I. SYNTHESIS AND PURIFICATION OF BENZ[a]ANTHRACENE

II. FRIEDEL-CRAFTS REACTION APPLIED TO AROMATIC ETHERS AND CROTONIC ACID

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TO

My departed Father

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PART I

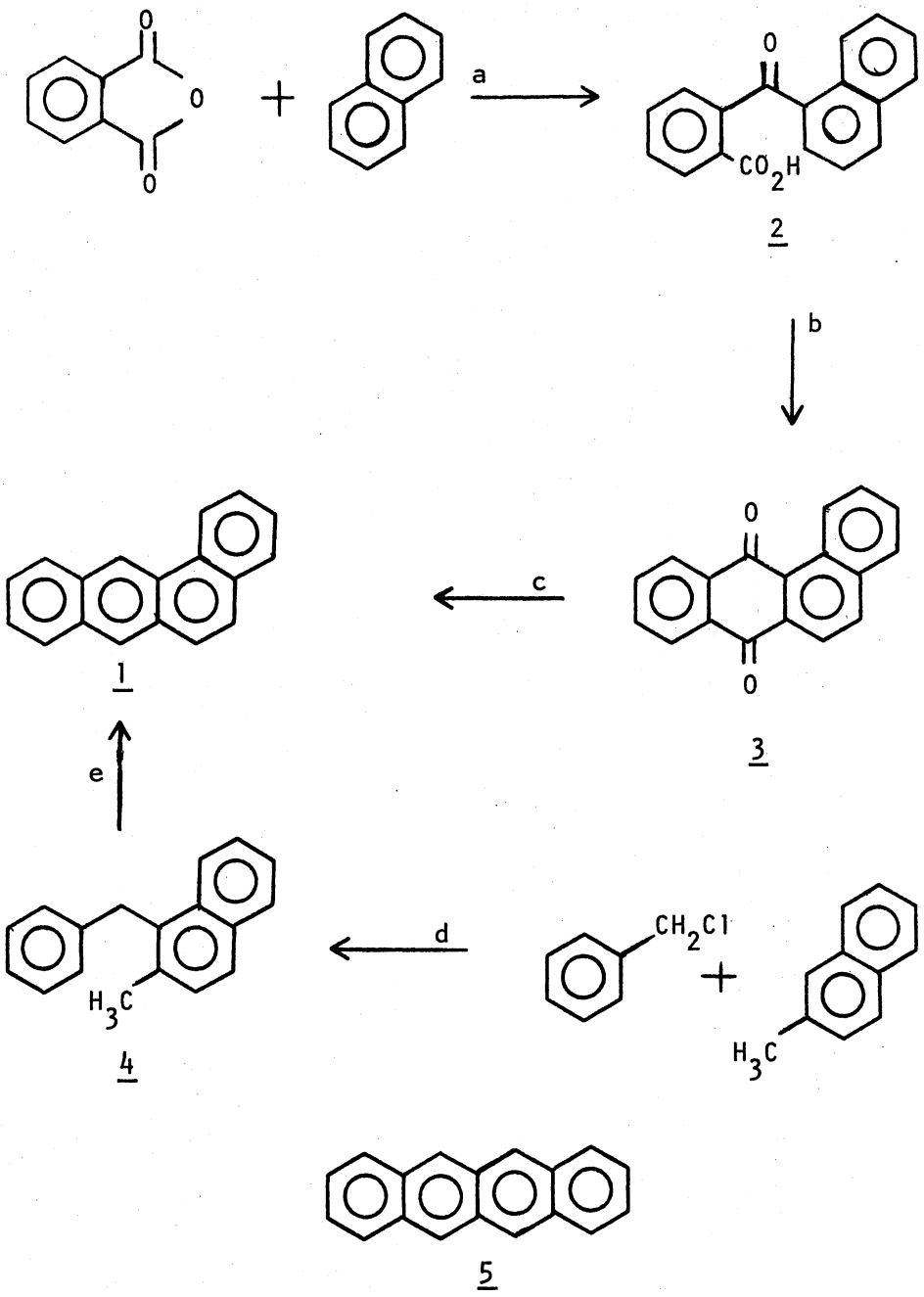
SYNTHESIS AND PURIFICATION OF BENZ[a]ANTHRACENE

CHAPTER I

INTRODUCTION AND HISTORICAL

Benz[a]anthracene (1) is a known carcinogen[1] and its carcinogenicity was determined through use of a variety of mice[2] and rats.[3] It was found that 1 produced skin tumors and lung tumors. Benz[a]anthracene (1) has been detected in cigarette smoke condensate,[4] polluted air and airborne particulates[5] found in industrial areas and large cities, automobile exhaust condensate,[6] coal tar,[7] smoked and broiled meat, fish, sausage, etc.,[8] sewage,[9] mineral oil,[10] roasted coffee and tea,[11] resins,[12] olive oil,[13] dust in gold mines,[14] roasted peanuts,[15] stack gases from pulp mills,[16] carbon black,[17] wood smoke from saw dust,[18] commercial soaps,[19] whiskey,[20] coconut oil,[21] and chemical and petrochemical waste water,[22] as well as petroleum.[23] Because of its widespread occurrence, a pure sample of 1 for use as a reference material was sought by the Environmental Protection Agency.[24]

Numerous syntheses of 1 have been described; some of these are cited below. It was first obtained by reduction with zinc dust and ammonia of 1,2-benzanthraquinone (3)[25] which in turn is prepared from phthalic anhydride and naphthalene, as shown in Figure 1. This route remains a reliable procedure for the preparation of 1 and it was used in our work. Benz[a]anthracene (1) was also prepared by distillation of 2 with zinc dust.[26]

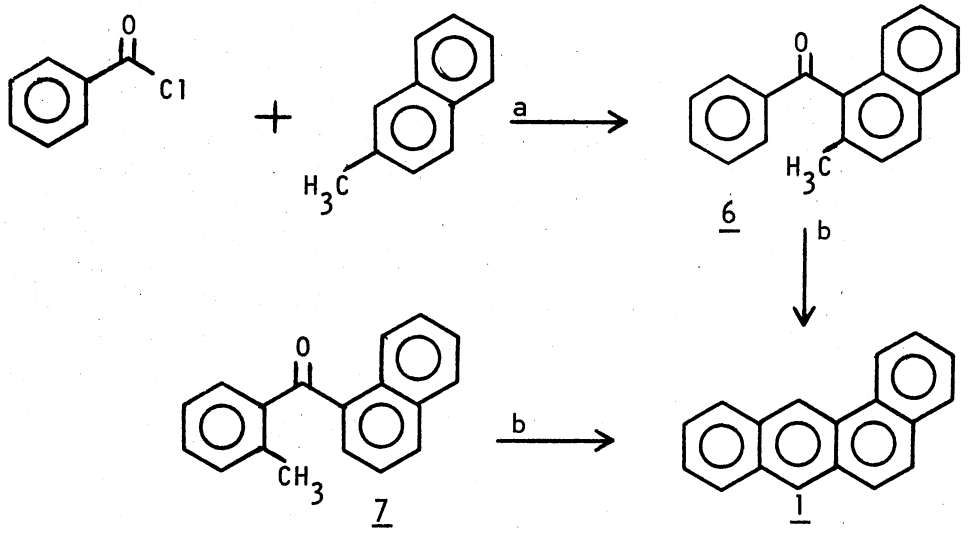


$^{a}AlCl_3$. $^{b}H_2SO_4,\Delta$. $^{c}Zn/NH_3$. $^{d}ZnCl_2$. $^{e}Zn,\Delta$.

Figure 1. Synthesis of 1

In another synthesis also shown in Figure 1, 2-methylnaphthalene is treated with benzylchloride in the presence of zinc chloride to give 1-benzyl-2-methylnaphthalene (4) which in turn yields 1 when distilled with zinc dust.

Some tetracene (5) is, however, also formed by rearrangement; this can be avoided as shown in Figure 2 by starting from 2-methyl-1-naphthylphenylketone (6),[27] which is readily obtained from the reaction of 2-methylnaphthalene, benzoyl chloride, and aluminum chloride.[28] A similar method for the preparation of 1 utilizes 1-naphthyl-o-tolylketone (7).[29]

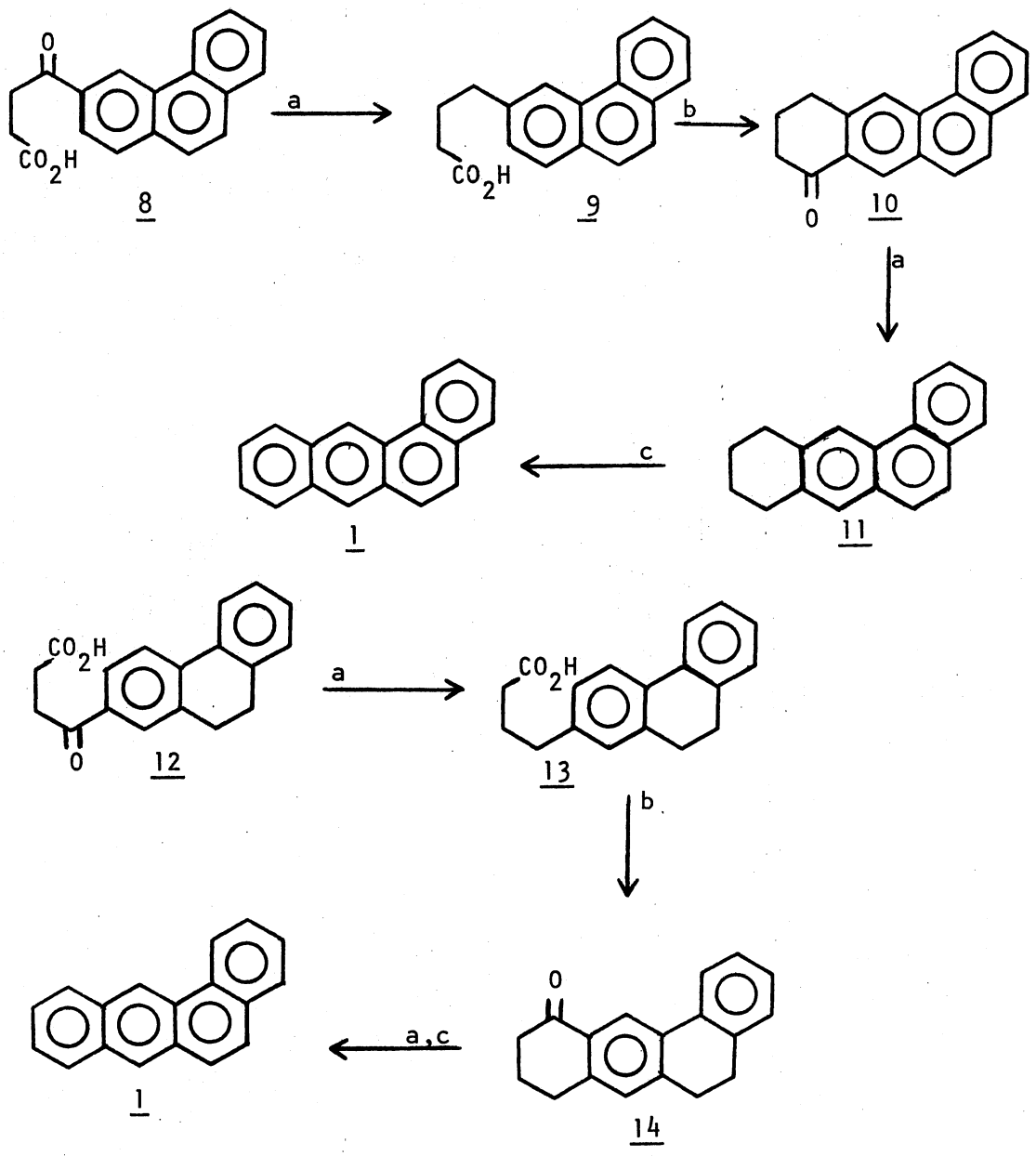


[a]$AlCl_3$. [b]Heating 2 hours at boiling temperature

Figure 2. Syntheses of 1

Another synthesis[30] of 1 starting with succinic anhydride, phenanthrene, and aluminum chloride yields, in addition to isomers, a ketonic acid (8). This acid, as shown in Figure 3, on reduction yields

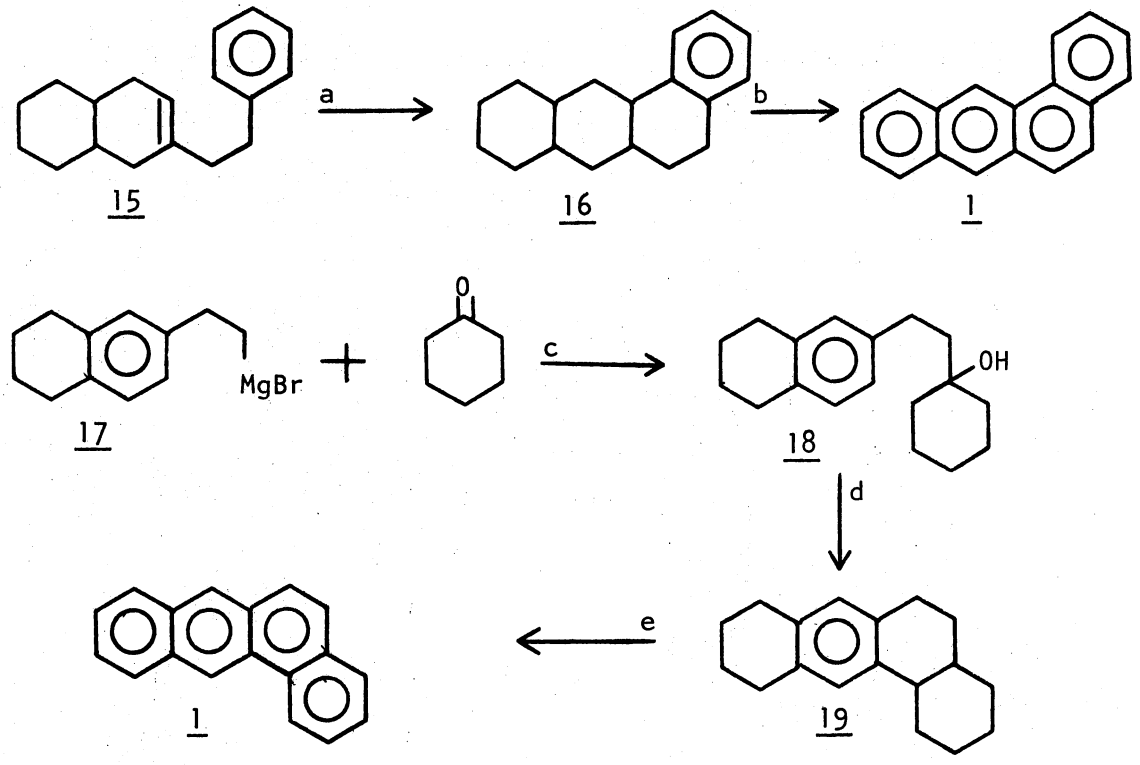
9 which can be cyclized to 10. Reduction of 10 to 11 and dehydrogenation gives 1. The isomeric acid 12, via reduction to 13 and ring-closure to 14, also yields 1.[31]



[a]Zn(Hg),HCl. [b]85% H_2SO_4. [c]Se,Δ.

Figure 3. Syntheses of 1

The Grignard reaction of 2-decalone with β-phenylethylmagnesium chloride and dehydration of the carbanol yields 15 which in the presence of aluminum chloride undergoes ring-closure to 16. This can be dehydrogenated to 1 with selenium as shown in Figure 4. This method was used by Cook and Hewett.[32]



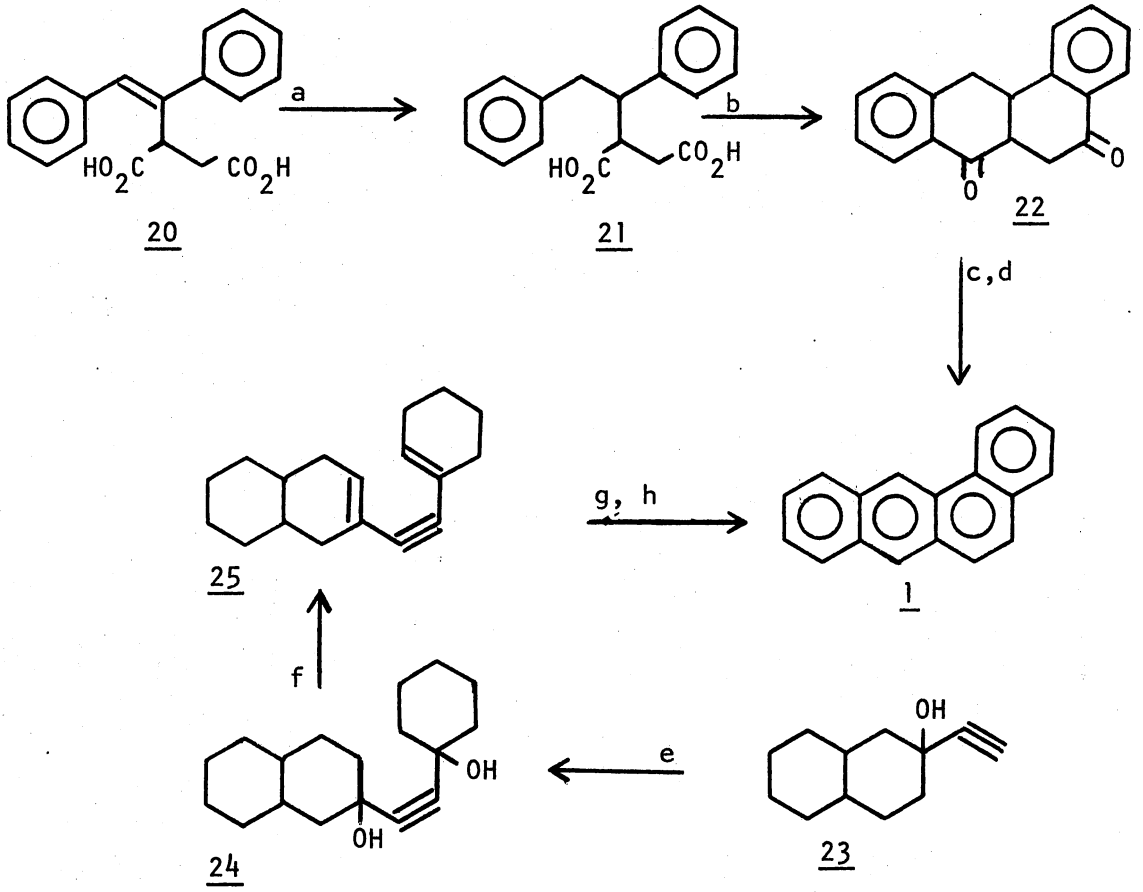
[a]$AlCl_3$ [b]Se. [c]ether [d]H_2SO_4 [e]Pd/C,300°.

Figure 4. Syntheses of 1

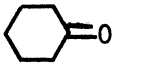
Mukherjee and Dabas[35] describe a variant of the method of Cook and Hewett[32] for making 1. This synthesis, also shown in Figure 4,

starts with β-(6-tetralyl)ethylmagnesium bromide (17).

In yet another synthesis, the succinic acid derivative 20 is first reduced to 21 which is then cyclized to 22 and thence converted to 1.[33]



[a] $Ni-Al,NaOH$. [b] HF. [c] $2H_2$. [d] $Pd/C,\Delta$.

[e] $2C_2H_5MgBr$,ether,  /base.

[f] $KHSO_4,\Delta$. [g] H_2SO_4. [h] Se.

Figure 5. Syntheses of 1

Trans-2-Decalone can be condensed with acetylene and potassium t-pentyloxide to 23, which after conversion to Grignard compound reacts with cyclohexanone to yield 24 as shown in Figure 5. Dehydration to 25, followed by ring-closure and dehydrogenation, yields 1.[34]

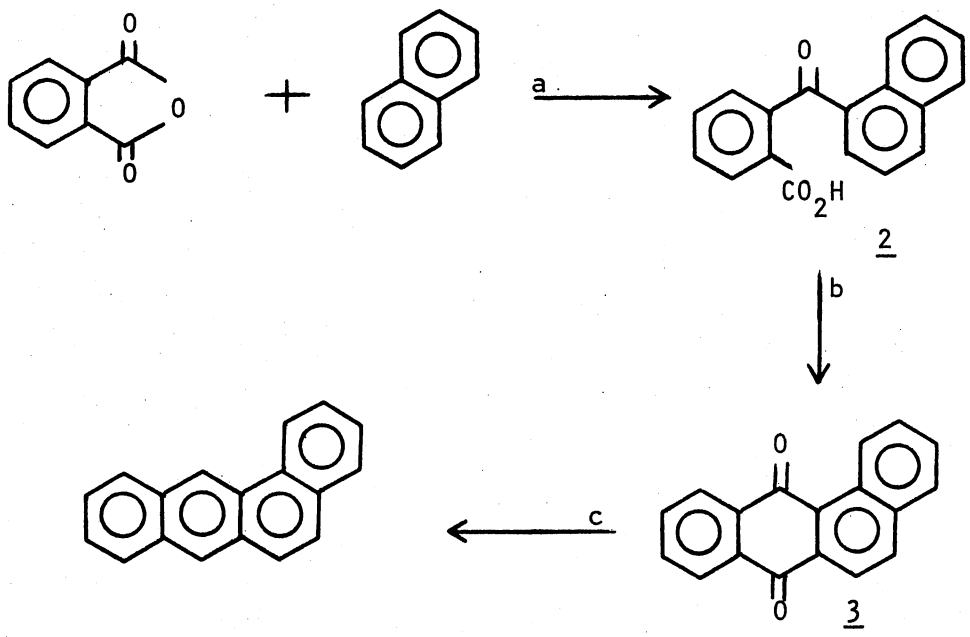
Badger and Cook[36] cyclized 2 to 3 by heating at 130° in the presence of C_6H_5COCl and treating cautiously with concentrated sulfuric acid. They finally reduced 3 by boiling with $SnCl_2$ and HCl and later aromatized the product to 1, with NaOH and zinc dust.

The preparation of 2-(1-naphthoyl)benzoic acid (2) according to the Friedel-Crafts reaction has been previously reported by Ador and Crafts,[37] Gabriel and Coleman,[25b] Graebe,[25c] and Heller and Schulke.[25d] In no case did the crude acid obtained by these investigators possess a high degree of purity. 1,2-Benzanthraquinone 3 was first prepared by Elbs[25a] and later by Gabriel and Coleman,[25b] Graebe,[25c] and Heller and Schulke.[25d] In the preparation of this compound, a maximum yield of 80 percent was obtained and a satisfactory purity was achieved only by recrystallizations involving a considerable loss in yield. Later Groggins and Newton[38] developed a modified process for the preparation of 2 and 3, which gave high purity and increased yields.

CHAPTER II

RESULTS AND DISCUSSION

The following scheme was used in our synthesis of 1.



[a] $AlCl_3$, o-dichlorobenzene. [b] PPA, Δ; or H_2SO_4 + H_3BO_3, Δ; or liq. HF.
[c] $Al[-O-C_6H_{11}]_3$, $C_6H_{11}OH$.

Napthalene and phthalic anhydride in equimolecular proportions

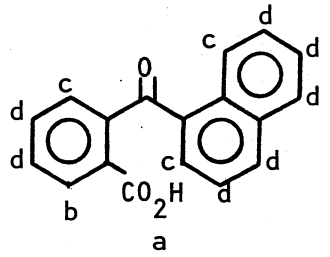
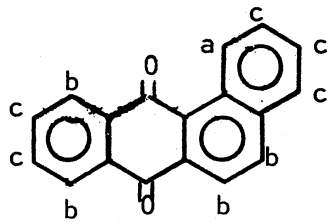
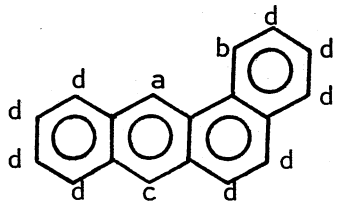
were condensed in the presence of aluminum chloride to give a 90 percent yield of 2-(1-naphthoyl)benzoic acid (2). o-Dichlorobenzene was used as solvent since it has been reported to aid in the selectivity of attack at the α-position.[38] Also o-dichlorobenzene does not condense with phthalic anhydride in the presence of aluminum chloride. A 10 percent excess of aluminum chloride relative to phthalic anhydride was found to be most suitable for the preparation of 2. The structure of 2 was verified by ir, mass, and pmr spectra. Proton magnetic resonance spectral data are given in Table I.

Once compound 2 was purified, methods of cyclization to 1,2-benzanthraquinone (3) were investigated. Different reagents (HF, H_2SO_4 and polyphosphoric acid) were tested in the ring-closure of 2 to 3. In the first attempt at cyclization, 95 percent sulfuric acid[38] was used and boric acid was added to inhibit sulfonation. The yield of 3 was only 54 percent and not 94 percent as claimed.[38] Considerable tarry material was obtained in the process. Moreover, it was very difficult to separate the product from the reaction mixture. Liquid HF was also used for cyclizing 2 to 3, but only a 15 - 20 percent yield was obtained. Snyder and Werber[39] used PPA for the cyclization of 2 to 3 and reported a 44 percent yield of recrystallized product. We also used PPA and obtained a 98 percent yield of crude 3.

1,2-Benzanthraquinone (3) was reduced and simultaneously aromatized to 1 using the Meerwein-Pondorff-Verley reaction. For this reaction aluminum tricyclohexoxide[40] was prepared by boiling pure aluminum turnings and dry cyclohexanol at its reflux temperature under a nitrogen atmosphere. Steam distillation was effective in removing cyclohexanol completely from the reaction mixture after reduction.

TABLE I

PROTON MAGNETIC RESONANCE SPECTRAL DATA OF 1, 2, AND 3

Compound	Number	Chemical Shifts (δ) and Assignments
	2	[a] 9.95(S, 1H, Ar-COOH) [b] 8.9 (d, 1H, Ar-H) [c] 7.9 (m, 3H, Ar-H) [d] 7.1-7.7 (m, 5, Ar-H)
	3	[a] 9.65 (d, 1, Ar-H) [b] 8.35-8 (m, 4, Ar-H) [c] 7.9-7.45 (m, 5, Ar-H)
	1	[a] 9.15 (S, 1, Ar-H)* [b] 8.8 (m, 1, Ar-H)* [c] 8.3 (S, 1, Ar-H)* [d] 7.9-7.4 (m, 9, Ar-H)*

*Sadtler Standard Spectra, 6018M, Sadtler Research Laboratories, Philadelphia, Pa.

Once 1 was prepared, different methods of purification were tried. The crude product was recrystallized from a mixture of glacial acetic acid and ethanol. It was then passed through neutral alumina in a Soxhlet apparatus in solution in isohexane to remove yellow color. The picrate of 1 was prepared and recrystallized from ethanol. The red-colored picric acid complex was decomposed by extraction through basic alumina in a Soxhlet apparatus. This yielded white crystals of 1. The ir and pmr spectra of 1 were compared with the standard Sadtler[42] spectral data. Spectra of this compound 1 are shown in the Appendix. Data from the proton magnetic resonance spectra of 1, 2, and 3 are given in Table I.

CHAPTER III

EXPERIMENTAL

Preparation of 2-(1-Naphthoyl)benzoic acid (2): 2-(1-naphthoyl)-benzoic acid was prepared according to the method of Groggins and Newton.[38] A 12-l. fluted flask was equipped with a mechanical stirrer, thermocouple, and nitrogen inlet. An 18-in. Vigreux column was also connected to the flask. This Vigreux column was fitted with a bubble trap containing benzene so that nitrogen flow could be observed. It also served as outlet for HCl gas. Naphthalene (833 g, 6.2 mol + 5% excess), 918 g (6.2mol) of sublimed phthalic anhydride, and 2500 ml of distilled o-dichlorobenzene were added to the flask. The exterior of the flask was warmed with a heat gun to dissolve the solid component of the mixture. The temperature of the reaction mixture was maintained at 0° throughout the reaction. Anhydrous aluminum chloride (1815 g, 13 mol + 10% excess) was gradually added to the flask over a period of three hours, with constant stirring. The reaction was run for another two hours, when the evolution of HCl gas had ceased. The product, a black tarry material, was poured onto ice (10 kg) and 10% HCl was added to solubilize the complex of aluminum salts. The mixture was transferred to a 22-l. two-necked flask and kept overnight. Steam was passed through the solution and 97% of the total o-dichloro-benzene (2415 ml) was recovered. The remaining solid was separated

from water and treated with 10% HCl five times and then washed three times with water. The hard mass was blended twice with water in a Waring blender whereupon a yellow powder was obtained. This powder was again washed with 12 l. of water, filtered out, and then partially dried under vacuum. The crude product was dissolved in 8 l. of toluene and 440 ml of water was removed by azeotropic distillation. The solid product which formed after cooling and washing four times with toluene, was filtered out and recrystallized from toluene to give 1540 g, mp 133-168°, (90% yield). After several recrystallizations from boiling toluene, a white powder was obtained. This showed mp 174-75° (lit.[38] 170-72°); ir spectrum (KBr) 3000, 2300, 1670, 1400, 1270, 908, 810, 775, 745, 685, 655 cm^{-1}; mass spectrum (70 eV.) m/e (rel. intensity) 276 (M^+, 41), 232(63), 231(38), 155(100), 127(76), 9(48); pmr spectrum ($DCCl_3$,100 MHz) δ 9.95(S, 1, Ar-COOH), 8.9 (d,1,Aromatic-H), 7.9(m,1,Ar-H), 7.1-7.7 (m,7,Ar-H).

Cyclization of 2-(1-Naphthoyl)benzoic acid (2): A three-necked 1-l. flask was equipped with a mechanical stirrer, thermometer, and heating mantle contained in a stainless steel bowl. PPA (240 g,115%) was heated to 90° and stirred continuously. A 25 g sample of 2 was added to the hot PPA gradually over a period of two hours and the temperature was maintained at 90°. The reaction mixture became pink at the beginning and gradually darkened. The reaction mixture eventually became black when all of the 2 was added. Heating was continued at 110° for another three hours. The flask was cooled to room temperature and the contents were poured onto ice water. The black product mixture was then stirred magnetically for an hour and

filtered. The residue, a greenish black solid, was washed with 250 ml of saturated sodium carbonate solution and then with 250 ml of water and then dried to a greenish solid. The crude product weighed 23 g (98%) and melted at 130-50°. This crude 3 was distilled in a Kugelrohr apparatus to give a yellow solid, mp 162-163°. Two recrystallizations from acetic acid gave golden-yellow 3, mp 167-69° (lit.[38] 169°); ir spectrum (KBr) 2300, 1650, 1565, 1450, 1370, 1300, 1270, 1160, 845, 765, 755, 708 $cm.^{-1}$; mass spectrum (70 eV.) m/e (rel. intensity) 258 (M^+,100), 230(33), 228(28), 202(48), 200(28), and 101(26); pmr spectrum ($DCCl_3$,100 MHz), δ 9.65 (d,1,Ar-H) 8.35-8.0 (m,4,Ar-H), 7.9-7.45 (m,5,Ar-H).

Reduction of 1,2-benzanthraquinone (3): 1,2-Benzanthraquinone (3) was reduced and aromatized using the Meerwein-Pondorff-Verley reaction.

Preparation of aluminum tricyclohexoxide:[40] A 2-l. three-necked fluted flask was fitted with a reflux condenser, mechanical stirrer, and heating mantle contained in a stainless steel bowl. Aluminum turnings (20 g), 400 ml of cyclohexanol distilled from calcium oxide, a trace of mercuric chloride, and two ml of carbon tetrachloride dried over $MgSO_4$ were mixed together with constant stirring. The mixture was refluxed (168°) for 24 hours under a nitrogen atmosphere, by which time all the aluminum had reacted, leaving a light gray precipitate in a clear solution which was used without further treatment. At the beginning of the reaction, considerable hydrogen gas was evolved and this was vented through the condenser.

A 40 g sample of 3 and 200 ml of dry cyclohexanol were added to the flask containing aluminum tricyclohexoxide. The reaction mixture was again refluxed for another 48 hours under a nitrogen

atmosphere, cooled, and poured onto cold water. Sufficient benzene (400 ml) was added to give a clear upper layer. The mixture was then stirred for two hours and acidified with 10% HCl to decompose the complex of aluminum salts. The suspension was filtered and the residue was extracted with benzene (100 ml). The combined yellow extracts, on steam distillation, afforded a yellow residual solid. The crude product was gummy and contained cyclohexanol. This appeared to be the sole product, but it was not easy to separate it quantitatively from cyclohexanol. The gummy yellow solid was then recrystallized thrice from a mixture of glacial acetic acid and ethanol to give 28 g (80%) of light yellow silky crystals, melting at 153-55° (lit.[41] 158-59°, colorless plates); ir spectrum (KBr), 2300, 950, 895, 880, 810, 780, 745, 685 $cm.^{-1}$; mass spectrum (70 eV.) m/e (rel. intensity) 228,(M^+ 100), 227(6), 226(20), 114(15), 113(3), and 100(10); pmr spectrum ($DCCl_3$, 100 MHz) δ 9.15 (S,1,Ar-H), 8.88 (m,1,Ar-H), 8.3 (S,1,Ar-H), 7.9-7.4 (m,9,Ar-H).

Purification of Benz[a]anthracene (1): Benz[a]anthracene (1) was further purified through its picrate. Picric acid (98 g) was first filtered into a 2-l. flask through Dicalite in a Soxhlet apparatus employing ethanol as a solvent. A 65 g sample of recrystallized 1 was added to the same Soxhlet and then extracted into the picric acid solution. Cooling caused deposition of red crystals of picrate. The picrate was then filtered out (120 g) and recrystallized twice from ethanol with the Soxhlet apparatus. The pure picrate was then dried under vacuum to give 108 g, melting at 140-142° (lit.[41] 141.5-142.5°). The red picrate was decomposed by extracting in a Soxhlet apparatus containing 300 g of basic alumina

with 1.5 l. of petroleum ether (bp 60-68°). A CO_2 atmosphere was maintained. The extraction was complete in 48 hours. On cooling, colorless crystals of 1, melting at 158.5-159.5° (lit.[41] 158-59°) were obtained.

PART II

FRIEDEL-CRAFTS REACTION APPLIED TO AROMATIC ETHERS AND CROTONIC ACID

CHAPTER IV

INTRODUCTION AND HISTORICAL

The Friedel-Crafts reaction is commonly considered to be a process of uniting two or more organic molecules through the formation of carbon-carbon bonds under the influence of strongly acidic metal halide catalysts such as aluminum chloride, boron trifluoride, ferric chloride and zinc chloride. Currently we consider Friedel-Crafts reactions to be any substitution, isomerization, elimination, addition, cracking, or polymerization taking place under the catalytic influence of Lewis acids (with or without co-catalyst) including proton acids. It is also unnecessary to limit the scope of Friedel-Crafts reaction to the formation of carbon-carbon bonds. The formation of carbon-oxygen, carbon-nitrogen, carbon-sulfur, carbon-halogen, carbon-phosphorous, carbon-boron, and carbon-deuterium bonds, all conform to the general Friedel-Crafts principle. The Friedel-Crafts and similar reactions all proceed through an electrophilic substitution mechanism.

Numerous Friedel-Crafts reactions have proven to be useful. 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.[43] He observed the formation of diphenylmethane and hydrogen chloride

during an 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 silver chloride. 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 products.

During an attempted synthesis of benzil, 'dibenzoyl', from benzoyl chloride in benzene, once again using silver to absorb the displaced chlorine, Zincke observed the formation of benzophenone.[44] 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 considerable potential.

Charles Friedel and James Crafts reinvestigated Zincke's work and found that the reactions were catalyzed by metal halides rather than metals.[45]

Since the Friedel-Crafts reaction covers a broad area of chemistry, as borne out by Olah's 5200-page treatise,[46] 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.

The Friedel-Crafts alkylation of aromatic rings involves the formation of Ar-C bonds via electrophilic attack of an alkyl action or at least at a highly polarized bond. Important alkylating agents are alkyl halides, olefins, and alcohols. The reactivity of alkyl halides is in the decreasing order: fluoride, chloride, bromide, and iodide. This order was determined by the reaction of the mixed dihalide (25) with benzene and BF_3 as shown below.[47]

$$C_6H_6 + \underset{\underline{25}}{FCH_2CH_2CH_2Cl} \longrightarrow \underset{\underline{26}}{C_6H_5CH_2CH_2CH_2Cl} + HF$$

Olefins are good alkylating agents, different only in that the overall reaction is an addition of Ar-H to a carbon-carbon double bond. Furthermore, alkylation will not occur with only a Lewis acid catalyst; a proton-donating co-catalyst is required.[48] Alcohols are more reactive than the alkyl halides towards Lewis acid catalysts. Proton acids, especially sulfuric acid, are often used rather than Lewis acids to cause alkylation via dehydration to generate an alkylcarbonium ion.[49]

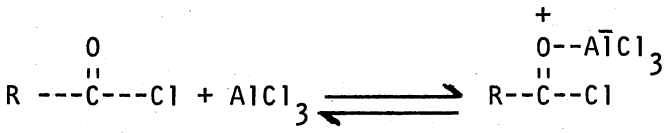
Aluminum chloride is the most commonly used catalyst, but many other Lewis acids have been used, as have many strong proton acids, particularly HF, H_2SO_4, and polyphosphoric acid. The more commonly used Lewis acids have been arranged in decreasing order of overall activity: $AlBr_3$, $AlCl_3$, $GaCl_3$, $FeCl_3$, $SbCl_5$, $ZrCl_4$, BCl_3, BF_3, and $SbCl_3$.[50]

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 does the substrate undergo multiple substitution as may be the case with alkylation. Acylation followed by a reduction of the ketone (27) is used frequently to prepare alkylbenzenes (28).

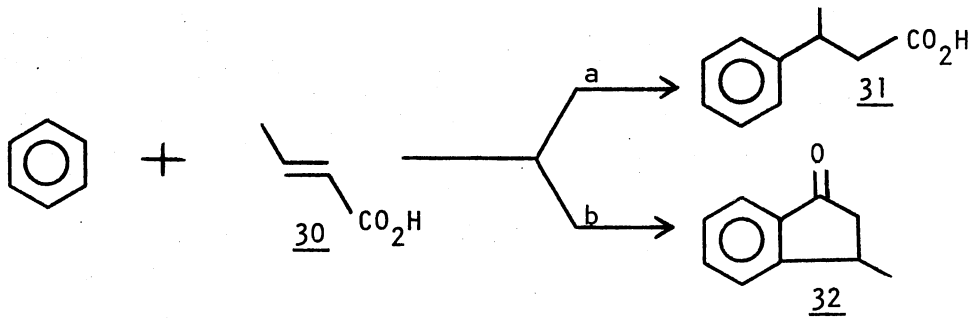
$$C_6H_6 + \underset{\underline{29}}{CH_3CH_2COCl} \longrightarrow \underset{\underline{27}}{C_6H_5COCH_2CH_3} \longrightarrow \underset{\underline{28}}{C_6H_5(CH_2)_2CH_3}$$

Acylation can be carried out with compounds containing almost any function which will lead to an acylium ion upon reaction with a

Lewis acid. Acyl halides, carboxylic acids, anhydrides, ketenes and esters have all been used as acylating agents.[51] The order of reactivity of acyl halides in acylation was found to be in decreasing order: I, Br, Cl, and F.[52] This order is opposite to that observed for the alkyl halides.[47] 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.

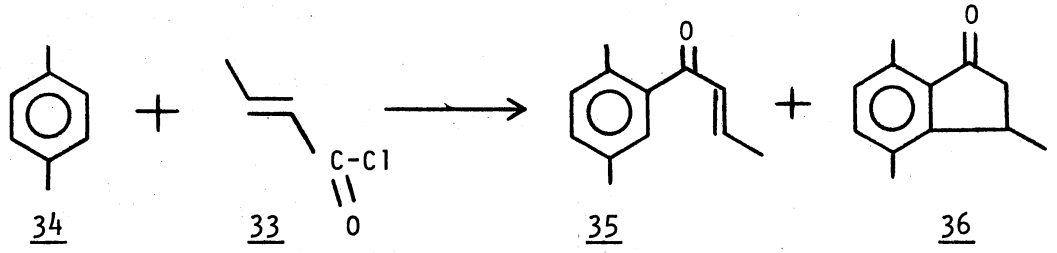


In 1909, it was reported that crotonic acid (30) reacted with one mole of aluminum chloride in benzene to give 3-phenylbutanoic acid (31).[53a] It was shown in 1943 that the use of three moles of $AlCl_3$ caused the further condensation of crotonic acid and benzene to 3-methylindanone (32).[53a]



$^{a}AlCl_3$(1 mol). $^{b}AlCl_3$(3 mol).

There are numerous examples showing that crotonyl chloride (33) 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 products.[56] Some pertinent examples have been included in Table II. The reaction of crotonyl chloride (33) with p-xylene (34) in the presence of aluminum chloride was found to give the products shown below.[57] In this case, acylation (35) appears to be the predominant reaction but is followed by cyclialkylation (36).



34 33 35 36

The reaction of crotonyl chloride (33) with p-methylanisole (37) 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 percent of the indanone (38) and 24 percent of the chromanone (39) as shown in the reaction scheme below.[58]

TABLE II

SELECTED FRIEDEL-CRAFTS REACTIONS OF UNSATURATED ACIDS AND ACID CHLORIDES

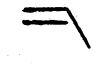
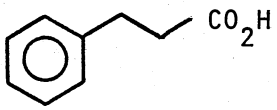
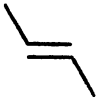
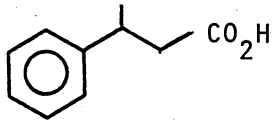
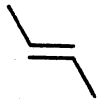
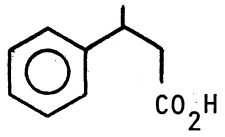
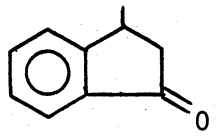
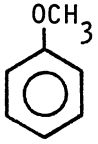
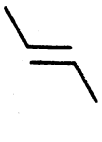
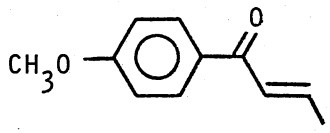
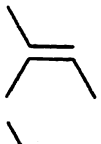
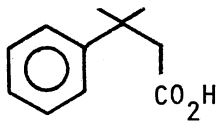
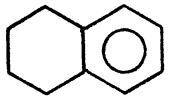
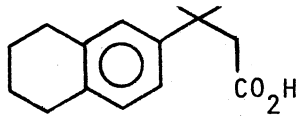
Substrate	Acyl Component	Catalyst	Percent Yield	Product(s)	Reference
		$AlCl_3$	--		53b
		$AlCl_3$	--		53a
		$AlCl_3$	63	 	53c
		PPA	80		53d
		$AlCl_3$	38		54a
		$AlCl_3$	70		54b

TABLE II (continued)

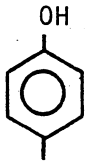
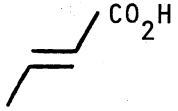
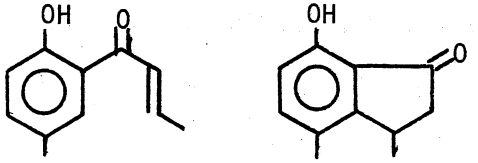
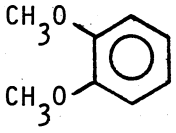
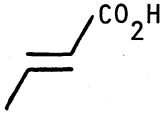
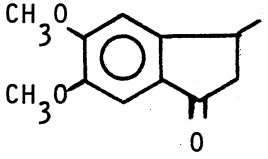
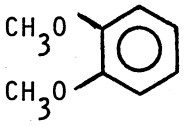
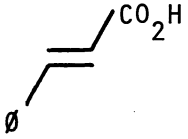
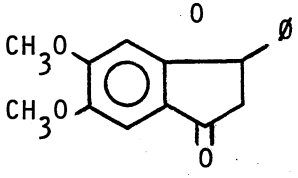
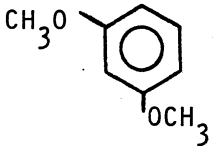
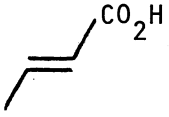
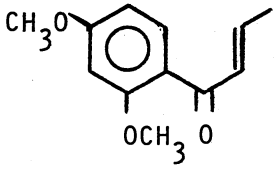
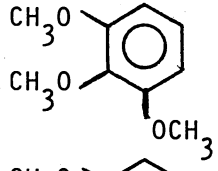
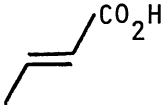
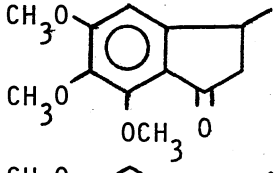
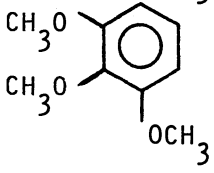
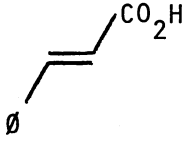
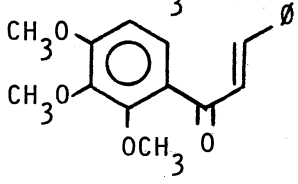
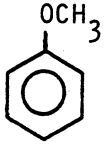
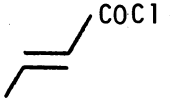
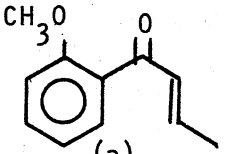
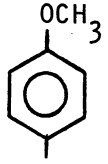
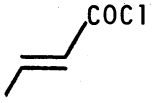
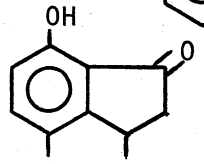
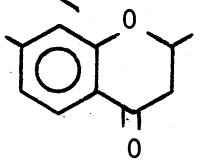
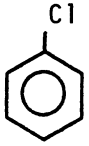
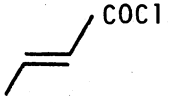
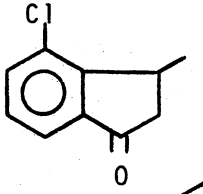
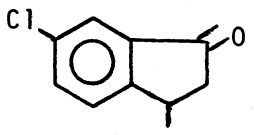
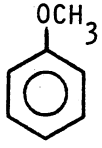
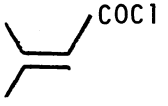
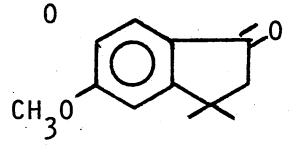
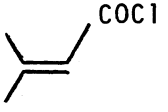
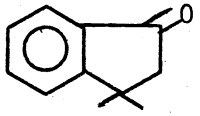
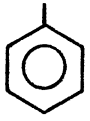
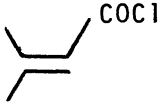
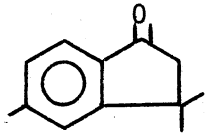
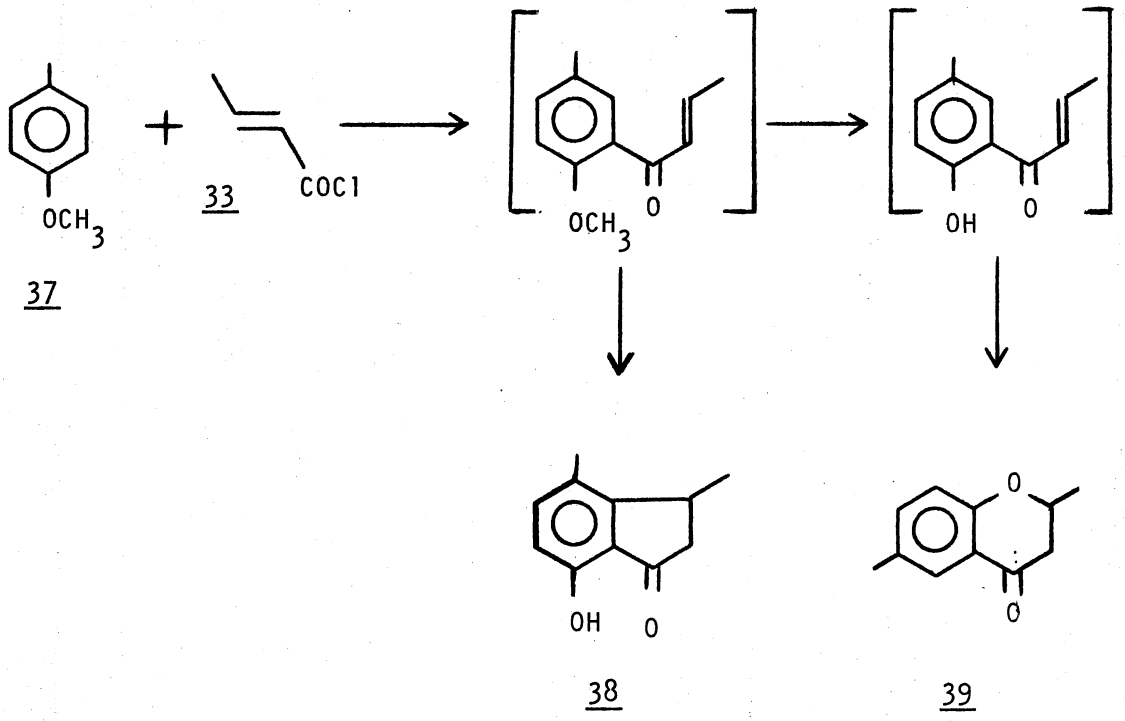
Substrate	Acyl Component	Catalyst	Percent Yield	Product(s)	Reference
		$AlCl_3$	96		61
		PPA	74		55
		PPA	76		55
		PPA	52		55
		PPA	11		55
		PPA	62		55

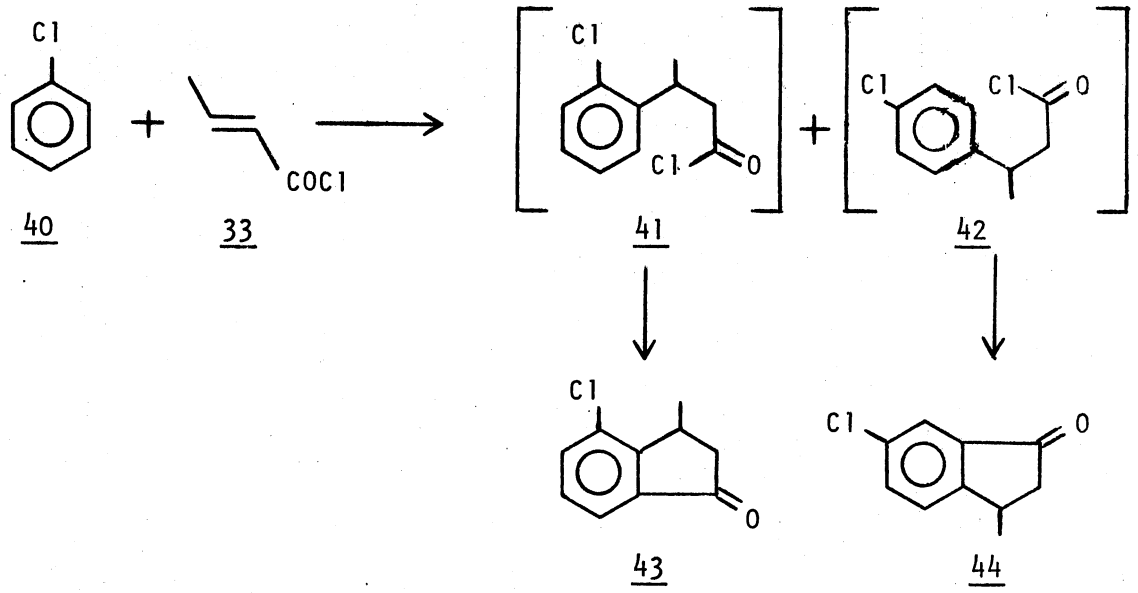
TABLE II (continued)

Substrate	Acyl Component	Catalyst	Percent Yield	Product(s)	Reference
		$AlCl_3$	48		58
		$AlCl_3$	(a)24 (b)19	(b)  (a) 	58
		$AlCl_3$	--	 	59
		$AlCl_3$	--		60
		$AlCl_3$	40		60
		$AlCl_3$	80		60



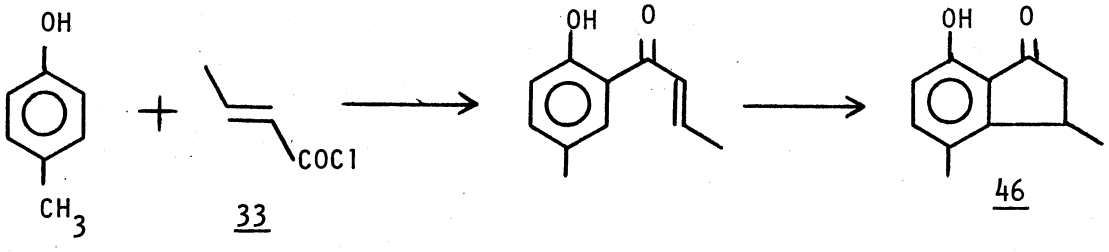
37 33 38 39

All the data presented thus far indicate that the acyl attack predominates over alkyl attack in reactions of the bifunctional crotonic acid (30). However, experiments carried out with crotonyl chloride (33) in chlorobenzene (40) in the presence of $AlCl_3$ gave the products shown below, apparently via alkylation (41, 42) followed by cycliacylation (43, 44).[59] This seems in conflict with the examples previously presented.



40 33 41 42 43 44

The reaction of p-cresol (45) and crotonic acid (30) in the presence of aluminum chloride was found to produce a major product shown to be 3,4-dimethyl-7-hydroxyindanone (46) by independent synthesis.[61] Optimum conditions were attained through the use of o-dichlorobenzene solvent and two molecules of aluminum chloride.



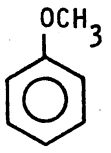
45 33 46

In this work, interest is centered upon the potential of crotonic acid as a bifunctional reagent in 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 are shown in Table II.

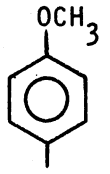
CHAPTER V

RESULTS AND DISCUSSION

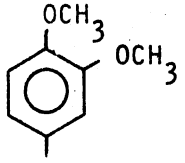
Polyphosphoric acid-catalyzed condensations of crotonic acid (30) with each of the following aromatic ethers were carried out in the presence of excess PPA (generally ten times by weight of the substrates) at 64-65°.



47

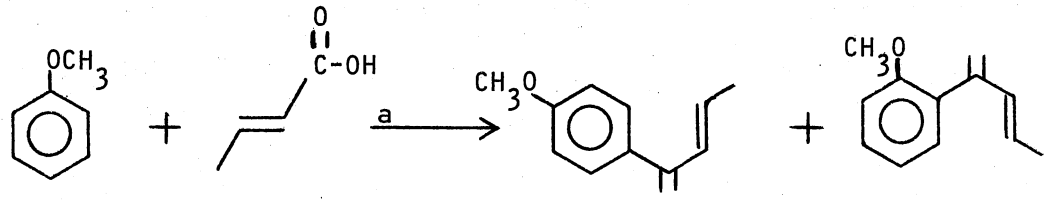


37

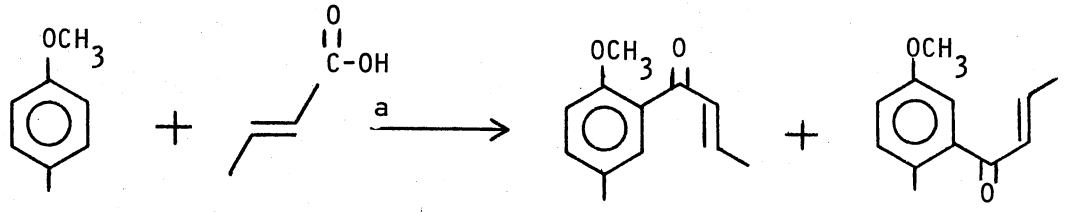


48

In each case, α,β-unsaturated ketones were the major products. Ethers 47 and 37 yield product mixtures because of ortho and para orientation. The ratios of these products were determined by glc analysis. These ratios are as shown except that in each case a third and smaller peak was observed (2-3%). Since the reaction products from 37 and 47 are liquid, the separation of each compound from the mixture was not attempted. It is to be expected that the electron-releasing methoxyl group would control the substitution in each case and that the acylation would probably take place predominantly at the para position in 47 becuase of steric effect. Therefore, the ketone 49 is probably the major product (92%). For ether 37 the para position is blocked by a methyl group and the presence of methoxyl group would cause substitution at the ortho position (meta to methyl group). Thus ketone 51 is probably the major product (94%).



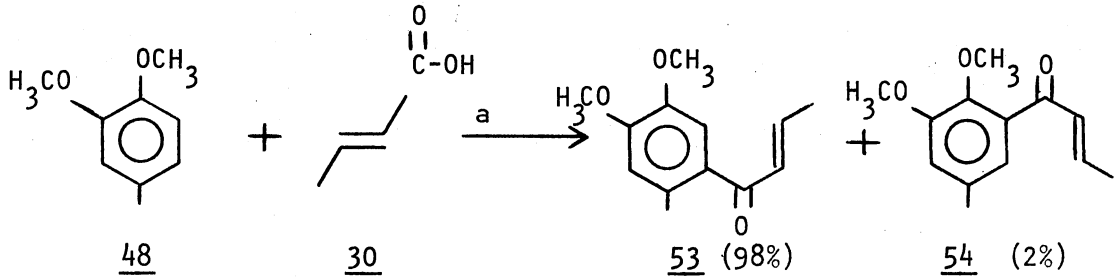
47 30 49 (92%) 50 (5%)



37 30 51 (94%) 52 (4%)

[a]PPA, 64°, Δ.

Considerable selectivity is obtained in the condensation involving ether 48 as shown below. Ketone 53 is the expected major product and 54 is the best choice for the minor product. Attack at the alternate position is sterically unfavorable.

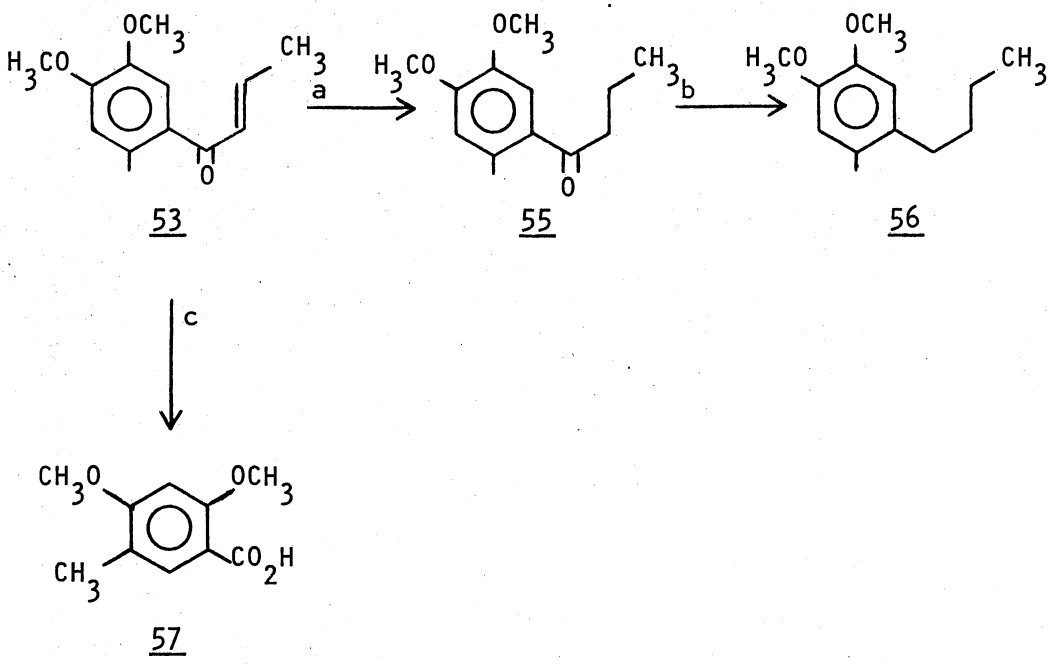


48 30 53 (98%) 54 (2%)

[a]PPA. 64°, Δ.

The crude product mixture from 48 is solid and the major isomer was successfully separated from the mixture by fractional crystallization from isohexane. The mother liquor was distilled to give a yellow liquid which failed to crystalize. It contains some 53, 54, and minor impurities.

The structure of 53 was established by the oxidation and reduction studies shown in the scheme below.



53 55 56 57

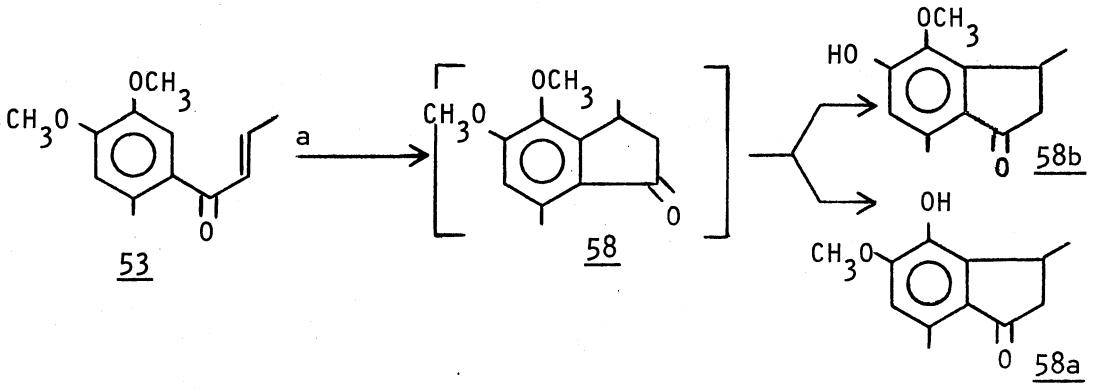
[a] H_2, Pd/C. [b] H_2NNH_2, OH^-, diethylene glycol. [c] $KMnO_4$

Compound 53 was hydrogenated in the presence of Pd/C to give 55. During this reduction the carbonyl group of 53 was also partially converted to a hydroxyl group. The hydroxyl was oxidized to 55 with

Jones reagent.[62] The progress of this oxidation treatment was readily followed by glc studies and it was continued until a single peak for 55 was observed. The near symmetry of 55 causes the expected pair of singlets in the aromatic proton region for p-hydrogens as shown in the Appendix. The spectral data are given in Table III. Wolff-Kishner reduction of 55 yielded the ether 56. As expected the pmr spectrum of the aromatic proton region changed since the two aromatic protons of 56 now experienced similar environments. Instead of a pair of singlets as seen in the spectrum of 55, a single peak at δ 6.5 is observed for 56.

The $KMnO_4$ oxidation of 53 in the presence of "dicocodimethylammonium chloride" catalyst gave 4,5-dimethoxy-2-methylbenzoic acid.[63] This molecule gives a pair of singlets similar to those found in the spectrum of 55. The spectral data for 57 are given in Table III.

Once compound 53 was identified, methods of cyclization to 4,5-dimethoxy-3,7-dimethyl-1-indanone (58) were sought. Different reagents (HF, PPA at 90° and Amberlyst-15) were tested for their ability to cause ring closure of 53 to 58, but only Amberlyst-15[64] proved to be an effective reagent in the cyclization.



53 58

[a]Amberlyst-15, xylene, 132°, Δ.

TABLE III

PROTON MAGNETIC RESONANCE SPECTRAL DATA

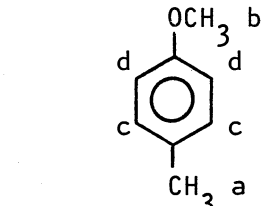
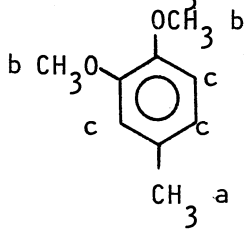
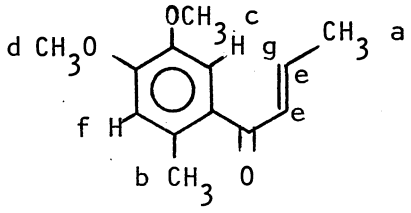
Compound	Number	Chemical Shifts (δ) and Assignments
	37	[a] 2.15 (s,3, Ar-CH_3) [b] 3.50 (s,3, Ar-OCH_3) [c] 6.70 (d,2, Ar-H) [d] 6.95 (d,2, Ar-H)
	48	[a] 2.20 (s,3, Ar-CH_3) [b] 3.65 (s,6, Ar-OCH_3)* [c] 6.60 (m,3, Ar-H)**
	53	[a] 1.9 (d,3, C-CH_3) [b] 3.4 (s,3, Ar-CH_3) [c] 3.85 (s,3, Ar-OCH_3) [d] 3.92 (s,3, Ar-OCH_3) [e] 6.55-6.80 (m,2,-CO-CH=CH-) [f] 6.7 (s,1, Ar-H) [g] 7.0 (s,1, Ar-H)

TABLE III (continued)

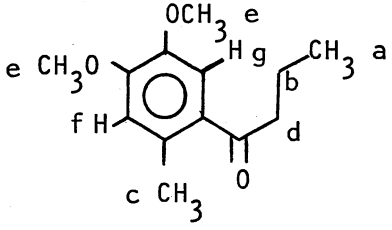
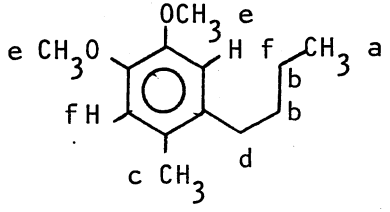
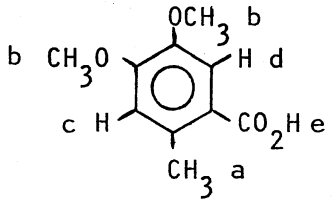
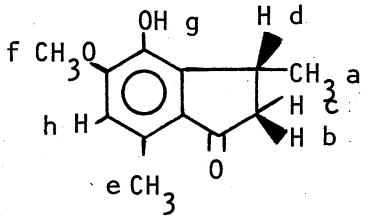
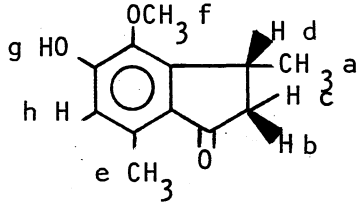
Compound	Number	Chemical Shifts (δ) and Assignments
	55	[a] 1.0 (t,3, C-CH_3) [b] 1.7 (m, 2, C-CH_2-C) [c] 2.5 (s,3, Ar-CH_3) [d] 2.8 (t,2,-CO-CH_2-C) [e] 3.9 (s,6, Ar-OCH_3)* [f] 6.7 (s,1, Ar-H) [g] 7.2 (s,1, Ar-H)
	56	[a] 0.95 (t,3, C-CH_3) [b] 1.2-1.6 (m,4,-C-CH_2-CH_2-C) [c] 2.2 (s,3, Ar-CH_3) [d] 2.5 (t,3, Ar-CH_2-C) [e] 3.8 (s,6, Ar-OCH_3)* [f] 6.5 (s,2, Ar-H)
	57	[a] 2.6 (s,3, Ar-CH_3) [b] 3.9 (d,6, Ar-OCH_3) [c] 6.7 (s,1, Ar-H) [d] 7.65 (s,1, Ar-H) [e] 11.60 (s,1, Ar-COOH)

TABLE III (continued)

Compound	Number	Chemical Shifts (δ) and Assignments
	58a	[a] 1.35 (d,3, C-CH_3) [b] 2.22 (q, 1, CO-CH-C)+ [c] 2.85 (q,1, CO-CH-C)+ [d] 3.50 (m,1, C-CH-C)+ [e] 2.55 (s,3, Ar-CH_3)+ [f] 3.9 (s,3, ArOCH_3) [g] 5.65 (s,1, Ar-OH) [h] 6.95 (s,1, Ar-H)
	58b	

*Unresolved pair of singlets
**Unresolved multiplet
+SADTLER Standard spectra, 3109M, Sadtler Research Laboratories, Philadelphia, PA.

Different solvents (benzene, toluene, xylene, and chlorobenzene) were used at their reflux temperatures. Only xylene and chlorobenzene were effective solvents in the cyclization process. In both cases, nearly 50 percent yield of cyclized product 58 was obtained. One of the methyl groups of 58 was lost during the cyclization with A-15 and the position of the cleavage was not determined. A considerable amount of tarry material was obtained during the cyclization process; this tar may be polymerized 53. A 100-ml portion of the solvent proved suitable for cyclization of 1 g of 53 to 58 in the presence of 1 g of A-15. Reduction of the solvent volume to 10 ml caused essentially complete conversion to polymer.

CHAPTER VI

EXPERIMENTAL

Preparation of p-cresyl methyl ether (37):[64] To a 5-l. three-necked fluted flask, fitted with an efficient stirrer, a dropping funnel, and a reflux condenser, a mixture of p-cresol (45) (203 g, 1.88 mol), sodium hydroxide (100 g, 2.5 mol) and 1 l. water were added. The mixture was cooled below 10° in an ice bath. Dimethyl sulfate (315 g, 2.5 mol) was added slowly to the flask over a period of one hour through the dropping funnel and the mixture was then heated for 30 minutes. A mixture of p-cresol (203 g, 1.88 mol) and sodium hydroxide (100 g, 2.5 mol) in 1 l. water was then added during 15 minutes. The reaction mixture was heated at reflux for 16 hours with continuous stirring and then allowed to cool overnight. The product layer (top) was separated and the aqueous layer was extracted with 300 ml of benzene. The combined extracts were washed twice with water (2X500 ml), dried ($MgSO_4$), filtered and distilled. The fraction distilling between 100-174° was redistilled to give 350 g (76%) of p-cresyl methyl ether, bp 173-74°; pmr spectrum ($DCCl_3$, 100 MHz) δ 2.15 (s,3,Ar-CH_3), 3.50 (s,3,Ar-OCH_3), 6.95 (d,2,Ar-H), 6.70 (d,2,Ar-H).

Preparation of 3,4-dimethoxytoluene (48):[64] The preceding procedure was used. Dimethyl sulfate (504 g, 4 mol) was added to a mixture of sodium hydroxide (320 g, 8 mol) and 4-methylcatechol (497 g, 4 mol) in 2.5 l. of water at 10° and then heated at reflux for

17 hours. The product was worked up as above to give 442 g (72%) of 3,4-dimethoxytoluene (48), bp 220-222°, pmr spectrum ($DCCl_3$, 100 MHz) δ 2.20 (s,3,Ar-CH_3), 3.65 (s,6,Ar-OCH_3), 6.60 (m,3,Ar-H).

Preparation of p-methoxycrotonophenone (49):[53d] Anisole (47) (21.6 g, 0.2 mol) and crotonic acid (30) (17 g, 0.2 mol) were added all at once to 210 g of PPA. The mixture was vigorously stirred with a mechanical stirrer and heated at 65° for 1.5 hours. The deep-red mixture was cooled and poured onto ice water (2 l.). The black tarry product mixture was stirred for 4 hours and then extracted with ether. The red extract was washed with saturated sodium carbonate solution and then with water. After drying ($MgSO_4$) the extract was distilled to give 23.3 g (63%) of light yellow oil. The product was shown by glc to be a mixture of three components. The p-isomer is probably the major isomer (92%); ir spectrum (thin film) 2900, 2000, 1650, 1600, 1500, 1440, 1300, 1170, 1110, 1020, 960, 920, 810 cm^{-1}; pmr spectrum ($DCCl_3$, 100 MHz) δ 1.85 (d,3,C-CH_3), 3.7 (s,3,Ar-OCH_3) 6.85 (d,2,Ar-H), 6.95 (d,2,Ar-H), 7.9 (m,2,-CH=CH-).

Preparation of 2-methoxy-5-methylcrotonophenone (51):
A mixture of p-methylanisole (37) (24.2 g, 0.2 mol) and crotonic acid (30) (17 g, 0.2 mol) was added to PPA (229 g). After stirring and heating at 64° for three hours, the black complex salt of PPA was decomposed as above. The product was extracted with ether and washed with sodium carbonate solution and water. The solvent was removed and the residue was fractionated to afford 20 g (53%) of yellow liquid. The product was a mixture of isomers as evidenced from glc analysis; the major isomer was 94% of the total mixture; ir spectrum (thin film): 2950, 1670, 1625, 1500, 1290, 1250, 1175, 1030, 815 cm^{-1} and pmr spectrum ($DCCl_3$, 100 MHz) δ 1.85 (d,3, C-CH_3),

2.2 (s,3,Ar-CH_3), 3.7 (s,3,Ar-OCH_3), 6.6-7 (m,3,Ar-H), 7.10-7.35 (m,-CO-CH=CH-).

Preparation of 3,4-dimethoxy-6-methylcrotonophenone (53): A mixture of 3,4-dimethoxytoluene (152 g, 1 mol) and crotonic acid (30) (86 g, 1 mol) was added all at one time to 2400 g of PPA. The temperature was maintained at 64° in a hot water bath and then heated for two hours with constant stirring. The black tarry product was worked up as above. The solvent was removed to give 160 g (73%) of brown solid. The crude mixture was shown by glc analysis to be composed of two products. 3,4-Dimethoxy-6-methylcrotonophenone was found to be the major isomer (98%) present. The crude product was blended with isohexane in a Waring blender, filtered, dried ($MgSO_4$), and finally distilled to give a pale yellow solid. After two crystallizations from boiling isohexane, the product formed white crystals of 53, mp 61-62°; ir (KBr) spectrum, 3330, 2925, 1650, 1600, 1430, 1260, 1200, 1150, 970, 910, 865, 780 $cm.^{-1}$; pmr spectrum ($DCCl_3$, 100 MHz) δ 1.9 (d,3, C-CH_3), 3.4 (s,3,Ar-CH_3), 3.85 (s,3,Ar-OCH_3) 3.92 (s,3,Ar-OCH_3), 6.55-6.80 (m,2,-CO-CH-CH-), 6.7 (s,1,Ar-H), 7.0 (s,1, Ar-H), mass spectrum (70eV) m/e (rel. intensity) 220(M^+, 39), 205(100), 206(16), 179(46), 174(12), 151(13), 121(13), 93(21), 61(20), 51(16), 41(33), 39(50) and 15(52).

Analysis: Calculated for $C_{13}H_{16}O_3$: 70.89%; H, 7.32%.
Found: C, 70.79%; H, 7.24%.

The red 2,4-dinitrophenylhydrazone (mp 217-220°) was prepared and recrystallized from ethanol.

The solvent was removed from the mother liquor and the brown liquid was distilled to give a yellow oil.

Hydrogenation of 3,4-dimethoxy-6-methylcrotonophenone (53): A 10 g sample of 3,4-dimethoxy-6-methylcrotonophenone in 250 ml of 95% ethanol containing 0.5 g of Pd/C was added to a stainless steel flask by introducing hydrogen gas and evacuating the flask with a vacuum pump. The pressure of hydrogen was kept at 30 pounds (approximately 2 atm. pressure) and the hydrogenation was continued for 2.5 hours at room temperature. A hydrogen atmosphere was maintained in the flask overnight. The black mixture was filtered through a bed of Dicalite to remove charcoal. The solvent was removed and distillation of resulting liquid gave 10 g (99%) of crude product. The carbonyl group of the crotonophenone (53) was partially reduced to the hydroxyl group as evidenced by glc trace and ir spectrum. The crude mixture was oxidized to 3,4-dimethoxy-6-methylbutryophenone (55) with Jones reagent[62] to remove alcohol impurity. Three crystallications from isohexane gave white crystals of 55, mp 53.5-54.5°; ir (KBr) spectrum, 2900, 1675, 1600, 1560, 1460, 1370, 1265, 1200, 1140, 1100, 1000, 895, 855, 760 $cm.^{-1}$, pmr spectrum ($DCCl_3$, 100 MHz) δ 1.0 (t,3, $C-CH_3$), 1.7 (m,2,$C-CH_2-C$), 2.5 (s,3,$Ar-CH_3$), 2.8 (t,2,$CO-CH_2-C$), 3.9 (s,6,$Ar-OCH_3$), 6.7 (s,1,Ar-H), 7.2 (s,1,Ar-H), mass spectrum (70eV.) m/e (rel. intensity), 222(M^+, 18), 180(11), 179(100), 151(11), 136(7), 93(8), 27(8), 18(19), 15(9).

Analysis: Calculated for $C_{13}H_{18}O_3$: C, 70.24%; H, 8.16%.
Found: C, 70.27%; H, 8.23%.

Wolf-Kishner Reduction of 3,4-dimethoxybutyrophenone (55): A 2.2 g sample of 55 (0.01 mol), 1 g KOH, 10 g of 85% hydrazine hydrate, and 100 g of diethylene glycol were added to a stainless steel flask, fitted with a Dean-Stark trap and a reflux condenser. The mixture was heated

for 3.5 hours under a nitrogen atmosphere. The product mixture was cooled, diluted with 500 ml of water and then extracted with 2 X 200 ml of ether. The ether extract was dried ($MgSO_4$), concentrated, and distilled to give 0.6 g of 2-butyl-4,5-dimethoxytoluene (56), which was passed through basic alumina using isohexane to remove yellow color. This showed pmr spectrum ($DCCl_3$, 100 MHz) δ 0.95 (t,3, C-CH_3), 1.2-1.6 (m,4,C-CH_2-CH_2-C), 2.2 (s,3,Ar-CH_3), 2.5 (t,3,Ar-CH_2-C), 3.8 (s,6,Ar-OCH_3), 6.5 (s,2,Ar-H).

Oxidation of 3,4-dimethoxy-6-methylcrotonophenone (53):[63]

3,4-Dimethoxy-6-methylcrotonophenone (53) (5.5 g 0.25 mol) was added to a stirred mixture of 50 ml of benzene, 5 g of "dicocodimethylammonium chloride," 16 g (0.1 mol) of $KMnO_4$, and 100 ml of water at such a rate that the temperature was maintained at 40-45° (0.5 hour). After addition was complete, the mixture was stirred for an additional 0.5 hour. Excess permanganate was destroyed by addition of sodium sulfite solution. The reaction mixture was filtered to remove MnO_2 and acidified with dilute HCl (10%). The MnO_2 cake was washed with 100 ml of benzene, which was also used to wash the aqueous phase of the filtrate. The combined benzene solutions were shaken with 100 ml of the 10% NaOH solution. The aqueous alkaline phase was washed with ether and then acidified with 10% hydrochloric acid. The carboxylic acid which separated was taken up in 100 ml of ether, and the ethereal solution was dried ($MgSO_4$). Evaporation of ether left 2.1 g (43%) of 4,5-dimethoxy-2-methylbenzoic acid 57, mp 144-145°; ir spectrum (KBr) 2950 (broad), 2600, 1700, 1625, 1585, 1540, 1475, 1380, 1280, 1220, 1175, 1090, 990, 930, 880, 850, 780, 760 $cm.^{-1}$; pmr spectrum ($DCCl_3$, 100 MHz) δ 2.6 (s,3,Ar-CH_3), 3.9 (s,6,Ar-OCH_3), 6.7 (s,1,Ar-H),

7.65 (s,1,Ar-H), 11.6 (s,1,Ar-COOH).

Cyclization of 3,4-dimethoxy-6-methylcrotonophenone (53): To a magnetically stirred solution of 10 g of 3,4-dimethoxy-6-methylcrotonophenone in 1 l. of o-xylene, 10 g of A-15[65] was added. The reaction mixture was heated at reflux[66] (132°) for 42 hours until the starting material was consumed as evidenced by glc analysis. The black mixture was then cooled, filtered and steam distilled to remove o-xylene. The ether extract of the crude product was dried ($MgSO_4$) and the solvent was removed to give 5 g (50%) of yellow crude oil. The crude product was distilled in a Kugelrohr apparatus to give 4 g light yellow liquid which solidified after a few hours. The yellow solid after two recrystallizations from boiling isohexane gave light yellow crystals of either 4-hydroxy-5-methoxy-3,7-dimethyl-1-indanone (58a) or 5-hydroxy-4-methoxy-3,7-dimethyl-1-indanone (58b). During cyclization one methyl group was lost and the position of cleavage was not determined. The compound showed mp 92.5-93.5°; ir spectrum (KBr) 3200, 2900, 1670, 1585, 1500, 1450, 1350, 1300, 1145, 1080, 1000, 880, 835 $cm.^{-1}$; pmr spectrum ($DCCl_3$, 100 MHz) δ 1.35 (d,3,C-CH_3), 2.22 (q,1,CO-CH-), 2.85 (q,1,CO-CH-). 3.50 (m,1,-C-CH-C), 2.55 (s,3,Ar-CH_3), 3.9 (s,3, Ar-OCH_3), 5.65 (s,1,Ar-OH), 6.95 (s,1,Ar-H); mass spectrum (70eV) m/e (rel. intensity), 207(11), 206(M^+,81), 192(11), 181(85), 163(9), 103(9), 91(18), 77(14), 65(9), 53(8), 51(11), 39(15), 28(13), 18(100), 17(29), 15(31) were obtained.

Analysis: Calculated for $C_{13}H_{16}O_3$: C, 70.89%; H, 7.32%.
Found: C, 70.59%; H, 7.13%.

BIBLIOGRAPHY AND NOTES

1. (a) G. Barry, J. W. Cook, G. A. D. Haslewood, C. L. Hewett, I. Hieger, and E. L. Kennaway, Proc. Royal Soc. (London), B117, 318 (1935).

   (b) I. Hieger, Am. J. Cancer, 28, 552 (1936).

   (c) W. E. Bachmann, J. W. Cook, A. Dansi, C. G. M. D. Worms, G. A. D. Haslewood, C. L. Hewett, and A. M. Robinson, Proc. Royal Soc. (London), B123, 343 (1937).

   (d) A. Muller, L. Kahofer, G. D. Miller-Aichhotz, and W. Ruzha, Monatsh 86, 16 (1955).

   (e) S. Newkomm, Oncologia, 10, 107 (1957).

   (f) A. Y. Meyer, and E. D. Bergmann, Phys-Chem. Mech. Carcinog. Proc. Int. Sym., 1968, 78 (Pub. 1969).

2. (a) M. J. Shear, and J. Leiter, J. Natl. Cancer Inst., 2,241 (1941).

   (b) I. Berenblum, Cancer Research, 5, 561 (1945).

   (c) T. W. Lees, and J. C. Lees, Cancer, 3, 580 (1950).

   (d) P. E. Steiner, and J. H. Edgcomb, Cancer Research, 12,657 (1952).

   (e) Ibid., 15, 632 (1955).

   (f) F. J. C. Roe, and M. H. Salaman, Brit. J. Cancer, 9,177 (1955).

   (g) I. Berenblum, and N. Hanan, Brit. J. Cancer, 9, 268 (1955).

   (h) F. G. Bock, and M. Burnham, Cancer Research, 21, 510 (1961).

   (i) D. H. Adams, Brit. J. Cancer, 13, 704 (1959).

   (j) J. L. Stevenson, and E. V. Hamm, Am. Ind. Hyg. Assoc. J., 26, 475 (1959).

   (k) V. Duuren, L. Benjamin, A. Sivak, B. M. Golsmith, C. Katz, and S. Melchionne, J. Nat. Cancer Inst., 44(5), 1167 (1970).

   (l) E. Boyland, and P. Sims, Int. J. Cancer, 2, 500 (1967).

   (m) E. Bingham and H. L. Falk, Arch. Environ. Health, 19(6), 779 (1969).

3. (a) J. Pataki, C. Duguld, P. W. Rabideau, H. Huisman, and R. G. Harvey, J. Med. Chem., 14, 940 (1971).

(b) M. Guerin, P. Lazar, and I. Chouroulinkov, C. R. Soc. Biol., 165, 2255 (1971).

(c) A. E. Freeman, E. K. Weisburger, J. H. Weisburger, R. G. Wolford, J. M. Manyak, and R. J. Huebuer, J. Natl. Cancer Inst., 51, 799 (1973).

4. (a) H. Lettre and A. Jahn, Naturwissenschaften, 42, 210 (1955).

(b) M. J. Lyons, Nature, 117, 630 (1956).

(c) J. Bennet, and S. Neukomm, Helv. Chim. Acta., 39, 1724 (1956).

(d) A. J. Lindsey, Brit. J. Cancer, 11, 192 (1957).

(e) A. Pietzech, Naturwissenschaften, 45, 445 (1958).

(f) E. L. Wynder, and D. Hoffmann, Cancer, 12, 1079 (1959).

(g) A. Pietzsch, Pharmazie, 14, 446 (1959).

(h) C. Pyriki, R. Muller, and W. Moldenhann, Ber. Inst. Tabakforsch Dresden, 7(1), 81 (1960).

(i) J. Ahlman, Acta. Pathol. Microbiol. Scand., 43, 379 (1958).

(j) J. A. S. Gilbert, and A. J. Lindsey, Brit. J. Cancer, 10, 642 (1956).

(k) K. Setsuo, and K. Masonori, Gann., 57, 317 (1966).

(l) I. G. Mokhnachev, V. P. Pisklov, S. R. Nauch-Issled, and V. Nauch-Issled, Inst. Tab. Makhorki, 155, 53 (1970), via C. A. 78, 40598t, 1973.

(m) H. J. Klimisch, W. Szoun, and Z. Fresenius, Anal. Chem., 1973, 265(1), 7.

(n) V. D'Arrigo, and L. Laghi, Quad. Merceol., 11(2), 27 (1972), via C. A. 78, 13833j, 1973.

5. (a) V. C. Shore, and M. Katz, Anal. Chem., 28, 1399 (1956).

(b) H. O. Hettche, Staub., 25, 365 (1965).

(c) Z. Morlin, and M. Kertesz-Saringer, Egeszegtudomany, 9, 349 (1956), via C. A. 78, 114883f, 1973.

(d) L. Demai, and M. Corn, J. Air Pollution Control Assoc., 16, 67 (1966).

(e) E. Sawicki, T. W. Stanley, W. C. Elbert, and J. D. Pfaff, Anal. Chem., 36, 497 (1964).

(f) G. Grimmer, and A. Hilderblandt, J. Chromatog., 20, 89 (1965).

(g) A. Liberti, G. P. Caronti, and V. Cantuli, J. Chromatog., 15, 141 (1964).

(h) E. Sawicki, T. R. Hauser, W. Elbert, F. T. Fox, and J. E. Meeker, Am. Ind. Hyg. Assoc. J., 23, 137 (1962).

(i) J. M. Colucci, and C. R. Begeman, Environ. Sci. Tech., 5, 145 (1971).

(j) G. J. Cleary, and J. L. Sullivan, Med. J. Aust., 52-I(2), 758 (1965).

(k) H. Matsushita, Y. Esumi, and K. Yamada, Bunseki Kagaku, 19, 961 (1970), via C. A. 74, 145943x, 1971.

(l) J. R. Sibru, R. L. Catalina, and A. Singerman, Rev. Aso. Bioquim. Argent., 32, (170-171), 66 (1967), via C. A., 69, 38531m, 1968.

(m) H. Watanabe, and K. Tomita, Intl. Clean Air Congr. Proc. (London), Part I, 226 (1966).

(n) P. Valori, and A. Grella, Nuovi Ann. Ig. Microbiol., 17, 264 (1966), via C. A. 66, 107993r, 1965.

(o) L. Zoccolillo, A. Liberti, and D. Brocco, Atmos. Environ., 1972, 6(100), 715 (1972).

(p) J. M. Colucci, and C. R. Begeman, Proc. Intl. Clean Air Congr., 2nd 1970, H. M. Englund, editor, Academic Press, New York, 1971.

(q) O. Hettche, Ver. Deut. Ing. Z., 114, 346 (1972).

(r) R. C. Lao, R. S. Thomas, and L. DuBois, Anal. Chem., 45, 908 (1973).

(s) M. Kertesz-Saringer, and Z. Morlin, Egeszegtudomany, 16, 392 (1972), via C. A. 78, 114883f, 1973.

(t) Y. Abdoh, N. Aghdaie, M. R. Darvich, and M. H. Khoragami, Atmos. Environ. 6, 947 (1972).

(u) G. Chatot, R. Dangy-Caye, and R. Fontages, J. Chromatogr., 72, 202 (1972).

(v) G. Chatot, R. Dangy-Caye, and R. Fontages, Atmos. Environ., 7, 819 (1973), via C. A. 79, 149145q, 1973.

(w) M. Cigula, M. Fugas, and F. Valic, Arch. Hig. Rada Toksikol, 23, 199 (1972), via C. A. 79, 107819g, 1973.

(x) R. Penny, Intl. Symp. Identification Meas. Environ. Pollut. (Proc.), 1971, 130.

(y) R. J. Gordon, and R. J. Brayan, Environ. Sci. Tech., 7, 1050 (1973).

6. (a) M. J. Lyons, and H. Johnston, Brit. J. Cancer, 11, 60 (1957).

(b) J. M. Colucci, and C. R. Begeman, J. Air Pollution Control, 15(3), 113 (1965).

(c) M. J. Lyons, Natl. Cancer Inst. Monograph No. 9, 193 (1962).

(d) G. M. Badger, J. K. Donnelly, and T. M. Spotswood, Aust. J. Chem., 16, 392 (1963).

(e) P. A. Kenline, C. J. Conlee, R. L. Cummins, and V. J. Konopinski, Arch. Environ. Health, 14, 429 (1967).

(f) R. Gladen, Chromatographia, 5, 236 (1972).

(g) G. S. Hoffman, Jr., R. L. Willis, G. H. Patterson, and E. S. Jacobs, Am. Chem. Soc., Div. Petrol. Chem. Prepr., 16(2), E-36 (1971).

(h) G. Grimmer, A. Hilderbrandt, H. Boehnke, and O. Erdoel Kohle, Erdgas Petrochem. Brennst-Chem., 25, 531 (1972).

(i) G. Grimmer, and H. Boehnke, Fresenius Z. Anal. Chem., 261, 310 (1972).

(j) R. A. Brown, T. D. Searl, W. H. King, W. A. Dietz, and J. M. Kelliher, U. S. Natl. Tech. Inform. Serv., P. B. Rep., 1971, No. 219025/456pp, via C. A. 79, 96392j, 1971.

7. (a) J. W. Cook, C. L. Hewett, and I. Hieger, J. Chem. Soc., 1933 396.

(b) O. Kruber, Ber. 74B, 1688 (1941).

(c) O. G. Eizen, and I. Kh. Arro, Vopnosy Onkol, 5, 160 (1957), via C. A. 53, 20469i, 1959.

(d) E. K. Diel, F. D. Breuil, and R. A. Glen, J. Eng. Power, 89 276 (1967).

(e) A. S. Filatova, and A. I. Kuzmihykh, Vop. Gia. Prof. Patol Tsvet. Chern., 1971, 114, viz, Zh. Met., 1971, Abstract No. 11G155, via C. A. 76, 131081u, 1972.

(f) V. Dolansky, J. Mostecky, and M. Pool, Sb. Vys. Sk. Chem-Tech., Praze, Tech., Paliv., D26, 71 (1972), via C. A. 78, 113719v, 1973.

(g) H. Matsushita, Y. Edumi, A. Susuki, and T. Honda, Bunseki Kagaku, 21, 1471 (1972), via C. A. 79, 106670q, 1973.

8. (a) W. Ljinsky, and P. Shubik, Toxicol. Appl. Pharmacol., 7, 337 (1965).

(b) J. W. Howand, R. T. Teaque, R. H. White, and B. E. Fry, J. Assn. Offic. Anal. Chem., 49, 595 (1966).

(c) Y. Masuda, K. Moni, and M. Kuratsure, Gann., 57, 133 (1966).

(d) G. Grimmer, and A. Hilderbrandt, Z. Krebsforsch, Z., 69, 223 (1967).

(e) A. J. Malanoski, E. L. Greenfield, J. M. Worthington, and C. J. Bernes, J. Assn. Offic. Anal. Chem., 51, 114 (1968).

(f) J. Filipovic, and L. Toth, Fleischwirtschaft, 51, 1323 (1971).

(g) T. Fazio, R. H. White, and J. W. Howard, J. Assoc. Offic. Anal. Chem., 56, 68 (1973).

(h) L. Toth, and W. Blaas, Fleischwirtschaft, 52, 1121 (1972).

(i) F. Petuely, Scr. Med. Fac. Med. Univ. Brun., Purkyniance, 46(2), 87 (1973), via C. A. 80, 56309b, 1974.

9. (a) P. Wedgwood, and R. L. Cooper, Analyst, 80, 652 (1955).

(b) P. Wedgwood, Water. Sanit. Engr., 2, 515 (1952).

10. (a) W. Carruthers, and A. G. Douglas, Nature, 162, 256 (1961).

(b) K. Soos, and V. Cieleszky, Color Ert., 11(5-6), 100 (1969), via C. A. 71, 79820q, 1969.

(c) I. Muntean, and N. Mosescu, Chim. Anal. (Bucharest), 1(14), 237 (1971), via C. A. 76, 115749n, 1972.

(d) K. Soos, Elemiszervizsgalti Kozlem, 18(1-2), 45 (1972), via C. A. 78, 2846q, 1973.

11. (a) G. Pertoldi-Marletta, Atti. Conv. Reag. Aliment., 1st Conv. Maz. Qual., 4th Thieste, 678 (1965), (Pub. 1966), via C. A. 71, 2272e, 1969.

(b) G. Grimmer, and A. Hilderbrandt, Deut. Lebensm-Rundsch, 62, 19 (1966).

(c) U. Bracco, Riv. Ital. Sostanze Grasse, 50(6), 166 (1973).

12. (a) J. Firket, and A. Malter, Bull. Assoc. Franc. Etude Cancer, 29, 24 (1940).

(b) H. Werner, J. Wurziger, and R. Ristow, Deut. Lebensm-Rundsch, 60, 133 (1964).

13. W. Ciusa, G. Nebbia, A. Bruccelli, and E. Volpones, Riv. Ital. Sostanze Grasse, 42(4), 175 (1965).

14. J. S. Harrington, and B. T. Commins, Chem. Ind. (London), 1427 (1964).

15. H. M. B. Ballschmieter, Fette, Seifen, Anstrichm, 71, 521 (1969).

16. E. R. Hendrickson, C. G. Walker, and V. D. Chapnerker, Am. Ind. Hyg. Assoc. J., 24, 121 (1963).

17. (a) A. J. Lindsay, M. A. Philips, and D. S. Wilinson, Chem. Ind. (London), 1365 (1958).

(b) E. Wolfrum, J. N. Roffman, and H. Nickel, Fresenis Z. Anal. Chem., 268, 19 (1974).

18. S. K. Rhee, and L. J. Bratzler, J. Food Sci., 33, 626 (1968).

19. V. D'Arrigo, and G. Marchesini, Riv. Ital. Sostanze Grasse, 48(6), 324 (1971), via C. A. 75, 131000w, 1971.

20. M. Yoshito, M. Kazuko, H. Tomio, and K. Masanori, Gann, 57 547 (1966).

21. G. Giernoth, and H. E. Rost, Chem. Ind. (London), 2002 (1967).

22. (a) M. I. Stepanova, R. I. Ilina, Y. K. Shaposhnikov, Zh. Anal. Khim., 27, 201 (1972), via C. A. 77, 105369v, 1972.

(b) K. P. Ershova, and I. M. Mints, Gig. Sanit., 33(a), 52 (1968), via C. A. 69, 109670u, 1968.

23. (a) I. S. Kireeva, and N. Y. Yanysheva, Gig. Naselem. Mest. Resp. Mezhvedom, Sb. 1970, No. 9, 113 ref. Zh. Khim, 1971, Abstract No. 81473, via C. A. 76, 131121g, 1972.

(b) H. Matsushita, Y. Esumi, and A. Suzki, Bunseki Kagaku, 21, 331 (1972), via C. A. 80, 5460m, 1974.

24. Environmental Protection Agency, Grant No. R803097.

25. (a) K. Elbs, Ber., 19, 2209 (1886).

(b) S. Gabriel, and J. Coleman, Ibid., 33, 446 (1900).

(c) G. Graebe, Justus Liebigs Ann. Chem., 340, 254 (1905).

(d) G. Heller, and K. Schulke, Ber., 41, 3627 (1908).

26. G. Graebe, Justus Liebigs Ann. Chem., 340, 254 (1905).

27. K. Dziewonski, and E. Ritt, Bull. Int. Acad. Polon. Sci. Letters, A181 (1927).

28. Fr. Meyer, and A. Sieglitz, Ber., 55, 1852 (1929).

29. (a) I. G. Farbenindustrie AG, Brit. Patent 251270 (1926): C 1928 II, 1820; L. F. Fieser and E. M. Dietz, Ber., 62, 1827 (1929).

(b) L. F. Fieser, and E. M. Dietz, Ber., 62, 1827 (1929).

30. R. D. Haworth, and C. R. Mavin, J. Chem. Soc., 1933, 1012.

31. H. Burger, and E. Mosettig, J. Am. Chem. Soc., 59, 1302 (1937).

32. J. W. Cook, and C. L. Hewett, J. Chem. Soc., 1934, 370.

33. M. S. Newman, and R. T. Hart, J. Am. Chem. Soc., 69, 298 (1947).

34. C. S. Marvel, D. E. Pearson, and L. A. Patterson, J. Am. Chem. Soc., 62, 2659 (1940).

35. S. M. Mukherjee, and K. S. Dabas, Indian J. Chem., 9, 1192 (1971).

36. G. M. Badger, and J. W. Cook, J. Chem. Soc., 1939, 802.

37. Ador and Crafts, Bull. Soc. Chim., 34, 531 (1800).

38. P. H. Groggins, and H. P. Newton, Ind. Eng. Chem., 22, 157 (1930).

39. H. R. Snyder, and F. X. Werber, J. Am. Chem. Soc., 71, 2967 (1950).

40. S. Coffey, and V. Boyd, J. Chem. Soc., 1954, 2468.

41. (a) J. W. Cook, J. Chem. Soc., 1931, 2524.

(b) K. Brass, and K. Fanta, Ber., 69, 1 (1936).

(c) L. F. Fieser, and E. B. Hershberg, J. Am. Chem. Soc., 59, 2502 (1937).

42. SADTLER STANDARD SPECTRA, Sadtler Research Laboratories, Philadelphia, Pa., NMR No. 6018M, IR Nos. 1124, 9258.

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

44. T. Zincke, Ber., 6, 137 (1873).

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

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

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

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

49. Ref. 46, Vol. II.

50. K. E. Russell, J. Am. Chem. Soc., 81, 4834 (1959).

51. Ref. 46, Vol. III.

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

53. (a) J. F. Eijkman, Chem. Weekblad, 5, 655 (1909).

(b) H. Hopff, Germ. Pat., 666,466 (October 20, 1938).

(c) C. F. Koelsch, H. Hochmann, and C. D. Leclaire, J. Am. Chem. Soc., 65, 59 (1956).

(d) Sukh Dev, J. Ind. Chem. Soc., 33, 703 (1956).

54. (a) E. Bergman, H. Tanbadel, and H. Weiss, Ber., 64, 1499 (1931).

(b) L. I. Smith, and Chien-Pen Lo, J. Am. Chem. Soc., 70, 2215 (1948).

55. (a) F. H. Marquardt, Helv. Chim. Acta., 48, 1476 (1965).

(b) F. H. Marquardt, Ibid., 48, 1490 (1965).

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

57. K. Von Auwers, Justus Liebigs Ann. Chem., 502, 282 (1933).

58. (a) K. Von Auwers, and E. Lammerhirt, Ibid., 421, 1 (1920).

(b) K. Von Auwers, Ber., 44, 3692 (1911).

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

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

61. J. D. Weaver, Jr., "I. Phenol-Deoxygenation Via Catalytic Hydrogenolysis. II. Friedel-Crafts Reaction of p-Cresols and Crotonic Acid. III. Synthesis of Non-isoprenoid Nepetalinic Acid," Ph. D. Thesis, Oklahoma State University, 1973.

62. E. J. Eisenbraun,"Org. Syn.," Collective Vol. V, 310, John Wiley and Sons, London, 1973.

63. C. M. Starks, J. Am. Chem. Soc., 93, 195 (1971).

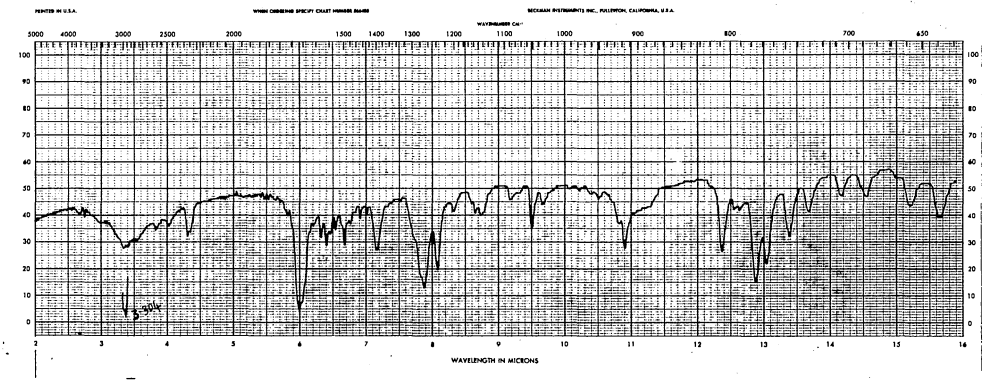
64. G. S. Heirs, and F. D. Hager, "Org. Syn.," Collective Vol. I, 58, John Wiley and Sons, 2nd ed., 1948.

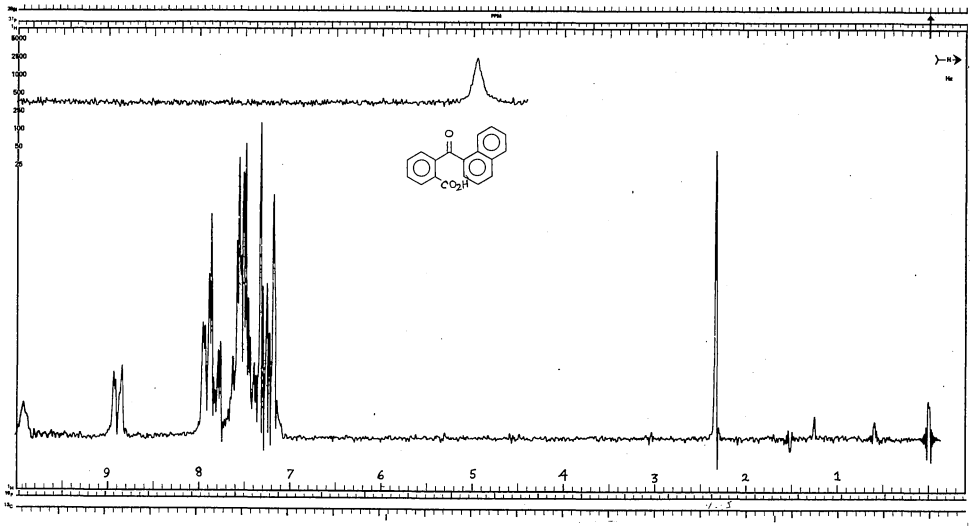
65. A gift from the Rohm and Haas Company.

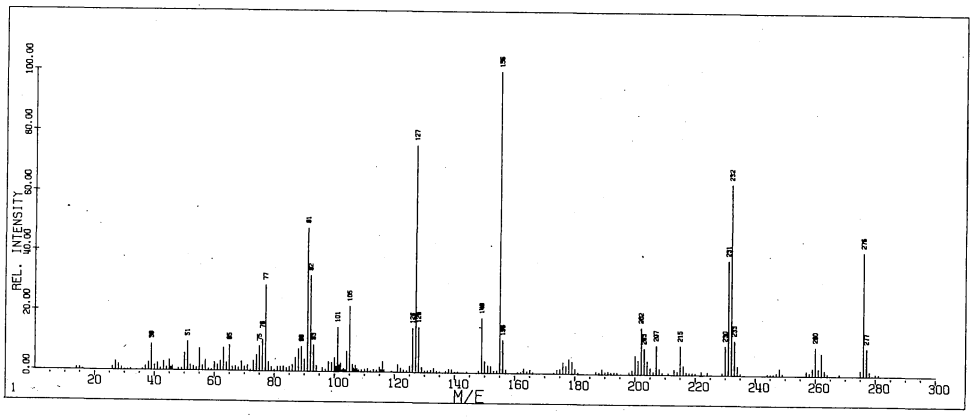
66. Rohm and Haas Company, Technical Bulletin, Ion Exchange Department, IE-94, May, 1962, A-15 decomposes above 150°.

APPENDIX

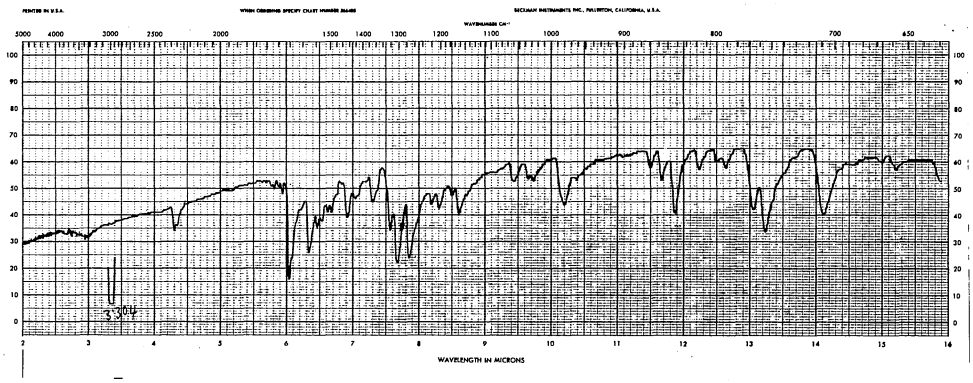
SPECTRA OF SELECTED COMPOUNDS

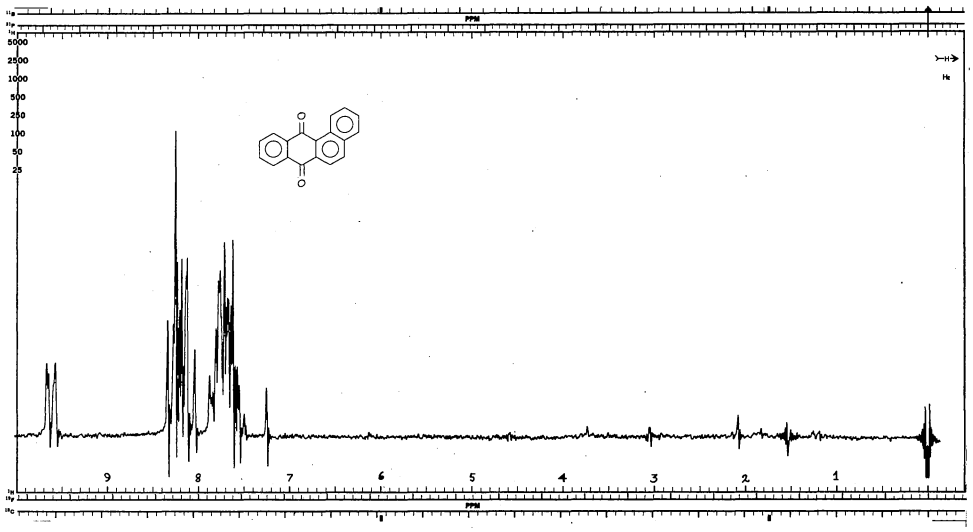


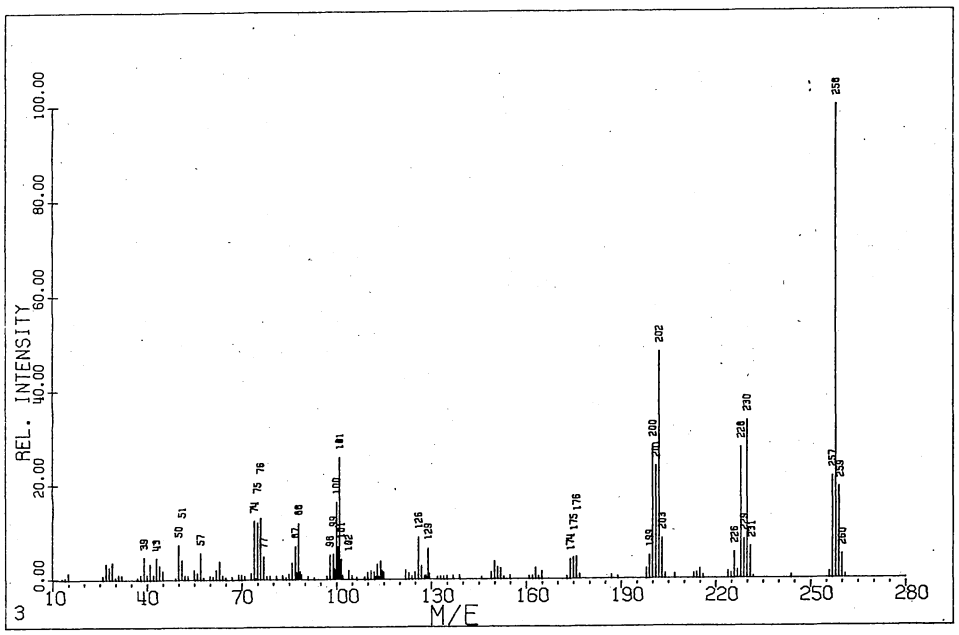




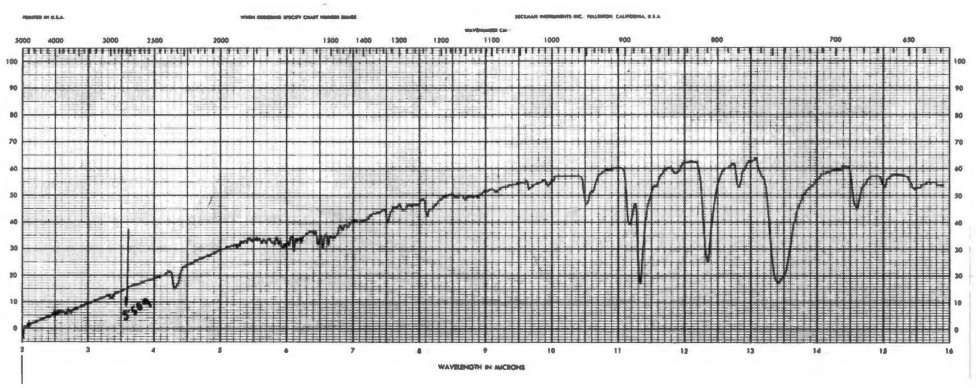
Spectra of 2-(1-Naphthoyl)benzoic acid (2)

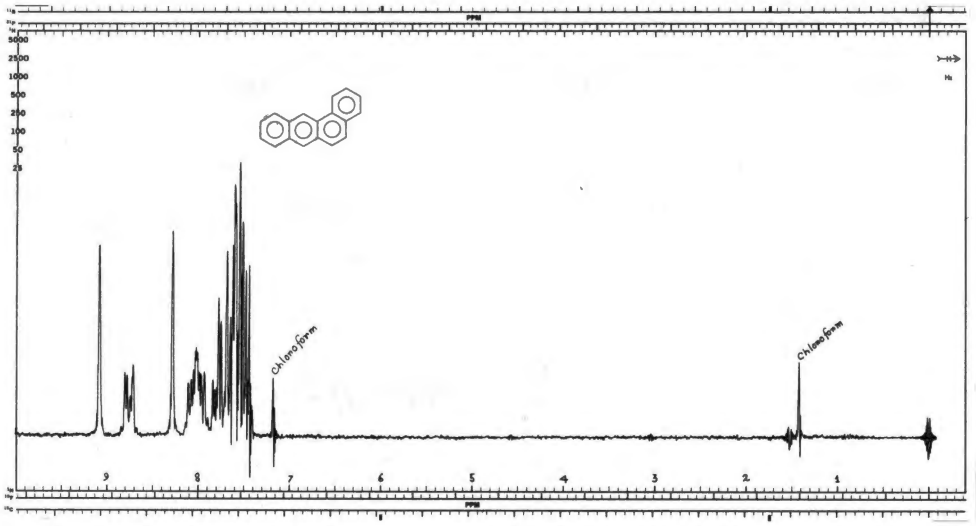


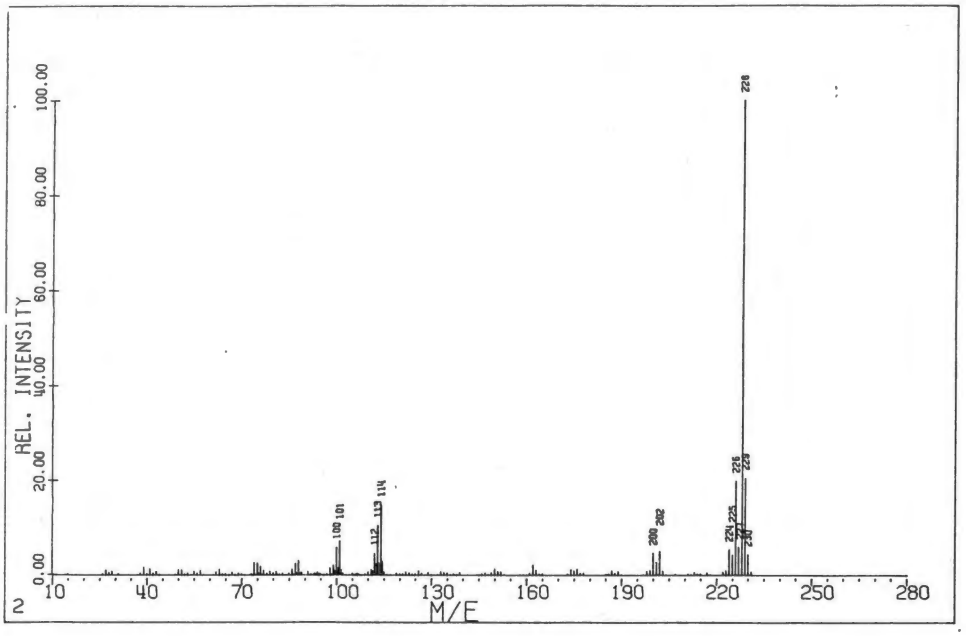




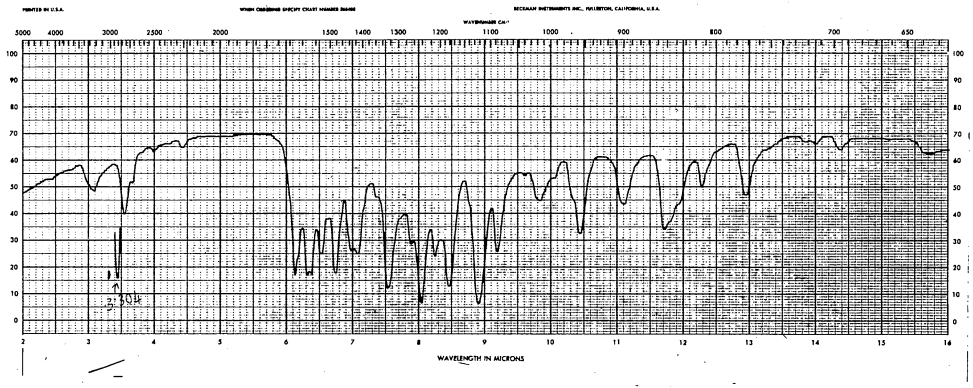
Spectra of 1,2-Benzanthraquinone (3)

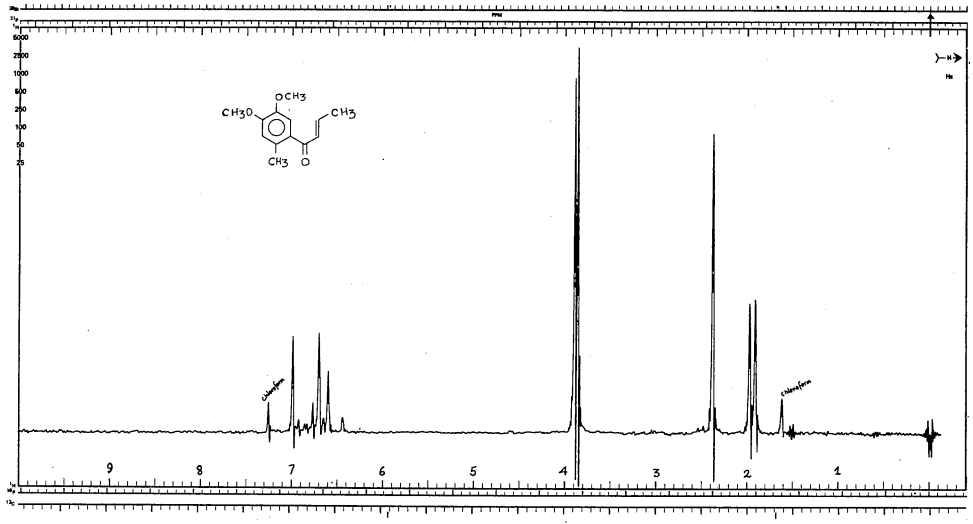


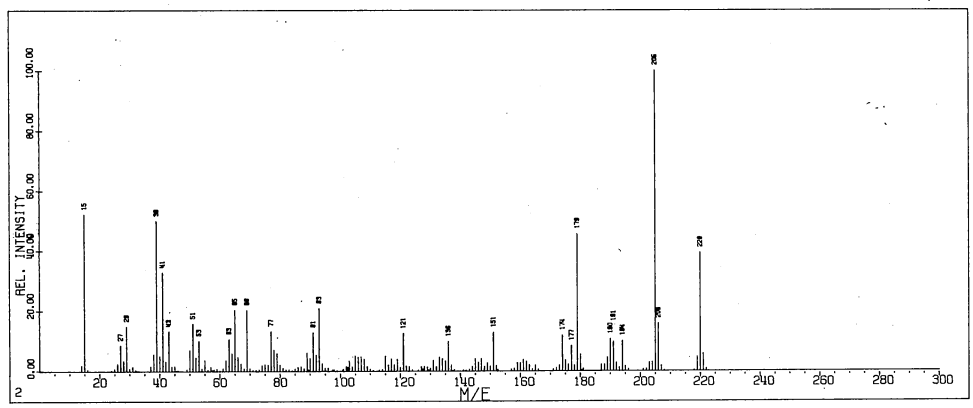




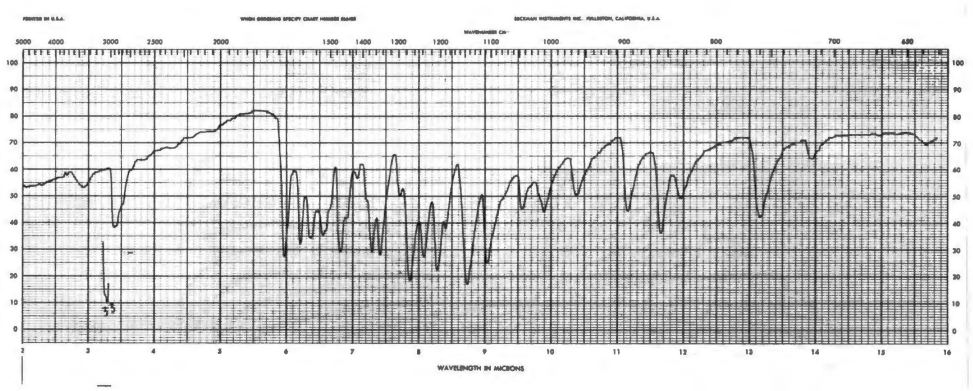
Spectra of Benz[a]anthracene (1)

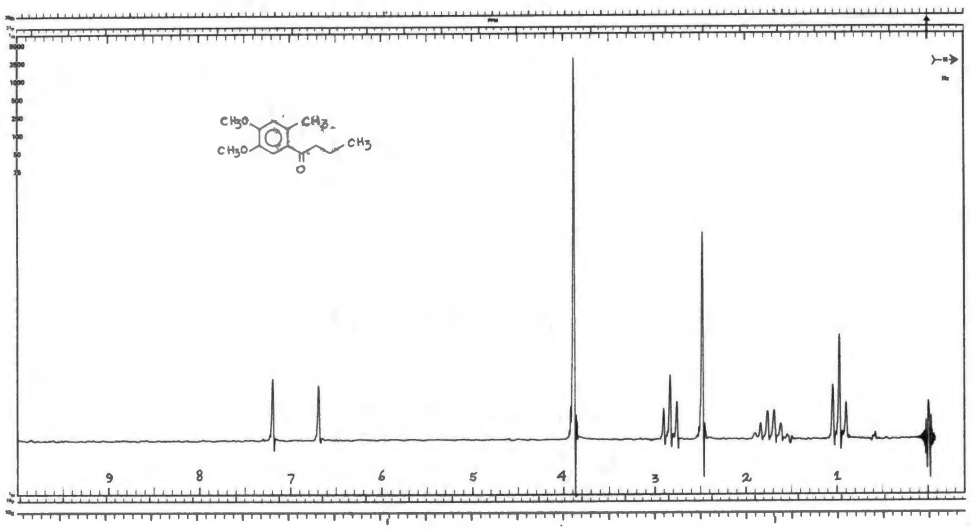


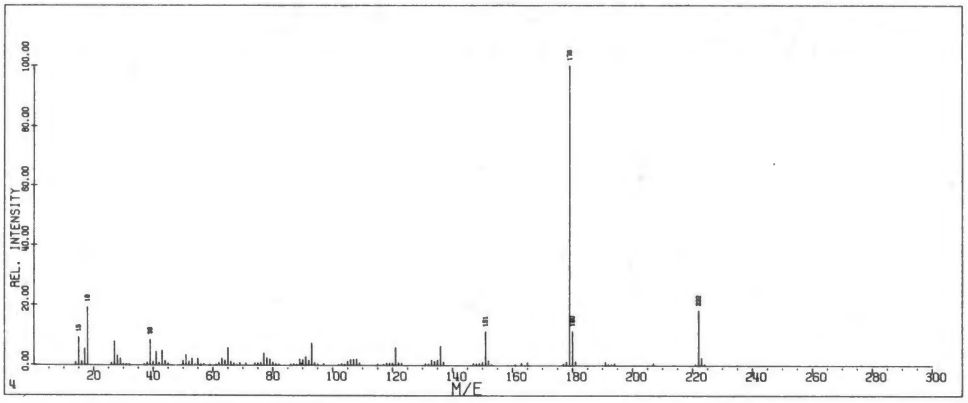




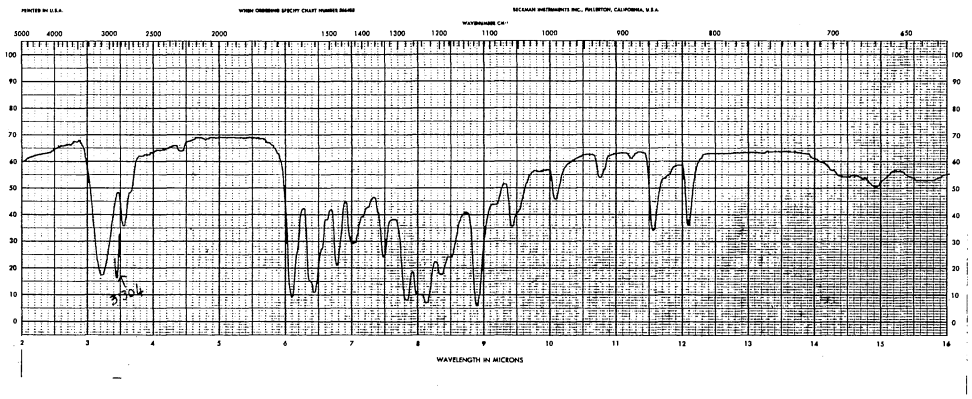
Spectra of 3,4-dimethoxy-6-methycrotonophenone (53)

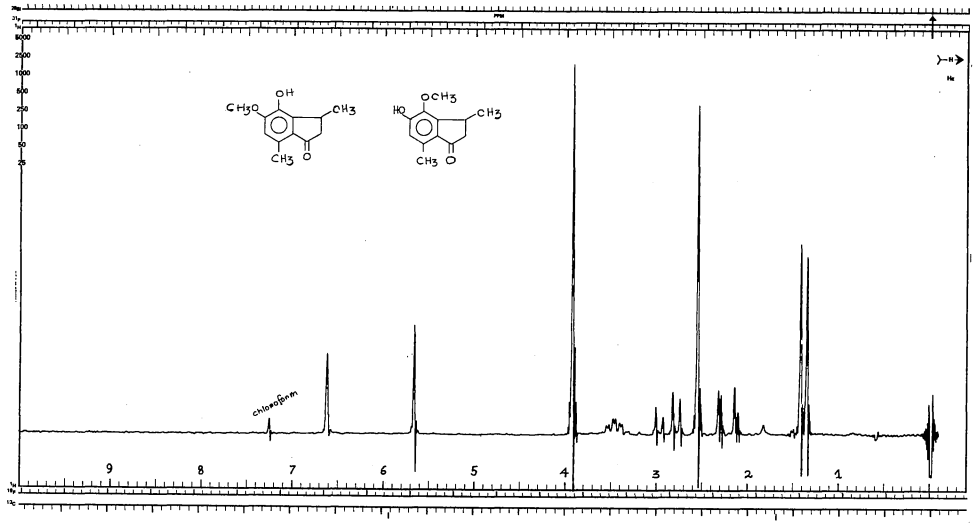


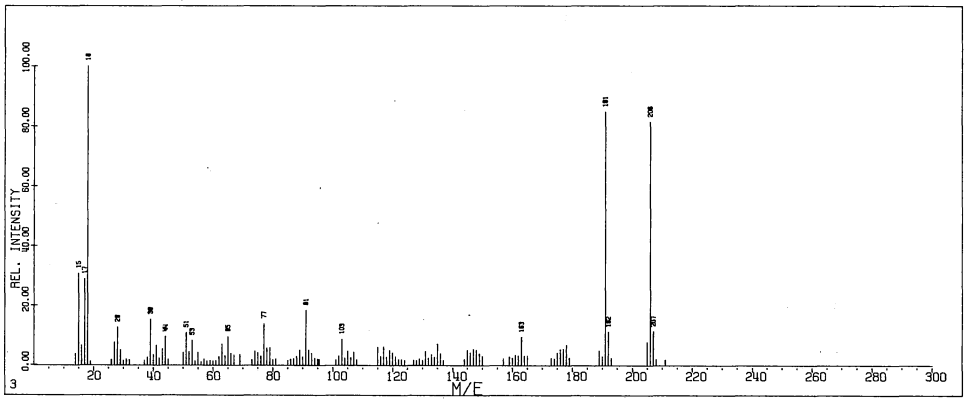




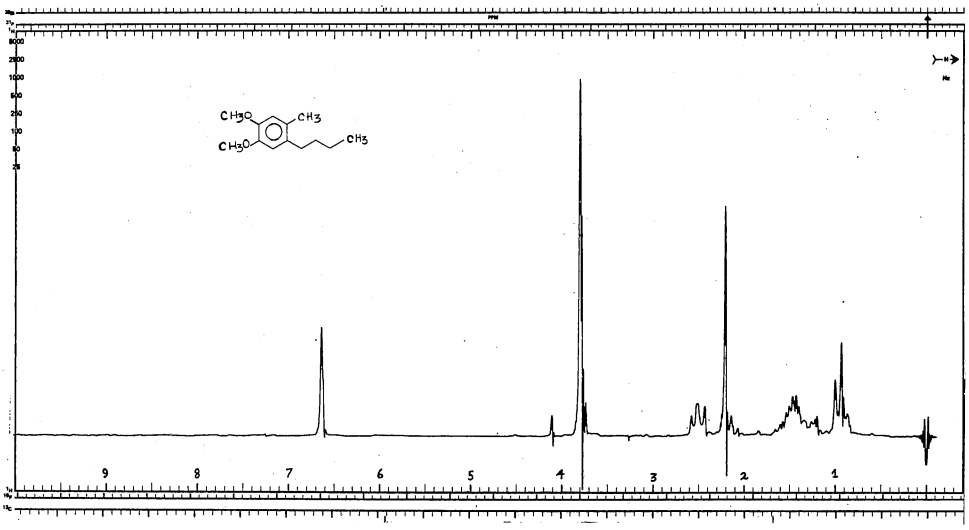
Spectra of 3,4-dimethoxy-6-methylbutyrophenone (55)



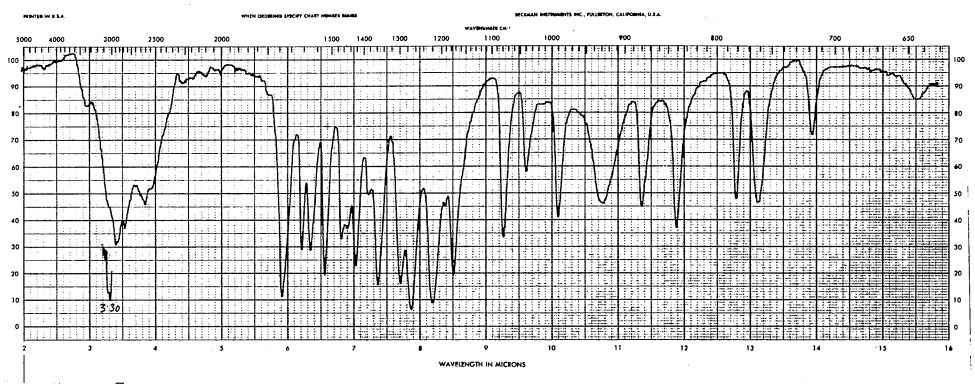


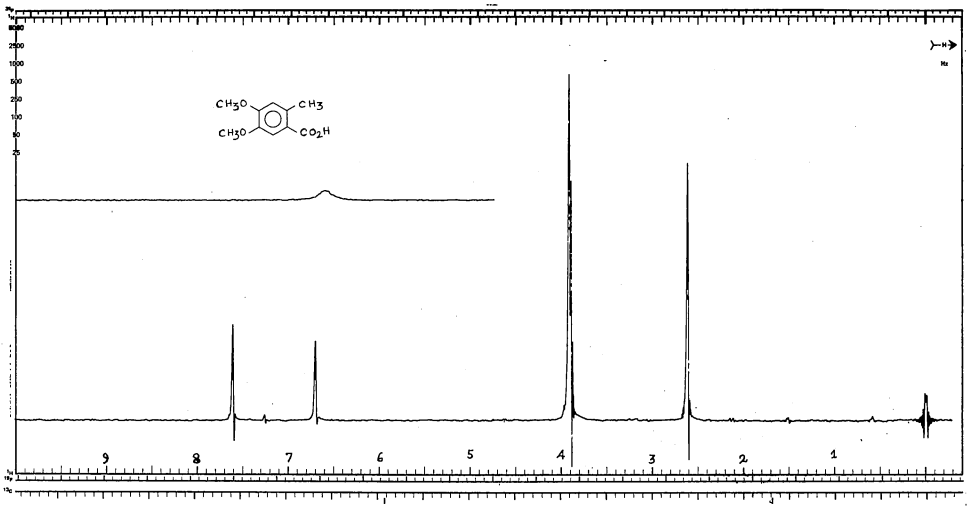


Spectra of 4-hydroxy-5-methoxy-3-,7-dimethyl-1-indanone (58a), or
4-methoxy-5-hydroxy-3-,7-dimethyl-1-indanone (58b)



Spectrum of 2-butyl-4,5-dimethoxytoluene (56)





Spectra of 4,5-dimethoxy-2-methylbenzoic acid (57)

VITA

Fahim Ud-Din Ahmed

Candidate for the Degree of

Master of Science

Thesis: I. SYNTHESIS AND PURIFICATION OF BENZ[a]ANTHRACENE

II. FRIEDEL-CRAFTS REACTION APPLIED TO AROMATIC ETHERS AND CROTONIC ACID

Major Field: Chemistry

Biographical:

Personal Data: Born in Shyampur, Mymensingh, Bangladesh, March 1, 1944, son of Mr. and Mrs. Dabir Ud-Din Ahmed.

Educational: Graduated from Melandah High School, Mymensingh, in 1962, received Bachelor of Science with Honours and Master of Science degree in Chemistry in 1968 and 1970, respectively, from Dacca University; attended Summer Science Institute in June, 1973, at Rajshahi University, Bangladesh; admitted to the Graduate College of Oklahoma State University, in fall, 1973; completed the requirements for the Master of Science degree at Oklahoma State University in July, 1975

Professional: Lecturer in Chemistry, Government B. M. College, Barisal, 1970-72; Government A. M. College, Mymensingh, 1972-73, Bangladesh; Graduate Teaching Assistant, Oklahoma State University, 1973-75; Graduate Research Assistant, American Petroleum Institute, Oklahoma State University, 1974; Graduate Research Assistant, the Environmental Protection Agency, Oklahoma State University, 1975; Summer Research Fellow, Dow Chemical Company, Oklahoma State University, summer, 1975; Member of Phi Lambda Upsilon, Honorary National Chemical Society.