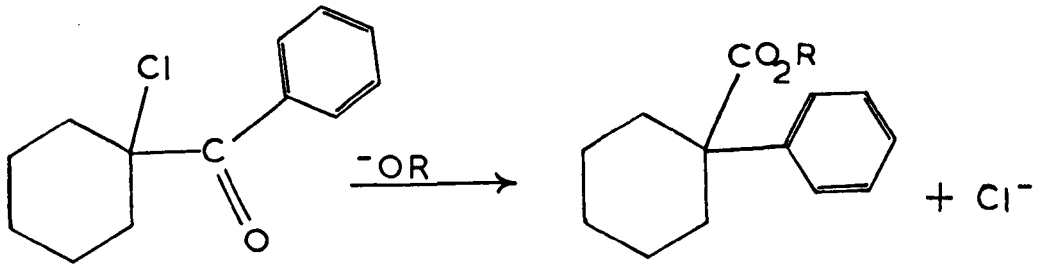
In order to explain these results, Loftfield[54] postulated the intermediate formation of a substituted cyclopropanone (XCVI), in which

C_2 and C_β are equivalent. This is formed by internal substitution within the carbanion XCVII. (Scheme 45)



Scheme 45

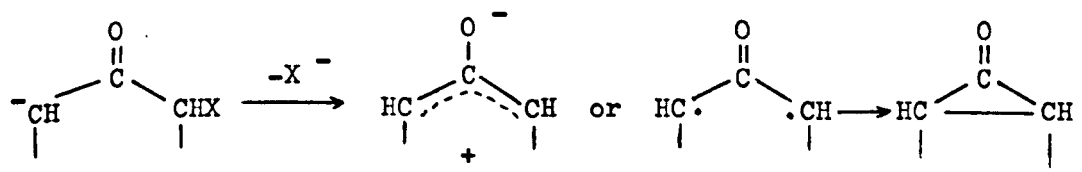
However, although this mechanism cannot operate in the case of an α-halo ketone where the non-halogenated α-carbon bears no hydrogen atom, 1-benzoyl cyclohexyl chloride (XCVIII) is found to rearrange with ease to the ester XCIX (Scheme 46). In this case, perhaps, a benzylic-type pathway is followed.



XCVIII XCIX

Scheme 46

Another implication of the Loftfield mechanism is that a stereospecific Favorskii rearrangement would result. This, however, is not always observed and loss of stereochemistry has been explained by the mechanism, Scheme 47,[55-58] according to which the enolate anion (C) undergoes S_N1 elimination of halide ion to give as an intermediate, a species variously represented as a mesomeric zwitterion (CI) or as a "no-bond" canonical form of a cyclopropanone (CII). Subsequent collapse of this species to the more stable cyclopropanone (CIII) would lead to the product. (Scheme 47)

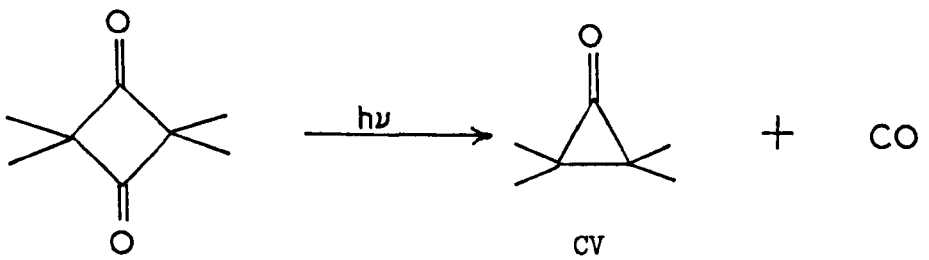


C CI CII CIII

Scheme 47

At least two mechanisms must operate in this reaction, therefore; perhaps a benzilic-type pathway being followed when the "cyclopropanone" pathway is excluded.

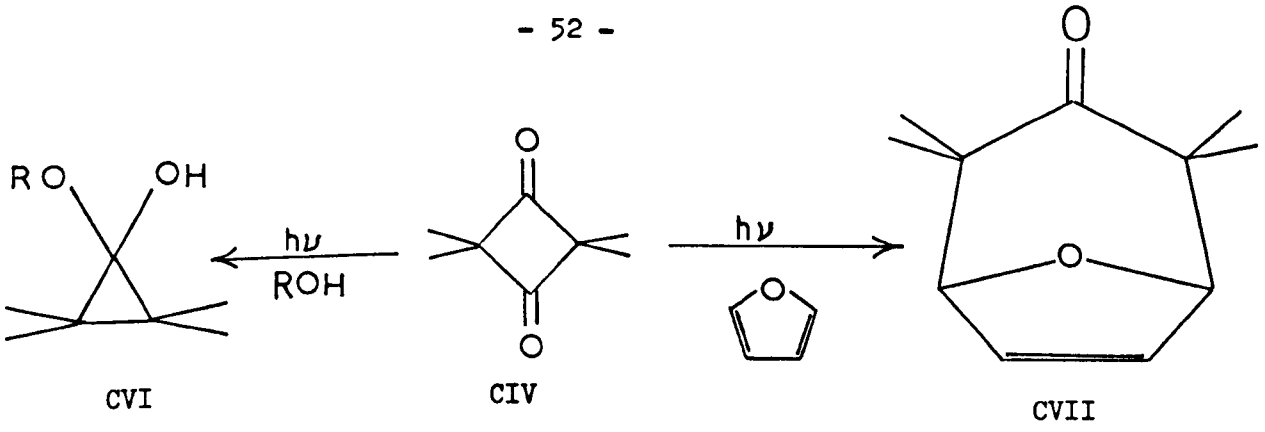
The possibility of cyclopropanones being intermediates in the Favorskii rearrangement, and the theoretical interest surrounding these small-ring compounds has provoked much discussion and research in the last decade. Until recently no successful preparation of a cyclopropanone had been reported in the literature although a number of attempts have been recorded.[59] The formation of tetramethyl cyclopropanone (CV) as an intermediate in photolyzed solutions of tetramethylcyclobutanedione (CIV) has been proposed by several workers.[60-64] (Scheme 48)



CIV CV

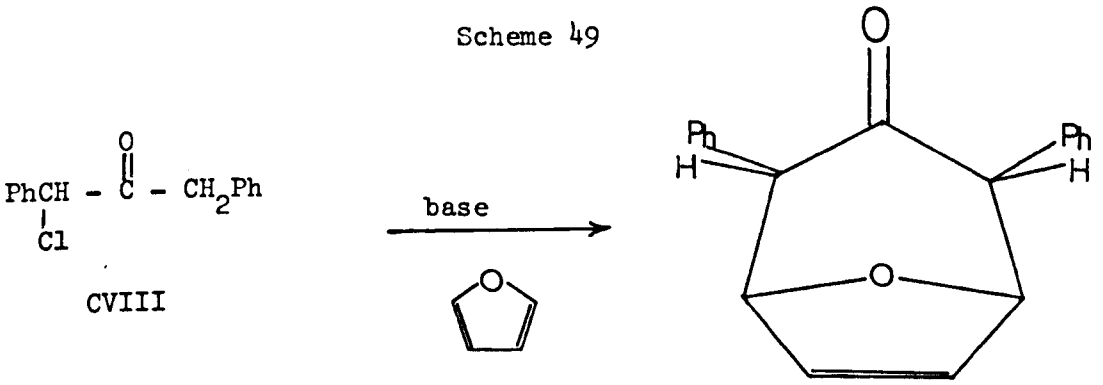
Scheme 48

Evidence for the intermediacy of CV has been obtained from photolyses of CIV in ethanol[61] or methanol[63,64] when the hemiketals CVI (R = Et or Me) are obtained in 35% and 70 - 80% yields, respectively. (Scheme 49). When the photolyses are carried out in the presence of a diene, such as furan, the adduct CVII is formed.[60,61,63,64] (Scheme 49). The formation of this type of adduct from the reaction of the chloroketone CVIII with 2,6-lutidine, in the presence of furan, has also been reported.[57] (Scheme 50)



CVI CIV CVII

Scheme 49



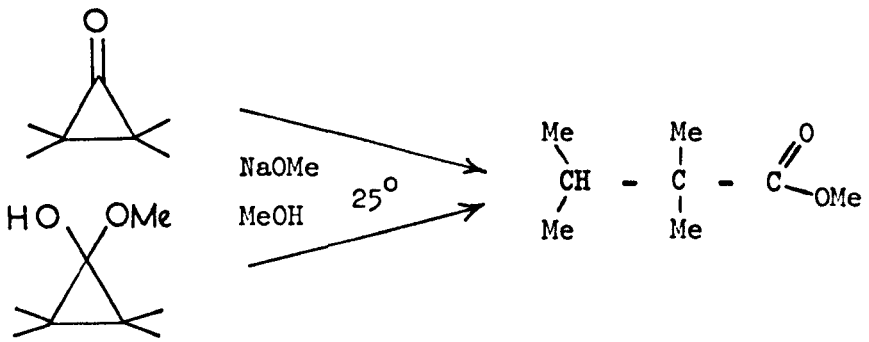
CVIII

Scheme 50

By rapid scanning of photolysed solutions of CIV a C = O stretching frequency at 1840 cm^{-1} has been detected;[62] this band could be characteristic of a cyclopropanone.

Turro and co-workers[64] have prepared an almost pure solution of tetramethylcyclopropanone (10%) in pentane by reduced pressure distillation after photolysis. They reacted portions of this solution with furan, methanol and ethereal lithium aluminium hydride to yield CVII, CVI (R = Me) and 2,3-tetramethylcyclopropanol, respectively. Tetramethylcyclopropanone and its methyl hemiketal have been found to rearrange smoothly to Favorskii products on treatment with sodium

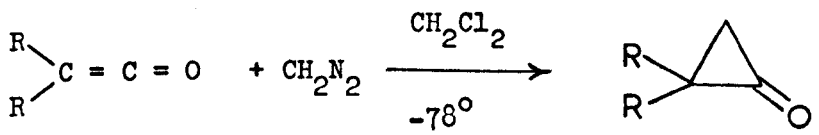
methoxide in methanol.[65] (Scheme 51)



~ 97%

Scheme 51

Cyclopropanone[67] (CIX, R = H) and 2,2-dimethylcyclopropanone[66] (CIX, R = Me) have been prepared by the addition of a methylene dichloride solution of diazomethane to keten and dimethyl keten, respectively, at -78°. (Scheme 52). Both compounds showed a band in the infrared, characteristic of a strained ketone; - dimethylcyclopropanone (1815 cm^{-1}); cyclopropanone (1813 cm^{-1}).

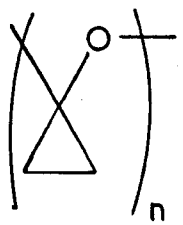


CIX

Scheme 52

Cyclopropanone has also been reported to be formed by the

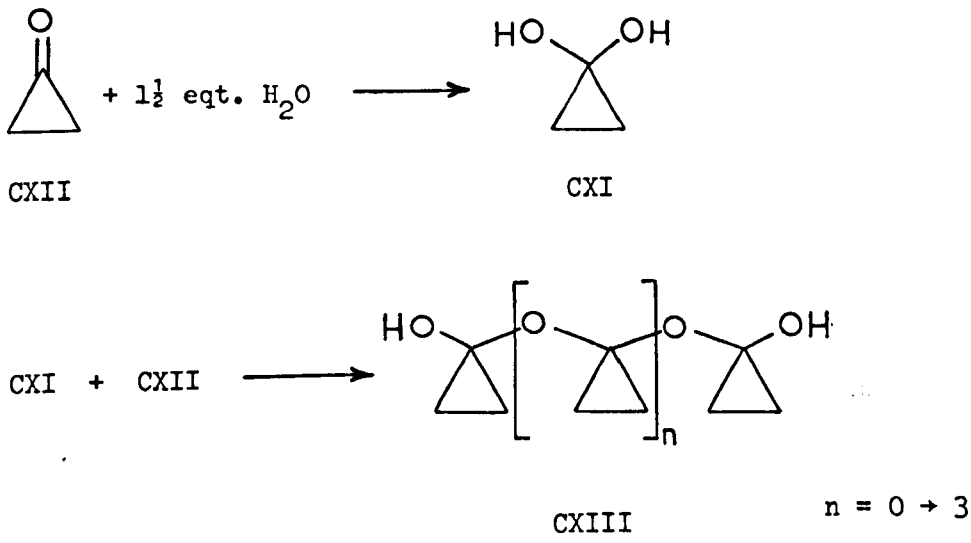
photolysis of a mixture of diazomethane and keten in a solid nitrogen matrix[69] and also by reaction of diazomethane with excess keten in liquid propane at -78°.[68] In the latter case excess keten and solvent were evaporated after the reaction and the residue distilled under reduced pressure to yield 20% cyclopropanone, contaminated with some cyclobutanone formed by subsequent addition of diazomethane to cyclopropanone.[68] Samples prepared in this way were found to be stable for a few days at -78° but a rapid strongly exothermic polymerisation takes place above 0°, or even below, if traces of water are present. The resulting polymer is a stable white solid which melts at 166.5 - 169.5° and is thought to have the structure CX.[67,68] Its molecular weight was found to be about 9,500 by means of an ultra-centrifuge.



CX

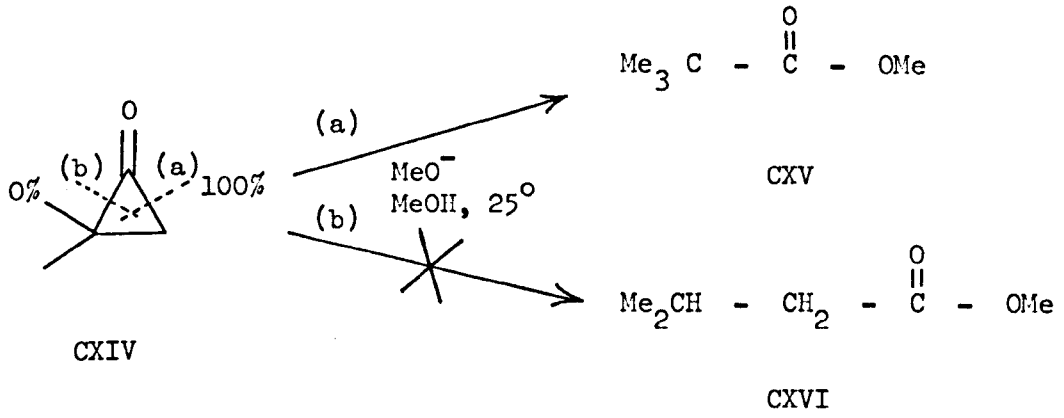
Acetic anhydride and acetyl chloride have been found to inhibit the polymerisation of methylene dichloride solutions of cyclopropanone. When these compounds are present in molar quantities, solutions of cyclopropanone possess a half-life of the order of days at room temperature.[73] Presumably they act as scavengers for traces of moisture or bases which could initiate the polymerisation.[73]

Solutions of cyclopropanone - which can be handled more easily than the neat liquid - have been reacted with a number of nucleophilic reagents. Reaction with one and a half equivalents of water yields the hydrate (CXI) which will react with cyclopropanone (CXII) to give the polymeric compound (CXIII) (Scheme 53).[70]



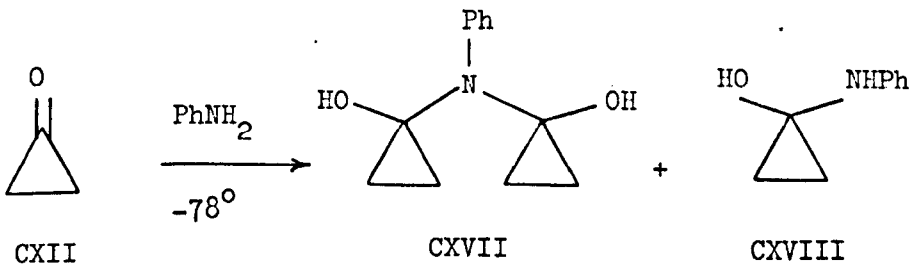
Scheme 53

Both cyclopropanone[67] and 2,2-dimethylcyclopropanone[66] react with methanol to give the corresponding hemiketal. 2,2-Dimethylcyclopropanone (CXIV) has also been allowed to react with sodium methoxide in methanol solution and methyl trimethylacetate (CXV) has been recovered in yields of greater than 70%.[66] No methyl isopropylacetate (CXVI) was detected; a result consistent with the formation of the most stable carbanion by exclusive bond cleavage of bond (a) after attack of base on the cyclopropanone.[66] (Scheme 54). Such a preference is predicted from results of Favorskii rearrangement of unsymmetrical α-halo ketones.[53]



Scheme 54

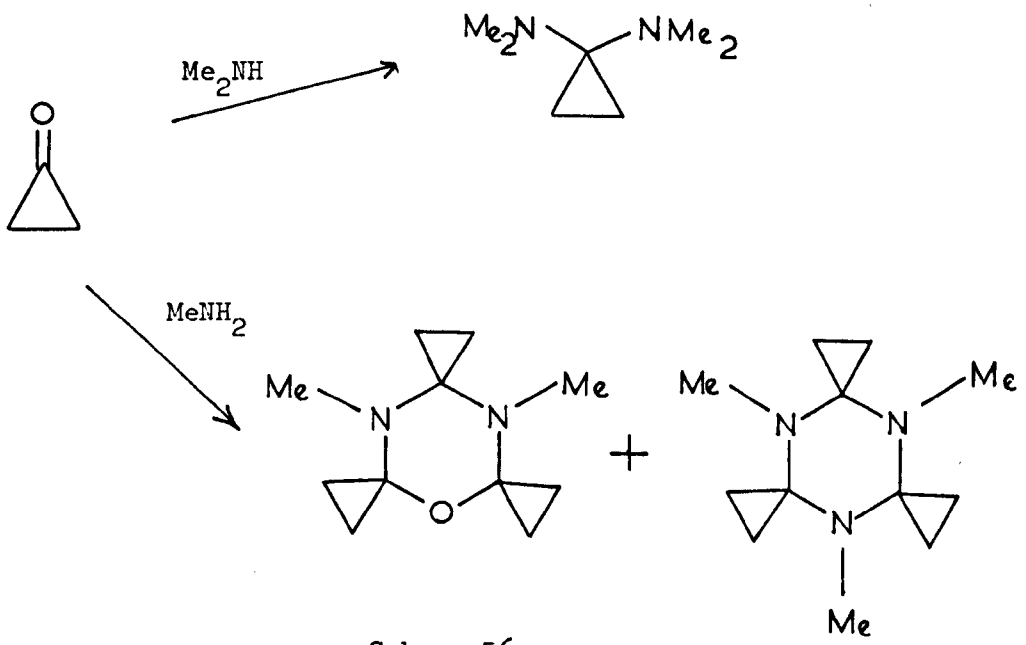
Reaction of a methylene dichloride solution of cyclopropanone (CXII) with one equivalent of aniline at -78° results in the immediate formation of N,N-bis-(1-hydroxycyclopropyl)-aniline (CXVII) (33%) and 1-anilino-1-hydroxycyclopropane (CXVIII) (66%). Treatment of CXII with two equivalents of aniline under similar conditions yields CXVIII as major product (95%) and CXVII as minor product (< 1%)[74] (Scheme 55).



Scheme 55

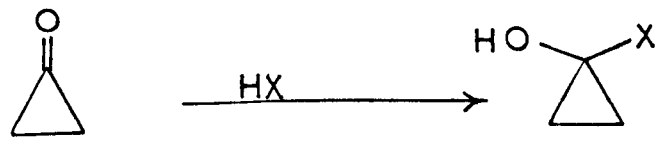
Addition of mono- and di-methylamines to cyclopropanone give

the products shown in Scheme 56.[71]



Scheme 56

Cyclopropanone has been found to react with an excess of acetic acid[72,73] or hydrogen chloride[73] or hydrogen cyanide[72] to give the compound CXIX (where X = OAc or Cl or CN)[72,73] (Scheme 57).

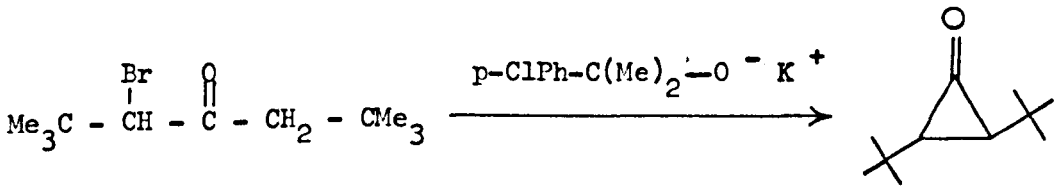


X = $OCOCH_3$, Cl, CN.

CXIX

Scheme 57

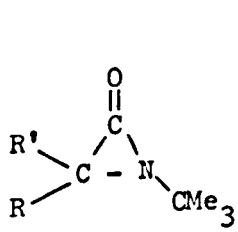
Pazos and Green[75] report the preparation and characterization (including elemental analysis) of trans-2,3-di-t-butylcyclopropanone (CXX), which has a melting point of 24 - 26° and is moderately stable in the absence of nucleophiles. It was prepared in 20-40% yield by the reaction of α-bromodineopentyl ketone (CXXI) with the potassium salt of p-chlorophenyldimethylcarbinol (Scheme 58). The infrared spectrum shows a C = O stretching frequency at 1822 cm^{-1} and reaction with benzyl alcohol gives the corresponding hemiketal.



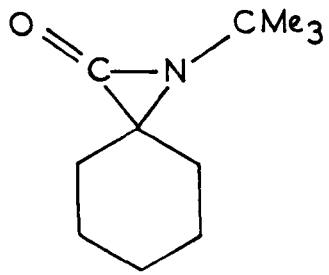
CXXI CXX

Scheme 58

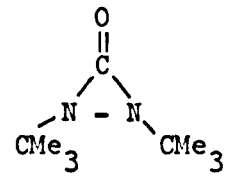
Similar stability of tertiary-butyl substituted three-ring compounds is found in the α-lactam (aziridinone) series: CXXII (R' = H, R = Ph;[78] R' = R = Me;[79b] R' = H, R = CMe_3)[76] and CXXIII;[79a] and in the 2,3-diazacyclopropanone (diaziridinone), CXXIV.[77]



CXXII

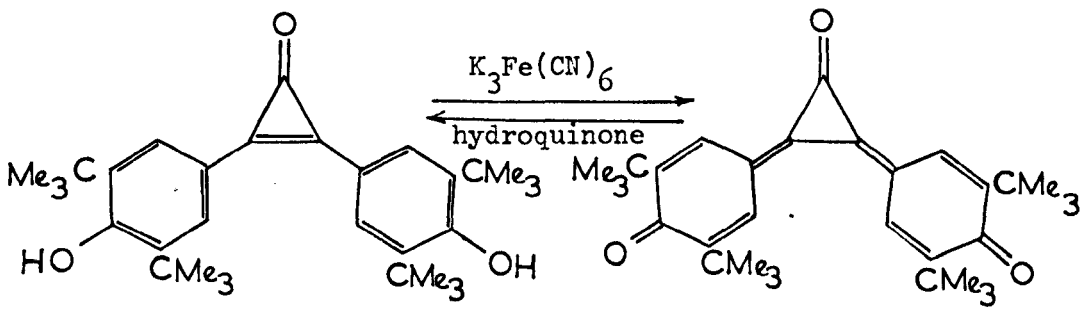


CXXIII



CXXIV

The diquinocyclopropanone, CXXV, has been synthesized by the reaction of the cyclopropenone, CXXVI, with aqueous basic potassium ferricyanide.[80] (Scheme 59). However, this compound does not represent a true cyclopropanone system since each carbon atom is in a state of sp^2 hybridisation.

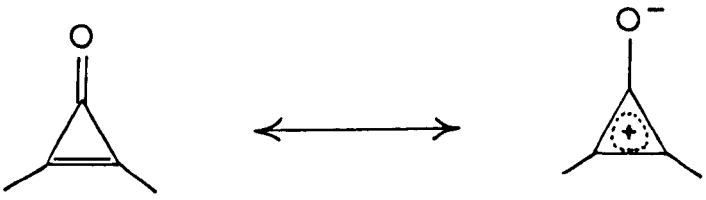


CXXVI CXXV

Scheme 59

In contrast to the cyclopropanones, cyclopropenones, the other class of three-membered ring ketones, are relatively stable. The chemistry of cyclopropenones and cyclopropylium compounds has been reviewed recently, by Krebs.[81]

Although cyclopropenone, the parent compound, has not yet been prepared, a number of disubstituted derivatives have been isolated and found to be relatively stable. The stability can be attributed to the delocalisation of electron density that can be achieved in the cyclopropenone molecule through the resonance contribution of the zwitter ion, CXXVIII.



CXXVII CXXVIII

This is in contrast to classical theories which would predict that the cyclopropanone system should be the more stable since it is less sterically strained.

Cyclopropenones possess aromatic character and obey Huckel's rule, i.e. they possess $(4n + 2)\pi$ electrons, where $n = 0$.

PART II

DISCUSSION SECTION

A. Formation of 1-Ethoxyvinyl Esters.

(1) Carboxylic acids:

Wasserman and Wharton[5] have prepared a number of 1-ethoxyvinyl esters, in high yields, by allowing the corresponding acid to react with an excess of ethoxyacetylene, either alone or in the presence of a mercuric salt as catalyst (ca. 10^{-2} molar quantity). It has been claimed that best results are obtained by use of the mercuric salt of the particular acid which is involved in the reaction: however, in the present work, mercuric acetate, which is commercially available, was used for all experiments without any obvious detriment to the yields and purity of the products.

1-Ethoxyvinyl esters (CXXIX) of pivalic acid, propionic acid and benzoic acid were prepared by dropwise addition of a solution of the acid to an ice-cooled solution of ethoxyacetylene (two-molar excess) containing mercuric acetate catalyst (ca. 10^{-2} molar). (Scheme 60)

In the preparation of 1-ethoxyvinyl dichloroacetate, ethoxyacetylene was used in a 0.25 molar excess in the absence of catalyst. (Scheme 60)

The solvent in all cases, was methylene dichloride which had been dried over calcium chloride and distilled before use. Ethoxyacetylene was distilled from potassium hydroxide pellets before use (b.p. 50 - 52°), and the carboxylic acid involved was purified by distillation (under reduced pressure), or dried under vacuum for a number of hours. The addition of the acid to ethoxyacetylene took place at 0°, or below, and the solution was then stirred at room temperature for a few hours.

$$HC \equiv COEt + RCO_2H \longrightarrow H_2C = C(OCOR)(OEt)$$

$$R = C_6H_5,\ CH_3CH_2,\ (CH_3)_3C,\ CHCl_2 \qquad \text{CXXIX}$$

Scheme 60

The crude 1-ethoxyvinyl carboxylates (CXXIX) were purified by distillation, under reduced pressure, through a short Vigreux column or a short column packed with Fenske helices. Yields ranged from 60 to 90%. The esters were characterised by spectral and elemental analysis.

The infrared spectra all exhibited the strong doublet in the 1650 - 1800 cm^{-1} region, which is characteristic of 1-ethoxyvinyl carboxylates:-

1-ethoxyvinyl pivalate: 1670, 1760 cm^{-1}

1-ethoxyvinyl propionate: 1675, 1775 cm^{-1}

1-ethoxyvinyl dichloroacetate: 1680, 1740 cm^{-1}

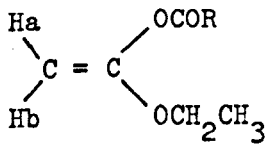
1-ethoxyvinyl benzoate: 1675, 1725 cm^{-1}

The nuclear magnetic resonance (n.m.r.) spectra showed a triplet for the methyl protons of the ethoxy group at about 8.6τ and a quartet for the methylene protons of the ethoxy group at about 6.0τ. In the n.m.r. spectrum of 1-ethoxyvinyl propionate and 1-ethoxyvinyl pivalate the absorptions of the vinyl protons appeared as a single peak superimposed on the methylene quartet: no splitting was discernable. In the n.m.r. spectra of 1-ethoxyvinyl benzoate and 1-ethoxyvinyl dichloroacetate, however, complex splitting, superimposed on the methylene quartet, was apparent. This is in accord with what appears to be the general case for the spin-spin coupling of the vinyl protons of 1-ethoxyvinyl carboxylates. In the case of esters of aliphatic carboxylic acids where R (CXXIX) is relatively small, the absorptions of the vinyl protons appear as a singlet (e.g. R = CH_3,[88] CH_2CH_3, CMe_3). Where R contains an aromatic ring or other bulky electronegative group then complex splitting is observed (e.g. R = Ph, p-NH_2-Ph,[88] -CH=CH-Ph,[88] -CH_2-Ph,[37] CCl_3,[88] $CHCl_2$). In some cases this splitting can be recognised as a typical AB quartet.

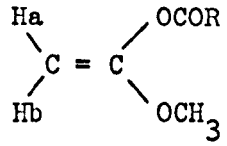
The vinyl protons of the keten acetal, CXXX, absorb at an unusually high field position away from the methylene quartet (at 5.94τ). Here the AB pattern is clearly discernible with peaks at 6.68, 6.74, 6.82, 6.90τ.[88]

1-Methoxyvinyl esters (CXXXI) have been reported to show AB

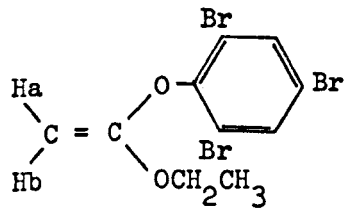
splitting in the three cases studied (R = CH_3, C_6H_5, CF_3).[20]



CXXIX

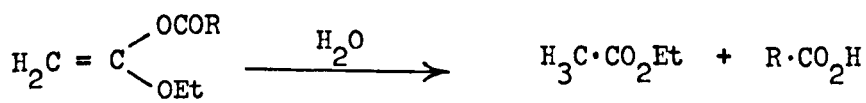


CXXXI



CXXX

The 1-ethoxyvinyl esters of pivalic, propionic, dichloroacetic and benzoic acids proved to be relatively stable liquids which hydrolysed at differing rates in contact with moist air (Scheme 61) but could be kept indefinitely under anhydrous conditions: 1-ethoxyvinyl dichloroacetate was the most unstable to moist air.

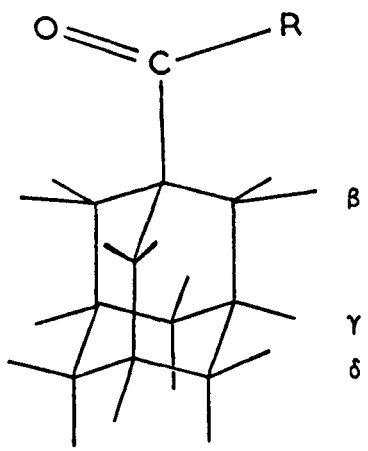


Scheme 61

(2) 1-Adamantanecarboxylic acid:

The properties and chemistry of adamantane, tricyclo $[3,3,1,1^{3,7}]$ decane, and some of its derivatives have recently been reviewed by Fort and Schleyer.[89] The same workers have also made a study of the proton magnetic resonance spectra of some fifty adamantane derivatives and have shown that this is a quick and effective method for the identification of adamantanes.[90]

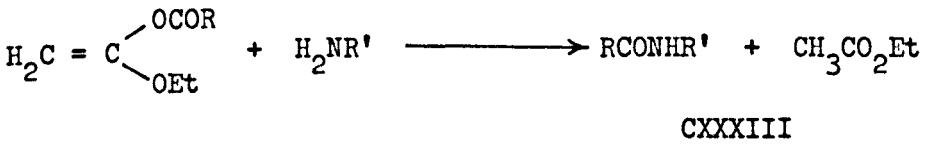
CXXXII



The object of the present study was to prepare a number of derivatives of 1-adamantane-carboxylic acid (CXXXII) (available from Aldrich Laboratories, U.S.A.) which contain an aromatic ring system in the side chain and to examine the affect, if any, on the absorptions of the protons of the adamantane nucleus. If, in these compounds, the aromatic ring spends an appreciable amount of time in the vicinity of the adamantane protons then the anisotropic effect of the ring could cause a downfield shift in the n.m.r. absorptions of these protons, particularly the β protons (CXXXII).

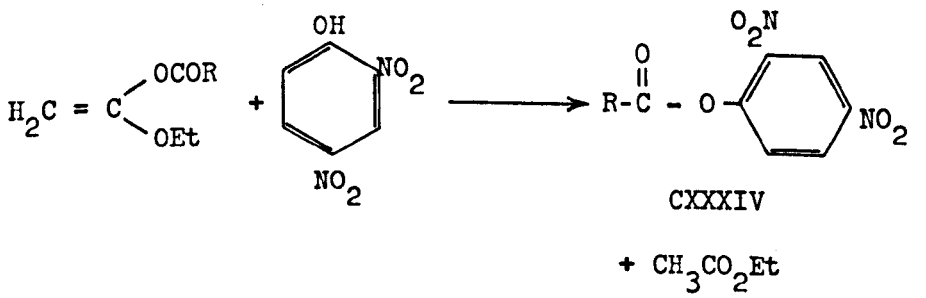
A simple synthetic route to compounds of this type via the 1-ethoxyvinyl ester was available. 1'-Ethoxyvinyl 1-adamantanecarboxylate, a low melting solid (m.p. 34 - 35°), was prepared by the usual method and purified by distillation under reduced pressure. The infrared spectrum showed strong peaks at 1673 and 1763 cm^{-1}, characteristic of a 1-ethoxyvinyl carboxylate, and the n.m.r. spectrum showed an unsplit peak, superimposed on the methylene quartet, for the absorptions of the vinyl protons.

1-Ethoxyvinyl adamantanecarboxylate was allowed to react with the amines, aniline, β-naphthylamine and benzylamine, and the corresponding amides (CXXXIII) obtained (Scheme 62); and with 2,4-dinitrophenol when the 2,4-dinitrophenyl ester (CXXXIV) was obtained (Scheme 63).



R = adamantyl; R' = C_6H_5, $C_6H_5CH_2$, or 1-naphthyl

Scheme 62



R = adamantyl

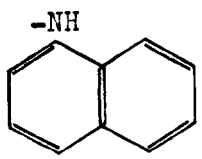
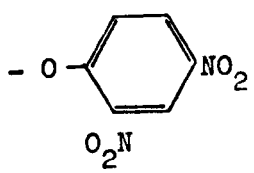
Scheme 63

The reactions with aniline and benzylamine were conducted without solvent, a solution of 1-ethoxyvinyl adamantanecarboxylate in an excess of the amine being heated at 80° for about 1 hour. The corresponding amides were obtained in 98 and 88% yields, respectively, and were characterised by spectral and elemental analysis. 1-Ethoxyvinyl adamantanecarboxylate was reacted with N-1-naphthylamine and 2,4-dinitrophenol, respectively, by heating a solution of the two reactants in methylene dichloride, under reflux for about one hour.

The absorptions of the protons of the adamantane nucleus in the n.m.r. spectra are shown in the following table, along with the absorptions in 1-adamantanecarboxylic acid and 1'-ethoxyvinyl 1-adamantanecarboxylate.

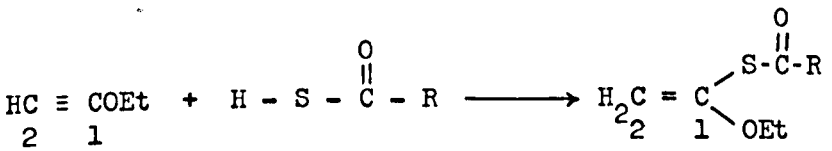
These measurements show no significant differences between the absorption positions of the adamantane protons in the derivatives, CXXXII, compared with those of 1-adamantanecarboxylic acid. Therefore it can be concluded that, in these compounds, the aromatic ring system spends little time in the vicinity of the protons on the adamantane skeleton.

Chemical Shifts (τ) of Adamantane Protons in Derivatives of 1-Adamantane Carboxylic Acid (CXXXII)

Substituent R CXXII	β and γ protons absorptions (τ)	δ protons absorption (τ)
-OH	8.06, 7.89 (partially resolved)	8.26
$-O-\overset{\overset{CH_2}{\|\|}}{C}-OEt$	8.02 (unresolved)	8.23
$-NHC_6H_5$	7.99, 7.82 (partially resolved)	8.22
$-NHCH_2C_6H_5$	8.06, 7.82 (partially resolved)	8.25
	7.86 (unresolved)	8.15
	7.85 (unresolved)	8.15

(3) Thiolic Acids:

Banks and Cohen[10] have reported that the thiolic acids, thiolacetic acid and thiolbenzoic acid, react with an excess of ethoxyacetylene to give the corresponding 1-ethoxyvinyl esters (CXXXV) in high yield (Scheme 64). This is analogous to the reaction of a carboxylic acid with ethoxyacetylene.



CXXXV

Scheme 64

When attempts were made to reproduce these reactions, in the present work, it was found that a free-radical mode of addition often competed with the ionic addition which had been previously observed; and sometimes free-radical addition can occur to the complete exclusion of ionic addition. The prediction that the 1-ethoxyvinyl ester should be the sole product of an ionic addition is in accord with Markovnikov's rule. The ethoxyacetylene molecule is polarised in the sense shown in CXXXVI; thus in an ionic addition reaction a proton should become attached at C_2.

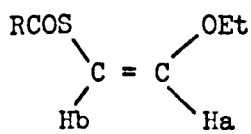
CXXXVI

When redistilled thiolacetic acid (Koch-Light Laboratories) was allowed to react with an excess of ethoxyacetylene, a 56% yield of 2-ethoxyvinyl thiolacetate (CXXXVII) was obtained after distillation of the crude product, under reduced pressure. (Scheme 65). V.p.c. analysis of the crude product indicated that no 1-ethoxyvinyl thiolacetate had been formed. 2-Ethoxyvinyl thiolacetate, a liquid of slightly higher boiling point than the 1-isomer, was characterised by its infrared and n.m.r. spectra, its mass spectra, and by elemental analysis. The infrared spectrum showed strong peaks at 1695 cm^{-1} and 1635 cm^{-1} for the absorptions of the C = O group and the C = C group, respectively, and a peak of medium intensity at 3090 cm^{-1} corresponding to the C - H stretch of the olefinic protons. The ester was identified as <u>cis</u>-2-ethoxyvinyl thiolacetate from its n.m.r. spectrum since the olefinic protons appeared as a pair of doublets (3.55, 4.42τ) with a coupling constant (J) of approximately 6 c.p.s. (CXXXVII)

$$HC \equiv COEt + HS - \overset{\overset{O}{\|}}{C} - R \longrightarrow \overset{\overset{O}{\|}}{RCSCH = CHOEt}$$

CXXXVII

Scheme 65

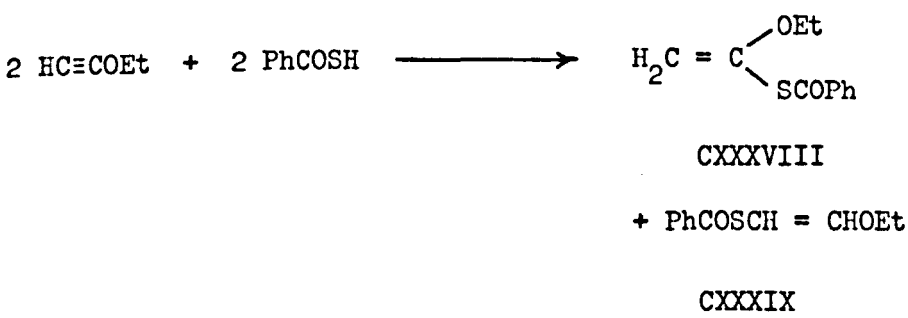


Jab ~ 6 c.p.s.

CXXXVII

Formation of 2-ethoxyvinyl thiolacetate by a stereospecific trans free-radical addition is supported by the fact that when the reaction was repeated in the presence of hydroquinone, a radical scavenger, in an atmosphere of dry nitrogen, in the dark, a 71% yield of 1-ethoxyvinyl thiolacetate was obtained. Thiolacetic acid was purified, before use, by distillation from a small amount of hydroquinone, in the dark, in an atmosphere of dry nitrogen. There was no trace of 2-ethoxyvinyl thiolacetate found in the crude product (v.p.c. analysis and n.m.r. spectral analysis).

Similar experiments were performed using thiolbenzoic acid and ethoxyacetylene, but with different results. In all cases a mixture of 1-ethoxyvinyl thiolbenzoate (CXXXVIII) and 2-ethoxyvinyl thiolbenzoate (CXXXIX) were formed (Scheme 66).

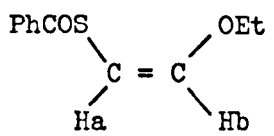


Scheme 66

The first experiment performed, when no special precautions were taken against free-radical intermediates, yielded a crude mixture of the 1- and 2-isomers in the ratio of 4 : 1 from v.p.c. analysis. Distillation, under reduced pressure, gave pure 1-ethoxyvinyl thiolbenzoate

in 25% yield. The infrared spectrum showed strong peaks at 1680 cm^{-1} and 1740 cm^{-1}. In the infrared spectra of both 1-ethoxyvinyl thiolacetate and 1-ethoxyvinyl thiolbenzoate the lower frequency band is slightly more intense. The n.m.r. spectrum of 1-ethoxyvinyl thiolbenzoate showed an unsplit peak at 6.06τ, superimposed on the methylene quartet, for the absorptions of the vinyl protons.

However the results of the above experiment could not be reproduced. When the reaction was repeated on a larger scale in the presence of small amounts of hydroquinone, in the dark, in an atmosphere of dry hydrogen the 1- and 2-isomers were formed in a ratio of 3 : 2, from v.p.c. analysis and n.m.r. spectral analysis. The n.m.r. spectrum of the mixture shows distinct absorptions for the ortho protons of the two isomers:- 1.56 - 1.82τ, complex splitting, for 1-ethoxyvinyl thiolbenzoate; and 1.86 - 2.05, complex splitting, for 2-ethoxyvinyl thiolbenzoate: the meta- and para- aromatic protons of the two isomers have overlapping absorptions. The olefinic protons appear as an AB quartet (5.15, 5.18, 5.24, 5.27τ) for the 2-isomer and an unsplit peak at 6.06τ, superimposed on the methylene quartet for the 1-isomer. The 2-ethoxyvinyl ester formed was identified as <u>cis</u>-2-ethoxyvinyl thiolbenzoate (CXXXIX), from the n.m.r. spectrum (Jab ~ 3 c.p.s.).



Jab ~ 3 c.p.s.

CXXXIX

Distillation of the mixture, under reduced pressure through a Vigreux column or a column packed with glass helices produced no separation of the isomers and an attempted distillation through an Annular Teflon Spinning Band column (Nester-Faust) resulted in decomposition of the 1-ethoxyvinyl ester because of prolonged heating at 150 - 200°. Pure samples of 2-ethoxyvinyl thiolbenzoate were obtained from this distillation.

An attempt to separate the isomers on an alumina column resulted in hydrolysis of the 1-isomer. No 1-ethoxyvinyl thiolbenzoate was recovered from the column, although samples of 2-ethoxyvinyl thiolbenzoate, uncontaminated with the 1-isomer were obtained. Some benzoic acid was also recovered from the column.

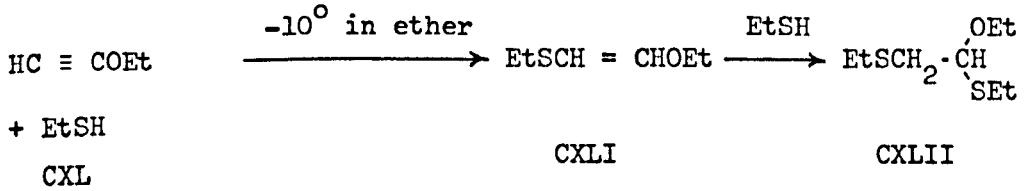
A variety of other reaction conditions were tried such as lower temperatures for the reaction (down to -30°), and other solvents (e.g. ether, benzene). The thiolbenzoic acid, used in the reaction, was purified by careful fractional distillation, under reduced pressure, and decolourised by distillation from Linseed oil which produced a colour change from deep-red to pale yellow. However, none of these measures produced any significant increase in the yield of the 1-ethoxyvinyl ester; the ratio of the 1-isomer to the 2-isomer never exceeding 3 : 2.

It was noticed that solutions of these isomers when allowed to evaporate in the air slowly deposited white crystals of benzoic acid, a hydrolysis product.

Experiments with thiolbenzoic acids were not continued beyond this stage.

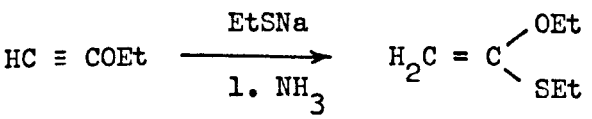
Free-radical addition reactions are well known in the chemistry of organic sulphur compounds. Some reactions of thiols and thiolic acids with acetylenes have been reported in the literature.[91,92,93]

The addition of thiols to ethoxyacetylene has been studied.[92] Ethanethiol (CXL) reacts with ethoxyacetylene to produce much cis and a little trans-1-ethoxy-2-(ethylthio) ethene (CXLI). This could also add a second molecule of ethanethiol to yield 1-ethoxy-1,2-bis(ethylthio) ethane (CXLII) (Scheme 67). Hydroquinone was found to inhibit the reaction.[92] Similar reactions were performed with other thiols.



Scheme 67

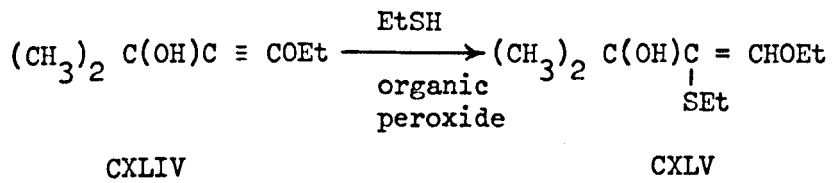
The corresponding 1-addition product (CXLIII) could be prepared by the reaction of sodium ethanethiolate, in liquid ammonia, with ethoxyacetylene (Scheme 68).[92]



CXLIII

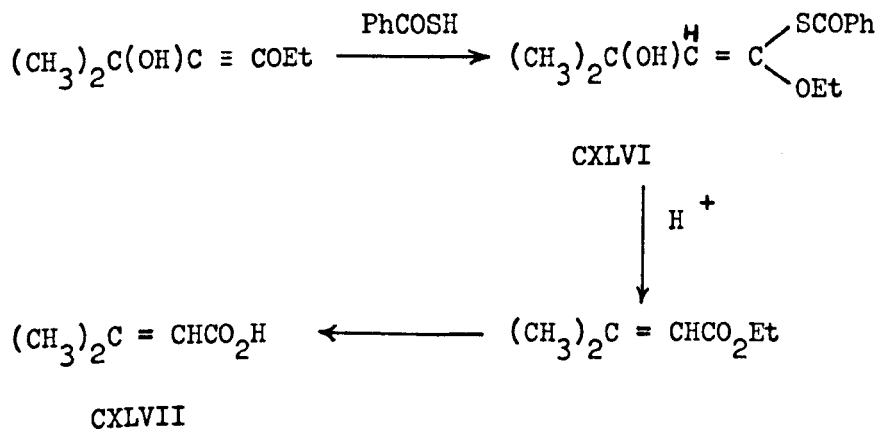
Scheme 68

The ethoxyethynylcarbinol, CXLIV, (prepared from BrMgC≡COEt and acetone) undergoes addition of ethanethiol, in the presence of di-t-butyl peroxide, to give the mono-adduct, CXLV, (Scheme 69);[91] whereas reaction with thiolbenzoic acid, even in the presence of organic peroxide, favours an ionic mechanism to yield the adduct, CXLVI, which was not isolated but which rearranged and was hydrolysed to give β,β-dimethylacrylic acid (CXLVII) (Scheme 70).[91]



CXLIV CXLV

Scheme 69



CXLVII

Scheme 70

When thiolacetic acid reacts with monosubstituted acetylenes (CXLVIII, R = C_4H_9, C_6H_5, p-$MeOC_6H_5$, $MeOCH_2$) either alone, or under the influence of organic peroxides or irradiation with ultra-violet light, mono-adducts (CXLIX) and di-adducts are produced by radical addition reactions (Scheme 71).[93]

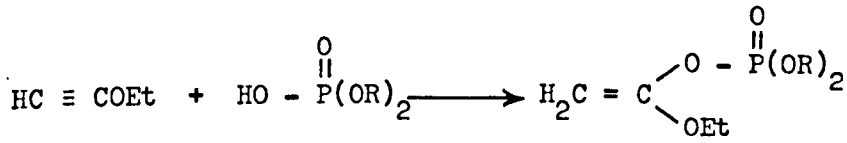
$$RC \equiv CH + CH_3COSH \longrightarrow RCH = CHSCOCH_3$$

CXLVIII CXLIX

Scheme 71

(4) Diphenylphosphinic acid:

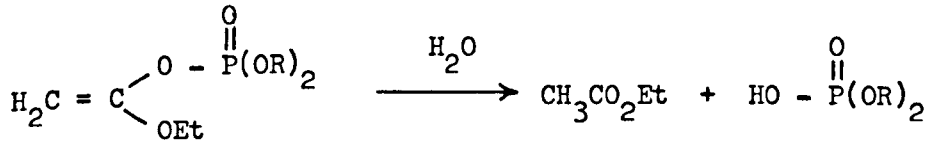
The 1-ethoxyvinyl phosphates (CL, R = C_6H_5, $C_6H_5CH_2$, p-$NO_2C_6H_5$) have been prepared by the reaction of the corresponding phosphate with an excess of ethoxyacetylene.[6,7] (Scheme 72). Elemental analyses were obtained for two esters (CL, R = C_6H_5, $C_6H_5CH_2$), and the other ester (CL, R = p-$NO_2C_6H_5$) was characterised by spectral analysis. These esters were found to be much less stable than their carboxylic analogues, undergoing facile hydrolysis on contact with moist air (Scheme 73).[6,7]



CL

$R = C_6H_5$, $C_6H_5CH_2$, $p\text{-}NO_2C_6H_5$

Scheme 72



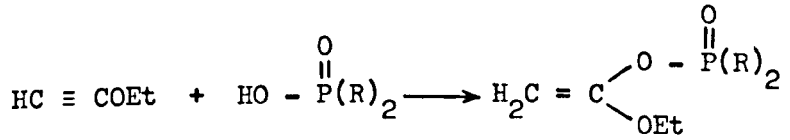
CL

Scheme 73

The object of the present work was to investigate the reactions of phosphinic acids with ethoxyacetylene and attempt to isolate the 1-ethoxyvinyl phosphinates. (CLI) (Scheme 74).

Diphenylphosphinic acid (K. and K. Laboratories, U.S.A.) was rigorously dried and allowed to react with a ten-molar excess of ethoxyacetylene, by addition of the solid acid to a methylene dichloride solution of ethoxyacetylene. Spectral analysis indicated the formation of 1-ethoxyvinyl diphenyl phosphinate, (CLI, $R = C_6H_5$) in almost quantitative yield (Scheme 74). The crude reaction product, a pale brown liquid, was distilled under reduced pressure to yield a clear colourless

liquid which proved to be too unstable for elemental analysis.



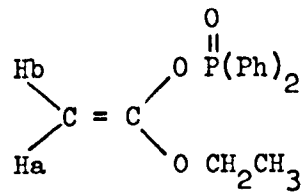
$R = C_6H_5$ CLI

Scheme 74

The infrared spectrum showed an intense absorption at 1665 cm^{-1} of the $C = CH_2$ stretching frequency, and a weak absorption at 1740 cm^{-1} which has not been assigned. As has been mentioned before, the two peaks in the 1650 - 1800 cm^{-1} region of the infrared spectrum are very characteristic of 1-ethoxyvinyl esters but although the upper frequency band can be assigned to the carbonyl stretching frequency in the case of the 1-ethoxyvinyl carboxylates and thiolates, no such assignment can be made for the 1-ethoxyvinyl esters of sulphonic, sulphuric, phosphoric and phosphinic acids. This band is notably weaker in 1-ethoxyvinyl esters of the phosphorus acids being of medium intensity for 1-ethoxyvinyl diphenylphosphate (1735, 1665 cm^{-1}) and now of weak intensity for 1-ethoxyvinyl diphenylphosphinate.

The n.m.r. spectrum of 1-ethoxyvinyl diphenylphosphinate shows the expected complex absorptions for the aromatic protons and a triplet for the methyl protons of the ethoxy group. In the region 5.9 - 6.5τ there is a region which can be analysed as the quartet of the methylene protons of the ethoxy group superimposed on a complex splitting pattern.

The complex pattern arises from the spin-spin coupling of the vinyl protons (CLI, Ha, Hb) with one another, and allylic spin-spin coupling of each of the vinyl protons with the phosphorus atom.



CLI

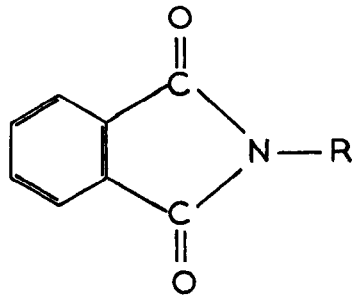
Coupling of protons with phosphorus through a number of bonds has been reported in many cases in the literature. For the system (H - C = C - O - P), which is the one present in 1-ethoxyvinyl diphenylphosphinate, coupling constants (J) of ca. 2 c.p.s. for cis coupling and 1 c.p.s. for trans coupling have been measured.[94] Also allylic coupling through the following systems has been observed:-[95] H - C - C = C - P; H - C = C - C - P; H - C - C ≡ C - P; H - C ≡ C - C - P; and even homoallylic coupling in the cases:-[95] H - C - C = C - C - P; H - C - C = C - O - P.

The absorptions of the vinyl protons of 1-ethoxyvinyl diphenylphosphate show a similar complex splitting pattern.[88]

On exposure of 1-ethoxyvinyl diphenylphosphinate to moist air, for even short periods, a white deposit of diphenylphosphinic acid was formed and the odour of ethyl acetate could be detected. Although small samples were completely hydrolysed in the air, after about one minute, they could be stored for long periods in sealed glass phials which had been flushed out with dry nitrogen.

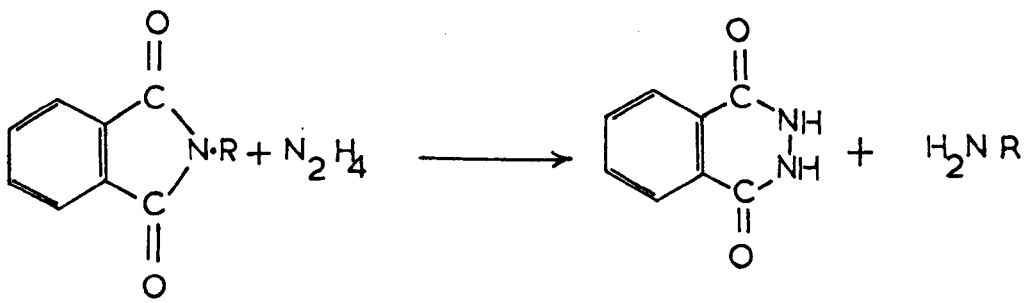
B. Reactions of 1,2-dicarboxylic acids with ethoxyacetylene, alone; and in the presence of amines, and of amino-acids: N-protection of amino-acids.

The phthaloyl group has been used quite widely for protecting the amino groups of α-amino-acids and peptides (CLII) during peptide synthesis.[102]



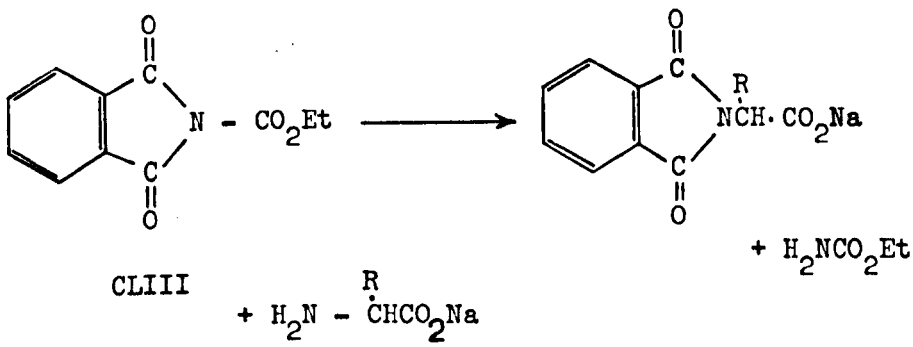
CLII

In contrast with other N-acyl-α-amino acids, the N-phthaloyl derivatives can be converted to stable acid chlorides that can be used as activated carboxyl components in peptide coupling.[102] The phthaloyl group can be subsequently removed, without affecting peptide bonds, by treatment with hydrazine;[102] this can be effective even under mild, neutral, conditions.[96] (Scheme 75)



Scheme 75

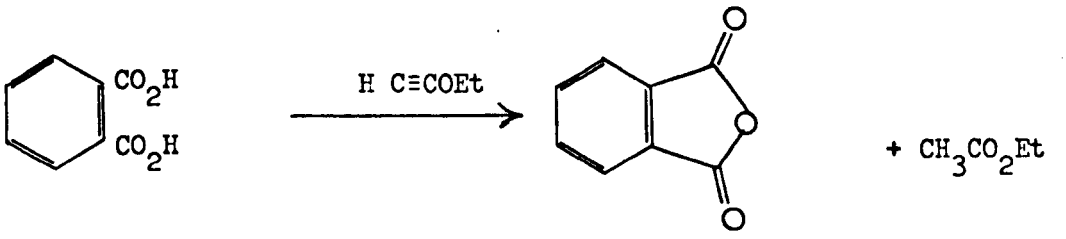
Methods of forming N-phthaloyl peptides, however, often suffer from a lack of general application or require rather drastic reaction conditions which might cause racemization of the optically active α-carbon atom. The method originally used by Sheehan and Frank[97] was to fuse the amino-acid and phthalic anhydride together but this often leads to racemized products. A better method, developed recently by Nefkens and co-workers,[98] uses the reagent N-ethoxycarbonyl-phthalimide, (CLIII), obtainable from a salt of phthalimide and ethyl chloroformate in dimethylformamide, and appears to be general in application. A suspension of the reagent in dilute sodium bicarbonate (or carbonate) solution readily reacts with the amino group of α-amino-acids to give the desired phthaloyl derivatives. (Scheme 76)



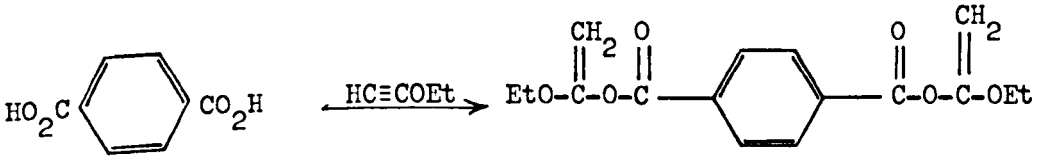
Scheme 76

Banks[11,19] has shown that when phthalic acid is allowed to react with an excess of ethoxyacetylene the intramolecular anhydride (CLIV) is formed (Scheme 77) whereas terephthalic acid yields the di-1-ethoxyvinyl

ester (CLV, Scheme 78). The proximity of the carboxyl groups in phthalic acid presumably accounts for the difference in the course of the reactions.

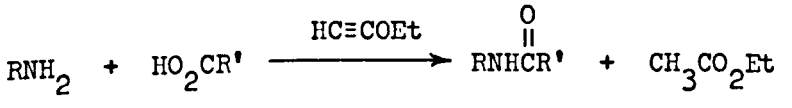


Scheme 77



Scheme 78

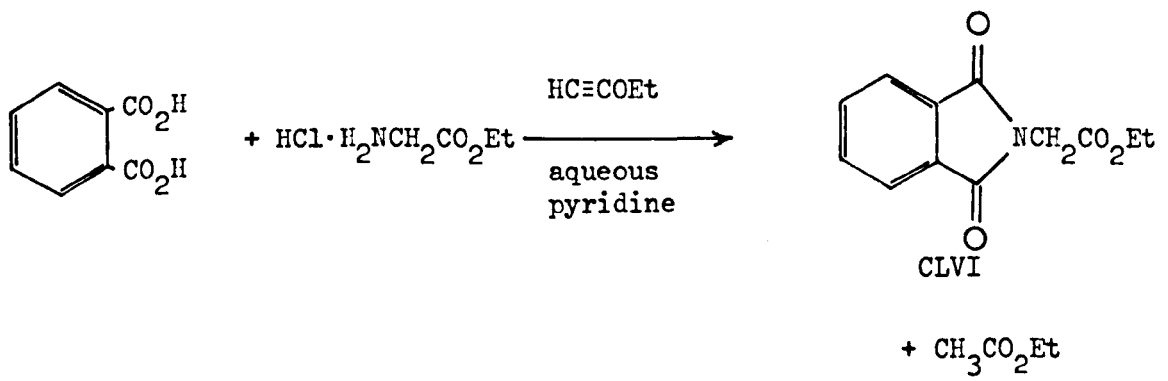
Although ethoxyacetylene had been used to form peptide links without isolation of the intermediate 1-ethoxyvinyl esters (Scheme 79) it had not been used to form the N-protected amino-acids themselves.



Scheme 79

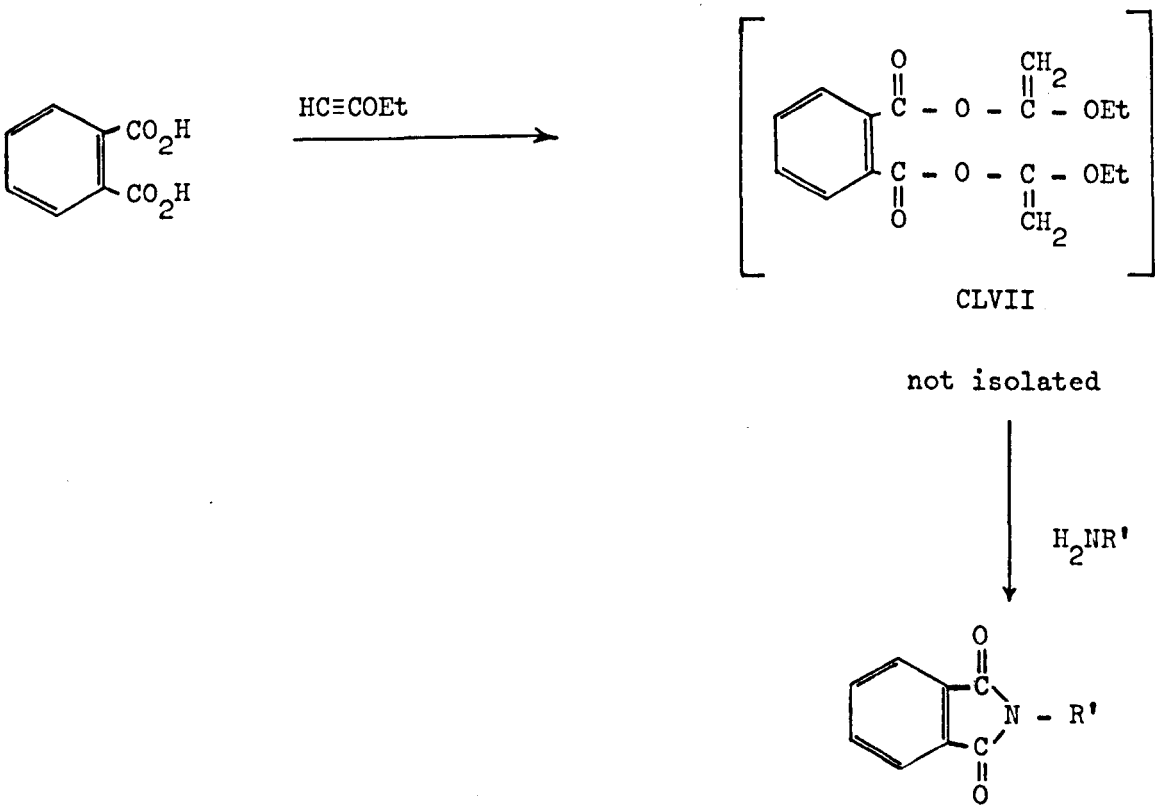
When phthalic acid was allowed to react with ethoxyacetylene

in the presence of amino-acids or amino-acid esters (or their hydrochlorides) either in anhydrous or aqueous solution, the corresponding N-phthaloyl derivatives are obtained smoothly and in good yield.[19] Thus N-phthaloylglycine ethyl ester (CLVI) was prepared in 93% yield by allowing a solution of phthalic acid in dilute aqueous pyridine to drip into an aqueous solution of glycine ethyl ester hydrochloride and excess ethoxyacetylene, cooled in an ice-bath.[19] (Scheme 80). Crystalline N-phthaloylglycine ethyl ester precipitated after stirring for several hours at room temperature. Ethyl acetate is a by-product of the reaction and this forms a separate layer on top of the aqueous layer in the reaction mixture.



Scheme 80

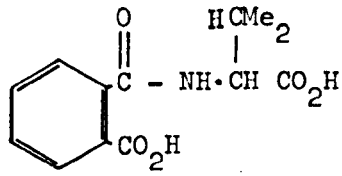
The reaction may proceed <u>via</u> the intermediate formation of the di-1-ethoxyvinyl ester of phthalic acid (CLVII) which then reacts with the amino group of the amino-acid to form the N-phthaloyl derivative. (Scheme 81).



Scheme 81

Using this reaction the N-phthaloyl derivatives of glycine (54%), L-phenylalanine methyl ester (84%) and D,L-alanine ethyl ester (50%) were also prepared.[19] In the reaction involving L-phenylalanine methyl ester Banks[11] has shown that the amino-acid undergoes no racemization.

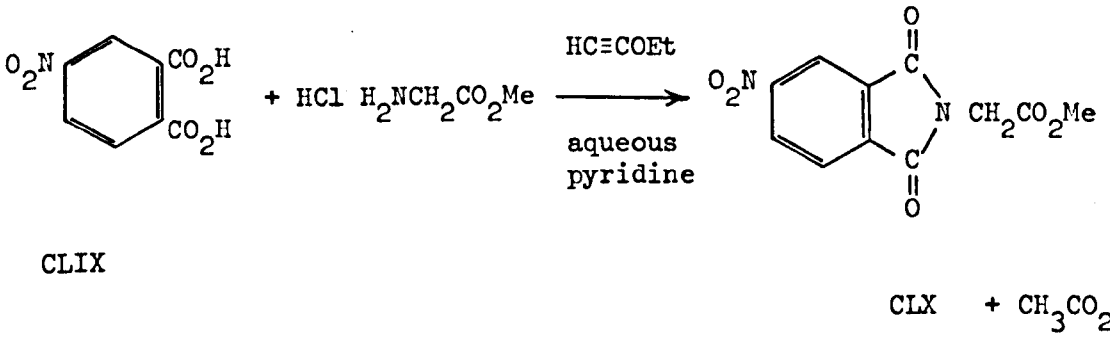
Attempts to prepare the N-phthaloyl derivative of D,L-valine ethyl ester, however, yielded only the corresponding phthalamic acid (CLVIII).[42]



CLVIII

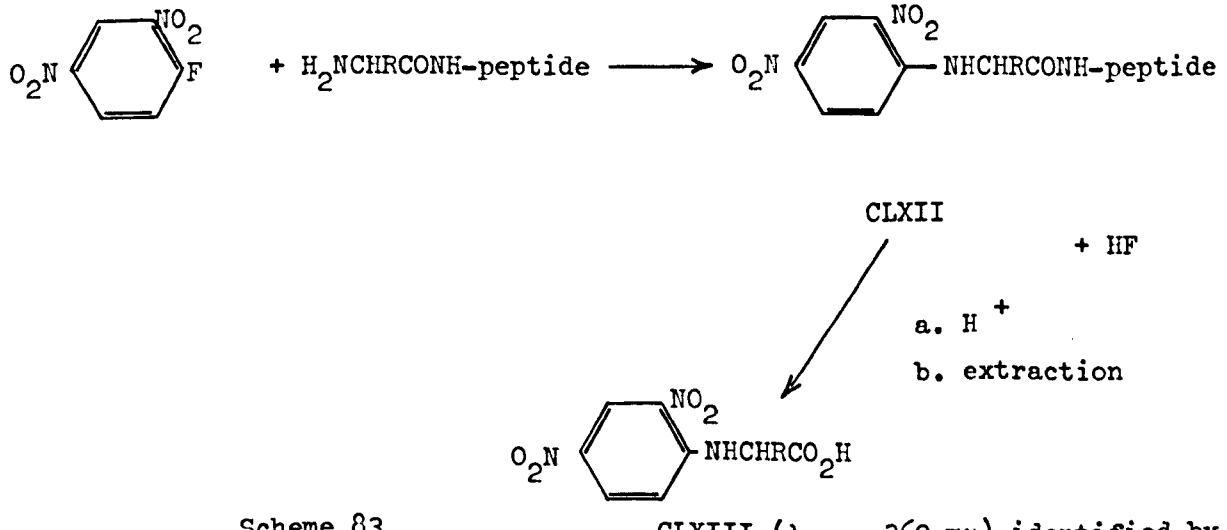
Reaction of an α-amino-acid (or its ester hydrochloride) with phthalic acid in the presence of ethoxyacetylene seems to offer an attractive route to N-phthaloylamino-acids since it takes place under mild conditions (0° or below) and is accompanied by little, or no, racemization. In order to extend the scope of this synthetic route, similar uses of substituted phthalic acids and the 1,2-dicarboxylic acids, maleic acid and succinic acid were investigated.[19]

Using the same reaction conditions as before, 4-nitrophthalic acid (CLIX) was allowed to react with glycine methyl ester hydrochloride in the presence of an excess of ethoxyacetylene. N-4-Nitrophthaloylglycine methyl ester (CLX) was crystallised in 62% yield from the crude reaction product. The n.m.r. spectrum showed complex splitting for the aromatic protons (1.23 - 1.92τ), a singlet for the methylene protons at 5.45τ and a singlet for the methyl protons at 6.16τ.



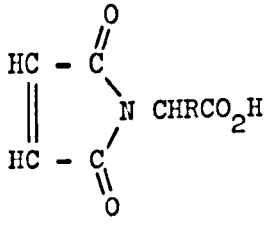
Scheme 82

Unfortunately this derivative was not sufficiently deeply coloured to act as an easily visible spot on paper chromatography. It seems clear, however, that suitably substituted phthalic acids could be used for this purpose in an analogous way to Sanger's dinitrophenylation technique. (Scheme 83)

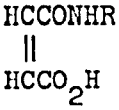


Scheme 83

The formal similarity between phthalimide and maleimide suggests that maleimido-acids (CLXIV) might be applied to the synthesis of peptides as with phthalimido-acids. Removal of the maleoyl group by, for example, ozonolysis can be envisaged. However none of the required maleimido-acids (CLXIV) is known and the literature records only six maleamic-acids (CLXV, R = o-, m-, p- $C_6H_4CO_2H$,[99] CH_2CO_2H[100,101] CH_2CO_2Et,[101] $CHMeCO_2H$[101]) derived from the corresponding amino-acids.

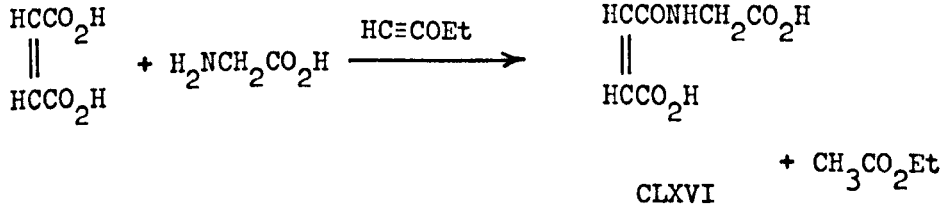


CLXIV



CLXV

Reaction of maleic acid with ethoxyacetylene in the presence of glycine in aqueous solution gave the maleamic-acid, maleyl glycine (CLXVI) in 85% yield. (Scheme 84)



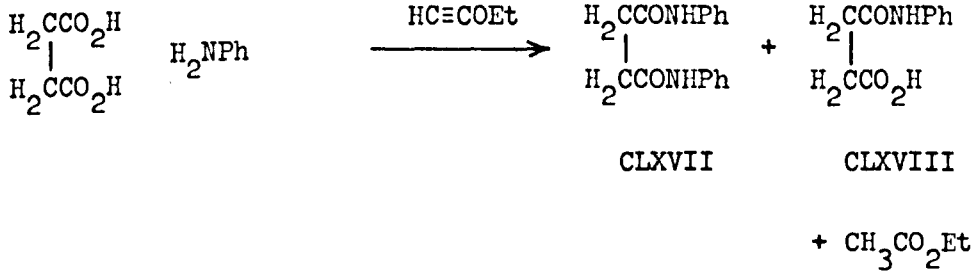
Scheme 84

The infrared spectrum showed a weak absorption at 3300 cm^{-1}

from the N-H stretching frequency, a strong amide carbonyl absorption at 1680 cm^{-1} (Amide I band) and another strong carbonyl absorption at 1720 cm^{-1}. The vinyl protons appeared as an unsplit peak at 3.65τ (D_2O) in the n.m.r.

Similarly, reaction with aniline under the same conditions gave maleanilic acid (N-phenylmaleamic acid) in 98% yield.

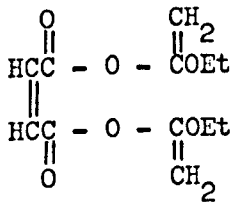
When succinic acid was allowed to react with ethoxyacetylene, in the presence of aniline, N,N'-diphenylsuccinamide (CLXVII) (17.5%) and N-phenylsuccinamic acid (CLXVIII) (56%) were isolated from the reaction mixture (Scheme 85).



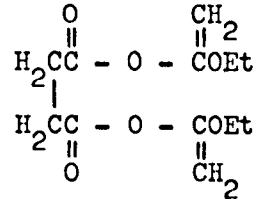
Scheme 85

Failure to cyclize maleamic acids to maleimide derivative using a wide variety of dehydrating agents has been reported in the literature.[101] Similar reaction conditions are successful in cyclizing phthalamic-acids to phthalimide derivatives.

Attempts were made to isolate the di-1-ethoxyvinyl esters of maleic acid (CLXIX) and succinic acid (CLXX).



CLXIX



CLXX

Maleic acid was allowed to react with an excess of ethoxyacetylene in methylene dichloride solution. The crude product after evaporation of volatile components showed peaks in the infrared spectrum which are characteristic of 1-ethoxyvinyl esters:- 1780 cm^{-1} (broad, strong), 1680 cm^{-1} (strong). However a weak band at 1850 cm^{-1} indicated an appreciable amount of maleic anhydride was also present. An attempt to distil the mixture resulted in decomposition of the ester: the black residue showed only anhydride peaks in the 1600 - 1900 cm^{-1} region of the infrared spectrum.

The experiment was repeated in an atmosphere of dry nitrogen, using anhydrous ether as solvent. In this case the product, a viscous orange liquid, gave a better resolution in the infrared spectrum showing strong peaks at 1680 cm^{-1} and 1760 cm^{-1} as expected for di-1-ethoxyvinyl maleate, and a strong peak at 1785 cm^{-1} and a weak peak at 1855 cm^{-1} indicating a considerable amount of the intramolecular anhydride was also present.

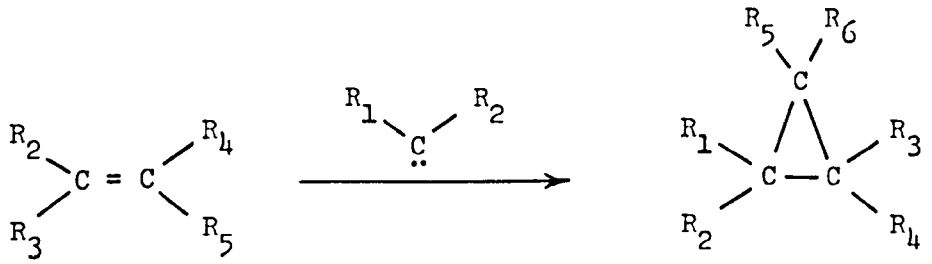
Similar experiments with succinic acid and ethoxyacetylene

gave, after distillation (115 - 118° at 0.6 mm.) a low melting solid. The n.m.r. spectrum showed complex splitting 5.8 - 6.2τ, an unsplit peak at 7.12τ and a triplet at 8.62τ integrating as 4 : 2 : 3. There was also a singlet at 6.91τ from the succinic anhydride impurity. This integrated as 0.8 of a proton indicating that about 20% of the anhydride was present. The infrared spectrum showed strong peaks at 1675 cm^{-1} and 1775 cm^{-1} and a weak anhydride peak at 1865 cm^{-1}.

A sample of the mixture was dissolved in aniline and heated at 80° for 4 hr. Formation of ethyl acetate was detected during the reaction, and N,N'-diphenylsuccinamide was recovered in 80% yield on evaporation of the excess aniline.

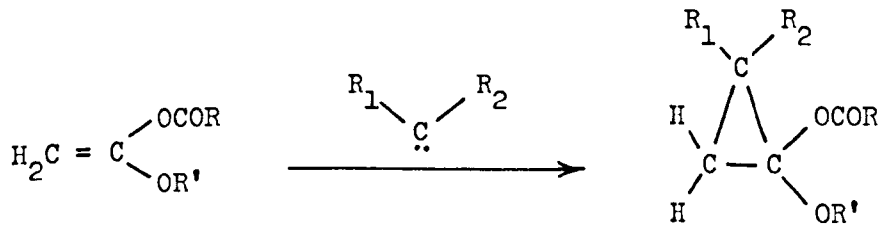
C. Formation and Reactions of Cyclopropanone Acylals.

The reaction of an alkene with a carbene or carbene-like intermediate represents a general synthetic route to derivatives of cyclopropane. (Scheme 86)



Scheme 86

If the alkene involved in this reaction were a 1-alkoxyvinyl ester (CLXXI) then the cyclopropane obtained would be a cyclopropanone acylal (CLXXII) (Scheme 87)



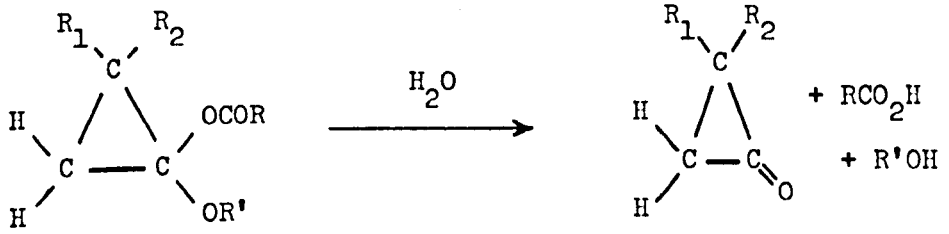
CLXXI CLXXII

Scheme 87

Since acylals, in general, are easily converted to the parent ketone by hydrolysis under acid, basic or even neutral conditions, the

acylal, CLXXII, should on hydrolysis yield the corresponding cyclopropanone (CLXXIII) (Scheme 88).

However, because of the high reactivity of the cyclopropane ring towards electrophiles, and the low thermal stability of some known cyclopropanones, a careful choice of reaction conditions would be necessary to avoid cleavage of the ring.

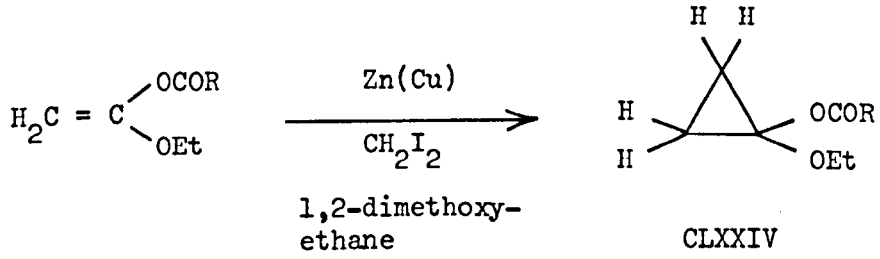


CLXXII CLXXIII

Scheme 88

The aims of the present work were to prepare the cyclopropanone acylal system (CLXXII) and to attempt to convert it to the cyclopropanone system (CLXXIII) with a view to isolating the cyclopropanone or demonstrating its formation as an intermediate.

Wasserman and Clagett[45] have prepared the cyclopropanone acylals (CLXXIV) 1-ethoxycyclopropyl acetate (R = CH_3, 35% yield) and 1-ethoxycyclopropyl benzoate (R = C_6H_5, 19% yield), by reaction of the corresponding 1-ethoxyvinyl ester with methylene di-iodide and zinc-copper couple in the presence of 1,2-dimethoxyethane (glyme) (Scheme 89).



CLXXIV

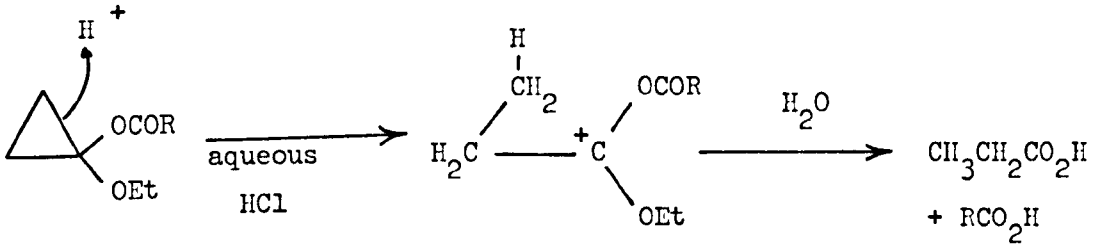
Scheme 89

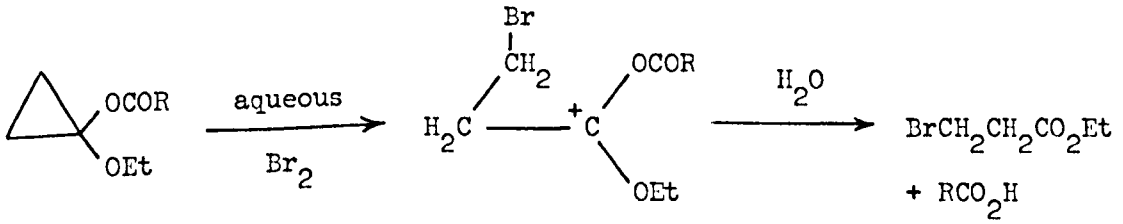
This reaction, which constitutes a general stereospecific 1,2-addition to give cyclopropanes was developed by Simmons and Smith.[85] They have shown that the reaction does not involve a free carbene intermediate but that the methylene-transfer step takes place through a stable organozinc intermediate, probably $(ICH_2)_2$ $Zn.ZnI_2$, which reacts in a kinetically bimolecular process with alkenes to give a cyclopropane and zinc iodide. This mechanism rationalises the observed rigorous stereospecificity of the reaction and the absence of any competing reactions involving insertion of methylene into carbon-hydrogen bonds.

Wasserman and Clagett[45] found that it was essential to use 1,2-dimethoxyethane in their reaction (in an amount equimolar to the methylene di-iodide) to precipitate zinc iodide, which would otherwise catalyse the cleavage of the cyclopropane ring.

The cyclopropanone acylals, CLXXIV, are distillable liquids (under reduced pressure), stable under neutral conditions, but on treatment with acidic or basic reagents facile ring-cleavage occurs. Reaction with dilute aqueous hydrochloric acid gives propionic acid and the

corresponding carboxylic acid while treatment with aqueous bromine gives ethyl β-bromopropionate and the corresponding carboxylic acid (Scheme 90).



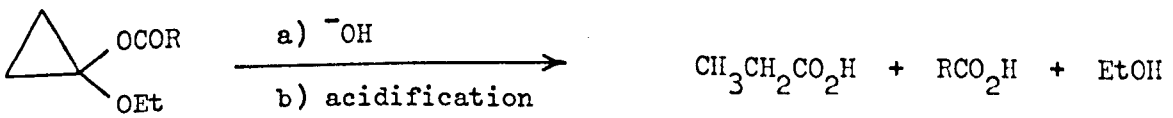


CLXXIV

R = CH_3, C_6H_5

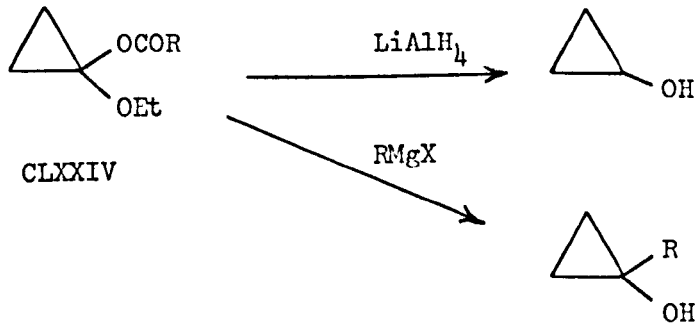
Scheme 90

Hydrolysis with dilute alkali gives propionic acid and either acetic or benzoic acid. (Scheme 91)



Scheme 91

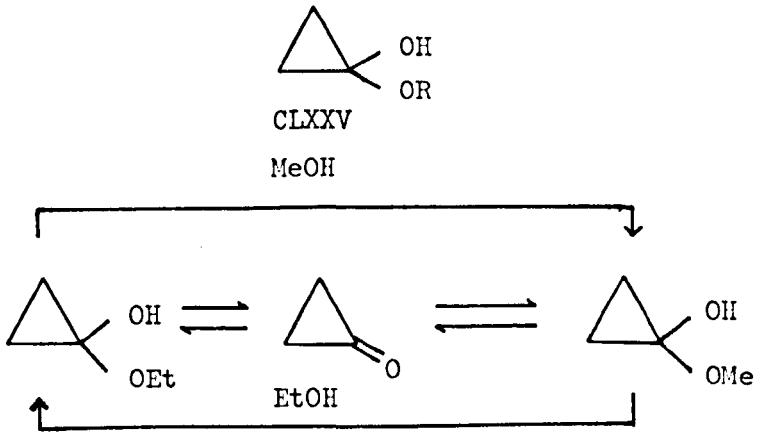
Cyclopropanol was formed in the reaction of 1-ethoxycyclopropyl esters, CLXXIV, with excess of lithium aluminium hydride in ether[45] (Scheme 92), and reaction with an excess of a Grignard reagent (Scheme 92, R = Ph or cyclopentadienyl, X = Br; R = CH_3, X = I) gave rise to the corresponding 1-substituted cyclopropanol.[45,46]



Scheme 92

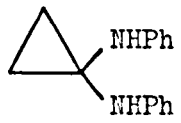
The formation of cyclopropanone as a transient intermediate in the reaction with Grignard reagents has been suggested.[45]

1-Ethoxycyclopropyl acetate, when allowed to react with an excess of methanol at 25° gives cyclopropanone methyl hemiketal (CLXXV, R = Me) (64% yield) along with methyl acetate and methyl propionate. With ethanol, the ethyl hemiketal (CLXXV, R = Et) is formed. This rearranges, above 65°, or on standing in inert solvents to form ethyl propionate. Either one of the hemiketals is converted to the other on standing with an excess of the corresponding alcohol (Scheme 93). A cyclopropanone-hemiketal equilibrium has been invoked to explain this conversion (Scheme 93).[46]



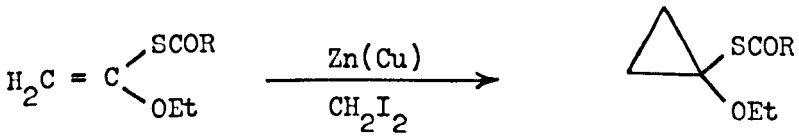
Scheme 93

Reaction of aniline with cyclopropanone ethyl hemiketal at 25° gave 1,1-dianilinocyclopropane (CLXXVI) in 48% yield.[46]



CLXXVI

In the course of the present work an attempt was made to extend the work of Wasserman and Clagett to the thio analogues (CLXXVIII) of the cyclopropanone acylals, prepared from the corresponding 1-ethoxy-vinyl thiolcarboxylate, CLXXVII (Scheme 94).



CLXXVII CLXXVIII

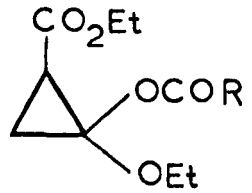
Scheme 94

As a trial experiment the 1-ethoxyvinyl ester of propionic acid was reacted with methylene di-iodide and zinc-copper couple, in boiling ether, in the presence of 1,2-dimethoxyethane. An exothermic reaction occurred and after heating the mixture under reflux for 44 hr., the solution was filtered free of catalyst and extracted with saturated aqueous sodium chloride. The ether was evaporated to yield a red-brown liquid. This was fractionally distilled and a fraction showed no olefinic absorptions in the infrared and a strong ester carbonyl absorption at 1760 cm^{-1}. A weak absorption at 1820 cm^{-1} showed the presence of anhydride impurity which was confirmed by v.p.c. analysis. The liquid could not be purified by distillation and a sample decomposed in an attempted preparative gas chromatography separation. A correct elemental analysis could not be obtained.

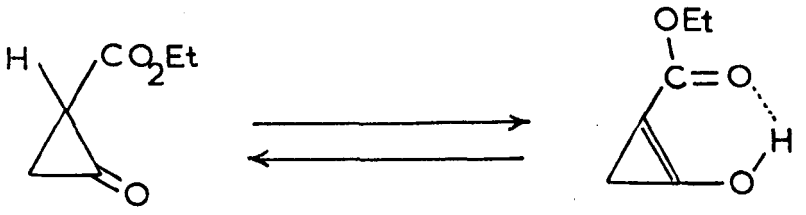
The experiment was repeated using 1-ethoxyvinyl thiolacetate. However when an attempt was made to distil the crude product, (a yellow liquid) at 100°, 28 mm., extensive decomposition occurred and a black tar was formed in the distillation flask. The pressure was reduced to 0.1 mm. but nothing distilled over.

At this stage experiments with zinc-copper couple and methylene di-iodide were discontinued, and attention was focused on the 2-ethoxycarbonylcyclopropanone acylal system (CLXXIX) which might give rise to what is possibly a more stable cyclopropanone system (CLXXX). It was thought worthwhile to investigate the possibility of stabilisation of

2-ethoxycarbonylcyclopropanone by intramolecular hydrogen bonding in the tautomeric enol form (CLXXXI).



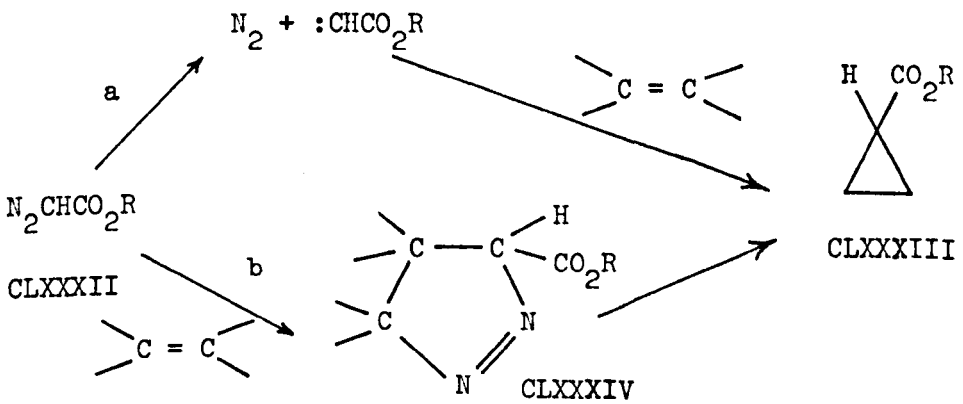
CLXXIX



CLXXX CLXXXI

D. Formation of 2-Ethoxycarbonylcyclopropanone Acylals.

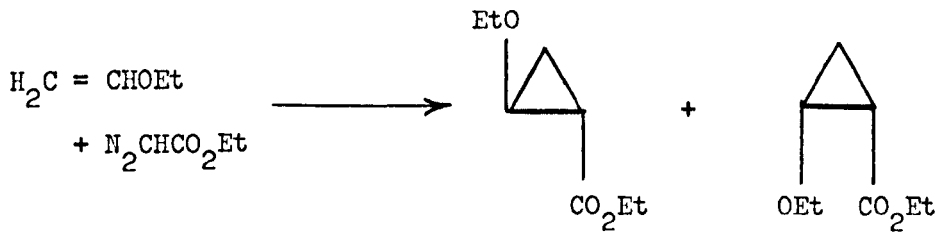
Ethyl diazoacetate (CLXXXII) has been allowed to react with alkenes to yield the corresponding ethoxycarbonylcyclopropanes (CLXXXIII). Kirmse[105] has reviewed the subject. Two possible reaction paths may be followed: the diazo ester may first lose nitrogen to give a carbene intermediate which adds to the alkene (Scheme 95, path a); or, alternatively, the diazo compound may add to the alkene with formation of a pyrazoline (CLXXXIV) which thermally decomposes to the same cyclopropane (Scheme 95, path b). Pyrazoline intermediates are most likely to occur in thermal reactions of diazo esters with polar double bonds.



Scheme 95

When two isomers can be formed, the less crowded arrangement of substituents is preferred.[106,107] The ratio of the two isomers, however, depends on the carbene precursors. Discrimination in favour of the less

hindered product has been found to be more pronounced with ethoxycarbonylcarbene produced by copper or cupric sulphate catalysis than with ethoxycarbonylcarbene generated by photolysis: an example is the addition of ethoxycarbonylcarbene to ethyl vinyl ether where the corresponding yields of isomers are as shown in Scheme 96.[107]



Scheme 96

Catalysis by copper or cupric sulphate also favours the 1,2-addition reaction rather than insertion into a carbon-hydrogen bond.[107]

The influence of the catalyst has been explained in terms of a copper complex of the carbene. This complexing is thought to increase the bulk of the intermediate but to leave the vacant orbital relatively free.

There are no reports (up to 1968) in the literature of ethyl diazoacetate having been allowed to react with 1-alkoxyvinyl esters although reactions with some vinyl ethers[107,108] and vinyl acetate[109] to form the corresponding cyclopropane derivative have been reported. In

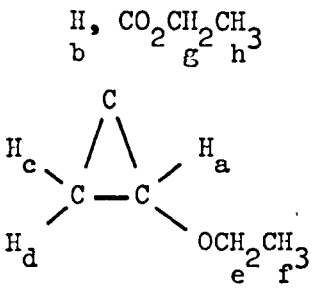
fact the only reported addition of carbene-like intermediates to 1-alkoxyvinyl esters is the previously mentioned work of Wasserman and Clagett,[45,46] using zinc-copper couple and methylene di-iodide. No 2-ethoxycarbonylcyclopropanone acylals are known.

In order to obtain spectral information and to test reaction conditions, ethyl diazoacetate, which had been prepared from ethyl glycinate hydrochloride,[82] was allowed to react with ethyl vinyl ether in the presence of anhydrous cupric sulphate. According to Dyakonov and Lugovtsova[108] the reaction will proceed in boiling ethyl vinyl ether, best yields (ca. 70%) of cyclopropanes being obtained with purified ethyl diazoacetate (steam distilled), although crude ethyl diazoacetate also gives the required product, but in lower yield (ca. 44%).

However, in the present work, no reaction occurred when ethyl vinyl ether was used as solvent as evidenced by the absence of gas evolution. The experiment was repeated in boiling benzene with ethyl vinyl ether in a ten-molar excess. After removal of volatile components pure 1-ethoxy-2-ethoxycarbonylcyclopropane (b.p. 68 - 69° at 9.5 mm., lit. 68.5 - 70° at 9.0 mm.) distilled in 27% yield. It was shown to be a mixture of isomers (ratio 8 : 3) by v.p.c. analysis. No attempt was made to separate the isomers.

The infrared spectrum of the cyclopropane, CLXXXV, shows a strong ester carbonyl absorption at 1725 cm^{-1}. The n.m.r. spectrum shows complex splitting in the region 5.6 - 6.6τ which can be analysed into two

methylene quartets (H_g, 5.90τ; H_e, 6.42τ) with shoulders from the isomer in lower concentration. Superimposed on these quartets is a complex splitting pattern from the ring-proton H_a, of the two isomers. The complex splitting pattern in the region 8.2 - 9.0τ consists of two methyl triplets (H_h, 8.75; H_f, 8.83τ) and a large number of lines for the ring protons H_b, H_c, H_d of the two isomers.



CLXXXV

A by-product in this reaction, and in many other pyrolyses of ethyl diazoacetate, is diethyl fumarate: the presence of this in the second distillation fraction is indicated by the infrared absorption at 1650 cm^{-1}.

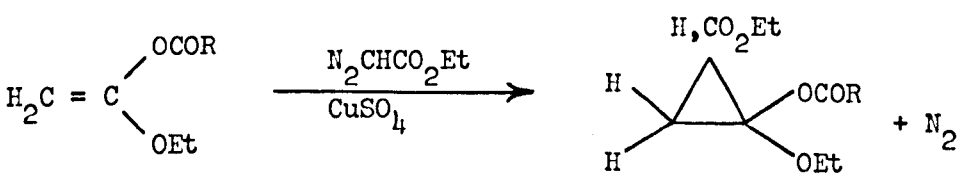
In the literature there are two general infrared correlations claimed for cyclopropane compounds. One is the asymmetric stretching frequency of the cyclopropane methylene, C-H, bonds which appears as a medium intensity band, ca. 3050 cm^{-1}; and the other is a skeletal vibration frequency which shows a medium strength absorption in the region 1050 - 1005 cm^{-1}. However the latter band is obscured in oxygenated

compounds and hence was useless in this work. The other band was found to have little diagnostic value being weak or absent in the compounds studied.

Although cyclopropane, itself, absorbs as high as 9.78τ in the n.m.r. spectrum the presence of electron withdrawing groups attached to the ring results in a very wide range of absorption positions.

In the present work the presence of the cyclopropane ring was established by the complex splitting observed in the n.m.r. spectrum and the formation of succinic acid or one of its derivatives as a degradation product. Confirmation of structure was obtained from the elemental analysis and the infrared spectrum.

The 2-ethoxycarbonylcyclopropanone acylals (CLXXXVI), 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (R = C_6H_5), propionate (R = CH_3CH_2) and dichloroacetate (R = $CHCl_2$), were prepared by pyrolysis of ethyl diazoacetate in the presence of the corresponding 1-ethoxyvinyl ester and anhydrous cupric sulphate catalyst (Scheme 97).



R = C_6H_5, CH_3CH_2, $CHCl_2$

CLXXXVI

Scheme 97

The reaction was performed by dropwise addition of a solution of approximately equal volumes of ethyl diazoacetate and 1-ethoxyvinyl ester, in dry benzene, to a boiling benzene solution of 1-ethoxyvinyl ester containing anhydrous cupric sulphate catalyst. The 1-ethoxyvinyl ester was present in a two to three-molar excess. The progress of the reaction could be followed by observation of the nitrogen evolution and the colour change from yellow to red-brown.

The following table gives the percentage yields, boiling points, ester carbonyl stretching frequencies in the infrared spectrum, and the ratio of isomers obtained (determined by v.p.c. analysis; silicon grease column) for the prepared cyclopropanone derivatives.

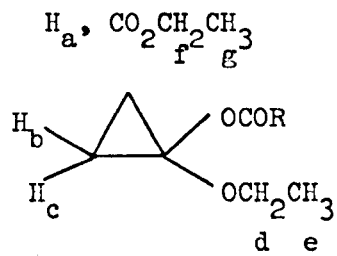
Compound	b.p.	$\nu_{max.}$ (cm^{-1})	Ratio of isomers	Yield %
PhCOOR	110° (1×10^{-3} mm.)	1730	3 : 2	15
CH_3CH_2COOR	$82\text{-}84.5^{\circ}$ (0.25 mm.)	1735	3 : 1	26
$Cl_2CHCOOR$	$96\text{-}112^{\circ}$ (5×10^{-3} mm.)	1740	9 : 1	33

R = 1-ethoxy-2-ethoxycarbonylcyclopropyl

No attempts were made to separate the isomers. The percentage yields recorded refer to pure products obtained after distillation: crude yields were much higher.

The n.m.r. spectra show the two regions of complex splitting

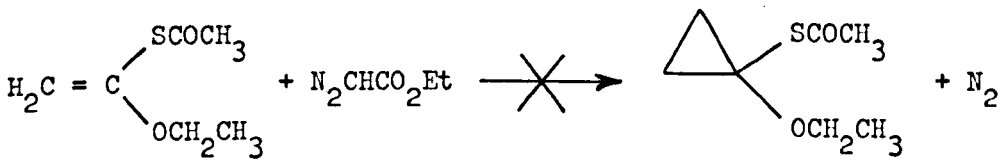
(apart from aromatic splitting) - 5.6 - 6.5τ and 7.4 - 9.1τ. The lower field region contains the two methylene quartets from the ethoxy methylene protons, H_d and H_f (CLXXXVII); sometimes the quartets were partially superimposed. The upper field region contains the two methyl triplets from the ethoxy methyl protons, H_e and H_g, and a large number of lines arising from the multiple splitting of the ring-protons, H_a, H_b, H_c, in both of the isomers. The methylene quartets of the less favoured isomer are clearly discernable as shoulders on the main peaks in the case of the benzoate ester.



CLXXXVII

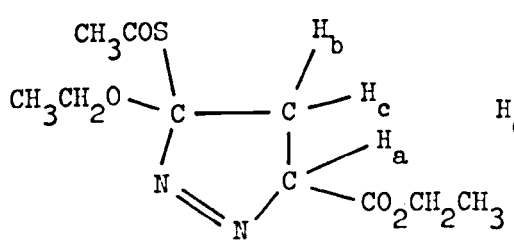
An attempt was made to prepare the thio analogue, CLXXXVIII, by reaction of 1-ethoxyvinyl thiolacetate with ethyl diazoacetate in the presence of anhydrous cupric sulphate catalyst (Scheme 98). During the reaction, which was conducted in boiling benzene, a colour change from yellow to red-brown was observed. The crude product, a red-brown liquid was distilled at 0.35 mm. to yield a fraction, b.p. 82 - 84°, which showed two peaks (ratio 7 : 1) on v.p.c. analysis. This product was shown to contain nitrogen and the elemental analysis approximated to that of a pyrazoline with either the structure CLXXXIX or CXC, although the former

is the more likely reaction product.

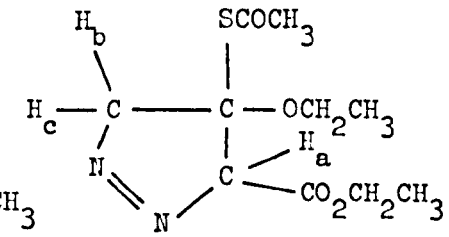


CLXXXVIII

Scheme 98



CLXXXIX



CXC

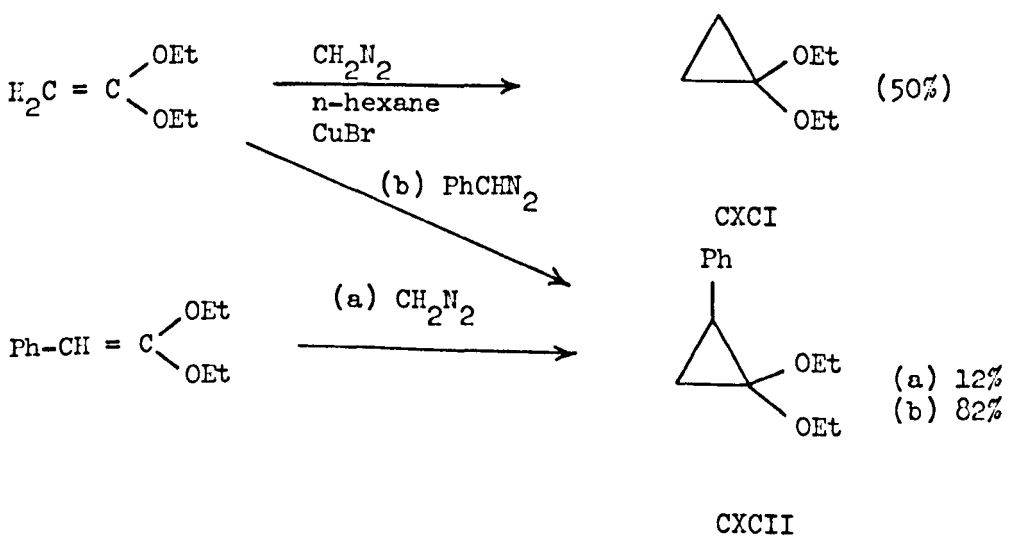
The infrared spectrum shows a strong ester carbonyl peak at 1725 cm^{-1} and a weak band at 1630 cm^{-1} with a shoulder at 1600 cm^{-1}. The N=N stretching frequency has been reported to occur as a peak of variable intensity in the region 1575 - 1630 cm^{-1}. The n.m.r. spectrum showed complex splitting in the region 5.3 - 6.7τ, a singlet at 7.08τ, and complex splitting in the region 7.45 - 8.80τ. The integration approximated to that expected for the pyrazoline, the ring-proton, H_a, appearing in the low-field region and the ring-protons, H_b and H_c, appearing in the high-field region. The complex splitting pattern observed

would seem to fit the pyrazoline, CLXXXIX, better.

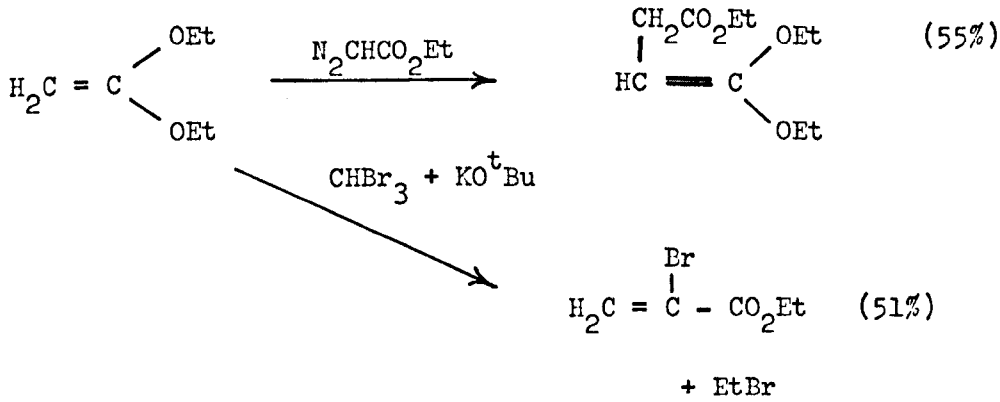
It did not prove possible to decompose the suspected pyrazoline to the corresponding cyclopropane derivative and nitrogen; no gas evolution was observed and at 150° the liquid decomposed to a black tar.

Experiments with 1-ethoxyvinyl thiolcarboxylates were not continued beyond this stage.

Dull and Abend[52] have successfully prepared the cyclopropanone ketals, CXCI and CXCII, from the corresponding keten acetal and either diazomethane or phenyldiazomethane (Scheme 99) but could not isolate any cyclopropane derivative from the reaction of keten diethylacetal with ethyl diazoacetate either in boiling n-hexane with cuprous bromide catalyst or in boiling benzene with copper catalyst. Instead a product arising from carbon-hydrogen bond insertion was obtained (Scheme 100). Similarly, reaction of keten diethylacetal with dibromocarbene (from bromoform and potassium t-butoxide) yielded ethyl α-bromoacrylate (Scheme 100): 2,2-dibromocyclopropanone was postulated as an intermediate.[52]

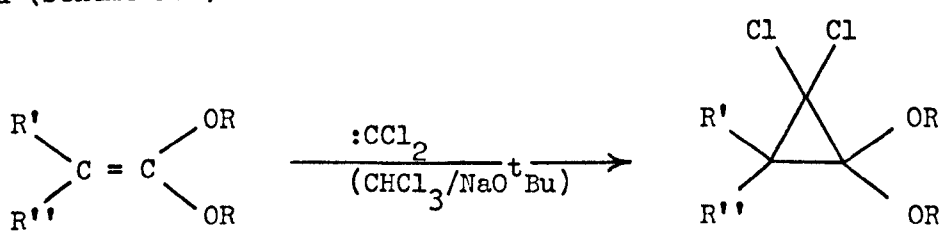


Scheme 99



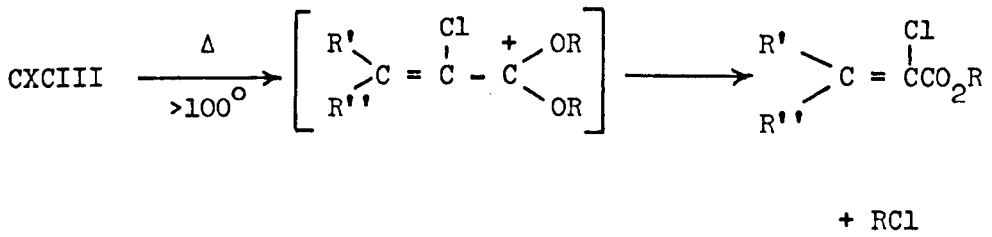
Scheme 100

McElvain and Weyna[51] have prepared a large number of dichlorocyclopropanone acetals (CXCIII) from the corresponding keten acetals (CXCIV) by reaction with dichlorocarbene. They found that, above 100°, pyrolysis to the corresponding α-chloroacrylic ester occurs in quantitative yield (Scheme 101).



CXCIV

CXCIII

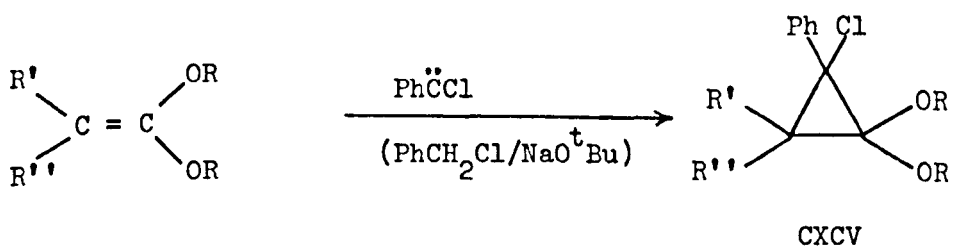


When R = Et; R' = R'' = H. When R = Me; R' = R'' = H; R' = R'' = Me; R' = Me, R'' = H; R' = Et, R'' = H; R' = nC_3H_7, R'' = H.

Scheme 101

The dichlorocyclopropanone acetal, CXCIII, (R = Et; R' = R'' = H), can be dechlorinated to cyclopropanone diethylacetal by treatment with sodium in t-butanol.

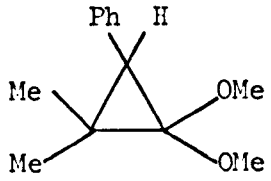
The monochlorocyclopropanone acetals, CXCV (R' = R'' = Me; R = Me and R' = R'' = H; R = Et), were similarly prepared by reaction of phenylchlorocarbene with the corresponding keten acetal (Scheme 102).



CXCV

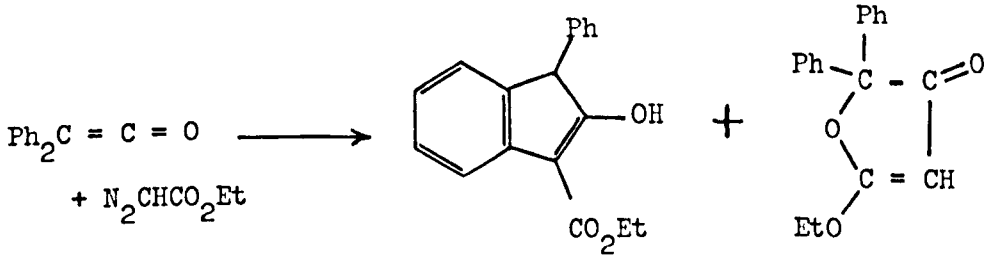
Scheme 102

The cyclopropanone acetal, CXCVI, was prepared by treatment of the monochloro precursor with sodium in t-butanol.

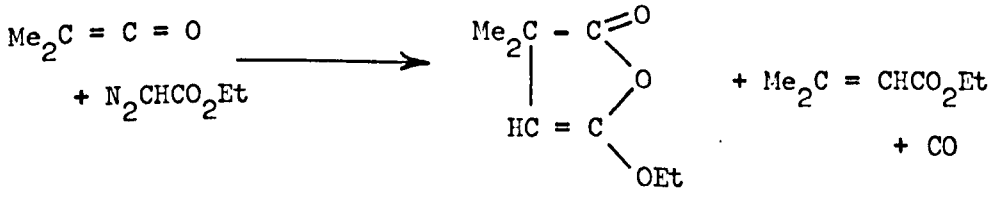


CXCVI

Reaction of a keten with ethyl diazoacetate would seem to offer a direct route to 2-ethoxycarbonylcyclopropanones, since cyclopropanone and dimethylcyclopropanone have been prepared using diazomethane. However, when Kende[113] allowed ethyl diazoacetate to react with diphenyl and dimethylketen no cyclopropane derivatives were obtained. The reactions, instead, took the courses shown in Schemes 103 and 104.

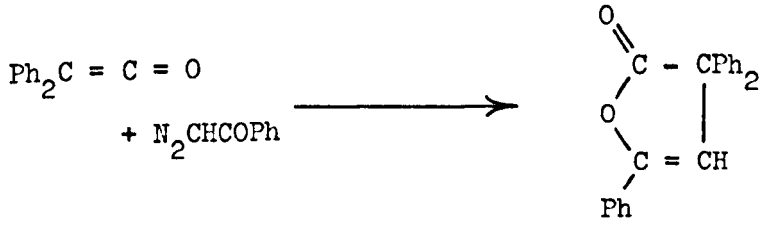


Scheme 103



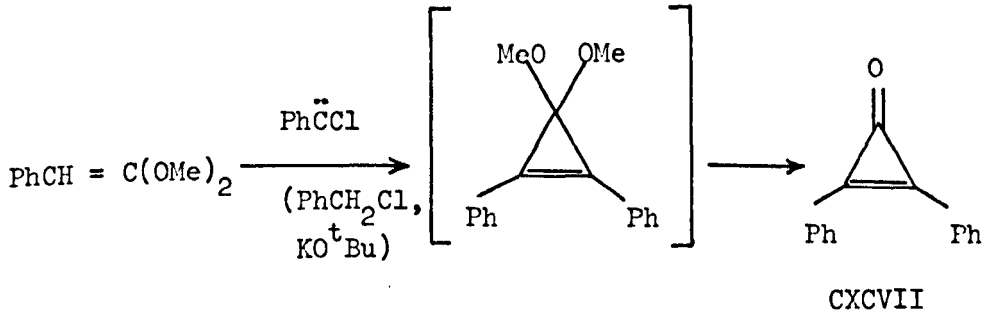
Scheme 104

Diphenylketen on reaction with diazoacetophenone yields a β,γ-butenolide, again apparently a product of 1,3-dipolar addition (Scheme 105).[114]

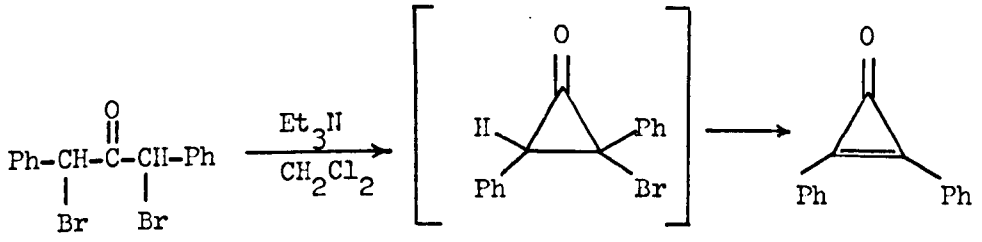


Scheme 105

Diphenylcyclopropenone (CXCVII) has been prepared by Breslow and co-workers,[110,111] by two routes, one of which probably involves a cyclopropanone intermediate. One method involves the addition of phenylchlorocarbene to phenylketen dimethylacetal (Scheme 106)[110] and the other the action of organic base on α,α'-dibromodibenzylketone (CXCVIII) (Scheme 107).[111]



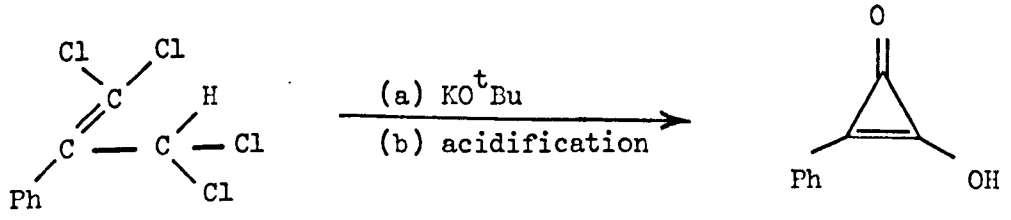
Scheme 106



CXCVIII CXCVII

Scheme 107

The only known hydroxycyclopropenone, CXCIX, was prepared by the cyclization of 1,1,3,3-tetrachloro-2-phenylpropene (CC) with potassium t-butoxide. (Scheme 108).[112] Phenylhydroxycyclopropenone (CXCIX) (m.p. 244 - 245°) appeared to be an associated dimer in dioxan (from osmometric molecular weight determinations) but the sodium salt in water was monomeric and dissociated.[112]



CC CXCIX

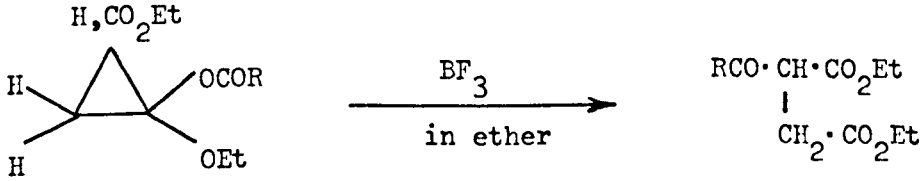
Scheme 108

E. Reactions of 2-Ethoxycarbonylcyclopropanone Acylals.

Several experiments were carried out including acidic, basic and neutral hydrolysis, boron trifluoride catalysis, and pyrolysis, but no evidence for the formation of 2-ethoxycarbonylcyclopropanone was found. The products isolated in all cases could be interpreted as resulting from facile ring cleavage reactions.

Rearrangement catalysed by boron trifluoride:

The 1-ethoxy-2-ethoxycarbonylcyclopropyl esters (CCI) of benzoic acid and dichloroacetic acid were found to rearrange spontaneously at room temperature, in the presence of boron trifluoride in ether, to give diethyl 2-benzoylsuccinate (CCII, R = C_6H_5) and diethyl 2-dichloroacetylsuccinate (CCII, R = $CHCl_2$) respectively, in almost quantitative yields. (Scheme 109)



CCI

R = C_6H_5, $CHCl_2$

CCII

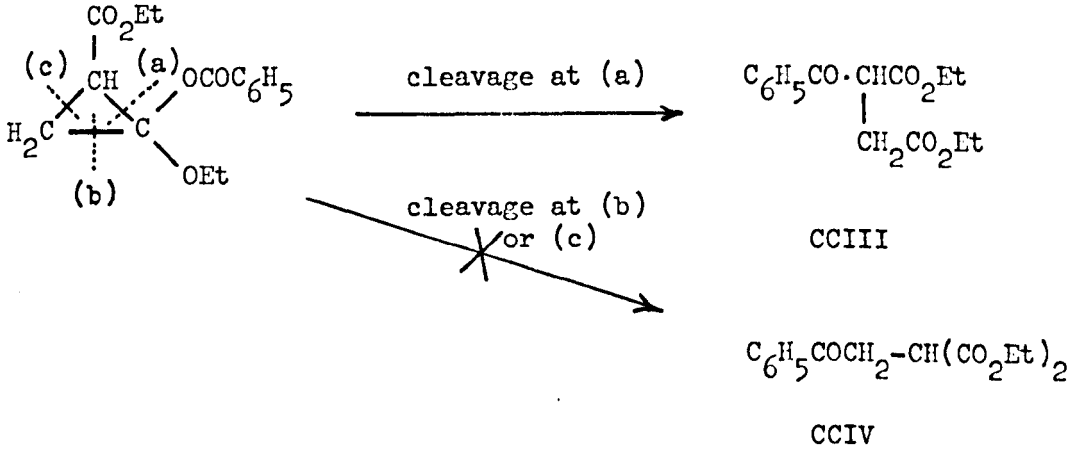
Scheme 109

The reactions were carried out in ether solution, a few drops of boron trifluoride etherate being added to the magnetically stirred

solution. In the presence of trace quantities of water, diethyl succinate and either benzoic acid or dichloroacetic acid are also formed.

The products were unambiguously characterised by their infrared spectra, n.m.r. spectra, elemental analyses, and in one case (CCII, R = C_6H_5) by chemical degradation.

Hydrolysis of the reaction product (CCII, R = C_6H_5) by boiling aqueous potassium hydroxide yielded succinic acid (72%) and benzoic acid (74%) (Scheme 111). Since β-keto esters undergo acid cleavage with hot, concentrated alkali, this reaction confirms that the structure of the reaction product is diethyl 2-benzoylsuccinate. The other possible product in this type of ring cleavage reaction is the isomer diethyl 2-phenacylmalonate (Scheme 110, CCIV) which would yield 3-benzoylpropionic acid with hot, concentrated alkali. (Scheme 111)



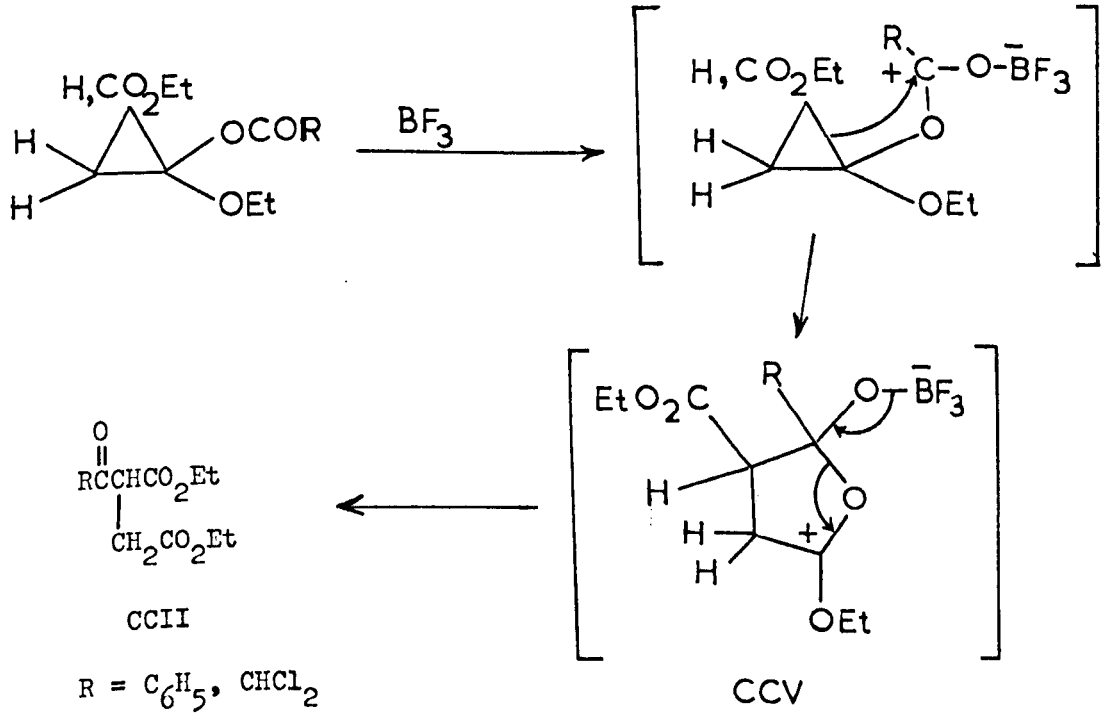
Scheme 110

CCIII $\xrightarrow[\text{alkali}]{\text{hot, conc.}}$ $PhCO_2H + (CH_2CO_2H)_2 + EtOH$

CCIV $\xrightarrow[\text{alkali}]{\text{hot, conc.}}$ $PhCOCH_2CH_2CO_2H + CO_2$

Scheme 111

This boron trifluoride catalysed rearrangement can be formulated as a nucleophilic attack on the carbon atom of the polarised carbonyl group of the acid residue, by the electrons of the cyclopropane ring causing ring cleavage. An unstable intermediate, such as CCV, may be formed and then rearrange with elimination of the boron trifluoride molecule to give the acyl or aroyl-succinic acid ester (CCII) (Scheme 112).



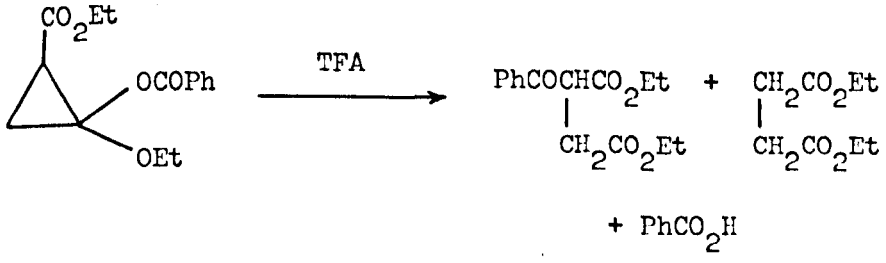
Scheme 112

1-Ethoxy-2-ethoxycarbonylcyclopropyl dichloroacetate under the same conditions rearranged almost quantitatively to diethyl 2-dichloroacetylsuccinate (CCII, R = $CHCl_2$). Its infrared spectrum showed a strong ester carbonyl peak at 1735 cm^{-1} and the n.m.r. spectrum was as expected.

Acid Hydrolysis:

Treatment of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (CCII, R = C_6H_5) with a small amount of trifluoroacetic acid at room temperature led to the same rearranged product as before. Diethyl 2-benzoylsuccinate was formed rapidly and in almost quantitative yield: the conversion was seen to be almost instantaneous by monitoring with n.m.r. and v.p.c.

Similarly diethyl 2-benzoylsuccinate was one of the products when an ether solution of the benzoate ester was shaken with concentrated hydrochloric acid. The other products were benzoic acid and diethyl succinate arising from competing nucleophilic attack by a molecule of water (Scheme 113).

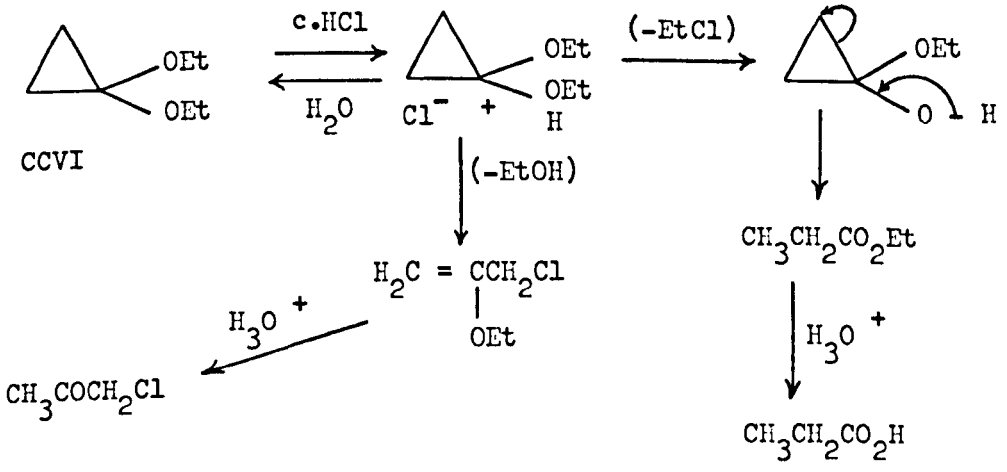


Scheme 113

V.p.c. analysis showed that diethyl succinate and diethyl 2-benzoylsuccinate were formed in a ratio of 1 : 3.

1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate remained unchanged in the presence of acetic acid, either at 80° for 60 hr., or at room temperature for several weeks.

McElvain and Weyna[51] found that cyclopropanone diethylacetal, CCVI, was soluble in concentrated hydrochloric acid and could be recovered unchanged after 30 min. at room temperature. On boiling the solution a mixture of chloroacetone (34%), ethyl propionate (12%) and propionic acid (30%) was obtained which can be rationalised as shown in Scheme 114.



Scheme 114

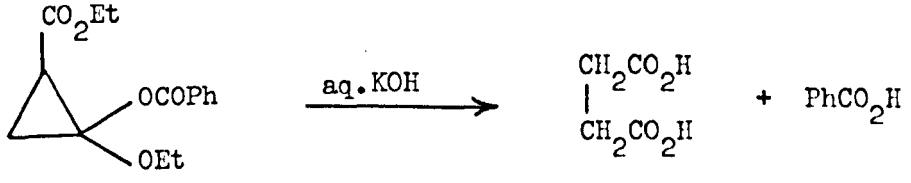
With anhydrous hydrogen chloride at 95° ethyl propionate was the only product.

Lipp and co-workers[59] have reported that cyclopropanone hydrate rearranged slowly on standing and more rapidly on heating to propionic acid.

As mentioned previously Wasserman and Clagett[45] observed similar transformations with 1-ethoxycyclopropyl esters.

Basic hydrolysis:

Hydrolysis of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate by 50% aqueous potassium hydroxide led to benzoic acid and succinic acid (Scheme 115). The formation of the succinic acid skeleton can be regarded as additional confirmation of the cyclopropane structure.



Scheme 115

Similarly Wasserman and Clagett[45] isolated propionic acid and benzoic acid from the alkaline hydrolysis of 1-ethoxycyclopropyl benzoate (Scheme 116).

Scheme 116

When 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate was shaken with 2% aqueous potassium hydroxide for 3 hr., complete hydrolysis occurred and benzoic acid (70%) and succinic acid (63%) were isolated. A small amount of liquid, which was obviously aliphatic in view of its spectrum, was also obtained.

Neutral hydrolysis:

1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate remained unchanged in 20% aqueous acetone solution after either three weeks at room temperature or 25 hr. at the boiling point. Similarly no change was observed in solutions in aqueous or absolute methanol and ethanol over several weeks in contrast to the experiments of Wasserman and Clagett[46] with 1-ethoxycyclopropyl benzoate (and acetate) and alcohols.

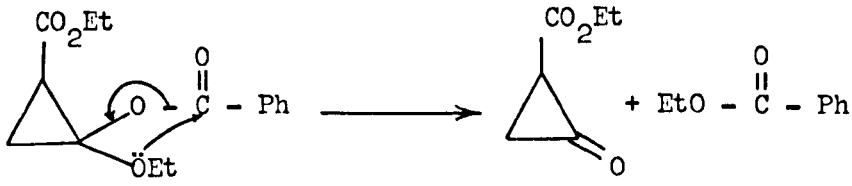
However, 1-ethoxycarbonylcyclopropyl dichloroacetate was completely decomposed after 15 hr. in 20% aqueous acetone solution. The products obtained were the ring cleavage products - diethyl succinate, dichloroacetic acid and diethyl 2-dichloroacetylsuccinate.

Pyrolysis:

Solutions of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate in carbon tetrachloride and di-n-butyl ether were kept at 35° and 134° for a number of days. No change in the starting material was observed from v.p.c. analysis. At 298° in diethyl phthalate the solution turned red-brown after 3 hr. and v.p.c. analysis showed the formation of a large

number of products.

It had been hoped to initiate, by heat, an intramolecular rearrangement of the type shown in Scheme 117. This would give rise to 2-ethoxycarbonylcyclopropanone and ethyl benzoate.



Scheme 117

Other experiments:

Attempts were made to form other derivatives of 2-ethoxycarbonylcyclopropanone. However no crystalline product was isolable from reactions with 2,4-dinitrophenylhydrazine or p-nitrophenylhydrazine.

When 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate was heated in excess aniline, at 80°, for 8 hr., a homogeneous solution resulted but no reaction had occurred from v.p.c. analysis. On heating the solution under reflux for 1 hr. and cooling, benzanilide crystallised, but v.p.c. analysis of the aniline solution showed it to be a very complex mixture.

Similar experiments were attempted with imidazole in boiling diethyl ether solution and di-n-butyl ether solution but no crystalline product could be precipitated in either case.

PART III

EXPERIMENTAL SECTION

Infrared spectra of solids were determined either as paraffin mulls, or in carbon tetrachloride solution; and of liquids, either as a liquid film or in carbon tetrachloride solution. The spectra were recorded on one of the following instruments:- Perkin Elmer Infracord; Perkin Elmer 221; Unicam SP200G; Perkin Elmer 257G.

Ultraviolet spectra of 95% ethanol solutions were recorded on either a Unicam SP700 or SP800 spectrometer.

Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R10 60 mc/s instrument. When spectra of solutions in deuterochloroform or carbon tetrachloride were determined, tetramethylsilane (T.M.S.) was used as an internal standard. For solutions in deuterium oxide, an external standard of T.M.S. in carbon tetrachloride was used.

Analytical vapour phase chromatography (v.p.c.) was carried out on a Pye series 104 chromatograph using mainly a 4 ft. spiral glass column (i.d. $\frac{1}{8}$") packed with 5% silicon grease (S.E. 30) on Chromosorb G. Occasionally the following columns were also used:- 5 ft. spiral copper

column (i.d. $\frac{1}{8}$") packed with 10% polyethyleneglycol adipate (P.E.G.A.) on white diatomaceous earth (60 - 72 mesh) (dimethylchlorosilane (D.M.C.S.) treated); 5 ft. spiral copper column (i.d. $\frac{1}{8}$") packed with 10% diethyleneglycol succinate (D.E.G.S.) on Chromosorb G; 5 ft. spiral copper column (i.d. $\frac{1}{8}$") packed with 3% Apiezon L on Chromosorb G (D.M.C.S. treated).

Preparative vapour phase chromatography was carried out on a Pye series 105 chromatograph using a 30 ft. spiral glass column (i.d. $\frac{1}{4}$") packed with 25% silicon grease (S.E. 30) on white diatomaceous earth (60 - 72 mesh) (D.M.C.S. treated).

Melting points were determined on a Kofler hot stage and are therefore corrected.

Elemental analyses were carried out by either Mr. J. Boulton of the University of Keele on an F. and M. carbon/hydrogen/nitrogen analyser, or by Drs. Weiler and Strauss of Oxford.

A. Preparations of Some 1-Ethoxyvinyl Esters.

Ethoxyacetylene used in this work was prepared by a modification of the method used by Nazarov and co-workers.[18] It was stored at -10°.

Preparation of Ethoxyacetylene: (1) 1,2-Dibromo-1-ethoxyethane: Ethyl vinyl ether (190 g., 250 ml.) was slowly added to stirred and cooled (-20 to -30°) bromine (422 g., 136 ml.). The resulting 1,2-dibromo-1-ethoxyethane was used without further purification. (2) 2-Bromo-1-ethoxyethylene: Diethylaniline (928 g., 988 ml.) was stirred and heated to 105° under a reduced pressure of 18 mm. The 1,2-dibromo-1-ethoxyethane was added dropwise over the course of 3 hr., during which the 2-bromo-1-ethoxyethylene distilled over into an ice-cooled flask. On fractional distillation of the product 2-bromo-1-ethoxyethylene (ca. 260 g.) distilled at b.p. 45 - 50° at 18 mm. (3) Ethoxyacetylene: 2-Bromo-1-ethoxyethylene (260 g.) and powdered potassium hydroxide (520 g.) were stirred and heated to about 110° when ethoxyacetylene distilled rapidly into an ice-cooled flask. The product was fractionally distilled to give ethoxyacetylene (ca. 95 g., ca. 50% from ethyl vinyl ether) b.p. 51 - 53°.

Preparation of 1-Ethoxyvinyl Pivalate: Pivalic acid was distilled before use. Ethoxyacetylene was distilled from potassium hydroxide pellets. A

solution of pivalic acid (10.2 g., 0.10 mole) in anhydrous methylene dichloride (10 ml.) was allowed to drip into an ice-cooled solution of ethoxyacetylene (17.5 ml., 14.0 g., 0.2 mole) in methylene dichloride (200 ml.) containing mercuric acetate (0.60 g., 0.002 mole), in suspension. The mixture was stirred magnetically and the addition was complete after 30 min. Stirring was continued for a further 30 min. and then the excess of ethoxyacetylene and the methylene dichloride were removed at 60°. The residue was distilled through a Vigreux column (4 cm.) at 26 mm. in an atmosphere of dry nitrogen. 1-Ethoxyvinyl pivalate (13.1 g., 76%) distilled over as a clear colourless liquid (b.p. 68 - 73° at 26 mm). A sample was purified for analysis by distillation through a short column packed with Fenske multi-turn glass helices.

$\nu_{max.}$ (liquid film): 1670 cm^{-1} (s) (C = CH_2), 1765 cm^{-1} (s) (C = O).

n.m.r. ($CDCl_3$): τ5.92 - 6.28 (complex splitting: a singlet, 6.23, superimposed on a quartet, 6.10, J ~ 7 c.p.s.); 8.58 - 8.82 (complex splitting: a singlet, 8.75, superimposed on a triplet, 8.70, J ~ 7 c.p.s.); integrating in the ratio 1 : 3 (theoretical 1 : 3).

Found : C, 63.06; H, 9.64%.

$C_9H_{16}O_3$ requires : C, 62.76, H, 9.36%.

Preparation of 1-ethoxyvinyl propionate: A solution of redistilled propionic acid (7.4 g., 0.10 mole) in methylene dichloride (10 ml.) was allowed to drip into an ice-cooled solution of ethoxyacetylene (17.5 ml.,

14.0 g., 0.20 mole) in methylene dichloride (200 ml.), containing mercuric acetate (0.60 g., 0.002 mole) over 30 min. The solution was stirred for 1 hr.; the volatile components removed at 60°; and the residue distilled at 16 mm. to yield 1-ethoxyvinyl propionate, b.p. 45 - 46° (13.0 g., 90%).

$\nu_{max.}$ (liquid film): 1675 cm^{-1} (s) (C = CH_2); 1775 cm^{-1} (s) (C = O).

n.m.r. ($CDCl_3$): τ 5.92 - 6.33 (complex splitting: a singlet, 6.27; superimposed on a quartet, 6.10, J ~ 7 c.p.s.); 7.55 (quartet, J ~ 7 c.p.s.) 8.52 - 8.93 (complex splitting, 2 partially superimposed triplets, J ~ 7 c.p.s.); integrating as 2 : 1 : 3 (theoretical, 2 : 1 : 3).

Found : C, 58.06; H, 8.10%.

$C_7H_{12}O_3$ requires : C, 58.31; H, 8.39%.

Large scale preparation of 1-ethoxyvinyl benzoate: A solution of dried benzoic acid (48.8 g., 0.4 mole) in methylene dichloride (50 ml.) was allowed to drip into an ice-cooled solution of ethoxyacetylene (53 g., 66 ml., 0.8 mole) in methylene dichloride (300 ml.); containing mercuric acetate catalyst (1.3 g., 0.004 mole). The addition was complete after 1 hr. The solution was stirred for 2 hr. at room temperature and then worked-up in the usual way. 1-Ethoxyvinyl benzoate (68 g., 88%) distilled at 72 - 73°, at 0.2 mm.

$\nu_{max.}$ (liquid film): 1675 cm^{-1} (s); 1750 cm^{-1} (s).

n.m.r. ($CDCl_3$): τ 1.6 - 1.8 and 2.2 - 2.6 (complex splitting); 5.78 - 6.15 (complex splitting); 8.61 (triplet, J ~ 7 c.p.s.); integrating in

the ratio 5 : 4 : 3 (theoretical 5 : 4 : 3).

Found : C, 68.62; H, 6.33%.

Calc. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29%.

Large scale preparation of 1-ethoxyvinyl dichloroacetate: Dichloroacetic acid (25.8 g., 16.6 ml., 0.2 mole) was reacted with ethoxyacetylene (17.5 g., 22.0 ml., 0.25 moles), with no catalyst present, to yield 1-ethoxyvinyl dichloroacetate (24.3 g., 61%), b.p. 50 52° at 0.3 mm.

$\nu_{max.}$ (liquid film): 1680 cm^{-1} (s); 1795 cm^{-1} (s).

n.m.r. ($CDCl_3$): 23.83 (singlet); 5.80 - 6.16 (complex splitting); 8.62 (triplet, J ~ 7 c.p.s.); integrating in the ratio 1 : 4 : 3 (theoretical 1 : 4 : 3).

Preparation of 1-ethoxyvinyl diphenylphosphinate: Diphenylphosphinic acid was dried at 120°, 0.1 mm., for 10 hr. Diphenylphosphinic acid (2.2 g., 0.01 mole) was added, over the course of 2 hr. to a magnetically stirred solution of ethoxyacetylene (10 ml., 8 g., 0.11 mole) in dry methylene dichloride (30 ml.), containing a small amount of mercuric acetate as catalyst. The addition of the solid acid was made from a container connected to the reaction flask by means of a flexible tube and the whole apparatus was continuously flushed with dry nitrogen. The heterogeneous mixture was stirred vigorously and after a total stirring time of 4 hr. all the acid had dissolved to give a pale yellow

solution. Volatile components were removed at 50°, initially under slightly reduced pressure and finally at 20 mm. The residue was a yellow brown viscous liquid which was identified as 1-ethoxyvinyl diphenylphosphinate.

$\nu_{max.}$ (CCl_4): 1665 cm^{-1} (s); 1740 cm^{-1} (w).

n.m.r. ($CDCl_3$): τ 1.7 - 2.5 (complex splitting); 5.9 - 6.5 (complex splitting); 8.82 (triplet, J ~ 7 c.p.s.); integrating in the ratio 10 : 3.7 : 3.1 (theoretical 10 : 4 : 3).

A sample of crude 1-ethoxyvinyl diphenylphosphinate was distilled in a bulb-tube at 150°, 0.1 mm., to yield a clear colourless liquid. This proved to be too unstable to be analysed, however, since on exposure to moist air a white solid began to form immediately and small samples were completely hydrolysed after about a minute. The solid was identified as diphenylphosphinic acid from its melting point, infrared spectrum and elemental analysis.

Found : C, 66.0; H, 4.87%.

Calc. for $C_{12}H_{11}PO_2$: C, 66.0; H, 5.15%.

Crude 1-ethoxyvinyl diphenylphosphinate could be stored for long periods in a sealed glass phial which had been flushed with dry nitrogen.

Preparation of 1'-ethoxyvinyl 1-adamantanecarboxylate: 1-Adamantanecarboxylic acid was dried at 70°, 0.1 mm., for 1 hr. 1-Adamantanecarboxylic acid (4.71 g., 0.026 mole) in dry methylene dichloride (20 ml.)

was added dropwise to a stirred solution of ethoxyacetylene (3.2 g., 4.0 ml., 0.046 mole) in dry methylene dichloride (50 ml.) containing a small amount of mercuric acetate as catalyst. The addition took place at room temperature, over 15 min., and the solution was stirred for a further 4 hr. at room temperature. Volatile components were removed at 60° and the residue, a yellow liquid (ca. 10 ml.) was fractionally distilled through a Vigreux column (4 cm.) to yield a clear colourless liquid (b.p. 82 - 90° at 0.06 mm.), which solidified on standing. This was identified as 1'-ethoxyvinyl 1-adamantanecarboxylate (6.2 g., 95%). A fraction of boiling point range 85 - 89°, 0.06 mm., and m.p. 34 - 35°, was characterised.

$\nu_{max.}$ (CCl_4): 1673 cm^{-1} (s); 1763 cm^{-1} (s).

n.m.r. ($CDCl_3$): τ 5.95 - 6.33 (complex splitting: a singlet, 6.33, superimposed on a quartet, 6.12, J ~ 7 c.p.s.); 8.02 (broad unsplit peak); 8.23 (broad unsplit peak), 8.65 (triplet, J ~ 7 c.p.s.); integrating in the ratio 4 : 9 : 6 : 3 (theoretical 4 : 9 : 6 : 3).

Found : C, 72.32; H, 8.95%.

$C_{15}H_{22}O_3$ requires : C, 71.97; H, 8.86%.

Preparation of 1-adamantanecarboxyanilide (N-phenyl-1-adamantanecarboxyamide): 1-Ethoxyvinyl 1-adamantanecarboxylate (0.5 g., 2 m.mole) was heated at 80° with redistilled aniline (5 ml.) for 1 hr. The ester slowly dissolved and on cooling white crystals separated (m.p. 198 - 200°). These were recrystallised from aqueous methanol to yield

1-adamantanecarboxyanilide (N-phenyl-1-adamantanecarboxyamide)

m.p. 199 - 200° (Lit. 196.5 - 197.5) (0.5 g., 98%).

n.m.r. ($CDCl_3$): τ 2.25 - 2.85 (complex splitting); 7.82 and 7.98 (sharp singlet and broad singlet, respectively - not fully resolved); 8.22 (broad singlet); integrating in the ratio 6 : 10 : 6 (theoretical 6 : 10 : 6, for N-H proton absorbing in the region 2.25 - 2.85τ).

Found : C, 80.3; H, 8.04; N, 5.4%.

Calc. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49%.

Preparation of N-benzyl-1-adamantanecarboxyamide: 1'-Ethoxyvinyl 1-adamantanecarboxylate (0.56 g., 2.2 m.mole) was heated with benzylamine (2 ml., ca. 20 m.mole) at 80° for 1 hr. The ester slowly dissolved and on cooling white crystals separated. These were recrystallised twice from aqueous methanol to yield N-benzyl-1-adamantanecarboxyamide, m.p. 174 - 175°, (0.52 g., 88%).

n.m.r. ($CDCl_3$): τ 2.62 (broad singlet); 4.0 (broad); 5.47, 5.56 (doublet, J ~ 5 c.p.s.); 7.82 - 8.25 (complex splitting; partially resolved into sharp singlet at 7.82; broad singlet at 8.06; and broad singlet at 8.25); integrating in the ratio 5 : 1 : 2 : 15 (theoretical 5 : 1 : 2 : 15).

Found : C, 80.6; H, 8.25; N, 5.4%.

$C_{18}H_{23}NO$ requires : C, 80.25; H, 8.61; N, 5.20%.

Preparation of N-1'-naphthyl-1-adamantanecarboxyamide: 1'-Ethoxyvinyl 1-adamantanecarboxylate (0.25 g., 1 m.mole) and 1-naphthylamine (0.14 g.,

1 m.mole) were dissolved in methylene dichloride (2 ml.) and heated at reflux for 1 hr. On cooling, some solid crystallised out as needles and on concentrating the solution and cooling more solid crystallised. This was recrystallised three times from aqueous methanol to yield N-1'-naphthyl-1-adamantanecarboxyamide, m.p. 252 - 254° (0.27 g., 82%).

n.m.r. ($CDCl_3$): τ 1.85 - 2.60 (complex splitting); 7.86 (broad singlet); 8.15 (broad singlet); integrating as 8 : 9 : 6 (theoretical 8 : 9 : 6, for N-H proton absorbing in the region 1.85 - 2.60).

Found : C, 82.3; H, 7.32; N, 4.6%.

$C_{21}H_{23}NO$ requires : C, 82.58; H, 7.59; N, 4.59%.

Preparation of 2',4'-dinitrophenyl 1-adamantanecarboxylate: 2,4-Dinitrophenol (0.18 g., 1 m.mole) and 1'-ethoxyvinyl 1-adamantanecarboxylate (0.28 g., 1.1 m.mole) were dissolved in methylene dichloride (2 ml.) and heated at reflux for 1 hr. The volatile components were removed under reduced pressure and the remaining yellow solid was recrystallised twice from methanol to yield 2',4'-dinitrophenyl 1-adamantanecarboxylate, m.p. 156 - 157° (0.30 g., 86%).

n.m.r. ($CDCl_3$): τ 0.9 - 1.45 and 2.35 - 2.55 (complex splitting); 7.85 (broad singlet); 8.15 (broad singlet); integrating as 1 : 3 : 2 (theoretical 1 : 3 : 2).

Found : C, 59.1; H, 4.92; N. 7.8%.

$C_{17}H_{18}N_2O_6$ requires: C, 58.95; H, 5.24; N, 8.09%.

B. Experiments with Thiolic Acids and Ethoxyacetylene: Thiolacetic Acid: (1) Reaction with ethoxyacetylene under usual conditions: Ethoxyacetylene was redistilled from potassium hydroxide pellets before use. Thiolacetic acid was distilled in an atmosphere of dry air. Thiolacetic acid (6.0 ml., 6.42 g., 0.085 mole) in methylene dichloride (10 ml.) was allowed to drip into a cooled (0°), and magnetically stirred, solution of ethoxyacetylene (15.2 g., 19.0 ml., 0.22 mole) in methylene dichloride (60 ml.), over 30 min. The reaction mixture was stirred for 10 hr. at room temperature and then the volatile components were removed at 60°. The residue, an orange liquid, was fractionally distilled to yield the following fractions at 4 mm. (1) 70 - 74° (7.2 g.) (2) 80 - 100° (3) 100 - 120°. Fraction (1), the major fraction, was identified as 2-ethoxyvinyl thiolacetate (7.2 g., 56%).

$\nu_{max.}$ (liquid film): 1635 cm^{-1} (s) (C = C); 1695 cm^{-1} (s) (C = O); 3090 cm^{-1} (m) (C = C - H)

n.m.r. ($CDCl_3$): τ 3.55, 4.42 (pair of doublets, J~ 6 c.p.s.); 6.02 (quartet, J ~ 7 c.p.s.); 7.65 (singlet); 8.70 (triplet, J ~ 7 c.p.s.); integrating in the ratio 1 : 1 : 2 : 3 : 3 (theoretical 1 : 1 : 2 : 3 : 3).

Mass spectral analysis gave a molecular weight of 146 and an empirical formula $C_6H_{10}O_2S$.

Found : C, 48.91; H, 6.81; S, 21.98%.

$C_6H_{10}O_2S$ requires : C, 49.32; H, 6.89; S, 21.90%.

(2) Reaction with ethoxyacetylene in the presence of hydroquinone, in the dark, and in an atmosphere of dry nitrogen: Thiolacetic acid was distilled through a column (8 cm. x 1 cm.) packed with multi-turn glass helices, in an atmosphere of dry nitrogen, in the dark. Ethoxyacetylene was distilled from potassium hydroxide pellets before use. Thiolacetic acid (2.23 g., 0.03 mole) in dry methylene dichloride (4 ml.) with hydroquinone (1 mg.) in suspension was added over the course of 1 hr. to cooled (0°) and magnetically stirred solution of ethoxyacetylene (7.3 g., 0.1 mole) in dry methylene dichloride (5 ml.) with hydroquinone (3 mg.) in suspension. The apparatus had previously been flushed out with dry nitrogen and a slow flow of dry nitrogen was maintained throughout the experiment. Light was excluded from the apparatus. After the addition, the resulting orange solution was stirred at room temperature for 17 hr. Volatile components were removed at 60° to leave a golden liquid which was distilled under reduced pressure to yield 1-ethoxyvinyl thiolacetate (3.1 g., 71%), b.p. 49 - 52° at 5.5 mm.

$\nu_{max.}$ (liquid film): 1680 cm^{-1} (s), 1714 cm^{-1} (s), (the lower frequency band being slightly more intense).

n.m.r. ($CDCl_3$): τ 6.05 (quartet, J ~ 7 c.p.s.), 6.15 (singlet), 7.36 (singlet), 8.65 (triplet, J ~ 7 c.p.s.); integrating in the ratio 4 : 2.9 : 3.1 (theoretical 4 : 3 : 3).

Found : C, 49.45; H, 7.15; S, 21.70%.

Calc. for $C_6H_{10}O_2S$: C, 49.32; H, 6.89; S, 21.90%.

Thiolbenzoic Acid: (1) Preparation of 1-ethoxyvinyl thiolbenzoate: Thiolbenzoic acid was redistilled under reduced pressure (b.p. 44° at 0.2 mm.), before use. Thiolbenzoic acid (7.0 g., 0.05 mole) in dry methylene dichloride (10 ml.) was added over the course of 30 min. to a cooled (0°) and magnetically stirred solution of ethoxyacetylene (10 ml., ca. 0.1 mole) in methylene dichloride (50 ml.) containing a small amount of mercuric acetate as catalyst. The mixture was stirred for 12 hr. at room temperature, the volatile components removed at 60° and the residue, an orange oil, was fractionally distilled under reduced pressure (0.2 mm) to yield the following fractions:- (1) 80 - 89° (0.71 g.) (2) 89 - 90° (1.92 g.) (3) 94 - 113° (2.94 g.). A very viscous dark red oil remained in the distillation flask. Fractions (1) and (2) were shown to be pure 1-ethoxyvinyl thiolbenzoate (2.63 g., 25%).

$\nu_{max.}$ (liquid film): 1680 cm^{-1} (s); 1740 cm^{-1} (s), (the lower frequency band being slightly more intense).

n.m.r. ($CDCl_3$): τ 1.66 - 1.75 and 2.35 - 2.56 (complex splitting); 6.04 (quartet, $J \sim 7$ c.p.s.) and 6.06 (singlet); 8.64 (triplet, $J \sim 7$ c.p.s.); integrating in the ratio 5 : 4 : 3 (theoretical 5 : 4 : 3).

Found : C, 63.30; H, 5.65%.

Calc. for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.80%.

Fraction (3) was found to be a mixture containing 1-ethoxyvinyl thiolbenzoate and 2-ethoxyvinyl thiolbenzoate. The crude yield of 1-ethoxyvinyl benzoate was shown to be approximately 80% by v.p.c. analysis.

(2) Attempted large scale preparation of 1-ethoxyvinyl thiolbenzoate: Thiolbenzoic acid was distilled at 20 mm. in an atmosphere of dry nitrogen in the dark and a middle fraction taken. The acid which was orange-red in colour did not lose colour appreciably on distillation. Thiolbenzoic acid (20.8 g., 0.15 mole) in methylene dichloride (20 ml.), which had been redistilled from calcium chloride, with hydroquinone (1 mg.) in suspension, was allowed to drip into cooled (0°) and magnetically stirred ethoxyacetylene (40 ml., 32 g., 0.46 mole) in methylene dichloride, with hydroquinone (3 mg.) in suspension. The addition took place over 1 hr. and the reaction mixture was stirred for 4 hr. at room temperature. The experiment was performed in an atmosphere of dry nitrogen, in the dark. Volatile components were removed at 80° and the residue, a deep orange liquid, was fractionally distilled at 0.2 mm. to yield the following fractions:- (1) $80 - 110^{\circ}$ (2) $110 - 112^{\circ}$ (3) $112 - 114^{\circ}$. V.p.c. analysis and n.m.r. spectral analysis showed that all three fractions were mixtures of 1-ethoxyvinyl thiolbenzoate (55%) and 2-ethoxyvinyl thiolbenzoate. The n.m.r. spectrum of the mixture showed complex absorptions in the ranges:- τ 1.66 - 1.75; 1.85 - 2.05; and 2.35 - 2.56; an AB quartet with peaks at 5.15, 5.18, 5.24, 5.27 and a singlet at 6.06, superimposed on the methylene quartet.

Distillation through a Vigreux column, or a column packed with glass helices, effected no purification and attempted distillation through a spinning-band column decomposed the 1-ethoxyvinyl ester, although

a small amount of pure 2-ethoxyvinyl thiolbenzoate could be obtained.

$\nu_{max.}$ (liquid film): 1600 cm^{-1} (broad, strong); 1685 cm^{-1} (broad, strong), 1740 cm^{-1} (w).

n.m.r. ($CDCl_3$): τ 1.85 - 2.05 and 2.35 - 2.56 (complex splitting); 5.01, 5.04, 5.10, 5.13 (AB quartet); 5.88 (quartet J ~ 7 c.p.s.); 8.62 (triplet J ~ 7 c.p.s.); integrating in the ratio 5 : 2 : 2 : 3 (theoretical 5 : 2 : 2 : 3).

An attempt was made to separate the two esters on an alumina column but the only compounds which were recovered from the column were 2-ethoxyvinyl thiolbenzoate and benzoic acid indicating that hydrolysis had taken place.

(3) Further experiments were carried out using thiolbenzoic acid which had been decolourised by distillation from linseed oil (colour change from deep red to straw); and using other solvents, such as ether and benzene. The reaction was also carried out at a variety of temperatures from -30° to 25°. However in every case a mixture of isomers was obtained, containing on average about 65% of the 1-ethoxyvinyl ester from n.m.r. spectral analysis.

C. The N-Protection of Amino-acids by Use of 1,2-Dicarboxylic Acids and Ethoxyacetylene.

Preparation of N-phthaloylglycine ethyl ester: Phthalic acid (3.32 g., 0.02 mole) and redistilled pyridine (4.60 g., 0.06 mole) in water (50 ml.) were allowed to drip into a magnetically stirred solution of glycine ethyl ester hydrochloride (2.78 g., 0.02 mole) and ethoxyacetylene (14.0 g., 0.20 mole) in water (20 ml.) which was cooled in an ice-bath. The addition was complete after 1 hr.; the solution was allowed to warm to room temperature and was stirred for 8 hr. The needles which had formed during this time were filtered off, washed with cold 95% ethanol and dried. The two-phase solution (ethyl acetate and water) was evaporated under reduced pressure to yield a yellow oil which on trituration with ethanol yielded white crystals. These were recrystallised from ethanol. The combined crystalline product was identified as N-phthaloylglycine ethyl ester (4.32 g., 93%), m.p. 114 - 114.5° (lit. 111 - 113°).

$\nu_{max.}$ (CCl_4): 1727 cm^{-1} (s); 1760 cm^{-1} (s); 1782 cm^{-1} (w). (1st peak stronger than 2nd peak).

n.m.r. ($CDCl_3$): τ 2.17 (complex splitting), 5.57 (unsplit), 5.78 (quartet, $J \sim 7$ c.p.s.), 8.70 (triplet, $J \sim 7$ c.p.s.), integrating in the ratio 4 : 2 : 2 : 3 (theoretical, 4 : 2 : 2 : 3).

Found : C, 62.2; H, 4.67; N, 5.7%.

Calc. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01%.

Preparation of N-4-nitrophthaloylglycine methyl ester: 4-Nitrophthalic acid (4.22 g., 0.02 mole) and pyridine (2.0 g., 0.03 mole) in water (20 ml.) were added during 1 hr. to glycine methyl ester hydrochloride (2.52 g., 0.02 mole) and ethoxyacetylene (9.6 g., 0.14 mole) in water (20 ml.), cooled in an ice-water bath. The mixture was stirred and allowed to warm to room temperature after the addition had been completed. After 8 hr. stirring, a yellow oil separated. Solvents were removed by evaporation under reduced pressure, leaving an oily solid which yielded a pale yellow powder (5.0 g.), m.p. 121 - 125°, on trituration with methanol. The methanol solution was kept at 0° for 2 days, after which a further 1.49 g. of the pale yellow solid had precipitated. A sample of this solid was recrystallised twice from methanol (charcoal), to give a very pale yellow solid, m.p. 124 - 125°, which was identified as N-4-nitrophthaloylglycine methyl ester (crude yield 6.59 g., 62%).

$\nu_{max.}$ (CCl_4): 1735 cm^{-1} (s); 1763 cm^{-1} (s); 1790 cm^{-1} (w). (1st peak stronger than 2nd peak).

n.m.r. ($CDCl_3$): τ 1.23, 1.25, 1.78, 1.92 (complex splitting); 5.45 (unsplit), 6.16 (unsplit), integrating in the ratio 2.9 : 2.0 : 3.1 (theoretical, 3 : 2 : 3).

$\lambda_{max.}$ (95% EtOH): 236 mμ (ε 1.89 x 10^4).

Found : C, 50.3; H, 2.9; N, 10.5%.

$C_{11}H_8N_2O_6$ requires : C, 50.01; H, 3.05; N, 10.60%.

Reaction of phthalic acid with hydrazine hydrate and ethoxyacetylene:

Phthalic acid (1.66 g., 0.01 mole) and hydrazine hydrate (0.50 g., 0.49 ml., 0.01 mole) in water (30 ml.) were allowed to drip into magnetically stirred ethoxyacetylene (5.0 ml., ca. 0.05 mole) over the course of 1 hr. After a short time the reaction mixture became warm and it was cooled in an ice-bath. It was then stirred for 2 days at room temperature when a white solid (1.18 g.) was precipitated. This was recrystallised from glacial acetic acid and identified as N-phthalimido-phthalimide (1.18 g., 82%) m.p. > 300° (lit., > 300°)

$\nu_{max.}$ (paraffin mull): 1740 cm^{-1} (s) (C = O).

$\lambda_{max.}$ (95% EtOH): 222.5 mμ (ε 9.18 x 10^4); 295 mμ (ε 6.49 x 10^3).

Found : C, 65.6; H, 2.87; N, 9.4%.

Calc. for $C_{16}H_8N_2O_4$: C, 65.75; H, 2.76; N, 9.59%.

Reaction of maleic acid with glycine and ethoxyacetylene: Maleic acid (2.32 g., 0.02 mole) and glycine (1.50 g., 0.02 mole) in water (30 ml.) were allowed to drip into magnetically stirred ethoxyacetylene (17.5 ml. 14.0 g., 0.2 mole) which was cooled in an ice-water bath. The addition took place over one hour and the solution was stirred for a further 8 hr. at room temperature. Precipitation of a white solid had been observed after stirring for about 30 min. and this was filtered off, washed with acetone, and recrystallised from butan-2-ol. It was identified as dibasic acid, maleyl glycine, m.p. 187 - 188° (lit., m.p. 189 - 190°; 186 - 187°). The filtrate from the reaction mixture was evaporated under reduced

pressure to yield a yellow oil which on trituration with acetone gave more maleyl glycine (total yield, 2.9 g., 85%).

$\nu_{max.}$ (paraffin mull): 1680 cm^{-1} (s) (Amide I band); 1720 cm^{-1} (s) (C = O), 3300 cm^{-1} (m) (N - H).

n.m.r. (D_2O): τ 3.65 (unsplit), 5.25 (HDO), 6.25 (unsplit), integrating in the ratio 1 : 1 (theoretical 1 : 1).

Found : C, 41.50; H, 4.03; N, 7.72%.

Calc. for $C_6H_7NO_5$: C, 41.62; H, 4.05; N, 8.09%.

Reaction of maleic acid with aniline and ethoxyacetylene: Ethoxyacetylene (3.20 g., 0.05 mole) was added to a stirred homogeneous mixture of maleic acid (1.16 g., 0.01 mole) and redistilled aniline (1.00 g., 0.01 mole). After about 15 min. the mixture became warm and an oily yellow solid began to separate. Stirring was continued for 3 hr., and volatile components were removed by evaporation under reduced pressure. The yellow powder remaining was recrystallised three times from 95% ethanol and identified as maleanilic acid (N-phenylmaleamic acid) (1.70 g., 98%), m.p. 187 - 199° (lit. 187 - 187.5°, 198°).

Found : C, 62.9; H, 4.6; N, 7.3%.

Calc. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33%.

Reaction of succinic acid with aniline and ethoxyacetylene: Ethoxyacetylene (3.2 g., 4 ml., 0.05 mole) was added to a solution of succinic

acid (1.18 g., 0.01 mole) and redistilled aniline (1.00 g., 0.01 mole) in water (5 ml.). After stirring for 30 min. an oily yellow solid began to separate. The mixture was stirred for 20 hr. when the liquid phase had separated into an upper red-brown layer (ethyl acetate) and a lower yellow aqueous layer.

The ethyl acetate was evaporated; water (150 ml.) was added and the remaining mixture boiled, cooled to room temperature and filtered to yield a solid which was identified as the di-anilide of succinic acid, N,N'-diphenylsuccinamide, (0.2 g., 17.5%), m.p. after recrystallising twice from 95% ethanol (charcoal), 232 - 233° (lit. 230°).

Found : C, 71.3; H, 5.91; N, 10.2%.

Calc. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44%.

The aqueous filtrate was evaporated under reduced pressure to yield a light-brown solid which after recrystallising twice from water (charcoal) was identified as succinanilic acid (N-phenylsuccinamic acid), (0.9 g., 56%), m.p. 145 - 146° (lit. 144.5 - 145.5°).

Found : C, 61.9; H, 5.37; N, 6.9%.

Calc. for $C_{10}H_{11}O_3N$: C, 62.16; H, 5.74; N, 7.25%.

Attempted preparation of di-1-ethoxyvinyl maleate. A. Using methylene dichloride as solvent: Maleic acid was dried for 6 hr. at 100°, 0.1 mm. pressure. Ethoxyacetylene was redistilled from potassium hydroxide pellets. Maleic acid (0.07 g., 6 m.mole) was added to a solution of

ethoxyacetylene (0.4 g., 0.5 ml., 60 m.mole) in dry methylene dichloride (5 ml.) containing a small amount of mercuric acetate as catalyst. The suspension was stirred magnetically, at room temperature, for 15 hr. when a clear straw coloured solution resulted. The volatile components were removed under reduced pressure, at 50°, in an atmosphere of dry nitrogen and a viscous orange liquid remained. An infrared spectrum of this liquid showed a weak band at 1850 cm^{-1}, a very strong band at about 1780 cm^{-1}, with shoulders at 1795 cm^{-1} and 1755 cm^{-1} and a slightly less intense band at 1680 cm^{-1}. Attempts to distil the crude mixture of maleic anhydride and di-1-ethoxyvinyl maleate, under reduced pressure in an atmosphere of dry nitrogen were unsuccessful; the product decomposed and turned black. The residue showed only anhydride peaks in the 1600 - 1900 cm^{-1} region of the infrared spectrum.

B. Using anhydrous ether as solvent: Maleic acid (0.07 g., 6 m.mole) was added to a solution of ethoxyacetylene (0.8 g., 1.0 ml., 120 m.mole) in ether dried over sodium (3 ml.) containing a catalytic amount of mercuric acetate. The suspension was cooled in an ice-bath and stirred magnetically for 4 hr. in an atmosphere of dry nitrogen and then stirred for a further 16 hr. at room temperature. A straw coloured solution remained and when volatile components had been removed, the residue was a viscous orange liquid. The infrared spectrum showed strong peaks at 1680 cm^{-1} and 1760 cm^{-1} as expected for di-1-ethoxyvinyl maleate but this was contaminated by a considerable amount of maleic anhydride as

evidenced by the strong peak at 1785 cm^{-1} and the weak peak at 1855 cm^{-1}.

Attempted preparation of di-1-ethoxyvinyl succinate: Succinic acid was dried for 3 hr. at 100° and 0.1 mm. pressure. EThoxyacetylene was redistilled from potassium hydroxide pellets. Succinic acid (1.18 g., 0.01 mole) was added to a solution of ethoxyacetylene (4.8 g., 6.0 ml., 0.06 mole) in dry methylene dichloride (120 ml.), containing mercuric acetate (5 mg.) as catalyst. A flow of dry nitrogen was maintained throughout the experiment. The suspension was stirred vigorously by means of a magnetic stirrer for five days when nearly all of the solid had dissolved to give a red-brown solution. The liquid was decanted and volatile components were removed at 60° initially, under slightly reduced pressure and finally at 20 mm. A mixture of a red-brown viscous liquid and colourless crystals remained. The oil was dissolved in dry ether and the crystals filtered off and identified as unreacted succinic acid (94 mg.) by comparison of the infrared spectrum with that of an authentic sample, and from its m.p. The filtrate was transferred to a distillation flask, the ether removed, and the remaining oil distilled at 0.6 mm. The distillate, a low melting solid, all distilled in the range 115 - 118° (0.6 mm.): the residue was a dark red-brown tar. The distillate was analysed to be di-1-ethoxyvinyl succinate (0.8 g., ca. 30%) contaminated with about 20% of succinic anhydride which could not be separated by distillation.

$\nu_{max.}$ (liquid film): 1675 cm^{-1} (s) (C = CH_2); 1775 cm^{-1} (s) (C = O); 1865 cm^{-1} (w) (anhydride C = O).

n.m.r. ($CDCl_3$): τ 5.8 - 6.2 (complex splitting); 7.12 (unsplit), 8.62 (triplet), integrating as 4 : 2 : 3 (theoretical 4 : 2 : 3): anhydride impurity appeared as a singlet at 6.91τ integrating as 0.8.

Reaction with aniline: Di-1-ethoxyvinyl succinate (50 mg.) was dissolved in redistilled aniline (5 ml.) and heated at 80° for 4 hr. Some droplets of clear liquid, with a fruity ester-like odour, formed on the lower part of the condenser during this time: this was identified as ethyl acetate by comparison of infrared spectra. Aniline was removed under reduced pressure (0.1 mm.) at 60° leaving a white crystalline solid. This was recrystallised twice from ethanol, m.p. 230 - 231° (lit. m.p. 230°) and identified as N, N'-diphenylsuccinamide (40 mg., 80%).

Found : C, 71.60; H, 5.91; N, 10.2%.

Calc. for $C_{16}H_{16}O_2N_2$: C, 71.62; H, 6.01; N, 10.44%.

D. Experiments with Ethyl Diazoacetate and Alkenes.

Ethyl diazoacetate was prepared from ethyl glycinate hydrochloride, by the method developed by Searle,[82] and was used without further purification.

Reaction of ethyl diazoacetate with ethyl vinyl ether in the presence of anhydrous copper sulphate as catalyst. (a) Using no solvent: Commercial ethyl vinyl ether was distilled from sodium wire before use. A mixture of approximately equal volumes of ethyl diazoacetate (10.0 g., 0.088 mole) and ethyl vinyl ether was allowed to drip into a boiling mixture of ethyl vinyl ether (130 ml.) and anhydrous copper sulphate (0.3 g.) over a period of 30 min. The yellow solution was heated under reflux for 2 hr. but the absence of gas evolution indicated that the required pyrolysis of the ethyl diazoacetate had not taken place. This reaction mixture was not investigated further: instead, a solvent of higher boiling point was used.

(b) Using benzene as solvent: A mixture of approximately equal volumes of ethyl diazoacetate (10.0 g., 0.088 mole) and ethyl vinyl ether was allowed to drip into a boiling mixture of ethyl vinyl ether (80 ml.) and anhydrous benzene (200 ml.) containing anhydrous copper sulphate (0.3 g.) over a period of 30 min. The temperature in the reaction flask was 60°. After a few minutes nitrogen evolution was observed and the colour of the solution changed from yellow to brown. The solution was heated under reflux for 4 hr.; the catalyst was filtered off, and volatile components

removed under a slightly reduced pressure at 60°. The crude residue, a brown liquid, was fractionally distilled (9.5 mm.) through a short Vigreux column to yield two fractions:- 68 - 69° (3.8 g.) and 75 - 83° (0.9 g.). The first fraction was shown to be a mixture of two components, by v.p.c. analysis (silicon grease; P.E.G.A.; D.E.G.S.). These were identified as cis and trans isomers of 1-ethoxy-2-ethoxycarbonylcyclopropane (3.8 g., 27%).

$\nu_{max.}$ (liquid film): 1725 cm^{-1} (s) (C = O).

n.m.r. (CCl_4): τ 5.6 - 6.6 (complex splitting); 8.2 - 9.0 (complex splitting); integrating in the ratio 5 : 9.3 (theoretical 5 : 9).

Found : C, 60.6; H, 9.23%; no nitrogen.

Calc. for $C_8H_{14}O_3$: C, 60.74; H, 8.93%.

V.p.c. analysis of the crude reaction mixture showed that 1-ethoxy-2-carboethoxycyclopropane was formed in approximately 60% yield and that the isomers were in a ratio of 8 : 3. The infrared spectrum of fraction 2 showed a strong absorption at 1725 cm^{-1} and a weak olefinic absorption at 1650 cm^{-1}.

Reaction of ethyl diazoacetate with 1-ethoxyvinyl benzoate in the presence of anhydrous copper sulphate as catalyst: Ethyl diazoacetate (6.3 g., 0.054 mole) and an approximately equal volume of 1-ethoxyvinyl benzoate, in dry benzene (10 ml.), were allowed to drip into a boiling solution of 1-ethoxyvinyl benzoate (31.5 g., 0.163 mole, including the volume mixed with ethyl diazoacetate) in dry benzene (40 ml.) containing anhydrous

copper sulphate (0.3 g.), over 45 min. Immediate reaction was indicated by the evolution of nitrogen and a colour change from yellow to brown. The solution was heated under reflux for 1½hr. after the addition had been completed and was then filtered and the benzene distilled off at 50° (200 mm.), through a short Vigreux column. The bulk of the excess of 1-ethoxyvinyl benzoate (ca. 25 ml.) then distilled at 72°, 0.2 mm., and the remaining reddish-brown liquid (ca. 10 ml.) was fractionally distilled at a reduced pressure of 1.0×10^{-3} mm. using a micro-distillation apparatus to yield the fractions:- (1) 62 - 63° (2) 63 - 100° (3) 100 - 108° (4) 110° (5) 110 - 120°. A red-brown tar (ca. 1 ml.) remained in the distillation flask. V.p.c. analysis (silicon grease column) of the distillation fractions showed fraction 4 to be a mixture of two components (ratio 3 : 2) which were identified as isomers of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (2.2 g., 15%).

$\nu_{max.}$ (liquid film): 1730 cm^{-1} (s) (C = O).

n.m.r. (CCl_4): τ 1.7 - 2.0 and 2.2 - 2.6 (complex splitting); 5.7 - 6.3 (complex splitting 6 peaks, 2 overlapping quartets, J ~ 7 c.p.s.); 7.5 - 8.9 (complex splitting + methyl triplet, J ~ 7 c.p.s.); integrating in the ratio 6 : 4 : 9.1 (theoretical 6 : 4 : 9).

Found : C, 65.00; H, 6.24%; no nitrogen.

$C_{15}H_{18}O_5$ requires : C, 64.73; H, 6.52%.

The total yield of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate was approximately 40% (v.p.c. analysis).

Reaction of ethyl diazoacetate with 1-ethoxyvinyl propionate, in the presence of anhydrous copper sulphate as catalyst: A solution of approximately equal volumes of ethyl diazoacetate (4.6 g., 0.040 mole) and 1-ethoxyvinyl propionate in dry benzene (5 ml.) was allowed to drip into a boiling solution of 1-ethoxyvinyl propionate (12 g., 0.083 mole, in all) in dry benzene (20 ml.) containing anhydrous copper sulphate catalyst (0.2 g.). Immediate nitrogen evolution occurred and the solution was refluxed for 2 hr. when the colour changed from yellow to red-brown. The solution was filtered, volatile components removed, and the residue, a red-brown oil was distilled under reduced pressure to yield the following fractions:-

at 8.5 mm. (1) 60° (2) 60 - 61° (3) 61 - 63°;

at 1.2 mm. (4) 64 - 66°;

at 0.4 mm. (5) 82° (6) 87°.

Fractions 4, 5 and 6 were redistilled at 0.25 mm. to give the fractions:- (i) 67 - 79°; (ii) 79 - 82°; (iii) 82 - 84.5°; (iv) 85 - 88°; (v) 88 - 92°; (vi) 92 - 100°.

Fraction (iii) was identified as a mixture of two isomers of 1-ethoxy-2-ethoxycarbonylcyclopropyl propionate, (in ratio of 3 : 1 from v.p.c.) (2.4 g., 26%).

$\nu_{max.}$ (liquid film): 1735 cm^{-1} (s) (C = O).

n.m.r. (CCl_4): τ 5.6 - 6.5 (complex splitting; 7 peaks (with shoulders) from 2 partially superimposed quartets, J ~ 7 c.p.s.); 7.4 - 9.1 (complex splitting which includes 2 methyl triplets, J ~ 7 c.p.s.); integrating in the ratio 2 : 6.8 (theoretical 2 : 7).

Found : C, 57.2; H, 7.81%; no nitrogen.

$C_{11}H_{18}O_5$ requires : C, 57.38; H, 7.88%.

Preparation of 1-ethoxy-2-ethoxycarbonylcyclopropyl dichloroacetate:

A solution of ethyl diazoacetate (5.7 g., 0.05 mole) and an approximately equal volume of 1-ethoxyvinyl dichloroacetate in dry benzene (20 ml.) was allowed to drip into a boiling solution of 1-ethoxyvinyl dichloroacetate (26.0 g., 0.13 mole in all) in dry benzene (40 ml.) containing anhydrous copper sulphate (0.1 g.). The amber colour of the solution deepened and nitrogen was evolved. The addition took place over 45 min. and heating under reflux was continued for 3 hr. The solution was then filtered and volatile components were removed at 60°, under slightly reduced pressure. The residue was then distilled at 0.3 mm. to remove most of the unchanged 1-ethoxyvinyl dichloroacetate (b.p. 50 - 52°). Distillation was continued under a reduced pressure of 5×10^{-3} mm. to yield the following fractions:- (1) 43° (2) 86° (3) 96 - 106° (4) 106 - 112° (5) 112 - 118° (6) 118 - 130°. Fractions 3 and 4 were found to be mixtures of two components (ratio 1 : 9) identified as isomers of 1-ethoxy-2-ethoxycarbonylcyclopropyl dichloroacetate (4.7 g.,33%).

$\nu_{max.}$ (liquid film): 1740 cm^{-1} (s) (C = O).

n.m.r. (CCl_4): τ 3.98 (singlet); 5.6 - 6.3 (complex splitting); 7.4 - 8.9 (complex splitting); integrating in the ratio 1 : 4 : 9 (theoretical 1 : 4 : 9).

Found : C, 41.81; H, 4.75%; no nitrogen.

$C_{10}H_{14}O_5Cl_2$ requires: C, 42.1; H, 4.90%.

Reaction of ethyl diazoacetate with 1-ethoxyvinyl thiolacetate, in the presence of anhydrous copper sulphate as catalyst: A solution of approximately equal volumes of ethyl diazoacetate (3.4 g., 0.030 mole) and 1-ethoxyvinyl thiolacetate in anhydrous benzene (10 ml.) was allowed to drip into a boiling solution of 1-ethoxyvinyl thiolacetate (9.6 g., 0.060 mole, including the volume mixed with ethyl diazoacetate) in anhydrous benzene (50 ml.) containing anhydrous copper sulphate (10 mg.). The addition took place over 45 min. in an atmosphere of dry nitrogen. The solution, which was now red-brown was boiled for a further 2 hr. and then the benzene was evaporated, initially at atmospheric pressure, and finally at 40 mm. The resultant red-brown liquid (ca. 18 ml.) was then distilled at 0.35 mm. to give the following fractions:- (1) 22 - 27°; (2) 27 - 32°; (3) 32 - 66°; (4) 66 - 82°; (5) 82 - 84°; (6) 92 - 100°.

Fractions 1 and 2 were shown to be pure 1-ethoxyvinyl thiolacetate and fraction 3 was also mainly the starting material (v.p.c. analysis). The other major fraction, fraction 5, showed two peaks (ratio 7 : 1) on v.p.c. analysis (silicon grease column).

$\nu_{max.}$ (liquid film): 1630 cm^{-1} (w) with a shoulder at 1600 cm^{-1} (w); 1725 cm^{-1} (s) (C = O).

n.m.r. ($CDCl_3$); τ 5.3 - 6.7 (complex splitting) 7.08 (singlet); 7.45 - 8.80 (complex splitting); integrating in the ratio 4.3 : 3.5 : 2.3 : 6.0 (theoretical 5 : 3 : 2 : 6).

Found : C, 43.10; H, 5.02; N, 11.95; S, 17.75%.

$C_{10}H_{16}O_4S$ requires : C, 51.7; H, 6.9; S, 13.8%.

$C_{10}H_{16}O_4N_2S$ requires: C, 46.1; H, 6.14; N, 12.3; S, 10.8%.

E. Experiments with 2-Ethoxycarbonylcyclopropanone Acylals.

(1) Intramolecular rearrangement catalysed by boron trifluoride etherate.

(a) 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (30 mg.) was dissolved in anhydrous ether (0.5ml and one drop of boron trifluoride etherate was added. The solution became warm and turned red-brown. It was transferred to a bulb-tube, the ether removed under slightly reduced pressure, and the resultant red viscous liquid was distilled at 0.03 mm., using a mercury diffusion pump. A colourless liquid was collected in the second bulb at an air-bath temperature of 130°. This was identified as diethyl 2-benzoylsuccinate (lit. b.p. 192 - 3°, 10 mm.) by spectral analysis, elemental analysis and chemical degradation.

$\nu_{max.}$ (liquid film): 1690 cm^{-1} (s) (conj. C = O); 1735 cm^{-1} (s) (C = O); 3070 cm^{-1} (w) (arom. C - H).

n.m.r. (CCl_4): τ 1.7 - 2.0 and 2.25 - 2.65 (complex splitting); 5.16 (triplet, J ~ 8 c.p.s.); 5.88 (quartet, J ~ 7 c.p.s.); 7.02 (doublet, J ~ 8 c.p.s.); 8.81 and 8.89 (two triplets, J ~ 7 c.p.s.); integrating in the ratio 5.1 : 1 : 4 : 2 : 6 (theoretical 5 : 1 : 4 : 2 : 6).

Found : C, 64.61; H, 6.65%.

Calc. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52%.

The crude yield of diethyl 2-benzoylsuccinate was almost quantitative from v.p.c. analysis.

Degradation of diethyl 2-benzoylsuccinate: Diethyl 2-benzoylsuccinate (58 mg.) was heated at reflux with 50% aqueous potassium hydroxide solution (2 ml.) for 2 hr. On acidification with concentrated hydrochloric acid a white solid which was identified as benzoic acid was precipitated. The solution was extracted with ether (3 x 20 ml.) and the ether solution dried and evaporated to yield a further quantity of benzoic acid (total yield 20 mg., 74%). After purification by sublimation the infrared spectrum was identical with that of an authentic sample of benzoic acid and the m.p. was 122 - 123° (lit. 122°). The aqueous layer from the ether extraction was evaporated to dryness, under reduced pressure, extracted with hot acetone (3 x 10 ml.) and filtered. On evaporation of the acetone a white solid was obtained which was identified as succinic acid (18 mg., 72%) m.p. 184 - 185°, after recrystallisation, (lit. m.p. 185°).

(b) 1-Ethoxy-2-ethoxycarbonylcyclopropyl dichloroacetate: The reaction was conducted as before and the product, a brown viscous liquid, distilled at 120°, 0.3 mm., to yield a colourless liquid which was identified as diethyl 2-dichloroacetylsuccinate.

$\nu_{max.}$ (liquid film): 1735 cm^{-1} (s) (C = O).

n.m.r. (CCl_4): τ 3.53 (singlet); 5.38 - 5.95 (complex splitting); 7.04 (doublet J ~ 7 c.p.s.); 8.68 and 8.72 (2 triplets, J ~ 7 c.p.s.) integrating in the ratio 1 : 5 : 2 : 6) (theoretical 1 : 5 : 2 : 6).

Found : C, 41.85; H, 4.63%.

$C_{10}H_{14}O_5Cl_2$ requires: C, 42.11; H, 4.94%.

(2) Intramolecular rearrangement of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate catalysed by trifluoroacetic acid. Trifluoroacetic acid (4 drops) was added to a solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (20 mg.) in carbon tetrachloride (0.5 ml.). Immediate quantitative conversion to diethyl 2-benzoylsuccinate was observed by monitoring the reaction by v.p.c. and n.m.r. analysis. The carbon tetrachloride was evaporated and the residue distilled to yield diethyl 2-benzoylsuccinate which was characterised by spectral comparison with an analysed sample.

(3) Attempted hydrolyses of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate.

(a) Under acidic conditions. (i) Hydrochloric acid: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (220 mg. 0.8 m.mole) in ether (1 ml.) was shaken with concentrated hydrochloric acid (0.5 ml.) for 30 min. V.p.c. analysis showed that total decomposition of the starting material had occurred giving rise to two new products. The volume of the ether layer was made up to 10 ml. and the aqueous layer separated: the ether layer was washed with water (5 x 10 ml.), dried over magnesium sulphate, and the ether evaporated. The residue was distilled to yield diethyl succinate, diethyl 2-benzoylsuccinate and benzoic acid (20 mg. 20%) which sublimed during the distillation. The products were identified by their infrared and n.m.r. spectra and by v.p.c. comparison with authentic samples. From v.p.c. analysis it was found that diethyl succinate and diethyl 2-benzoylsuccinate had been formed in a ratio of 1:3.

(ii) Acetic acid: Glacial acetic acid (0.5 ml.) was added to a solution of 1-ethoxy-2-carboethoxycyclopropyl benzoate (20 mg.) in ether (0.5 ml.) and the mixture shaken. After standing for several weeks at room temperature, v.p.c. analysis showed that the starting material was unchanged. The solution was then heated at 80° for 60 hr. but v.p.c. analysis again showed only unchanged starting material.

(b) Under basic conditions. (i) Sodium carbonate: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (20 mg.) was added to 10 ml. of a 5% solution of sodium carbonate in water and the mixture shaken for 2 days. At the end of this period the mixture was still two phases and all the starting material was recovered unchanged by ether extraction.

(ii) 50% aqueous potassium hydroxide: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (196 mg.) was added to 5 ml. of a 50% solution of potassium hydroxide in water and the mixture was heated at 80° for 3 hr. A pale yellow homogeneous solution was formed. The solution was acidified to pH 5 with 10% hydrochloric acid and extracted with ether (5 x 10 ml.). The ether extract was dried and evaporated to yield benzoic acid (62 mg., 72%) m.p. 121 - 122° (lit. 122°). The aqueous layer was evaporated to dryness under reduced pressure and the solid residue extracted with hot acetone (5 x 10 ml.). Evaporation of the acetone yielded succinic acid (40 mg., 66%) m.p. 182 - 183° (lit. 182°). The infrared spectra of both acids were found to be identical with those of authentic samples.

(iii) 2% aqueous potassium hydroxide: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (1.24 g., 4.5 m.mole) was shaken with 2% aqueous potassium hydroxide (40 ml.). After 3 hr. a homogeneous solution had been formed. The alkaline solution was extracted with ether (5 x 10 ml.) and then continuously extracted with ether for 24 hr. The ether extracts were dried ($MgSO_4$) and evaporated leaving no residue. The aqueous solution was acidified to pH 5 with 2% hydrochloric acid and extracted with ether (5 x 10 ml.) to yield, after evaporation of the ether, benzoic acid (190 mg.), which was identified by its melting point and infrared spectrum. The acidified solution was then continuously extracted with ether for 24 hr. On evaporation of the dried ether a mixture of a solid and a liquid (67 mg.) resulted. This mixture was distilled in a bulb-tube under a reduced pressure of 2×10^{-5} mm. (mercury diffusion pump). At an oil-bath temperature of about 90° the solid (~ 20 mg.) which was identified as benzoic acid sublimed. A clear colourless liquid distilled at 140°. This liquid showed only one peak on v.p.c. analysis (silicon grease column). Its n.m.r. spectrum was complex but clearly showed the absence of the cyclopropane ring system: the structure could not be fully elucidated. The acidified solution was continuously extracted with ether for a further 52 hr. when 125 mg. of benzoic acid were recovered. The solution was then evaporated to dryness under reduced pressure and the solid residue was continuously extracted with chloroform, in a Soxhlet extractor, for 12 hr. Succinic acid, which was identified by its melting point and infrared

spectrum, was deposited in the flask of the extractor during this period and a further quantity was recovered on evaporation of the chloroform. The total amount of succinic acid recovered was 336 mg. (63%) and the total amount of benzoic acid recovered was 290 mg. (70%).

(c) Under neutral conditions. (i) Aqueous acetone: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (~ 10 mg.) was dissolved in aqueous acetone (20%) and left for 3 weeks at room temperature. V.p.c. analysis showed that the starting material was unchanged. Boiling the solution under reflux for 25 hr. produced no change in the starting material. (ii) Aqueous ethanol and methanol: Solutions of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (~ 10 mg.) in aqueous ethanol and methanol were left for several weeks at room temperature. V.p.c. analysis showed that the starting material was unchanged. Similarly no reaction occurred in solutions of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate in absolute ethanol and absolute methanol.

(4) Hydrolysis of 1-ethoxy-2-ethoxycarbonyl dichloroacetate under neutral conditions. 1-Ethoxy-2-ethoxycarbonyl dichloroacetate (0.82 g.) was dissolved in acetone (25 ml.) and distilled water (8 ml.) was added. The homogeneous solution was stirred for 8 hr. when v.p.c. analysis showed that all the starting material had been decomposed. Most of the acetone was evaporated under reduced pressure and a yellow oil separated. Ether (20 ml.) was added and the ether layer separated. The aqueous layer was extracted with a further quantity of ether (2 x 20 ml.) and the combined

ether solutions were dried ($MgSO_4$). V.p.c. analysis of the ether solution showed three major peaks in the ratio 2 : 3 : 1): their retention times were identical with those of dichloroacetic acid, diethyl succinate and diethyl 2-dichloroacetylsuccinate, respectively. The aqueous layer was evaporated under reduced pressure when no residue remained. The ether was evaporated and the residue was distilled in a bulb-tube at 0.2 mm. At 60 - 70°, air-bath temperature, a clear colourless liquid distilled. From v.p.c. this was a mixture of diethyl succinate and dichloroacetic acid. Extraction of an ether solution with saturated aqueous sodium bicarbonate yielded pure diethyl succinate:-

$\nu_{max.}$ (liquid film): 1730 cm^{-1} (s)

n.m.r. ($CDCl_3$): τ 5.75 (quartet); 7.32 (singlet); 8.72 (triplet); integrating in the ratio 2 : 2 : 3 (theoretical 2 : 2 : 3).

Acidification of the aqueous extract and ether extraction yielded dichloroacetic acid.

$\nu_{max.}$ (liquid film): 1750 cm^{-1} (s);

n.m.r. ($CDCl_3$): τ 2.1 (broad O-H); 3.90 (singlet).

The distillation residue was shown to consist of a mixture of diethyl succinate, dichloroacetic acid and diethyl 2-dichloroacetylsuccinate by v.p.c. analysis. Extraction of an ether solution with saturated sodium bicarbonate yielded a mixture of diethyl succinate and diethyl 2-dichloroacetylsuccinate.

$\nu_{max.}$ (liquid film): 1730 cm^{-1} (s);

n.m.r. ($CDCl_3$): τ 3.53 (singlet); 5.38 - 5.95 (complex splitting);

7.04 (doublet); 8.6 - 8.9 (complex splitting).

(5) Attempted preparations of derivatives of 2-ethoxycarbonylcyclopropanone.

(a) 2,4-Dinitrophenylhydrazone: 2,4-Dinitrophenylhydrazine (40 mg., 0.2 m.mole) was dissolved in 5 ml. ethanol by adding concentrated hydrochloric acid. This solution was added to a solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (30 mg., 0.11 m.mole) in ethanol (1 ml.) and the mixture was heated under reflux for 12 hr. No crystalline product was isolated on cooling the solution.

(b) p-Nitrophenyl hydrazone: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (84 mg., 0.3 m.mole) was added to a solution of p-nitrophenyl hydrazine (45.5 mg., 0.3 m.mole) in ethanol (5 ml.) containing 1 drop of glacial acetic acid. The solution was heated under reflux for 3 days. No crystalline product was isolated on cooling the solution. Aqueous acetic acid (20%) was added but again no solid crystallised.

(6) Experiments with amines.

(a) Aniline: 1-Ethoxy-2-ethoxycarbonylcyclopropyl benzoate (50 mg.) was added to aniline (5 ml.) and the mixture was heated at 80° for 8 hr. A homogeneous solution was obtained but v.p.c. analysis showed that the starting material remained unchanged. The solution was heated under reflux for 1 hr. and then cooled to 0° when benzanilide (30 mg., 83%), m.p. 162 - 3° (lit. 163°), crystallised out. V.p.c. analysis of the aniline

solution showed a mixture of several products.

(b) Imidazole: A solution of imidazole (30 mg.) in diethyl ether (5 ml.) was added to a solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (30 mg.) in diethyl ether (1 ml.) and the resulting solution was heated under reflux for several hours. No crystalline product was obtained. The experiment was repeated in boiling di-n-butyl ether but again no crystalline product could be obtained.

(7) Pyrolysis experiments.

(a) 35°: A solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate (30 mg.) in carbon tetrachloride was kept at 35° for 7 days. V.p.c. and n.m.r. analysis showed that the starting material was unchanged.

(b) 134°: A solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate ($\sim$ 10 mg.) in di-n-butyl ether (2 ml.) was refluxed for 3 days. V.p.c. analysis showed that the starting material remained unchanged.

(c) 298°: A solution of 1-ethoxy-2-ethoxycarbonylcyclopropyl benzoate ($\sim$ 10 mg.) in di-ethyl phthalate (5 ml.) was refluxed for 3 hr. The solution turned red-brown and v.p.c. analysis showed a complex mixture of products.

(F) Experiments with Zinc-copper Couple and Methylene Di-iodide.

Zinc-copper couple was prepared by the method of Shank and Schechter.[83,84] The zinc dust used was analytical reagent grade obtained from the Mallinckrodt Chemical Company (U.S.A.). Methylene di-iodide (Eastman Kodak) was distilled (30 mm.) before use and stored over bright iron wire.

Reaction of zinc-copper couple and methylene di-iodide with 1-ethoxyvinyl propionate. Zinc-copper couple (8.4 g., 0.12 g. atom of zinc) in anhydrous ether (80 ml.) was stirred magnetically and a few small crystals of iodine were added. The iodine colour was discharged almost immediately and methylene di-iodide (26.9 g., 8.2 ml., 0.10 mole) and 1,2-dimethoxy ethane, (9.02 g., 10.4 ml., 0.10 mole) which had been distilled from sodium wire, were added. This mixture was then stirred magnetically and heated at reflux for 30 min. 1-Ethoxyvinyl propionate (15 g., 0.104 mole) in dry ether (20 ml.) was added dropwise over 30 min. After about 20 min. a vigorous exothermic reaction set in and it was necessary to discontinue heating for 15 min. Finally the mixture was stirred and heated under reflux for 44 hr. The zinc-copper couple was filtered off and washed with ether (2 x 20 ml.) and the combined ether solutions were extracted with saturated aqueous sodium chloride (3 x 20 ml.). The sodium chloride solutions were extracted with ether (2 x 30 ml.) and the total ether

extract was dried ($MgSO_4$) and then the ether and other volatile components were removed at 60° under slightly reduced pressure. The residue, a red-brown liquid, was distilled at 19 mm. through a Dufton column (12 cm.) to remove unchanged 1-ethoxyvinyl propionate (b.p. 40 - 45°) and then three fractions were collected:- (1) 70 - 75°; (2) 75 - 77°; (3) 77 - 80° (19 mm.). Fraction 2 was tentatively identified as consisting mainly of 1-ethoxycyclopropyl propionate contaminated with propionic anhydride, which could not be separated by distillation:- (Found: C, 57.61%; H, 8.38%: $C_8H_{14}O_3$ requires: C, 60.74%; H, 8.92%; Calc. for $C_6H_{10}O_3$ (anhydride): C, 55.37%, H, 7.75%). The infrared spectrum of fraction 2 showed a strong absorption at 1760 cm^{-1} and a weak absorption at 1820 cm^{-1}. Purification of samples by preparative v.p.c. was unsuccessful due to decomposition of the sample.

Reaction of zinc-copper couple and methylene di-iodide with 1-ethoxyvinyl thiolacetate. The experiment was performed as before, using:- 1-ethoxyvinyl thiolacetate (1.19 g., 7.5 m.mole); methylene di-iodide (2.42 g., 9 m.mole); 1,2-dimethoxyethane (0.81 g., 9 m.mole); and zinc-copper couple (0.7 g., 10 mg. atom zinc). An attempted distillation of the crude product, a yellow liquid, at 28 mm. resulted in extensive decomposition; a black tar was formed in the distillation flask and nothing could be distilled over, even at 0.1 mm.

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