1961

The chemistry of 3-acetyl-3, 4-phenacylidenecoumarin

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THE CHEMISTRY OF 3-ACETYL-3,4-PHENACYLIDENECOUMARIN

by

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In Charge of Major Work

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Signature was redacted for privacy.

Dean of Graduate College

Iowa State University
Of Science and Technology
Ames, Iowa

1961

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INTRODUCTION

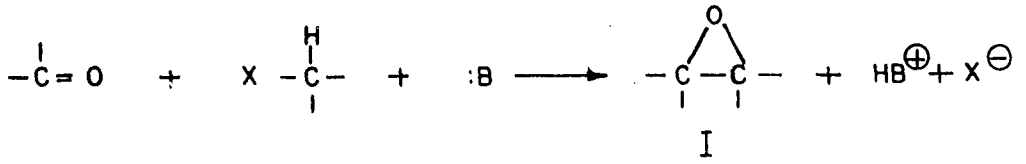
The Darzens reaction has been extensively studied since the turn of the Twentieth Century. The scope and limitations of the reaction were determined by Darzens in the early 1900's, and in recent years, the stereochemistry and mechanism of the condensation have received ample investigation. The vinylogous Darzens reaction, on the other hand, has received sparse attention, and indeed, its existence is still in doubt today.

The purpose of this research was to investigate the chemistry and constitution of 3-acetyl-3,4-phenacylidene-coumarin, and the validity of the vinylogous Darzens reaction in the condensation of 3-acetylcoumarin with phenacyl halides.

HISTORICAL

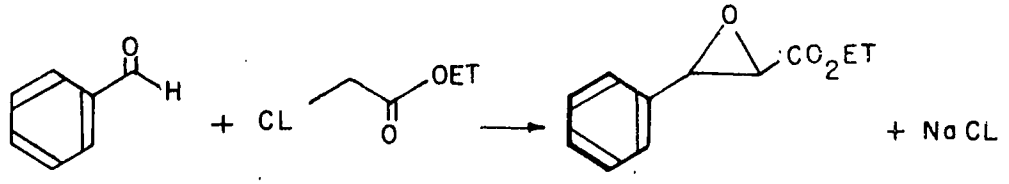
The Darzens Reaction

The Darzens reaction is defined as the condensation of a halomethylene compound with an aldehyde or ketone in the presence of base to yield an oxirane ring (I) by the elimination of hydrogen halide, i,e.,



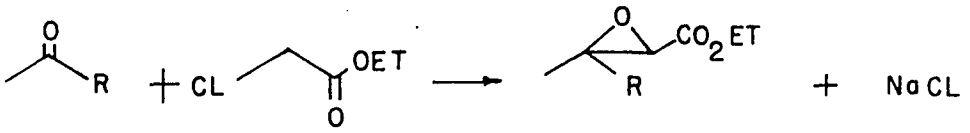
I

In 1892, Erlenmeyer (1) announced the first synthesis of an epoxy or glycidic ester (II) by the condensation of benzaldehyde with ethyl α-chloroacetate (III) in the presence of sodium:



III II

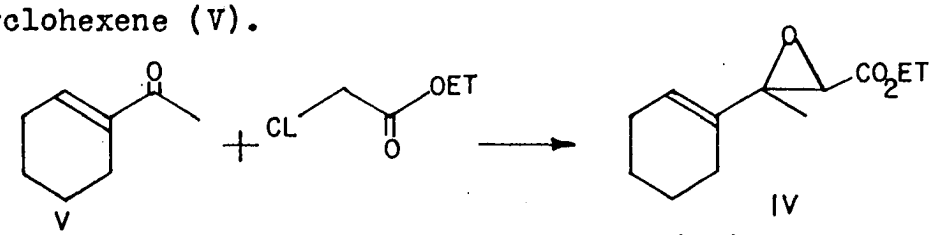
The condensation was extensively investigated by Darzens (2-14) in the early 1900's, as a consequence of which the reaction was given his name. Darzens (2) demonstrated the generality of the condensation in regard to the use of ketones in 1904:



R= methyl, isohexyl, heptyl, nonyl, phenyl, β-phenylethyl and p-isobutylphenyl

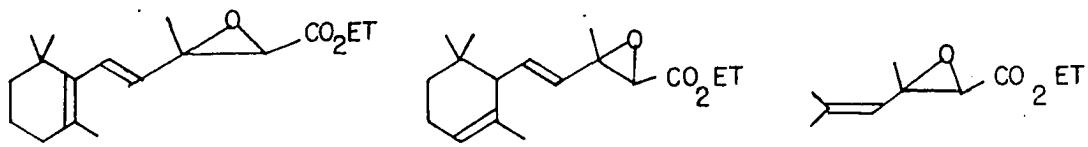
In 1906, Darzens (4) investigated the condensation of aldehydes with α-haloesters, and demonstrated the reaction to be general for aldehydes also. The aromatic aldehydes, benzaldehyde, anisaldehyde, piperonal and furfural, gave high yields of the corresponding epoxyesters. On the other hand, the aliphatic aldehydes, formaldehyde, acetaldehyde, propionaldehyde and isovaleryaldehyde, were found to give low yields of the epoxyesters.

The condensation of α,β-unsaturated ketones with ethyl α-chloroacetate was also studies by Darzens and other investigators. Darzens and Rost (9) reported the preparation of the glycidic ester of 1-acetyl-1-cyclohexene (IV) by the condensation of ethyl α-chloroacetate with 1-acetyl-1-cyclohexene (V).



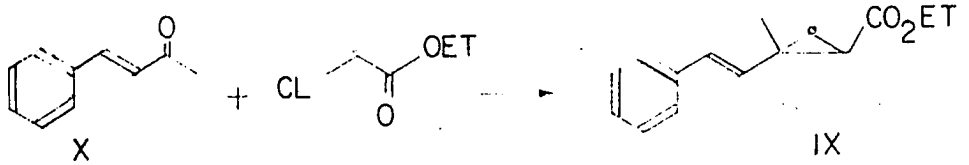
V IV

In recent years, Heilbron and coworkers (15), and Linnell and Shen (16) have investigated the condensation of α, β-unsaturated ketones with α-haloesters. Heilbron, et al have reported the preparation of the glycidic esters of α-ionone (VII), β-ionone (VI), and mesityl oxide (VIII):



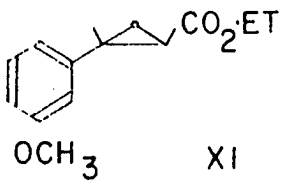
VI VII VIII

Linnell and Shen have also prepared the glycidic ester of benzalacetone (IX) by the condensation of benzalacetone (X) with ethyl α-chloroacetate:

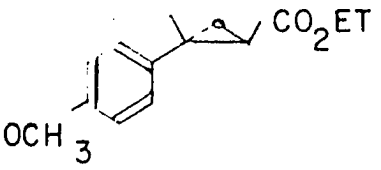


X IX

In recent years the German chemists, Nerdel and Fröhlich (17) have investigated the condensation of m-methoxyacetophenone and p-methoxy-acetophenone with ethyl α-chloroacetate, and have obtained a satisfactory yield of the glycidic esters, ethyl β-methyl- β-(m-methoxyphenyl)- α,β-epoxypropionate (XI) and ethyl β-methyl-β-methyl- β -p-methoxyphenyl)-α,β-epoxypropionate (XII). Nerdel and Fröhlich have also prepared ethyl β-methyl-β(m-nitrophenyl)-α,β-epoxypropionate, and ethyl β-(m-nitrophenyl)-α,β-epoxypropionate by the condensation of m-nitroacetophenone and m-nitrobenzaldehyde with



XI



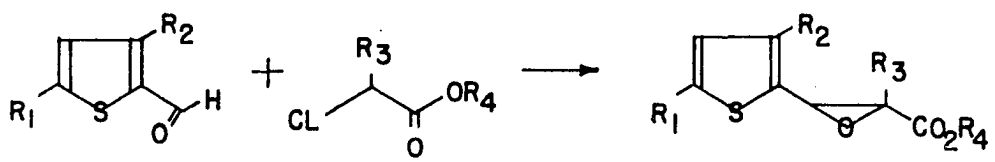
ethyl α-chloroacetate.

The Russian workers, Martynov and Ol'man (18) have supplemented the work of Nerdel and Fröhlich by condensing ethyl α-chloroacetate with several substituted benzal-

dehydes. The Russians have prepared the glycidic esters of o-nitrobenzaldehyde, m-nitrobenzaldehyde, p-nitrobenzaldehyde, and p-chlorobenzaldehyde.

In 1905, Darzens (3,4) investigated the condensation of ethyl α-chloropropionate with aldehydes and ketones, and found this α-chloroester to exhibit the same behavior in condensations as α-chloroacetates. Darzens has prepared the α-methyl glycidic esters of acetone, methyl ethyl ketone, methyl propyl ketone, methyl hexyl ketone, and acetophenone. Aldehydes such as benzaldehyde, anisaldehyde, piperonal, furfural, acetaldehyde, propionaldehyde and isovalerylaldehyde have also been found to condense favorably with ethyl α-chloropropionate.

In 1952, Dullaghan and Nord (19) have employed ethyl α-chloropropionate and methyl α-chloroacetate in the preparation of the glycidic esters of 2-thenaldehyde and substituted 2-thenaldehydes (XIII):



XIII

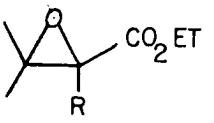
XIII

a) R_1=hydrogen b) R_1=ethyl c) R_1=ethyl d) R_1=chloro
R_2=methyl R_2=hydrogen R_2=hydrogen R_2=hydrogen
R_3=methyl R_3=hydrogen R_3=methyl R_3=hydrogen
R_4=ethyl R_4=methyl R_4=ethyl R_4=methyl

e) R_1=chloro f) R_1=hydrogen g) R_1=hydrogen h) R_1=hydrogen
R_2=hydrogen R_2=hydrogen R_2=hydrogen R_2=methyl
R_3=methyl R_3=hydrogen R_3=methyl R_3=hydrogen
R_4=ethyl R_4=methyl R_4=ethyl R_4=methyl

In recent years, Morris and Young (20) have investigated the α-chloroesters, ethyl α-chloropropionate, ethyl α-chlorobutyrate, ethyl α-chlorovalerate, and ethyl α-chlorocaproate by preparing the substituted glycidic ester (XIV a-d) of acetone.

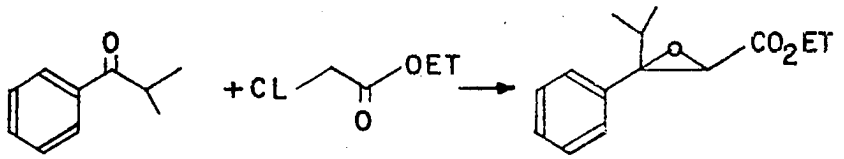
XIV a) R = methyl
b) R = ethyl
c) R = propyl
d) R = butyl



XIV

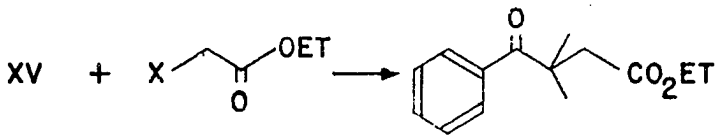
Although ethyl α-chloroacetate has become the most popular halo component in the Darzens reaction, α-bromoacetate and α-iodoacetate have also been used (21). The yields of glycidic esters are somewhat lower if the α-bromo- or α-iodoesters are employed; the lower yields have been explained by the greater reactivity of the bromo-and iodo-

esters to SN_2 displacement. Haller and Ramart - Lucas (22) have illustrated the fact that alkylation of the carbonyl component is enhanced by using ethyl α -bromoacetate and ethyl α -iodoacetate. When isopropyl phenyl ketone (XV) is condensed with ethyl α -chloroacetate, the Darzens product (XVI) prevails,



XV XVI

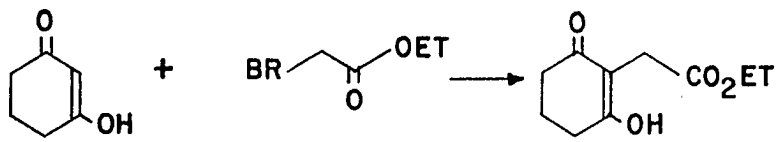
however, when ethyl α -chloroacetate is replaced by ethyl α -bromoacetate or ethyl α -iodoacetate, only the alkylated ketone (XVII) is recovered:



XVII

X = Br, I

Stetter, Dierichs, and Siehnhold (23, 24) have also reported C-alkylation to be the predominate reaction in the condensation of ethyl α -bromoacetate with dihydroresorcinol (XVIII).

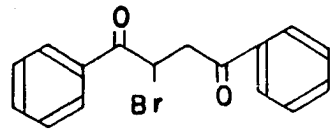


XVIII

The condensation of ethyl α-bromophenylacetate with acetone has been shown by Morris, et al. (25) not to afford a glycidic ester. An analysis of the reaction mixture disclosed that the bromoester was degraded to a mixture of ethyl phenylacetate, ethyl 2,3-diphenylmaleate, and ethyl 2,3-diphenylsuccinate.

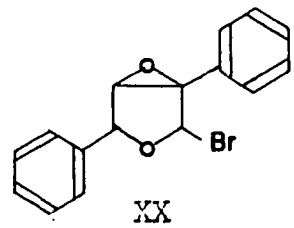
The Darzens reaction with complex α-haloesters has proven to be unsuccessful. Yarnall and Wallis (26) have attempted to condense ethyl α,β dichloropropionate with cyclohexanone and have found no evidence of a Darzens product. Apparently, the ethyl α,β dichloropropionate undergoes elimination to yield ethyl α-chloroacrylate. The Darzens reaction between acetophenone and ethyl α-chloro- ββ-diethoxypropionate has also been unsuccessful, as Oroshnik and Spoerri (27) were unable to isolate products.

The Darzens reaction involving an α-haloketone as the halomethylene component was first discovered by Fritz (28) in 1895. In attempting to prepare α-ethoxyacetophenone by the solvolysis of α-bromoacetophenone, Fritz discovered that α-bromoacetophenone condensed with itself. Fritz named the condensation product, diphenacyl bromide, and assigned the structure of the compound as 1,5-diphenyl-2-bromo-1,4 butadione (XIX).



XIX

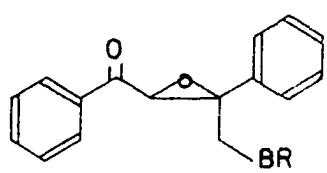
Paal and coworkers (29, 30) studied the condensation in 1903, and discovered that two isomeric diphenacyl bromides were formed in the reaction; the isomeric diphenacyl bromides were designated as α-and β-diphenacyl bromides. Paal then extended the condensation by preparing the α-and β-diphenacyl chlorides, and the α-and β-diphenacyl iodides. In 1913, Widman (31) investigated the diphenacyl halides and rejected the structure proposed by Fritz. Widman discovered that if he treated β-diphenacyl bromide with acetyl chloride, he obtained a product that was identical with a product obtained by treating β-diphenacyl chloride with acetyl bromide. On the strength of this reaction, and other degradative evidence, Widman proposed the tetrahydrofuran structure, 2-bromo-3,4-epoxy-3,5 diphenyltetrahydrofuran (XX).



XX

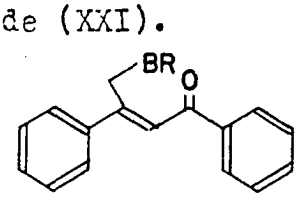
The structure of the diphenacyls was not investigated again until 1952, when Berson (32) and Wasserman (33)

demonstrated that the tetrahydrofuran structure proposed by Widman to be incorrect. Berson based his investigation on spectroscopic means, and discovered the infra-red and ultraviolet spectra of the diphenacyl halides were incompatible with the structure outlined by Widman. The spectra was compatible however, with an epoxyketone and thus Berson proposed the structure of the diphenacyl bromides to be the normal Darzens product, 4-bromo-1,3-diphenyl-2,3-epoxy-1-butanone (XXI).



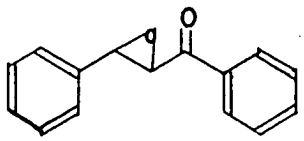
XXI

Wasserman and coworkers (33) investigated the structure of the diphenacyl bromides at approximately the same time, and agreed completely with the Berson structure. The structure of α-diphenacyl bromide was confirmed by synthesis in 1954 by the work of Stevens, Church, and Traynelis (34). The synthesis consisted of the preparation of bromo-dypnone (XXII) by the action of NBS on dypnone, and the subsequent oxidation of bromo-dypnone by alkaline hydrogen peroxide to the α-diphenacyl bromide (XXI).



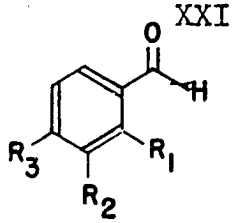
XXII

After the initial research by Fritz on α-bromoacetophenone, Widman investigated the condensation of α-haloacetophenones with aldehydes. Widman (35) discovered that benzaldehyde condensed with α-chloroacetophenone in the presence of sodium hydroxide or sodium ethoxide to produce 1,3-diphenyl-2,3-epoxy-1-propanone (XXIII).



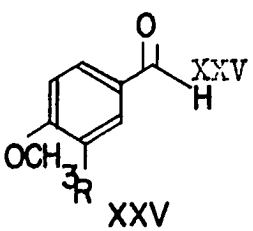
XXIII

The scope and limitations of the condensation between phenacyl halides and aldehydes remained for Bodforss (36,37) to investigate. The reaction proved to be general for benzaldehydes substituted with electron-withdrawing groups, (XXIV-XXVIII) but did not proceed with



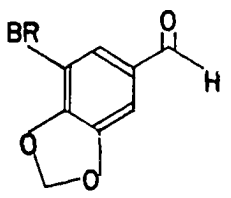
XXIV

XXIV a) R_1=hydrogen R_2=hydrogen R_3=hydrogen
b) R_1=nitro R_2=hydrogen R_3=hydrogen
c) R_1=hydrogen R_2=nitro R_3=hydrogen
d) R_1=hydrogen R_2=hydrogen R_3=nitro
e) R_1=hydrogen R_2=hydrogen R_3=chloro

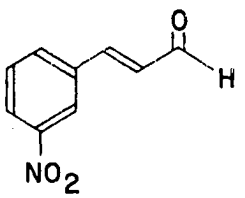


XXV

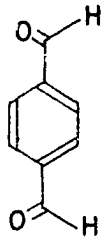
XXV a) R-bromo
b) R-nitro



XXVI



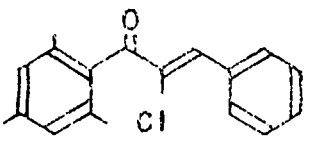
XXVII



XXVIII

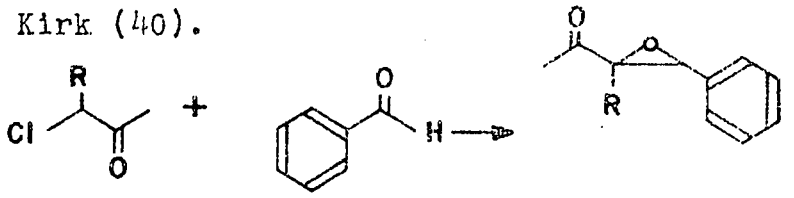
the aliphatic aldehydes, acetaldehyde and isobutyraldehyde, or the substituted benzaldehydes, anisaldehyde, piperonal, cinnamaldehyde, and p-tolualdehyde.

The effect of substituents on the aromatic ring of the α-haloacetophenones on the condensation with benzaldehyde has been extensively studied by Jörlander (38). The condensation of benzaldehyde with p-amino α-chloroacetophenone, p-acetamino-α-chloroacetophenone, 2-acetamino-6-methyl-α-chloroacetophenone, 2-methyl-5-acetamino-α-chloroacetophenone, and 3-acetamino-4-methyl-α-chloroacetophenone was shown to occur in high yield by Jörlander. The reaction was also successful in the condensation of benzaldehyde with 2-methoxy-5-chloro-α-chloroacetophenone, 2,4-dimethoxy-α-chloroacetophenone, and 4-phenyl-α-chloroacetophenone. The methylated acetophenones, 3,4-dimethyl-α-chloroacetophenone, and 2,4-dimethyl-α-chloroacetophenone condensed with benzaldehyde in the normal manner. However 2,4,6-trimethyl-α-chloroacetophenone did not yield the epoxy-ketone, but instead afforded the aldol product (XXIX).



XXIX

In recent years, the Darzens reaction between aliphatic α-haloketones and aldehydes has been studied by several investigators. The condensation of α-chloroacetones with benzaldehyde to produce the epoxyketones (XXX_a, XXX_b) has been reported by Temnikova and Martynov (39) and Kwart and Kirk (40).

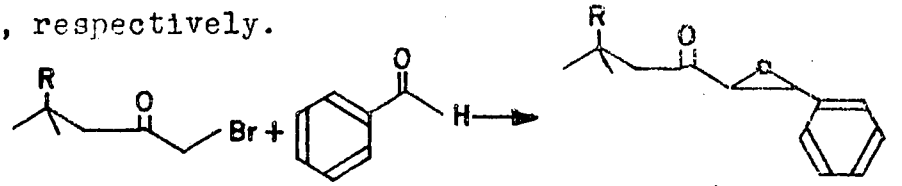


XXX

XXX_a) R = hydrogen

b) R = methyl

The branch-chained α-bromoketones, 1-bromo-3-methyl-2-butanone and 1-bromo-3,3-dimethyl-2-butanone, have been condensed with benzaldehyde by Temnikova and Kropachev (41,42) to yield 1-phenyl-1,2-epoxy-4-methyl-3-pentanone (XXXIa), and 1-phenyl-1,2-epoxy-4,4-dimethyl-3-pentanone (XXXIIb), respectively.

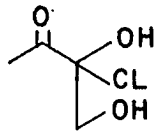


XXXI

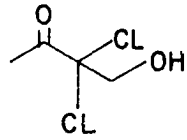
XXXIa) R = hydrogen

b) R = methyl

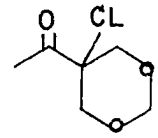
The condensation of formaldehyde with α-chloroacetone has been studied by Hurd, McPhee, and Morey (43). The condensation has been shown not to yield the normal Darzens product, but instead yields a mixture of three products, 2-acetyl-2-chloro-1,3-dihydroxypropane (XXXII), 4-hydroxy-3,3-dichloro-2-butanone (XXXIII), and 5-acetyl-5-chloro-1,3-dioxane (XXXIV).



XXXII

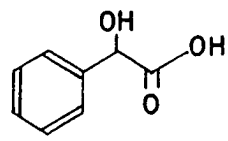


XXXIII



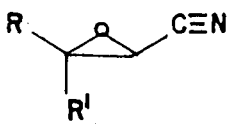
XXXIV

The α-haloketones have also been shown to undergo other side reactions under the conditions of the Darzens reaction. Campbell and Khanna (44) have discovered the formation of 1,2-dibenzoylethylene and 1,2-bis-(o-nitrobenzoyl)-ethylene in the base treatment of α-bromoacetophenone and α-bromo-o-nitroacetophenone. Eaborn (45) has shown phenacyl chloride to undergo an auto-oxidation reduction reaction in the presence of base to yield mandelic acid (XXXV).



XXXV

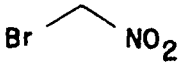
Since the initial discovery of the Darzens reaction in 1892, many halocompounds have been found to condense with carbonyl compounds in the same manner. Bodforss (46) in 1919 showed that α-haloamides could be substituted for α-haloesters and ketones by condensing N-phenyl-α-chloroacetamide with benzaldehyde to yield N-phenyl-3-phenyl-2,3-epoxypropanamide. In recent years, Martynov and Shchelkunov (47,48) have synthesized α,β-epoxy-nitriles (XXXVI) by the condensation of chloroacetonitrile with ketones:



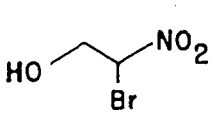
XXXVI

XXXVI a) R = methyl, R' = methyl
b) R = methyl, R' = ethyl
c) R = propyl, R' = ethyl
d) R = phenyl, R' = phenyl
e) R = isobutyl, R' = isobutyl
f) R = phenyl, R' = methyl

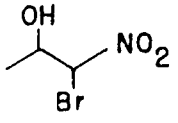
The Darzens reaction has also been reported by Ballester (49) to proceed with α-halomethylene sulfones and carbonyl compounds. Maas (50) has discovered that α-bromonitromethane (XXXVII) condenses with formaldehyde and acetaldehyde to form 2-bromo-2-nitro-1-ethanol (XXVIII), and 1-bromo-1-nitro-2-propanol (XXXIX).



XXXVII



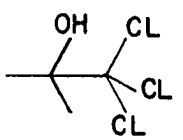
XXXVIII



XXXIX

Newman and Magerlein (51) have reported that the p-toluenesulfonic acid group may be used instead of a halogen in the Darzens reaction, since they have prepared ethyl α,β-epoxycyclohexylideneacetate by the condensation of ethyl α-(p-toluenesulfonyl)-acetate and cyclohexanone.

The first condensation between a carbonyl component and an α-halocomponent not containing a carbonyl system was discovered by Willgerodt (52) in 1881. Willgerodt condensed acetone with chloroform and isolated the halogen containing compound, 1,1,1-trichloro-2-methyl-2-propanol (XL).

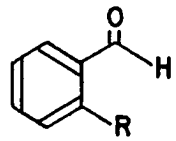


XL

In 1897, Jocicz (53) demonstrated that benzaldehyde condensed with chloroform to form 1,1,1-trichloro-2-phenyl-2-ethanol, and Levedev (54) synthesized 1,1,1-trichloro-2-(o-methoxyphenyl)-2-ethanol by condensing o-methoxybenzaldehyde and chloroform. The scope and limitations of the condensation of chloroform and ketones were investigated by Weizman, Bergman, and Sulzbacher (55) in 1948. They discovered the condensation to occur quite readily with acetone, methyl ethyl ketone, cyclohexanone, acetophenone, and methyl isobutyl ketone. Benzophenone was the only ketone which did not condense with chloroform. The con-

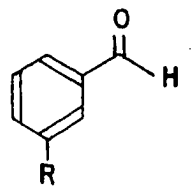
densation of chloroform and branch-chained ketones has been studied by Lombard and Boesch (56) in 1953. They have discovered that steric requirements for the reaction are very important, since methyl isobutyl ketone yield only an 18% conversion to 1,1,1-trichloro-2,4 dimethyl-2-pentanol, methyl propyl ketone, methyl n-pentyl ketone, and methyl n-hexyl ketone give a 10% yield of the chloroform addition products. Lombard and Boesch have found that severely sterically hindered ketones such as diisobutyl ketone and diisopropyl ketone do not condense with chloroform.

Howard (57) and Howard and Castles (58) have prepared 1,1,1-trichloro(p-chlorophenyl)-2 ethanol and 1,1,1-trichloro-(o-chlorophenyl)-2-ethanol by the condensation of chloroform with p-chlorobenzaldehyde and o-chlorobenzaldehyde. Cristol and Harms (59) have prepared the trichlorohydrins of o-bromobenzaldehyde, o-tolualdehyde, and o-methoxybenzaldehyde. Bergmann, Ginsburg, and Lavie (60) have prepared the trichlorohydrins of several substituted benzaldehydes, and have found the condensation to be general for ortho-, meta-, and para- substituted benzaldehydes (XLI, XLII, XLIII).

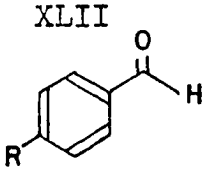


XLI

XLI a) R = methyl
b) R = methoxy
c) R = chloro



XLII



XLIII

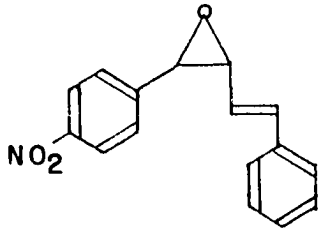
XLII a) R = methyl
b) R = methoxy
c) R = chloro

XLIII a) R = methyl
b) R = methoxy
c) R = chloro

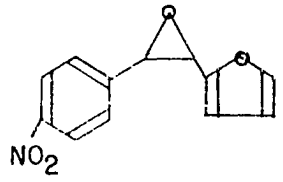
Bergmann, Ginsburg, and Lavie have observed the Cannizzaro reaction to occur with 2-and 4-Nitrobenzaldehydes, and o-phenylbenzaldehyde, instead of the condensation with chloroform. Howard (61) has also found that the aliphatic aldehydes, formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, and isovaleraldehyde do not condense with chloroform, but undergo self-condensation instead.

The trihalomethanes, bromoform and iodoform, have also been found by Ekeley and Klemme (62) to condense with aldehydes and ketones, however the yield of trihalohydrins is lower with these halides.

Certain benzyl and benzal halides have also been reported to undergo the Darzens reaction. Kleucker (63) has described the preparations of 1-(p-nitrophenyl)-2-(p-stryryl)-epoxyethane (XLIV) and 1-(p-nitrophenyl)-2-(2-furanyl)-epoxyethane (XLV) by the condensation of p-nitrobenzyl chloride with cinnamaldehyde and furfural, respectively.

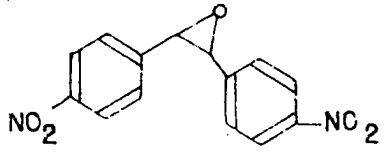


XLIV



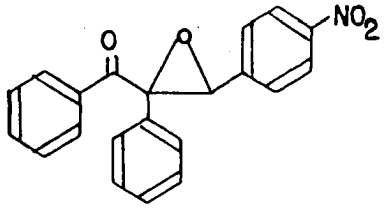
XLV

The condensation of p-nitrobenzyl chloride with p-nitrobenzaldehyde to prepare 1,2-di(p-nitrophenyl)-epoxy-ethane (XLVI) has been reported by Bergmann and Hervey (64).

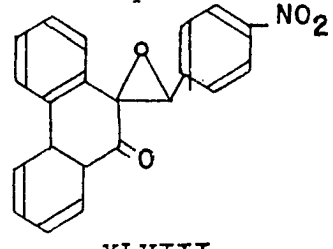


XLVI

Hahn (65) has prepared the epoxy-ketones (XLVII, XLVIII) by the condensation of p-nitrobenzyl chloride with the 1,2-diketones, benzil and phenanthraquinone.

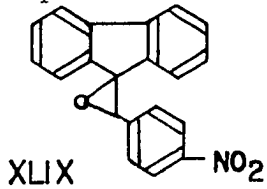


XLVII



XLVIII

Bergmann and Hervey (64) have shown that 9-chloro-fluorene may be used as a halomethylene component in the Darzens reaction by condensing 9-chlorofluorene with p-nitro-benzaldehyde to prepare p-nitrobenzal-9-fluorene oxide.



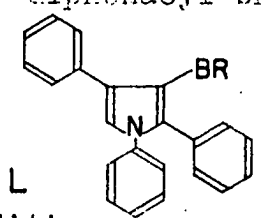
XLIX

Several basic reagents have been used to effect the Darzens reaction. Sodium and a drop of alcohol was employed by Erlenmeyer (1), while Darzens investigated the scope of the reaction with sodium ethoxide. In recent years, sodium methoxide (39,40), sodium amide (66), sodium hydride (67), diisopropylamino magnesium bromide (68), and potassium t-butoxide (69) have been employed. Johnson, et al (70), have compared the effectiveness of potassium t-butoxide and sodium ethoxide, and have found potassium t-butoxide to be the superior reagent. Widman (35) has discovered sodium hydroxide to be effective in condensing α-chloroacetophenone with benzaldehyde, and most of the chloroform condensations (52-62) have been carried out with this reagent. Potassium carbonate has also seen limited use as a condensing agent (63).

The stereochemistry of the Darzens reaction has not received extensive study. The early work by Fritz (28), Paal (29,30), Widman (31), and Kleucker (63) have demonstrated that both cis and trans isomers are formed in the reaction. The work on the α-and β-diphenacyl halides by Widman (31) and Berson (32) has also indicated a base-catalyzed isomerization of the epoxy-compounds under the conditions of the reaction. Berson has found a ratio of 8α-to 5β-diphenacyl bromides, when α-bromoacetophenone is treated with one mole of sodium ethoxide, and only the β-

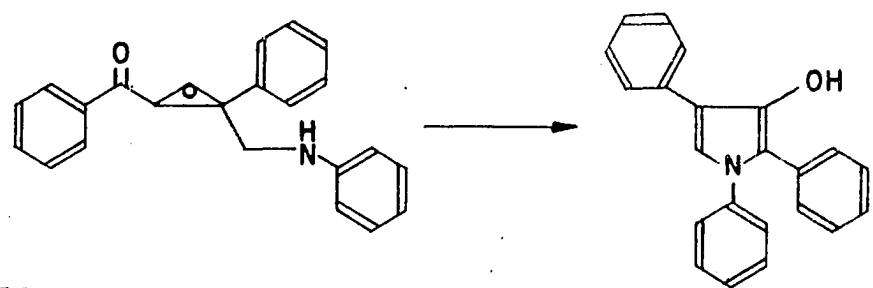
isomer when excess sodium ethoxide is used.

The first Darzens products to be extensively studied stereochemically were the α-and β-diphenacyl bromides. Wasserman and Brous (71) investigated the stereochemistry of these epoxyketones by employing a stereospecific reaction that was developed by Widman (31). Widman had discovered that α-diphenacyl chloride and α-diphenacyl bromide were converted to 3-halo-1,2,4-triphenylpyrrole by aniline, whereas the β-isomers under the same conditions yielded 3-hydroxy-1,2,4-triphenylpyrrole. Wasserman and Brous repeated the Widman reaction on α-diphenacyl bromide under milder conditions and isolated 3-bromo-1,2,4-triphenyl-pyrrole (L). The β-diphenacyl bromide,



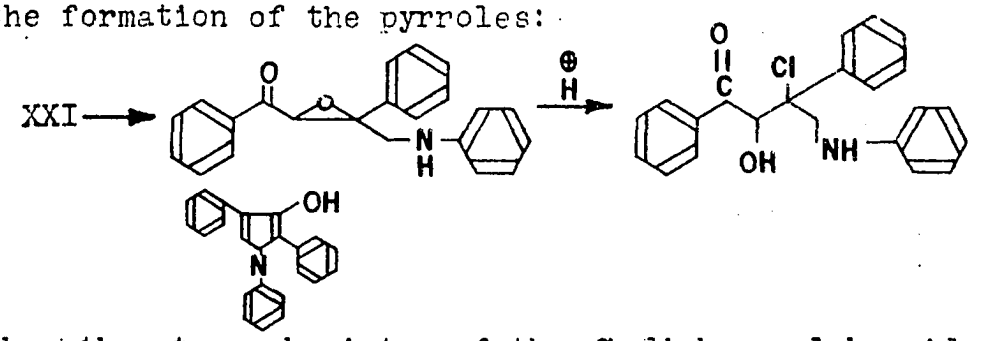
L

under identical conditions, was converted to an anilino derivative (LI), which on acid treatment at room temperature was converted into 3-hydroxy-1,2,4-triphenylpyrrole.

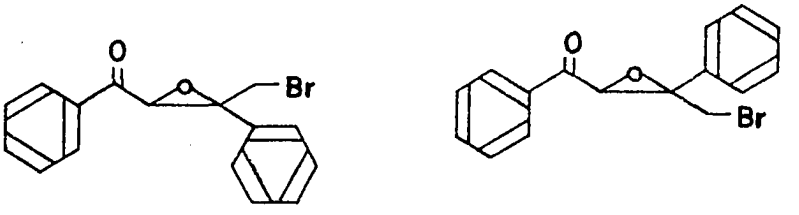


LI

Thus the α-diphenacyl bromide must have a cis arrangement of the bromomethylene and benzoyl groups to facilitate the formation of the pyrrole, wheras the β-isomer must have the trans arrangement. Opening of the epoxide would allow the formation of the pyrroles:



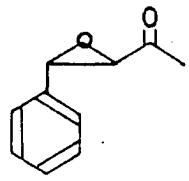
Thus the stereochemistry of the α-diphenacyl bromide (LII) and β-diphenacyl bromide (LIII) must be the following:



LII LIII

The stereochemistry of the α-and β-diphenacyl halides was also studied independently by Stevens and Traynelis (72), and they verified the assignments of configuration made by Wasserman and Brous.

In recent years, Kwart and Kirk (40) have investigated the stereochemistry of 4-phenyl-3,4-epoxy-2-butanone (LIV), and they have discovered the Darzens reaction between benzaldehyde and α-chloroacetone to give exclusively the trans-glycidic ketone.



LIV

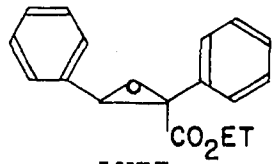
The steric arrangement was proven by the reduction of transbenzalacetone with lithium aluminum hydride followed by oxidation of the olefin (LV) by perbenzoic acid to 4-phenyl-3,4-epoxy-2-butanol (LVI).

LV LVI

The epoxy-alcohol (LVI) proved to be identical with the product obtained by sodium borohydride treatment of the Darzens product (LIV).

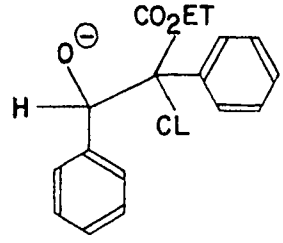
Dahn and Loewe (73) have also reported the exclusive formation of the trans isomer in the condensation of m-nitrobenzaldehyde with ethyl α-chloroacetate. The Darzens product, ethyl β-(m-nitrophenyl)- α,β-epoxypropionate was shown to have the trans arrangement by stereospecific synthesis: additions of hypobromous acid to ethyl trans-m-nitrocinnamate followed by elimination of hydrobromic acid.

Zimmerman and Ahramjian (74) have discovered the stereochemistry of α,β-diphenyl-α,β-epoxypropionate to have a cis arrangement of the diphenyl groups (LVII). Since both threo and erythro isomers of ethyl 2-chloro-3-hydroxy-2,3-diphenylpropionate give the same product, Zimmerman has



LVII

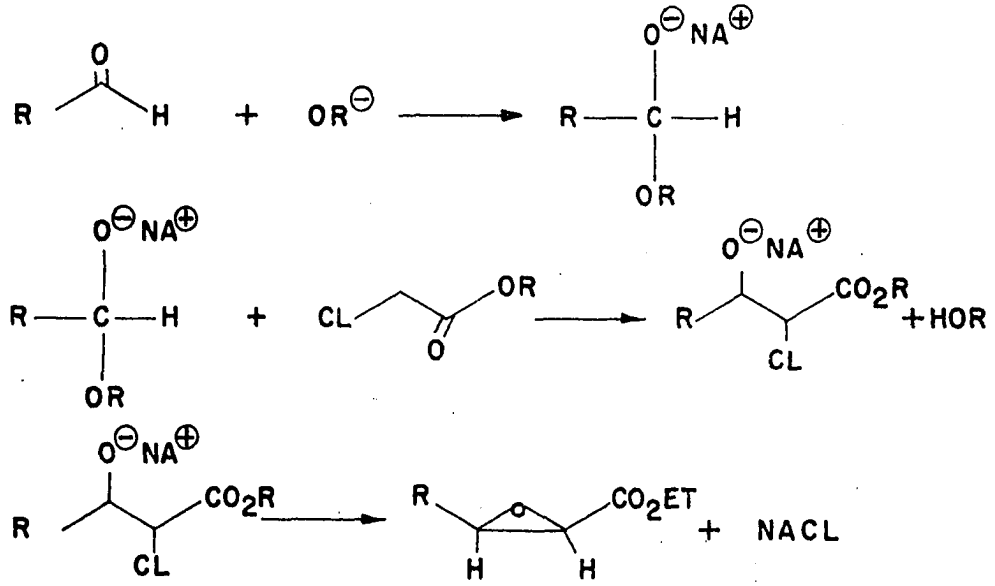
concluded that the stability of the aldol intermediate (LVIII) anion determines the stereochemistry of the reaction:



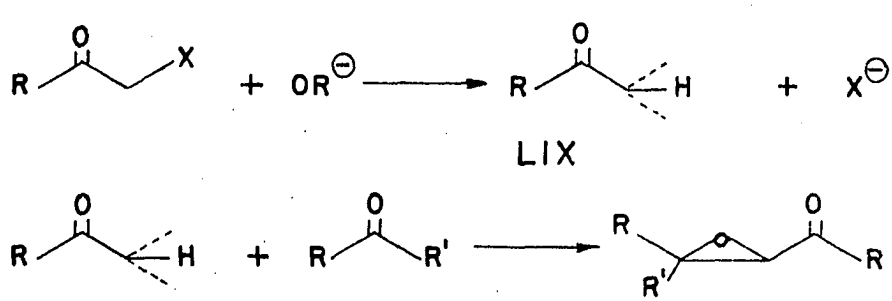
LVIII

Since the Darzens reaction was first discovered in 1892, several mechanisms have been proposed to explain the reaction; most of these may be conveniently summarized as four distinct mechanisms: 1) the displacement mechanism, 2) the bivalent radical or carbene mechanism, 3) the ketyl mechanism, and 4) the enolate anion mechanism.

The displacement mechanism was first proposed by Erlenmeyer (1) and later by Claisen (66); the mechanism involved the addition of the alkoxide ion to the carbonyl component, which is then displaced by the haloester:



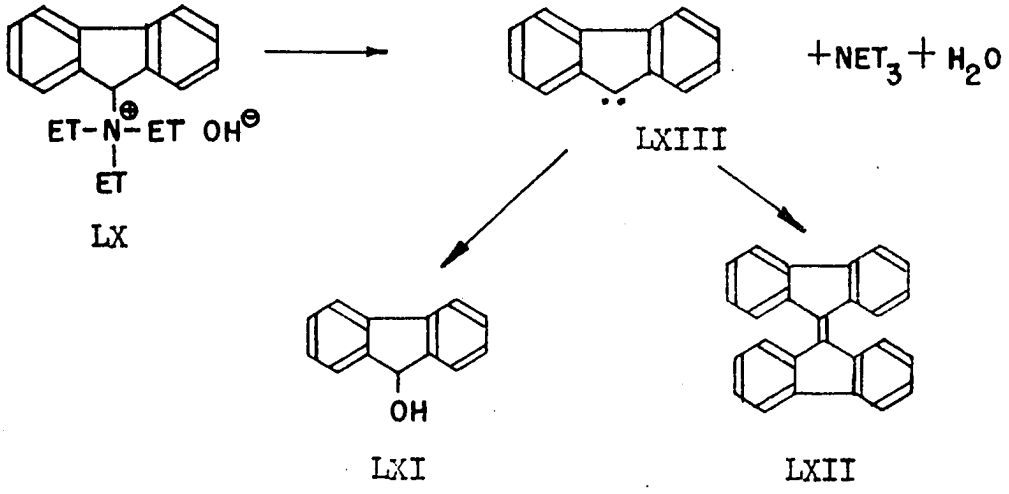
The bivalent radical or carbene mechanism was theoretically conceived by Nef (75) in 1897, and employed by Bodforss (36,37) in 1918 to explain the condensations of α-haloacetophenones with carbonyl compounds. The first step in this mechanism involves the α-elimination of hydrogen halide acid to form a bivalent radical or carbene (LIX) followed by addition of the bivalent radical to the carbonyl component:



LIX

In recent years, the bivalent radical or carbene mechanism has received experimental support from Ingold and Hine.

Ingold and Jessop (76) have pyrolyzed triethyl fluoryl ammonium hydroxide (LX), and they have isolated 9-hydroxy-fluorene (LXI) and difluoryl-ethylene (LXII). They proposed the mechanism to be an α-elimination producing a six-electron intermediate (LXIII) that either combines with itself or adds water:



Hine (77) has studied the kinetics of the base-catalyzed hydrolysis of chloroform, and has proposed a carbene mechanism for the reaction:

$$HCCl_3 + OH^{\ominus} \longrightarrow {}^{\ominus}CCl_3 + H_2O$$

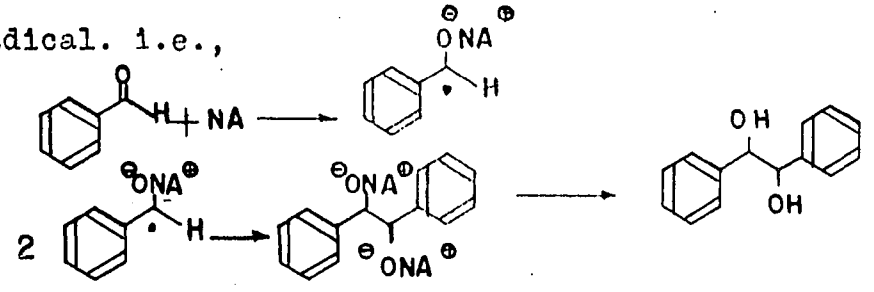
$$C^{\ominus}Cl_3 \longrightarrow :CCl_2 + Cl^{\ominus}$$

$$:CCl_2 + OH^{\ominus} \longrightarrow CO + HCO_2^{\ominus}$$

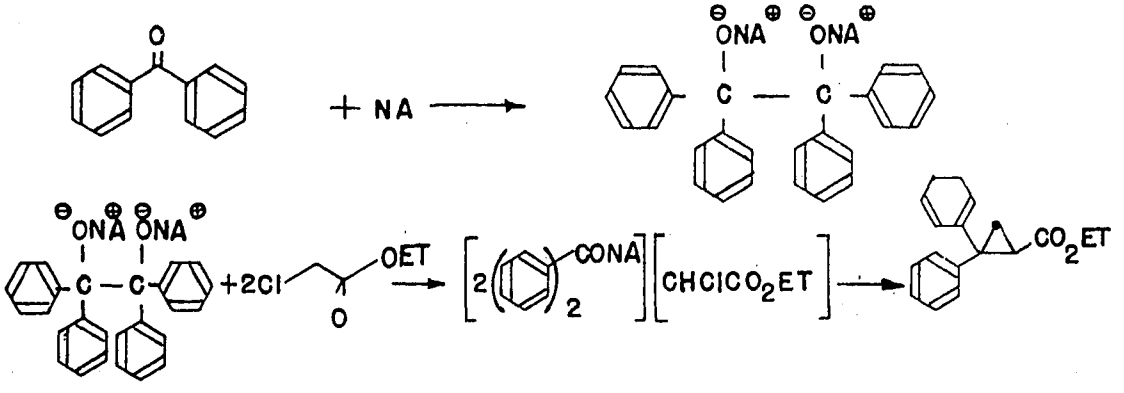
The carbene mechanism for the hydrolysis of chloroform has received support from the work of Sakamoto (78); he has investigated the rate of deuterium exchange of chloroform in base, and has found the rate of exchange to be faster than the rate of hydrolysis which is consistent with the

mechanism proposed by Hine.

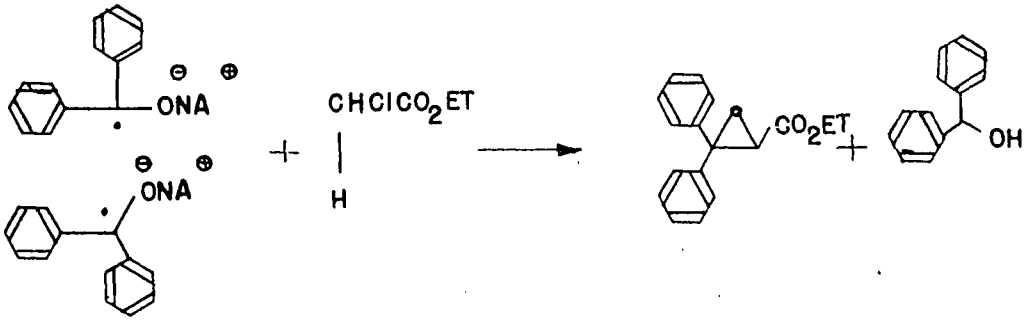
The ketyl mechanism was first proposed by Blicke (79) in 1924 to explain the reaction of benzaldehyde with sodium to afford hydrobenzoin. The mechanism comprises a one electron transfer from sodium to benzaldehyde forming the benzyl radical which then combines with another benzyl radical. i.e.,



Fourneau and Billeter (80) in 1939 extended the ketyl mechanism to the Darzens reaction in explaining the condensation between diphenyl ketone and ethyl α-chloroacetate. The mechanism comprises two separate reactions occurring simultaneously. One reaction involves the formation of the sodium salt of hydrobenzoin which complexes with ethyl α-chloroacetate:

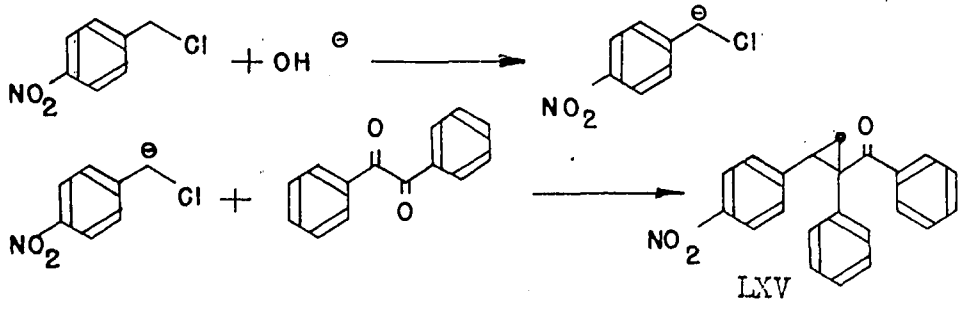


The intermediate complex then combines to form the epoxide. The second reaction involves two molecules of the intermediate benzhydryl free radical (LXIV) combining with a molecule of ethyl α-chloroacetate to form the glycidic ester and benzhydryl alcohol:



LXIV

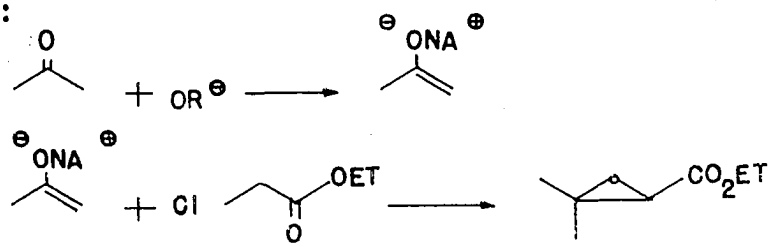
The enolate anion mechanism was proposed by Hahn (65) in 1929 to explain the condensation of p-nitrobenzyl chloride with benzil to yield 1,2-diphenyl-3-(p-nitrophenyl) -2,3-epoxy-1-propanone (LXV). The mechanism involves the formation of the carbanion reagent and displacement of halide ion:



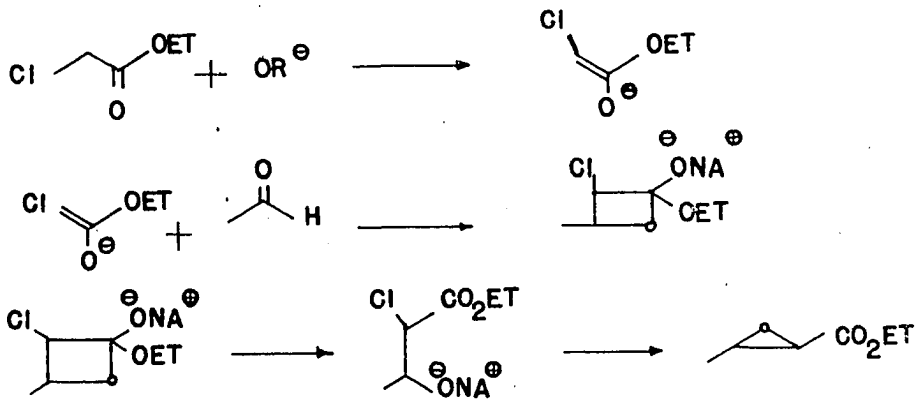
LXV

Since the initial proposal of the enolate anion mechanism, several investigators have proposed various modifications of the mechanism. In 1931, Rutowski and Dajew (81) proposed

the formation of the enolate anion of the carbonyl component in the condensation of acetone with ethyl α-chloroacetate:

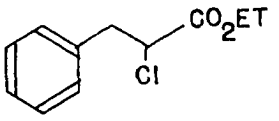


The formation of the enolate anion of ethyl α-chloroacetate was proposed by Scheibler and Tutundzitach (82) in the condensation of ethyl α-chloroacetate with acetaldehyde:



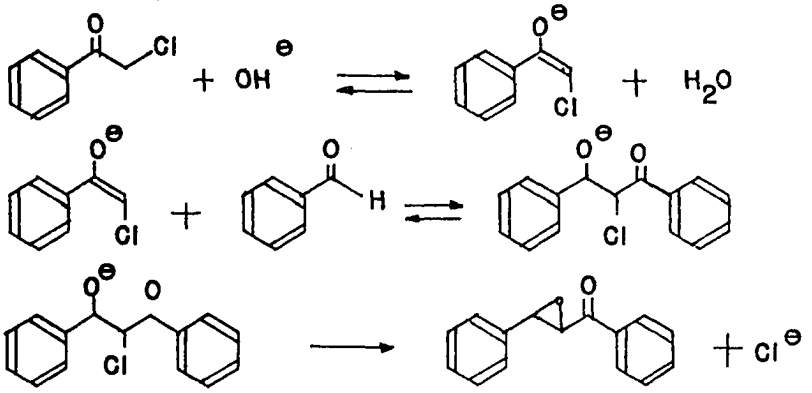
The enolate anion of ethyl α-chloroacetate has been shown to exist in basic solutions, since Newman and Magerlein (83) have synthesized ethyl α-chlorohydrocinnamate (LXVI) bh the alkylation of ethyl α-chloroacetate with benzyl chloride. Newman has also reported that 79% of the theoretical amount of ammonia is evolved when an ether solution of ethyl α-chloroacetate is treated with sodium amide, thus giving additional evidence for the existence of

the enolate anion under Darzens reaction conditions.

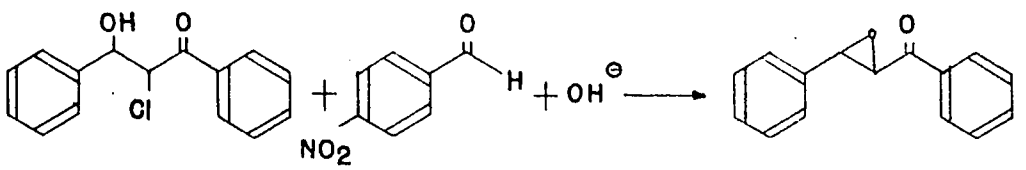


LXVI

Recently, the dinetics of the Darzens reaction between α-chloroacetophenone and benzaldehyde have been reported by Ballester and Bartlett (84). The reaction was discovered to be third order with the rate-determining step including benzaldehyde, α-chloroacetophenone, and hydroxide ion, and the investigators have proposed the following scheme for the reaction:

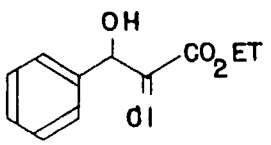


Ballester (85) has demonstrated the oxirane ring formation to be faster than the reverse aldol step, by the base treatment of 1,3 diphenyl-2-chloro-3-hydroxy-1-propanone (LXVII) in the presence of p-nitrobenzaldehyde; the reaction led to 1,3-diphenyl-2,3-epoxy-1-propanone (LXVIII), and not a trace of 1-phenyl-3-(p-nitrophenyl)-2,3-epoxy-1-propanone.



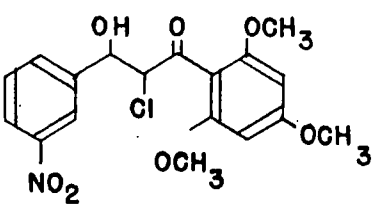
LXVII LXVIII

In recent years, the enolate anion mechanism has received additional proof by the isolation of the intermediate halohydrins. Munch - Peterson (66) has isolated ethyl 2-chloro-3-hydroxy-3-phenylpropionate (LXIV) in the condensation of ethyl α-chloroacetate with benzaldehyde.



LXIX

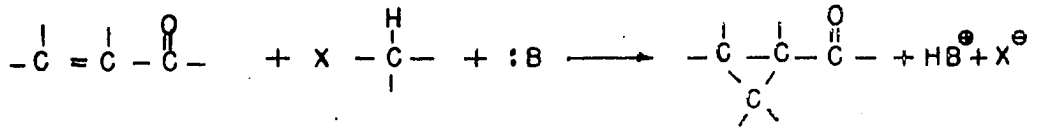
Ballester (86) has also isolated the chlorohydrin, 1-(2,4,6-trimethoxyphenyl)-3-(m-nitrophenyl)-2-chloro-3-hydroxy-1-propanone (LXX), in the condensation of m-nitrobenzaldehyde with α-chloro-(2,4,6-trimethoxy)-acetophenone. Ballester has also shown the intermediate chlorohydrin to afford a quantitative yield of epoxy-ketone on treatment with base.



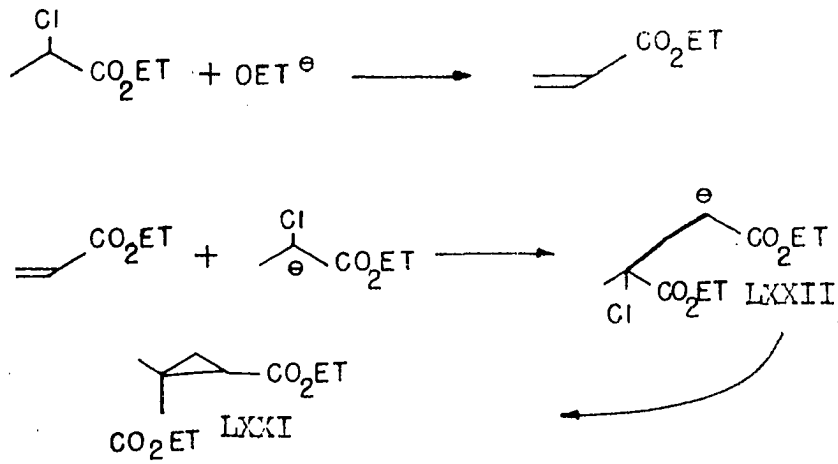
LXX

The Vinylogous Darzens Reaction

The vinylogous Darzens reaction may be defined as the condensation of a halomethylene compound with an α,β unsaturated aldehyde or ketone in the presence of base to yield a cyclopropane ring by the elimination of halide ion, i.e.,

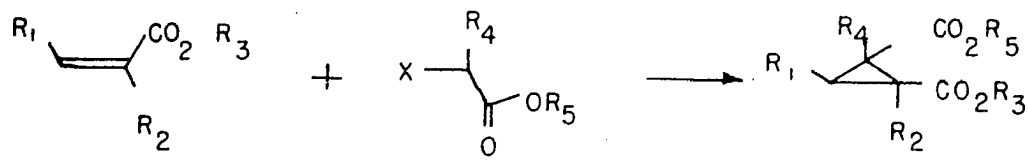


The vinylogous Darzens reaction has not received extensive investigation as in the case of the Darzens reaction; in fact, the earlier work by Darzens (9), Heilbron (15), Linnell and Shen (16), and Kleucker (63) had cast doubt on the existence of such a reaction. In recent years, however, the vinylogous Darzens reaction has received support from the investigations of Deutsch and Buchman, and McCoy. Deutsch and Buchman (87) have discovered the formation of 1-methyl-1,2-dicarboethoxy-cyclopropane (LXXI), when ethyl α -chloropropionate was treated with sodium ethoxide, The reaction was rationalized on the assumption that elimination of hydrogen chloride had yielded ethyl acrylate, which had been attacked by the enolate anion of ethyl α -chloropropionate in a Michael reaction and the resulting new enolate anion (LXXII) had displaced chloride to form the cyclopropane ring, i.e.,



The assumption was supported by the experimental fact that ethyl acrylate condensed with ethyl α-chloropropionate to yield 1-methyl-1,2-dicarboethoxycyclopropane in high yield.

In recent years, McCoy (88) has synthesized several 1,2-dicarboethoxylcyclopropanes (LXXIII) by the condensation of α,β-unsaturated esters with α-haloesters:



LXXIII

LXXIII

a) R_1=hydrogen
R_2=hydrogen
R_3=methyl
R_4= hydrogen
R_5=ethyl

b) R_1=hydrogen
R_2=hydrogen
R_3=methyl
R_4=methyl
R_5= methyl

c) R_1=hydrogen
R_2=methyl
R_3=ethyl
R_4=hydrogen
R_5=ethyl

a) X = chloro or bromo b) X = chloro c) X = chloro

d) R_1=hydrogen
R_2=methyl
R_3=ethyl
R_4=methyl
R_5=methyl
X =chloro

e) R_1=methyl
R_2=hydrogen
R_3=ethyl or methyl
R_4=hydrogen
R_5=ethyl
X =chloro

f) R_1=methyl
R_2=hydrogen
R_3=ethyl
R_4=methyl
R_5=methyl
X =chloro

The reaction was shown to be general for both α-and β-substituted acrylic esters; the only α,β-unsaturated ester that would not condense was ethyl fumarate. McCoy has investigated the stereochemistry of the cyclopropyl compounds by comparing them with cyclopropane-1,2-dicarboxylic acids of known configuration. He has discovered the cis isomer to be present in the highest yield in most cases.

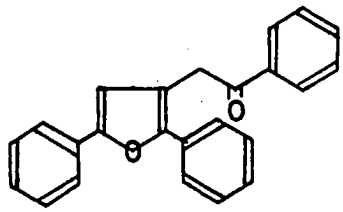
The reaction of α,β-unsaturated esters with α-haloesters was employed by Mousseron and Fraisse (89) synthesis of 1-isopropyl-1,2-dicarboethoxycyclopropane, and 1-ethyl-1,2-dicarboethoxycyclopropane; they prepared the cyclopropane compounds by the condensation of ethyl acrylate with ethyl 2-bromo-3-methylbutanoate and ethyl 2-bromobutanoate, respectively.

Mousseron, et al., (90) have also investigated the condinsation of ethyl α-chloroacetate and ethyl α-bromo-

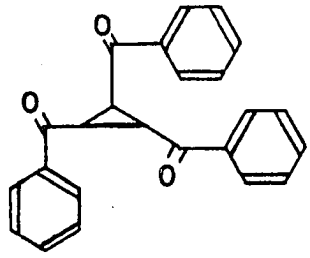
malonate with several α,β unsaturated compounds. The condensation of ethyl α-chloroacetate with ethyl acrylate was found to occur quite readily, however the condensation did not occur with acrolein, acrylonitrile, crotonaldehyde, and ethyl cinnamate. The α,β unsaturated esters, ethyl crotonate, ethyl α-methylacrylate, ethyl maleate, and ethyl fumarate, condensed with ethyl α-chloroacetate to afford a low yield of the cyclopropane compounds. The α-haloester, ethyl α-bromomalonate, was found to condense with ethyl acrylate and acrylonitrile, but did not condense with ethyl crotonate, ethyl α-methylacrylate, and ethyl cinnamate. Mousseron, et al., also studied the condensation of ethyl α-bromomalonate with several α,β unsaturated aldehydes and ketones. The vinylogous Darzens reaction was found to occur in the condensation of ethyl α-bromomalonate with acrolein, crotonaldehyde, and methyl vinyl ketone, but failed with α-methylacrolein.

The first example of a vinylogous Darzens reaction was reported in 1903 by Paal and Schulze (91). In the synthesis of α-and β-diphenacyl iodides by the self-condensation of α iodo-acetophenone, Paal and Schulze isolated a small amount of high melting solid which analyzed for $C_{24}H_{18}O_3$. Due to the facts that the compound did not reduced potassium permerganate, and yielded 2,5-diphenyl-3-phenacylfuran (LXXIV) upon zinc reduction followed by acid

treatment, Paal and Schultze proposed the structure to be 1,2,3-tribenzoyl-cyclopropane (LXXV).

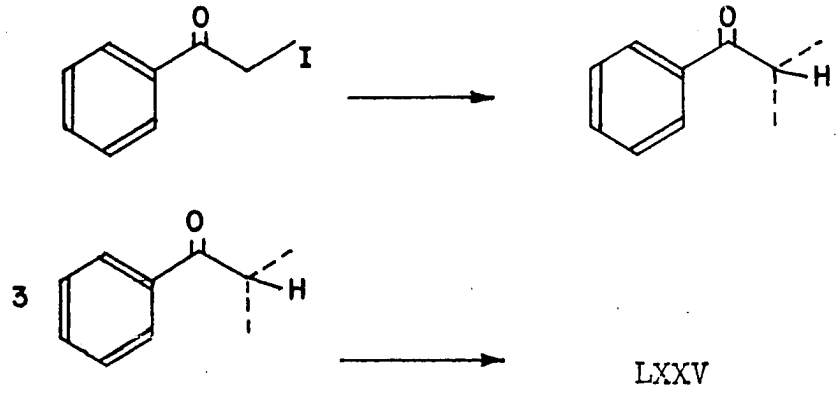


LXXIV



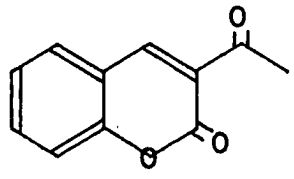
LXXV

The mechanism of the reaction was postulated by Paal and Schultz to be comprised of a bivalent radical that combines with two other bivalent radicals:



LXXV

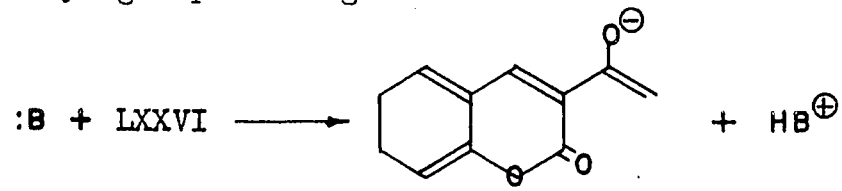
In 1918 Widman (92) investigated the condensation of the $\alpha\beta$ unsaturated ketone, 3-acetylcoumarin (LXXVI), with α-haloacetophenone. Widman (93) began his study of 3-acetylcoumarin in 1902, when he investigated the effect of



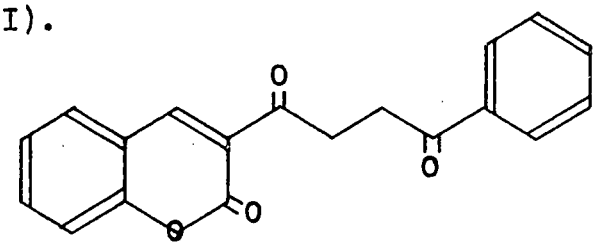
LXXVI

sodium hydroxide and other bases on 3-acetylcoumarin.

In the course of his investigation, he postulated that base reacts with 3-acetylcoumarin by removing the α-hydrogen of the acetyl group forming the enolate anion:



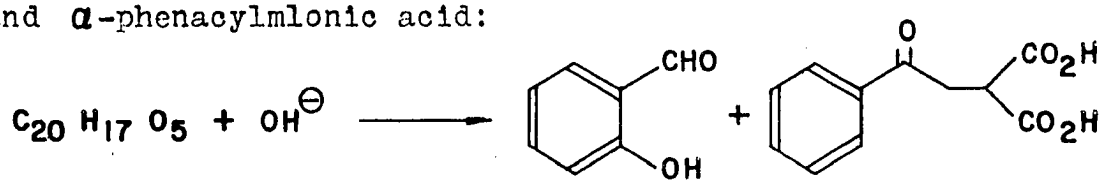
In order to prove his postulate, Widman attempted to alkylate basic solutions of 3-acetylcoumarin with alkyl halides. Widman (92) began his alkylation studies by treating a sodium hydroxide solution of 3-acetylcoumarin with ethyl iodide; the alkylation failed and 3-acetylcoumarin was recovered unchanged. The alkylation was then tried with α-chloroacetone and Widman found that he could not isolate any recognizable products. Widman then employed α-bromo- and α-chloroacetophenone in the presence of sodium ethoxide, and found the alkylation to proceed smoothly to lead to a compound whose composition corresponded to the phenacyl derivative of the enolate anion of 3-acetylcoumarin (LXXVII).



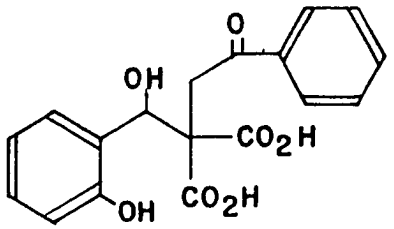
LXXVII

It soon became evident that this structure could not be correct, since potassium pernanganate was not reduced, even

under refluxing acetone conditions, and the iodoform test was positive, At approximately the same time, Widman (94) extended the reaction by condensing 3-carboethoxycoumarin with α-bromoacetophenone, and he isolated a product similar to the 3-acetylcoumarin condensation product, a $C_{20}H_{17}O_5$ compound. Degradation of this compound by sodium hydroxide hydrolysis gave two recognizable fractions, salicylaldehyde and α-phenacylmlonic acid:

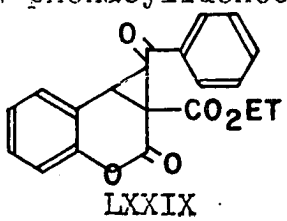


A $C_{18}H_{16}O_7$ compound (LXXVIII) was also isolated from the hydrolysis which was assumed to be the precursor of salicylaldehyde and α-phenacylmalonic acid, namely:



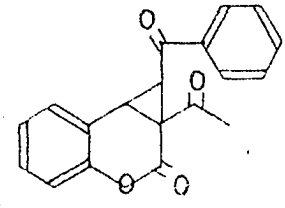
LXXVIII

Based on the results of the hydrolysis and the fact that potassium permanganate was not reduced, Widman deduced the structure of the 3-carboethoxycoumarin condensation product to be 3-carboethoxy-3,4-phenacylidenecoumarin (LXXIX).



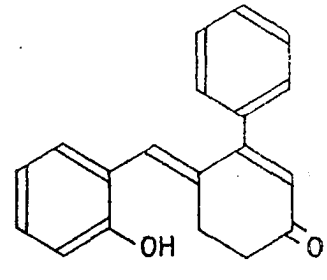
LXXIX

In like manner, the condensation product of 3-acetylcoumarin with α-chloroacetophenone was suggested to be 3-acetyl-3,4-phenacylidenecoumarin (LXXX).



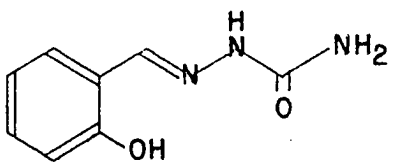
LXXX

The chemistry of 3-acetyl-3,4-phenacylidenecoumarin was shown by Widman (95) to be quite interesting. Hydrolysis of 3-acetyl-3,4-phenacylidenecoumarin with 10% sodium hydroxide led to a $C_{18}H_{14}O_2$ compound which was assigned the structure of 3-phenyl-4-(o-hydroxybensal)-2-cyclopenten-1-one (LXXXI). Widman discovered that 3-acetyl-3,4-phenacylidenecoumarin did not react normally with the carbonyl reagents hydroxylamine hydrochloride, semicarbazide hydrochloride, and hydrazine hydrochloride, since only a monoxime and mono-semicarbazone could be prepared. Since the oxime of 3-acetyl-3,4-phenacylidenecoumarin gave a positive iodoform test, Widman proposed that the aromatic ketone may have reacted, thus leaving the acetyl linkage intact.



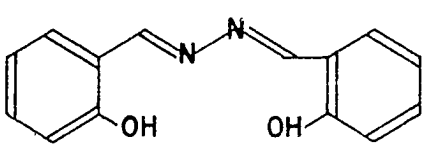
LXXXI

Widman attempted to prepare the disemicarbazones of the coumarin compound by refluxing an acetic acid solution of the compound with two moles of semicarbazide hydrochloride. However extensive degradation of the molecule led to the semicarbazone of salicylaldehyde (LXXXII). Widman found the



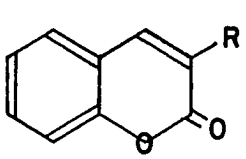
LXXXII

same type of degradation to occur with hydrazine hydrochloride, since a solution of the compound with two moles of hydrazine hydrochloride produced salicylidene azine (LXXXIII)



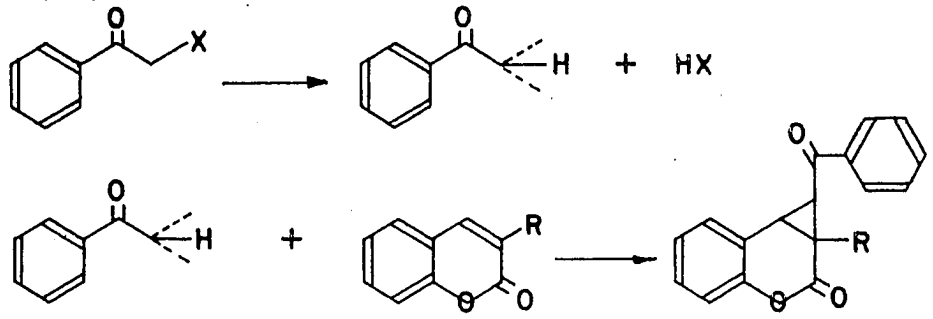
LXXXIII

The scope of the reaction of α,β-unsaturated ketones with phenacyl halides was investigated by Widman (96). He found the reaction to be applicable only to a limited number of ketones. The reaction succeeded for 3-acetyl-, 3-benzoyl-, 3-propionyl-, 3-cyano-, 3-carboethoxy-, and 3-carbomethoxy-coumarins:

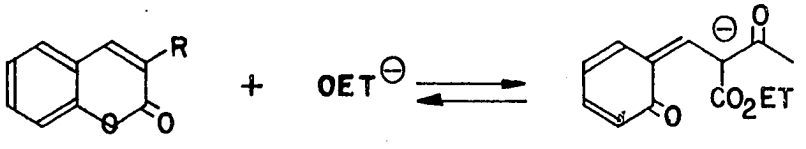


R = acetyl, benzoyl, propionyl, cyano, barboethoxy, carbomethoxy.

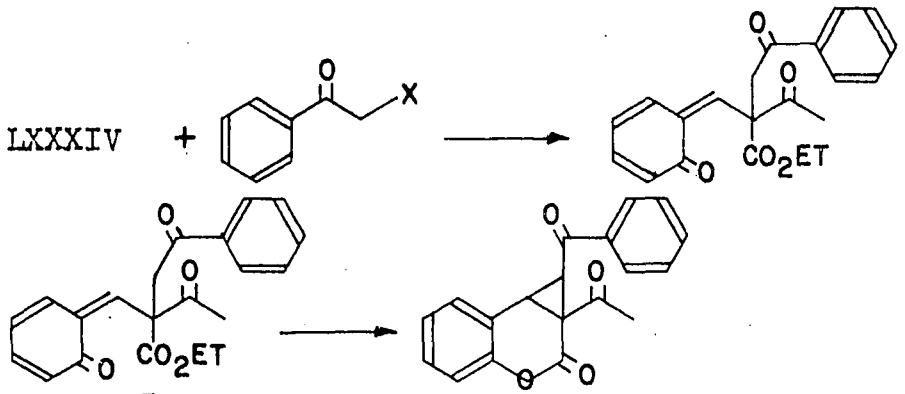
The reaction did not succeed for coumarin, 3-methyl-, 3-phenyl-, and 4-carboethoxycoumarin. On the basis of this evidence Widman first believed the reaction to proceed by a bivalent radical adding to the ethylene linkage of the 3-acylcoumarin.



Widman (96) tested his hypothesis by condensing several substituted ethylenes, ethyl fumarate, ethyl maleate, ethyl 2,3-dicarboethoxymaleate, ethyl benzalacetoacetate, ethyl benzalmalonate, ethyl o-ethoxybenzalacetoacetate, and ethyl p-methoxybenzalacetoacetate, with α-chloroacetophenone. However, none condensed. As a consequence, the bivalent radical mechanism was discarded in favor of the following mechanism (96). His scheme involved opening of the lactone with base to the o-quinoid structure (LXXXIV), internal displacement of halide and recyclization to a coumarin system:



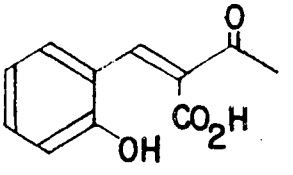
LXXXIV



In the course of his investigation of the scope of the reaction, Widman (94) condensed several substituted phenacyl halides with 3-acylcoumarins. Widman prepared 3-acetyl-3,4-anisylidenecoumarin, 3-benzoyl-3,4-anisylidenecoumarin, and 3-carboethoxy-3,4-anisylidenecoumarin by condensing 3-acetyl-,3-benzoyl-, and 3-carboethoxycoumarin with α-chloro-p-methoxyacetophenone. The phenacyl halides, α-chloro-o-methoxyacetophenone, α-bromo-m-nitroacetophenone, and 1-(α-chloroacetyl)-napthalene, were also discovered to condense with 3-acylcoumarins. Widman prepared 3-acetyl-3,4-(o-methoxyphenacylidene)-coumarin, and 3-acetyl-3,4-napthacylidenecoumarin by the condensation of 3-acetylcoumarin with α-chloro-o-methoxyacetophenone and 1-(α-chloroacetyl)-napthaline. He also prepared 3-carboethoxy-3,4-(n-nitrophenacylidene)-coumarin by the condensation of 3-carboethoxycoumarin with α-bromo-m-nitroacetophenone.

The reaction between 3-acylcoumarins and phenacyl halides remained dormant until 1938, when Bodforss (97)

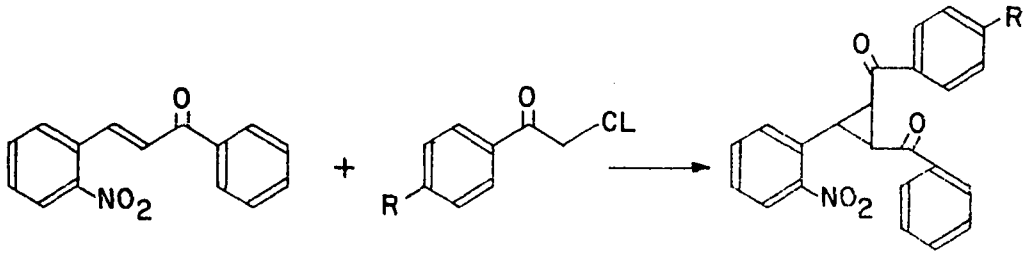
refuted the mechanism proposed by Widman. Bodforss rejected the existence of the o-quinoid structure (LXXXIV) proposed by Widman, and supported his claim by three experimental facts. Firstly, the o-quinoid structure is a ketone derivative and would be expected to polymerize in the presence of oxygen, whereas alkaline solutions of 3-acetylcoumarin were shown to be stable to air. Secondly, conductance studies on alkaline solutions of 3-acetylcoumarin showed the existence of a moderately strong acid having a pK_a of this value, the acidity may be due to the formation of 3-acetyl-coumarinic acid (LXXXV).



LXXXV

Thirdly, the ultraviolet spectrum of an alkaline solution of 3-acetylcoumarin is almost identical with the spectrum of an alkaline solution of o-hydroxybenzalacetone, thus indicating the opening of the lactone to form 3-acetyl-coumarinic acid. Since Bodforss could not find any experimental evidence to support the o-quinoid structure, he rejected Widman's claim that the coumarin lactone was required for the formation of the cyclopropyl ring. Bodforss contended that any α,β unsaturated carbonyl system should

react with phenacyl halides, and he supported his proposal by synthesizing 1-(o-nitrophenyl)-2,3-dibenzoylcyclopropane ($LXXXVI_a$) and 1-(o-nitrophenyl)-2-benzoyl-3-(p-methoxybenzoyl)-cyclopropane ($LXXXVI_b$) by condensing o-nitrobenzalacetone with phenacyl chloride and α-chloro-p-methoxyacetophenone. Bodforss then attempted to extend the



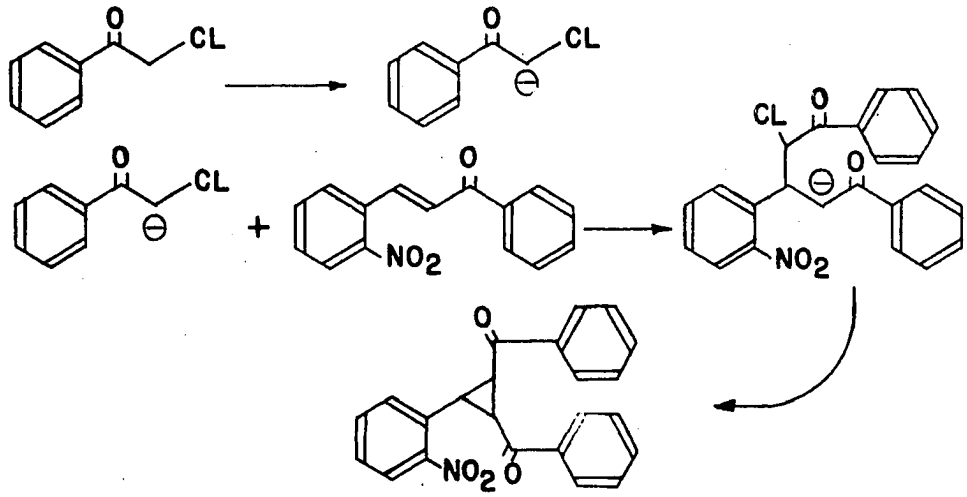
$LXXXVI_a$) R = hydrogen

b) R = methoxy

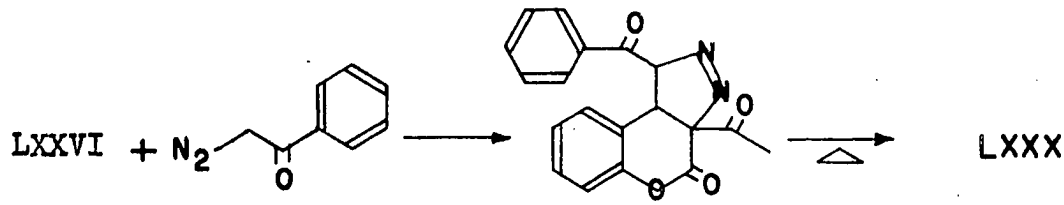
reaction to several α,β-unsaturated carbonyl compounds such as benzalacetophenone, cinnamlacetophenone, dibenzalacetone, ethyl p-nitrobenzalmalonate, 1,1-dibenzoyl-2-phenyl-ethylene, ethyl o-nitrocinnamate, di-m-nitrobenzalacetone, and carvone, but could not isolate crystalline products.

Bodforss then proposed the mechanism of the condensation of o-nitrobenzalacetophenone with phenacyl halides to consist of an enolate anion combining with the α,β-unsaturated ketone.

Earlier this year, Wawzonek and Morreal (98) reinvestigated the chemistry and constitution of 3-acetyl-3,4-phenacylidenecoumarin. The cyclopropane structure was

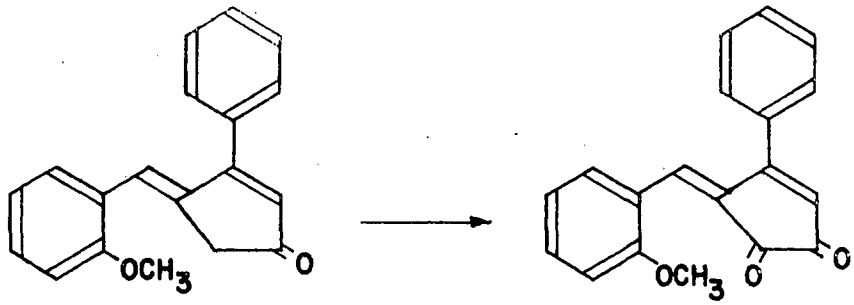


confirmed by synthesis from 3-acetylcoumarin and diazoacetophenone, the intermediate pyrazoline (LXXXVII) being pyrolyzed to give the cyclopropane ring:



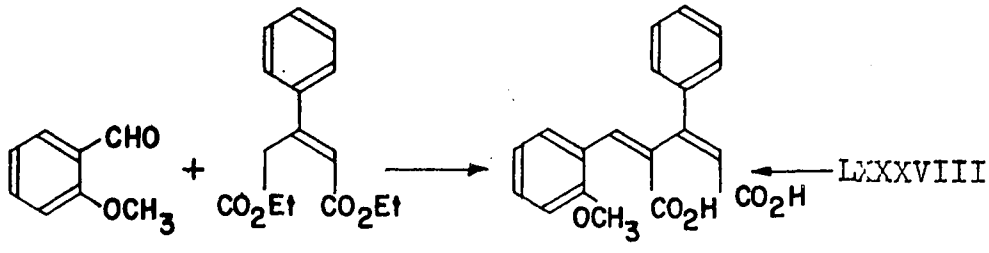
LXXXVII

The base catalyzed degradation of 3-acetyl-3,4-phenacylideneocoumarin was also reinvestigated by the University of Iowa chemists. Widman (95) had assigned the structure of the degraded compound to be 3-phenyl-4-(o-hydroxybenzal)-2-cyclopenten-1-one, and this assignment was shown to be correct by a series of chemical transformations. Wawzonek and Morreal converted the hydrolyzed product to its methyl ether by treating it with dimethyl sulfate and alkali. The methyl ether of the compound was then oxidized to the diketone (LXXXVIII) by selenivm dioxide:

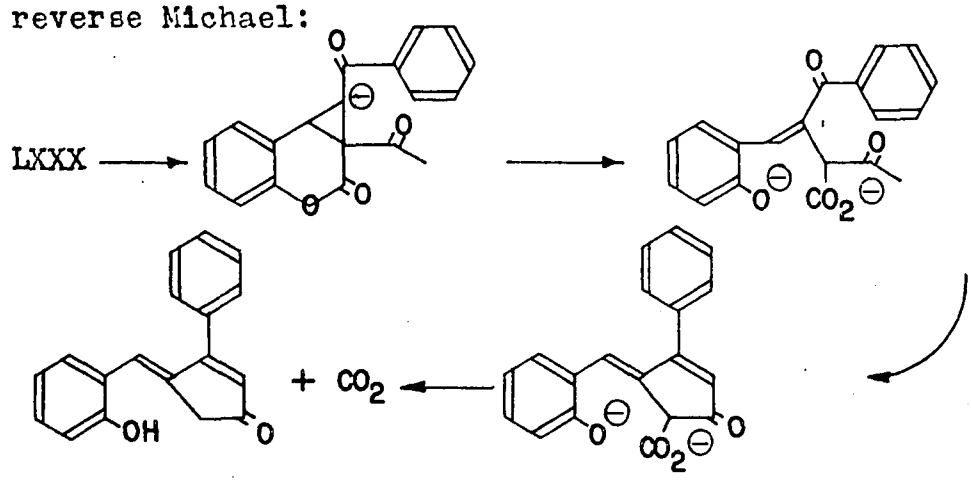


LXXXVIII

The diketone (LXXXVIII) was then oxidized by alkaline hydrogen peroxide to give β-phenyl-α-(o-methoxybenzal)-glutaconic acid (LXXXIX), which proved to be identical with a sample synthesized by the condensation of diethyl β-phenyl-glutaconate with o-methoxybenzaldehyde:

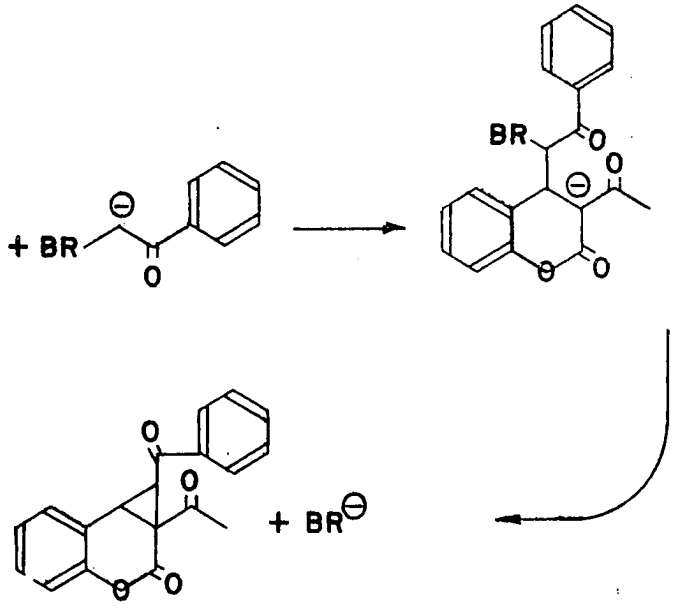


The effect of sodium hydroxide on 3-acetyl-3,4-phenacylideneecoumarin was proposed to consist of an abstraction of a proton from the α-carbon of the benzoyl group followed by a reverse Michael:



Wawzonek and Morreal reaffirmed the conclusions reached by Bodforss concerning the mechanism of the condensation of 3-acetylcoumarin with α-bromoacetophenone, and concluded the reaction to proceed by means of a vinylogous Darzens scheme:

LXXVI



DISCUSSION

The structure elucidation of 3-acetyl-3,4-phenacyliden-coumarin, as reported by Widman (92-96) required further investigation, since Widman employed non-specific oxidative and hydrolytic reactions in examining the structure of the coumarin compound. The bulk of the chemical proof rested on two facts, namely the inability of the coumarin to reduce potassium permanganate, and the hydrolysis of the compound to afford α-phenacylmalonic acid and salicylaldehydrate (94).

Although the Baeyer test for unsaturation has been found to be fairly reliable over the years, the test has been known to give anomalous results with certain unsaturated systems. The Baeyer test has been known to be upset by steric hindrance, since several tetra-substituted ethylenes give a negative test, and in recent years the test has been shown to be sensitive to the purity of the unsaturated substrate. Ipatieff, Thompson, and Pines (99) have reported the Baeyer test in acetone to be dependent upon the purity of the ethylene compound since a purified sample of α-pinene fails to reduce potassium permanganate, whereas an impure sample of the olefin affords a positive test. Thus the Baeyer test does not constitute a rigorous proof for the presence or absence of unsaturation, but only provides a qualified proof which must be supplemented by other more specific tests for unsaturation.

The hydrolysis of 3-acetyl-3,4-phenacylidenecoumarin to afford α-phenacylmalonic acid does not prove the existence of the cyclopropane ring, since several alternate structures could be visulized to hydrolyze to the same intermediate under strong base treatment. However, the isolation of α-phenacylmalonic acid does constitute proof of the attachment of the phenacyl group to carbon-3 in some manner, since the alkylation of carbon-3 during the hydrolysis would be very difficult to rationalize.

The cyclopropane structure for the coumarin compound also does not satisfy the experimental evidence concerning the formation of carbonyl derivatives with hydroxylamine hydrochloride and semicarbazide hydrochloride. Widman has established that the dioximes and disemicarbazones of the coumarin cannot be prepared. Since an examination of a model of the cyclopropane compound did not appear to exclude the formation of dicarbonyl derivatives, the proposed structure appeared in doubt.

The validity of the cyclopropane structure was also questionable on theoretical grounds, since the reaction of α-halomethylene compounds with α,β-unsaturated aldehydes and ketones has been shown to afford the Darzens product in most cases. Thus the occurrence of the vinylogous Darzens reaction in the condensation of 3-acetylcoumarin with α-haloacetophenone appeared doubtful.

The condensation of 3-acetylcoumarin with α-chloroacetophenone in the presence of sodium ethoxide was found to occur in exactly the same manner as described by Widman in 1918. The reaction was interesting in two respects. First, the ethanol solution of 3-acetylcoumarin and α-chloroacetophenone turned an orange-red color with every drop of sodium ethoxide solution, wherein the color would remain for one or two seconds and then disappear. Second, the reaction appeared to be very fast since the yield of the reaction was not altered by allowing the condensation to proceed for fifteen, thirty or sixty minutes. Spectroscopic investigation of the coumarin afforded interesting but inconclusive evidence concerning the structure of the compound. The infrared spectrum displayed three bands in the carbonyl region, namely a strong band at 5.75 μ, a moderate band at 5.88μ, and a sharp but weak band at 5.99μ. The 5.75μ band was tentively assigned to the lactone carbonyl, since coumarin and 3-acetylcoumarin are known to contain a similar band. The 5.88μ band was assigned to the saturated ketone, while the remaining 5.99μ band could be assigned to the aromatic ketone or another unknown functional group in the molecule. The cyclopropane structure is supported by certain aspects of the spectrum, but refuted by other aspects of the spectrum. The positions of the 5.88μ and 5.99μ bands for the cyclopropane structure are supported by the fact that cyclopropyl methyl ketone (100) and cyclopropyl phenyl

ketone (101) display 5.87μ and 5.96μ bands, respectively. However, the intensities of the bands involved are not consistent with the cyclopropane formulation. The intensities of carbonyl compounds have been found to be as characteristic of the carbonyl function as the position of absorption. Marion, Ramsay, and Jones (102) have investigated the intensity of several ketonic carbonyl groups in steroids, and showed these groups to possess molecular extinction coefficients between 350 and 1350, whereas the esters have an intensity range between 350 and 770. On this basis the cyclopropane structure seems not acceptable, since, in fact the magnitudes of the intensities of the ketones and the lactone are just reversed in the compound under consideration.

The ultraviolet spectrum of the coumarin disclosed that the 3-acetylcoumarin chromophore had been altered, since the condensation product showed absorption at $\lambda = 254 m\mu$ ($\epsilon = 15,600$) whereas 3-acetylcoumarin showed absorption at $\lambda = 298 m\mu$ ($\epsilon = 13,200$).

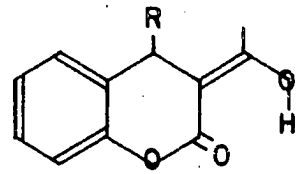
The chemical investigation into the structure of the coumarin compound was initiated on an oxidative and hydrolytic note. The original qualitative studies by Widman were repeated and completely verified in that the coumarin proved to be inert to potassium permanganate, but reacted readily with sodium hypoiodite to give an iodoform test. The oxidative reactions were supplemented by attempting to brominate the

coumarin. However, the compound was found to be unreactive, even if allowed to stand for twelve hours in the presence of the halogen. Since Widman had investigated the base-catalyzed hydrolysis of the coumarin, an acid-catalyzed hydrolysis was tried in the hope that the reaction would complement the basic hydrolysis, and thus give insight into the structure of the compound. However, the reaction did not succeed, since the coumarin was discovered to be inert to 5% sulfuric acid.

Since the oxidative and hydrolytic reactions were not very helpful in disclosing the structure, a reductive approach to the problem was attempted. The coumarin system was exposed to catalytic hydrogenation using 5% palladiumcharcoal as the catalyst, and the coumarin was found to take up two moles of hydrogen, and to be converted to a tetrahydro derivative analyzing for $C_{19}H_{18}O_4$. The infra-red spectrum of the product disclosed 2.8μ, 5.75μ bands and a shoulder at 5.84μ. Thus the 5.99μ band of the coumarin starting material had disappeared on hydrogenation, and a new hydroxyl peak at 2.8μ had appeared. However, the spectrum at 5.75-5.85μ was not resolved and therefore difficult to appraise. The ultraviolet spectrum revealed sparse information on the structure of the compound, since it was only characteristic of a benzenoid system.

The hydrogenated compound was then tested with ferric chloride, since it was conceivable that an acetoacetic ester

(XC) had been produced in the reduction.



R = C_8H_9O

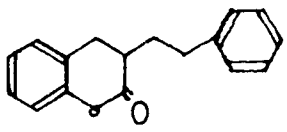
XC

The ferric chloride test afforded interesting but confusing information. When a chloroform solution of the compound was exposed to the reagent, a negative result was recorded, which however became positive when the solution was allowed to stand for ten or fifteen minutes. The test was further complicated by the fact that an almost instantaneous test was observed when a drop of pyridine was added to the ferric chloride solution.

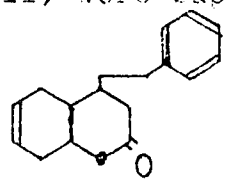
The tetrahydro compound was then exposed to an acetic anhydride-pyridine mixture in an attempt to acetylate the alcohol, but it readily decomposed. Acetylation without basic catalyst led to recovery of starting material.

On the assumption that the hydroxyl group of the reduced compound was benzylic and hence hydrogenolytically removable, the substance was exposed to further reduction. Its hydrogenation proceeded very sluggishly over a 72-hour period in which it was observed to absorb approximately one mole of hydrogen. The hydrogenation product analyzed for a $C_{17}H_{16}O_2$ compound indicating the loss of two carbon atoms and an oxygen atom. This suggested the loss of the acetyl group. Therefore,

The new product had to be either 3-(β-phenylethyl) dihydrocoumarin (XCI) or 4-(β-phenylethyl)-dihydrocoumarin (XCII). The two proposed structures (XCI and XCII) were supported by



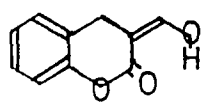
XCI



XCII

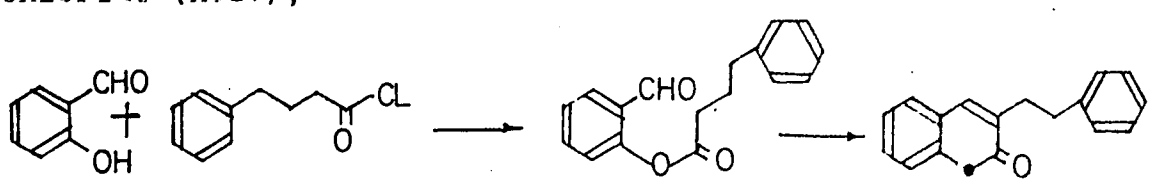
the infra-red spectrum of the compound since only a single carbonyl band at 5.70μ was observed.

In order to prove the structure of the hexahydro desacetyl compound, its synthesis was attempted. The lacitone (XCI) was believed to be the correct structure, since the infra-red spectrum of the tetrahydro precursor contained a 5.75μ band and a shoulder at 5.84μ, whereas the spectrum of 3-acetyldihydrocoumarin (XCIII), an acetyl system unsubstituted at carbon-3, contained only a single band at 5.98μ. The first approach to the synthesis was concerned with the



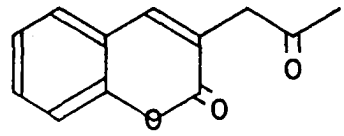
XCIII

esterification of salicylaldehyde with γ-phenylbutyryl chloride (XCIV),



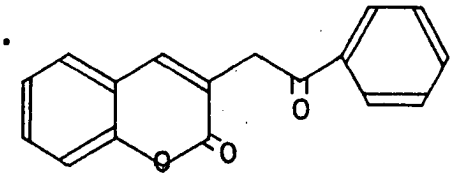
XCIV XCV XCVI

Perkin condensation of the resulting ester (XCV) into 3-(β-phenylethyl)-coumarin (XCVI), and hydrogenation of the latter. However, while the esterification reaction proceeded readily, the Perkin step did not succeed. Mostly starting material was recovered. An alternate scheme was modeled after the synthesis of 3-acetonyl-coumarin (XCVII) by Marrian and Russell (103). They had condensed salicylaldehyde with levulinic acid in the presence of sodium acetate and acetic anhydride. It appeared that simple substitution of levulinic



XCVII

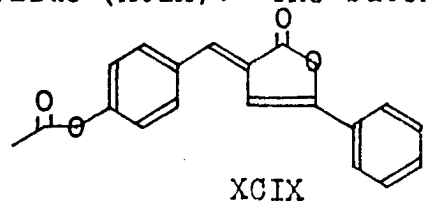
acid by β-benzoylpropionic acid should afford 3-phenaceyl-coumarin (XCVIII).



XCVIII

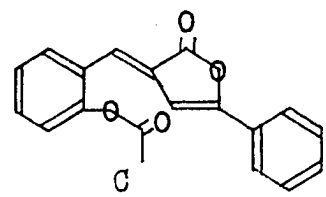
The condensation was tried and found to yield an orange compound analyzing as $C_{19}H_{14}O_4$. The product showed two carbonyl bands in the infra-red, a 5.60μ and 5.65μ band, and the ultraviolet spectrum of the compound revealed two maxima at 250mμ(log ε 4.56) and 395mμ(log ε 4.67). A survey of the literature concerning β-benzoylpropionic acid revealed that the condensation of aromatic aldehydes with this keto-acid had been extensively studied by Schueler and Hanna (104) and

Filler and Hebron (105). Schueler and Hanna had condensed a number of substituted aromatic aldehydes with β-benzoylpropionic acid, one of which was p-hydroxybenzaldyde which afforded an orange compound, α-(p-acetoxybanzal)-γ-phenyl-Δ,β,γ-butenolide (XCIX). The butenolide (XCIX) possessed



XCIX

an ultraviolet spectrum, two maxima at 252mμ(log ε 4.32)and 395mμ(log ε 4.49) that was almost identical with the spectrum of the compound obtained from the condensation of salicylaldehyde with β-benzoylpropionic acid: Thus the $C_{19}H_{14}O_4$ compound appeared to be α-(o-acetoxybenzal)-γ-phenyl-Δβγ-butenolide (C).

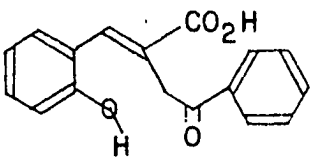


C

A chromatographic investigation of the mother liquor of the condensation revealed a yellow compound which analyzed as $C_{17}H_{12}O_3$. The compound contained a 5.80μ and a 5.95μ band in the infra-red, and a ultraviolet maximum at 272mμ (ε = 11,800). This indicated that this compound was the anticipated 3-phenacylcoumarin (XCVIII).

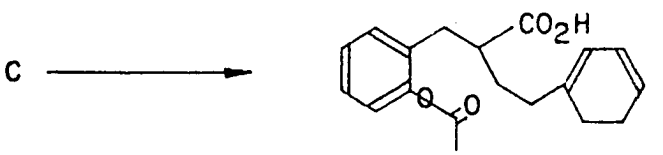
The chemistry of the butenolide was investigated to a limited extent. It was hydrolyzed by hydrobromic acid to 3-phenacylcoumarin. The hydrolysis of the compound with sodium

hydroxide was found to afford the ocumaric acid, α-phenacyl-o-hydroxycinnamic acid (CI).



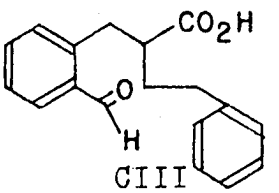
CI

The synthesis of the hexahydrodesacetyl degradation product (XCI) was then continued. Hydrogenation of the butenolide over 5% palladium-charcoal led to the carboxylic acid (CII). Hydrolysis of the latter by 48% hydrobromic acid gave a mixture of 3- β-phenylethyl-dihydrocoumarin (XCI)



CII

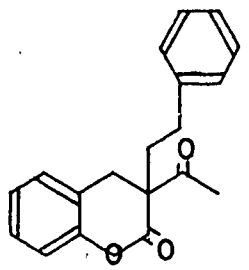
and α-β-phenylethyl-o-hydroxyhydrocinnamic acid (CIII), which afforded a lactone on acetic anhydride treatment. The



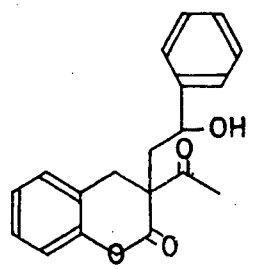
CIII

lactone, 3- (β-phenylethyl)-dihydrocoumarin, proved to be identical with the hexahydro-desacetyl product (XCI) obtained from two hydrogenations of 3-acetyl-3,4-phenacylidenecoumarin. This synthesis showed that in the initial alkylation of 3-acetylcoumarin by α-chloroacetophenone a new carbon-carbon bound had been formed at least at carbon 3.

While proof of the structure of the hexahydro product also settled the position of most substituents of its tetrahydroprecursor, it shed no light on the location of the latter's hydroxyl group. A modified hydrogenation of the tetrahydro compound, hydrogen and 5% palladium charcoal and five drops of sulfuric acid afforded an oil. Its infra-red spectrum, 5.75μ and 5.84μ bands indicated two carbonyl groups and hence could be assigned the keto-lactone structure (CIV).



CIV

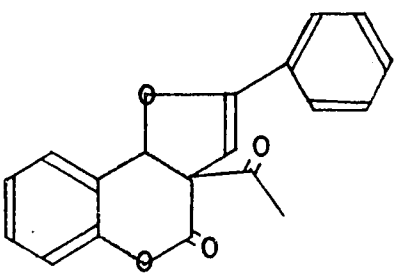


CV

Whereas structure (CV) seemed to fit the tetrahydro compound, three facts were not readily reconcilable with the formulation: a) the compound's surprizingly slow rate of hydrogenolysis, b) its unusual behavior toward ferric chloride and c) its decomposition during base-catalyzed acetylation. However, these data were not incompatible with alternate structure (CVIII), although its formation by hydrogenation of the Widman condensation product was not apparent. As a consequence, the cyclopropane formula (LXXX) of the latter was put in doubt.

Widman had postulated the condensation of 3-acetylcoumarin with α-chloroacetophenone to proceed by way of the o-quinoid

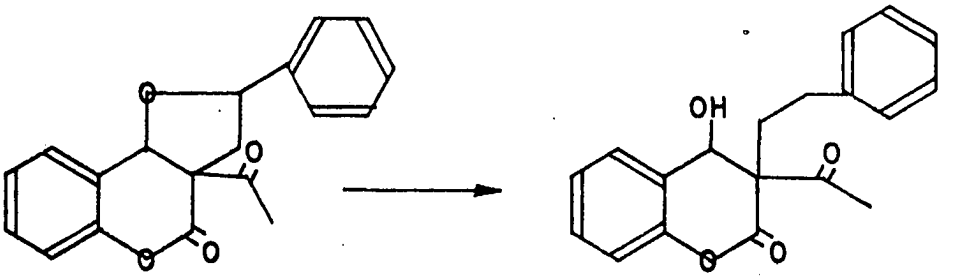
intermediate (LXXXIV). This mechanism seemed reasonable, since Widman discovered that the reaction did not occur in α,β unsaturated systems that did not contain the coumarin system. However, intramolecular base-catalyzed condensation of the quinonemethine (LXXXIV) with its own aromatic ketone side chain need not lead only to the cyclopropane structure (LXXX). The enol ether (CVI) is another likely reaction product.



CVI

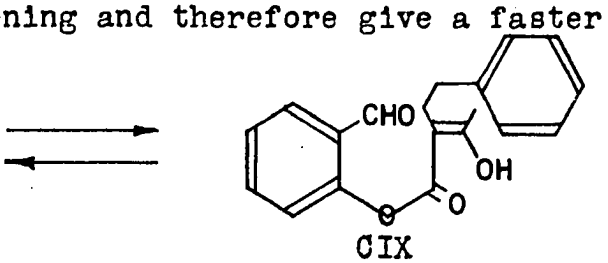
The enolether structure (CVI) in no way contradicted the experimental data of Widman or of the present hydrogenation work. Hydrolysis of the enolether would afford an α-phenacylacetoacetate derivative comparable to the hydrolysis of the carboethoxy-coumarin compound (LXXIX) reported by Widman. The fact that only mono-carbonyl derivatives of the coumarin compound can be prepared is also in support of the enolether structure. Hydrogenation of the enolether would afford an α-phenacylacetoacetate derivative comparable to the hydrolysis of the carboethoxy-coumarin compound (LXXIX) reported by Widman. The fact that only mono-carbonyl derivatives of the coumarin compound can be prepared is also in support of the enolether structure. Hydrogenation of the

enolether would be expected to proceed through the tetrahydrofuran derivative (CVI) to the aldol product (CVIII). The hydrogenolysis at carbon-2 would be expected in preference to C-O fission at carbon-5, since the former site is less



CVII CVIII

sterically hindered. The aldol product would be expected to accumulate in the reaction mixture since the alcohol would resist ready reduction due to the proximity of a quaternary carbon at carbon-3. Results of qualitative tests carried out on the tetrahydro compound could be explained easily in terms of the aldol structure. The Lewis acid, ferric chloride, would be expected to catalyze the retro-aldol reaction affording the open-chain aldehyde-acetoacetic ester (CIX) and thus freeing an enol to give a characteristic ferric chloride test. Addition of pyridine would be expected to help the ring-opening and therefore give a faster ferric

CVIII 

CIX

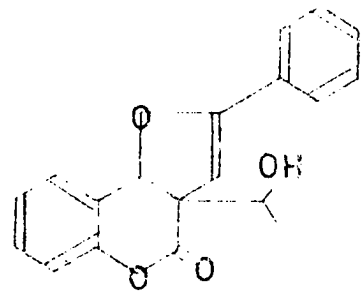
chloride test. The base-catalyzed acetylation might lead conceivably to decomposition of the labile aldehyde-

acetoacetic ester, while mild acetylation might not succeed because of the nature of the alcohol. The loss of the acetyl group in the exhaustive hydrogenation of the tetrahydro compound to 3-(β-phenylethyl)-dihydrocoumarin (XCI) is not as easily explained on the basis of the aldol structure as on structure (CV). In either case the acetyl loss can be rationalized only by assuming a palladium-induced intramolecular transacetylation toward this hydroxyl group prior to hydrogenolysis. Such C-toO acetyl migration is more reasonable for (CV) than for CVIII). Since the structure of the tetrahydro compound was still unsettled, a Fehling's test was chosen to differentiate between (CV) and CVIII). It was felt that should the compound be (CVIII), it would hydrolyze to salicylaldehyde and oxidize to salicylic acid, whereas were it the benzylic alcohol (CV), it would not reduce Fehling's solution. While a qualitative Fehling's test proved positive, a quantitative experiment, unfortunately, failed to reveal salicylic acid among the reaction products.

The difficulties associated with attempts of a rigorous structure proof of the tetrahydro compound cased a return of experimental emphasis to the structure elucidation of its presursor, the product of the condensation of phenacyl chloride with 3-acetylcoumarin. By now its structure was limited to that proposed by Widman (LXXX) or the enolether (CVI). To achieve this solution, an examination of the

mono-oxime derivative of the coumarin compound was undertaken. Since the cyclopropane structure contains two carbonyl components, the oxime could arise from either group, however, in the enolether case the methyl ketone must give rise to the oxime, therefore, the infra-red spectrum of the oxime may shed some light on the structure of the coumarin compound. The oxime was prepared by the addition of two moles of hydroxylamine hydrochloride to one mole of the coumarin as described by Widman. The infra-red spectrum of the mono-oxime displayed two carbonyl bands, a 5.75μ and a 5.99μ band, whereas the 5.88μ band present in the coumarin compound was missing, thus indicating that the methyl ketone had condensed with the hydroxylamine hydrochloride. Thus the oximation did not solve the problem since both compounds contain the methyl ketone group and, therefore, the structures cannot be differentiated on this basis.

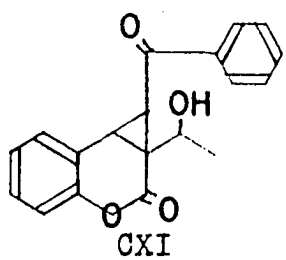
The coumarin then was exposed to sodium borohydride reduction. The hydride product was not isolated as such, but was treated with hydrobromic acid. On the basis of an enolether structure the reduction would have expected to give alcohol (CX) and acid hydrolysis of the latter should have afforded 3-phenacylcoumarin and acetaldehyde. The acid hydrolysis was found to lead to extensive polymerization. However, chromatographic separation of the reaction mixture afforded a 20% yield of 3-phenacylcoumarin unfortunately the



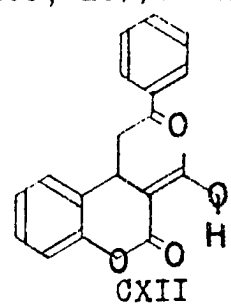
CX

low yield made the result inconclusive since incomplete reduction of diacyl cyclopropane (LXXX) to ketol (CXI) and fragmentation of the latter in a manner analogous to that of (CXI) could be visualized also to yield 3-phenacylcoumarin.

A survey of the literature of dihydrocoumarins revealed that 3-acetyl-4-phenacyldihydrocoumarin (CXII) had been synthesized by Heilbron, et al., (106, 107). This compound



CXI

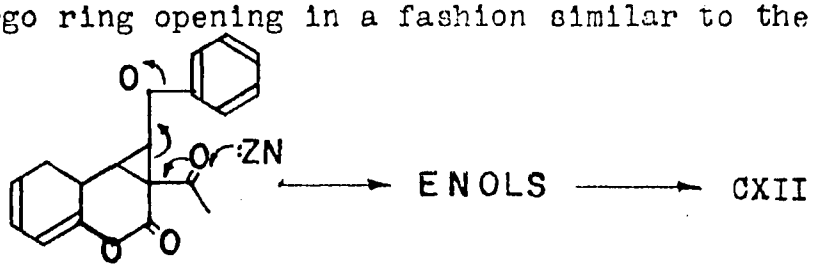


CXII

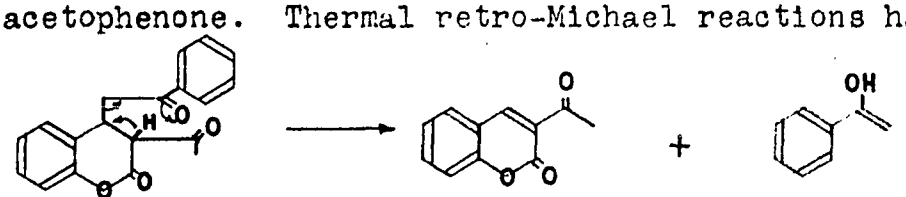
was significant since zinc-acetic acid reduction of the cyclopropane structure should afford the same compound. Zinc reduction was then attempted and found to yield a brown amorphous substance that resisted purification by recrystallization. The carbonyl region of its infra-red spectrum revealed little about the compound because the bands were not well defined. However, the compound did give a positive ferric chloride test. Purification of the compound was then tried by

sublimation, however the compound was found to decompose thermally into 3-acetylcoumarin and acetophenone. The latter was identified as its 2,4-dinitrophenylhydrazone.

These results, like many of the earlier results, may be explained on the basis of both structures. In the case of the cyclopropane structure, the 1,2-diketocyclopropane system would undergo ring opening in a fashion similar to the zinc



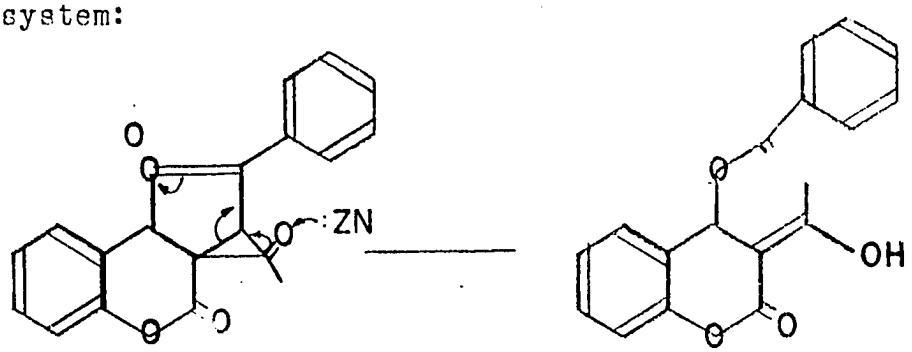
reduction of 1,2-dibenzoylcyclopropane to 1,5-diphenyl-1,5-pentadione reported by Allen, et al., (108). The 3-acetyl-4-phenacylidihydrocoumarin then would undergo a thermal retro-Michael reaction upon sublimation to give 3-acetylcoumarin and acetophenone. Thermal retro-Michael reactions have been



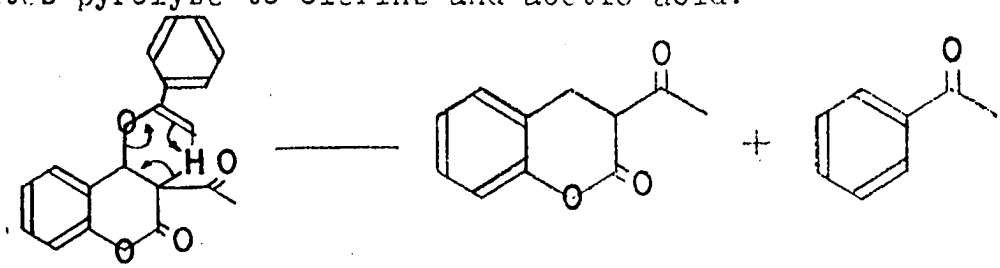
reported by several investigators. Meerwein (109) reported the pyrolysis of 2,3-diphenyl-5-keto-4-propionoxy-1-hexanal to α , β diphenylacrolein and acetonyl propionate. In recent years, Achtermann (110) and Cornforth, et al., (111) have degraded terpenes and sterols by thermal retro-Michael reactions.

In the case of the enolether structure conjugate acid of the enolether would undergo reduction to the acetoacetic

ester system:



The resulting acetoacetic ester system would undergo pyrolysis to 3-acetylcoumarin and acetophenone in the same manner as acetates pyrolyze to olefins and acetic acid:



At this stage of the investigation of the coumarin compound, its synthesis and identity with Widman's structure were reported by Wawzonek and Morreal (98). These workers employed the standard method of cyclopropane preparation, by the addition of diazoacetophenone to 3-acetylcoumarin to form the pyrazoline (LXXXVII); and pyrolysis of the latter to the cyclopropane system. The first step of the synthesis is beyond reproach since the addition of diazo-systems to α, β-unsaturated systems has been extensively studied (112, 113, 114). The second step of the synthesis, the pyrolysis is open to some question, since cyclopropane systems are known to rearrange on heating; e.g. vinyl cyclopropane rearranges to cyclopentene under pyrolytic conditions (115). The

reverse of this rearrangement has also been reported in a similar system. Shuiken (116) has reported the thermal rearrangement of dihydrofuran to cyclopropyl methyl ketone:

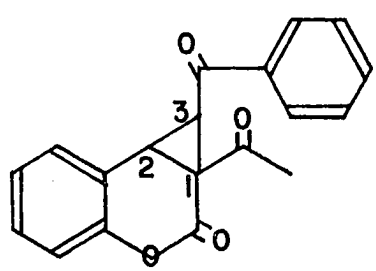
Thus the thermal rearrangements cited in these cases may indicate that an equilibrium exists between the cyclopropyl and five-membered ring systems, and the position of equilibrium may depend to a fair extent on the nature of the substituents. Therefore, the synthesis does not constitute a rigorous proof for the cyclopropane structure.

Since the chemical, spectroscopic, and synthetic data could not distinguish between the two postulated structures, a tool more specific in its nature, was required to indicate the structure of the coumarin compound. The problem appeared to be ideally suited for nuclear magnetic resonance analysis since the cyclopropane ring hydrogens absorb at a characteristic portion of the spectrum and the spectra of the two compounds would be substantially different. The NMR spectrum of the compound was investigated and showed to be composed of a signal at 7.45 p.p.m. was assigned to the methyl hydrogens of the acetyl group; the four signals in the 5.79-6.69 p.p.m.

range indicated vicinal hydrogens which are splitting each other to form and AB or two-spin system. The remaining series of signals at 2.51-2.85 p.p.m. was assigned to the benzene hydrogens. The intensity ratio of the methyl hydrogens to the four signals of the vicinal hydrogens indicated a ratio of three hydrogens to two. Thus the spectrum is consistent only with a system that has two hydrogens in proximity of each other, and therefore, the coumarin compound must indeed possess the cyclopropane structure (LXXX).

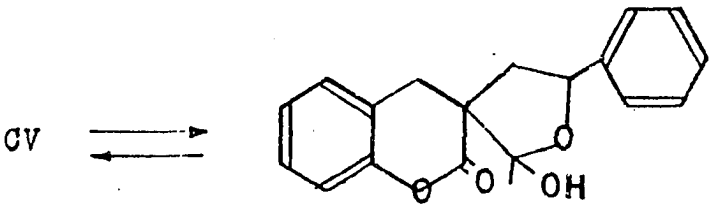
The chemistry of 3-acetyl-3,4,-phenacylidenecoumarin is very intriguing since an a priore explanation of the results was almost impossible. However hindsight has always been more kind to the organic chemist, and this case is no exception.

The catalytic hydrogenation of 3-acetyl-3,4-phenacylidenecoumarin would be expected to proceed via the cleavage of the C-2-C-3 bond of the cyclopropane ring, since that carbon-carbon bond is more sterically available to the approach of the catalyst then the other two carbon-carbon bonds:



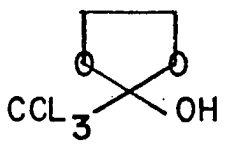
However, the resistance of the 3-acetyl-3-(β-hydroxy-β-(phenylethyl)-dihydrocoumarin (CV) to further hydrogenation

would not be anticipated, since benzylic alcohols are known to undergo hydrogenolysis to the hydrocarbon. This resistance may be explained by the formation of the hemiketal which may be preferred to the open-chained system, i.e.,

CV 

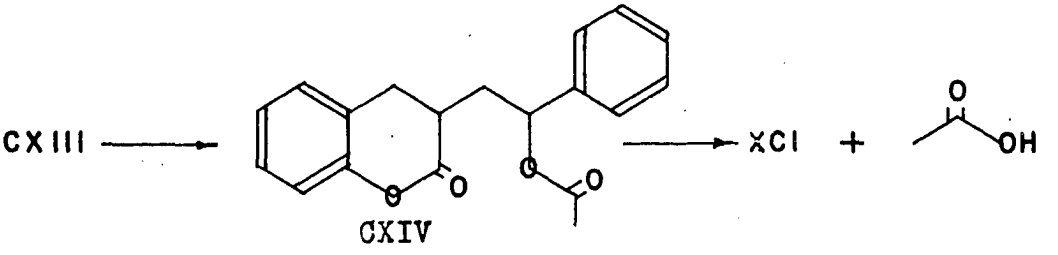
CXIII

The infra-red spectrum supports this claim since the 5.82 band is not well resolved, but is present as a shoulder. The hemiketal form may be the stable form in the solid state, and in equilibrium with the hydroxyketone form in solution. This phenomenon has been known for some time and is best exemplified by the sugar series. The sugar fructose exists as the five-membered hemiketal in the solid state, and is in equilibrium with the ketone in solution (117). In recent years, certain hydroxy-esters have been found to exist in the form of a cyclic carbonate, Meerwein (118) has reported that -hydroxyethyl trichloroacetate also exists in the cyclic carbonate form, i.e.,



The rate of hydrogenolysis of the carbon-oxygen bond in the hemiketal form would be exceedingly slow since the furan derivative (CXIII) is tetra-substituted, making catalyst approach to the benzyl carbon unfavorable.

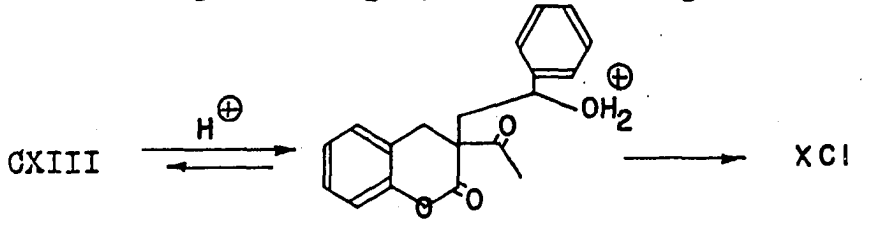
The exhaustive catalytic hydrogenation of the tetrahydrocoumarin to afford 3-(β-phenylethyl)-dihydrocoumarin may also be explained on the basis of the hemiketal. The formation of the hemiketal leads to a β-hydroxylactone (CXIII) which can undergo a retro-Claisen reaction to afford the acetate (CXIV) which, in turn, is hydrogenolyzed to the final product. The



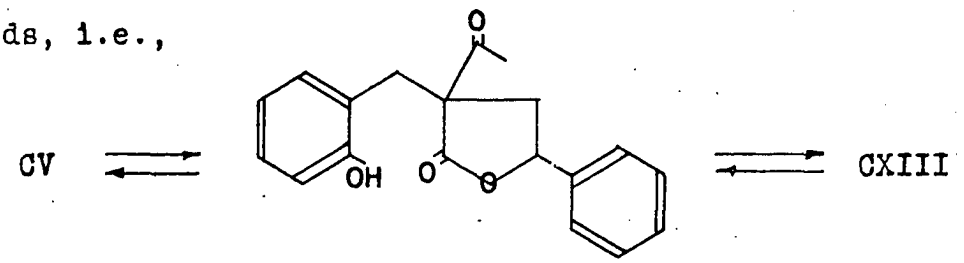
CXIV

reaction is catalyzed by the traces of base usually present on metal catalysts since the catalysts are prepared in a basic medium. The reaction is probably accelerated by the easing of steric strain in the system, since the reaction involves the removal of a substituent from a quaternary carbon atom. This type of transacylation reaction has been reported in the sugar series many times (119, 120, 121).

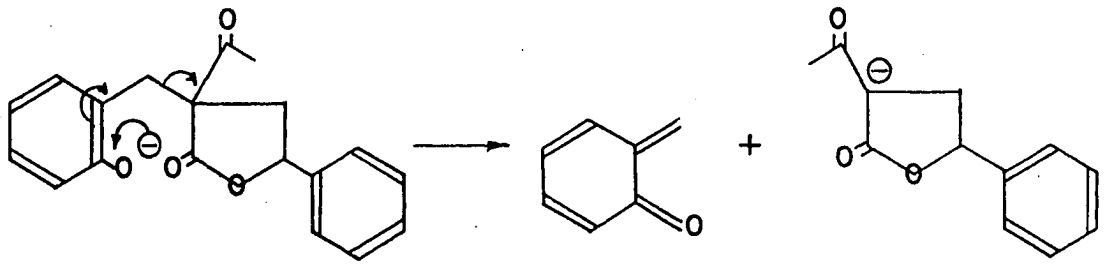
The acid-catalyzed hydrogenation of the tetrahydrocoumarin would neutralize the traces of base present on the catalyst and would, therefore, terminate the retro-Claisen reaction. The hydrogenation of the tetrahydro-coumarin can be visualized as proceeding by the following scheme:



The inability of the tetrahydro-coumarin to afford the acetate by the acetic anhydride treatment may also be due to the hemiketal formation. The hemiketal formation would in effect produce a tertiary carbinol which would be sterically incapable of reacting with the anhydride. The decomposition of the tetrahydro-coumarin by base-catalyzed acetylation may involve the hydroxyl groups interacting in a manner different than in the hemiketal formation. Since it is conceivable that the hydroxyl group can interact with the lactone as well as the ketone, an equilibrium surely exists among three compounds, i.e.,



The basic catalyst would pick off the phenolic hydrogen forming the phenoxide system (CXV) which might displace the enolate anion (CXVI). The quinone methine (CXVII) produced



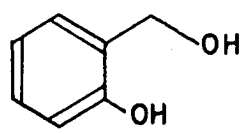
CXV CXVII CXVI

in the reaction would polymerize with itself or unreacted phenol. The driving-force in this reaction would be again the relieving of steric strain on the quaternary carbon atom

by the removal of a substituent.

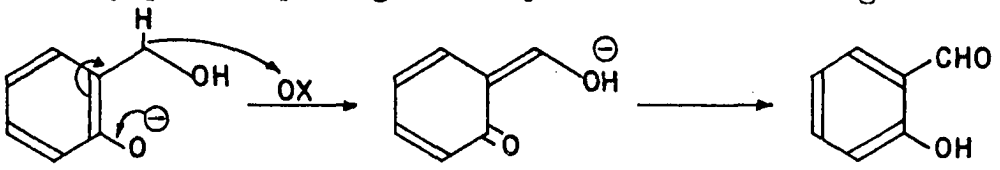
The results obtained with ferric chloride can be rationalized on the basis of the equilibration of the tetrahydrocoumarin to the phenol (CXV). The transesterification should be catalyzed by the Lewis acid, ferric chloride, thus freeing the phenol to complex with the ferric salt.

The positive Fehling's test on the tetrahydro-coumarin was the most unexpected result of all of the structure studies. The test has not been extensively studied, but the generalization that benzylic alcohols or phenols do not give a positive test has been found to be valid. The answer to the reaction may lie with the base decomposition of the molecule. The strong base present in the Fehling's solution would open the lactone to form the phenoxide system (CXV). If the same cleavage of the phenoxide, as in the case of acetylation, is employed then the cleavage will give an o-quinonemethine. The latter most likely would polymerize in the same manner as in the acetylation reaction or undergo β-addition of hydroxide ion to form o-hydro-oxybenzyl alcohol i.e.,

CXVII + OH $\rightleftharpoons$ 

Were the β-addition of hydroxide to occur, it is conceivable that the phenoxide anion of o-hydroxybenzyl alcohol could facilitate the oxidation of the alcohol to salicylalde-

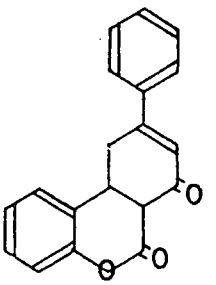
hyde by participating in a hydride transfer e.g.:



The salicylaldehyde would then undergo normal oxidation to salicylic acid under Fehling's conditions. To test this hypothesis, o-hydroxybenzyl alcohol were exposed to the Fehling's test. The test was positive with both o-and p-substituted alcohols, whereas the meta compound gave a negative test. Since only the ortho and para phenolic hydroxy group can help in the oxidation, these results support the proposed mechanism.

The catalytic hydrogenation of 3-acetyl-3,4-phenacylidene-coumarin led to the cleavage of a carbon-carbon bond of the cyclopropane ring to afford 3-(β-phenylethyl)-dihydrocoumarin. If a reaction could be devised that would cleave one of the other carbon-carbon bonds in the cyclopropane ring to a recognizable system, then the two reactions would complement each other and prove the existence of the cyclopropane ring. The zinc-acetic acid reduction appeared to be ideal since the reaction would afford 3-acetyl-4-phenacyldihydrocourmarin, a compound that had been synthesized several years earlier. The product afforded by the zinc reduction of 3-acetyl-3,4-phenacylidene-coumarin could not be crystallized and very little information on the compound had been gained. Since the zinc product was hard to handle, the original synthetic

work of Heilbron and Hill (122) was repeated in order to obtain an authentic sample of the coumarin. The synthesis consisted of a Michael addition of ethyl acetoacetate to o-hydroxychalcone in the presence of sodium ethoxide. The coumarin compound reported by Heilbron could not be isolated; a compound was isolated from the reaction mixture in a 10 percent yield that analyzed for $C_{19}H_{14}O_3$ and had an 5.70μ band and a 5.99μ band in the infra-red. The compound appeared to be the aldol condensation product of the desired compound, i.e.,

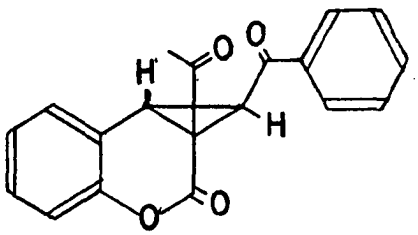


CXVIII

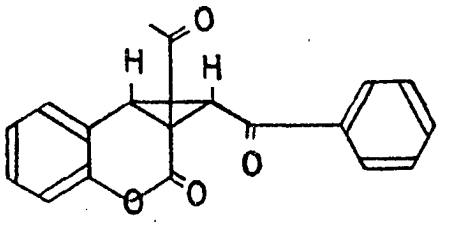
Since the product from the zinc reduction of 3-acetyl-3,4-phenacylidenecoumarin must have been 3-acetyl-4-phenacyl-dihydrocoumarin, having yielded 3-acetylcoumarin and acetophenone on pyrolysis, a sodium ethoxide treatment of it should afford the same aldol product as the one that arose from the condensation of o-hydroxychalcone and ethyl acetoacetate. However, while the condensation was tried several times, no aldol product (CXVIII) could be isolated. The only recognizable product was 3-acetylcoumarin, thus indicating that a retro-Michael reaction had occurred instead of the expected aldol condensation. An examination of the synthesis

of the aldol product by the Michael addition of ethyl aceto-acetate to o-hydroxychalcone revealed that the condensation proceeded in very low yield. At first it was assumed that the Michael addition was slow. However, on an examination of the reaction mixture a 30 percent yield of 3-acetylcoumarin was discovered, thus indicating the predominance of the retro-Michael reaction even in this case.

The stereochemistry of 3-acetyl-3,4-phenacylidenecoumarin had not been investigated by Widman or Wawzonek and Morreal. The cyclopropane system can possess one of two possible stereochemical forms: (CXIXa), (CXIXb). Some chemical information on the stereochemistry had been obtained from the structure work. The sodium borohydride reduction indicated



CXIXa



CXIXb

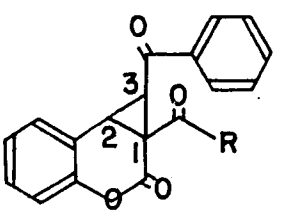
that the phenyl ketone is sterically hindered to some extent, since approximately 20 percent of the ketone survived reduction. This supposition received support from the earlier work done by Widman (95) concerning the carbonyl derivatives of the cyclopropane compound. Widman had reported that the coumarin afforded only mono-carbonyl derivatives with hydroxylamine hydrochloride and semicarbzide hydrochloride. All

attempts to prepare the di-carbonyl derivatives under more rigorous conditions resulted in decomposition of the molecule. The infra-red spectrum of the oxime of the coumarin compound disclosed that only the methyl ketone had been oximated; the phenyl ketone remained intact. Thus indicating that the aromatic ketone is sterically hindered. Since, 1,4 dicarbonyl compounds react with hydrazine to form azines, this reaction appeared to be capable of distinguishing between the two steric possibilities because only the cis-arrangement (CXIXa) could form the azine. Unfortunately the coumarin gave a complex mixture on attempted hydrazone formation. The spectroscopic data accumulated earlier in the discussion of the structure of 3-acetyl-3,4-phenacylidenecoumarin also gave some qualitative indication of the stereochemistry of the compound. The infra-red spectrum disclosed that the intensities of the ketones were anomalous. The fact that both the methyl ketone and phenyl ketone had anomalous intensities, whereas the lactone intensity was normal suggested a neighboring-group interaction of the two ketones possible only in a cis arrangement.

The NMR spectrum has been found to be a useful tool in the study of stereochemistry. The spin-spin coupling constant, J, has been found to depend on the type of hydrogens involved in the interaction. In the cyclohexane series, the spin-spin coupling constant has a value between 6-10c/s for 1,2-diaxial

hydrogens. The constant for 1,2-axial-equatorial hydrogens is lower, between 2-3 c/s (123). The same effect is observed in the penta-acetates of glucose, mannose, and galatose (123). The spin-spin coupling constant in these cases ranges from 6-8 c/s for the diaxial interaction, and 2-3 in the axial-equatorial interaction. The cyclopropane case however, is ambiguous, since the cis 1,2 dihydrogens and the trans 1,2 dihydrogens have been found to give the same spin-spin coupling constant. 6.3c/s. for cis-and trans-dibromocyclopropane reported by Jackman (124). The spin-spin coupling constant for 3-acetyl-3,4-phenacylidene-coumarin has been found to be 10c/s. Thus the NMR suggests a cis arrangement of acetyl and benzoyl groups, but unfortunately does not prove it rigorously.

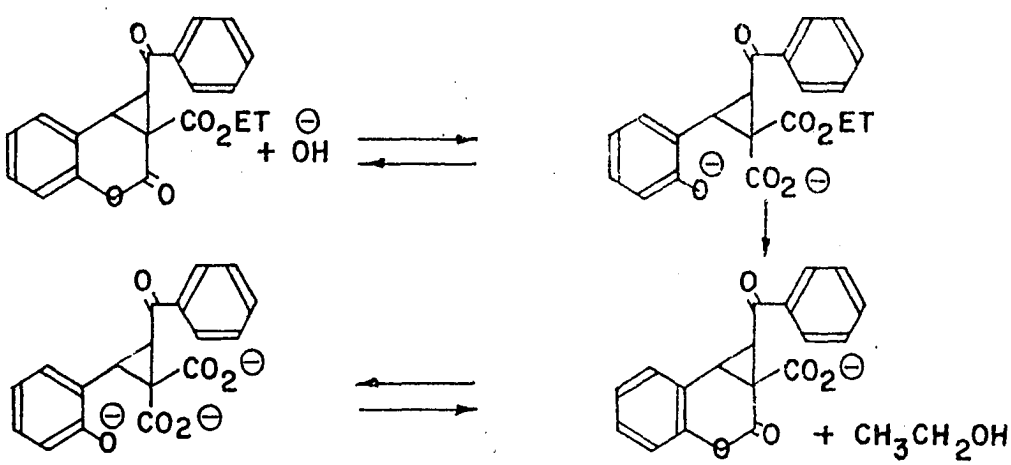
The reactions of 3-acetyl-3,4-phenacylidenecoumarin and related compounds are quite interesting since the cyclopropane ring has been opened in all of the three possible ways: Widman (94) has reported the cleavage of the carbon-2 carbon-3 bond of 3-carboethoxy-3,4-phenacylidene-coumarin by base hydrolysis. The cleavage of the carbon-1 carbon-2 bond of 3-acetyl-3,4-phenacylidenecoumarin by base hydrolysis has



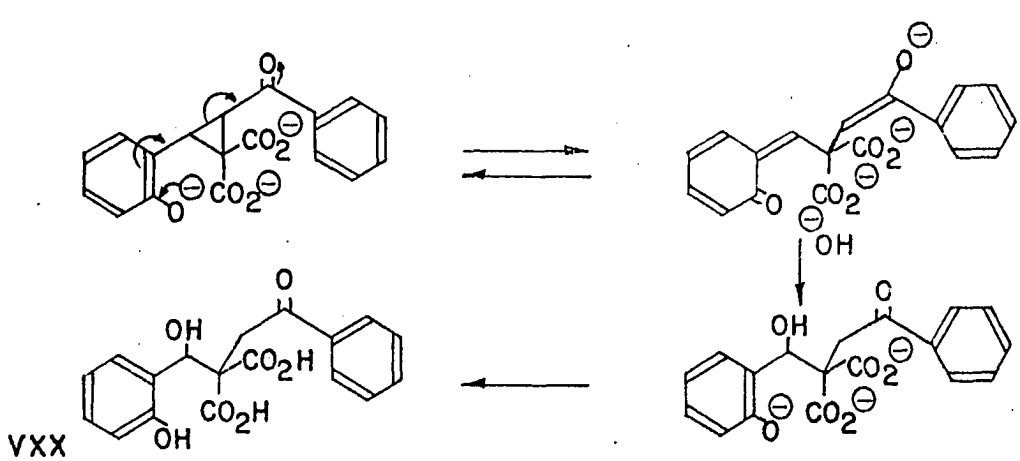
R = methyl
α = ethoxyl

also been studied by Wawzonek and Morreal (98), and zinc-acetic acid reduction of 3-acetyl-3,4-phenacylidenecoumarin in this laboratory has led to the cleavage of the carbon-1 carbon-3 bond.

Although Widman did not comment on the mechanism of hydrolysis of 3-carboethoxy-3,4-phenacylidenecoumarin, the mechanism is probably comprised of an opening of the lactone followed by hydrolysis of the carboethoxy group, the cyclopropane ring is than cleaved to afford the more stable



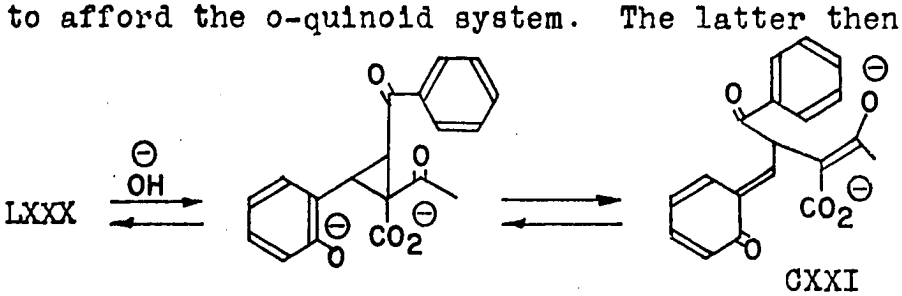
enolate anion, namely the enolate anion of the phenacyl group, i.e.,



VXX

On acidification, the intermediate hydroxy-acid (CXX) would undergo a retro-aldol reaction to afford salicylaldehyde and α-phenacylmalonic acid in order to relieve the steric strain associated with carbon-3.

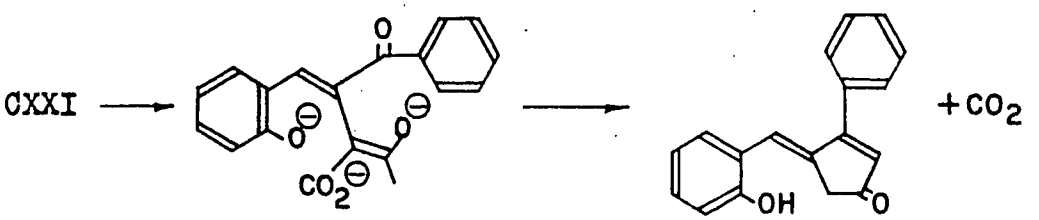
The cleavage of the carbon-1 carbon-2 bond of 3-acetyl-3, 4-phenacylidenecoumarin to afford 3-phenyl-4-(o-hydroxybenzal)-cyclopenten-1-one (LXXXI) was postulated by Widman in 1918. The reaction was re-examined last year by Wawzonek and Morreal and the Widman assignment of structure was found to be correct. The mechanism of the reaction was assumed by Wawzonek and Morreal to involve a retro-Michael (see pp. 47), since the reaction was analogous to the cyclopropane ring cleavage discovered in 1,1 dicarbomethoxy-2-benzoyl-3-phenylcyclopropane by Kohler and Conant (125). The reaction can be equally explained by the mechanism employed to explain the hydrolysis of 3-carboethoxy-3,4-phenacylidecoumarin. The first step of the reaction is the cleavage of the lactone followed by the cleavage of the carbon-1-carbon-2 bond by phenoxide participation to afford the o-quinoid system. The latter then



CXXI

stabilizes itself by an abstraction of a proton from the phenacyl group to afford the o-hydroxychalcone system (CXXII),

which then undergoes intramolecular aldol reaction, dehydration, and decarboxylation to the cyclopentenone system.



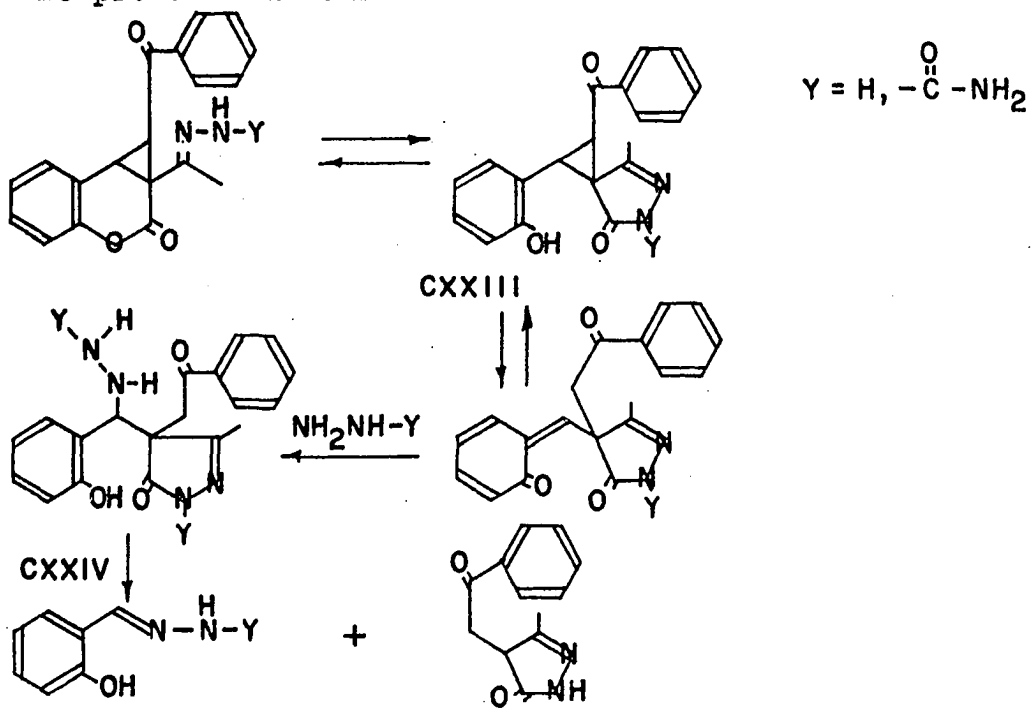
CXXII

The base-catalyzed degradations of 3-carboethoxy- and 3-acetyl-3,4-phenacylidenecoumarin proceeds by the same pathway differing only in the carbon-carbon bond that is cleaved in the cyclopropane ring. This difference between the two reactions can be rationalized by examining the stability of the intermediates involved in the reactions. The cleavage of the carbon-1 carbon-2 bond would be preferred to the cleavage of the carbon-2 carbon-3 bond, since the former cleavage would relieve the steric strain associated with carbon-3. However, in the hydrolysis of 3-carboethoxy-3,4-phenacylidenecoumarin the cleavage of the carbon-1 carbon-2 bond would involve the formation of an unstabilized anion. Thus the cyclopropane ring strain is released by the cleavage of the carbon-2 carbon-3 bond. In the hydrolysis of 3-acetyl-3,4-phenacylidenecoumarin, the cleavage of the carbon-1 carbon-2 bond leads to the most stable intermediate, the acetoacetate anion (CXXI).

The cleavage of the carbon-2 carbon-3 bond of the cyclopropane ring was discovered to occur quite readily by zinc-

acetic acid reduction. The mechanism of the reduction has been discussed earlier. The reaction is another example of the drive to relieve the strain of the cyclopropane ring and that of the quaternary carbon-3.

The cleavage of the carbon-2 carbon-3 bond may also be occurring in the reactions of the semicarbazone and hydrazone of 3-acetyl-3,4-phenacylideneccoumarin. Widman had attemped to prepare the di-carbonyl derivatives, however he found the coumarin degraded to the derivatives of salicylaldehyde (95). The reaction appears to involve the formation of the derivative of the acetyl group leaving the benzoyl group intact. The derivative may then interact with the lactone, forming the phenol-amide system. (CXXIII). The phenol then undergoes further cleavage in complete analogy with the previous discussions:



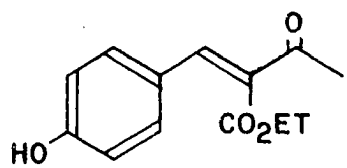
The mechanism of the condensation of 3-acetylcoumarin with α-chloroacetophenone was postulated by Widman to involve the opening of the lactone to afford the o-quinoid structure (LXXXIV). The mechanism was supported by two facts: firstly, a red-orange color was noted during the condensation which corresponded to the formation of the o-quinone-methine system, and secondly the condensation was observed not to occur with several similar α,β-unsaturated systems that did not contain the coumarin ring.

In 1938, Bodforss reinvestigated the mechanism of the condensation, and rejected the Widman mechanism in favor of a vinylogous Darzens mechanism. Bodforss supported his mechanism by two facts. Firstly, he could not find any chemical or spectroscopic evidence to support the o-quinone-methine, and secondly, he was able to condense o-nitrochalcone with α-chloroacetophene to afford the vinylogous Darzens product, 1-(o-nitrophenyl) -2-3-dibenzoylcyclopropane.

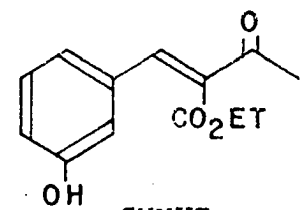
This year Wawzonek and Murreal favored the vinylogous Darzens mechanism, but did not offer any experimental evidence to support it.

Since Widman and Bodfross had attempted to extend the condensation to sixteen other α,β-unsaturated carbonyl compounds, and had discovered only one carbonyl compound to condense in a vinylogous Darzens manner, the Widman mechanism appears most reasonable. Corroboration of the Widman

mechanism could be attained by the condensation of α-chloroacetophenone with two similar unsaturated compounds: one compound containing the elements necessary for the formation of the quinone-methine system in the presence of base, and the second compound being similar to the first system, but unable to afford a quinone-methine intermediate. The two chalcones, ethyl p-hydroxybenzalacetoacetate (CXXV) and ethyl m-hydroxybenzalacetoacetate (CXXVI) appeared to be ideally suited for this purpose. The anion of the p-hydroxychalcone system (CXXV) as represented in (CXXXVII) is exceedingly

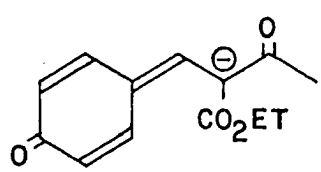


CXXV



CXXVI

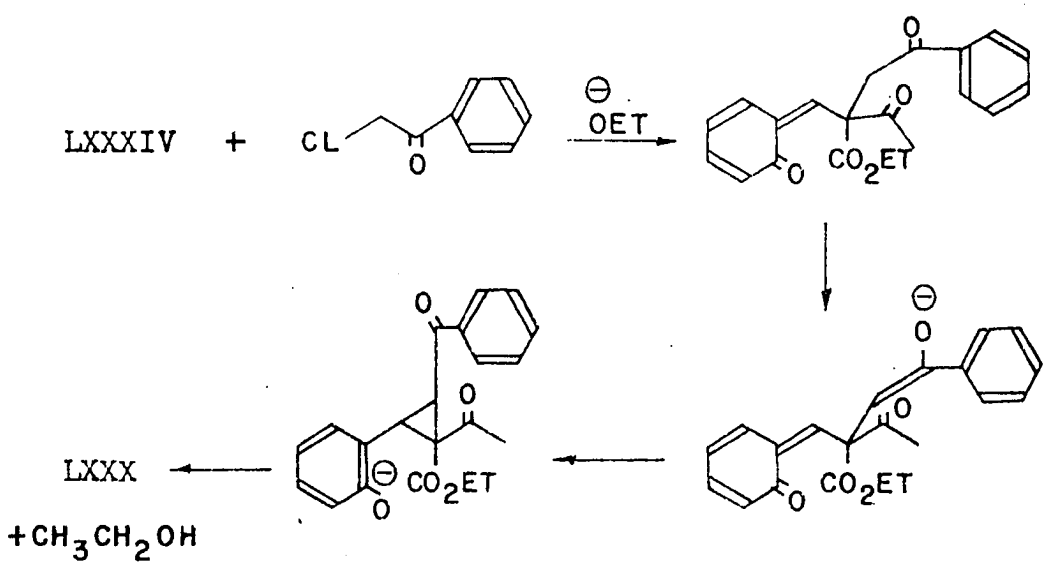
similar to the quinone-methine intermediates of both the synthesis and base-catalyzed degradations of 3-acetyl-3,4-phenacylidenecoumarin. Hence, CXXVII might be expected to yield a cyclopropane derivative with sodium ethoxide and α-chloroacetophenone. However, the meta-substituted chalcone



being unable to form a quinone-methine intermediate would be expected merely to undergo phenyl ether formation. Unfortunately neither chalcone yielded anything other than starting

material on exposure to α-chloroacetophenone and sodium ethoxide in as short a reaction time as had been necessary to convert 3-acetylcoumarin to 3-acetyl-3,4-phenacylidene-coumarin.

Although no direct proof can be offered for the Widman mechanism, it still is the only mechanism that is consistent with all experimental facts. The mechanism can be assumed to consist of a fast formation of the phenoxide ion (LXXXIV) by ethoxide ion attack on the coumarin carbonyl group of 3-acetylcoumarin and its alklation, in a slow step, at carbon-3.

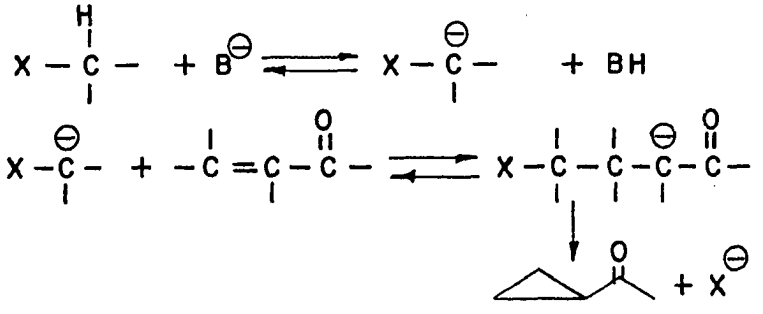


Sodium ethoxide then abstracts a proton from the phenacyl and the resulting enolate anion undergoes an intramolecular Michael reaction producing the cyclopropane ring. Internal extrusion of ethoxide ion from the thus-form phenoxide salt finally reforms the coumarin system.

Bodforss' objection to the Widman mechanism was based on

his ability to obtain a cyclopropane derivative from the condensation of o-nitrochalcone with α-chloroacetophenone and sodium ethoxide. Repetition of the Bodforss reaction led only to a 10 percent yield of a condensation product (85 percent recovery of o-nitrochalcone), in contrast to the high yield obtained in the coumarin series. A similar reaction with p-nitrochalcone was even less successful, yielding only a 90 percent recovery of starting material. In the absence of any knowledge about the structure of the Bodforss product it is uncertain if Bodforss' reaction has any relevance to the Widman reaction.

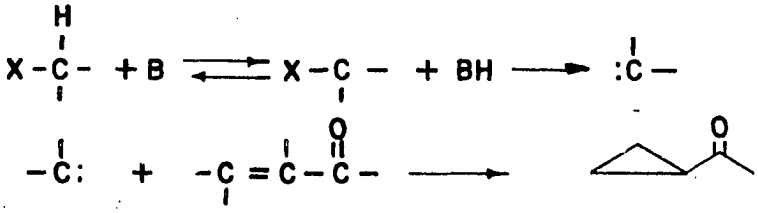
The vinylogous Darzens reaction may be occurring by three distinct mechanisms, the enolate anion, carbene, and displacement mechanisms. The enolate anion mechanism involves the abstraction of a proton from the halo-component and subsequent addition of the anion to the β-carbon of the unsaturated carbonyl component. The resulting anion then displaces internally halide ion effecting ring closure, i.e.



This mechanism has received support from the investigations of Deutsch and Buchman (87), McCoy (88,126), and Mousseron and Fraisse (89). They have investigated the condensations

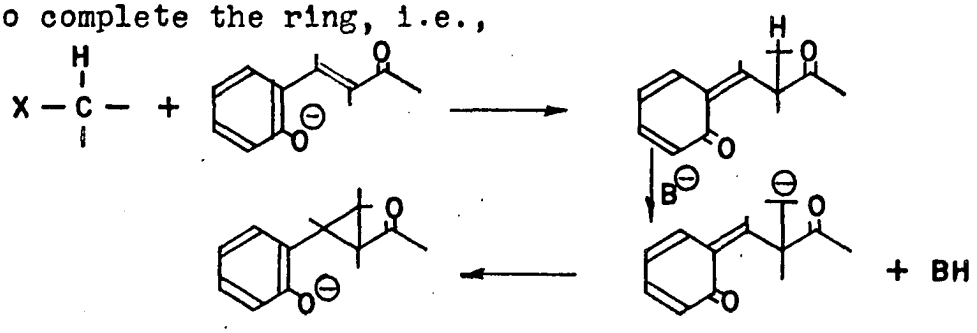
of α,β-unsaturated esters with α-haloacetates, and have reported high yields of the cyclopropane compounds.

The carbene mechanism, like the enolate anion mechanism, involves an initial abstraction of a proton from the halo-component. However the second step is a dehalogenation to afford the carbene. The carbene then adds across the double bond to form the cyclopropane derivative, i.e.,



Ballester (85) has investigated this mechanism in the Darzens reaction, but has found it not to be involved. However, the mechanism has been suggested by Closs and Closs (127) to explain the condensation of 1,2-dimethylpropenyllithium with methylene chloride to afford 1,3,3-trimethylcyclopropene. While the carbene mechanism may be applicable no experimental evidence for its support is available.

The displacement mechanism involves an initial displacement of the halide by the double bond of the o-hydroxycinnamyl system. Base then abstracts a proton from the halo-component to complete the ring, i.e.,



SPECTRA

Ultraviolet spectra were run in 95% ethanol using a Beckman model DU quartz spectrophotometer and a Cary recording spectrophotometer. Infrared absorption spectra were recorded using a Perkin - Elmer Infracord spectrophotometer.

Figure 1. Spectra

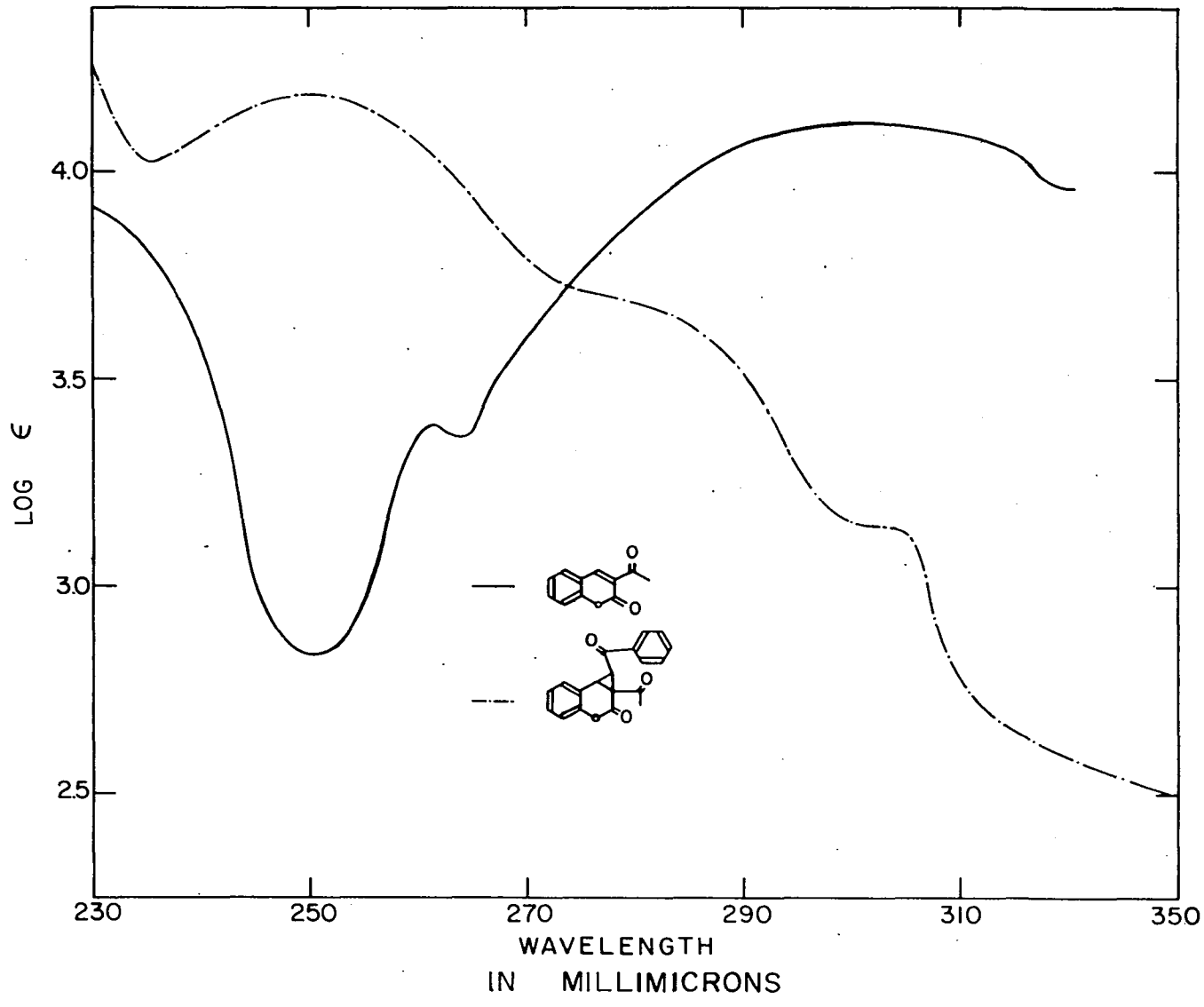

4.0
3.5
3.0
2.5
LOG ε
230
250
270
290
310
350
WAVELENGTH
IN MILLIMICRONS

Figure 2. Spectra

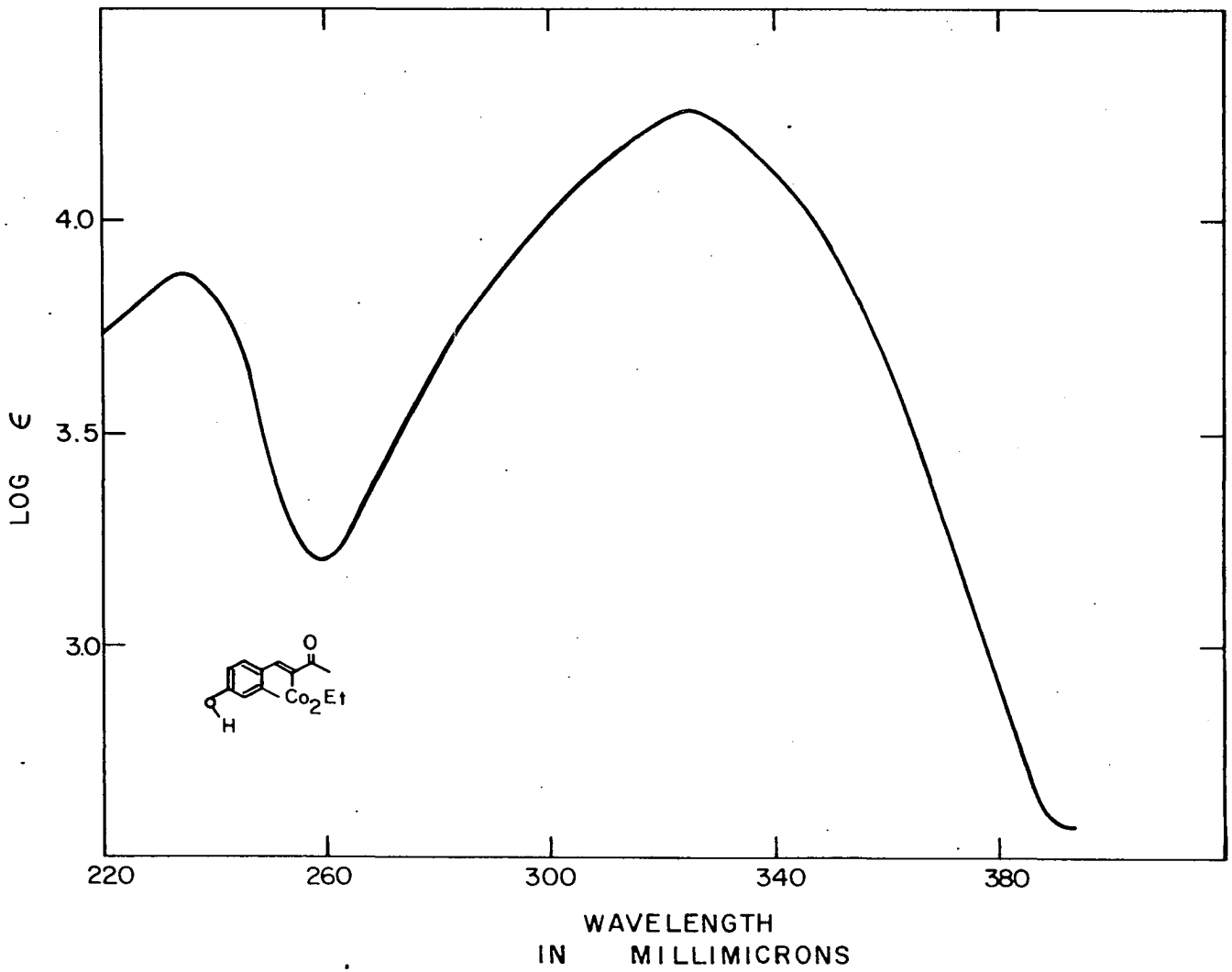

4.0
3.5
3.0
LOG ∈
220
260
300
340
380
WAVELENGTH
IN MILLIMICRONS
O
Co2Et
O
H

Figure 3. Spectra

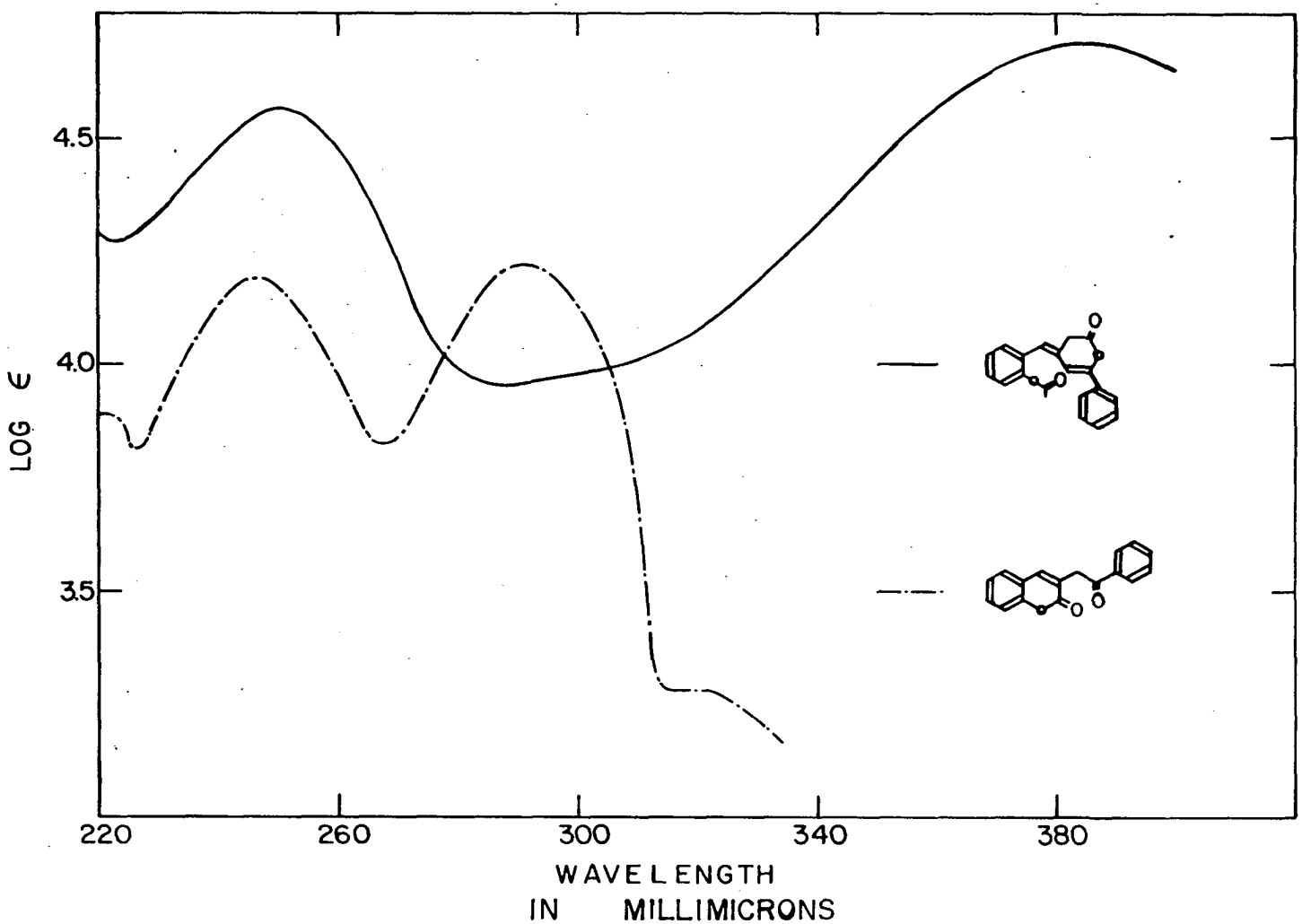

4.5
4.0
3.5
LOG ∈
220
260
300
340
380
WAVELENGTH
IN MILLIMICRONS

Figure 4. Infra Red Spectra

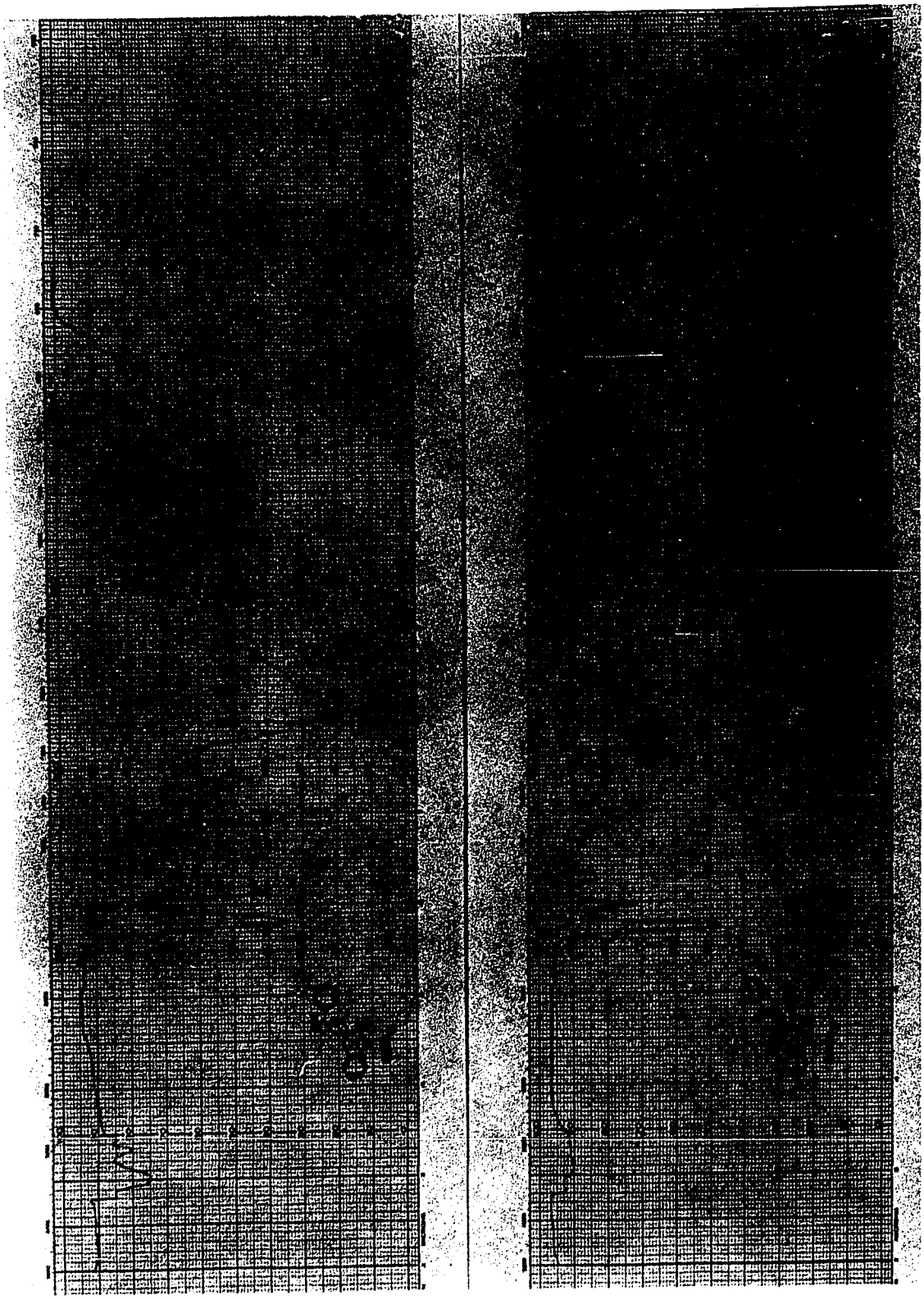


Figure 5. Infra Red Spectra

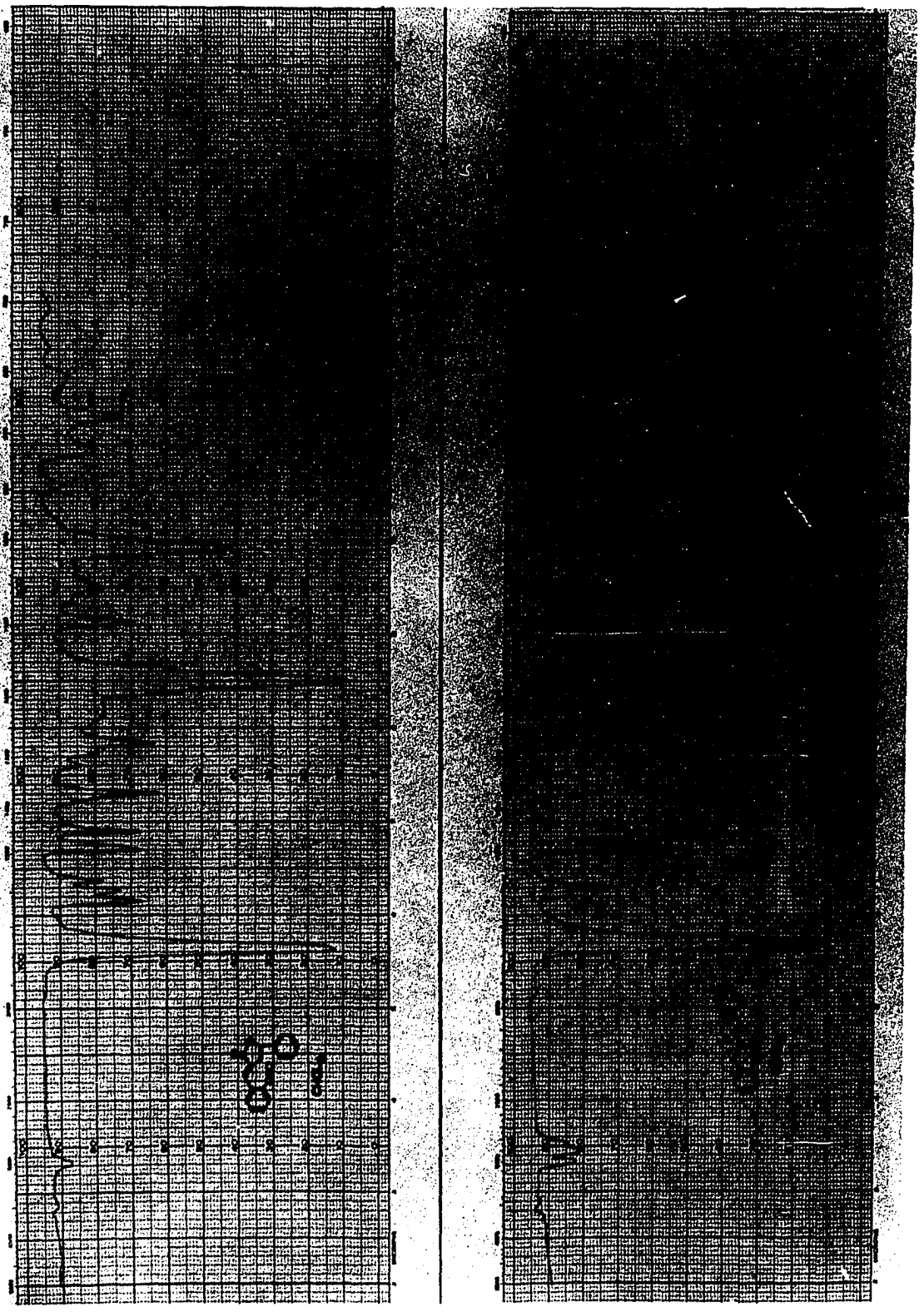


Figure 6. Infra Red Spectra

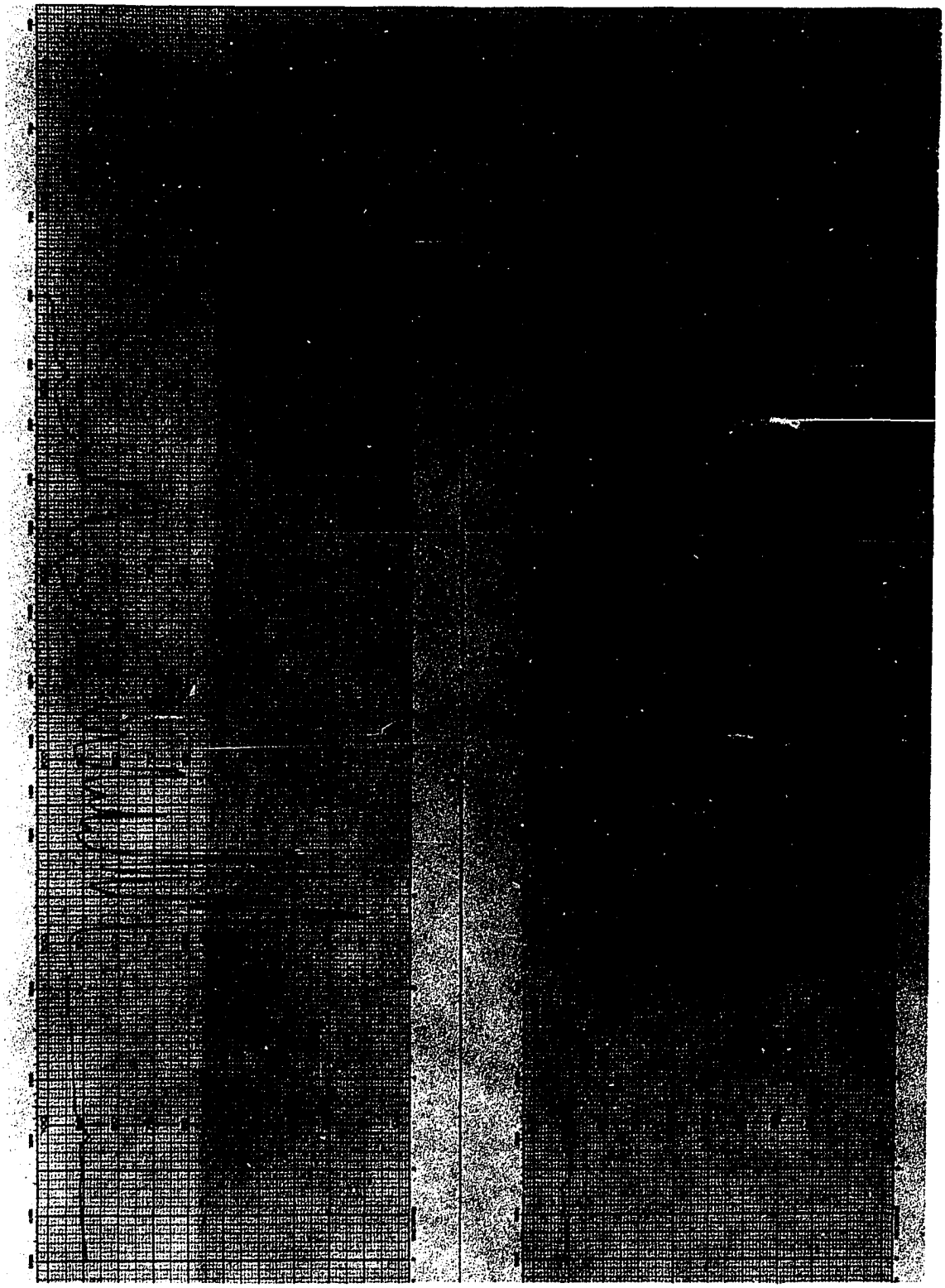


Figure 7. Infra Red Spectra

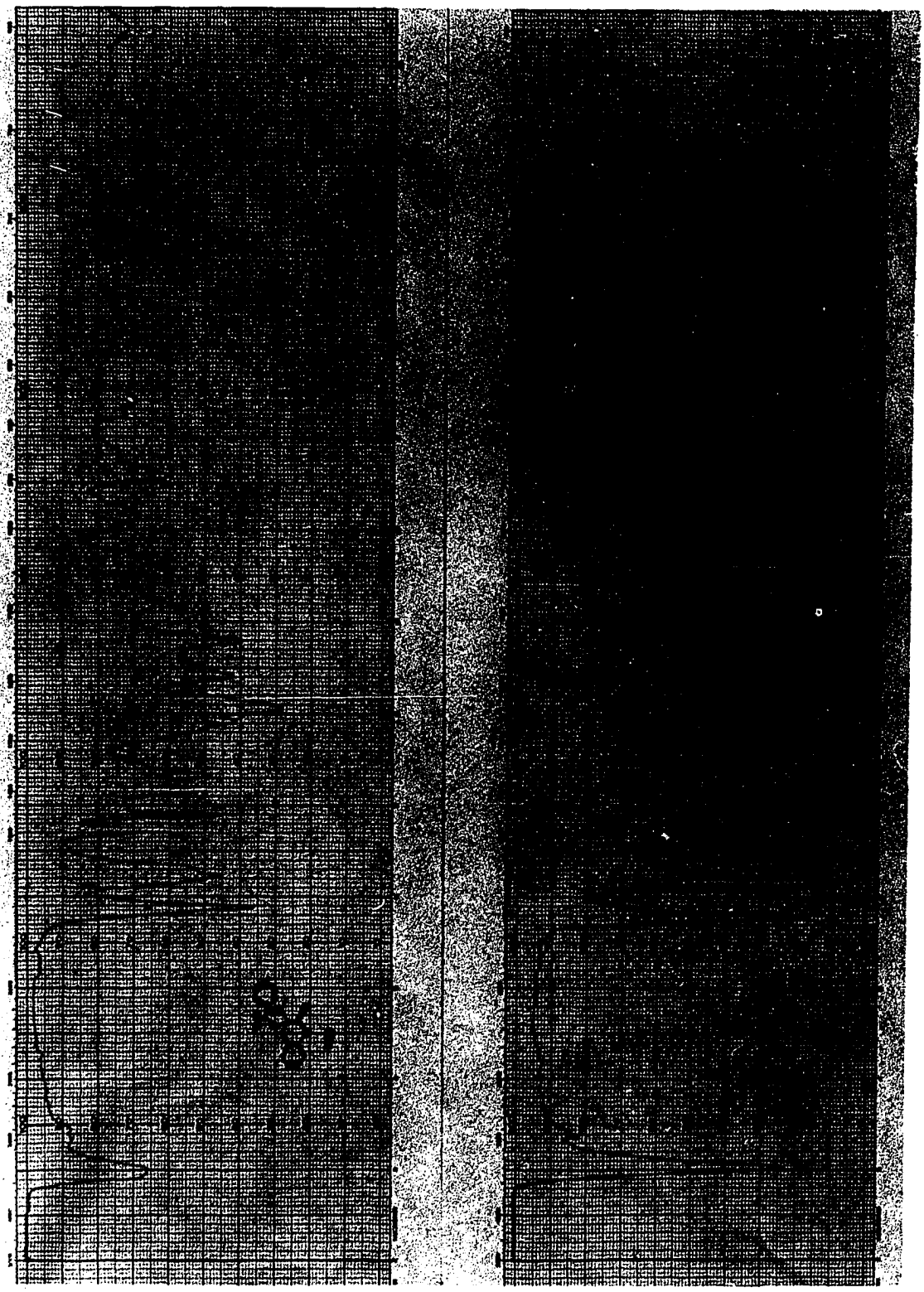


Figure 8. Infra Red Spectra

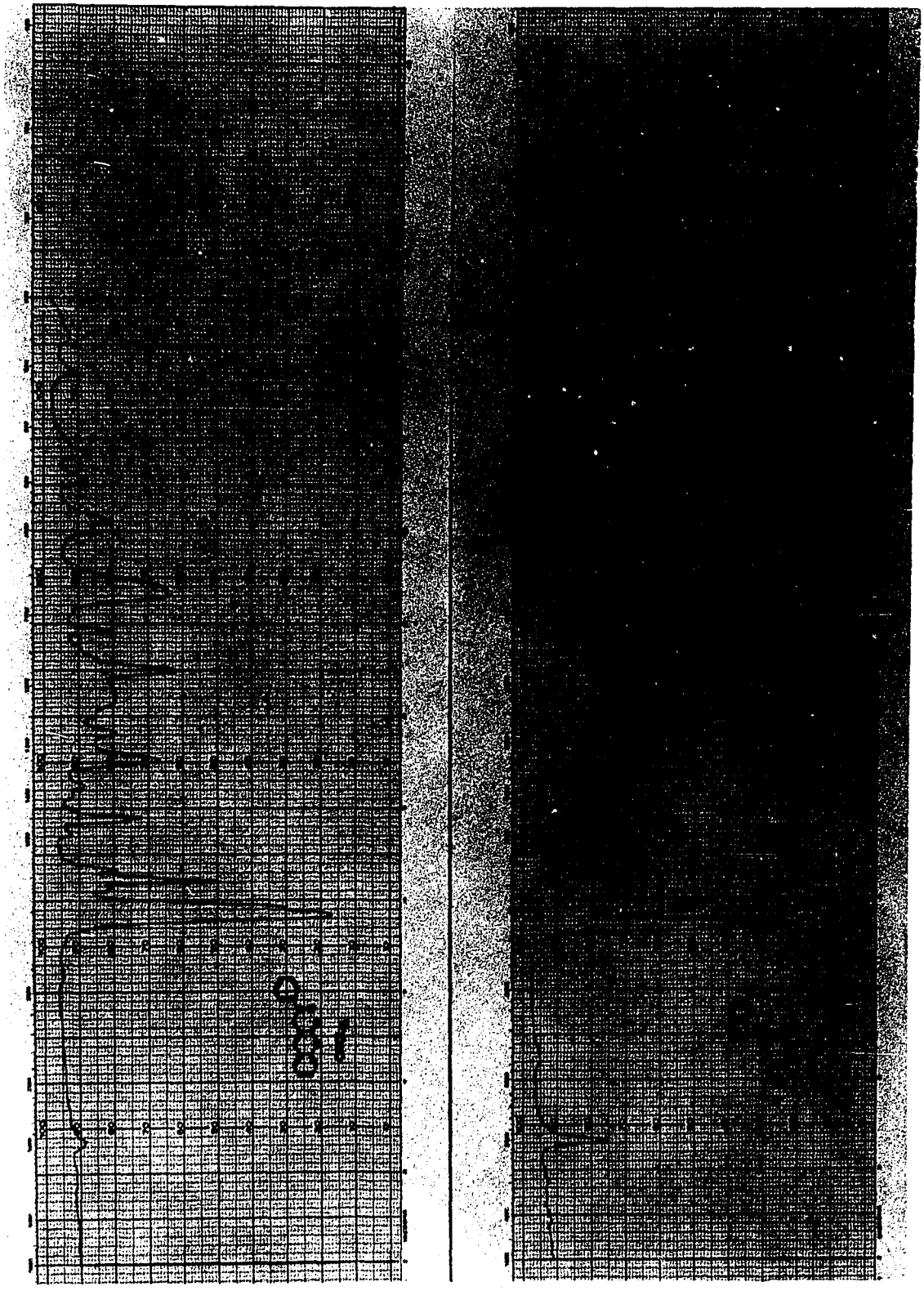


Fig. 1

Figure 9. Infra Red Spectrum

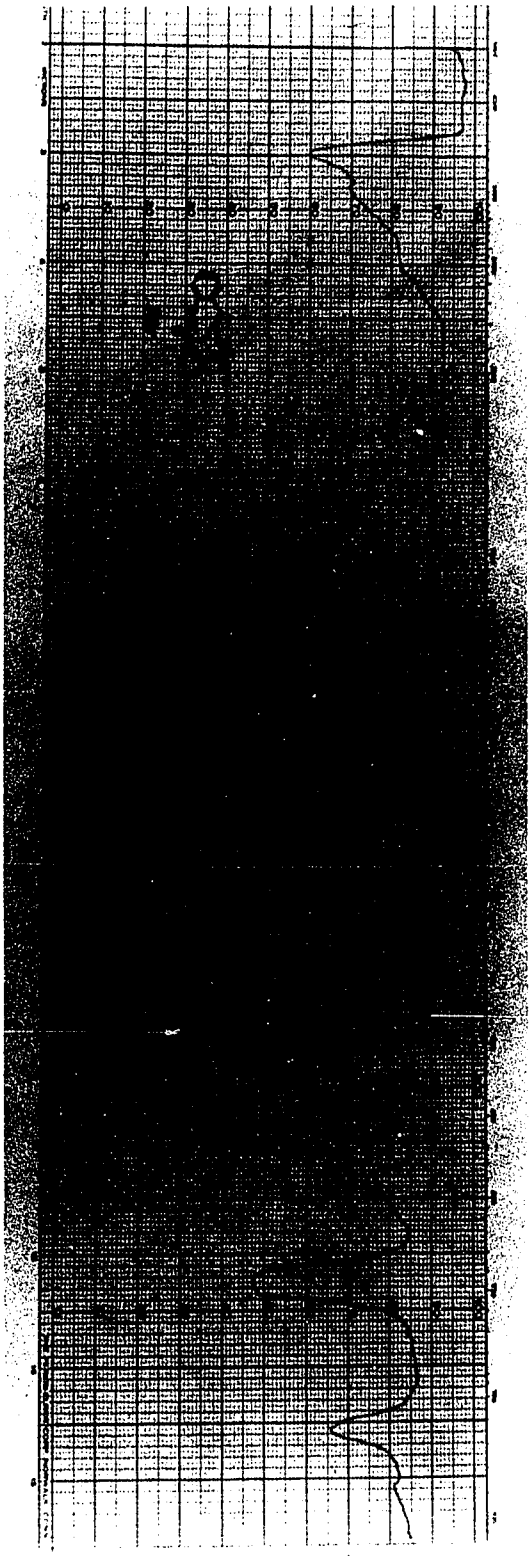
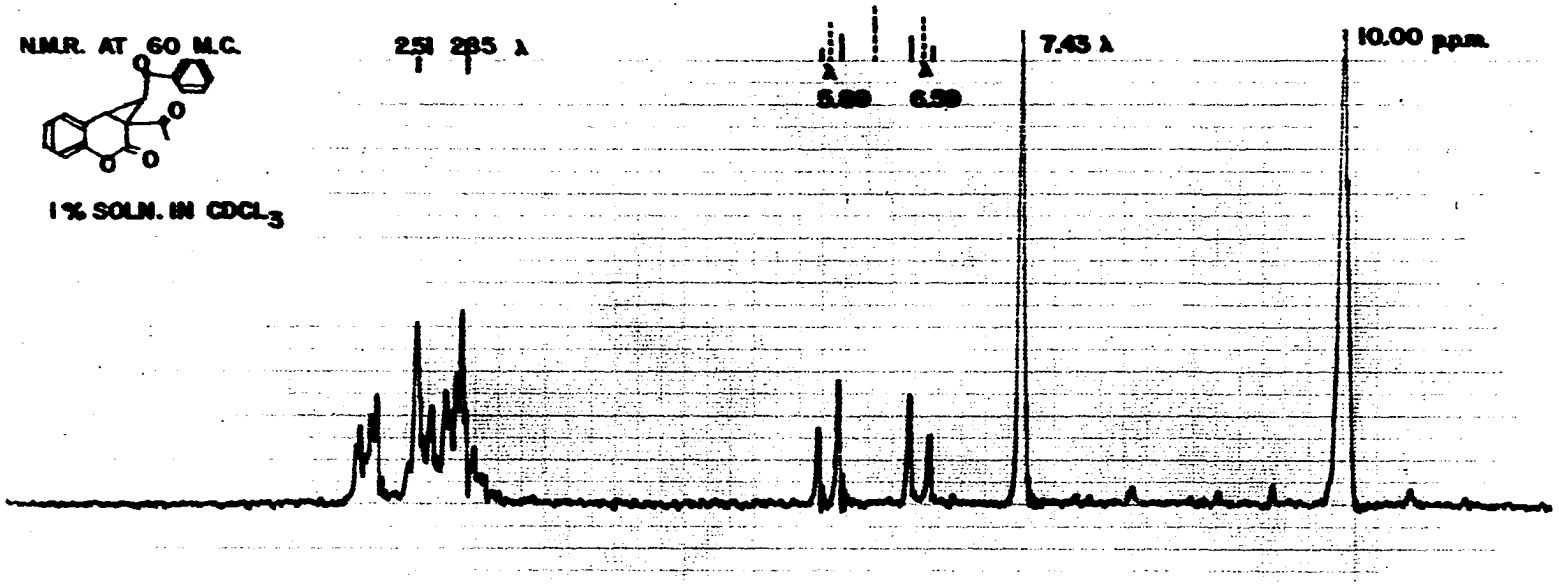


Figure 10. N.M.R. Spectrum


N.M.R. AT 60 M.C.
1% SOLN. IN $CDCL_3$
251 285 λ
7.43 λ
10.00 ppm.

EXPERIMENTAL

All melting points and boiling points are corrected unless otherwise stated. The term petroleum ether refers to the petroleum fraction of b. p. 60-70°. Ultraviolet spectra were measured in 95% ethanol solution with a Cary recording spectrophotometer and a Beckmann model DU quartz spectrophotometer. Micro-analyses were determined by the Strauss and Weiler Microanalytical Laboratory, Oxford, England, and the Midwest Microlab. Inc., Indianapolis, Indiana.

Absorbents for Chromatography

Activated alumina, 80-280 mesh, was allowed to stand with ethyl acetate for 24 hours, then washed with water and methanol, and dried at 100° for 24 hours.

The Celite-silicic acid absorbent was prepared by mixing equal weights of Celite and 100 mesh silicic acid.

3-Acetylcoumarin

Freshly distilled salicyaldehyde (11.0 ml., 0.1 mole) was mixed with ethyl acetoacetate (13.0 ml., 0.1 mole), and the mixture was dissolved in 95% ethanol (25 ml.). The solution was then cooled in an ice bath to 0°, and piperidine (1 ml.) was added. After one hour the mixture had completely solidified into an orange-yellow solid. The solid was mixed with water and the resulting slurry was filtered. The solid

was washed with three 50 ml. portions of water and dried. The crude solid (17.3 g., 92%), m.p. 110°-120° was crystallized from ethanol-water and the purified compound melted between 120-121°.

Ultraviolet spectrum

λ max = 298 mμ (ϵ 133,300)

3-Acetyl-3,4-phenacylidenecoumarin

The Widman procedure(95) was modified. A mixture of 3-acetylcoumarin (15.0 g., .08 mole) and α-chloroacetophenone (12.4 g., .08 mole) was placed into 250 ml. of absolute ethanol. The ethanol solution was refluxed until solution was complete. The hot solution was then allowed to cool to 65°. At this time a sodium ethoxide solution (1.84 g. of sodium in 50 ml. of absolute ethanol) was added dropwise to the stirred solution over a period of 45-60 minutes. After the addition of sodium ethoxide solution was complete, the solution was allowed to stir for fifteen minutes. Whenever the solution was not neutral at this point, a few drops of glacial acetic acid were added. The neutral solution was allowed to stand at room temperature for one hour after which time 3-acetyl-3,4-phenacylidenecoumarin and sodium chloride had crystallized from the solution. The solids were filtered and washed with three 20 ml. portions of 95% ethanol. The solids were treated with hot ethyl acetate and the resulting

solution was decanted from the sodium chloride. The ethyl acetate solution was then evaporated and afforded almost pure 3-acetyl-3,4-phenacylidenecoumarin (11.5 g., 46%), m.p. 183°-185°. The coumarin was soluble in benzene, chloroform, and acetic acid, and insoluble in 95% ethanol and carbon tetrachloride. The compound was crystallized from ethyl acetate-95% ethanol, m.p. 184°-185°.

Ultraviolet spectrum

λ max. 254 mμ (ϵ 14,800)

Hydrogenation of 3-Acetyl-3,4-phenacylidenecoumarin

A solution of 1.0 g. of 3-acetyl-3,4-phenacylidenecoumarin in 100 ml. of ethyl acetate was hydrogenated over 100 mg. of 5% palladium-charcoal at room temperature and atmospheric pressure. The hydrogenation was allowed to continue over a 24 hour period. The solution was then filtered and the solvent removed by evaporation at room temperature. The oily residue was crystallized from 95% ethanol-water, afforded 3-acetyl-3-(β-hydroxy-β-phenylethyl)-dihydrocoumarin (.700 g., 73%), m.p. 152-153°.

Anal. Calc. for $C_{19}H_{18}O_4$: C, 73.54; H, 5.81
Found: C, 73.39; H, 6.00

Hydrogenation of 3-Acetyl-3-(β-hydroxy-β-phenylethyl)-dihydrocoumarin

A solution of 0.500 g. of 3-acetyl-3-(β-hydroxy-β-phenylethyl)-dihydrocoumarin in 25 ml. of ethyl acetate was hydrogenated over 100 mg. of 5% palladium-charcoal at room temperature and atmospheric pressure. The hydrogenation was sluggish and absorbed hydrogen over a 72 hour period. The catalyst was removed by filtration, the solvent evaporated at room temperature and the residue crystallized from 95% ethanol-water. The crystalline solid, 3-(β-phenylethyl)-dihydrocoumarin (0.355 g., 87%) melted between 81-82°.

Anal. Calc. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39
Found: C, 80.73; H, 6.95

Preparation of α-(o-Acetoxybenzal-γ-phenyl-Δβ, γ-butenolide and 3-Phenacylcoumarin

Freshly distilled salicylaldehyde (1 ml., 0.0095 mole, β-benzoylpropionic acid (1.69 g., 0.0095 mole), and fused sodium acetate (1.56 g., 0.019 mole) were dissolved in 30 ml. of acetic anhydride. The solution was heated on a steam bath for two hours, and then allowed to stand at room temperature for 12 hours. The solution was then diluted with 30 ml. of water and heated on a steam bath for 30 minutes. The red solution was diluted with water and extracted several times with ether until the last ether extract was colorless. The ether layer was then evaporated to dryness and the resulting

red crystalline solid (705 mg.) m.p. 170°-174°, was crystallized from ethyl acetate-95% ethanol. The recrystallized orange solid, α-(o-acetoxybenzal)-γ-phenyl-Δβ,γ-butenolide melted between 173-174°. The mother liquor was evaporated to dryness on a steam bath under vacuum. The red residue was dissolved in benzene and chromatographed on alumina. Elution with petroeum ether led to 130 mg. of α-(o-acetoxybenzal)-α-phenyl-Δβ,γ-butenolide. Elution with 3:1 benzene-ether led to 102 mg. (5) of 3-phenacylcoumarin, m.p. 159°-163°. Crystallization of the compound from acetone-water raised the m.p. to 163°-164°.

The total yield of α-(o-acetoxybenzal)-γ-phenyl-Δβ,γ-butenolide was 835 mg. (30%).

α-(o-Acetoxybenzal)-γ-phenyl-Δβ,γ-butenolide

Anal. Calcd. for $C_{19}H_{14}O_4$: C, 74.45: H, 4.60 Found: C, 74.28; H, 4.86

Ultraviolet spectrum λ max 250 mμ (ε 36,000); λ max 385 mμ (ε 49,300)

3-Phenacylcoumarin

Anal: Calcd. for $C_{17}H_{12}O_3$: C, 77.27; H, 4.55 Found: C, 77.27; H, 4.83

Ultraviolet spectrum λ max 247 mμ (ε 13,100); λ max 290 mμ (ε 14,800)

Acid Hydrolysis of α-(o-Acetoxybenzal)-γ-phenyl-Δβ, γ-butenolide

A solution containing α-(o-acetoxybenzal)-γ-phenyl-Δβ,γ-butenolide (500 mg.), 5 ml. of 48% hydrobromic acid and 10 ml. of water in 25 ml. of glacial acetic acid was refluxed for six hours. The solution was then cooled to room temperature and poured into 100 ml. of water. The resulting solution was extracted with chloroform until the last chloroform layer was colorless. The chloroform solution was washed with two 25 ml. portions of water, dried over magnesium sulfate, and evaporated to dryness at room temperature. A solid, 3-phenacylcoumarin (302 mg., 71%), crystallized on evaporation of the solvent. The compound was identified by a comparison of its infra-red spectrum with that of an authenic sample and a lack of mixed melting point depression.

Basic Hydrolysis of α-(o-Acetoxybenzal)-γ-phenyl-Δβ, γ-butenolide

An ethanolic solution containing α-(o-acetoxybenzal)-γ-phenyl-Δβ,γ-butenolide (500 mg.) and potassium hydroxide (180 mg.) in 5 ml. of water was refluxed for two hours. The solution was then cooled, and acidified with concentrated hydrochloric acid. Upon dilution of the solution with water α-phenacyl-o-hydroxycinnamic acid (99 mg., 22%) crystallized from the reaction mixture. The compound was recrystallized from 95% ethanol-water, m.p. 191°-192°.

Ultraviolet spectrum λ max 243 (ϵ 12,900); λ max 310 (ϵ 4,510)
Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96 Found:
C, 72.13; H, 4.99

Synthesis of 3-(β-Phenylethyl)-dihydrocoumarin

A solution of α-(o-acetoxybenzal)-γ-phenyl-$\Delta\beta$, γ-butenolide (500 mg., 0.0016 mole) in 50 ml. if ethyl acetate was hydrogenated over 100 mg. of palladium-charcoal at room temperature and atmospheric pressure. The catalyst was removed by filtration, and the resulting solution was evaporated to dryness at room temperature. The oily residue, α-(β-phenylethyl)-o-acetoxyhydrocinnamic acid was not isolated but hydrolyzed directly. The residue was dissolved in 50 ml. of glacial acetic acid, then 10 ml. of 48% hydrobromic acid and 10 ml. of water were added, and the mixture was refluxed for four hours. The solution was cooled, diluted with water and extracted with three 25 ml. portions of chloroform. The chloroform solution was dried with magnesium sulfate and then evaporated to dryness. The resulting oil was a mixture of 3-(β-phenylethyl)-dihydrocoumarin and α-(β-phenylethyl)-o-hydroxyhydrocinnamic acid. The mixture was dissolved in 50 ml. of acetic anhydride and distilled until approximately 10 ml. of acetic anhydride remained. The remaining acetic anhydride was removed by evaporating the solution under vacuum. The residue was crystallized from

95% ethanol-water, and afforded 0.282 g. (71%) of 3-(β-phenylethyl)-dihydrocoumarin, m.p. 81°-82°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.55; H, 6.67

Found: C, 75.00; H, 6.69

Zinc Reduction of 3-Acetyl-3,4-phenacylidenecoumarin

Method A

A 500 mg. sample of 3-acetyl-3,4-phenacylidenecoumarin was dissolved in 25 ml. of glacial acetic acid, and the solution was cooled to 0° in an ice bath. One ml. of concentrated hydrochloric acid was then added to the solution followed by one gram of zinc. The resulting solution was swirled for three minutes in the ice bath, and then allowed to stand at room temperature for ten minutes. The excess zinc was removed by filtration and the resulting solution was diluted with water. Upon the addition of water, an amorphous yellow solid precipitated. The solid was filtered, and sublimed at 160° and 1.5 mm. pressure. The resulting sublimate (62 mg., 20%) was identified as 3-acetylcoumarin. The residue of the sublimation was dissolved in benzene and chromatographed on alumina. The petroleum ether fraction was concentrated and diluted with 95% ethanol. The resulting solution was then poured into a 95% ethanol solution containing 2,4-dinitrophenylhydrazine (100 mg.). After a few minutes the 2,4-dinitrophenylhydrazone (96 mg.), crystallized from

the solution. The derivative was identified as the 2,4-dinitrophenylhydrazone of acetophenone by comparison with an authenic sample.

Method B

The method of C. F. H. Allen (108) was employed in this reduction. The 3-acetyl-3,4-phenacylidenecoumarin (500 mg.) was dissolved in 15 ml. of glacial acetic acid and one ml. of water. Zinc dust (2.0 g.) was then added to the solution and the mixture was refluxed for one hour. The solution was cooled, filtered, and evaporated to dryness under vacuum. The resulting oil was dissolved in 25 ml. of absolute ethanol containing 400 mg. of sodium, and stirred for 12 hours under an atmosphere of nitrogen. The solution was then acidified with glacial acetic acid and evaporated to dryness under vacuum. The residue was dissolved in 15 ml. of benzene and chromatographed on alumina. Elution with 1:1 benzene-ether led to 61 mg. of 3-acetylcoumarin.

Oximation of 3-Acetyl-3,4-phenacylidenecoumarin

A solution consisting of hydroxylamine hydrochloride (0.239 g.) in 2 ml. of water was added to 25 ml. of ethyl acetate containing 3-acetyl-3,4-phenacylidenecoumarin (500 mg.). The solution was made homogeneous by the addition of sufficient 95% ethanol. The homogeneous solution was then allowed to stand at room temperature for 12 hours. The

solution was concentrated at room temperature until it became turbid. Thereupon it was allowed to stand at room temperature until crystallization was complete. The impure 3-acetyl-3,4-phenacylidenecoumarin oxime (305 mg.) melted between 225°-230°. Recrystallization from 95% ethanol-water gave crystals which melted between 229°-230°.

Sodium Borohydride Reduction of 3-Acetyl-3,4-phenacylidenecoumarin Followed by Acid Hydrolysis

The method described by Fieser (120) was employed. A 95% ethanol solution of 3-acetyl-3,4-phenacylidenecoumarin (500 mg.) was treated with sodium borohydride (100 mg.). After addition of the latter, the solution was allowed to stand for 10 minutes at room temperature. Approximately 10 ml. of water was added to the solution, and the solution was boiled for 10 minutes. The resulting solution was neutralized by the dropwise addition of glacial acetic acid. The product was not isolated, but hydrolyzed directly. The solution was acidified with 5 ml. of 48% hydrobromic acid and refluxed for four hours. The resulting solution was cooled and diluted with water and extracted with chloroform. The extract was dried over magnesium sulfate and evaporated to dryness at room temperature. The oily residue was dissolved in 20 ml. of benzene and chromatographed on alumina. Elution with 1:1 benzene-ether afforded yellow crystals of a compound (97 mg., 23%), m.p. 160°-164°, which were identified as 3-phenacylcou-

marin.

o-Nitrobenzalacetophenone

A dioxane solution containing o-nitrobenzaldehyde (3.0 g; .02 mole), acetophenone (4 ml.), and 5 ml. of concentrated hydrochloric acid was refluxed for 12 hours. At the end of the heating period, the solution was cooled and diluted with water until the solution became turbid. The resulting solution was then allowed to stand at room temperature until crystallization was complete, leading to yellow needles, o-nitrobenzalacetophenone (4.04 g., 80%), m.p. 123°-124°.

The Condensation between o-Nitrobenzalacetophenone and α -Chloroacetophenone

The method devised by Bodforss (97) was employed in the condensation, however the work-up of the reaction was modified. A solution of o-nitrobenzalacetophenone (2.05 g.) and α -chloroacetophenone (1.5 g.) in dioxane (20 ml.) and acetone (20 ml.) was prepared by warming, then a solution of sodium ethoxide (0.23 g. in absolute ethanol) was added dropwise to the stirred solution. The addition was complete at the end of a 15 minute period, but the solution was allowed to stir for 15 minutes more. It was acidified with concentrated hydrochloric acid and evaporated on a steam bath under vacuum. The brown residue was triturated with methanol, and almost immediately a yellow semi-crystalline solid precipitated.

The solid was crystallized from dioxane-water and identified as o-nitrobenzalacetophenone (1.70 g.). The filtrate was evaporated to dryness in vacuum, and the residue was dissolved in 10 ml. of warm benzene and chromatographed on alumina. Elution with 3:1 benzene-petroleum ether yielded a compound (50 mg.), m.p. 166°-176°, that was described by Bodforss to be 1-(o-nitrobenzyl)-2,3-dibenzoylcyclopropane. The compound was crystallized from 95% ethanol-water which raised the melting point to 176°-177°.

p-Nitrobenzalacetophenone

A solution of p-nitrobenzaldehyde (3.0 g.) and acetophenone (4 ml.) in dioxane was treated with 5 ml. of concentrated hydrochloric acid in the same manner as reported in the preparation of o-nitrobenzalacetophenone. The yellow product (4.3 g., 85%), was crystallized from dioxane and water, m.p. 165°-166°.

Attempted Condensation of p-Nitrobenzalacetophenone with α-Chloroacetophenone

A solution of p-nitrobenzalacetophenone (2.05 g.) and α-chloroacetophenone (1.5 g.) was treated in the same manner as that reported for the condensation of o-nitrobenzalacetophenone with α-chloroacetophenone. After the reaction was complete, the solution was evaporated to dryness on a steam bath under vacuum. The resulting residue was triturated with

a few ml. of methanol. The yellow solid, p-nitrobenzalacetophenone (1.83 g., 90%), precipitated from the methanolic solution. The filtrate was evaporated to dryness, dissolved in 20 ml. of benzene and chromatographed on alumina. Elution with benzene afforded 50 mg. of p-nitrobenzalacetophenone; however further elutions did not reveal any other products.

Ethyl p-Hydroxybenzalacetoacetate

A solution of p-hydroxybenzaldehyde (2.44 g., .02 mole) and ethyl acetoacetate (3.5 ml.) in 25 ml. of 95% ethanol was cooled to 0° in an ice bath. Piperidine (10 drops) was added and the solution was allowed to stand. The solution set to a solid mass after an hour, yielding 3.70 g. (80%) of ethyl p-hydroxybenzalacetoacetate, m.p. 136°-137°. The compound was crystallized from 95% ethanol.

Ultraviolet spectrum λ max. 239 (ϵ 13,100); λ max 328 (ϵ 18,300)

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02

Found: C, 66.65; H, 6.05

Attempted Condensation of Ethyl p-Hydroxybenzalacetoacetate with α-Chloroacetophenone

A solution of sodium ethoxide (.23 g. in absolute ethanol) which was added dropwise to a stirred solution of ethyl p-hydroxybenzalacetoacetate (2.34 g.) and α-chloroacetophenone (1.55 g.) in 100 ml. of absolute ethanol. The

solution then was stirred for 15 minutes, concentrated at room temperature until it became turbid and allowed to stand until crystallization was complete. The resulting yellow solid was filtered and identified as ethyl p-hydroxybenzal-acetoacetate (2.06 g.). The filtrate was evaporated dryness, and the oily residue was identified as ethyl p-hydroxybenzal-acetoacetate and α-chloroacetophenone by infra-red and ultraviolet analysis.

Ethyl m-Hydroxybenzalacetoacetate

A solution of m-hydroxybenzaldehyde (1.22 g.) and ethyl acetoacetate (1.5 ml.) in 25 ml. of 95% ethanol was treated with 20 drops of piperdine. The reaction was carried out in the same manner as in the condensation of p-hydroxybenzalde-hyde with ethyl acetacetate. The solution was evaporated to dryness and the residue dissolved in chloroform. The chloro-form extract was washed with three 25 ml. portions of 5% hydrochloric acid and dried over magnesium sulfate. The solution was evaporated to dryness, and the brown residue dissolved in 20 ml. of benzene and chromatographed on Celite-silicic acid. Elution with 1:1 ether-methanol yielded a light brown oil. The oil, ethyl m-hydroxybenzalacetoacetate (1.4 g., 61%) distilled between 198°-205° at 1.5 mm. pressure with decomposition.

Attempted Condensation of Ethyl m-Hydroxybenzalacetoacetate with α-Chloroacetophenone

The condensation was carried out in the same manner as that reported in the condensation of ethyl p-hydroxybenzal-acetoacetate with α-chloroacetophenone. A solution of ethyl m-hydroxybenzalacetoacetate (1.17 g.) and α-chloroaceto-phenone (.78 g.) in 50 ml. of absolute ethanol was treated with sodium ethoxide (120 mg. of sodium in absolute ethanol). The resulting solution was evaporated to dryness. The residue was shown to be ethyl m-hydroxybenzalacetoacetate by its infra-red spectrum.

3-Acetyldihydroucoumarin

A solution of 3-acetylcoumarin (500 mg.) in 50 ml. of ethyl acetate was hydrogenated at room temperature and atmos-pheric pressure in the presence of 100 mg. of 5% palladium-charcoal. The catalyst was removed by filtration and the solution was evaporated to dryness. The residue was sublimed at 85% and 1.5 mm. pressure to afford a white crystalline solid (400 mg., 60%), m.p. 62°-63°.

The Reactions of o-Hydroxybenzyl, m-Hydroxybenzyl and p-Hydroxybenzyl Alcohols with Fehling's Solution

o-hydroxybenzyl alcohol

A solution of salicylaldehyde (.1 ml.) in 95% ethanol was reduced by sodium borohydride (100 mg.) using the Feiser

method. After the excess sodium borohydride was destroyed, the solution was made alkaline by the addition of a few drops of sodium hydroxide. The solution was then treated with 6 ml. of Fehling's solution and boiled for ten minutes. The color of the Fehling's solution changed from blue to yellow indicating a positive test. Similar tests were negative in the meta case and positive in the para case.

SUMMARY

The structure assigned by Widman to the product of the reaction between 3-acetylcoumarin and phenacyl halides and sodium ethoxide has been reinvestigated and verified by chemical and spectroscopic means.

Data on the catalytic hydrogenation and zinc reduction of the coumarin are presented, structures of the products are proposed, and postulated mechanisms for their formation are discussed.

The synthesis of 3-alkyldihydrocoumarins by a reaction similar to an azlactone synthesis is presented.

A discussion of the stereochemistry of 3-acetyl-3,4-phenacylidenecoumarin is presented.

The mechanism of the condensation of 3-acetylcoumarin with α-haloacetophenones is illustrated.

The scope and limitations of the vinylogous Darzens reaction are discussed.

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