RING CLEAVAGE OF 3-HYDROXY-2,2,4-TRIMETHYL-3-PENTENOIC ACID β-LACTONE BY THE ANION OF DIISOPROPYL KETONE

By

ROBERT BURTON HANSON

Bachelor of Arts

Oklahoma State University

Stillwater, Oklahoma

1963

Submitted to the faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the degree of
DOCTOR OF PHILOSOPHY
July, 1967

RING CLEAVAGE OF 3-HYDROXY-2,2,4-TRIMETHYL-3-PENTENOIC ACID β-LACTONE BY THE ANION OF DIISOPROPYL KETONE

Thesis Approved:

K. D. Berlin
Thesis Adviser

O C Dermer

E J Eisenbraun

Fremont Harris

N. N. Durham
Dean of the Graduate College

ACKNOWLEDGMENTS

The author is indeed deeply grateful for the encouragement, counsel and guidance provided by Dr. K. Darrell Berlin during the course of this study, not to mention his invaluable assistance which made possible the herein documented research.

The author also wishes to express appreciation to Dr. Claude H. Dungan, Monsanto Chemical Company, St. Louis, Missouri, for determination of some high resolution nuclear magnetic resonance spectra and for several invaluable molecular weight determinations. Also deepest thanks are extended to those herein unnamed fellow graduate students of Dr. Berlin's with whom I had the pleasure to work.

Gratitude is also extended to the Oklahoma State University Department of Chemistry, the Research Foundation, and to the National Science Foundation for financial assistance during the course of my studies.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

LIST OF ILLUSTRATIONS

Plate Page

Infrared Spectra

Nuclear Magnetic Resonance Spectra

INTRODUCTION

Ring cleavage of β-lactones by certain anionic reagents is well known, although ring opening by Grignard reagents is not well documented. Recent experimental evidence presented in this Laboratory revealed the possibility of the presence of a dicarbanion form of diisopropyl ketone in condensation of phenyl Grignard reagent and 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone. Furthermore the production (in fair yields) of two compounds of highly unusual structure, a cyclic ketol and an acyclic triketone, suggested dicarbanion intermediates. Since from previous mechanistic considerations the condensation of the lactone with phenyl Grignard reagent was believed to involve anion species which condensed with additional lactone, the use of excess lactone might possibly increase the yields of the ketol and triketone. Moreover, the anion species could be carbonated giving acids if the ketone-enol equilibrium favored the ketone form. In addition, spectral data and chemical and elemental analysis might lead to a structural assignment for the ketol and the triketone.

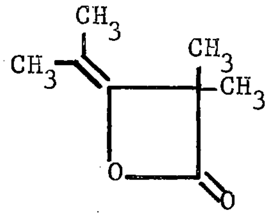
CHAPTER I

HISTORICAL

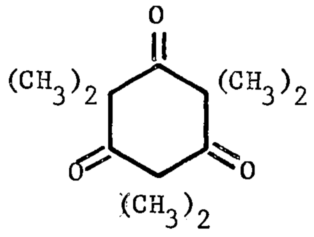
Recent Chemistry of the β-Lactone Dimer of Dimethylketene

Since the preparation of the β-lactone dimer I of dimethylketene, many reactions of this lachromatory, moderately stable liquid compound have been reported. Examples are: aminolysis, hydrolysis and alcoholysis and reactions with anions such as methoxide and those from active methylene compounds. Reactions with other nucleophiles and polymerization will not be discussed but have been reviewed in part by Zaugg.[88]

Various trimers, tetramers and polymers of dimethylketene have been prepared. A stable trimer of dimethylketene, 2,2,4,4,6,6-hexamethyl-1,3,5-cyclohexanetrione (II) is formed by a base-catalyzed reaction of the ketene, its dimers or its polymers.[15,65]

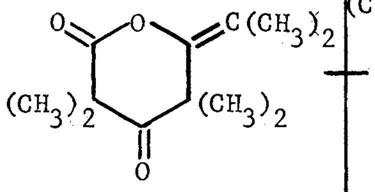


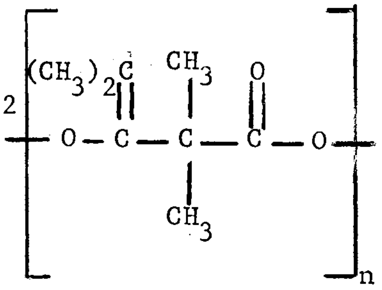
I

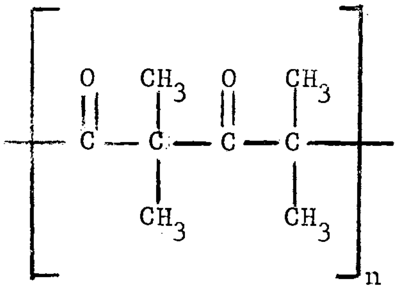


II

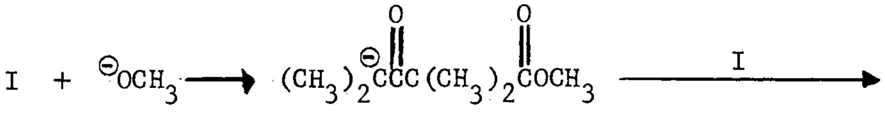
A less stable trimer of dimethylketene, 5-hydroxy-2,2,4,4,6-pentamethyl-3-oxo-5-heptenoic acid 5-lactone, has been synthesized by base-catalyzed disproportionation of the β-lactone dimer of dimethylketene, 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (I).[14] In the



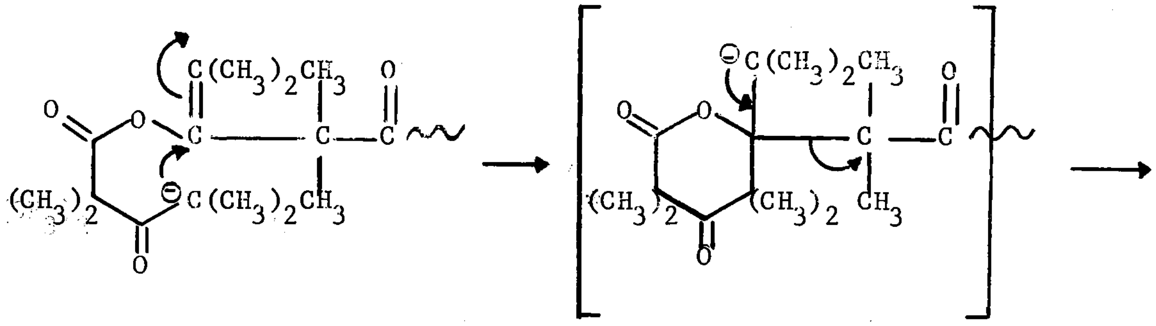


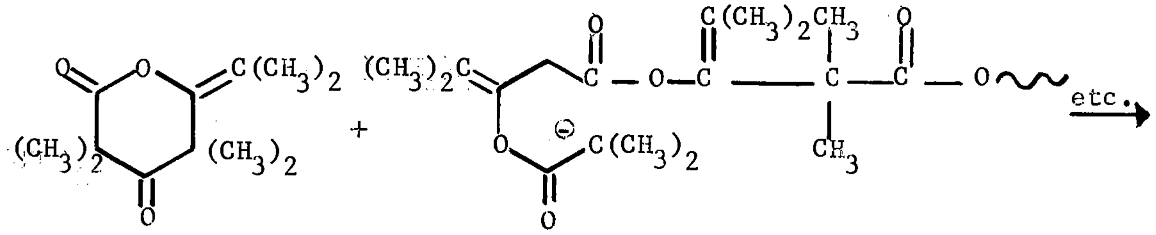


absence of labile hydrogen atoms, lactone I reacts with strong bases such as a sodium alkoxide to form an enolate anion.[42] With less than equivalent amounts of base, other products are formed. A polyester conceivably is obtained from lactone I by simple ring opening; propagation is reported to proceed through the enolate anion rather than the carboxylate anion. Reaction at the oxygen atom of the enolate anion produces a polyester, whereas reaction at the carbon atom would possibly yield a polyketone. This latter type of attack would lead to triketone II. With a strong base such as sodium methoxide and a low temperature (boiling ether), only the polyester is formed. With a slightly weaker base such as sodium hydroxide, the polyester is reported to form exothermally in boiling lactone I. Further heating of the mixture to 200-250° without removal of lactone I converts the polyester into a mixture of the trimers.

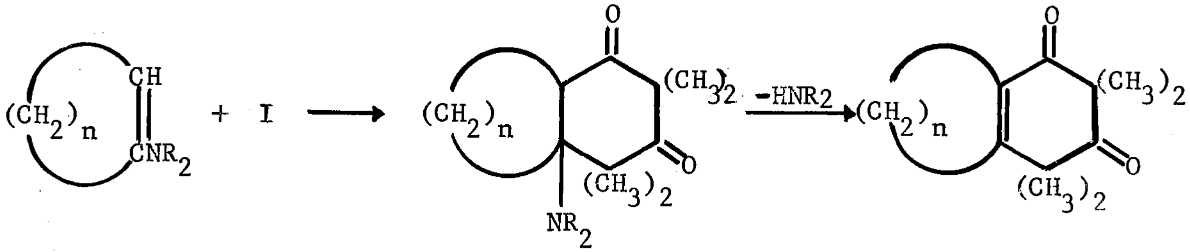


$$I + {}^{\ominus}OCH_3 \longrightarrow (CH_3)_2\overset{\ominus}{C}\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow{\quad I \quad}$$

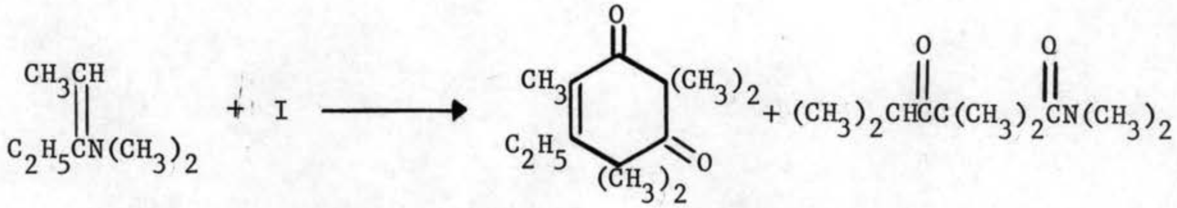




Recently, Martin and co-workers[57] have reported that lactone I condenses with cyclic enamines to give highly substituted carbocyclic ring compounds. 1-(1-Cyclohexen-1-yl)pyrrolidine and lactone I when heated

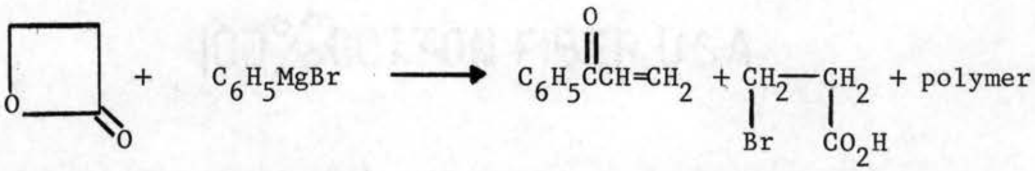


for several hours on a steam bath under nitrogen, gave hexahydro-2,2,4,4-tetramethyl-4a-(1-pyrrolidinyl)-1,3-(2H,4H)-naphthalenedione in good yield (80%). This adduct was reported to decompose slowly when stored at room temperature. 1-Ethyl-N,N-dimethylpropenylamine and lactone I reacted to give a cyclic, unsaturated diketone and an amide.



β-Lactones and Their Reactions With Grignard Reagents

Gresham and co-workers in 1949 reported the first evidence of ring cleavage of a β-lactone by Grignard reagents.[27] When β-propiolactone and phenyl Grignard reagent (1:1) were allowed to condense at -6°, products from O-alkyl and O-acyl ring opening were observed. A small amount of polymer (9.6%), β-bromopropionic acid (43%) and phenyl vinyl ketone (21.2%) were isolated. Phenyl vinyl ketone may have arisen through spontaneous dehydration of the intermediate, β-hydroxypropiophenone.



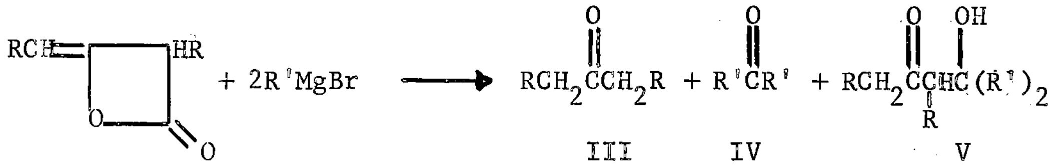
Methylmagnesium iodide condensed with β-propiolactone (1:1) to give β-iodopropionic acid, [a neutral oil which exhibited a large boiling range, 29-78°/25-28mm], a small amount of polymer and methyl vinyl ketone. Benzylmagnesium chloride and β-propiolactone gave polymer (22.4%), β-chloropropionic acid (16.1%) and 4-phenylbutanoic acid (32.4%). However the remaining 20% of the reaction mixture was not completely identified.

Stuckwisch and Bailey[75] found that allylmagnesium bromide and β-propiolactone gave 5-hexenoic acid in fair yield (54%). This product was the only compound isolated, however.

When phenyllithium and β-propiolactone were allowed to condense at 0°, the diaddition product [1,1-diphenyl-1,3-propanediol (40%)] and phenyl vinyl ketone (45%) were the only compounds isolated. When two equivalents of n-butyllithium and one equivalent of the lactone were used, the corresponding diaddition product was the sole product isolated from the reaction mixture.

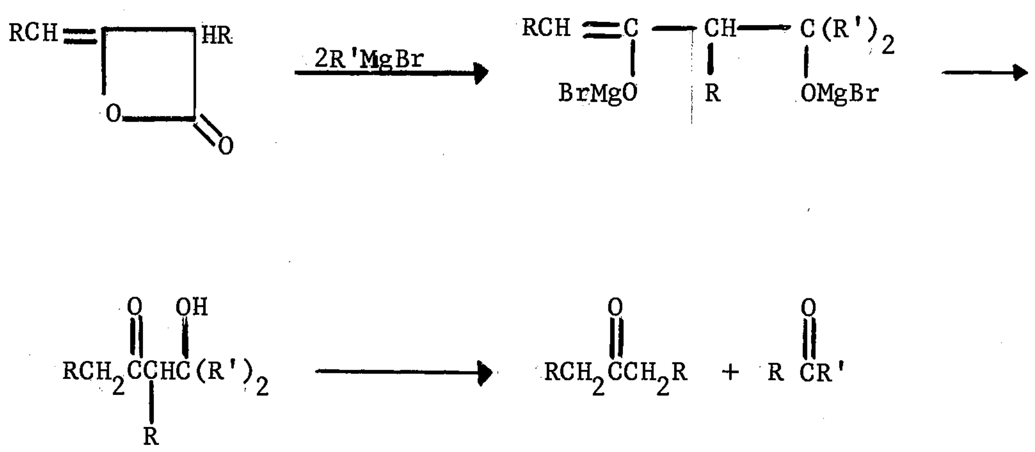
Many investigations of the reactions of aldoketene dimers have been carried out, but only a few have dealt with their reactions with Grignard reagents. Reid and Croszos have reported that solid ethylketene dimer, which is stated to have the structure of 2,4-diethyl-1,3-cyclobutanedione, behaved abnormally in a Grignard machine yielding 1.3 active hydrogens along with less than two additions to carbonyl groups.[66]

Nightingale and Turley[61] found that when a two-mole excess of phenyl Grignard reagent was added to the β-lactone dimer of n-butylketene, three products were isolable, these arising from O-acyl ring cleavage of the lactone. Benzophenone (16%) (IV, R' = C_6H_5), 6-undecanone (III, R = n-C_4H_9) and 5-(diphenylhydroxymethyl)-6-undecanone (V, R = n-C_4H_9) were found.



n-Hexylketene dimer (β-lactone) reacted with excess of phenyl Grignard reagent to give 7-(diphenylhydroxymethyl)-8-pentadecanone (V, R = n-C_6H_{13}) as the only isolated product. The remainder of the reaction mixture was thought to contain 8-pentadecanone and benzophenone which could not be separated. The β-lactone dimer of n-octylketene and excess phenyl Grignard reagent gave products analogous to those reported for n-butylketene dimer and phenyl Grignard reagent.

An excess of the aliphatic Grignard reagents (ethyl, n-butyl, n-octyl) condensed with the aldoketene dimers to yield the simple ketones III and IV, but none of the diaddition, product V could be isolated from the high-boiling residues. The mechanism of the formation of the two ketones has been formulated as involving a simple retrograde aldo



V III IV

reaction of V either during the reaction or during the hydrolysis of the Grignard complex.

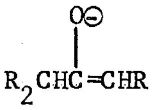
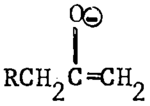
It was reported from this Laboratory[5] that an excess of phenyl, o-tolyl and 1-naphthyl Grignard reagents condensed with the β-lactone dimer I, and high-boiling β-diketones were produced in yields of less than 50%. The remaining portion of the reaction mixture in each case was complex, with more than 15 components detectable by gas liquid chromatography (GLC).

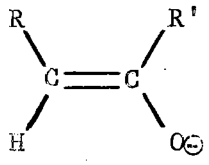
Recent Carbanion Enolate Chemistry

Because of the insurmountable task of sifting through the literature and extracting all information on enolate carbanion chemistry, this discussion will be limited to important work which has been published within the past decade.

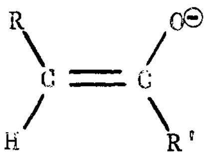
The use of acid chlorides and anhydrides for the acylation of ketones having an α-hydrogen atom has been reported as a convenient route to many β-diketones.[48,10] With acid chlorides, the condensation is usually effected by means of basic reagents such as sodium alkoxides, sodium hydride and sodium amide; with acid anhydrides, a Lewis acid such as boron trifluoride is generally employed. O-Acyl derivatives are formed in these reactions, but the conditions can be controlled so that favorable yields of 1,3-diketones can be obtained. Several authors have proposed one-stage mechanisms,[51,52,63] while other data has led to a proposed circular transfer mechanism.[79]

The acylation of enolate carbanions formed from the reaction of an aliphatic ketone and sodium amide has been found to be sensitive to the molar ratio of acid halide (or anhydride) to ketone-base.[60] Benzoyl chloride,sodium amide and acetone, when combined in a 1:2:2 ratio, respectively, gave chiefly the 1,3-diketone, but when a 2:1:1 ratio of reactants was employed, the major product was the enol ester. With a more sterically hindered ketone, such as 2,6-dimethyl-4-heptanone, enol ester formation predominated. Increased hindrance in a substituted ketone tends to stabilize the enol structure.[24]

House and Kramer[52] have performed extensive investigations on enolate anion compositions of reaction mixtures obtained from acyclic unsymmetrical ketones. The base-solvent system used for the conversion of the ketones was triphenylmethylpotassium in 1,2,-dimethoxyethane. Two methods were used for measuring the enolate concentrations. One consisted of quenching part of the reaction mixture with a solution of deuterioacetic acid-deuterium oxide followed by analysis of the formed monodeuterated ketones (mixture) by mass spectrometry. In all cases, the recovered ketones contained no significant amount of dideuterated species. The second method used to measure the composition of the enolate solutions consisted of adding solutions of the enolates to an excess of acetic anhydride with the formation of enol acetates. In all cases the enol acetates were the major products of the reaction along with small amounts of recovered ketone. The authors reported no evidence for the existence of C-acylated products. Several generalizations were made: (1) acyclic ketones of the type $R_2CHCOCH_2R$ form the less highly substituted enolates  $R_2CH\overset{O^{\ominus}}{\overset{|}{C}}=CHR$ as the predominate structural isomer in the equilibrium mixture; (2) ketones of the type RCH_2COCH_3 form approximately equal amounts of the structurally isomeric enolates if R is an unbranched alkyl group and form mostly the less highly substituted enolate  $RCH_2\overset{O^{\ominus}}{\overset{|}{C}}=CH_2$ if R is a branched alkyl group; (3) cyclic ketones, 1-methylcyclohexanone and 1-methylcyclopentanone, afford approximately equal amounts of the structurally isomeric enolates; (4) where stereoisomeric enolates of types VI and VII are possible, the latter structure



VI

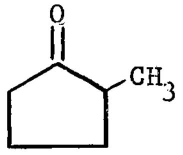


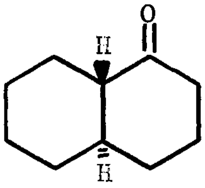
VIII

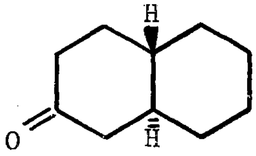
will predominate. An enhanced preference for the less highly substituted enolate in equilibrium mixtures involving lithium enolates was also reported.

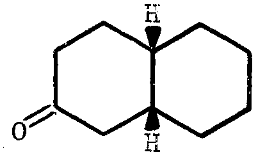
Alkylation of enolate anions has been found to be improved by the use of dimethyl ethers of ethylene glycol.[90] The activity of the carbanion was increased by coordination of the solvent with the cation. Solutions of this type have been found to be conductors of electricity, whereas solutions of carbanions associated with metallic cations as aggregates in aromatic hydrocarbons or diethyl ether have been found not to conduct an electric current.

In several other studies,[73,67,85] ketone enolate anions which had been generated in the absence of either a relatively acidic proton-donating solvent or an excess of the ketone appeared not to produce equilibrium mixtures of enolate anions. This failure to equilibrate was notable when lithium enolates were involved. Further studies along this same line have been done by House and Trost.[53] It was found that the potassium enolates of several cyclic ketones equilibrated much faster than did the corresponding lithium derivatives in a 25-100 mole % excess of the ketone. Triphenylmethylpotassium or the lithium analogue were used to form the enolates.



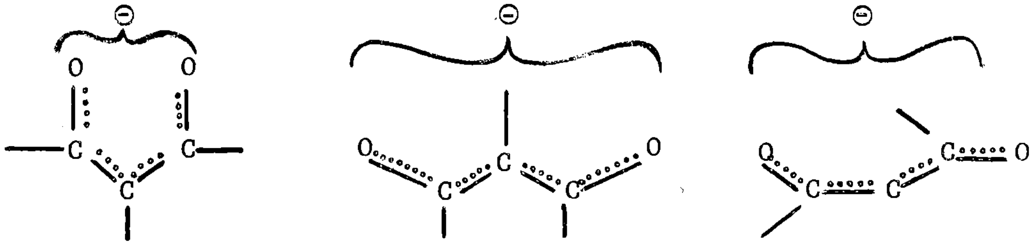






The base-solvent system lithium in liquid ammonia has been used extensively for the conversion of α,β-unsaturated ketones[73,74] and steroids[84,56,89,86] into the corresponding enolate anions. These latter species have been trapped by alkylation and carbonation.

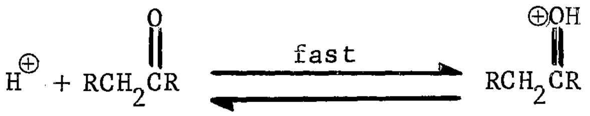
Theoretically, anions derived from acyclic β-dicarbonyl compounds can exist in any one or all of three plane-parallel molecular orbital systems which can be termed U-shaped, W-shaped and sickle-shaped.



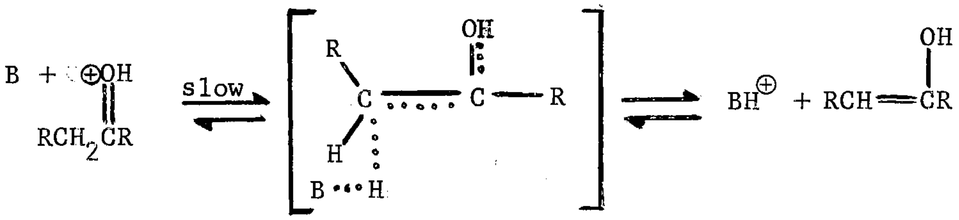
Representative examples unequivocally possessing the latter structure are not known. Ultraviolet spectroscopy was used to determine that acyclic enolates primarily exist in the U-shaped ion pairs.[89]

Infrared spectroscopy studies have been made on the free enolate ions of acetylacetone and diacetylacetonitrile. Diacetylacetonitrile in contrast to acetylacetone was shown to exist completely as the enol form.[86]

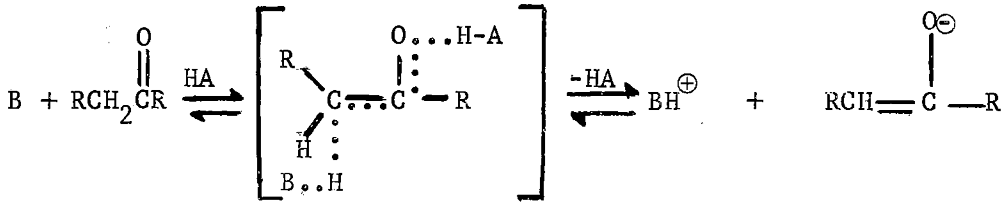
Acids and bases catalyze enolization of ketones by similar mechanisms. In the presence of strong acids, a ketone is converted reversibly to its conjugate acid; loss of an alpha proton occurs by reaction with a nucleophile in the rate-determining step to give the corresponding enol. Enolization by strong bases involves reaction of a base and a ketone with



$$H^{\oplus} + RCH_2\overset{\overset{\displaystyle O}{\|}}{C}R \underset{}{\overset{\text{fast}}{\rightleftharpoons}} RCH_2\overset{\overset{\displaystyle \oplus OH}{\|}}{C}R$$



assistance of weak electrophiles present to yield the enolate anion.

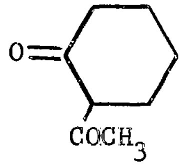
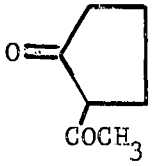


Bromine titration, infrared (IR) and ultraviolet (UV) spectroscopy and more recently NMR analysis[12] of β-dicarbonyl compounds have been used to determine the percent of enolization.

The K_a values found in Table I are important to the understanding of some of the work described in the Discussion section.

TABLE I

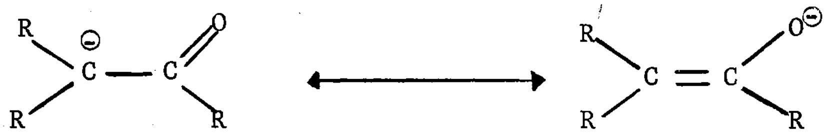
ACIDITY CONSTANTS FOR PSEUDO ACIDS AT 25° IN WATER[64,50]

Carbonyl Compound	K_a[a]	Carbonyl Compound	K_a[a]
CH_3COCH_3	$\sim 10^{-20}$	$CH_3COCH_2COCF_3$	2×10^{-5}
$CH_2(COCH_3)_2$	1.0×10^{-9}	$C_6H_5COCH_2COCF_3$	1.5×10^{-7}
$CH(COCH_3)_3$	1.4×10^{-6}		8.1×10^{-11}
$CH_3COCH_2COCH_3$	1.0×10^{-9}		
$CH_3COCH(CH_3)COCH_3$	1.0×10^{-11}		1.5×10^{-8}
$CH_3COCH_2COC_6H_5$	4×10^{-10}		
CH_3COCH_2CHO	1.2×10^{-6}	$CH_2(CHO)_2$	1.0×10^{-5}

[a] This is gross acid constant uncorrected for enol content.

Potentiometric methods have also been used for the determination of pK_a values for several substituted β-diketones at different temperatures.[19] The acidity values were found to decrease with increasing temperature.

In order for there to be any contribution of structures (shown below) to the total hybrid of an enolate anion, it has been found that the



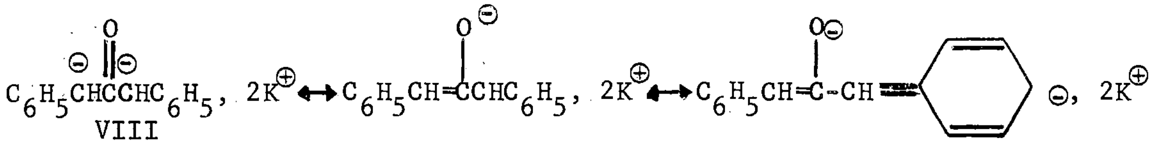
$>C{=}C{\leftarrow}\overset{\ominus}{O}$ system and the three atoms attached directly thereto lie at least very nearly in the same plane.[50,17]

Proton removal from an asymmetric carbon atom to form a carbanion results in racemization. The charge of the carbanion (ambident carbanions) is known to be largely concentrated on the oxygen of the carbonyl group (the more electronegative element), and proton capture undoubtedly occurs there much faster than on carbon.[20]

Dicarbanions of Monoketones, 1,3-Diketones and β-Ketoaldehydes

Intermediates in which two negative charges have been generated on two vicinal or nonvicinal atoms in the same molecule have been formed from a variety of compounds. When the charges are on carbon atoms, the anions are more precisely labeled dicarbanions.

The first dicarbanion of an acyclic ketone reported in the literature was prepared by Hauser and Harris.[45] They found that the reaction of dibenzyl ketone with two equivalents of potassium amide in liquid ammonia produced dark red dicarbanion VIII. The dark red color of species VIII suggested that the hybrid possessed properties

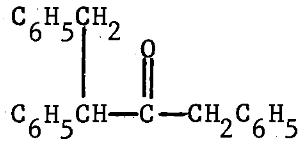


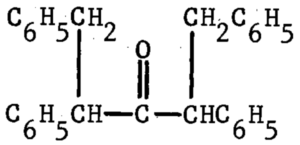
$C_6H_5\overset{\ominus}{C}H\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}HC_6H_5,\ 2K^{\oplus} \leftrightarrow C_6H_5CH{=}\overset{O^{\ominus}}{\overset{|}{C}}\overset{\ominus}{C}HC_6H_5,\ 2K^{\oplus} \leftrightarrow \dots$

VIII

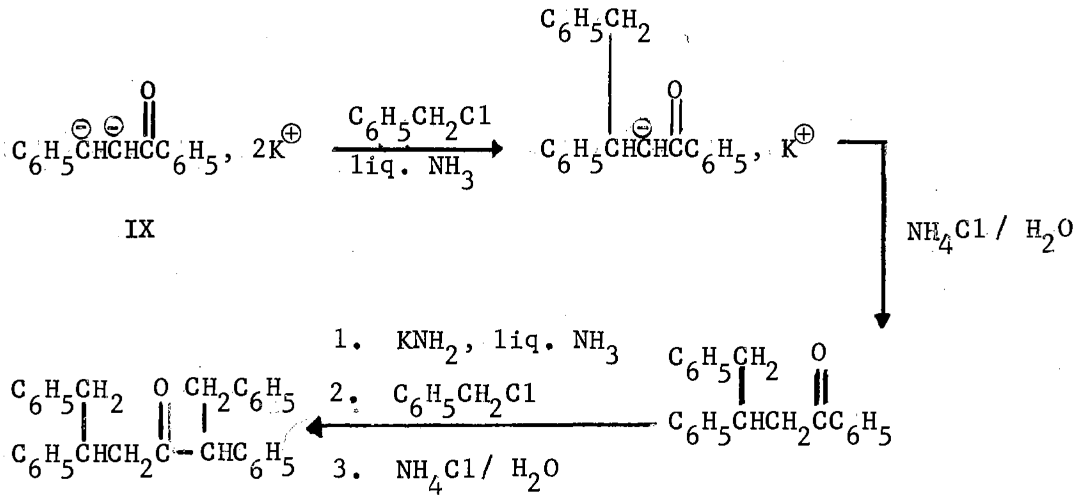
characteristic of not only an enolate anion resonance form, but it is likely that the phenyl group makes significant contributions.[47]

Dicarbanion VIII, when treated with one molar equivalent of benzyl chloride, gave a high yield of the monoalkylated product whereas the monovalent precursor species of VIII under the same conditions gave a mixture of products. Supposedly the dicarbanion VIII exhibits much greater basic and nucleophilic strength than the monovalent species. Essentially pure dibenzylated derivative was obtained when dicarbanion VIII was treated with two equivalents of benzyl chloride. A monoconjugate addition product was obtained in excellent yield when VIII was condensed with ethyl cinnamate. The monocarbanion precursor of VIII failed to give any appreciable conjugate addition product.


$C_6H_5CH(CH_2C_6H_5)-C(=O)-CH_2C_6H_5$

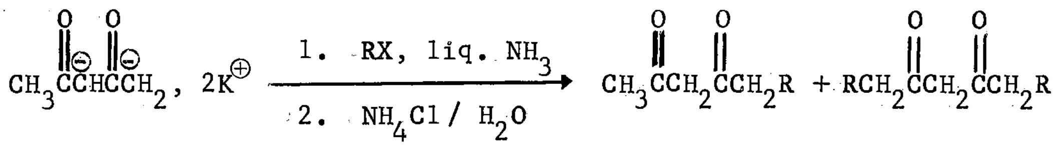

$C_6H_5CH(CH_2C_6H_5)-C(=O)-CH(CH_2C_6H_5)C_6H_5$

Benzalacetophenone was found to undergo rapid reductive metalation with two equivalents of potassium amide in liquid ammonia to form black dicarbanion IX.[35] The dipotassio salt of IX when allowed to react with benzyl chloride (one equivalent) gave the β-alkylated product in good



yield. This product may be further metalated and the resulting carbanion treated with benzyl chloride to yield the dibenzylated derivative. A γ-hydroxy ketone was formed when IX was condensed with benzophenone.

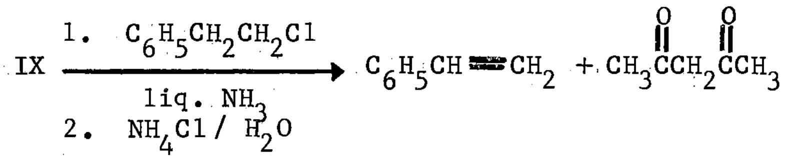
Acetylacetone undergoes conversion to a dicarbanion when treated with two equivalents of potassium amide in liquid ammonia.[46] The species was monoalkylated with several primary halides, a secondary and tertiary halide to give terminal alkylated products.[58,29] Along with the monoalkylated derivative a small amount of a dialkylated product was



$$\mathrm{CH_3\overset{O}{C}\overset{\ominus}{C}H\overset{O}{C}\overset{\ominus}{C}H_2,\ 2K^{\oplus}} \xrightarrow[\mathrm{2.\ NH_4Cl/\ H_2O}]{\mathrm{1.\ RX,\ liq.\ NH_3}} \mathrm{CH_3\overset{O}{C}CH_2\overset{O}{C}CH_2R + RCH_2\overset{O}{C}CH_2\overset{O}{C}CH_2R}$$

detected in the reaction mixtures. When analyzed structurally, the dialkylated products were observed to contain the alkylated group on the terminal ends of the ketone. The mechanism of formation of the dialkylated compounds has been postulated to involve metal-hydrogen exchange.[28] When a secondary halide, isopropyl bromide, combined with IX the yield of the monoalkylated β-diketone was 27%; with t-butyl bromide the alkylation failed.

In contrast to the typical primary halides, β-phenylethyl chloride, which has a relatively reactive β-hydrogen, failed to alkylate



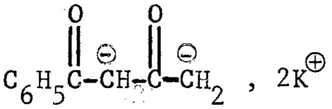
$$\mathrm{IX} \xrightarrow[\substack{\mathrm{liq.\ NH_3} \\ \mathrm{2.\ NH_4Cl/\ H_2O}}]{\mathrm{1.\ C_6H_5CH_2CH_2Cl}} \mathrm{C_6H_5CH{=}CH_2 + CH_3\overset{O}{C}CH_2\overset{O}{C}CH_3}$$

dicarbanion IX. Instead the halide underwent β-elimination to form styrene (89%) with most of the ketone being recovered.

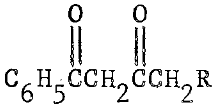
Benzhydryl chloride, which has a more reactive α-hydrogen than benzyl chloride, also failed to alkylate dicarbanion IX. The halide instead underwent self-alkylation accompanied by β-elimination to form tetraphenylethylene (98%).

In addition, the dicarbanion of acetylacetone, IX, has been reported to undergo phenylation with bromobenzene (benzyne intermediate) to form 1-phenyl-2,4-pentanedione in low yields (13%).[46] However the terminal derivative was formed (92%) when disodioacetylacetone and diphenyliodonium chloride were brought together in a 2:1 molar ratio, respectively. The mechanism of the reaction has been postulated to involve the formation of a radical anion and the phenyl radical which combine to give the terminal product.[30]

Benzoylacetone, not unlike acetylacetone, has undergone analogous reactions. When treated with two equivalents of potassium amide in liquid ammonia, conversion to a dicarbanion was realized. The divalent species has been treated with one equivalent of benzyl chloride to give the terminal benzylated derivative Xa (77%). Triketone Xb was obtained (58%) by condensing the dicarbanion with methyl benzoate; terminal acid Xc was afforded (58%) by adding the dicarbanion to a slurry of pulverized Dry Ice. It was added that carbonation possibly occured at C-3 but decarboxylation took place during workup of the reaction mixture. Ketol Xd was prepared by condensing the dicarbanion with benzaldehyde and the



$C_6H_5\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H-\overset{O}{\overset{\|}{C}}-\overset{\ominus}{C}H_2$, $2K^{\oplus}$

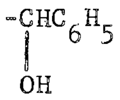


$C_6H_5\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2R$

Xa, R = $CH_2C_6H_5$

b, R = COC_6H_5

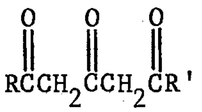
c, R = CO_2H

d, R = 

$-\underset{\underset{OH}{|}}{C}HC_6H_5$

product was isolated as its copper chelate in an overall yield of 28%.[46]

Aroylations of β-diketones to form 1,3,5-triketones has been performed; structure proof of the compounds was afforded by elemental analyses, enol tests and cyclizations to 4-pyrones and 4-pyridones.[55,32] The general procedure for effecting the aroylations involved the addition of the β-diketone to two molar equivalents of potassium amide in liquid ammonia followed by the addition of one-half of an equivalent of an appropriate ester. In all cases, yields of the triketones were reported



$$\mathrm{R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}R'}$$

a. $R = CH_3$, $R' = C_6H_5$

b. $R = CH_3$, $R' = p\text{-}ClC_6H_4\text{-}$

c. $R = C_6H_5$, $R' = C_6H_5$

d. $R = C_6H_5$, $R' = p\text{-}ClC_6H_4\text{-}$

e. $R = C_6H_5$, $R' = p\text{-}CH_3OC_6H_4\text{-}$

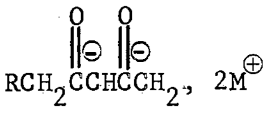
f. $R = C_6H_5$, $R' = 3$ - pyridyl

to be fair to good (40-62%). In addition, 2-acetylcyclohexanone, 2-acetylcyclopentanone and o-hydroxyacetophenone were converted to their corresponding dicarbanions and aroylated at the terminal position with an appropriate ester, although the yields were lower than for the acylic triketones. A mechanism (three-step) was offered to explain the formation of the triketones which was an adaptation of the method used in the acylations of ketones with esters (by alkali amides) to form β-diketones.[48]

The dilithio derivatives of acetylacetone and benzolacetone have also been aroylated.[87] The dilithio salt of benzolacetone was studied as the attempted condensation of either the dipotassio or disodio salt failed to give a condensation product when treated with phenyl propionate. Apparently the dicarbanions merely removed the α-hydrogen of the ester. However by using the dilithio salts, condensation products (> 40%) with ethyl acetate and higher esters were obtained; with the disodio or dipotassio salts the reactions failed.

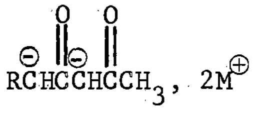
Excess sodium hydride has also been used for the preparation of 1,3,5-triketones from several β-diketones and an appropriate ester.[59] A comparison of the methods of arylation using excess sodium hydride in boiling monoglyme and potassium amide in liquid ammonia to effect the condensations, revealed that in most cases the sodium hydride method was superior, as yields of the triketones were far higher than for the potassium amide experiments. However for carbonation, benzylation and aldol-type condensations the potassium amide in liquid ammonia method is reported to be superior. Although four possible mechanisms involving initial formation of a monocarbanion were postulated for the condensations using sodium hydride in boiling monoglyme, no explanation for the increased yields of the triketones was provided.

In contrast to the situation of acetylacetone and benzoylacetone, two different dicarbanions XI and XII can arise from certain unsymmetrical β-diketones depending on whether a methyl or 5-methylene hydrogen undergoes the secondary ionization.[39,31] It was shown by Meyer and



$$\mathrm{RCH_2\overset{\overset{O}{\|\ominus}}{C}CH\overset{\overset{O}{\|\ominus}}{C}CH_2,\ 2M^{\oplus}}$$

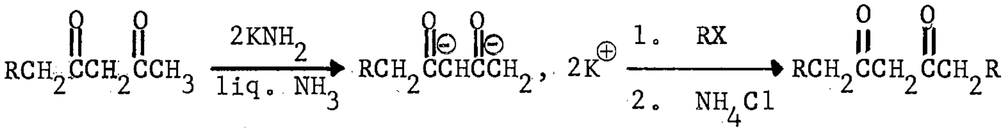
XI



$$\mathrm{\overset{\ominus}{R}CH\overset{\overset{O}{\|\ominus}}{C}CH\overset{\overset{O}{\|}}{C}CH_3,\ 2M^{\oplus}}$$

XII

Hauser[58] that 6-phenyl-2,4-hexanedione can be benzylated through a dicarbanion of type XI, yielding 1,7-diphenyl-3,5-heptanedione in 65% yield. No products corresponding to alkylation of dicarbanion XII were obtained. The β-diketone, 2,4-tridecanedione, was converted to its dicarbanion with two molar equivalents of potassium amide in liquid ammonia and alkylated with one equivalent of n-octyl bromide to give β-diketone XIIIb (71%). The dicarbanion of 6-phenyl-2,4-hexanedione underwent butylation with n-butyl bromide to give β-diketone XIIIc (67%). Structure proof of the compound was established by IR analysis of its copper chelate and an independent synthesis involving the condensation of methyl hydrocinnamate with methyl amyl ketone.



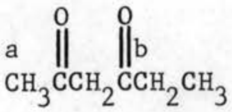
$$\mathrm{RCH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[liq.\ NH_3]{2KNH_2} RCH_2\overset{\overset{O}{\|\ominus}}{C}CH\overset{\overset{O}{\|\ominus}}{C}CH_2,\ 2K^{\oplus} \xrightarrow[2.\ NH_4Cl]{1.\ RX} RCH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2R}$$

XIIIa, R = R' = $CH_2C_6H_5$

b, R = R' = n-C_8H_{17}

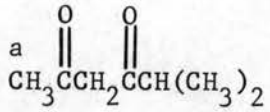
c, R = $CH_2C_6H_5$, R' = n-C_4H_9

Further studies of alkylation of unsymmetrical β-diketones have shown that structural effects have an influence on the position alkylated.[31]



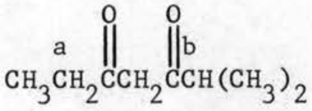
$\overset{a}{CH_3}\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}\overset{b}{CH_2}CH_3$

XIV



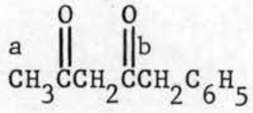
$\overset{a}{CH_3}\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH(CH_3)_2$

XV



$CH_3\overset{a}{CH_2}\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}\overset{b}{CH}(CH_3)_2$

XVI

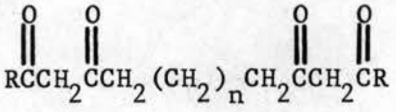


$\overset{a}{CH_3}\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}\overset{b}{CH_2}C_6H_5$

XVII

Compound XIV was converted to the dicarbanion with two equivalents of sodium amide in liquid ammonia and the disodio salt treated with one equivalent of methyl iodide. Gas chromatographic analysis of the reaction mixture indicated that terminal alkylation at position a occurred to a far greater extent than at position b. The yield of the terminal methylated diketone was 89% while the product arising from alkylation at b was 11%. The dicarbanions arising from ketones XV and XVI, when methylated under the same conditions as for the dicarbanion of XIV, formed the methylated product from alkylation at position a in 99% yield. The product ratios of the alkylated products obtained from the dicarbanion of XVI were not analyzed by GLC as the isomers could not be separated. However, analysis by GLC of the products obtained from alkaline cleavage of the components present in the reaction mixture gave only traces of pinacolone. The authors surmised that pinacolone would have been formed from base degradation of the reaction mixture if XVI had been alkylated at position b. Under identical conditions, the dicarbanion derived from compound XVII underwent exclusive methylation, n-butylation and benzylation at position b. The disodio salts of the β-diketones were used in preference to the potassio salts as the latter were found to undergo rapid metal-hydrogen exchange with the monopotassio salts of the alkylation products.

Terminal bis-β-diketones have been prepared by treating the dicarbanions derived from acetylacetone, benzoylacetone and other related β-diketones with 1,3-dibromopropane and higher methylene halides.[34] A two-fold alkylation of benzoylacetone was accomplished by condensing the dicarbanion with α,α'-dibromo-*o*-xylene and α,α'-dichloro-*p*-xylene. The reaction was reported to fail with ethylene and methylene halides.



$$R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2(CH_2)_nCH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}R$$

a. $R = C_6H_5$; $n = 3$

b. $R = C_6H_5$; $n = 4$

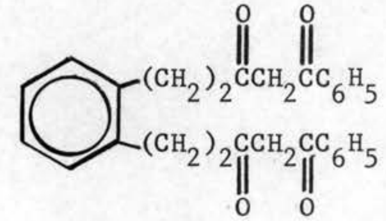
c. $R = CH_3$; $n = 3$

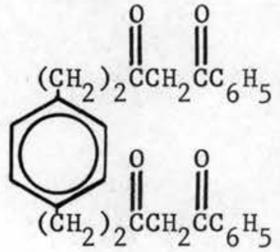
d. $R = CH_3$; $n = 4$

e. $R = CH_3$; $n = 9$

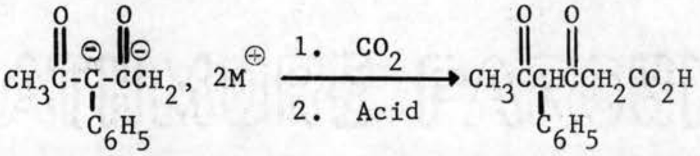
f. $R = CH_3$; $n = 10$

g. $R = C_6H_5(CH_2)_2$; $n = 4$



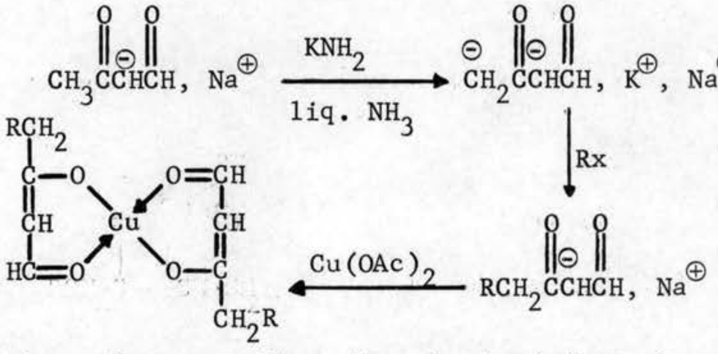


The dicarbanion derived from 3-phenyl-2,4-pentanedione has been shown to be less reactive than the dicarbanion derived from acetylacetone, as benzylation attempts on the former failed to give any appreciable benzylated product.[62] This relative sluggishness toward alkylation has been attributed to lower solubility of the dicarbanion in liquid ammonia and/or a lower nucleophilicity of the dicarbanion because of contributing structures in which the phenyl group participates in delocalizing part of the charge. Although the terminal benzylated derivative of 3-phenyl-2,4-pentanedione was obtained (16%) when its dicarbanion (in liquid ammonia) was treated with benzyl chloride, the yield was increased to 50-60% when the solvent system was changed to pyridine containing a small amount of liquid ammonia. No explanation was given as to the function of pyridine in increasing the yield of the terminal derivative. Preformed benzylpyridinium chloride, when added to the dicarbanion, gave no benzylated product. Aroylation of the dicarbanion in liquid ammonia with methyl benzoate gave the corresponding triketone in a yield of 14%, but the yield of the triketone was increased to 47% when the reaction was run in pyridine containing a little liquid ammonia. Carbonation of the dicarbanion was accomplished by pouring a solution of the dicarbanion in ether over a large excess of pulverized Dry Ice. The terminal acid was obtained in 26% yield.



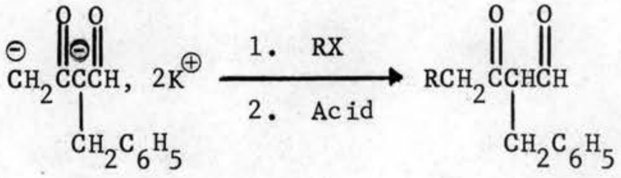
$$\mathrm{CH_3\overset{\overset{O}{\|}}{C}-\underset{\underset{C_6H_5}{|}}{\overset{\ominus}{C}}-\overset{\overset{O}{\|}}{C}\overset{\ominus}{C}H_2,\ 2M^{\oplus}\xrightarrow[\text{2. Acid}]{\text{1. }CO_2}CH_3\overset{\overset{O}{\|}}{C}\underset{\underset{C_6H_5}{|}}{C}H\overset{\overset{O}{\|}}{C}CH_2CO_2H}$$

The monosodio salt of acetoacetaldehyde has been converted to a dicarbanion with one equivalent of potassium with one equivalent of potassium amide in liquid ammonia and the resulting species treated with benzyl, methyl, n-butyl and n-octyl halides giving the corresponding alkylated monocarbanions which were converted to their copper chelates.[36]



In addition, the monosodio salts obtained from the reaction of the dicarbanion with benzyl and methyl halides were converted to cyanopyridones by treatment with cyanoacetamide.

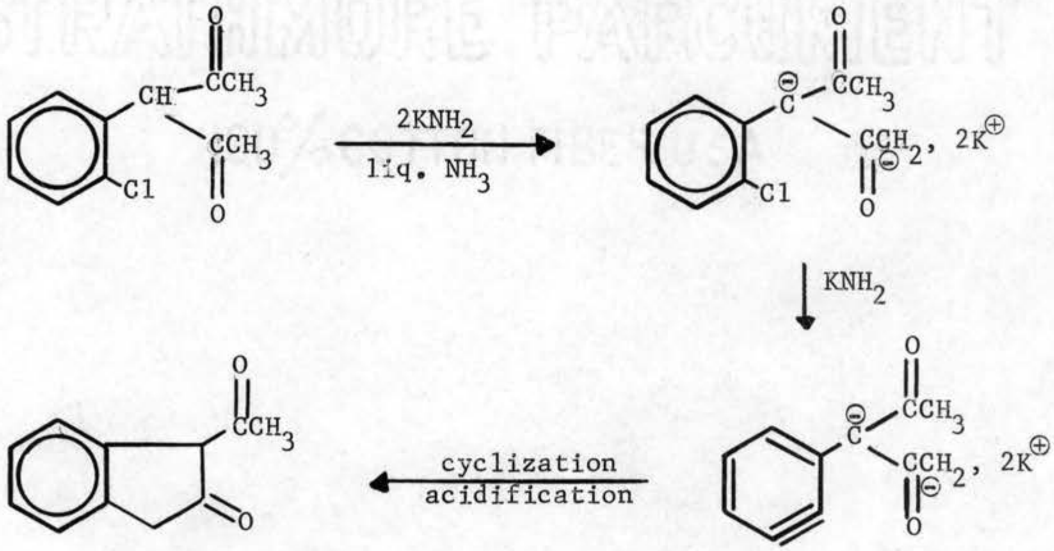
α-Benzylacetoacetaldehyde was converted to a dicarbanion with two equivalents of potassium amide in liquid ammonia and alkylated with benzyl and n-butyl halides to yield the corresponding terminal alkylated derivative in yields of 51 and 27% respectively.[36] That the alkylation



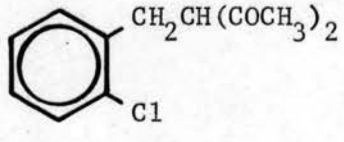
$$\overset{\ominus}{\mathrm{C}}\mathrm{H_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{CH_2C_6H_5}}{\overset{\ominus}{\mathrm{C}}}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H},\ 2\mathrm{K}^{\oplus} \xrightarrow[\text{2. Acid}]{\text{1. RX}} \mathrm{RCH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\underset{\mathrm{CH_2C_6H_5}}{\mathrm{C}}\mathrm{H}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{H}$$

products of the dicarbanion were the terminal derivatives, was supported by positive enol tests with ferric chloride and by IR spectral data.

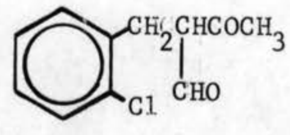
A benzyne-dicarbanion intermediate was reported to arise when o-chlorophenyl β-diketone XVIII was slowly treated with excess potassium amide in liquid ammonia.[40] The intermediate formation of the dicarbanion



in the reaction mixture was indicated as a transient green color was observed. Indirect evidence that the two-fold ionization to form the dicarbanion preceded dehydrohalogenation was the lack of any appreciable amination which would have been expected if a benzyne were produced first. Similarly o-substituted derivatives XIX and XX when converted to corresponding dicarbanions were cyclized to six-membered ring compounds.

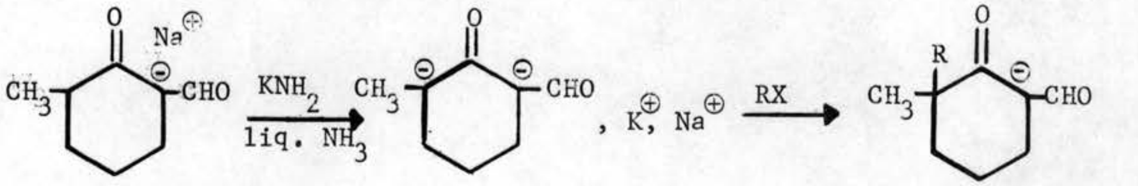


XIX

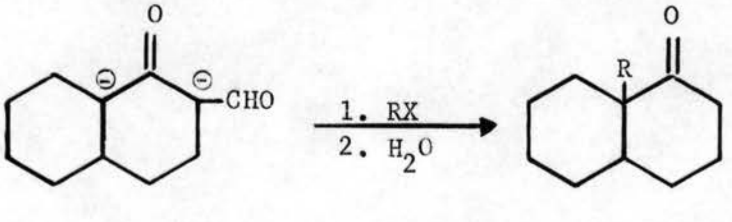


XX

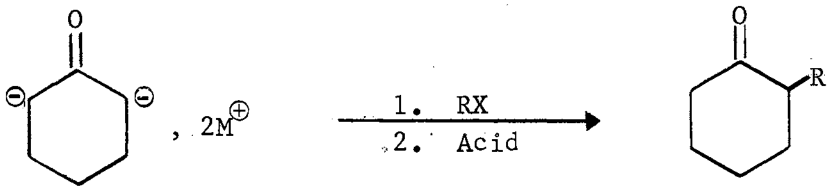
Dicarbanions of compounds other than acyclic ones have been prepared from α-formylcyclic ketones.[39,9] The monosodio salt of 2-formyl-6-methylcyclohexanone was changed to the dicarbanion with an equivalent of potassium amide in liquid ammonia. Benzylation of the dicarbanion and

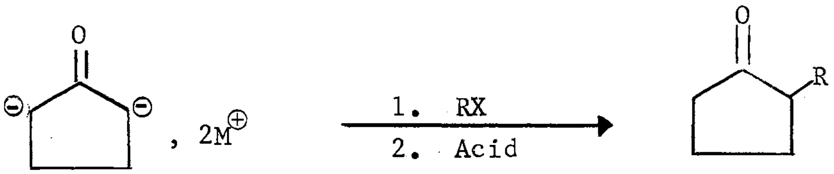


subsequent deformylation with aqueous sodium hydroxide gave 2-benzyl-2-methylcyclohexanone (50%). Methylation and n-butylation of the dicarbanion offered analogous products after deformylation. All three of the 2-alkyl-2-methylcyclohexanones were detected by GLC and NMR to be uncontaminated with the isomeric 2,6-disubstituted ketone. This method of angular alkylation has been reported to be superior to direct alkylation of a 2-substituted cyclohexanone, which produces a mixture of the 2- and 6-alkylation products as well as higher alkylated derivatives. Likewise, alkylation of the dicarbanion of 2-formyl-1-decalone with methyl, n-butyl and benzyl halides offered only the 9-alkyldecalones uncontaminated with any of the 2-alkylated product. Single diastereoisomers were



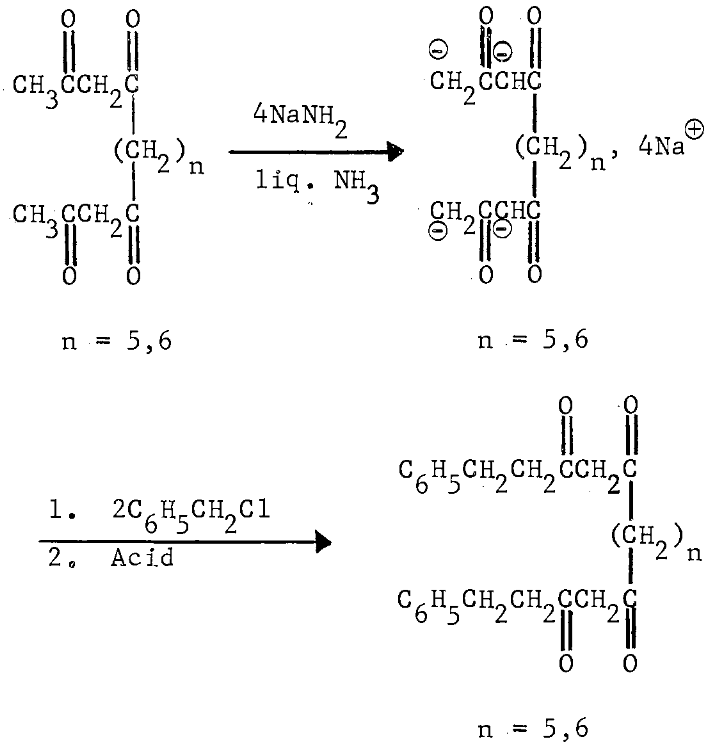
reported for the benzyl and *n*-butyl derivatives, but GLC indicated a 46:54 mixture of the *cis* and *trans* isomers from the methylation experiment. The butyl derivative was shown to contain a *cis*-fused ring system by reduction of its ethylene thioketal under Wolff-Kishner conditions to 9-butyl-*cis*-decalin. Direct alkylation of 1-decalone has been reported to give chiefly the 2-alkyl derivative rather than the 9-alkyl derivative. Pure 2-alkylated products, as indicated by GLC, have been prepared from the dicarbanions of cyclopentanone and cyclohexanone. The method is



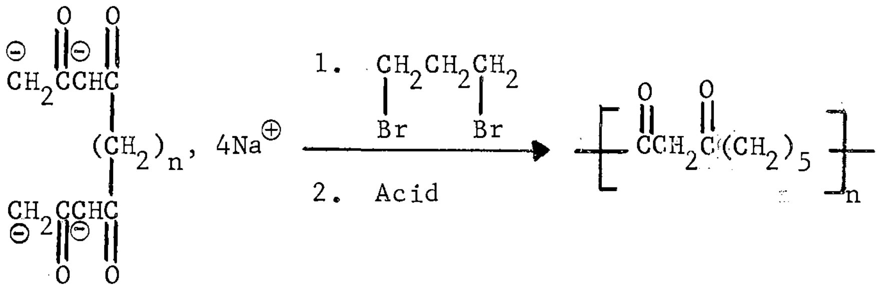


reported to be superior to direct alkylation of these systems by means of strong bases.

Certain bis-β-diketones have been converted by four molar equivalents of sodium amide in liquid ammonia to their tetrasodio salts which

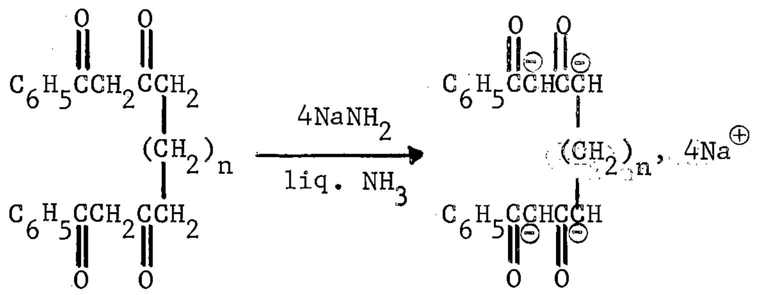


were condensed with certain electrophilic reagents.[33] Benzyl chloride when condensed with the tetrasodio salt gave a 67% yield of the diterminal derivative. Polymer formation was observed when 1,3-dibromopropane was condensed with the tetrasodio salt. The polymer was reported to be

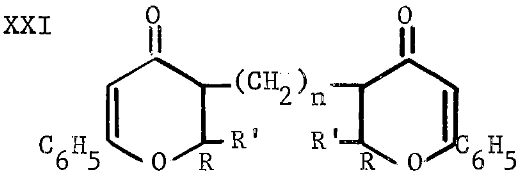


poly(1,3-octanedione) with a molecular weight of 1800 indicating an average value of n to be 12 to 13.

Bis-β-diketones XXIa and b were reported to form the tetrasodio salts when the compounds were treated with four equivalents of sodium amide in liquid ammonia. The diadducts obtained from the condensation



XXI

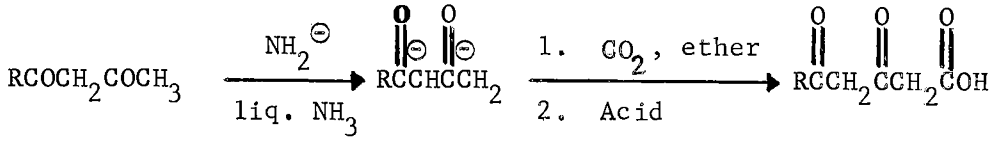


a, n = 3; R,R' = C_6H_5

b, n = 4; R = H, R' = $C_6H_4OCH_3$-p

of the tetrasodio salt with benzophenone and anisaldehyde were reported to be difficult to crystallize and were thus treated with methanolic hydrochloric acid to give the corresponding bisdihydro pyrones.

Carboxylations of dicarbanions derived from a large number of β-diketones have been carried out by the addition of lumps of Dry Ice to



$$RCOCH_2COCH_3 \xrightarrow[\text{liq. } NH_3]{NH_2^{\ominus}} R\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H\overset{O}{\overset{\|}{C}}\overset{\ominus}{C}H_2 \xrightarrow[\text{2. Acid}]{\text{1. } CO_2\text{, ether}} R\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OH$$

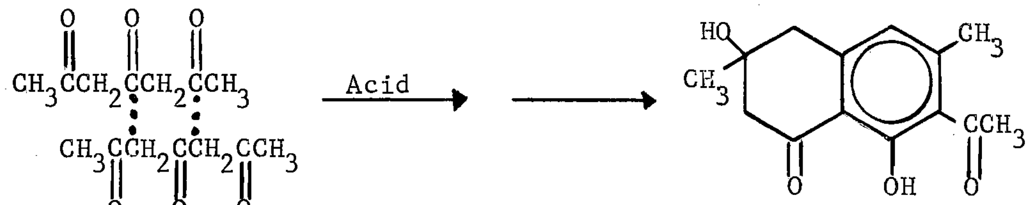
a. R = C_6H_5	a. R = C_6H_5
b. R = CH_3	b. R = CH_3
c. R = $C_6H_5CH_2CH_2$	c. R = $C_6H_5CH_2CH_2$
d. R = $(CH_3)_2CHCH_2$	d. R = $(CH_3)_2CHCH_2$
e. R = $C_6H_5CH{=}CH$	e. R = $C_6H_5CH{=}CH$
f. R = $(C_6H_5)_2C{=}CH$	f. R = $(C_6H_5)_2C{=}CH$
g. R = H	g. R = H
h. R = C_2H_5O	h. R = C_2H_5O

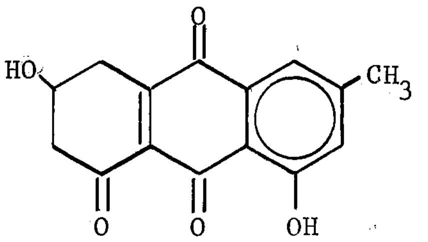
a mixture containing the dicarbanion. The yields of terminal acids in all cases were below 55%.[37]

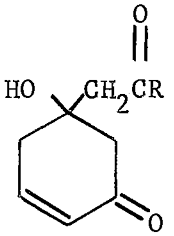
Poly-β-Carbonyl Compounds

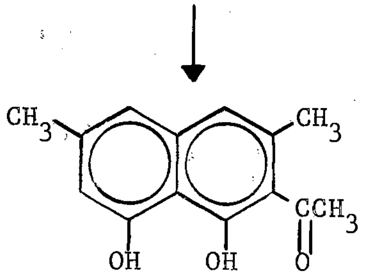
Linear β-polyketones and analogous compounds, although not extensively investigated, have been shown to undergo condensation to more complex sturctures, some of which are related in type to substances found in nature. The ease of some of these reactions led Collie in 1907[16] to suggest that such compounds might be intermediates in some biosynthetic processes and might be derived from acetic acid.

Birch and co-workers,[6] in a reinvestigation of Collie's earlier work, condensed two equivalents of the barium salt of 2,4,6-heptanetrione under weakly acidic conditions to form a yellow compound $C_{14}H_{14}O_3$









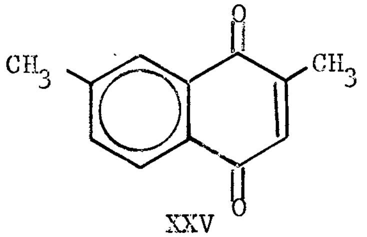
XXII

XXIII

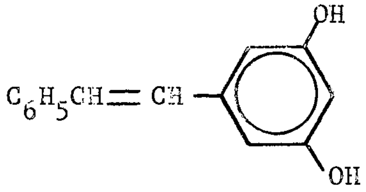
XXIV

assigned structure XXIV. In addition, two intermediate compounds were identified by UV data. Similarly, natural compounds containing hydroxycyclohexenone structures XXII and XXIII (R$\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}$ = oleoyl) were readily aromatized by dehydration.

Chimaphilline (XXV) from Ericaceae species is an example of a natural product which has been postulated as arising by intermolecular condensations between β-polyketones or poly keto acids.

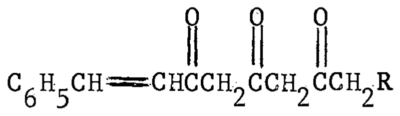


XXV



XXVI

It was suggested that the flavonoid constituents of pines could be correlated with the pinosylvin (XXVI) derivatives on the basis of a common origin from cinnamic acid and three acetate units through the intermediate (XXVII; R = CO_2H). However, no indication of the formation of

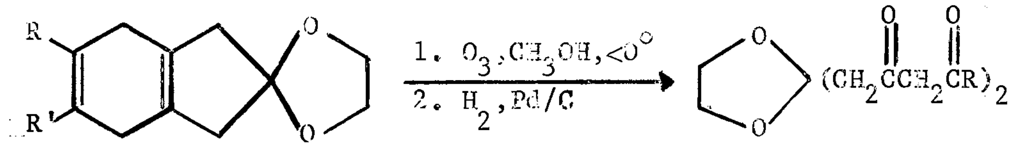


$$C_6H_5CH{=}CH\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2R$$

XXVII

pinosylvin (XXVI) was found when compound XXVII was treated with alkali under a variety of conditions.[1]

Ozonolysis has also been found to lead to poly-β-carbonyl compounds. The ozonide of ketal XXVIIIa was hydrogenated to give the tetraketone



XXVIIIa, R = R' = H

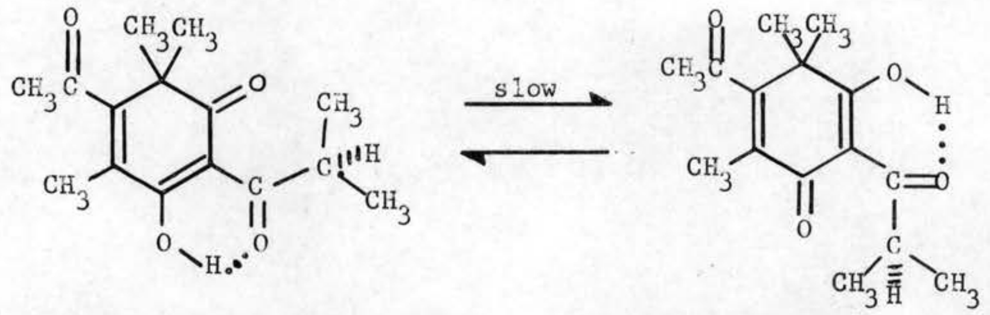
b, R = R' = CH

XXIXa, R = R' = H

b, R = R' = CH_3

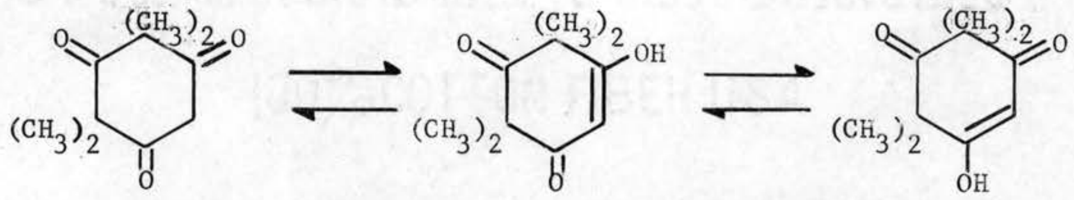
XXIXa. Similarly hydrogenation of the ozonide of ketal XXVIIIb gave tetraketone XXIXb.[8]

Tasmanone, a constituent of the essential oils of Eucalyptus tasmanica Blakely and E. camfieldi Maiden, apparently exists as a tautomeric mixture of two enolic forms since its titration curve showed



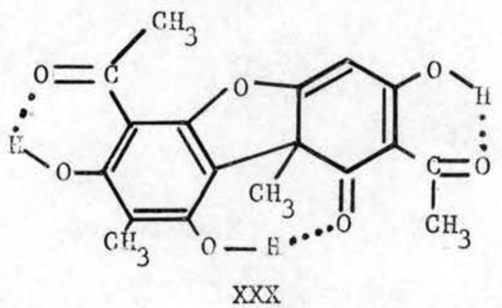
a pronounced hysteresis effect on back-titration, and in its NMR spectrum the signals of most of the groups of protons were doubled, with the intensity of one of each pair half that of the other. Addition of a small amount of diethylamine to a chloroform solution containing tasmanone produced a coalescence of the signals attributed to the two tasmanone tautomers.[6]

The NMR spectrum of syncarpic acid, in deuterochloroform, reveals that the acid exists almost entirely in the keto form. However, in

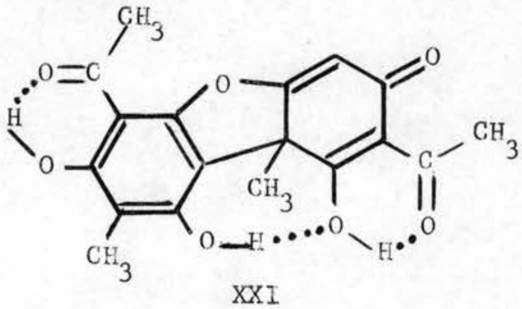


acetone-d_6 solution the substance is almost entirely in the enol form (92%).[6]

In the case of unsic acid, it has been shown by NMR analysis[23] that only one enolic form exists which is either XXX or XXXI. Form XXX has been reported to be likely the more stable one, not only because it



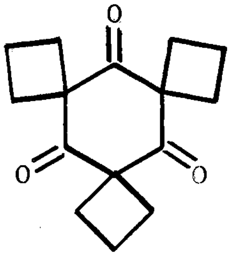
XXX

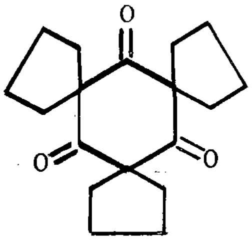


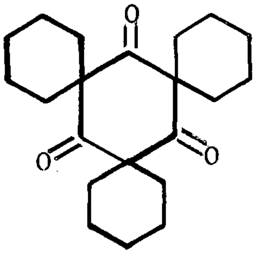
XXI

contains a conjugated system, but also because the hydrogen bonding in XXXI might be expected to be less stable than in XXX in which all three hydroxy groups are bonded to individual carbonyl groups.

Recently, several trispiro triketones were synthesized by base catalysis of the dimer of trimethyleneketene, tetramethyleneketene dimer, and pentamethyleneketene dimer. Alcoholysis, in the presence of a catalytic amount of sodium ethoxide, of the trispiro compounds led to acyclic β,δ-diketo esters.[65]



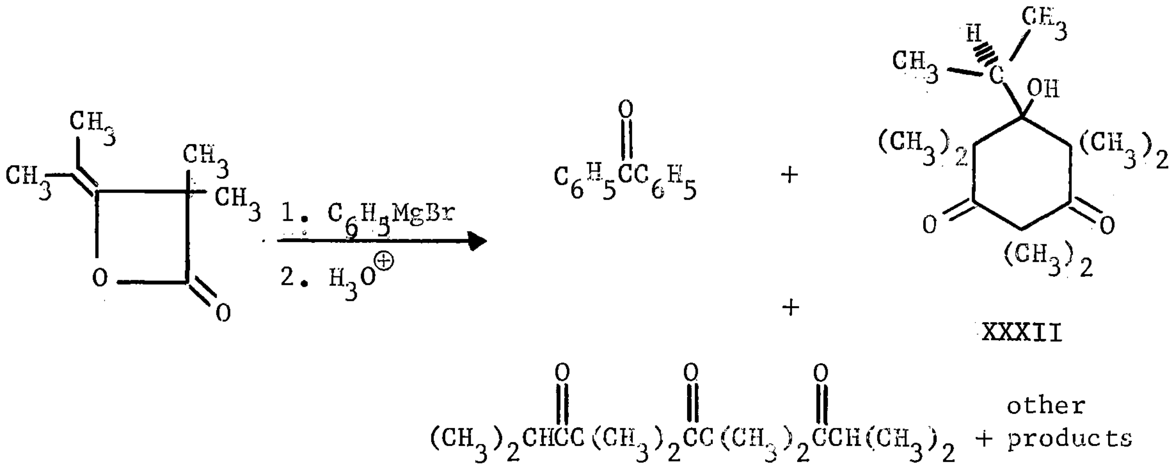




CHAPTER II

DISCUSSION OF RESULTS AND CONCLUSIONS

A study of the condensation of 3-hydroxy-2,2,4-trimethyl-3-pentenoic acid β-lactone (I) with phenyl Grignard reagent was undertaken because previous experiments performed in this Laboratory[5] gave support for the presence of the dicarbanion of diisopropyl ketone in the reaction mixture. In addition, this dianion intermediate was surmised to be involved in the formation of a ketol XXXII and a triketone XXXIII.

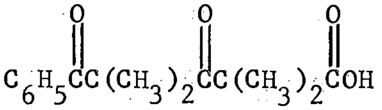


XXXII

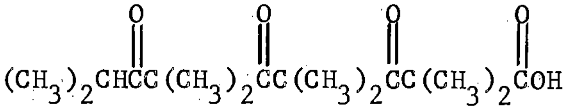
XXXIII

Since one mole of lactone in theory is consumed by two moles of Grignard reagent, excluding secondary processes such as cleavage or reduction of products, a 1:1 mole ratio of lactone I and Grignard reagent should provide 0.5 mole of the anion or dianion of diisopropyl ketone, which in turn may react with the remaining 0.5 mole of lactone I to give a new anion or dianion. This has been accomplished although an excess of lactone I was used because insufficient reaction (diaddition) was observed, and an increase in the yield of ketol was noted. The reaction mixture, was found to contain, in addition to benzophenone and the ketol XXXII, more than a dozen minor components including the triketone XXXIII (GLC analysis).

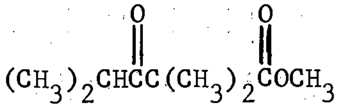
Carbonation of the reaction mixture of phenyl Grignard reagent and lactone I in ether gave acid XXXIV, XXXV and an oil. The oil was


$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH}$

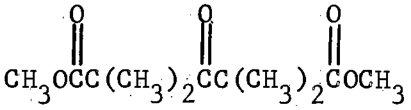
XXXIV


$\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH}$

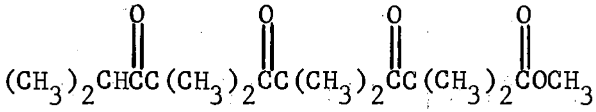
XXXV


$\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3}$

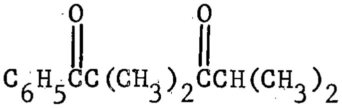
XXXVI


$\mathrm{CH_3O\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3}$

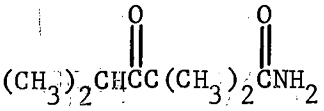
XXXVII


$\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3}$

XXXVIII


$\mathrm{C_6H_5\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}CH(CH_3)_2}$

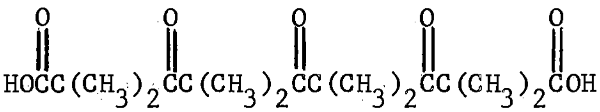
XXXIX


$\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}NH_2}$

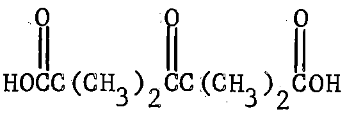
XL

treated with diazomethane; esters XXXVI, XXXVII, and XXXVIII, diketone XXXIX, amide XL and triketone XXXIII were found in the reaction mixture.

Carbonation of the reaction mixture of phenyl Grignard reagent and lactone I in tetrahydrofuran gave acids XLI, XLII and an oil. The oil

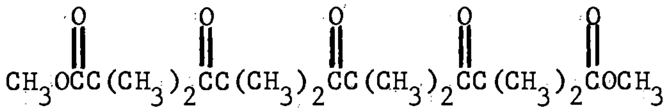

$\mathrm{HO\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH}$

XLI


$\mathrm{HO\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH}$

XLII

when treated with diazomethane gave esters XXXVI, XXXVII, and XXXVIII, diketone XXXIX, amide XL and triketone XXXIII. A mixture of acids LXI and XLII treated with diazomethane gave diesters XLII, XLIII, and XXXVII.

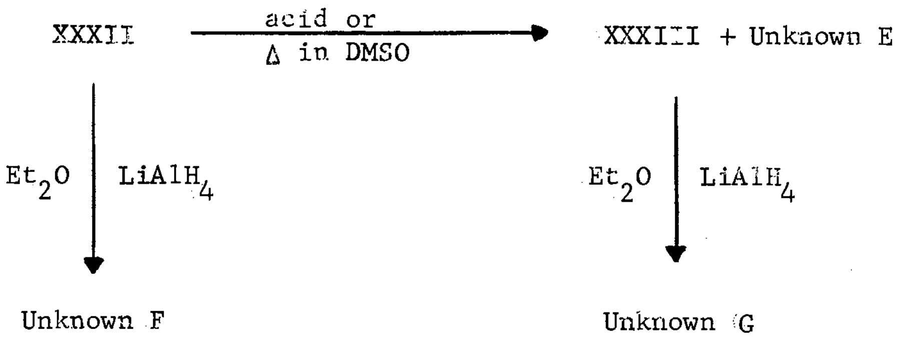


$$CH_3O\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$$

XLIII

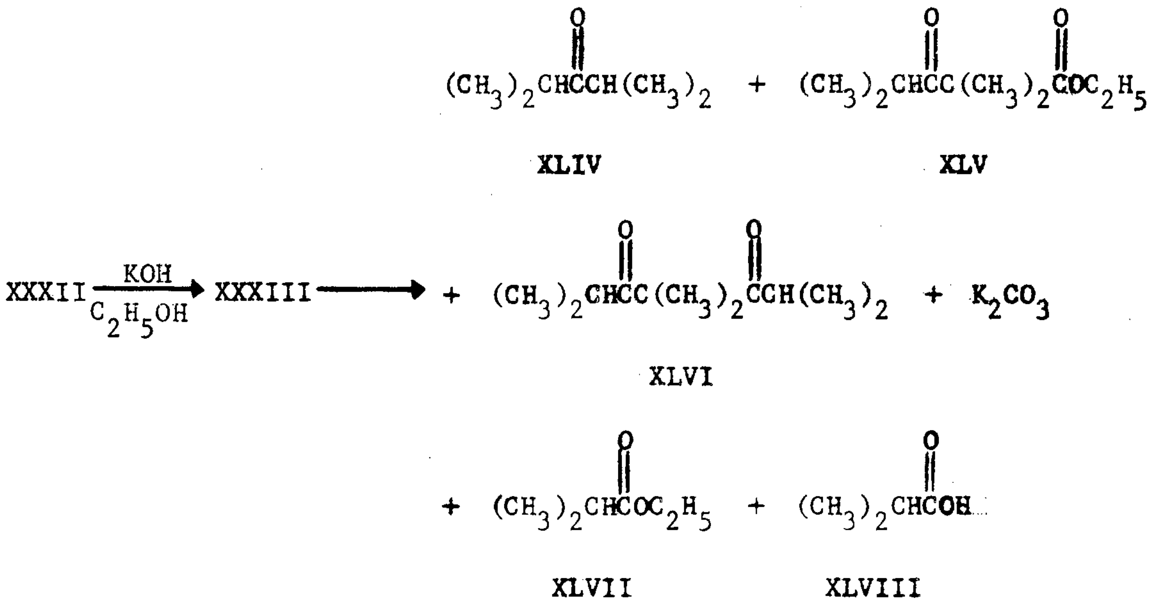
Lactone I with methyl and ethyl Grignard reagents produced complex reaction mixtures but good yields of triketone XXXIII. Lactone I and t-butyl Grignard reagent gave a complex reaction mixture, with amide XL being isolated and triketone XXXIII detected in the reaction mixture.

Acid hydrolysis of ketol XXXII gave triketone XXXIII and unknown E, while heating ketol XXXII in DMSO yielded triketone XXXIII and a trace of unknown E. Thermolysis of XXXII gave XXXIII in quantatative yield.



Ketol XXXII and lithium aluminum hydride gave a solid product, unknown F. The same reducing agents converted triketone XXXIII to a solid compound, unknown G.

Base degradation in ethyl alcohol of triketone XXXIII gave diisopropyl ketone (XLIV), ethyl 2,2,4-trimethyl-3-oxovalerate (XLV), 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI), potassium carbonate, ethyl isobutyrate (XLVII) and isobutyric acid (XLVIII). Base degradation of ketol XXXII



$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}CH(CH_3)_2 \quad + \quad (CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}OC_2H_5$$

XLIV XLV

$$XXXII \xrightarrow[C_2H_5OH]{KOH} XXXIII \longrightarrow + \quad (CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}CH(CH_3)_2 \quad + \quad K_2CO_3$$

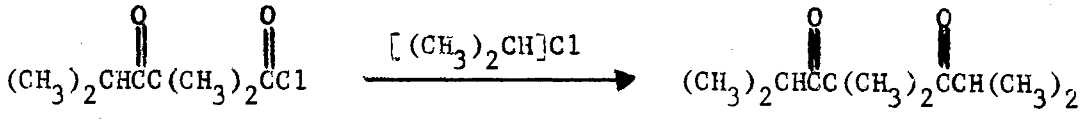
XLVI

$$+ \quad (CH_3)_2CH\overset{\overset{O}{\|}}{C}OC_2H_5 \quad + \quad (CH_3)_2CH\overset{\overset{O}{\|}}{C}OH$$

XLVII XLVIII

in ethyl alcohol gave rise to the same products as from triketone XXXIII except that triketone XXXIII was detected in the reaction mixture.

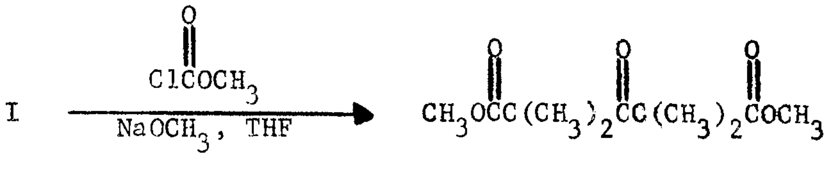
Diketone XLVI was prepared by condensing 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX) with diisopropylcadmium. Dimethyl 2,2,4,4-



$$(CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}Cl \xrightarrow{[(CH_3)_2CH]Cl} (CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}CH(CH_3)_2$$

XLIX XLVI

tetramethyl-3-oxoglutarate (XXXVII) was prepared by the reaction of



$$I \xrightarrow[NaOCH_3,\ THF]{Cl\overset{\overset{O}{\|}}{C}OCH_3} CH_3O\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}OCH_3$$

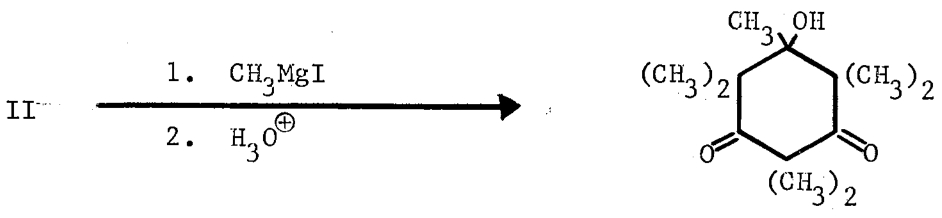
XXXVII

lactone I with methyl chloroformate in the presence of sodium methoxide.

Hexamethyl-1,3,5-cyclohexanetrione (II) and isopropyl Grignard reagent, in the presence of magnesium bromide and isopropyllithium,

$$\text{II} \xrightarrow[\text{or } (CH_3)_2CHLi]{(CH_3)_2CHMgBr\ (\text{in MgBr})} \text{XXXIII} + \text{other products}$$

respectively, gave triketone XXXIII and several other products. Methyl Grignard reagent and II gave hydroxy diketone L.



L

The original condensation of lactone I and phenyl Grignard reagent was performed utilizing various molar ratios of the lactone I to the Grignard reagent. In all cases except where the molar ratio of lactone I to phenyl Grignard reagent was 0.8:1, ketol XXXII could be crystallized directly from the reaction mixture and the compound easily purified (see Experimental section). Evidently, XXXII was present in the 0.8:1 reaction of I and phenyl Grignard reagent in too low yield to crystallize directly. Removal of most of the products, excluding ketol XXXII, was effected by treatment of the reaction residue with Girard's T reagent.

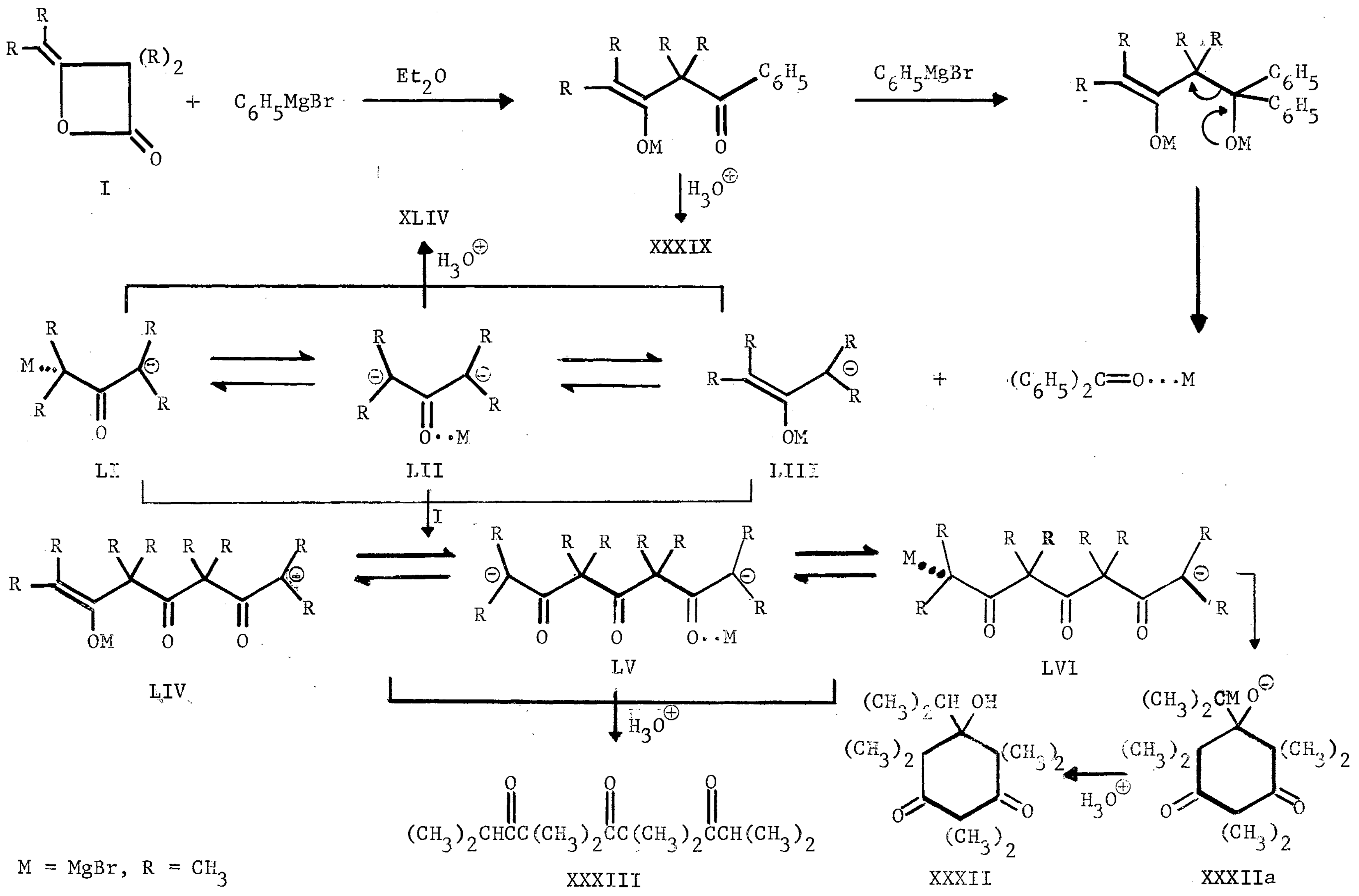
This process resulted in the eventual isolation of several grams of pure ketol XXXII.

A molar ratio of 1:1.2 for phenyl Grignard reagent and lactone I was found to give the maximum amount (30.1%) of ketol XXXII. When the molar concentration of I was raised above 1.2, the yield of ketol XXXII dropped slightly. The general procedure used for effecting the condensation was to add the lactone I to the chilled Grignard solution, stir the mixture and then heat at reflux. Hydrolysis of the mixture was performed at room temperature with aqueous ammonium chloride solution because at ice-salt bath temperatures, the mixture solidified to a large extent and stirring became difficult. In general, workup of the reaction mixture proceeded smoothly unless the reaction mixture, after hydrolysis, was stirred vigorously and then extracted immediately. Separation of layers was exceedingly slow when this latter process was tried.

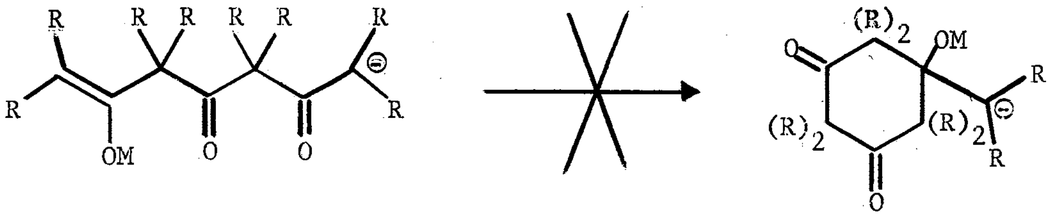
Since the 1:1.2 mole condensation of lactone I and phenyl Grignard reagent was frequently used for the preparation of ketol XXXII, the reaction residue left after the removal of this compound was analyzed by GLC. Benzophenone (40.1%) was found to be the major component, in addition to more than a dozen other components including diisopropyl ketone (XLIV) (4%), 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX) (8%) and triketone XXXIII (4%).

Both methyl and ethyl Grignard reagents, when condensed with lactone I, gave complex reaction mixtures, with only the ethyl Grignard run providing ketol XXXII. Both reaction mixtures, via GLC analysis were shown to contain triketone XXXIII in good yields. No explanation is offered as to the high yield (60%) of the triketone XXXIII and the trace amount of ketol XXXII (ethyl Grignard run). Thus, the condensation of ethyl and methyl Grignard reagents with lactone I needs further investigation. t-Butyl Grignard reagent and lactone I also gave a complex reaction mixture (GLC analysis). A small amount of 2,2,4-trimethyl-3-oxovaleramide (XL) was obtained from the reaction mixture, and the structure of the compound was supported by NMR (Plate XXXI) and IR (Plate IX) analyses. Triketone XXXIII was also identified as one of the products. Amide XL is postulated to arise from the reaction of aqueous ammonium chloride solution on lactone I during hydrolysis of the reaction mixture.

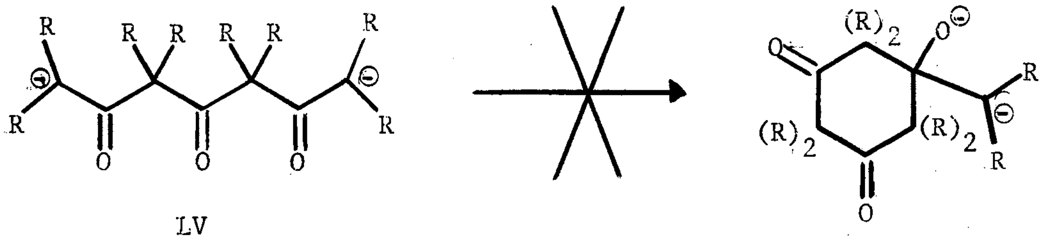
The mechanism of formation of XXXII and XXXIII and several other products from the reaction of I and phenyl Grignard reagent is believed to involve initial cleavage of the lactone I by one mole of the phenyl Grignard reagent. A second mole of Grignard may add to give an intermediate which undergoes retrograde aldol-type cleavage to yield benzophenone and an anion of diisopropyl ketone, species LI, LII and/or LIII. These carbanion-enolate or dicarbanion intermediates may react with additional lactone I giving rise to new anion intermediates LIV, LV and LVI. Which of the species LI, LII or LIII condenses with the lactone I to form anions LIV, LV or LVI cannot be determined from the present data, but LI and LIII are perhaps better candidates than LII because of the presence of two negative charges on LII. Hydrolysis of the reaction mixture with aqueous ammonium chloride solution gives ketol XXXII and triketone XXXIII in relatively low yields. The structure LVI may be favored over LIV and LV because ring closure of the latter two species


I
C6H5MgBr
Et2O
C6H5
OM
H3O⊕
XXXIX
XLIV
LI
LII
LIII
(C6H5)2C=O···M
LIV
LV
LVI
(CH3)2CHCC(CH3)2CC(CH3)2CCH(CH3)2
XXXIII
XXXII
XXXIIa
(CH3)2CH OH
(CH3)2CM O⊖
(CH3)2

M = MgBr, R = CH_3



LIV



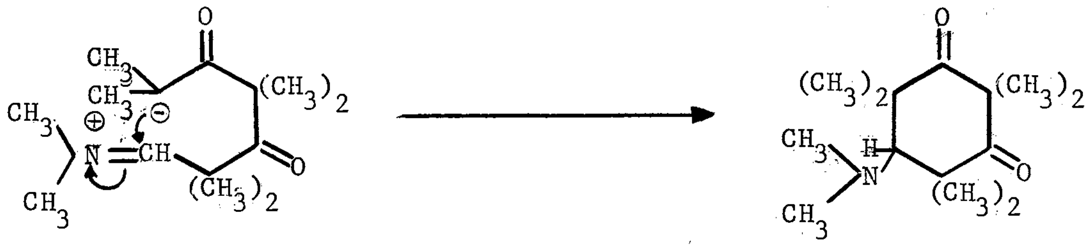
LV

R = CH_3

would give a tertiary carbanion the stability of which may be less than that of XXXIIa. The stability of the enol forms LIII and LIV compared to keto forms LI, LV and LVI cannot be evaluated from the present data; thus a definite designation of LIV, LV or LVI as the precursor of XXXIIa is not possible. Since GLC indicates a complex reaction mixture, the anions LI, LII, LIII, LIV, LV and LVI may be involved in other reaction sequences.

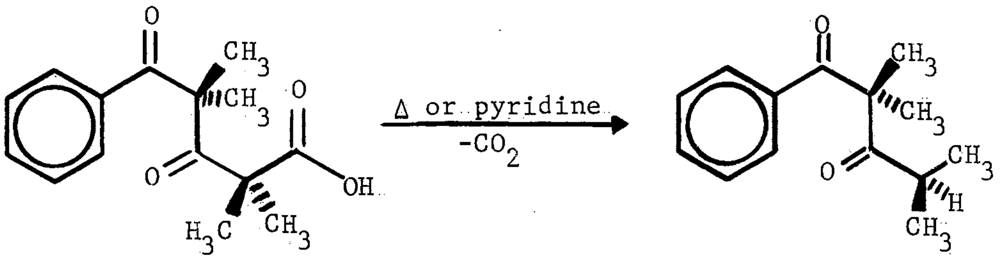
When tetrahydrofuran was used as a solvent for the condensation of lactone I and phenyl Grignard reagent, solvation of the Grignard complex was observed. Initially upon heating, the reaction mixture became a dark red-brown solution. The yield of ketol XXXII in this reaction was found to be lower than in the condensation of phenyl Grignard reagent and lactone I in ethyl ether.

A cyclization similar to that shown for XXXIIa has been observed in the formation of 5-dimethylamino-2,2,4,4,6,6-hexamethyl-1,3-cyclohexanedione (LVII).[44] Cyclization of the carbanion intermediate in this case



involves attack on a carbon atom of an enamine salt rather than a carbonyl carbon atom.

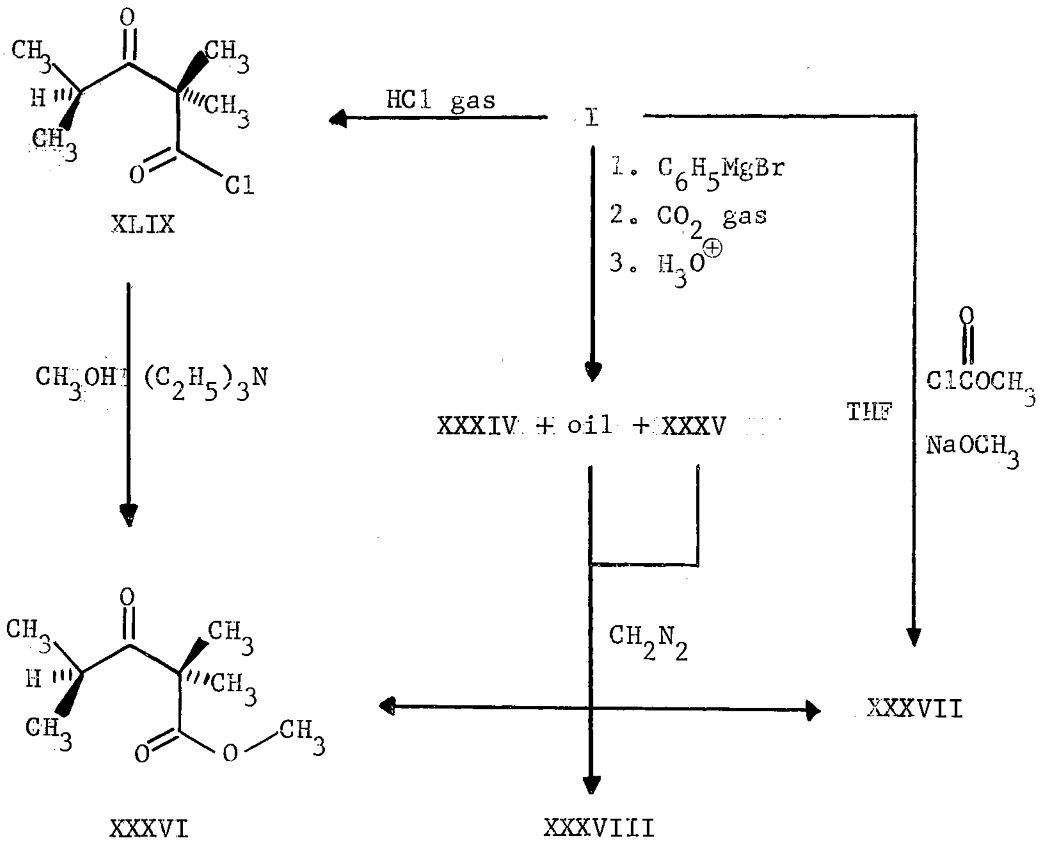
In order to demonstrate the intermediacy of species LI, LII, LIII, LIV, LV and LVI the reaction mixture of phenyl Grignard reagent and lactone I was carbonated. Carbon dioxide gas was bubbled through the ethereal reaction mixture. No noticeable reaction was observed, but the mixture had the appearance of caramel candy with layers of white material. Workup of the reaction afforded a monoacid, 5-phenyl-2,2,4,4-tetramethyl-3,5-dioxovaleric acid (XXXIV), in low yield and a brown



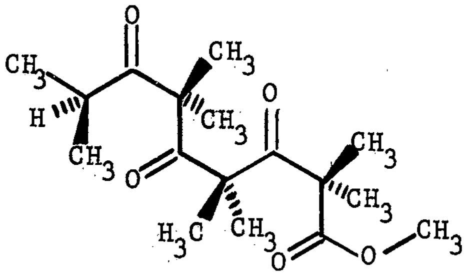
XXXIV

XXXIX

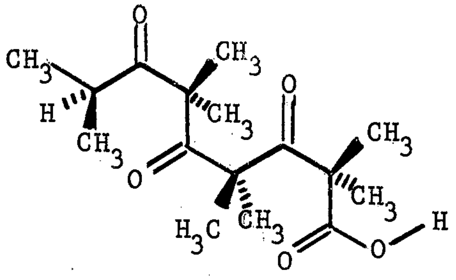
viscous oil. The structure of monoacid XXXIV was supported by IR, NMR (Plates III and XXIV) and elemental analyses (see Tables III, IV and V). The NMR spectrum (pyridine-d_5) had to be taken quickly as compound XXXIV rapidly (10-15 minutes) decomposed into diketone XXXIX. Thermolysis of acid XXXIV at its melting point gave the diketone XXXIX in quantitative yield. IR and NMR analyses (Plates IV and XXV - Tables IV and V) further support the known structure of diketone XXXIX.[5] The aforementioned oil was treated with diazomethane and afforded a complex reaction mixture. GLC analysis revealed the presence of methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI), dimethyl 2,2,4,4-tetramethyl-3-oxoglutarate (XXXVII), 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX), 2,2,4-trimethyl-3-oxovaleramide (XL), triketone XXXIII and methyl 2,2,4,4,6,6,8-heptamethyl-3,5,7-trioxononanoate (XXXVIII).



Ester XXXVI was prepared by treating lactone I with anhydrous hydrogen chloride gas,[79] followed by esterification of 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX) with methanol in the presence of triethylamine[4] to give the ester XXXVI in good yields. The structure of acid chloride XLIX was supported by NMR and IR data (Plates XXXVI and XVI). NMR and IR spectral data (Plates XXXVII and XVII) authenticated the structure of ester XXXVI. Methyl chloroformate and sodium methoxide with lactone I in tetrahydrofuran gave ester XXXVII in fair yield.[78] Authentication of its structure was afforded by physical data, including IR (Plate XVIII) and NMR (Plate XXXVIII) analyses (Tables IV and V). Ester XXXVIII was obtained in the pure form by preparative GLC and its structure elucidated by NMR (Plate XXXVII), IR (Plate VI) and elemental analyses (see Tables III, IV, and V). The presence of triketone XXXIII in the reaction mixture is attributed to decarboxylation of acid XXXV, probably during workup of the reaction mixture.



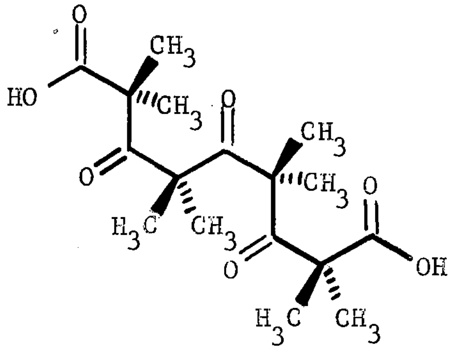
XXXVIII



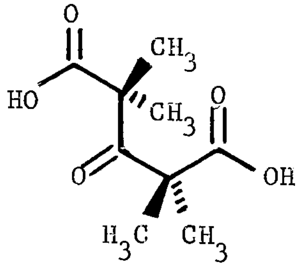
XXXV

Acid XXXV was produced when the oil obtained from an identical carbonation experiment was allowed to stand for several weeks. The compound precipitated and was identified as 2,2,4,4,6,6,8-heptamethyl-3,5,7-trioxononanoic acid (XXXV) by elemental analysis, IR (Plate V) and NMR (Plate XXVI) spectral data (Tables III, IV and V).

When the condensation of phenyl Grignard reagent and lactone I was performed in ethyl ether and the solvent displaced by tetrahydrofuran, carbonation of the resulting red-brown solution gave a mixture of acids



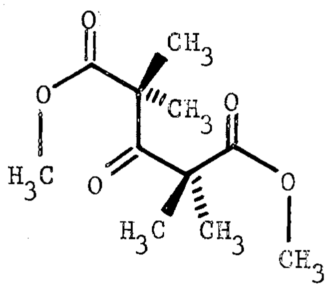
XLI



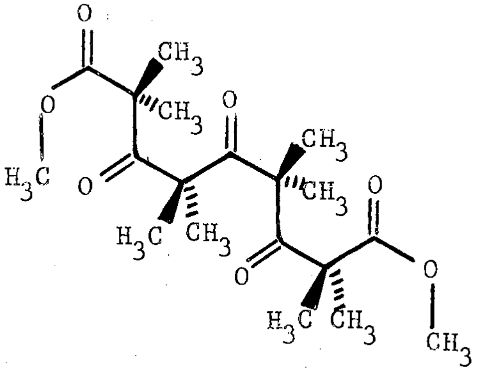
XLII

XLI, XLII and an oil. Although the mixture of XLI and XLII had a relatively sharp melting point (134-135.5^{o} dec.), both NMR and GLC analyses of a sample of the mixture revealed the presence of two compounds. The GLC chromatogram revealed two peaks which were identified as arising from diisopropyl ketone (XLIV) and triketone XXXIII. Apparently the acids decarboxylated on the column. A sample of pure XLI was obtained by repeated recrystallization of a sample of the acid mixture from benzene. Elemental analysis, NMR (Plate XXVIII) and IR (Plate VII) spectral data support the structure of this acid, 2,2,4,4,6,6,8,8-octamethyl-3,5,7-trioxo-1,9-nonanedioic acid (XLI), (see Tables III, IV and V).

A sample of a mixture of acids XLI and XLII was treated with diazomethane. Diester XLIII precipitated from the resulting golden-colored oil as a white solid. NMR (Plates XXIX and XXX), IR (Plate VIII) and elemental analyses support the proposed structure of dimethyl 2,2,4,4,6,6,8,8-octamethyl-3,5,7-trioxo-1,9-nonanedioate (XLIII). GLC analysis of



XXXVII

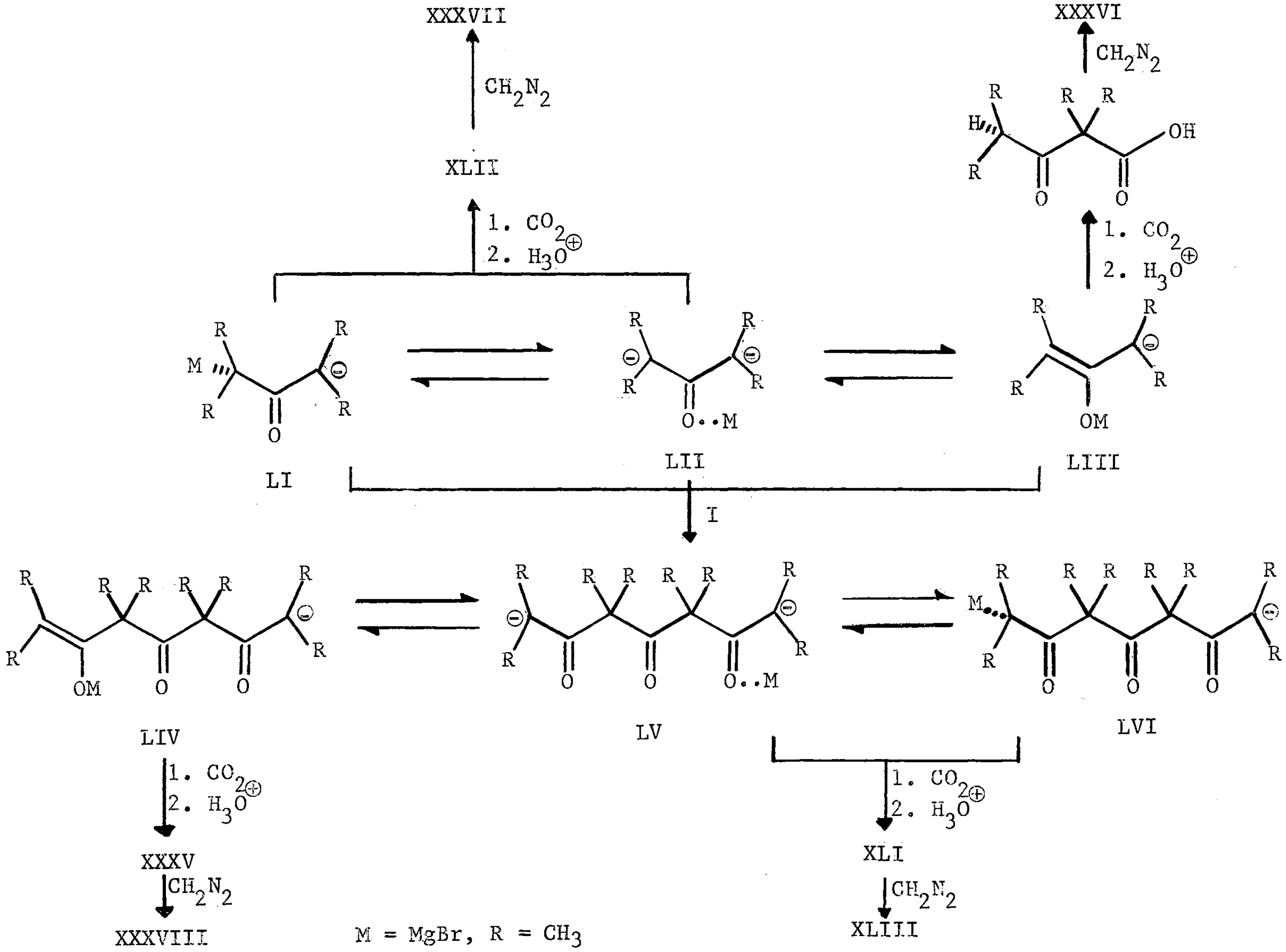


XLIII

the filtrate obtained from the removal of diester XLII showed only one peak; mixed injection with an authentic sample identified it as dimethyl 2,2,4,4-tetramethyl-3-oxoglutarate (XXXVII).

The NMR spectra of diesters XXXVII and XLIII (Plates XXXIX, XXX and XXXVIII) are unusual, since magnetic nonequivalence of the ester methyl protons in the ester group and of the internal gem-dimethyl protons is observed. Both compounds seem to have a preferred conformation and one can only speculate as to the true stereochemistry of both molecules. However, a conformation in which the carbonyl groups are trans-oriented and the gem-dimethyl groups are staggered would imply less dipole-dipole interactions between these groups and represents one possible conformation. At a temperature above 50°, the difference in the field position of the ester methyl protons in diester XLIII increased 2 c.p.s. Perhaps at a lower temperature, say 0°, these two singlets might coalesce.

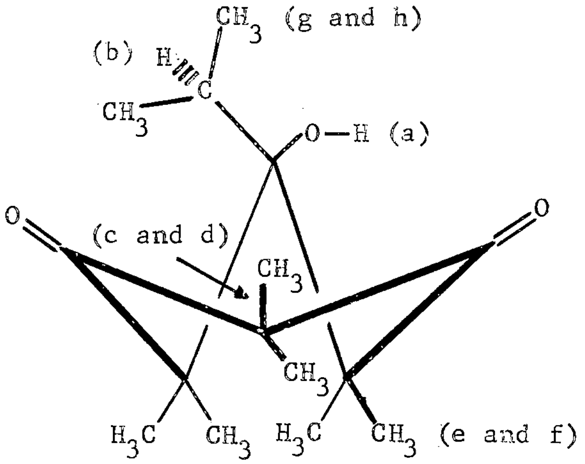
The equilibrium that is postulated between LI, LII and LIII, LIV, LV and LVI is based upon the fact that the ratio of monoacid (precursor of ester XXXVI) to diacid XLII (precursor of diester XXXVII) remained


XXXVII
CH$_2$N$_2$
XLII
1. CO$_2$
2. H$_3$O$^\oplus$
XXXVI
CH$_2$N$_2$
1. CO$_2$
2. H$_3$O$^\oplus$
LI
LII
LIII
I
LIV
LV
LVI
1. CO$_2$
2. H$_3$O$^\oplus$
XXXV
CH$_2$N$_2$
XXXVIII
1. CO$_2$
2. H$_3$O$^\oplus$
XLI
CH$_2$N$_2$
XLIII

M = MgBr, R = CH$_3$

fairly constant in all runs in ethyl ether. This suggests that the anions have a common precursor and that variation in the efficiency of carbonation is minimal. It is not possible to establish whether LI or LII is the precursor of the dicarboxylic acid XLII, but it is not unreasonable to suggest that LIII is carbonated to give the monoacid which esterified gives ester XXXVI. Likewise, whether species LV or LVI is the precursor of diacid XLI cannot be evaluated with the present data; again it is not unreasonable to assume that LIV is carboxylated to give monoacid XXXV and esterification of this compound gives ester XXXVIII. When the carbonation of the reaction mixture of lactone I and phenyl Grignard reagent was performed in tetrahydrofuran, an increase in the ratio of diacid XLII (precursor of diester XXXVII) to monoacid (precursor of ester XXXVI) was noted. This could be a result of increased solvation of all reactants or a shift in the equilibrium between LI and LII or LIII. These arguments receive some support from experimental data. Carbonation of the original condensation product (in ethyl ether) was performed in a heterogeneous reaction mixture, but use of tetrahydrofuran i.e., permitted carbonation in a homogeneous system. The condensation of lactone I and phenyl Grignard reagent in tetrahydrofuran at 68° gave a lower yield of ketol XXXII than when performed in ethyl ether. If a shift in the equilibrium between LI and LII or LIII and LVI, LIV or LV occurred at this higher temperat re, ketol XXXII should have been formed in a higher yield. As suggested earlier, dianion species LVI cyclizes giving XXXIIa which upon hydrolysis yields XXXII. However, the original condensation in tetrahydrofuran was performed only once, and because of insufficient data, this one condensation cannot be expected to disprove our arguments. Furthermore many condensations (1:1.2) between phenyl Grignard reagent and lactone I were effected in order to prepare ketol XXXII. Although the lactone I was distilled before using and the yields of phenyl Grignard reagent were generally above 95%, the yield of ketol XXXII varied from 15-30.1%. Many explanations can be adduced for such a range of yields; thus the lower yield of ketol XXXII obtained when tetrahydrofuran was used as the solvent cannot be a basis for stating that this is the highest possible yield of ketol XXXII with this solvent system.

A maximum yield (30.1%) of ketol, 5-hydroxy-2,2,4,4,6,6-hexamethyl-5-isopropyl-1,3-cyclohexanedione (XXXII), was obtained once when phenyl Grignard reagent and lactone I were combined in a molar ratio of 1:1.2. The compound was easily crystallized directly from the reaction mixture; purification was relatively simple. Elemental analysis (Table III) indicated an empirical formula of $C_{15}H_{26}O_3$ with a molecular weight of 253 (Monsanto Chemical Company, Inc., St. Louis, Missouri). Infrared absorptions (Plate II) occurred at 3460 (hydroxyl group) 1692 (carbonyl group:shoulder at 1718), 1390 and 1378 cm.$^{-1}$ (isopropyl group) with several other sharp bands as found in Table IV. The NMR spectrum (100 M.c.) displayed signals in benzene (Plate XXI) at δ1.90 (singlet), 1.43 (doublet:J = 7 c.p.s.), 1.19 (doublet:J = 6 c.p.s.) and 0.91 (doublet: J = 6.5 c.p.s.) in a ratio of 1:6:12:6 respectively. At a sweep width of 500 c.p.s., the peaks representing the proton of the tertiary hydrogen were easily discernible but no assignment in regard to their relative field position was made. When the NMR spectrum (60 M.c.) of ketol XXXII was determined in pyridine-d_5 (Plate XXIII), an enhanced chemical shift placed the heptet of proton b at δ2.38 clearly outside the area of the methyl resonances. Further NMR studies [100 M.c., at a sweep width

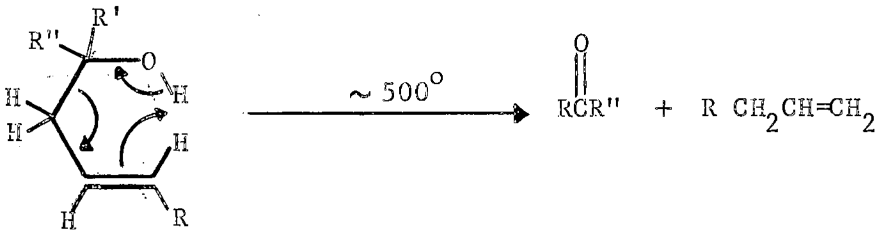


XXXII

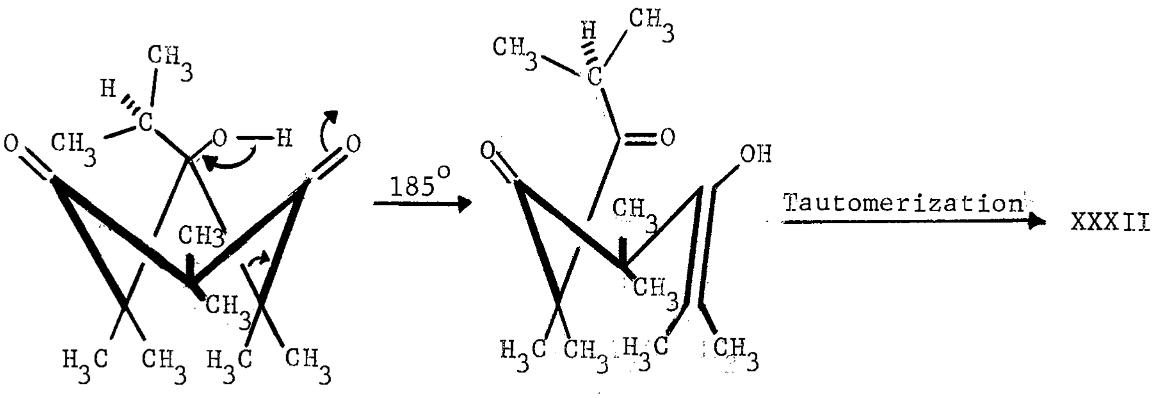
of 250 c.p.s. and a spectrum amplitude of 6000] of ketol XXXII (Plate XXII) revealed the finer points of the previous spectrum (Plate XXI). In benzene, five of the theoretical seven peaks of the expected heptet for proton b on XXXII were revealed. The doublet at δ1.43 has been assigned to methyl group protons c and d, while the doublet at δ1.19 is due to methyl protons e and f and the doublet at δ0.91 to the methyl protons of the isopropyl group g and h. Decoupling protons g and h from the tertiary proton b (-273.3 c.p.s.). [and the reverse decoupling] resulted in the collapse of the doublet due to protons g and h and the heptet due to the proton b, respectively, to singlets. These decoupling experiments show that the protons g and h are the true protons on an isopropyl group. Splitting of the gem-dimethyl resonances may result from a preferred conformation imposed upon the system by steric requirement of the isopropyl group and geometric stipulations of the 1,3-dicarbonyl system. It is rather interesting to note that the isopropyl group of ketol XXXII apparently experiences only one environment. Drieding models infer that a chair conformation for ketol XXXII is rigid and has imposing 1,3-interactions of axial methyl groups. However, a twisted-chair form can be constructed, in which interactions of non-bonded groups are reduced (structure shown on page 48). Although the twisted-chair form may imply a rigid system for ketol XXXII, an NMR analysis in a suitable solvent at low temperature would resolve whether the molecule is rigid or is flipping through all possible forms faster than the sweep rate of the instrument (2 c.p.s./sec.). An X-ray analysis of ketol XXXII would provide knowledge of the true conformation of this molecule in the solid state. Because of a lack of a model similar to XXXII, assignment of the proton resonances c and d and e and f to individual methyl groups could not be determined. This situation is not met in the NMR spectrum of II, which displays two sets of magnetically equivalent, internal gem-dimethyl groups as one signal. Dipole moment studies indicate that triketone II probably exists in a twisted flexible boat conformation. This form shows an equivalency of all methyl groups.[18]

Treatment of ketol XXXII with aqueous hydrochloric acid gave two products which were detected in the reaction mixture by GLC analysis. Attempted distillation of this mixture did not afford any pure compound. However, both products were obtained in the pure form by preparative GLC (see Experimental section). The first peak collected from the Autoprep unit was labeled unknown E. Although the mass spectrum of this compound indicated a molecular weight of 236 [thus probably a dehydration product of ketol XXXII], elemental analysis did not lead to the molecular formula $C_{15}H_{24}O_2$ as expected (see Table III). The IR spectrum (Plate X) indicates the presence of a vinylic methylene group and possibly a five-membered ring (carbonyl absorptions at 1722 - shoulder at 1748 cm.$^{-1}$). The NMR spectrum (Plate XXXII) also shows a terminal methylene group (see Table V), but the rest of the spectrum suggests a rather complex system. A 100 M.c. spectral analysis and decoupling experiments might be helpful in resolving the structure of unknown E. The second peak collected from the Autoprep unit was identified by spectral data as triketone XXXIII. Dehydration of ketol XXXII with potassium acid sulfate likewise gave unknown E and triketone XXXIII. Attempted solvolytic dehydration of XXXII with dimethyl sulfoxide[80] at 178° for nine hours resulted in a 98% conversion to triketone XXXIII. The trace product accompanying XXXIII was identified by GLC analysis as unknown E.

Thermolysis of ketol XXXII at 185° for one hour gave triketone XXXIII in quantitative yield. Although pyrolysis of this type is rare in the literature, an anology may be found in the pyrolysis of β-hydroxy olefins, which is believed to involve a cyclic mechanism.[2]



As stated previously, models imply that nonbonded interactions are minimal in the twist conformation of XXXII but the hydroxyl proton a can rotate close to an oxygen atom of a β-carbonyl group. One rationale for the apparent lower activation energy for thermal conversion of XXXII to



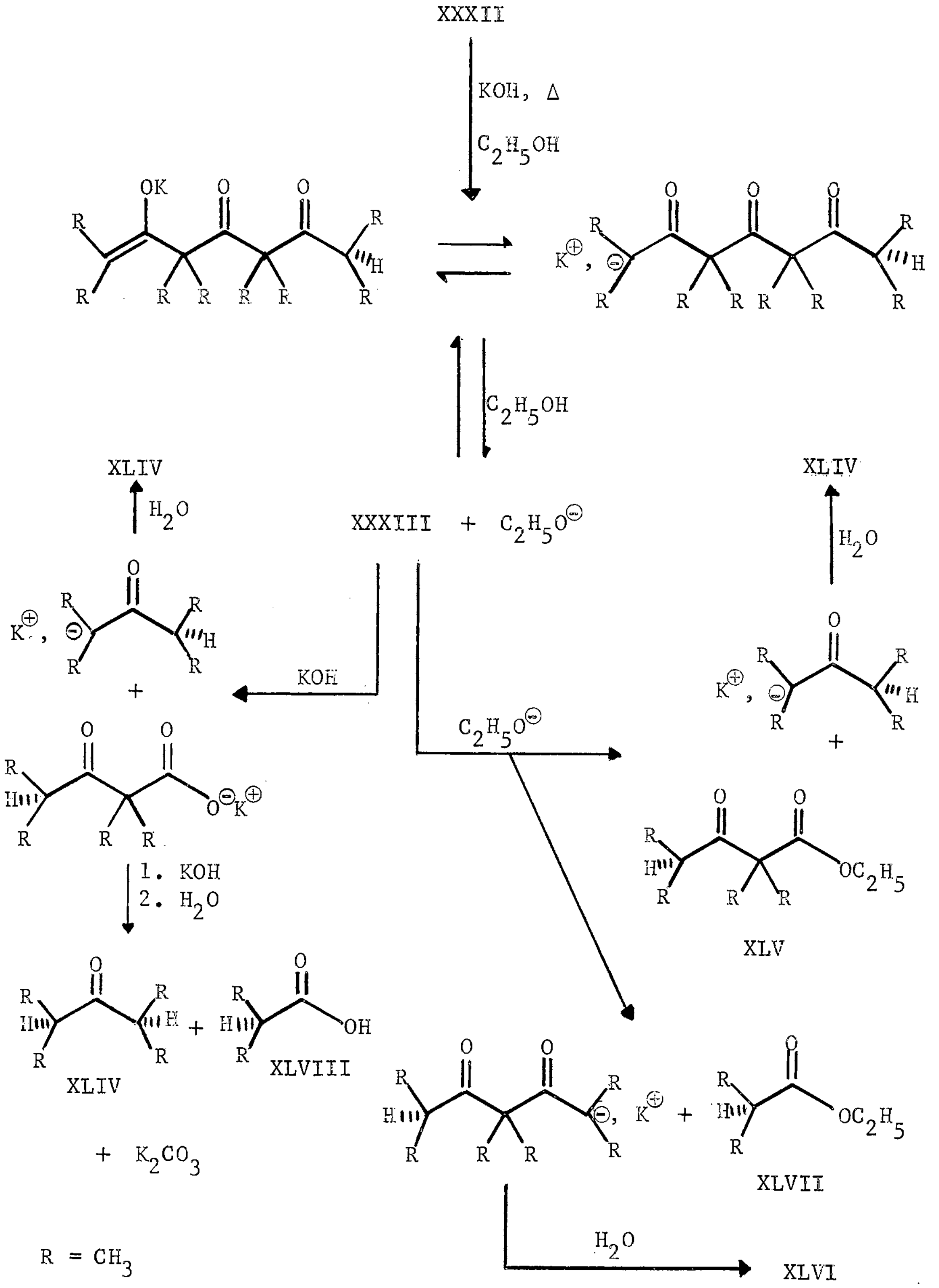
XXXII

triketone XXXIII compared to the analogous pyrolysis of β-hydroxy olefins is perhaps found in the conformational rigidity of the ring in XXXII, which increases the strain.

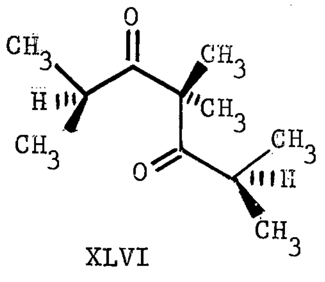
In attempts to prepare ketol XXXII, hexamethyl-1,3,5-cyclohexanetrione (II) was treated with isopropyl Grignard reagent (in the presence of magnesium bromide)[76] and isopropyllithium, respectively. The reaction mixture obtained from the isopropyl Grignard reaction was shown to contain [GLC analysis] triketone XXXIII in low yield; starting material [triketone II] was largely recovered. A slightly improved yield of triketone XXXIII was observed by GLC analysis of the reaction mixture of isopropyllithium and triketone II. Several other products including triketone II were also present in the reaction mixture.

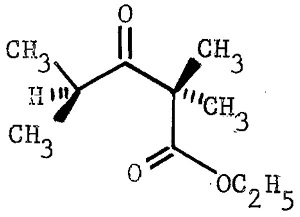
Ring closure of triketone XXXIII was attempted using sodium methoxide and sodium hydride as bases. It could not be established from GLC analysis of the two reaction mixtures obtained, that ketol XXXII was not one of the many products present. Triketone XXXIII was identified in the aqueous portion (after hydrolysis of the reaction mixture and workup of the aqueous layer) of the reaction mixture and its presence can be explained in several ways: inferior procedure for processing the reaction mixture, carbanion formation of triketone XXXIII and subsequent hydrolysis yielding XXXIII, or cyclization of triketone XXXIII giving ketol XXXII, after hydrolysis, with subsequent decomposition of XXXII on the GLC column. When an ethereal solution of pure ketol XXXII was placed on a GLC column, a chromatogram representative of a decomposition pattern was observed with a large peak having the same retention time as triketone XXXIII was noticed.

By using an excess of potassium hydroxide in absolute ethanol, ketol XXXII was degraded into three compounds, diisopropyl ketone (XLIV), isobutyric acid (XLVIII) and potassium carbonate. Because of the rather large amount of potassium carbonate that precipitated, it was anticipated that using equimolar quantities of ketol XXXII and base would produce intermediary products that might be isolated. This was verified; the 1:1 reaction of XXXII with potassium hydroxide in absolute ethanol gave (after hydrolysis) triketone XXXIII, ethyl isobutyrate (XLVII), ethyl 2,2,4-trimethyl-3-oxovalerate (XLV), diisopropyl ketone (XLIV), 2,2,4,4-tetramethyl-3,5-heptanedione(XLVI), potassium carbonate and a trace of isobutyric acid (XLVIII). Since XXXIII was present in the reaction mixture the mechanism of the reaction is postulated as involving initial ring opening of ketol XXXII to yield the monocarbanion of XXXIII. Since hydroxide ion would be totally consumed in the initial step, ethoxide ion is believed to form and become a competitive base. Although attack by base at the carbonyl carbon atom in XXXII could occur, no simple mechanism can be written which would involve the formation of triketone XXXIII. Diisopropyl ketone (XLIV), triketone XXXIII, isobutyric acid (XXXVIII), and ethyl isobutyrate (XLVII) were detected by GLC analysis of the reaction mixture. Diketone XLVI and β-oxoester XLV were isolated in pure form by preparative GLC. The structure of diketone XLVI was supported by IR (Plate XV) and NMR (Plate XXV) analyses.

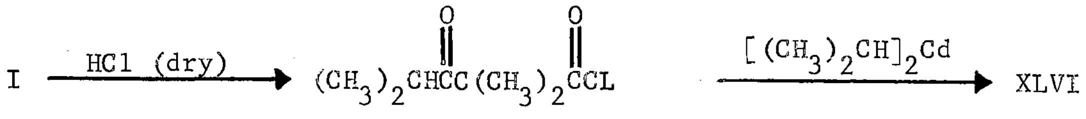


Additional proof for structure XLVI was obtained when the compound was


XLVI


XLV

synthesized by treating 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX) with diisopropylcadmium. The structure of ester XLV was substituted by IR (Plate XIV) and NMR (Plate XXXIV) analyses.

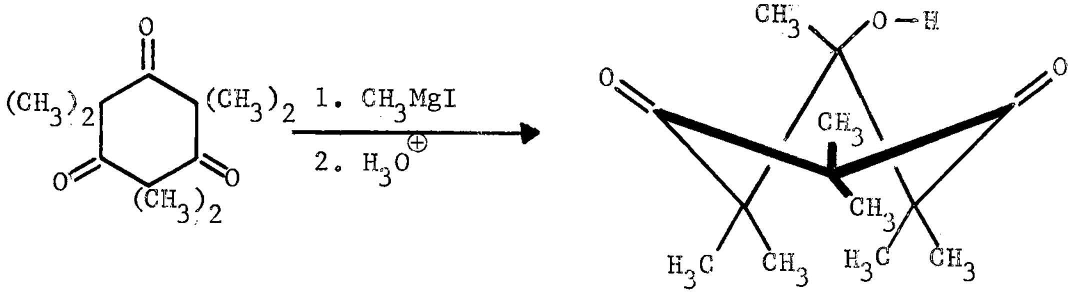


$$\mathrm{I} \xrightarrow{\text{HCl (dry)}} (CH_3)_2CH\overset{\overset{O}{\|}}{C}C(CH_3)_2\overset{\overset{O}{\|}}{C}CL \xrightarrow{[(CH_3)_2CH]_2Cd} \mathrm{XLVI}$$

XLIX

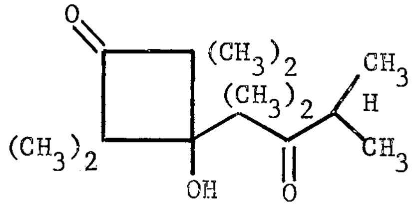
Lithium aluminum hydride, when allowed to react with ketol XXXII, gave a gas (probably hydrogen-no IR absorptions), a rather viscous oil, and a white solid (Unknown F) in low yield. The IR (Plate XII) spectrum of this solid indicated no carbonyl bonds, and the initial evidence suggested that reduction of both carbonyl groups of ketol XXXII had occurred. However, elemental analysis (Table III) does not fit the molecular formula $C_{15}H_{30}O_3$ which the triol should possess. The NMR analysis (for δ values see Experimental section) offers little help in evaluating the structure of this compound because of the complexity and poor resolution of the signal patterns. Because of the large volume of gas (hydrogen?) given off, hydride abstraction of the hydroxyl proton of ketol XXXII may be the initial reaction.

In an effort to prepare a model similar to XXXII, hexamethyl-1,3,5-cyclohexanetrione (II) was allowed to condense with methyl Grignard reagent. The solid product L obtained had an IR (Plate XIX) spectrum which bore a striking resemblance to that of ketol XXXII (see Table IV). The NMR spectrum (Plates XXXIX and XL) further support the structure of this compound, 5-hydroxy-2,2,4,4,5,6,6-heptamethyl-1,3-cyclohexanedione (L).

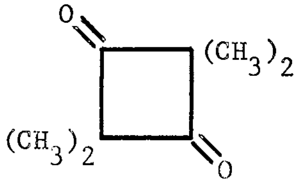


II L

Although ketol XXXII possesses carbonyl groups, normal procedures[70] to prepare an oxime, 2,4-DNP or semicarbazone derivatives failed. In contrast, a compound such as LVII, which could be envisioned as an alternate structure for ketol XXXII, might be expected to form carbonyl derivatives as does diketone LVIII.[83] Attempted esterification of ketol XXXII with acetic anhydride in pyridine[11] was also unsuccessful, with most of XXXII being recovered.

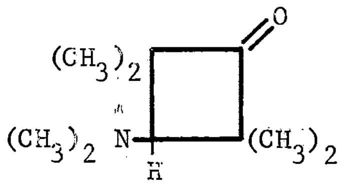


LVII

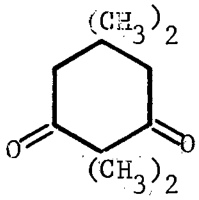


LVIII

Good evidence in favor of the six-membered diketone structure XXXII, is afforded by IR data. A band at 1779 cm.$^{-1}$ was recorded for the carbonyl groups[44] in LIX while LVIII exhibits a doublet at 1745 and 1721 cm.$^{-1}$, triketone II has a broad band at 1698 cm.$^{-1}$. For comparison,



LIX



LX

XXXII has a peak at 1694 cm.$^{-1}$ with a sharp band of lower intensity at 1718 cm.$^{-1}$ (see Table IV). Most convincing was the similarity of the carbonyl absorptions of LX to those of XXXII, as twin carbonyl peaks were reported for the former at 1718 and 1688 cm.$^{-1}$ in chloroform.[21] The spectrum of XXXII in potassium bromide or chloroform contained the two bands mentioned previously for the carbonyl groups in nearly identical positions to those in LX.

In previous discussion in this chapter, it was noted that the triketone, 2,4,4,6,6,8-hexamethyl-3,5,7-trioxononanetrione (XXXIII) was obtained initially by preparation GLC of the reaction mixture from acidolysis and dehydration of ketol XXXII. Elemental analysis (Table III) of triketone XXXIII indicates an empirical formula of $C_{15}H_{26}O_3$ and a molecular weight of 254 (Monsanto Chemical Company, Inc., St. Louis, Missouri) nearly identical to that of ketol XXXII. Infrared absorptions (Plate XI) are visible at 1700 (carbonyl group:shoulder at 1722), 1390 and 1378 cm.$^{-1}$ (gem-dimethyl groups) along with several other sharp intense bands at 1018 and 988 cm.$^{-1}$ (Table IV). The NMR spectrum (Plate XXXIII) revealed a simple pattern in carbon tetrachloride at δ3.08 (multiplet:J = 7 c.p.s.), 1.34 (singlet) and 1.05 (doublet:J = 7 c.p.s.).

When triketone XXXIII was boiled in a three-mole excess of 2,4-DNP reagent for 17 hours, recovery of XXXIII was quantitative. This is unusual since diisopropyl ketone(XLIV) gives a derivative although the reaction is slow.[49] Attempted preparation of an oxime and a semicarbazone also failed. A solid derivative was obtained when XXXIII was treated with phenyldrazine but the product could not be purified.

Triketone XXXIII and lithium aluminum hydride, when combined at 0° gave a white solid unknown G, and a viscous yellow oil. Like unknown F, obtained from the lithium aluminum hydride-ketol XXXII experiment, unknown G has an IR spectrum (Plate XIII) containing no carbonyl absorption. Also like unknown F, elemental analysis (Table III) of unknown G did not correspond to a molecular formula of $C_{15}H_{32}O_3$. The NMR spectrum in pyridine-d_5 was poorly resolved (see Experimental section for δ values) and offered no help in elucidating the structure of unknown G.

Triketone XXXIII was prepared in low yield (4%) by the Claisen condensation of methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI) and diisopropyl ketone (XLIV) in the presence of sodium methoxide. Unfortunately, using sodium amide and sodium hydride as bases with XXXVI did not give triketone XXXIII as indicated by GLC analysis of the reaction mixtures. Sodium hydride was found to have converted diisopropyl ketone(XLIV) into diisopropylmethanol. This latter reaction is rather unusual as it has been reported[77] that the ketone evolves hydrogen gas (80%) when treated with sodium hydride in toluene at 120° for 5 hours. Most of the ketone

XLIV was recovered after workup of the reaction mixture.

A 1:1 mole reaction of XXXIII with ethanolic potassium hydroxide gave products identical to those found from the same reaction with ketol XXXII except that XXXIII was totally consumed in the former case. Using an excess of potassium hydroxide only diisopropyl ketone (XLIV), isobutyric acid (XXVIII) and potassium carbonate were isolated. A mechanism for formation of products is representative of a classic attack on the carbonyl carbon atom which is known to occur in 1,3-diketone systems[82] as summarized on page 23.

CHAPTER III

EXPERIMENTAL[a-e]

Preparation of Phenylmagnesium Bromide. A 2-l. three-necked flask was equipped with a mechanical stirrer, a condenser with drying tube ($CaCl_2$), a thermometer, and a pressure-equalizing funnel connected to an anhydrous, deoxygenated[72] nitrogen supply. The entire system was swept with nitrogen for 30 minutes and 24.00 g. (1 g.-atom) of magnesium was placed in the flask with just enough anhydrous ether to cover the metal. The addition funnel was charged with 157.02 g. (1.0 mole) of bromobenzene and approximately 10 ml. was added to the flask. When the reaction had been initiated by gentle crushing of the metal with a stirring rod, 400 ml. of anhydrous ether was quickly added to the

---

[a] All melting points are corrected; all boiling points are uncorrected. Skelly Solvent F boiled at 30-60°.

[b] The infrared spectra were determined on a Beckman IR-5A as films on sodium chloride cells or as potassium bromide pellets unless otherwise specified.

[c] The nuclear magnetic resonance spectra were determined on a Varian A-60 high resolution spectrometer with a field-sensing stabilizer ("Super-Stabilizer"). Tetramethylsilane was used as an internal standard.

[d] Gas chromatographic analyses were performed using an Aerograph Hy-Fi Model A-500, Varian-Aerograph Hy-Fi Model 1520 with a hydrogen flame ionization detector and an Aerograph Model A-700 Autoprep unit from Wilkens Instrument and Research, Inc., Walnut Creek, California.

[e] The microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee and Midwest Microlab, Inc., Indianapolis, Indiana.

reaction flask and 150 ml. of ether added to the bromobenzene. With stirring, under nitrogen, the bromobenzene-ether solution was added over a period of 2 hours. When the addition was complete, 200 ml. of ether was added and the reaction mixture was heated under gentle reflux for 3 hours. After cooling, the mixture was filtered through a glass wool plug into a graduated cylinder continuously flushed with nitrogen. The volume was adjusted to 850 ml. with ether, and two 1-ml. aliquots were withdrawn and added to 50.00 ml. of aqueous hydrochloric acid (0.1029 meq./1 ml.). The acid mixture was titrated to a phenolphthalein end point with aqueous sodium hydroxide (0.1024 meq./ 1 ml.).[26] The yield was 0.989 mole (98.9%).

Reaction (1:0.8) of Phenyl Grignard Reagent and Lactone I - Run 1. One mole of phenylmagnesium bromide (98%) was prepared by the method described in the previous experiment. The Grignard solution was placed in a 2-l., three-necked flask equipped with a mechanical stirrer, condenser with drying tube ($CaCl_2$) a thermometer, and a pressure-equalizing funnel. A solution of lactone I[f] (118.3 g., 0.84 mole) dissolved in 175 ml. of anhydrous ether was added dropwise with stirring under dry nitrogen. The flask was kept in an ice-salt bath during the 2-hour addition period to keep the reaction mixture below 15°. The brown mixture was allowed to warm to room temperature, and the resulting orange mixture was stirred overnight. The lemon-orange mixture, which now contained a pale-white granular precipitate, was heated at reflux for 5 hours, allowed to come to room temperature and then hydrolyzed by slow dropwise (to control foaming) addition of 300 ml. of 20% aqueous ammonium chloride

---

[f] Eastman Chemical Products, Inc., Kingsport, Tennessee, b.p. 170°/ 730 mm. See IR (Plate I) and NMR (Plate XX) spectra.

TABLE II

GLC COLUMN SPECIFICATIONS

Title	Length (ft.)	Diameter (in.)	Packing	Mesh	Substrate[a]
CA[b]-1	6	1/8	6% Silicone-30	80/100	G
CA-2	6	1/8	6% Silicone-30	60/80	W
CA-3	6	1/8	5% Silicone-30	60/80	G
CA-4	6	1/8	6% SE-30	80/100	W
CA-5	6	1/8	6% SE-30	80/100	G
CA-6	6	1/8	4% Silicone-30	80/100	G
CA-7	ç	1/8	5% UCON Polar	80/100	W
CA-8	5	1/4	5% Silicone Rubber	80/100	G
CA-9	8	1/4	5% Silicone-30	60/80	G
CA-10	6	1/4	5% Silicone-30	80/100	G
CA-11	6	1/8	10% Silicone Rubber	80/100	G
CA-12	6	1/8	5% SE-30	60/80	G
CP[c]-1	20	3/8	30% DEGS	60/80	W

TABLE II (CONTINUED)

Title	Length (ft.)	Diameter (in.)	Packing	Mesh	Substrate[a]
CP-2	10	3/8	15% DEGS	60/80	W

[a] G = DMCS - treated Chromosorb G; W = Chromosorb W

[b] Analytical columns used on the hydrogen flame detection unit

[c] Refers to columns used on the Autoprep unit

TABLE III

PHYSICAL PROPERTIES OF PRODUCTS

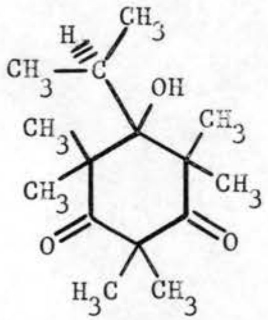
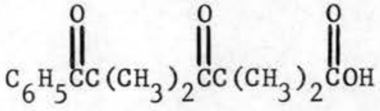
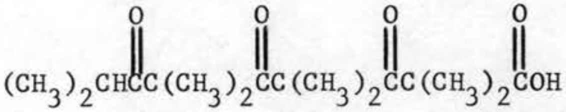
Compound	m.p., °C	Yield	Analysis (percent)			
			Calculated		Found	
			C	H	C	H
 XXXII	147.5-149	30.1 (max.)	70.86	10.23	70.83 71.18	10.30 10.32
 $C_6H_5\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ XXXIV	148.5-150	3	68.68	6.92	68.61 68.03	6.80 6.87
 $(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ XXXV	74.5-75.5	20	64.43	8.72	64.73	8.80

TABLE III (CONTINUED)

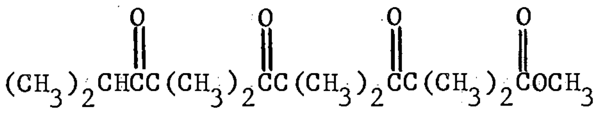
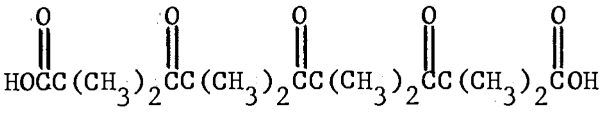
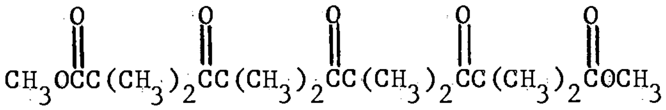
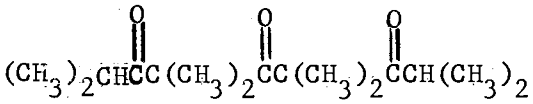
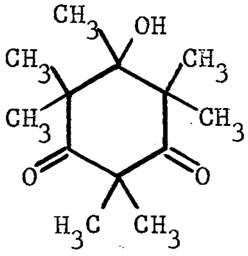
Compound	m.p., °C	Yield	Analysis (percent)			
			Calculated		Found	
			C	H	C	H
 $(CH_3)_2CH\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}OCH_3$ XXXVIII	. . . .	18	65.38	8.97	65.17	8.77
 $HO\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}OH$ XLI	121-122	2.5	59.64	7.60	59.35	7.20
 $CH_3O\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}OCH_3$ XLIII	74-75	3.5	61.60	8.10	61.64	8.13
Unknown E	. . . .	. . . .	. . . .	. . . .	75.14	10.01
 $(CH_3)_2CH\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}C(CH_3)_2\overset{\overset{O}{\parallel}}{C}CH(CH_3)_2$ XXXIII	19-21	4	70.86	10.23	70.94 71.64	10.24 10.08

TABLE III (CONTINUED)

Compound	m.p., °C	Yield	Analysis (percent) Calculated C	Analysis (percent) Calculated H	Analysis (percent) Found C	Analysis (percent) Found H
Unknown F	196-198	....	....	....	68.60 68.68	11.46 11.56
Unknown G	121-122	....	....	....	67.05	11.75
 L	97.5-98.5	....	69.03	9.73	68.64	9.60

---

[a] Yields are based on lactone I

[b] Refractive index of compound XXXVIII is $n^{23}D$ 1.4641

TABLE IV

INFRARED ABSORPTION BANDS (cm.$^{-1}$) OF PRODUCTS

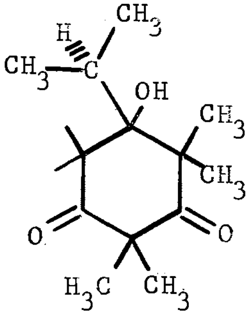
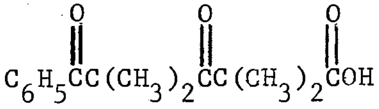
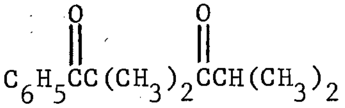
Compound	Hydroxyl	Carbonyl	Gem-dimethyl	Additional Bands
 XXXII	3460	1692 (shoulder at 1718)	1390, 1378	1071, 1000, 982, 960
 $C_6H_5\overset{O}{\overset{\parallel}{C}}C(CH_3)_2\overset{O}{\overset{\parallel}{C}}C(CH_3)_2\overset{O}{\overset{\parallel}{C}}OH$ XXXIV	3300	1720 (shoulder at 1746)	....	1390, 1305, 1175, 1095, 979, 768, 707
 $C_6H_5\overset{O}{\overset{\parallel}{C}}C(CH_3)_2\overset{O}{\overset{\parallel}{C}}CH(CH_3)_2$ XXXIX	......	1672 (shoulder at 1718)	1390, 1370	1252, 1045, 1000, 754, 706

TABLE IV (CONTINUED)

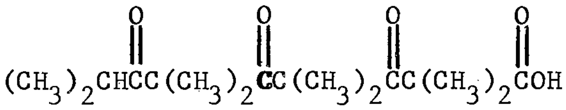
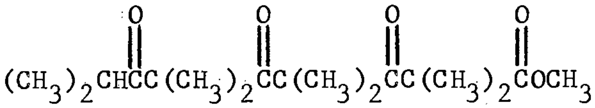
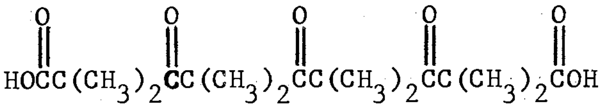
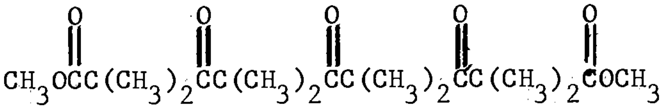
Compound	Hydroxyl	Carbonyl	Gem-dimethyl	Additional Bands
 $(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ XXXV	3000 (broad)	1738, 1703	. . . .	1273, 1243, 1115-1130, 1038, 996
 $(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$ XXXVIII	. . . .	1757, 1721, 1699	1390, 1372	1265, 1155, 983
 $HO\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OH$ XLI	2900 (broad)	1755, 1700	. . . .	1305, 1120, 1070, 1043, 1007, 935, 690
 $CH_3O\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3$ XLIII	. . . .	1752, 1733, 1700	1390, 1379	1278, 1060, 988, 837

TABLE IV (CONTINUED)

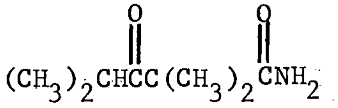
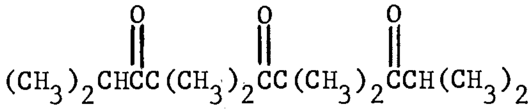
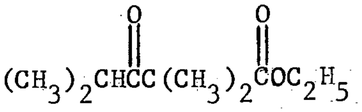
Compound	Hydroxyl	Carbonyl	Gem-dimethyl	Additional Bands
 $(CH_3)_2CH\overset{O}{\overset{\Vert}{C}}C(CH_3)_2\overset{O}{\overset{\Vert}{C}}NH_2$ XL	3430, 3218[a]	1675 (broad)	. . . .	1397, 1268, 1097, 1043, 810, 768
Unknown E	. . . .	1722 (shoulder at 1748)	. . . .	1639, 1266, 1070, 995, 902
 $(CH_3)_2CH\overset{O}{\overset{\Vert}{C}}C(CH_3)_2\overset{O}{\overset{\Vert}{C}}C(CH_3)_2\overset{O}{\overset{\Vert}{C}}CH(CH_3)_2$ XXXIII	. . . .	1700 (shoulder at 1722)	1390, 1378	1351, 1096, 1002, 989
Unknown F	3400 (broad)	. . . .	. . . .	1490, 1393, 1290, 950, 874
Unknown G	3035 (broad)	. . . .	1396, 1378	1470, 1113, 1025, 795
 $(CH_3)_2CH\overset{O}{\overset{\Vert}{C}}C(CH_3)_2\overset{O}{\overset{\Vert}{C}}OC_2H_5$ XLV	. . . .	1718 (shoulder at 1737)	1390, 1370	1265, 1148, 1041

TABLE IV (CONTINUED)

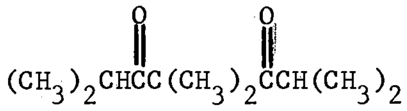
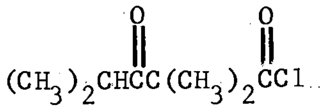
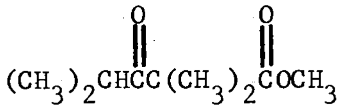
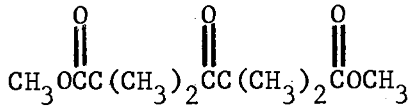
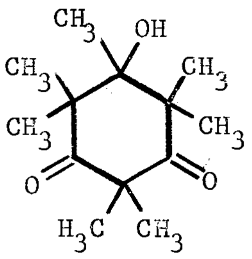
Compound	Hydroxyl	Carbonyl	Gem-dimethyl	Additional Bands
 $\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}CH(CH_3)_2}$ XLVI	. . . .	1703 (shoulder at 1721)	1390, 1377	1097, 1019, 1000
 $\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}Cl}$ XLIX	. . . .	1788, 1725	1390, 1373	1099, 1046, 945, 754
 $\mathrm{(CH_3)_2CH\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3}$ XXXVI	. . . .	1725 (shoulder at 1742)	. . . .	1269, 1157, 1043
 $\mathrm{CH_3O\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}C(CH_3)_2\overset{O}{\overset{\|}{C}}OCH_3}$ XXXVII	. . . .	1775 (shoulder at 1723)	. . . .	1246, 1144, 1037, 1024, 790-760 (broad)

TABLE IV (CONTINUED)

Compound	Hydroxyl	Carbonyl	Gem-dimethyl	Additional Bands
 L	3510	1690 (shoulder at 1720)	. . . .	1328, 1289, 1204, 1025, 995, 913

Compounds XXXII, XXXIV, XXXV, XLI, XLIII, XL, unknown F, unknown G, and L, (KBr pellets).

Compounds XXXIII, XXXVI, XXXVIII, XXXIX, unknown E, XLV, XLVI and XLIX, (NaCl cells).

Compound XXXVII, ($CHCl_3$ solution).

[a] Bands at 3430, 3212 cm.$^{-1}$ are due to amide linkage.

TABLE V

NMR CHEMICAL SHIFTS AND COUPLING CONSTANTS OF PRODUCTS

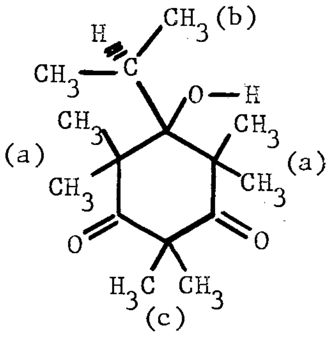
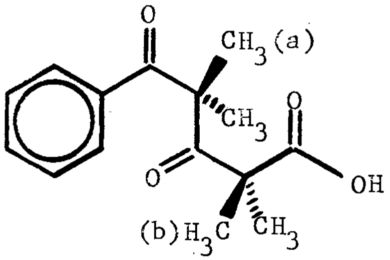
Compound	Plate	Solvent	δ(values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 XXXII	XXI		1.90 s	. . . .	OH
			1.43 d	7.0	CH_3 (c)
	XXIII	benzene	1.19 d	6.0	CH_3 (a)
			0.91 d	6.5	CH_3 (b)
	XXII	pyridine-d_5	2.38 h	6.5	H
 XXXIV	XXIV	pyridine-d_5	9.80 s	. . . .	OH
			7.83-7.21	. . . .	C_6H_5
			1.66 s	. . . .	CH_3 (a)
			1.38 s	. . . .	CH_3 (b)

TABLE V (CONTINUED)

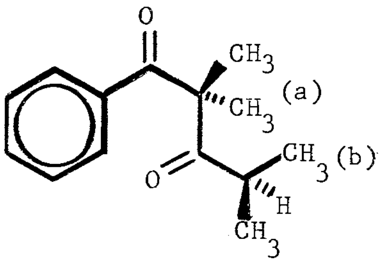
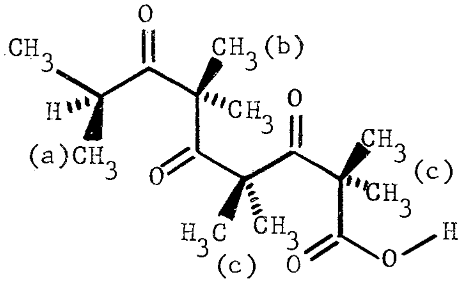
Compound	Plate	Solvent	δ (values) (p.p.m.)[1]	J (c.p.s.)	Assignment
 XXXIX	XXV	CCl_4	7.71, 7.38(m)	. . . .	C_6H_5
			2.73(h)	7.0	H
			1.44(s)	. . . .	CH_3 (a)
			0.90(d)	7.0	CH_3 (b)
 XXXV	XXVI	$CDCl_3$	11.66 s	. . . .	OH
			3.19 h	6.5	H
			1.59 s (split)	2.5	CH_3 (c)
			1.28 s	. . . .	CH_3 (b)
			1.06 d	6.5	CH_3 (a)

TABLE V (CONTINUED)

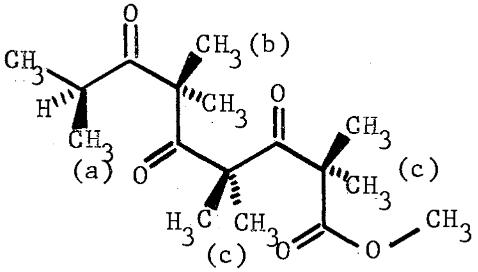
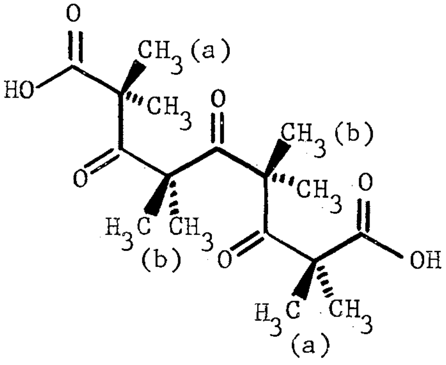
Compound	Plate	Solvent	δ (values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 XXXVIII	XXVII	$CDCl_3$	3.69 s	. . . .	OCH_3
			3.09 h	6.5	H
			1.41 s	. . . .	CH_3 (c)
			1.38 s	. . . .	CH_3 (b)
			1.06 d	6.5	CH_3 (a)
 XLI	XLI	$CDCl_3$	11.96 s	. . . .	OH
			1.57 s	. . . .	CH_3 (a)
			1.54 s	. . . .	CH_3 (a)
			1.45 s	. . . .	CH_3 (b)
			1.39 s	. . . .	CH_3 (b)

TABLE V (CONTINUED)

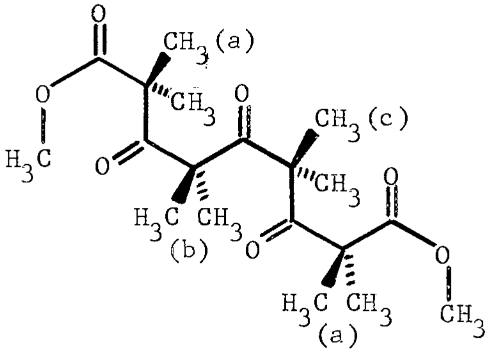
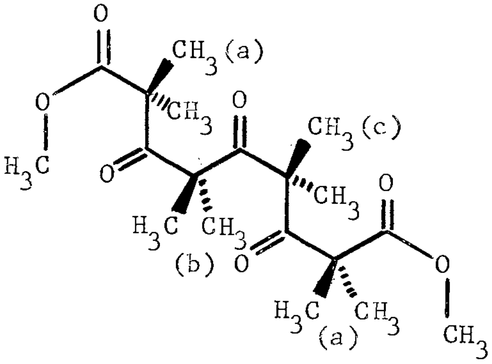
Compound	Plate	Solvent	δ(values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 XLIII	XXIX	benzene	3.39 s 3.39 s[2]	. . . .	OCH_3
			3.37 s 3.36 s	. . . .	OCH_3
			1.46 s	. . . .	CH_3 (a)
			1.42 s	. . . .	CH_3 (b or c)
 XLIII	XXX	$CDCl_3$	3.79 s	. . . .	OCH_3
			3.70 s	. . . .	OCH_3
			1.56 s	. . . .	CH_3 a
			1.54 s	. . . .	CH_3
			1.45 s	. . . .	CH_3 b or c
			1.34 s	. . . .	CH_3

TABLE V (CONTINUED)

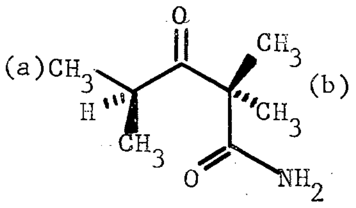
Compound	Plate	Solvent	δ (values) (p.p.m.)^1	J(c.p.s.)	Assignment
 XL	XXXI		6.56 (broad)	. . . .	NH_2
			3.19 h	7.0	H
			1.44 s	. . . .	CH_3 (b)
			1.09 d	7.0	CH_3 (a)
Unknown E	XXXII	$CDCl_3$	5.07 s	. . . .	. . . .
			4.86 s	. . . .	. . . .
			2.21 h	6.5	. . . .
			1.79 s	. . . .	. . . .
			1.35 s	. . . .	. . . .
			1.26 s	. . . .	. . . .
			1.15 s	. . . .	. . . .
			0.99 d	6.5	. . . .
			0.71 d	7.0	. . . .

TABLE V (CONTINUED)

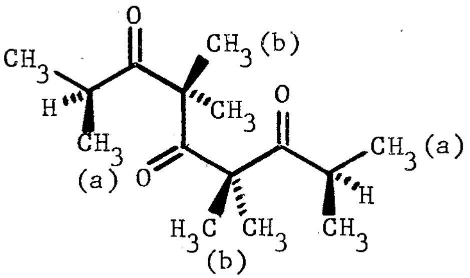
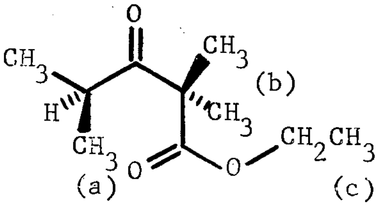
Compound	Plate	Solvent	δ (values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 XXXIII	XXXIII	CCl_4	3.08 h	6.5	H
			1.34 s	. . . .	CH_3 (b)
			1.04 d	6.5	CH_3 (a)
 XLV	XXXIV	CCl_4	4.17 g	7.0	$-CH_2-$
			2.84 h	6.5	H
			1.29 s	. . . .	CH_3 (b)
			1.25 t	7.0	CH_3 (c)
			1.05 d	6.5	CH_3 (a)

TABLE V (CONTINUED)

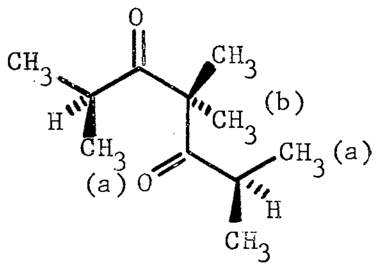
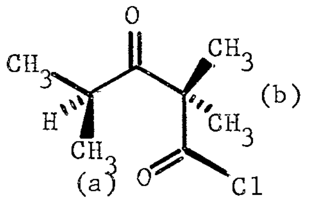
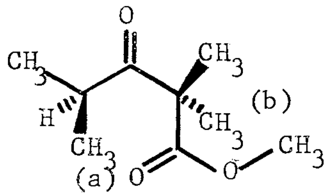
Compound	Plate	Solvent	δ(values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 XLVI	XXXV	CS_2	3.86 h	7.0	H
			1.33 s	. . . .	CH_3 (b)
			1.03 d	7.0	CH_3 (a)
 XLIX	XXXVI	neat	3.05 h	7.0	H
			1.52 s	. . . .	CH_3 (b)
			1.13 d	7.0	CH_3 (a)
 XXXVI	XXXVII	neat	3.73 s	. . . .	OCH_3
			2.92 h	6.5	H
			1.32 s	. . . .	CH_3 (b)
			1.03 d	6.5	CH_3 (a)

TABLE V (CONTINUED)

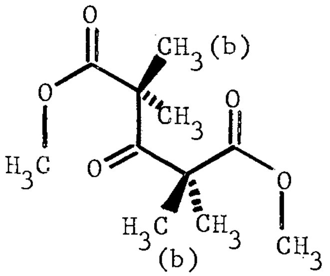
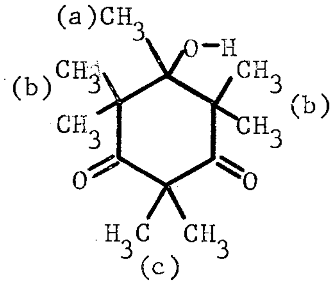
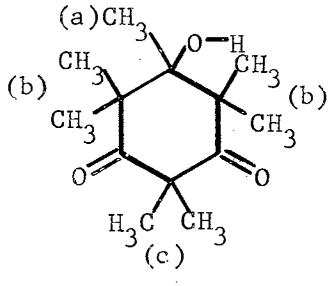
Compound	Plate	Solvent	δ(values) (p.p.m.)^1	J(c.p.s.)	Assignment
 XXXVII	XXXVIII	CCl_4	3.79 s	. . . .	OCH_3
			3.67 s	. . . .	OCH_3
			1.54 s	. . . .	CH_3 (b)
			1.30 s	. . . .	CH_3 (b)
 L	XXXIX	pyridine-d_5	6.49 s	. . . .	OH
			1.54 s	. . . .	CH_3 (c)
			1.38 s	. . . .	CH_3 b
			1.33 s	. . . .	CH_3
			1.17 s	. . . .	CH_3 (a)

TABLE V (CONTINUED)

Compound	Plate	Solvent	δ (values) (p.p.m.)[1]	J(c.p.s.)	Assignment
 L	XL	benzene	2.30 s	. . . .	OH
			1.38 d	6.5	CH_3 (c)
			1.15 s	. . . .	CH_3
			0.91 s	. . . .	CH_3 b
			0.88 s	. . . .	CH_3(a)

---

[1] The multiplicity of each peak is indicated as follows: singlet, s; doublet, d; triplet, t; quartet, q; and heptet, h.

[2] Delta (δ) values for ester methyl group protons when sample was heated above 50°.

solution. When approximately 150 ml. of the ammonium chloride solution had been added, the reaction subsided and the rest of the ammonium chloride solution was added rapidly. The two-layered mixture (yellow-green organic layer) was poured into an additional 100 ml. of the ammonium chloride solution. The mixture was allowed to stand overnight and then extracted with three 200-ml. portions of ether. The yellow organic extracts were combined, dried ($MgSO_4$) and filtered under suction; the ether was removed under aspirator pressure giving approximately 112 ml. of a yellow oily liquid. No precipitate formed when the liquid was chilled overnight.

In an attempt to separate the components of the previous reaction mixture a 1-liter, three-necked flask equipped as usual, except for an addition funnel was charged with 50.0 g. of the reaction residue, 50.0 g. (0.38 mole) of Girards' T reagent, 50 ml. of glacial acetic acid and 500 ml. of methanol. The solution (yellow in color) was heated under reflux for 3.5 hours, allowed to cool to room temperature and then treated with 5% aqueous sodium hydroxide solution until a pH of about 8 was obtained in the solution. Water (100 ml.) was added and the mixture was extracted with 300 ml. of ether. The organic layer was dried ($MgSO_4$) and filtered; removal of the solvent under aspirator pressure gave an oily liquid. Chilling the liquid overnight resulted in the precipitation of a white solid. The solid was filtered from the mixture, washed with hot water (100 ml.) and recrystallized from a minimum amount of hot benzene-cyclohexane (1:1) to give 2.84 g. (1.8%) of rectangular crystals. From the infrared (IR) (Plate II), nuclear magnetic resonance (NMR) (Plates XXI, XXII and XXIII) spectra, and physical data, the structure of this compound was assigned as that of ketol XXXII, the properties of which are found in Tables III, IV and V.

Reaction (1:1) of Phenyl Grignard Reagent and Lactone I - Run 2. The apparatus and procedure used in this experiment were identical to those described in the previous experiment. The lactone I (140.1 g., 1.0 mole) was added to the chilled Grignard solution. After the reaction period, workup of the reaction mixture afforded a yellow liquid which deposited a white solid when chilled; 7.26 g. (4.7%) of ketol XXXII was obtained, mixture m.p. 147.5-149° with a sample from Run 1 (benzene-n-heptane solution).

Reaction (1:1.2) of Phenyl Grignard Reagent and Lactone I - Run 3. One mole of phenylmagnesium bromide was prepared (96%) as before. The Grignard solution was cooled to 0°, and 168.12 g. (1.2 mole) of lactone I in 175 ml. of ether (anhydrous) was added as described in the previous experiments. The reaction mixture was treated as previously outlined for Run 1. The oily yellow-brown liquid (approximately 110 ml.), when chilled overnight, afforded a white solid which was washed as before and recrystallized from benzene-n-heptane solution (1:1) to give 45.95 g. (yield, 30.1%) of ketol XXXII; mixture m.p. 148-149° with the sample obtained from Run 1.

The mother liquor obtained from the removal of ketol XXXII was analyzed by GLC (CA-1). The following compounds were identified and their yields, based on lactone I, were obtained by repeated injections with known standard solutions and calculations of peak area ratios. Compounds identified were: diisopropyl ketone (XLIV) (4%), lactone I (13%), 2,2,4-trimethyl-3-oxovaleramide (XL) (1.5%), biphenyl (3.5%), 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX) (8%), triketone XXXIII (4%) and benzophenone (40.1%). Retention times at 139° were:

diisopropyl ketone (XLIV), 2 minutes; lactone I, 2.5 minutes; amide XL, 3 minutes; biphenyl, 6 minutes; diketone XXXIX, 36 minutes; triketone XXXIII, 41 minutes; benzophenone, 48 minutes.

In an experiment practically identical to that described above, lactone I (182.1 g., 1.3 mole) was added to one mole of phenyl Grignard reagent (Run 4). Normal reaction conditions and workup (see page 60) of the reaction mixture gave (after purification), 38.42 g. (23.6%) of ketol XXXII, mixture m.p. 148-149° with a sample obtained from Run 1.

The reaction of one mole of phenyl Grignard reagent and lactone I (210.2 g., 1.5 mole - Run 5) gave 38.79 g. (23.6%) of ketol XXXII, mixture m.p. 148-149° with a sample obtained from the previous run.

Condensing one mole of phenyl Grignard reagent (98%) with 280.2 g. (2.0 mole) of lactone I (run 6) gave 39.00 g. (23.9%) of ketol XXXII; mixture m.p. 148-149° with a sample obtained from the previous run.

Carbonation of 1:1.2 Reaction Mixture of Phenyl Grignard Reagent and Lactone I. One mole of phenylmagnesium bromide was prepared (97.5%) and combined with 168.12 g. (1.2 mole) of lactone I as previously described. The brown mixture was allowed to warm to room temperature and then heated at reflux for 3.5 hours. When the contents of the flask had attained room temperature, gaseous carbon dioxide was bubbled into the stirred orange mixture for 27 hours. During the first 2 hours of carbonation, the mixture became increasingly difficult to stir because of a very viscous brown material which formed on the bottom of the reaction vessel. During the remainder of the carbonation, however, the brown substance solidified and stirring became easier. A lemon-colored reaction mixture finally resulted; this was decomposed at room temperature with aqueous ammonium chloride as usual. The resulting golden colored, jelly-like mixture was stirred at room temperature for 1 hour and then extracted with three 300-ml. portions of 1:1 ether-benzene solution. The combined yellow organic extracts (T) were now extracted with three 300-ml. portions of saturated sodium bicarbonate solution; the bicarbonate extracts were washed with two 100-ml. portions of ether-benzene (1:1) solution, and the organic washings were added to the original organic layer (T). After the sodium bicarbonate extracts were acidified to a pH of 1 with aqueous 6N hydrochloric acid (130 ml.), the mixture was extracted with three 150 ml.-portions of ether-benzene solution (1:1). These combined organic extracts (brown in color) were dried ($MgSO_4$), and filtered under suction. When about 75% of the solvent had been removed from the filtrate (under aspirator pressure), a white solid formed in the flask. The flask was chilled and the solid filtered out.

After being washed successively with water (75 ml.) and benzene (75 ml.), the solid was dissolved in hot acetone and reprecipitated by the addition of cold water. A snow-white solid was obtained - 8.36 g. (3% - based on lactone I); m.p. 148.5-150°. Physical properties (Table III) and IR (Plate III) and NMR (Plate XXIV) spectral data (see Tables IV and V led to the structure assignment of acid XXIV for this compound.

The purity analysis of the acid was demonstrated by GLC [(CA-2 - Table II] analysis. Only one peak was observed on the chromatogram; this was found to have the same retention time as 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX). This was varified by a mixed injection with a known sample of the diketone XXXIX, and peak reinforcement was observed. Apparently decarboxylation of the acid occurred on the column.

A 1.0-g. (0.004 mole) sample of the acid was placed in a large test tube having a side-arm outlet. The test tube was fitted with a thermometer which extended into the solid and with a rubber hose connected to a small piece of glass tubing immersed in a solution of 10% aqueous calcium hydroxide. The test tube was slowly heated on a sand bath to 155° where the temperature was held for 1 hour. Smoky vapors were observed to rise in the test tube with bubbles emerging from the end of the glass tube in the calcium hydroxide solution. After 1 hour of heating, the calcium hydroxide solution contained a milky white precipitate. When the test tube was cool (room temperature), the IR spectrum (Plate IV) and the NMR (Plate XXV) spectrum of the contents in the tube were identical to those of an authentic sample of 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX). The mother liquor obtained from the removal of acid XXXIV was further concentrated on a rotary evaporator to give 25.02 g. of a viscous light brown oil. This acid mixture was treated with diazomethane as described in a later experiment (page 85).

The original organic extracts (T) were concentrated under aspirator pressure to yield 90 ml. of a yellow-colored oil. GLC (CA-11) analysis revealed the presence of benzophenone (44%), and small amounts of lactone I, biphenyl, and bromobenzene as the only components present. Retention times at 161° were: bromobenzene, 2 minutes; lactone I, 2.7 minutes; biphenyl, 4.5 minutes; and benzophenone, 30 minutes.

In another essentially identical carbonation experiment, the organic layer obtained from the acidified bicarbonate extracts was stripped of solvent under aspirator pressure and the oily liquid was bottled and stored. Weeks later it was observed that the bottle contained a white precipitate. The solid was filtered from the mixture and washed with 10 ml. of Skelly Solvent F and 10 ml. of warm water. A solution of the compound in hot acetone yielded a white solid on the addition of cold water; 125 mg. of the solid was obtained, m.p. 74.5-75.5°. Elemental analysis and IR (Plate V) and NMR (Plate XXXVI) spectral data identified the compound as monoacid XXXV, (see Tables III, IV, and V).

Esterification of Acid Material (Page 84) Obtained From the Carbonation of the Reaction Mixture of Phenyl Grignard Reagent and Lactone I. A 1-liter one-necked flask, equipped with a 12-inch modified Claisen U-tube, a thermometer and a condenser, was charged with a solution of 4.4 g. (0.11 mole) of sodium hydroxide pellets dissolved in 35 ml. of water, 85 ml. of capitol and 275 ml. of ether. The flask was cooled to 0° by means of an ice-salt bath. EXR-101(N,N'-dinitroso-N,N'-dimethylterephthalamide), 12.0 g. (containing inert filler), was funneled into the flask rapidly. The mixture (two layers) was allowed to come to room temperature and then was slowly heated until the ether-diazomethane distilled slowly. The distillate was caught in a 250-ml. flask (chilled by Dry Ice) containing 25.0 g. of the acid material obtained from carbonation of reaction mixture of phenyl Grignard reagent and lactone I - (page 84). Distillation was continued until the distillate was water-white. Heating was discontinued, and the apparatus was allowed to stand for 1 hour. The ether was removed from the receiver flask under aspirator pressure to give 24.97 g. of a light yellow oil. GLC analysis (CA-3) of the residue revealed the presence of a many-component reaction mixture. Compounds were identified by mixed injections with authentic samples and yields were based on lactone I: methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI) (6%), 2,2,4-trimethyl-3-oxovaleramide (XL) (2%), dimethyl 2,2,4,4-tetramethyl-3-oxoglutarate (XXXVII) (1%), triketone XXXIII (16%), and 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX) (2%). Retention times at 161° were: ester XXXVI, 0.5 minute; amide XL, 1.3 minutes; ester XXXVII, 2.1 minutes; diketone XXXIX, 1.4 minutes; triketone XXXIII, 16.3 minutes. Seven other small peaks observed in the chromatogram were not identified. However, the compound representing the largest peak (18% - from peak area ratios) and having a retention time on the column of 49 minutes was isolated in the pure state by injecting twenty 165-ml. samples of the reaction residue (dissolved in 15 ml. of ether) onto a column in the Autoprep GLC unit (CP-1). Settings on the chromatograph were as follows: Column, 189°; helium flow, $>$ 600 cc./min.; injector, 265°; collector, 270°; detector, 310°. Retention time for the compound on the prep column was 72 minutes. The small amount of a viscous, light brown-colored liquid obtained was analyzed for purity by GLC (CA-4). The chromatogram showed only one peak present; retention time at 150° was 19 minutes. The structure of this compound was assigned as that of ester XXXVIII from IR (Plate VI), NMR (Plate XXVII) and elemental analyses. (See Tables III, IV and V).

<u>Reaction (1:1.2) of Phenyl Grignard Reagent and Lactone I in Tetrahydrofuran - Run 7</u>. One mole of phenyl Grignard reagent was prepared (99%) and combined with 168.12 g. (1.2 mole) of lactone I in a manner similar to that previously described. The brown mixture was allowed to warm to room temperature and the addition funnel was removed. A Claisen head with a thermometer was attached to the flask, and the ether was slowly distilled out through a short path condenser until a slurry formed in the distillation flask. Dry anhydrous tetrahydrofuran (THF) (750 ml.) was added, and the solution was distilled until the

temperature of the contents in the flask reached 68°. The brownish-red solution was heated at reflux for 10 hours, then allowed to cool to room temperature and was further stirred for 12 hours. The mixture was decomposed at room temperature by the dropwise addition of 350 ml. of 20% aqueous ammonium chloride solution with violent foaming. The resulting yellow-green mixture was extracted with three 300-ml. portions of ether; the organic extracts were combined, dried ($MgSO_4$) and filtered with suction. When the solvent was removed by distillation, approximately 100 ml. of a yellow oil remained. The oil was dissolved in 100 ml. of Skelly Solvent F and chilled overnight with the subsequent formation of a white precipitate. The white solid was filtered from the solution and washed with hot water (75 ml.) and cold Skelly Solvent F (75 ml.). Solution of the solid occurred in hot benzene from which precipitation was effected by the addition of cold n-heptane, giving 22.07 g. (15%) of ketol XXXII, mixture m.p. 148-149° with a sample obtained from Run 1.

Carbonation of 1:1.2 Reaction Mixture of Phenyl Grignard Reagent and Lactone I in Tetrahydrofuran. One mole of phenylmagnesium bromide was prepared (97%) and combined with lactone I (168.12 g., 1.2 mole) in a manner as previously described in Run 3. The ether was distilled from the flask as described in the previous experiment (page 86) and dry THF (750 ml.) added to the slurry until the temperature of the contents in the flask reached 68°. The brownish-red solution was heated under reflux for an additional 7 hours and allowed to cool to room temperature; then carbon dioxide gas was bubbled into the solution for 24 hours. After 15 minutes of carbonation, the temperature of the solution rose 14° and remained at 41° for 0.5 hour. The temperature of the solution then slowly fell to room temperature (27°) where it remained for the duration of the carbonation. The brown-red mixture containing a small amount of chunky white precipitate was hydrolyzed at room temperature by the dropwise addition of 300 ml. of 20% aqueous ammonium chloride solution (as before). Workup of the reaction mixture was practically the same as that described for the experiment cited on page 82. Filtration under suction, of the organic extracts obtained from the acidified bicarbonate extracts, followed by removal of most of the solvent by distillation, gave a white precipitate. The mixture was chilled overnight and the solid was filtered out and washed with warm water (50 ml.) and then cold Skelly Solvent F (50 ml.). The solid (8.60 g.) had a melting point of 134-135.5 (dec.); its purity was checked by GLC analysis (CA-5) and the presence of two peaks was observed. These peaks were identified as arising from diisopropyl ketone (XLIV) and triketone XXXIII in a ratio of 1:9 respectively. Retention times at 147° were: diisopropyl ketone (XLIV), 2.5 minutes; triketone XXXIII, 17 minutes. The IR spectrum of the solid contained absorptions (both hydroxyl and carbonyl regions) which indicated the presence of a carboxylic acid group. A small amount of the solid (4 g.) was repeatedly recrystallized from benzene and gave some solid (100 mg.) which melted sharply (121-122°). GLC analysis of this solid material (same column and temperature as cited above) showed only one peak that corresponded to the retention time of triketone XXXIII. Apparently decarboxylation occurred on the column. Structure proof of this diacid XLI was further obtained from elemental analysis (Table III), NMR (Plate XXVIII) and IR (Plate VII) spectral data (Tables IV and V).

The mother liquor (filtrate obtained from the removal of the above acid mixture) was further concentrated on a rotary evaporator giving

39.05 g. of a light brown oil which was treated with diazomethane in a later experiment (page 89).

The remaining 4.0 g. of the acid mixture was treated with 1.2 g. of diazomethane (prepared as before - page 85). A light golden-colored oil was obtained and was dissolved in 8 ml. of Skelly Solvent F. The solution, when chilled, deposited a white solid which was filtered out and washed with cold Skelly Solvent F (10 ml.). Dissolving the precipitate in hot benzene and then allowing the solution to cool gave clear platelets (2.64 g.), m.p. 74-75°. IR (Plate VIII) and NMR (Plates XXXIX and XXX) spectral data and elemental analysis (Tables III, IV and V) substantiate its proposed structure of diester XLIII. Analysis (GLC, CA-5) of the mother liquor obtained from the removal of diester XLIII revealed only one peak on the chromatogram. It was identified as diester XXXVII by mixed injection with an authentic sample. The original organic extracts were stripped of solvent under aspirator pressure to give 109 ml. of a golden-colored oil. GLC analysis (same column and temperature as cited above - page 89), showed the presence of only benzophenone (45%), and small amounts of bromobenzene, biphenyl, and lactone I. Retention time was: benzophenone, 29 minutes. The yield of benzophenone was based on lactone I.

<u>Esterification of Acid Material (Page 87) Obtained From the Carbonation of the Reaction Mixture of Phenyl Grignard Reagent and Lactone I in THF</u>. Diazomethane (12.0 g.) was prepared (as previously described - page 85) and slowly distilled into a solution of 25.0 g. of the acid material (page 87) dissolved in 75 ml. of ether cooled in Dry Ice. The solution in the receiver flask was allowed to attain room temperature; then the ether was removed under aspirator pressure to yield 24.83 g. of

a red-colored oil. GLC analysis (CA-3) revealed the presence of many components. Compounds identified by mixed injections with authentic samples were: methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI) (4%), dimethyl 2,2,4,4-tetramethyl-3-oxoglutarate (XXXVII) (8%), 2,2,4-trimethyl-3-oxovaleramide (XL) (2%), triketone XXXIII (13%), 1-phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX) (2%), and ester XXXVIII (12%). Yields are based on lactone I and retention times on the column are the same as those obtained from the treatment of the acid mixture received from the carbonation of the reaction mixture of phenyl Grignard Reagent and lactone I - page 82, with diazomethane.

Reaction (1:1.9) of Methyl Grignard Reagent[h] and Lactone I. The apparatus, procedure and workup used for this experiment were identical to those used for the reaction of lactone I with phenyl Grignard reagent. Lactone I (91.07 g., 0.65 mole) was added to methyl Grignard reagent (0.33 mole by titration). The amber-colored oil (approximately 55 ml.) was chilled but no precipitate formed. Analysis of the oil by GLC (CA-6) disclosed the presence of more than a dozen components. Triketone XXXIII (70%) was identified by mixed injection with an authentic standard solution of this compound. Retention time at 178° was: triketone XXXIII, 8 minutes. No attempt was made to identify any of the other components present in the reaction mixture.

Reaction (0.30:1.0) of Ethyl Grignard Reagent[h] and Lactone I. The procedure used for this experiment is identical to that described for the reaction of phenyl Grignard reagent and lactone I. Ethyl Grignard reagent (0.15 mole) was chilled to 0° and lactone I (70.0 g., 0.5 mole)

---

[h] Arapahoe Chemicals Inc., Boulder, Colorado, concentration (in ether), 3 molar.

added over a period of 1.5 hour. Reaction conditions and workup of the reaction mixture were essentially the same as described for the reaction of phenyl Grignard reagent and lactone I (page 60). Chilling the yellow oil (50.09 g.) gave a white solid. The precipitate was filtered from the mixture and recrystallized from benzene-n-heptane solution to give 123 mg. of ketol XXXII, mixture m.p. 148-149°. GLC analysis (CA-3) of the filtrate revealed a complex reaction mixture with nearly 20 components observed on the chromatogram. A major component of the reaction mixture was identified as triketone XXXIII (60%) by mixed injection with an authentic standard solution. Retention time at 162° was: triketone XXXIII, 8 minutes. No attempt was made to identify any of the other peaks indicated on the chromatogram.

Preparation of t-Butyl Grignard Reagent.[54] A 1-liter three-necked flask equipped as usual for Grignard formation was charged with 12.00 g. (0.5 g.-atom) of magnesium shavings; and the metal was covered with 90 ml. of anhydrous ether. t-Butyl bromide (68.51 g., 0.50 mole) was placed in the addition funnel and approximately 5 ml. was added to the flask. When the reaction had been initiated by gentle crushing of the metal with a stirring rod, ether (250 ml.) was quickly introduced into the flask and ether (250 ml.) was added to the addition funnel. The procedure from this point was nearly identical to that used for the preparation of phenyl Grignard reagent (page 59). Titration led to a calculated yield of 82% (0.41 mole).

Reaction (1:1.15) of t-Butyl Grignard Reagent and Lactone I. The t-butyl Grignard reagent (0.41 mole) was placed in a 2-liter three-necked flask (same apparatus as described in the previous experiment) and chilled to 0° using an ice-salt bath. Lactone I (91.07 g., 0.65 mole) diluted with 250 ml. of anhydrous ether was added dropwise with stirring, under nitrogen over a period of 1.5 hours. The addition was not exothermic. The resulting dark-green mixture was allowed to come to room temperature; heat was applied and the mixture held at reflux for 12 hours, without noticeable color change. The flask was chilled in an ice-salt bath to 0° and the reaction mixture decomposed by adding 500 ml. of aqueous 20% ammonium chloride solution. The resulting yellow-green mixture was extracted with three 250-ml. portions of ether. The solvent extracts were dried ($MgSO_4$) and filtered under suction; the ether was removed under water aspirator pressure to give 97.12 g. of a yellow oil. A solid was deposited when the oil was chilled. When filtered from solution and recrystallized from benzene-n-heptane solution (1:1) there was obtained 1.52 g. of 2,2,4-trimethyl-3-oxovaleramide (XL), mixture m.p. 107-109° (with an authentic sample). IR (Plate IX) and NMR (Plate XXXI) spectral data further support this known structure (see Tables IV and V). GLC analysis (CA-3) of the mother liquor obtained from the filtration of this compound disclosed the presence of more than 15 components. Mixed injection (authentic standard solution) identified one of the components as triketone XXXIII (no yield measured. Retention time at 167° was: triketone XXXIII, 8 minutes.

Sublimation of Ketol XXXII. Ketol XXXII, 5.0 g. (0.02 mole) was placed in a 10-inch sublimation gun and heated at 150°. Vacuum was then applied and heating was continued until the temperature reached 190°/0.45 mm. Heating was maintained to hold this temperature and pressure, with a white solid coating the cold finger at the end of 30 minutes. Heating was discontinued and the tube was allowed to cool to room temperature under vacuum. The vacuum was then slowly removed and the cold finger carefully withdrawn from the apparatus. The very hard and very nicely crystalline solid had the appearance of small uncut diamonds. The melting point (148-149°), and the sharp bands observed in the IR spectrum identified the material as ketol XXXII.

Attempted Preparation of Carbonyl Derivatives[70] of Ketol XXXII and Triketone XXXIII. A. 2,4,-Dinitrophenylhydrazone. Ketol XXXII (1.0 g., 0.004 mole) was placed in a large test tube along with 20 ml. of 2,4-DNP reagent.[68] The test tube was stoppered and vigorously shaken for 15 minutes. When no precipitate formed, the test tube was attached to a water condenser and heated for 6 hours on a steam bath. The orange solution was poured into a 1:1 mixture of water and cracked ice. An oil formed on top of the ice mixture but could not be made to crystallize, even when allowed to stand for 1 week.

B. Oxime. Hydroxylamine hydrochloride (0.25 g., 0.003 mole) dissolved in 15 ml. of water was placed in a large test tube. Ketol XXXII (1.0 g., 0.004 mole) and 10 ml. of 10% aqueous sodium hydroxide were added along with 2 ml. of ethanol until a clear solution formed. A condenser was attached, and the contents of the tube were heated on a steam bath for 3 hours. The tube was chilled in an ice bath, but crystallization did not occur and could not be induced by scratching the sides of the test tube with a stirring rod.

C. Semicarbazone. Ketol XXXII (1.0 g., 0.004 mole) was dissolved in 10 ml. of ethanol in a large test tube. Water was then added until the solution became faintly turbid. Semicarbazide hydrochloride (1.0 g., 0.001 mole) and 1.5 g. of sodium acetate were then added and the mixture vigorously shaken for 30 minutes. Because no precipitate formed, the contents of the tube were heated in a beaker of boiling water for 10 minutes; when cool no precipitate formed. The tube was chilled in a beaker containing ice, but crystallization did not occur.

Identical procedures as described above were followed in attempts to prepare derivatives of triketone XXXIII. In all cases, attempts to induce the formation of crystals were of no avail. A solid product was obtained, however, when 1.0 g. (0.004 mole) of triketone XXXIII and 3.0 g. (0.028 mole) of phenylhydrazine, dissolved in 25 ml. of ethanol, were heated at reflux in a test tube for 12 hours; however, the solid product obtained could not be purified. Recrystallization using benzene, ethanol, acetone and chloroform as solvents failed to give a pure product.

Attempted Acylation of Ketol XXXII With Acetic Anhydride in Pyridine.[11] Ketol XXXII 4.86 g. (0.02 mole) was placed in a 100-ml. one-necked flask fitted with a mechanical stirrer and a condenser with drying tube ($CaCl_2$). Pyridine (23 ml.) and acetic anhydride (7 ml.) were added in that order and the mixture was heated at reflux for 15 hours. The reaction mixture turned brown after 1.5 hours. The mixture was then chilled in an ice bath for 1 hour and poured into 100 ml. of distilled water. The brown solution was treated with powdered sodium carbonate (9.78 g.) until evolution of carbon dioxide ceased. Ether-benzene solution (250 ml.-1:1 ratio) was used to extract the mixture. The solvent extracts were washed successively with two 200-ml. portions of 1N hydrochloric acid, 170 ml. of 10% sodium bicarbonate solution and finally 100 ml. of water. The organic layer was then dried ($MgSO_4$) and filtered under suction. When most of the solvent had been removed by distillation, a white precipitate formed. The solid was filtered out and washed successively with 50 ml. of water and Skelly Solvent F

(60 ml.). Dissolving the material in hot benzene and precipitating it by the addition of cold n-heptane gave 4.79 g. (98% recovery) of snowy white crystals, mixture m.p. 148-149° with a sample of ketol XXXII from Run 1 - page 60.

Acid Hydrolysis of Ketol XXXII. A 250-ml. single-necked flask equipped with a mechanical stirrer and reflux condenser with drying tube ($CaCl_2$) was charged with 150 ml. of aqueous 6N hydrochloric acid and 10 g. (0.039 mole) of ketol XXXII. The mixture was boiled for 6 hours. The ketol seemed to dissolve after the mixture had been heated for 0.5 hour, and a yellow liquid formed on top of the solution. The mixture was allowed to cool to room temperature and was then extracted with 250 ml. of ether. The yellow organic layer was dried ($MgSO_4$), and filtered; the ether was removed to give 9.83 g. of a yellow liquid. GLC analysis (CA-4) revealed the presence of two components. Retention times at 167° were: unknown E, 12 minutes; triketone XXXIII, 16 minutes. Two grams of the residue were dissolved in an equal volume of ether and chromatographed on the Autoprep unit (CP-2). Settings on the chromatograph were as follows: column, 190°; helium flow, 300 cc./min.; injector, 255°; collector, 280°; detector, 305°. Twenty-five 100-ml. injections of the ether solution of the reaction residue were placed on the column and both unknown E (retention time, 26 minutes) and triketone XXXIII (retention time, 30 minutes) were collected in small glass collector tubes immersed in a Dry Ice - acetone bath. During the first few injections it was found that both materials readily yielded aerosols when emerging from the collection port. By using a stainless steel L-shaped tube, wrapped with an electric heating tape, connected to a number 19 hypodermic needle, the amount of aerosol was reduced and the efficiency of collection greatly increased.

After the twenty-fifth injection, the tubes were allowed to warm to room temperature and the partially solidified material present in each tube was washed into separate vials with ether. Analysis of both solutions by GLC (CA-4 - temperature 167°) indicated only one peak from the solution containing triketone XXXIII. However, the solution containing unknown E was shown to be contaminated with approximately 2% of triketone XXXIII. It was evident that peak separation was not large enough or the technique for collection was poor. So, the column temperature was dropped to 185° and twenty 100-ml. injections were placed on the column, care being taken to wash the needle in acetone before each collection. GLC analysis (same column and temperature as cited above) indicated that both compounds collected were pure, as only one peak was observed for each sample. Elemental analysis and IR (Plate X) and NMR (Plate XXXII) spectral data are given in Tables III, IV and V for unknown E. The structure of triketone XXXIII was deduced from data like that given above. IR (Plate XI, NMR (Plate XXXIII) data and results of analysis are also shown in Tables III, IV and V.

<u>Dehydration of Ketol XXXII</u>. An intimately ground mixture of 20.0 g. (0.078 mole) of ketol XXXII and 20.0 g. (0.14 mole) of freshly fused potassium acid sulfate was placed in a 250-ml. one-neck flask equipped as in the previous experiment. The mixture was heated slowly by means of a sand bath and began to melt at 105°. When the temperature reached 110°, the mixture had entirely liquified and had turned purple. Slow heating was continued until the temperature of the mixture reached 155° where it was thus held for 1 hour. At this temperature, droplets of water could be seen condensing on the sides of the flask and the

condenser. The melt was allowed to cool to room temperature; 250 ml. of ether was added and the mixture was filtered. The filtrate was treated with solid sodium bicarbonate until the mixture was neutral to litmus. Extraction of the mixture with 300 ml. of ether followed. The ether extract was dried ($MgSO_4$) and filtered. Removal of the ether from the filtrate on a rotary evaporator gave 19.39 g. of a brown oil. GLC analysis (CA-7) of the oil revealed two components present. Retention times at 163° were: unknown E, 18 minutes; triketone XXXIII, 20 minutes. Approximate area ratios of the components showed the yields of these to be about 40 and 60% respectively.

Distillation of 18 g. of the brown oil using a short-path Kontes distillation apparatus appeared to be unsuccessful. Fractions were taken at 115-118°, 118-120°, 120-126° and 126-129°/3.5 mm. Each fraction consisted of about 4 ml. of a clear colorless liquid. GLC analysis (same column and temperature as cited above) of each fraction still showed the presence of two components, but the peak attributed to unknown E decreased steadily in the higher-boiling fractions and was present to the extent of only about 5% in the highest-boiling fraction.

Each fraction was dissolved in 5 ml. of Skelly Solvent F and chilled overnight. An oily solid was deposited in each fraction and was removed by filtration. The precipitate obtained from the highest-boiling fraction was washed with 10 ml. of cold Skelly Solvent F and analyzed by GLC (same column and temperature as cited above). Again two components were observed, but the amount of unknown E was estimated to be only about 3%.

A quantitative analysis was performed on the reaction residue by making repeated injections of the residue (1.0027 g. in 25 ml. of ether) alternately with a prepared standard solution (1.0080 g. of triketone XXXIII in 25 ml. of ether). From the molar concentration of triketone XXXIII obtained from the standard solution, and from the observed peak area of this component obtained from the standard solution and from the reaction mixture, the yield of triketone XXXIII was found to be 62%. The yield of unknown E was 38% since it was the only other component detected by GLC.

Attempted Dehydration of Ketol XXXII with Dimethyl Sulfoxide.[81] Ketol XXXII (13.90 g., 0.055 mole) was placed in a 200-ml. three-necked flask equipped as in the previous experiment. Dimethyl sulfoxide (30.03 g., 0.385 mole) was funneled into the flask and the solution was heated in an oil bath to 178° and held at this temperature for 11 hours. The brown solution was allowed to cool to room temperature and was then poured into 150 ml. of water. The solution was extracted with three 100-ml. portions of ether-benzene solution (1:1). Filtration of the dried ($MgSO_4$) extracts gave a light yellow solution which was concentrated under aspirator pressure to give 13.79 g. of a yellow liquid. GLC analysis (CA-8) disclosed the presence of only one peak along with a trace impurity. By mixed injection with a standard solution, the peak was identified as that corresponding to triketone XXXIII (98%). The impurity was identified as unknown E. Retention times at 160° were: triketone XXXIII, 5 minutes; unknown E, 3 minutes.

Thermolysis of Ketol XXXII. A 50-ml. flask equipped like that described for the experiment cited on page 95 was charged with 5.0 g. (0.02 mole) of ketol XXXII. The flask was slowly heated and the ketol liquified at 151°. Further heat was applied until the temperature of the contents in the flask reached 185°. The light brown liquid was heated at this temperature for 1 hour, then allowed to cool to room temperature. The IR spectrum of the liquid (4.96 g.) was identical to that of triketone XXXIII. GLC analysis (CA-4) disclosed only one peak on the chromatogram. By a mixed injection with an authentic sample, the compound was identified as triketone XXXIII. Retention time at 165° was 17 minutes.

Reaction of Ketol XXXII with Lithium Aluminum Hydride. A 1-liter three-necked flask equipped similarly as that described for phenyl Grignard preparation with the exception of a glass tube outlet connected to a gas buret (filled with water), was charged with 200 ml. of anhydrous ether and 1.74 g. (0.044 mole) of lithium aluminum hydride; the grey suspension was chilled to 0° in an ice-salt bath with stirring, under nitrogen. After passing nitrogen through the system for 15 minutes, the nitrogen flow was stopped and 25.00 g. (0.098 mole) of ketol XXXII dissolved in 100 ml. of anhydrous ether was added dropwise. With each drop of the solution of ketol XXXII a large volume of gas was liberated as bubbles were observed to rise to the top of the gas buret. After the addition (1 hour), which was quite exothermic, the grey mixture was stirred for 1 hour at 0°, then decomposed at this temperature by adding dropwise 100 ml. of ethyl acetate followed by water (60 ml.). The white, gelatinous slurry was filtered (difficult) and the filtrate extracted with two 200-ml. portions of ether-benzene solution (1:1). The solvent extracts were combined, dried ($MgSO_4$) and filtered. Solvent was stripped from the mother liquor under aspirator pressure until approximately 40 ml. of solution remained. The solution was chilled to cause deposition of a white solid. The precipitate was filtered out and washed with 50 ml. of Skelly Solvent F followed by 20 ml. of chloroform. The solid (4.57 g.), unknown F, m.p. 196-198° was shown to be pure by GLC analysis (CA-9). Only one compound was observed with a retention time at 204° of 12 minutes.

The NMR spectrum (pyridine-d_5) was poorly resolved but indicated a singlet at δ5.47 superimposed on a very broad hump at δ5.25, three singlets at δ3.75, δ3.58, δ3.10, two more singlets at δ2.90 and δ2.80, a multiplet (heptet) centered at δ0.94 (J = 6 c.p.s.) and finally a doublet centered δ0.78 (J = 7 c.p.s.). The IR spectrum (Plate XII) was simple but poorly resolved (see Table IV for analysis).

The filtrate obtained from the removal of unknown F was further concentrated on a rotary evaporator and gave 20.33 g. of a thick brown oil. No attempt was made to analyze this residue. IR analysis of the gas evolved from the residue showed no peaks - it was probably hydrogen.

Reaction of Triketone XXXIII with Lithium Aluminum Hydride. The apparatus used for this experiment was identical to that described in the previous experiment. Lithium aluminum hydride (1.59 g., 0.042 mole) suspended in 200 ml. of anhydrous ether was placed in the flask. The addition of triketone XXXII (10.0 g., 0.04 mole), diluted with 100 ml. of anhydrous ether, the reaction conditions, and the method of work-up of the reaction mixture were the same as those described in the previous experiment. No noticeable gas evolution was observed. A solid was obtained from the chilled, partially concentrated organic layer. When recrystallized from benzene, a white solid, unknown G (3.62 g.) was isolated, m.p. 121-122°. The IR spectrum (Plate XIII) ana analysis are shown in Tables III and IV. All peaks observed in the NMR spectrum (pyridine-d_5) were very poorly resolved. Broad singlets were observed at δ7.55, δ6.12, δ5.77, δ4.03, δ3.79, δ3.39, a multiplet centered at δ2.13 (J = 6 c.p.s.), another singlet at δ1.33 and a singlet at δ1.13 with shoulders at δ1.25 and δ1.06.

The mother liquor obtained from the removal of this compound was further concentrated under aspirator pressure and gave 6.29 g. of a yellow viscous oil. The residue was not analyzed further.

The (1:1) Reaction of Triketone XXXIII with Potassium Hydroxide in Ethyl Alcohol. A 100-ml. three-necked flask equipped like that described for Grignard preparations (page 59) was charged with 3.00 g. (0.012 mole) of triketone XXXIII diluted with 40 ml. of absolute ethanol. The solution was stirred under nitrogen for 15 minutes; a solution of 0.672 g. (0.012 mole) of potassium hydroxide dissolved in 20 ml. of absolute ethanol was added over a period of 45 minutes. During the addition of the first few drops of the potassium hydroxide solution, the color of the contents in the flask became yellow-brown, but the temperature did not rise. Heat was applied and the solution heated to reflux, and the rest of the potassium hydroxide solution added to the boiling solution. After the addition was complete, the mixture was further heated at reflux an additional hour. The flask, which now contained a white precipitate, was allowed to cool to room temperature, then chilled for 1 hour in an ice-salt bath. The mixture was filtered and the filter cake was washed with 10 ml. of ether and the washings added to the filtrate. After the solid (0.53 g.) was dried in air, it was identified as potassium carbonate by comparing its IR spectrum to that of an authentic sample. The mother liquor was poured into 50 ml. of distilled water, and the brown mixture was extracted with two 125-ml. portions of ether. The ether was distilled from the solution until

22.5 ml. (measured) of liquid remained. GLC analysis of this solution (CA-3) disclosed the presence of a 4-component system. The first two peaks, identified by mixed injections with authentic samples (standard solutions) were due to: ethyl isobutyrate (XLVII) (10%) and diisopropyl ketone (XLIV) (43%); retention times at 86° were: ethyl isobutyrate (XLVII), 0.8 minutes; diisopropyl ketone (XLIV), 0.95 minutes. Two peaks representing 24 and 19% (peak area ratios) of the reaction mixture had retention times at 86° of 16.8 and 23 minutes, respectively. The solution containing the residue was further concentrated by distillation to a yellow-brown oil which was dissolved in 5 ml. of ether. Chromatography of the solution was effected on the Autoprep unit (CP-2). Temperature settings on the unit were as follows: column, 152°; injector, 233°; collector, 295°; and detector, 312°. The helium flow rate was 93 cc./min. Twenty-five 250-ml. injections of the ether solution were placed on the column and materials corresponding to both of the unknown peaks, having retention times of 7.3 and 10 minutes respectively, were collected in the same manner as that described previously for the collection of unknown E and triketone XXXIII, page 95. Spectral data (Tables IV and V) [IR (Plate XIV), NMR (Plate XXXIV) analysis] identified one of the compounds as ethyl 2,2,4-trimethyl-3-oxovalerate (XLV). Spectral data (Tables IV and V) [IR (Plate XV) and NMR (Plate XXXV)] also identified the other compound as 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI).

The aqueous layer was acidified with 2 ml. of aqueous 6N hydrochloric acid, and the resulting brown solution was extracted with 100 ml. of ether. The organic layer was dried ($MgSO_4$), filtered under suction and the ether was removed by distillation until 7 ml. (measured) of solution remained. GLC analysis (same column as used above) revealed the presence of only isobutyric acid (XLVIII) (3.5% - based on lactone I obtained by alternate injections with standard solution). Retention time at 89° was: isobutyric acid (XLVIII) 1.0 minute.

In another experiment, triketone XXXIII (2.35 g., 0.009 mole) and 20 ml. of a solution containing 20.0 g. (0.36 mole) of potassium hydroxide dissolved in 80 ml. of methanol were heated at reflux for 4 hours. Workup of the reaction mixture from this point was identical to that described in the previous run. Potassium carbonate (0.54 g.) was obtained and identified by comparing its IR spectrum to that of an authentic sample. GLC analysis (same column and temperature as above) of the residue obtained from the distillation of the filtrate revealed the presence of only diisopropyl ketone (XLIV). Analysis (CA-3) of the residue obtained from the distillation of the organic extracts received from the acidified aqueous layer showed isobutyric acid (XLVIII) as the only compound present.

The (1:1) Reaction of Ketol XXXII with Potassium Hydroxide in Ethyl Alcohol. The procedure and apparatus for this reaction [using 21.50 g. (0.084 mole) of ketol XXXII and 4.50 g. (0.084 mole) of potassium hydroxide] were essentially identical to those described in the previous experiment. Filtration of the reaction mixture gave 3.61 g. of potassium carbonate. The filtrate was poured into 225 ml. of water, and the resulting mixture was extracted with three 150-ml. portions of 1:1 ether-benzene solution. The solvent extracts were combined, dried ($MgSO_4$) and filtered under suction. Distillation of the organic layer afforded an oily residue which was diluted to 25 ml. with ether. GLC analysis (same column as cited in the previous experiment) revealed a

5-component system. Compounds identified were: ethyl isobutyrate (XLVII) (5%), diisopropyl ketone (XLIV) (30%), ethyl 2,2,4-trimethyl-1,3-oxovalerate (XLV) (18%), 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI) (11%), and triketone XXXIII (35%). Retention times at 86° were: ethyl isobutyrate (XLVII), 0.8 minutes; diisopropyl ketone (XLIV), 0.95 minutes; ethyl 2,2,4-trimethyl-3-oxovalerate (XLV), 16.8 minutes; 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI) 23 minutes. Retention time at 165° was: triketone XXXIII, 17.3 minutes.

Workup (see previous experiment) of the aqueous layer revealed only a trace of isobutyric acid (XLVIII) when analyzed by GLC (same column and temperature as previously described for this part of the experiment cited earlier).

In a similar experiment as described for the (1:1) reaction, ketol XXXII (20.0 g., 0.08 mole) was combined with a solution composed of 40.0 g. (0.71 mole) of potassium hydroxide dissolved in 160 ml. of methanol. Reaction conditions and workup of the reaction mixture were essentially identical to those described in the previous experiments. The reaction mixture when filtered gave 10.0 g. of potassium carbonate. The filtrate obtained (containing ether) was dried ($MgSO_4$) and suction-filtered. Removal of the solvent by distillation gave a light yellow liquid. Further distillation using a short-patch apparatus gave one main fraction (4.95 g.) b.p. 124-126/744 mm. which was identified as diisopropyl ketone (XLIV) by comparing its IR spectrum with that of an authentic sample. Distillation of the ether extracts obtained from the acidified aqueous layer gave 3.90 g. of a foul-smelling liquid, b.p. 138-140°/744 mm. The IR spectrum of this liquid was identical to that of an authentic sample of isobutyric acid (XLVIII). The small amount of dark residue accompanying each distillation was not analyzed.

Preparation of 2,2,4-Trimethyl-3-oxovaleryl Chloride(XLIX).[8] Lactone I (195.0 g., 1.39 mole) was placed in a 500-ml. three-necked flask equipped with a mechanical stirrer, a thermometer, and a Dry Ice condenser. Hydrogen chloride gas was bubbled slowly into the stirred lactone through a glass frit. Any excess hydrogen chloride vapors which were not liquified by the Dry Ice condenser passed through the side arm of the condenser and into a 1-liter flask containing approximately 500 ml. of water. The contents in the reaction flask turned red in color after 30 minutes of reaction, and the temperature of the solution rose 7° during that time. The hydrogen chloride gas was passed through the lactone I for 24 hours with the temperature of the contents in the flask slowly falling to room temperature (26°). The maroon-colored solution was distilled through a 50-cm. Vigreux column, and gave a small amount of forerun (5 ml.) between 100-170°, with two large fractions taken at 171-180° and 181-184°/744 mm. Both latter fractions were shown to be contaminated with lactone I as the IR spectra of both cuts indicated absorptions in the carbonyl region that were observed in the spectrum of the lactone I. All fractions and the small amount of dark residue in the distillation flask were combined and hydrogen chloride gas passed through the solution for an additional 16 hours.

During this additional reaction period, a 1-liter three-necked flask, equipped with a water inlet tube, a glass stopper, and a Claisen U-tube, was filled halfway with ¼-inch glass helices. A funnel was placed on top of a 24-inch glass column bearing a side arm and the apparatus arranged so that the Claisen U-tube extended halfway into the funnel. The water was turned on and its rate of flow controlled so that only one or two helices at a time passed through the U-tube and into the column. The total time to pack the column was 5.5 hours. The column was washed with acetone and allowed to drip-dry. After the 16-hour reaction period, the red solution was distilled through the column. The column was heated just enough that vapors rose to the top of the column but did not distill. After this preliminary equilibration period, heating was increased and the liquid allowed to distill. Three clear, colorless fractions were taken at 169-179°, 180-185° and 186-187°/735 mm. The main fraction, b.p. 186-187°/735 mm. [lit.[79] 85-86/23 mm.] - yield 110 g. (49%), was shown to contain no lactone I. [See IR (Plate XVI) and NMR (Plate XXXVI) spectra, Tables IV and V for data on acid chloride XLIX].

Preparation of Diisopropylcadmium[69] and its Reaction With 2,2,4-Trimethyl-3-oxovaleryl Chloride (XLIX). Isopropyl Grignard reagent (0.5 mole; 87% by titration), prepared in essentially the same manner as those Grignard reagents previously described, was chilled to -10° in a Dry Ice - acetone bath. Pulverized cadmium chloride (49.0 g., 0.27 mole) which was previously dried at 120° for 1 week was added in 2-3 g. portions over a period of 25 minutes, under nitrogen with stirring. The contents of the flask (grey in color) were allowed to warm to room temperature and turned brown in color and finally to dark brown (almost black). The dark mixture was heated at reflux for 45 minutes and then ether was rapidly distilled from the flask through a short-path condenser. When a slurry formed in the distilling flask, 350 ml. of anhydrous benzene was added and an additional 75 ml. of solution distilled from the reaction flask. The dark mixture was then cooled to -7° (Dry Ice-acetone bath) and 83.25 g. (0.5 mole) of 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX) dissolved in 50 ml. of dry benzene was added over a period of 0.5 hour. The resulting black mixture was boiled for 3.5 hours, cooled to 10° in an ice-bath and decomposed by the dropwise addition of 250 ml. of 20% aqueous ammonium chloride. The resulting mixture (two layers) was extracted with three 200-ml. portions of benzene. The organic extracts were combined and dried ($MgSO_4$), and the solvent was removed under aspirator pressure to give 82.96 g. of a light brown liquid. GLC analysis (CA-10) revealed 8 peaks on the chromatogram, 6 of which were not identified. Compounds identified were: 2,4,4,5-tetramethyl-3,5-heptanedione (XLVI) (29% - peak area ratio) and unreacted acid chloride (XLIX) (43% - obtained from alternate injections with a standard solution). Retention times at 66° were: 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX), 15 minutes; 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI), 32 minutes. The residue (10 ml.) was diluted with 5 ml. of ether and chromatographed on the Autoprep unit (CP-2). Temperature settings on the unit were: column, 150°; injector, 245°; collector, 250°; detector, 305°. Helium flow rate was 95 cc./min. Ten 85-μl. injections of the ether solution were placed on the column. The compound which represented the peak having a retention time of 11 minutes were caught in a small collector tube (in a manner like that described previously - page 95). The IR spectrum of this compound was identical to that of an authentic sample of 2,4,4,6-tetramethyl-3,5-heptanedione (XLVI).

<u>Preparation of Methyl 2,2,4-Trimethyl-3-oxovalerate (XXXVI)</u>. The procedure used for the preparation of this sample was similar to the method of Berlin and Austin for the preparation of diphenylphosphinic esters.[9] A 1-liter flask, equipped like that described on page 59 for Grignard formation, was purged with nitrogen and charged with 80.75 g.

(0.50 mole) of 2,2,4-trimethyl-3-oxovaleryl chloride (XLIX) dissolved in 200 ml. of anhydrous ether; triethylamine (50.60 g., 0.50 mole) diluted with 150 ml. of anhydrous ether was added dropwise to the stirred solution of acid chloride over a period of 1 hour. Methanol (22.40 g., 0.70 mole) was then added dropwise to the white, slightly opaque mixture over a period of 45 minutes. Stirring became difficult during the addition of the methanol owing to the formation of the amine hydrochloride. Heat was applied to the flocculent heterogeneous mixture which was kept under reflux for 1.5 hours. The mixture was allowed to cool to room temperature and stand overnight and then filtered under suction. The filtrate was washed with a total of 750 ml. of 10% aqueous sodium bicarbonate solution. The organic layer was washed with two 700-ml. portions of water and then dried ($MgSO_4$). Filtration followed by removal of solvent on a rotary evaporator gave 54 ml. of a light yellow liquid. Distillation through an 18-inch silver-jacketed tantalum wire-packed column gave forerun fractions at 65-90° (3 ml.) and 90-180° (4 ml.). The principal fraction distilled at 188-189.5°/729 mm. [lit.[43] 88-91/22 mm.]: yield 59.42 g. (76%) [$n^{20}D$ 1.4215; lit.[10] $n^{20}D$ 1.4244]. It was checked for purity by GLC analysis (CA-11). Only one peak was observed. Retention time at 138° was: methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI), 0.9 minutes. IR (Plate XVII) and NMR (Plate XXXVII) spectral data (Tables IV and V) further substantiate this known structure.

Preparation of Dimethyl 2,2,4,4-Tetramethyl-3-oxoglutarate (XXXVII). The procedure used for the preparation of this compound was identical to that given in Eastman Technical Data Report No. X-129.[79] The quantities of materials used were: lactone I (46.65 g., 0.34 mole), sodium methoxide (18.60 g. 0.34 mole) and 31.50 g. (0.33 mole) of methyl chloroformate. The ester XXXVII was isolated (47.00 g., 62%), b.p. 110-112°/6 mm, $n^{20}D$ 1.4481, [lit. b.p. 97-98/3 mm., $n^{20}D$ 1.4470 - 1.4480], as a clear colorless liquid. The IR (Plate XVIII) and NMR (Plate XXXVIII) spectra are consistent with the structure of this known compound (see Tables IV and V).

Attempted Claisen Condensation of Methyl 2,2,4-Trimethyl-3-oxovalerate(XXXVI) with Diisopropyl Ketone(XLIV). A. Sodium Methoxide as the Condensing Agent.[78] Sodium methoxide (25.056 g., 0.464 mole) and 100 ml. of dry methanol were placed in a 500-ml. flask equipped like that for Grignard formation (page 59). Diisopropyl ketone (XLIV) (12.104 g., 0.116 mole) was added to the stirred mixture over a period of 45 minutes. Methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI) (20.00 g., 0.116 mole) was added dropwise over a period of 1 hour. Neither the addition of the ketone XLIV nor the addition of ester XXXVI was exothermic, so heat was applied and the mixture was heated under reflux for 18 hours. After standing overnight, the mixture was chilled in an ice bath and 350 ml. of ice water was added. The mixture was extracted with three 125-ml. portions of ether and the ether extracts combined and dried ($MgSO_4$). The organic extracts were filtered and the solvent was removed by distillation. The residue, very light tan in color, was analyzed by GLC (CA-3). Compounds identified by mixed injections with solutions of known samples were: diisopropyl ketone (XLIV) (near quantitative recovery) and a small amount of methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI). Retention times at 160° were: methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI), 0.4 minutes; diisopropyl ketone (XLIV), 0.6 minutes.

The aqueous layer was acidified and extracted with ether. After drying ($MgSO_4$), and filtering, the ether was distilled until 50 ml.

(approximately) of solution remained. GLC analysis (same column as above) showed that methyl isobutyrate was the major component along with trace amounts of six other compounds. One of these was identified by mixed injection with a known standard as triketone XXXIII, but this compound was present to an extent of only 4% in the reaction mixture. Retention time at 160° was: triketone XXXIII, 9 minutes. The other peaks observed in the chromatogram were not identified.

B. Sodium Hydride as Condensing Agent.[71] The apparatus was identical to that used in the preceding experiment. The quantities used in this run were identical to that of the previous experiment except that sodium hydride (3.84 g., 0.116 mole) was used in place of sodium methoxide. GLC analysis (same column and temperature as in part A) of the initial organic solution revealed the presence of diisopropyl ketone (XLIV) (35% recovery - from alternate injections with known standard solution), methyl 2,2,4-trimethyl-2-oxovalerate (XXXVI) (near quantitative recovery), and diisopropylmethanol (50% - from peak area ratios). Retention time at 160° was: diisopropylmethanol, 0.3 minutes. No triketone XXXIII was detected by GLC.

C. Sodium Amide as the Condensing Agent.[41] Same procedure and apparatus was used in this experiment as in the previous experiment except that 3.12 g. (0.081 mole) of sodium amide, 4.56 g. (0.040 mole) of diisopropyl ketone (XLIV) and 14.00 g. (0.081 mole) of methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI) were the quantities used. GLC analysis (same column and temperature as cited in parts A and B) of the initial organic solutions revealed the presence of only diisopropyl ketone (XLIV) and methyl 2,2,4-trimethyl-3-oxovalerate (XXXVI). GLC analysis of the extracts (ether) obtained from the acidified aqueous layer showed no triketone XXXIII present. There were several small peaks observed in the chromatogram but no attempt to identify any of them was made.

Reaction of Diisopropyl Ketone (XLIV) with Sodium Hydride.[77] Diisopropyl ketone (XLIV) (4.00 g., 0.035 mole) dissolved in 25 ml. of anhydrous ether along with 1.68 g. (0.070 mole) of sodium hydroxide were placed in a 50-ml. one-necked flask equipped like that described for the thermolysis of ketol XXXII (page 98). The mixture was heated at reflux for 16 hours under nitrogen, with the color of the contents in the flask becoming dark brown. After the flask had cooled to room temperature, the mixture was poured into 100 ml. of ice water. Normal workup followed.

The aqueous layer was acidified with 6.5 ml. of 6N hydrochloric acid, with the brown color of the solution vanishing. The other extracts (150 ml.) were dried ($MgSO_4$), filtered and distilled until approximately 5 ml. of solution remained. Analysis of this solution by GLC (CA-10) revealed diisopropylmethanol as the major component (55% - peak area ratio) along with a trace amount of diisopropyl ketone (XLIV). Retention time at 91° was: diisopropylmethanol, 0.8 minutes.

Attempted Ring-Closure of Triketone XXXIII. Triketone XXXIII (1.00 g., 0.004 mole) was placed in a 50-ml. one-necked flask equipped like that described in the previous experiment. Sodium methoxide (0.432 g., 0.008 mole) was added along with 20 ml. of anhydrous ether to the flask and the suspension heated under reflux for 11 hours. The brown-colored mixture was allowed to attain room temperature, then slowly poured into 75 ml. of ice water. Extraction with three 75-ml. portions of ether was followed by combining the organic layers, drying ($MgSO_4$) and distillation until approximately 5 ml. of solution remained.

GLC analysis (CA-12) revealed the presence of only triketone XXXIII. Retention time at 169° was: triketone XXXIII, 7 minutes.

The aqueous layer was acidified with 5.6 ml. of aqueous 6N hydrochloric acid and the colorless solution was extracted with three 75-ml. portions of ether. The combined, dried ($MgSO_4$) organic layers were distilled until approximately 5 ml. of solution remained. No precipitate formed when the solution was chilled. GLC analysis (same column and temperature as above) disclosed the presence of many components in the reaction mixture. One peak was identified, by mixed injection with a standard solution, as arising from triketone XXXIII. This compound may have arisen by poor techniques in working up the reaction mixture, or ketol XXXII may have been present in the reaction mixture and produced triketone XXXIII as a decomposition product when GLC analysis was performed on the reaction mixture. Ketol XXXII when analyzed for purity by GLC (CA-11), column temperature 158°, gave a chromatogram representative of a decomposition pattern.

Ring closure of triketone XXXIII (1.00 g., 0.004 mole) was also attempted using sodium hydride (0.192 g., 0.008 mole) as the base. The reaction mixture was worked up exactly like that from the sodium methoxide run - page 111. GLC analysis (same column and temperature as described above) revealed the presence of triketone XXXIII in the initial organic extracts. Analysis by GLC of the organic extracts obtained from the acidified aqueous layer showed a multi-component system. Triketone XXXIII was also identified as present in the reaction mixture, and the same explanation for its appearance may also apply here as in the sodium methoxide run - page 111.

Preparation of Hexamethyl-1,3,5-cyclohexanetrione (II). The procedure used for the preparation of this sample was essentially the same as that given in Eastman Technical Data Report No. X-129.[79] A 500-ml. one-necked flask equipped like that cited previously for the acid hydrolysis of ketol XXXII (page 95) was charged with 140.1 g. (1.0 mole) of lactone I and 2.28 g. (0.042 mole) of sodium methoxide. Heat was applied until the contents of the flask reached a temperature of 90°. At this temperature an exothermic reaction began and the reaction mixture boiled violently for 10 minutes. When the reaction began to subside, heat was applied and the brown-colored reaction mixture held at reflux for 1 hour. After the contents in the flask had cooled to 100°, the mixture was poured into 1 liter of water and the heterogeneous mixture was rapidly stirred. Filtration gave a solid material consisting of white needle-shaped crystals and many pieces of a brown polymeric-like material. The brown substance was removed from the white crystals with a pair of tweezers (tedious) and discarded. A solution of the white solid in hot ethanol gave a white precipitate upon the addition of cold water. The precipitate was washed with hot water (100 ml.) and dried (atmosphere) to give 94.32 g. (68%) of hexamethyl-1,3,5-cyclohexanetrione (II), mixture m.p. 79-80° with an authentic sample.

Preparation of Isopropyl Grignard Reagent.[13] A 300-ml. three-necked flask equipped for Grignard formation (see page 59) was charged with 2.40 g. (0.10 g.-atom) of magnesium shavings and enough ether to cover the metal. Isopropyl bromide (12.30 g., 0.10 mole) was placed in the addition funnel. From this point the procedure and reaction conditions were identical to that for the preparation of phenyl Grignard reagent. The yield was 0.078 mole (78%).

Attempted Condensation of Isopropyl Grignard Reagent with Hexamethyl-1,3,5-cyclohexanetrione (II) in the Presence of Magnesium Bromide.[76] A 1-liter three-necked flask equipped for Grignard formation (see page 59) was charged with magnesium shavings (2.40 g., 0.10 mole) and 85 ml. of anhydrous ether and bromine (16.00 g., 0.10 mole) was added dropwise to the stirred mixture. A vigorous, exothermic reaction occurred after the addition of each drop of bromine. After the addition (1.5 hours), hexamethyl-1,3,5-cyclohexanetrione(II) (20.00 g., 0.10 mole) dissolved in 90 ml. of anhydrous ether was added to the brown magnesium bromide solution, under nitrogen, over a period of 1 hour. The resulting mixture (two layers) was stirred for 15 minutes, then isopropylmagnesium bromide (0.078 mole; prepared in the previous experiment - page 113) was added slowly to the mixture over a period of 2 hours. The addition of the Grignard solution was exothermic as evidenced by the gentle boiling of the mixture. After the addition, the yellow mixture was stirred overnight at room temperature, then heated under reflux for 12 hours. The mixture was cooled to 0° in an ice-salt bath and decomposed by the dropwise addition (to control foaming) of 125 ml. of 20% anueous ammonium chloride solution; the ether extracts were combined, dried ($MgSO_4$) and filtered under suction. Distillation of the organic layer afforded 19.86 g. of a yellow liquid. The liquid, when analyzed by GLC (CA-10) was found to contain starting material (ketone II) -92% - peak area ratio, and three other components. One of the peaks was identified by mixed injection with an authentic sample as triketone XXXIII (4%). The other three peaks were not identified. Retention times at 165° were: hexamethyl-1,3,5-cyclohexanetrione (II), 9 minutes; triketone XXXIII, 15.5 minutes. Chilling the yellow liquid afforded a white precipitate which could not be further purified by recrystallization.

Preparation of Lithium Dust. The procedure is essentially the same as that of Bartlett, Swain and Woodward.[3] A 500-ml. three-necked flask equipped with a high-speed mechanical stirrer, a condenser with drying tube ($CaCl_2$), and a nitrogen inlet tube was charged with 110 ml. of mineral oil (Fisher paraffin oil, white and heavy), and 2.0 g. (0.28 mole) of freshly chipped lithium. The contents of the flask were heated until the lithium began to melt; the mixture was stirred vigorously until the metal dispersed into droplets. Heating and stirring were discontinued and the contents were allowed to cool to room temperature. The mineral oil was removed by sucking it from the flask (by means of a vacuum pump) through a glass frit. The lithium dust was washed with four portions of Skelly Solvent F (100 ml. each) and the Skelly Solvent F removed through the glass frit. The lithium dust was finally suspended in 100 ml. of Skelly Solvent F and used in the next experiment.

Preparation of Isopropyllithium.[25] Using the same apparatus as described in the previous experiment, isopropyl chloride (9.8 g., 0.125 mole) dissolved in 100 ml. of dry Skelly Solvent F was placed in the addition funnel and added dropwise to the suspension of lithium dust (0.28 mole) held at reflux in the Skelly Solvent F. After the addition (45 minutes), the contents of the flask which were charcoal-black in color, were heated at reflux an additional 0.5 hour. At the end of this period, an exothermic reaction began and the mixture boiled gently without any external heating for 0.5 hour. After the reaction had subsided, the mixture was stirred for 1 hour. Titration (as in experiment 1) indicated a yield of 72% (0.072 mole).

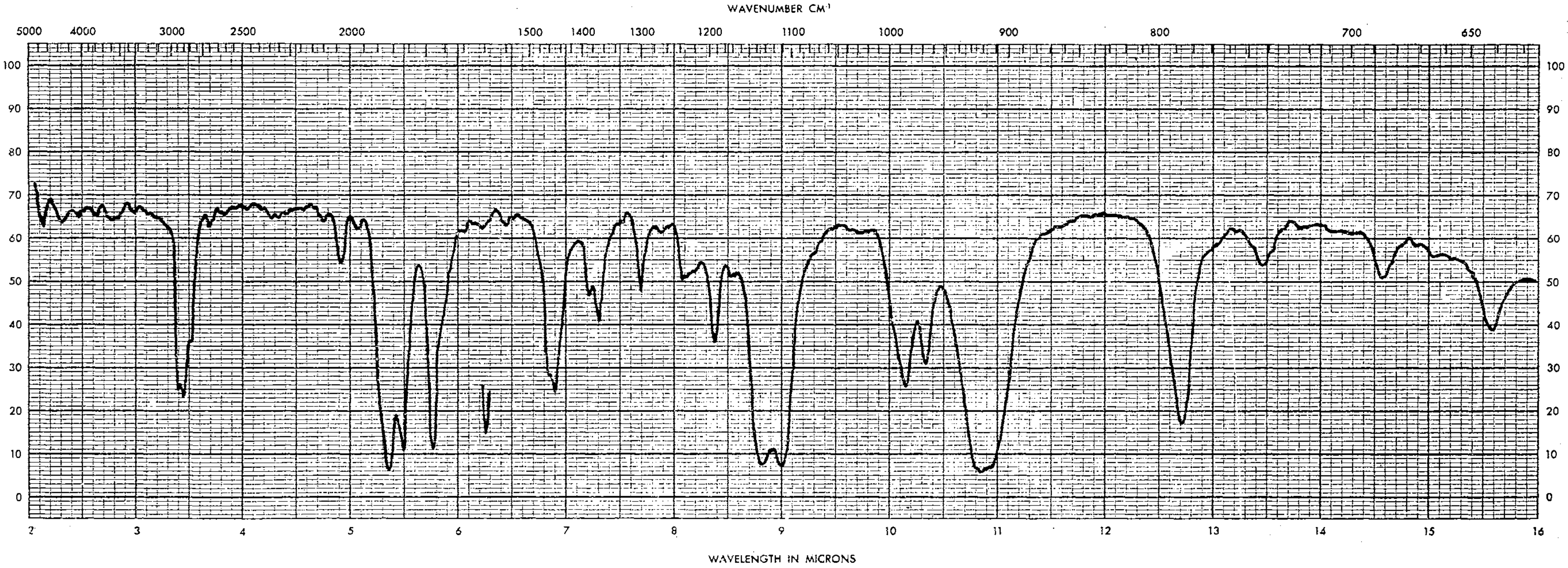
Reaction of Isopropyllithium with Hexamethyl-1,3,5-cyclohexanetrione (II). A 500-ml. three-necked flask (equipped as in the previous experiment) was charged with 20.00 g. (0.10 mole) of hexamethyl-1,3,5-cyclohexanetrione (II) and 100 ml. of dry Skelly Solvent F; the contents of the flask were chilled to -30° in a Dry Ice - acetone bath. The isopropyllithium (0.072 mole - 206 ml.) solution prepared in the previous experiment was added to the contents of the flask over a period of 1 hour. The addition was slightly exothermic, and the color of the mixture became grey. After the addition, the mixture was allowed to warm to room temperature and was further stirred for 12 hours. Water (175 ml.) was added dropwise to decompose the grey mixture (not exothermic) followed by an extraction of the mixture with two 150-ml. portions of ether - Skelly Solvent F solution (1:1). The organic extracts were combined, dried ($MgSO_4$), filtered under suction and stripped of solvent on a rotary evaporator to give 19.90 g. of a light yellow liquid. Chilling the liquid gave a precipitate, but recrystallization attempts using a number of solvents (benzene, ether, acetone, chloroform) gave no pure product. GLC analysis (CA-10) of the reaction residue showed starting material (ketone II) present (53%), triketone XXXIII (8%) and two other peaks which were not identified. Retention times at 162° were: hexamethyl-1,3,5-cyclohexanetrione (II), 10 minutes; triketone XXXIII, 16.5 minutes. Yields of triketones II and XXXIII were based on a comparison of peak area ratios of the compounds present in the reaction mixture to those obtained from standard solutions of these compounds.

Condensation of Methyl Grignard Reagent[h] with Hexamethyl-1,3,5-Cyclohexanetrione (II). Hexamethyl-1,3,5-cyclohexanetrione (II) (20.00 g., 0.10 mole) dissolved in 125 ml. of anhydrous ether was added dropwise to the stirred solution over a period of 2.5 hours. The addition was slightly exothermic, and the color of the contents in the flask initially were lemon colored, but at the end of the addition had changed to milky white. After the mixture, containing a white precipitate, had been allowed to warm to room temperature, the mixture was heated to a boil and was maintained thus for 12 hours. The flask was chilled to 5° by means of an ice bath, and the mixture decomposed by the dropwise addition of 100 ml. of 20% aqueous ammonium chloride solution. The ether extracts (300 ml.) were combined, dried ($MgSO_4$) and filtered. Distillation (removal of solvent) gave 19.91 g. of a yellow liquid. Chilling the liquid deposited a white solid which was filtered out. The precipitate was recrystallized from benzene-n-heptane solution (1:1) to give (after drying in air), 14.84 g. (69%) of a fine white powder. IR (Plate XIX) and NMR (Plates XXXIX and XL) spectral analyses allowed the compound to be assigned the structure of new ketol L (see also Tables III, IV and V). GLC analysis (CA-10) of the filtrate obtained from the removal of this compound disclosed only starting material (ketone II) present. Retention time of ketone II at 160° was 10.5 minutes.

---

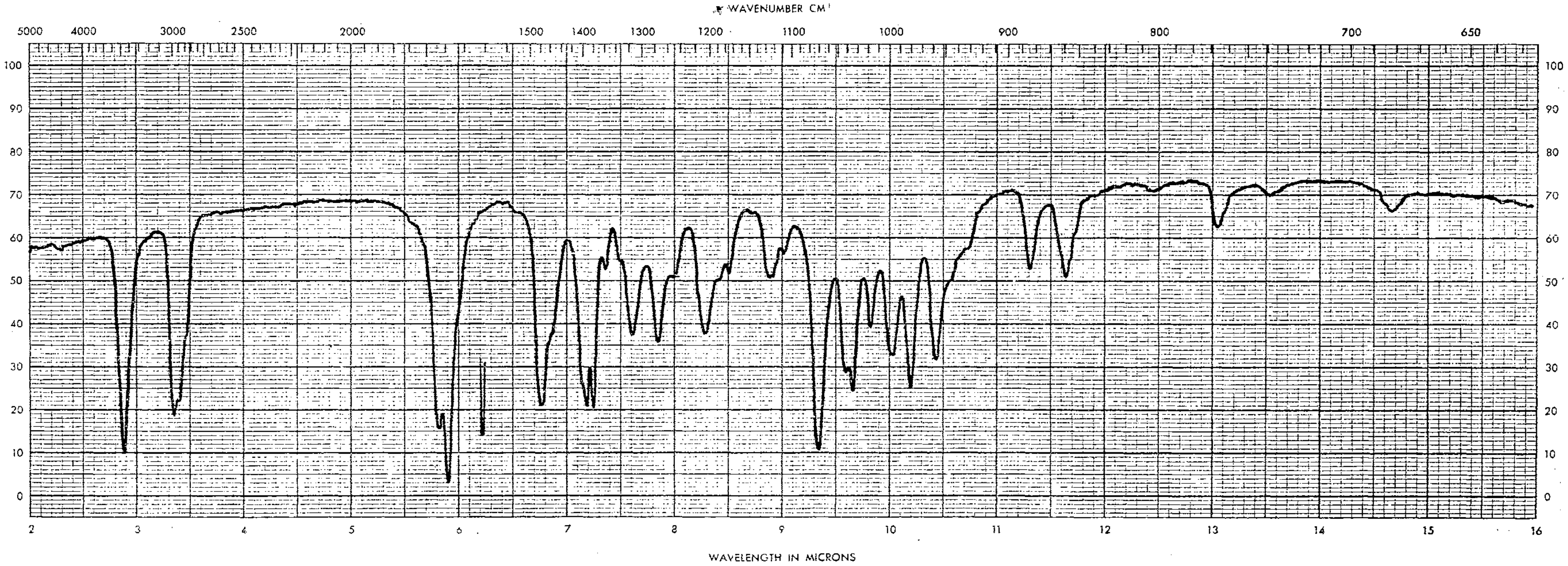
[h] Ibid, page 90.

Plate I



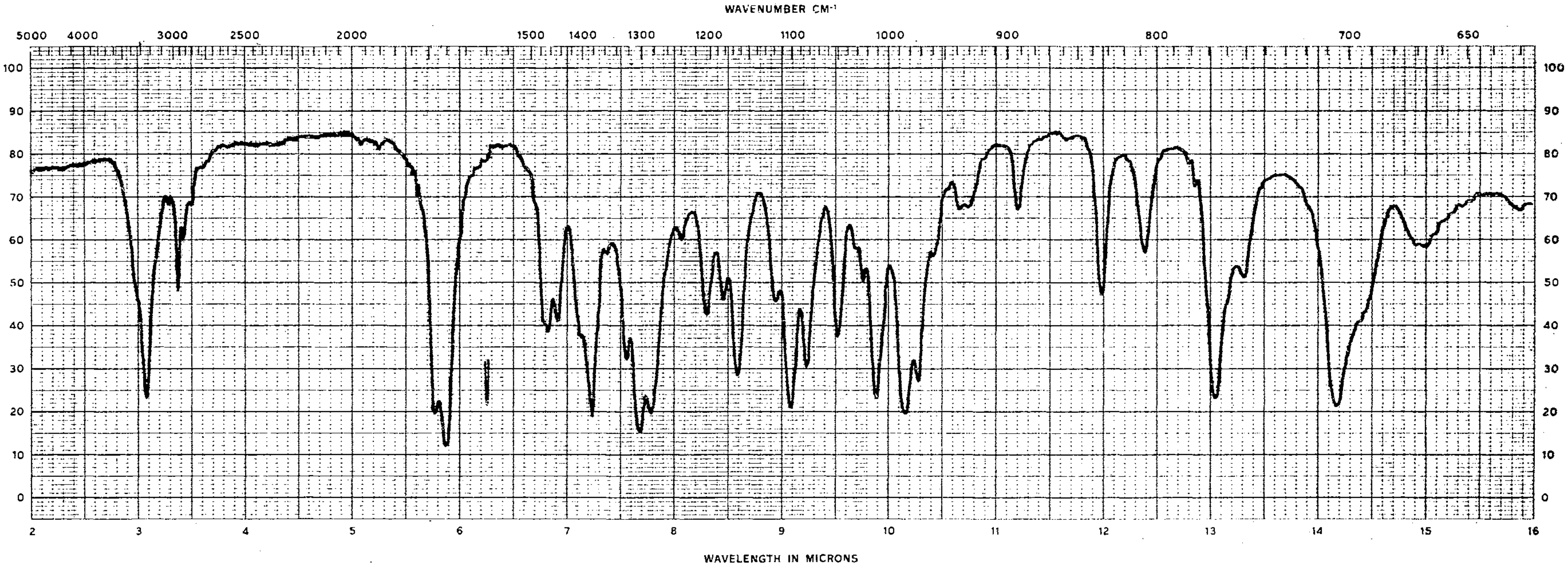
3-Hydroxy-2,2,4-trimethyl-3-pentenoic Acid β-Lactone (I), Film on NaCl Plates

Plate II



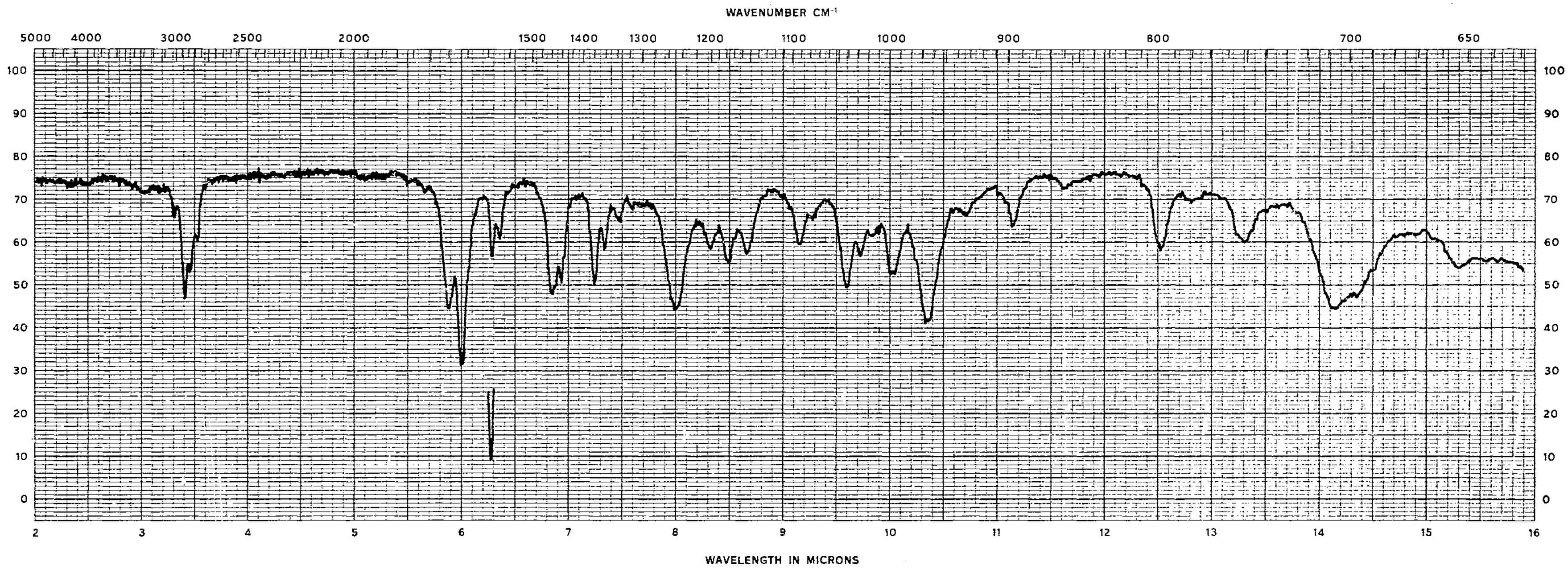
5-Hydroxy-2,2,4,4,6,6-hexamethyl-5-isopropyl-1,3-cyclohexanedione (XXXII), KBr Pellet

Plate III



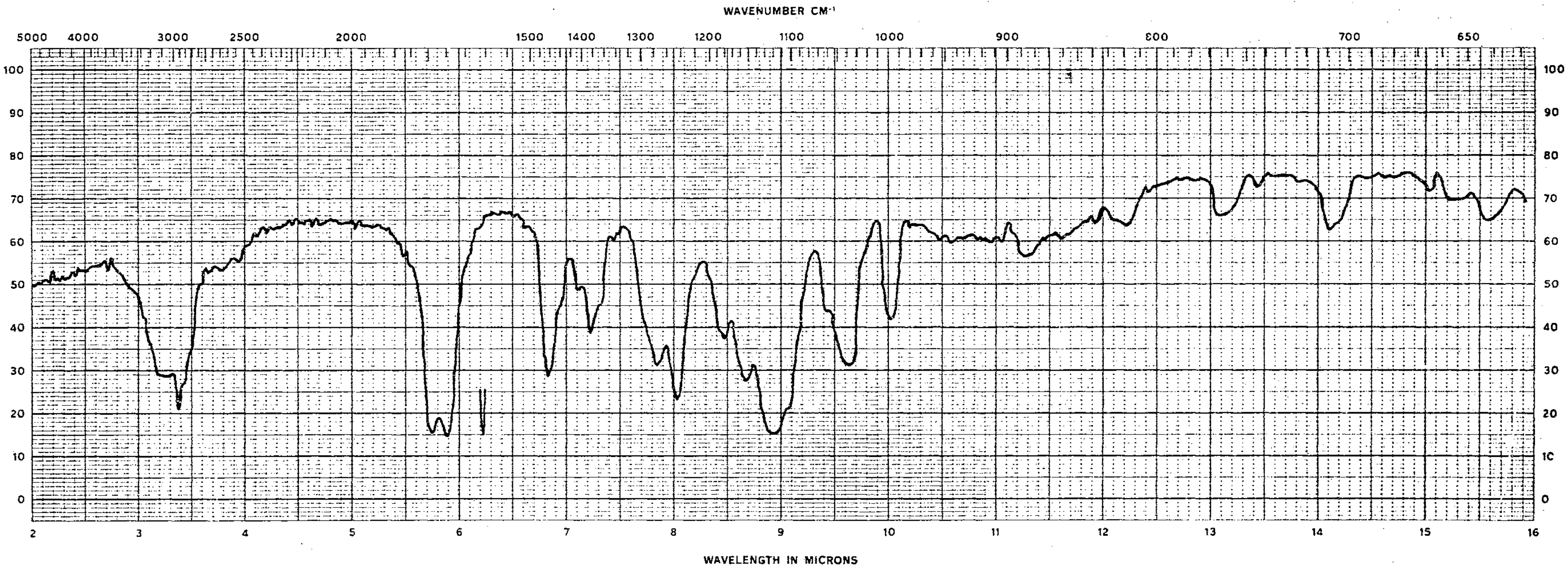
5-Phenyl-2,2,4,4-tetramethyl-3,5-dioxovaleric Acid (XXXIV), KBr Pellet

Plate IV



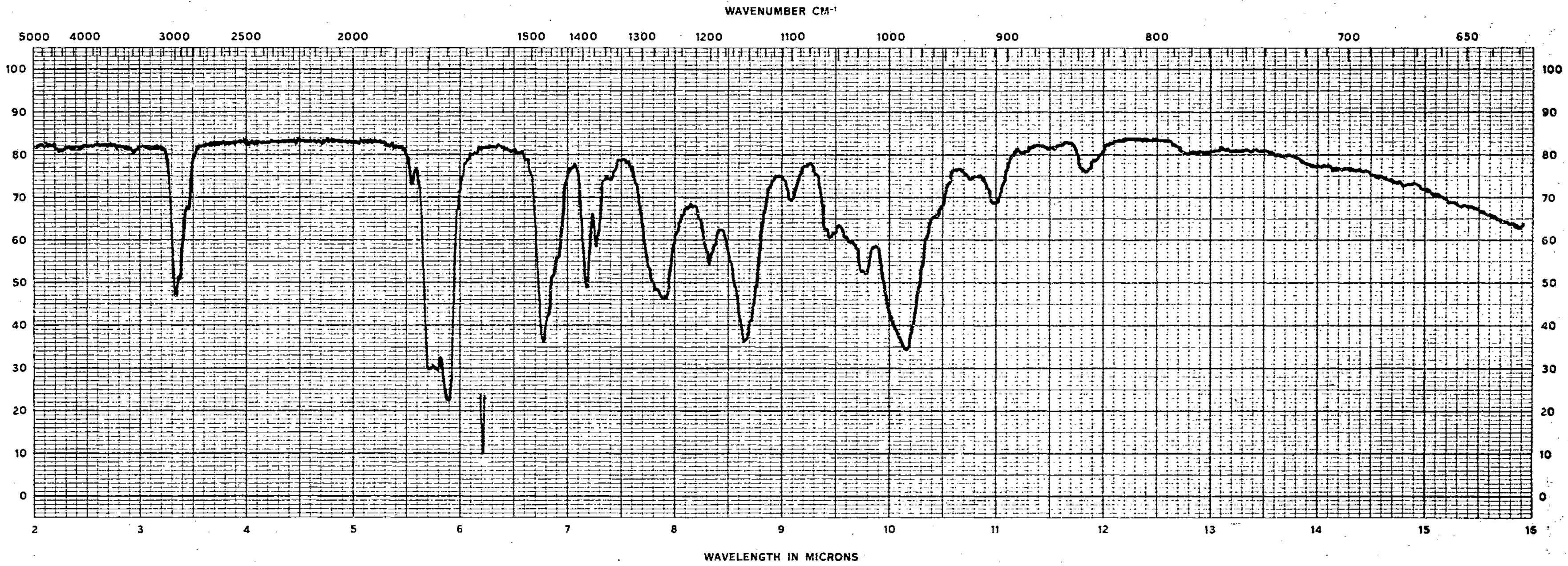
1-Phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX), Film on NaCl Plates

Plate V



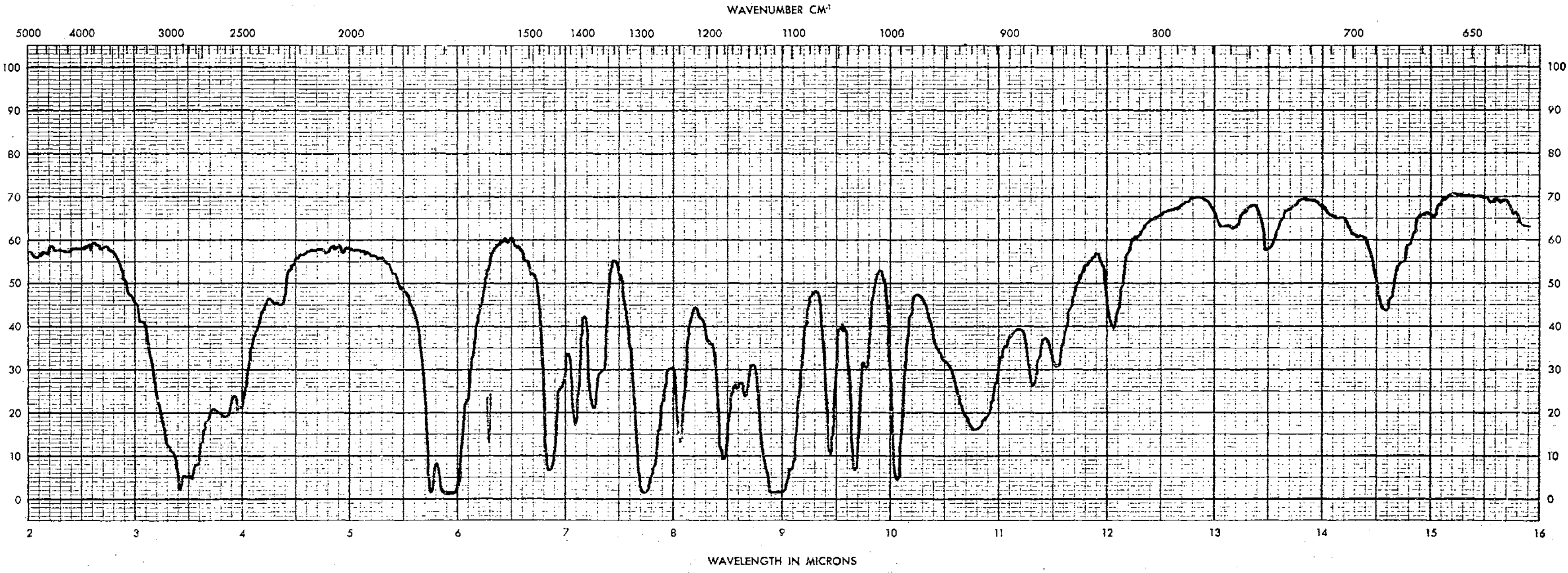
2,2,4,4,6,6,8-Heptamethyl-3,5,7-trioxononanoic Acid (XXXV), KBr Pellet

Plate VI



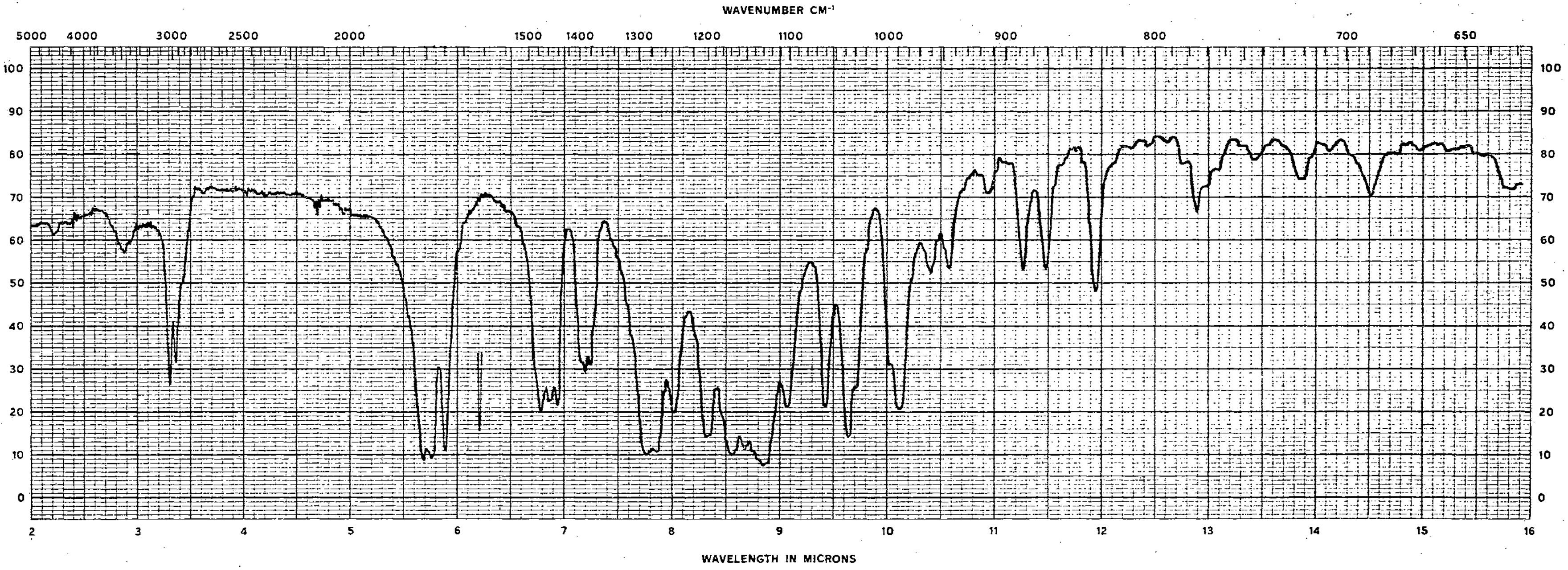
Methyl 2,2,4,4,6,6,8-Heptamethyl-3,5,7-trioxononanoate (XXXVIII), Film on NaCl Plates

Plate VII



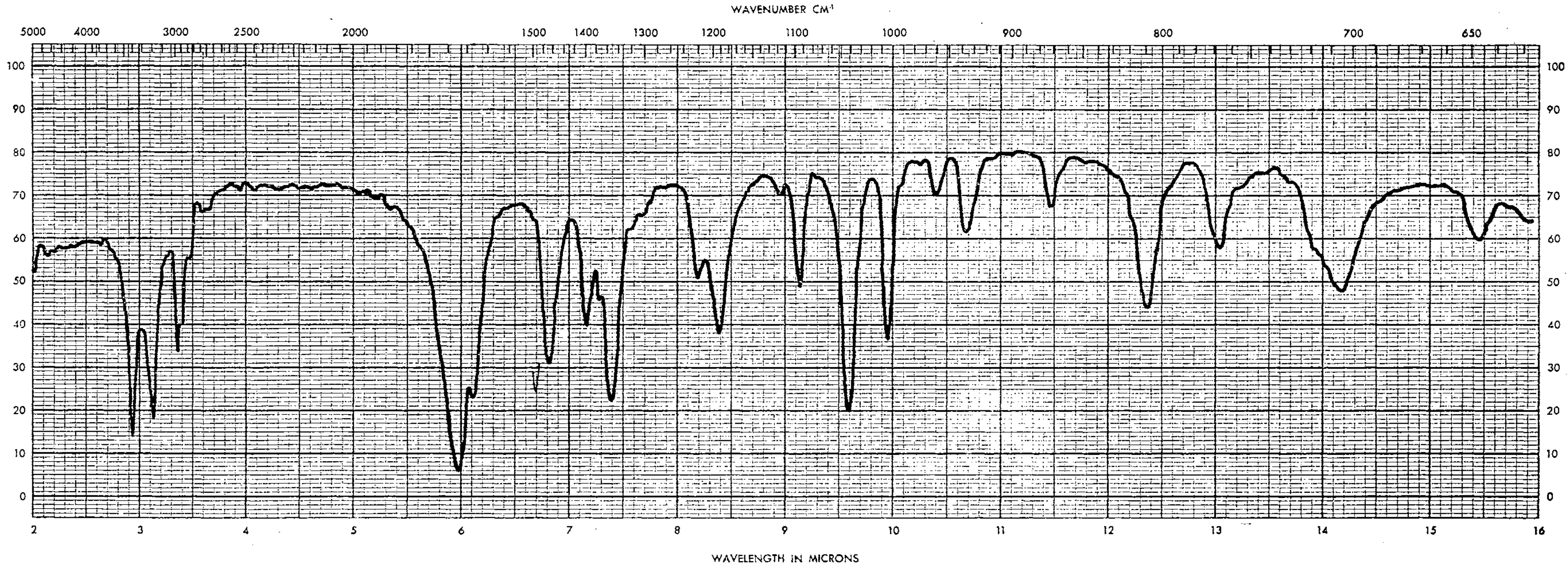
2,2,4,4,6,6,8,8-Octamethyl-3,5,7-trioxo-1,9-nonanedioic Acid (XLI), KBr Pellet

Plate VIII



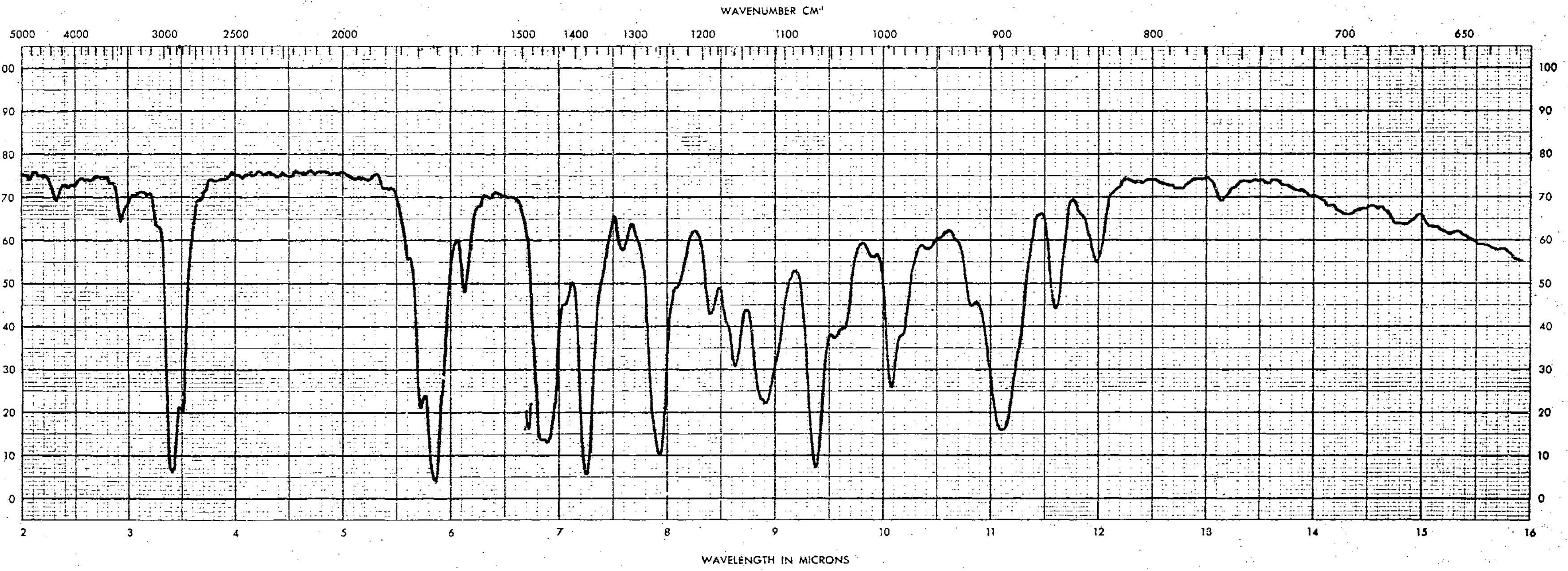
Dimethyl 2,2,4,4,6,6,8,8-Octamethyl-3,5,7-trioxo-1,9-nonanedioate (XLIII), KBr Pellet

Plate IX



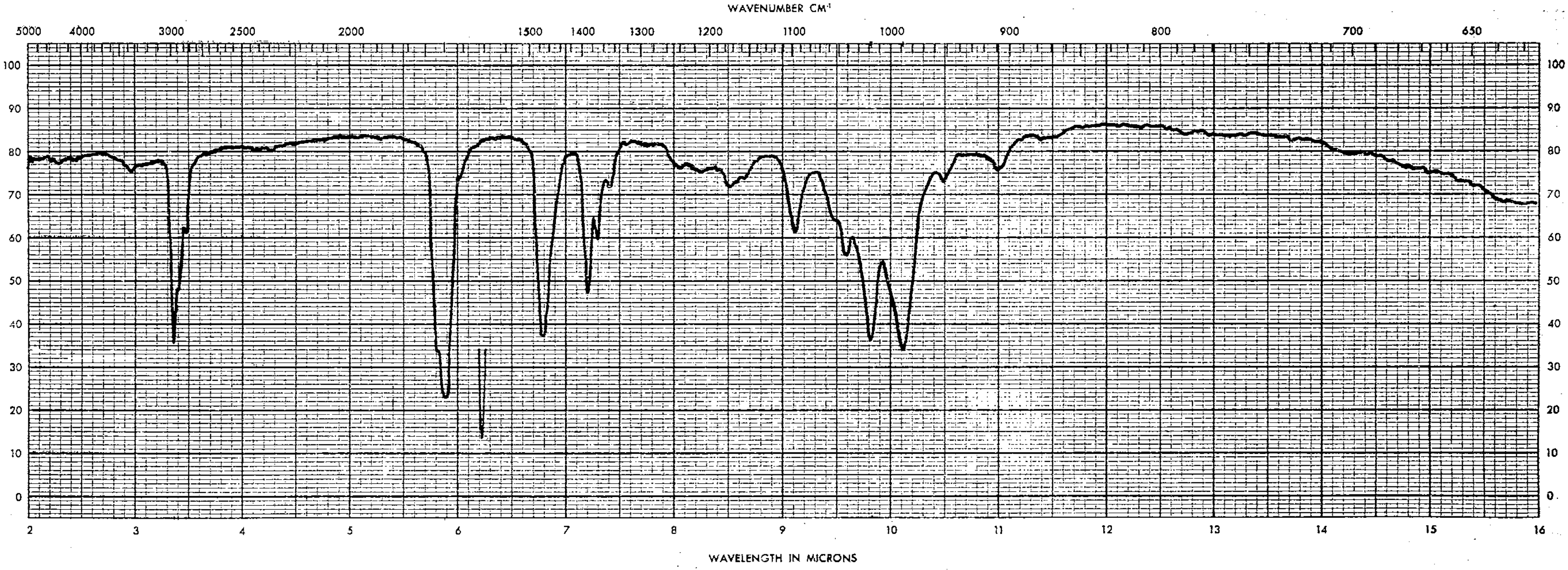
2,2,4-Trimethyl-3-oxovaleramide (XL), KBr Pellet

Plate X



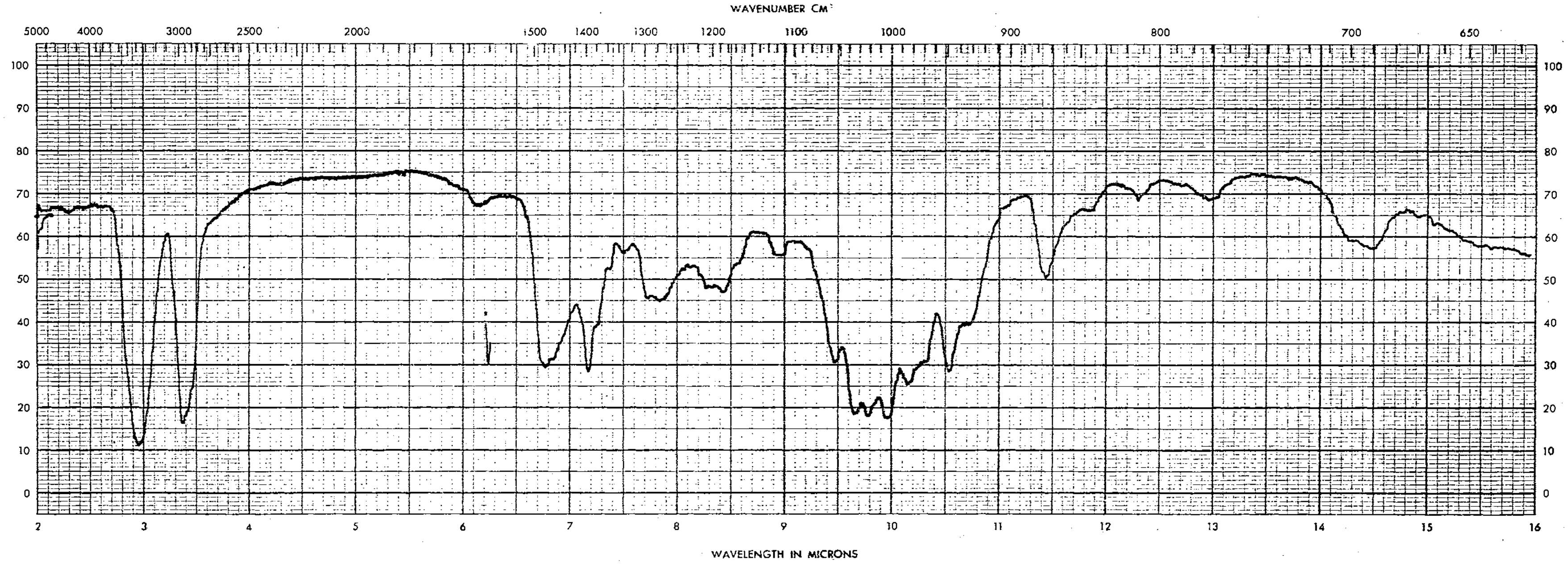
Unknown E, Film on NaCl Plates

Plate XI



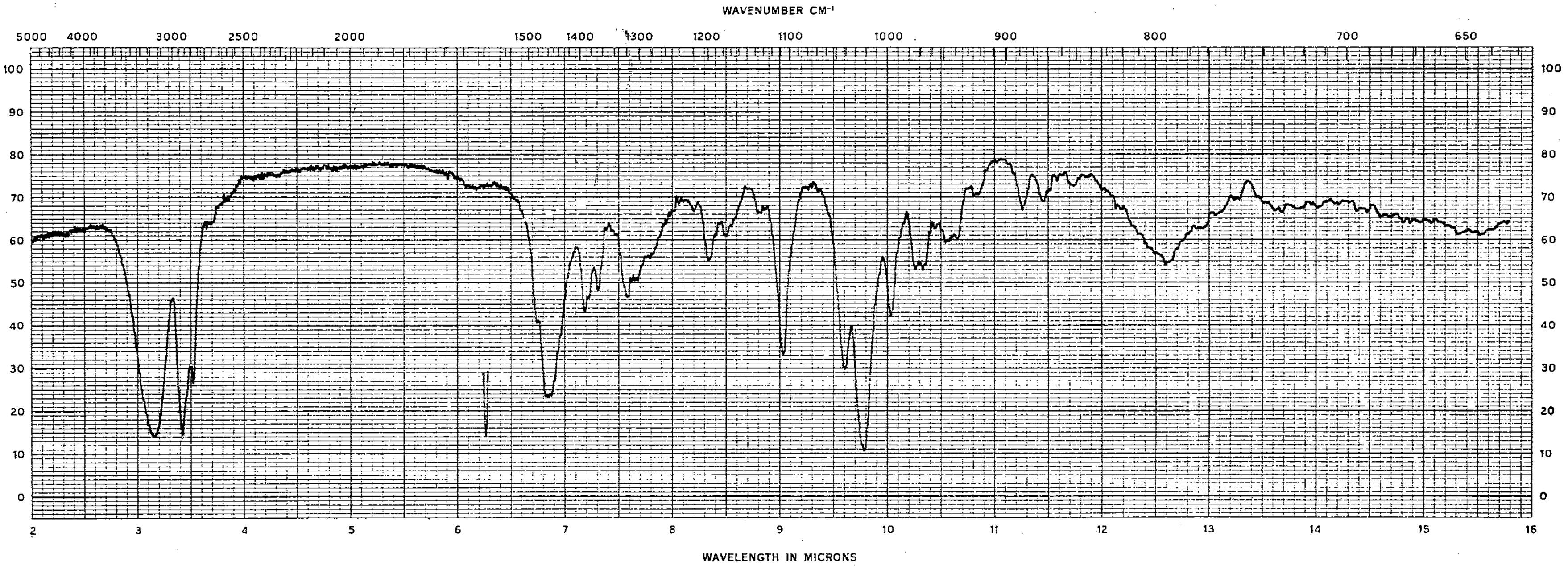
2,4,4,6,6,8-Hexamethyl-3,5,7-nonanetrione (XXXIII), Film on NaCl Plates

Plate XII



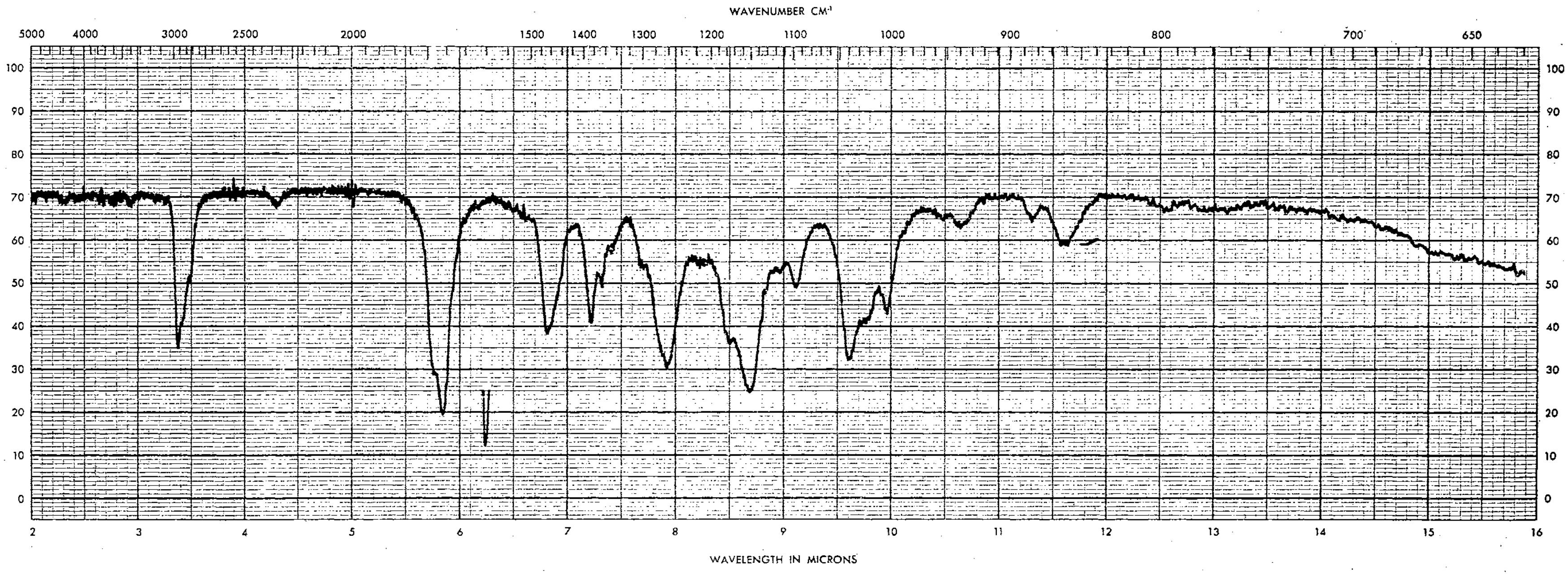
Unknown F, KBr Pellet

Plate XIII



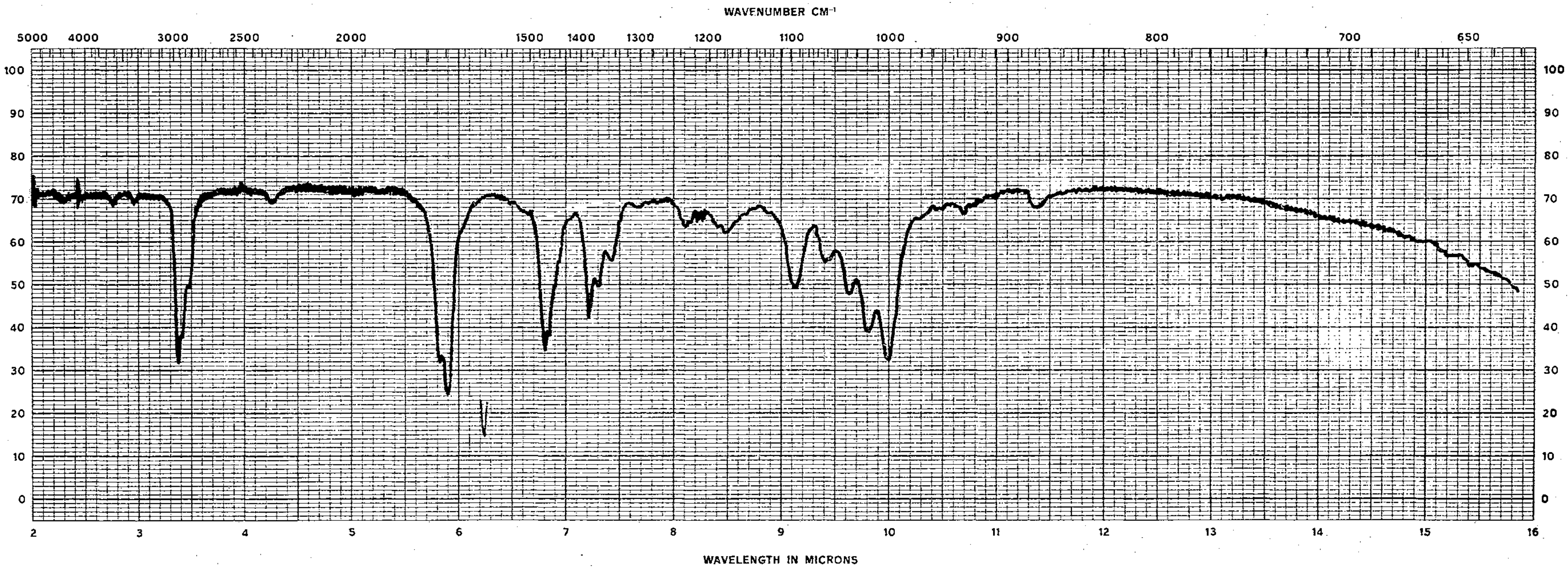
Unknown G, KBr Pellet

Plate XIV



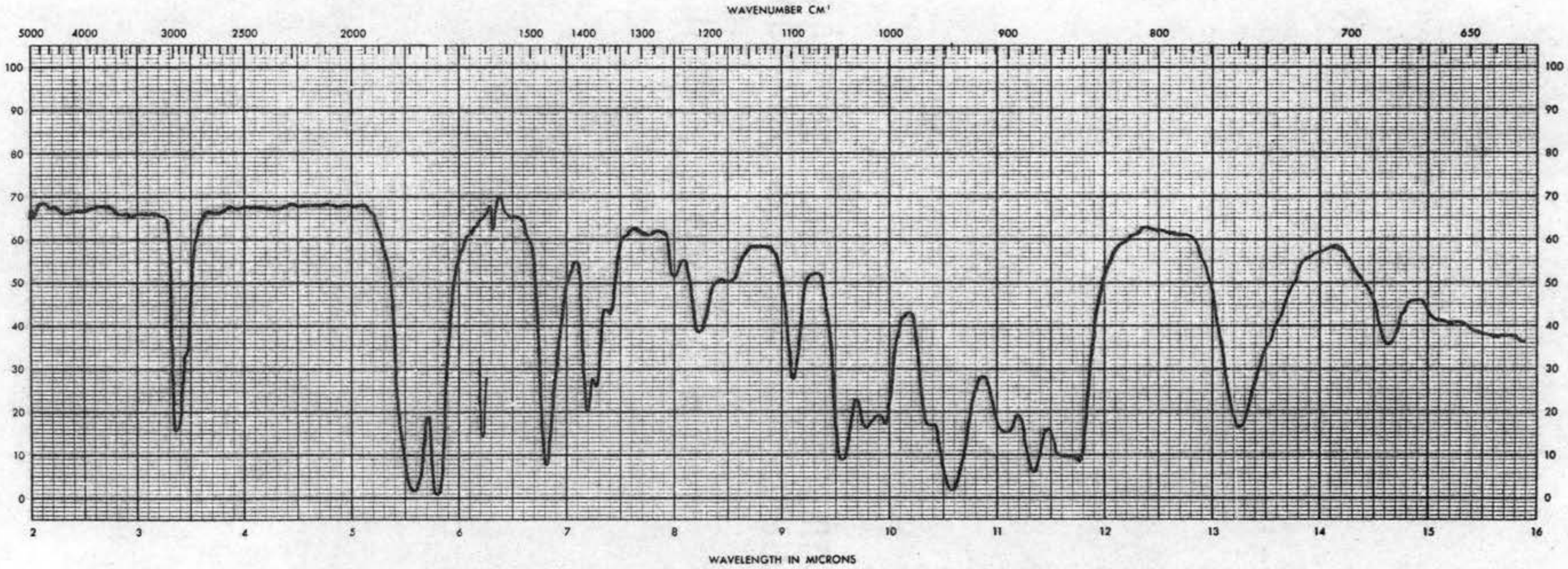
Ethyl 2,2,4-Trimethyl-3-oxovalerate (XLV), Film on NaCl Plates

Plate XV



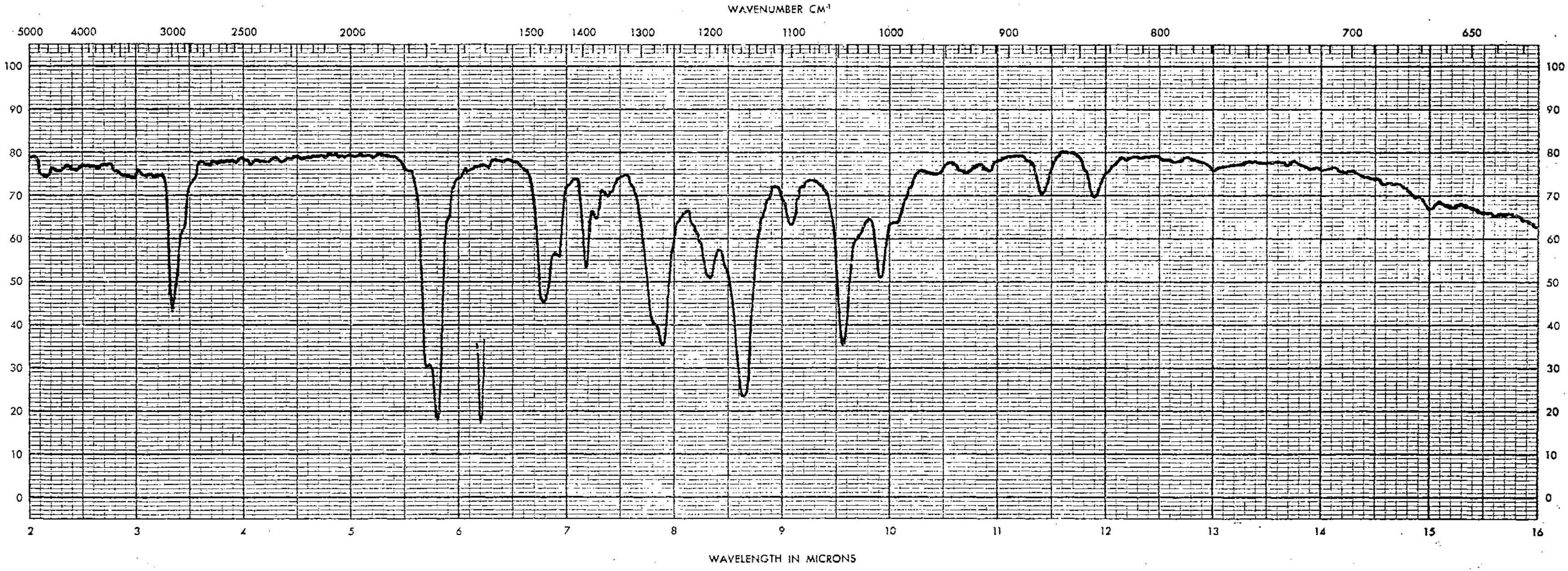
2,4,4,6-Tetramethyl-3,5-heptanedione (XLVI), Film on NaCl Plates

Plate XVI



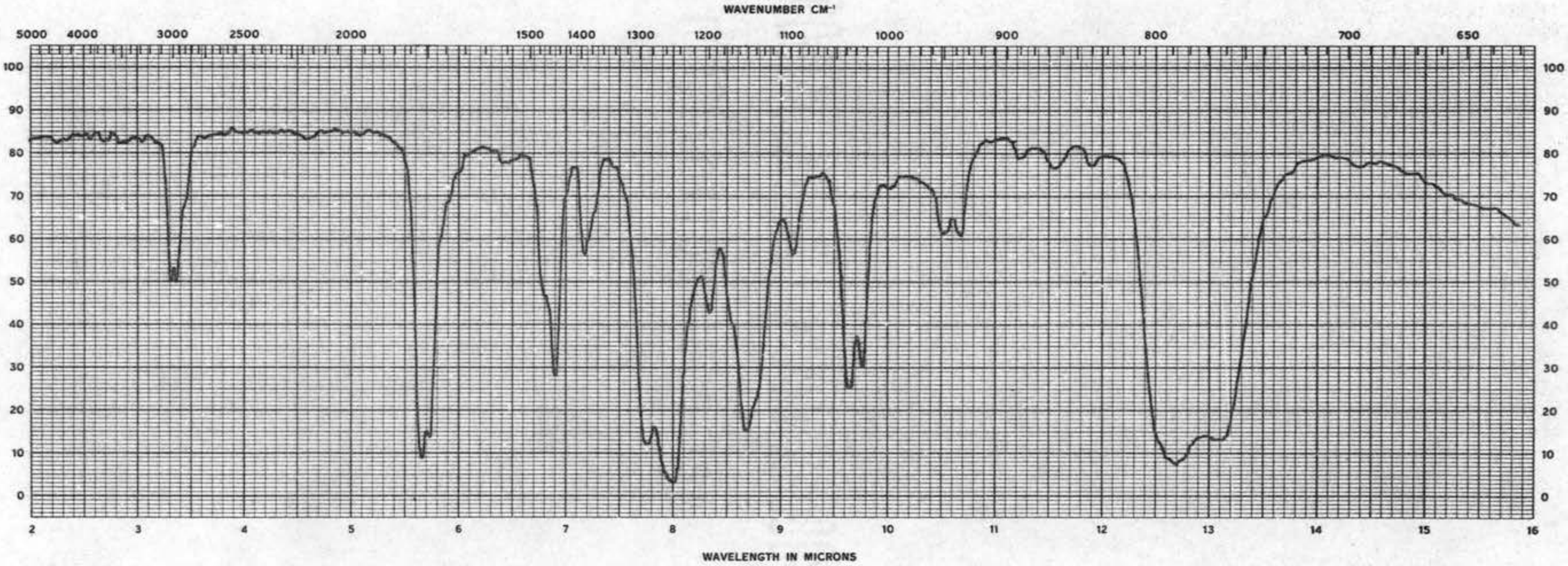
2,2,4-Trimethyl-3-oxovaleryl Chloride (XLIX), Film on NaCl Plates

Plate XVII



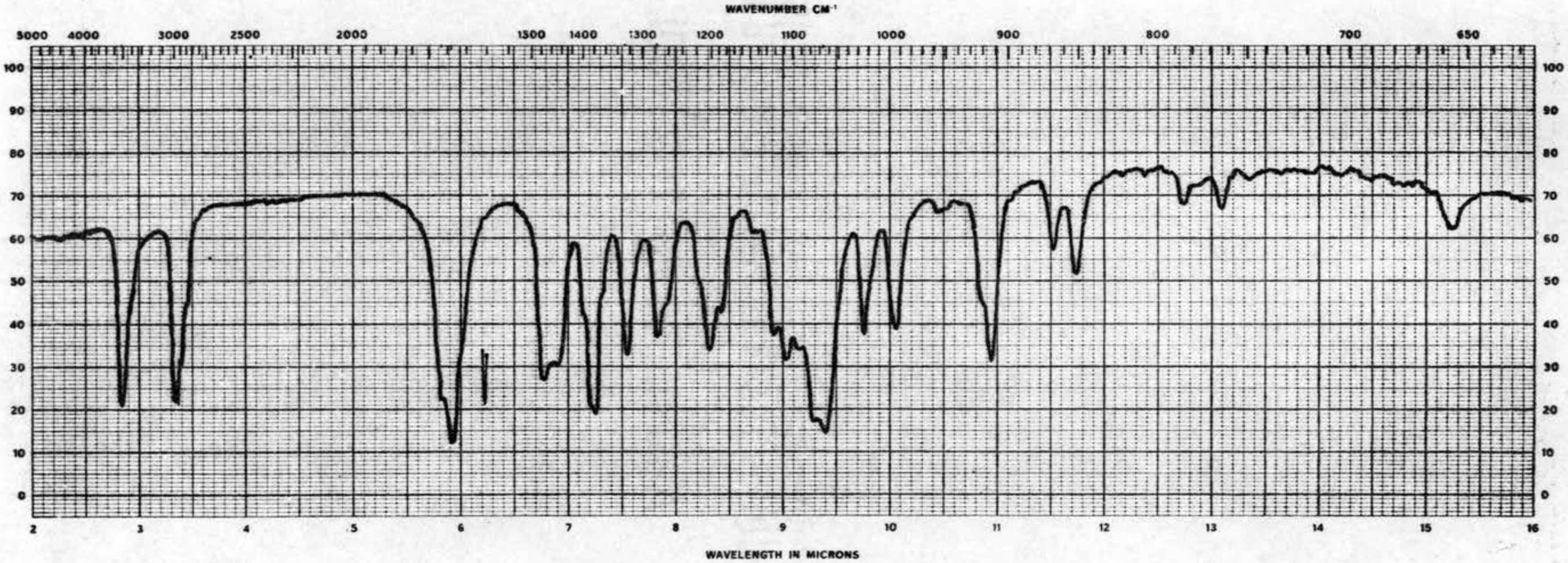
Methyl 2,2,4-Trimethyl-3-oxovalerate (XXXVI) Film on NaCl Plates

Plate XVIII



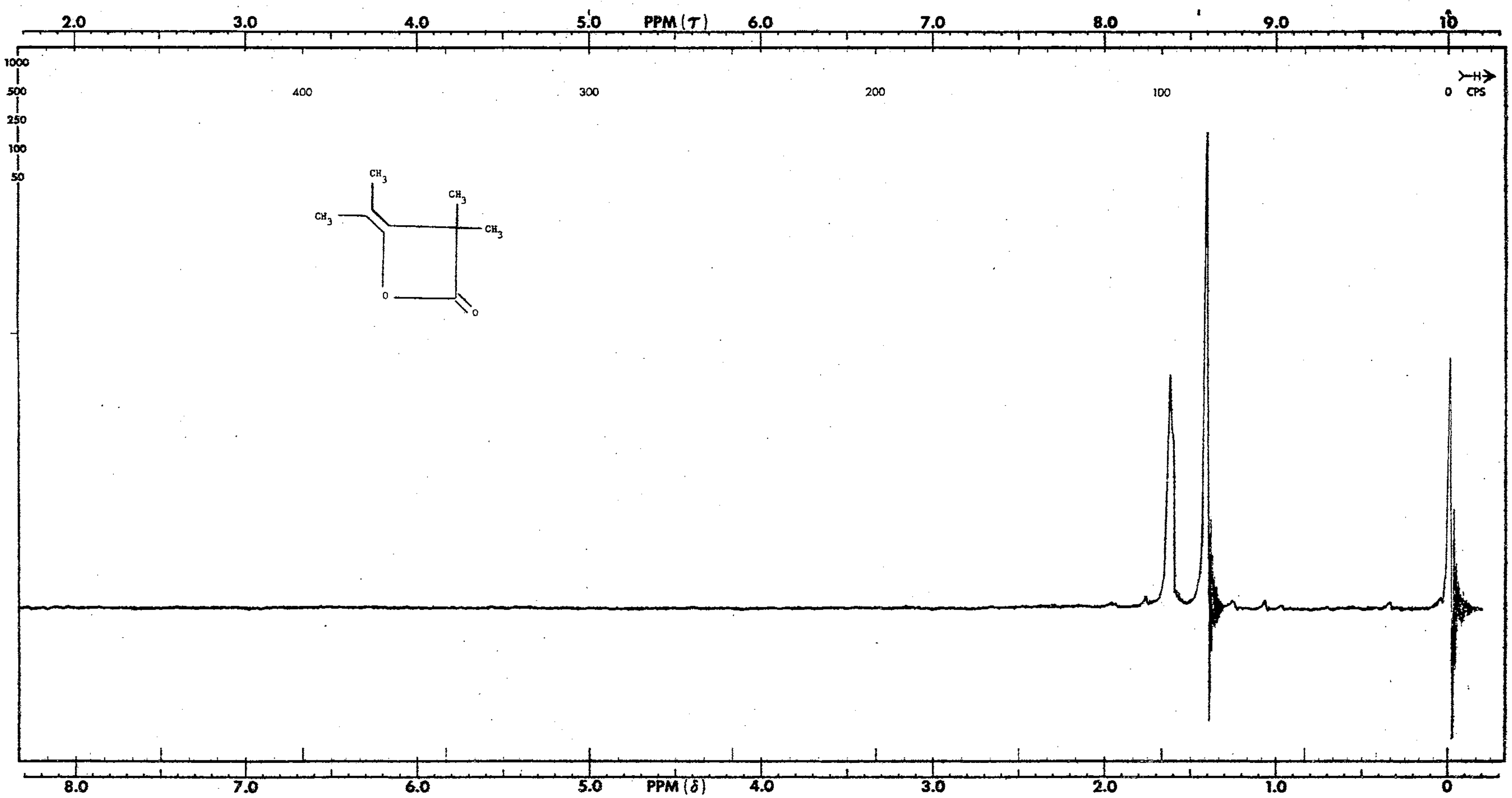
Dimethyl 2,2,4,4-Tetramethyl-3-oxoglutarate (XXXVII), Chloroform Solution

Plate XIX



5-Hydroxy-2,2,4,4,5,6,6-heptamethyl-1,3-cyclohexanedione (I), KBr Pellet

Plate XX

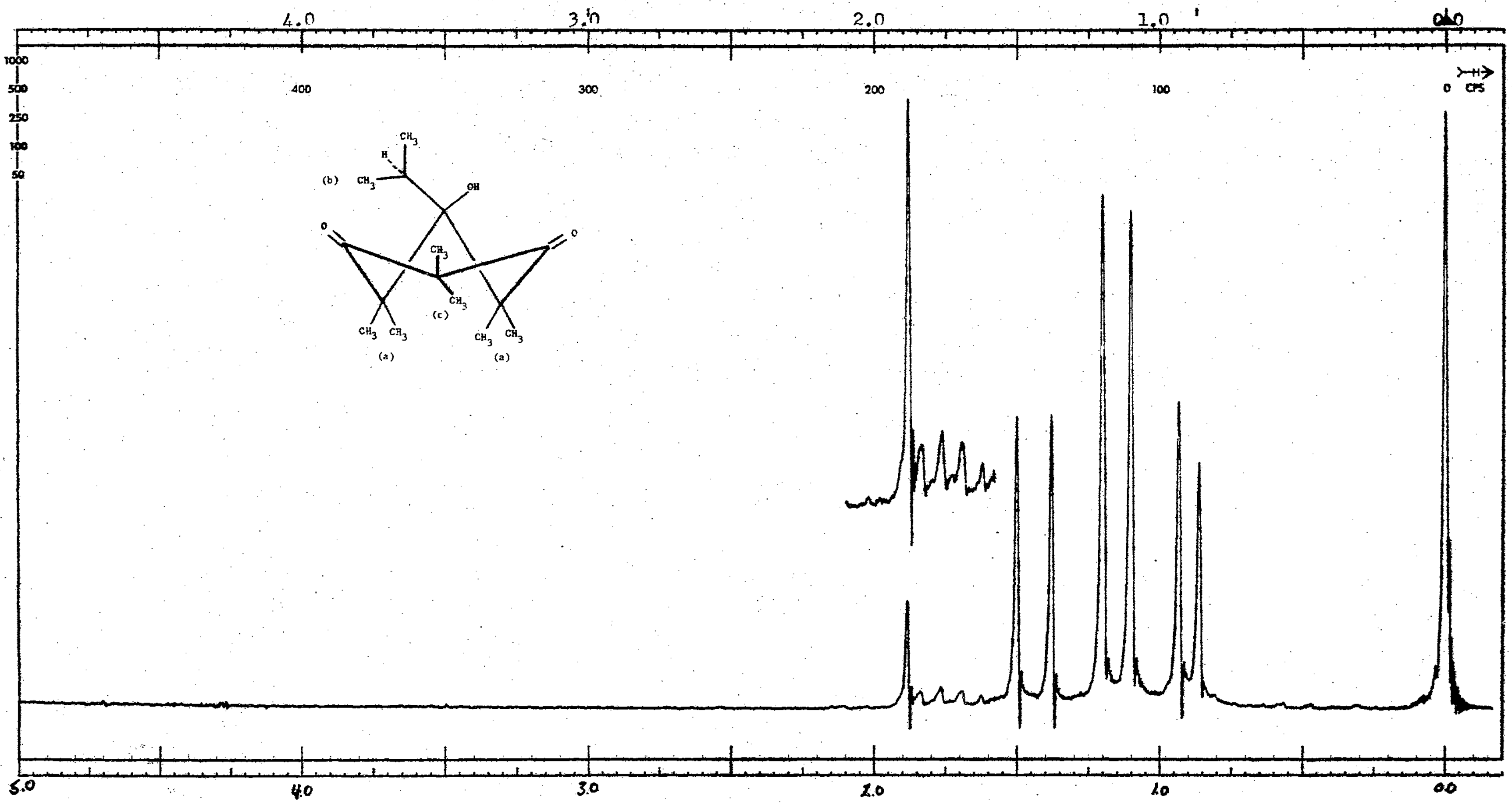


3-Hydroxy-2,2,4-trimethyl-3-pentenoic acid β-Lactone (I)

Solvent..........CCl_4 R. F. Field......0.05 mG S.W............500 cps S.A..................3.2

F.B...........4.0 cps S.T..............250 cps S.O............000 cps I.A...................off

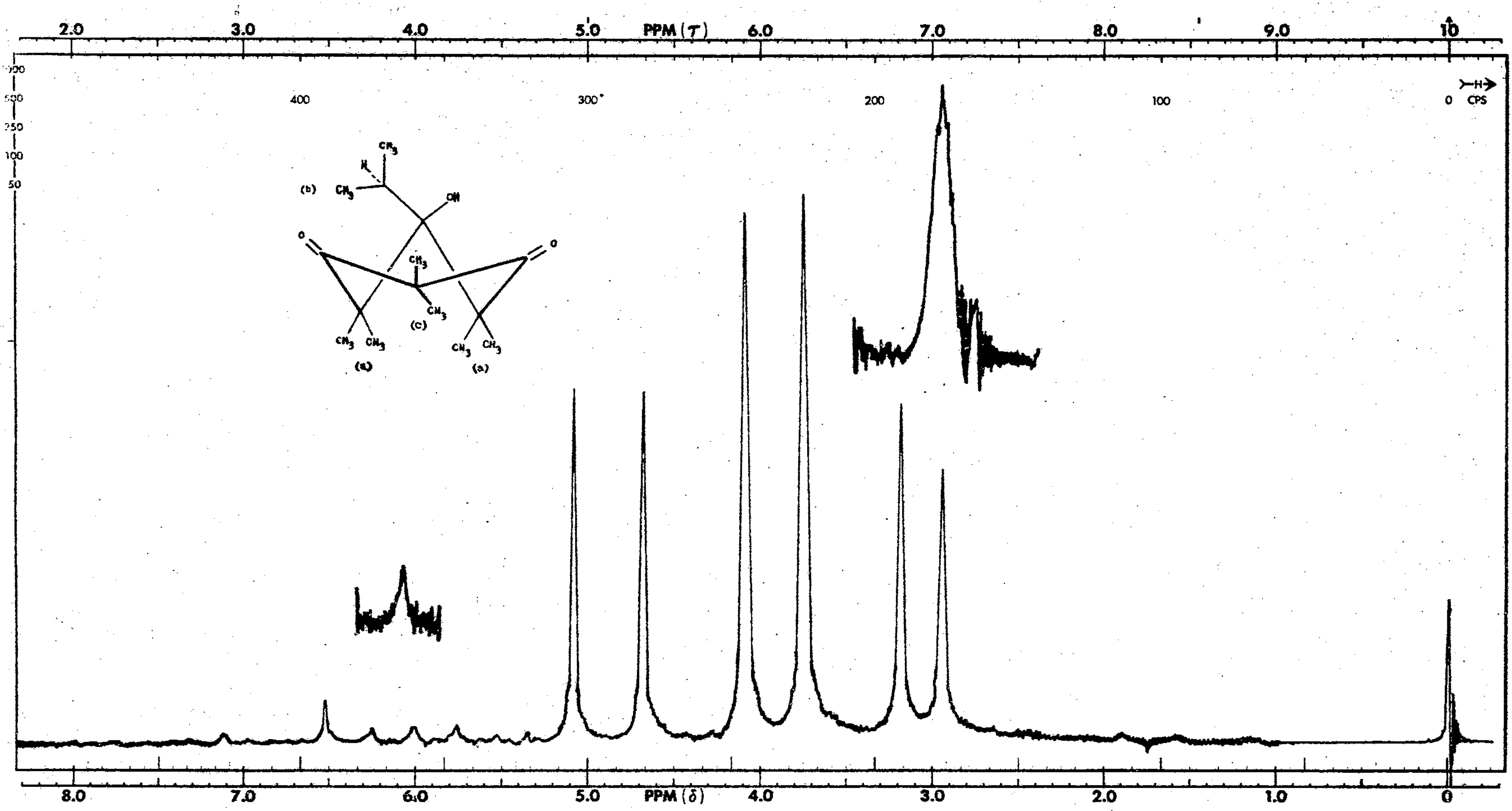
Plate XXI



5-Hydroxy-2,2,4,4,6,6-hexamethyl-5-isopropyl-1,3-cyclohexanedione (XXXII)

Solvent......Benzene
F.R.........20.0 cps
R. F. Attn.........26 db
S.T.............250 sec
S.W...........500 cps
S.O...........000 cps
L.S...............Benzene

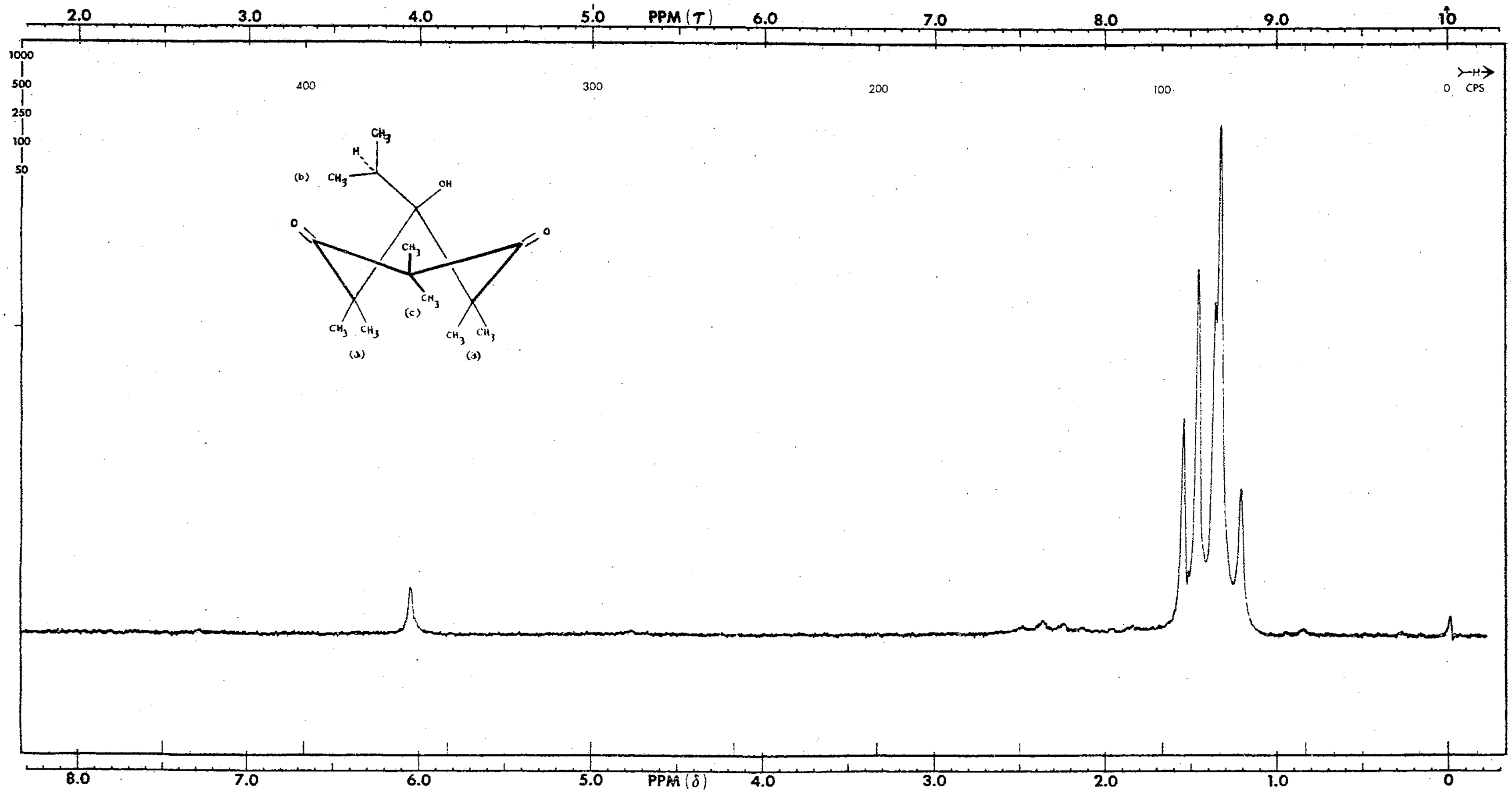
Plate XXII



5-Hydroxy-2,2,4,4,6,6-hexamethyl-5-isopropyl-1,3-cyclohexanedione (XXXII)

Solvent......Benzene
F.R.........10.0 cps
R. F. Attn.........17 db
S.T.............500 sec
S.W...........250 cps
S.O...........000 cps
S.A.................6000
L.S...............Benzene

Plate XXIII



5-Hydroxy-2,2,4,4,6,6-hexamethyl-5-isopropyl-1,3-cyclohexanedione (XXXII)

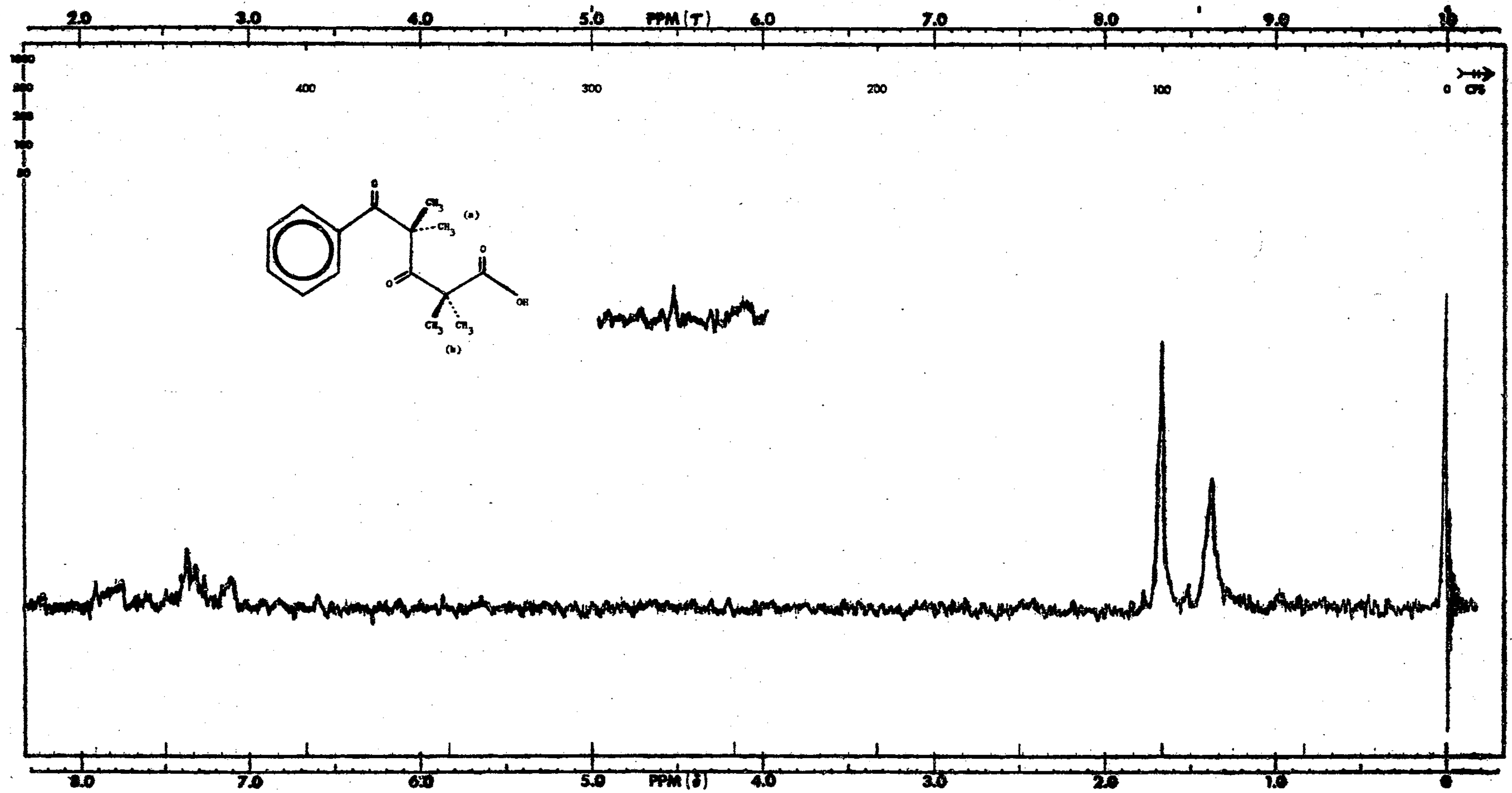
Solvent..Pyridine-d_5
F.B...........4.0 cps

R. F. Field......0.05 mG
S.T.............250 sec

S.W............500 cps
S.O............000 cps

S.A..................1.6
I.A..................off

Plate XXIV



5-Phenyl-2,2,4,4-tetramethyl-3,5-dioxovaleric acid (XXXIV)

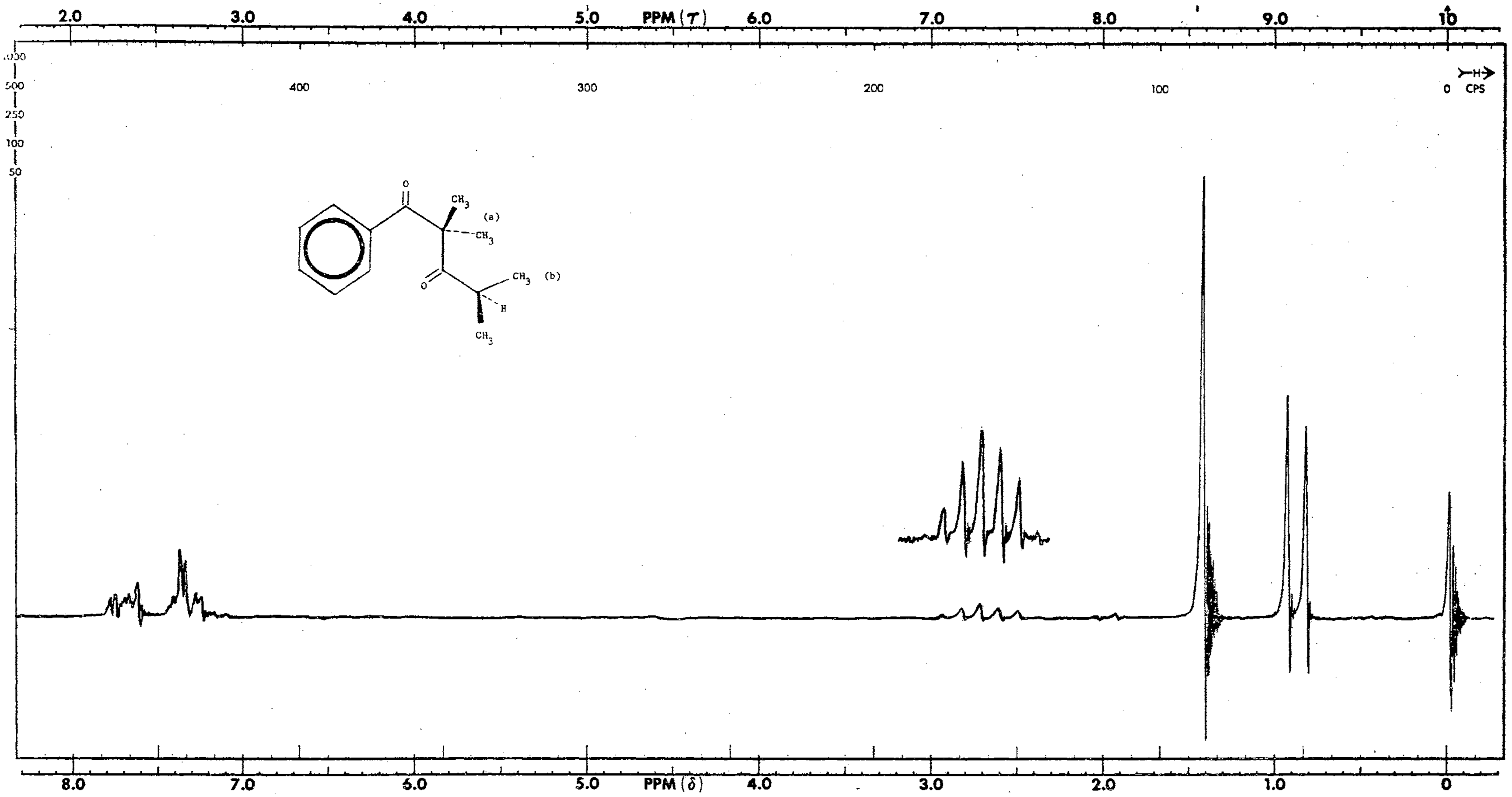
Solvent..Pyridine-d$_5$.
F.B..........4.0 cps

R. F. Field......0.02 mG
S.T.............250 sec

S.W..........-500 cps
S.O..........482 cps

S.A..................6.3
I.A..................off

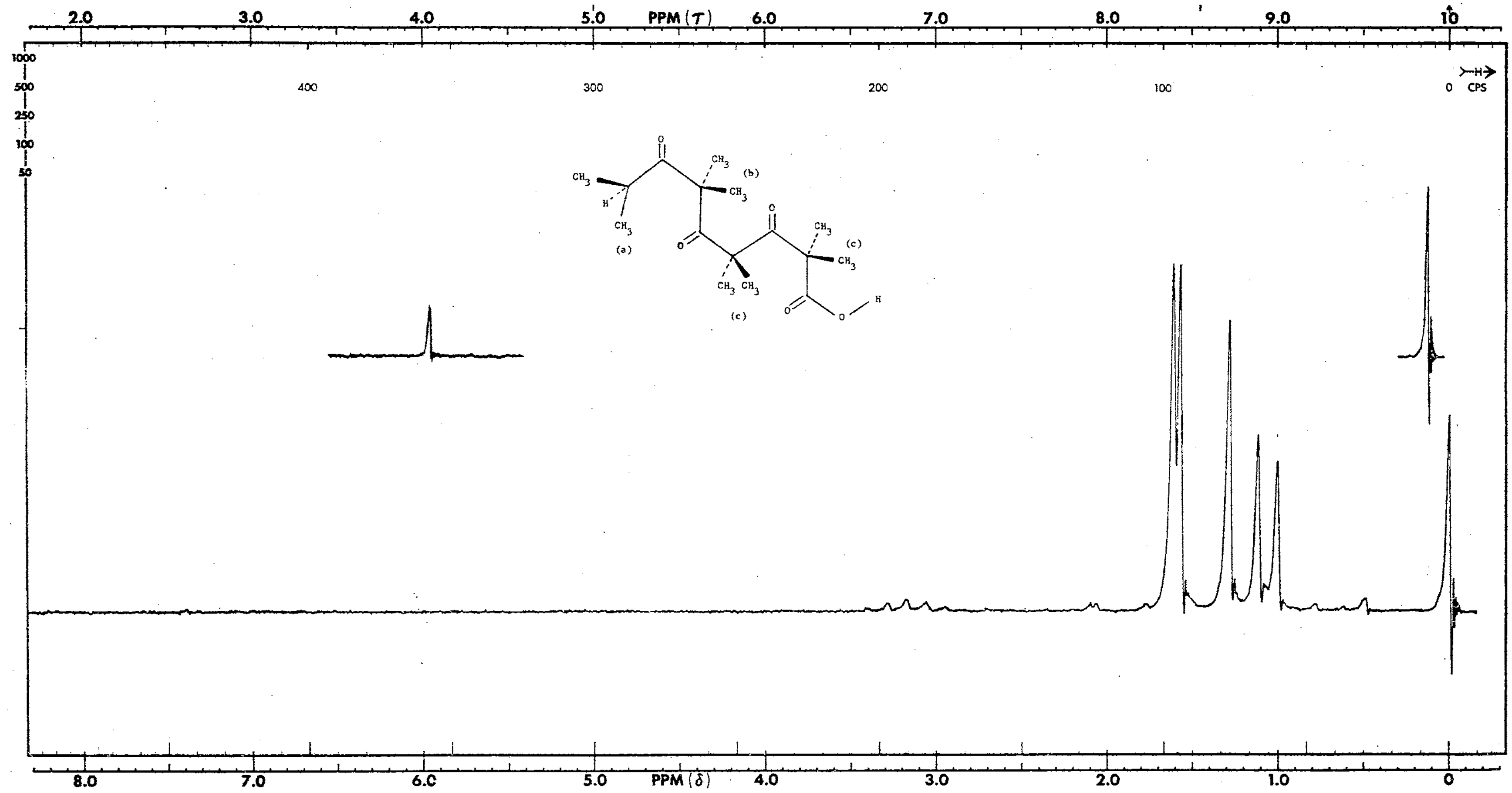
Plate XXV



1-Phenyl-2,2,4-trimethyl-1,3-pentanedione (XXXIX)

Solvent..........CCl_4
F.B...........4.0 cps
R. F. Field......0.05 mG
S.T..............250 sec
S.W............500 cps
S.O............000 cps
S.A...................1.0
I.A...................off

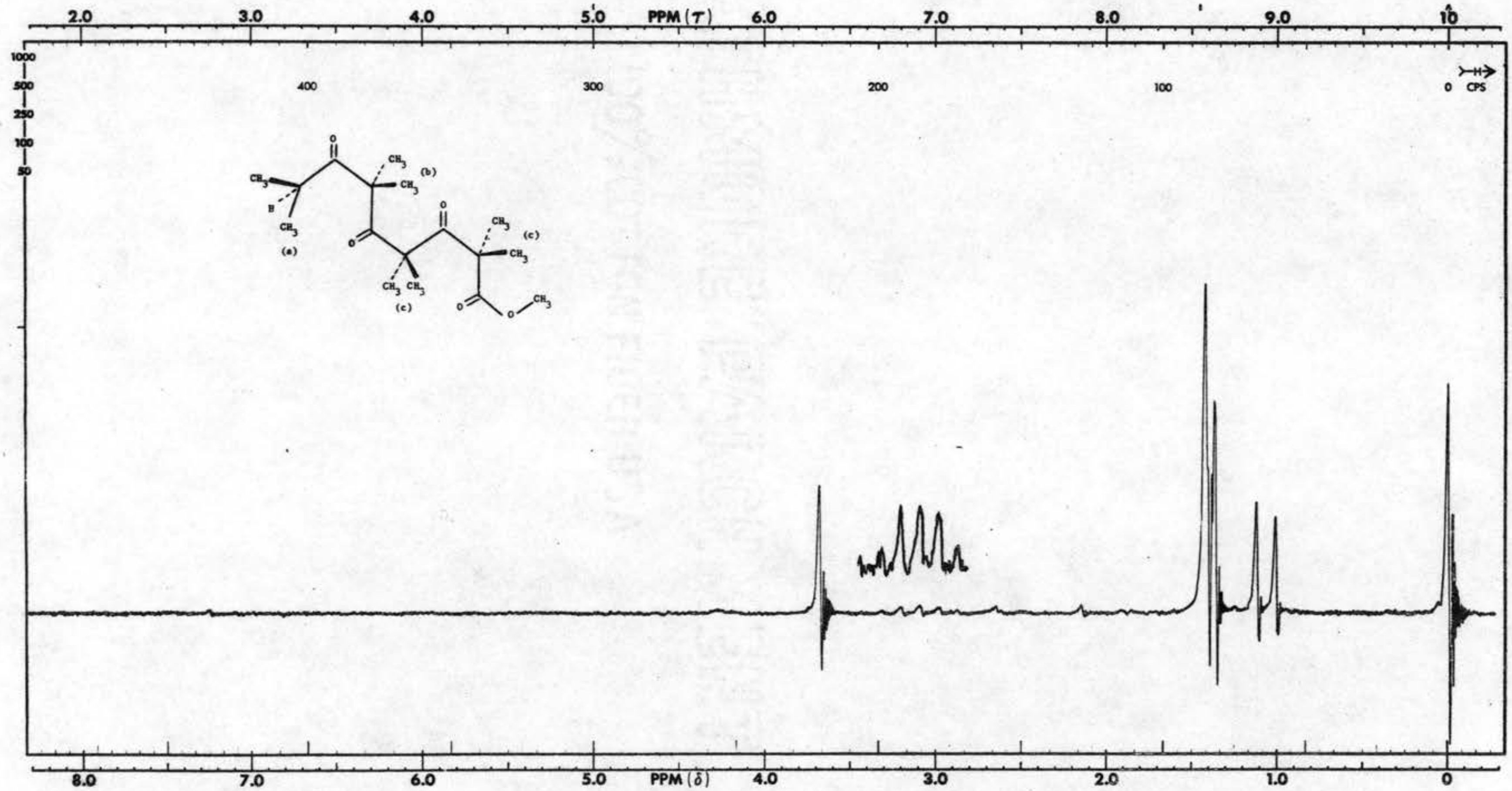
Plate XXVI



2,2,4,4,6,6,8-Heptamethyl-3,5,7-trioxononanoic acid (XXXV)

Solvent.........$CDCl_3$
R. F. Field......0.05 mG
S.W...........500 cps
S.A..................2.5
F.B...........4.0 cps
S.T.............250 sec
S.O...........000 cps
I.A..................off

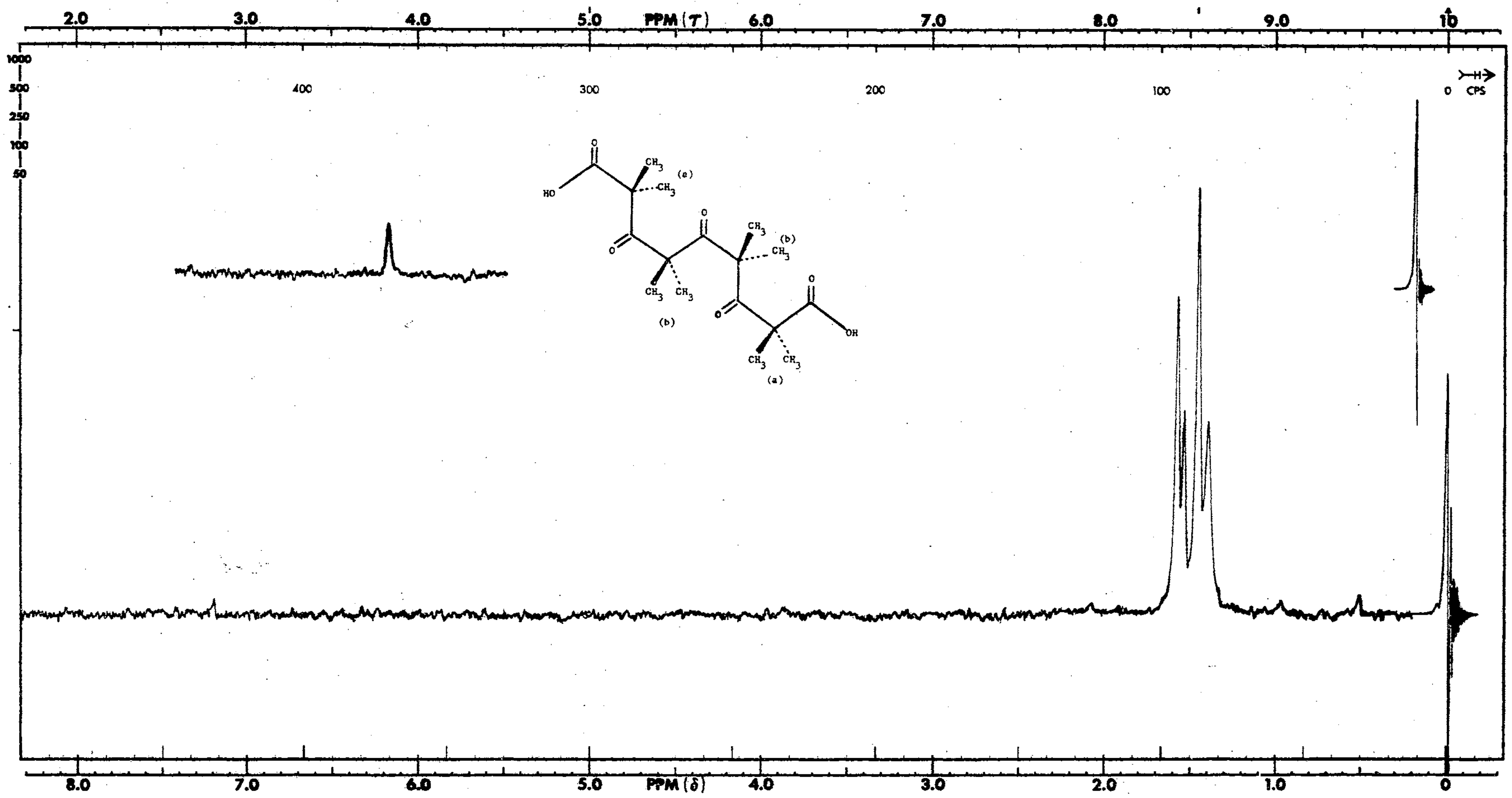
Plate XXVII



Methyl 2,2,4,4,6,6,8-Heptamethyl-3,5,7-trioxononanoate (XXXVIII)

Solvent........CDCl$_3$
R. F. Field......0.05 mG
S.W..........500 cps
S.A..................2.5
F.B...........4.0 cps
S.T.............250 cps
S.O..........000 cps
I.A..................off

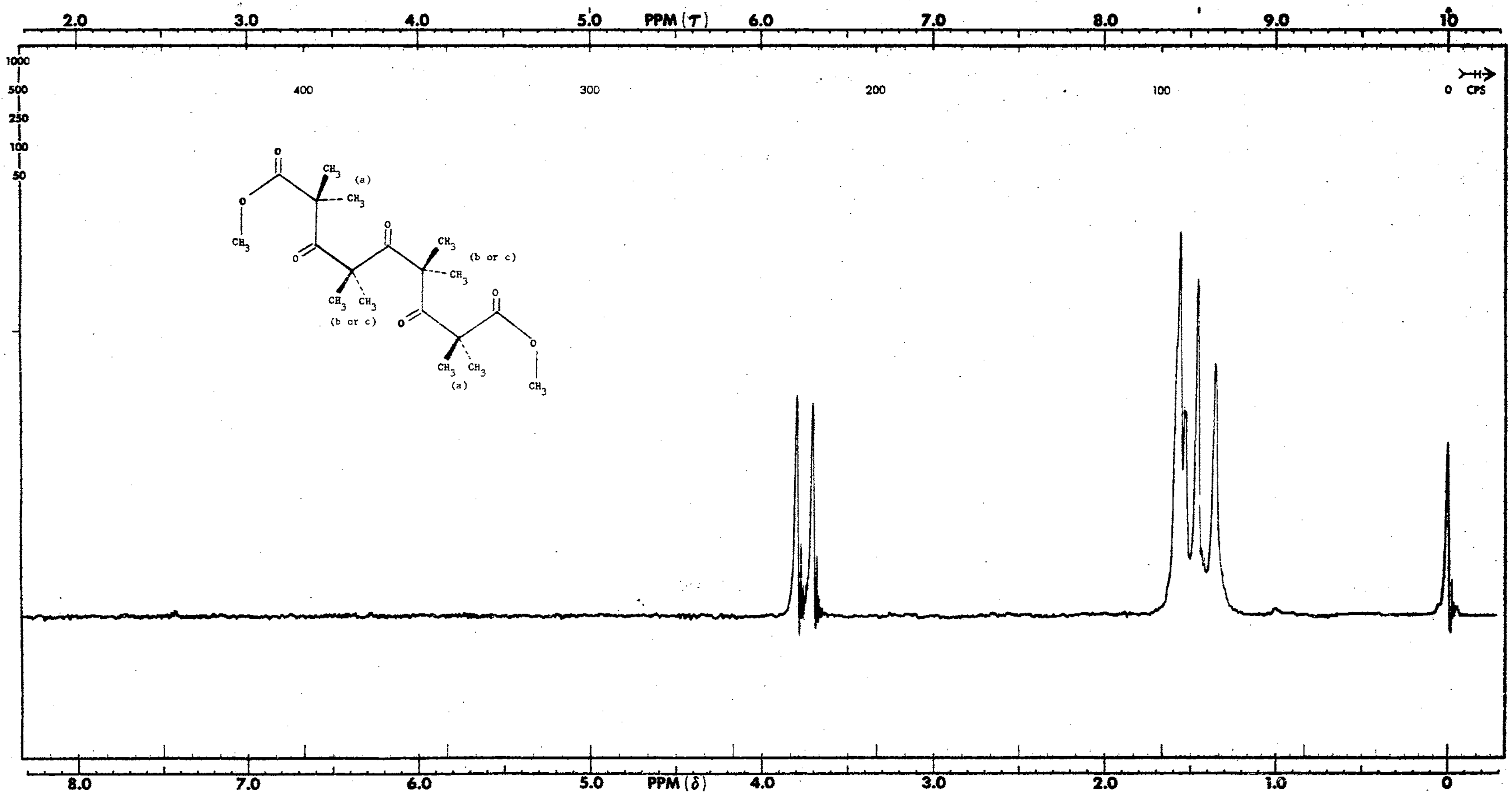
Plate XXVIII



2,2,4,4,6,6,8,8-Octamethyl-3,5,7-trioxo-1,9-nonanedioic acid (XLI)

Solvent........CDCl$_3$
F.B..........1.0 cps
R. F. Field.....0.018 mG
S.T.............250 cps
S.W.....500, 1000 cps
S.O..........000 cps
S.A..................10
I.A.................off

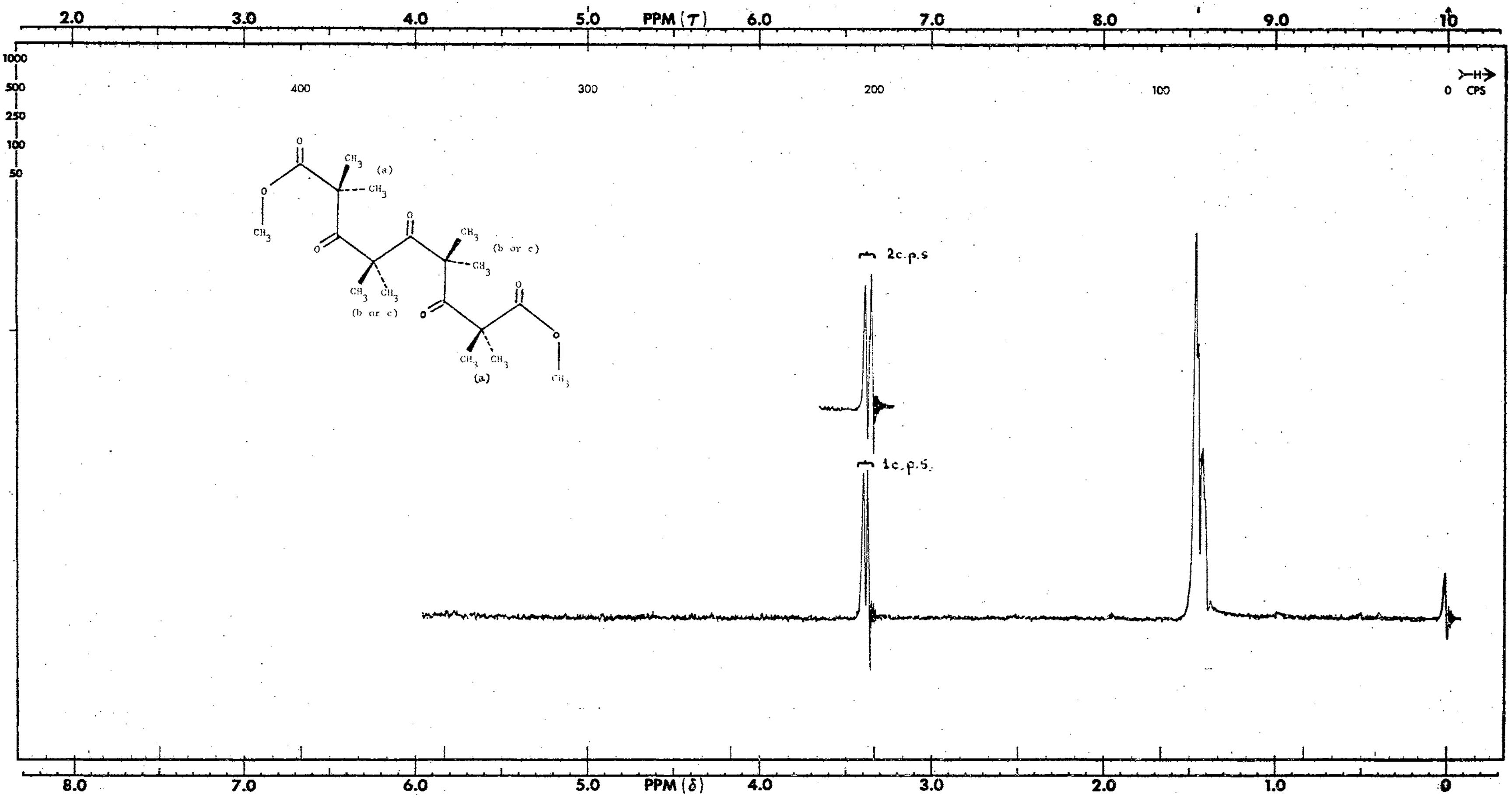
Plate XXIX



Dimethyl 2,2,4,4,6,6,8,8-Octamethyl-3,5,7-trioxo-1,9-nonanedioate (XLIII)

Solvent.........$CDCl_3$	R. F. Field......0.05 mG	S.W...........500 cps	S.A..................3.2
F.B...........4.0 cps	S.T.............250 cps	S.O...........000 cps	I.A..................off

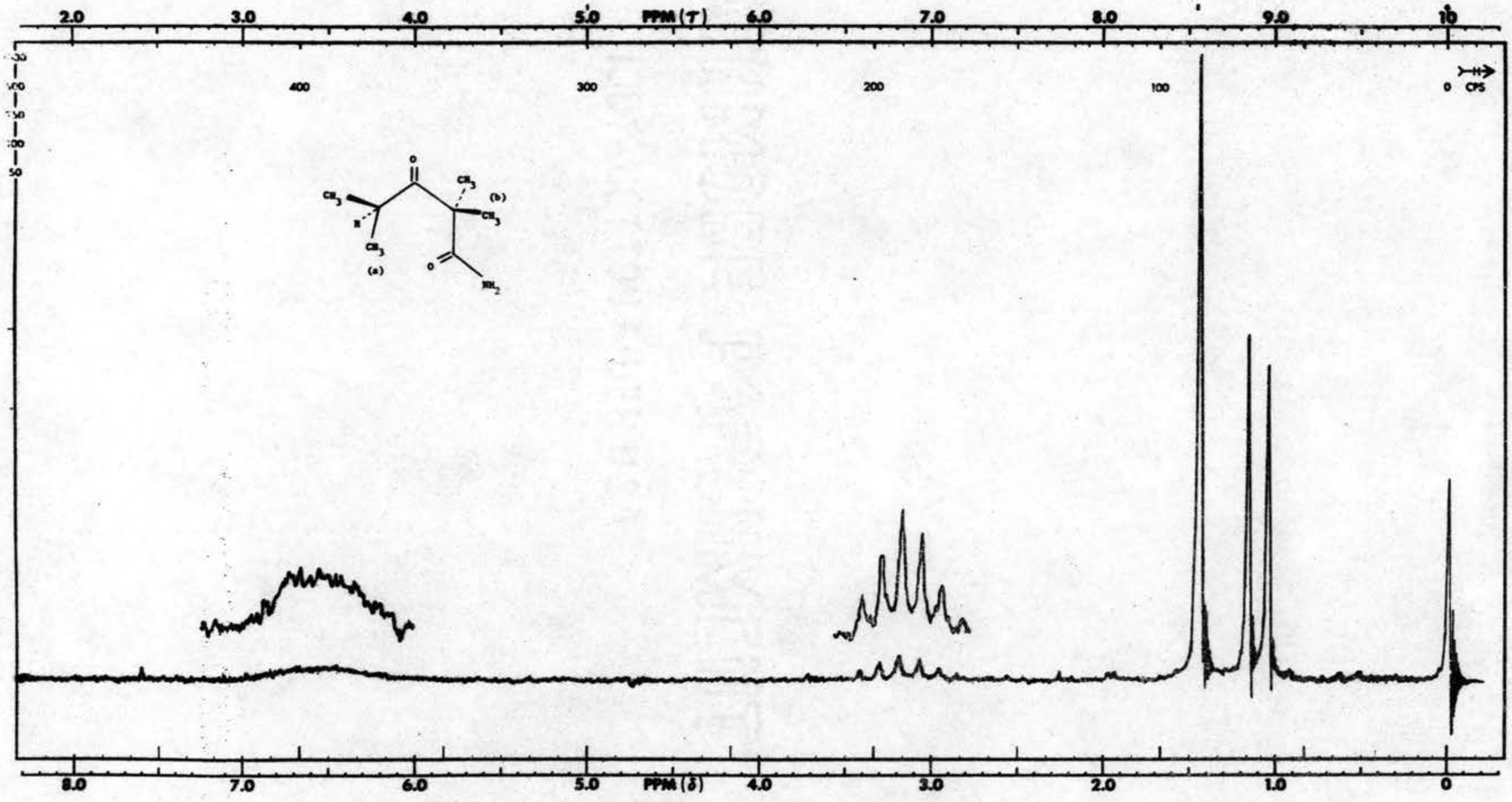
Plate XXX



Dimethyl 2,2,4,4,6,6,8,8-Octamethyl-3,5,7-trioxo-1,9-nonanedioate (XLIII)

Solvent........Benzene
R. F. Field......0.03 mG
S.W..........-500 cps
S.A...................2.6
F.B...........4.0 cps
S.T.............250 sec
S.O...........493 cps
I.A...................off

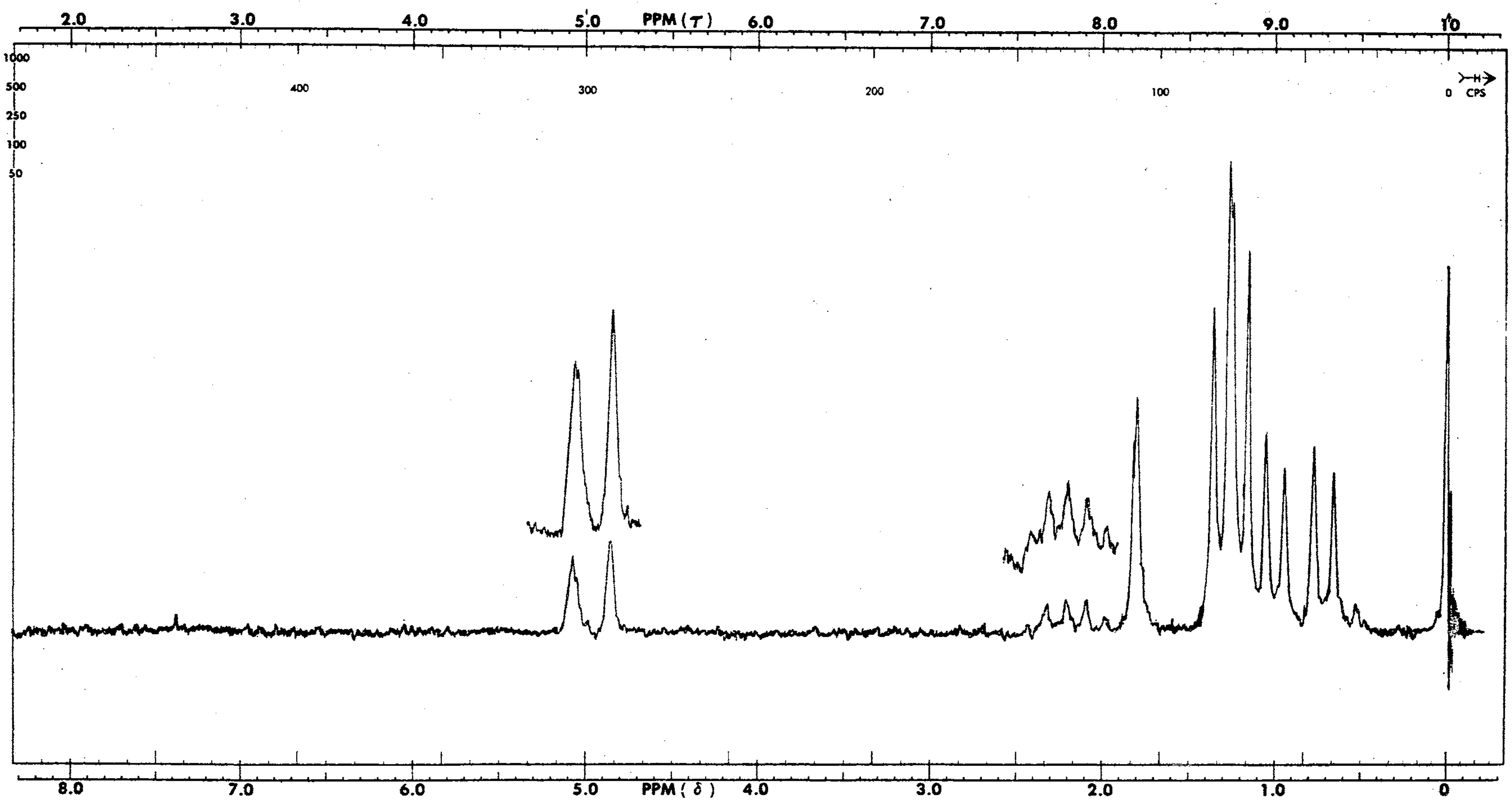
Plate XXXI



2,2,4-Trimethyl-3-oxovaleramide (XL)

Solvent..........$CDCl_3$
F.B.......2.0, 0.4 cps
R. F. Field......0.05 mG
S.T..............250 sec
S.W...........500 cps
S.O............35 cps
S.A..............2.0, 24
I.A..................off

Plate XXXII



Unknown E

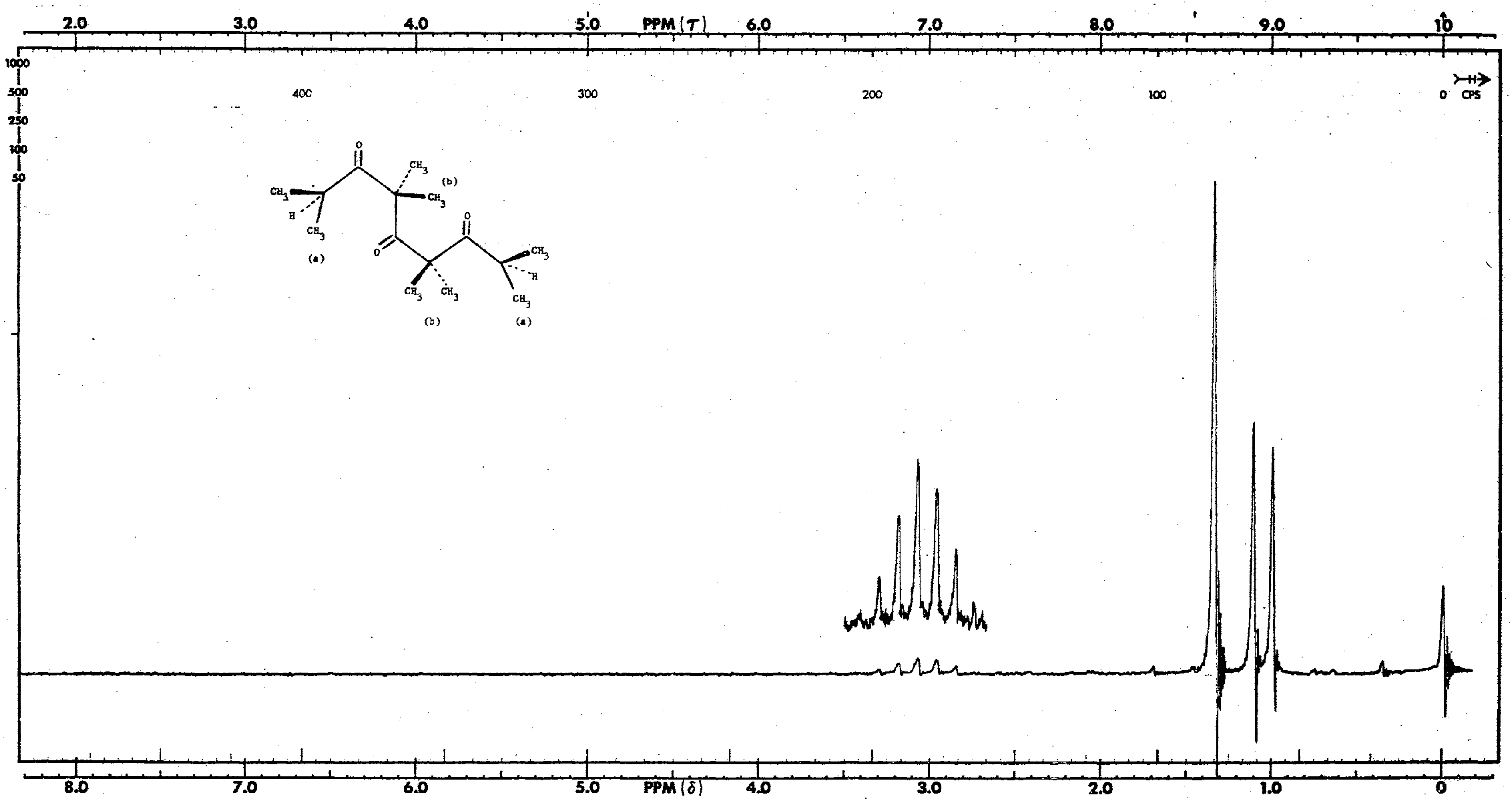
Solvent..........CDCl$_3$
F.B...........1.0 cps

R. F. Field......0.05 mG
S.T.............250 sec

S.W...........500 cps
S.O...........003 cps

S.A.................6.3
I.A.................off

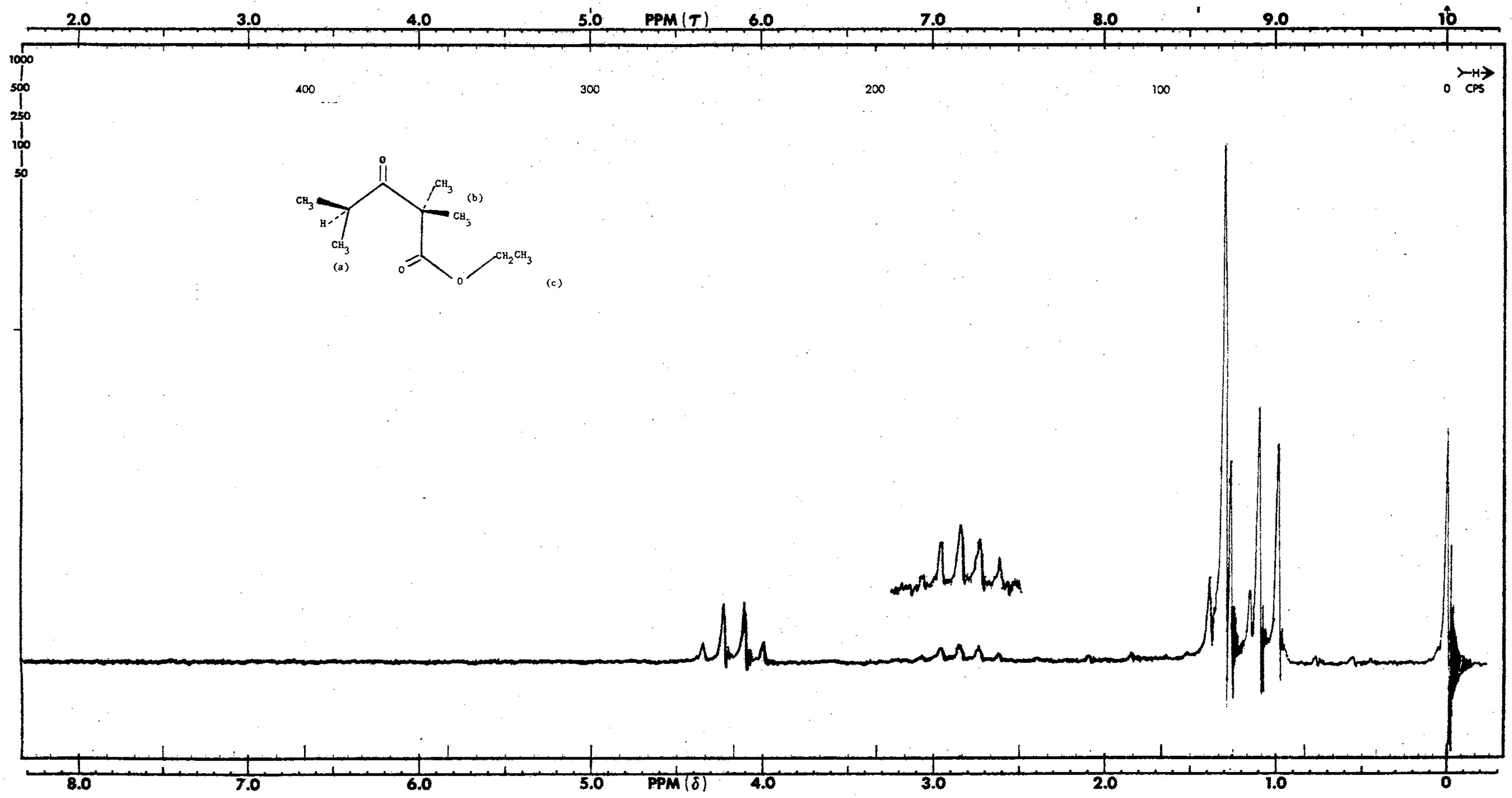
Plate XXXIII



2,4,4,6,6,8-Hexamethyl-3,5,7-nonanetrione (XXXIII)

Solvent..........CCl_4	R. F. Field......0.05 mG	S.W...........500 cps	S.A...................1.0
F.B............4.0 cps	S.T.............250 cps	S.O............49 cps	I.A...................off

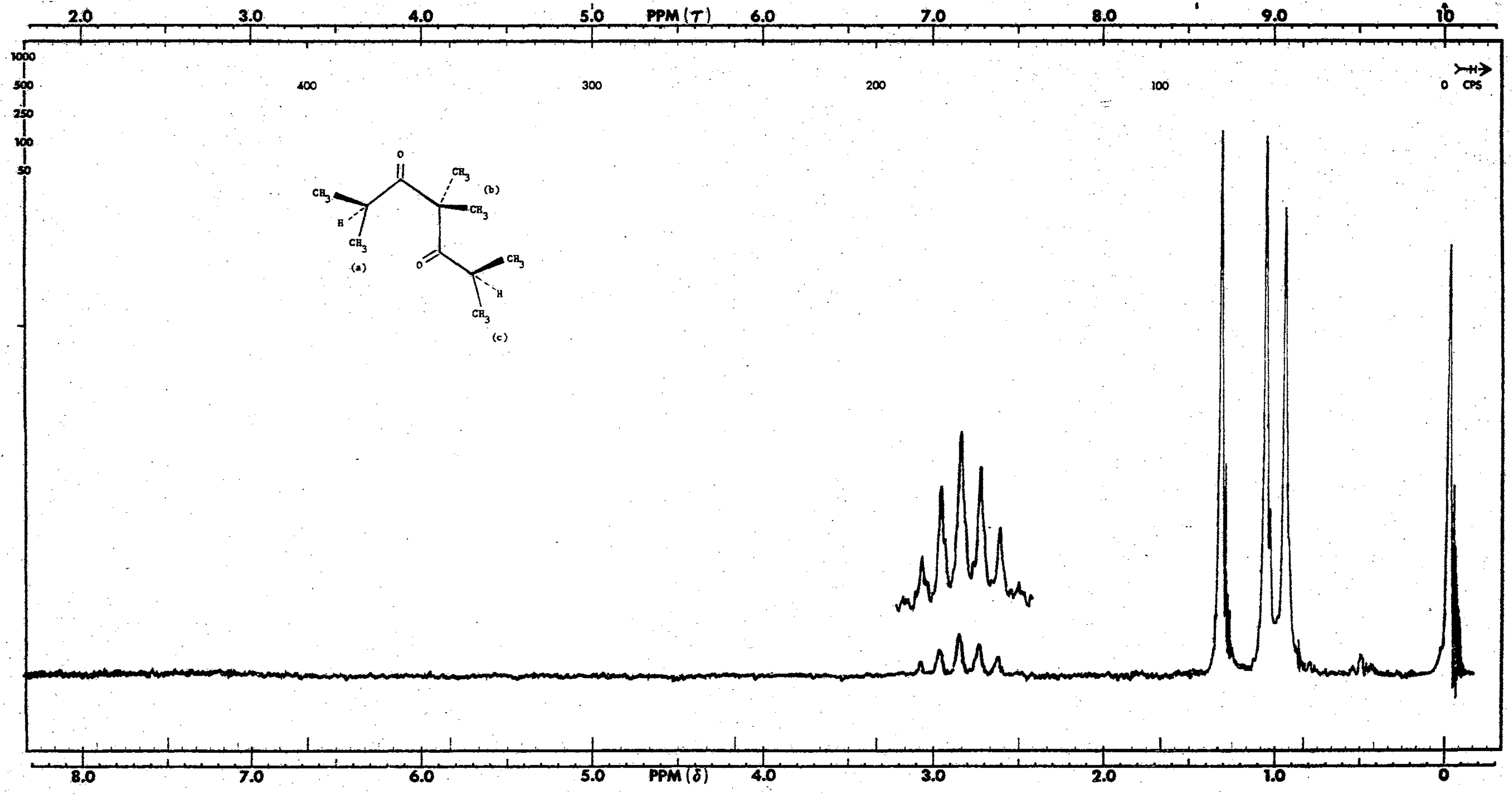
Plate XXXIV



Ethyl 2,2,4-trimethyl-3-oxovalerate (XLV)

Solvent...........CCl$_4$ R. F. Field......0.05 mG S.W...........500 cps S.A..................1.6
F.B...........4.0 cps S.T..............250 sec S.O...........000 cps I.A..................off

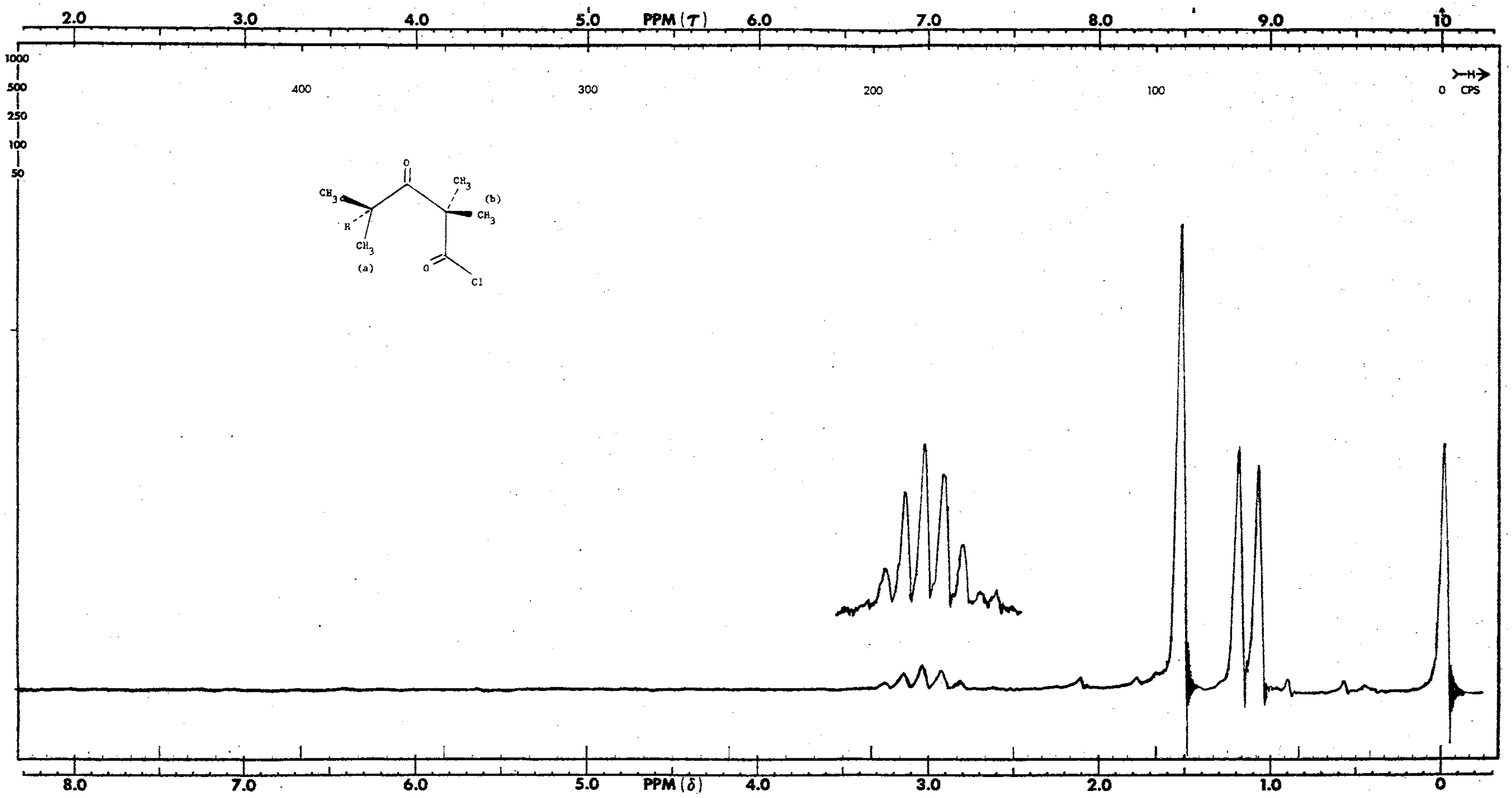
Plate XXXV



2,4,4,6-Tetramethyl-3,5-heptanedione (XLVI)

Solvent............CS$_2$ R. F. Field......0.05 mG S.W...........500 cps S.A..............4.0, 20
F.B.......2.0, 0.4 cps S.T.............250 sec S.O...........000 cps I.A.................off

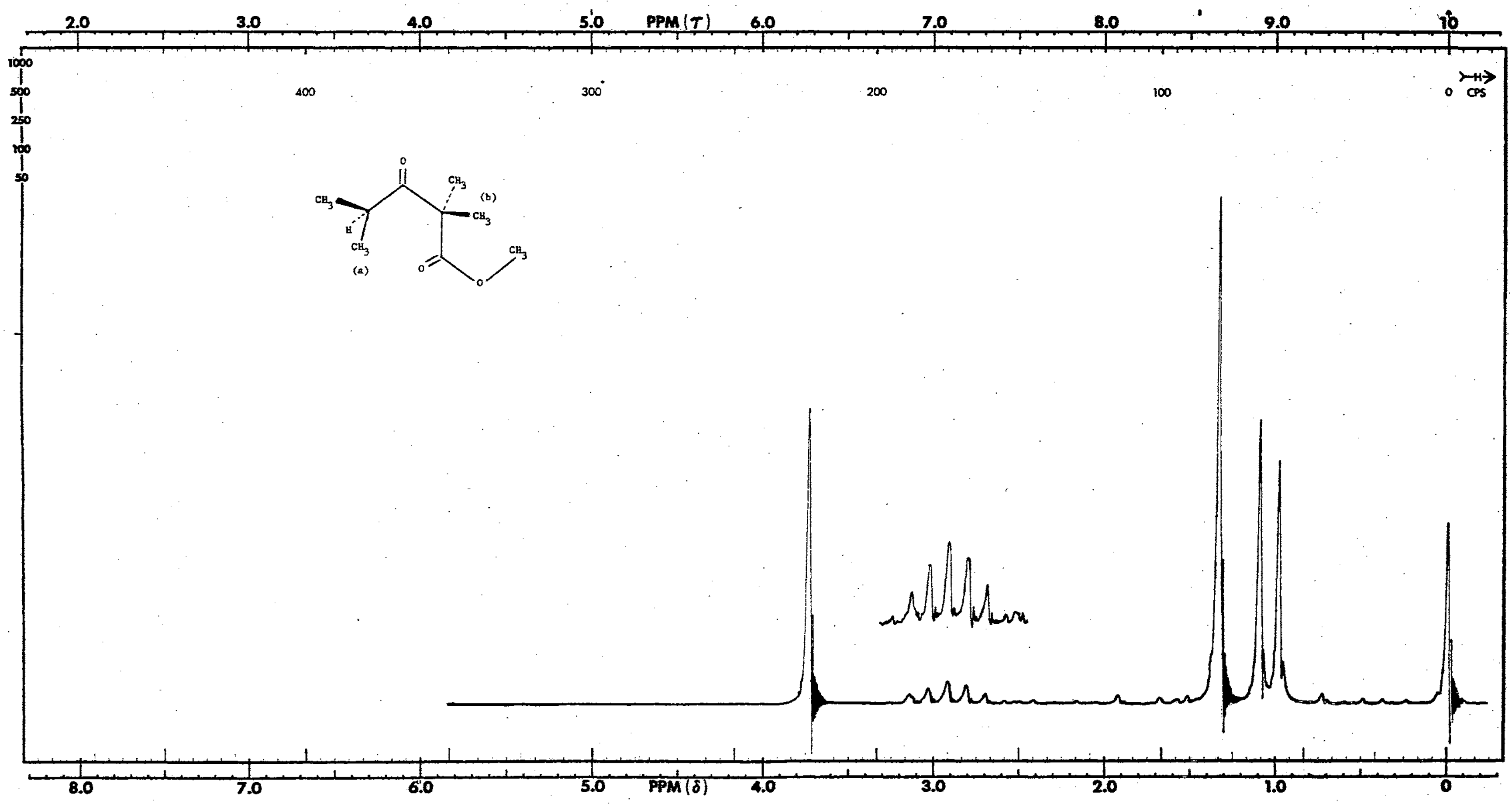
Plate XXXVI



2,2,4-Trimethyl-3-oxovaleryl Chloride (XLIX)

Solvent............Neat R. F. Field......0.22 mG S.W...........500 cps S.A..................0.8
F.B............4.0 cps S.T.............250 sec S.O...........000 cps I.A..................off

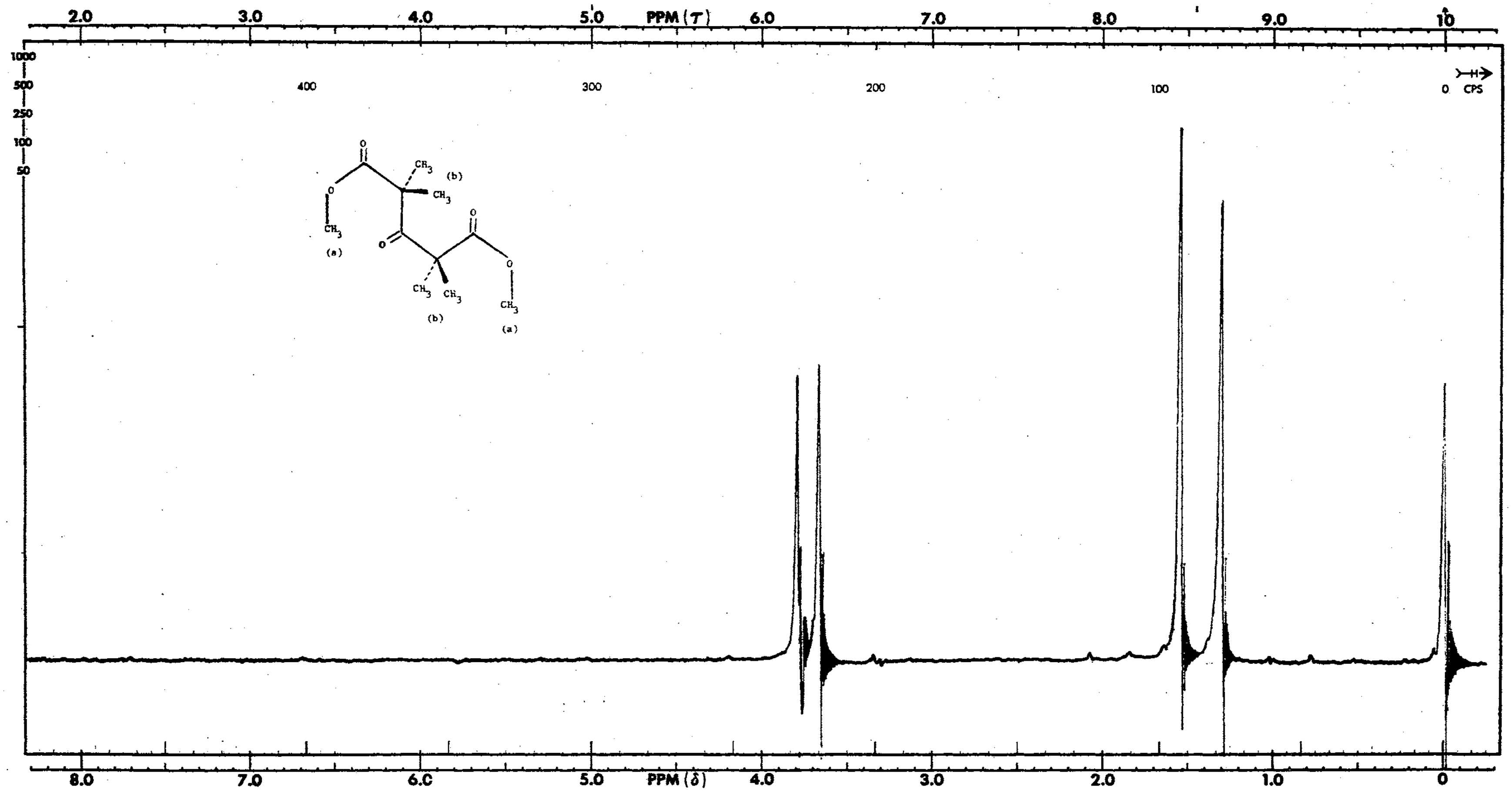
Plate XXXVII



Methyl 2,2,4-Trimethyl-3-oxovalerate (XXXVI)

Solvent............Neat   R. F. Field......0.02 mG   S.W..........500 cps   S.A..............0.5, 2.0
F.B..............2.0 cps   S.T..............250 sec   S.O...........000 cps   I.A..................off

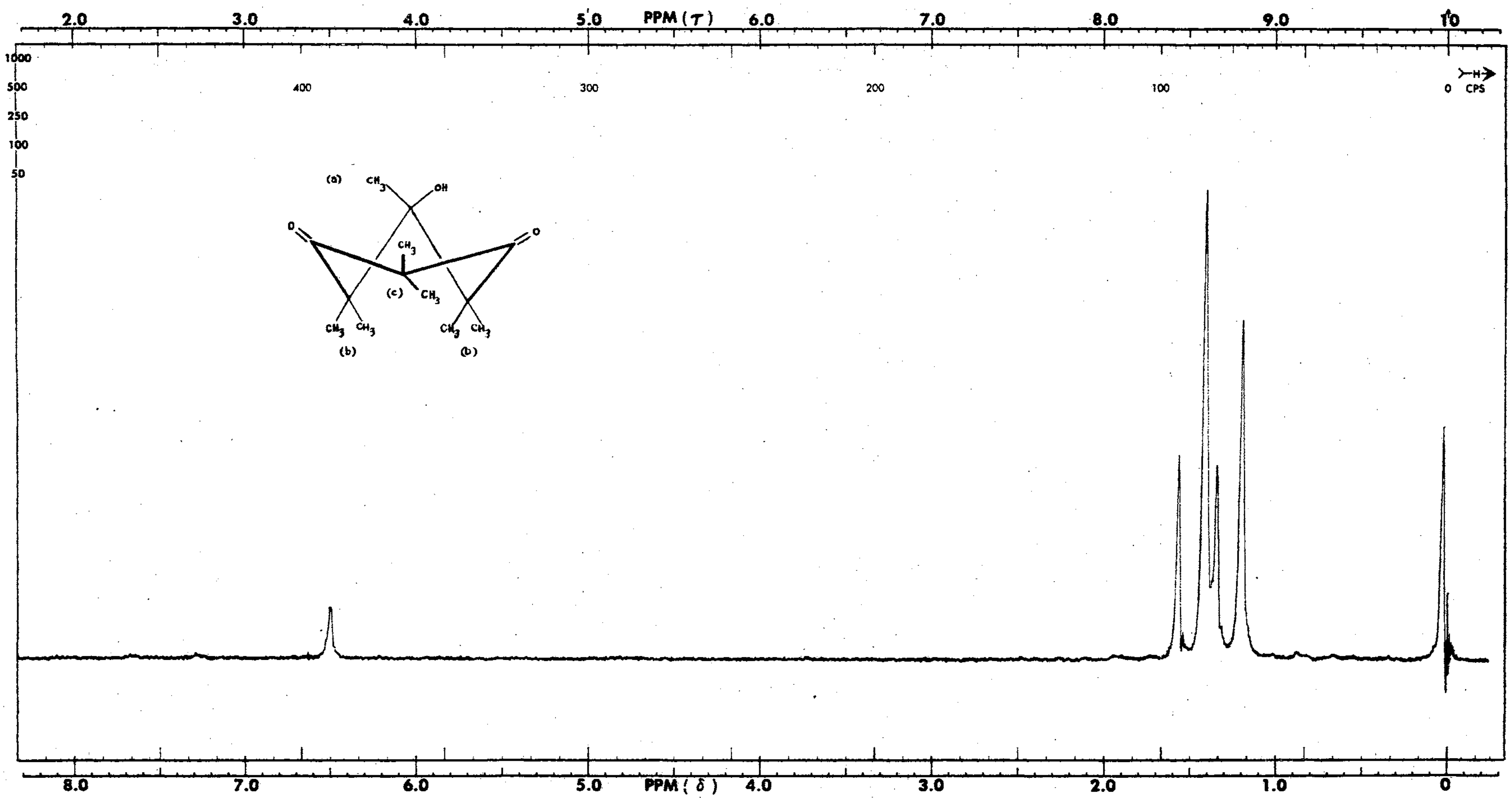
Plate XXXVIII



Dimethyl 2,2,4,4-Tetramethyl-3-oxoglutarate (XXXVII)

Solvent..........CCl_4	R. F. Field......0.05 mG	S.W...........500 cps	S.A..................1.6
F.B...........4.0 cps	S.T.............250 sec	S.O...........002 cps	I.A..................off

Plate XXXIX

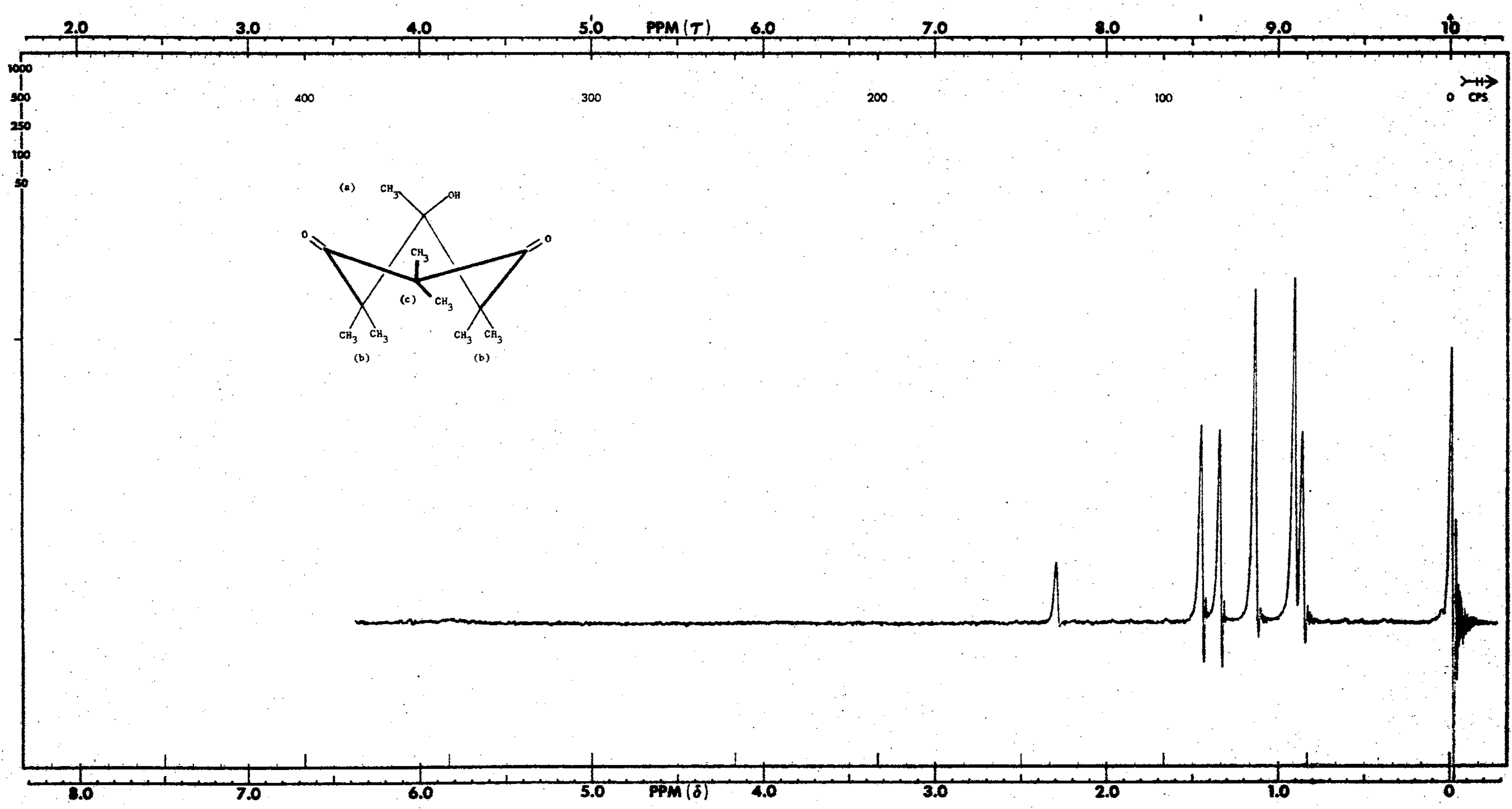


5-Hydroxy-2,2,4,4,5,6,6-heptamethyl-1,3-cyclohexanedione (L)

Solvent...Pyridine-d_5 R. F. Field......0.05 mG S.W..........500 cps S.A.................1.2

F.B............4.0 cps S.T.............250 sec S.O..........365 cps I.A.................off

Plate XL



5-Hydroxy-2,2,4,4,5,6,6-heptamethyl-1,3-cyclohexanedione (L)

Solvent........Benzene	R. F. Field......0.05 mG	S.W...........500 cps	S.A..................2.5
F.B............400 cps	S.T.............250 sec	S.O...........000 cps	I.A..................off

BIBLIOGRAPHY

1. Anderton, K. and Richards, R. W., J. Chem. Soc., 2543 (1965).

2. Arnold, R. T. and Smolinsky, G., J. Am. Chem. Soc., 82, 4918 (1960).

3. Bartlett, P. D., Swain, C. G., and Woodward, R. B., J. Am. Chem. Soc., 63, 3230 (1941).

4. Berlin, K. D., Austin, T. H., and Nagabhushanam, M., J. Org. Chem., 30, 1267 (1965).

5. Berlin, K. D. and Cooper, M. H., J. Org. Chem., 29, 2057 (1964).

6. Bick, I. R. C. and Horn, D. H. S., Aust. J. Chem., 18, 1405 (1965).

7. Birch, A. J., Cameron, D. W., and Richards, R. W., J. Chem. Soc., 4395 (1960).

8. Birch, A. J., Fitton, P., Smith, C. C., Steere, D. E. and Stelfox, A. R., J. Chem. Soc., 2209 (1963).

9. Boatman, S., Harris, T. M., and Hauser, C. R., J. Am. Chem. Soc., 87, 82 (1965).

10. Breslow, D. S. and Hauser, C. R., J. Am. Chem. Soc., 62, 2385 (1940).

11. Buchis, G., Scharch, M., Witteran, V., and White, D. M., J. Am. Chem. Soc., 81, 1968 (1959).

12. Burdett, J. L. and Rogers, M. T., J. Am. Chem. Soc., 86, 2105 (1964).

13. Carlin, R. B. and Smith, L. O., Jr., J. Am. Chem. Soc., 68, 2007 (1947).

14. Clark, R. D., J. Org. Chem., 32, 399 (1966).

15. Clark, R. D. (to Eastman Kodak Co.), U.S. Patent 3,173,954 (March 16, 1965); Nations, R. G. (to Eastman Kodak Co.), U.S. Patent 3,091,642 (May 28, 1963).

16. Collie, J. N., J. Chem. Soc., 91, 1806 (1907).

17. Cram, D. J., "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp. 86-94.

18. Dale, J., J. Chem. Soc., 1028 (1963).

19. Diard, M. and Rumpf, P., Bull. Soc. Chim. France, 1645 (1962).

20. Eigen, M., Angew. Chem. (Intern. Ed. Engl.), 3, 1 (1964).

21. Eistert, B. and Reiss, W., Chem. Ber., 87, 92 (1954).

22. Erickson, J. L. E., Collins, F. E., Jr., and Owens, B. L., J. Org. Chem., 31, 480 (1966).

23. Forsen, S., Nilson, M., and Wachtmeister, C. A., Acta Chem. Scand. 16, 583 (1962).

24. Fuson, R. C., Chadwick, D. H., and Ward, M. L., J. Am. Chem. Soc., 68, 389 (1946).

25. Gilman, H., Langham, W., and Moore, F., J. Am. Chem. Soc., 62, 2327 (1940).

26. Gilman, H., Zoellner, E., and Dickey, J., J. Am. Chem. Soc., 51, 1576 (1929).

27. Gresham, T. L., Jansen, J. E., Sharer, F. W., and Bankert, R. A., J. Am. Chem. Soc., 71, 2807 (1949).

28. Hampton, K. G., Harris, T. M., and Hauser, C. R., J. Org. Chem., 28, 1946 (1963).

29. Hampton, K. G., Harris, T. M., and Hauser, C. R., J. Org. Chem., 30, 61 (1965).

30. Hampton, K. G., Harris, T. M., and Hauser, C. R., J. Org. Chem., 31, 1035 (1966).

31. Hampton, K. G., Harris, T. M., and Hauser, C. R., J. Org. Chem., 31, 663 (1966).

32. Hampton, K. G., Harris, T. M., Harris, C. M., and Hauser, C. R., J. Org. Chem., 30, 4263 (1965).

33. Hampton, K. G. and Hauser, C. R., J. Org. Chem., 30, 2934 (1965).

34. Hampton, K. G., Light, R. J., and Hauser, C. R., J. Org. Chem., 30, 1413 (1965).

35. Hamrick, P. J., Jr. and Hauser, C. R., J. Am. Chem. Soc., 81, 493 (1959).

36. Harris, T. M., Boatman, S., and Hauser, C. R., J. Am. Chem. Soc., 85, 3273 (1963).

37. Harris, T. M. and Harris, C. M., J. Org. Chem., 31, 1032 (1966).

38. Harris, T. M. and Hauser, C. R., J. Am. Chem. Soc., 81, 1160 (1959).

39. Harris, T. M. and Hauser, C. R., J. Am. Chem. Soc., 84, 1751 (1962).

40. Harris, T. M. and Hauser, C. R., J. Org. Chem., 29, 1391 (1964).

41. Harris, S. R. and Levine, R., J. Am. Chem. Soc., 71, 1120 (1949).

42. Hasek, R. H., Clark, R. D., Elam, E. U., and Nations, R. G., J. Org. Chem., 27, 3106 (1962).

43. Hasek, R. H., Elam, E. V., Martin, J. C., and Nations, R. G., J. Org. Chem., 26, 700 (1961).

44. Hasek, R. H. and Martin, J. C., J. Org. Chem., 28, 1468 (1963).

45. Hauser, C. R. and Harris, T. M., J. Am. Chem. Soc., 79, 6342 (1957).

46. Hauser, C. R. and Harris, T. M., J. Am. Chem. Soc., 80, 6360 (1958).

47. Hauser, C. R. and Harris, T. M., J. Am. Chem. Soc., 81, 1154 (1959).

48. Hauser, C. R., Swamer, F. W., and Adams, J. T., "Organic Reactions," VIII, 59 (1954), J. Wiley and Sons, Inc., New York, N. Y.

49. Herzog, H. L. and Buchman, E. R., J. Org. Chem., 16, 99 (1951).

50. Hine, J., "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 237.

51. House, H. O. and Kramer, V., J. Org. Chem., 27, 4146 (1962).

52. House, H. O. and Kramer, V., J. Org. Chem., 28, 3362 (1963).

53. House, H. O. and Trost, B. M., J. Org. Chem., 30, 1341 (1965).

54. Kharasch, M. S., Hancock, J. W., Nudenberg, W., and Tawney, P. O., J. Org. Chem., 21, 322 (1956).

55. Light, R. J. and Hauser, C. R., J. Org. Chem., 25, 538 (1960).

56. Malhotra, S. K. and Ringold, H. J., J. Am. Chem. Soc., 85, 1538 (1963).

57. Martin, J. C., Burpitt, R. D., and Hostettler, H. U., J. Org. Chem., 32, 210 (1967).

58. Meyer, R. B. and Hauser, C. R., J. Org. Chem., 25, 158 (1960).

59. Miles, M. L., Harris, T. M., and Hauser, C. R., J. Org. Chem., 30, 1007 (1965).

60. Muir, W. M., Ritchie, P. D., and Lyman, D. J., J. Org. Chem., 31, 3790 (1966).

61. Nightingale, D. V. and Turley, R. H., J. Org. Chem., 26, 2656 (1961).

62. O'Sullivan, W. I. and Hauser, C. R., J. Org. Chem., 25, 1110 (1960).

63. Parker, A. J., Quart. Rev. (London), 16, 163 (1963).

64. Pearson, R. G. and Dillon, R. L., J. Am. Chem. Soc., 75, 2439 (1953).

65. Pregaglia, G. F. and Binaghi, M., J. Org. Chem., 28, 1152 (1963).

66. Reid, E. B. and Groszos, S. J., J. Am. Chem. Soc., 75, 1655 (1963).

67. Schaub, R. E. and Weiss, M. J., Chem. Ind. (London), 2003 (1961).

68. Schmutzler, R. and Reddy, G. S., Inorg. Chem., 4, 191 (1965).

69. Shichiro, A. and Nakazawa, Y., J. Pharm. Soc. Japan, 76, 1401 (1956).

70. Shriner, R. L., Fuson, R. C., and Curtin, D. Y., "The Systematic Identification of Organic Compounds," J. Wiley and Sons, New York, N. Y., 1956.

71. Sprague, J. M., Beckham, L. J., and Adkins, H., J. Am. Chem. Soc., 56, 2665 (1934).

72. Stone, H. W. and Hume, D. N., Ind. Eng. Chem., Anal. Ed., 11, 598 (1939).

73. Stork, G., Rosen, P., and Goldman, N. L., J. Am. Chem. Soc., 83, 2965 (1961).

74. Stork, G., Rosen, P., Goldman, N., Coombs, R. V., and Tsuji, T., J. Am. Chem. Soc., 87, 275 (1965).

75. Stuckwisch, C. G. and Bailey, J. V., J. Org. Chem., 28, 2362 (1963).

76. Swain, C. G. and Boyler, H. B., J. Am. Chem. Soc., 73, 870 (1951).

77. Swamer, F. W. and Hauser, C. R., J. Am. Chem. Soc., 68, 2647 (1946).

78. Swamer, F. W. and Hauser, C. R., J. Am. Chem. Soc., 72, 1352 (1950).

79. "Technical Data Report No. X-129," Eastman Chemical Products, Inc., Kingsport, Tennessee, 1961.

80. Toromanoff, E., Bull. Soc. Chim. France, 799 (1961).

81. Traynelis, V. I., Hergenrather, W. L., and in part with Hanson, H. J., and Valicenti, J. A., J. Org. Chem., 29, 123 (1964).

82. Wasserman, H. H. "Steric Effects in Organic Chemistry," Editor, Newman, M. S., Chapt. 7, J. Wiley and Sons, Inc., New York, N. Y., 1956.

83. Wedekind, E. and Weisswange, W., Ber. 39, 1631 (1906).

84. Weiss, M. J., Schaub, R. E., Allen, G. R., Jr., Polleto, J. F., Pidacks, C., Conrow, R. B., and Cascia, C. J., Tetrahedron, 20, 357 (1964).

85. Weiss, M. J., Schaub, R. E., Polleto, J. F., Allen, G. R., Jr., and Cascia, C. J., Chem. Ind. (London), 118 (1963).

86. Wierzchowski, K. L. and Shugan, D., Spectrochem. Acta., 21, 943 (1965).

87. Work, S. D. and Hauser, C. R., J. Org. Chem., 28, 725 (1963).

88. Zaugg, H. E., "Organic Reactions," VIII, 322 (1954), J. Wiley and Sons, Inc., New York, N. Y.

89. Zaugg, H. E. and Schaefer, A. D., J. Am. Chem. Soc., 87, 1857 (1965).

90. Zook, H. D. and Russo, T. J., J. Am. Chem. Soc., 82, 1258 (1960).

VITA

Robert Burton Hanson

Candidate for the Degree of

Doctor of Philosophy

Thesis: RING CLEAVAGE OF 3-HYDROXY-2,2,4-TRIMETHYL-3-PENTENOIC ACID β-LACTONE BY THE ANION OF DIISOPROPYL KETONE

Major Field: Organic Chemistry

Biographical:

Personal Data: The author was born in Jackson Heights, New York on May 3, 1941, the son of Robert Andrew and Ruth Burton Hanson. On August 11, 1965, he married Barbara Suzanne Logsdon.

Education: The author graduated from Will Rogers High School in Tulsa, Oklahoma, in 1959. In September, 1959, he entered Oklahoma State University, Stillwater, Oklahoma, where he received a Bachelor of Arts Degree in Chemistry in August, 1963. In September, 1963, he was admitted to the Graduate School of Oklahoma State University, Stillwater, Oklahoma, where he completed the requirements for the Doctor of Philosophy degree in July, 1967.

Professional experience: The author served as a graduate teaching assistant from the fall of 1963 to January, 1967. He was a recipient of a Department Fellowship during the summer of 1965 and served as an NSF "trainee" from September, 1966, to July, 1967.

Membership in professional societies: The author is a member of Phi Lambda Upsilon.