SYNTHESIS OF γ-OXOACIDS FROM α,β-UNSATURATED KETONES

By

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SYNTHESIS OF γ-OXOACIDS FROM

α,β-UNSATURATED KETONES

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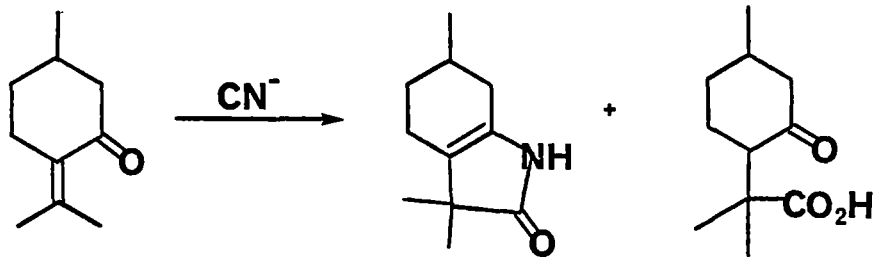
CHAPTER I

INTRODUCTION AND HISTORICAL

This study of the synthesis of γ-oxoacids through treatment of α,β-unsaturated ketones and their relationship to β,γ-enelactams was suggested by the earlier work of Lapworth[1] in which (+)pulegone (**1**) was treated with cyanide ion and in the process the enelactam **2** and the γ-oxoacid **3** were obtained as shown below.

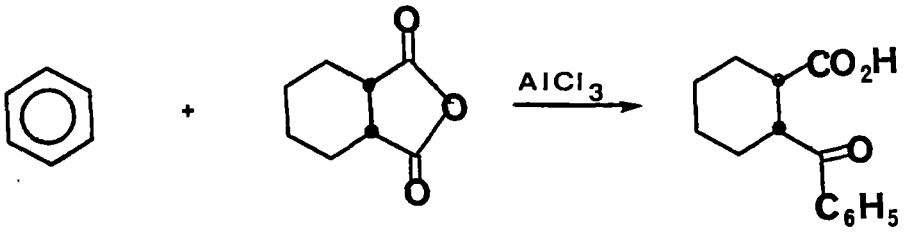


1 **2** **3**

The discussion of this reaction will be treated in the next chapter. To gain an appreciation of the effectiveness of this reaction in producing **2** and **3**, a literature search of major methods of γ-oxoacid synthesis was made. These synthesis routes constitute the Introduction and Historical portion of this thesis and are presented with examples as follows.

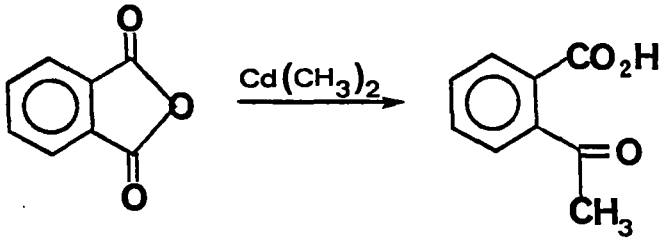
Friedel-Crafts Synthesis

The Friedel-Crafts synthesis involving aromatic hydrocarbon(s), anhydride(s) and aluminum chloride catalyst is probably the most widely used synthesis route to γ-oxoacids but it is restricted to aromatic hydrocarbons. A typical example[2a,b] is shown on the next page.



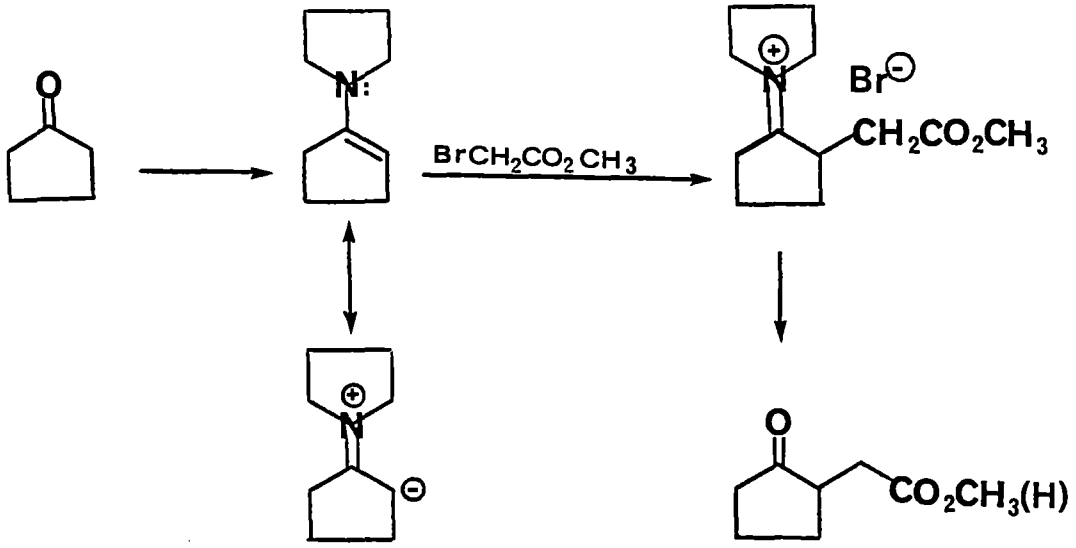
Grignard Reagent

The Grignard reagent (RMgX) has been used to prepare γ-oxoacids from substituted succinic anhydrides. However, in some cases the reaction of a second mole cannot be halted and this results in a lactone rather than a γ-oxoacid. Dimethyl cadmium[3] is more selective and provides an effective route as shown below.



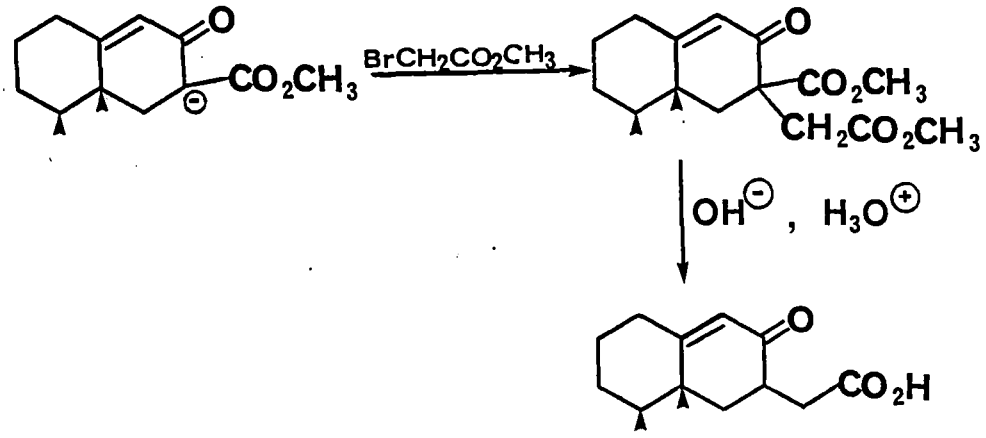
Enamine Reaction

The invention of the Stork enamine reaction[4] applied to ketones, provided one of the better methods for the synthesis of γ-oxoacids or γ-oxoesters. A typical example is presented below in which the enamine is prepared from cyclopentanone and pyrrolidine and then used to prepare the γ-oxoester.



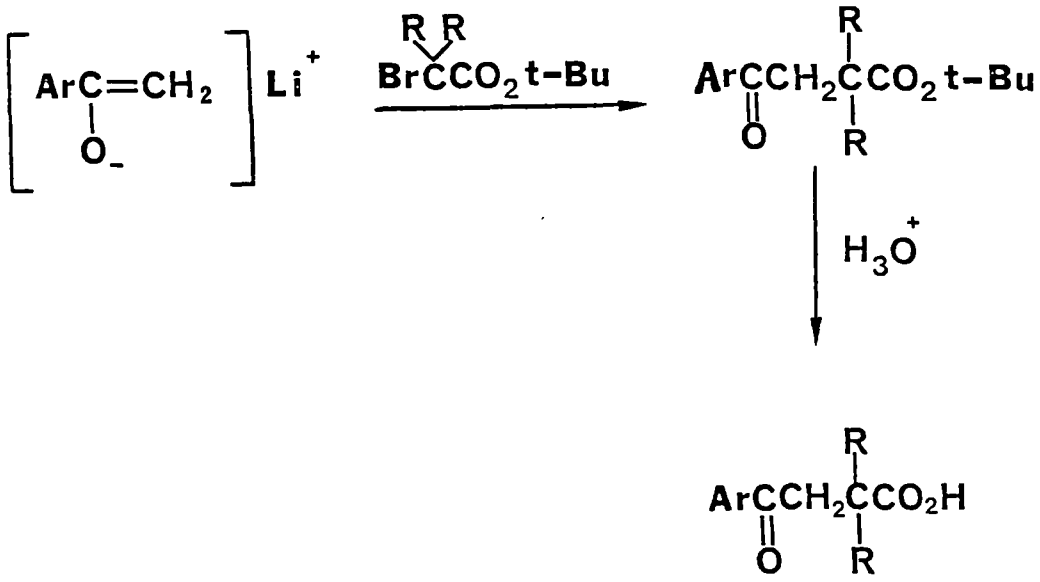
Synthesis via β-Oxoester

Alkylation of an anionic center will also provide γ-oxoester which can be hydrolyzed to the corresponding γ-oxoacid. This reaction has some similarity to the Stork reaction. However, it only will be successful if the anionic center is easily produced and sufficiently stabilized as shown in the following example.[5]



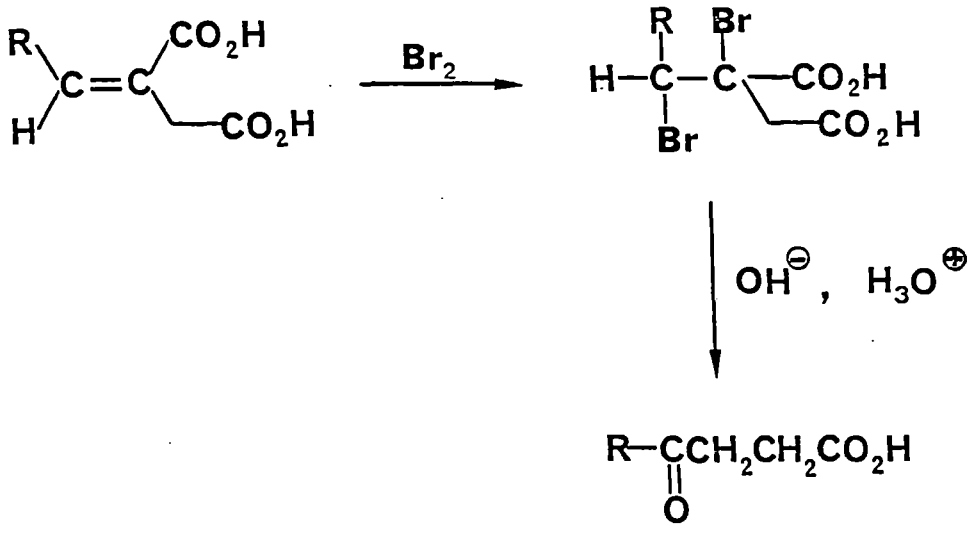
Synthesis via Lithio Derivative

The following procedure[6] has been reported to be effective for the synthesis of highly substituted γ-oxoacids. The needed ketones are readily prepared through acylation of aromatic hydrocarbons.



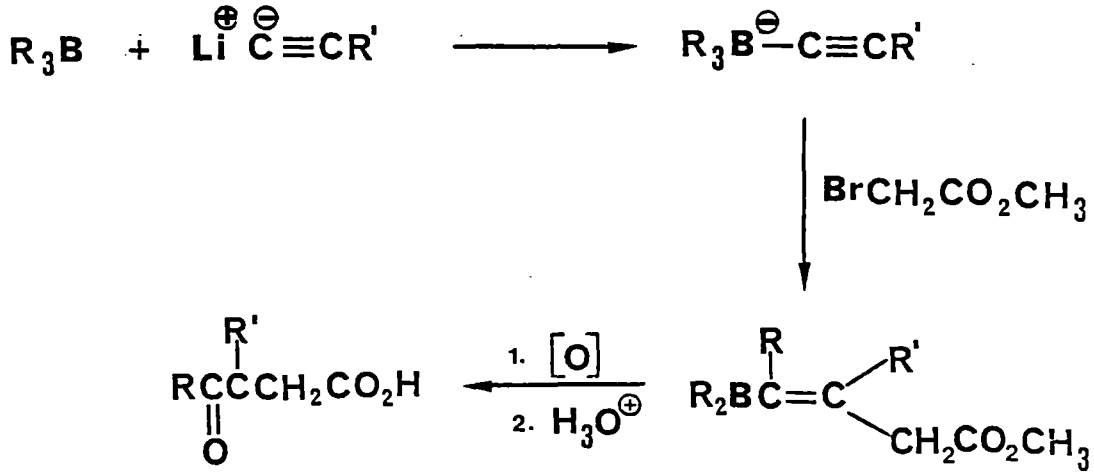
Bromination of Alkylidenesuccinic Acids

Aldehydes readily react with dimethylsuccinate in the presence of a strong anhydrous base to form alkylidene succinates. Hydrolysis of this product provides an alkylidene succinic acid. As shown below,[7] bromination of an alkylidene succinic acid provides the expected dibromo derivative which undergoes debromination and decarboxylation to the salt of a γ-oxoacid.



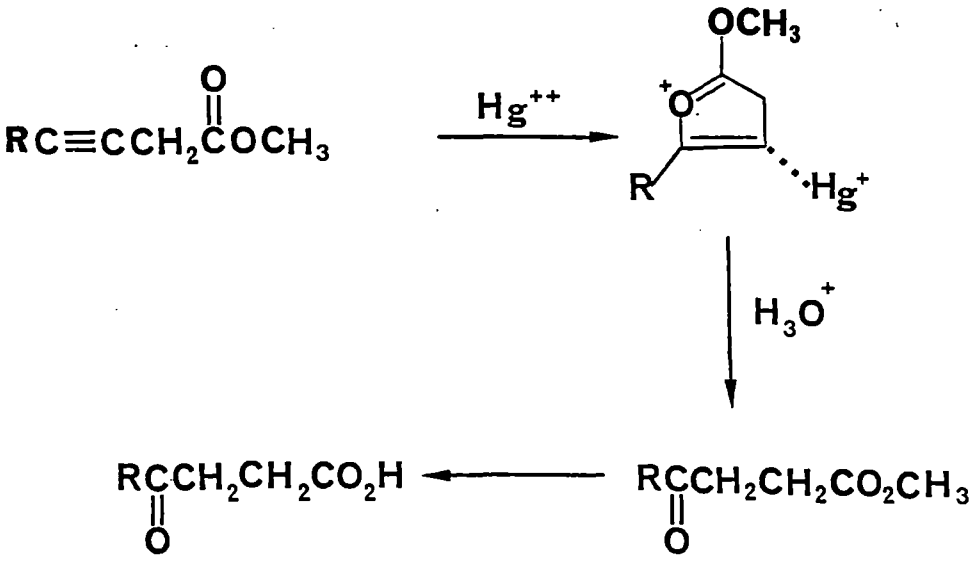
Hydroboration of Acetylenic Compound

Hydroboration of acetylenic compounds and subsequent alkylation provides an intermediate borane with a residual double bond. This is an advantage in the synthesis of ketones and has successfully been extended to γ-oxoacids as shown below.[8]



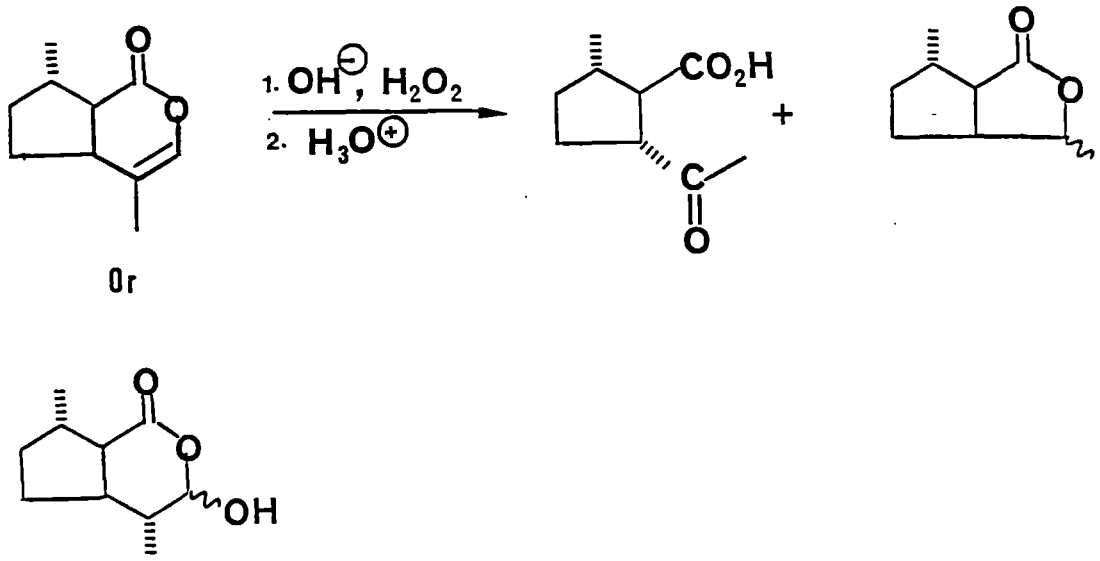
Mercuric Ion-promoted Hydration

Acetylenic compounds are readily hydrolyzed to ketones in the presence of mercuric ion and acid. This approach has been used to synthesize γ-oxoacids from acetylenic esters. The placement of oxygen at the γ-position is believed to be controlled by the cyclic intermediate shown in the following sequence.[9]



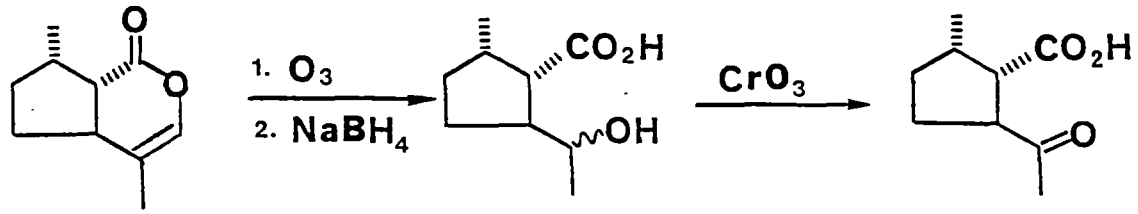
Oxidative Degradation with Hydrogen Peroxide in Alkali

γ-Oxoacids, on occasion, are obtained from oxidative degradation of natural products. Nepetonic acid was formed from nepetalic acid and/or nepetalactone in the sequence shown below.[10]



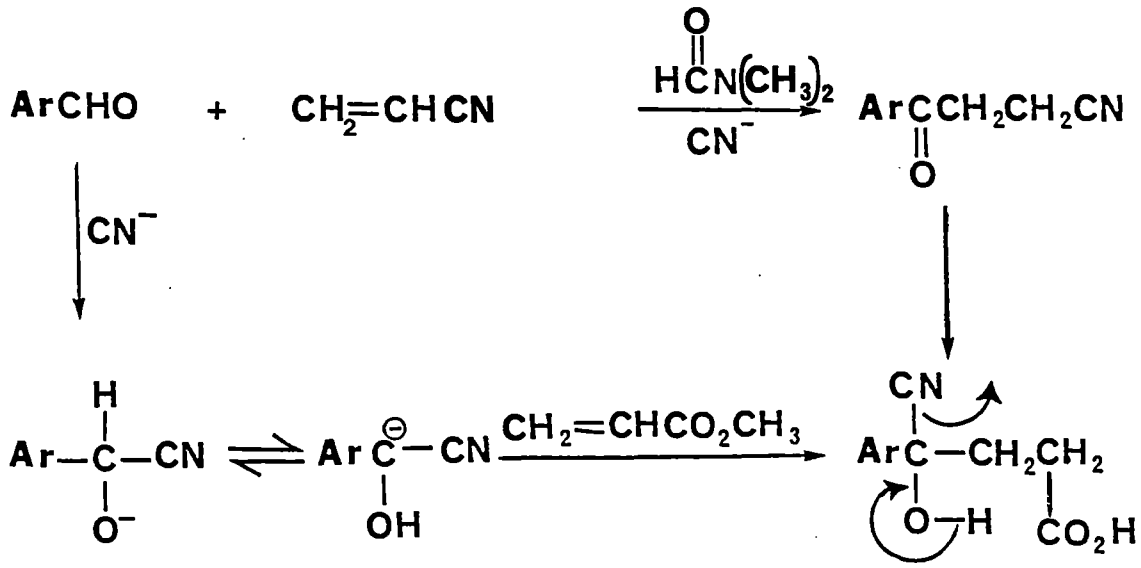
Oxidative Degradation with Ozone

An alternative degradation was applied to an isomer of nepetalactone which in turn provided an isomer of the nepetonic acid shown above. The success of this degradation, shown below,[11] is dependent upon the stereochemistry. If a trans ring junction were not present, the intermediate hydroxy acid would have lactonized and consequently a lactone would have formed.



Cyanide Catalyzed Addition of Aldehydes to Activated Double Bonds

Cyanide, as will be described under Results and Discussion, was selected as a reagent for addition to α,β-unsaturated ketones to ultimately provide γ-oxoacids. Cyanide ion also has been used as a catalyst in the synthesis of γ-oxoacids.[12] In the following example the γ-oxonitrile is later hydrolyzed to the corresponding γ-oxoacid.



CHAPTER II

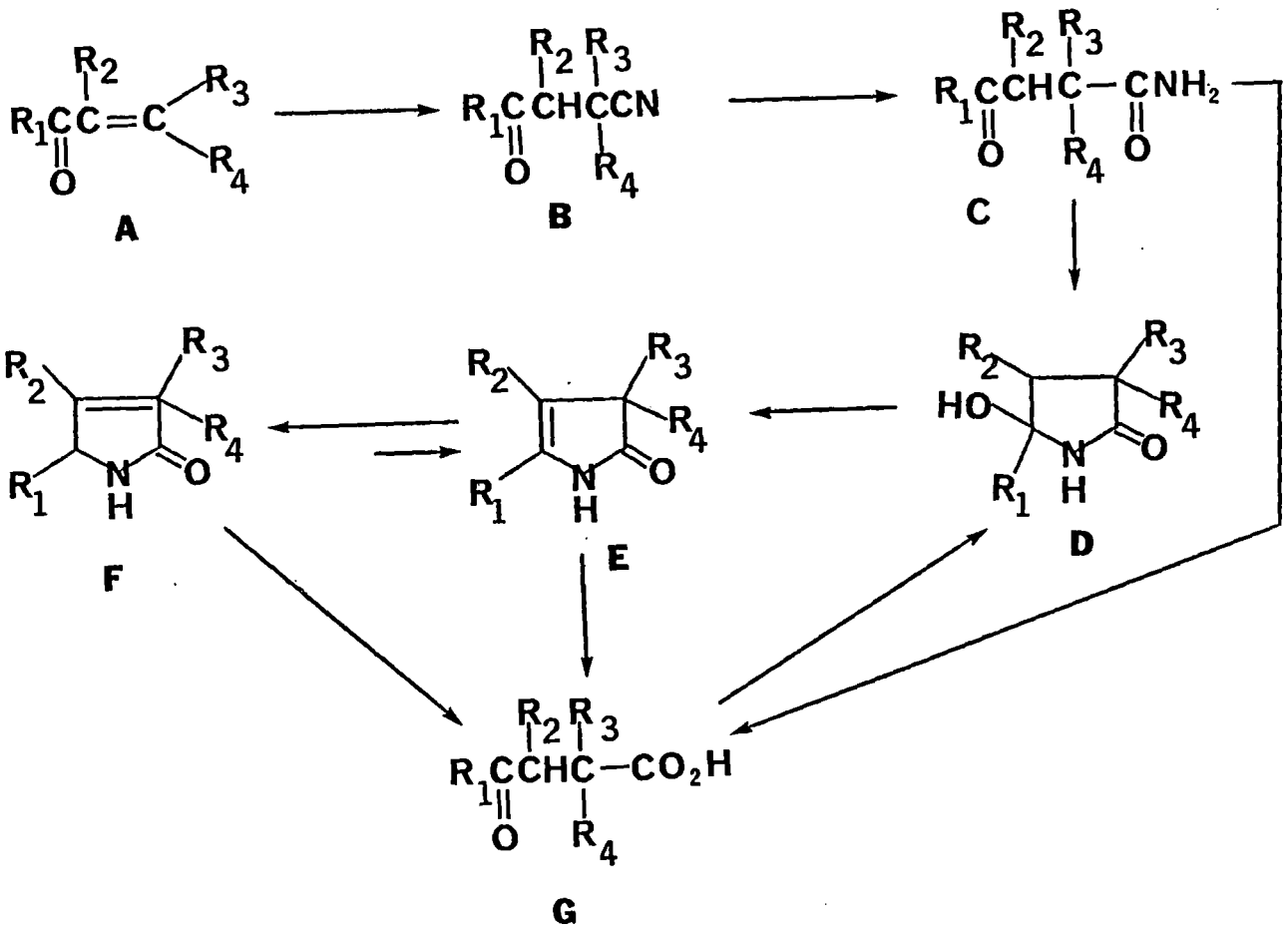
RESULTS AND DISCUSSION

The general route for the preparation of γ-oxoacids from α,β-unsaturated ketones is outlined in Scheme I. The types of intermediates obtained are also presented. Addition of cyanide ion to α,β-unsaturated ketones yields γ-oxonitriles. This result is not the case for every reaction. Depending on the reaction conditions, the product also could be one of the following compounds: γ-oxonitrile, γ-oxoamide, γ-hydroxylactam enelactams or γ-oxoacid shown as B, C, D, E or F, and G respectively in Scheme I. Under mild reaction conditions, the reaction will stop at the formation of γ-oxonitrile. Subsequent hydrolysis by the alkaline reaction mixture will convert the γ-oxonitrile as shown in Scheme I to the γ-oxoamide which may further hydrolyze to the salt of a γ-oxoacid or the γ-oxoamide may cyclize to form a hydroxylactam which in turn dehydrates to an enelactam. The enelactam is capable of isomerizing to the α,β-unsaturated lactam or hydrolyzing to the desired γ-oxoacid.

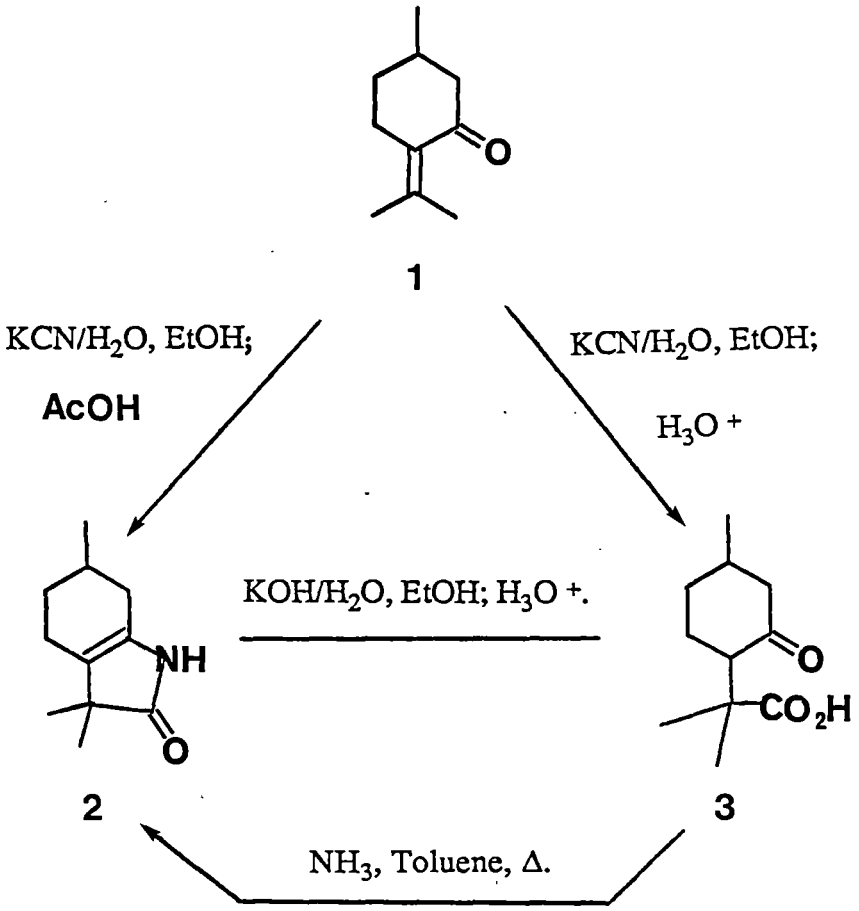
As will be shown, γ-oxoacids may be converted to enelactam by treating γ-oxoacids with ammonia. This reaction has not been studied extensively and one of the objectives of the current work was to explore the conversion of γ-oxoacids to enelactams. Widely varying results can be obtained and this variation is largely the result of structure differences in the γ-oxoacids as well as the stability of the enelactams.

Reaction with (R)-(+)-Pulegone (**1**)

The reaction sequence for the preparation of γ-oxoacid (**3**) from (+)-pulegone (**1**) is outlined in Scheme II.



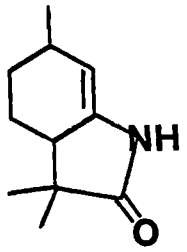
Scheme 1


O
1
KCN/H2O, EtOH;
AcOH
KCN/H2O, EtOH;
H3O +
KOH/H2O, EtOH; H3O +.
NH
O
O
CO2H
2
3
NH3, Toluene, Δ.

Scheme II

(+)-Pulegone (1) is commercially available. Addition of cyanide to (+)-pulegone yields the cyanomenthonecyanohydrin. But the reaction is very slow. According to Lapworth,[1] (+)-pulegone was partially converted to cyanomenthonecyanohydrin when the reaction in alcoholic potassium cyanide was allowed to continue for one week. Applying heat to the system causes the conversion of (+)-pulegone to the enelactam (2) or to the corresponding menthone oxoacid (3) depending on the reaction conditions used. Refluxing (+)-pulegone with potassium cyanide in ethanol for half an hour followed by treatment with acetic acid for another half hour yielded the enelactam (2). On the other hand, if the reaction was allowed to continue for 5h and without treatment with acetic acid, the reaction proceeded to the sodium salt of γ-oxoacid (3). For the second reaction, (+)-pulegone was first converted to 2 which on prolonged heating hydrolyzed to the γ-oxoacid 3. The enelactam (methonecarboxylic anhydramide) 2, may be regarded as formed by the dehydration of menthonecarboxylic amide.

The placement of the double bond in the lactam 2 was established by ^{1}H NMR. No ethylenic hydrogen was observed in the region between 4-7 δ. Therefore, the possibility of the formation of compound 4, shown below, is eliminated.



4

The γ-oxoacid 3, obtained from the above reaction, was a 50:50 mixture of cis and trans forms. The yield for the γ-oxoacid was 44% when the starting compounds was (+)-pulegone or 70% when starting from the lactam (2).

The possibility of converting the acid 3 to the lactam 2 was also examined. It was found that the enelactam 2 could be obtained when a solution of menthonecarboxylic acid (3) in refluxing toluene, was treated with ammonia.

Preparation of 1-Acetyl-1-cyclohexene (**6**)

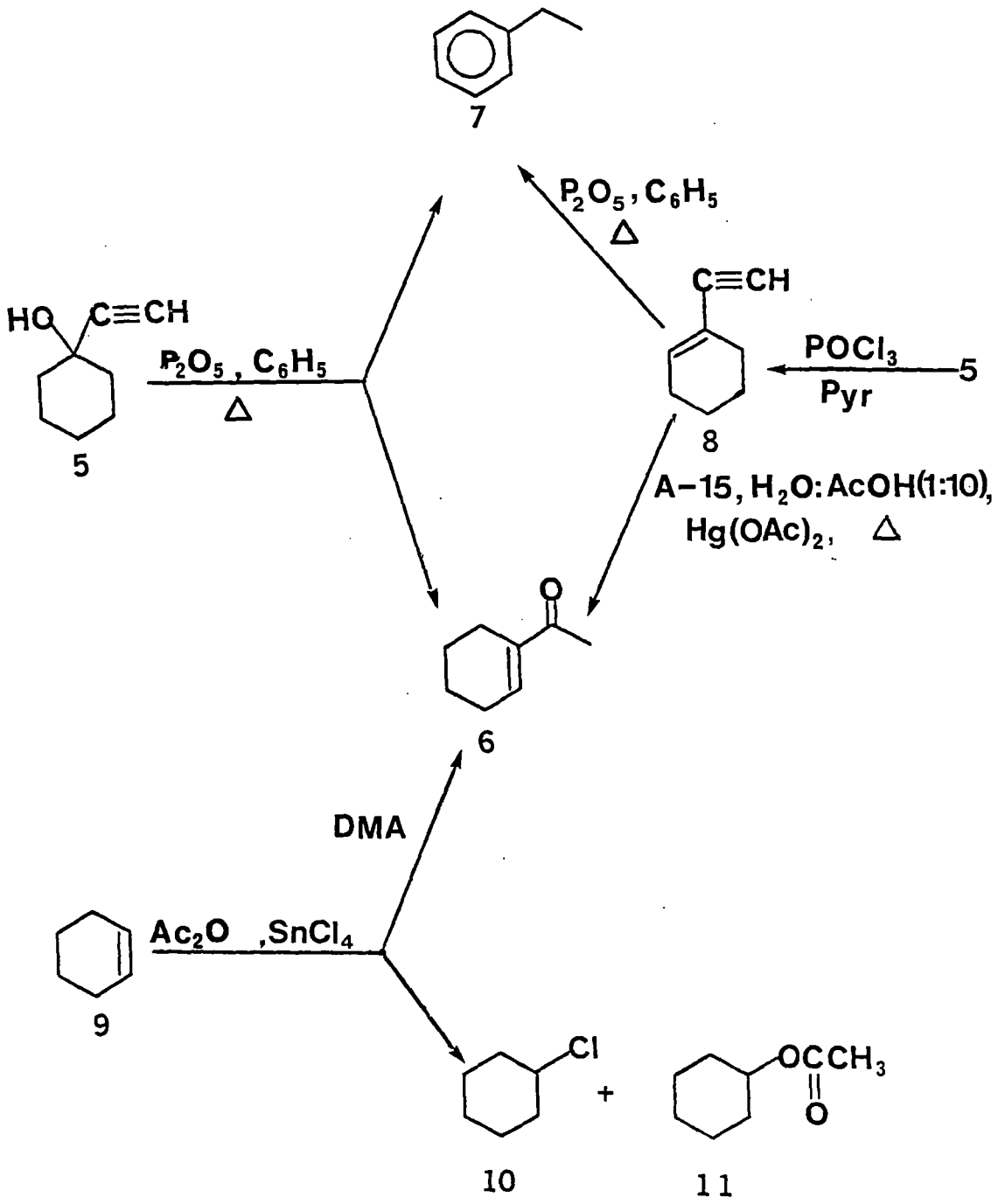
In addition to (+)-pulegone (**1**), 1-acetyl-1-cyclohexene (**6**) was selected for study. This α,β-unsaturated ketone was selected because it represents a considerably different structural type from that of (+)-pulegone. It was anticipated that the stability and ease of formation of the intermediate γ-oxonitrile, γ-oxoamide, γ-hydroxylactam, β,γ-enelactam and α,β-enelactam (B, C, D, E and F, respectively) of Scheme I also would differ significantly. 1-Acetyl-1-cyclohexene is commercially available. However, the quantity needed for the projected study required that it be prepared.

Two synthesis routes for the preparation of **6** were used. These are shown in Scheme III.

1-Acetyl-1-cyclohexene (**6**) usually is prepared through acid-catalyzed isomerization[13] of commercially available 1-ethynyl-1-cyclohexanol (**5**) or by Friedel-Crafts acetylation of cyclohexene (**9**). In the latter reaction, stannic chloride is considered to be the most effective reagent.[14] Our experience with both routes has shown that the preparation of **6** from **5** is the better choice. The selection of these routes was based on higher yield, greater purity, cheaper reagents and overall greater convenience.

The acid catalyzed isomerization of **5**→**6**, generally known as the Rupe rearrangement,[13] has been carried out using a broad variety of acidic reagents including acetic acid with added sulfuric acid,[13] phosphoric acid,[13] aqueous sulfuric acid,[13] sulfuric acid in ethanol,[13] Dowex-50 in refluxing acetic acid:water (10:1),[15a,15b,15c] P_2O_5 in refluxing benzene,[16] and Nafion -H in refluxing carbon tetrachloride.[17]

As pointed out above, 1-acetyl-1-cyclohexene (**6**) is commercially available and the cost of the needed quantity promoted its preparation. The preparation of **6** from **5** using P_2O_5 in refluxing benzene was tried first because of the described convenience and the reported yield.[16] However, this reaction failed to give more than 66% conversion in the specified 2.5h of reflux. The reaction was repeated twice with the same result. A subsequent time trial provided the GC data in Table I used to construct Figure 1. This


7
P_2O_5, C_6H_5
Δ
C≡CH
HO C≡CH
P_2O_5, C_6H_5
Δ
5
$POCl_3$
Pyr
5
8
A–15, H_2O: AcOH(1:10),
$Hg(OAc)_2$, Δ
O
6
DMA
Ac_2O, $SnCl_4$
9
Cl
+
$OCCH_3$
O
10
11

Scheme III

TABLE I

CONVERSION OF 1-ETHYNYL-1-CYCLOHEXANOL (**5**) TO 1-ACETYL-1-CYCLOHEXENE (**6**) USING P_2O_5 IN REFLUXING BENZENE

Reaction Time	%		
(h)	5	6	7
0.0	100	0	0
0.25	94	5	1
0.75	75	21	4
1.0	66	27	7
1.5	51	40	9
2.0	41	47	12
2.5	34	53	13
3.0	28	59	13
4.0	18	67	15
5.0	14	71	15
6.0	10	75	15
8.0	6	78	16

GC Analysis was done on an OV-101 interior coated column at 100 °C.

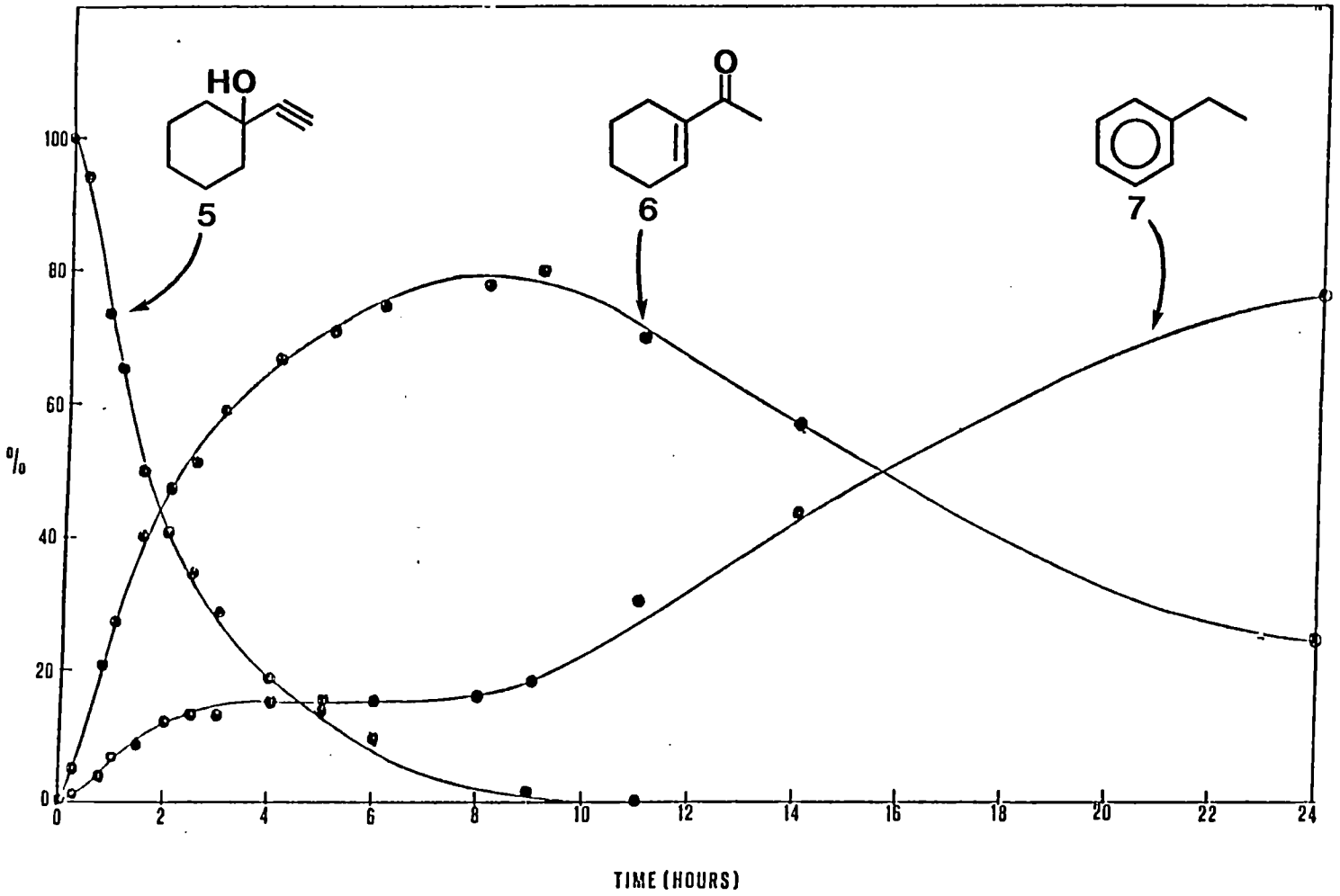


Figure 1. Acid Catalyzed Conversion of 1-Ethynyl-1-cyclohexanol (**5**) to 1-Acetyl-1-cyclohexene (**6**).

shows that some **5** persists through 8h of reflux. With this reaction time, the production of **6** and the major impurity, found to be ethylbenzene (**7**), appeared to level off. Addition of fresh P_2O_5 at 8h and at 14h caused an increase in the formation of **7** with a corresponding decrease in **6**. The changes are shown in Fig. 1 at the corresponding times. Also, a later experiment with pure **6** in the presence of P_2O_5 in refluxing benzene showed that **7** was formed at the expense of **6**.

Initially 1-ethynyl-1-cyclohexene (**8**), rather than **7** was considered to be the side product in the preparation of **6** from **5** using P_2O_5. However, the GC retention time of **8**, prepared from **5**, was found to be different from that of **7**. Also, the conversion of **8** to **6** has been reported to be slow compared to that of **5** to **6** in the presence of Dowex-50 in aqueous acetic acid.[15a,15b,15c] Treatment of **5** with P_2O_5 in refluxing benzene for 2h gave **6** and **7** (22:72) with 6% unreacted **5**. When **5** was treated for 15 minutes with Amberlyst-15 (A-15) in refluxing acetic acid:water (10:1) in the presence of mercuric ions, **6** was the sole product with no observable **7** as shown by GC studies. The reaction conditions using A-15 are an adaptation of Newman's Dowex-50 procedure with the minor modification of substituting A-15 for Dowex-50.[15a,15b,15c]

Newman reported[15a,15b,15c] that prior treatment of Dowex-50 with mercuric ions accelerated the conversion of **5** to **6**. Thus, as shown in Table II, addition of a catalytic quantity of mercuric acetate, directly to the reaction mixture, accelerated the conversion of **5** to **6** in the presence of A-15 in refluxing acetic acid:water (10:1). While no studies were carried out, it appears that prior preparation of the mercuric ion treated sulfonic acid resin is not essential.

Since **8** was not observed as a product, in the preparation of **6** from **5**, using A-15 and since **8** is not converted to **7** under the same conditions, it appears that A-15 in refluxing acetic acid:water (10:1) is regiospecific in the formation of **6** from **5**, in regard to **7** and **8**, as compared to treatment of **5** with P_2O_5 in refluxing benzene. These results are summarized in Scheme III. The identity of **7** as a reaction product was established through

TABLE II

CONVERSION OF 1-ETHYNYL-1-CYCLOHEXANOL (**5**) TO 1-ACETYL-1-CYCLOHEXENE (**6**) USING A VARIETY OF ACIDIC REAGENTS

Run	Reagent	h	Yield %	Purity %[a]
1	A-15 in refluxing benzene	5	[b]	—
2	Water:acetic acid (1:10)	2	[b]	—
3	Water:acetic acid (1:10) with added mercuric acetate	2	[b]	—
4	A-15 in refluxing acetic acid:water (10:1)	2	80	98
5	A-15 in refluxing acetic acid:water (10:1) and mercuric acetate	1	82	98
6	A-15 in refluxing benzene	2.5	66[c]	60-65[d]
7	Nafion-H in refluxing CCl_4	15	84	≥96[e]

[a]Purity determined by GLC using a 1/8" x 6' column containing 5% SP 2100 (OV-101) on 100/120 mesh Supelcoport (1-1989) using a Varian 3400 TC instrument equipped with integrator.

[b]No reaction.

[c]Triplicate runs under these conditions.

[d]Accompanied by 35-40% of **5**.

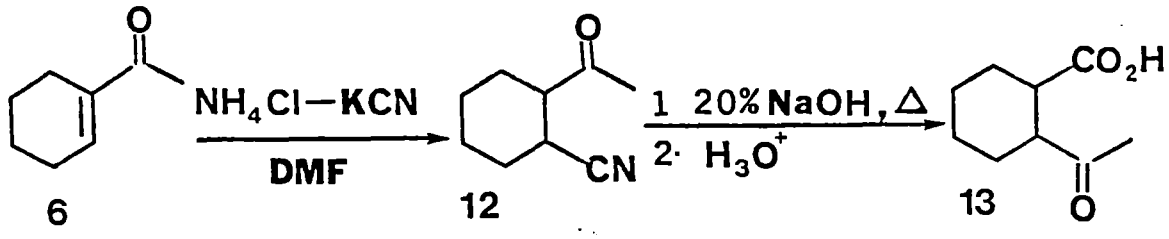
[e]For Lit. result c.f. ref. 17.

comparison studies with authentic material using GC-MS as well as ^{1}H- and ^{13}C-NMR spectroscopy. It was previously reported that **7** is a side product in the synthesis of **6** from cyclohexene and acetic anhydride in the presence of a mixture of P_2O_5 and phosphoric acid.[18]

The $SnCl_4$ acetylation of cyclohexene using Royal's procedure[14] was carried out. This process was reported to provide pure **6**, free of 2-chloro-1-acetylcyclohexane. However, the reaction product, in an ether solution, continued to evolve HCl fumes despite a prior wash with aqueous sodium bicarbonate. Half of this sample was concentrated and distilled. Again HCl fumes were observed. A GC study on OV-101 showed this mixture to contain **10**:**11**:**6** in the ratio (43:15:42) in that order of emergence from the GC column. The remaining half of the sample was concentrated and then heated in the presence of N,N-dimethylaniline[14] to eliminate and remove chloride. This treatment greatly decreased the relative concentration of the GC peak assigned to **10** and changed the **10**:**11**:**6** ratio to 4:20:76. Infrared studies of this mixture showed bands at 1640 cm^{-1}, 1680 cm^{-1} and 1740 cm^{-1} indicative of the presence of **6** and **11**. Their presence also was supported by the appearance of peaks at 200.6 and 170.1 ppm, consistent with the ^{13}C NMR resonances of **6** and **11**. These studies show that the use of the Friedel-Crafts synthesis of **6** can only be of value if the presence of **10** and **11** is not objectionable since extensive fractionation is required for the preparation of pure **6**.

Reaction with 1-Acetyl-1-cyclohexene (**6**)

Scheme IV represents the reaction sequence for the preparation of 2-acetylcyclohexane carboxylic acid (**13**) from 1-acetyl-1-cyclohexene (**6**) via the formation of 1-acetyl-2-cyanocyclohexane (**12**).



Scheme IV

Addition of cyanide to 1-acetyl-1-cyclohexene (**6**) was done according to the procedure described by Nagata and coworkers.[19] The cyanation was carried out with two mole equivalents of potassium cyanide and 1.5 mole equivalents of ammonium chloride in dimethylformamide. The excess of ammonium hydroxide which was produced by consumption of cyanide ion, was liberated as ammonia by heating. Thus the reaction mixture was maintained at minimal basicity. This procedure permits formation of γ-oxonitrile without hydrolysis to C, D, E or F of Scheme I. The IR spectrum of **12** showed the expected strong absorption peak of C≡N at 2250 cm^{-1} and C=O stretch at 1710 cm^{-1}. The mass spectrum showed the molecular ion peak of 1-acetyl-2-cyano cyclohexane **12** at 151.

The γ-oxonitrile **12**, prepared using the above method, was obtained as a mixture of cis- and trans-1-acetyl-2-cyano cyclohexane **12a** and **12b**. This mixture of γ-oxonitrile was used to prepare the corresponding γ-oxoacid **13** (2-acetylcyclohexane carboxylic acid) as predominately the trans isomer **13b**. The cis form of **12**, obtained from another route, on heating in the presence of NH_3 in toluene isomerized to the trans form and hydrolysis in 20% NaOH followed by acidification yielded predominantly the trans-1-acetylcyclohexane carboxylic acid (**13b**). Stirring γ-oxoacid **13b** with ammonia, using the conditions applied to the γ-oxoacids of pulegone, did not give the expected lactam as it did in the conversion of **3** to **2**.

CHAPTER III

EXPERIMENTAL

All melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 196 IR Spectrophotometer. Proton NMR spectra were determined at 300 MHz on Varian XL-300 using tetramethyl silane as internal standard in $CDCl_3$ solvent. The ^{13}C NMR spectra were obtained at 75 MHz on Varian XL-300. Chemical shifts are reported in ppm using tetramethylsilane as an internal standard. Mass spectra were obtained on a CEC 21-110B with 3/12 NOVA Data System and on J&W db-5 2091 Gas Chromatograph-Mass Spectrometer (30mm x .25mm 0.1 μm film with split injection of 1:4).

Preparation of Menthonecarboxylic Anhydramide (2) from (+)-Pulegone (1)

A solution of potassium cyanide (25g, 0.385 mol) in water (30 mL) was added to a 500 mL, three-necked, round-bottomed flask equipped with a condenser, thermometer, and magnetic stirrer. A N_2 atmosphere was maintained throughout the experiment. To the flask was added a solution of (+)-pulegone (45g, 0.296 mol) in 95% ethanol (75 mL). Stirring and heating at reflux (84°C) was continued for 30 minutes. The reaction mixture was cooled to 51°C, glacial acetic acid (60g, 1.0 mol) was added, the mixture was refluxed for another 30 minutes, cooled, and poured into 1 liter water, extracted with ether (2 x 250 mL), dried ($MgSO_4$) and concentrated to give 43g crude product. Kugelrohr distillation gave 30 g of menthonecarboxylic anhydramide (2) in 85% yield based on the reacted (+)-pulegone; mp 160-163°C [lit.[1] mp 164-165°C]; ^1H NMR ($CDCl_3$) δ 9.40 (s, 1H), 2.44-

2.64 (m, 1H), 1.96-2.03 (m, 2H); 1.90-2.20 (m, 4H), 1.14 (s, 6H), 1.01-1.03 (d, 3H); ^{13}C NMR ($CDCl_3$) ppm 186.8, 131.2, 120.3, 46.6, 30.8, 30.1, 28.8, 22.2, 21.7, 19.3; IR (nujol) 3200 cm^{-1} (NH), 1710 cm^{-1} (C=O), 1670 cm^{-1} (C=C); mass spectrum m/z (relative abundance) M^+ 179 (29), 169 (6), 165 (11), 164 (100), 137 (7), 136 (9), 122 (14), 94 (10), 77 (6), 69 (53), 67 (6), 51 (6), 41 (9), 39 (5).

Preparation of Menthonecarboxylic Anhydramide (2) from Menthonecarboxylic Acid (3)

Menthonecarboxylic acid (2.0g, 0.01 mol) was added to a 50 mL, two-necked, round-bottomed flask equipped with a condenser, magnetic stirrer and thermometer. Toluene (10 mL) was then added to the flask, and the solution was flushed with ammonia gas. At the end of 10 minutes, the reaction mixture formed a white-gel which melted on heating. Heating at higher temperature (95°C) caused the reaction mixture to foam. The refluxing was continued for 1h, then concentrated by distilling out toluene, extracted with ether (100 mL), washed with $NaHCO_3$ (2 x 100 mL), and reextracted with $NaHCO_3$ and with ether (100 mL). The ether layers were combined, dried ($MgSO_4$), filtered, and concentrated to give menthonecarboxylic anhydramide (1.2g, 86%); based on reacted menthonecarboxylic acid.

Preparation of Menthonecarboxylic Acid (3) from Menthonecarboxylic Anhydramide (2)

A solution of menthonecarboxylic anhydramide (2) (1.79g, 0.01 mol) in 95% ethanol (40 mL) was added to a solution of potassium hydroxide (2.24g, 0.04 mol) in water (30 mL) in 300 mL, three-necked, round-bottomed flask, equipped with a condenser, magnetic stirrer and thermometer. A N_2 atmosphere was maintained throughout the experiment. The reaction mixture was refluxed for 5h, cooled, and concentrated by distilling off ethanol. The residue was diluted with water (200 mL), acidified (450 mL of 10% HCl),

extracted with ether (2 x 100 mL), washed with water (2 x 100 mL), dried ($MgSO_4$), filtered, and concentrated to give 1.5g of crude product. Kugelrohr distillation gave a mixture of cis- and trans-menthonecarboxylic acid (**3**) (1.4g, 70%).

Preparation of Menthonecarboxylic Acid (**3**) from
(+)-Pulegone (**1**)

A solution of (+)-pulegone (45g, 0.296 mol) in 95% ethanol (75 mL) was mixed with a solution of potassium cyanide (25g, 0.384 mol) in water (35 mL) and the whole mixture were refluxed for 5h. Ethanol was then removed by distillation while keeping the water level in the flask constant. The reaction mixture was then cooled, diluted with water (1000 mL), acidified (10% HCl), extracted with ether (2 x 250 mL), washed with water (4 x 250 mL), dried ($MgSO_4$), and concentrated to give 32 g of crude product. Kugelrohr distillation gave a mixture of cis- and trans-menthonecarboxylic acid (26g, 44%).

Preparation of 1-Acetyl-1-cyclohexene (**6**) from
1-Ethynyl-1-cyclohexene (**8**)

1-Ethynyl-1-cyclohexene (5g, 0.047 mol) was added to a 300 mL, two-necked, round-bottomed flask equipped with a condenser and a magnetic stirrer. To the flask was added acetic acid (15 mL) in water (1.5 mL), A-15 (2.5g) and mercuric acetate (10 mg). The reaction mixture was stirred and heated to reflux. At the end of 15 minutes, the reaction mixture turned purple. Gas chromatography indicated that the reaction contained only traces of starting material. The reaction mixture was then extracted (twice) with ether, washed with $NaHCO_3$, then water (twice), dried ($MgSO_4$), and concentrated by distilling ether at atmospheric pressure. Distillation (Kugelrohr) gave 1-acetyl-1-cyclohexene (**6**) (4.7g, 80%): bp 80-90°C (32mm) [lit.[14] bp. 65-69°C (5mm)]; ^1H NMR ($CDCl_3$) δ 6.88-6.98 (m, 1H), 2.10--2.32 (m, 8H), 1.30-1.68 (m, 3H); ^{13}C NMR ($CDCl_3$) ppm 197.9, 140.4, 139.8, 26.3, 25.0, 23.3, 22.2, 22.0; IR (neat) 1660 cm^{-1} (C=O) 1640 cm^{-1} (C=C);

mass spectrum m/z (relative abundance) M^+ 124 (43), 109 (66), 79 (31), 77 (11), 53 (22), 43 (79), 41 (15), 39 (11).

The above procedure was repeated without using mercuric acetate. Kugelrohr distillation gave 1-acetyl-1-cyclohexene (3.4g, 58%).

Preparation of 1-Ethynyl-1-cyclohexene (**8**)

1-Ethynylcyclohexene used in the above experiment was obtained from the dehydration of 1-ethynyl-1-cyclohexanol.[15c] A solution of phosphorus oxychloride (55 mL) in dry pyridine (55 mL) was added slowly to a solution of 1-ethynyl-1-cyclohexanol (100g) in dry pyridine (150 mL) in a flask fitted with a stirrer, thermometer, and a reflux condenser. Nitrogen was allowed to flow throughout the experiment. At the end of two hours, the reaction mixture was quite viscous. After heating (85-92°C) for an additional 2h, the reaction mixture was cooled, added to 400g of cracked ice, extracted twice with isohexane, dried ($MgSO_4$), filtered, and concentrated. The crude product (66g) was distilled (Kugelrohr) to give 1-ethylnyl-1-cyclohexene (64g, 76%) with traces of pyridine, 1-ethynyl-1-cyclohexanol, and 1-acetyl-1-cyclohexene being present. These impurities were removed by passing the material through an acidic alumina column. 1-Ethynyl-1-cyclohexene; bp. 52-57° (25 mm) [lit.[15c] bp 53-56°C (40 mm)]; IR (neat) 3300 cm^{-1} (=CH), 2100 cm^{-1} (C≡C), 1635 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 6.02-6.20 (m, 1H), 2.62-2.78 (m, 1H), 1.90-2.20 (m, 4H), 1.40-1.76 (m, 4H); ^{13}C NMR ($CDCl_3$) ppm 136.3, 120.4, 85.8, 74.9, 32.0, 29.4, 26.0, 22.2; mass spectrm m/z (relative abundance) M^+ 106 (70), 105 (39), 91 (100), 79 (28), 78 (82), 77 (32), 65 (28), 63 (18), 52 (31), 51 (36), 50 (24), 30 (48).

Preparation of Acetyl-1-cyclohexene (6) From 1-Ethylnyl-1-cyclohexanol (5)[15a]

1-Ethylnyl-1-cyclohexanol (21g, 0.169 mol) was added to a 300 mL, 2-necked flask fitted with a condenser and a magnetic stirrer. To the flask also was added acetic acid (50 mL) in water (5 mL), A-15 (10g), and mercuric acetate (25 mg). The reaction mixture was stirred, refluxed for one hour, filtered, neutralizd with sodium hydroxide solution (30 mL of 50% NaOH diluted in 200 mL water) and extracted with ether (200 mL) twice. The combined ether extracts was washed once with $NaHCO_3$ solution, twice with water, dried ($MgSO_4$), filtered, and concentrated by distillation at atmospheric pressure. Vacuum distillation gave 14.2g (68%) of 1-acetyl-1-cyclohexene at 67-90° (24 mm).

Reaction of 1-Ethynyl-1-cyclohexanol (5) with P_2O_5 in Refluxing Benzene

The treatment of **5** with P_2O_5 in refluxing benzene was carried out exactly as described[16] except that the reaction was continued beyond the prescribed 2.5h. The collected data were used to prepare Figure 1.

Preparation of 1-Acetyl-1-cyclohexene (6) from Cyclohexene (9)

Cyclohexene (123g, 1.5 mol) was added to a 1-liter, three-necked, round-bottomed flask equipped with condenser, thermometer, mechanical stirrer, and a dropping funnel. The system was protected by a calcium chloride tube and a N_2 atmosphere was maintained throughout the experiment. The flask was immersed in an ice bath, and $SnCl_4$ (260.5g, 1.0 mol) was added. The flask was further cooled to 2°C before acetic anhydride (102g, 1.0 mol) was added dropwise via the dropping funnel. The temperature of the reaction mixture varied between 16-22°C during the 35 minutes addition. Stirring in the ice bath was continued for 15 minutes. The thick reddish-brown reaction mixture was then poured

onto 300-400g of cracked-ice extracted with ether (500 mL) and washed with water three times (300 mL, 500 mL, 500 mL). The yellowish water layer was reextracted with ether and washed with 10% HCl (200 mL). The ether layers were combined and washed once with $NaHCO_3$ (300 mL), dried ($CaCl_2$), and filtered through $MgSO_4$. The ether layer was then divided into two parts. One part was kept aside for dimethylaniline treatment. Another, was concentrated by distilling ether at atmospheric pressure. Kugelrohr distillation gave 85g (95%; based on one half of the reaction mixture) of a mixture of cyclohexyl chloride (43%), cyclohexyl acetate (15%) and 1-acetyl-1-cyclohexene (40%). This mixture gave acidic fumes to moist pH paper.

Dimethylaniline Treatment

The reaction mixture was concentrated by distilling ether and treating with N,N-dimethylaniline (100 mL) at the same time. The reaction mixture was refluxed with dimethylaniline for 3 hours at 182°C, cooled, washed with 10% HCl (500 mL), washed with water, dried ($CaCl_2$), concentrated and vacuum distillation to give 1-acetyl-1-cyclohexene 26.6g (30%). GC showed a single peak.

Preparation of 1-Acetyl-2-cyanocyclohexane

(12a) and (12b)

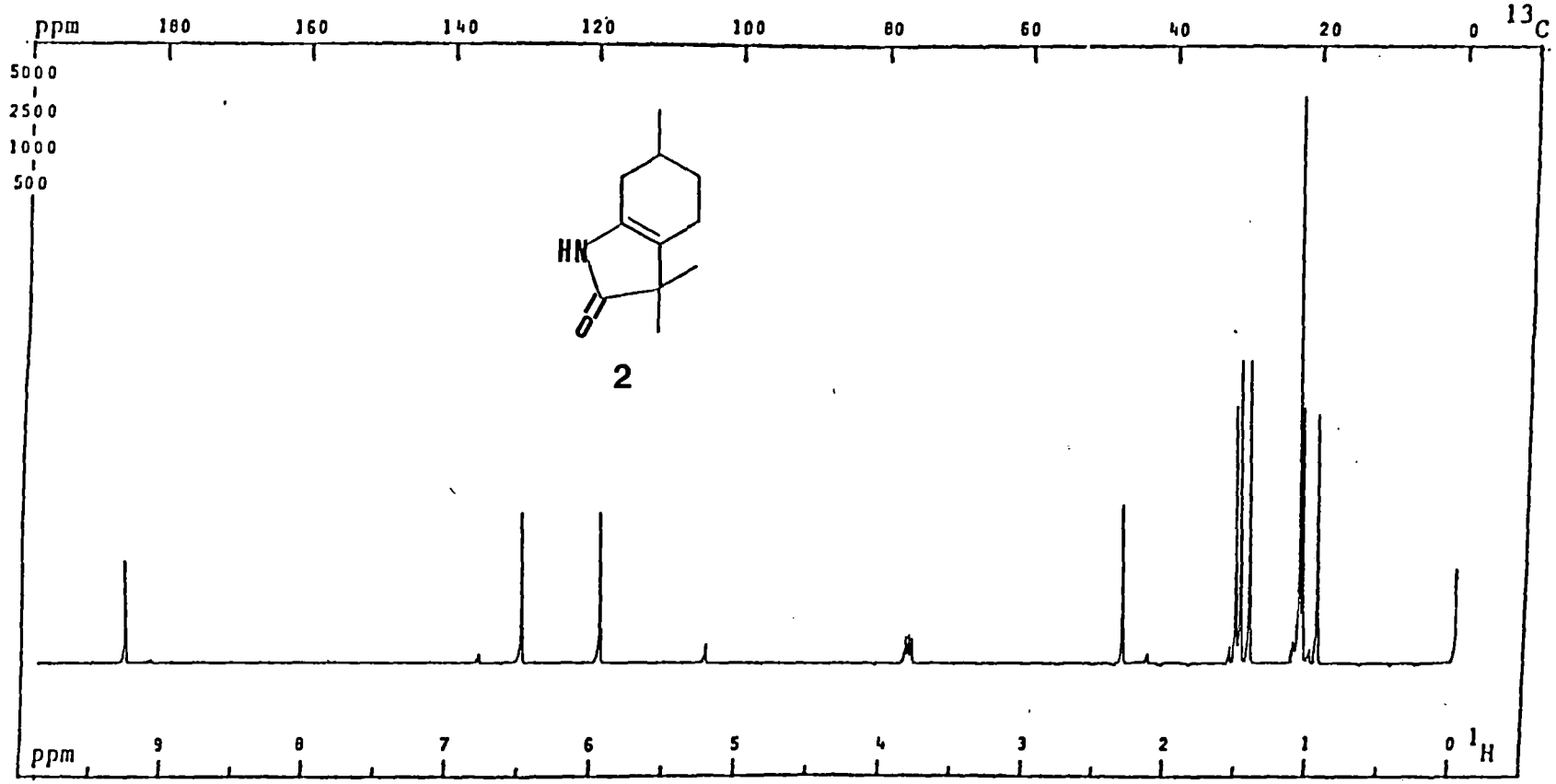
Ammonium chloride (3.2g, 0.06 mol) and potassium cyanide (5g, 0.08 mol) were added to a 500-mL, 3-necked, round-bottomed flask equipped with a condenser, thermometer and a magnetic stirrer. A nitrogen atmosphere was maintained throughout the experiment. Water (30 mL) was added, and the stirring started. A solution of 1-acetyl-cyclohexene (5g, 0.04 mol) in dimethylformamide (160 mL) was then added. The cloudy reaction mixture was heated to reflux at 100°C for 8 hours, cooled, and the solvent concentrated under vacuum. Water (100 mL) was added to the residue which was extracted three times (3x100 mL) with dichloromethane. The extracts were combined,

dried ($MgSO_4$), filtered and concentrated. Kugelrohr distillation gave 5g (85%) of a mixture of cis and trans 1-acetyl-2-cyanocyclohexene (**12a**) and (**12b**). IR (neat) 2250 ml^{-1} (C≡N), 1710 cm^{-1} (C=O), mass spectrum m/z (relative abundance) M^+ 151 (2), 123 (3), 109 (3), 108 (4), 82 (12), 81 (9), 80 (5), 67 (9), 54 (6), 53 (5), 52 (2), 44 (2), 43 (100), 41 (8).

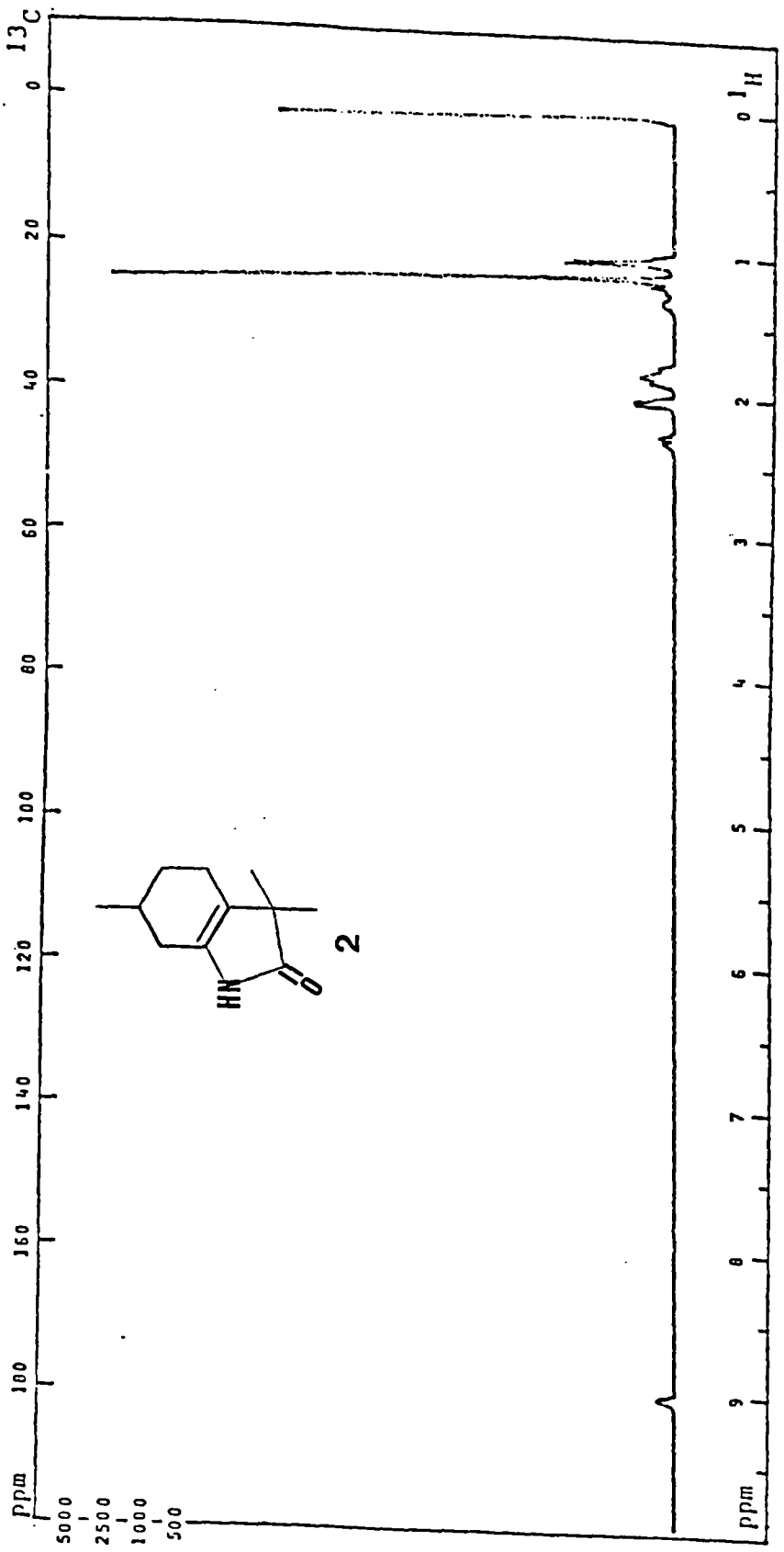
Preparation of 2-Acetylcyclohexanecarboxylic Acid (**13**)

The mixture of cis- and trans-γ-oxonitriles **12a** and **12b** from the above experiment was used in the following hydrolysis.[20]

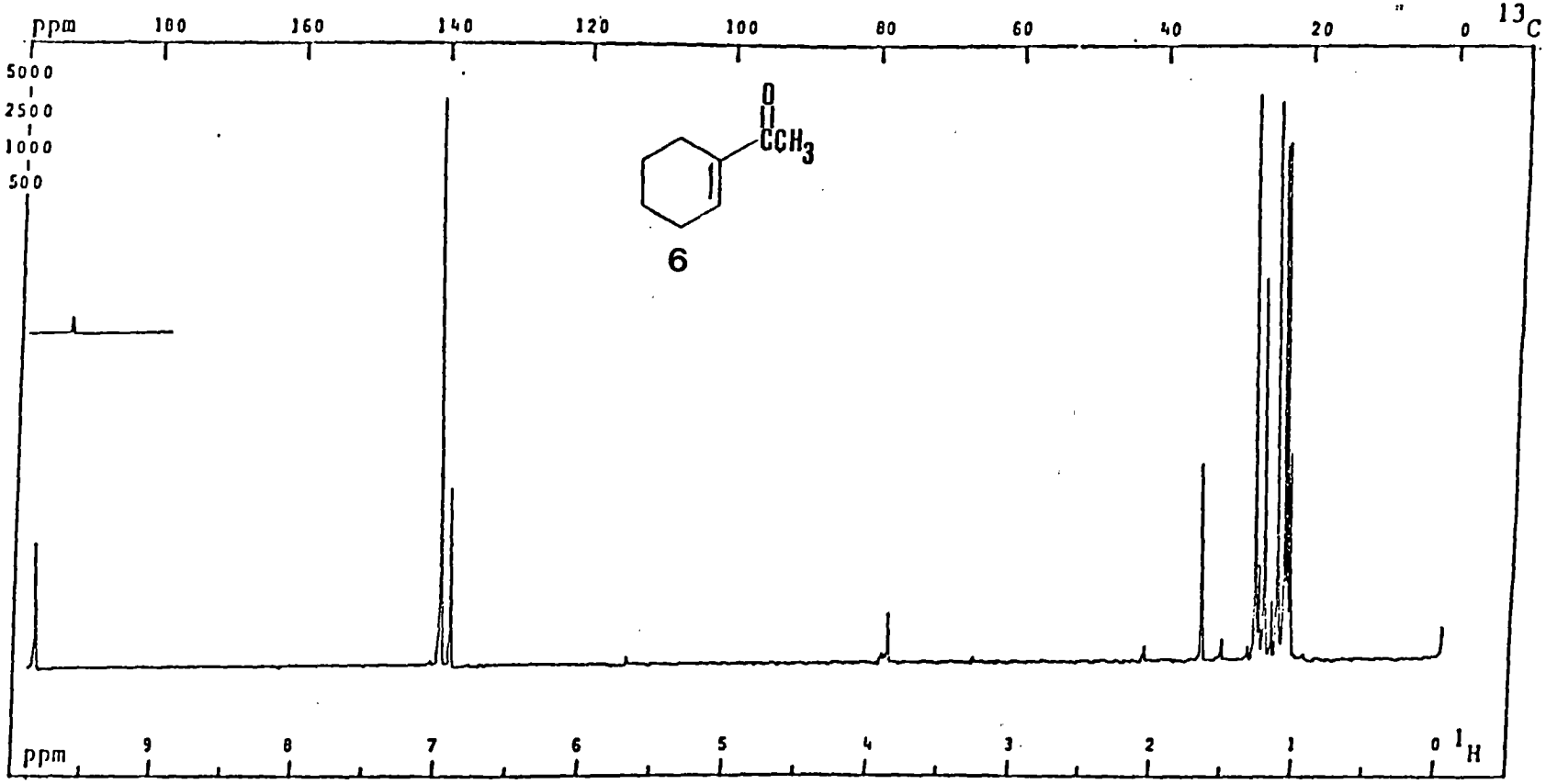
1-Acetyl-2-cyanocyclohexane (5g, 0.033 mol) was added to a cylindrical stainless steel flask equipped with condenser, thermometer, and magnetic stirring bar. A nitrogen atmosphere was maintained throughout the experiment. Sodium hydroxide (25 mL of 20% NaOH) was then added and this mixture was stirred and heated at reflux between 99-103°C for 2h. The cooled reaction mixture was transferred to a separatory funnel and extracted with ether (2x25 mL) and the ether layer was washed with water (2x25 mL). The combined ether layers were dried ($MgSO_4$), filtered, and stripped to give an oily yellow crude product (1.0g, 12%). The water layer was acidified (400 mL of 10% HCl), extracted with ether (2x100 mL) washed with water (3x100 mL), dried ($MgSO_4$), filtered, and concentrated to give exclusively trans-2-acetyl-cyclohexane carboxylic acid (**13b**) (3.0g, 47%) mp. 124-127 °C; ^1H NMR ($CDCl_3$) δ 9.01 (s, 1H), 2.47-2.68 (m, 2H), 2.09 (s, 3H), 1.65-2.08 (m, 4H), 1.01-1.41 (m, 4H); ^{13}C NMR ($CDCl_3$) ppm 211.0, 181.4, 51.8, 44.0, 28.9, 28.6, 28.3, 25.5, 25.4; IR (nujol) 2300-3450 cm^{-1} (broad OH), 1700 cm^{-1} (C=O); mass spectrum m/z (relative abundance) M^+ 170 (11), 155 (16), 152 (11), 124 (13), 109 (24), 81 (100), 67 (42), 54 (14), 53 (11), 51 (66), 43 (96), 41 (15).



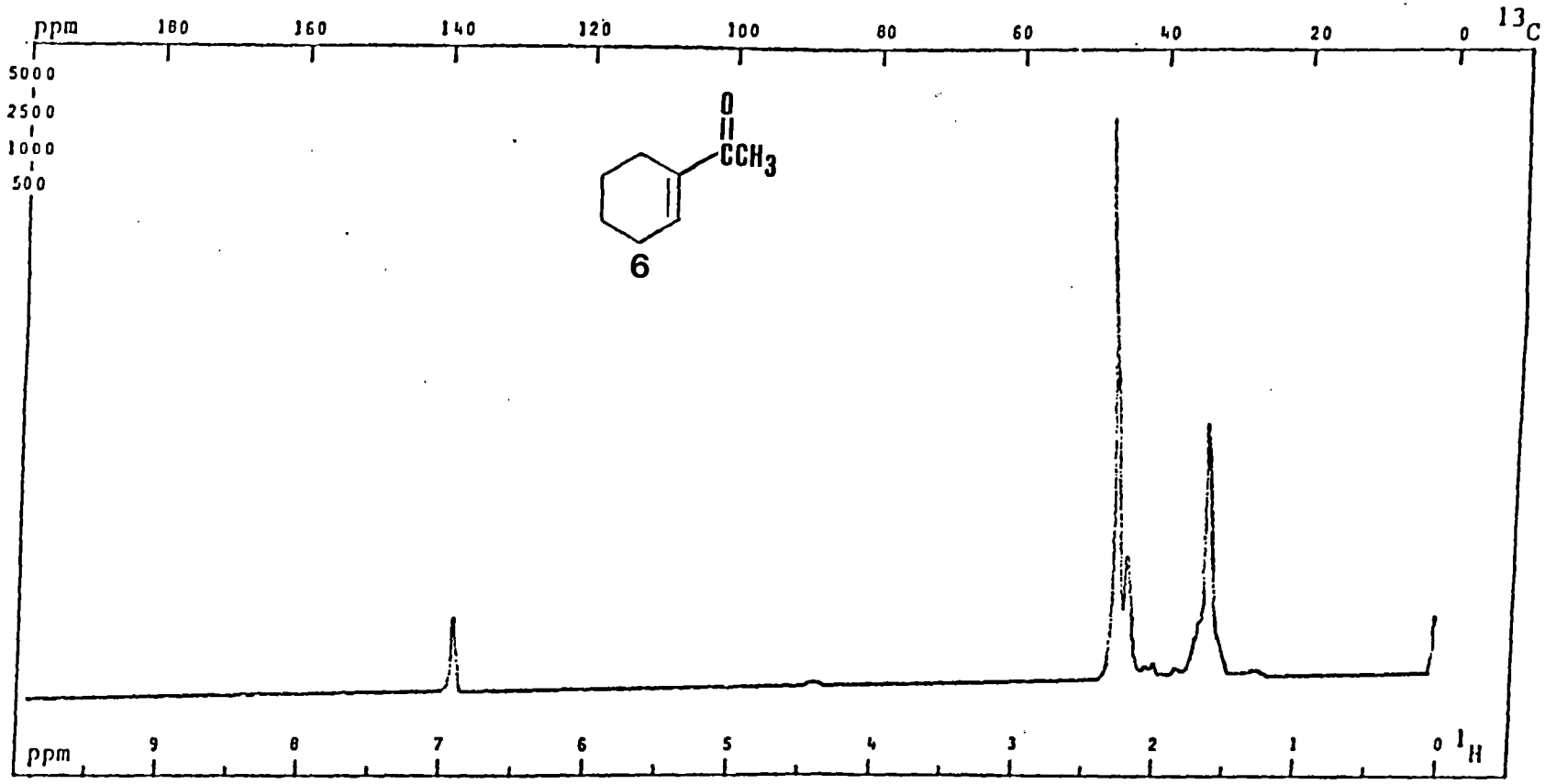
Spectrum 1. ^{13}C NMR of Menthonecarboxylic Anhydramide (2).



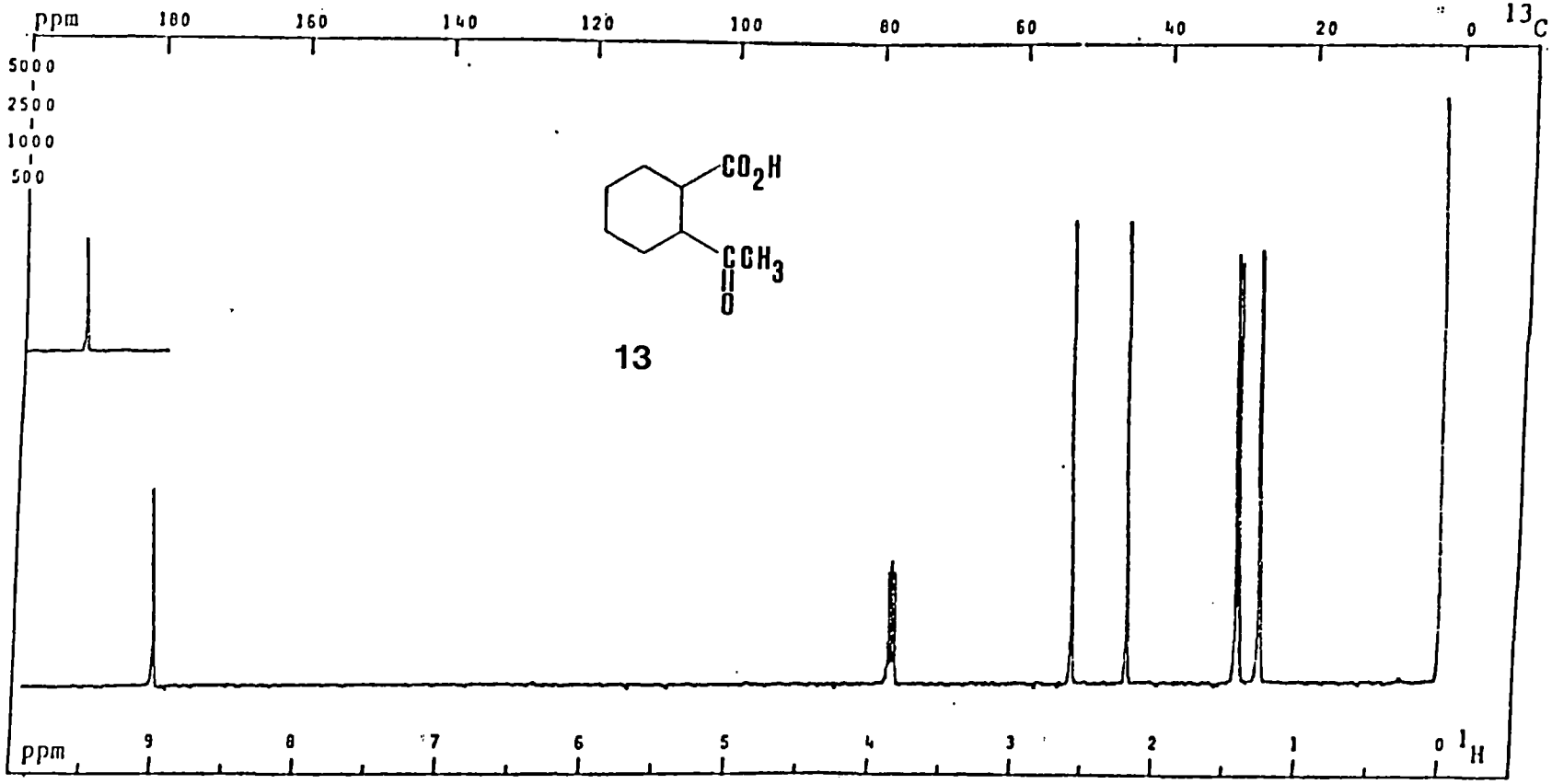
Spectrum 2. ^{1}H NMR of Menthonecarboxylic Anhydramide (2).



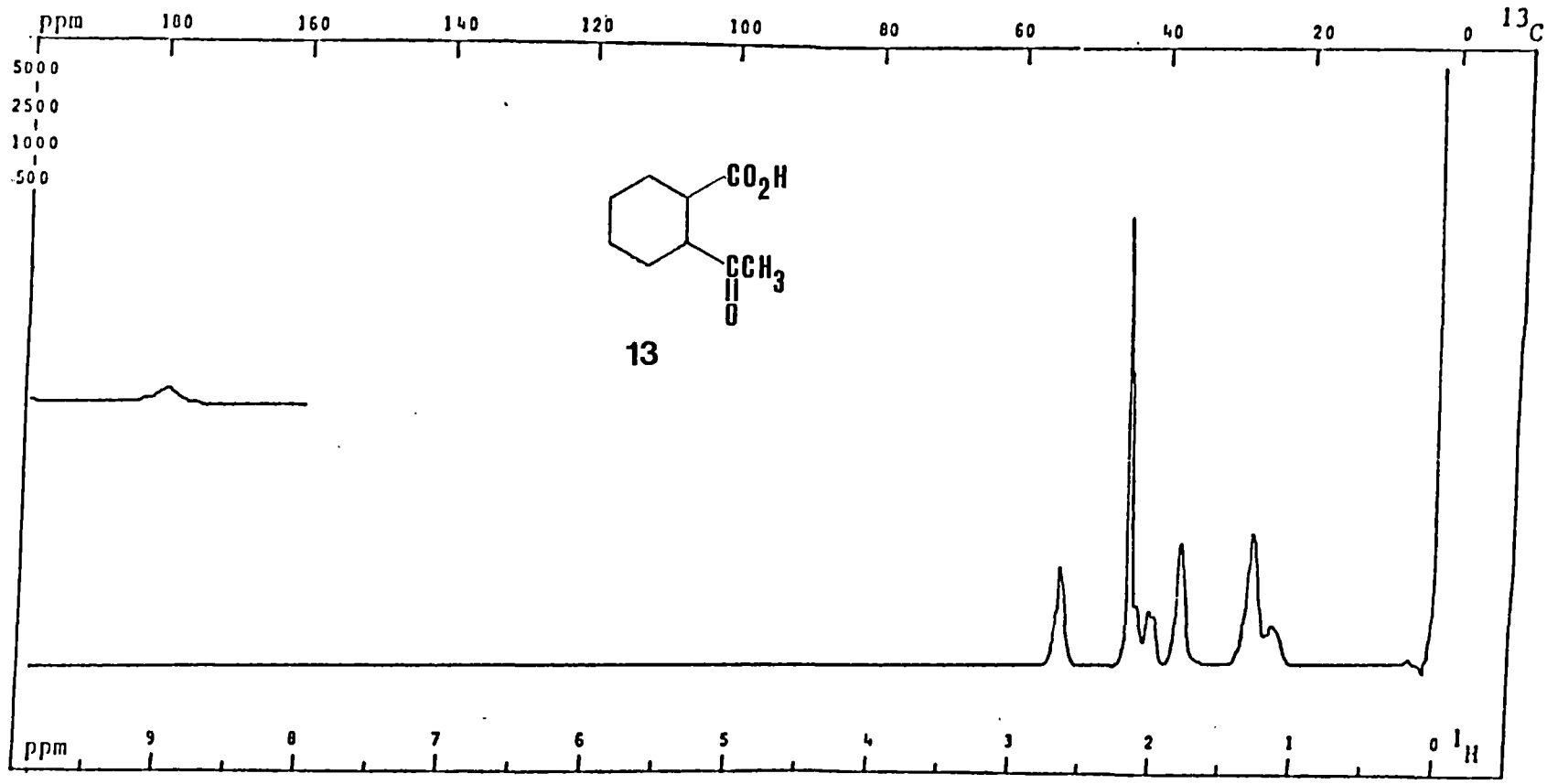
Spectrum 3. ^{13}C NMR of 1-Acetyl-1-cyclohexene (**6**).



Spectrum 4. ^{1}H NMR of 1-Acetyl-1-cyclohexene (**6**).



Spectrum 5. ^{13}C NMR of 2-Acetylcyclohexane Carboxylic Acid (**13**).



Spectrum 6. ^{1}H NMR of 2-Acetylcyclohexane Carboxylic Acid (**13**).

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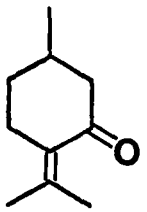
APPENDIX

GLOSSARY OF STRUCTURES



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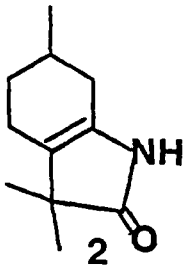

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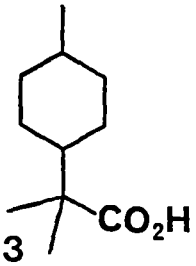

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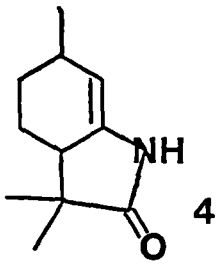

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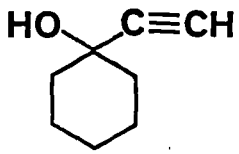

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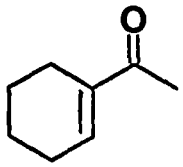

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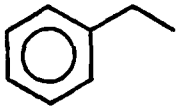

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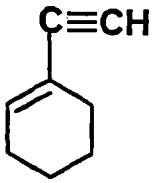

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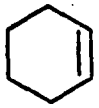

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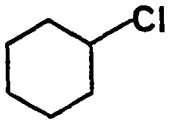

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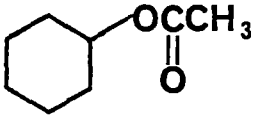

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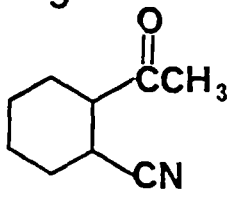
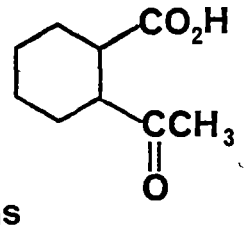


12a, cis
12b, trans



13a, cis
13b, trans

VITA

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Master of Science

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