I. PHENOL DEOXYGENATION VIA CATALYTIC HYDROGENOLYSIS

II. FRIEDEL-CRAFTS REACTION OF p-CRESOL AND CROTONIC ACID

III. SYNTHESIS OF NONISOPRENOID NEPETALINIC ACIDS

By

Jimmie Dean Weaver, Jr.

Bachelor of Science

Southwestern State College

Weatherford, Oklahoma

1968

Submitted to the Faculty of the Graduate College
of the Oklahoma State University
in partial fulfillment of the requirements
for the Degree of
DOCTOR OF PHILOSOPHY
July, 1973

I. PHENOL DEOXYGENATION VIA CATALYTIC HYDROGENOLYSIS

II. FRIEDEL-CRAFTS REACTION OF p-CRESOL AND CROTONIC ACID

III. SYNTHESIS OF NONISOPRENOID NEPETALINIC ACIDS

Thesis Approved:

E J Eisenbraun
Thesis Adviser

Ernest M. Hodnett

Horacio A. Mottola

Kenneth Carraway

N. N. Durham
Dean of the Graduate College

ACKNOWLEDGEMENTS

I am appreciative of the patience, encouragement, and able counsel of my research adviser, Dr. E. J. Eisenbraun, during the course of this study. I am also grateful to Dr. O. C. Dermer for advice and for having read and made many helpful suggestions during the preparation of this thesis.

I thank Dr. L. E. Harris, Enviromental Protection Agency, for his friendship and his efforts in obtaining gas chromatographic-mass spectrometric data.

I also thank Drs. K. Berlin, G. Gorin, E. Hodnett, H. Mottola, and N. Purdie for their friendship and willingness to aid me during this study.

I wish to express thanks to my many friends for having made this study pleasurable and especially to Drs. J. Burnham, W. Duncan, W. Harms, D. Morris, and T. Snider.

I am grateful to the American Petroleum Institute and Oklahoma State University for partial financial support during my graduate work.

TO

My Parents,

who have done everything for their children

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PART I

PHENOL DEOXYGENATION VIA CATALYTIC HYDROGENOLYSIS

CHAPTER I

INTRODUCTION AND HISTORICAL

In 1897 Sabatier reported that finely divided nickel in a hydrogen atmosphere have a high reducing strength.[1] This early observation led to the development of one of the more significant synthetic tools available to the organic chemist, catalytic hydrogenation.

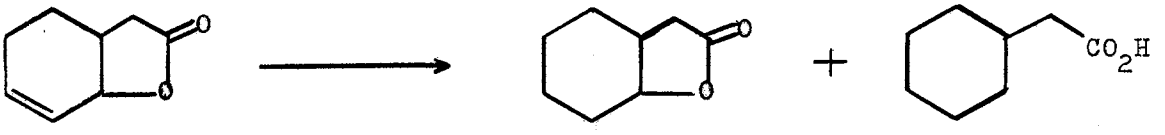
The term hydrogenation has at times been applied to any reaction involving the use of hydrogen. However, there are at least two explicit types of reactions in which hydrogen is incorporated into a compound--addition and substitution.

The name hydrogenation has evolved to mean the addition of hydrogen to multiple bonds of olefins, acetylenes, arenes, and carbonyl groups, as well as to other types of unsaturation. Considerable effort has been invested in the study of catalytic hydrogenation since the reaction is of great importance both industrially and academically. These studies have yielded valuable information allowing choice of suitable conditions, solvents, and catalysts. The mechanism of hydrogenation is not fully understood because the kinetics of heterogeneous catalysis are inherently difficult to interpret. However, recent advances in homogeneous catalysis are providing a more complete understanding of catalytic hydrogenation. Several comprehensive reviews are available.[2,3,4]

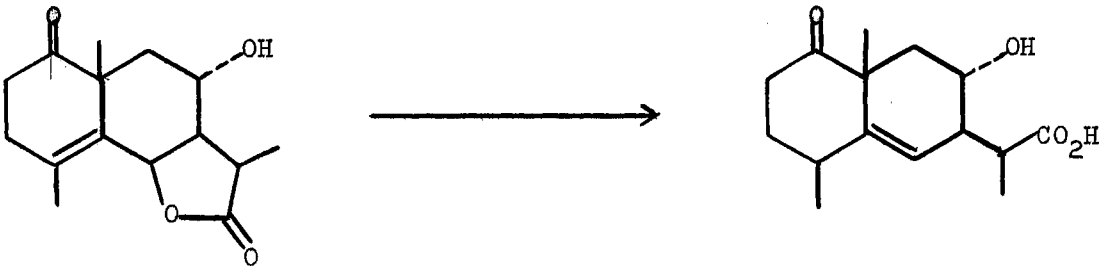
Hydrogenolysis may be defined as the substitution of hydrogen for another atom. Some cycloalkanes may be cleaved to form alkanes by the

substitution of hydrogen for carbon.[5] Reactions of this type find broad use in industry. The more commonly hydrogenolyzed bonds are those linking carbon to hetero atoms (C-X, C-O, C-N, and C-S) in compounds containing halogen, hydroxyl, acetal, and amino groups, and in thio compounds.

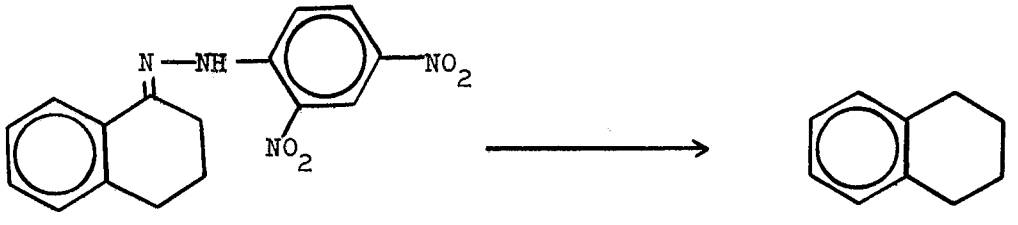
Hydrogenolysis of these groups occurs most readily when they are located at an allylic or a benzylic position. Hydrogenolysis of allylic groups is often accompanied by competitive hydrogenation of the double bond. Frequently, hydrogenation of the double bond follows hydrogenolysis. For example, 2-hydroxycyclohex-3-enylacetic lactone was reported to give a 71% yield of the hydrogenolysis product, cyclohexylacetic acid, when it was exposed to hydrogen in ethanol in the presence of Adams catalyst.[6] However, when the same reaction was carried out in acetic acid as the solvent, the yield dropped to 55% with a corresponding increase in that of the saturated lactone.[7]



In some cases, hydrogenolysis can be carried out without saturation of double bonds. These reactions are often complicated by double bond migration, especially in nonaromatic, allylic systems as illustrated by the hydrogenolysis of Ψ-santonin with palladium on carbon in acetic acid as shown on the following page.[8]

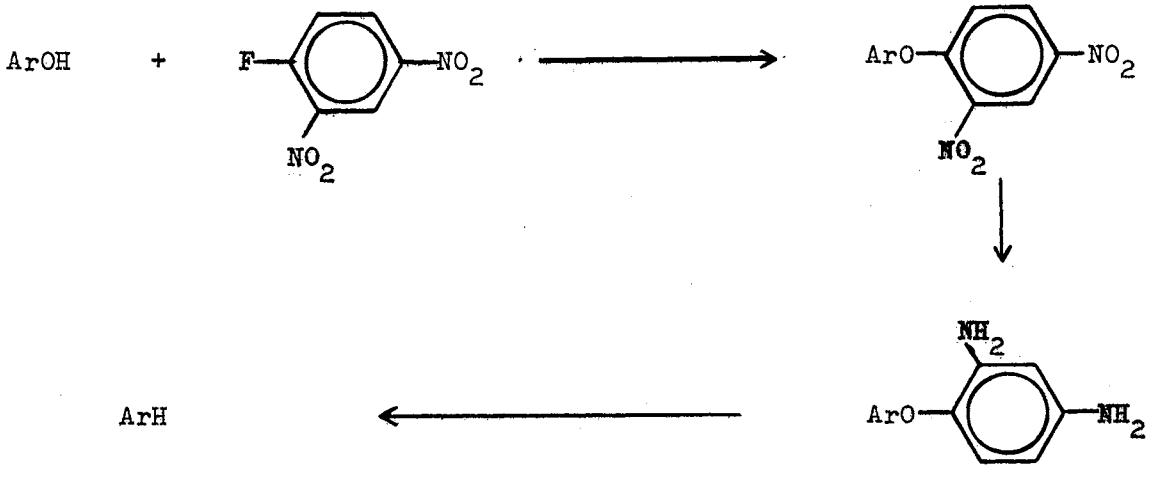


Hydrogenolysis of benzylic alcohols,[9] halides,[10] esters,[9] and aromatic ketones and their derivatives occurs in a more predictable manner than with the corresponding allylic systems. The latter process may involve partial hydrogenation and rearrangement as pointed out previously, whereas the benzylic system is more resistant to hydrogenation. Hydrogenolysis of aromatic ketones and their derivatives is particularly useful for the preparation of high-purity arenes as illustrated by the reduction of the 2,4-dinitrophenylhydrazone of 1-tetralone in acetic acid with palladium on carbon catalyst to give a 95% yield of tetrahydronaphthalene as shown below.[11]



The hydrogenolysis of phenols with removal of the hydroxyl groups is a main topic of this thesis. Until very recently there have been few reported techniques for the removal of phenolic hydroxyl groups without hydrogenation of the aromatic ring.

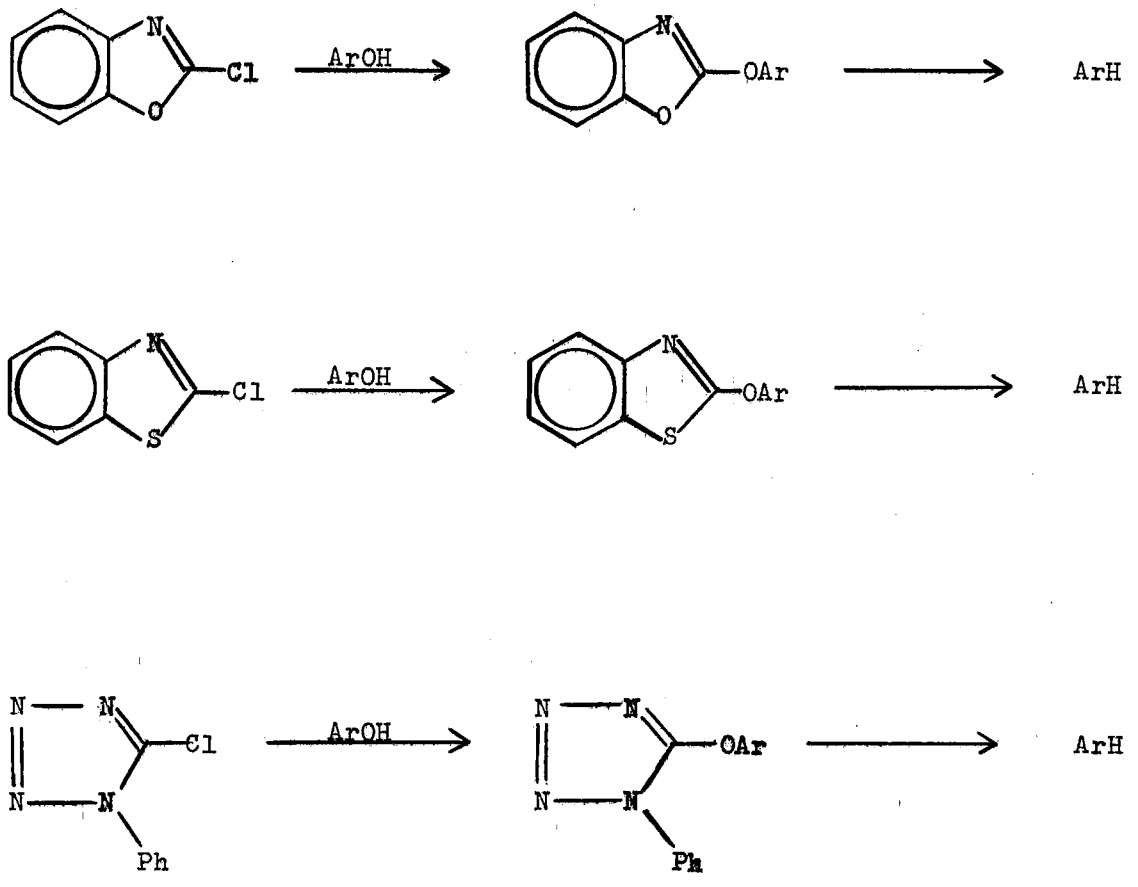
One of these methods involves the sodium-ammonia reduction of diaryl ethers, which results in cleavage to an arene and a phenol.[12] Taking advantage of this observation, Pirkl and Zabriskie in 1964 published a procedure for the removal of phenolic hydroxyl groups.[13] In order to control the direction of cleavage, the phenol was converted to the 2,4-dinitrophenyl aryl ether by reaction with 2,4-dinitrofluorobenzene in dimethylformamide-benzene mixture, sodium hydride being used as the base, as shown below. The nitro groups were then reduced with hydrogen over palladium to give the diamino ether, and subsequent further reduction with sodium and ammonia gave the deoxygenated arene. This reaction, in addition to requiring several steps, is mostly restricted to those phenols having a methoxyl or phenyl group in the <u>ortho</u> position.



The catalytic hydrogenation of phenols to the corresponding cyclohexanols has been known for many years to produce small amounts of cyclohexanes as hydrogenolysis by-products. A great deal of study has been given to this reaction, mostly to find conditions to minimize hydrogenolysis of substituted phenols.[14,15]

Amino, hydroxyl, alkoxyl, and carboxyl substituents in phenols tend to increase hydrogenolysis of the phenol while alkyl substituents appear not to affect the reaction much.[16] The catalyst used has been found to have a profound effect upon the extent of hydrogenolysis, hydrogenolysis being favored by Group VIII metals in decreasing order: iridium, platinum, palladium, rhodium, and ruthenium.[14] Most compounds give different ratios of hydrogenation to hydrogenolysis when solvents are changed but no generalizations can be made. Hydrogenolysis is generally enhanced by mineral acids as well as by an increase in the reaction temperature.[17] There have been at least three possible mechanisms suggested. The hydroxyl may be lost by (a) hydrogenolysis of the aryl-oxygen bond before any reduction of the ring, (b) after partial reduction of the ring, or (c) at the same time as reduction of the ring. There is evidence indicating that each pathway occurs to some extent and that no single mechanism accommodate all the required data.[14]

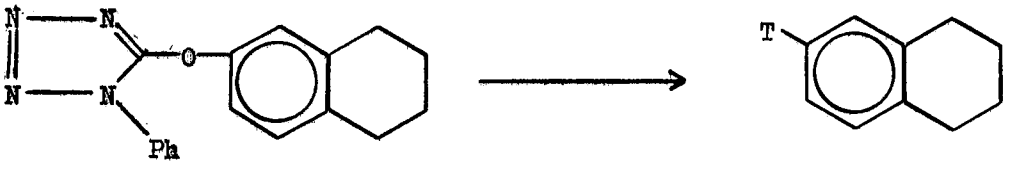
In 1966 Musliner and Gates reported that phenols could by deoxygenated under mild conditions by the catalytic hydrogenolysis of certain heterocyclic ethers.[18] To date this procedure remains the most general and consistent method for the removal of phenolic hydroxyls. The reaction of 2-chlorobenzoxazole, 2-chlorobenzothiazole, or 1-phenyl-5-chlorotetrazole with various phenols in acetone and potassium carbonate yields the heterocyclic ethers as shown on the following page.



Hydrogenolysis of the above ethers in benzene, ethanol, or tetrahydrofuran gave excellent to poor yields of arenes using palladium on carbon as the catalyst. The hydrogenolyses generally occurred without further reduction of the arenes produced, thus providing a useful method for removing phenolic oxygen. However, substituents in certain positions on the phenol were found to produce a lower yield of the arenes and in many cases, the hydrogenolysis occurred in the "undesired direction". That is, the starting phenol was produced. The mechanism was not discussed.[18]

In some cases, the hydrogenolysis products poison the catalyst, thus requiring high catalyst ratios. This was particularly common for the benzoxazolyl ethers, which required as high as 50% catalyst/substrate in some instances.[18]

The use of these derivatives in deoxygenation procedures is receiving attention. Jagt, Hollander, and Zanten reported in 1971 that the 6 position of 1,2,3,4-tetrahydronaphthalene was labeled with tritium by the catalytic tritiumolysis of the phenyltetrazolyl ether of 5,6,7,8-tetrahydro-2-naphthol.[19]



CHAPTER II

DISCUSSION AND RESULTS

We sought a high-purity sample of 1,7-dimethylindan (4) for use as a standard hydrocarbon by the American Petroleum Institute. In order to obtain 4, the deoxygenation of 1,7-dimethyl-4-indanol (2), which was conveniently available via a Clemmensen reduction of 3,4-dimethyl-7-hydroxyindanone (1), was studied. This reaction scheme is illustrated in Figure 1.

The indanone 1 was prepared in high purity from a novel Friedel-Crafts cyclization reaction of p-cresol and crotonic acid. Discussion of this reaction will be deferred until Chapter V.

Clemmensen reduction conditions necessary for the conversion of 1 to 2 were modified considerably from the ordinary procedure. Rather than mossy zinc, zinc dust was amalgamated. Also a homogeneous solvent system was used and the reaction mixture was stirred vigorously. These conditions usually favor the formation of pinacols[20] but in this case the indanol 2 was obtained in 81% yield in less than one hour. Normally, Clemmensen reductions require several hours.

The reaction of 2-chlorobenzoxazole with 2 proceeded smoothly in acetone. Potassium carbonate was used to absorb the hydrogen chloride produced by the formation of 2-benzoxazolyl 7-(3,4-dimethylindanyl) ether (3). The reaction mixture was distilled under reduced pressure to give a 69% yield of the colorless, crystalline ether 3.

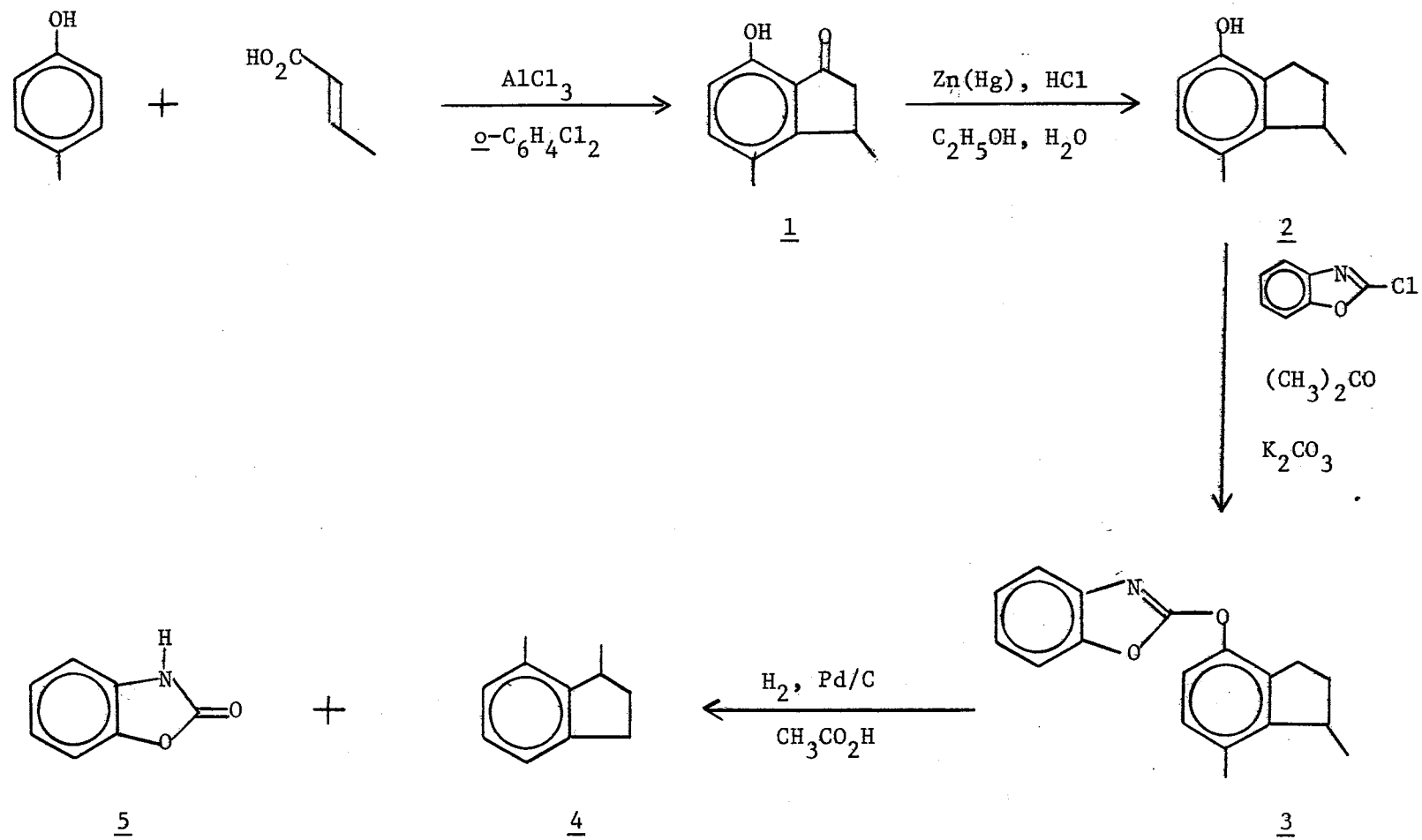


Figure 1. Reaction Scheme for the Synthesis of 1,7-Dimethylindan (4).

Hydrogenolysis of 3 proceeded smoothly in ethyl acetate using palladium on carbon as the catalyst to give a nearly quantitative yield of the indan 4 and 2-benzoxazolone (5). This method appears ideal for the preparation of high-purity hydrocarbons since the two products from the hydrogenolysis are easily separated and no perhydrogenation products are observed.

Acetic acid, generally recognized as a good hydrogenolysis solvent, gave a reduced yield (70%) of 4. Gas chromatographic analysis of the hydrogenolysis reaction mixture gave the chromatogram shown in Figure 2. The peaks were found to correspond to 4, an unknown later identified as 7, followed by 2, and 3 in the order of their emergence.

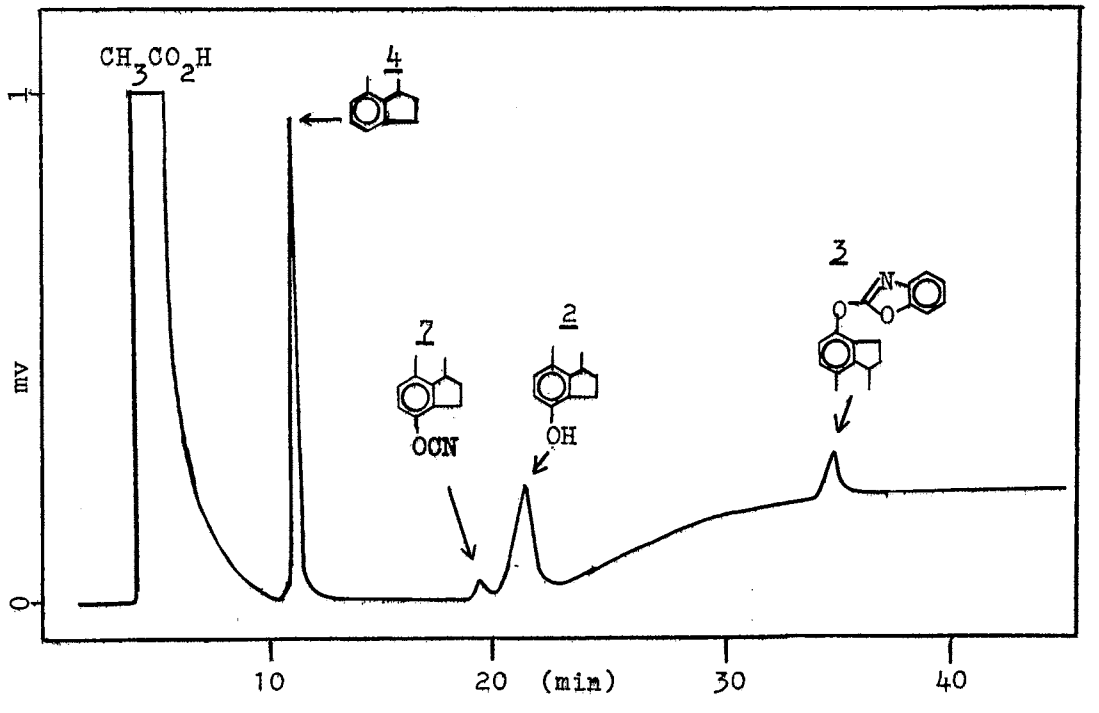


Figure 2. Gas Chromatoghram of the Reaction Mixture from Hydrogenolysis of 3 in Acetic Acid.[21]

The thermal stability of the ether 3 on the gc column was established using the column conditions[21] described in the previous analysis. This indicated that the phenol 2 was formed during the reaction and not by thermal degradation during gc analysis. Furthermore, 3 was stirred in acetic acid under the conditions of the hydrogenolysis reaction and was found to be stable.

The formation of the starting phenol was not completely unexpected since it had been previously noted that hydrogenolysis may occur in the "undesired manner".[18] However, the infrared spectrum of the distilled hydrocarbon 4 showed a strong absorption band at 4.45 μ indicative of a triply bonded impurity.

There are three hetero atom arene bonds present in the benzoxazolyl ether 3 shown in Figure 3, and these bonds should be expected to undergo hydrogenolysis, but probably at greatly different rates. Examination of the possible modes of hydrogenolysis of each of these hetero atom arene bonds allow prediction of the potential intermediates 6 and 7 shown in Figure 3.

Hydrogenolysis of the indanyl-oxygen bond (Figure 3, cleavage a and pathway a) leads to the hydrocarbon 4. This is the desired hydrogenolysis and obviously is favored under the reaction conditions presented. Hydrogenolysis of the oxygen-arene bond (cleavage c and pathway c) leads to the phenylcarbamate 6. Formation of a triply bonded species (e.g. 7) is rationalized if hydrogenolysis should occur at the nitrogen-arene bond (cleavage b and pathway b) with a subsequent loss of phenol to yield the indanyl cyanate 7.

In order to confirm any of these postulates, it became necessary to synthesize the proposed intermediates (6 and 7) and subject them to

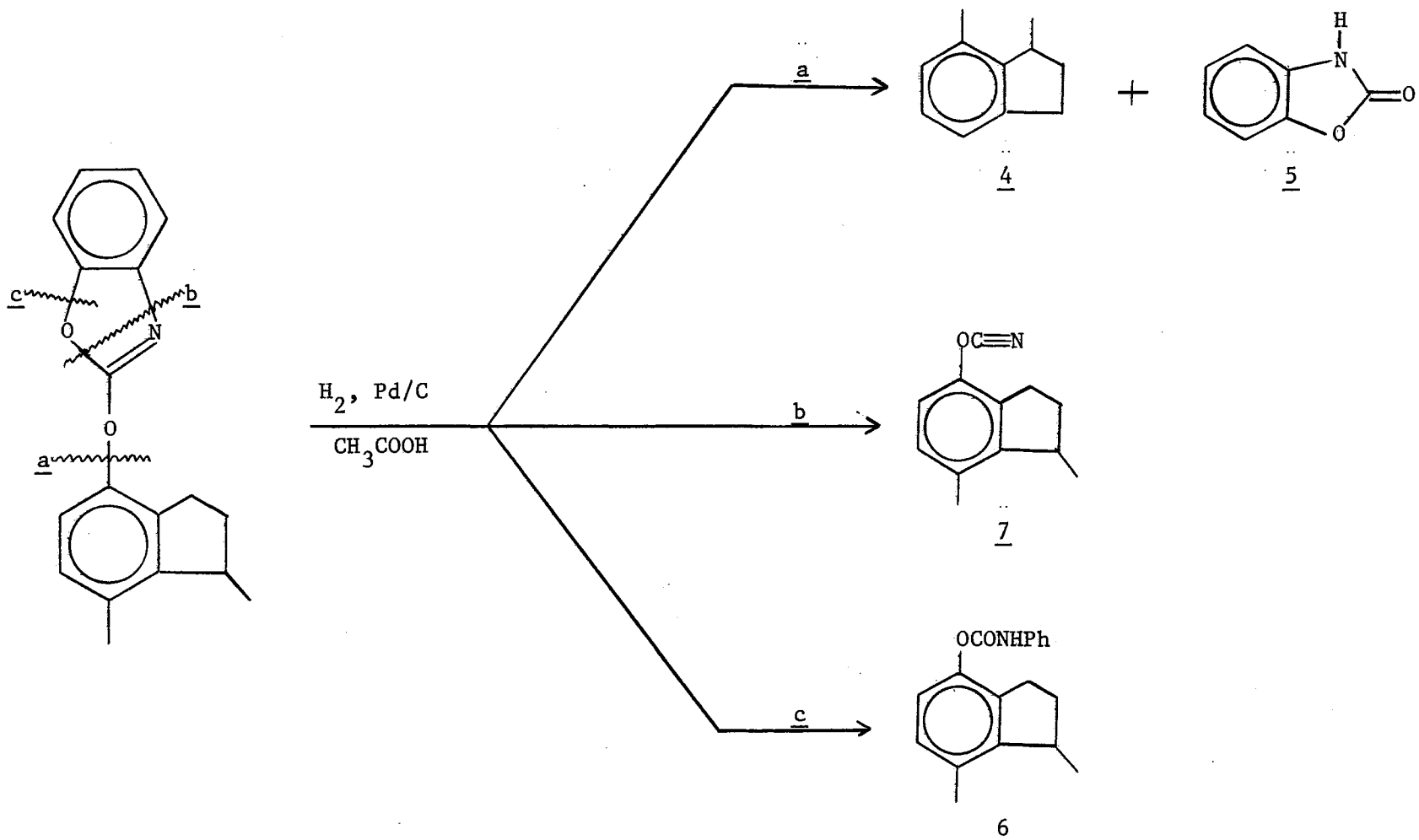
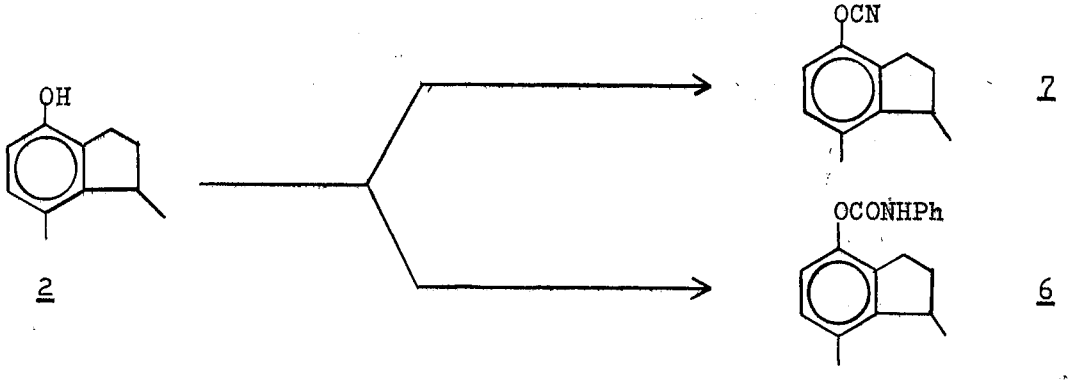


Figure 3. Possible Pathways for the Hydrogenolysis of 3.

independent hydrogenolyses and thus determine their role in the reaction of 3 with catalyst and hydrogen. The cyanate 7 was prepared in 96% yield by the reaction of 2 with cyanogen bromide in acetone. The carbamate 6 was prepared in 41% yield by the reaction of 2 with phenyl isocyanate in refluxing benzene.



2 7 6

A trace of 7 was added to a sample of 1,7-dimethylindan (4) and the infrared spectrum of the mixture was obtained. This spectrum was identical with the spectrum of 4 obtained previously from the hydrogenolysis in acetic acid. Futhermore, the gc retention time of the cyanate 7 was identical with that of the second peak obtained upon gc determination of the products of hydrogenolysis in acetic acid as shown in Figure 2. Injection of a mixture confirmed the identity of the retention times. The mass spectrum of the cyanate 7 (obtained by use of a combination gc-ms instrument[22]) was the same as the one obtained for the unknown in the hydrogenolysis in acetic acid. This evidence supports the intermediacy of the cyanate 7. Although its concentration in the reaction mixture

appeared to be less than 1%, its presence as a reaction intermediate is significant since a hydrogenolysis of this type has not been reported previously.

The cyanate 7 was subjected to the same hydrogenolysis conditions in acetic acid as used previously in the conversion of 3 to 4. The only product detected by qualitative gc analysis was 2. In contrast, 7 was inert to hydrogenolysis in ethyl acetate. Thus, in acetic acid 7 is a possible intermediate leading to the starting phenol 2. Although 3 may be hydrogenolyzed by pathway b, Figure 3, to form the cyante 7, this cleavage ultimately leads to the formation of the starting phenol 2. Thus, hydrogenolysis occurs in the "undesired manner".

If, indeed, the cyanate 7 is an intermediate, then the carbamate 6 must also be considered as a potential intermediate although there is no direct gc evidence supporting its intermediacy. Hydrogenolysis of 6 in ethyl acetate did not occur, and in fact, 6 was recovered quantitatively. However, hydrogenolysis in acetic acid proceeded slowly to form the indan 4 as well as some cyclohexenylamines. Gas chromatographic studies of the mixtures were complicated by the fact that 6 proved to be unstable to column conditions. It thermally rearranged to form 2 and phenyl isocyanate. In fact, 6 was found to decompose at 270° in a Pyrex glass melting point tube. When stainless steel filings were added, the sample decomposed below 200°. This prompted the preparation of a glass gc column, but to no avail since such analysis of 6 remained unsucessful. Glass liners for the stainless steel injection ports probably would have solved this problem.

Although the intermediacy of 6 could not be confirmed by gc, greater success was realized using thin-layer chromatography. Another

hydrogenolysis of 3 in acetic acid was interrupted before the reaction was complete and the mixture was steam distilled. Previously, a mixture of 3, 5, and 6 had been shown to be stable in boiling aqueous acetic acid and non-volatile in the presence of steam. The steam distillation pot residue was extracted with ether and the ether solution was chromatographed on silical gel.[23] Figure 4 illustrates the results. Although the carbamate 6 was not isolated from the hydrogenolysis mixture, 6 did have the same Rf value as one of the components of the mixture.

The gravimetrically determined yield of 4 from the hydrogenolysis of 6 in acetic acid was found to be 70% based upon the 78% of 6 consumed in the reaction. The results from the various hydrogenolyses of the postulated intermediates are summarized in Table I.

The preceding evidence suggests that all three of the postulated pathways are operative, but at very different rates depending upon the solvent used. When the hydrogenolysis was carried out in ethyl acetate, a non-protonating solvent, the rate at which the indanyl-oxygen bond (Figure 3, cleavage a) was hydrogenolyzed apparently was very large compared to the rates along the other two pathways, b and c. When acetic acid, a protonating solvent, is used pathways b and c become competitive with a. The need for high catalyst/substrate ratios for the hydrogenolysis of benzoxazolyl ethers[18] may stem from the poisoning effect of cyclohexenylamines formed as by-products via pathway c, amines having been well established as palladium poisons.[24]

Perhaps the observed solvent effect results from the protonation of the benzoxazolyl ether 3 and the existence of the equilibrium suggested in Figure 5. Protonations of this type have been known to facilitate hydrogenolytic removal of allylic and benzylic groups.[25]

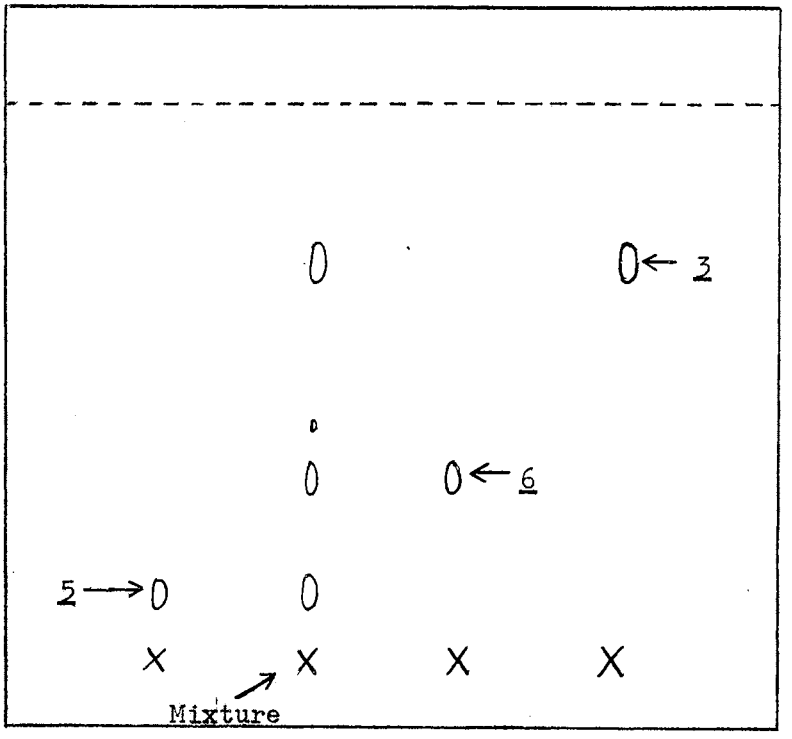


Figure 4. Thin-Layer Chromatogram of the Non-Steam-Volatile Compounds from the Hydrogenolysis of 3 in Acetic Acid[23].

TABLE I

HYDROGENOLYSIS PRODUCTS OF PROPOSED INTERMEDIATES

Substrate	Solvent	Products	% Yield[a]
7	ethyl acetate	7	100
7	acetic acid	2	100
6	ethyl acetate	6	100
6	acetic acid	4	70[b]

[a]Determined by gc analysis.[26] [b]Determined gravimetrically and based upon recovered 6.

A literature survey failed to reveal previous accounts of the hydrogenolysis of phenylcarbamates. Since phenylcarbamates are conveniently prepared and easily purified, it seemed worthwhile to investigate the possibility of using this reaction as a general method to deoxygenate phenols.

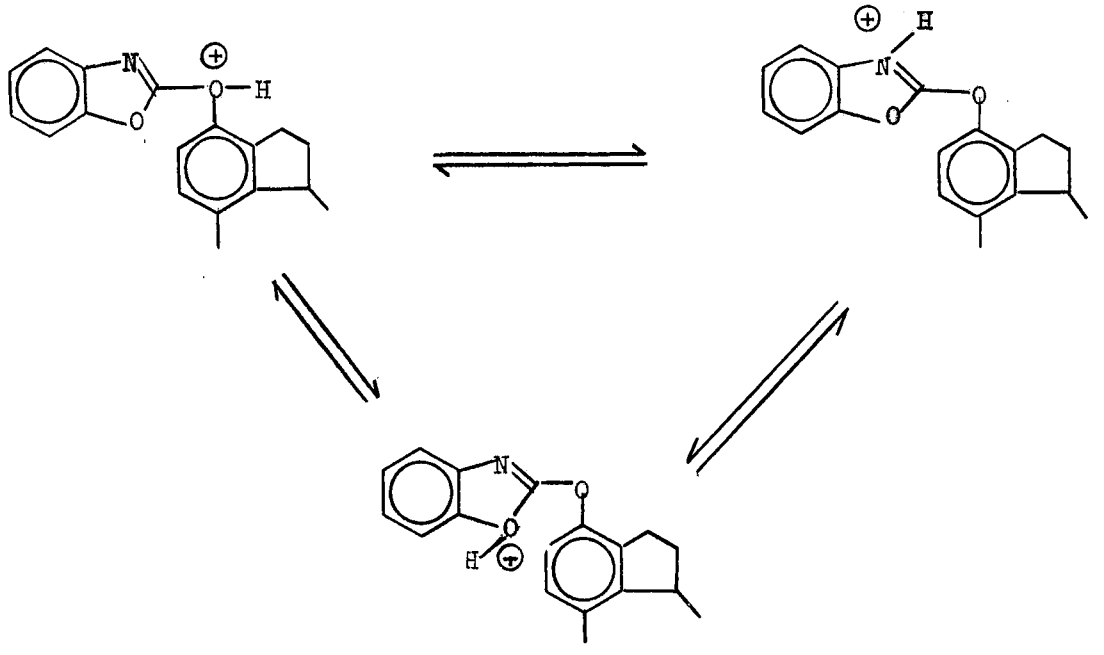


Figure 5. Possible Protonated Forms of 3.

A series of methyl- and dimethylphenols were combined with phenyl isocyanate to form the respective phenylcarbamates in excellent yields as shown in Table II. The carbamates were invariably crystalline and easily purified by recrystallization.

It has been previously noted that the more hindered phenols often

give hydrogenolysis in the "undesired manner."[18] No substituent effects of this nature were observed during the hydrogenolysis of the series shown in Table III. The rate at which the hydrogenolysis proceeded and the overall yield were indeed affected as can be observed from these data. Alkyl substituents in ortho positions decreased the extent of hydrogenolysis.

The uptake of hydrogen during the hydrogenolysis of the series of carbamates was monitored and the volume of hydrogen used was plotted against time. A typical plot is shown in Figure 6. It should be noted that hydrogen was consumed rapidly for the first portion of the reaction, which was generally 3 to 6 hours.

TABLE II

PRODUCTS FROM THE REACTION OF PHENYL ISOCYANATE AND VARIOUS PHENOLS

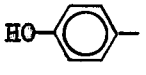
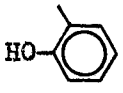
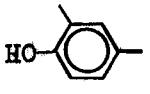
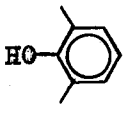
Phenol	% Yield carbamate	Mp °C
	93	114-115
	89	148-149
	90	99-100
	93	144-145

TABLE III

HYDROGENOLYSIS OF VARIOUS PHENYLCARBAMATES

Substrate R-OCONHPh R=	% Arene[a] Produced	Recovered Carbamate (g)	Carbamate Used (mol)	% Arene[b]	Reaction Time (hrs)
p-$CH_3C_6H_4$-	34.7	2.9	.009	82.5	18
o-$CH_3C_6H_4$-	49.0	3.3	.029	73.0	24
2,4-$(CH_3)_2C_6H_3$-	9.7	6.6	.014	28.8	48
2,6-$(CH_3)_2C_6H_3$-	4.5	7.8	.009	20.6	72

[a]Actual yield as determined by gc analysis. [b]Yield based upon the recovered phenylcarbamate.

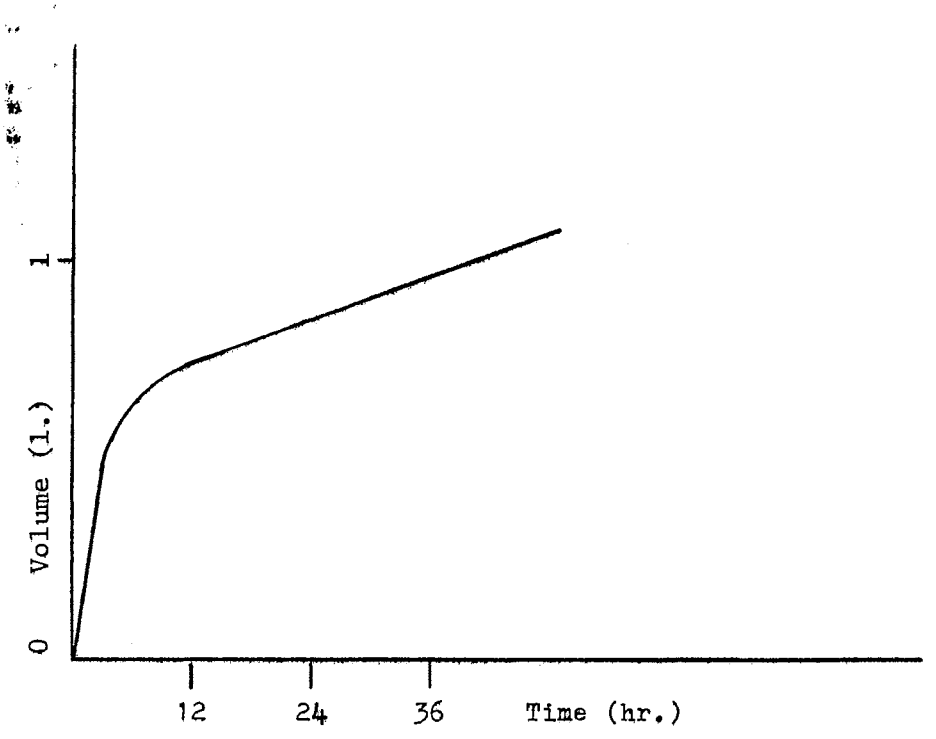


Figure 6. Rate of the Hydrogenolysis of 2,4-Dimethylphenyl Phenylcarbamate.

Amines are known to be effective palladium catalyst poisons and since cyclohexenylamines are being produced during the hydrogenolysis of the phenylcarbamate, it was surmised that the reaction proceeded rapidly until the limited amount of catalyst was saturated with the amine.[24] Beyond this point the rate would depend upon the rate of absorption-desorption of the amine and the competition between the amine and the substrate for the catalyst. Evidence supporting this postulate was obtained by carrying out the hydrogenolysis of the p-methylphenyl phenylcarbamate in acetic acid for 12 hours at 52° using various catalyst/substrate ratios. The data summarized in Table IV show that an increased catalyst/substrate ratio increased the yield for the 12-hour period.

TABLE IV

THE EFFECT OF VARYING THE CATALYST RATIO UPON HYDROGENOLYSIS OF 4-METHYLPHENYL PHENYLCARBAMATE[a]

% Catalyst w/w[b]	% Arene	% Recovered Carbamate
10	23	70
20	35	58
30	49	38
40	66	29
50	73	14

[a]All reactions were carried out in acetic acid for 12 hours at 52°. [b]10% palladium on activated carbon. [c]Determined by gas chromatographic analysis.[26]

Another consideration is that in order for the reaction to proceed effectively, the solvent must dissolve the reactants, products, and intermediates in order to prevent saturation of the catalyst surface or trapping the catalyst inside a coating of products. The choice of solvent has already been shown to be a significant factor in the hydrogenolysis. A series of solvents were selected for the hydrogenolysis of 2,4-dimethylphenyl phenylcarbamate. The data are presented in Table V. It should be noted that dimethylformamide shows promise as a useful hydrogenolysis solvent in that there was an increase from 10% to 85% in hydrogenolysis with a 25% reduction in the required time.

TABLE V

SOLVENT EFFECT IN THE HYDROGENOLYSIS OF 2,4-DIMETHYLPHENYL PHENYLCARBAMATE

Solvent	Reaction time (Hrs.)	% Arene
Ethyl acetate	72	0
Acetic acid	48	10
Dimethylformamide	12	85

The hydrogenolysis of this series of phenylcarbamates proceeded to give the respective arenes in fair yields. The hydrogenolysis by-products formed were mainly cyclohexylamine and cyclohexenylamines. In addition, small amounts of benzyl acetate (from the hydrogenolysis of the methylphenyl phenylcarbamates) and 3-methylbenzyl acetate (from the hydrogenolysis of the dimethylphenyl phenylcarbamates) were formed. It is believed that these acetates are formed via side-chain acetoxylation of a transitatory intermediate formed during hydrogenolysis of the phenylcarbamates.

The use of phenylcarbamates as derivatives to deoxygenate phenols should be considered because of their ease of preparation and purification. The yields of hydrogenolysis are somewhat lower than from that of the corresponding benzoxazolyl ethers. However, in view of the current cost of 2-chlorobenzoxazole compared to that of phenyl isocyanate and the care required in the preparation of benzoxazolyl ethers, the carbamate route appears advantageous.[27]

CHAPTER III

EXPERIMENTAL

Preparation of 1,7-Dimethyl-4-indanol (2) via Clemmensen Reduction of 1.-- Powdered zinc (200 g) was amalgamated by treatment with 4 g of $HgCl_2$ in 300 ml of water and 50 ml of 37% HCl with stirring for 30 min. The solution was decanted and the amalgam was twice washed with water. The indanone 1 (40 g) was dissolved in 200 ml of ethanol and the solution added to a reaction vessel containing the amalgam, 200 ml of water, and 200 ml of 37% HCl. The mixture was refluxed for one hour while being stirred vigorously. The solution was decanted, the amalgam was washed with ether several times, and these washings were added to the ether extract of the decanted material. The combined ether solutions were dried with Na_2SO_4 and evaporated. The resulting oil was distilled at 92° (0.7 mm) to give an 81% yield of 2: ir (neat) 3.05, 3.40, 6.04, 6.24, 6.70, 6.88, 7.90, 9.54, 10.96, and 12.35 μ; mass spectrum m/e (rel intensity) 162 (24), 147 (100), 132 (20), 115 (15), and 91 (24); pmr (CCl_4) δ 6.48 (q, 2, ArH), 5.92 (s, 1, ArOH), 3.19 (m, 1, $-C\underline{H}CH_3$), 2.72 (m, 2, $ArCH_2-$), 2.17 (s, 3, $ArCH_3$), 1.90 (m, 2, $-CH_2-$), and 1.10 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{11}H_{14}O$:[69] C, 81.44; H, 8.70. Found C, 81.44; H, 8.71.

2-Benzoxazolyl 7-(3,4-Dimethylindanyl) Ether (3).[18]-- This compound was prepared by combining 200 ml of anhydrous acetone containing 16.2 g

(0.10 mol) of 2, 16 g (0.14 mol) of 2-chlorobenzoxazole, and 28 g (0.20 mol) of anhydrous potassium carbonate and heating the mixture under reflux with stirring under a nitrogen atmosphere for 12 hr. The reaction mixture was filtered to remove salts and the filtrate was concentrated on a rotary evaporator. The residue was distilled at reduced pressure (0.03 mm) and the fraction distilling at 163-165° was collected; it crystallized upon cooling. Recrystallization from 95% ethanol gave colorless, crystalline 3: ir (neat) 3.42, 6.16, 6.38, 6.74, 7.39, 7.60, 8.14, 8.42, 8.55, 12.29, and 13.44 μ; mass spectrum m/e (rel intensity) 279 (1), 144 (58), 143 (30), 130 (25), 129 (100), 128 (45), 115 (34), 91 (17), 77 (21), 51 (16), and 39 (10); pmr (CCl_4) δ 7.40-6.85 (m, 6, ArH), 3.38-3.12 (m, 1, $ArC\underline{H}CH_3$), 3.06-2.78 (m, 2, $ArCH_2$-), 2.25 (s, 3, $ArCH_3$), 2.42-1.58 (m, 2, $-CH_2-$), and 1.21-1.14 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.13. Found: C, 77.18; H, 6.10.

General Hydrogenolysis Procedure.-- The hydrogenolyses were carried out with 10% palladium on carbon catalyst obtained from Engelhard Industries. The ratio of catalyst to compound was 0.2 unless stated otherwise. The solvents used were either ethyl acetate, acetic acid, or dimethylformamide and the amount of solvent was such that the substrate was 5-10% of the solution. The reactions were carried out in a 500 ml fluted flask, stirred magnetically, and the temperature was maintained by a stirred oil bath. The hydrogen pressure was maintained at slightly greater than one atmosphere by use of a leveling bulb containing water. Unless otherwise stated, the hydrogenolyses were carried out until the rate of uptake of hydrogen became insignificant (see Figure 6). The hydrogenolyses mixtures were filtered through Dicalite to remove the

catalyst and the yields of hydrocarbons were determined by gc analysis[26]. The substrates were recovered by diluting the acetic acid or dimethylformamide solutions with 3-6 volumes of water and removing the precipitated starting material by filtration. The hydrocarbons were isolated by extracting the filtrates with petroleum ether, drying (Na_2SO_4), and distilling. When ethyl acetate was used, careful distillation yielded both the hydrocarbon and the starting material.

Preparation of 1,7-Dimethylindan (4).-- Hydrogenolysis of 3 as described above using ethyl acetate as the solvent resulted in a quantitative yield of the benzoxazolone 5 and a 98% yield of 4: bp 88° (16 mm); ir (neat) 3.31, 3.41, 6.46, 6.88, 7.30, 7.72, 9.36, 13.10, and 13.36 μ; mass spectrum m/e (rel intensity) 146 (18), 131 (100), 116 (15), 115 (20), and 77 (8); pmr (neat) δ 7.00-6.71 (m, 3, ArH), 3.30-2.95 (m, 1, $ArC\underline{H}CH_3$), 2.93-2.48 (m, 2, $ArCH_2$-), 2.17 (s, 3, $ArCH_3$), 2.20-1.45 (m, 2, $-CH_2-$), and 1.09-1.02 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.40; H, 9.60.

Preparation of 1,7-Dimethyl-4-cyanatoindan (7).[28]-- A 11.0-g (0.1-mol) sample of cyanogen bromide and 16.2 g (0.1 mol) of 1 were dissolved in 250 ml of anhydrous acetone, added to a 500 ml fluted flask, and cooled to 0°. Triethylamine (10.1 g, 0.1 mol) was added dropwise through an addition funnel to the stirred mixture at a rate such that the temperature remained below 10°. The mixture was stirred for an additional 10 min. after addition was completed. Triethylammonium bromide was filtered from the reaction mixture and the filtrate was concentrated on a rotary evaporator. The resulting oil was distilled to give 18 g (96%) of 7: bp 92° (0.5 mm); ir (neat) 3.40, 4.45, 6.76, 8.18, 8.68,

11.2, and 12.2 μ; mass spectrum m/e (rel intensity) 187 (46), 172 (100), 130 (28), 129 (49), 128 (29), and 115 (25); pmr (CCl_4) δ 6.99 (q, 2, ArH), 3.30 (m, 1, $ArC\underline{H}CH_3$), 2.96 (m, 2, $ArCH_2$-), 2.27 (s, 3, $ArCH_3$), and 1.15 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{12}H_{13}$: C, 76.97; H, 7.00. Found C, 77.12; H, 7.20.

General Preparation of Carbamates.-- The general procedure was carried out by dropwise addition (0.5 hr.) of 0.1 mol of phenyl isocyanate to a stirred mixture of 0.1 mol of phenol and 100-200 ml of benzene. A nitrogen atmosphere was maintained throughout the reaction. After addition was completed, the temperature was increased to reflux and maintained for 4-6 hr. The hot solution was poured into a large beaker, and upon cooling, the carbamate crystallized. It was removed by filtration and washed with petroleum ether. The carbamates were recrystallized from either ethanol or benzene. Individual properties are listed in Table IV except for 6.

Preparation of 4-(1,7-Dimethylindanyl) Phenylcarbamate (6).-- This compound was prepared in 41% yield as described in the above procedure: mp 122-123°; ir (nujol) 3.05, 5.85, 6.23, 6.46, 8.12, and 13.27 μ; mass spectrum m/e (rel intensity) 281 (1), 145 (50), 144 (35), 129 (100), 128 (92), 127 (38), 115 (53), 105 (48), 91 (43), 77 (22), and 41 (18); pmr (CCl_4) δ 7.00 (m, 8, ArH), 3.28 (m, 1, $ArC\underline{H}CH_3$), 2.84 (m, 2, $ArCH_2$-), 2.26 (s, 3, $ArCH_3$), 1.78 (m, 2, $-CH_2-$), and 1.16 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81. Found C, 77.00; H, 6.90.

PART II

FRIEDEL-CRAFTS REACTION OF p-CRESOL AND CROTONIC ACID

CHAPTER IV

INTRODUCTION AND HISTORICAL

The Friedel-Crafts reaction is often broadly defined as the formation of carbon-carbon bonds via Lewis acid catalysis. Even this simple statement does not indicate the vast scope of the reaction. Not only are carbon-carbon bonds formed but also carbon-hetero atom bonds may be formed with Lewis acids or some protonic acids as catalysts. The Friedel-Crafts and similar reactions are all related in proceeding through an electrophilic substitution mechanism.

The numerous reactions using Friedel-Crafts reactions have proven to be very productive. Major processes for the production of high-octane gasoline, cumene, synthetic rubber, plastics, and detergents are but a few applications of Friedel-Crafts chemistry.

The alkylation reaction was first reported in 1869 by Zincke.[29] He observed the formation of diphenylmethane and hydrogen chloride during the attempted preparation of 2-phenylpropanoic acid from benzyl chloride and chloroacetic acid. This reaction was carried out in a sealed tube using benzene solvent in the presence of silver to form a silver halide with any liberated chlorine. He also discovered that the reaction proceeded under milder conditions if iron or zinc was substituted for silver and that toluene and xylene as solvents readily gave similar reaction products.

During an attempted synthesis of benzil, "dibenzoyl", from benzoyl chloride in benzene, once again using silver to absorb the expected chlorine, Zincke reported the formation of benzophenone.[30] Thus, he was one of the very first to observe both the alkylation and acylation reactions. It was evident, however, that he did not realize the cause of the reactions nor their vast potential.

Charles Friedel and James Crafts became acquainted while studying under Wurtz in France. In later colaboration, they investigated the effects of aluminum chloride on pentyl chloride and found that in the presence of benzene, pentylbenzene was produced. They demonstrated that Zincke's reactions were catalyzed by metal halides rather than metals. Their first discoveries were reported to the Chemical Society of France in 1877.[31] Subsequently, they published over sixty papers concerning the reactions which now bear their names. Not only did they demonstrate that the metal halide was a required catalyst, but they also showed the relative activities of several metal halides and they established the utility of the reaction for the preparation of alkylarenes and aromatic ketones, the cracking of hydrocarbons, and similar reactions. An excellent biographical survey of the Friedel-Crafts literature is available.[32]

Since the Friedel-Crafts reaction covers a broad area of chemistry as borne out by Olah's 5200-page treatise, discussion in this work will be limited to a brief description of the alkylation and acylation reactions and the conditions required to effect these reactions.[32]

The Friedel-Crafts alkylation of aromatic rings involves the formation of Ar-C bonds via electrophilic (with respect to the aromatic compound) attack of an alkyl cation or at least a highly polarized bond. Important alkylating agents are alkyl halides, olefins, and alcohols.

The reactivity of the alkyl halides is in decreasing order: fluoride, chloride, bromide, and iodide. This order was determined by the reaction of mixed dihalides with benzene and BF_3 as shown below.[33]

$$C_6H_6 + FCH_2CH_2CH_2Cl \longrightarrow C_6H_5CH_2CH_2CH_2Cl + HF$$

Di- and trihalides generally react with more than one molecule of the aromatic compound when the halogens are the same and often it is impossible to prevent this reaction from occurring. An illustrative example is the reaction of benzene with chloroform to form triphenylmethane in the presence of aluminum chloride as shown below.

$$C_6H_6 + CCl_3H \longrightarrow (C_6H_5)_3CH + HCl$$

Olefins are very good alkylating agents, different only in that the overall reaction is an addition of Ar-H to a C-C double bond. Furthermore, alkylation will not occur with only a Lewis acid catalyst; a proton-donating cocatalyst is required.[34]

Alcohols are more reactive than the corresponding alkyl halides, but more catalyst is required since the catalyst complexes with the hydroxyl group. Proton acids, especially sulfuric acid, are often used rather than a Lewis acid to cause alkylation via dehydration to generate an alkylcarbonium ion.[35]

Many other types of compounds have been used as alkylating reagents. More notable among these are the cyclic ethers, especially ethylene oxide, in which the ring can be opened by acid catalysis to form an alkylcarbonium ion that will cause the substitution of $-CH_2CH_2OH$ for a hydrogen on the aromatic ring. Esters have been used, but these reactions are generally complicated by competing acylations. Some other types of compounds used with success are: ethers, mercaptans, sulfides, thiocyanates, alkyl sulfates, sulfonic esters, and strained cycloalkanes.[35]

The reactivities for all types of reagents correspond dirctly to the relative stability of the carbonium ions generated. These reactivities in dereasing order are: allyl and benzyl, tertiary, secondary, and primary.[36]

Aluminum chloride is the most commonly used catalyst, but many other Lewis acids have been used, as have many strong proton acids, particularly HF and H_2SO_4. The overall activity of the more commonly used Lewis acids has been arranged in decreasing order: $AlBr_3$, $AlCl_3$, $GaCl_3$, $FeCl_3$, $SbCl_5$, $ZrCl_4$, BCl_3, BF_3, and $SbCl_3$.[37] However the order of catalyst activity often can vary depending on the substrate, solvent, and other conditions. Most reaction procedures using $AlCl_3$ or other Lewis acid call for anhydrous acid. Several chemists have actually shown that very dry, pure $AlCl_3$ does not catalyze the Friedel-Crafts reactions effectively until a small amount of a proton source is added.[38]

Friedel-Crafts alkylation is sometimes complicated by the fact that the alkylated products are usually more reactive towards alkylation than the starting aromatic compound, thus leading to polyalkylation. However, the activating effect of most simple alkyl groups (e.g., ethyl and

isopropyl) is such that aromatics with these substituents are only 1.5-3 times as reactive as benzene so that by careful control of conditions, high yields of monoalkylated products can be obtained.[39] It has also been shown that polyalkylation often results from the preferential solubility of alkylbenzenes in the catalyst layer where the reaction is occurring. The use of excess arene, a more suitable solvent, higher temperatures, or high-speed stirring can solve this problem.[40]

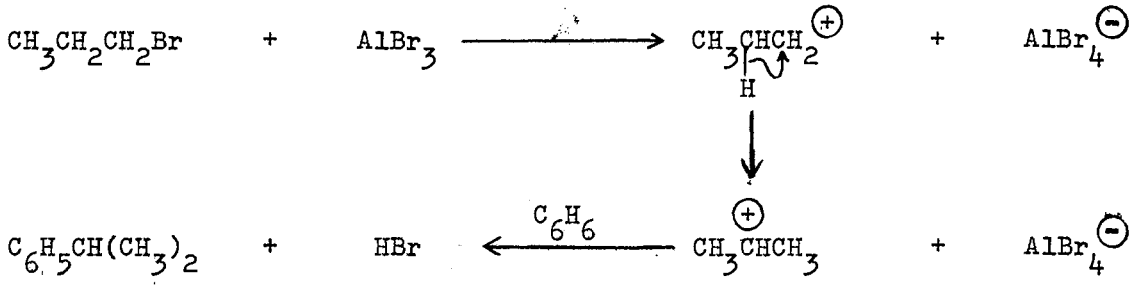
Functional groups which normally activate an aromatic ring for electrophilic substitution (OH, OR, NH_2, etc.) often do not facilitate the Friedel-Crafts alkylation. The electron-releasing ability of these groups is partially nullified by their complexation with the Lewis acid catalyst as shown for phenol.

$$C_6H_5OH + AlCl_3 \rightleftharpoons C_6H_5\overset{\oplus}{O}H\overset{\ominus}{A}lCl_3$$

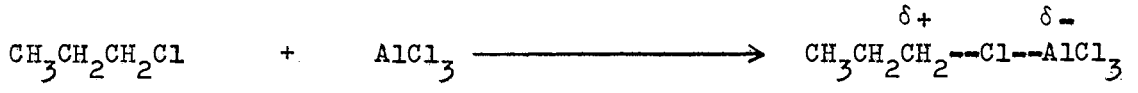
Phenols, however, generally can be alkylated, and in the ortho-para positions as expected, but alkylation of aromatic amines is rarely achieved. Meta-directing groups usually deactivate the ring so that alkylation, like other electrophilic substitutions, is unfavored and the electrophile often is degraded and/or polymerized.

Alkylations are many times complicated because of rearrangements of the reagents. For example, n-propyl bromide reacts with benzene in the presence of $AlBr_3$ to give almost exclusively isopropylbenzene as shown on the following page.[41] Obviously, the attacking electrophile is not the initially formed n-propyl cation, but rather the isopropyl cation.

This is an example of alkyl rearrangement via hydride transfer as illustrated. Migration of alkyl groups has also been observed.

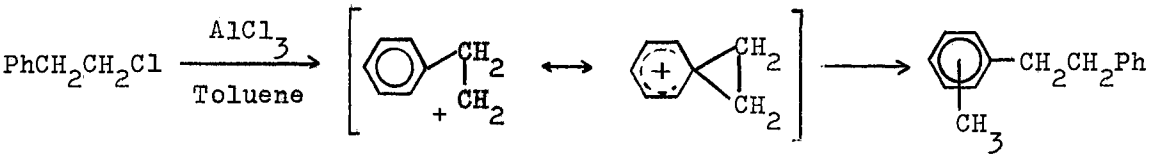


The reaction of n-propyl chloride with benzene in the presence of $AlCl_3$ gives predominantly n-propylbenzene when carried out at room temperature.[41] A rationalization is that the C-Cl bond is more difficultly cleaved to form the carbonium ion than is the C-Br bond. Instead of the C-Cl bonds being cleaved, it is polarized by the $AlCl_3$ as shown below. The complex containing the polarized bond acts as the electrophile.

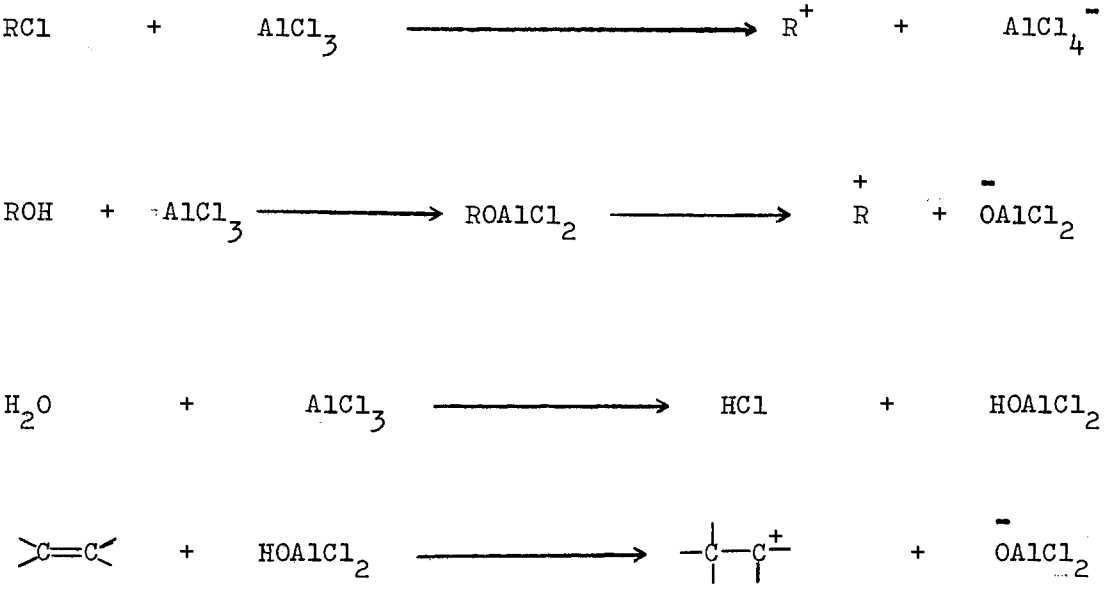


Some other evidence supporting carbocations as the attacking electrophiles has been obtained by isotopic labeling experiments. For example, $Ph^{14}CH_2CH_2Cl$ with toluene gave the product shown, in which each of the ethane carbons possessed about 50% of the labeling.[42] This scrambling indicates that both of the ethane carbons are equally strong

electrophiles. This observation led to the postulation of the non-classical carbonium ion shown below.



The carbonium ion is generated by the reaction of the Lewis acid with the alkylating agent. The three major alkylating reagents react with aluminum chloride as shown. Notice that olefins are special in that they require a proton source in order to form the active catalyst to generate the carbonium ion. Olefins generally follow Markovnikov's rule



In many cases it is believed that the carbonium ion is not free, but rather exists as a member of a tight ion pair. This accounts for the observation that the same alkyl halide is often more active with $AlCl_3$ than with $FeCl_3$ and that the kinetics are third order: first order each in aromatic substrate, attacking reagent, and catalyst.[43]

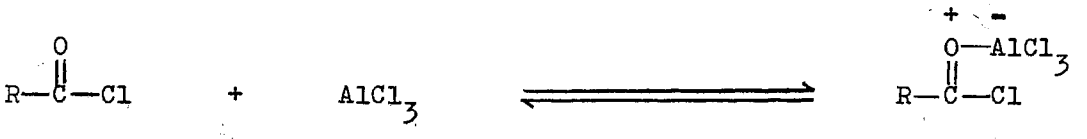
One of the most important methods for the preparation of aryl ketones is the Friedel-Crafts acylation. There are generally fewer complications with the acylation reaction because the electrophile does not rearrange nor the substrate undergo multiple substitution as may be the case with alkylation. Acylation followed by a reduction of the ketone is used frequently to prepare alkybenzenes as illustrated for the preparation of propylbenzene.

$$+ \quad CH_3CH_2COCl \longrightarrow PhCOCH_2CH_3 \longrightarrow Ph(CH_2)_2CH_3$$

Acylations can be carried out with compounds containing almost any function which will lead to an acylium ion upon reaction with a Lewis acid. For example, acyl halides, carboxylic acids, anhydrides, ketenes, and esters have all been used as acylating agents.[44] Esters, however, generally give mixtures resulting from the competing alkylation reaction.

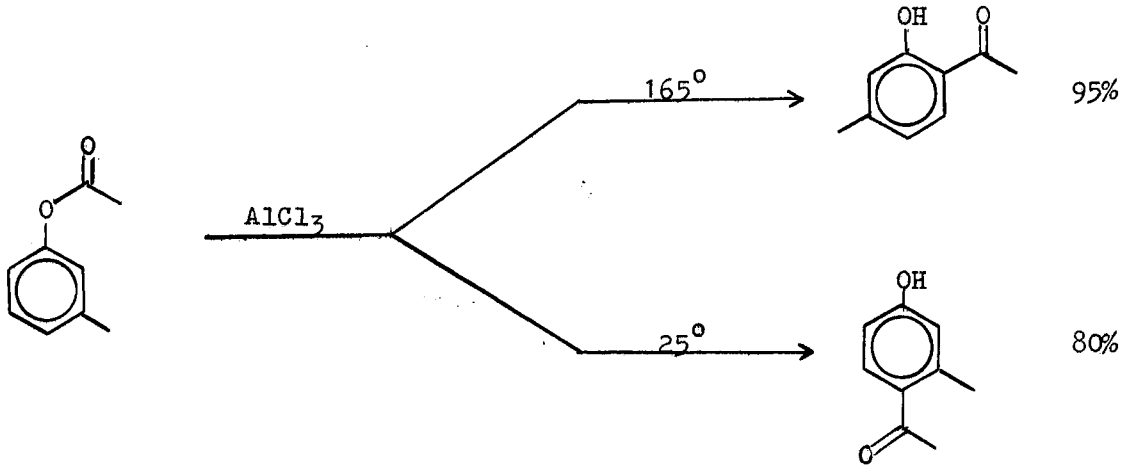
The order of reactivity of acyl halides in acylation was found to be in decreasing order: I, Br, Cl, and F.[45] Notice that this order is

opposite to that observed for the alkyl halides.[33] The Lewis acid catalysts required for the acylation show essentially the same order of reactivity as in the alkylation reaction. However, acylations generally require more than one mole of catalyst since the first mole is spent in the formation of complexes as illustrated below.

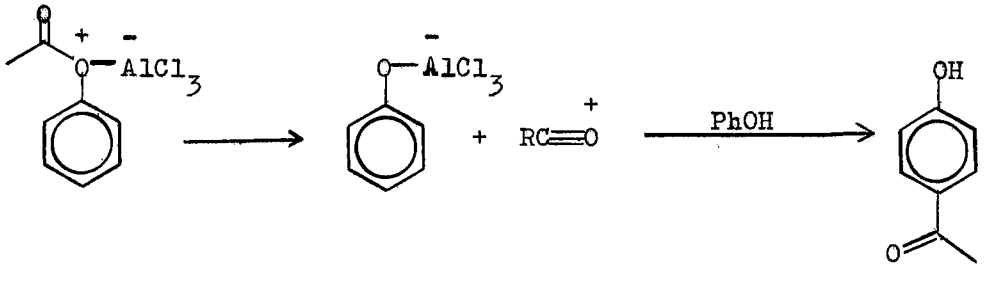


Aromatic substrates containing ortho-para-directing groups, including alkyl, hydroxy, alkoxy, halogen, and acetamido groups, are easily acylated to give almost exclusively the para products. This is believed to be due to the steric effects of the relatively large acyl ion. When aromatic amines and phenols are used, there generally is competition by the nucleophilic nitrogen or oxygen atoms for the acyl ion to give the N- and O-acylated products. However, the O-acylated products can be converted to the ordinary acylated products via a rearrangement known as the Fries rearrangement.

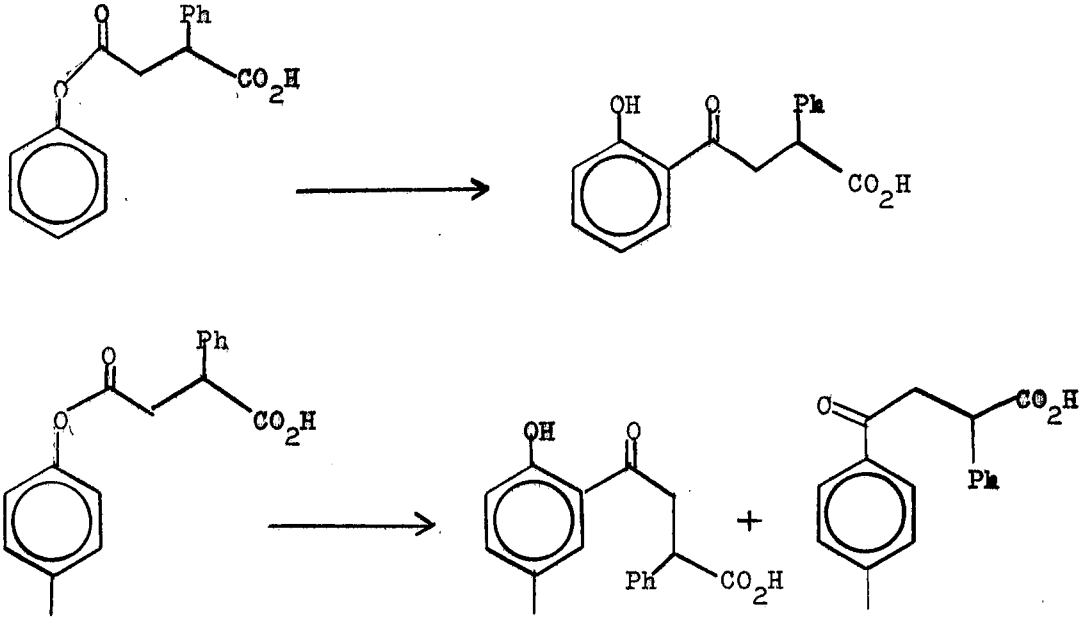
The esters of phenols are easily converted into ortho- and para-acylphenols. Often, conditions can be chosen to give a preponderance of one isomer or the other as illustrated for 3-methylphenyl acetate in the presence of aluminum chloride on the following page.[46]



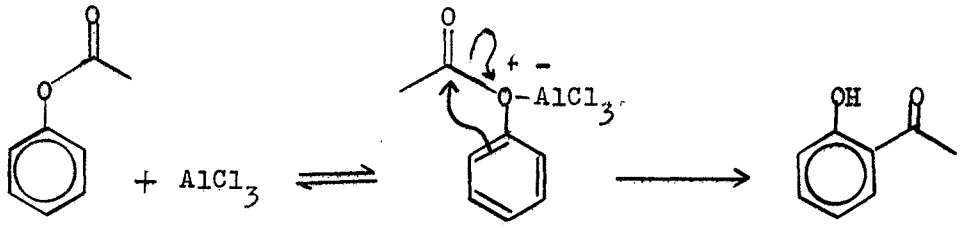
The exact mechanism of the Fries rearrangement remains unknown, but it is believed that there are at least two mechanisms operative. These are the inter- and intramolecular rearrangements. The intermolecular rearrangement generally gives a product distribution like the ones obtained from Friedel-Crafts acylations, para substitution products being predominant.[47] This is believed to occur as depicted below.



Evidence supporting intra- versus intermolecular rearrangement is obtained by carrying out the Fries rearrangement in the presence of another active aromatic compound. If there is any incorporation of the additional substrate, then the rearrangement is probably intermolecular. As an example, the two esters shown below were rearranged using $AlCl_3$ in toluene. Notice that only the second compound gave incorporation of toluene.[48]

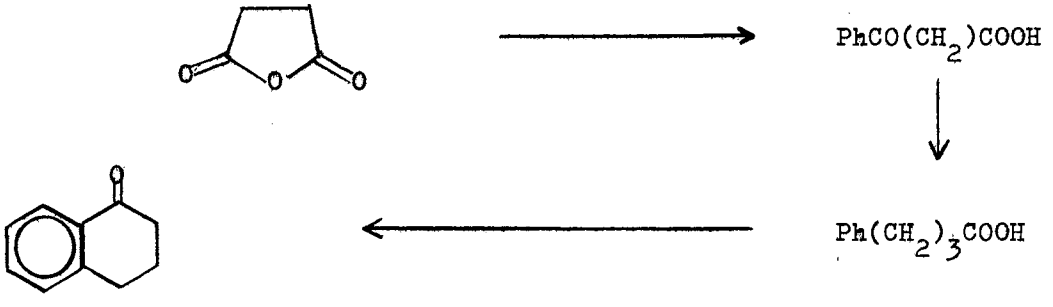


The rearrangement to give ortho isomers is thought to proceed by an intramolecular mechanism.[47] The reaction intermediates are shown on the following page.



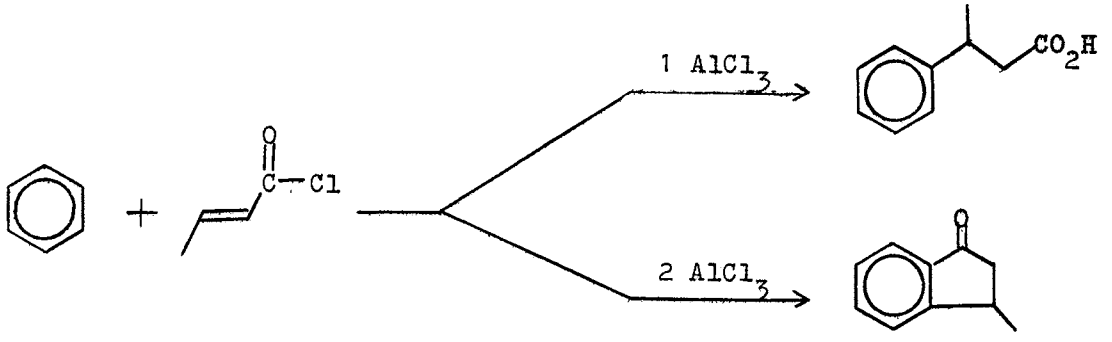
A few generalizations can be made about the conditions which control the ortho-para ratio. Generally, higher temperature favors the ortho product. The ortho-para ratio has been shown to be a function of the aluminum chloride/substrate ratio. High-polarity solvents favor the formation of para products.[49]

Both alkylation and acylation of arenes with bifunctional reagents have been used extensively for the preparation of bicyclic systems either in single- or multi-step synthesis. An illustrative example is the Haworth reaction, shown below. This reaction is used for the preparation of 1-tetralone by carrying out an acylation with succinic anhydride and subsequently reducing the ketone. The acid is then cyclized via another acylation reaction catalyzed by a strong protonic acid catalyst.



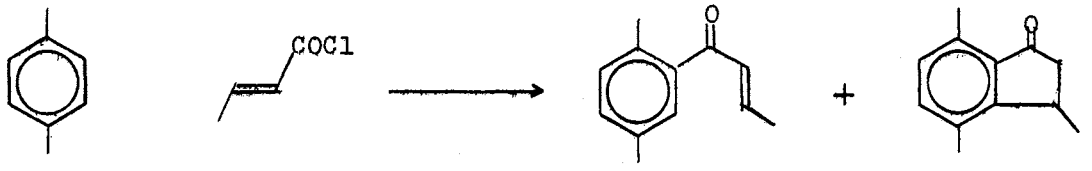
In this work, interest is centered upon the potential of crotonic acid as a bifunctional reagent to be used in a Friedel-Crafts cyclization to indanones. There have been previous examples using crotonic acid and crotonyl chloride to prepare substituted 3-methylindanones and similarly, 3,3-dimethylindanones from 2,2-dimethylacrylic acid. In many cases, however, these reactions were accompanied by chromanone formation. Several reactions of this type have been tabulated in Table VI.

In 1909, it was reported that crotonic acid reacted with one mole of aluminum chloride in benzene to give 3-phenylbutanoic acid.[50a] It was shown in 1943 that the use of three moles of aluminum chloride caused the condensation of crotonic acid and benzene to 3-methylindanone.[50c]

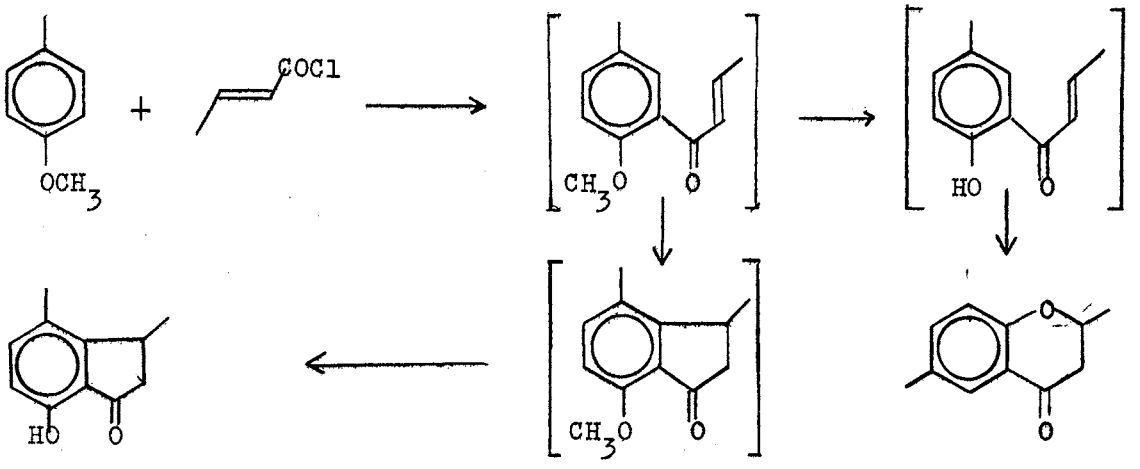


There are numerous examples showing that crotonyl chloride gives the normal acylation products in most cases. Also, phenolic esters of crotonic acid have been shown to rearrange in the normal manner to give mainly the ortho acyl product.[52] Some pertinent examples have been

included in Table VI. There are three notable exceptions to normalcy listed. The reaction of crotonyl chloride with p-xylene in the presence of aluminum chloride was found to give the products shown below.[53] In this case, acylation appears to be the predominant reaction but is followed by a cylialkylation.



The reaction of crotonyl chloride with p-methylanisole in the presence of one mole of $AlCl_3$ gave the expected acyl derivative. However, with an excess of $AlCl_3$, cyclization occurred to give 19% of the indanone and 24% of the chromanone as shown in the reaction scheme below.[54]



All the data presented thus far indicate that the acyl attack predominates over alkyl attack in reactions of the bifunctional crotonic acid. However, experiments carried out with crotonyl chloride in chlorobenzene in the presence of $AlCl_3$ gave the products shown below, apparently via an alkylation followed by a cyliacylation.[55] This seems in conflict with the examples previously presented.

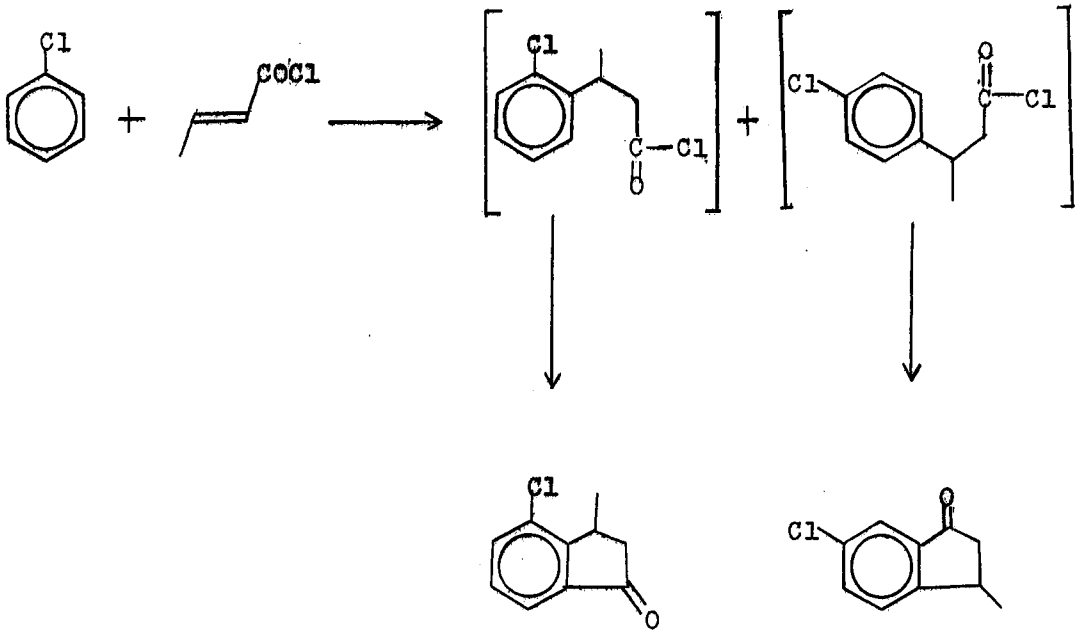


TABLE VI

SELECTED FRIEDEL-CRAFTS REACTIONS OF UNSATURATED ACIDS AND ACID CHLORIDES

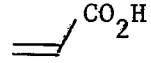
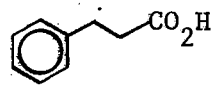
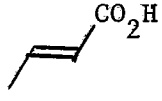
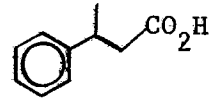
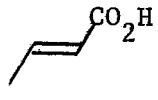
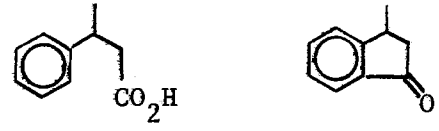
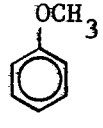
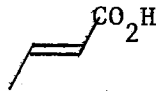
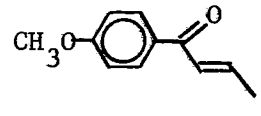
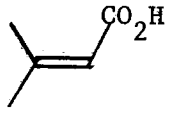
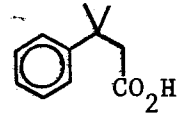
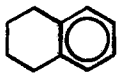
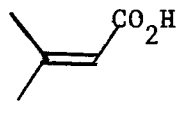
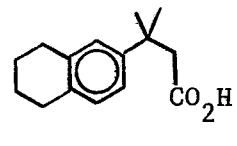
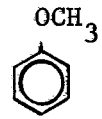
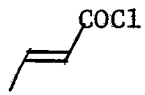
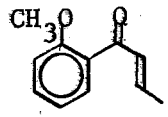
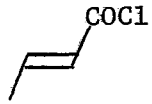
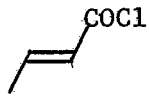
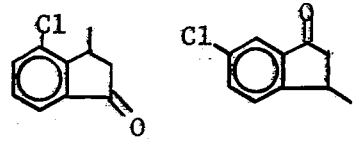
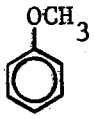
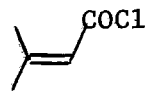
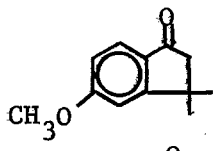
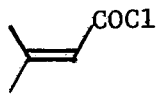
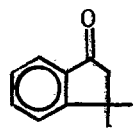
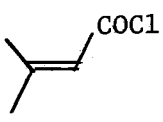
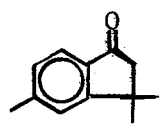
Substrate	Reagents	Catalyst	Products	Reference
		$AlCl_3$		50b
		$AlCl_3$		50a
		$AlCl_3$		50c
		PPA		50d
		$AlCl_3$		51a
		$AlCl_3$		51b

TABLE VI (Continued)

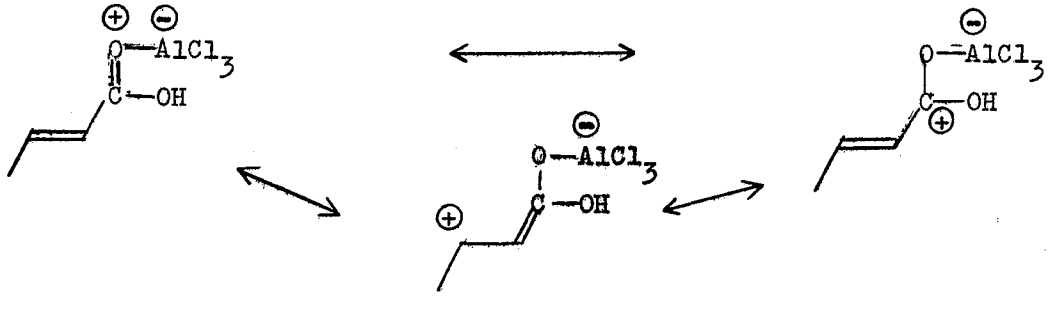
Substrate	Reagents	Catalyst	Products	Reference
		$AlCl_3$		54
		$AlCl_3$		54
		$AlCl_3$		55
		$AlCl_3$		56
		$AlCl_3$		56
		$AlCl_3$		56

CHAPTER V

DISCUSSION AND RESULTS

The reactions of crotonic acid and benzene noted in Chapter IV indicated that this Friedel-Crafts reaction could be controlled to give either 3-phenylbutanoic acid or 3-methyl-1-indanone.[50c] The cycliaddition of crotonic acid to p-cresol appeared to be an attractive method for the preparation of a substituted indanone to be used as a synthetic intermediate to be discussed in Chapter VII.

If complexation of aluminum chloride with crotonic acid proceeds in a fashion similar to that suggested for other acids and the double bond behaves like similar α,β-unsaturated systems, the prediction of both alkylation and acylation via the ion depicted below seems resonable. The reaction of this complex with p-cresol allows the prediction of several possible reaction intermediates, pathways, and products which are shown in Figure 7.



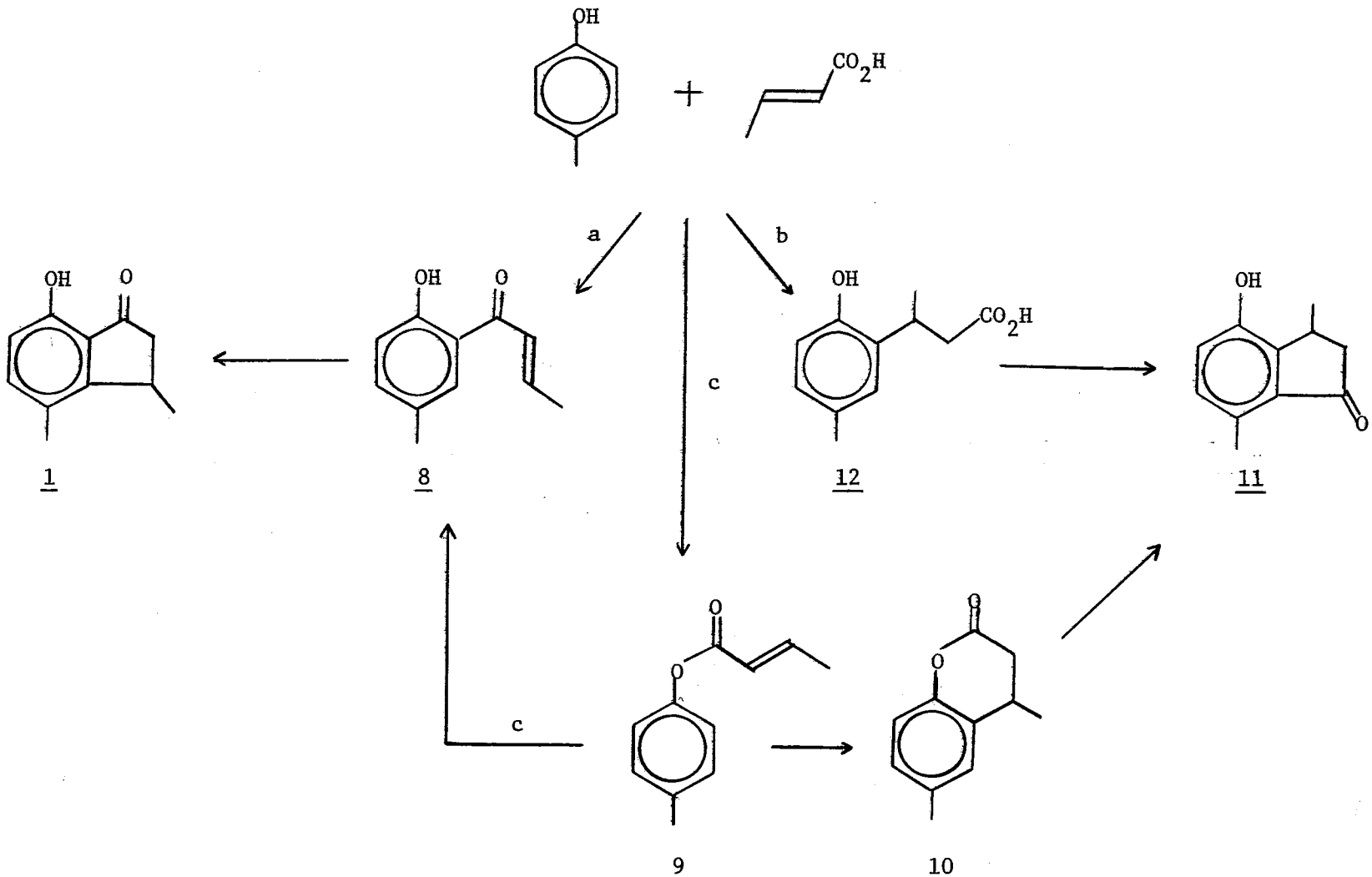


Figure 7. Reaction Products and Intermediates from the Friedel-Crafts Reaction of p-Cresol and Crotonic Acid

The Friedel-Crafts reaction of crotonic acid with p-cresol was carried out under conditions similar to those described by Koelsch, Hochmann, and LeClaire for the preparation of 3-methylindanone.[50c] Equal molar amounts of the reagents were warmed to form a solution to which was cautiously added three moles of aluminum chloride at a rate such that the temperature was kept below 50°. After addition was complete the mixture was slowly heated, during which there was a mild evolution of hydrogen chloride such as was also noted during the addition process. When the temperature reached 90-100°, an exothermic reaction began which was difficult to control. This spontaneous reaction raised the temperature to 140-180°. During this period, copious evolution of hydrogen chloride took place. The reaction mixture became so viscous as to prevent stirring and thus a severe foaming problem resulted. Upon cooling, the mixture formed a difficultly soluble glass which greatly complicated the work-up. Only one major product was isolated and its properties corresponded to the previously described 1.[54]

The present collective knowledge of the Friedel-Crafts reaction allows a reasonable doubt that the previous preparation of 1 actually produced this compound.[54] This earlier preparation (1911) is outlined in Figure 8. It involves the esterification of p-cresol with 2-bromobutanoyl bromide to form the ester 13. This ester was treated with $AlCl_3$ at 130° for four hours. This treatment was apparently expected to give the Fries rearrangement and subsequent cyclialkylation to 1. A scrutiny of this reaction scheme and consideration of the reaction conditions suggest the possibility of rearrangement to the isomeric indanone 11 shown in Figure 8.

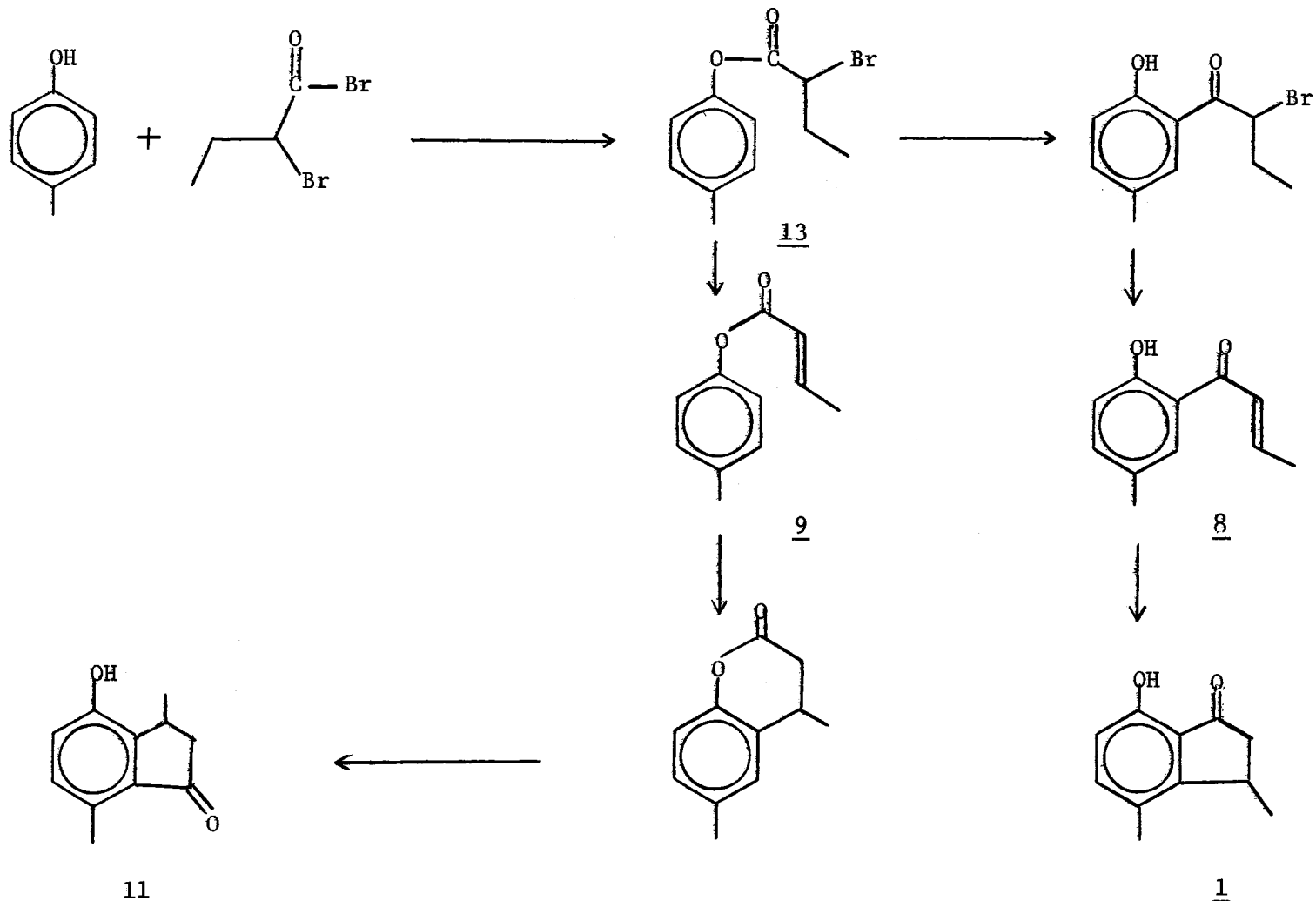


Figure 8. Reaction Scheme for the Synthesis of 1 and Possible Competing Reactions.

Since the structure of 1 was uncertain, we sought evidence to confirm it. The Friedel-Crafts reaction product was shown to be a phenolic ketone by the ordinary qualitative methods. The use of nmr spectroscopy was unsucessful in confirming the structure, and unambiguous syntheses were required.

The Friedel-Crafts reaction product was proven to be 1. This was done by reduction of the ketone via a Clemmensen reduction and the deoxygenation of the resulting phenol by the catalytic hydrogenolysis its benzoxazolyl ether to 1,7-dimethylindan (4) as shown in Figure 4.

An authentic sample of 4 was prepared by a series of reactions which are known to proceed without rearrangement. These are described in Figure 9. This sample of 4 was found to be identical with that obtained via the Friedel-Crafts reaction and subsequent steps.

In addition, the methyl ether of 11 was prepared, also by well established reactions as shown in Figure 10, and found not to be the same as the methyl ether of 1.

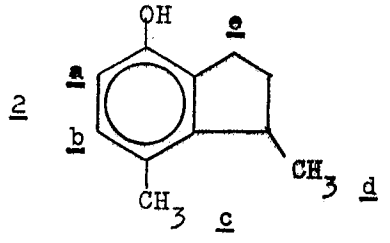
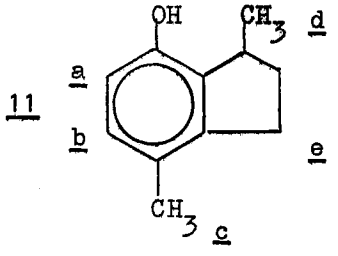
Additional confirmative data was obtained by a relatively new nmr technique which involves the use of a magnetic-shift reagent. These reagents have been shown to complex with hetero atoms and cause a change in the magnetic enviroment of the molecule; thus a shift is observed for the nmr absorptions. The amount of shift observed is inversely proportional to the distance of the absorbing proton from the complexation site.[57]

This study was performed on the phenol 2 resulting from a Clemmensen reduction of 1. The two possible structures considered and the data obtained are shown in Table VII.[58a] If 2 is indeed the correct structure, the observed shift for protons e should be greater than that

for d since the e protons are closer to the complexation site. This is observed and indicates structure 2 since the d and e protons of 11 should give the opposite observation.

TABLE VII

EFFECT OF SIEVERS REAGENT ON THE NMR SPECTRUM OF 2

Possible Structures	Proton[a]	Observed Shift (Hz)[b]
 2	a	29
	b	8
	c	5
 11	d	6
	e	24

[a] As labeled on the possible structures. [b] 2.32% Sievers reagent,[58b] 3.25% phenol in CCl_4.

The structure of the Friedel-Crafts reaction product is therefore established to be 1 and not 11. In fact, 11 has not been detected in the reaction mixture. Attempts to show the presence of some of the suggested intermediates (8 and 9, Figure 7) were successful by qualitative gas chromatographic analysis.

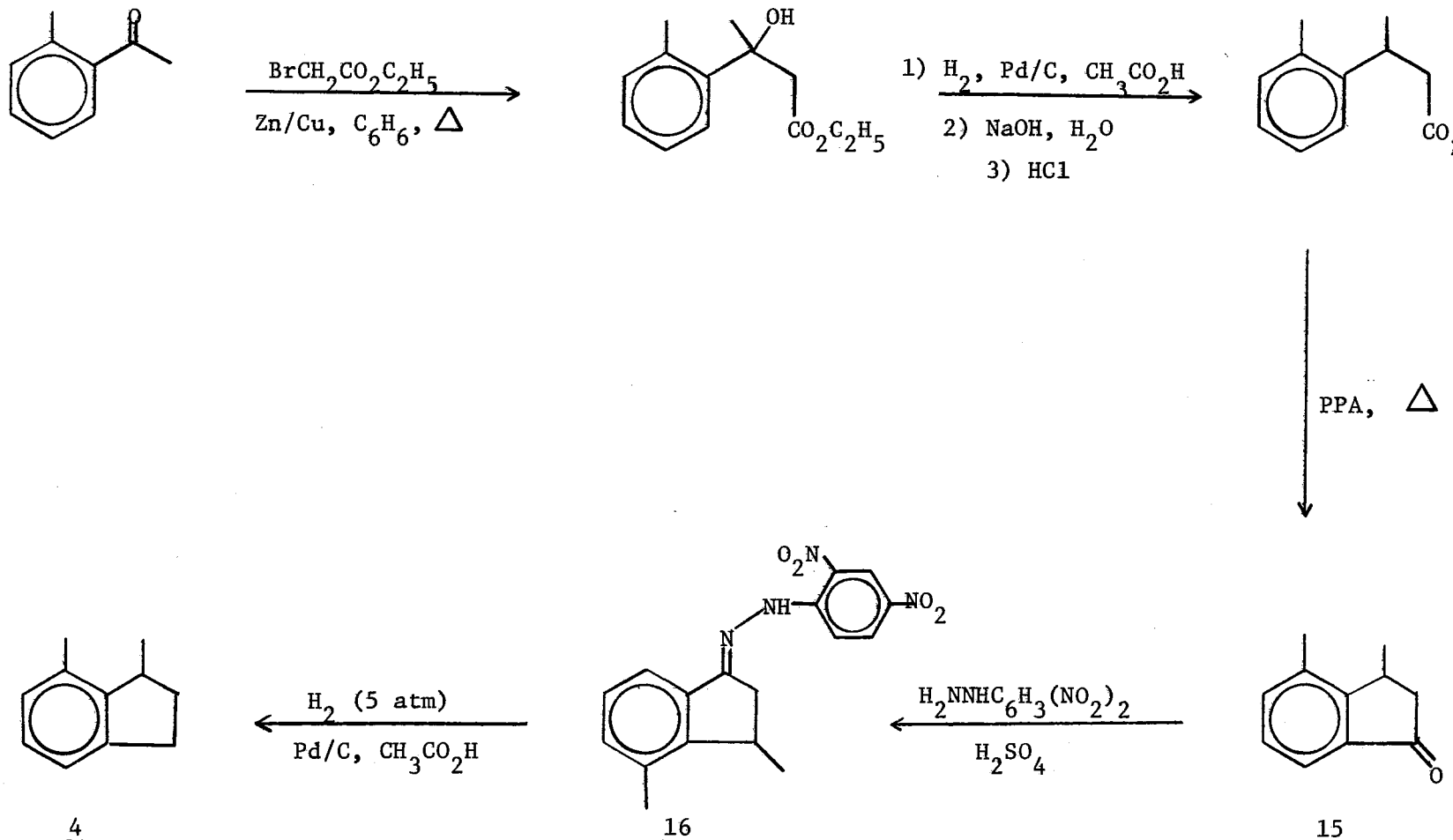


Figure 9. Synthesis of 1,7-Dimethylindan (4).

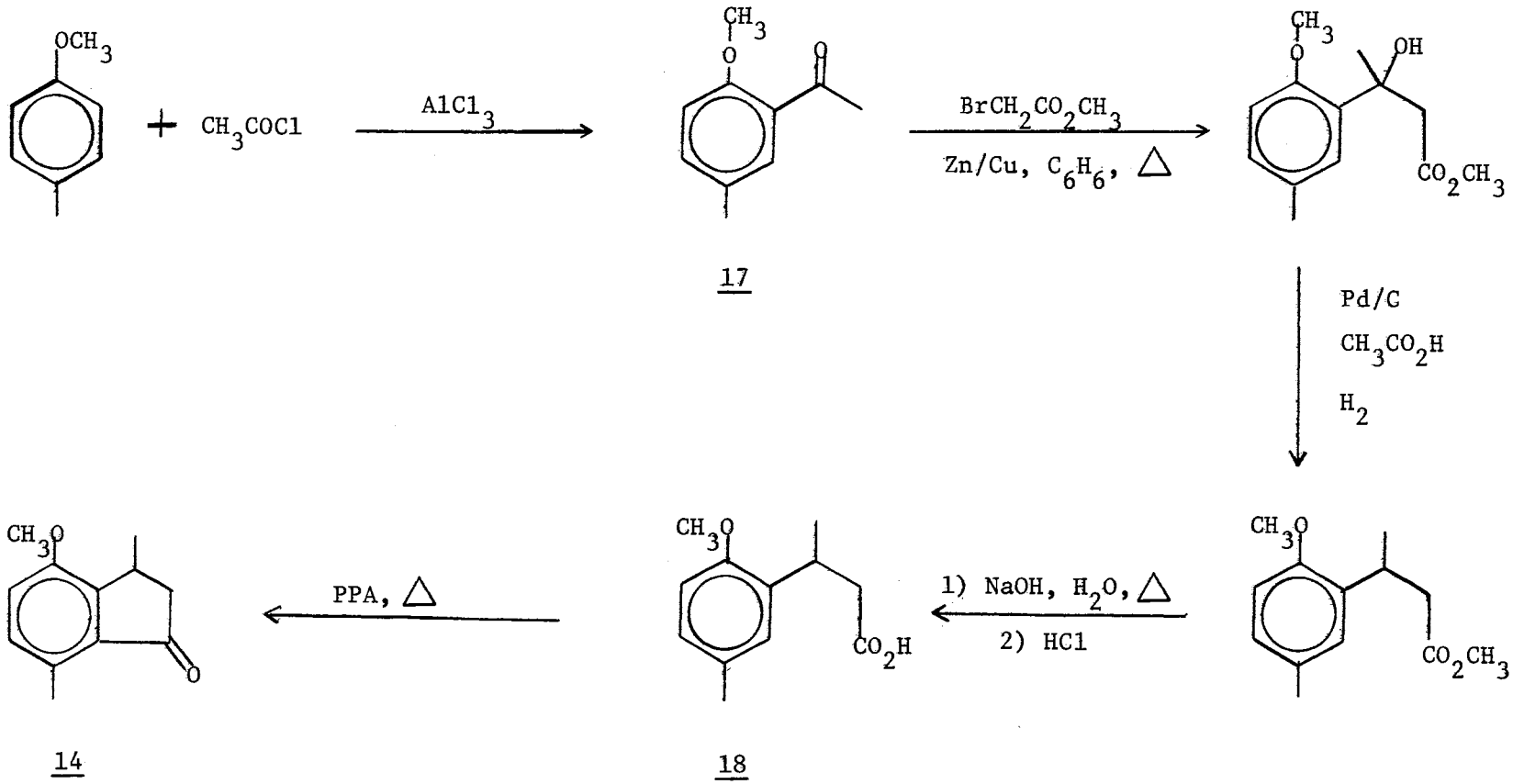


Figure 10. Synthesis of 3,7-Dimethyl-4-methoxyindanone (14).

Samples of the Friedel-Crafts reaction mixture were taken at various times during the reaction. Early in the reaction (during the addition of $AlCl_3$) there was found to be a mixture of p-cresol, crotonic acid, and p-methylphenyl crotonate (9). Later in the reaction and becoming more predominant as the temperature was increased was the Fries rearrangement product 8. Attempts to detect the acid 12 by extraction with sodium bicarbonate, acidification, extraction with ether, and treatment with diazomethane revealed only methyl crotonate. The presence of 1 was not detected until the exothermic reaction had begun. When the reaction had reached completion, the relative amounts of 8 and 9 were small compared to the product 1. In some instances, higher molecular weight substances were observed. These, presumably, are polymeric in nature.

The failure to detect the acid 12 or the indanone 11 seems to rule out pathway b (Figure 7) as the possible alkylation and subsequent cyclicacylation route. The acylation of p-cresol appears to be the favored reaction. Whether the acylphenol 8 is formed via a direct acylation of the aromatic ring (pathway a) or via a Fries rearrangement (pathway c) is not known. Both pathways lead to the same product under the reaction conditions and in all probability, at the elevated temperatures, both pathways are operative.

Although this reaction gave the indanone 1 in a one-step reaction, there are several disadvantages in its use as shown by the erratic yields obtained. For example, five one-mole reactions carried out consecutively on the same day using the same reagents and conditions gave 50, 36, 27, 27, and 0% yields of 1. Furthermore, for one-mole reactions, a 22-liter vessel was required to contain the reaction mixture. It was therefore essential to develop a method to moderate this reaction.

The reaction failed to produce 1 in any of the more commonly used Friedel-Crafts solvents: nitroethane, nitrobenzene, and chlorobenzene. However, o-dichlorobenzene at reflux was found to have the desired properties. With this solvent, the reagents and products were soluble, the boiling point was above the maximun temperature normally obtained during the reaction, and the reaction was moderated so that it proceeded smoothly at reflux temperature to give good, reproducible yields of 1.

The optimum ratio of catalyst to other reactants was determined and found to be 1:1:2 of p-cresol, crotonic acid, and aluminum chloride as shown in Table VIII. It should be noted that this reaction requires one less mole of aluminum chloride than reported necessary to produce 3-methylindanone from benzene and crotonic acid.[51]

The discovery of conditions which allow this reaction to be easily carried out made it possible to prepare 3,4-dimethyl-7-hydroxyindanone (1) for use in other studies.

TABLE VIII

OPTIMUM CATALYST-TO-SUBSTRATE RATIO[a]

Aluminum Chloride (moles)	% Yield of 1
1	0
2	96
3	20
4	5

[a]One mole of p-cresol and one of crotonic acid along with catalyst, were refluxed for 8 hours in 300 ml of o-dichlorobenzene. The product was isolated by steam distillation.

CHAPTER VI

EXPERIMENTAL

Preparation of the 3,4-Dimethyl-7-hydroxyindanone (1).-- An 86-g (1.0-mol) sample of crotonic acid and 108 g (1.0 mol) of p-cresol were dissolved in 200 ml of o-dichlorobenzene. This solution was added to a dry 2-l. flask equipped with reflux condenser, thermometer, magnetic stirring bar, and magnetic stirrer. Anhydrous $AlCl_3$ (260 g, 2.0 mol) was added in small portions over a 30 min period. The temperature during the addition was maintained below 30° by surrounding the reaction flask with an ice-water bath when necessary. The last half-portion of $AlCl_3$ was added rapidly (5-10 min). After addition was completed, the solution was stirred for 30 min at room temperature. The temperature was slowly increased until reflux was obtained (ca. 180°) and was maintained for 4-8 hr during which time there was a mild evolution of HCl and the solution color became deep red. The solution was then cooled and poured on ice (0.5-1 kg), and concentrated hydrochloric acid was added until the pH was 2-4. The isolation of 1 was conveniently carried out by any of three methods. Method A. The acidified mixture was extracted with ether and the extract was steam distilled. The product, 1, steam distilled slowly and crystallized in the collection flask. This product was filtered out and recrystallized from ethanol. Method B. The mixture was extracted with ether and the extract dried (Na_2SO_4) and concentrated on a rotary evaporator at 100°. The resulting

oil was distilled under reduced pressure to give 1. Method C. The mixture was extracted with ether and the ether extract was washed with 10% NaOH. The product, 1, precipitated as a yellow sodium salt which was recrystallized from hot water. The phenol, 1, may be released from the salt with HCl. The yields obtained from this reaction are 70-90%. The product had: mp 52-53° [lit.[54a,b] 53-54°]; ir (neat) 2.98, 3.41, 5.97, 6.20, 8.59, 9.83, 11.1, 11.9, and 14.9 μ; mass spectrum m/e (rel intensity) 176 (50), 135 (55), 117 (100), 80 (60), 77 (30), and 41 (60); pmr (CCl_4) δ 6.82 (q, 2, ArH), 3.32 (m, 1, $ArC\underline{H}CH_3$), 2.80 (m, 2, $-COCH_2-$), 2.25 (s, 3, $ArCH_3$), and 1.29 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H, 6.86. Found: C, 75.09; H, 6.87.

Preparation of 1,7-Dimethylindan (4).-- To a 1-l. flask equipped with mechanical stirrer, addition funnel, reflux condenser, and nitrogen atmosphere was added 7 g of powdered zinc-copper couple. Benzene (40 ml) containing 13.4 g (0.1 mol) of o-methylacetophenone and 16.7 g (0.1 mol) of ethyl bromoacetate was placed in the addition funnel. About 10 ml of this solution was added to the zinc-copper couple and the stirred mixture was heated gently until an exothermic reaction was initiated. Reflux was maintained by the slow addition (30 min) of the remaining solution. After addition was completed, the mixture was heated at reflux for 1 hr. The reaction mixture was washed with cold 10% H_2SO_4. The benzene solution was dried (Na_2SO_4) and distilled to give 15 g of the unsaturated ester. This sample was treated with hydrogen (1 atm) in 100 ml of acetic acid containing 1 g of Pd/C (10%) until the uptake of gas had ceased (3 hr). The catalyst was removed from the mixture by filtering through Dicalite and the filtrate was concentrated by rotary

evaporation. The resulting oil was refluxed for 2 hr in 50 ml of water containing 13.5 g (0.2 mol) of KOH. The mixture was acidified and extracted with ether. The ether extract was dried (Na_2SO_4), concentrated, and distilled to give 7.1 g of 3-(2-methylphenyl)butanoic acid. Cyclization of this acid was effected by adding it to 20 g of PPA (polyphosphoric acid) and stirring for 30 min at 60°. An additional 20 g of PPA was added and the temperature was increased to 90° for 30 min. This mixture was then added to 500 ml of ice-water and subsequently extracted with ether. The ether extract was evaporated, the resulting oil was dissolved in ethanol, and the 2,4-dinitrophenylhydrazone of the ketone 15 was prepared. The hydrazone was recrystallized two times from ethanol to give 6 g of 16. This sample was hydrogenated in 50 ml of acetic acid with 0.5 g of Pd/C (10%) at 5 atm for 4 hr. The catalyst was removed by filtration and the filtrate was diluted with 5 volumes of water. This mixture was extracted with petroleum ether (bp 44°) and the petroleum ether extract was flushed through a column of acidic alumina with petroleum ether. This solution was concentrated by distillation to give 0.5 g of 1,7-dimethylindan (4): bp 88° (16 mm); ir (neat) 3.31, 3.41, 6.46, 6.88, 7.30, 7.73, 9.36, 13.10, and 13.36 μ; mass spectrum m/e (rel intensity) 146 (18), 131 (100), 116 (15), 115 (20), and 77 (8); pmr (neat) δ 7.00-6.71 (m, 3, ArH), 3.30-2.95 (m, 1, $ArC\underline{H}CH_3$), 2.93-2.48 (m, 2, $ArCH_2$-), 2.17 (s, 3, $ArCH_3$), 2.20-1.45 (m, 2, $-CH_2-$), and 1.09-1.02 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.40; H, 9.60.

Preparation of 3,7-Dimethyl-4-methoxyindanone (14).-- A Friedel-Crafts acylation was performed using 1023 g (8.4 mol) of p-methylanisole,

655 g (8.4 mol) of acetyl chloride, and 1117 g (8.41 mol) of $AlCl_3$. The reagents (except $AlCl_3$) were placed in a 12-l. flask equipped with mechanical stirrer, thermocouple, reflux condenser, and a nitrogen atmosphere. The $AlCl_3$ was then added in small portions at a rate (1 hr) such that the temperature was maintained below 35° by use of an ice bath. This mixture was stirred for 1 hr after addition was completed. The reaction mixture was poured on ice (2-3 kg) and the resulting mixture was steam distilled. The distillate was extracted with petroleum ether and benzene. The solvents were removed by rotary evaporation and the resulting oil was distilled at 105° (2.2 mm) to give 621 g of 17. A 32.8-g (0.2-mol) sample of the ketone 17 and 33.6 g (0.22 mol) of methyl bromacetate were dissolved in 80 ml of benzene and this solution was cautiously added to 14 g of zinc-copper couple in a flask equipped with reflux condenser, mechanical stirrer, and a pressure-equalizing addition funnel. The reaction was carried out under a nitrogen atmosphere. Reaction was initiated by the addition of a small amount of the benzene solution to the zinc-copper couple and heating gently until an exothermic reaction began and was maintained by the addition of the remaining solution over a 1-hr. period. The reaction mixture was refluxed for 1 additional hr, cooled and washed with cold 10% H_2SO_4. The benzene extract was dried (Na_2SO_4) and concentrated on a rotary evaporator. The resulting oil (35.7 g) was hydrogenated in 150 ml of acetic acid with 2 g of Pd/C (10%) at 1 atm until the up-take of hydrogen had ceased (3 hr). The mixture was filtered through Dicalite and the acetic acid was removed by rotary evaporation. The residue was refluxed for 4 hr in 100 ml of 20% NaOH. Acidification, extraction with ether, drying (Na_2SO_4), and distillation yielded 22.8 g of the acid 18.

This acid was added to 70 g of PPA at 90° and the mixture was stirred for 30 min. An additional 70 g of PPA was added and stirring was continued for 30 additional min. This mixture was added to 500 g of ice and extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated by rotary evaporation. The resulting oil was distilled to give 13.7 g of the keton 14 in an overall yield of 35%: bp 108° (2 mm); ir (neat) 3.41, 5.87, 6.19, 7.90, 9.50, and 12.34 μ; mass spectrum m/e (rel intensity) 190 (78), 175 (24), 161 (100), 145 (20), 115 (25), 103 (16), and 91 (25); pmr (CCl_4) δ 6.96-6.70 (q, 2, ArH), 3.80 (s, 3, $ArOCH_3$), 3.05-3.18 (m, 1, $ArC\underline{H}CH_3$), 3.84-2.96 (m, 2, $-CH_2-$), 2.44 (s, 3, $ArCH_3$), and 1.30-1.25 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.76; H, 7.38.

The 2,4-dinitrophenylhydrazone of 14 (mp 279-280° dec) was prepared and crystallized from ethanol.

Preparation of 3,4-Dimethyl-7-methoxyindanone (31).-- A 30.0-g sample of 1 and 25.0 g of dimethyl sulfate was added to 200 ml of 20% NaOH. This mixture was stirred and refluxed for 12 hr. At the end of this period the mixture was extracted with ether. The ether extract was dried (Na_2SO_4) and concentrated by rotary evaporation. The product was recrystallized from ethanol to give 18 g (48%) of the ether 31: mp 76-78°; ir (neat) 3.42, 5.88, 6.30, 7.84, 9.63, and 12.34 μ; pmr (CCl_4) δ 7.21-7.57 (q, 2, ArH), 3.84 (s, 3, $ArOCH_3$), 4.48-4.16 (m, 1, $ArC\underline{H}CH_3$), 3.88-2.00 (m, 2, $-COCH_2-$), 2.29 (s, 3, $ArCH_3$), and 2.32-2.24 (d, 3, $ArCHC\underline{H}_3$).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.56; H, 7.36.

The 2,4-dinitrophenylhydrazone of 31 (mp 253-255° dec) was prepared and crystallized from ethanol.

Preparation of 2'-Hydroxy-5'-methyl-2-butenophenone(8).[54]-- To a mixture of 18 g (0.15 mol) of p-cresol and 15.3 g (0.15 mol) of crotonyl chloride in 150 ml of carbon disulfide was added 4 g of $AlCl_3$ in small portions over a period of 1 hr. The mixture was stirred for an additional hour after addition was completed. This mixture was poured on 100 g of ice. This mixture was extracted with ether and the extract was distilled to give 10.6 g of 8: bp 125° (1.5 mm); mp 65-66°; ir (Nujol) 2.98, 6.04, 6.28, 8.42, 9.70, 10.39, and 12.08 μ; pmr (CCl_4) δ 7.44 (s, 1, ArOH), 7.24-7.00 (m, 3, ArH), 6.82-6.72 (m, 2, vinylic), 2.26 (s, 3, $ArCH_3$), and 2.02-1.96 (d, 3, $CHCH_3$).

Preparation of p-Methylphenyl Crotonate (9).[52]-- To a 21.6-g (0.2-mol) sample of p-cresol in 50 ml of anhydrous benzene was added dropwise 20.8 g (0.2 mol) of crotonyl chloride (1.5 hr). This solution was stirred and refluxed for 8 hr. After cooling, this solution was added to 100 ml of ice-water and the benzene layer was separated. The benzene solution was washed with 10% NaOH and water, dried (Na_2SO_4), and distilled to give 20.0 g of 9: bp 94° (1.3 mm); ir (neat) 3.46, 5.78, 6.04, 6.64, 8.32, 8.64, 9.07, 10.30, and 12.25 μ; pmr (CCl_4) δ 7.20-6.75 (m, 4, ArH), 6.01-6.78 (m, 2, vinylic), 2.25 (s, 3, $ArCH_3$), and 1.85-1.76 (d, 3, $CHCH_3$).

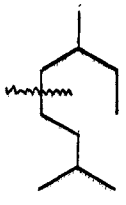
PART III

SYNTHESIS OF NONISOPRENOID NEPETALINIC ACID

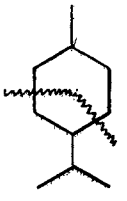
CHAPTER VII

INTRODUCTION AND DISCUSSION

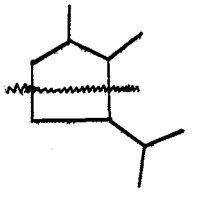
From the beginning of chemical research, there has been enthusiastic interest in the study of naturally occurring compounds. Many plant odors have been shown to be due to C_{10} compounds classified as terpenes and terpenoids. These may be visualized as made up of isoprene units as shown below for I, II, and III. Much of the basic chemistry of types I and II and similar monoterpenoids except type III was established prior to 1920.[59]



I



II



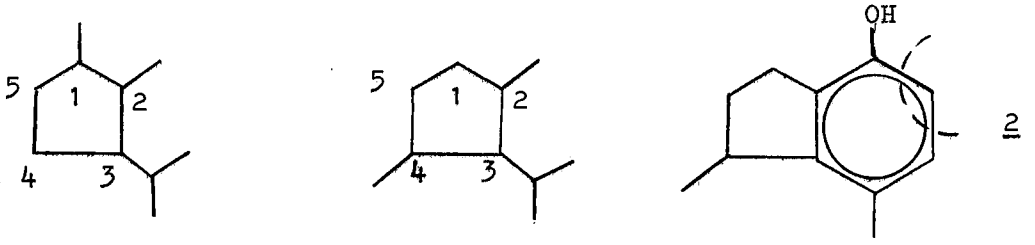
III

Since the early 1950's, however, numerous methylcyclopentane monoterpenoids (structure type III) have been isolated and described. Many of these have been shown to be physiologically active as defense chemicals, communication chemicals, and pheromones in insects and animals.[60]

The first compound of this type to be fully characterized was nepetalactone. Nepetalactone was found to be a major constituent of the oil of catnip and responsible for its excitation of cats. This oil was isolated by steam distillation of the catnip plant, Nepeta Cataria. An elegent structure proof and stereochemical assignment was made by McElvain and Eisenbraum.[61,62,63] The key to the assignment of the stereochemistry of nepetalactone and many subsequently described metylcyclopentane monoterpenoids was the assignment of the nepetalinic acids.[60] Two of the nepetalinic acids (mp 85° and 117°) have also been shown to be present in the oil of catnip.[62]

An early synthesis of nepetalinic acid was accomplished by the reaction scheme shown in Figure 11. The condensation of 3-bromobutyne with ethyl 3-methyl-2-oxocyclopentanecarboxylate afforded the acetylenic ketoester 19. Hydration of the acetylenic bond and hydrolysis of the ester gave the diketone 20. Base-catalyzed condensation of 21 with benzaldehyde yielded the benzylidene derivative 22 which upon ozonolysis gave a racemic form of nepetalinic acid (23).[64]

It became of interest to demonstrate the utility of the phenol 2, derived from the Friedel-Crafts reaction of p-cresol and crotonic acid described in Chapter V, in the synthesis of nonisoprenoid cyclopentane monoterpenoids. These compounds are nonisoprenoid with a methyl group normally located at the 1-position appearing at the 4-position as shown on the following page. It should be noted that the phenol 2 has the nonisoprenoid carbon skeleton. It would also be of interest to compare the physiological activities of the synthesized isomers with the authentic methylcyclopentane monoterpenoids but such assay is not within the scope of this study.



The utility of the phenol 2 is sufficiently demonstrated by the synthesis of nonisoprenoid nepetalinic acid 30. This synthesis was carried out as outlined in Figure 12 and involves the high-pressure catalytic hydrogenation of the phenol 2 to the alcohol 24 in nearly quantitative conversion. A Jones oxidation of 24 resulted in a mixture of ketones corresponding to the structure of 25 in 85% yield. The benzylidene derivative of the ketone 25 was prepared by condensation with benzaldehyde. This derivative, 26, was formed in 94% yield but remains as inseparable mixture of isomers. Ozonolysis of 26 and decomposition of the ozonide in alkaline hydrogen peroxide gave the dicarboxylic acid 27 upon acidification. This acid was esterified with diazomethane to give the diester 28. A Dieckmann condensation of 28 was effected with sodium methoxide in methanol to give the beta-keto ester 29. Oxidation of 29 with hydrogen peroxide in alkali followed by acidification afforded a mixture of stereoisomeric forms of nonisoprenoid nepetalinic acid 30. The separation of one racemate was accomplished via the formation of an insoluble barium salt. This behavior is reminiscent of the formation of an insoluble barium salt of α-nepetalinic acid, mp 85°.[62]

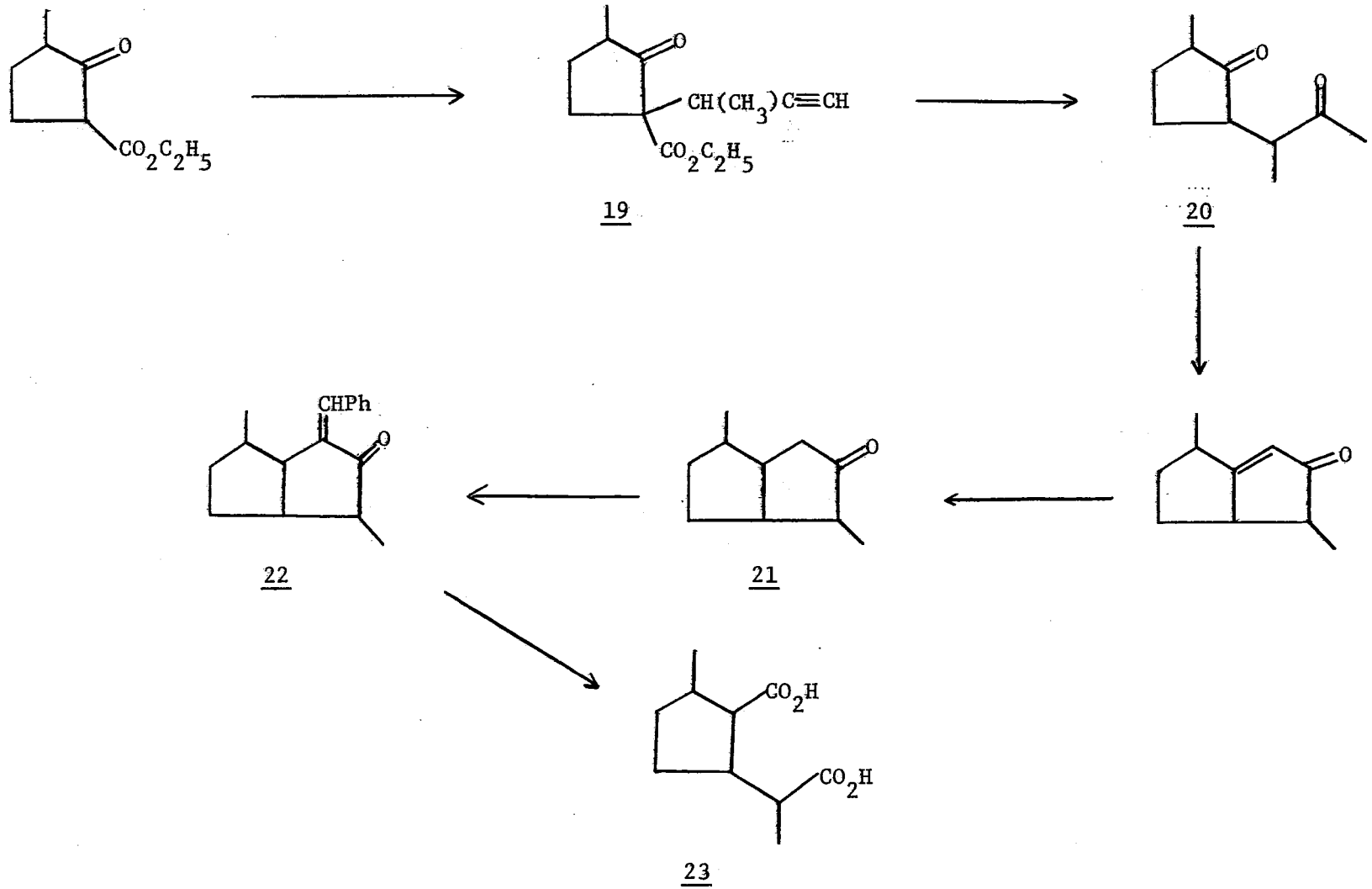
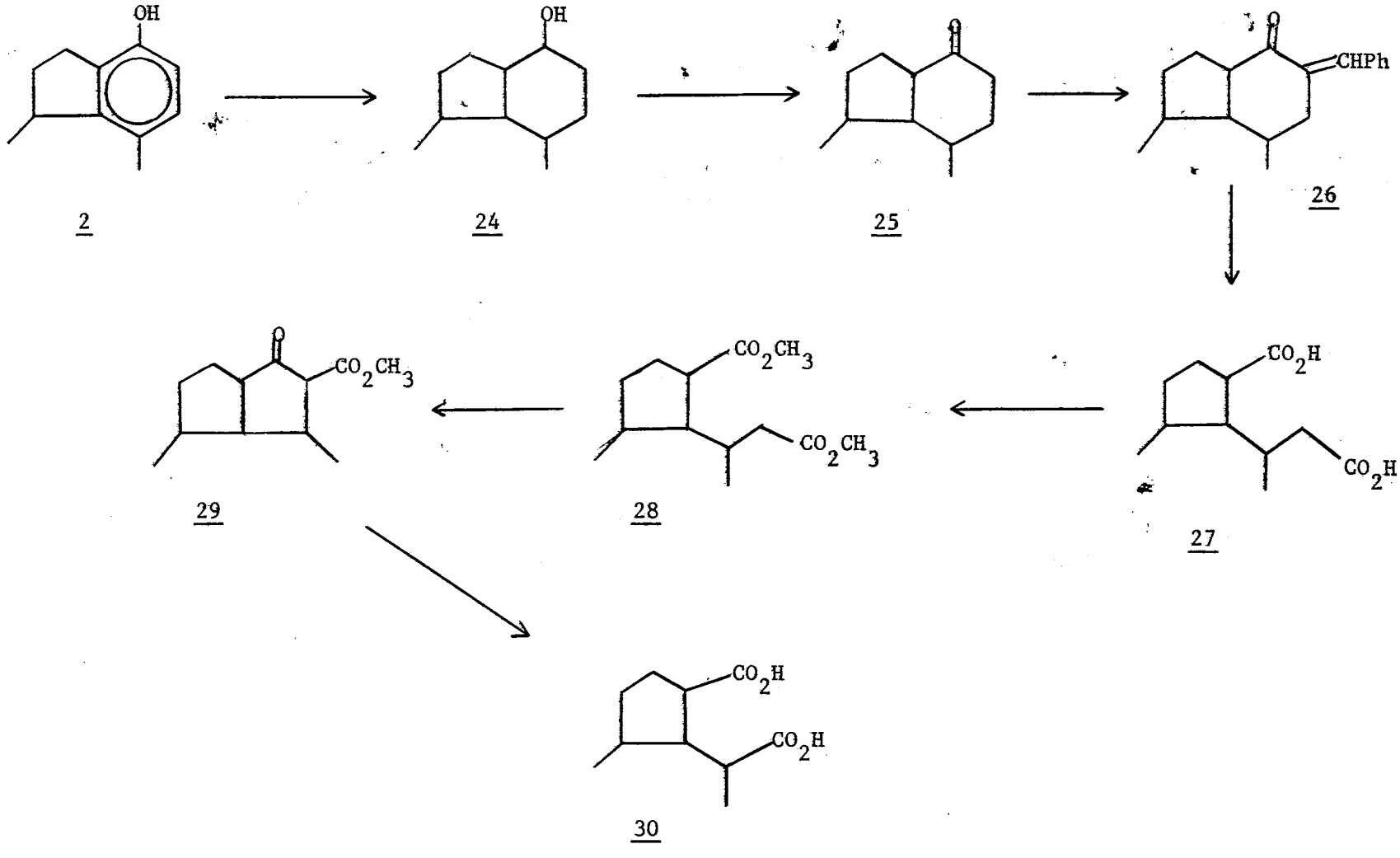


Figure 11. Synthesis of Nepetalinic Acid.



2 24 25 26 27 28 29 30

Figure 12. Synthesis of the Nonisoprenoid Nepetalinic Acid 30.

CHAPTER VIII

EXPERIMENTAL

Catalytic Hydrogenation of 1,7-Dimethyl-4-indanol (2).-- An 82-g sample of 2 was dissolved in 1.5 l. of 95% ethanol containing 4 g of Pd/C (10%). This mixture was treated with hydrogen at 2000 psi and 200° for 6 hr.[65] The reaction mixture was filtered through Dicalite and the solvent was distilled off at atmospheric pressure. Distillation at reduced pressure afforded 79 g (95%) of the stereoisomeric mixture 24: bp 90° (0.7 mm); ir (neat) 2.99, 3.43, 3.49, 6.90, 7.28, 9.65, and 10.30 μ.

Jones Oxidation of 1,7-Dimethyl-4-hexahydroindanol (24).-- Jones reagent[66] was added dropwise to 100 ml of acetone containing 20 g of 24. The stirred reaction mixture was kept below 5° with a salt-ice bath. The addition was stopped when a red-brown color persisted. Isopropyl alcohol was added dropwise until the red-brown color was discharged. The reaction mixture was filtered to remove salts and acetone was removed by rotary evaporation. The resulting oil was distilled to give 15 g (75%) of an isomeric mixture of 1,7-dimethyl-4(5H)-tetrahydroindanone (25): bp 85-95° (1.9 mm); ir (neat) 3.42, 5.88, 6.88, 7.26, 8.75, 9.95, 10.48, and 11.68 μ.

Preparation of the Benzylidene Derivative of 25.-- A mixture containing 18.3 g (0.11 mol) of 25, 23.2 g (0.22 mol) of freshly distilled benzaldehyde, 44 ml of ethanol, 13 ml of water, and 13 ml of 10% NaOH

was stirred for 72 hr. This mixture was extracted with ether, dried (Na_2SO_4), and distilled to give 24 g of a mixture of stereoisomeric formes of 26 (94%): bp 150-170° (0.15 mm); ir (neat) 3.41, 3.49, 5.95, 6.23, 6.91, 8.47, 8.63, 10.77, 11.12, 13.26, and 14.42 μ.

Preparation of 3-(2-Carboxy-5-methylcyclopentane)-3-methylpropanoic acid (27).-- A 24-g (0.09-mol) sample of 26 was dissolved in 200 ml of dichloromethane and subjected to treatment with ozone at Dry ice-acetone temperature until an excess ozone was indicated by change in color of the dichloromethane solution to blue-green (2 hr). This solution was cautiously poured into a stirred solution containing 50 ml of 30% H_2O_2 and 200 ml of 20% NaOH and the whole was stirred for an extra hr after addition was completed. This mixture was then extracted with ether to remove the neutral compounds and the aqueous layer was made acidic with concentrated HCl. The benzoic acid by-product was removed by steam distillation of the acidified aqueous layer. The steam-distilled residue was extracted with ether, dried (Na_2SO_4), and concentrated by rotary evaporation to give 16.8 g (89%) of a mixture of the stereoisomeric dicarboxylic acids 27. Attempted crystallizations of 27 were unsuccessful: ir (neat) 2.8-3.8, 5.88, 6.99, 7.24, and 8.10 μ.

Esterification of 27 to the Dimethyl ester 28.-- An etheral solution of diazomethane was added to 16 g of 27 until the yellow color of diazomethane persisted. The solvent was removed by rotary evaporation and the product was distilled to give 17 g of the isomeric methyl 3-(2-(methoxycarbonyl)-5-methylcyclopentane)-3-methylpropanoate (28): bp 115° (0.2 mm); ir (neat) 3.43, 5.79, 6.90, 7.29, and 8.60 μ.

Dieckmann Condensation of the Diester 28.[67]-- A 1.6-g sample of freshly cut sodium metal was added to 30 ml of anhydrous methyl alcohol,

freshly distilled from powdered Mg. To the resulting solution was added 15.5 g of the diester 28. This mixture was refluxed for 10 hr in an apparatus consisting of a 250 ml flask, magnetic stirring bar, reflux condenser, and a drying tube. Approximately one-half of the solvent was removed by distillation. About 50 ml of dry toluene was added and the remaining methyl alcohol was removed by azeotropic distillation at 64°. When the distilling temperature reached 110° (boiling point of toluene) the mixture was cooled and made acidic with 10% acetic acid. This mixture was extracted with ether and the ether extract was washed with saturated $NaHCO_3$ and water and dried (Na_2SO_4). The solvent was removed by rotary evaporation. Distillation resulted in 10.1 g of the beta-keto ester 29: bp 120° (5 mm); ir (neat) 2.96, 3.41, 5.80, 6.06, 6.20, 6.92, 7.29, 8.11, and 8.68 μ.

Oxidation of 29 to the Nonisoprenoid Nepetalinic Acid (30).[68] -- A 10.1-g sample of the ester 29 was added to a stirred solution of 40 ml of water, 20 ml of 30% H_2O_2, and 4 g of NaOH and stirred for 1 hr. This solution was extracted with ether. The aqueous layer was made acidic and extracted with ether. The ether layer was then shaken with saturated $Ba(OH)_2$. A white precipitate, presumably the barium salt, was formed immediately and was removed by filtration and washed with water. The product was regenerated by treating the salt with 10% HCl and extracting with ether. The ether was dried (Na_2SO_4) and removed by rotary evaporation. The resulting material upon recrystallization from ethanol gave 2.7 g of 2-(2-carboxy-5-methylcyclopentane)-2-methylacetic acid (30). Gc analysis of the methyl ester indicated that 30 is a single racemate: mp 120° (dehydration); ir (Nujol) 2.80-4.10, 5.92, 7.27, 8.26, and 10.80 μ; pmr (CCl_4) δ 3.04-2.55 (m, 2, C<u>H</u>COOH), 2.30-

0.88 (m, 6, $-CH_2-$ and $C\underline{H}CH_3$), 1.30-1.23 (d, 3, $C\underline{H}_3CH-$), and 1.08-1.02 (d, 3, $C\underline{H}_3CHCOOH$).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.72; H, 7.97.

BIBLIOGRAPHY AND NOTES

1. P. Sabatier and J. Senderens, Compt. Rend., 124, 1358 (1897).

2. R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, Inc., New York, 1965.

3. M. Freifelder, "Practical Catalytic Hydrogenation", Wiley-Interscience, New York, 1971.

4. P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, 1971.

5. Ref. 3, page 524.

6. J. Meinwald, M. C. Seidel, and B. Cadoff, J. Amer. Chem. Soc., 80, 6303, (1958).

7. J. Meinwald and E. Frauenglass, ibid., 82, 5235, (1960).

8. W. G. Dauben and P. Hance, ibid., 77, 2451 (1955).

9. A. M. Kham, F. J. McQuillin, and I. Jardine, J. Chem. Soc., 136 (1967).

10. S. H. Weber, R. J. Kleipool, and D. B. Spoelstra, Rec. Trav. Chim., 76, 193 (1957).

11. J. W. Burnham and E. J. Eisenbraun, J. Org. Chem., 36, 737 (1971).

12. D. H. R. Barton, N. J. Holness, and W. Klyne, J. Chem. Soc., 2456 (1949).

13. W. H. Pirkle and J. L. Zabriskie, J. Org. Chem., 29, 3124 (1964).

14. P. N. Rylander and D. R. Steele, Engelhard Industries, Inc., Technical Bulletin, 6, 41 (1965).

15. P. N. Rylander and N. Himelstein, ibid., 8, 53 (1967).

16. H. A. Smith and B. L. Stump, J. Amer. Chem. Soc., 83, 2739 (1961).

17. J. H. Billman and J. A. Buchler, Proc. Indiana Acad. Sci., 63, 120 (1953).

18. W. J. Musliner and J. W. Gates, Jr., J. Amer. Chem. Soc., 88, 4271 (1966).

19. P. J. Van Der Jagt, W. Den Hollander, and B. Zanten, Tetrahedron, 27, 1049 (1971).

20. W. P. Duncan, J. E. Rusell, and E. J. Eisenbraun, J. Org. Chem, 37, 142 (1972).

21. Qualitiative analyses were carried out using a 0.123-in. (o.d.) x 8-ft stainless steel column containing 80-100 mesh, acid-washed DMCS-treated Chromosorb W coated with 5% of UCW-98 silicone rubber in a Hewlett-Packard 5750 instrument, either isothermally or with a temperature program as required.

22. These analyses were performed by Dr. L. E. Harris using a Varian 1400 gas chromatoghraph in conjunction with a Finigan 1015 mass spectrometer.

23. Thin-layer chromotoghaphy experiments were performed using non-activated Eastman Chromatogram Sheets (silica gel) and were developed with a 9:1 mixture of petroleum ether and benzene.

24. Ref. 3, page 29.

25. Ref. 3, page 401.

26. Quantitative analyses were performed using a 0.25-in. (o.d.) x 12-ft copper column containing 80-100 mesh, acid-washed Chromosorb W coated with 25% Carbowax 20M on a Beckmann GC-2A instrument operating at an appropiate temperature. Concentrations were determined by comparing peak heights and/or peak areas to those of solutions of known concentration.

27. J. D. Weaver, E. J. Eisenbraun, and L. E. Harris, Chem. Ind. (London), 187 (1973).

28. R. Stroh and H. Gerber, Angew. Chemie, 72, 1000 (1960).

29. T. Zincke, Ber., 2, 737 (1869).

30. T. Zincke, ibid., 6, 137 (1873).

31. C. Friedel and J. Crafts, Bull. Soc. Chim. France, 27, 530 (1877).

32. G. A. Olah, "Friedel-Crafts and Related Reactions", Interscience Publishers, New York, 1963, Volumes I-V.

33. G. A. Olah and S. J. Kuhn, J. Org. Chem., 29, 2317 (1967).

34. C. J. Plank and D. M. Nace, Ind. Eng. Chem., 47, 2374 (1955).

35. Ref. 32, Volume II.

36. J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry", W. A. Benjamin, Inc., New York, 1965, Page 184.

37. K. E. Russell, J. Amer. Chem. Soc., 81, 4834 (1959).

38. Ref. 32, Volume 1, page 205.

39. G. A. Olah, S. J. Kuhn, and S. H. Flood, J. Amer. Chem. Soc., 84, 1688 (1962).

40. A. W. Francis, Chem. Rev., 43, 257 (1948).

41. J. March, "Advances in Organic Chemistry: Reactions, Mechanisms, and Structure", McGraw-Hill, New York, 1968.

42. M. A. McMahon and S. C. Bunce, J. Org. Chem., 29, 1515 (1964).

43. S. U. Choi and H. C. Brown, J. Amer. Chem. Soc., 85, 2596 (1963).

44. Ref. 32, Volume III.

45. Y. Yamase, Bull. Chem. Soc. Japan, 34, 480 (1961).

46. A. Liberles, "Introduction to Theoretical Organic Chemistry", MacMillan Co., New York, 1968, page 648.

47. Ref. 32, Volume III, page 499.

48. A. M. El-Abbady, F. G. Baddar, and A. Labib, J. Chem. Soc., 1083 (1961).

49. Ref. 32, Volume III, page 507.

50. (a) J. F. Eijkman, Chem. Weekblad, 5, 655 (1909); (b) H. Hopff, Germ. Pat. 666,466 (Oct. 20, 1938); (c) C. F. Koelsch, H. Hochmann, and C. D. LeClaire, J. Amer. Chem. Soc., 65, 59 (1943); (d) Sukh Dev, J. Indian Chem. Soc., 33, 703 (1956).

51. (a) E. Bergmann, H. Taubadel, and H. Weiss, Ber., 64, 1499 (1931); (b) L. I. Smith and Chien-Pen Lo, J. Amer. Chem. Soc., 70, 2215 (1948).

52. A. B. Sen and V. S. Misra, J. Indian Chem. Soc., 26, 339 (1949).

53. K. von Auwers, Ann., 502, 282 (1933).

54. (a) K. von Auwers and E. Lammerhirt, ibid., 421, 1 (1920); (b) K. von Auwers, Ber., 44, 3692 (1911).

55. I. G. Farbenindustrie A.-G., Brit. Pat. 288,441 (1927) via C. A., 23, 606 (1929).

56. Buu-Hoi and R. Royer, Bull. Soc. Chim. France, 812 (1947) via C. A., 42, 3382 (1948).

57. C. S. Springer, Jr., D. W. Meek, and R. E. Sievers, Inorg. Chem., 6, 1105 (1967).

58. (a) Nmr Spectra were obtained with a Varian XL-100 or A-60 instrument. Peak position are in terms of ppm downfield from internal TMS standard. (b) Sievers reagent, available from Aldrich, is 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione, europium (III).

59. G. W. K. Cavill, Rev. Pure Appl. Chem., 10, 169 (1960).

60. C. W. K. Cavill, "Cyclopentanoid Terpene Derivaties", W. I. Taylor and A. R. Battersby, eds., Marcel Dekker, Inc., New York, 1969, Volume II, Chapter 3, page 203.

61. S. M. McElvain, R. D. Bright, and P. R. Johnson, J. Amer. Chem. Soc., 64, 1828 (1942).

62. S. M. McElvain and E. J. Eisenbraun, ibid., 77, 1599 (1955).

63. R. B. Bates, E. J. Eisenbraun, and S. M. McElvain, ibid., 80, 3420 (1958).

64. T. Sakan, A. Fujino, F. Murai, A. Suzui, and Y. Betsugan, Bull. Chem. Soc. Japan, 22, 1737 (1960).

65. High-pressure hydrogenations were carried out in a one-gallon autoclave, Autoclave Engineers, Magnedrive, Model AFP-150.

66. E. J. Eisenbraun, Org. Syn., 45, 28 (1965).

67. K. Sisido, K. Utimoto, and T. Isida, J. Org. Chem., 29, 2781 (1964).

68. E. J. Eisenbraun, G. H. Adolphen, K. S. Schorno, and R. N. Morris, ibid., 36, 414 (1971).

69. Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

VITA

Jimmie Deam Weaver, Jr.

Candidate for the Degree of

Doctor of Philosophy

Thesis: I. PHENOL DEOXYGENATION VIA CATALYTIC HYDROGENOLYSIS
II. FRIEDEL-CRAFTS REACTION OF p-CRESOL AND CROTONIC ACID
III. SYNTHESIS OF NONISOPRENOID NEPETALINIC ACID

Major Field: Chemistry

Biographical:

Personal Data: Born in Oklahoma City, Oklahoma, July 10, 1945, the son of Jimmie D. and Rhama E. Weaver.

Education: Graduated from Carnegie High School, Carnegie, Oklahoma, in 1963; attended Bethany Nazarene College, Bethany, Oklahoma, 1963-65; received the Bachelor of Science degree from Southwestern State College, Weatherford, Oklahoma, in June, 1968, with a major in Chemistry and minor in Mathematics; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in July, 1973.

Professional Experience: Graduate Teaching Assistant, Oklahoma State University, 1968-73; member of American Chemical Society and Phi Lambda Upsilon.