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The object of this work was to explore the generality of acetic anhydride-perchloric acid catalyzed C-acylations, to determine experimental conditions which maximize C-acylation, and to further elucidate the mechanism by which the C-acylation occurs.

The ability of acetic anhydride-perchloric acid systems to effect C-acylation of cyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone was demonstrated; the C-acylation yields are 36%, 40%, and 36% respectively. A reaction time of three hours with 1M acetic anhydride and 10^{-1}M perchloric acid in a solvent of low dielectric constant and weak electron donating power such as chloroform gives maximum C-acylation. The molar ratio of 1:10:1 for ketone : acetic anhydride : perchloric acid was found best for C-acylation. Tar formation is a considerable problem and material balance studies indicate from 65% - 82% recovery of material.

Several mechanistic possibilities are examined including: direct C-acylation of the enol form of the ketone, C-acylation of the enol acetate, and rearrangement of the enol acetate as possible mechanisms for the C-acylation of ketones in acetic anhydride-perchloric acid catalyzed systems. The direct C-acylation of the enol form of the ketone is found to be the mechanism most consistent with all the experimental data.

PERCHLORIC ACID CATALYZED ACYLATIONS

by

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TABLE OF CONTENTS

Part	Page
Title Page	i
Approval Page	ii
ACKNOWLEDGEMENTS	iii
TABLE OF CONTENTS	iv
LIST OF TABLES	vi
LIST OF FIGURES	vii
I. INTRODUCTION	1
II. EXPERIMENTAL	11
A. General	11
B. Preparation of Enol Acetates with Isopropenyl Acetate	11
1. Cyclohexen-1-yl acetate	11
2. α-Acetoxystyrene	12
3. 3-Methyl and 5-Methylcyclohexen-1-yl acetates	12
4. 2-Acetylcyclohexen-1-yl acetate	13
C. Acetic Anhydride-Perchloric Acid Reagents	14
1. Reagent 1	14
2. Reagent 2 and 3	14
3. Reagent 4	14
4. Reagent 5	14
5. Reagent 6	14
6. Reagent 7	15
7. Reagent 8	15
8. Reagent 9	15
D. Acetic Anhydride-Perchloric Acid Catalyzed Acylations	15
1. α-Acetoxystyrene	15
2. Cyclohexanone	16
a. Reaction with Reagents 1 through 7	16
b. Reaction with Reagent 8	18
c. Reaction with Reagent 9	20
3. Cyclohexen-1-yl acetate	20
4. 2-Methylcyclohexanone	21
5. 3-Methylcyclohexanone	22
6. 4-Methylcyclohexanone	23
E. Tar Formation	24

III. DISCUSSION OF RESULTS 26

IV. SUMMARY AND CONCLUSIONS 45

V. BIBLIOGRAPHY 47

LIST OF TABLES

Table		Page
1.	Perchloric Acid Reagents	15
2.	Relative Product Ratios from the Reaction of Cyclohexanone and Reagent 5	17
3.	Relative Product Ratios from the Reaction of Cyclohexanone and Reagents 6 and 7	18
4.	Product Identification and Material Recovery from Cyclohexanones and Reagent 8	36

LIST OF FIGURES

Figure	Title	Page
1.	Barton's Proposed O-Acetylation Mechanism	2
2.	O-Acylation of 10α-Des-A-cholestan-5-one	3
3.	Acetylation Products from Androstenone	4
4.	Proposed C-Acylation Mechanisms of Ketones via Acetic Anhydride-Perchloric Acid Reagents	5
5.	Acetylation Products from 17β-Hydroxy-androst-4-en-3-one	6
6.	C-Acylation of 17β-Acetoxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-lactone	7
7.	O-Acylation of Ketones According to Libman and Mazur	8
8.	Ketone O-Acylation Via Acetylium Perchlorate	8
9.	C-Acylation Pathways of Cyclohexanone Via Boron Trifluoride	9
10.	Possible Reaction Sequences for Formation of 2-Acetyl-cyclohexanone from Cyclohexanone	30
11.	Mechanism for Hydrolysis of Cyclohexen-1-yl Acetate by Perchloric Acid	34
12.	Nmr Spectrum 3-methylcyclohexen-1-yl acetate and 5-methylcyclohexen-1-yl acetate mixture	38
13.	Nmr Spectrum 3-methylcyclohexen-1-yl acetate	39
14.	Nmr Spectrum 5-methylcyclohexen-1-yl acetate	40
15.	Nmr Spectrum 3-methyl-2-acetylcyclohexanone and 5-methyl-2-acetylcyclohexanone mixture	41
16.	Nmr Spectrum 3-methyl-2-acetylcyclohexen-1-yl acetate	42
17.	Nmr Spectrum 5-methyl-2-acetylcyclohexen-1-yl acetate	43
18.	Acetic Anhydride-Perchloric Acid Catalyzed Acylation of Cyclohexanone	46

I. INTRODUCTION

The use of acetic anhydride-perchloric acid mixtures has been known for some time to O-acylate ketones to yield enol acetates and to C-acylate ketones and certain aromatic systems. Burton and Praill[1] propose that the acetylium cation, Ac^+, is the acylating species. The acetic anhydride molecule, according to Burton and Praill[1] is protonated by the strong acid and the acetylium cation is produced by elimination of acetic acid:

$$H^+ + Ac_2O \rightleftarrows Ac_2OH^+ \rightleftarrows Ac^+ + AcOH \qquad (1)$$

This acetic anhydride perchloric acid reagent was used to obtain a Friedel-Crafts type acylation of anisole to p-methoxyacetophenone. The important point from Burton and Praill[1] is the experimental evidence put forth for Ac^+ as an acylating species. Whereas acetic anhydride and perchloric acid were found to give acetylation of phenols, a reagent mixture of acetic acid and perchloric acid without the anhydride did not acetylate phenols. Thus $AcOH_2^+$ was ruled out as an acylating species. Also anisole was found to be converted into p-methoxyacetophenone in amounts greater than the molar amount of perchloric acid present. Thus the acylating agent must be regenerated. Burton and Praill[1] considered the reaction to be:

$$C_6H_5OMe + Ac^+ \longrightarrow MeOC_6H_4COMe + H^+ \qquad (2)$$

Reaction (2) then being followed by (1) to regenerate the Ac^+ acylating reagent. The p-methoxyacetophenone formed underwent further reaction to yield tars which were not identified; 80-90% of the materials were accounted for in products of reaction.

Using the work of Burton and Praill[1] as a basis, Barton et. al.[2] investigated the use of acetic anhydride and perchloric acid to O-acylate the ketone, 3β-acetoxyallopregnane-11:20-dione into the mono enol acetate at C-20. The desired product was obtained in yields of 67-85% depending upon the solvent utilized. Lower dielectric solvents gave higher yields so long as a homogeneous system could be maintained. Barton and co-workers[2] hypothesized the following mechanism:

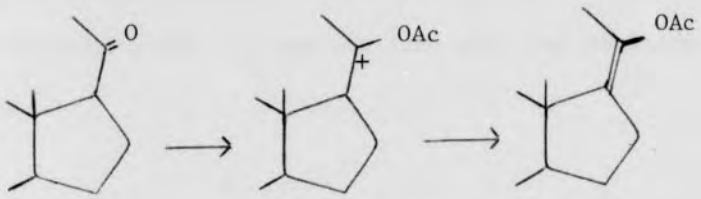


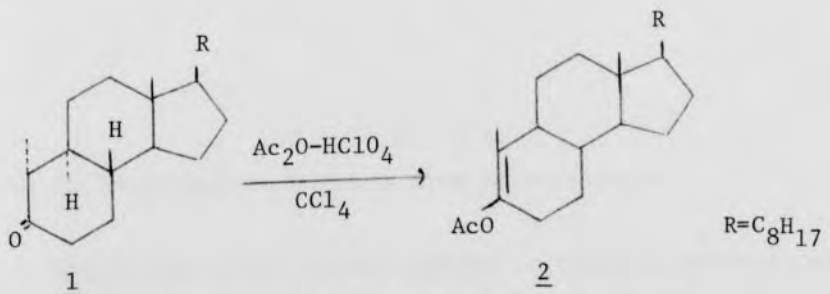
Figure 1. Barton's Proposed O-Acetylation Mechanism

The dependence of the yield of enol acetate upon the dielectric constant of the solvent was proposed to be due to the destabilization of the intermediate carbonium ion which then would quickly lose a proton to yield the enol acetate. Barton et. al.[2] imply that the acetylium ion,

Ac^+, directly acylates the ketone rather than the enol form.

In 1955 Burton and Praill[3] reviewed acylation reactions and included a section on perchloric acid-acetic anhydride reagents. At the date of the review, O-acylation of ketones and C-acylation of certain aromatic compounds and quinones had been reported. The existence of the acetylium ion Ac^+ as the acylating agent had been generally accepted. The possibility of $AcOH_2^+$ as the acylating agent had been discounted, and Ac_2O itself had not been considered as an acylation agent for either O- or C- acylation.

Using the method of Barton et. al.[2] Berkoz, Chavez, and Djerassi[4] O-acylated 17β-hydroxy-4α-methyl-5α-androstan-3-one and obtained 80-90% conversion to enol acetate in an approximate 2:1 ratio of Δ^3-enol acetate to Δ^2-enol acetate. Also utilizing the same experimental reagent[2] Hartshorn and Jones[5] O-acylated 10α-Des-A-cholestan-5-one, 1, and obtained only one enol acetate, 2, in 70% yield.

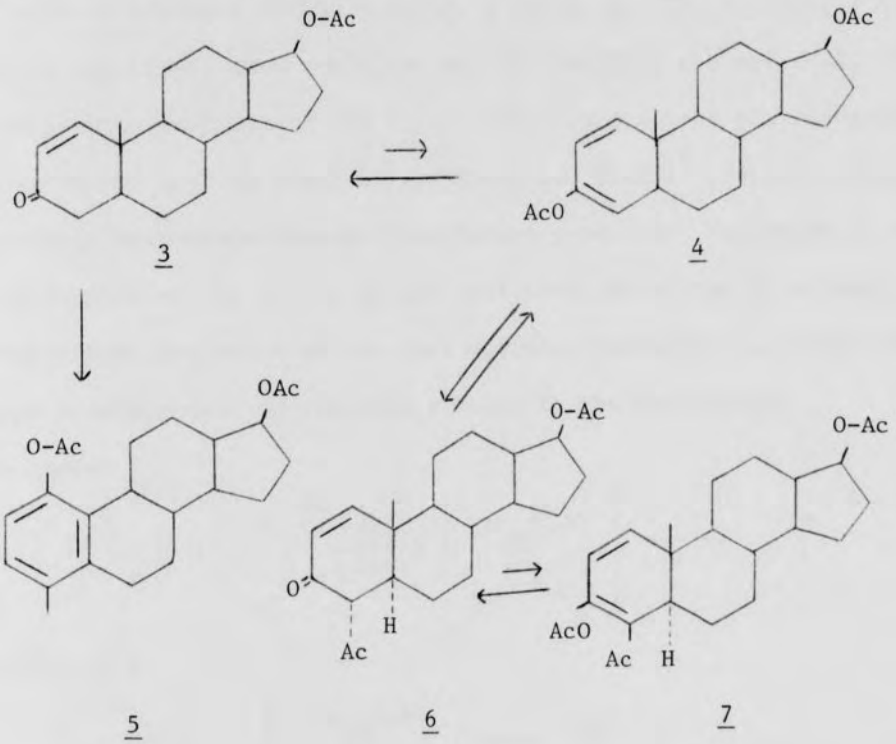


1 2

Figure 2. O-Acylation of 10α-Des-A-cholestan-5-one

Schenk and Fritz[6] used a reagent of acetic anhydride and perchloric acid in ethyl acetate to quantitatively determine phenols, thiols and amines from their acetates. Edwards and Rao[7] used an acetic anhydride-

perchloric acid in ethyl acetate reagent to obtain enol lactonization and enol acetylation of a number of steroidal systems. Rodig and Zanati[8] using one of the systems described by Edwards and Rao[7], obtained from androstenone, 3, the materials shown in Figure 3.



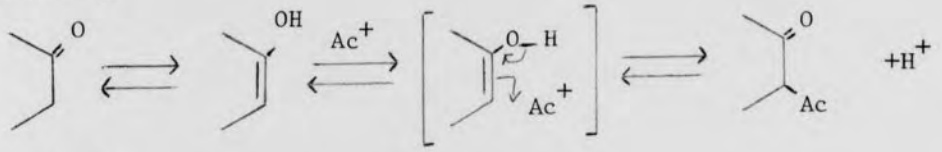
3 4 5 6 7

Figure 3. Acetylation Products from Androstenone

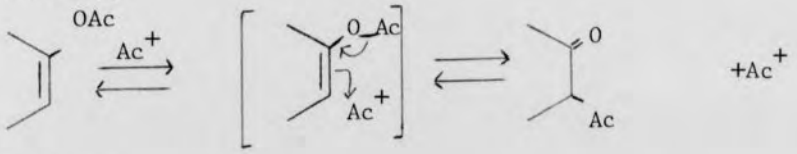
Using thin layer chromatography to identify products and estimate relative ratios, Rodig and Zanati found that similar product yields were obtained when 3 and 4 were used as starting materials. Using 6 and 7 as starting material, an equilibrium was reached after 2.5 hours in which mostly 6 was present; in this experiment none of 3, 4, or 5 was found. The relative proportion of C-acylation product

6 to O-acylation product 4 continued to increase throughout the 3.5 hour reaction time. The amount of 6 and 4 became equal after 2.5 hours. After a 4 hour reaction period the products were isolated by column chromatography and identified by spectral methods. The relative yields of products were: 3 (46%), 4 (11%), 5 (3%), 6 (15%), 7 (3.5%). Rodig and Zanati thus could account for 78.5% of the material. The C-acylation products of the type 6 and 7 were a type not reported by Edwards and Rao[7] in their work. Rodig and Zanati[8] proposed three possible mechanisms for the C-acylation products: Mechanism A, direct C-acylation of the ketone in its enol form; Mechanism B, Friedel-Crafts type acylation of the enol acetate; Mechanism C, Claisen-Haase type rearrangement of the enol acetate to the β-diketone.

Mechanism A



Mechanism B



Mechanism C

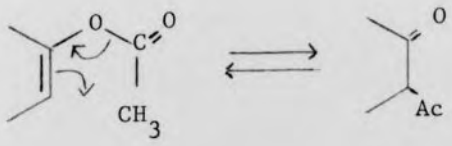


Figure 4. Proposed C-Acylation Mechanisms of Ketones via Acetic Anhydride-Perchloric Acid Reagents

Previously Gorodetsky and co-workers[9] had found the enol acetate to be an intermediate in the C-acylation of ketones via acetic anhydride and BF_3-etherate. In view of the findings of Gorodetsky[9], Rodig and Zanati felt that Mechanism B was the mechanism obtaining in the C-acylation of androstenone. Similarly, Liston and Toft[10] used a perchloric acid-acetic anhydride reagent in a benzene-carbon tetrachloride solvent system to obtain C-acylation of 17β-Hydroxy-androst-4-en-3-one, 8, as shown in Figure 5.

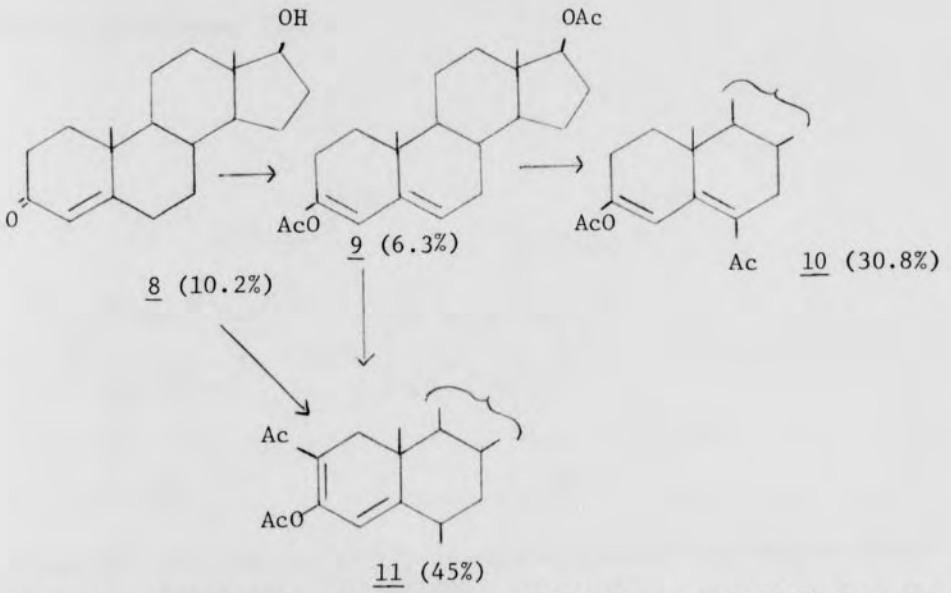
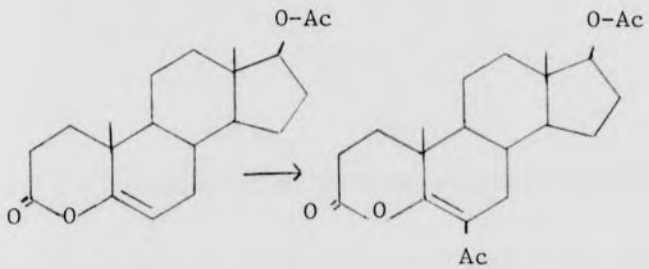


Figure 5. Acetylation Products from 17β-Hydroxy-androst-4-en-e-one

Liston and Toft used the lack of C-acylation at C-4 as evidence against Mechanism C, the rearrangement acylation. Parallel experiments using 8 and 9 as starting materials gave similar product mixtures with a slight increase (10.5%) in 10 when ketone, 8, rather than enol acetate, 9, was used as a starting material.

The similarity of product mixtures, in the opinion of Liston and Toft, indicated that both Mechanism A and Mechanism B obtain in the reaction and the increased formation of 10 from 8 was due to the operation of Mechanism A, the direct C-acylation of the ketone in its enol form, in the reaction. In a later paper, Rao, Burdett, and Edwards[11], utilizing a reagent stronger in both acetic anhydride and perchloric acid than previously[7], demonstrated the C-acylation of a steroidal enol lactone, 17β-acetoxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-lactone, (12).



12 13

Figure 6. C-Acylation of 17β-Acetoxy-3,5-seco-4-norandrost-5-en-3-oic acid 3,5-lactone

Dorofeenko, Dulenko, and Antoneko[12] obtained C-acylation of cyclohexanone in low yield (7-8%) using boiling acetic anhydride and cyclohexanone with catalytic amounts of magnesium perchlorate. Dorofeenko and co-workers ascribed the activity of their reagent to the generation of $Ac^+ ClO_4^-$, but did not propose any mechanism for the C-acylation of cyclohexanone.

The acid catalyzed O-acylation of ketones by acetic anhydride to give enol acetates had been generally regarded[13] as an attack by the acylating species on the small amount of enolic form of the ketone. A proton transfer agent was considered necessary to maintain a small amount of enol present in the system. However, Libman and Mazur[14] demonstrated that the O-acylation of ketones occurs through attack of anhydrides or mixed anhydrides on the keto form of the ketone as shown in Figure 7.

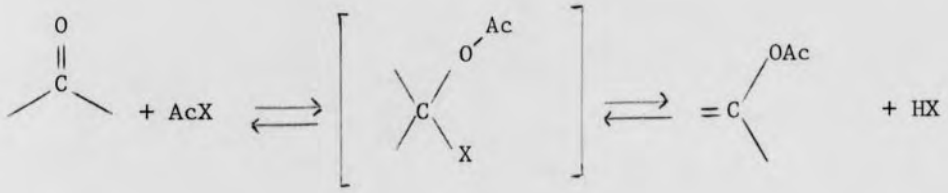


Figure 7. O-Acylation of Ketones According to Libman and Mazur

According to the O-acylation scheme of Libman and Mazur, the O-acylation of a ketone via acetic anhydride and perchloric acid would yield an enol acetate as shown in Figure 8.

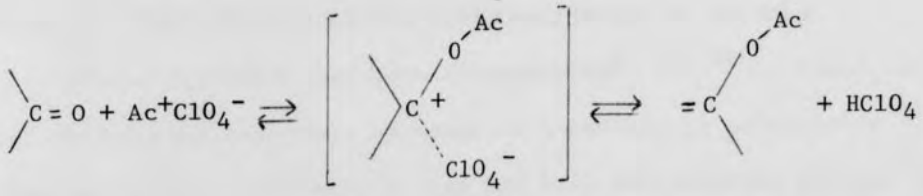


Figure 8. Ketone O-Acylation Via Acetylium Perchlorate

In working with boron trifluoride C-acylation of cyclohexanone, Hauser and co-workers[15] demonstrated that the β-diketone, 2-acetyl-

cyclohexanone arises through two mechanisms, direct C-acylation of the ketone and C-acylation of the anol acetate with subsequent loss of an acetyl moiety. Hauser's proposed pathways are shown in Figure 9.

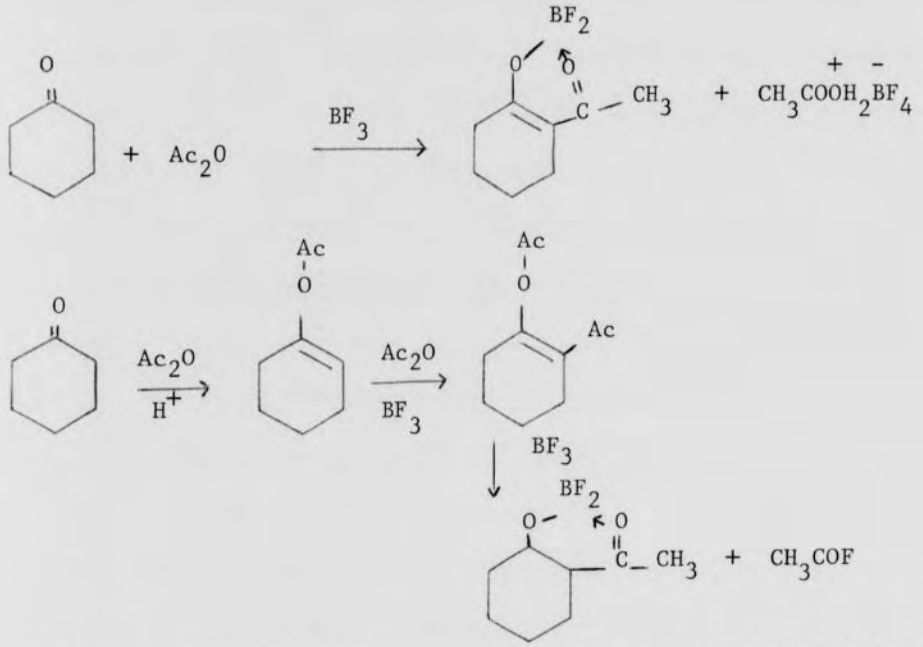


Figure 9. C-Acylation Pathways of Cyclohexanone Via Boron Trifluoride

Hauser's proposed C-acylation mechanisms of cyclohexanone by boron trifluoride correspond to Mechanism A and Mechanism B (Figure 4) in the acetic anhydride-perchloric acid C-acylation of ketones.

Thus C-acylation has been demonstrated[8, 10, 11] to occur, at least in steroidal systems, by means of a perchloric acid-acetic anhydride reagent. However, it had not been demonstrated whether the C-acylation was a general reaction with synthetic possibilities similar to boron trifluoride. The work described hereafter is aimed at finding the optimum conditions for C-acylation of some ketones and

enol acetates with perchloric acid and acetic anhydride and also at shedding more light on the mechanism or mechanisms involved.

II. EXPERIMENTAL

A. General

Infrared spectra were recorded on a Perkin Elmer Model 221 double-beam spectrophotometer. Gas chromatography was carried out on a Hewlett-Packard Research Chromatograph, Model 5750, helium carrier gas at 80 cc/min flow rate, 150 milliamp bridge power, 280° injection port temperature, 320° detector temperature, thermal conductivity detector. The gas chromatographic column used unless otherwise noted was 10% Carbowax 20M, 10 ft. by 1/4 inch O.D. on 60-80 mesh chromosorb W, acid washed, and treated with DMCS. Nmr spectra were obtained on a Varian A 60 A using $CDCl_3$ solvent. Mass spectra were obtained on a CEC 21103 C using 70 volts ionizing current.

All reagents were ACS reagent grade and all solvents were reagent grade or chromatoquality and were used without further purification except hexane and methylene chloride which were drum grade and were distilled and chromatographed on silicic acid prior to use.

B. Preparation of Enol Acetates with Isopropenyl Acetate

Enol acetates were prepared from reaction of the ketone and isopropenyl acetate with p-toluenesulfonic acid catalyst according to the method of Hagemeyer and Hull[16].

1. Cyclohexen-1-yl acetate

A solution of 24.5g (0.25 mole) cyclohexanone, 37.5g (0.37 mole) isopropenyl acetate and 0.5g p-toluenesulfonic acid were heated to

reflux on a Vigreux column 15cm long. The reflux was continued until acetone ceased to be given off. The pot material was washed twice with sodium bicarbonate solution, separated from the aqueous phase, and dried over anhydrous magnesium sulfate. The material distilling between 80-82°/15mm (lit.[16] b.p. 96°/50mm) was collected, and 19.3g (55%) cyclohexen-1-yl acetate was obtained; ir (KBr) 3.40, 3.50, 5.70, 5.90, 6.95, 7.35, 7.75, 8.25, 8.95, 9.35, 9.60, 9.90, 10.85, 11.10, 11.10, 11.70, 12.50, 12.80, 13.15μ.

2. α-Acetoxystyrene

A solution of 37.5g (0.37 mole) of isopropenyl acetate, 30.0g (0.25 mole) of acetophenone and 0.5g of p-toluenesulfonic acid were heated to reflux on a Vigreux column 15cm long. The reflux was continued until acetone ceased to be given off. The pot material was washed twice with sodium bicarbonate solution, separated from the aqueous phase, and dried over anhydrous magnesium sulfate. The fraction distilling at 118°/15mm (lit.[16] b.p. 85°/2mm) weighed 14.8g (37%); nmr ($CDCl_3$) δ2.15 (s, 3, $-O-\overset{O}{\overset{\|}{C}}-\underline{CH_3}$), 5.0 (d, 1, J=2Hz, $-\overset{O}{\overset{|}{C}}=C\overset{H}{\underset{H}{\diagup\diagdown}}$) 5.41 (d, 1, J=2Hz, $-\overset{|}{C}=C\overset{H}{\underset{H}{\diagup\diagdown}}$) and 7.35 ppm (m, 5, $\underline{C_6H_5}$).

3. 3-Methyl- and 5-Methylcyclohexen-1-yl acetates

A solution of 28.0g (0.25 mole) of 3-methylcyclohexanone, 37.5g (0.37 mole) isopropenyl acetate, and 0.5g p-toluenesulfonic acid were heated to reflux on a Vigreux column 15cm long. Acetone was removed by distillation. The organic material was washed with sodium bicarbonate solution, separated from the aqueous phase, dried over anhydrous magnesium sulfate. Distillation yielded 26.9g (70%) of isomeric 3-

methyl and 5-methylcyclohexen-1-yl acetates b.p. 76-77°/12.5mm; ir (KBr) 3.40, 3.50, 5.70, 5.90, 6.85, 6.95, 7.35, 8.25, 8.90, 9.35, 9.50, 9.95, 10.20, 10.95, 11.10, 11.50, 11.75, 12.95μ; nmr ($CDCl_3$) δ1.0 (d, 3, J=5Hz + J=7Hz $C\underline{H}_3$) 1.9 (m, 6, $C\underline{H}_2$), 2.09 (s, 3, $O\text{-}\overset{O}{\overset{\|}{C}}\text{-}C\underline{H}_3$), 5.30 ppm (m, 1, =C<u>H</u>-). Gas chromatography allowed separation of the two isomers found to be in the ratio 5-methyl- to 3-methyl- 1.00 to 0.75; 5-methylcyclohexen-1-yl acetate; nmr ($CDCl_3$) δ1.0 (d, 3, J=5Hz $C\text{-}C\underline{H}_3$), 1.65 (m, 3, $C\underline{H}_2$ [C-4], C<u>H</u> [C-5], 2.0 (m, 4, $C\underline{H}_2$ [C-3 and C-6]), 2.10 (s, 3, $O\text{-}\overset{O}{\overset{\|}{C}}\text{-}C\underline{H}_3$), 5.40 ppm (m, 1, =C<u>H</u>-); 3-methylcyclohexen-1-yl acetate; nmr ($CDCl_3$) δ1.0 (d, 3, J=7Hz, $C\text{-}C\underline{H}_3$), 1.7 (m, 5, $C\underline{H}_2$ [C-4, C-5], C<u>H</u> [C-3], 2.05 (m, 2, $C\underline{H}_2$ [C-6], 2.10 (s, 3, $O\text{-}\overset{O}{\overset{\|}{C}}\text{-}C\underline{H}_3$) and 5.3 ppm (m, 1, =C<u>H</u>-).

4. <u>2-Acetylcyclohexen-1-yl acetate</u>

A solution of 17.5g (0.125 mole) of 2-acetylcyclohexanone 18.5g (0.18 mole) of isopropenyl acetate and 0.25g of p-toluenesulfonic acid were heated to reflux on a Vigreux column 15cm long. The reflux was continued until acetone ceased to be given off. The pot material was washed twice with sodium bicarbonate solution, separated from the aqueous phase, and dried over anhydrous magnesium sulfate. The evaporated organic residue weighed 20.9g. A distillation of 19.9g of the organic material yielded 17.0g of distillable materials, and the remainder was a tarry, black residue. The fraction distilling at 120-125°/6mm (lit.[15] 126-129/10mm) was 9.9g (22%) 2-acetylcyclohexen-1-yl acetate; ir (KBr) 3.40, 3.50, 5.65, 5.90, 6.00, 6.05, 7.00, 7.35, 7.80, 7.95, 8.25, 8.50, 8.65, 9.05, 9.30, 9.70, 9.95, 10.20, 10.65, 10.95μ;

nmr ($CDCl_3$) δ1.70 (m, 4, $C\underline{H}_2$ [C-4 and C-5] 2.3 (m, 4, $C\underline{H}_2$ [C-3 and C-6]), 2.19 (s, 3, O-C-CH_3) 2.25 (s, 3, -C-CH_3).

C. Acetic Anhydride-Perchloric Acid Reagents

1. Reagent 1

To 40 ml of ethyl acetate was added 0.05 ml of 70% perchloric acid and 4.8 ml of acetic anhydride, and the solution was made up to 50 ml with ethyl acetate. The resulting solution was 1M in acetic anhydride and 1.2×10^{-2}M in perchloric acid.

2. Reagents 2 and 3

These reagents were the same as Reagent 1 except benzene and carbon tetrachloride respectively were used as solvents.

3. Reagent 4

This reagent was prepared similarly to reagent 1 using 0.05 ml of 70% perchloric acid and 9.6 ml of acetic anhydride. The resulting solution was 1.2×10^{-2}M in perchloric acid and 2.0M in acetic anhydride.

4. Reagent 5

To 80 ml of ethyl acetate was added 0.84 ml of 70% perchloric acid and 9.6 ml of acetic anhydride, and the resulting solution was made up to 100 ml with ethyl acetate. The resulting solution was 10^{-1}M in perchloric acid and 1.0M in acetic anhydride.

5. Reagent 6

This reagent was prepared similarly to reagent 5 using 0.84 ml of 70% perchloric acid and 4.8 ml of acetic anhydride. The resulting solution was 10^{-1}M in perchloric acid and 0.5M in acetic anhydride.

6. Reagent 7

This reagent was prepared similarly to reagent 5 using 0.84 ml of 70% perchloric acid and 38.4 ml of acetic anhydride. The resulting solution was 10^{-1}M in perchloric acid and 4.0M in acetic anhydride.

7. Reagent 8

This reagent was the same as Reagent 5 in chloroform solvent.

8. Reagent 9

Into 50 ml of ethylene chloride was placed 0.93 ml of 70% perchloric acid and 5 ml of 20% fuming sulfuric acid. Assuming 90% of the perchloric acid to be in the methylene chloride[17, 18], 5 ml of the methylene chloride phase would be equal to 0.001 mole of perchloric acid.

D. Acetic Anhydride-Perchloric Acid Catalyzed Acylations

1. α-Acetoxystyrene

To 0.100g (0.0062 mole) of α-acetoxystyrene was added 10 ml of

TABLE 1

Perchloric Acid Reagents

Reagent	$HClO_4$ Conc.	Ac_2O Conc.	Solvent	Reagent	$HClO_4$ Conc.	Ac_2O Conc.	Solvent
1	10^{-2}M	1.0M	EtOAc	6	10^{-1}M	0.5M	EtOAc
2	10^{-2}M	1.0M	C_6H_6	7	10^{-1}M	4.0M	EtOAc
3	10^{-2}M	1.0M	CCl_4	8	10^{-1}M	1.0M	$CHCl_3$
4	10^{-2}M	2.0M	EtOAc	9	0.2M	0	CH_2Cl_2
5	10^{-1}M	1.0M	EtOAc				

of Reagent 1, and the solution was allowed to stand at room temperature for 30 minutes. The solution was then washed with saturated sodium bicarbonate, dried over magnesium sulfate, evaporated to one milliliter and analyzed by gas chromatography. Only acetophenone, identified by retention time comparison, was found in the reaction mixture.

The experiment was repeated using Reagents 2 and 3. Again, only acetophenone was found.

2. Cyclohexanone

a. Reaction with Reagents 1 through 7

To 0.100g (0.00102 mole) of cyclohexanone was added 10 ml of Reagent 1, and the solution was allowed to stand at room temperature for periods ranging from 10 minutes to 24 hours. After workup as for α-acetoxystyrene, only cyclohexanone and cyclohexen-1-yl acetate were found in significant amounts by gas chromatographic analysis. The cyclohexen-1-yl acetate was identified by retention time comparison and ir comparison with the authentic sample prepared previously.

Reaction of cyclohexanone with Reagents 2, 3, and 4, and increasing the ratio of Reagent 1 to 20 ml per 1.00g of cyclohexanone did not result in any new product formation.

To 1.00g (0.0102 mole) of cyclohexanone was added 100 ml of Reagent 5 and allowed to stand for 35 minutes, 1 hour, 3 hours, 8 hours, and 24 hours. After the reaction time was complete, the reaction mixture was washed with 80 ml of saturated sodium bicarbonate. Twenty grams of solid sodium bicarbonate was added. The aqueous phase was separated

and back extracted with 3 x 75 ml of ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and the filtrate was evaporated in a rotary evaporator. The residue was very dark and viscous. A new product, identified as 2-acetylcyclohexanone by gas chromatographic retention time, ir, and nmr comparison with a commercial (Eastman) sample of 2-acetylcyclohexanone, was detected. Using relative peak area ratios from gas chromatographic analysis on Carbowax 20M as a measure, the relative product yields of cyclohexanone, cyclohexen-1-yl acetate, and 2-acetylcyclohexanone are shown in Table 2.

TABLE 2

Relative Product Ratios from the Reaction of Cyclohexanone and Reagent 5

Reaction Time	Residue Weight	Product Ratios		
		Cyclohexanone	Cyclohexen-1-yl Acetate	2-Acetylcyclohexanone
35 min	1.45g	10	84	6
1 hr	1.31g	10	71	19
3 hr	1.17g	10	48	42
8 hr	1.75g	17	28	55
24 hr	1.81g	31	trace	69

The three hour reaction procedure for cyclohexanone with Reagent 5 was repeated using Reagents 6 and 7. The results are shown in Table 3.

TABLE 3

Relative Product Ratios from the Reaction of

Cyclohexanone and Reagents 6 and 7

Reagent	Residue Weight	Product Ratios: Cyclohexanone	Cyclohexen-1-yl Acetate	2-Acetylcyclohexanone
6	0.98g	20	62	18
7	2.41g	trace	trace	trace

In no case was an attempt at materials balance made. It should be stated that the dark, tarry nature of the residue was noted in every case, and with Reagent 7 the products of reaction would not elute from the gas chromatograph.

The spectral data for 2-acetylcyclohexanone obtained by gas chromatographic trapping from the product mixture of cyclohexanone and Reagent 5 was : ir (KBr) 3.40, 3.50, 5.90, 6.25, 6.95, 7.10, 7.35, 7.65, 7.95, 8.10, 8.80, 9.35, 10.25, 10.55, 11.45, 11.75 and 12.20μ; nmr ($CDCl_3$) δ1.72 (m, 4, $\underline{CH}_2$ [C-4 and C-5]), 2.12 (s, 3, $\overset{O}{\overset{\|}{C}}-\underline{CH}_3$), 2.30 (m, 4, $\underline{CH}_2$ [C-3 and C-6]), 16.1 ppm (s, 1, -O-H); mass spectrum (70 eV) m/e 140, 125, 112, 98, 97, 70, 69, 55 and 43.

b. Reaction with Reagent 8

To 1.00g (0.0102 mole) of cyclohexanone was added 100 ml of Reagent 8. The solution was allowed to stand at room temperature for three hours after which time the reaction was quenched with 80 ml of saturated sodium bicarbonate solution and 20g of solid sodium bicarbonate. The aqueous phase was backwashed with 3 x 75 ml of chloroform.

The combined organic phases were dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated to a constant weight of 1.64g in a rotary evaporator. Gas chromatographic analysis of the residue showed a 2:1 ratio of 2-acetylcyclohexanone to cyclohexanone and no cyclohexen-1-yl acetate. This reaction with Reagent 8 was repeated and a residue of 1.27g was obtained. The residue was chromatographed on a 15cm x 2.5cm silicic acid column. Four fractions were taken using 150 ml of solvent for each fraction (95:5 Hexane: ether; 95:5 Hexane: ether; 50:50 Hexane:ether; 100 ether). The tarry residue atop the column was then eluted with methanol. The first four fractions eluted had a combined weight of 0.74g and a gas chromatography peak area ratio of 36:0:55:9 cyclohexanone: cyclohexen-1-yl acetate: 2-acetylcyclohexanone: 2-acetylcyclohexen-1-yl acetate. The latter material was identical in retention time and ir and nmr spectra with the 2-acetylcyclohexen-1-yl acetate prepared from 2-acetylcyclohexanone. Comparison of equimolar amounts of cyclohexanone, cyclohexen-1-yl acetate, 2-acetylcyclohexanone, and 2-acetylcyclohexen-1-yl acetate showed that there was no difference in their molar sensitivity in gas chromatographic analysis on Carbowax 20M. Hence, the peak area ratio can be taken as a molar product ratio. This means that the molar recovery of material was 23% cyclohexanone, 36% 2-acetylcyclohexanone and 6% 2-acetylcyclohexen-1-yl acetate for a total of 65% material recovery.

c. Reaction with Reagent 9

To 10 ml of methylene chloride containing 5 ml of Reagent 9 and 0.1g (0.001 mole) cyclohexanone was added dropwise with stirring 0.96 ml of acetic anhydride in 10 ml of methylene chloride. The addition was accomplished over a 30 minute period. The reaction mixture was kept at ice-bath temperature throughout the reaction. After the addition was complete, the solution was neutralized with sodium bicarbonate and the organic phase separated and evaporated to about one milliliter. Gas chromatographic analysis of the residue indicated that the dark material was mostly tars; however, some small peaks corresponding to cyclohexanone and 2-acetylcyclohexanone were observed.

3. Cyclohexen-1-yl acetate

Reaction of 0.100g of cyclohexen-1-yl acetate with 10 ml of Reagent 1 yielded a product ratio the same as from cyclohexanone and Reagent 1 under similar conditions.

A solution of 1.43g (0.0102 mole) of cyclohexen-1-yl acetate was allowed to react with 100 ml of Reagent 5. The reaction was quenched after three hours and worked up as described for cyclohexanone. The ratio of cyclohexanone: cyclohexen-1-yl acetate: 2-acetylcyclohexanone was 18:49:33.

A solution of 1.43g (0.0102 mole) of cyclohexen-1-yl acetate was allowed to react with 100 ml of Reagent 8. The reaction was quenched after three hours and worked up as described for cyclohexanone. The ratio of cyclohexanone: cyclohexen-1-yl acetate: 2-acetylcyclohexanone was 1:0:2; the same ratio obtained using cyclohexanone.

A solution of 1.43g (0.0102 mole) of cyclohexen-1-yl acetate in 100 ml of 10^{-1}M perchloric acid in ethyl acetate was allowed to stand at room temperature for 3 hours. The reaction mixture was worked up by the normal procedure. Gas chromatographic analysis indicated that the tarry residue contained cyclohexanone, a trace of cyclohexen-1-yl acetate and no 2-acetylcyclohexanone.

A solution of 0.140g (0.001 mole) of cyclohexen-1-yl acetate in 5 ml of methylene chloride and 5 ml (0.001 mole $HClO_4$) of Reagent 9 were allowed to stand at room temperature for two hours. At the end of two hours the solution was washed with sodium bicarbonate, evaporated to approximately one milliliter on a rotary evaporator, and analyzed by gas chromatography. The ratio of cyclohexanone: cyclohexen-1-yl acetate: 2-acetylcyclohexanone was 56:3:41.

4. 2-Methylcyclohexanone

A solution of 1.14g (0.0102 mole) of 2-methylcyclohexanone was mixed with 100 ml of Reagent 8 and allowed to stand at room temperature for three hours. The reaction was then quenched, and the product dried, evaporated, weighed (1.38g), and analyzed via silicic acid column chromatography and gas chromatography as described for cyclohexanone and Reagent 8. Indentification of the reaction products from 2-methylcyclohexanone is incomplete. The recovered material weighed 1.38g and the relative gas chromatographic peak areas and spectral data are given: 2-methylcyclohexanone (3%); 2-methylcyclohexen-1-yl acetate (41%): ir (KBr) 3.40, 3.50, 5.70, 5.80, 6.95, 7.35, 7.90, 8.25, 8.80, 9.05, 9.25, 9.40, 9.60, 9.95, 10.05, 10.70, 10.95,

11.15, 11.30, 11.55, 11.75, 11.95, 12.25, and 13.70μ; nmr ($CDCl_3$) δ1.52 (s, 3, C-$\underline{CH}_3$), 1.62 (m, 4, $\underline{CH}_2$ [C-4 and C-5]), 2.05 (m, 4, $\underline{CH}_2$ [C-3 and C-6]), and 2.10 ppm (s, 3, O-$\overset{O}{\overset{\|}{C}}$-$\underline{CH}_3$). Another major product (33%) had the following spectra: ir (KBr) 2.85, 3.40, 3.50, 5.80, 5.90, 6.90, 7.30, 7.40, 7.60, 8.05, 8.60, 8.80, 8.90, 9.05, 9.20, 9.45, 9.65, 9.90, 10.20, 10.50, 10.90, 11.20, 11.70, 13.15μ; nmr ($CDCl_3$) δ1.25 (d?, 3, J=4Hz), 1.7 (m, 6), 2.10 (d?, 3, J=1Hz), and 2.4 ppm (m, 2). A second unidentified major product (18%) had the following spectra: ir (KBr) 3.40, 3.50, 5.75, 6.95, 7.30, 7.75, 7.90, 8.10, 8.45, 9.05, 9.60, 9.85, 10.20, 10.50, 11.40, 11.75, 13.45μ; nmr ($CDCl_3$) δ1.48 (s), 1.6 (m), 2.03 (s), 2.09 (s), and 2.1 ppm (m). Another 5% (by gas chromatographic peak area) was divided among three small peaks upon which no spectral measurements were made.

5. 3-Methylcyclohexanone

A solution of 1.14g (0.0102 mole) of 3-methylcyclohexanone was mixed with 100 ml of Reagent 8 and allowed to stand at room temperature for three hours. The reaction was quenched, and the product dried, evaporated, and analyzed via silicic acid column chromatography and gas chromatography as described for cyclohexanone. The products identified and the yield were 7% 3-methylcyclohexanone, 7% 5-methyl-cyclohexen-1-yl acetate and 3-methylcyclohexen-1-yl acetate in a 1:2 ratio, 40% isomeric β-diketones 3-methyl-2-acetylcyclohexanone and 5-methyl-2-acetylcyclohexanone, 2.5% 3-methyl-2-acetylcyclohexen-1-yl acetate and 8.5% 5-methyl-2-acetylcyclohexanone. The 5-methylcyclo-hexen-1-yl acetate and 3-methylcyclohexen-1-yl acetate were identical

in gas chromatographic retention time, ir, and nmr spectra with authentic samples made by isopropenyl acetate acetylation of 3-methylcyclohexanone. Spectral data for the mixture of isomeric β-diketones 3-methyl-2-acetylcyclohexanone and 5-methyl-2-acetylcyclohexanone was: ir (KBr) 3.40, 3.45, 5.75, 5.85, 6.20, 6.85, 7.05, 7.25, 7.35, 7.50, 7.75, 8.05, 8.65, 8.75, 9.10, 9.30, 9.80, 10.00, 10.40, 10.50, 10.70, 11.20, 11.45, and 12.40μ; nmr ($CDCl_3$) δ1.00 (d, 3, $C-\underline{CH}_3$, J=5Hz), 1.73 (m, 3, $\underline{CH}_2$ [C-4] and $\underline{CH}$ [C-5]) 2.10 (s, 3, $C-\underline{CH}_3$), 2.34 (m, 4, $\underline{CH}_2$ [C-3 and C-6]), and 16.1ppm (s, 1, $\underline{OH}$). This last nmr appears to be the nmr mainly of 5-methyl-2-acetylcyclohexanone. The nmr spectrum of 5-methyl-2-acetylcyclohexen-1-yl acetate was: nmr ($CDCl_3$) δ1.0 (d, 3, $C-\underline{CH}_3$, J=5Hz), 1.7 (m, 3, $\underline{CH}_2$ [C-4] and $\underline{CH}$ [C-5]), 2.20 (s, 3, $O-C-\underline{CH}_3$), 2.27 (s, 3, $-C-\underline{CH}_3$), and 2.3 ppm (m, 4, $\underline{CH}_2$ [C-3 and C-6]). The nmr spectrum of 3-methyl-2-acetylcyclohexen-1-yl acetate was: nmr ($CDCl_3$) δ1.00 (d, 3, $C-\underline{CH}_3$, J=7Hz), 1.7 (m, 4, $\underline{CH}_2$ [C-4 and C-5]) 2.18 (s, 3, $O-C-\underline{CH}_3$), 2.2 (m, 3, $\underline{CH}_2$ [C-6] and $\underline{CH}$ [C-3]), and 2.25 ppm (s, 3, $-C-\underline{CH}_3$).

6. 4-Methylcyclohexanone

A solution of 1.14g (0.0102 mole) of 4-methylcyclohexanone was mixed with 100 ml of Reagent 8 and allowed to stand at room temperature for three hours. The reaction was quenched, and the product was dried, evaporated, and analyzed via silicic acid and column chromatography as described for cyclohexanone. The products identified and the yield were 31% 4-methylcyclohexanone; 1% 4-methylcyclohexen-1-yl acetate: ir (KBr) 3.45, 3.50, 5.45, 5.95, 6.90, 6.95, 7.35, 7.70, 7.75, 8.20, 8.95, 9.20, 9.65, 9.85, 10.00, 10.65, 11.05,

12.10, 12.25, 12.60, 13.10μ; nmr ($CDCl_3$) δ0.97 (d, 3, J=5Hz, CH-C<u>H</u>$_3$), 1.65 (m, 3, C<u>H</u>$_2$ [C-5] and C<u>H</u> [C-4]), 2.1 (m, 4, C<u>H</u>$_2$ [C-3 and C-6]), 2.10 (s, 3, O-$\overset{O}{\overset{\|}{C}}$-C<u>H</u>$_3$) and 5.32 ppm (m, 1, =C<u>H</u>-); 36% 4-methyl-2-acetylcyclohexanone: ir (KBr) 3.45, 3.50, 5.80, 5.90, 6.25, 6.85, 7.10, 7.40, 7.60, 7.70, 7.80, 8.05, 8.20, 8.70, 8.85, 9.20, 9.75, 9.85, 9.95, 10.55, 10.75, 11.85, 12.45, 13.90; nmr ($CDCl_3$) δ1.03 (d, 3, J=5Hz, CH-C<u>H</u>$_3$), 1.72 (m, 3, C<u>H</u>$_2$ [C-5] and C<u>H</u> [C-4]), 2.10 (s, 3, $\overset{O}{\overset{\|}{C}}$-C<u>H</u>$_3$), 2.35 (m, 4, CH_2 [C-3 and C-6], and 16.1 ppm (s, 1, -O<u>H</u>); 14% 4-methyl-2-acetylcyclohexen-1-yl acetate: ir (KBr) 3.40, 3.50, 5.70, 5.90, 6.00, 6.05, 6.90, 7.05, 7.70, 7.95, 8.05, 8.15, 8.30, 8.50, 8.65, 9.00, 9.15, 9.30, 9.60, 9.75, 9.95, 10.30, 10.60, 10.80, 11.10, 11.35, 13.35, 13.65μ; nmr ($CDCl_3$) δ1.01 (d, 3, J=5Hz, CH-C<u>H</u>$_3$) 1.7 (m, 3, C<u>H</u>$_2$ [C-5] and C<u>H</u> [C-4]), 2.20 (s, 3, O-$\overset{O}{\overset{\|}{C}}$-$CH_3$) 2.26 (s, 3, $\overset{O}{\overset{\|}{C}}$-$CH_3$), and 2.3 ppm (m, 4, CH_2 [C-3 and C-6]). A total of 82% of the material was accounted for by this analysis.

E. Tar Formation

The dark, tar fraction from the reaction of cyclohexanone and Reagent 8 was eluted from the silicic acid column by using methanol: ir (KBr) 3.0, 3.40, 5.85, 6.90, 7.35, 8.25, 9.20μ. The nmr spectrum had only broad bands.

To each of the following was added 10 ml of a 10^{-1}M perchloric acid in ethyl acetate solution: 0.10g cyclohexanone, 0.14g cyclohexen-1-yl acetate, 0.14g 2-acetylcyclohexanone, 0.18g 2-acetylcyclohexen-1-yl acetate, and 0.10 ml acetic anhydride. After twenty four hours the solution containing 2-acetylcyclohexanone had darkened considerably.

The solutions containing cyclohexen-1-yl acetate and 2-acetylcyclohexen-1-yl acetate had darkened slightly. The other two solutions and the 10^{-1}M perchloric acid solution had not darkened. The darkened solutions were chromatographed on silicic acid in capillary pipettes; first ether and then methanol was used as eluents. The methanol fractions were evaporated, and ir spectra were made on the residues: cyclohexen-1-yl acetate methanol fraction, ir (KBr) 2.85, 3.40, 5.85, 6.15, 6.90, 7.35, 8.20, 9.20μ; 2-acetylcyclohexanone methanol fraction, ir (KBr) 2.95, 3.45, 5.85, 7.25, 7.35, 8.20, 9.20μ; and 2-acetyl-cyclohexen-1-yl acetate methanol fraction, ir (KBr) 2.80, 5.85, 6.05, 7.0, 7.4, 9.20μ.

III. DISCUSSION OF RESULTS

The first problem in studying the C-acylation of ketones with acetic anhydride-perchloric acid systems was to determine the conditions which would maximize C-acylation. Three materials were chosen for the initial starting materials: cyclohexanone, cyclohexen-1-yl acetate, and α-acetoxystyrene. Since Rodig and Zanati[8] had obtained C-acylation of androstenone using a reagent which was 1M in acetic anhydride and 1.2×10^{-2}M in perchloric acid in ethyl acetate solvent, a system described by Edwards and Rao[7] for obtaining O-acylation of steroidal ketones, this reagent was tried first. The reagent hydrolyzed the α-acetoxystyrene to acetophenone and gave a mixture of cyclohexanone and cyclohexen-1-yl acetate from both cyclohexanone and cyclohexen-1-yl acetate. Using the latter two starting materials, trace amounts of materials other than the ketone or enol acetate were detectable by gas chromatography; but the amounts were too small for trapping and identification. Reaction times varying from 10 minutes to 24 hours were tried, but no significant C-acylation occurred. In order to determine whether increasing the reagent to starting material ratio (1:10:0.12 molar ratio of cyclohexanone: acetic anhydride: perchloric acid initially) would enhance C-acylation, the amount of reagent used was doubled (1:20:0.24 molar ratio) and the molarity of the acetic anhydride was doubled (1:20:0.12 molar ratio); but C-acylation was not induced by these changes. In other experiments carbon tetrachloride and benzene were utilized as solvents, but again no C-acylation was found using cyclohexanone as starting material, and α-acetoxystyrene was again hydrolyzed to acetophenone. The reagent system was then altered to 1M acetic

anhydride and 10^{-1}M perchloric acid in ethyl acetate. This reagent gave appreciable C-acylation product, 2-acetylcyclohexanone, when reacted with cyclohexanone. However, the reaction product was very dark and tarry, indicating that appreciable material might have been lost by polymerization of some sort. The reaction time was varied and the ratio of products was determined (Table 2). By referring to Table 2, one can see that the O-acylation occurs rapidly while the C-acylation occurs slowly and reduces the relative O-acylation yield. The product ratios in Table 2 do not take into account loss of material due to tar formation. The experimental data presented in Table 2 sheds little light upon the mechanism or mechanisms by which C-acylation occurs. Mechanism A (Fig. 4) in which the enol is directly C-acylated is consistent with the fact that the increased perchloric acid concentration in Reagent 5 would tend to shift the keto-enol equilibrium toward the enol thus increasing the amount of enol available for C-acylation. Mechanism B (Fig. 4) in which the enol acetate is C-acylated is consistent with the fact that the β-diketone increases directly as the enol acetate decreases. This relationship suggests that the enol acetate may be intermediate in the β-diketone formation. Mechanism C (Fig. 4) in which the enol acetate rearranges to the β-diketone is also consistent with the direct increase of β-diketone formation as the enol acetate decreases as shown in Table 2.

A comparison reaction was run using cyclohexen-1-yl acetate with Reagent 5. The resulting product ratio after three hours was 18:49:33 ketone: enol acetate: β-diketone as compared to the 10:48:42 ratio after three hours reaction time from cyclohexanone and Reagent 5. The increased relative proportion of 2-acetylcyclohexanone in the reaction with cyclohexanone indicates that Mechanism A is at least partially operative and that C-acylation is occurring via direct C-acylation of the ketone, probably in its enol form. Otherwise, one would expect the C-acylation product to be greater from the enol acetate starting material. Liston and Toft[10] also found a slight (10.5%) increase in the C-acylation product of 17β-hydroxyandrost-4-en-3-one when the ketone rather than the enol acetate was utilized as starting material. Had Mechanism B or C been totally the pathway to C-acylation, one would expect an increase in the C-acylation product from the enol acetate as starting material.

A further indication that Mechanism C is not operative is that when cyclohexen-1-yl acetate was reacted with perchloric acid in ethyl acetate, the major product was cyclohexanone and none of the β-diketone was found. This later experiment does not rule out the rearrangement mechanism because one could argue that the acetic anhydride is necessary to maintain the equilibrium of the ketone to enol acetate, which is the fast reaction, and that the enol acetate rearrangement to the β-diketone, which is the slow reaction, is thus not observed.

In an effort to determine what factor acetic anhydride concentration might play, the reagent system was changed; and instead of 1.0M acetic anhydride, 0.5M and 4.0M acetic anhydride were used. The results are given in Table 3. The decrease of C-acylation with decreased acetic anhydride in the 0.5M reagent does not help distinguish between Mechanism A and Mechanism B because one could argue that lessened anhydride would lessen the enol acetate present and thus, if Mechanism B obtained, would lessen the β-diketone formation. Likewise, if Mechanism A obtained the decrease of Ac^+ concentration would result in lessened β-diketone formation. Material loss through tar formation was the main result of 4.0M anhydride reagent. Thus no mechanistic conclusions were obtained.

The role played by the solvent in the reaction needed to be investigated. Three solvents, chloroform, carbon tetrachloride, and benzene, were chosen, but of these three only chloroform gave a homogenous solution with 1M acetic anhydride and 10^{-1}M perchloric acid. The dielectric constants of these two systems, acetic anhydride-perchloric acid in ethyl acetate and acetic anhydride-perchloric acid in chloroform, are not too different; the dielectric constant of chloroform is 4.8 at 20°[19] and the dielectric constant of ethyl acetate is 6.0 at 25°[16]. However, there is considerable difference in the basicity of the two solvents. Using the electron donating power of the solvent as a measure of basicity and defining benzene as $\Delta\nu_D=0$, Kagiya, Sumida, and Inoue[20] found chloroform to have a $\Delta\nu_D=-17$ and ethyl acetate to have a $\Delta\nu_D=39$. Thus ethyl acetate is

far more basic than chloroform. When the reaction was accomplished in chloroform as a solvent, all other conditions being the same as with ethyl acetate solvent, a 1:2 ratio of cyclohexanone to 2-acetylcyclohexanone was obtained with only trace amounts of cyclohexen-1-yl acetate found by comparison of gas chromatographic peak areas. When the reaction was repeated in chloroform, using cyclohexen-1-yl acetate as starting material, after three hours the same 1:2 ratio of ketone to β-diketone was found. As with the ethyl acetate procedure, the reaction product was very dark. If Mechanism B or Mechanism C were the only operative mechanisms it would seem that an increase of proportion of β-diketone would have been observed by starting with the enol acetate; this was not the case. Again, however, one could argue that the equilibrium between ketone and enol acetate is very rapid and that the β-diketone formation is very slow so that the systems are identical with regard to C-acylation whether one starts with the ketone or the enol acetate as indicated in Figure 10.

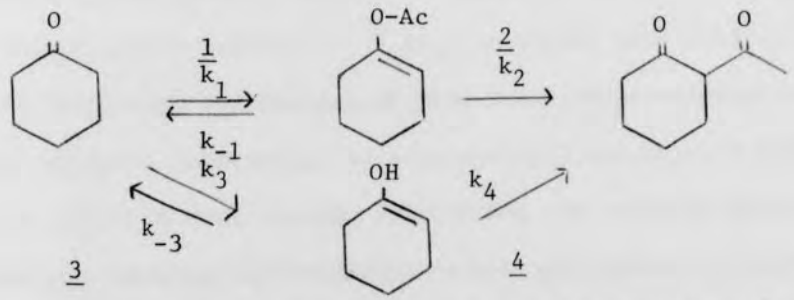


Figure 10. Possible Reaction Sequences for Formation of 2-Acetylcyclohexanone from Cyclohexanone

Thus if $k_{-1} >> k_2$ then the relative yield of β-diketone would be the same whether one started with ketone or enol acetate even if Mechanism B or Mechanism C obtained. From the point of view that Mechanism A is the route to C-acylation, one would expect the same ketone to diketone equilibrium if k_{-1} were very large and could maintain a high concentration of ketone and enol form of ketone present in the system. Thus no definite conclusions can be drawn from this evidence. The great variation in ketone: enol acetate: β-diketone ratio between the two solvents is, however, worthy of speculation. Starting with the ketone and referring to Figure 10, one would expect that in less basic solvent systems one would have a pronounced effect upon the equilibria 1 and 3. In chloroform, the less basic solvent, the proportion of material going through equilibrium 3 would be greater. That equilibrium 3 is not the initial step of O-acylation has been demonstrated by Libman and Mazur[14] and Libman, Sprecher, and Mazur[21] who show that the enol acetate is formed from the keto form of the ketone via a gem-diester. It is demonstrated by Mazur and co-workers[14, 21] that, although some acid is necessary in order to obtain elimination of HOAc from the gem-diester to give the enol acetate, increasing the acid strength too greatly reduces the total yield of enol acetate by reducing the relative amount of keto form present. Although the evidence is not conclusive, it seems that Mechanism A is totally or together with Mechanism B partially responsible for the C-acylation, otherwise one would have expected, according to Figure 10, a decrease in C-acylation with increased acid strength of the system. This is consistent with what Liston and Toft[10] proposed

except they implied that, if a dual mechanism exists, Mechanism B is probably more important than Mechanism A. Another experiment was conducted to determine whether Mechanism A was indeed the route for C-acylation. If the ketone were placed in solution with perchloric acid without acetic anhydride, a keto-enol equilibrium would be established as shown in equilibrium 3 Figure 10. If acetic anhydride were then added, the acetylium ion would be formed and C-acylate the enol form to a greater extent than if the acetic anhydride-perchloric acid reagent were added to the ketone because the acetic anhydride might not have the chance to O-acylate the keto form as proposed by Mazur and co-workers[14, 21]. There is, however, a problem in this approach. Given that the enol form will be present to a greater extent if the ketone is placed in strong acid solution, equilibrium 3 (Fig. 10) may be faster than Ac^+ formation in which case the anhydride would detect more of the keto form than acetylium ion would detect enol form. There is reason to believe, based upon this work and that of others[8, 10] that k_4 (Fig. 10) is small, and that equilibria 1 and 3 are fast. At any rate, the experiment was run in methylene chloride with anhydrous perchloric acid prepared as described by Klages and Hegenberg[17] with the result that there was a great loss of material and the products formed were dark and tarry and not eluted from the gas chromatograph. It seems most likely that what occurred was either an aldol condensation of the cyclohexanone or some type of polymerization reaction of the acylation products as have been previously noted in this work. The aldol

type condensation would not be unexpected since Libman, Sprecher, and Mazur[22] detected this type of condensation product when 3-oxo-steroids were placed in strong acid solution.

Another experiment was conducted using the anhydrous perchloric acid solution in which equimolar amounts of perchloric acid and cyclohexen-1-yl acetate were allowed to react for two hours. Upon workup, the reaction products were found to be cyclohexanone and 2-acetylcyclohexanone with a trace of cyclohexen-1-yl acetate. The occurrence of C-acylation in this system proves that Mechanism B is not necessary for C-acylation because in this dilute solution, 0.1M in cyclohexen-1-yl acetate and 0.1M in $HClO_4$, it is doubtful whether enough of the acetylium ion, Ac^+, could be generated in solution to C-acylate the remaining enol acetate; especially since, from Table 3, it is seen that reducing the acetic anhydride concentration from 1.0M to 0.5M greatly reduces the C-acylating ability of the reagent. In this system Ac^+ would necessarily be less than 0.1M. These results therefore negate the likelihood of Mechanism B in C-acylation. This leaves a choice between Mechanisms A and C. It would be easy to assume Mechanism C is occurring merely as an acid catalyzed rearrangement of the enol acetate. However, previous results in this work and elsewhere[10] indicate that C-acylation is lessened when the enol acetate rather than the ketone is used in acetic anhydride and perchloric acid systems and no C-acylation was found when 70% perchloric acid was placed in ethyl acetate with cyclohexen-1-yl acetate. These last two pieces of experimental

evidence tend to discount the likelihood that Mechanism C is the route for C-acylation. Instead, it could happen that trace amounts of water in the system catalyze the hydrolysis of enol acetate via the mechanism proposed by Noyce and Pollack[23]. In the presence of perchloric acid, cyclohexanone could be expected to be found largely in the enol form. The perchloric acid could also lead to acetylium ion formation during the hydrolysis as shown in Figure 11. In methylene chloride, which has a low dielectric constant (9.08 at 20°[19]) and is not a basic solvent ($\Delta\nu_D$=-12[20]), the acetylium ion and the enol form of the cyclohexanone would be trapped in the same solvent cage and thus lead directly to C-acylation according to Mechanism A.

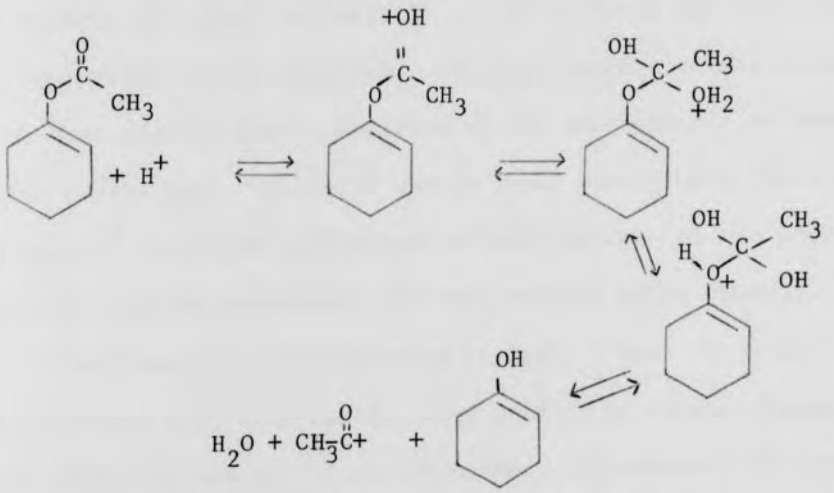


Figure 11. Mechanism for Hydrolysis of Cyclohexen-1-yl Acetate by Perchloric Acid

No experiment has been conducted which definitely indicates that only Mechanism A, B, or C is operative. However, several experiments have strongly indicated against Mechanism B and Mechanism C,

especially the lowered C-acylation yield when using enol acetate as a starting material rather than ketone and the occurrence of C-acylation in an "anhydrous" methylene chloride system with equimolar enol acetate and perchloric acid. It thus seems that Mechanism A, the C-acylation of the ketone in its enol form by attack of acetylium ion, is the mechanism most consistent with the data given here and elsewhere[8, 10].

Utilizing Reagent 8 which gave maximum C-acylation and minimum tar formation as judged by discoloration of the reaction mixture, the products of acylation of cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone were investigated. The results are given in Table 3. A new product, the enol acetate of the β-diketone was detected. The enol acetate of the β-diketone could have arisen from C-acylation of the enol acetate or O-acylation of the β-diketone. The later course seems more likely since Rodig and Zanati[8] found the β-diketone and enol acetate of the β-diketone to be in equilibrium without the enol acetate being present.

The product yields reported in Table 3 were obtained by cleaning the polymeric tars from the reaction product by column chromatography. Using authentic samples of cyclohexanone, cyclohexen-1-yl acetate, 2-acetylcyclohexanone and 2-acetylcyclohexen-1-yl acetate, it was determined that the molar sensitivities of these materials as measured by gas chromatography on Carbowax 20M was the same. Thus the gas chromatography peak area was taken as the molar ratio of products in the analyzed fractions. The reaction products from cyclohexanone

TABLE 4

Product Identification and Material Recovery

from Cyclohexanones and Reagent 8

Ketone Starting Material	Reaction Products and % Yield				
	Ketone	Enol Acetate	β-Diketone	β-Diketone enol Acetate	% Material Accounted For
Cyclohexanone	23%	trace	36%	6%	65%
2-Methylcyclohexanone[a]	3%	41%[b]	33%[c]	18%[c]	---
3-Methylcyclohexanone	7%	7%[d]	40%[e]	11%[f]	65%
4-Methylcyclohexanone	31%	1%	36%	14%	82%

a. Percentages are relative gas chromatographic peak areas, not yields.

b. Only 2-methylcyclohexen-1-yl acetate, no 6-methylcyclohexen-1-yl acetate found.

c. Unidentified material(s).

d. 2:1 ratio of 5-methylcyclohexen-1-yl acetate to 3-methylcyclohexen-1-yl acetate.

e. Mostly 5-methyl-2-acetylcyclohexanone according to nmr data.

f. 2.5% 3-methyl-2-acetylcyclohexen-1-yl acetate, 8.5% 5-methyl-2-acetylcyclohexen-1-yl acetate.

were identified by spectral comparison (ir and nmr) and gas chromatography retention time comparison to authentic samples. Product identification from 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone was made by comparison of retention time and ir and nmr spectra with the analagous material from cyclohexanone. The assumption that the enol acetate of 2-methylcyclohexanone was totally enolized toward the methyl was based upon the lack of a vinyl proton signal in the nmr. The assignment of isomeric products from 3-methylcyclohexanone was based upon the nmr assignment of protons on the cyclohexanone ring (Figures 12-17); those protons adjacent to the ring double bond are shifted further downfield. Also the more strained 3-methyl products were detectable by the increased splitting of the methyl signal (J=7Hz for 3-methyl and J=5Hz for 5-methyl isomers). The difference in J values was also reported by Descotes and Querou[24] who reported the J=5Hz for 5-methyl-2-acetylcyclohexanone and J=7Hz for 3-methyl-2-acetylcyclohexanone. Descotes and Querou also reported the C=C of the enol at ν=1610 cm^{-1} for the 5-methyl product and 1600 cm^{-1} for the 3-methyl product. The β-diketone product from 3-methylcyclohexanone had ir and nmr data more consistent with the 5-methyl isomer than with the 3-methyl isomer, and no separation of the gas chromatographic peak could be effected by lowering the column temperature or changing from Carbowax 20M to SE-30 columns. The C-acylation product from 3-methylcyclohexanone is probably mostly 5-methyl-2-acetylcyclohexanone.

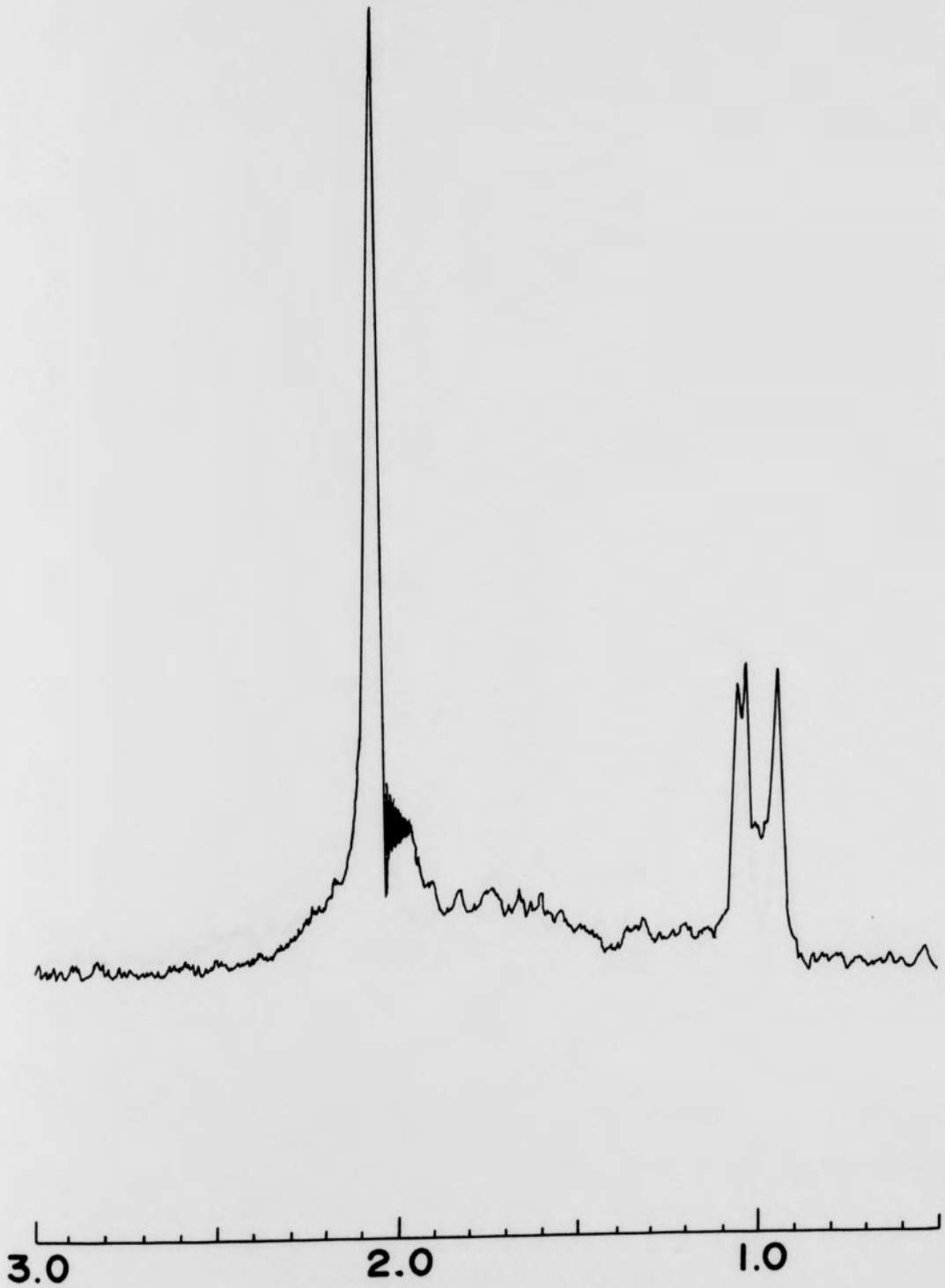


Figure 12. Nmr Spectrum 3-methylcyclohexen-1-yl acetate and 5-methylcyclohexen-1-yl acetate mixture.

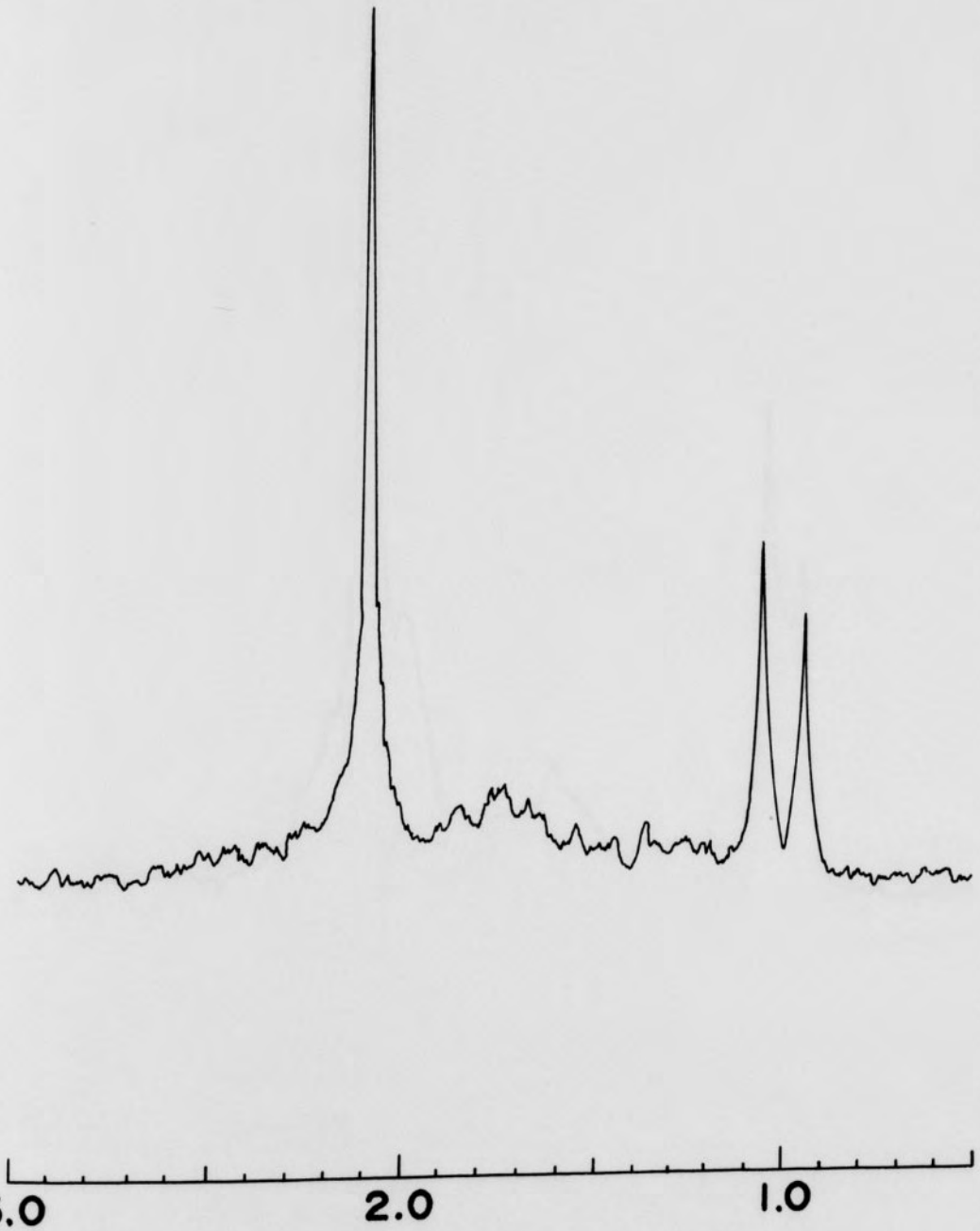


Figure 13. Nmr Spectrum 3-methylcyclohexen-1-yl acetate.

Figure 14. Nmr Spectrum 5-methylcyclohexen-1-yl acetate.

Figure 15. Nmr Spectrum 3-methyl-2-acetylcyclohexanone and 5-methyl-2-acetylcyclohexanone mixture.

Figure 16. Nmr Spectrum 3-methyl-2-acetylcyclohexen-1-yl acetate.

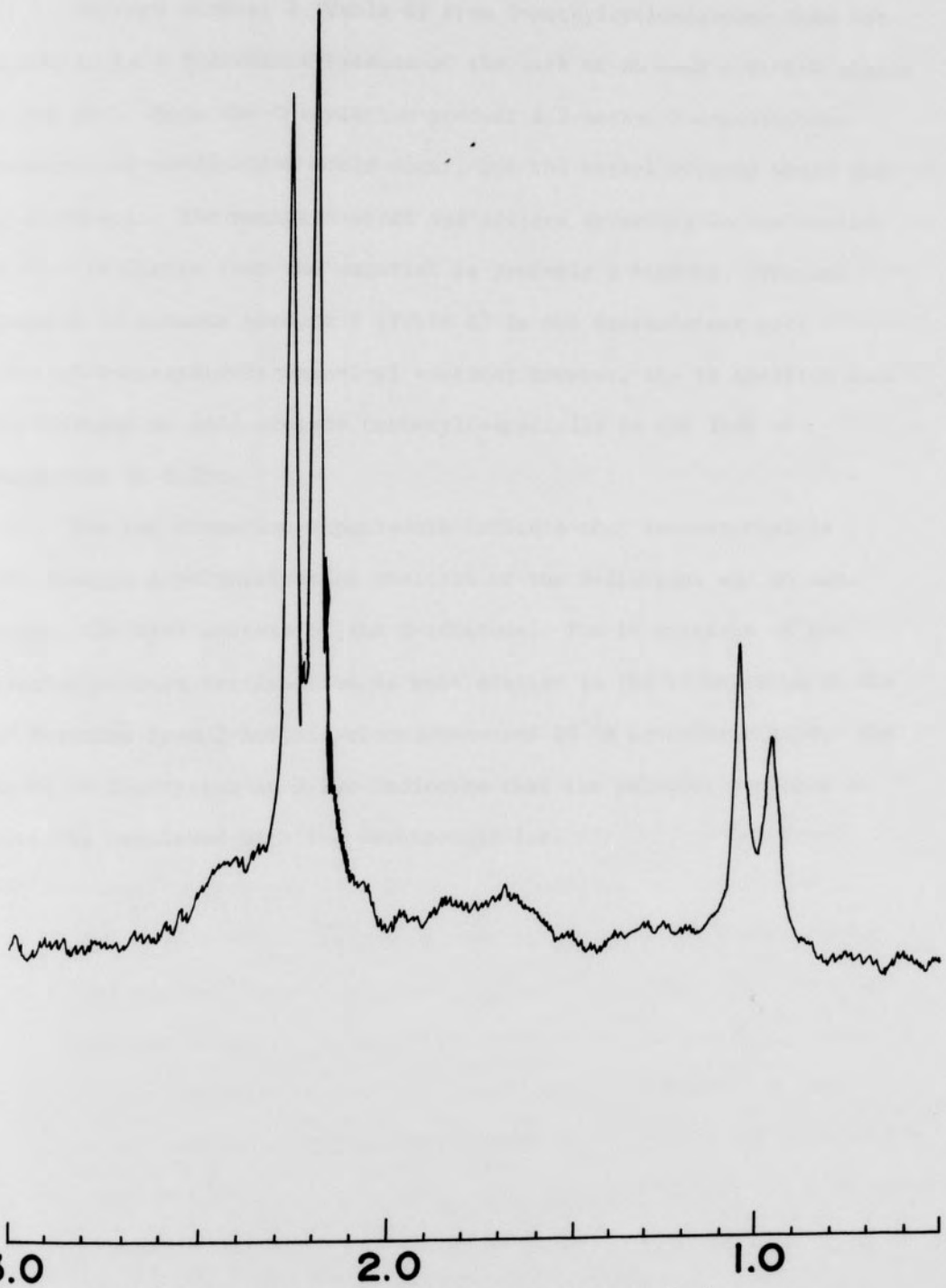


Figure 17. Nmr Spectrum 5-methyl-2-acetylcyclohexen-1-yl acetate.

Unknown product 1 (Table 4) from 2-methylcyclohexanone does not appear to be a β-diketone because of the lack of an enol hydrogen signal in the nmr. Were the C-acylation product a 2-methyl-2-acetylcyclohexanone, no enolization would occur, but the methyl protons would not be a doublet. The methyl doublet and acetate or methyl ketone doublet at δ2.1 indicates that the material is probably a mixture. The nmr spectrum of unknown product 2 (Table 4) is not inconsistent with 2-methyl-6-acetylcyclohexen-1-yl acetate; however, the ir spectrum does not indicate an enol acetate carbonyl especially in the lack of absorption at 8.25μ.

The tar formation experiments indicate that the material is lost through a polymerization reaction of the β-diketone and to some extent, the enol acetate of the β-diketone. The ir spectrum of the reaction product tar fraction is most similar to the ir spectrum of the tar fraction from 2-acetylcyclohexanone and 10^{-1}M perchloric acid. The strong ir absorption at 9.20μ indicates that the polymer, probably an aldol, is complexed with the perchlorate ion.

IV. SUMMARY AND CONCLUSIONS

The object of this work was to explore the generality of acetic anhydride-perchloric acid catalyzed C-acylations, to determine experimental conditions to maximize C-acylation, and to further elucidate the mechanism by which acetic anhydride and perchloric acid C-acylations occur.

The ability of acetic anhydride-perchloric acid systems to effect C-acylations of non-steroidal ketones was demonstrated using cyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone in which the C-acylation yields were 36%, 40%, and 36% respectively. The use of the same reaction mixture was tried on 2-methylcyclohexanone, but the products of this reaction have not been completely identified and the presence of a C-acylation product has not been confirmed.

The parameters investigated in the optimization study were: time, acetic anhydride concentration, perchloric acid concentration, and solvent effects. A constant problem was the formation of tars during the course of the reaction. The time factor seemed very important; the C-acylation required approximately three hours to reach a maximum. Reducing the acetic anhydride concentration below 1M drastically affected the C-acylation yield, while increasing the acetic anhydride concentration above 1M caused tar formation to be so great that little else was found in the reaction mixture. A perchloric acid concentration of at least 10^{-1}M was found to be necessary for appreciable C-acylation to occur. The effect of solvent is major; O-acylation was minimized and C-acylation was maximized by using solvents which were poor dielectrics and poor bases.

Chloroform was determined to be the most suitable solvent.

Previous workers[8, 10] considered three possible mechanisms (A, B, and C, Fig. 4) for C-acylation: the direct C-acylation of the ketone in its enol form, the C-acylation of the enol acetate, the rearrangement of the enol acetate. The previous workers[8, 10] favored Mechanism B, the C-acylation of the enol acetate. This work however shows that Mechanism A, the direct C-acylation of the ketone in its enol form is the mechanism most consistent with all of the available data. The flow diagram and material yield for the acylation of cyclohexanone as proposed from this work is shown in Figure 18.

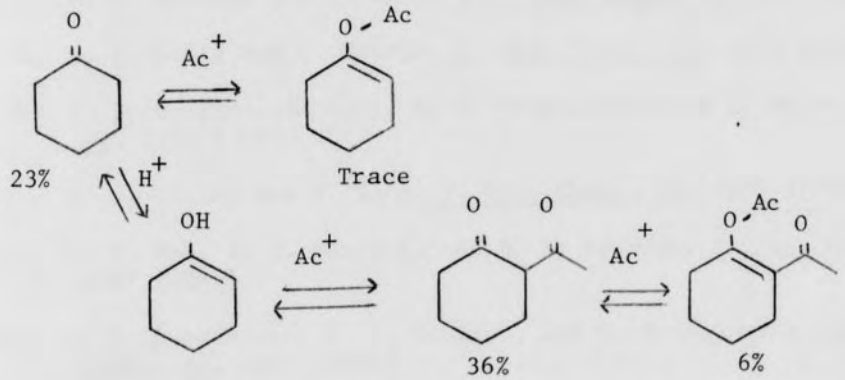


Figure 18. Acetic Anhydride-Perchloric Acid Catalyzed Acylation of Cyclohexanone.

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