POLYMERS OF α-KETO-γ-LACTONES

by

CHAI-YUN C. CHANG

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1978

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

August 28, 1978 — Richard A. Wiley
date — Chairman of Examining Committee

12 September 1978 — David C. Locke
date — Executive Officer

Richard A. Wiley

J. Meyerson

Norman Sutin
Supervisory Committee

The City University of New York

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor Richard H. Wiley for his support, encouragement, and guidance during the course of this investigation as well as the preparation of this thesis.

I would also like to thank Professors M.H.J. Wijnen and Nan-Loh Yang, members of my thesis committee for their interest and the generosity of their time.

I am indebted to my parents and family for their faith and continual encouragement.

Finally, I wish to thank my husband, Tze-Hsiang, for his encouragement, understanding and help through all these years of my graduate studies at City University of New York.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

1. INTRODUCTION

Polymers containing reactive groups have been intensively studied in recent years.[1] The polymer containing reactive groups can undergo chemical reaction to make new derivatives which possess completely different properties from their parent polymers. It is also possible to make a new polymer which is not accessible through direct polymerization of the monomer by the chemical reaction of the polymer containing reactive group.

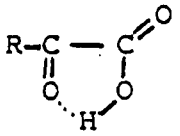
It is the objective of this work to make polymer containing reactive group, by selective polymerization of monomers with multi-functional groups. We have applied the polymerization study on (a) α-Ketoacids (b) γ-lactone of citroylformic acid (dimer of oxalacetic acid) (c) α-Keto-γ-lactones.

In addition, new characterization data of α-keto-γ-lactones are analyzed.

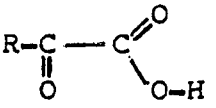
1.1 α-Ketoacids

α-Ketoacids exhibit in complexes properties which are not shown by the free acid.[2,3] In homopolar solvents α-ketoacids form intramolecular resonance stabilized proton chelate rings between the carboxy and α-carbonyl group. This was especially manifested at low concentrations (mole fraction <0.03) by an increased tendency to break up the polymer or dimer structures in favor of monomer forms. This feature, characteristic for α-oxoacids and not found in γ-oxoacids, decreased with increasing methylation of

pyruvic acid. Spectroscopic examinations also shown that with increasing dilution and temperature the open-chain form 2 became increasingly important. In the presence of



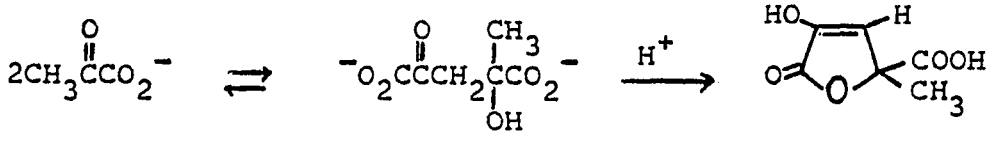
1



2

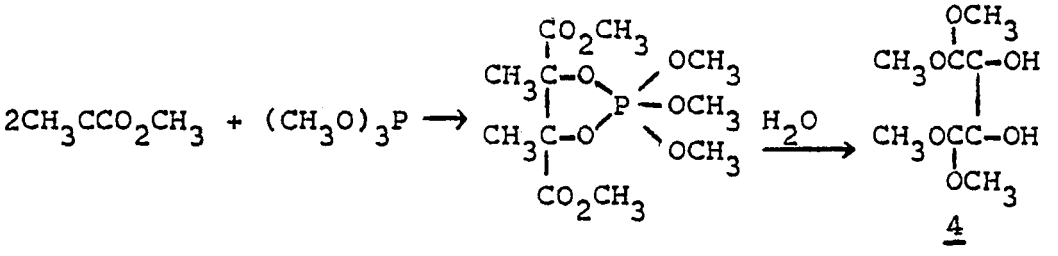
complexing metal ions, halogenation as well as deuteration of β-CH bonds of α-oxoacids was considerably accelerated. The order of effectiveness of acceleration[3,4] was H < Cd < Zn < Co < Ni < Cu < Al. This effect depended on acid-catalyzed influence of the rate of transformation of the keto into the enol form.

However, under the influence of divalent heavy metal ions such as Ba(II), Zn(II), Hg(II), Co(II), Ni(II), the pyruvate ion[5,6] also formed highly insoluble polymeric salts having a metal to pyruvate ratio of 1:2. On the basis of isolation of α-ketovalerolactocarbonic acid 3 from solutions of these salts dissolved in strong acid, Wolff[5] had concluded that these compounds are salts of dimeric pyruvate. The reaction mechanism of Ni(II) and Zn(II) catalyzed pyruvate dimerization was proposed by Leussing[7] via a two-step reaction: enolate formation of complexed pyruvate followed by addition of a second pyruvate to the complexed enolate (carbanion).



3

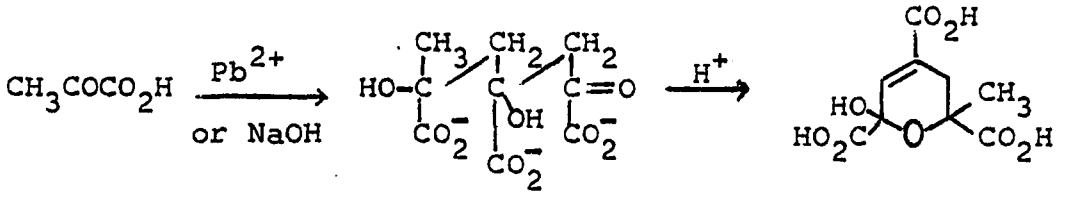
While, two moles of methyl pyruvate reacted with one mole of trimethyl phosphite to give a cyclic saturated oxyphosphorane,[8] which upon hydrolysis gave a liquid mixture of the two diastereometric dimethyl C,C-dimethyl-tartrates 4 .



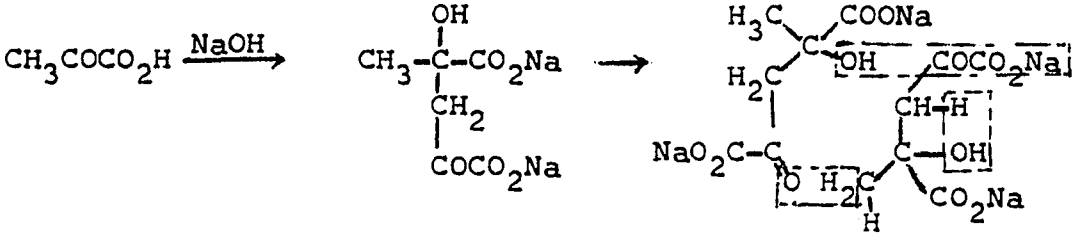
4

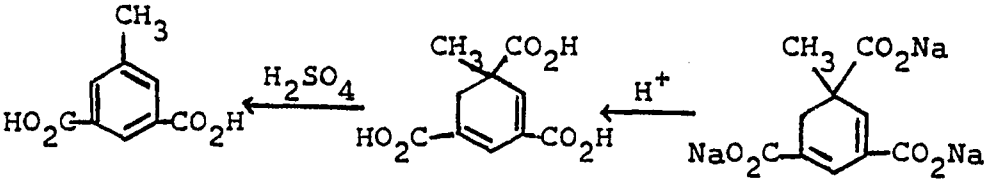
It has been shown[9-11] that the alkali treatment of pyruvic acid gives aldol condensation products with two, three, four or more molecules. The double condensate lactonized upon conversion to the free acid on ion-exchange resin to give α-keto-γ-valerolactocarbonic acid 3 . The triple condensate lactolizes to parapyruvic acid 5 (2-methyl-6-hydroxy-3-dihydropyran, 2,4,6-tricarboxylic acid). The quadruple condensate showed a reaction course involving loss of water and ring formation followed by hydrolysis and loss of oxalic acid to give methyldihydro-

trimesic acid 6 and uvitic acid 7 . At higher temperatures and higher concentration of alkalies ring formation to methyldihydrotrimesic acid 6 occured to a greater extent.



5



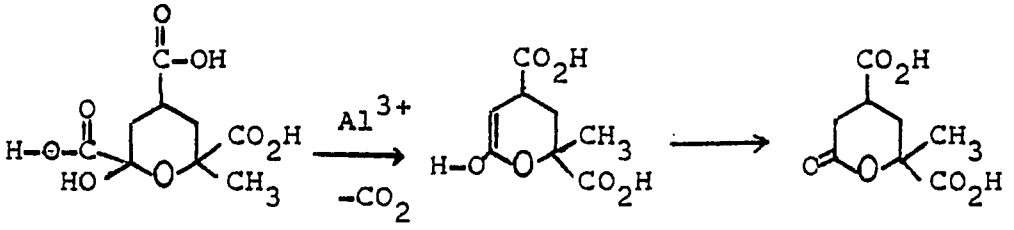


7 6

Under the same conditions metapyruvic acid 3 and parapyruvic acid 5 are partly converted to pyruvic acid.

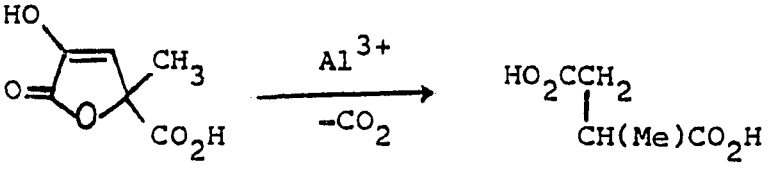
Aqueous pyruvic acid was decarboxylated[12] by aluminum(III) salts proceeded in all probability via the intermediate parapyruvic acid 5 which is formed, preferen-

tially in the presence of complex-forming metal ions, by an aldol-type condensation of 3 moles of pyruvic acid. The resulting hypothetical decarboxylated product rearranges subsequently to the γ-lactone 8 of α-methyl-α-hydroxy-β'-carboxyl-adipic acid. Metapyruvic acid 3 is decarboxy-



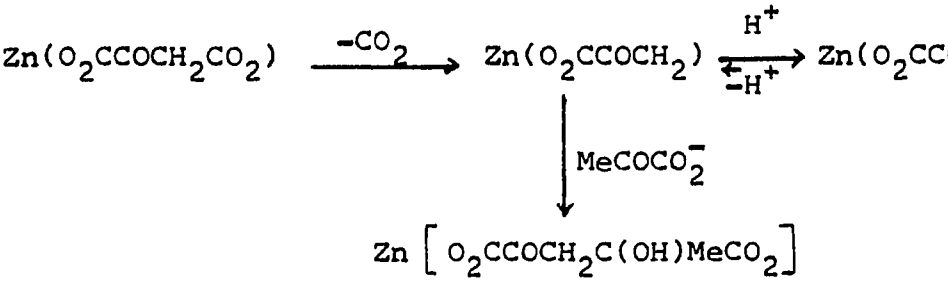
5 8

lated apparently by the same mechanism to methyl succinic acid.



3

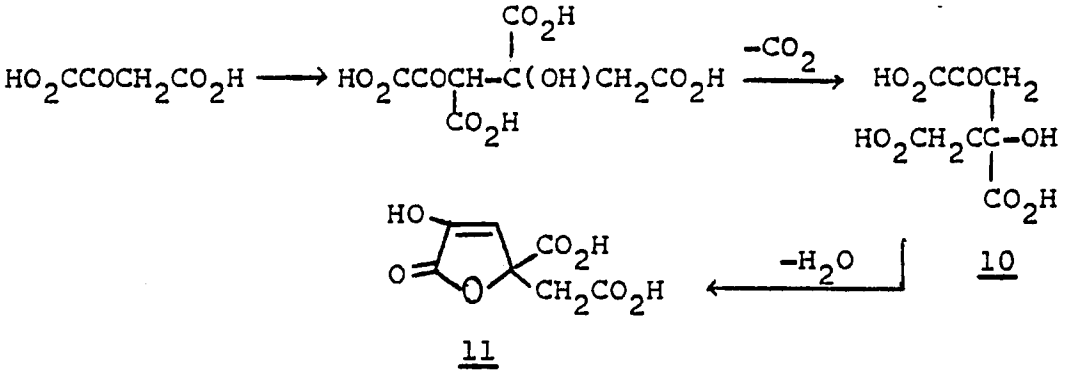
In Zn(II)-catalysed decarboxylation[13,14] of oxaloacetate, the pyruvate dimer (metapyruviate 9) was induced. It is inferred that the induced formation of



9

metapyruvate occurs after Zn(oxalacetate) has lost CO_2, but before the final decarboxylated product pyruvate is formed.

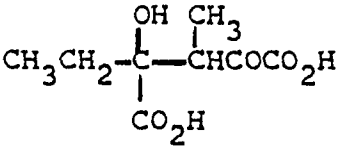
Kumler[15] had study the NMR of oxalacetic acid and found that some other peaks besides the absorption peak for oxalacetic acid were present in the water solution spectrum. These peaks were not due to impurities in the original oxalacetic acid. Some other species were evidently formed when pure oxalacetic acid was placed in water. It was later proved by Wiley and Kim[16] with the isolation of the dimer (Citroyl formic acid 10) which was formed from aldol condensation of 2 moles of oxalacetic acid, with the loss



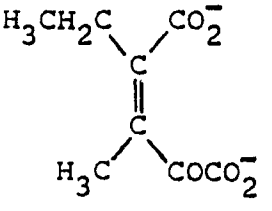
of carbon dioxide. The reaction goes in high yield at pH 3-7, 25-30°C and in aqueous media. The citroyl formic acid 10 is converted to its lactone 11 by dehydration.

In the presence of Zn(II) ion or proton-catalyst, the α-ketobutyric acid was dimerized[17] by aldol condensation. This dimer 12 exists in two diastereometric forms. The possible mechanism involving 2:1 or higher

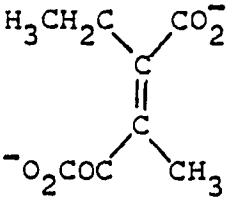
complexes of α-ketobutyric acid, Zn(II) ion serves to catalyze the enolization of α-ketobutyric acid, so that when one of α-ketobutyric acid complex is enolized, another is close by in the coordination sphere to condense with it. The dimer 12 can be gradually dehydrated in the presence of Zn(II) to form an unsaturated compound, perhaps the dehydrated dimer 13a and 13b.



12



13a

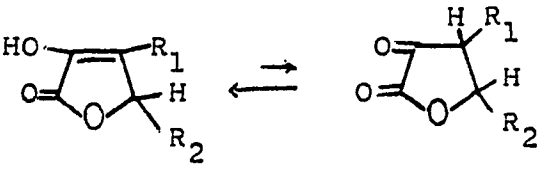


13b

The α-keto acids form self-condensation products, most of them are dimers. Pyruvic acid gives tetramer at higher concentration of alkalies. There are possibly some higher polymers which are not separated. Separation of the higher polymer of pyruvic acid was attempted. Further condensation reaction of the dimer of oxalacetic acid (γ-lactone of citroyl formic acid 10) was also studied at different (a) reaction temperatures (b) reaction times (c) concentration of the lactone in solution.

1.2 Polymers of α-keto-γ-lactones

α-Tetronic acids are β or γ-substituted derivatives of the parent acid 14. This form normally predominates in the tautomeric system 14 ⇄ 15: non-enolisable forms, i.e. those disubstituted in the β-positions possess very



14 15

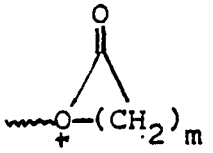
different properties. The polymerizations of α-tetronic acids are especially interest because of their multiple functional groups-lactone, enol, carbon-carbon double bond, which may be in competition with one another for polymerization. Under suitable conditions, α-tetronic acids may be selectively polymerized through one functional group, thus, the polymers obtained will contain reactive functional groups. It is proper to review the polymerizations on these functional groups before discussing the results of our study on polymerization of α-tetronic acids.

1.2.1 Polymerization of lactones

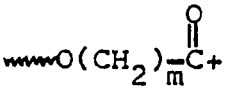
Lactones undergo ring-opening polymerization to polyesters with the use of a variety of cationic and anionic catalysts.[18]

The cationic polymerization proceeds via attack on

monomers by a propagating center which is either the oxonium ion 16 or the acylium ion 17 formed by unimolecular ring-opening of the oxonium ion. The anionic polymerization probably proceeds by acyl oxygen cleavage

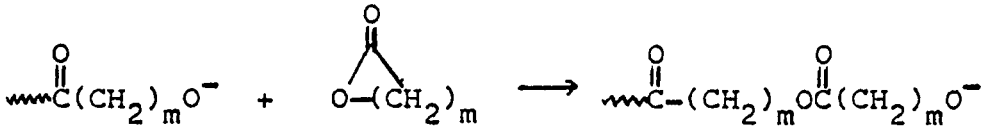


16

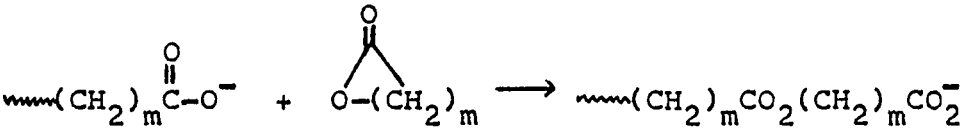


17

of the ring. This mechanism is consistent with the fact that the base saponification of esters generally proceeds by means of acyl oxygen cleavage, i.e. cleavage of the bond between the carbonyl carbon and the non-carbonyl

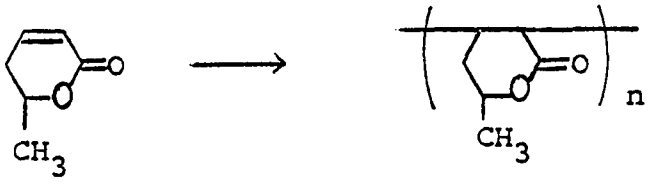


oxygen. However, alkyl oxygen cleavage has been suggested for the reactions of some lactones and their polymerization may proceed[19] by way of the carboxylate anion as the propagating center.



In the absence of any termination reactions, the system should lead to 'Living polymer' and the molecular weight of the polymer should be inversely related to the concentration of the active catalyst species.

Longi[20] and co-workers have examined the anionic polymerization of unsaturated lactones. The lactone of 5-hydroxy-2-hexenoic acid was found to polymerize in the presence of metal amidic compounds. The soluble polymer was found to have been generated exclusively through reaction of the double bond to generate polymers of the structure 18.



18

In view of this result, it is interesting that Ohse and Cherdron[21] investigated the polymerization of β-substituted-β-lactones in the presence of zinc alkyls. They found that this polymerization was so specific that even when a second polymerizable group (vinyl or epoxy) was present, polymerization proceeded exclusively via the lactone group. The substituted β-propiolactones which they investigated and the resulting polymer structure as demonstrated through infrared spectra were shown in Fig. 1:

These polymers could be readily prepared at room temperature. Even in those cases where the substituted functional group is known to be polymerized by zinc alkyls (e.g. epoxy group) the lactone ring was selectively attacked.

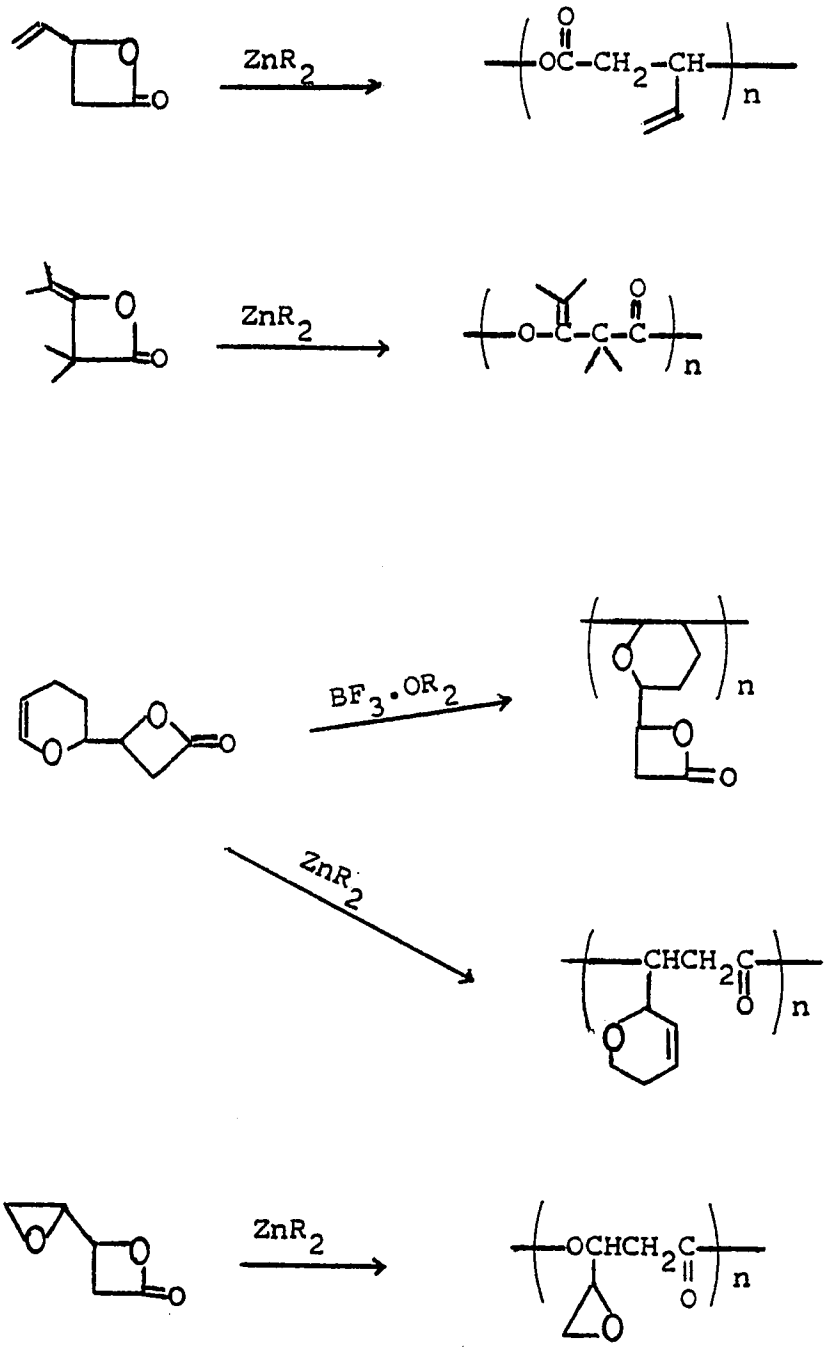


Fig.1: Polymerization of β-lactones

Cox and Hostettler's study[22] on the effect of ring substitution and susceptibility to polymerization have shown that ring substitution of lactones tend to stabilize the ring relative to the polymer and the total number of organic substituents attached to the carbon atoms contained in lactone ring should not exceed four and preferably should not exceed three. This observation is undoubtedly a consequence of the thermodynamic stability of the ring. It is also probable that the location and size of the ring substituents will have a pronounced influence on polymerization rate.

It is significant that, of the simple unsubstituted lactones, only γ-butyrolactone is apparently not polymerizable under conditions where the four-, six, and seven-membered rings readily homopolymerize.

1.2.2 Polymerization of alkenes

A wide range of carbon-carbon double bonds undergo chain polymerization[24] by radical or ionic initiators. Whether an alkene polymerized by radical, anionic, or cationic initiator depends on the inductive and resonance characteristics of the substituent present. The effect of the substituents manifests itself by its alteration of the electron-cloud density on the double bond and its ability to stabilize the possible radical, anion, or cation formed.

Electron-pushing substituents such as alkoxy, alkyl, alkenyl and phenyl increase the electron density on the carbon-carbon double bond and facilitate its bonding

to a cationic species. Further, these substituents stabilize the cationic propagating species by resonance. Thus, monomers such as isobutylene, styrene, methyl vinyl ether and isoprene undergo polymerization by cationic initiators. The effect of alkyl groups in facilitating cationic polymerization is weak and it is only the 1,1-disubstituted alkenes which undergo cationic polymerization.

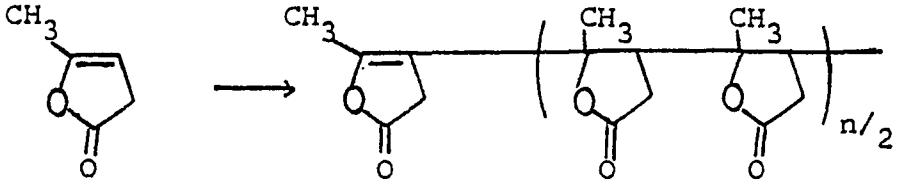
Electron-withdrawing substituents such as cyano and carbonyl (aldehyde, ketone, acid, or ester) facilitate the attack of an anionic species by decreasing the electron-density on the double bond. These substituents also stabilize the propagating anionic species by resonance. Alkenyl and phenyl substituents, although electron-pushing inductively, can resonance stabilize the anionic propagating species. Thus, monomer such as styrene and 1,3-butadiene can therefore, undergo anionic as well as cationic polymerization.

Contrary to the high selectivity shown in cationic and anioinc polymerization, radical initiators bring about the polymerization of almost any carbon-carbon double bond. Radical species are neutral and do not have stringent requirements for attacking the π-bond or for the stabilization of the propagating radical species. Resonance stabilization of the propagating radical occurs with almost all substituents. Thus, almost all substituents are able

to stabilize the propagating radical by delocalization of the radical over two or more atoms.

1.2.3 Polymerization of α,β-unsaturated-γ-lactones

The first attempt to polymerize unsaturated γ-lactone were made by Marvel and Levesque.[25] From the lactone of γ-hydroxyangelic acid 19 , with BF_3.ether as the initiator, these authors obtained a dark red, tacky mass having a molecular weight of 800-900 (ebullioscopic). In addition to γ-lactone groups, the polymer still contained about 25% of its hydroxy and carboxyl groups.

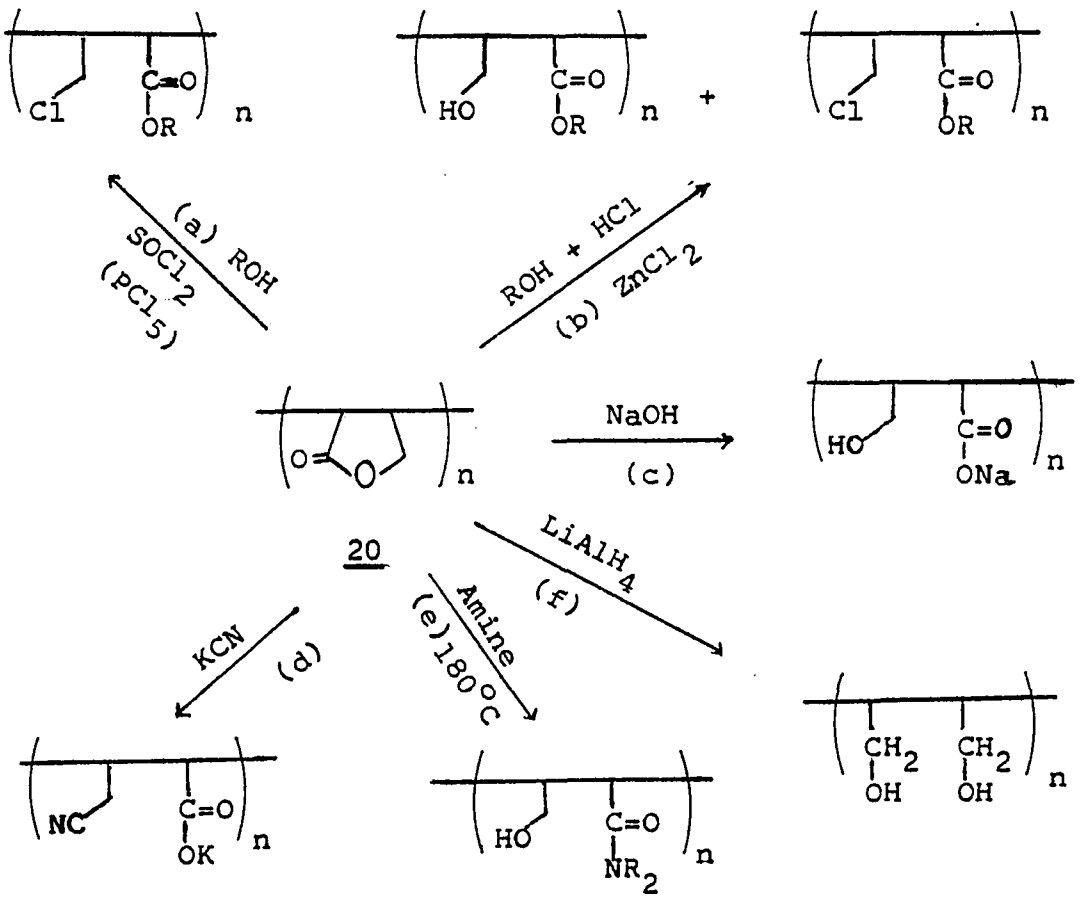


19

Ohse and Cherdron[26] had obtained solid polymers from unsaturated-γ-lactone of γ-hydroxycrotonic acid, with triethylamine as the initiator. The polymer are only soluble in strongly polar solvents (dimethylformamide or formic acid). On the basis of the IR spectrum (The γ-lactone absorption at 1765cm^{-1} is retained, and the absorption of C=C bond at 1675cm^{-1} disappears). The polymers were assigned to have structure 20.

The poly-lactone 20 reacts with inorganic acid halides (e.g. PCl_5 or $SOCl_2$) to give polymeric γ-halogen-oacyl halides, from which the esters of the γ-halogeno

acids can be directly obtained by treatment with alcohol (Scheme 1a). In the presence of $ZnCl_2$, poly-lactone 20 reacts with HCl to give the polymeric ester of the γ-hydroxy-carboxylic acid and a little of the ester of the γ-chlorocarboxylic acid are formed (Scheme 1b). The



Scheme 1 : Reactions of poly-γ-hydroxycrotonolactone

poly-lactone 20 dissolves in aqueous sodium hydroxide solution to give the sodium salt of the corresponding

polymeric γ-hydroxy acid (Scheme 1c). The original polymer is recovered on acidification. Reaction of potasium cyanide with poly-lactone 20 in anhydrous dimethyformamide gives the salt of the γ-cyanocarboxylic acid (Scheme 1d). Poly-lactone 20 also reacts with an exess of the amine in organic solvents to give polymeric γ-hydroxycarboxamide (Scheme 1e). Upon reduction with $LiAlH_4$, poly-lactone 20 gives a water-soluble polymer of 2-butene-1,4-diol (Scheme 1f).

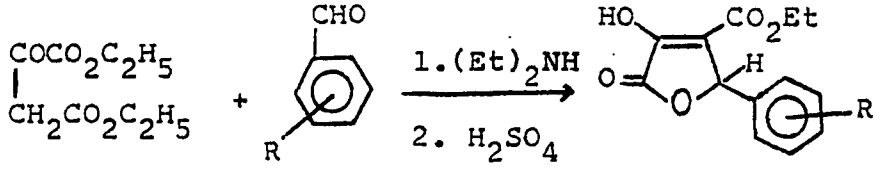
1.2.4 Syntheses of α-Tetronic acids

The field of α-tetronic acids, after a thorough synthetic exploration in the forties by Schinz and co-workers,[27-29] has gained in interest recently as its representatives were encountered among the degradation products of the important antibiotic, cephalosporin C[30], and were subsequently utilized as intermediates in the total synthesis of the cephalosporin C nucleus.[31-37] Some of α-tetronic acids which possess intense aroma have been used as food flavoring agents.[38-44] There are several methods of preparing α-tetronic acids:

1.2.4.1 Condensation of ethyl oxalacetate with aldehyde

The first preparation of a α-tetronic acid was done by Wislicenus,[45] who prepared α-keto-β-carbethoxy-γ-phenyl-γ-butyrolactone (ketophenylparaconic ester) 21 by condensation of ethyloxalacetate with benzaldehyde in presence of diethylamine, followed by acidification. Gault successfully obtained ketoanisylparaconic ester, ketoortho-

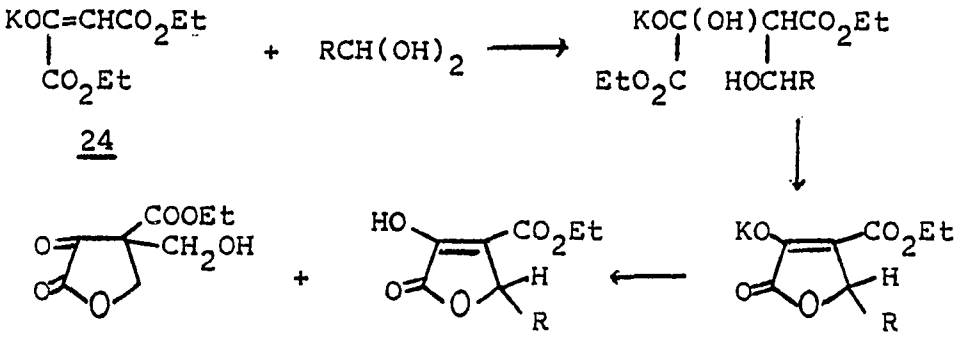
nitrophenylparaconic ester 22, ketometanitrophenylparaconic ester 23 , ketoparaoxyphenylparaconic ester by applying Wislicenus' method to substituted benzaldehyde. However, the ethyl oxalacetate condensed with salicylaldehyde under the influence of diethylamine giving, not a ketoarylparaconic ester, but salicylidenemonoxalacetic ester by the elimination of one molecule of water.



21 (R=H)
22 (R=o-nitro-)
23 (R=m-nitro-)

Later, Gault[47] modified the method by condensation of ethyl potassium oxalacetate 24 with formaldehyde to form α-ketoparaconic ester 25 and a side product β-hydroxymethyl-α-ketoparaconic ester 26, resulting from 1 mole of 24 and 2 moles of formaldehyde. Compound 26 decomposed on heating to 25 and formaldehyde. Similarly, the γ-alkyl ketoparaconic esters were obtained from the reaction of 24 with appropriate aldehydes.[48] It is assumed by Gault that the aldehyde reacts in the hydrated form, adding to the enolic double bond of 24 and the unstable enol thus formed spontaneously and simultaneously loses

1 mole of water and 1 mole of alcohol with formation of ketoparaconic ester.



24

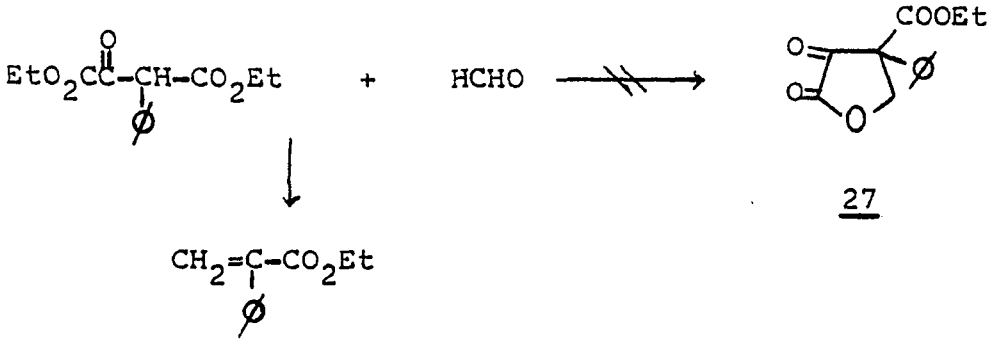
26 25 (R=H)

The α-keto-β-carbethoxy-γ-alkyl-γ-butyrolactone can be degraded by cleavage of ketoester with acid to the corresponding α-keto-γ-alkyl-γ-butyrolactone with free β-position.[27-29] The cleavage of ketoester becomes more difficult with higher γ-alkyl groups. The α-keto-β-carbethoxy-γ-aryl -γ -butyrolactones can not be degraded by the reaction with acid to α-keto-γ-aryl-γ-butyrolactones.

1.2.4.2 Condensation of ethyl oxalate with ester followed hydroxyalkylation

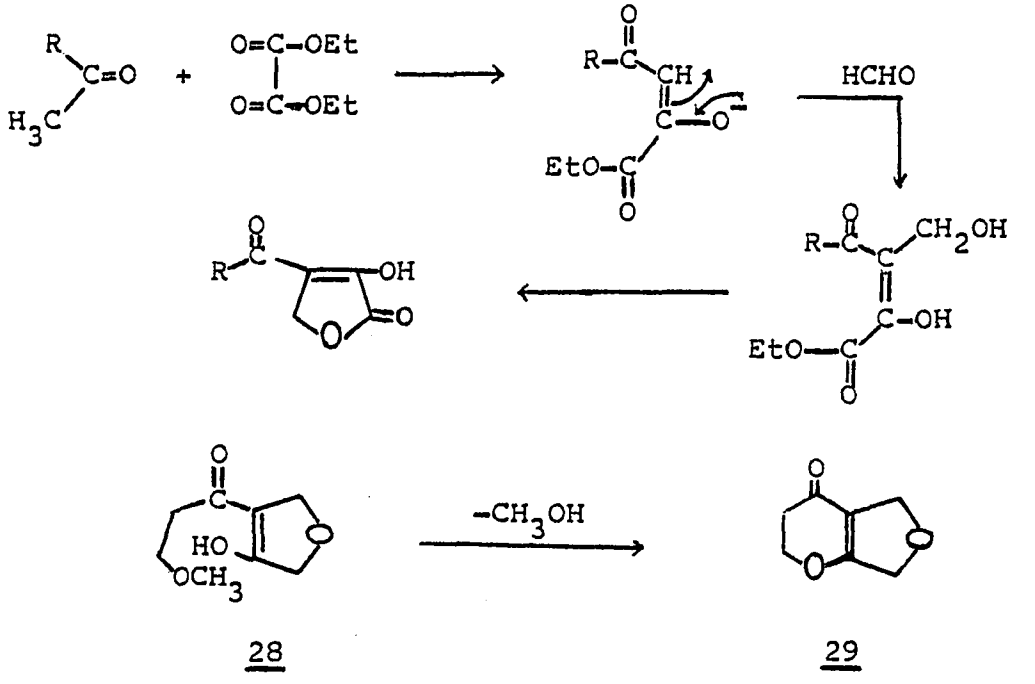
Reaction of diethyl oxalate with ethyl propionate in the presence of sodium ethoxide gives ethyl ethoxalyl-propionate which was then condensed with formaldehyde to give α-keto-β-carbethoxy-β-methyl-γ-butyrolactone. Similarly, reaction of diethyl oxalate with appropriate ester followed by further condensation with proper

aldehydes can give resonable yield of α-keto-β-carbethoxy-β-alkyl-γ-alkyl-γ-butyrolactones. However, reaction of ethyl phenyloxalacetate with formaldehyde did not give the expected product- α-keto-β-carbethoxy-β-phenyl-γ-butyrolactone 27 , and only ethyl-α-phenylacrylate was obtained. Schinz[49] suggested that the ethyl-α-phenylacrylate was formed by decomposition of 27 in basic media. It was later studied by Galantay and co-worker,[50] they found that the intermediary hydroxymethyl products was unstable under the mild basic condition, which underwent fragmentation to the acrylic ester derivatives.



27

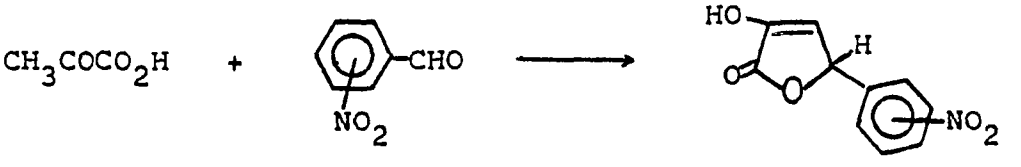
Couquelet[51,52] extended the Schinz's method to methyl ketones by treating acetophenone with diethyl oxalate to give ethyl benzoyl pyruvate which was then hydroxymethylated to give α-keto-β-benzoyl-γ-butyrolactone. With α-keto-β-methoxypropionoyl-γ-butyrolactone 28 , it is possible to cause ring closure to give the corresponding reduced γ-pyrone butenolide 29 by elimination of methanol.[51,53]



28 29

1.2.4.3 Condensation of α-ketoacid with aldehydes

Acid-catalysed condensation of o-nitrobenzaldehyde with 2 equivalent of pyruvic acid gives the enol-lactone 30 in 60-80% yield.[55] Parallel experiments with m-nitro-

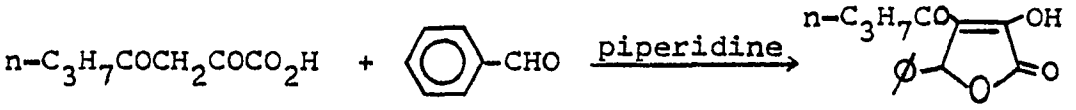


30 (o-nitro-)
31 (m-nitro-)

benzaldehyde resulted in rather poor yield of mixtures difficult to separate. Using either hydrogen chloride or methanesulfuric acid as catalysts, the expected γ-lactone of 2,4-dihydroxy-4-(m-nitrophenyl)-crotonic acid 31 was

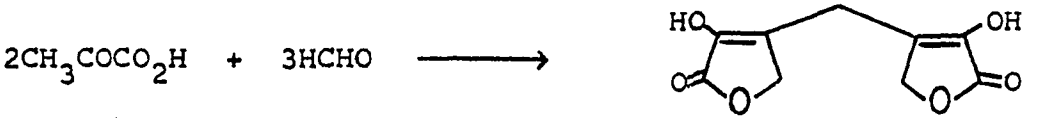
obtained in 23-51% yield. With a minor product m-nitrobenzylidenepyruvic acid.

Condensation of 2-oxobutyric acid with aldehydes in the presence of concentrated sulfuric acid is reported[57] to give α-keto-γ-alkyl-γ-butyrolactones. Condensation of butyrylpyruvic acid with aromatic aldehydes in the presence of piperidine leads to the formation of α-tetronic acids 32.[58]



32

However, the condensation of pyruvic acid with formaldehyde in the presence of acid did not give the expected α-tetronic acid, a methylene bis-α-tetronic acid was obtained.[59-61]

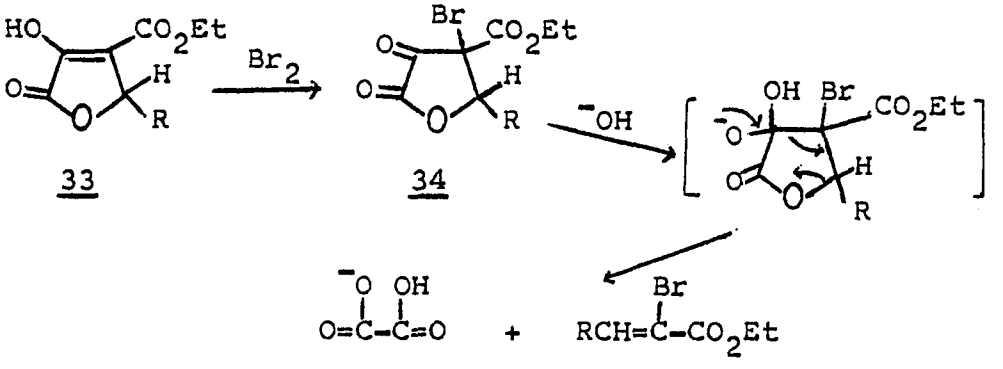


1.2.5 Reactions of α-keto-γ-lactones

1.2.5.1 Reactions of α-keto-β-carbethoxy-γ-alkylbutyrolactones

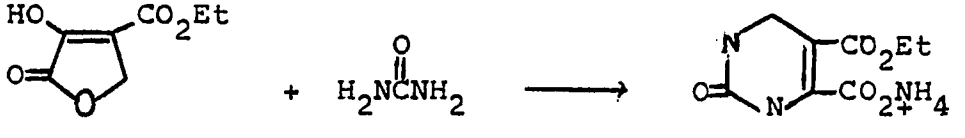
α-Keto-β-carbethoxy-γ-alkylbutyrolactones 33 can be brominated in aqueous methanol to form α-keto-β-

bromo-β-carbethoxy-γ-alkylbutyrolactones 34. Treatment of 33 with aqueous potassium bicarbonate, potassium hydroxide, ammonium hydroxide or phenylhydrazine splits out oxalic acid as the salt or hydrazide and forms ethyl-α-bromoacrylate.[62-64] The reaction is proceeded by way of

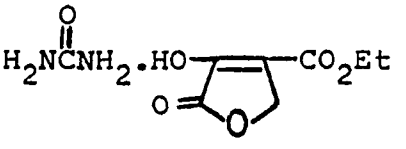


alkaline cleavage of the carbon-carbon bond followed by elimination of a hydrogen oxalate ion to give the β-alkyl α-bromoacrylic ester.

Fusing 1 mole of α-keto-β-carbethoxy-γ-butyrolactone 25 and 2 moles of urea gives 2-oxo-1,2,3,4-tetrahydro-5,6-pyrimidine dicarboxylic acid monoethyl ester mono-NH_4 salt.[65] Under certain conditions, the fusion of



25

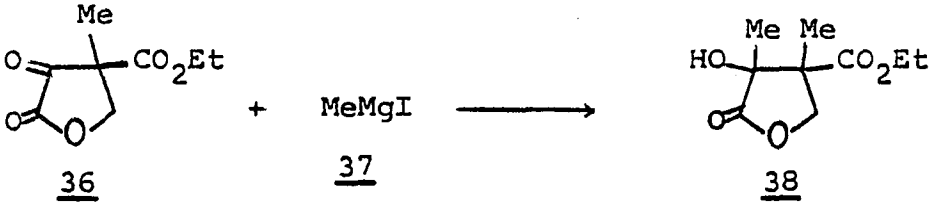


35

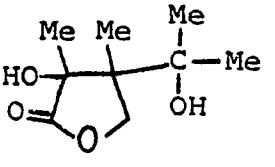
lactone 25 and urea leads to a 1:1 addition product, which is considered to be urea enolate 35.

1.2.5.2 Reaction of α-keto-β-methyl-β-carbethoxy-γ-butyrolactone (36)

Addition of an equimolar amount of MeMgI 37 to lactone 36, gave α,β-dimethyl-α-hydroxy-β-carbethoxy-γ-butyrolactone 38.[66] With 3 moles of MeMgI to 1 mole of lactone 36, α,β-dimethyl-α-hydroxy-β-(1-hydroxyisopropyl)-γ-butyrolactone 39 was obtained. The reversed procedure (addition of an equimolar amount of 36 to 37) gave a mixture of products resulting from the initial excess of MeMgI 37.



36 37 38

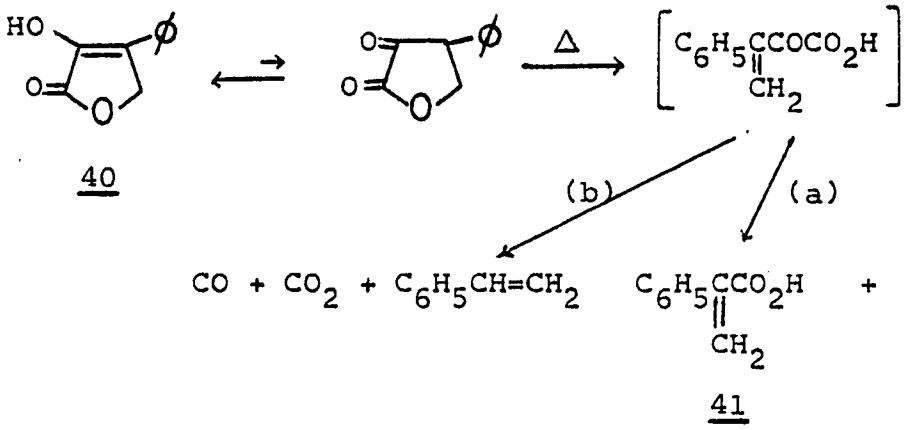


39

1.2.6 Pyrolysis of α-keto-γ-lactone derivatives

When α-keto-β-phenyl-γ-lactone 40 was heated,[67] carbon monoxide and carbon dioxide were evolved, and a mixture of atropic acid 41 and styrene was formed. The mechanism was proposed that the lactone 40 was first

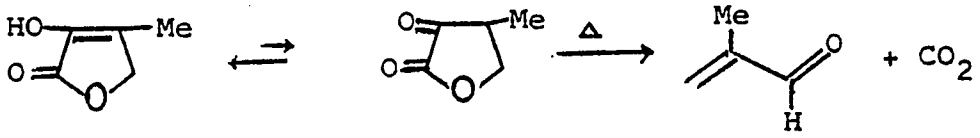
converted to phenylmethylene pyruvic acid which then underwent (a) by decarboxylation to give atropic acid 41 (b) by decarbonylation and decarboxylation to give styrene.



40

41

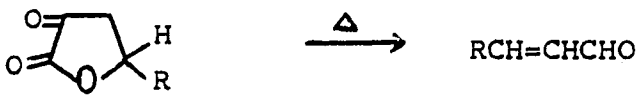
However, in Schinz's report, pyrolysis of α-keto-β-methyl-γ-butyrolactone 43 at 300°C only α-methyl acrolein 44 was obtained, which was produced by decarboxylation of the lactone 43.



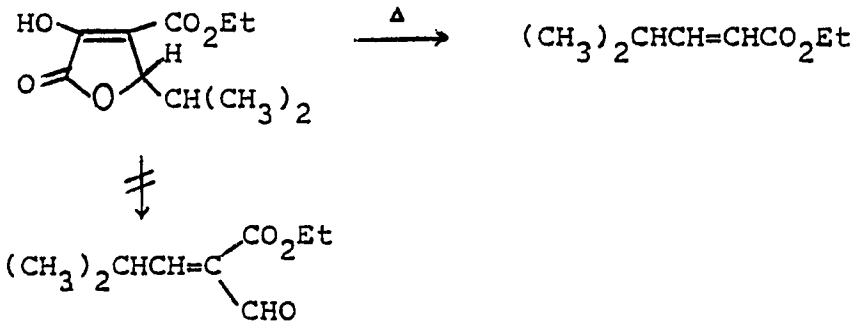
43

44

Also, upon pyrolysis of γ-alkylsubstituted α-keto-γ-lactones, β-alkyl acrolein was obtained in low yield (6-30%).



But, pyrolysis of enol-lactone with a carbethoxyl group on β-position, did not give the expected acrolein. Upon pyrolysis of α-keto-β-carbethoxy-γ-isopropyl-γ-butyrolactone 45, the β-isopropyl ethyl acrylate was separated in 30% yield.



2. EXPERIMENTAL

2.1 Reactions of Pyruvic acid

2.1.1 Preparation of α-keto-γ-valerolactone-γ-carboxylic acid (3)

The pyruvic acid was distilled under reduced pressure. The pyruvic acid was obtained by collecting the fraction boiled at 62-70°C/14mm. The residue obtained from distillation was allowed to stand at room temperature overnight. The oily residue was solidified. The solid was washed with benzene. The compound had MP=117-118°C (lit[9] 118°C), NE = 80.2 (calc. 79). Mass spectra : m/e at 158 (molecular ion), 113 ($M-CO_2H$), 85 (M-COOH-CO), 70 (CH_2COCO).

2.1.2 Preparation of γ-lactone of α-hydroxy-α-methyl-γ-carboxyl-adipic acid (5)

To 70 ml of 10% solution of pyruvic acid was added 70 ml of 25% solution of lead acetate, the solution was allowed to stand overnight at room temperature (25-30°C). The lead-salt of para-pyruvic acid was filtered and washed with water. The lead salt was neutralized with 6N sulfuric acid. The lead sulfate was filtered. The filtrate was evaporated under reduced pressure. The oily residue was then dried under high vacuum to give yellow-porous solid. The crystalline product 5 as reported by Waldmann[9] was not obtained. The porous solid had NE = 99.2. This is probably the decarboxylated product-lactone 8 (Calc. 101) from the title compound.

2.1.3 Preparation of methyldihydrotrimesic acid (6)

Pyruvic acid (5g, 0.057moles) was added dropwise to an ice-cold solution of 11g (0.275 moles) of sodium hydroxide in 20 ml of water. The color of solution was changed to pale yellow. The solution was refluxed on steam bath for three hours. The color became deep orange and a yellow precipitate was formed. The precipitate was filtered. The filtrate was acidified with conc. HCl (ca. 25 ml), the precipitate of MDTA 6 was collected and recrystallized from ethanol at temperature below 60°C. The yield was 1.5g (46.6%). MP = 218-225°C (dec.) (lit.[10] 253°C). NE = 80.1 (calc. 75.3). Repeated recrystallization did not improve the melting point. NMR (acetone-d_6): 1.08ppm(s, 3H), 2.73ppm(AB quartet, 2H), 7.40ppm(broad, 7H). The compound may be a hydrated MDTA 6.

2.1.4 Preparation of 2-methoxy-6-methyl-2,4,6-tricarbomethoxy-5,6-dihydropyran

A mixture of 50 ml of 10% pyruvic acid and 50 ml of 25% lead acetate was allowed to stand at room temperature for 4 days. The lead salt of parapyruvic acid was collected and acidified with 6N sulfuric acid, the lead sulfate was filtered. The filtrate was evaporated under reduced pressure. The oily residue was then dried under high vacuum to give yellow-porous solid. The solid was dissolved in 100 ml of anhydrous ether, the solution was cooled in ice-bath. A solution of diazomethane in ether was added dropwise to the ice-cold solution until the yellow color persisted. The

solution was stirred for one hour. After evaporation of the solvent, a viscous oil was obtained. Mass spectra showed m/e at 271($M-OCH_3$), 243 ($M-CO_2CH_3$), 211, 183, 169, 141, 127. NMR (CCl_4): 1.56ppm (t, 3H), 3.26ppm (d, 3H), 3.30ppm (m,2H), 3.68ppm (d, 3H), 3.78ppm (d, 6H), 6.73ppm (1H, m). There are some absorption peaks from impurity around 1.1-2.95ppm.

2.2 Reactions of citroyl formic acid lactone

2.2.1 Preparation of citroylformic acid lactone (11)

A solution of 15g of oxaloacetic acid in 50 ml of water was adjusted to pH=3 with 20% sodium hydroxide (3.3ml) and allowed to stand overnight at 25-30°C. Carbon dioxide was evolved during the period. The solution was decationized by passing through an acidified ion-exchange resin (300 meq Dowex 50W-X8) and evaporated to dryness under a vacuum evaporator at 35°C. The final drying was completed in a vacuum desiccator over anhydrous calcium sulfate to give 8g. The dried residue was partially dissolved in a minimum amount (25 ml) of warm, dry acetone. Nitromethane (dry, about 4 volumes) was added to incipient cloudiness. The mixture was filtered and the solution was allowed to stand at room temperature to deposit crystals. Recrystallization gives the pure lactone of citroylformic acid, MP=167-171°C(dec.), turn brown at 164°C (lit.[16] 160-164°C), NE = 69.2 (calc. 67.9).

2.2.2 Methylation of citroylformic acid lactone (11)

A mixture of 0.7g of title compound 11 and 30 ml of anhydrous ether was cooled in ice-bath. A diazomethane

solution (0.02 moles in 35 ml of anhydrous ether) was added dropwise to the ice-cold mixture until the yellow color persisted. The solution was stirred for one hour. The solution was heated in a water-bath at 35°C to expel excess diazomethane, the solvent was removed. The oily residue was solidified on standing. The solid was washed with cold ether. The ester has MP= 75-76.5°C, NMR (acetone-d_6): 3.17ppm (AB quartet, 2H, $-CH_2CO_2CH_3$), 3.69ppm, 3.77ppm, 3.85ppm (s, 9H,$-CO_2CH_3$), 6.15ppm (s, 1H, vinyl H). Mass spectra: m/e at 244.0556 (molecular ion, calc. 244.0581 for $C_{10}H_{12}O_7$), 213, 200, 185, 143, 115, 101, 57.

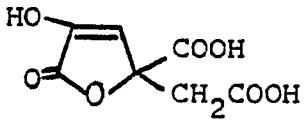
2.2.3 Methylation of trimethyl oxalocitrolactone ester

A mixture of 0.5g of the title compound and 25 ml of anhydrous ether was cooled in ice-bath. A diazomethane solution (0.02 moles in 35 ml of ether) was added dropwise to the ice-cold mixture until the yellow color persisted. The solution was allowed to stand overnight under the hood to expel excess of diazomethane, the ether was also evaporated off. The white solid was washed with cold ether. The product has MP=85-89°C, mass spectra: m/e at 302, 271, 258, 243, 211, 201, 199, 185, 173, 143, 115.

2.2.4 Condensation reactions of citroylformic acid lactone (11)

Citroylformic acid lactone 11 (0.5g) was dissolved in 5 ml of nitromethane and 2 ml of acetone, the solution was refluxed for 20 minutes. The precipitate was collected

Table 1 : Reaction data of citroylformic acid lactone 11



11

Solvent	Conc. g/ml	Reaction temp.(^oC)	Reaction time(hrs.)	Neutralization equivalent
				68.22
THF	1	67	2.5	75.00
THF	1.3	67	10.0	76.59
THF	22.8	67	2.0	86.83
EtOAc	1	77	3.0	71.92
CH_3CN	5	81.6	0.5	72.48
CH_3NO_2	2.86	90-98	15(min.)	70.04
CH_3NO_2	1.4	90-98	1.0	83.46
CH_3NO_2/ acetone	20	90-98	20(min.)	95.89
CH_3NO_2	1.3	101	4.0	106.58
Dioxane	20	101	10(min.)	80.68
Dioxane	20	101	3.0	90.50

and the solvent of the filtrate was evaporated off. Both the precipitate and residue were vacuum dried and titrated with 0.100N sodium hydroxide solution. The higher neutralization equivalent of the two components was recorded. Similar reactions were run by varying the concentration of the solution, solvent, and reaction time.

All condensation reactions of lactone 11 with pertinent data are presented in Table 1.

2.2.5 Methylation of poly-(citroylformic acid lactone)

The citroyl formic acid lactone 11 (5.5g) obtained from condensation of oxalacetic acid was dissolved in 12 ml of warm, dry acetone, 50 ml of nitromethane was added to incipient cloudiness. The mixture was filtered and the filtrate was allowed to stand at room temperature to deposit crystals. The crystals were filtered, the filtrate was concentrated to give second crops of crystals. The mother liquor was evaporated to give oily residue. The residue was dried under vacuum overnight. The oil was titrated with 0.100N sodium hydroxide solution. NE= 86.58. A mixture of 0.5g of oily residue and 30 ml of anhydrous ether was cooled in ice-bath. A solution of diazomethane in ether was added slowly to the ice-cold mixture until the yellow color persisted. The mixture was stirred for one hour in ice-bath After evaporation of the ether, a viscous oil was obtained. Mass spectra showed m/e at 443, 393, 381, 344, 330, 312, 301, 299, 272, 261, 257, 229, 185, 171. The lactone was polymerized with decarboxylation.

2.3 Preparation of α-keto-γ-lactones

The ethyl sodium oxalacetate used in the preparation was recrystallized from methanol. There was no detectable amount of ester exchange from the NMR spectra of the condensation products.

2.3.1 α-Keto-β-carbethoxy-γ-butyrolactone (25)

To a suspension of 14.7g (0.07 moles) of ethyl sodium oxalacetate in 80 ml of water at 5°C was added 6.5 ml (0.08 moles) of 38% formaldehyde. The mixture was stirred at room temperature for several hours. The resulting mixture was then acidified with 6N H_2SO_4. The white precipitate was filtered, washed with ice-water and recrystallized from benzene. The yield was 9.6g (78.1%). MP= 107-108°C (lit.[47] 108°C), uv $\lambda_{max}^{methanol}$= 254mu (ϵ =11,500), 302mu (ϵ =3,125). NMR (acetone-d_6): 1.32ppm (t, 3H, $-OCH_2\underline{CH_3}$), 4.26 (q, 2H, $-O\underline{CH_2}CH_3$), 4.93ppm (s, 2H, $-OCH_2-$, ring proton), 8.71ppm (broad singlet, 1H, enol H).

2.3.2 α-Keto-β-carbethoxy-γ-methyl-γ-butyrolactone (46)

A solution of 6.3 ml (0.12 moles) of acetaldehyde in 10 ml of water was added slowly to an aqueous suspension of 21g (0.1 moles) of ethyl sodium oxalacetate in 100 ml of water at 5°C (white precipitate was formed), stirred at 5-10°C for 2 hours and at room temperature overnight. The resulting mixture was then acidified with 18 ml of 6N sulfuric acid and extracted with 150 ml of ether. The ether layer was dried over anhydrous sodium sulfate. After evapo-

ration of ether, the residue was distilled under reduced pressure. The product was collected at 108-112°C (1mm) (lit.[28] 108-115°C at 0.15mm). NE = 186.4 (calc. 186). NMR (acetone-d_6): 1.37ppm (t, 3H, $-OCH_2\underline{CH_3}$), 1.54ppm (d, 3H $-\dot{C}H\underline{CH_3}$), 4.38ppm (q, 2H, $-O\underline{CH_2}CH_3$), 5.17ppm (q, 1H, $-\dot{C}\underline{H}CH_3$) 8.65ppm (broad singlet, 1H, enol H).

2.3.3 <u>α-Keto-β-carbethoxy-γ-ethyl-γ-butyrolactone(47)</u>

To a suspension of 31g (0.15 moles) of ethyl sodium oxalacetate in 200 ml of water at 0-5°C was added 6g (0.17 moles) of propionaldehyde. After stirring at room temperature for 10 hours (white precipitate was formed), the mixture was acidified with 6N sulfuric acid and extracted with ether. The ether layer was dried over anhydrous sodium Sulfate. The ether was removed by evaporator. The residue was distilled under reduced pressure, 19.6g of the lactone <u>47</u> (65.3%) was collected at 112-115°C (0.5-1mm) (lit.[28] 121-125°C at 0.5mm). NMR (acetone-d_6): 0.97ppm (t, 3H, $-\dot{C}HCH_2\underline{CH_3}$), 1.38ppm (t, 3H, $-OCH_2\underline{CH_3}$), 2.00ppm (m, 2H, $-\dot{C}H\underline{CH_2}CH_3$), 4.37ppm (q, 2H, $-O\underline{CH_2}CH_3$), 5.12ppm (AB quartet, 1H, $-O\dot{C}\underline{H}C_2H_5$), 8.77ppm (broad, 1H, enol H).

2.3.4 <u>α-Keto-β-carbethoxy-γ-(n-propyl)-γ-butyrolactone (48)</u>

A solution of freshly distilled butyradehyde (20 ml, 0.23 moles) in 25 ml of ethanol was added slowly to an aqueous suspension of 44.5g (0.21 moles) of ethyl sodium oxalacetate in 200 ml of water. After stirring at room temperature for 10 hours (white precipitate was formed), the

mixture was acidified with 35 ml of 6N sulfuric acid and extracted with three 100 ml portions of ether. The combined ether layer was dried over anhydrous sodium sulfate. The ether was removed by evaporator. The residue was distilled under reduced pressure, 26g of the lactone 48 (57.8%) was collected at 120-130°C (1mm) (lit.[28] 131-133°C at 0.1mm).

2.3.5 Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)] (49)

To an ice-cold mixture of 26.5g (0.12 moles) of ethyl sodium oxalacetate in 200 ml of water was added 10.5 ml of 40% glyoxal solution. The mixture was stirred at 0-5°C for 2 hours (clear light-brown solution) and stirred at room temperature for several hours. The mixture was then acidified with 6N sulfuric acid. The white precipitate was collected and recrystallized from ethanol. The yield was 7g (34.1%). MP = 195-201°C (dec. turn brown at 178°C, lit.[72] 192°C). NMR (acetone-d_6): 1.38ppm (t, 3H, $-OCH_2\underline{CH_3}$), 4.43ppm (q, 2H, $-OC\underline{H_2}CH_3$), 5.82ppm (s, 1H, $-OC\underline{H}-$, ring proton), 8.63ppm (broad, 1H, enol H). Mass spectra: m/e at 342 (molecular ion), 314, 252, 224, 194, 172, 143, 97, 69.

2.3.6 Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene (50)

A solution of 1.9g (0.014 moles) of terephthaldehyde in 20 ml of ethanol was added slowly to an aqueous suspension of 5.4g (0.026 moles) of ethyl sodium oxalacetate in 40 ml of water at 5°C. The mixture was stirred at room temperature for several hours. The resulting mixture

was acidified with 6N sulfuric acid. A white precipitate was formed. The precipitate was collected and recrystallized from ethanol. After recrystallization from ethanol, the lactone 50 was obtained in 46.4% yield (2.54g). MP= 192-195°C (dec., turn orange at 183°C). NMR (acetone-d_6) 1.13ppm (t, 3H, $-OCH_2\underline{CH_3}$), 4.07ppm (q, 2H, $-OC\underline{H_2}CH_3$), 6.04ppm (s, 1H, ring proton), 7.36ppm (s, 2H, phenyl H), 6.98ppm (broad, 1H, enol H). Mass spectra: m/e at 418 (molecular ion), 374, 346, 301, 276, 249, 213, 185, 149, 115, 105.

2.3.7 α-Keto-β-carbethoxy-γ-phenyl-γ-butyrolactone (21)

To an aqueous suspension of 12.4g (0.06 moles) of ethyl sodium oxalacetate in 80 ml of water at 10°C was added 7 ml of freshly distilled benzaldehyde. The mixture was stirred at 5-10°C for 2 hours and at room temperature for several hours (a white paste was formed). The resulting mixture was acidified with 16 ml of 6N sulfuric acid. The white precipitate was filtered and washed with ice-water. The yield was 9.6g (66.2%, recrystallized from ethanol). MP 105-106°C (lit.[46] 104-105°C). NMR (acetone-d_6): 1.12ppm (t, 3H, $-OCH_2\underline{CH_3}$), 4.11ppm (q, 2H, $-OC\underline{H_2}CH_3$), 6.08ppm (s, 1H, $-OC\underline{H}-$), 7.36ppm (s, 5H, phenyl H), 8.98ppm (broad, 1H, enol H). Mass spectra: m/e at 248 (molecular ion), 203, 175, 130, 115, 105, 102, 77.

2.3.8 α-Keto-β-carbethoxy-γ-(o-nitrophenyl)-γ-butyrolactone (22)

A mixture of 4.2g (0.03 moles) of o-nitrobenzaldehyde and 25 ml of ethanol was added slowly to a solution of 5.5g (0.025 moles) of ethyl sodium oxalacetate in 80 ml of ethanol. This was stirred for 4 hours. The resulting mixture was then acidified with 6N sulfuric acid. The precipitate was filtered and recrystallized from benzene/hexane. The yield was 5.4g (73.7%). MP 118-120°C (lit.[46] 118°C). NMR (acetone-d_6): 1.05ppm (t, 3H, $-OCH_2\underline{C}H_3$), 4.24ppm (q,2H, $-O\underline{C}H_2CH_3$), 7.1ppm (s, 1H, ring proton), 7.66-8.47ppm (m,5H, phenyl and enol H).

2.3.9 α-Keto-β-carbethoxy-γ-(m-nitrophenyl)-γ-butyrolactone (23)

A mixture of 4.2g (0.03 moles) of m-nitrobenzaldehyde and 25 ml of ethanol was added slowly to a solution of 5.5g (0.025 moles) of ethyl sodium oxalacetate in 80 ml of ethanol. This was stirred for 4 hours. The mixture was then acidified with 6N sulfuric acid. The precipitate was collected and recrystallized from benzene. The yield was 4.3g (58.7%). MP 96-101°C (lit.[46] 96°C). NMR (acetone-d_6): 1.14ppm (t, 3H, $-OCH_2\underline{C}H_3$), 4.2ppm (q, 2H, $-O\underline{C}H_2CH_3$), 6.36ppm (s, 1H, ring proton), 7.5-8.43ppm (m, 5H, phenyl and enol H). IR (Nujol): 1780cm^{-1} (C=O of γ-lactone), 1690cm^{-1} (C=O of β-ketoester), 1650cm^{-1} (C=C).

2.3.10 α-Keto-β-carbethoxy-γ-(p-nitrophenyl)-γ-butyrolactone (51)

A solution of 8.3g (0.055 moles) of p-nitrobenzaldehyde in 50 ml of ethanol was added slowly to an ice-cold solution of 11g (0.05 moles) of ethyl sodium oxalacetate in 50 ml of water. A beige-colored precipitate was formed immediately. This was stirred for 2 hours with 80 ml of ethanol was added to help stirring. The mixture was stored in refrigerator overnight. The resulting mixture was acidified with 6N sulfuric acid and stirred for 1 hour. The precipitate was collected and recrystallized from benzene. The yield was 12g (81.9%). MP 125.5-127°C (lit.[72] 125-126°C). NMR (acetone-d_6): 1.2ppm (t, 3H, $-OCH_2\underline{CH_3}$), 4.23ppm (q, 2H, $-OC\underline{H_2}CH_3$), 6.08ppm (s, 1H, ring proton), 7.46ppm, 8.17ppm (AB quartet, 4H, phenyl H), 8.34ppm (s, 1H, enol H) IR (Nujol): 3310cm^{-1} (enol OH), 1795cm^{-1} (C=O of γ-lactone), 1675cm^{-1} (C=O of β-ketoester), 1660cm^{-1} (C=C).

2.3.11 α-Keto-β-carbethoxy-γ-(o-hydroxyphenyl)-γ-butyrolactone (52)

Salicylaldehyde 3.15 ml (0.03 moles) was added slowly to an ice-cold solution of 5.5g (0.025 moles) of ethyl sodium oxalacetate in 50 ml of ethanol. The solution turned yellowish green upon addition. This was stirred at room temperature for 5 hours. The resulting mixture was acidified with 6N sulfuric acid. The solvent was evaporated off. The residue was solidified after standing overnight.

The solid was then recrystallized from chloroform. The yield was 4.6g (68.2%). MP 155-160°C (dec.). NMR (acetone-d_6): 1.27ppm (t, 3H, $-OCH_2\underline{C}H_3$), 4.20ppm (q, 2H, $-O\underline{C}H_2CH_3$), 7.16ppm (m, 4H, phenyl H), 7.78ppm (s, 1H, ring proton), 8.01ppm (broad, 2H, phenol and enol H). IR (Nujol): $3530cm^{-1}$ and $3200cm^{-1}$(OH strtching for phenol and enol), $1755cm^{-1}$ (C=O of γ-lactone). NE = 261.67 (calc. 264).

2.3.12 Reaction of p-methoxybenzaldehyde and ethyl sodium oxalacetate

A solution of 3.1 ml of p-anisaldehyde in 50 ml of ethanol was added slowly to a solution of 5.5g (0.025 moles) of ethyl sodium oxalacetate in 50 ml of water at 5°C. The mixture was stirred at room temperature overnight. A white precipitate was formed after stirring for 4 hours. The resulting mixture was then acidified with 6N sulfuric acid. Some oily liquid was formed. The mixture was extracted with ether, the ether layer was dried over anhydrous sodium sulfate. After evaporation of the ether, a brownish liquid was obtained. NMR (acetone-d_6): 1.21ppm (triplet), 3.85ppm (multiplet), 3.92ppm (singlet), 5.95ppm (singlet), 7.03ppm (multiplet), 7.46ppm (AB quartet). No further study was done.

2.3.13 Attempted reaction of N,N-dimethylaminobenzaldehyde and ethyl sodium oxalacetate

A solution of 4.5g (0.03 moles) of N,N-dimethylaminobenzaldehyde in 30 ml of absolute ethanol was added slowly to a solution of 5.5g (0.025 moles) of ethyl sodium oxalacetate in 80 ml of ethanol at 5°C. The mixture was heated at 60°C in a water-bath for 3 hours. After cooling, the mixture was acidified with conc. sulfuric acid. A white precipitate was formed upon addition of water to the acidified mixture. NMR of the solid in acetone-d_6 solution showed singlet at 2.96ppm(3H), AB quartet at 7.13ppm (2H). The compound was the starting material-N,N-dimethylaminobenzaldehyde.

2.3.14 α-Keto-β,β-dimethyl-γ-butyrolactone (53)

To a stirred solution of d,l-pantoylactone (13g, 0.1 moles) in benzene (100 ml), 8N CrO_3-H_2SO_4 solution[73] was added during 3 hours at 20-30°C. After stirring for another 2 hours, the mixture was extracted with benzene. The benzene layer was washed with saturated sodium sulfate and then dried over sodium sulfate. The solvent was removed in vacuo and the residue was recrystallized from ether to give 2.8g (21.5%) of the title compound. MP 66-68°C (lit.[76] 66-68°C). NMR ($CDCl_3$): 1.23ppm (s, 3H, $-CH_3$), 4.42ppm (s, 1H, $-OC\underline{H}_2-$). Mass spectra: m/e at 128 (molecular ion), 127, 100, 99, 70, 69, 56, 42, 39, 29,28.

2.3.15 α-Keto-γ-methyl-γ-butyrolactone (54)

The α-keto-β-carbethoxy-γ-methyl-γ-butyrolactone 46 (9.3g, 0.05 moles) stabilized with 50mg of hydroquinone, was heated at 110°C with 25 ml of conc. HCl, 30 ml of water and 15 ml of glacial acetic acid for 4 hours. The solvent was evaporated with an evaporator at 50-60°C. The residue was distilled under reduced pressure and 4.3g of the title compound was collected at 75-80°C (0.5-1mm). The compound was recrystallized from benzene/hexane. The yield was 3.5g (61%). MP 74-76°C (lit.[28] 70-73°C), uv λ max= 230mu (ϵ =10,560) in 95% ethanol. NMR (acetone-d_6): 1.76ppm (d, 3H, -OCHC$\underline{H}_3$), 5.43ppm (q, 1H, -OC$\underline{H}$CH$_3$), 6.78ppm (d, 1H, vinyl H), 9.05ppm (broad, 1H, enol H). Mass spectra: m/e at 114 (molecular ion), 99, 71, 70, 69, 58, 43, 39, 29, 28,27.

2.3.16 α-Keto-γ-ethyl-γ-butyrolactone (55)

The α-keto-β-carbethoxy-γ-ethyl-γ-butyrolactone 47 (7g) stabilized with 50mg of hydroquinone, was heated at 110°C with 20 ml of conc. hydrochloric acid, 10 ml of water and 10 ml of glacial acetic acid for 4 hours. The solvent was evaporated with an evaporator at 50-60°C (14mm). The residue was distilled under reduced pressure, 3.4g of the title compound was collected at 110-115°C (0.5-1 mm) (lit.[28] 79-80°C at 0.08 mm). The yield was 2.81g (62.1%) after recrystallization from benzene/hexane MP 43-46°C (lit. 43-45°C).[28] NMR (acetone-d_6): 0.91ppm (t, 3H, -CH$_2$C$\underline{H}_3$), 1.68ppm (m, 2H, -C$\underline{H}_2$CH$_3$), 4.86ppm (t, 1H, ring proton),

6.26ppm (d, 1H, vinyl H), 8.67ppm (broad, 1H, enol H).

2.3.17 α-Keto-γ-(n-propyl)-γ-butyrolactone (56)

The α-keto-β-carbethoxy-γ-(n-propyl)-γ-butyrolactone 48 stabilized with 100mg of hydroquinone, was heated at 110°C with 35 ml of acetic acid, 35 ml of water, and 50 ml of conc. hydrochloric acid for 4 hours. The solvent was removed by an evaporator at 50-60°C (14 mm). The residue was distilled under reduced pressure, 12.3g of the title compound (72.6%) was collected at 100-105°C (0.5-1 mm) (lit.[28] 98°C at 0.1 mm). NMR (acetone-d_6): 0.9-2.0ppm (m, 7H, $-OCHC_3\underline{H}_7$), 5.0-5.32ppm (m, 1H, $-OC\underline{H}C_3H_7$), 6.48ppm (d, 1H, vinyl H), 7.85ppm (broad, 1H, enol H).

2.3.18 Hydrolysis of α-keto-β-carbethoxy-γ-butyrolactone (25)

A mixture of 1.8g of lactone 25 in 9 ml of 5% sulfuric acid was refluxed for 3 hours. The resulting mixture was continuously extracted with ether for 18 hours. The ether layer was separated and dried over anhydrous sodium sulfate. After evaporation of the ether, the residue was sublimed under high vacuum. The white solid (α-keto-γ-butyrolactone 57) was collected at 50-70°C. The viscous residue (light yellow) was characterized: NMR (acetone-d_6): 1.0-1.5ppm (m, ester H), 3.7-4.8ppm (m, ester H), 3.48ppm (q, ester H), 4.94ppm (s) and 1.87-3.2ppm (broad unresolved peak), uv λmax = 248mu (ϵ =1,800) in 95% of ethanol. Mass

spectra: m/e at 381, 373, 345, 328, 301, 299, 273, 228, 227, 181. The lactone 25 is polymerized.

2.3.19 Hydrolysis of α-keto-β-carbethoxy-γ-methyl-γ-butyrolactone (46)

A mixture of 3.7g (0.02 moles) of the title compound, 10mg of hydroquinone and 30 ml of 10% sulfuric acid was refluxed for 3 hours. The resulting solution was extracted with ether in a Kutscher-Steudet extractor for 24 hours. The ether layer was dried over anhydrous magnesium sulfate. The ether was removed by an evaporator. The oily residue was chromatographed (silica gel, 10% MeOH in benzene) to give 2 fractions. Fraction 1: NMR ($CDCl_3$): 0.9-1.6ppm (m), saturated hydrocarbon. Fraction 2: white crystal, MP 134-140°C. NMR (acetone-d_6): 1.5ppm (t, 6H, $-OCHC\underline{H}_3$), 2.15ppm (q, 1H, J_1=10Hz, J_2=-14Hz), 3.12ppm (q, 1H, J_1=6Hz, J_2=-14Hz), 4.9ppm (m, 1H, $-OC\underline{H}CH_3$), 5.23ppm (q, 1H, J=6Hz, $-OC\underline{H}CH_3$), 6.05ppm (broad, 2H, $-O\underline{H}$). The NMR spectra showed similarity with the dimer of α-keto-γ-methyl-γ-butyrolactone 54.

2.3.20 Hydrolysis of α-keto-β-carbethoxy-γ-phenyl-γ-butyrolactone (21)

A mixture of 2.6g of the title compound with 10 ml of 5% sulfuric acid was refluxed for 24 hours. The precipitate was collected after cooling. The NMR data showed that the solid was the starting material.

2.3.21 α-Keto-β-methyl-γ-butyrolactone (58)

Methyl oxalate (60g, 0.5 moles) was added to a suspension of 27g (0.5 moles) of sodium methoxide in 150 ml of absolute ether. Ethyl propionate (53g, 0.52 moles) was then added dropwise to the mixture. The resulting mixture was refluxed for 3 hours. The solvent was removed under reduced pressure. The residue was dissolved in 80 ml of water and 43g of 35% formaldehyde solution was added to this solution portionwise with cooling. The solution was heated at 50°C for 1 hour and the resulting alcohol was removed from reaction by an evaporator. The solution was then acidified with 100 ml of conc. hydrochloric acid, 30 ml of water and 50mg of hydroquinone were added to the solution. The acidified solution was the refluxed for 4 hours. After cooling, the solution was extracted with 5 portions of 100 ml of ethyl acetate. The aqueous layer was continuously extracted with ether in a Kutscher-Steudel extractor. The combined organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was vacuum distilled. The main fraction collected at 80-92°C was oxalic acid. The title compound was collected at 25-40°C (2-4mm). The yield is 2.3g (5%). MP 89-90°C (lit.[29] 90-92°C). NMR ($CDCl_3$): 1.93ppm (t, 3H, methyl H), 4.54ppm (q, 2H, ring proton), 8.23ppm (s, 1H, enol H).

2.3.22 Attempted preparation of α-keto-β-carbethoxy-γ,γ-dimethyl-γ-butyrolactone

To a suspension of 5.4g (0.025 moles) of sodium ethyl oxalacetate in 40 ml of water was added 2.6 ml (0.035 moles) of ice-cold acetone at 0-5°C. The mixture was stirred at 0-5°C for one hour, then stirred at room temperature for 2 hours. The resulting mixture was then acidified with 4.3 ml of 6N sulfuric acid. The acidified solution was extracted with ether in a Kutscher-Steudel extractor for 10 hours. The ether layer was dried over anhydrous sodium sulfate, the ether was removed by an evaporator. The residue was a viscous liquid. NMR data indicated the acidified starting material-diethyl oxalacetate.

2.4 Polymerization of α-keto-γ-lactones

2.4.1 Pyrolysis of α-keto-γ-methyl-γ-butyrolactone(54)

α-Keto-γ-methyl-γ-butyrolactone (100mg) was placed in a pyrex glass tube which was evacuated and filled with nitrogen several times. The tube was then sealed under vacuum. After heating in an oil-bath at 115-120°C (evolution of gas) for 20 hours, the tube was cooled and opened. The yellowish solid was dissolved in acetone-d_6, NMR data showed saturated hydrocarbon absorptions around 1.35-1.84ppm. The solid may be polymer of propylene, which was formed by decarbonylation and decarboxylation of the title compound. Mass spectra also showed mass number at 210 (the dimer of lactone 54 less 1 mole of water) besides the

the background of poly-propylene (clusters of peaks, 14 mass unit (CH_2) apart, of decreasing intensity with increasing fragment weight up to 294).

2.4.2 Pyrolysis of α-keto-β-carbethoxy-γ-butyrolactone (25)

α-Keto-β-carbethoxy-γ-butyrolactone 25 (100mg) was placed in a pyrex glass tube (6mm in diameter) which was evacuated and filled with nitrogen several times. The tube was then sealed under vacuum. After heating in an oil-bath at 150-160°C (evolution of gas) for 2 hours, the tube was cooled and opened. The brownish solid was mixed with 10 ml of benzene, the insoluble material was filtered and sublimed under vacuum to remove the monomer. Mass spectra of the residue showed m/e at 453, 438, 382, 381, 353, 325, 299, 282, 281, 272, 255, 253, 227, 209, 199, 181, 173, 172. (calc. trimer 516, dimer, 344, monomer 172). The compound may undergo decarbonylation and decarboxylation to give ethyl acrylate which was then polymerized to give poly-(carbethoxyl ethylene) (calc. M.W of monomer 100).

2.4.3 Pyrolysis of α-keto-β,β-dimethyl-γ-butyrolactone (53)

α-Keto-β,β-dimethyl-γ-butyrolactone 53 (100mg) was placed in a pyrex glass tube which was evacuated and filled with nitrogen for several times. The tube was then sealed under vacuum. After heating in an oil-bath at 115-

125°C for 24 hours, the tube was cooled and opened. The solid was dissolved in acetone-d_6, NMR data showed peaks at 1.23ppm (s, 3H), 4.42ppm (s, 1H). The starting material was recovered.

2.4.4 Polymerization of α-keto-γ-methyl-γ-butyrolactone (54)

α-Keto-γ-methyl-γ-butyrolactone 54 (0.6g, 5.2 mmoles) was added into a stirred suspension of 5 mg of sodium methoxide in 15 ml of anhydrous ether. The mixture was then refluxed for 10 hours, and a white powdery solid was separated. The crude polymer was collected. MP 134-140°C. NE = 196.2. The yield was 0.5g (83.3%). The solid was chromatographed (silica gel, 10% MeOH/benzene) to give 0.3g of flaky white crystals after evaporation of solvent. MP 147-152°C. NE = 211.1 (calc. M.W. of dimer 228, dimer less 1 mole of water 210), uv λ max = 240mu (ϵ =6,068), IR (Nujol): 3200-3600cm^{-1}(maxi 3410cm^{-1}, OH stretching), 1785-1635cm^{-1} (maxi 1735cm^{-1}, C=O). NMR (acetone-d_6): 1.5ppm (t, 6H), 2.15ppm (q, 1H, J_1=10Hz, J_2=-14Hz), 3.12ppm (q, 1H, J_1=6Hz, J_2=-14Hz), 4.9ppm (m, 1H, -OC<u>H</u>CH_3), 5.23ppm (q, 1H, J=6Hz, -OC<u>H</u>CH_3), 6.05ppm (broad, 2H, -O<u>H</u>), pKa=7.6.

2.4.5 Copolymerization of bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)] and terephthaloyl chloride

To a solution of 3.42g (0.01 moles) of bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)] in 30 ml of tetrahydrofuran was added with stirring 2.8 ml of distilled triethylamine. The mixture was cooled in an ice-bath, a solution of 2.3g (0.01 moles) of terephthaloyl chloride in 25 ml of tetrahydrofuran was added to the ice-cold mixture in about 30 minutes. After the mixture was stirred for one hour, it is then diluted with 50 ml of solvent and the diluted mixture was poured into 250 ml of hexane in a beaker. The brownish product was collected and washed repeatedly with distilled water. IR (Nujol) showed C=O stretch overlapping around 1680-1800cm^{-1} and no carboxyl or enolic OH band. The solid is not soluble in chloroform, alcohol, or acetone.

2.4.6 Attempted copolymerization of bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene and terephthaloyl chloride

To a suspension of 4.18g (0.01 moles) of bis-lactone 50 in 25 ml of chloroform was added with stirring 2.8 ml of distilled triethylamine. The mixture was cooled in an ice-bath, a solution of 2.3g (0.01 moles) of terephthaloyl chloride in 25 ml of chloroform was added to the ice-cold mixture in about 30 minutes. After the mixture was stirred for one hour, it is then diluted with 50 ml of

chloroform and the diluted mixture was poured into 250 ml of hexane in a beaker. A viscous oil was obtained. The oil was mixed with 100 ml of acetone, white precipitate was formed. The precipitate was collected. IR (Nujol) showed single C=O stretch at 1690cm^{-1}, and NH^+ band at 2610cm^{-1}, the solid might be the triethylamine salt of terephthalic acid.

2.4.7 Attempted polymerization of α-keto-β-carbethoxy-γ-butyrolactone (25) using sodium ethoxide as catalyst

The title compound (0.86g, 5 mmoles) was dissolved in 20 ml of absolute ethanol. To this solution was added with stirring 0.5 ml of 0.105M sodium ethoxide in ethanol. The mixture was refluxed for 4 hours. After cooling, no precipitate was formed. The solvent was removed by an evaporator. The NMR data of the residue showed that the starting material was recovered.

2.4.8 Attempted polymerization of α-keto-β,β-dimethyl-γ-butyrolactone (53) using sodium ethoxide as catalyst

α-Keto-β,β-dimethyl-γ-butyrolactone 53 (0.64g, 5 mmoles) was dissolved in 20 ml of absolute alcohol. To this solution was added with stirring 0.1 ml of 0.21M sodium ethoxide in ethanol. The mixture was refluxed for 8 hours. No precipitate was formed after cooling. The

solvent was removed by an evaporator. The starting material (0.51g, 80%) was recovered.

2.4.9 Attempted polymerization of bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene using sodium ethoxide as catalyst

The title compound (2.1g, 5 mmoles) was mixed in a solution of 15 ml of tetrahydrofuran and 45 ml of absolute ethanol. To the resulting solution was added 0.2 ml of 0.105M sodium ethoxide in ethanol. The mixture was then refluxed for 20 hours. A white precipitate was formed after cooling. The solid was collected. The NMR data showed that the solid was the starting material.

2.5 Instrumentation

NMR spectra were measured using Varian A-60 or Hitachi Perkin-Elmer R-24 spectrometer. Spectra were obtained on either neat sample or in solution with TMS as internal standard. The following abreviations are used to describe NMR spectral bands reported herein: singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m), and

(parts per million, ppm, downfield from TMS).

Infrared spectra were recorded on Perkin-Elmer 521, polystyrene film was used for calibration. Only the most characteristic and prominent peaks are cited.

Mass spectra were obtained with a Varian M66, and calibrated with bromoform or perfluoralkane.

Ultraviolet and visible spectra were taken with a Cary Model 14 spectrophotometer in 95% ethanol or absolute methanol.

Melting points were determined on a Thomas capillary melting point apparatus, and were uncorrected.

Elemental Analysis were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York.

Ionization Constants - The classical ionization[55] constants of the acids were determined by pH titration, both in water and in 50% by volume methanol-water containing 0.2M Lithium chloride. The latter solvent permitted the use of more concentrated solutions and provided a medium of relatively constant ionic strength. The pK_a was determined from the mid-point of the titration curve where pK_a = pH. In methanol all pK values have relative rather than absolute validity. The neutralization equivalent was also obtained from the titration curve.

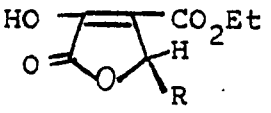
3. RESULTS AND DISCUSSION

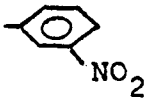
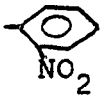
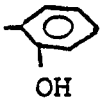
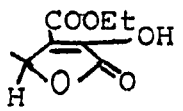
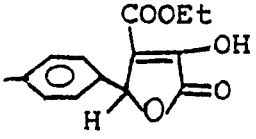
3.1 Preparation of α-keto-β-carbethoxy-γ-substituted-γ-butyrolactones

There are several ways of preparing α-keto-γ-butyrolactones. The method of Gault and Durand[47] was followed because of the readily available ethyl sodium oxalacetate. The Gault and Durand's method for the preparation of α-keto-β-carbethoxy-γ-butyrolactone from ethyl sodium oxalacetate and formaldehyde was slightly modified for the reaction with less soluble, less reactive aldehyde to give α-keto-β-carbethoxy-γ-substituted-γ-butyrolactones. The condensation of ethyl sodium oxalacetate proceeded readily in most cases in yield of 55-75%. The products are listed in Table 2. Condensation of substituted benzaldehyde with ethyl sodium oxalacetate gave the products which had same melting point with Gault's compounds[46] from condensation of diethyl oxalacetate and aldehydes in the presence of diethylamine. Characterization data (neutralization equivalent, acidity, IR, NMR and Mass spectra) also confirmed the structures which were assigned by Gault.

Along the preparation, two new compounds: α-keto-β-carbethoxy-γ-(o-hydroxyphenyl)-γ-butyrolactone 52, and bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene 50 were obtained.

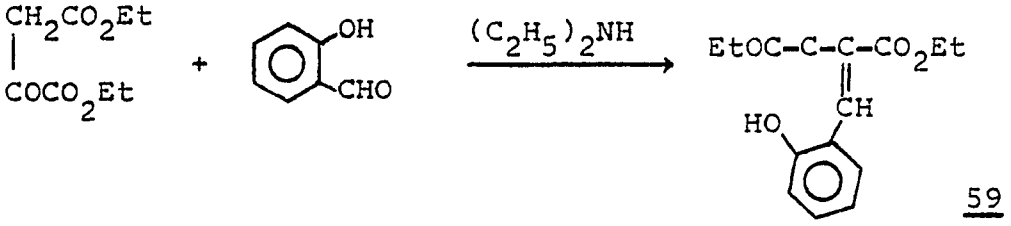
Table 2 : α -Keto- β -carbethoxy- γ -substitutedbutyrolactone



R	Yield %	BP °C	mm	MP °C	N.E. obs.	calc.
H	78.1	-		107-108	172.3	172
CH_3	71.2	108-112/	1	-	187.1	186
C_2H_5	65.3	112-115/	0.5-1	-	195.7	200
C_3H_7	57.8	120-130/	1	-		
	81.9			125.5-127	297.0	293
	58.7			96-101	292.7	293
	73.7			118-120	292.5	293
	68.2			155-160	261.7	264
	66.2			105-106	250.9	248
	34.1			195-201	170.7	171
	46.4			192-195	218.3	209

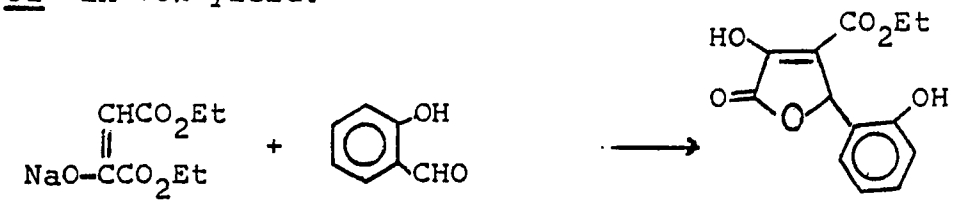
3.1.1 Preparation of α-keto-β-carbethoxy-γ-(o-hydroxyphenyl)-γ-butyrolactone (52)

Gault[46] reported that condensation of ethyl sodium oxalacetate and salicylic aldehyde in the presence of diethylamine gives, not a ketoaryparaconic ester 52 after acidification of the amino salt, but salicylidenemonooxalacetic ester 59 by the elimination of one molecule of water.



59

In our preparation, condensation of ethyl sodium oxalacetate and salicylic aldehyde in absolute ethanol, followed by acidification afforded ketoarylparaconic ester 52 in 70% yield.



The ketoarylparaconic ester 52 isolated after recrystallization was reasonably pure. The proton NMR (acetone-d_6) exhibits triplet for the methyl protons of ester at δ1.27ppm (3H, J = 7Hz), quartet for the methylene protons of ester at δ4.20ppm (2H, J = 7Hz), singlet for

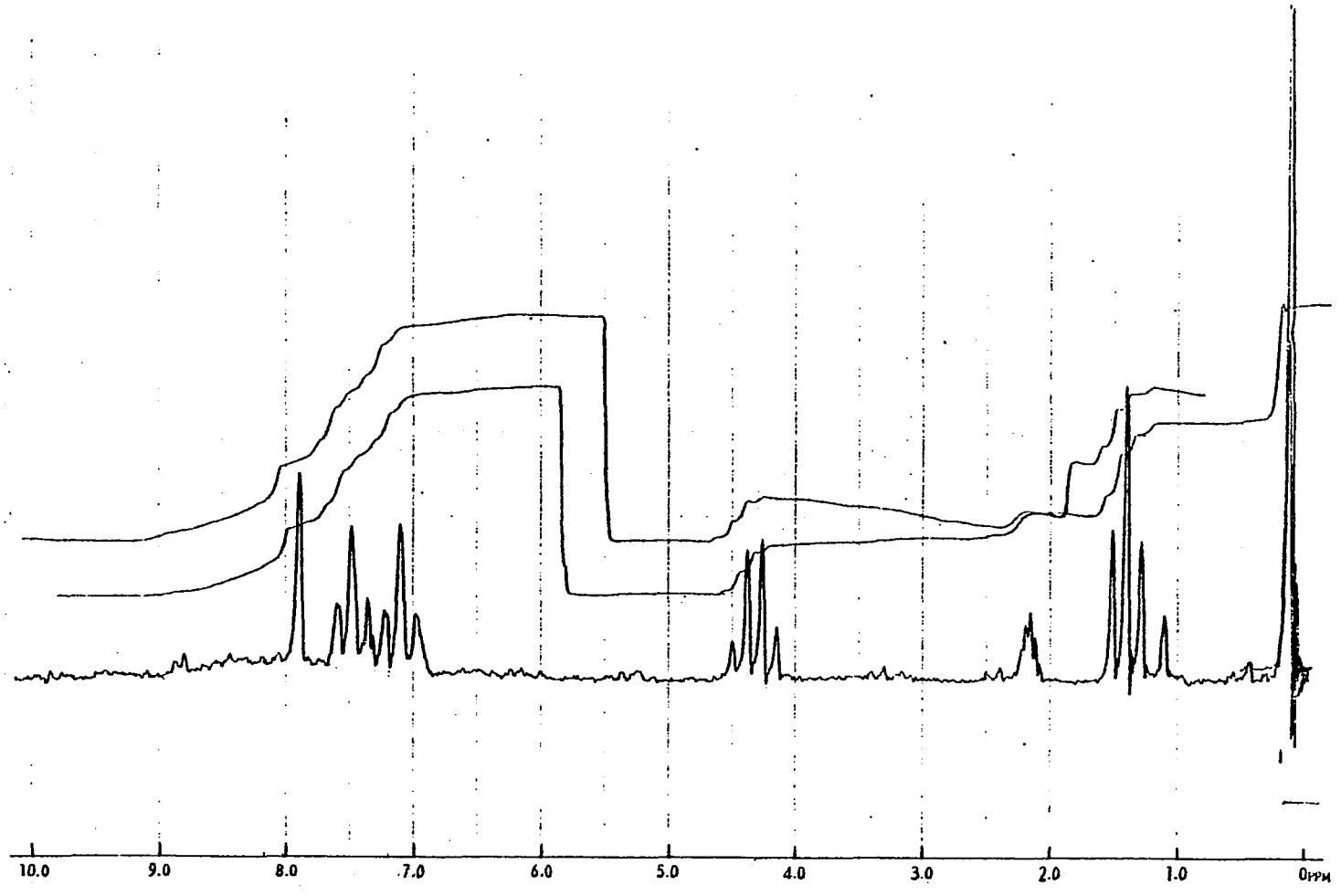
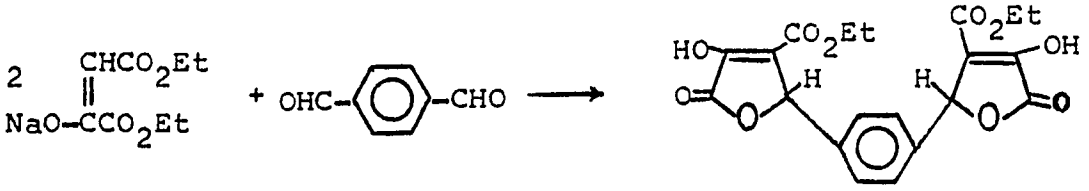


Fig. 2 : PMR spectrum of lactone 52 in acetone-d_6 solution at 60MHz

proton on lactone ring at δ 7.78ppm (1H), a broad singlet for hydroxyl proton centered at δ 8.01ppm (2H, exchangable with D_2O) and a multiplet for phenyl protons centered at δ 7.16ppm (4H). IR (Nujol) displays two hydroxy absorption at 3530cm^{-1} and 3200cm^{-1} corresponding to phenol and enol group respectively. The carbonyl absorption at 1755cm^{-1} - a characteristic absorption for α,β-unsaturated γ-lactone. Neutralization equivalent 261.67 (calc. 264) was obtained by titration. These characterization data are consistent with lactone structure 52 and exclude the possibility of Gault's ester 59.

3.1.2 Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene (50)

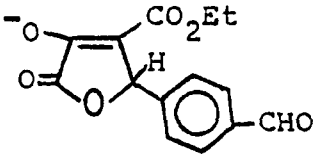
condensation of 2 moles of ethyl sodium oxalacetate and one mole of terephthaldehyde, gives bis-product 50 by double condensation.



50

The terephthaldehyde has two aldehyde groups, after first condensation of the ethyl sodium oxalacetate with one aldehyde, to form the intermediate 60, the aldehyde group in 60 can be in competition with unreacted terephthaldehyde for condensation, since the aldehyde group is expected

to be a stronger electron-withdrawer than the ester, the terephthaldehyde should be more reactive than the intermediate 60. If 1 mole of ethyl sodium oxalacetate was condensed with 1 mole of terephthaldehyde, the acid of 60 would be obtained.



60

The infrared spectra of compound 50 offer a strong evidence of hydroxy-lactone. Fig. 3 shows two hydroxy band at 3470cm^{-1} and 3280cm^{-1} for the enol group, two strong absorption at 1780cm^{-1} and 1750cm^{-1} corresponding to the γ-lactone and ester group.

The NMR spectra (acetone-d_6) in Fig. 4 shows a triplet for methyl protons of ester at 1.13ppm (3H, J = 7Hz), a quartet for methylene protons of ester at 4.12ppm (2H, J = 7Hz), a singlet for proton on lactone ring at 6.14ppm and a singlet for symmetric phenyl protons at 7.43ppm (2H), a broad absorption around 6.20-7.94 was confirmed by the integration of peak area as well as the proton exchange with D_2O, after addition of D_2O, a DHO peak was observed at 4.10ppm (Fig. 5). Mass spectra exhibit a very weak molecular ion at m/e 418. The fragmentation are summerized in Table 3.

The compound 50 decomposes to an orange viscous

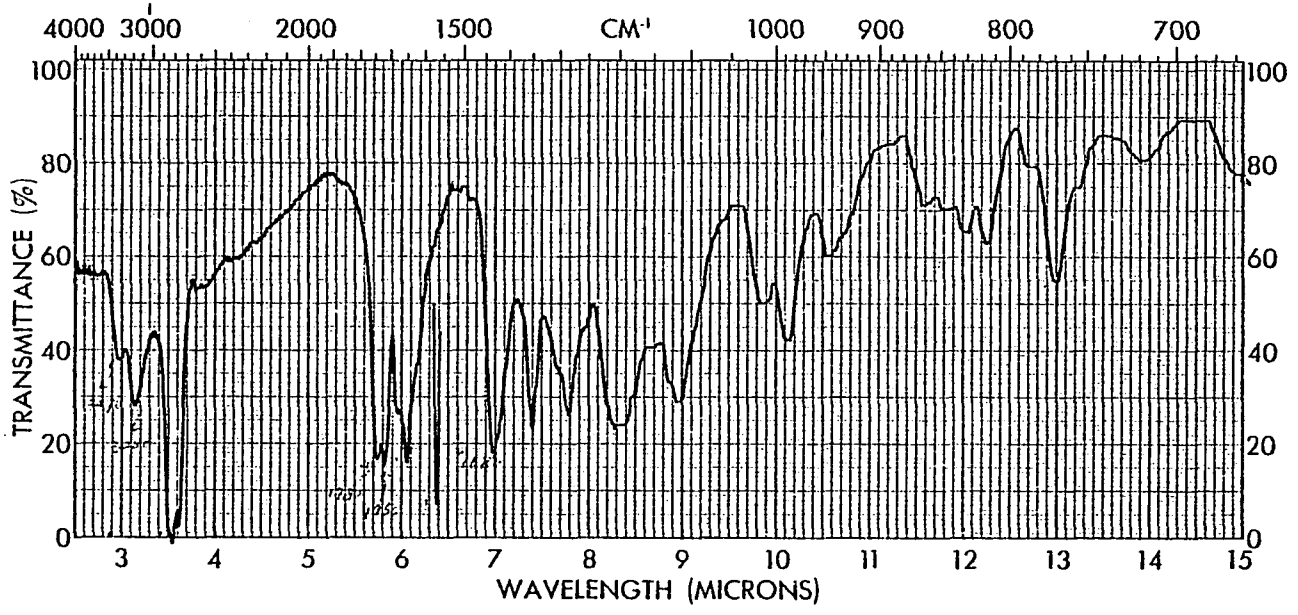


Fig. 3 : Infrared spectrum of Bis-lactone 50 in Nujol

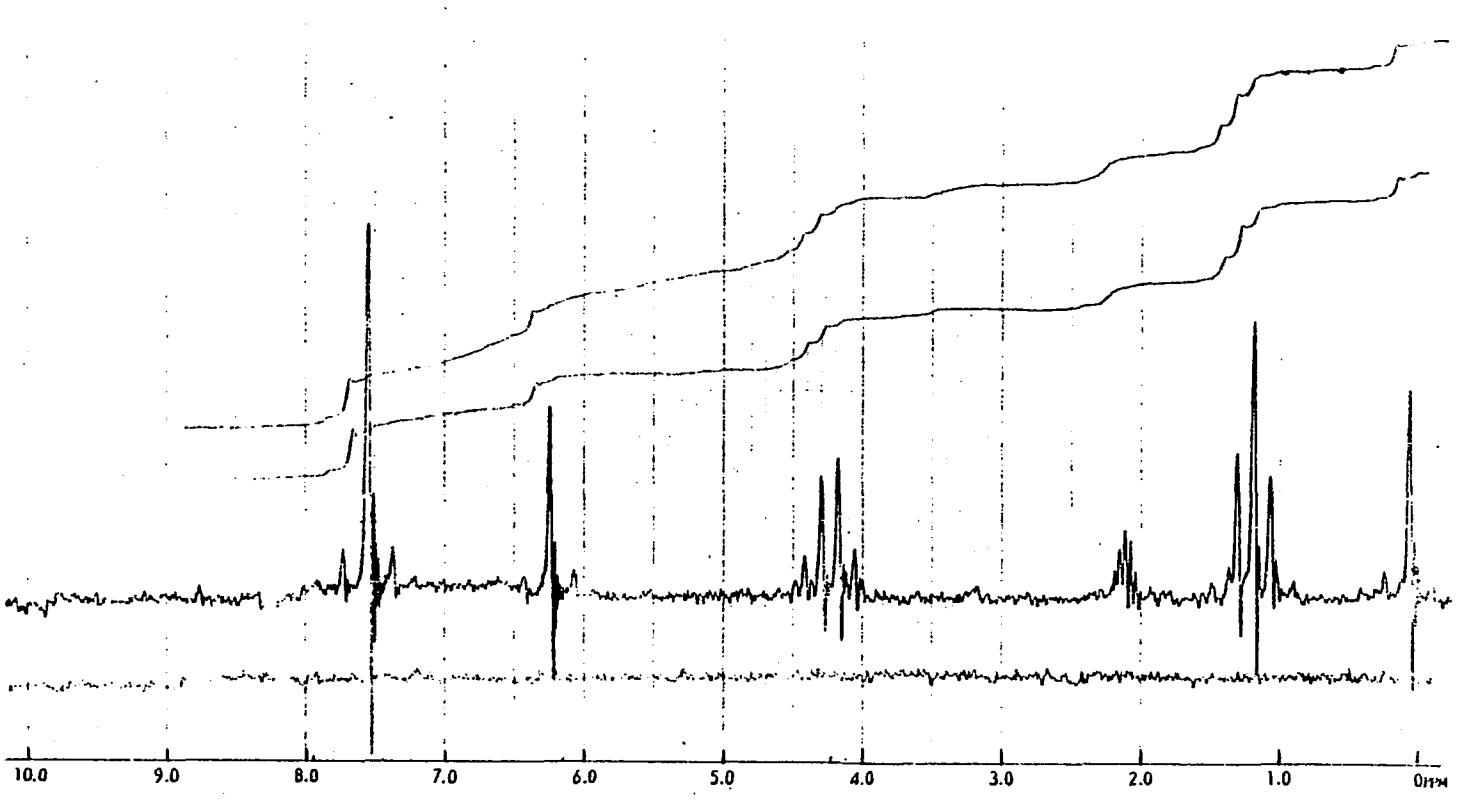


Fig. 4 : PMR spectrum of bis-lactone 50 in acetone-d_6 solution at 60MHz

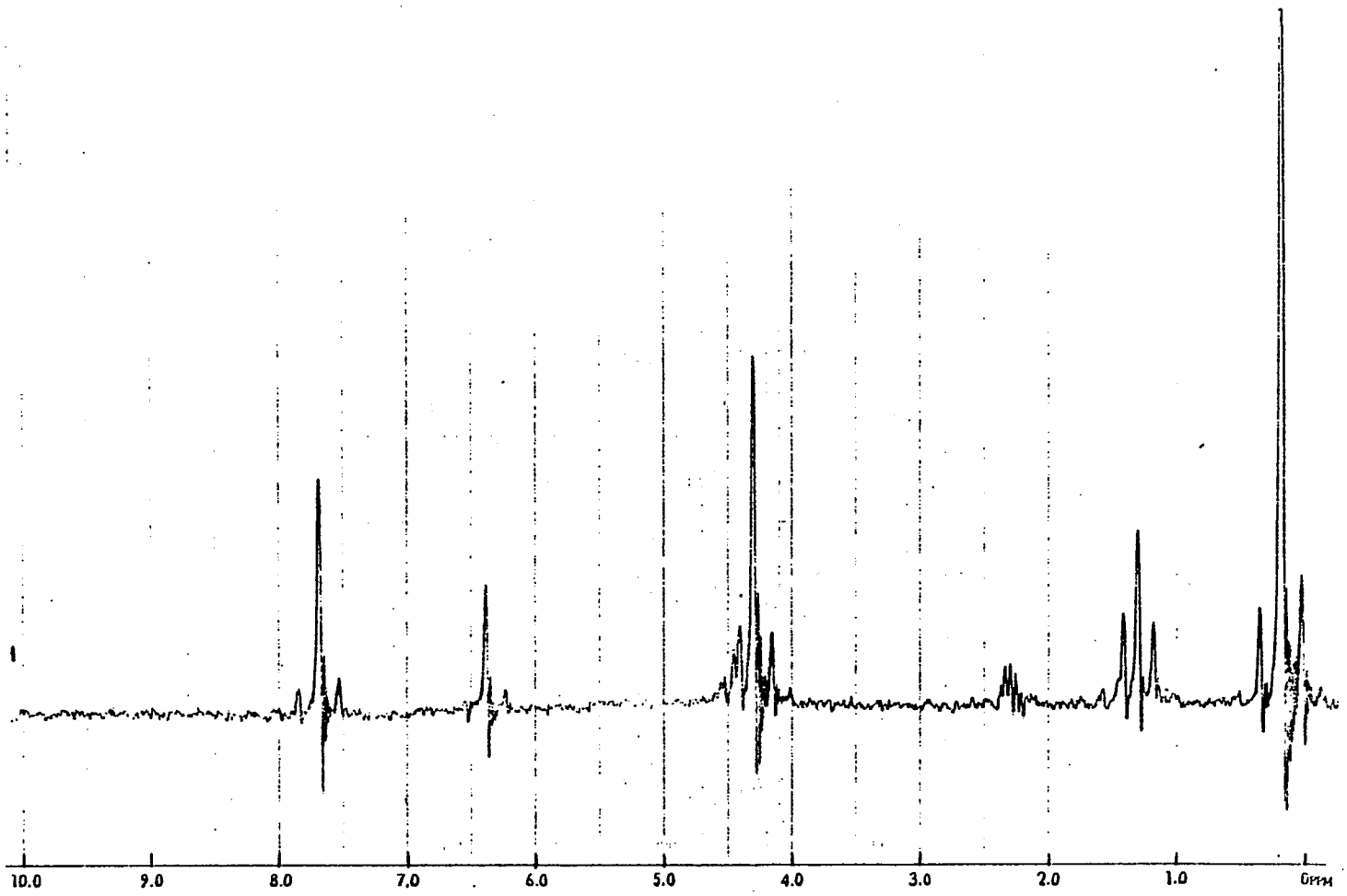
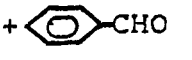
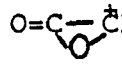


Fig. 5 : PMR spectrum of Bis-lactone 50 in acetone-d_6 and D_2O at 60MHz

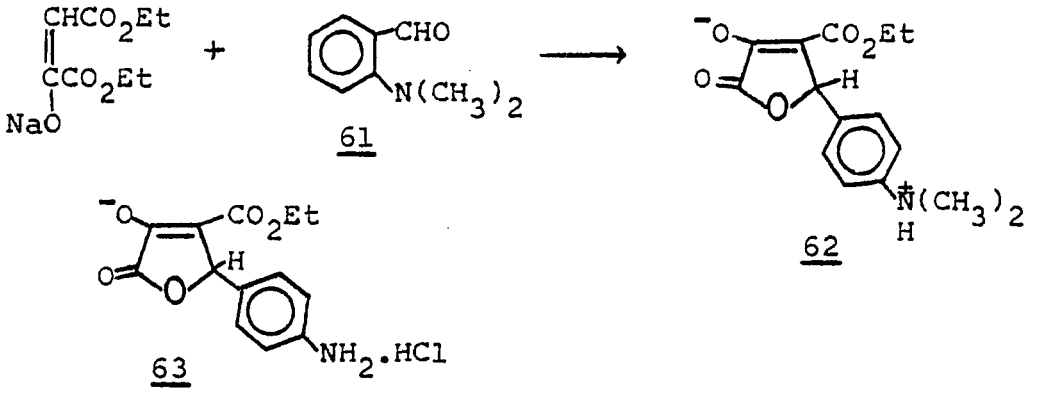
Table 3: m/e Values and relative intensities of abundant ions of bis-lactone 50

Mass no.	Intensity(%)	Comments
418	0.7	Molecular ion
374	1.1	$M-CO_2$
373	1.9	$M-OC_2H_5$
346	1.9	$M-CO-CO_2$
328	2.2	$M-OC_2H_5-CO_2H$
318	2.0	$M-2CO-CO_2$, or $M-CO_2C_2H_5-CO+H$
301	2.9	$M-CO_2C_2H_5-CO_2$
300	2.7	301-H
275	4.1	$M-CO_2C_2H_5-CO-C_2H_2O$
256	15.2	$M-CO_2Et-CO_2-OC_2H_5$
213	13.0	$328-(HO)HC=CCO_2Et$
205	11.1	$275-CO-CO_2$
199	7.0	$M-2CO_2Et-CO-CO_2-H$
185	13.0	$M-2CO_2Et-2CO_2+H$
171	9.1	M-115-2CO
157	10.1	185-CO
149	31.3	205-CO-CO
133	27.4	$205-CO-CO_2$
129	37.2	157-CO
115	30.9	$HO^{+}=C=CH(CO_2Et)$
111	47.1	129-OH-H
105	21.6	
97	86.5	115-OH-H
73	94.7	$+CO_2Et$
69	100.0	$\dot{O}=CCH=C=O$
57	90.8	
55	80.9	$CH_2=CHC=\dot{O}$

liquid with evolution of gas at melting point. Based on above spectra data, the lactone structure 50 was assigned.

3.1.3 Attempt to generate the α-keto-β-carbethoxy-γ-(p-N,N-dimethylaminophenyl)-γ-butyrolactone

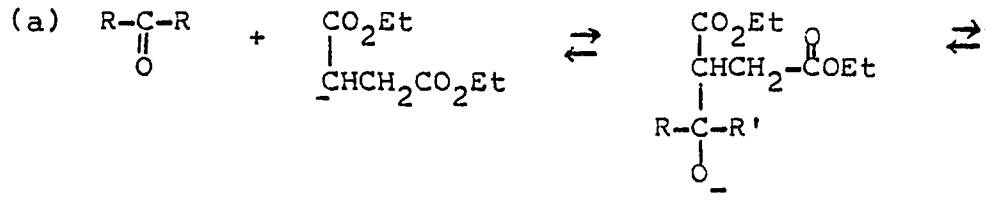
The condensation of aldehyde with ethyl sodium oxalacetate gives α-ketoparaconate, however, reaction of p-(N,N-dimethylamino)-benzaldehyde 61 with ethyl sodium oxalacetate, did not give the expected α-ketoparaconate 62

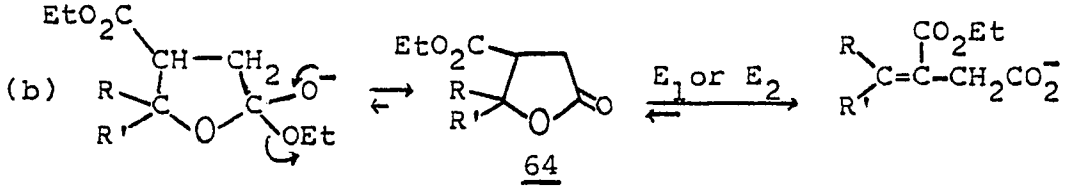


the aldehyde 61 and diethyl oxalacetate were recovered. The failure in this preparation may be explained as the instability of the product or the difficulty in separating the zwitterion ion 62. Since the compound 63 had been separated by hydrogenation of the γ-(p-nitrophenyl)-α-oxoparaconate 51 by Monsimer[72] as the hydrochloric salt, the compound 62 should also be stable and separable as a hydrochloric salt.

Stacy[64] suggested that the condensation of aldehyde and ethyl sodium oxalacetate resembles the Stobbe condensation. The reaction mechanism of Stobbe condensation[73-74] was proposed as in the sequence (a), (b) for (1) the fact

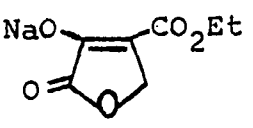
succinic esters react so much better than others (2) one ester group is always cleaved, and (3) the alcohol is not the product, but the olefin. In addition, intermediate lactone 64 has been isolated from the mixture.[75]



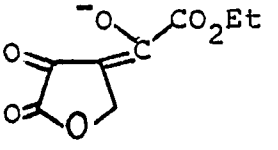


64

In condensation of aldehyde and ethyl sodium oxalacetate, the intermediate 65 is stabilized by the resonance between 65 and 66, which does not undergo further cleavage as in Stobbe condensation. But, Gault[47] proposed that aldehyde reacts in the hydrated form. For either



65



66

mechanism, the initial step should be the nucleophilic addition to the carbonyl group of the aldehyde. The reactivity of the aldehyde will then play an important role in initiating the reaction.

Jenck[76] studied a series of substituted benzaldehydes reacting with semicarbazide. At low pH's where the rate-limiting step is attack by the amine. Using a Hammet equation (c), exhibits $\rho = 0.91$, a negative σ_Z value for

(c) $\log K_Z = \rho\sigma + \log K_H$ Z : substituted aldehyde
H : benzaldehyde

the elctron-releasing group and a positive σ_Z value for the electron-withdrawing group, which means a electron-withdrawing substituents on the aldehyde will increase the rate of reaction and electron donors decrease it. Study of the dissociation constant of substituted benzoic acid,[77] set up $\rho = 1$, -0.66 of σ_Z value for p-amino group was observed, which is smaller than p-hydroxy (-0.37) and p-methoxy (0.27). This shows that p-amino group is a very good electron donor, which decreases the dissociation constant of benzoic acid.

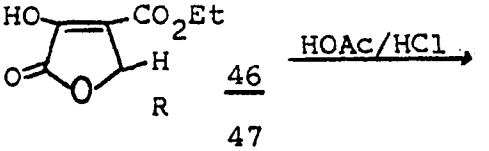
Based on above results, the failure of preparing compound 62 may be due to the strong electron-releasing character of N,N-dimethylamino group of the benzaldehyde.

This summarized the condensation of ethyl sodium oxalacetate with aldehyde, an electron withdrawing group on aldehyde will facilitate the condensation, while the electro donor will decrease it.

3.1.4 Acid-catalyzed decarboxylation of α-keto-β-carbethoxy-γ-substituted-γ-butyrolactones

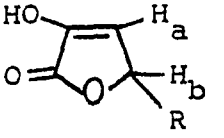
Acid-catalysed decarboxylation[27] of the β-alkyl-α-oxoparaconates, yields the corresponding α-tetronic acids, because it entails conversion of β-ketoacids into stable enolic compounds. Decarboxylation of ethyl γ-alkyl-α-oxoparaconates, which are already enolic, are more difficult with higher γ-alkyl group.

Hydrolysis of α-keto-β-carbethoxy-γ-butyrolactone 25 with dilute sulfuric acid give α-tetronic acid 57 in very low yield (5%) with polymeric material in 60% yield (the structure of the polymer will be discussed in later section). Hydrolysis of α-keto-β-carbethoxy-γ-methyl-γ-butyrolactone 46, did not give the expected γ-methyl-α-tetronic acid 54. Reaction of lactones 46, 47, 48 with mixture of acetic acid and hydrochloric acid gives the corresponding γ-alkyl-α-tetronic acids in 50-70% yield.



46
47
48

HOAc/HCl



54 R=CH_3
55 R=C_2H_5
56 R=C_3H_7

The NMR spectra (acetone-d_6) of α-ketolactone 54 is given in Fig. 6. The absorption of methyl protons show a doublet at δ1.54ppm (3H, J=7Hz), the absorption of enol proton shows a broad peak centered at δ8.64ppm (1H), the absorption of the proton H_b at δ4.98ppm (1H, J_{Ha-CH} =3Hz)

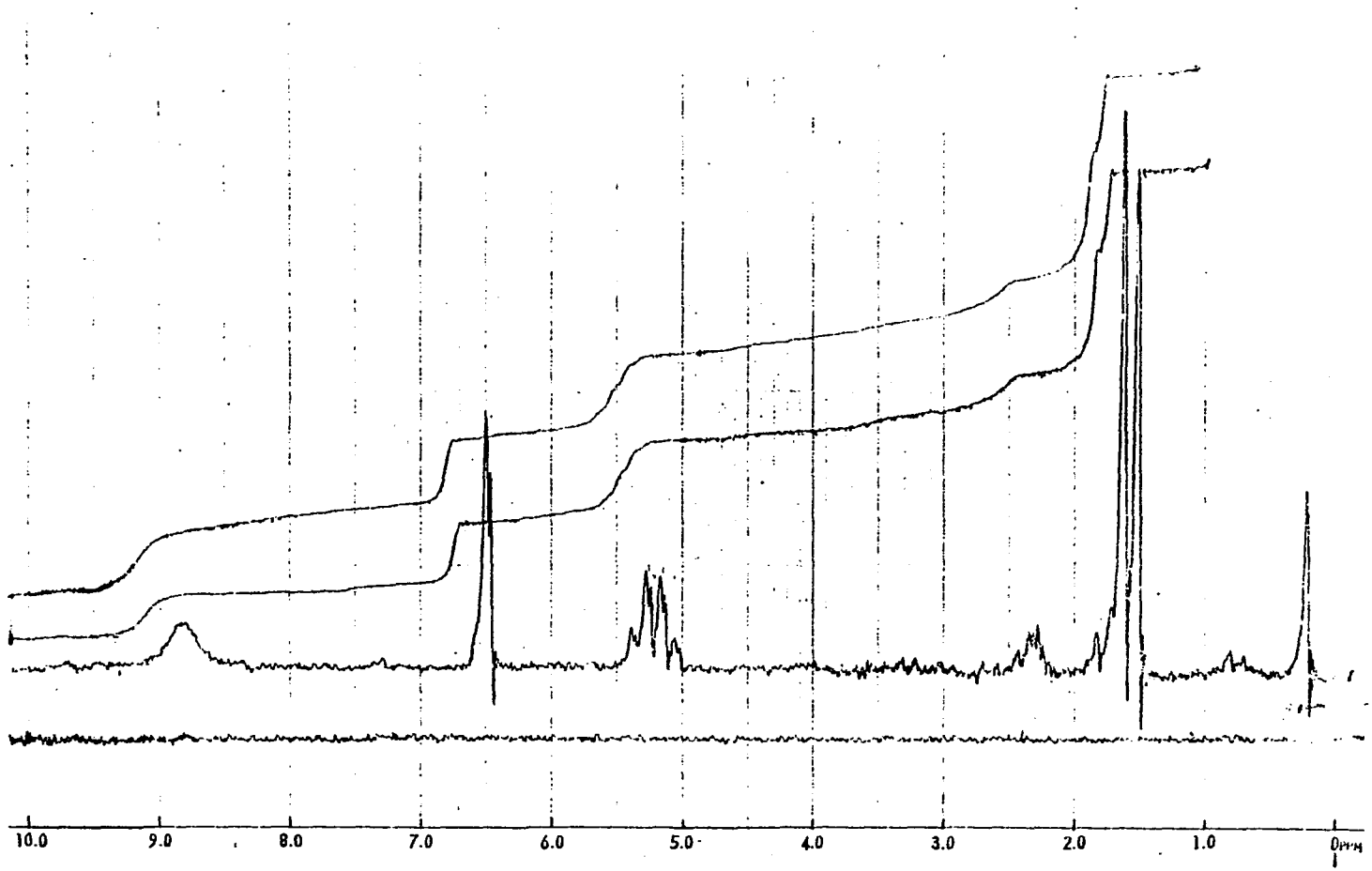


Fig. 6 : PMR spectrum of lactone 54 in acetone-d_6 solution at 60MHz

is split into a quartet (J=7Hz) with each component of which is split into a doublet (J=3Hz). The absorption of H_a is split into a doublet (J=3Hz) by the proton H_b at δ 6.78ppm. Thus the H_a-H_b dihedral angle is about 50°, this reveals a nearly planar structure for the lactone 54 with H_a on the plane, H_b and CH_3 above and below the plane at an angle of 109°. Legan[68] studied the microwave spectra of α,β-unsaturated-γ-lactone and showed that ring atoms and carbonyl oxygen are coplanar.[69] The hydroxy group on double bond should not affect the planarity of the ring, so the α-keto-γ-lactone should be also in planar structure.

The NMR spectra of lactone 55 exhibits a triplet for methyl protons at δ0.91ppm (3H, J=7Hz), multiplet for methylene protons at δ1.68ppm (2H, J=7Hz), a triplet with each component split into a doublet for H_b at δ4.86ppm (1H, J_{Hb-CH_3}= 7Hz, J_{Hb-Ha}=3Hz), a doublet for H_a at δ6.26ppm (1H, J=3Hz), and a broad singlet for enol group at δ8.67ppm (1H). The NMR spectrum of lactone 56 shows a more complex absorption for 2 methylene group centered at δ1.61ppm (4H), triplet for methyl proton at δ0.95ppm (3H, J=7Hz), a triplet with each component split into doublet for H_b at δ4.98ppm (1H, J_{Ha-Hb}=3Hz, J_{Hb-CH_2}=7Hz), a doublet for H_a at δ6.29ppm (1H, J=3Hz) and a broad singlet at δ7.68ppm (1H) for the enol group.

The NMR spectrum of lactones 54, 55, 56 is consistent with the structures that were assigned by Schinz.[49]

However, acid-catalysed decarboxylation of lactones

21, 49, 50 did not give the expected β-unsubstituted α-keto-γ-lactones. Suprin[62] reported that reaction of lactone 21 with 50% hydrochloric acid gave CO, CO_2 and some viscous product. The failure of decarboxylation of lactone 21, 49, 50 can be rationalized as the stability of the enolized lactones 21, 49, 50 which require more severe conditions for the decarboxylation. It is also possibly due to the instability of the expected decarboxylated products.

Suprin,[62,34] Green and co-worker reported base-catalysed cleavage and fragmentation of the α-tetronic acid ring, so the base-catalyzed hydrolysis and decarboxylation have not been studied.

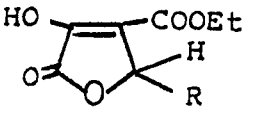
3.2 Characterization

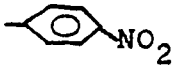
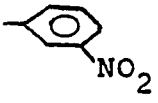
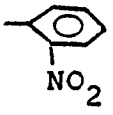
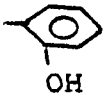
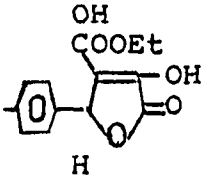
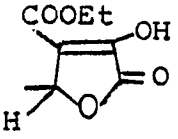
The α-keto-γ-lactones are characterized by their neutralization equivalent, dissociation constants and the infrared, nuclear magnetic resonance and mass spectra.

3.2.1 Nuclear magnetic resonance spectra of α-keto-β-carbethoxy-γ-substituted-γ-butyrolactones

The proton NMR spectra of α-keto-β-carbethoxy-γ-substituted-γ-butyrolactones are listed in Table 4. The proton absorption of the methyl group of the ethyl ester shows a triplet around δ 1.12-1.38ppm, and a quartet around δ 4.07-4.38ppm for the methylene group of the ester. The singlet for the proton in the lactone ring at δ 4.93ppm for lactone 25 is consistent with the chemical shift for

Table 4 : NMR data of α-keto-β-carbethoxy-γ-substitutedbutyrolactone (δ ppm, TMS)



Compd.	R	$-OCH_2\underline{CH_3}$	$-O\underline{CH_2}CH_3$	$-O\underline{CH}R$	-R	-OH
25	H	1.32	4.36	4.93	-	8.71
46	CH_3	1.37	4.38	5.17	1.54	8.65
47	C_2H_5	1.38	4.37	5.12	0.97(CH_3) 2.00(CH_2)	8.77
21		1.12	4.11	6.08	7.36	8.98
51		1.2	4.23	6.08	7.46 8.17	8.34
23		1.14	4.2	6.36	7.46	6.58
22		1.07	4.13	6.85	7.77	7.82
52		1.27	4.20	7.78	7.16	7.47
50		1.13	4.07	6.04	7.36	6.98
49		1.38	4.43	5.82	-	8.98

methylene group in the ring of α,β-unsaturated γ-lactone (δ 5.01ppm).[79] The proton absorption of the enol group shows a broad singlet centered around δ 6.98-8.98ppm.

The chemical shift of hydrogen in lactone ring are affected by the γ-substituents. Since the chemical shift highly dependent on the electron density about nucleus being observed, or associated with the atom to which it is bonded, as the electron density decreases, the nucleus experiences a greater deshielding and absorbs at lower field positions. A difference of 0.2ppm for the γ-alkyl substituted lactones 47, 48 and γ-unsubstituted lactone 25 is comparable to the difference of tertiary alkane (0.2ppm). A difference of 1.2ppm between the γ-phenyl substituted lactone 21 and γ-unsubstituted lactone 25 is also comparable to the difference between methyl group absorption of toluene and alkane (1.4ppm). Since the nitro group on the phenyl ring increases the electron-withdrawing effect, the proton would be expected to absorb at a lower field position. In comparing the chemical shifts of lactones 21, 22, 23, 51, the deshielding effect of hydrogen by nitrophenyl decreases as one goes from ortho to meta to the para-position, and the para-position being unaffected. This appears to be a good correlation between inductive effect on γ-carbon and deshilding effect of γ-hydrogen by nitrophenyl group.

The γ-hydrogen of the o-hydroxyphenyl-substituted lactone 52 absorbs at much lower field position (7.78ppm).

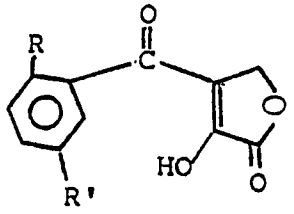
Though without a resonance effect, hydroxy-group shows a negative inductive effect which increase the electron-withdrawing effect of phenyl, but the chemical shift of the proton is lower than the expected value. Factors other than inductive effect should also be considered.

The NMR spectra of α-keto-β-benzoyl-γ-butyrolactones are shown in Table 5.[78] Without a substituent on γ-carbon, the chemical shifts of the methylene proton on lactone ring seem to be less affected by the β-substituent i.e. δ 5.00ppm (DMSO-d_6) for β-benzoyl substituents, δ 4.93ppm (acetone-d_6) for β-carbethoxyl substituent, δ 4.73ppm ($CDCl_3$) for lactone 58. The β-substituents are further away from the γ-hydrogen, smaller effect on chemical shift is expected.

3.2.2 Acidity of α-keto-γ-lactones

In carbonyl compounds, the ketone and enol forms are in equilibrium, and on the basis of bond energies alone, the keto-form is calculated to be more stable by about 15-18 Kcal/mole.[80] Thus for most systems the equilibrium lies well to the side of the keto-form. However, such calculations do not include steric effects, resonance effects, or solvent effects, all of which tend to change the value of the equilibrium constant and in some cases cause the enolic form to become more stable and a few materials exist entirely (at least as far as the measurements indicate) in the enolic form.

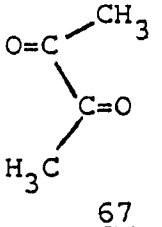
Table 5 : Chemical shifts (δ ppm, TMS) of protons in α-Keto-β-benzoyl-γ-butyrolactones (DMSO-d_6)



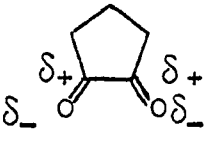
R	R'	$-CH_2OCO$	Ar	OH
H	H	5.01	7.62(5)	≃9
H	CH_3	5.01	7.28(2) 7.75(2)	≃9
H	OH	5.02	6.87(2) 7.79(2)	10.1
H	OCH_3	5.02	7.00(2) 7.87(2)	9.2
OCH_3	OCH_3	4.96	6.55(2) 7.35(2)	8.8
H	Cl	5.00	7.52(2) 7.84(2)	-
H	F	5.02	7.25(2) 7.88(2)	-

A comparison of the properties of α-diketones provides a convenient point for any discussion relating to enolization and acidity of the α-keto-γ-lactones. Table 6 shows the acidities of some α-diketones in water and the percentage of the enolic form in aqueous solution.

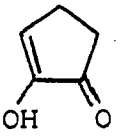
Cyclisation has a most remarkable influence on the degree of enolization of α-diketones, diacetyl $CH_3COCOCH_3$ exists almost exclusively as the keto form whereas 1,2-cyclopentanedione is 100 percent enolized. This is almost certainly a conformational effect. In the most stable conformation of biacetyl 67, the C=O dipoles are pointing in opposite directions with the negative oxygen atoms as



67



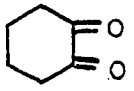
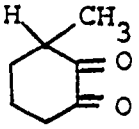
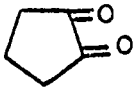
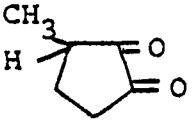
68



69

far from each other as possible. Because of the rigidity of the cyclopentane ring, however, the two carbonyl dipoles in 1,2-cyclopentanedione lie at an angle of only about 65°, and because of dipole-dipole and non-bonded interactions in the diketone which destabilize this keto-form 68. So, the compound adopts the enol-form 69 (which can be stabilized by resonance and hydrogen bonding) presumably in an attempt to relieve this electrostatically unsatisfactory situation. In 1,2-cyclohexanedione, the larger ring is

Table 6 : Enol content and acidity in some diketones and keto esters

Compound	% Enol in liquid	pK_E	Ref.
$CH_3COCH_2CO_2Et$	7.5	8.09	81
$CH_3COCH_2COCH_3$	80	8.13	81
	40	10.3	82
	60	11.23	82
	100	9.14	82
	100	9.60	82
$CH_3COCOCH_3$	5×10^{-3}	-	83

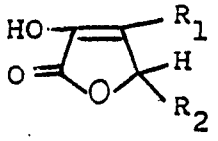
somewhat more flexible and the predominance of the enol form therefore not as great.

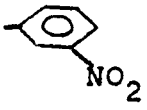
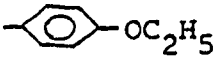
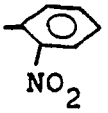
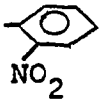
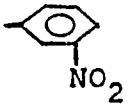
α-Tetronic acid in the crystalline state has been reported[84] to exist in the enol form and to have a pK of 7.0 (enol). Plattner has synthesized the β-methyl derivative which was studied by Schwarzenback and Wittwer[82] and was also found to exist as the enol in solid state and to have a pK of 7.77. The cyclic oxygen atom exerts an inductive effect through the γ-carbon atom and results in α-tetronic acid being a stronger acid than cyclopentane-1,2-dione (pK = 9.14).

Table 7 lists the values of the dissociation constants of some substituted α-tetronic acids prepared in this study together with some from other sources. With free β-position, α-keto-γ-lactones shows pK_a around 7 to 7.8. With bromo-group at β-position, the lactones show pK_a around 5.55 to 5.64, and with a carbethoxyl group at β-position, the lactones have pK_a around 3.30 to 4.15. The difference in acid strength is comparable to the α-substituted tetronic acids as shown in Table 8. The acid weakening or strengthening effect of groups substituted in α-position of tetronic acids is generally considered from their inductive effects.[77]

However, the conjugation effect may also be a factor of major importance in determining the acidities of β-carbethoxy-α-tetronic acids. The methylketene dimer 70

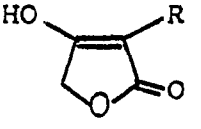
Table 7 : pK_a values of α-tetronic acids in 50% Methanol- 0.2M LiCl



R_1	R_2	pK_a	R_1	R_2	pK_a
$-CO_2Et$	$-H$	3.98	$-H$	$-H$	7.0[a]
$-CO_2Et$	$-CH_3$	4.07	$-H$	$-CH_3$	7.65
$-CO_2Et$	$-C_2H_5$	4.15	$-H$	$-C_2H_5$	7.77
$-CO_2Et$		3.85	$-CH_3$	$-H$	7.77[b]
$-CO_2Et$		3.75	$-Br$		5.55[c]
$-CO_2Et$		3.69	$-Br$		5.63[c]
$-CO_2Et$		3.52	$-Br$		5.64[c]
$-CO_2Et$		3.30	$-H$		7.25[d]
			$-H$		7.4[d]

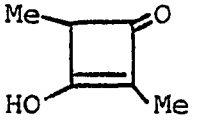
a. H. Hift, H. Mahler, J. Biological Chem. 901, (1952)
b. G. Schwarzenback, Helv. Chim. Acta, 30 663 (1947)
c. E.D. Stecher, et.al., J. O. C. 30 1800 (1964)
d. E.D. Stecher, et. al., JOC 26 2693 (1961)

Table 8 : Dissociation constants of tetronic acids[88]



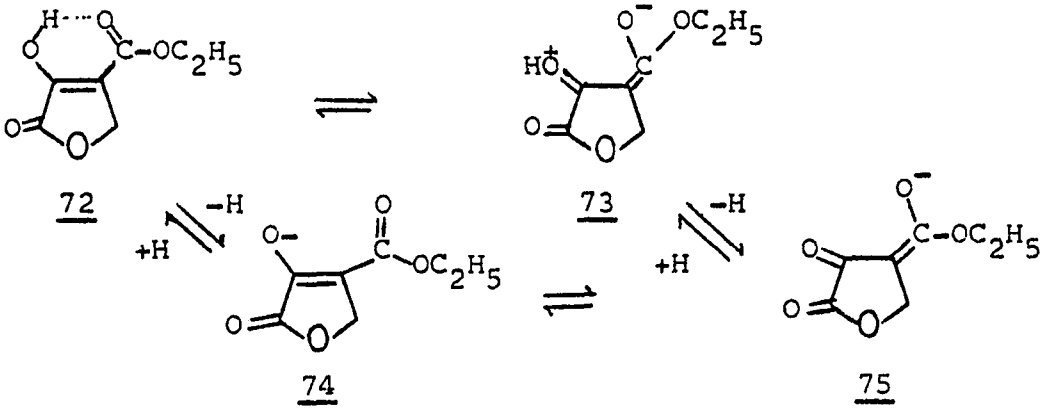
Acid	pK_a
Tetronic acid	3.76
α-Chlorotetronic acid	2.13
α-Bromotetronic acid	2.23
α-Methyltetronic acid	4.19
α-Ethoxycarbonyltetronic acid	1.8
α-Acetyltetronic acid	1.8

has pK_a ca. 2.8, which is about 100 times as strong as acetic acid. Since the keto group in this compound is sufficiently far from the hydroxyl group, so that the inductive effect may be considered relatively small, it seems that the high acidity in compound 70 is due largely to conjugation effects.[86]



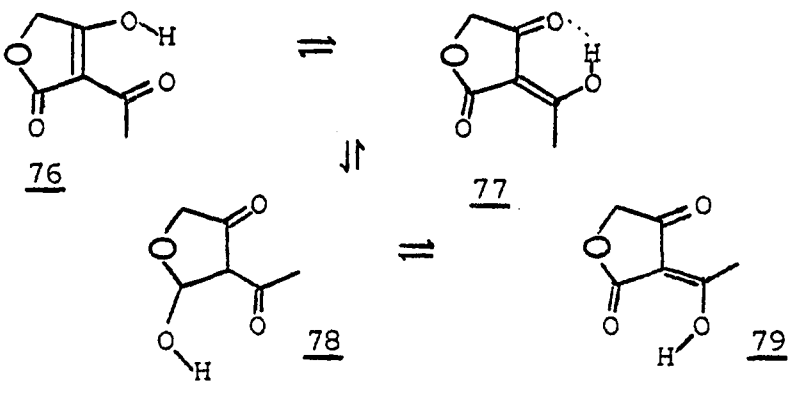
70

The β-carbethoxy-α-tetronic acid should also have this conjugation effect - that is, the ion formed as a result of dissociating hydrogen from hydroxy group should be stabilized by a resonance distribution of the charge between the oxygen atoms of the acidic hydroxyl group and



of the ester carbonyl group as in 72 - 75. This conjugation effect had been observed by Yamagashi and co-worker[87] on 90MHz NMR study of α-acetyl-tetronic acid. The different

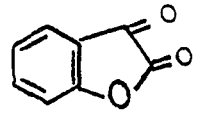
chemical shift for the methylene proton on the ring and the methyl proton of the acetyl group in the tautomers 76 - 79.



As the cyclic oxygen atom exerts an inductive effect through the γ-carbon atom, a γ-substituent should also be able to reinforce or compete with the inductive effect of the ring oxygen atom. As shown in Table 7, the β-carbethoxy-α-tetronic acids with γ-aryl substituents show stronger acidity than the β-carbethoxy-α-tetronic acids with γ-alkyl substituents.

3.2.3 Mass spectra of α-keto-γ-lactones

Although the mass spectra of a series of lactones and tetronic acids[88-92] had been reported, there is not much information available on the mass spectra of α-keto-γ-lactones. The only reported mass spectra on this class of compounds is the mass spectra of coumaran-2,3-dione 80, the fragmentation pattern[93] involving the consecutive loss



(M+) m/e 148

$\xrightarrow{-CO}$ m/e 120(100%) $\xrightarrow{-CO}$ m/e 92 $\xrightarrow{-CO}$ m/e 64

$\downarrow -H\cdot$

m/e 63

80

of three molecules of carbon monoxide followed by loss of a hydrogen atom to give m/e 63 as the stable end product. The α-keto-γ-lactones prepared in this study mostly exist as enol-lactone, without a benzene fusion on β- and γ-carbon. The mass spectra of these compounds exhibit some difference to the mass spectra of coumaran-2,3-dione 80.

The compounds studied are set out in Table 9-13, together with the intensity of the ion peak. All the compounds except the bis-product show strong molecular peak. The mass spectra are shown in Fig. 7-10.

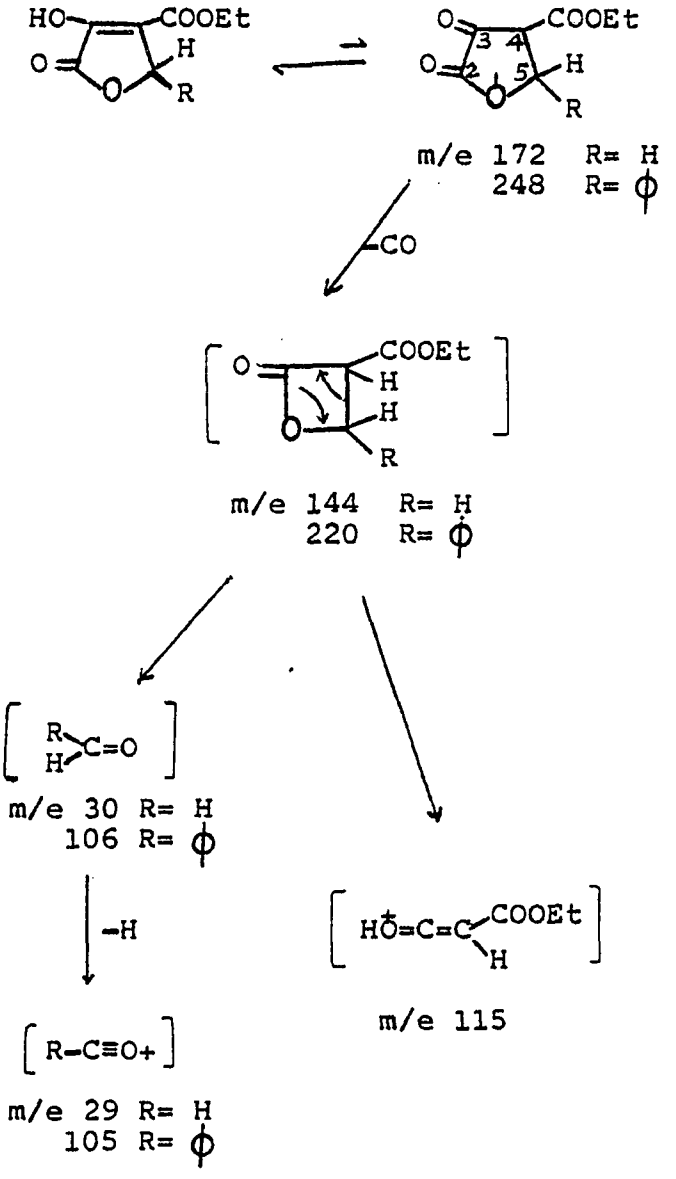
The predominant degradation routes for many of these compounds can be explained on the basis of three schemes. The first involving ketonization of the molecular

ion followed by elimination of carbon monoxide. The second involving rupture of C_5-R_3 bond prior to elimination of carbon monoxide. The third involving rupture of C_2-C_3 bond and loss of carbon dioxde. Also, in those cases where the ring system contains labile substituents, the loss of carbon monoxide or carbon dioxde occurs after modifications to the substituents had first taken place.

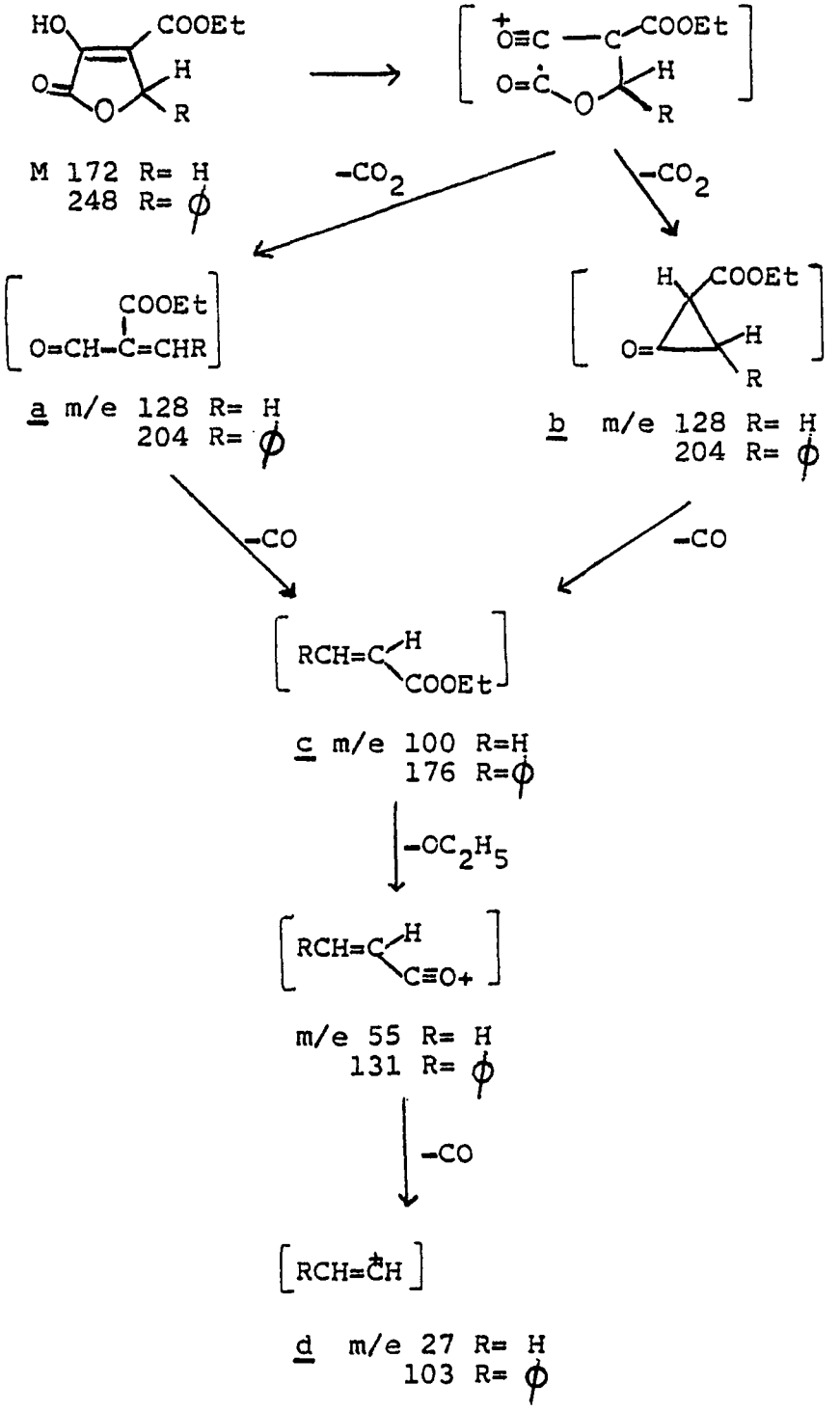
The fragmentation of α-keto-β-carbethoxy-γ-alkyl (or aryl)-γ-butyrolactones can be rationalized as in Scheme 2-4. Scheme 2 involves rupture of C_2-C_3 bond after ketonization, followed by elimination of carbon monoxide to give 4-membered lactone, which is then split to give ketene and aldehyde.

Labelling experiment by Friedman and Long[94] showed that in unsaturated γ-lactones, the ring oxygen was expelled, accompanied by a hydrogen shift. The loss of carbon monoxide in lactones 21, 25 is expected to come from α-keto group. Since the loss of ring oxygen is observed as fragment of CHO, the loss of CO in lactones 21, 25 should come from α-keto group. Scheme 3 involves the rupture of C_2-C_3 bond, followed by elimination of carbon dioxide. Loss of CO_2 from the molecular ion is an important fragmentation process for γ-butyro- and γ-valero-lactones resulting in the cyclopropane ions as the base peak.[94] In contrast to simple saturated γ-lactones, the unsaturated γ-lactone show relatively little loss of carbon dioxide from the parent ion.[95] The loss of CO_2 from lactones 21

Scheme 2 : Fragmentation path 1 of α-keto-β-carbethoxy-γ-butyrolaclactone



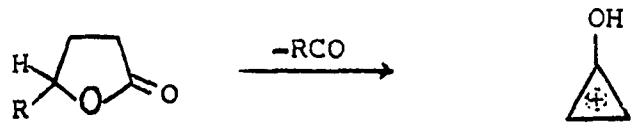
Scheme 3 : Fragmentation path 2 of α-keto-β-carbethoxy-γ-butyrolactones



and 25 exhibits relatively higher intensity (38.2%, 17.3%) than the α,β-unsaturated lactones. The loss of CO_2 from enol-lactones 21, 25 may be explained as rupture of weaker C_2-C_3 bond after ketonization, to form the cyclopropanone b which then lost CO to form acrylate c, this further fragments by loss of OC_2H_5 and CO to alkene ion d.

Scheme 4 involves rupture of R_2-C_4 bond, with loss of carbethoxy group to give e, which is then followed by transfer of hydrogen from C_5 to C_4 with subsequent C_4-C_5 and C_2-O_1 splitting to ion f.

The relative intense ion at m/e 69 is observed for both 21, 25 . The only possible composition of the fragment from both 21, 25 is C_3HO_2 , a fragment i or j is proposed from the loss of hydrogen in h . The fragment h had also been proposed by Haynes[91] in the mass spectra study of tetronic acids. Friedman and Long also observed similar fragment C_3H_3O in the mass spectra of γ-crotonolactone 81 and β-angelicalactone 82 . O^{18}-labelling study also shown that carbonyl oxygen atom incorporate to the cyclopropenoyl ions.

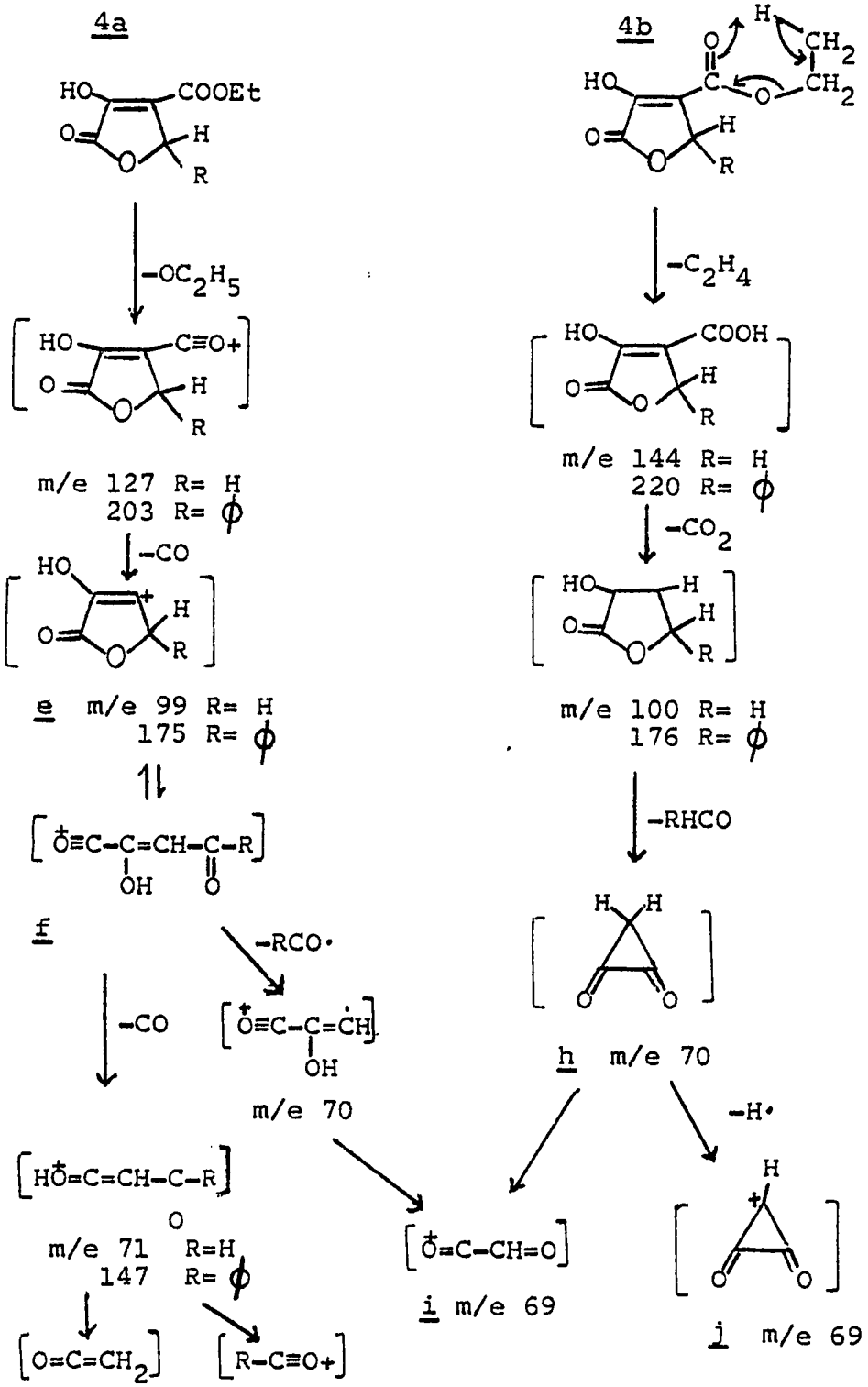


81 R = H
82 R = CH_3

m/e 55

The fragmentation of α-keto-γ-methyl-γ-butyrolactone 54 are shown in Scheme 5 to 7. The fragmentation

Scheme 4 : Fragmentation path 3 of α-keto-β-carbethoxy-γ-butyrolactones



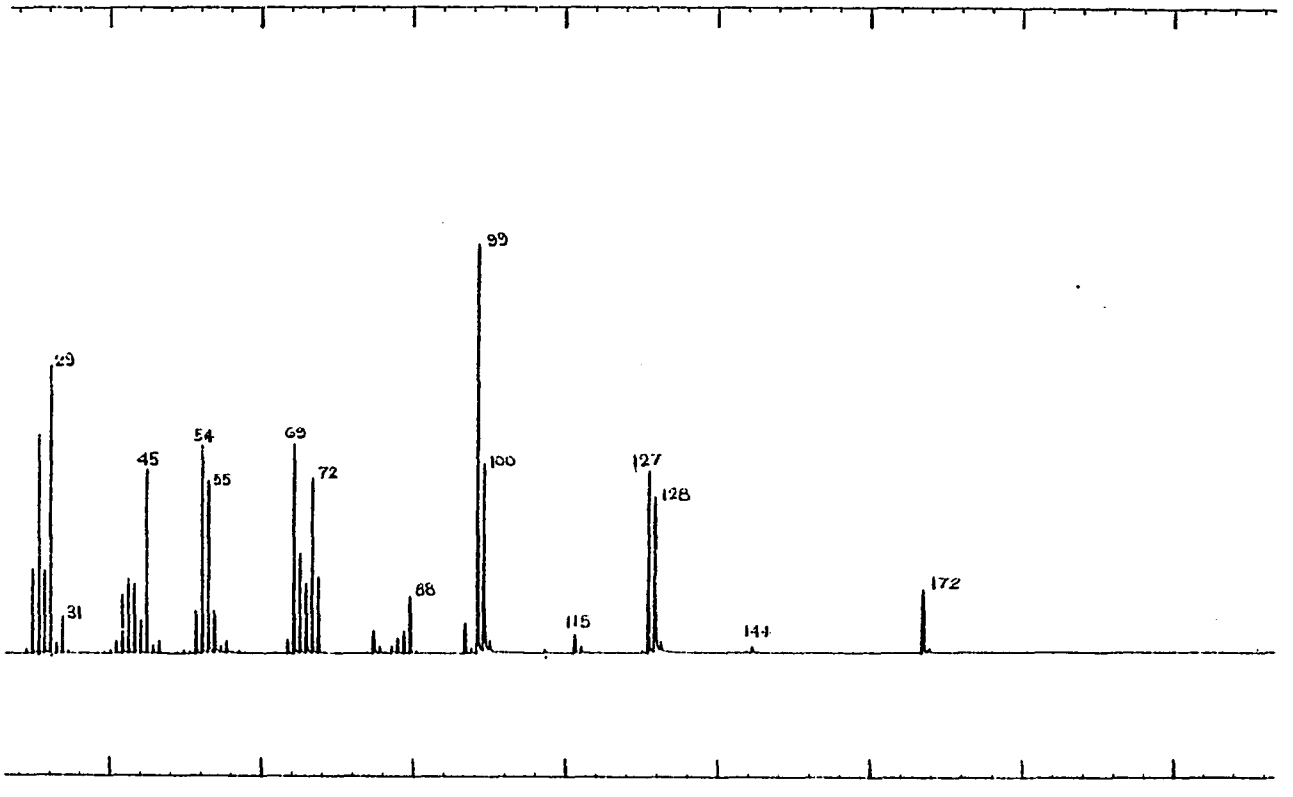


Fig. 7 : Mass spectrum of α-keto-β-carbethoxy-γ-butyrolactone 20

Table 9 : m/e Values and relative intensities (%) of mass spectra of α-keto-β-carbethoxy-γ-butyrolactone 20

Mass no.	Intensity(%)	Comments
172	15.8	Molecular ion
144	1.9	M - CO, or M-C_2H_4
143	0.7	M-CHO, or M-C_2H_5
128	38.2	M-CO_2
127	44.8	M-CO_2H, or M-OC_2H_5
100	46.6	M-CO-CO_2, or M-C_2H_4-CO_2
99	100.0	M-$CO_2C_2H_5$
73	19.0	+$CO_2C_2H_5$
72	43.0	C_2O_3
71	17.3	+O=COCH≡CH_2
69	50.9	$OC\overset{+}{C}H-CO$
55	41.9	$H_2C=CH-C=O^+$
54	51.1	$H_2C=C=C=O$
45	44.8	+CO_2H
42	16.5	$H_2C=C=O$
29	70.2	$HC\equiv O^+$
27	53.7	$H_2C=\overset{+}{C}H$

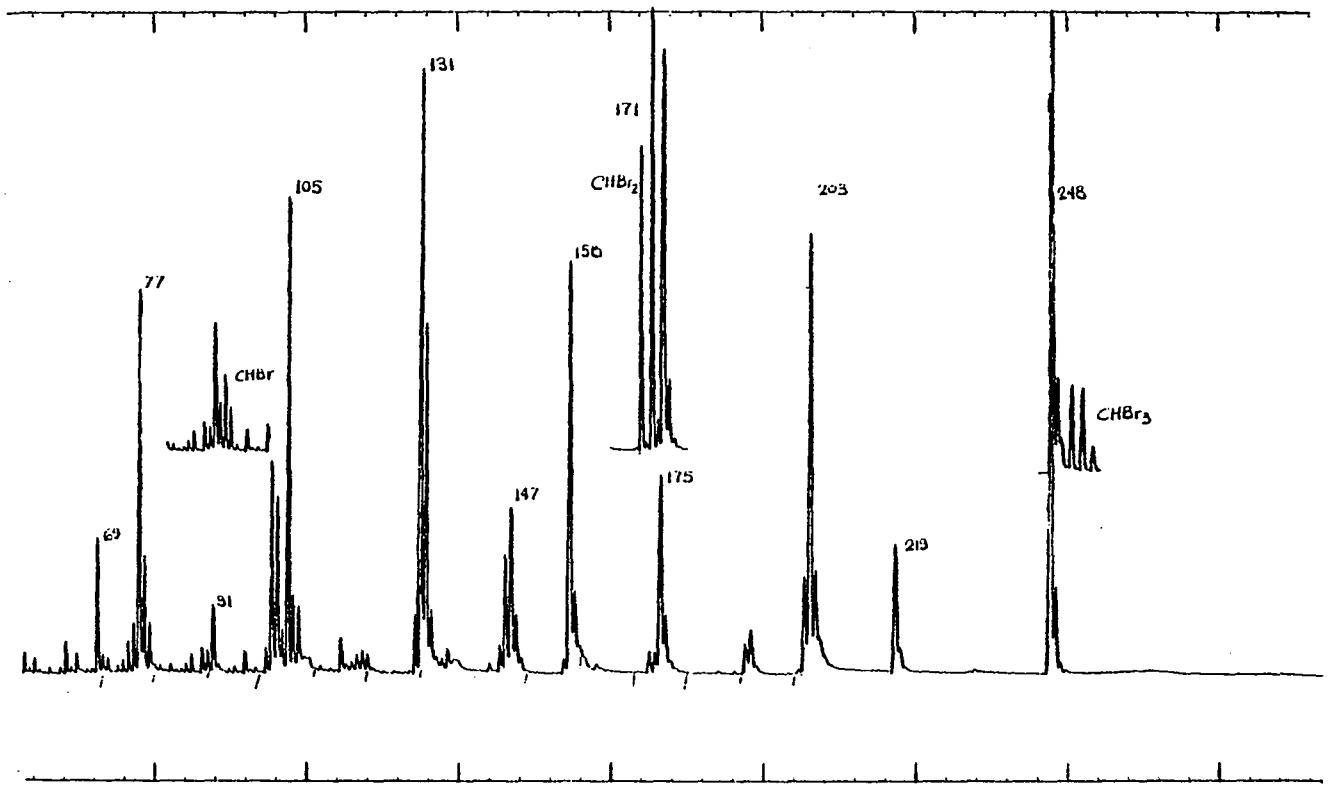
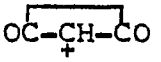


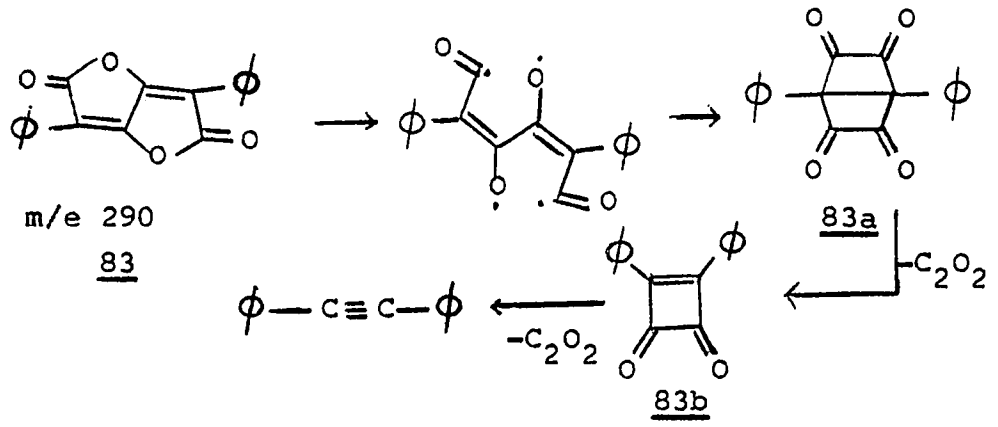
Fig. 7a: Mass spectrum of α-keto-β-carbethoxy-γ-phenyl-γ-butyrolactone 21

Table 10 : m/e Values and relative intensities of mass spectra of α-keto-β-carbethoxy-γ-phenyl-γ-butyrolactone 21

Mass no.	Intensity(%)	Comments
248	95.9	Molecular ion
220	4.6	M-CO, or M-C_2H_4
219	21.3	M-C_2H_5
204	17.3	M-CO_2
203	15.7	M-CO_2H or M-OC_2H_5
175	33.0	M-$CO_2C_2H_5$
158	68.0	M-$CO_2C_2H_5$-OH
147	27.4	M-$CO_2C_2H_5$-CO
146	19.8	147-H
131	57.9	ϕ HC=CH-C=O+
130	100.0	ϕ HC=C=C=O
115	5.6	$H\overset{+}{O}$=C=C(CO_2Et)H
105	78.7	ϕ-C=O+
103	29.4	ϕ CH=$\overset{+}{C}$H
102	35.0	103-H
91	11.7	
77	63.5	
69	22.3	

of lactone 54 are somewhat different from the fragmentation of 21 and 25 . For lactone 54 has no labil substituent-carbethoxyl group on β-position, a methyl group on γ-position is capable of α-cleavage as in Scheme 5. Cleavage α to the lactone oxygen and resultant loss of a methyl radical had also been observed in β-angelicalactone 82.[94] α-Cleavage may become increasingly important with larger substituents at C_5.[96] The intense ion at m/e 69 (base peak) can be the ion i as in Scheme 4b from the loss of aldehyde RHCO from α-ketolactone after ketonization or from the loss of carboxylic acid from the vinyl pyruvic acid which is the hydrogen rearrangement of lactone 54.

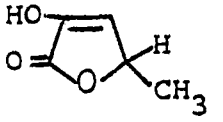
The fragment at m/e 58 may be expected from the simultaneous ejection of two molecules of carbon monoxide (or C_2O_2) or from the sequential loss of carbon monoxide.



A few reports on such fragmentation are found in the literature.[97-101] Letcher in studying mass spectra of pulvic

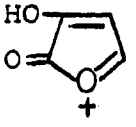
Scheme 5 :

Fragmentation path 1 of lactone 54



54 m/e 114

$-CH_3$



m/e 99

$-CO$

$HO^{+}=C=CHCHO$

m/e 71

$-H$

$O=C=CHCHO$

m/e 70

$O=C=\overset{+}{C}H$

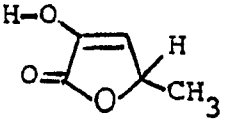
m/e 41

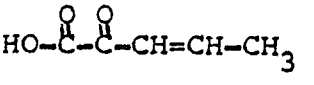
$H-C\equiv O^{+}$

m/e 29

Scheme 6 :

Fragmentation path 2 of lactone 54





k m/e 114

$-CO_2H$

$O=C-CH=CH-CH_3$

1 m/e 69 (100%)

$-CO$

$\overset{+}{C}H=CH-CH_3 \rightleftharpoons CH_2=\overset{+}{C}-CH_3$

m/e 41

$-H_2$

$CH_2=C=CH_2$

$\overset{+}{C}H=C=CH_2$

m/e 39

Scheme 7 : Fragmentation path3 for α-keto-γ-methyl-γ-butyrolactone

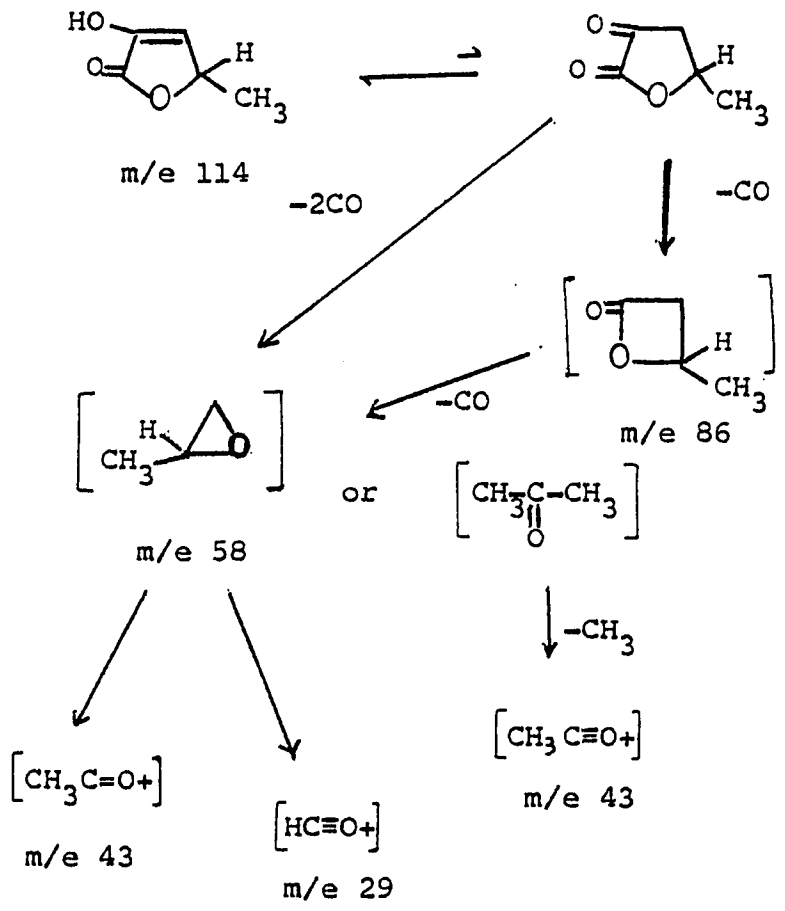


Table 11 : m/e Values and intensities of mass spectra of α-keto-γ-methyl-γ-butyrolactone 54

Mass no.	Intensity(%)	Comments
114	14.8	Molecular ion
99	10.3	$M-CH_3$
71	8.5	$M-CH_3-CO$
70	5.5	$M-CO_2$
69	100.0	$M-CO_2H$, $\overset{+}{O}\equiv C-CH=CHCH_3$
58	56.5	M-2CO
45	4.6	$+CO_2H$
44	7.6	CO_2
43	81.6	$CH_3C\equiv O+$
42	19.8	$CH_2=C=O$
41	42.4	$CH_3CH=\overset{+}{C}H$
39	27.2	$\overset{+}{C}H=C=CH_2$
29	11.2	$H-C\equiv O+$
28	9.2	C=O

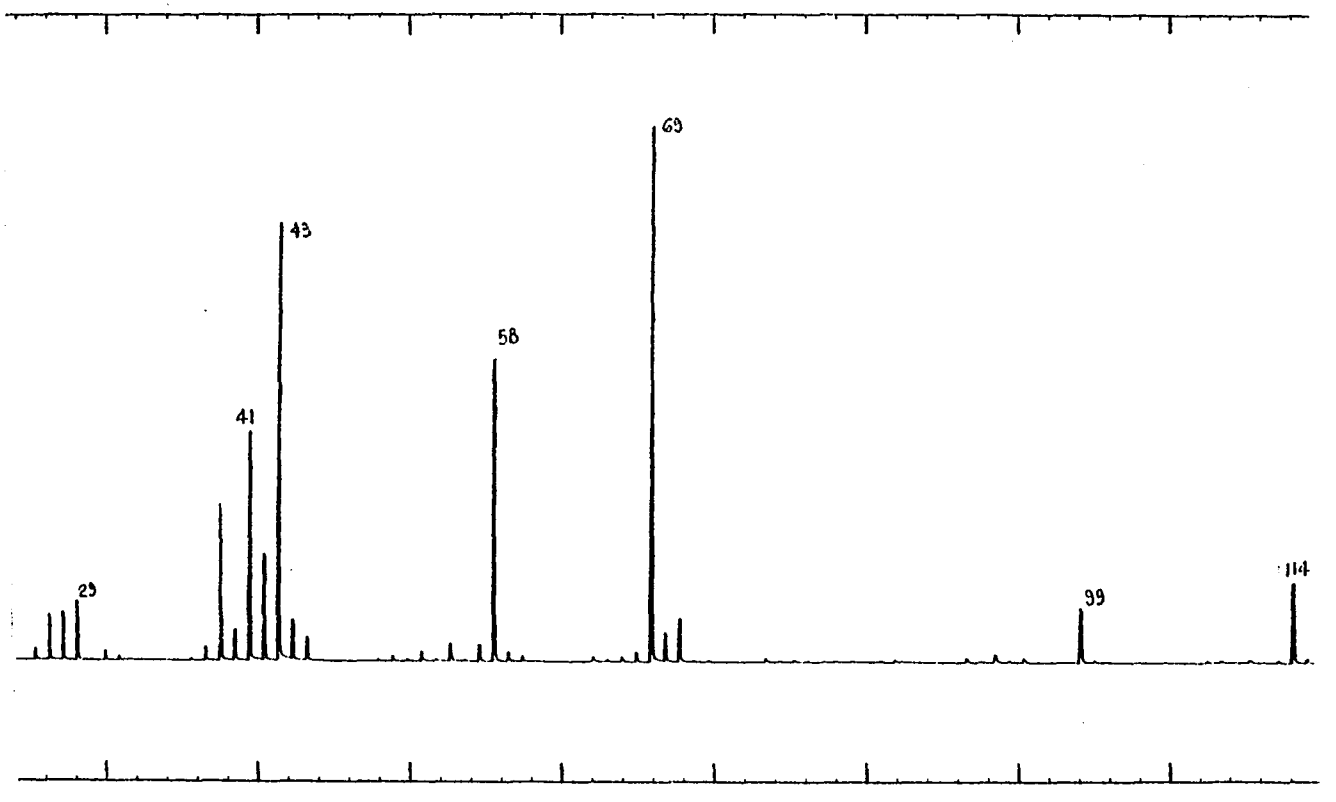


Fig. 8 : Mass spectrum of α-keto-γ-methyl-γ-butyrolactone

acid lactone 83, proposed a cyclic intermediate - α-diketone 83a was formed by rearrangement and a concerted loss of C_2O_2 to 83b was substantiated by the appropriate metastable ion. Since m/e at 86 for the single loss of carbon monoxide from lactone 54 has not been observed in substantial intensity. It is believed that the m/e 58 formed by simultaneous ejection of two molecules of CO (or loss of C_2O_2).

However, in the mass spectra of α-keto-β,β-dimethyl-γ-butyrolactone 53 , the m/e at 84 (with initial loss of carbon dioxide from molecular ion) was not observed. The fragmentation involves the elimination of carbon monoxide, followed by elimination of carbon monoxide, carbon dioxide or formaldehyde as shown in Scheme 8. A rather intense M-1 ion was observed in the spectra of lactone 53 , as a fragment from α-cleavage with the loss of hydrogen to give oxonium ion 53a, which was then followed by elimination of carbon monoxide as shown in Scheme 9.

Scheme 8 : Fragmentation path 1 of α-keto-β,β-dimethyl-γ-butyrolactone 53

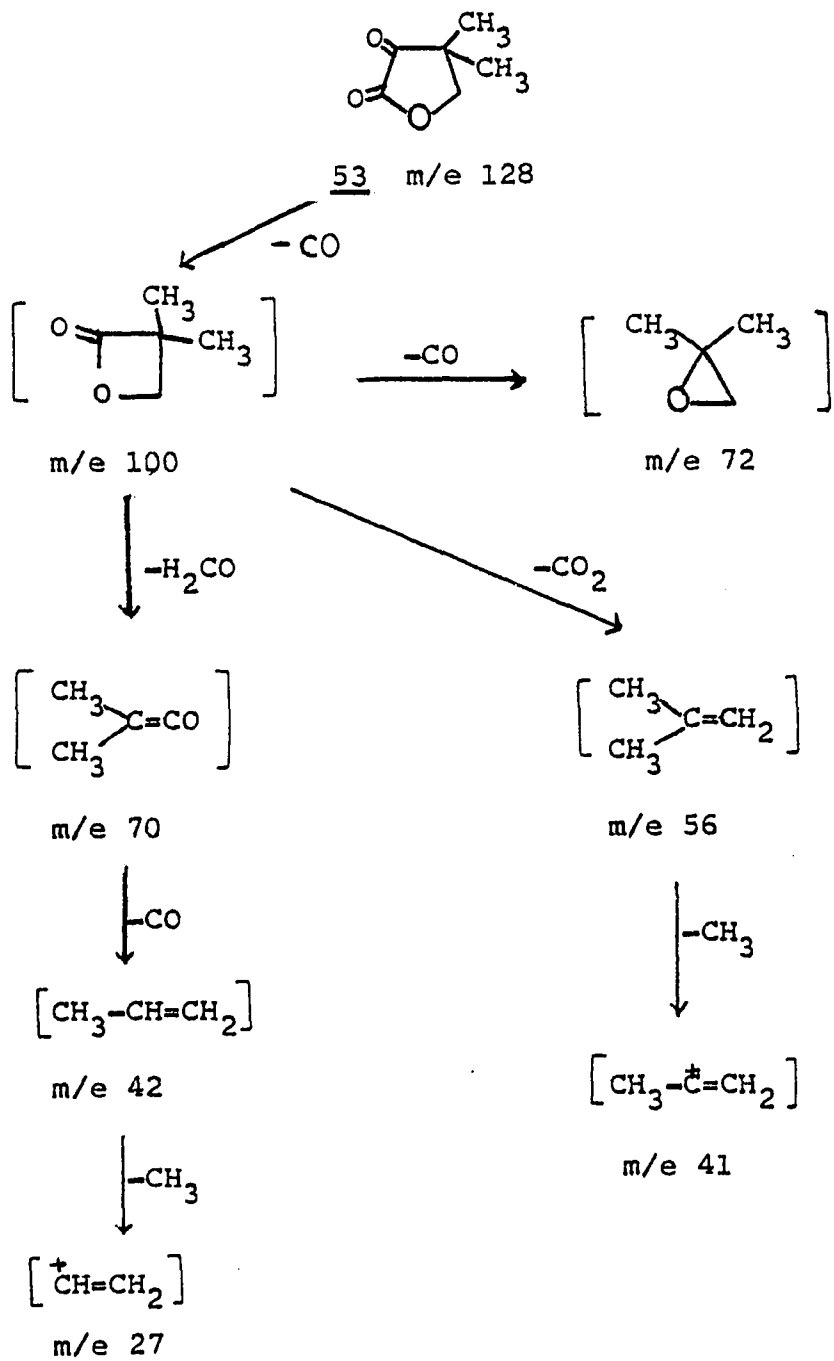


Table 12 : m/e Values and intensities of mass spectra of α-keto-β,β-dimethyl-γ-butyrolactone 53

Mass no.	Intensity(%)	Comments
128	86.4	Molecular ion
127	16.6	M-H
100	9.3	M-CO
99	21.4	M-CHO
70	75.0	$(CH_3)_2C=C=O$
69	30.7	70-H
56	61.4	$(CH_3)C=CH_2$
55	20.7	$CH_2=CH-C=O^+$
42	57.1	$CH_3-CH=CH_2$
41	100.0	$CH_3-\overset{+}{C}=CH_2$
39	38.6	$CH_2=C=CH_2$
29	36.0	$H-C\equiv O^+$
28	30.0	C=O
27	43.2	$CH_2=\overset{+}{C}H$

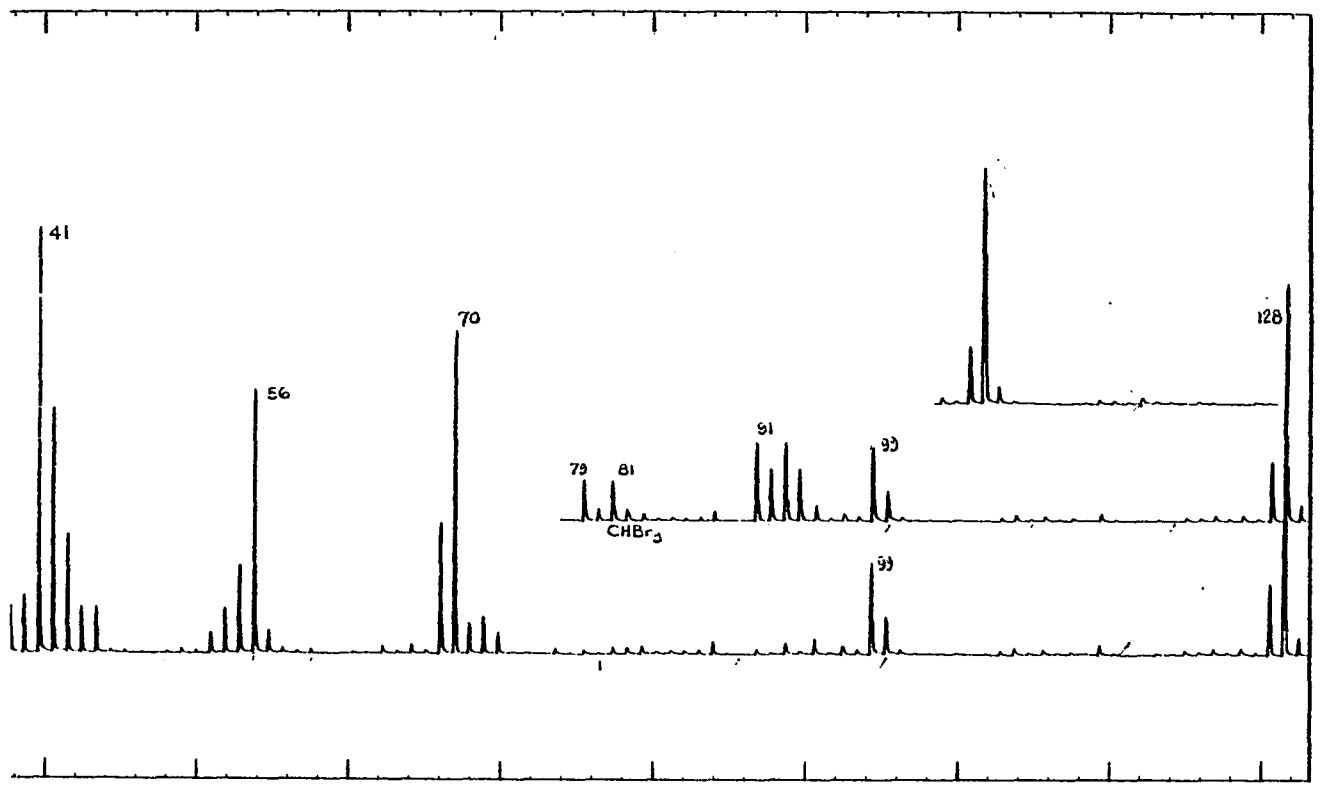
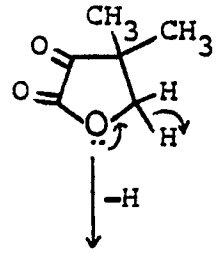
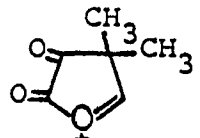


Fig. 9 : Mass spectrum of α-keto-β,β-dimethyl-γ-butyrolactone 53

Scheme 9 : Fragmentation path 2 of α-keto-β,β-dimethyl-γ-butyrolactone 53

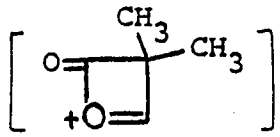


-H



53a m/e 127

-CO



m/e 99

-CO
-H

$[(CH_3)_2C=C=O]$

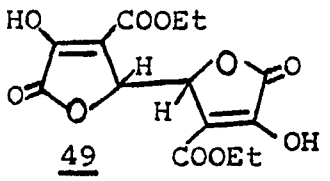
m/e 70

$-CH_3$

$[CH_3\overset{+}{C}=C=O]$

m/e 55

Table 13 : m/e values and intensities of mass spectra of bis-lactone 49



49

Mass no.	Intensity(%)	Comments
342	4.4	Molecular ion
324	1.8	$M-H_2O$
314	3.0	$M-CO$, $M-C_2H_4$
296	11.2	$M-H_2O-CO$
270	9.4	$M-CO_2C_2H_4$, $M-CO-CO_2$
252	5.8	$M-OH-CO_2C_2H_5$, or $M-H_2O-CO-CO_2$
224	28.0	$M-CO_2C_2H_5-OH-CO$
194	15.1	$224-C_2H_5+H$, $224-CO$
179	8.4	$224-OC_2H_5$, or $224-CO_2H$
172	91.4	
143	100.0	M-171-CO
126	68.8	143-OH
115	99.5	143-CO
98	27.5	$143-OC_2H_5$, $143-CO_2H$
97	92.5	98-H
70	49.9	$CH_2=CHCH_2CHO$
69	73.4	$CH_2=CHCH_2C\equiv O^+$
45	68.9	$\overset{+}{C}O_2H$, $\overset{+}{O}C_2H_5$
44	71.2	CO_2
29	59.4	CHO^+
28	46.3	C=O

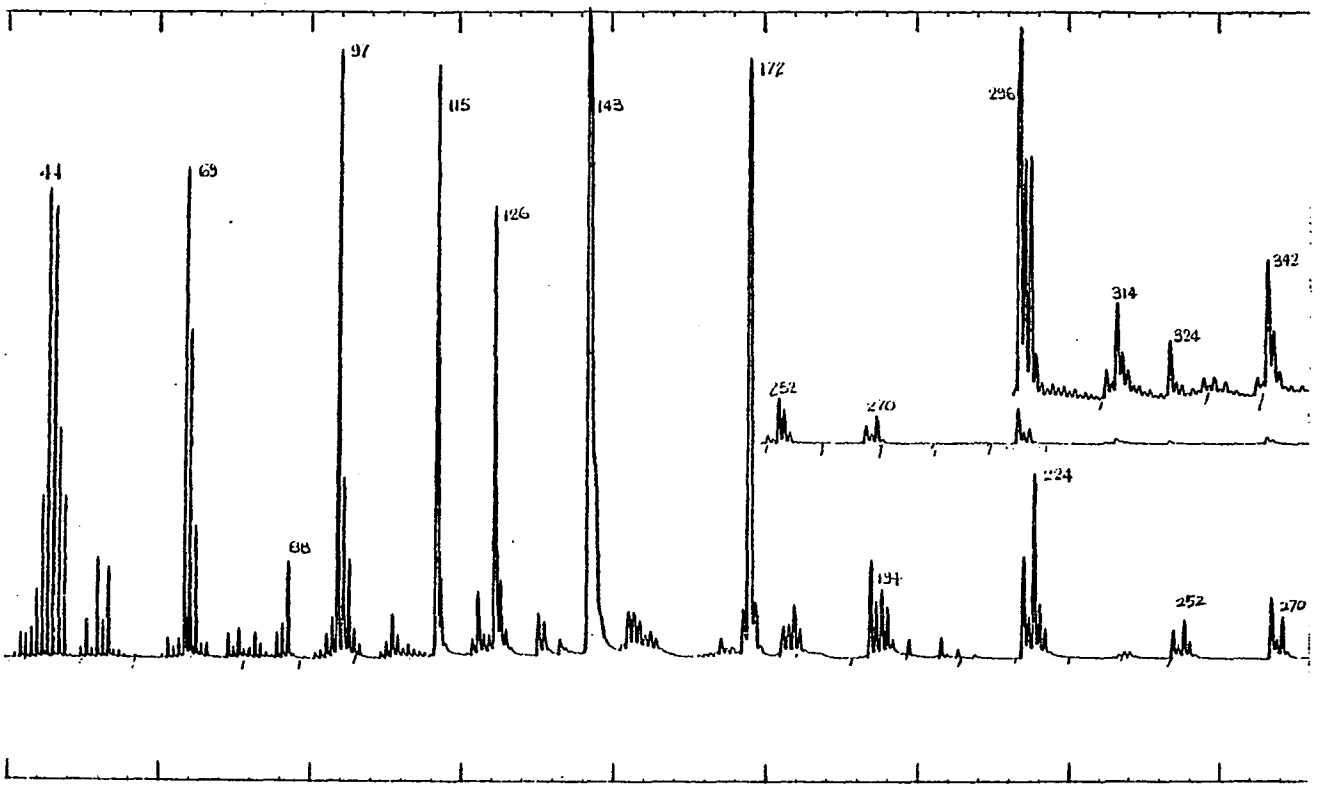


Fig. 10 : Mass spectrum of bis-lactone 49

3.3 Polymerization of α-keto-γ-lactones

No previous work on polymerization of α-keto-γ-lactones has been reported. Infering from their analogs (lactone, ketone, enol), three possible polymerization paths were proposed: (a) Ring-opening polymerization to give polyester, as in the saturated lactones which undergo ring-opening polymerization to polyesters with the use of a variety of cationic and anionic catalysts.[18] (b) Polymerization through reaction of the double bond, as in polymerization of α,β-unsaturated-γ-lactones, the lactone ring was retained, the polymer was generated exclusively through reaction of the double bond.[20,25,26] (c) Polymerization by Aldol-condensation of ketone group as in the condensation of pyruvic acid.[9-11] The polymer obtained from path (b) and path (c) should have same structure with retention of lactone ring.

3.3.1 Polymerization of α-keto-β-carbethoxy-γ-butyrolactone (25)

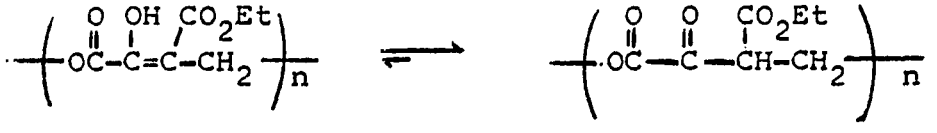
(a) By acid-catalyzed polymerization:

The polymer obtained from acid-catalyzed polymerization of lactone 25 is probable a low molecular weight polymers. The polymer was obtained from extraction with ether, which remove the high molecular weight fraction, sublimation of the compound under high vacuum should also remove the monomer. From the mass spectra of polymer as

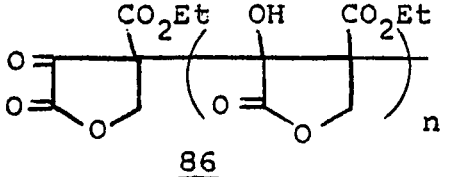
shown in Table 14, the ion peak at m/e 381 reveals a fragment from trimer of lactone 25.

The NMR spectra showed carbethoxyl group at δ 1.0-1.5ppm(m, 3H), δ 3.7-4.8ppm(m, 4H, methylene protons of ester and methylene protons on the ring), enol group at δ 8.13ppm(broad, 1H) with a quartet at δ 3.48ppm(0.4H), singlet at δ 4.94ppm(0.2H) and broad unresolved peaks around δ 1.87-3.2ppm. uv absorption shwoed λ max=248mu (ϵ =1,800) in 95% EtOH. The infrared spectra of the polymer showed OH absorption at 3500cm^{-1}, carbonyl absorption overlapping around 1710 to 1780cm^{-1}.

Lactone 25 seemed to be polymerized in dilute sulfuric acid before the cleavage of β-ketoester. The lactone 25 can undergo (a) ring-opening polymerization to give polymer 84 or (b) polymerization through the carbon-



84 85

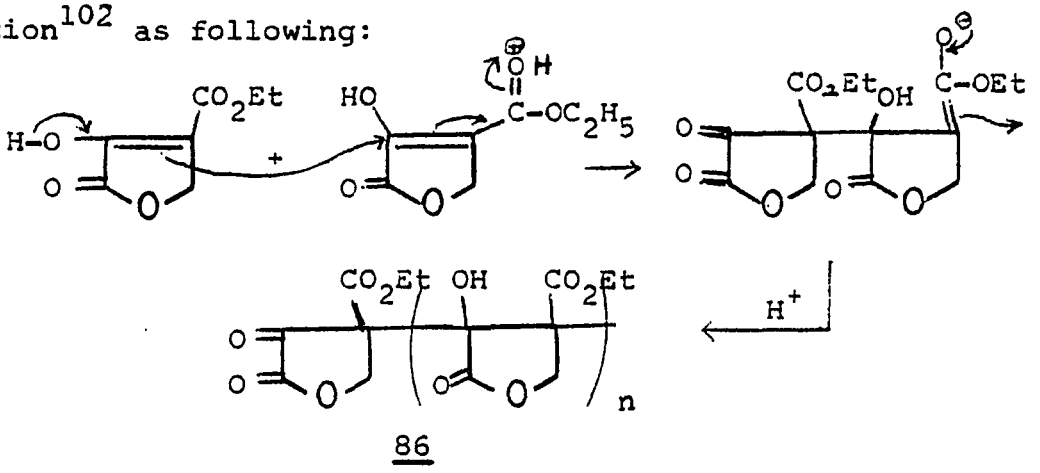


86

carbon double bond to give polymer 86.

For ring-opening polymerization product 84, the noncyclic β-ketoester may exist mostly in keto-form, as

in the acetoacetic ester $CH_3COCH_2CO_2Et$,[81] only 7.5% of the ester exist in enol form. The strong enol peak at δ 8.13ppm indicated the polymer exist mostly in enol-form, also infrared absorption at 1780cm^{-1} indicated a γ-lactone. We therefore prefer the polymer structure 86, which can be formed by acid-catalysed Michael-type addition[102] as following:



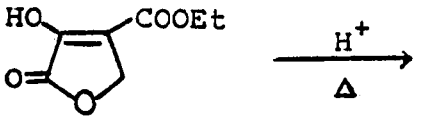
86

Since the reaction is a Michael-type addition, the polymer is believed to be head to tail polymer as in structure 86. The compound can also be stabilized by intra-hydrogen bonding between the hydroxyl group and the carbonyl group of the ester.

The mass spectra of the polymer 86 are summarized in Table 14. The ion peak at m/e 345(dimer+1) can be explained as the fragment 87 from the elimination of CO, CO_2 and $CH_2=\dot{C}CO_2Et$.

Rather high intensity at m/e 155 was observed in the mass spectra of polymer 86 , which is due to the loss

Table 14 : m/e Values and fragments of polymer 86



Mass no.	Intensity(%)	Comments
381	0.3	Trimer-$CO_2C_2H_5$, -OC_2H_5-OH
345	1.3	Trimer-171, dimer+H
328	1.5	345-OH
301	5.6	345-CO_2
299	1.5	Dimer-OC_2H_5
283	0.6	345-OC_2H_5-OH, or dimer-CO_2-OH
282	0.6	Dimer-CO_2-OH-H
273	6.7	Dimer-$CO_2C_2H_5$, or 345-CO-CO_2
255	2.0	Dimer-CO-CO_2-OH
227	18.8	345-$CO_2C_2H_5$-OH-CO
199	3.1	345-2$CO_2C_2H_5$, or 345-$CO_2C_2H_5$-CO-CO_2-H
181	5.5	345-2$CO_2C_2H_5$-OH-H
172	25.0	monomer
155	12.0	monomer-OH
144	3.0	172-CO
128	38.5	172-CO_2
127	100.0	172-CO_2H, or 172-OC_2H_5
115	10.4	172-CO-H_2CO
100	45.8	172-CO-CO_2
99	95.0	172-$CO_2C_2H_5$
72	41.7	172-CO_2Et-OH
69	40.6	C_3HO_2
55	70.3	$H_2C{=}CH{-}C{\equiv}O^+$

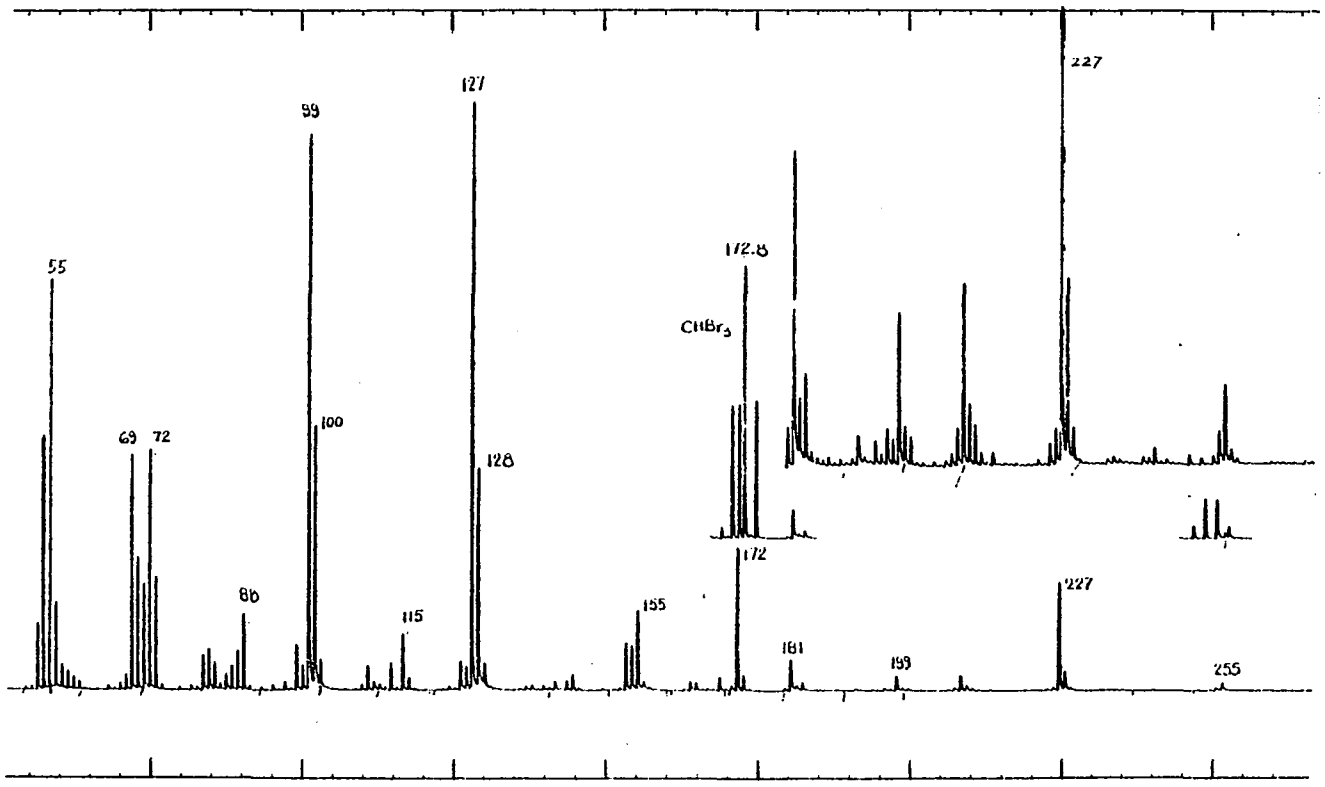


Fig. 11 : Mass spectrum of polymer 86 of α-keto-β-carbethoxy-γ-butyrolactone

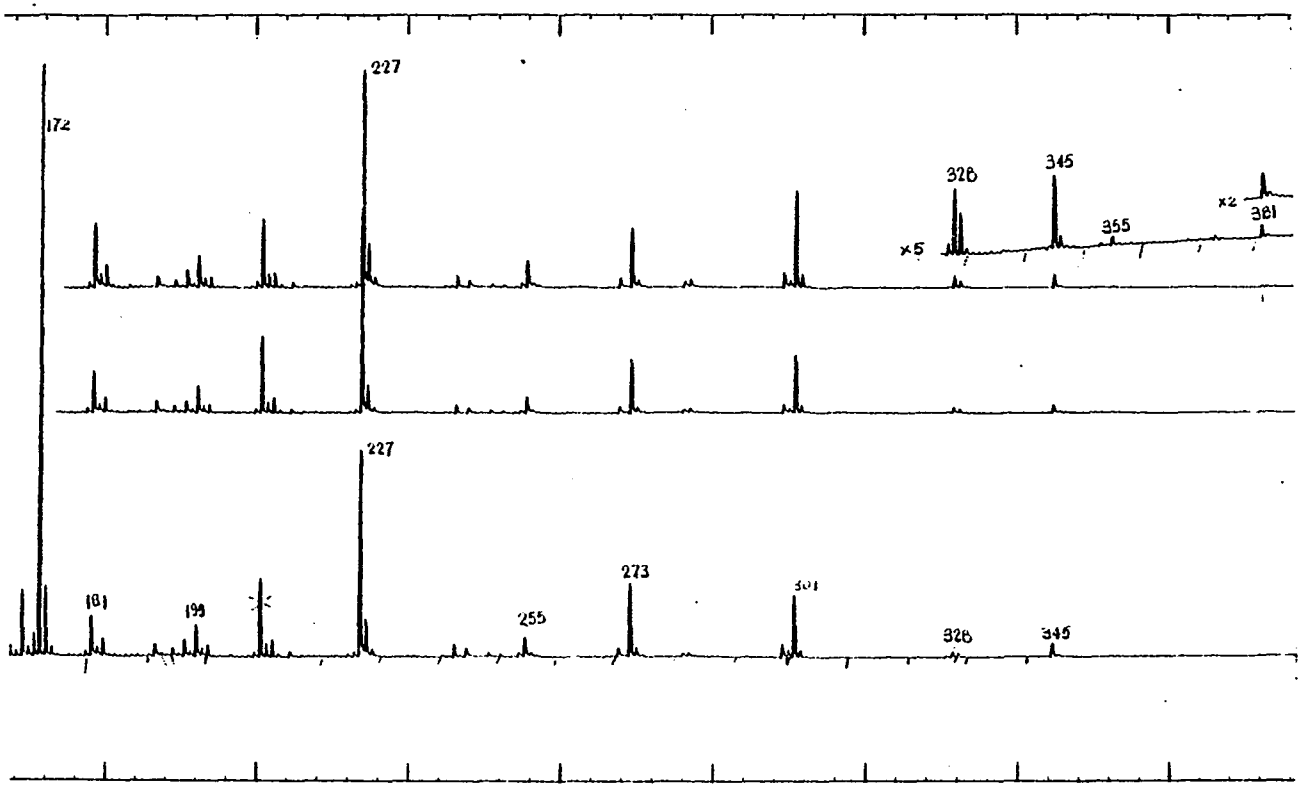
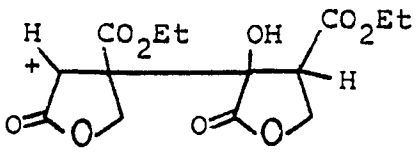


Fig. 11a : Mass spectrum of polymer (86) of α-keto-β-carbethoxy-γ-butyrolactone

of OH from 1 unit of lactone. The m/e at 155 is not detectable in mass spectra of the monomer lactone 25 due to fragmentation of monomer take place after ketonization. Also, the loss of OH from carbon-carbon double bond is less facile.

As observed in NMR spectra of polymer 86 , there are some unresolved peaks around δ 1.87-3.2ppm, which may be due to the polymer that was formed after decomposition of the monomer.



87

(b) By pyrolysis : The thermal polymerization should give polymer structure free from the contamination by catalysts. However, the mass spectra of thermal polymer of lactone 25 , showed a more complex spectra than that of the acid-catalysed polymer 86 . As shown in Table 15, in addition to the ion peaks (381, 299, 282, 255, 227, 199, 181, 172 etc.) observed in acid-catalysed polymer 86 , the mass spectra of thermal polymer also exhibits a lot of other numbers. Since gas evolution was observed in pyrolysis of lactone 25, it is believed that the polymerization is also accompanying by decomposition of the

lactone 25 . Schinz reported[28] that upon pyrolysis of α-keto-β-carbethoxy-γ-isopropyl-γ-butyrolactone at 290-310°C gave $(Me)_2CHCH=CHCO_2Et$ in 30% yield. Upon pyrolysis, lactone 25 may also undergo decarboxylation and decarbonylation to give ethyl acrylate which is then polymerized. The fragmentation of this poly-(ethyl acrylate) may be explained as followed:

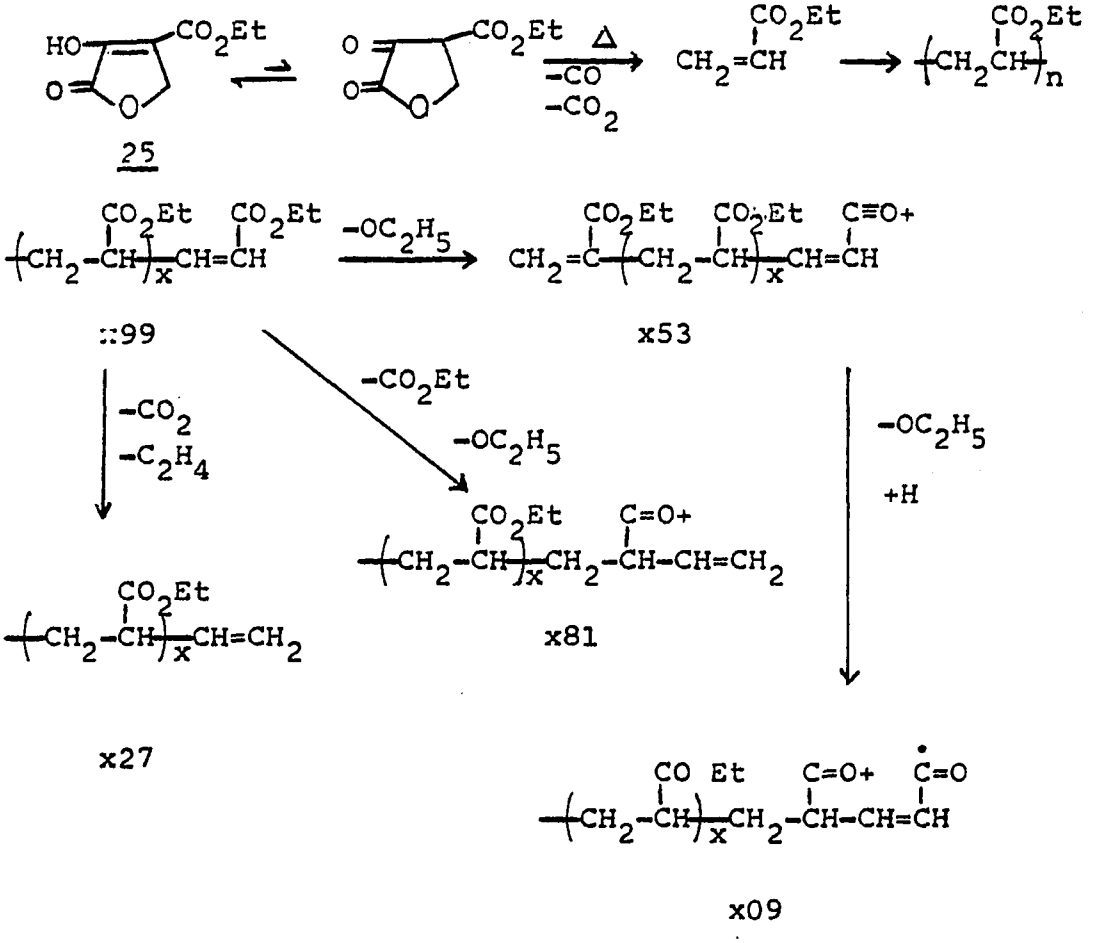


Table 14a: m/e Values and relative intensities of abundant ions of heated polymer of α-keto-β-carbethoxy-γ-butyrolactone

Mass no.	Intensity(%)	Mass no.	Intensity(%)
453	0.1	207	0.9
451	0.1	*199	2.5
438	0.1	198	1.3
409	0.1	*181	4.1
382	0.1	180	3.3
*381	0.1	173	1.6
354	0.1	*172	10.2
353	0.1	*144	2.2
337	0.1	128	31.4
325	0.1	127	1.9
309	0.1	115	5.1
*299	0.1	100	42.3
*282	0.2	99	100.0
281	0.8	88	11.7
272	0.3	72	36.5
263	0.3	69	48.2
*255	0.6	55	52.6
254	0.6	54	67.9
235	0.9	45	59.8
*227	2.6	43	28.5
226	1.1	31	37.9
209	0.7	29	71.5

* Same fragment had also been observed in acid-catalyzed polymerization of lactone 20

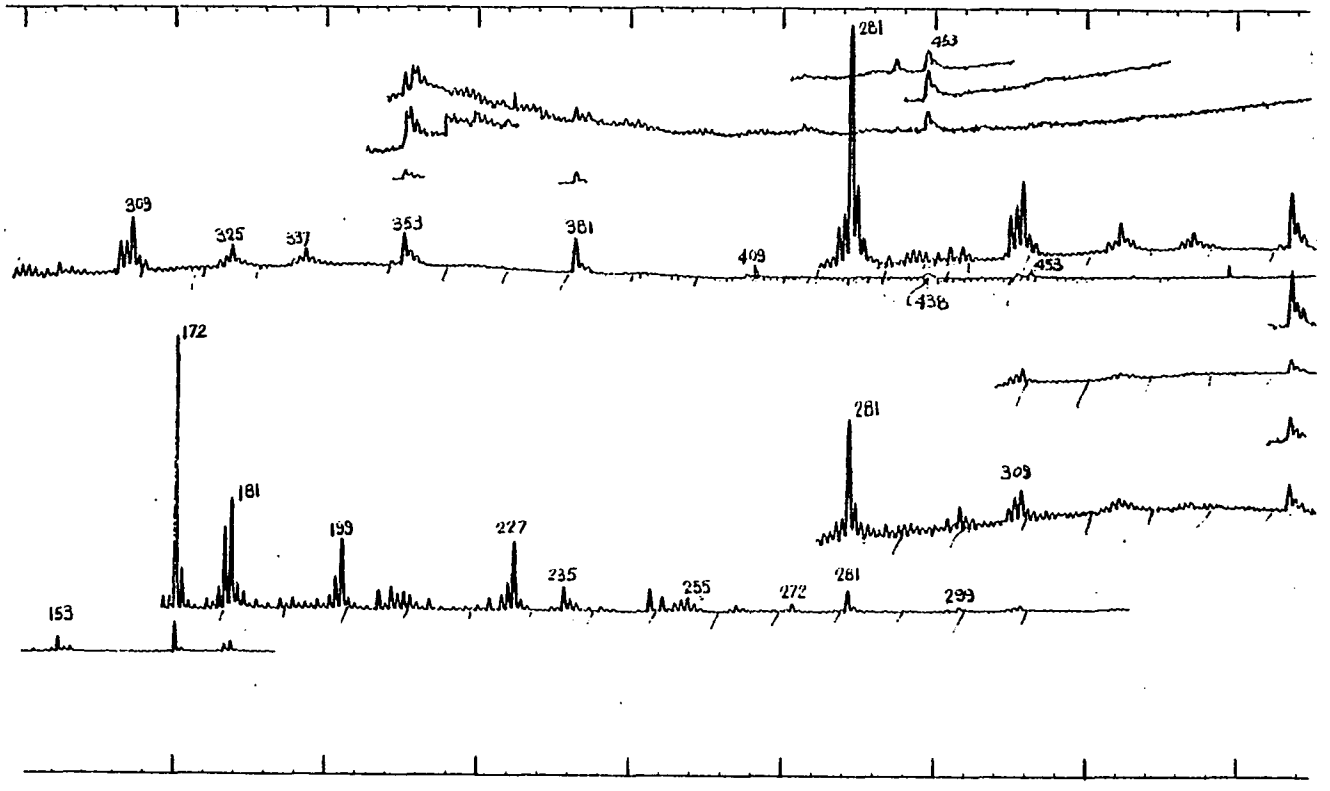


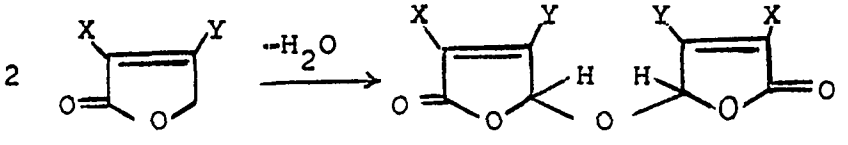
Fig. 11b : Mass spectrum of heated polymer of α-keto-β-carbethoxy-γ-butyrolactone

3.3.2 Polymerization of α-keto-γ-methyl-γ-butyrolactone (54)

The α-keto-γ-methyl-γ-butyrolactone has similar functional groups as the α-keto-β-carbethoxy-γ-butyrolactone 25 , except the free β-position. Without a carbethoxyl group on β-position, the lactone 54 should be more reactive. The study of polymerization of this lactone 54 should also be less complicated without a carbethoxyl group on β-position.

(a) Anionic polymerization: A white solid was obtained when α-keto-γ-methyl-γ-butyrolactone 54 was added into a stirring suspension of sodium methoxide in ether. The mass spectra of the product with highest ion peak at m/e 210, and a neutralization equivalent of 211.1 leads to an assumption of dehydrated dimer(a dimer less 1 mole of water).

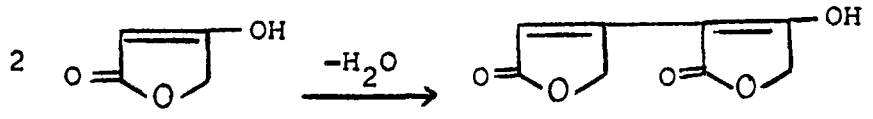
The dehydrated dimer bis-(3,4-dihalogeno-5-oxo-2,5-dihydrofuran-2-yl) ether 88 had been reported by Kovac and coworkers[105] from the dehydration of the



88

appropriate 3,4-disubstituted-5-hydroxyfuran-2-(5H)-ones.

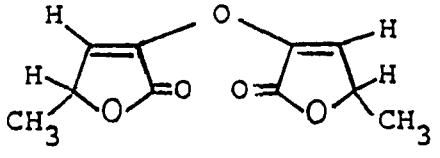
Anhydrotetronic acid 89 was also obtained by Wolff and Schwabe[106] by heating an aqueous solution of tetronic acid. The structure of anyhydrous acid $C_8H_6O_5$ was later



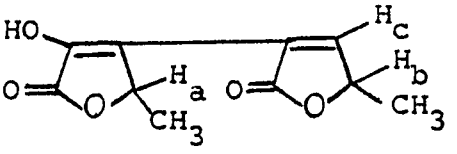
89

confirmed by Marrian and coworkers[107] as 89 .

The dimer of lactone 54 was first assumed to be the dehydrated compound 90 or 91[97]. The infrared absorption



90



91

at 1760cm^{-1} suggested retention of γ-lactone ring, and hydroxyl group at 3320cm^{-1} and 3450cm^{-1} indicated an enol structure 91 . The weak acidic character(pk_a=7.60) also suggested that the compound is an enol. However, NMR spectra at δ 4.7-5.1ppm(m, 1H, assigned to be Hb), δ 5.23ppm(q, 1H, assigned to be Ha), δ 3.12ppm(q, 1H) seemed to be a rather upfield chemical shift for vinyl proton Hc, and the triplet at δ 1.5ppm(6H) is a kind of peculiar, there is no compatible methylene group(according

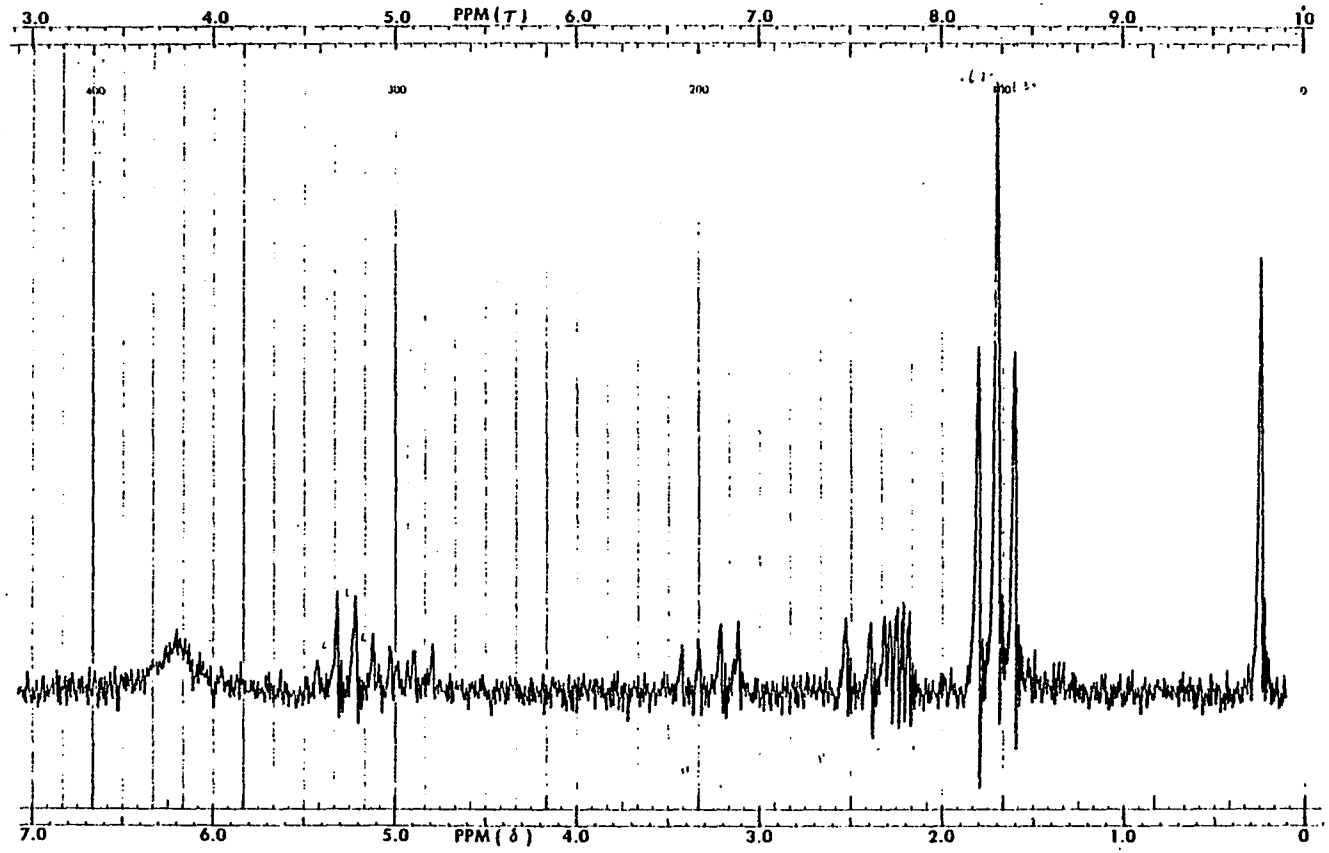
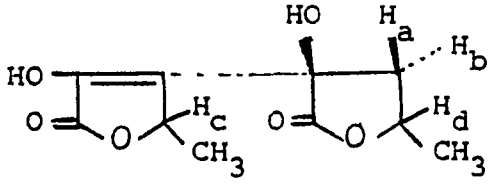


Fig. 12 : PMR spectrum of dimer of α-keto-γ-methyl-γ-butyrolactone in acetone-d_6 solution at 60MHz

to integration of peak area) which can be coupled with these protons. So, it is assumed that the two doublet for the methyl groups happend to have the difference of chemical shift equal to their coupling constant. (similar overlapping had also been observed in the NMR spectra of lactone 46 as in Fig. 12a,the triplet of the methyl protons of ester at δ1.60ppm was overlapped with the doublet of the methyl protons on the ring at δ1.78ppm). But, no proton can be assigned to the absorption around δ2.1-2.20ppm.

The carbon hydrogen analysis showed that the compound has composition of $C_5H_6O_3$. The compound may be a dimer without dehydration. The proton absorption around δ 2.1-2.20ppm was overlapped with the absorption of acetone-d_6. The NMR spectra of the dimer in D_2O indicated that the proton absorption at δ 2.15ppm was a AMX tpye quartet(1H, J_1=10Hz, J_2=14Hz). Careful examination of the NMR spectra lead to a dimer structure 92. The triplet at



92

δ 1.5ppm(6H, J= 6Hz) was assigned to be the overlapping of two doublet of methyl protons, the doublet of methyl

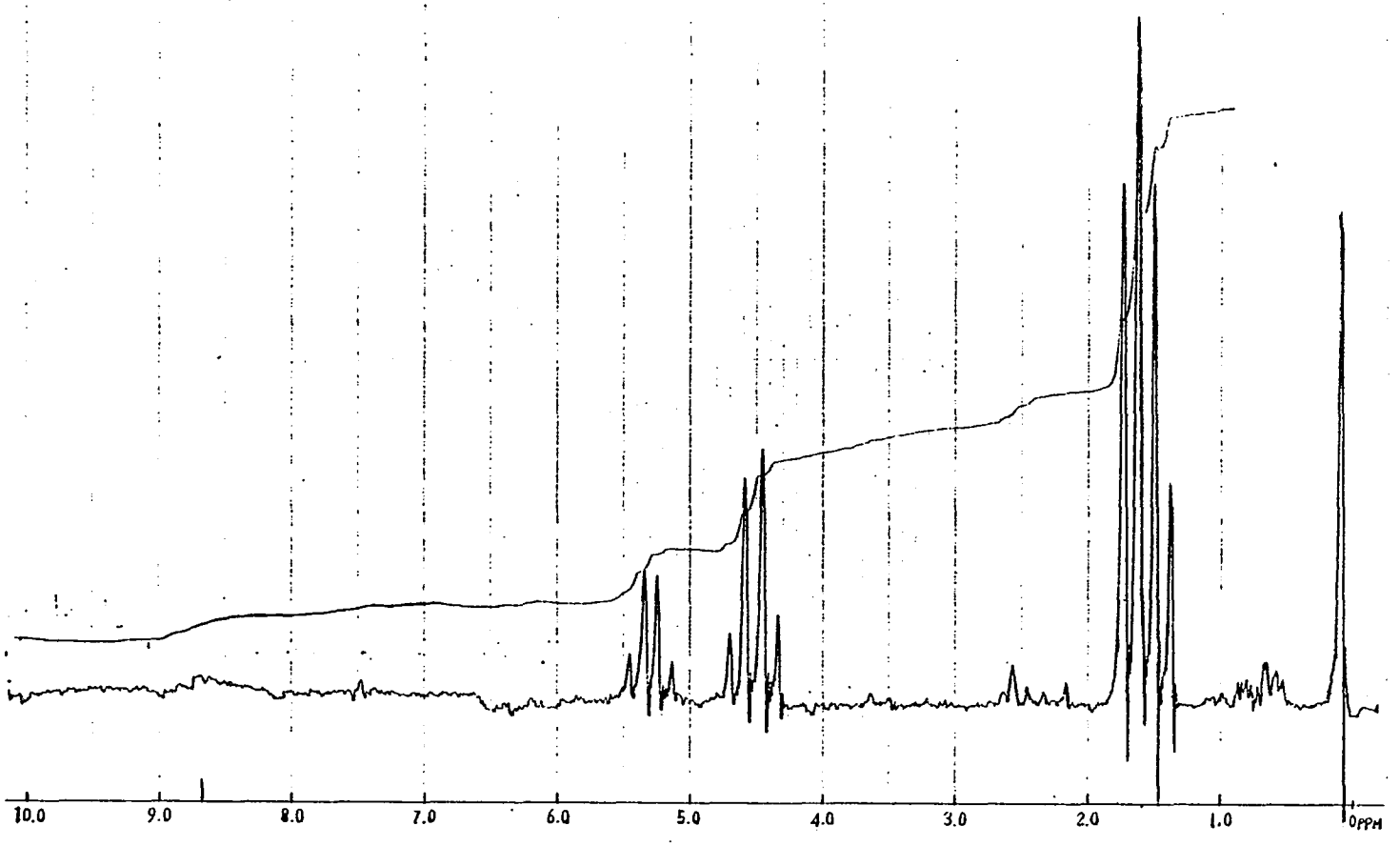


Fig. 12a : PMR spectrum of lactone 46 in choloroform-d at 60MHz

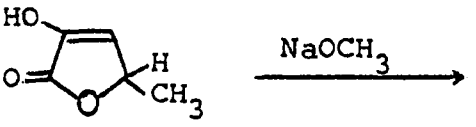
protons which coupled with Hd at δ 1.44ppm(3H, J=6Hz) and the doublet of methyl protons at δ 1.54ppm(3H, J=6Hz) which coupled with Hc, with the neighboring double bond, a downfield chemical shift is expected.

The AMX type quartet at δ 2.15ppm(1H, J_1=10Hz, J_2=-14Hz) is assigned to be Hb, another AMX type quartet at δ 3.12ppm(1H, J_1=6Hz, J_2=-14Hz) is assigned to be Ha, for the proton is closer to the hydroxyl group, a downfield chemical shift is expected. The geminal coupling constant (J=-14Hz) for Ha and Hb also consistent with the bond angle about 109°. A complex absorption at δ 4.7-5.1 ppm(m, 1H) is expected for Hd, which coupled with Ha, Hb and the methyl protons on the ring. The Hc absorption exhibits a clear quartet at δ 5.23ppm(1H, J=6Hz) for the only possible coupling with methyl protons. The enol and hydroxyl protons are absorbed at δ 6.05ppm(broad, 2H).

The absence of molecular ion at m/e 228 in the mass spectra of the dimer 92 may be due to the quick dehydration upon heating(a weak ion peak at m/e 228 has been observed in the mass spectra of heated dimer of lactone 54,which will be discussed in later section). The mass spectra of dimer 92 are summarized in Table 15, which is also consistent with the structure assigned.

(b) By pyrolysis: The lactone 54 was heated at 115-125°C for 24 hours, evolution of gas was observed and

Table 15 : m/e Values and relative intensities (%) of dimer of α-keto-γ-methyl-γ-butyrolactone



Mass no.	Intensity(%)	Comments
210	76.6	Dimer-H_2O
195	6.0	210-CH_3
192	18.0	210-H_2O
184	4.4	Dimer-CO_2
165	50.1	210-OH-CO
164	60.7	210-H_2O-CO
149	8.2	210-OH-CO_2
147	11.9	210-H_2O-CO_2H
139	34.8	210-CO-CH_3CO
121	19.6	139-H_2O, or 165-CO_2
114	8.3	Monomer
111	25.1	139-CO
97	14.2	210-monomer-H
95	33.0	139-CO_2
93	46.8	210-CH_3CHO-CO-CO_2H
77	22.4	121-CO_2
69	57.2	CH_3CH=CHC≡O+
43	100.0	CH_3CO

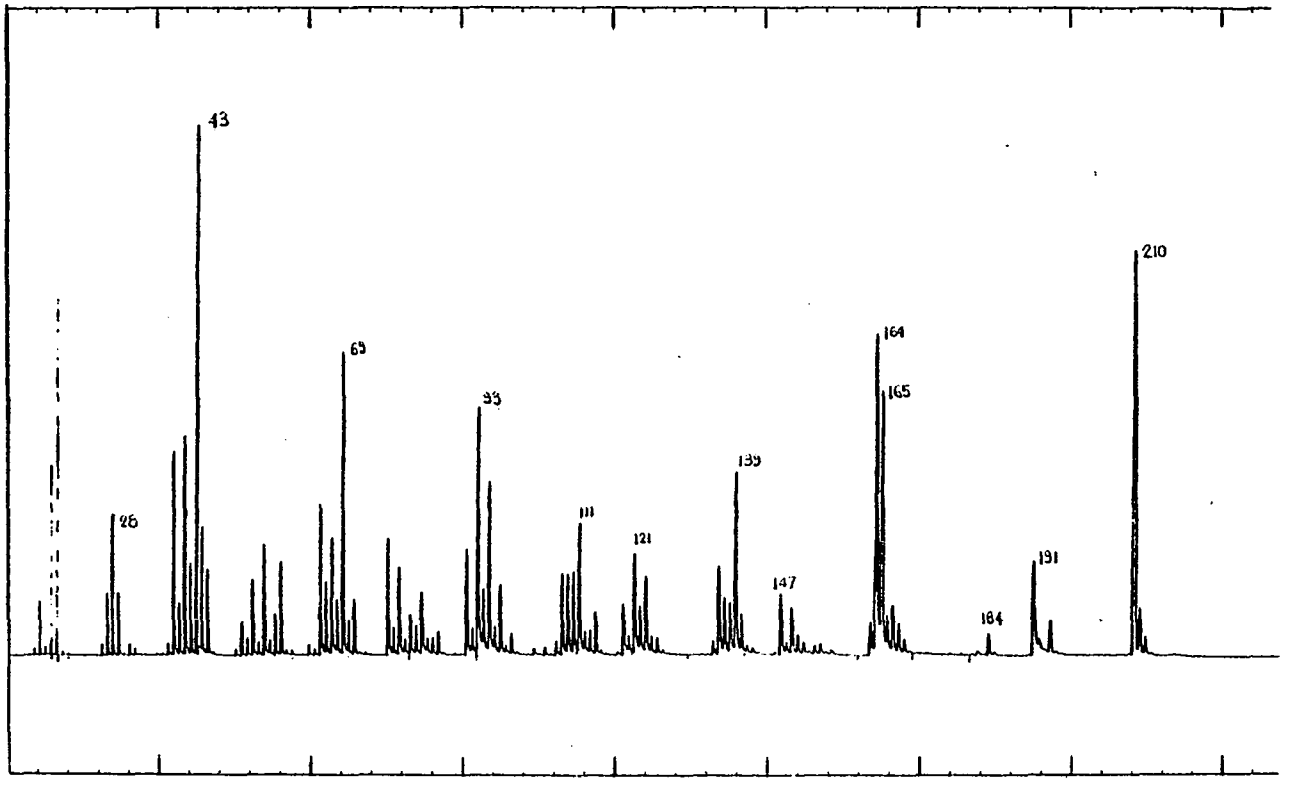
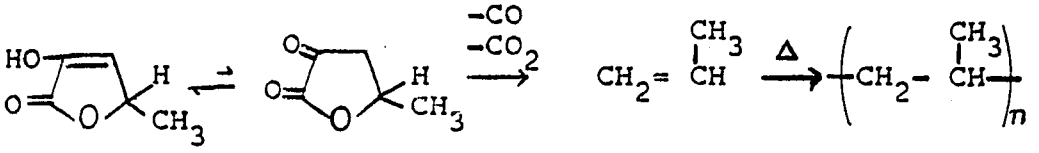


Fig. 13 : Mass spectrum of dimer of α-keto-γ-methyl-γ-butyrolactone

a yellowish tacky solid was obtained. The NMR of compound (Fig. 14) showed saturated hydrocarbon around δ 1.35-1.85ppm, the compound may be a polymer of propene which is formed by decarboxylation and decarbonylation of lactone 54.



The mass spectra obtained after background of polypropylene(Fig. 15) was summarized in Table 16. The mass spectra with m/e below 210 are similar to the of dimer 92(Fig. 16). The higher ion peak at m/e 324, 308, 280, 260, 236 indicated a trimer has also been formed in the thermal polymerization. The weak ion peak at m/e 228, confirmed that the dimer is not dehydrated.

(c) By acid-catalysed polymerization: Attempt in degradation of lactone 46 to lactone 54 with 10% sulfuric acid, give 50% of degradation product-lactone 54 , as shown in NMR spectra(Fig. 17). However, when the product was passed through silica gel column, completely different compounds were obtained as in comparison of the NMR spectrum. Two fractions were obtained after column chromatography. Fraction 1 showed saturated hydrocarbon around δ0.9-1.6ppm, which may be due to the decomposition

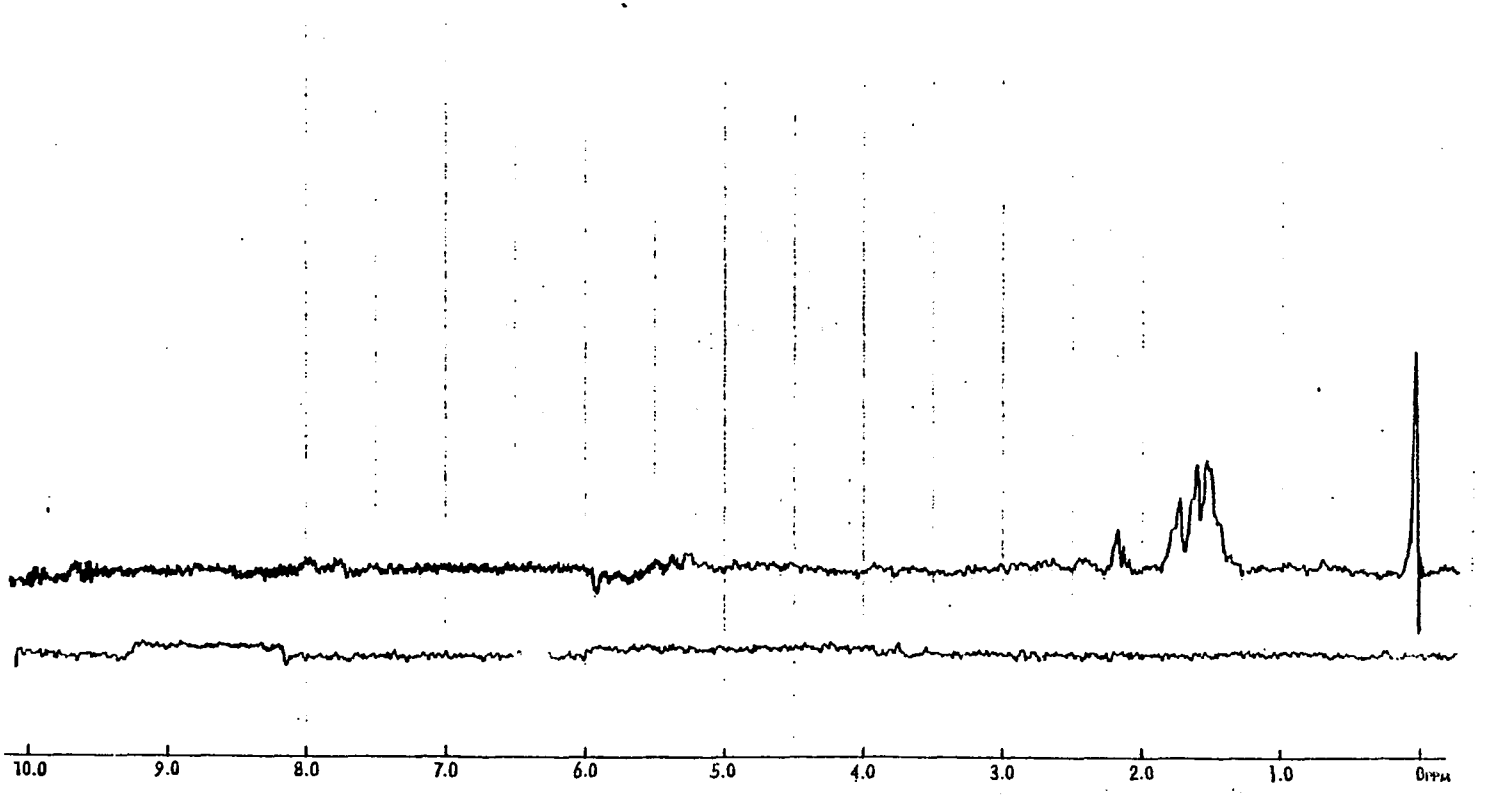


Fig. 14 : PMR spectrum of pyrolysis products of lactone 54 in Acetone-d_6 at 60MHz

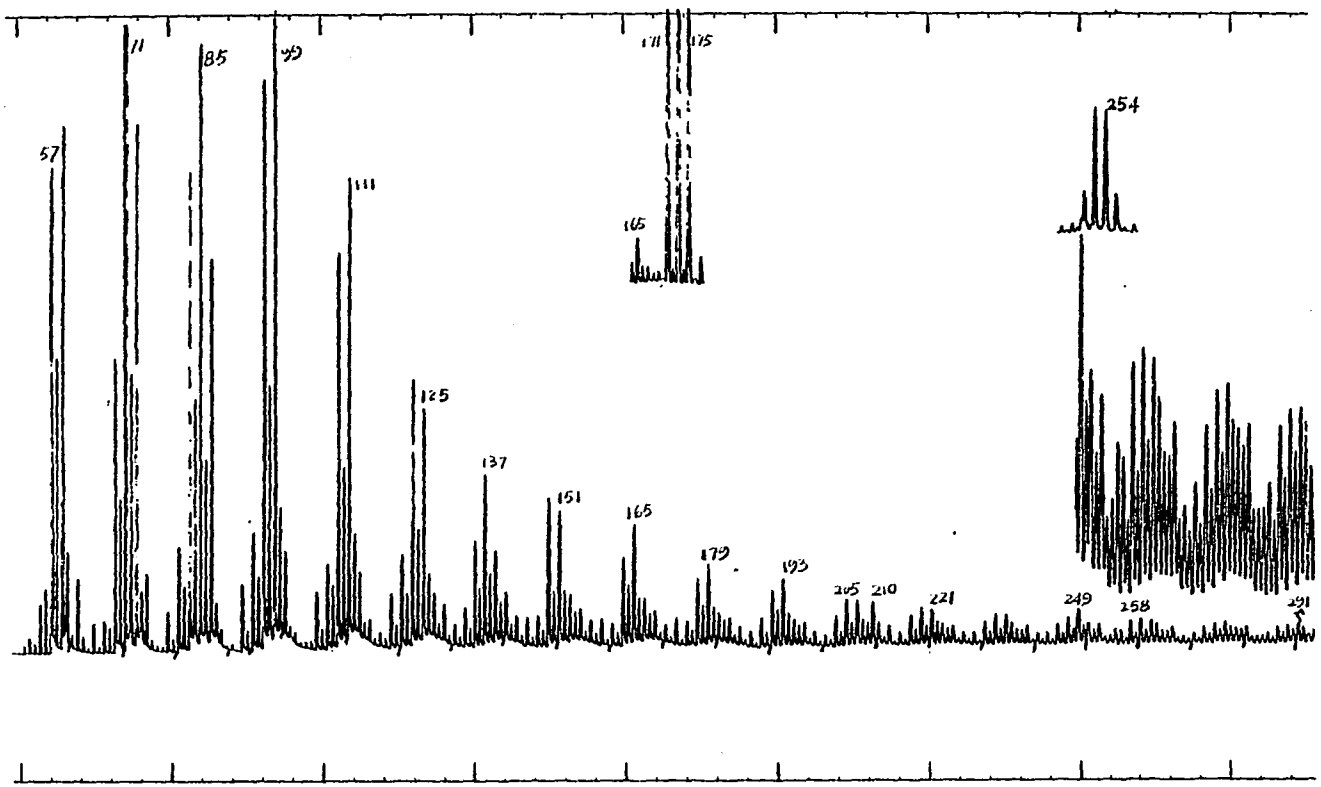


Fig. 15 : Mass spectrum of poly-propylene

Table 16 : m/e Values and relative intensities of abundant ions of pyrolysis products of α-keto-γ-methyl-γ-butyrolactone

Mass no.	Intensity(%)	Comments
324	0.2	Trimer-H_2O
308	0.2	Trimer-2OH
280	0.3	Trimer-H_2O-CO_2
262	0.3	Trimer-$2H_2O$-CO_2
236	1.6	Trimer-H_2O-$2CO_2$
228	.4	Dimer
218	1.2	236-H_2O
210	60.6	Dimer-H_2O
195	5.6	210-CH_3
192	12.9	210-H_2O
165	31.3	210-OH-CO
164	37.6	210-H_2O-CO
149	5.2	210-OH-CO_2
147	5.6	210-H_2O-CO_2H
139	11.5	210-CO-CH_3CO
121	9.4	139-H_2O, or 165-CO_2
114	20.0	Monomer
111	9.4	139-CO
95	34.1	139-CO_2
93	20.0	210-CH_3CHO-CO-CO_2H
69	100.0	$CH_3CH=CHC=O^+$
43	100.0	CH_3CO

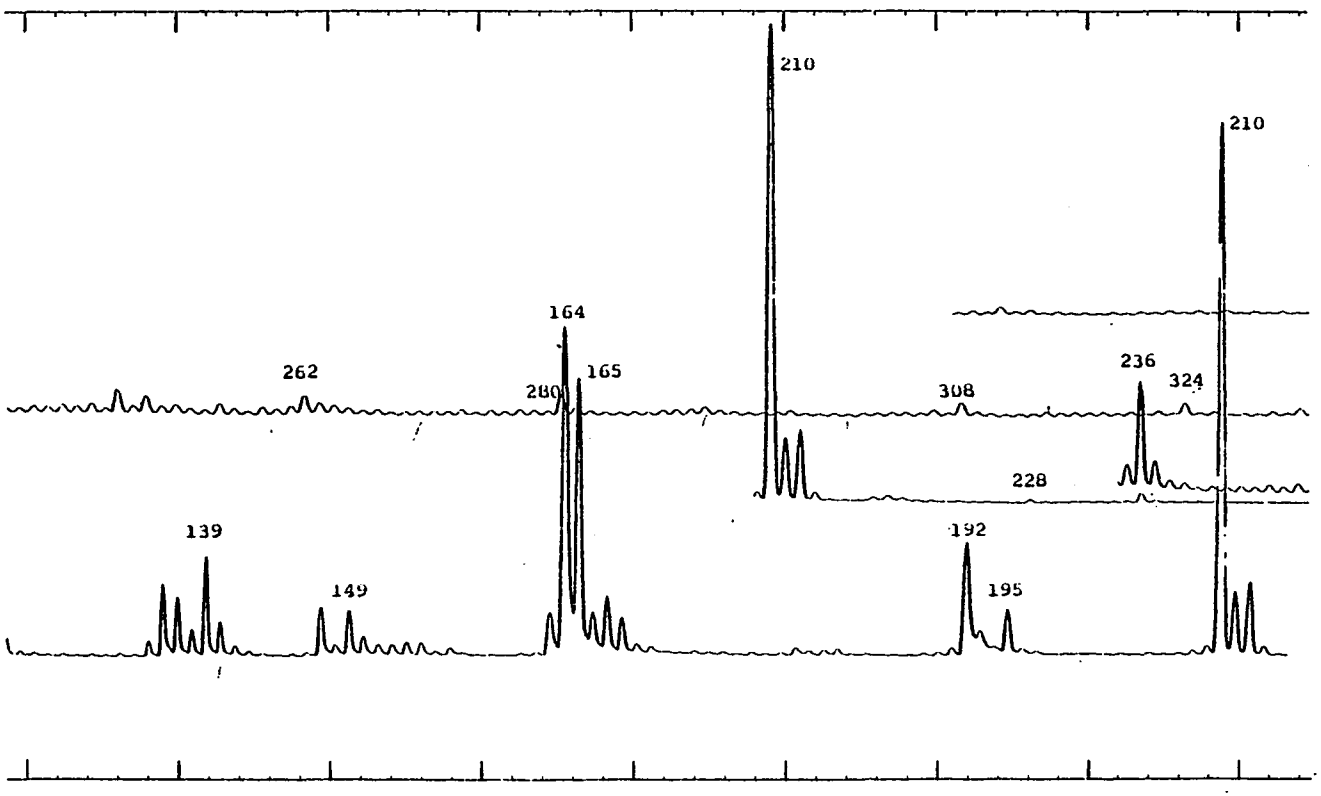


Fig.16 : Mass spectrum of pyrolysis products of α-keto-γ-methyl-γ-butyrolactone

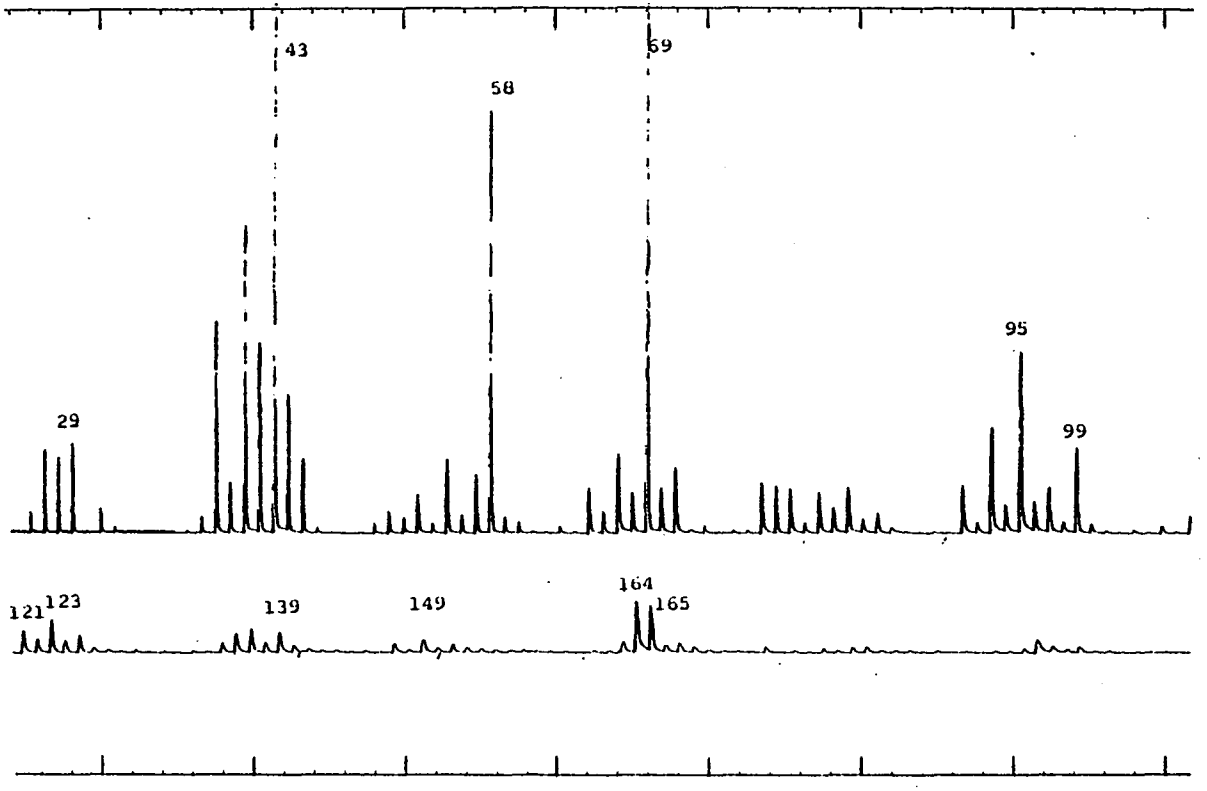


Fig.16a : Mass spectrum of pyrolysis products of α-keto-γ-methyl-γ-butyrolactone

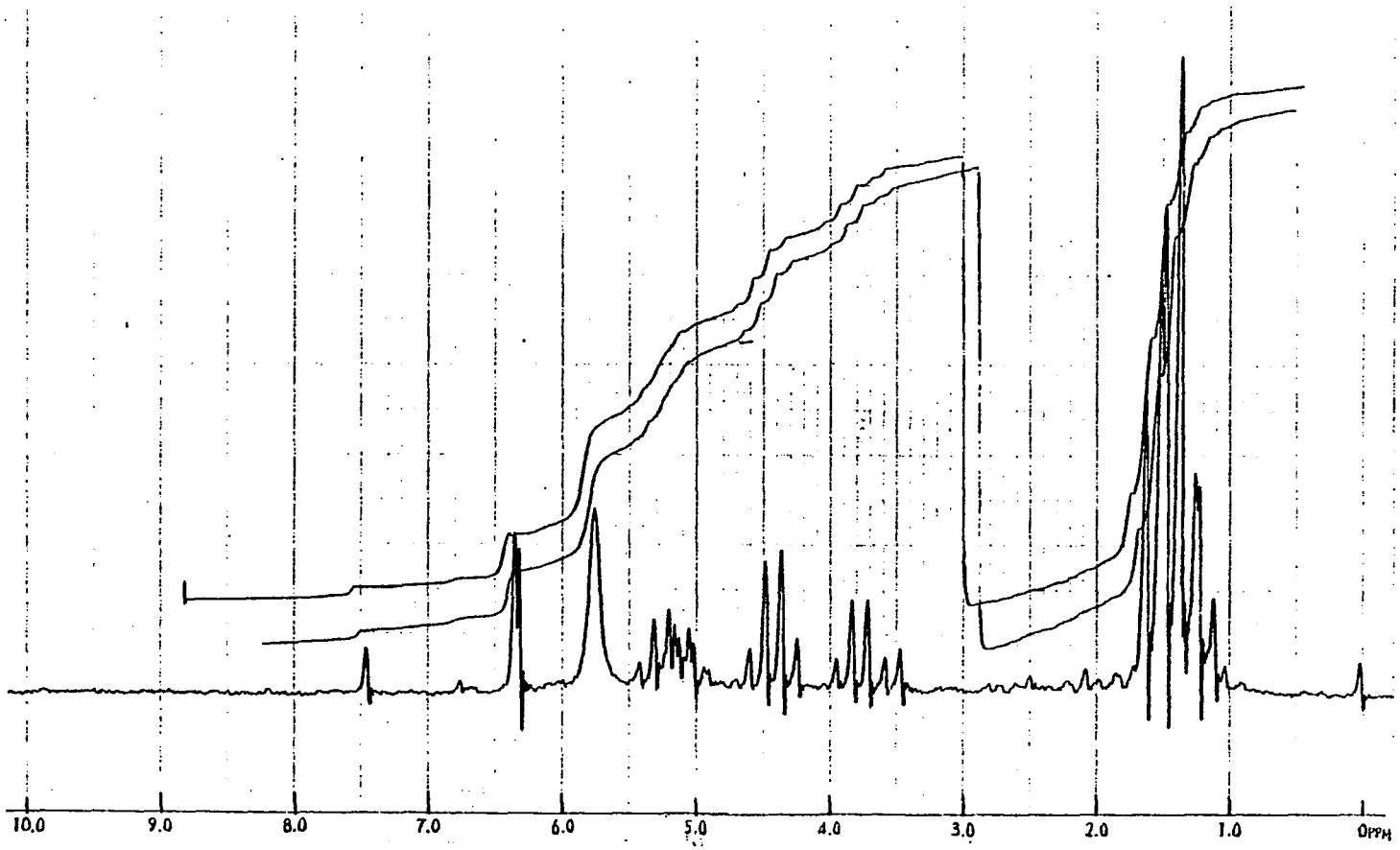
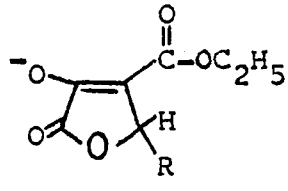


Fig. 17 : PMR spectrum of hydrolysis products of lactone 46 in acetone-d_6 at 60MHz

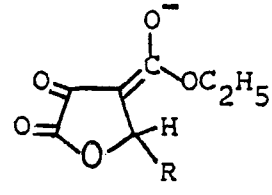
of lactone 54 . Fraction 2 showed identical NMR spectra to that of dimer 92 obtained from base-catalysed reaction of lactone 54 . As the acetaldehyde has been reported to be polymerized to high molecular weight polymers by using γ-alumina or high purity silica.[106-108] It is believed that the dimerization of lactone 54 was catalysed by silica gel in presence of acid.

3.3.3 Attempted polymerization of some α-keto-γ-butyrolactones

(a) α-Keto-γ-lactones with β-carbethoxyl group: Attempt on polymerization of lactones 25, 49, 50 with sodium ethoxide as catalyst was unsuccessful. The starting material was recovered in all cases. Failure of polymerization may be due to the formation of anion 93 which can be



93



94

stabilized by resonance distribution of the charge between the oxygen atoms of hydroxyl group and of the ester carbonyl group as in 93 and 94 .

(b) α-Keto-β,β-dimethyl-γ-butyrolactone 53 : The lactone 53 can not be polymerized either by pyrolysis or base-catalysed reaction. The starting material were recovered in both cases. The lactone 53 with two substituents on β-position can only exist in keto-form. The failure of polymerization may be due to the non-enolizable ketone group, which is less reactive than the enol group.

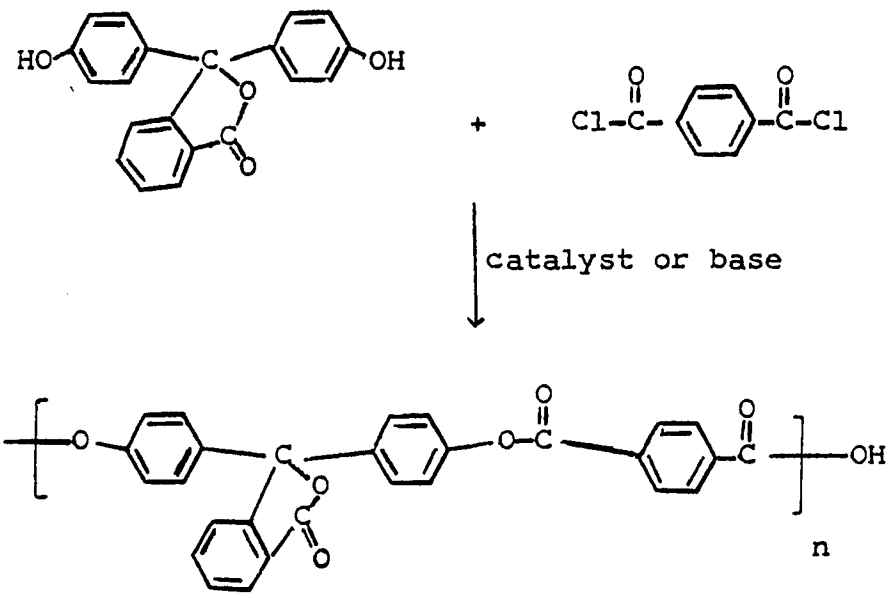
(c) α-Keto-γ-(n-propyl)-γ-butyrolactone 56 : The lactone 56 can not be dimerized under the same condition as in dimerization of α-keto-γ-methyl-γ-butyrolactone 54. Failure in obtaining anhydrotetronic

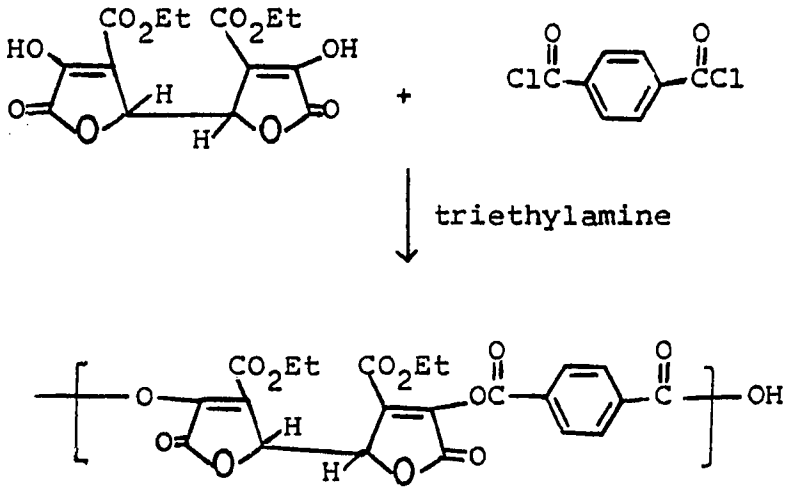
acid from γ-substituted tetronic acid was also reported by Marrian and co-workers,[105] and it had been suggested that steric factors may govern the course of reaction. As in lactone 56, the n-propyl group is a bulky group compare to methyl group. If the dimer of lactone 56 has the similar structure as dimer 92, steric interaction between n-propyl group and H_a or H_b would be expected. If the dimer of lactone 56 has the structure of dehydrated dimer 91, steric hindrance in the transition state 92 still prevent the dimerization. Failure of dimerization of lactone 56 can be attributed to the bulky n-propyl group which destabilized the dimer.

3.3.4 Copolymerization of bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)] (49)

Reaction of phenolphthalein 95 with terephthaloyl chloride in presence of triethylamine gives poly-(phenolphthalein terephthalate).[109] Since the enol has similar reactivity as phenol, reaction of dienol with terephthaloyl chloride should also give the polyester. Reaction of bis-lactone 49 with terephthaloyl chloride indeed give solid polymers, which are insoluble in chloroform, acetone, or alcohol. On the basis of the IR spectrum (C=O stretching overlapped around 1680-1800cm^{-1} and no carboxylic or enolic OH band) and the analytical data (composition $C_{11}H_8O_6$), this polymer is assigned the structure 96 . From the reactivity of enol group, the bis-lactone 49, 50 is

expected to form copolymer with diisocyanates, dicarboxylic acids or their derivatives, e.g. dichlorides of dicarboxylic acids.



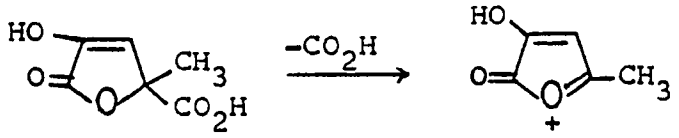


96

3.4 Reactions of pyruvic acid

The pyruvic acid obtained by distillation is reasonably pure. Mass spectra (Table 17) indicated no dimer in detectable amount. Pyruvic acid fragments by cleavage of the carbon-carbon bond between the two carbonyl groups, producing the base peak of the spectrum (m/e 43). The same m/e 43 fragment has also been observed in methyl pyruvate and pyruvaldehyde.

The mass spectra of α-keto-γ-valerolactocarbonic acid 3 - dimer of pyruvic acid (Table 18), showed similar fragmentation as that of α-keto-γ-methyl-γ-butyrolactone, except the base peak at m/e 113, which is formed by initial loss of γ-substituent ($-CO_2H$).



3 m/e 113 (100%)

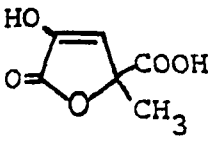
Methylation of parapyruvic acid 5 - trimer of pyruvic acid, did not give the crystalline product as reported by Schellenberger.[12] The mass spectra of the product (Table 19) indicated a mixture of methylated and unmethylated hydroxyl pyran 100, 100a.

no polymer other than reported ones has been separated upon reaction catalyzed by sodium hydroxide or by lead acetate.

Table 17 : m/e Values and relative intensities of abundant ions of pyruvic acid, methyl pyruvate, and pyruvaldehyde

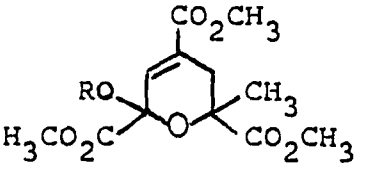
	$CH_3COCO\ H$		$CH_3COCO_2CH_3$		CH_3COCHO	
Mass no.	%	ions	%	ions	%	ions
102			9.8	M.		
88	5.0	M				
72					5.9	M
60	1.5	M−CO				
59			4.5	CO_2CH_3		
56	4.0	OCCO				
45	44.8	CO_2H				
44	18.5	CO_2				
43	100.0	CH_3CO	100.0	CH_3CO	100.0	CH_3CO
42	35.5	$CH_2{=}C{=}O$				
41	10.0	$H\overset{+}{C}{=}C{=}O$				
31			1.2	OCH_3		
29	29.5	$HC{\equiv}O^+$	7.8	$HC{\equiv}O^+$	47.5	$HC{\equiv}O^+$
28	15.0	C=O	3.3	CO	27.5	CO

Table 18 : m/e Values and relative intensities of abundant ions of α-ketovalerolactocarbonic acid 3

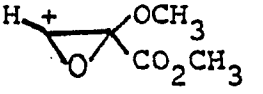
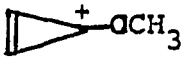


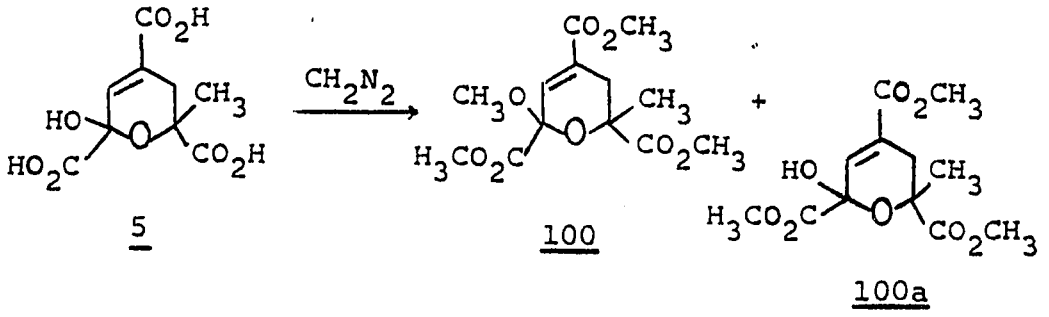
Mass no.	Intensity(%)	Comments
158	1.7	Molecular ion
130	2.2	M-CO
114	11.1	$M-CO_2$
113	100.0	$M-CO_2H$
102	3.7	M-2CO
99	4.4	$M-CH_3-CO_2$
86	21.7	$M-CO-CO_2$
85	34.7	$M-CO-CO_2H$
70	38.9	$M-CHO-CH_3CO$
69	18.9	$M-CO-CO_2H$
56	14.4	O=C=C=O
45	66.1	CO_2H
44	67.2	CO_2
43	19.4	CH_3CO
41	15.6	$M-CO-CO_2-CO_2H$
40	30.6	$CH_2=C=CH_2$
29	24.4	HC≡O+
28	10.7	CO

Table 19 : m/e Values and relative intensities of abundant ions of trimethyl-2-methoxy-6-methyl-3-dihydro-pyran-2,4,6-tricarboxylate



(R = H or CH_3)

Mass no.	Intensity(%)	Comments
302	-	Molecular ion
288	-	Molecular ion
271	6.9	302-OCH_3, or 288-OH
243	99.6	302-CO_2CH_3
229	11.5	288-CO_2CH_3
211	86.6	302-CO_2CH_3-OCH_3-H
201	25.3	288-CO_2CH_3-CO
187	19.8	288-CO_2CH_3-CH_2CO
184	18.4	288-CO_2CH_3-CO-OH
183	96.8	302-CO_2CH_3-CO_2CH_3-H
169	93.5	302-$CH_3COCO_2CH_3$-OCH_3
151	23.0	302-2CO_2CH_3-OCH_3-2H
141	35.9	302-2CO_2CH_3-CH_3CO
131	90.8	
127	100.0	302-2CO_2CH_3-CH_3CO-CH_2
115	24.4	$\overset{+}{C}H$=C(OCH_3)CO_2CH_3
99	22.6	$\overset{+}{C}H$=C(CH_3)CO_2CH_3
89	74.7	$\overset{+}{C}H_2CO_2CH_3$
69	29.5	
59	84.8	$\overset{+}{C}O_2CH_3$



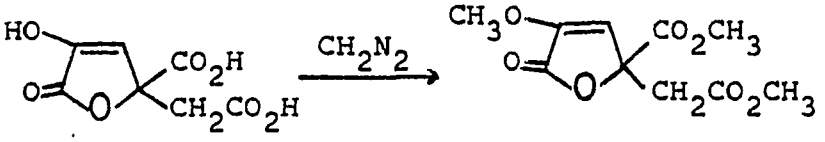
5 100 100a

3.5 Reactions of citroylformic acid lactone (11)

Lactone of citroylformic acid was prepared from self-condensation of oxalacetic acid by following Wiley and Kim's procedure.[16]

3.5.1 Methylation of citroylformic acid lactone

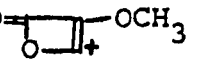
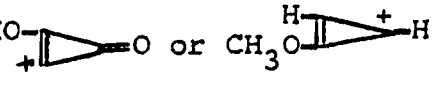
Methylation of lactone of citroylformic acid 11 with diazomethane, gives a colorless solid. The molecular weight (mass spectra) was found to be 244.0556 ($C_{10}H_{12}O_7$, theory 244.0581) with reference to the C_6F_9 peak at 242.9856 amu. Both hydroxyl groups of acid and enol are methylated.



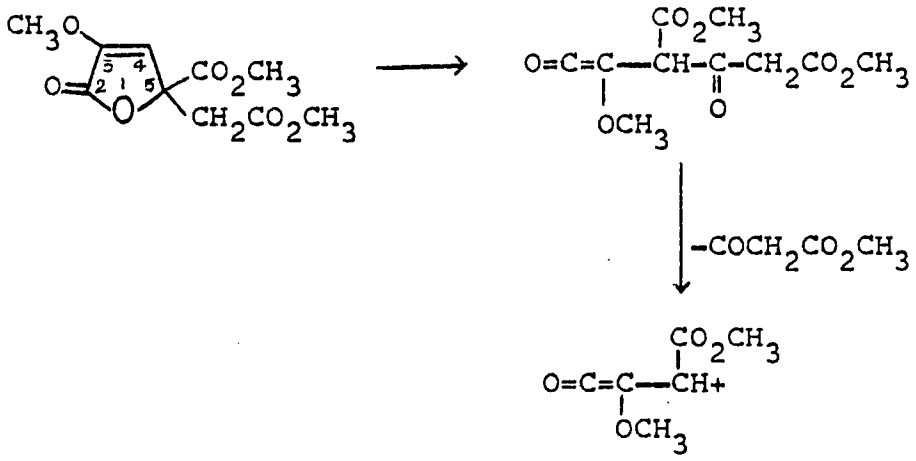
97

The fragmentation of methyl ether 97 (Table 20) confirms Schemes 2, 3 for fragmentation of α-keto-γ-lactones. Since the enol group is methylated, the initial

Table 20 : m/e Values and relative intensities of abundant ions of Trimethyl ester of citroylformic acid lactone 97

Mass no.	Intensity(%)	Comments
244	3.7	Molecular ion
229	2.3	$M-CH_3$
213	6.5	$M-OCH_3$
212	22.7	$M-OCH_3-H$
200	19.6	$M-CO_2$
199	9.3	$M-CO_2-H$
185	99.1	$M-CO_2CH_3$
184	28.5	$M-CO_2CH_3-H$
171	11.2	$M-CH_2CO_2CH_3$
157	22.9	$M-CO-CO_2CH_3$
143	100.0	$M-CH_2CO_2CH_3-CO$
141	45.8	$M-CO_2CH_3-CO_2$
127	100.0	$M-CH_2CO_2CH_3-CO_2$
115	62.6	$M-CH_2CO_2CH_3-2CO$
101	61.7	$\dot{O}\equiv CCH_2CO_2CH_3$
99	33.6	
69	65.9	
59	72.0	$\dot{C}O_2CH_3$
29	41.1	$HC\equiv O+$
28	43.9	CO

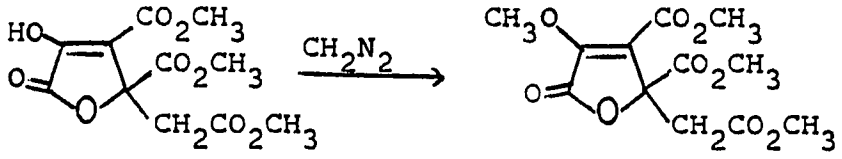
loss of carbon monoxide has not been observed (m/e 216), this confirms the proposed mechanism that carbon monoxide is eliminated from α-keto group, not from the carbonyl group of the lactone. The ion peaks at m/e 157 (loss of CO_2CH_3, CO), 143 (loss of $-CH_2CO_2CH_3$, CO) indicated that there is a migration of the γ-substituents, such rearrangements can be explained by using the principles extracted from the work of Friedman and Long.[94] Thus, the lactone ring is ruptured at C_2-O_1 bond (acyl oxygen cleavage) with simultaneous migration of a substituent at C_5 to C_4



Scheme 10 : Rearrangement path for ether 97

(Scheme 10). In this study, the methyl ether of trimethyl oxalocitrolactone ester 98 is also prepared by methylation of trimethyl oxalacitrolactone ester. The mass spectra of methyl ether 98 showed that with m/e below 200, the ether 98 has same fragments (199, 185, 157, 143, 141, 127, 115)

as that of the ether 97.



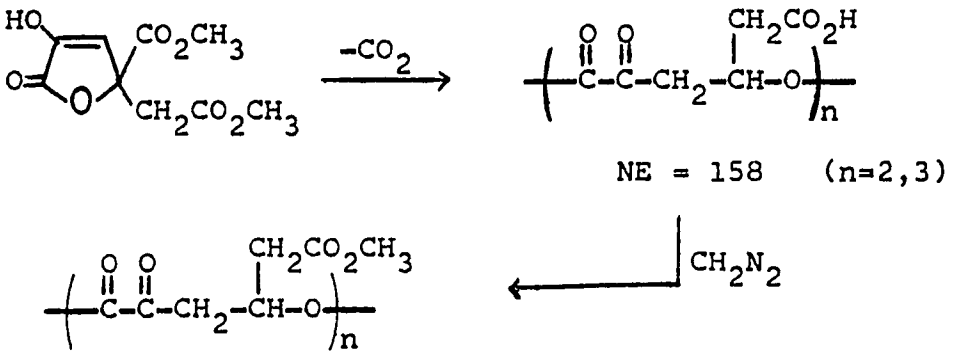
98

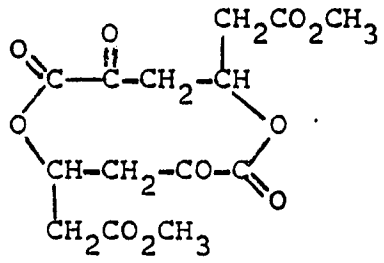
The NMR (acetone-d_6, TMS) of methyl ether 97 exhibits an AB quartet for the methylene protons at δ2.95ppm (H_a of AB quartet, 1H, J=17Hz), δ3.40ppm (H_b of AB quartet, 1H, J=17Hz), three sets of singlet for the methyl protons at δ3.69ppm (s, 3H, $-OCH_3$), δ3.77ppm (s, 3H, $-CH_2CO_2\underline{CH_3}$), δ3.85ppm (s, 3H, $-CO_2\underline{CH_3}$), and another singlet for vinyl proton at δ6.15ppm (s, 1H). This is also consistent with structure 97 for the trimethyl ester of citroylformic acid lactone 11.

3.5.2 Polymerization of citroylformic acid lactone (11)

Polymerization of citroylformic acid lactone was studied at different (1) reaction temperatures- by varying the refluxing solvent (2) reaction times (3) concentration of lactone 11 in solution. The degree of polymerization was based on neutralization equivalent which was obtained from titration of the resulting acids. The reaction data is listed in Table 1. The neutralization equivalent is increased by increasing concentration, reaction time, and

reaction temperature. With mixture of nitromethane and acetone as refluxing solvent, the neutralization equivalent seems to increase to the greater extent. Methylation of one of the reaction product (N.E.=86.5) with diazomethane, gives methyl ester. The mass spectra of resulting methyl ester (Table 21) showed ion peaks at m/e 443, 431, 381, 344, 330, 315, 313, 312, 301, 299, 287, 272, 271, 257 in addition to the major ion peaks of the methyl ester of monomer 97 . From polymerization study of α-keto-γ-lactones in the previous section, it is very unlikely for a lactone with bulky γ-substituent to be polymerized through carbon-carbon double bond. Thus, ring-opening polymerization is proposed for the reaction of lactone 11 with bulky γ-substituent. Besides, decarboxylation may also take place at high temperature. According to mass spectra (Table 21), the polymer is possibly formed by ring-opening polymerization after decarboxylation of lactone 11. The dimer formed by ring-opening polymerization may be cyclised to form 10-membered ring lactone 99.





99

The polymers were not separated from the monomer, an estimation of 25% polymers in the mixture based on calculation from the neutralization equivalent (monomer N.E.=67.3, after decarboxylation, N.E.=158).

Table 21 : Fragments of methyl ester of poly-citroyl-formic acid lactone

Mass no.	Comments
443	trimer-$CH_2CO_2CH_3$
431	trimer-CH_2CO-CH_3-CO
381	trimer-$2CO_2CH_3$-OH
344	dimer
330	dimer-CH_2
315	dimer-CO-H
313	dimer-OCH_3
312	dimer-OCH_3-H
301	dimer-CO_2+H, or dimer-CH_3-CO
299	dimer-CO_2-H
287	dimer-2CO-H
272	dimer-CO-CO_2
271	dimer-$CH_2CO_2CH_3$
257	dimer-$CH_2CO_2CH_3$-CH_2, or Dimer-CO_2CH_3-CO
244	monomer
243	monomer-H
229	monomer-CH_3
212	monomer-OCH_3-H
185	monomer-CO_2CH_3
171	monomer-$CH_2CO_2CH_3$
157	monomer-CO_2CH_3-CO

4. CONCLUSION

A variety of α-keto-γ-lactones were prepared by modified Gault and Durand's method for characterization study. Two new lactones - α-keto-β-carbethoxy-γ-(o-hydroxyphenyl)-γ-butyrolactone and bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene were synthesized. Following Schinz's method, the α-keto-β-carbethoxy-γ-alkyl-γ-butyrolactones can be degraded to their corresponding α-keto-γ-alkyl-γ-butyrolactones. In proton NMR spectra of α-keto-γ-lactones, all protons fall into the chemical shifts expected. The chemical shift of the proton in the lactone ring is affected by the γ-substituent. There appears to be a good correlation between the inductive effect on γ-carbon and the deshielding effect of γ-hydrogen by substituted phenyl group.

The α-keto-γ-lactones exist, when possible, in the enolic form, in which the dipole-dipole and non-bonded interactions in two carbonyl group can be relieved. The cyclic oxygen atom exerts an inductive effect through the γ-carbon atom and results in α-keto-γ-lactones being a stronger acid than cyclopentane-1,2-dione. An electron-withdrawing substituent on β-position increases the acidity of α-keto-γ-lactones. The stronger acidity of β-carbethoxyl-α-keto-γ-lactones may be due to the conjugation effect as well as the inductive effect. The γ-substituents can reinforce or compete with the inductive effect

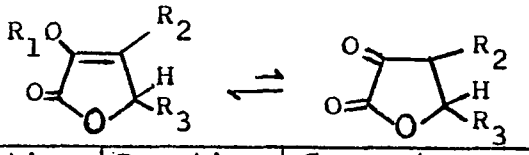
of ring oxygen atom on the γ-carbon atom. Thus, electron-withdrawing γ-substituent also increase the acidity of α-keto-γ-lactones.

The mass spectra of a number of α-keto-γ-lactones are studied. The predominant fragmentation routes for many of these compounds can be explained on the basis of three schemes. The first involving ketonization of the molecular ion followed by elimination of carbon monoxide. The second involving rupture of C_5-R_3 bond prior to elimination of carbon monoxide. The third involving rupture of C_2-C_3 bond and loss of carbon dioxide. Special structural features, provide alternate routes.

The polymerization reactions of α-keto-γ-lactones are summerized in Table 22. α-Keto-β-carbethoxy-γ-butyrolactone can be polymerized thermally or catalytically. The polymer obtained from acid-catalysed polymerization, showed retention of γ-lactone ring from IR spectrum. The polymer is formed by Michael-addition through carbon-carbon double bond. Mass spectra indicated that dimer and trimer have been formed. Thermal polymerization of α-keto-β-carbethoxy-γ-butyrolactone yields complex products. The major product - poly-ethylacrylate is formed after decarboxylation and decarbonylation of the lactone.

Polymerization of α-keto-γ-methyl-γ-butyrolactone by base-catalyst gives mostly colorless dimer. The lactone is dimerized across the carbon-carbon double bond

Table 22 : Polymerization of α-keto-γ-lactones



R_1	R_2	R_3	Catalyst system	Solvent	Reaction temp.	Reaction time	Comments
H	$-CO_2C_2H_5$	H	H_2SO_4	H_2O	reflux	4 hrs.	dimer, trimer and -tetronic acid
H	$-CO_2C_2H_5$	H	-	-	150-160°C	2 hrs.	dec., dimer, trimer poly-ethylacrylate
H	$-CO_2C_2H_5$	H	$NaOC_2H_5$	C_2H_5OH/THF	reflux	10 hrs.	no reaction
CH_3	CH_3	H	-	-	115-125°C	24 hrs.	no reaction
CH_3	CH_3	H	$NaOC_2H_5$	C_2H_5OH/ THF	reflux	10 hrs.	no reaction
H	H	CH_3	$NaOCH_3$	ether	reflux	10 hrs.	dimer
H	H	CH_3	-	-	120-125°C	24 hrs.	dec., dimer, trimer poly-propylene
H	H	CH_3	H_2SO_4/ silica	benzene/ methanol	R.T.	3 hrs.	dimer, poly-propylene
H	H	C_3H_7	$NaOCH_3$	ether	reflux	10 hrs.	no reaction
Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]			$NaOC_2H_5$	ethanol/ THF	reflux	10 hrs.	no reaction
			terephthaloyl Chloride	THF	R. T.	2 hrs.	copolymer
Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)]-1,4-benzene			$NaOC_2H_5$	ethanol/ THF	reflux	10 hrs.	no reaction

and the structure is assigned. The dimer and trimer of α-keto-γ-methyl-γ-butyrolactone can be obtained by thermal polymerization, however, the decarboxylation and decarbonylation are the predominant reactions, and polypropylene is the major product. Dimerization of α-keto-γ-methyl-γ-butyrolactone can also be catalysed by silica in presence of acid, the polypropylene and some unidentified polymers are also present besides the major product-dimer.

The α-keto-γ-lactones with β-carbethoxyl group can not be polymerized by base-catalyst, this may be due to the stabilization of anion by resonance. α-Keto-β,β-dimethyl-γ-butyrolactone can not be polymerized thermally or catalytically. Failure of polymerization may be attributed to the non-enolizable α-keto group, which is less reactive than the enol group. α-Keto-γ-(n-propyl)-γ-butyrolactone did not dimerized under the same condition as in dimerization of α-keto-γ-methyl-γ-butyrolactone. The bulky n-propyl group may prohibit the formation of the dimer.

Bis-[γ-(α-keto-β-carbethoxy-γ-butyrolactone)] with a dienol group can be copolymerized with terephthaloyl chloride to give polyester in presence of triethylamine. The bis-lactone is expected to form copolymer with diisocyanates, dicarboxylic acids or their derivatives under suitable conditions.

The lactone of citroylformic acid can be polymerized after decarboxylation of lactone. The product may be formed by ring-opening polymerization.

From this study, the polymerization of α-keto-γ-methyl-γ-butyrolactone seemed to be more plausible, for the higher reactivity, and less complicate structure. Carefully control of the reaction condition may give higher molecular weight polymer. The polymer with retention of γ-lactone ring is expected to give addition product upon reaction with the reagents which were used by Ohse and co-worker[26] in reactions of poly-γ-hydroxycrotonolactone.

5. BIBLIOGRAPHY

1. (a) W. Kern and R. C. Schulz, Angew. Chem. 69 153(1957) (b) G. Smets, Angew. Chem. 67 57 (1955).
2. (a) A. Schellenberger and K. Winter, Tetrahedron 27 5683-95 (1971); (b) A. Schellenberger, G. Oehme, Z. Physik. Chem. 227 112-20 (1964).
3. A. Schellenberger and K. Winter, Chem. Ber. 92 793-806 (1952).
4. A. Schellenberger, G. Oehme, J. Prakt. Chem. 24 239-45 (1964).
5. L. Wolff, Ann. Chem. 305 154 (1899).
6. A. W. K. DeJong, Rec. Trav. Chim. 20 81 (1901).
7. (a) D. L. Leussing, D. E. Tallman, JACS 91 6256 (1969). (b) D. L. Leussing, C. K. Stanfield, JACS 86 2805 (1964).
8. F. Rannirez, N. B. Desai, N. Ramanathan, Tet. Lett. 323, (1963).
9. E. Waldman, V. Prey, F. Jellinek, Monatsch. Chem. 85 872 (1953).
10. V. Prey, E. Waldman, H. Berbalk, Monatsch. Chem. 86 408 (1956)
11. D. M. Hughes and J. C. Reid, JOC 516 (1949).
12. A. Schellenberger, E. Pondany, Chem. Ber. 91 1781 (1958).
13. W. D. Covey and D. L. Leussing, JACS 96 3860 (1974).

14. B. Lillis, D. L. Leussing, JCS Chem. Comm. 397 (1975).

15. W. P. Kumler, Ernest Kun and J. Shooley, JOC 27 1165 (1961).

16. R. Wiley and K. S. Kim, JOC 38 3582 (1973).

17. E. H. Abbott and A. E. Martell, JACS 91 6931 (1969).

18. G. Odian, 'Principles of Polymerization' p497, McGraw-Hill, New York. (1970).

19. R. A. Patsiga, J. Macromol. Sci-Revs. Macromol. Chem. C1(2): 223 (1967).

20. P. Longi, F. Greco, and F. Mapelli, Chim. Ind. (Milan) 47 951 (1965).

21. H. Ohse and H. Cherdron, Makromol. Chem. 95 283 (1966).

22. K. C. Frisch and S. L. Reegen "Ring Opening Polymerization" p274, Marcel Dekker, New York and London (1969).

23. K. C. Frisch and S. L. Reegen "Ring Opening Polymerization: p256, Marcel Dekker, New York and London (1969).

24. G. Odian, "Principles of Polymerization" p163, McGraw-Hill, New York (1970).

25. Marvel and C. L. Levesque, JACS 61 1682 (1939).

26. H. Ohse, H. Cherdron and R. Palm, Angew. Chem. internat. Edit. 5 994-1000 (1966).

27. H. Schinz and M. Hinder, Helv. Chim. Acta 30 1439 (1947).

28. A. Rossi and H. Schinz, ibid. 31 473 (1948); 32 1967 (1949).

29. H. Schinz, F. Fleck, A. Rossi, M. Hinder, Helv. Chem.

Acta, 33 130 (1950).

30. E. P. Abraham, Quart. Rev. 21 231 (1967).

31. E. Galantay, A. Szabo and J. Fried, Tet. Lett. 415, (1963).

32. A. G. Long and A. F. Turner, ibid., 421 (1963).

33. E. Galantay, H. Engel, A. Szabo and J. Fried, JOC, 29 3560 (1964).

34. D. M. Green, A. G. Long, P. J. May and A. F. Turner, JCS 766 (1964).

35. G. C. Barrett, S. H. Eggers, T. R. Emerson and G. Lowe, JCS 788 (1964).

36. R. Heymes, G. Amiard and G. Nomine, C. R. Acad. Science, Ser. C, 263 170 (1966).

37. J.E. Dolfini, J. Schwartz and F. Weisenborn, JOC 34 1582 (1969).

38. P. Dietrich, E. Sundt, Swiss 482,415 (Cl, A.231, A24b, C11b).

39. A. Pittet, P. Rittersbacher and R. Muralidhara, J. Agr. Food.Chem. 18 928-32 (1970).

40. N. V. Chemische Fabrieh "Naarden" Neth. Appl. 70 01,653 (Cl. A231, C07d) 09 Aug. 1971, Appl. 05 Feb. 1970.

41. Saito, Chushin, H. Shimazaki, Y. Komata, CA 75: 117350d.

42. P. Dietrich, E. Sundt, CA 78: 146510y.

43. J. Batchelor, D. Clark, G. Tuey, CA 75: 77034d.

44. W. Roedel, U. Hempel, Nahrung 18 133-41 (1974).

45. W. Wislicenus, Ber 25 3448 (1892); 26 2144 (1893).

46. H. Gault, Bull. Soc. Chim. 3 1264-75.

47. H. Gault and R. Durand, Compt. Rend. 216 848 (1943).

48. G. Stacy and G. Wagner, JACS 74 909 (1952).

49. M. Hinder, H. Schinz and C. F. Seidel, Helv. Chim. Acta 30 1495 (1947).

50. E. Galantay, C. Hoffman, and N. Paolella, JOC 35 4277 (1970).

51. J. Couquelet, P. Tronche, Bull. Soc. Chim. Fr. 2015-17 (1968).

52. J. Couquelet, J. Boyer, C. R. Acad. Sci. 274 Ser. C 422 (1972).

53. A. Caudet, J. Couquelet and R. Vessiere, C. R. Acad. Sci. Ser. C, 270 1127 (1970).

54. A. Caudet, P. Tronche, R. Vessiere and J. Couquelet, Bull. Soc. Chim. Fr. 1707 (1973).

55. E. D. Stecher and E. Gelblum JOC 26 2693 (1961).

56. E. D. Stecher, A. Waldman and D. Fabiny, JOC 30 1800 (1964).

57. W. Roedel and U. Hempel, Nahrung 18 137 (1974).

58. K. Thomae, GmBH, British Patent 993-509 (1963); CA 60: 1702 (1964).

59. O. Kaltwasser, Ber. 29 2273 (1896).

60. E. Asahina, S. Terada, J. Pharm. Soc. Japan 502 855 (1923).

61. S. Olsen, G. Havre, Acta Chem. Scand. 8 47 (1954).

62. J. Suprin, Ann. Chim. 12 295 (1951).

63. C. H. Nield JACS 67 1145 (1945).

64. G. W. Stacy and G. D. Wagner, JACS 911 (1952).

65. M. Suquet, Ann. Chim. 8 545 (1953).

66. G. Ghilardi, H. Gault, Compt. rend. 234 337 (1952).

67. Hall, Hynes and Lapworth JACS 132 (1915).

68. A. C. Legon, Chem. Comm. 838 (1970).

69. S. Kovac, E. Solcaniova, JCS, Perkin II 108 (1973).

70. H. Gault and G. Gordon, Compt. rend. 245 971 (1957).

71. O. Nagse, Y. Hosokawa, M. Shimzu, Chem. Pharm. Bull. (Tokyo) 17 398 (Eng.) (1960).

72. H. G. Monsimer, U.S. 3,185,711 (Cl. 260-3436) may 25, 1965, CA 63: 9879 (1965).

73. Stobbe, Ann. 282 280 (1894).

74. Mille, Billet, Bull, Soc. Chim. (Fr.) 16 D297(1949).

75. Robinson and Seijo, JCS 582 (1941).

76. W. P. Jencks, "Progress in Physical Organic Chemistry", New York, Interscience, 1964, Vol. 2, p73.

77. A. Liberles, "Introduction to Theoritical Orgnic Chemistry" The Macmilliam Co., New York 1968, p91.

78. J. Couquelet, J. Boyer, C. R. Acad, Sci. Ser. C, 274 424 (1972).

79. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Chap. 3-3A, Pergamon Press. Oxford (1968).

80. E. S. Gould, "Mechanism and Structure in Organic Chemistry" Holt, Rinhart and Winston, New York, Chicago, San Francisco, Toronto, London (1959).

81. Schreck, JACS 71 1881 (1949).

82. G. Schwarzenback, C. Wittwer, Helv. Chim. Acta 30 663 (1947).

83. G. Schwarzenback, C. Wittwer, Helv. Ch . Acta, 30 669 (1947).

84. H. Hift, H. Mahler, J. Biological Chem., 901 (1952).

85. Kumler, JACS 60 859 (1938).

86. Woodward and Small, JACS 72 1297 (1950).

87. T. Yamagushi, K. Saito, T. Tsujimoto and H. Yuki, J. Heterocyclic Chem. 13 533 (1976).

88. E. Hankanenm, T. Moisio and P. Karbonen, Acta Chem. Scand. 69 1370 (1965).

89. W. H. McFadden, E.A. Pay and M. J. Diamond, Anal. Chem. 37 89 (1965).

90. B. J. Millard, Org. Mass Spectrom. 1 279 (1968).

91. L. J. Haynes, A. Kirkien-Konasiewick, A. G. Loudon, and A. Maccoll, Org. Mass Spectrom. 1 743 (1968).

92. J. A. Ballantine, R.G. Fenwick and V. Ferrito, Org. Mass Spectrom. 1 761 (1968).

93. J. H. Bowie and J. W. Morgan, Aust. J. Chem. 20 117 (1967).

94. L. F. Friedman and F. A. Long, JACS 75 2832 (1953).

95. Q. N. Porter and J. Baldes, "Mass Spectrometry of Heterocyclic Compounds" Wiley-Interscience, New York-London, p199.

96. W. H. Lunn, J. T. Edward, and S. Meyerson, Can. J. Chem. 44 279 (1966).

97. H. Nakata, Y. Hirata and A. Talematsu, Tet. Lett. 123 (1965).

98. R. M. Letcher, Org. Mass. Spectrom. 1 805 (1968).

99. R. M. Letcher, S. Eggers, Tet. Lett. 3541 (1967).

100. Y. Koyama, Y. Fukakusa, N. Kyomura and S. Yamagishi, Tet. Lett. 355 (1969).

101. B. Willhalm, A. F. Thomas, and F. Gautschi, Tetrahedron 20 1185 (1964).

102. J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" McGraw-Hill, New York, 1968, p568.

103. S. Kovac, E. Solcaniova, E. Beska and P. Rapos, JCS, Perkin II, 107 (1973).

104. Wolff and Schwabe, Annalen 291 251 (1896).

105. D. H. Marrian, P. B. Russell, A. R. Todd and W. S. Waring, JCS 1365 (1947).

106. J. Furukawa, T. Saegusa, and H. Tsuruta, Makro. Chem. 33 32 (1959).

107. J. Furukawa, J. Polymer Sci. 36 546 (1959).

108. K. Weissermel and W. Schmieder, Makro. Chem. 51 39 (1962).