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Synthesis and polymerization of vinylsalicylic acid derivatives and 2,4-dihydroxy-4-vinylbenzophenone.

David A. Tirrell
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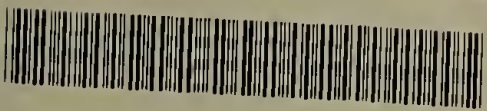
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SYNTHESIS AND POLYMERIZATION OF VINYLSALICYLIC ACID
DERIVATIVES AND 2,4-DIHYDROXY-4'-VINYL BENZOPHENONE

A Dissertation Presented

By

DAVID A. TIRRELL

Submitted to the Graduate School of the
University of Massachusetts in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

September 1978

Polymer Science and Engineering

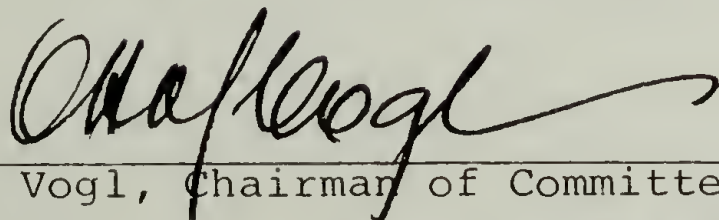
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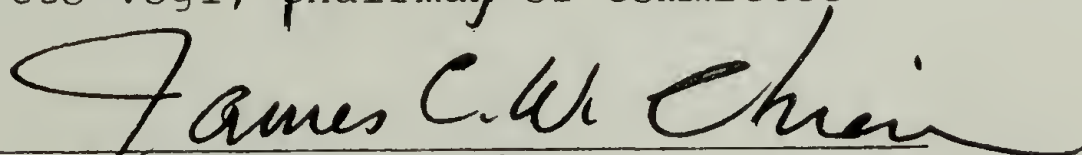
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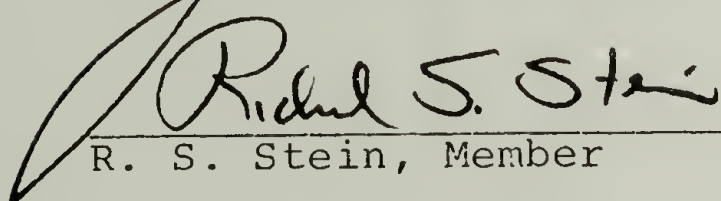
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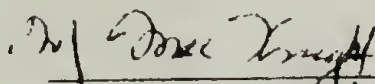
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Finally, the author would like to thank his laboratory coworkers, and in particular his contemporaries, Wally Deits and Steve Corley, for their cooperation and suggestions during the course of this research.

ABSTRACT

Synthesis and Polymerization of Vinylsalicylic Acid Derivatives and 2,4-Dihydroxy-4'-Vinylbenzophenone

(September 1978)

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S.B., Massachusetts Institute of Technology
M.S., University of Massachusetts

Directed by: Professor Otto Vogl

Several 4- and 5-vinylsalicylic acid derivatives and 2,4-dihydroxy-4'-vinylbenzophenone were synthesized, and their polymerization behavior investigated, with the objective of preparing novel polymeric ultraviolet absorbers and biologically-active polymers.

5-Vinylsalicylic acid and 5-vinylacetylsalicylic acid were prepared in overall yields of 26% and 12%, respectively, starting with methyl salicylate. Each monomer was successfully homopolymerized, and copolymerized with methacrylic acid, to give polymers of high molecular weight, using AIBN as the radical initiator.

Methyl 4-vinylsalicylate, 4-vinylsalicylic acid and 4-vinylacetylsalicylic acid were prepared in overall yields of 28%, 21% and 16%, respectively, starting with 3-ethylphenol. Radical polymerization of all three monomers was investigated. The first two of these compounds polymerized normally via radical initiation, giving soluble polymers

of high molecular weight. 4-Vinylacetylsalicylic acid gave gelled polymerization mixtures in tert-butanol and in dimethyl sulfoxide, using the same experimental procedure. A water-insoluble copper complex of poly(4-vinylsalicylic acid) was prepared. Methyl 4-vinylacetylsalicylate was also synthesized, in 35% yield, but no polymerization experiments were performed with this monomer.

2,4-Dihydroxy-4'-vinylbenzophenone was prepared in 33% yield from 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone, completing a five-step synthesis of this compound from p-ethylbenzoic acid, in an overall yield of 14%. Homopolymerization and copolymerizations of 2,4-dihydroxy-4'-vinylbenzophenone with methacrylic acid and with styrene were accomplished. The influence of the model compound, 2,4-dihydroxy-4'-ethylbenzophenone, on styrene polymerization was also investigated.

Fluorosulfonic acid and trifluoromethanesulfonic acid were investigated as potential catalysts for Fries rearrangement of methyl acetylsalicylate and acetylsalicylic acid. The objective of this investigation was preparation of the corresponding 3-acetyl derivatives, which would then be used for synthesis of 3-vinylsalicylic acid and its esters. However, no rearranged products were isolated.

Results of preliminary tests of antibacterial activity are reported for thirteen monomeric and polymeric derivatives of 5-vinylsalicylic acid.

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C H A P T E R I

INTRODUCTION

This dissertation describes the synthesis and polymerization of several vinylsalicylic acid derivatives and 2,4-dihydroxy-4'-vinylbenzophenone. The polymers obtained are of potential interest as biologically-active agents and as ultraviolet stabilizers.

As part of a general effort in the area of functional polymers, this work builds on that of D. Bailey¹ in the area of polymeric ultraviolet absorbers. The discussions given in this chapter are thus intended to be complementary to those of Bailey; repetition has been kept to a minimum.

Section A discusses, in very general terms, the principal synthetic routes to functional polymers. This is followed, in Sections B and C, by surveys of the prior art in the areas of polymeric salicylic acid derivatives and vinylbenzophenone polymers.

The concept of biologically-active polymers has recently been thoroughly reviewed,²⁻⁵ and thus is not treated in this chapter; however, the specific problem of the use of polymers in the prevention of light-induced damage to the skin forms the subject of Section D.

Section E discusses briefly the very broad spectrum

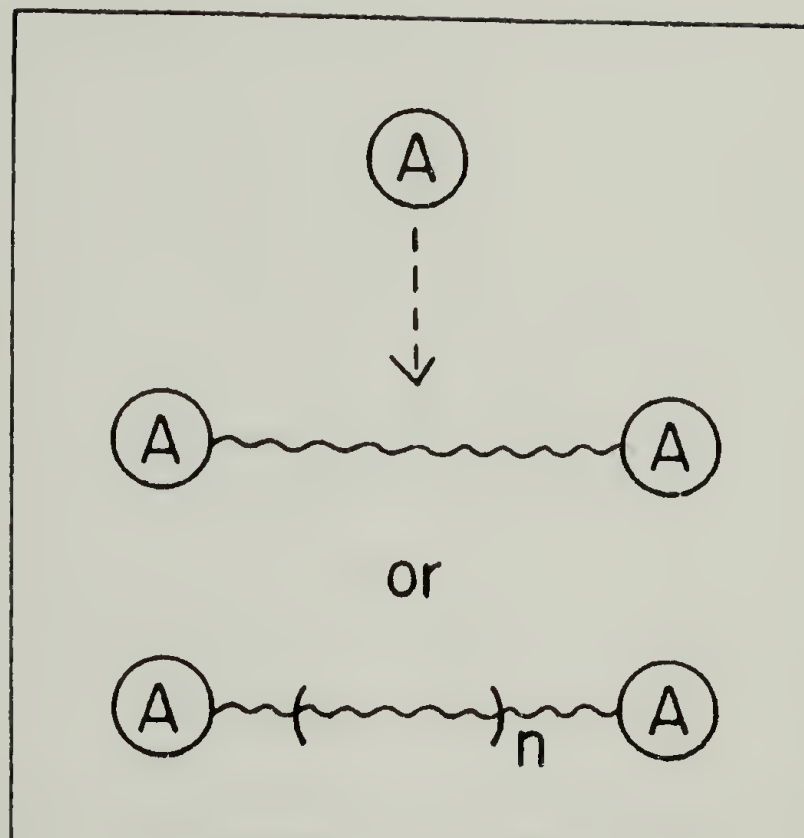
of biological activity displayed by salicylic acid derivatives, and is intended to provide a background for the evaluation of the polymeric derivatives prepared in this work. Finally, Section F treats a problem common to all of the polymerizations performed in the course of this research--that of retardation of radical polymerization by phenolic compounds.

A. Methods of Preparation of Functional Polymers

In view of the diverse applications of polymers bearing reactive functional groups, it is necessary to develop versatile synthetic methods which allow the introduction of the desired functional groups into polymer molecules with useful properties. Three synthetic approaches have been investigated in this laboratory:¹ (i) endcapping of oligomers, (ii) polymerization of functional monomers and (iii) reactions on polymers. Each of these methods is briefly discussed below.

Endcapping of oligomers is illustrated schematically in Figure 1. The active functional group is introduced as an endgroup in a moderate molecular weight compound by reaction with terminal reactive sites. This results in changes in the mobility, solubility, and total activity of the active group. Hydroxyl-terminated oligomers of ethylene oxide or butadiene serve as excellent substrates for this process, which offers the advantages of ready availability

Figure 1. Schematic illustration of synthesis of functional oligomers via endcapping reactions. (A) represents the active functional group.



and high purity of starting materials. In many cases, the products of such a process are crystalline as well, leading to high purity of reaction products. The method suffers somewhat, however, from a lack of versatility; it is difficult or impossible to introduce additional functional groups into the endcapped product.

The synthesis and polymerization of functional monomers are in many respects complementary to the endcapping approach; Figure 2 shows a schematic illustration. The complementarity arises from the essentially unlimited diversity of products that may be obtained from polymerization and copolymerization of functional monomers. On the other hand, the required monomer syntheses are often quite difficult, so that the "starting materials" for polymer synthesis are often difficult to obtain, and the functional monomer may not polymerize. As in the endcapping approach, purity of starting materials is generally quite good.

It is in the polymer reaction method that considerations of purity become most significant (Figure 3). Although this approach offers the advantages of selection of substrate polymers with desirable properties and of a versatility in the introduction of functional groups, it is absolutely necessary to avoid all side reactions involving the polymer chain, since the resultant impurities are covalently bound to the chain and therefore impossible to remove. For example, use of polymers as substrates for nucleophilic sub-

Figure 2. Schematic illustration of copolymerization of active monomer (A) with comonomer (C), for the synthesis of functional polymers.

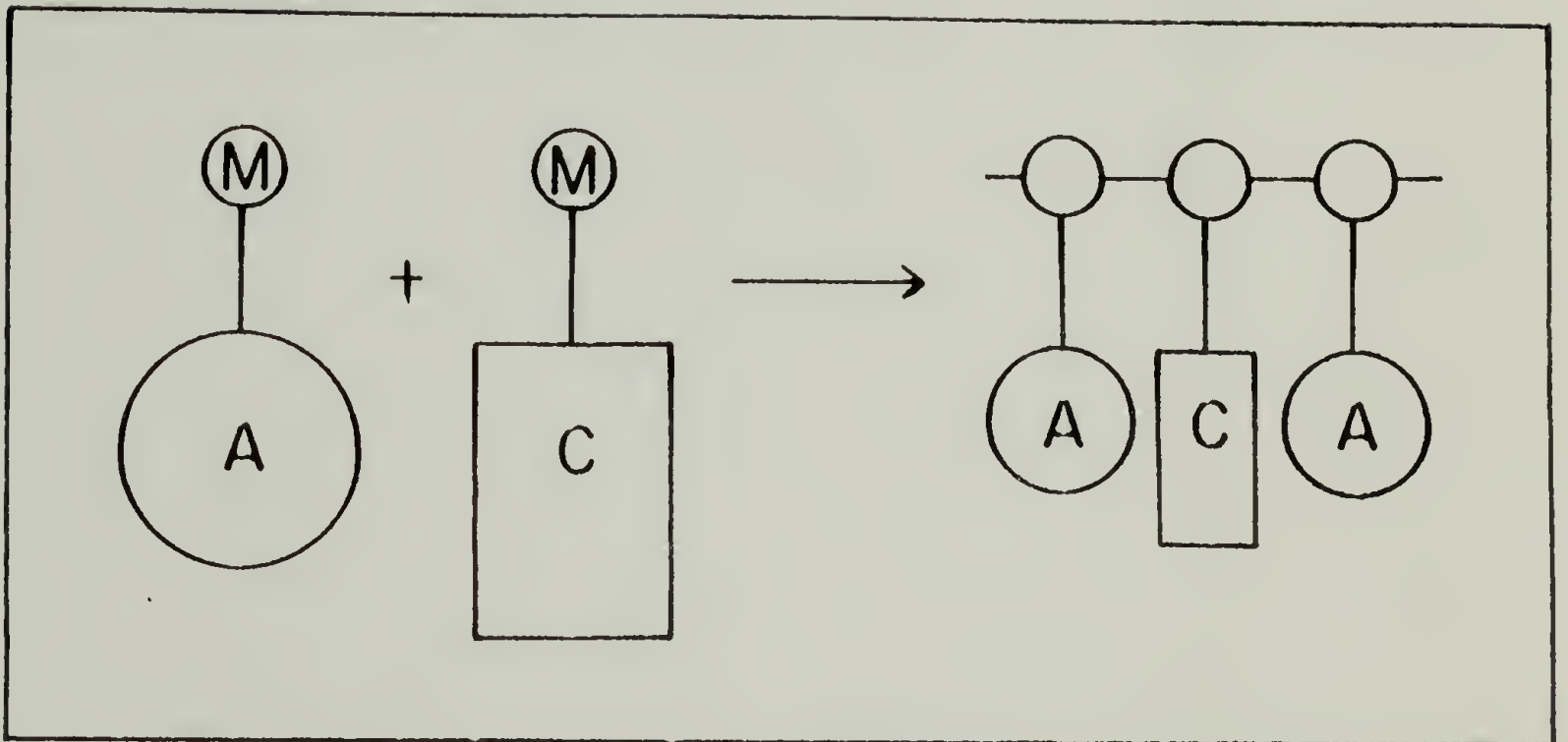
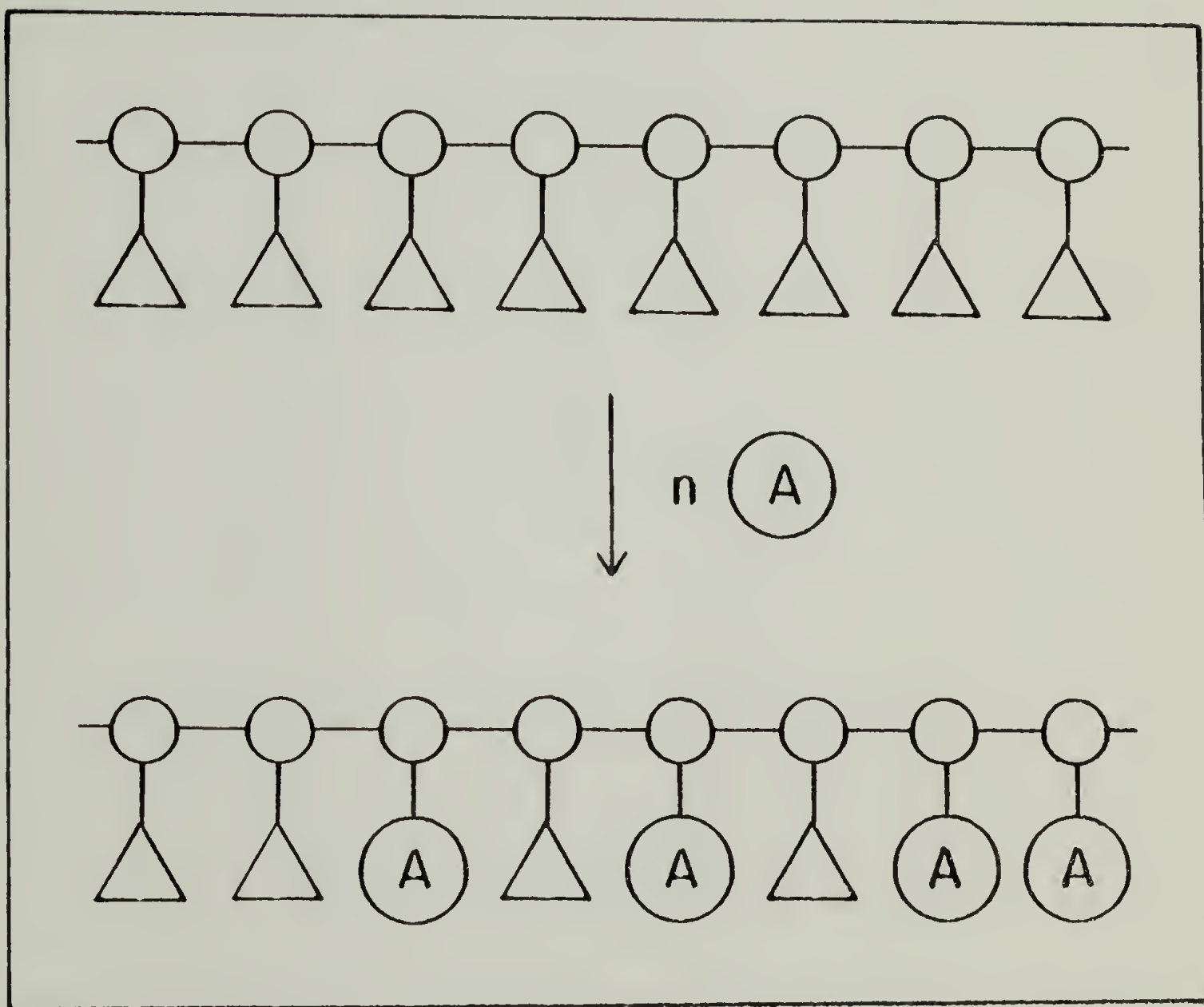


Figure 3. Synthesis of functional polymers via polymer reactions, schematic illustration. (A) is the active functional group.



stitution opens the door to competing elimination reactions, producing undesirable unsaturation in the polymer chain.

B. Preparation and Properties of Salicylic Acid Polymers

Salicylic acid polymers have been prepared by a variety of synthetic methods, and have been employed in rather diverse applications. Because of their relevance to the present work, only vinyl-type polymers of salicylic acid will be discussed in this section; the preparation of salicylic acid--formaldehyde copolymers and salicylic acid polyesters will not be treated. The following paragraphs discuss monomer synthesis and polymerization, and preparation via polymer reactions, and then give a brief outline of the applications of salicylic acid polymers. This discussion is intended to place in perspective the present work on the synthesis and polymerization of vinylsalicylic acid derivatives.

Synthesis of Salicylic Acid Polymers by Radical Polymerization. Salicylic acid polymers have been prepared by a number of radical polymerization techniques: (i) polymerization of methyl methacrylate in the presence of salicylic acid, (ii) polymerization of N-acryloyl or N-methacryloylaminosalicylic acids, (iii) polymerization of vinyl salicylate, vinyl acetylsalicylate or allyl salicylate, (iv) incorporation

of p-aminosalicylic acid into poly(vinyl acetate) by radical chain transfer, (v) polymerization of acryloyl- or methacryloyloxysalicylic acid, and (vi) polymerization of salicylic acid methacrylate.

In 1950, Shapiro reported that polymerization of methyl methacrylate in the presence of salicylic acid at 100°C gave copolymers containing up to 20% salicylic acid.⁶ These copolymers were shown to be useful as thermally curable resins. It is quite probable that salicylic acid units were incorporated by both chain transfer and transesterification, but no details were given.

The preparation and polymerization of N-acryloyl- and N-methacryloyl- derivatives of p-aminosalicylic acid have been undertaken in several laboratories,⁷⁻¹⁴ beginning with the work of Grieger in 1957.⁷ In the most detailed of these studies, Kennedy, et al.,⁹ prepared 4- and 5-acrylamidosalicylic acids, and examined radical polymerization of these compounds with AIBN as initiator. These authors reported complete inhibition of the polymerization in ethanol or in ethylene glycol, unless the acid group was ionized (at high pH) or complexed (with borate). No molecular weight data were given for the polymers obtained in this work.

Reppe¹⁵ and Hopff and Lussi¹⁶ prepared vinyl acetylsalicylate by direct vinylation of the acid in the presence of metal oxide catalysts, and Hardy and coworkers¹⁷ obtained

vinyl salicylate via transesterification of vinyl acetate. The latter group studied the kinetics of the polymerization of vinyl salicylate with AIBN as initiator, and determined a chain transfer constant of 8.0×10^{-3} for the monomer at 70°C. This is approximately a factor of ten greater than the transfer constant of vinyl benzoate,¹⁸ indicating that the phenol group makes a contribution to transfer in the polymerization of vinyl salicylate. Pizzirani and co-workers¹⁹ polymerized vinyl acetylsalicylate in bulk with benzoyl peroxide as initiator, and obtained in 40% yield a polymer of molecular weight 61,000. The glass transition temperature of the polymer was determined to be 60°C.

Hrabek²⁰ incorporated p-aminosalicylic acid into poly(vinyl acetate) through chain transfer, and then converted the polymer into a poly(vinyl alcohol). It was claimed that the salicylate units were present as endgroups in the polymer chains.

Chloromethylation of salicylic acid derivatives followed by reaction with potassium acrylate or potassium methacrylate has also been used to prepare polymerizable salicylic acids. Goldberg and coworkers prepared 3-methyl-5-(acryloyloxymethyl)salicylic acid via this route, and obtained homopolymers and copolymers with methyl acrylate by radical polymerization.²¹ Braun and Boudevska reported polymers of 5-(methacryloyloxymethyl)salicylic acid, prepared by a similar route.²² The latter workers stated that thorough

purification of chloromethylsalicylic acid was prevented by formation of condensation products.

Kotenko and coworkers prepared salicylic acid methacrylate, and reported studies of the pharmacological properties of homopolymers and copolymers of this monomer.²³

Preparation of Salicylic Acid Polymers by Polymer Reactions.

Only two fundamentally-different polymer reactions have been used for the preparation of salicylic acid polymers: ester formation and azo coupling.

Ushakov and coworkers, in their investigation of the anti-tuberculosis activity of p-aminosalicylic acid polymers, incorporated this unit into poly(vinyl alcohol) at levels of up to 10% by weight via a sodium methoxide-catalyzed transesterification of methyl p-aminosalicylate with the polymeric alcohol.²⁴ This reaction was then optimized by Varga and Wolkober, who achieved incorporation of 37 weight percent of salicylate ester units.²⁵ In related work, Ushakov's group esterified poly(vinyl alcohol) with N,O-diacetyl-p-aminosalicyl chloride in interfacial and solution systems, and obtained copolymers containing up to 23 weight percent of ester.²⁶ A similar reaction was used by Italian workers for the incorporation of 5-iodoacetyl-salicylate units into poly(vinyl alcohol),²⁷ and by Tocker in modification of partially-hydrolyzed copolymers of ethylene and vinyl acetate.²⁸

The preparation of salicylic acid polymers via coupling with diazotized polystyrene has been investigated in the Soviet Union.²⁹⁻³¹ The resulting polymers are of interest as complexing agents for metal ions.

Applications of Salicylic Acid Polymers. Salicylic acid polymers such as those described in the preceding paragraphs have been employed primarily in three areas: (i) in studies of the biological activity of synthetic polymers, (ii) in binding of biologically-important compounds such as enzymes and pharmaceuticals and (iii) as complexing agents for metal ions. These uses are discussed below. In addition, the literature contains isolated reports of the use of these polymers in the dyeing of fabrics,⁷ in photographic emulsions,³² and in pressure-sensitive adhesives.^{12,28}

Ushakov and coworkers reported, as early as 1961, that the poly(vinyl alcohol) ester of p-aminosalicylic acid showed in vitro activity against *Mycobacterium tuberculosis*.²⁴ Elimination of the acid from rabbits was found to require longer times than were required after administration of the monomeric form of the drug. Prolonged antibacterial activity was also observed in a p-aminosalicylic acid derivative bound to a polyaldehyde obtained by the oxidation of starch,³³ and a low level of antimicrobial efficiency against *M. tuberculosis* was reported by Hrabek for his poly-(vinyl alcohol) "endcapped" with p-aminosalicylic acid.²⁰

Kotenko and coworkers found that the pharmacological properties of salicylic acid methacrylate injected intravenously into rats were similar to those of free salicylic acid, but that the potency of the polymer was reduced.²³ Antiviral and interferonogenic activities were demonstrated by Abdukhodzhaev and coworkers for copolymers of N-vinylpyrrolidinone and N-acryloyl or N-methacryloylaminosalicylic acids.³⁴ Antiviral activity was determined against encephalitis in mice, and interferon induction was determined following intraperitoneal administration to mice. "Physiologically-active" copolymers of vinyl acetylsalicylate with monosaccharide vinyl derivatives were prepared by Lapenks and Shukin,³⁵ but this reference was available only in abstract form, and details were not provided.

Although the polymers described above represent a rather wide range of structures, it should be pointed out that all of these materials are at least somewhat susceptible to hydrolysis, since linkage of the active group to the polymer chain requires stability of ester, imide or amide bonds. Each of these functional groups may be hydrolyzed under physiological conditions. This is in contrast to the expected behavior of the vinylsalicylic acid derivatives prepared in the present work, in which the carbon-carbon linkage of the salicylate unit to the chain backbone should be quite resistant to breakdown. This makes possible the separation of physiological effects due to the polymer struc-

ture from those due to its hydrolysis products, and simplifies somewhat the evaluation of biological test data.

Salicylic acid polymers, in particular poly(N-acryloyl aminosalicylic acid) and poly(N-methacryloylaminosalicylic acid), have been used for the immobilization (or insolubilization) of biologically-important substances such as enzymes and antibiotics. Kennedy and coworkers³⁶⁻³⁸ used titanium or borate complexes of these polymers to couple proteins such as amylase, glucoamylase and pectinase, although the pectinase complex as found to be inactive.³⁶ This was ascribed to inhibition of the enzyme by the polymer. Selezneva studied the reversible sorption of the proteolytic enzyme terrilytin on poly(N-methacryloylaminosalicylic acid) as a function of pH, and found this polymer to be the most selective of the carboxylic resins tested.¹³ Kennedy's group has also used these polymers to render the antibiotics streptomycin and gentamicin insoluble.³⁹ The resultant complexes were effective against *S. pyogenes*, *S. faecalis*, *P. aeruginosa* and *E. coli*.

Many laboratories have investigated the metal complexation behavior of salicylic acid polymers. These studies were motivated by a desire for rapid, selective agents with high capacity, or by an interest in the properties (e.g. thermal properties) of the complexes themselves. The capacity and selectivity of complexation have been studied by Tolmachov,^{30,31} by Kuznetsova,¹⁰ and by Kennedy and coworkers.⁴⁰ The latter group found substantial selec-

tivity in complexation as a function of pH in poly(N-acryloylamino-salicylic acids). Essentially quantitative uptake of Fe(III), Cr(III), VO₂(II) and Cu(II) was observed at pH 2-5.5. Lower capacities for Ni(II), Co(II), Zn(II), Mg(II) and Cd(II) were noted at pH 4.5-6.0.

The properties of metal complexes of salicylic acid polymers are also of interest. These complexes have been reported to impart UV-resistance to polymer films⁴¹ and to improve the thermal stability of polymers.⁴² In addition, Braun used the reversibility of complexation to produce a reversibly cross-linked poly(5-methacryloyloxymethylsalicylic acid).²² This polymer was cross-linked through addition of Fe(III), but the cross-links could be destroyed by binding the iron in a complex with ethylene diamine tetraacetic acid.

C. Preparation and Properties of Vinylbenzophenone Polymers

In recent years a number of polymerizable 2-hydroxybenzophenones have been prepared, with the objective of developing polymeric ultraviolet absorbers. The most important route to these compounds utilizes the 4-hydroxyl group of 2,4-dihydroxybenzophenone to attach this unit to a reactive monomer capable of free radical, coordination, or ring-opening polymerization. Acrylates, methacrylates and epoxides have been employed as polymerizable substrates.⁴³⁻⁵⁶ Allyl bromides, p-chloromethylstyrene, and epichlorohydrin have

been used as substrates for displacement of halogen, yielding polymerizable ether derivatives of 2,4-dihydroxybenzophenone.⁵⁷⁻⁶⁰ A Claisen rearrangement of 2-allyloxybenzophenone has been used to prepare 3-allyl-2-hydroxybenzophenone, which was copolymerized with ethylene with partial deactivation of the catalyst.⁶¹

Perhaps more relevant to the present work, however, are published studies of the preparation and polymerization of vinylbenzophenone derivatives. The following paragraphs discuss problems of monomer synthesis and polymerization, and synthesis via polymer reactions, and give a brief survey of the applications of such polymers. This discussion is intended to place in perspective the present work on the synthesis and polymerization of 2,4-dihydroxy-4'-vinylbenzophenone.

Monomer Synthesis. The first preparation of 4-vinylbenzophenone appears to be that reported in a patent issued to Kenyon, Waugh and Unruh in 1955.⁶² In this work, vinylacetophenone was prepared by acetylating polystyrene and decomposing the resulting polymer under reduced pressure; a similar procedure gave the benzoylated derivative, 4-vinylbenzophenone. Although other syntheses have been reported, this method appears to have remained the most popular.

In 1956, Gensler, et al. reported an elegant synthesis of 2-vinylbenzophenone from phenyldihydroisoquinoline.⁶³

Treatment with dimethyl sulfate and sodium hydroxide provided a 54% yield of the vinylbenzophenone after distillation.

Reid, et al., employed this method, and reported preparation of the tosylhydrazone, followed by cyclization to the benzo-diazapene.⁶⁴ Although it was reported that 2-vinylbenzophenone polymerized readily during distillation or even on prolonged standing, no polymerization studies have been reported with this monomer.

Braun prepared 4-vinylbenzophenone in 60% yield from p-styrylmagnesium chloride and benzonitrile.⁶⁵

Pogosyan, Zhamkochyan and Matsoyan reported two related syntheses of 4-vinylbenzophenone in 1969.⁶⁶ 4-(2-Bromoethyl)benzoyl chloride was used to acylate benzene in the presence of aluminum chloride, giving an 81% yield of 4-(2-bromoethyl)benzophenone. Dehydrobromination was then accomplished in 90% yield with ethanolic potassium hydroxide. In a second synthesis, the intermediate 2-bromoethyl compound was prepared in 80% yield by acylation of 2-acetoxyethyl benzene with benzoyl chloride followed by hydrolysis and bromination. These workers have also reported studies of the rates of polymerization of 4-vinylbenzophenone,⁶⁷ and of the glass transition temperature of poly(4-vinylbenzophenone).⁶⁸

Polymerization of 4-Vinylbenzophenone Derivatives. Radical polymerization of 4-vinylbenzophenone derivatives appears to

proceed normally, except for an unusual concentration effect. Braun, et al. reported that bulk polymerization of 4-vinylbenzophenone produced insoluble, presumably cross-linked, polymers when the conversion exceeded about 10%.⁶⁹ This was also observed in Pinazzi's work on methoxylated derivatives.^{70,71} In contrast, solution polymerization gave soluble polymers, even up to 75% conversion. If, on the other hand, the solvent/monomer ratio exceeded about 15, only very small yields of polymer were obtained. Similar observations have been made in polymerization of 2-vinylfluorone,⁷² but the effect has not been explained.

Reactivity ratios for several 4-vinylbenzophenone derivatives in copolymerization with styrene have been determined; these are summarized in Table 1.

TABLE 1

Reactivity Ratios for 4-Vinylbenzophenone Derivatives^a

M ₂	r ₁	r ₂	Ref
4-Vinylbenzophenone (4-VB)	0.18 \pm 0.08	3.0 \pm 0.3	69
2-Methoxy -4' -VB	0.28 \pm 0.02	1.6 \pm 0.3	70
4-Methoxy-4' -VB	0.38 \pm 0.05	1.6 \pm 0.3	70
2,4-Dimethoxy-4' -VB	0.41 \pm 0.02	2.1 \pm 0.2	70

^aM₁ = Styrene

Synthesis of Poly(4-Vinylbenzophenones) by Polymer Reactions.

The polymer reaction approach has been used more frequently than the monomer synthesis route for the preparation of polymers of 4-vinylbenzophenone derivatives. This goes back to the patent of Kenyon et al., in 1955.⁶² The same laboratory reported the use of other acylating agents, in addition to benzoyl chloride, in 1958, in a patent covering "photosensitive polymers,"⁷³ and similar work was reported three years later by Kuznetsov, Prokhorova and Faizulline.⁷⁴ Braun studied the addition of poly(p-lithiostyrene) to a series of nitriles, and obtained, with benzonitrile, 58% conversion to benzophenone units after treatment of the intermediate ketimine with hydrochloric acid and methanol.⁷⁵ Tocker treated polystyrene with salicyl chloride under Friedel-Crafts conditions, and observed acylation of 70% of the monomer units.⁷⁶ This copolymer was then incorporated into poly(vinyl fluoride) to give a light-screening polymer film.

More recently, a first attempt to prepare 2-hydroxy-4'-vinylbenzophenone derivatives was made.^{70,71} This work is discussed in this section on polymer reactions because modification of the polymers was required to obtain the desired hydroxylated structures. The preparations of 2-methoxy-4'-vinylbenzophenone, 2,4-dimethoxy-4'-vinylbenzophenone and 4-methoxy-4'-vinylbenzophenone were achieved through the reactions of the corresponding methoxybenzalde-

hydres with p-styrylmagnesium chloride, followed by chromic acid oxidation to the ketone. These compounds were homopolymerized and copolymerized with styrene with a radical initiator to give high molecular weight polymers. In order to convert these polymers to useful ultraviolet absorbers with a free 2-hydroxyl group, it was necessary to demethylate the 2-position. This reaction could be forced to essentially 100% conversion with aluminum chloride in nitrobenzene, but only at the expense of a substantial decrease in molecular weight.

The same authors have recently described another polymer-reaction approach to this problem.⁷⁷ Poly(4-vinylbenzoyl chloride) was treated with resorcinol under Friedel-Crafts conditions, giving partial acylation and formation of a copolymer of 2,4-dihydroxybenzophenone and 4-vinylbenzoic acid. The extent of acylation was limited to approximately 20% in this reaction. Also described in this paper was a Fries arrangement of poly(3-methoxyphenylvinyl benzoate), giving polymers containing up to 50 mole percent 2-hydroxy-4-methoxy-4-vinylbenzophenone groups.

Applications of Vinylbenzophenone Polymers. Vinylbenzophenone polymers have been applied in several areas: (i) in studies of photodegradation and energy transfer in polymers, (ii) as parent polymers for grafting reactions, (iii) as light sensitive materials for use in photoresists, (iv) in chemical synthesis on polymer supports, (v) in purification

of organic materials, and (vi) as ultraviolet absorbers. The following discussion is a very brief survey of this work.

The photochemistry of poly(4-vinylbenzophenone) has been studied primarily by three groups. Searle et al., at Eastman Kodak, reported that the quantum efficiencies of stilbene photoisomerization were identical for reactions sensitized by 4-methylbenzophenone and by poly(4-vinylbenzophenone).⁷⁸ This was in agreement with earlier work on poly(vinylphenyl ketone),⁷⁹ and consistent with later work on poly(β -naphthoystyrene).⁸⁰ Poly(α -naphthoystyrene), however, was shown to sensitize the trans \rightarrow cis isomerization with lower efficiency than the model compound, p-ethyl β -naphthophenone.⁸⁰

Geuskens and coworkers have studied poly(4-vinylbenzophenone) and 4-vinylbenzophenone-styrene copolymers in the solid state and in solution. Inter- and intramolecular pinacol formation,⁸¹ energy transfer to naphthalene,^{82,83} and polarization of phosphorescence⁸⁴ were investigated. Geuskens has also reviewed the photodegradation of poly(vinylbenzophenone) and other polymers.⁸⁵

Hrdlovic and Lukac have reported two studies of poly(vinylbenzophenone) photochemistry.^{86,87} In a comparison of chemically-bound vs. added benzophenones as sensitizers for the addition of maleic anhydride to polystyrene, the copolymerized sensitizer gave the higher degree of photochemical addition.⁸⁶ This was ascribed to the higher

effective concentration of sensitizer in the polymer coil. These workers have also reported Stern-Volmer constants of poly(4-vinylbenzophenone) and related polymers.⁸⁷

Poly(4-vinylbenzophenone) has been used in a variety of ways to produce sites for grafting of monomers via anionic and photopolymerization. Treatment of the polymer with sodium metal in a polar solvent gives the polymeric ketyl, which has been used for grafting of acrylonitrile, methyl methacrylate, styrene and 2- and 4-vinylpyridines.^{65,88-90} Sodium naphthalene has been shown to be suitable for the preparation of parent polymers for grafting of aldehydes.⁹¹ Sumitomo and coworkers used a benzoylated polystyrene containing 4% benzophenone units for a photoinitiated grafting of methyl methacrylate.⁹²

Several modified forms of poly(4-vinylbenzophenone) have also been used by Braun and coworkers for anionic grafting. The polymeric anil was treated with sodium in THF and used for grafting of acrylonitrile, methyl methacrylate and styrene,⁹³ and reaction of poly(4-vinylbenzophenone) with methyl magnesium iodide followed by sulfuric acid produced p-vinyl-1,1-diphenylethylene units which served as highly efficient sites for grafting of the same monomers.^{94,95}

The literature contains several brief reports of the use of poly(4-vinylbenzophenone) and related polymers as light-sensitive materials for use in photoresists or in similar applications. Reynolds and Borden claim that poly-

mers containing thallated aryl groups are sensitive, positive-working resists, and may be prepared by thallation of the preformed polymer with thallium trifluoroacetate.⁹⁶

In a Japanese patent, Kato and Yamazaki claim the synthesis of a photodecomposable copolymer of 4-vinylbenzophenone and methyl methacrylate.⁹⁷

Two groups have used poly(4-vinylbenzophenone) for the preparation of supports for oligonucleotide synthesis. Hayatsu and Khorana benzoylated polystyrene to 30% conversion and treated the resulting polymer with p-methoxyphenyl magnesium bromide to give the trityl alcohol. Acetyl chloride was then used to form the trityl chloride group, which was used in a fashion analogous to the use of chloromethylated polystyrene in the Merrifield peptide synthesis.⁹⁸ An essentially identical preparation was carried out by Cramer and coworkers.⁹⁹

Baer used the ketyl form of a crosslinked poly(4-vinylbenzophenone) to remove acid impurities from organic solvents.¹⁰⁰

Tocker⁷⁶ and Pinazzi and coworkers¹⁰¹ claimed the use of poly(4-vinyl-2'-hydroxybenzophenones) as ultraviolet stabilizers, but no details were given.

D. Polymers in the Prevention of Light-Induced Damage to the Skin

The design of effective agents for prevention of the harmful effects of solar radiation requires consideration of a number of factors in addition to photochemical behavior. It is not sufficient to produce protective agents that absorb strongly in the ultraviolet and that possess pathways for nondestructive dissipation of the absorbed energy; in fact, it is most often not photochemical behavior that ultimately determines the success of a compound in this application. These additional considerations apply whether one is concerned with prevention of oxidative photodegradation of synthetic polymers, or with prevention of erythema ("sunburn") and cancer in the human skin. Bailey and Vogl¹⁰² have reviewed the use of polymers in the first of these two areas; the present discussion addresses the latter problem.

The problem of sunlight-induced damage to the skin is indeed severe. In addition to countless cases of painful sunburn, the U.S. Food and Drug Administration has recently expressed concern about the number of deaths due to sun-induced skin cancers in this country--1409 in 1973 by FDA figures--and has called for more stringent regulation of protective products.¹⁰³

The most direct method of protecting the skin from ultraviolet light-induced damage is to apply to its surface

a very thin layer of a substance that prevents transmission of the harmful radiation (a "sunscreen"). In order to function effectively, the sunscreen must perform satisfactorily in several respects. First of all, of course, the compound must exhibit appropriate photochemical behavior. It must possess a high extinction coefficient in the region of 300-310 nm, since the combination of erythema sensitivity [maximum at 297 nm¹⁰⁴] and solar radiation intensity makes this the most damaging radiation, and it must be reasonably stable, since degradation products may provide insufficient protection or may cause discoloration and staining. A reasonably sharp decrease in extinction coefficient at longer wavelength may also be desirable, since the "quick-tanning" of the skin due to oxidation of melanin is most effectively promoted by 340-360 nm radiation. There are many compounds known to exhibit these characteristics; the use of these compounds in sunscreen preparations has been reviewed.^{104,105} Among the most successful compounds are derivatives of p-aminobenzoic acid, salicylic acid, or 2,4,-dihydroxybenzophenone.

The protective agent must also possess a moderate degree of permanence in order to provide long-term protection without the inconvenience and expense of repeated application. The lifetime of a sunscreen compound on the skin is limited by two factors: removal by water or perspiration, and percutaneous absorption. The solubility characteristics

of the compound are critical in determining its effective lifetime.

When in place on the skin, the film of protective agent must be uniform, and free of defects or voids. This requires compatibility with the skin surface and with other substances in the sunscreen composition, in order to prevent phase separation or crystallization, since such processes result in unprotected areas on the skin surface. Similarly, the applied layer must remain fluid and continuous, and must not be removed by mechanical abrasion. It is largely this consideration that results in the widespread use of amyl p-(N,N-dimethylamino)benzoate in commercial sunscreen products; the amyl ester melts below -50°C and does not crystallize prior to or in use, whereas the ethyl ester melts near 65°C and provides much poorer protection.¹⁰⁴ Use of the dialkylamine rather than the primary aromatic amine offers additional advantages as well; alkylation results in a slight hypsochromic shift of the absorption maximum, making the spectral properties nearly ideal for sunscreen applications, and also prevents oxidation of the aromatic amine with its attendant discoloration and staining problems.

A final consideration in the design of suncreening agents is that of toxicity. The possibility of allergic reaction on the skin surface is obviously a problem, but in addition, systemic toxicity as a result of skin penetration must be considered. For example, increased levels of p-amino-

benzoic acid or salicylic acid are observed in urine 30 minutes after application of sunscreens containing esters of these acids,¹⁰⁴ so that systemic toxicity should not be ignored. Although sunscreens have been used without apparent ill effects for many years, topical application of related substances has caused medical problems; in particular, acute intoxication and poisoning have occurred following topical application of salicylic acid derivatives.^{106,107}

The use of polymers as protective agents in sunscreen formulations offers the prospect of improved performance with respect to three of the above-mentioned design criteria: permanence, compatibility, and toxicity. Permanence and compatibility may be favorably influenced by manipulation of molecular weight, solubility, and skin-binding properties, and the use of high molecular weight substances reduces the possibility of undesirable skin penetration.

That these potential advantages are recognized in industrial laboratories is apparent from the recent appearance of several patents dealing with sunscreen products containing synthetic polymers.¹⁰⁸⁻¹²⁰ Polymers have been used as additives to promote rapid drying and long-term performance; an ethylene-maleic anhydride copolymer¹⁰⁸ and a poly(N,N-dimethylacrylamide)¹⁰⁹ have been employed for these purposes. Of more direct relevance to the present work is the direct incorporation of ultraviolet absorbers into polymer chains via covalent bonds. Bailey and Vogl

have recently reviewed the field of polymeric UV absorbers;¹⁰² the following discussion highlights recent work aimed specifically at polymers for skin protection.

Noruse et al.¹¹⁰ produced polymeric UV absorbers for skin protection by reaction of aromatic isocyanates with Nylon 6 or Nylon 12; the polymers were reportedly nontoxic. Skoultchi and Meir^{111,112} prepared a series of 4-(N,N-dialkylamino)benzoic acid derivatives by alkylation of the free amine with excess allyl chloride, and copolymerized these allylic compounds with acrylic acid, hydroxypropyl acrylate, and methyl acrylate. Ciaudelli¹¹³ prepared sunscreen formulations containing a polyethyleneimine that was partially substituted with p-dialkylaminobenzoyl units; incorporation of the absorber up to 15% substitution was accomplished using the acid chloride of the desired p-dialkylaminobenzoic acid. Most active in this area has been the group at S.A. Oreal.¹¹⁴⁻¹¹⁸ Acrylamide derivatives of hydroxybenzophenones, benzylidene camphor, and hydroxycoumarins were prepared and polymerized by this group. Comonomers such as stearyl methacrylate or N-vinylpyrrolidone promoted compatibility with the skin, and the copolymers were reported to be long-lasting and non-absorbable. Copolymers of vinyl glycolate cinnamate and dimethylaminoethyl acrylate were quaternized with dimethyl sulfate and used in sunscreen oils. Recent work in this country has come from laboratories at Gillette and at the Colgate-Palmolive Co. Johnston¹¹⁹ reported that sunscreen

compositions containing polyvinylbutyrals containing up to 5% p-dimethylaminobenzoate units were not readily removed from the skin by contact with water, but that they were easily washed off with soap and water. These polymers were obtained by reaction of polyvinylbutyral with p-dimethylaminobenzoyl chloride. Gerecht and Epstein¹²⁰ stated that sunscreens containing a copolymer of N-allylsalicylamide and p-guanidylstyrene showed improved skin adhesion.

The use of polymeric ultraviolet absorbers in the prevention of light-induced damage to the skin clearly offers advantages in comparison with the use of traditional protective agents. In spite of these advantages, and in spite of the attractiveness of many patent claims, the author is unaware of the use of polymeric ultraviolet absorbers in commercial sunscreen products.

E. Biological Activities of Salicylic Acid and Acetylsalicylic Acid

This section is a very brief discussion of the biological activities of salicylic acid and acetylsalicylic acid (aspirin), and is intended to provide a background for the evaluation of the polymeric salicylic acid derivatives prepared in the present work. The literature in this area is staggering; a review by Gross and Greenberg in 1948 listed over four thousand references,¹⁰⁷ and the

relevant papers now number in the tens of thousands.¹²¹ Only the most important pharmacological actions of these compounds have been selected for discussion in this section. Because of the overwhelming importance of the use of aspirin in medicine, emphasis is placed on the activity of this compound. A brief treatment of the antibacterial action of salicylic acid is included at the end of this section because of its relevance to the antibacterial test data presented in Appendix A of this dissertation.

Aspirin has achieved its prominence among modern drugs by virtue of its broad spectrum of pharmacological action. Collier¹²¹ has presented a detailed pharmacological analysis of aspirin, and has enumerated the most significant of these actions: (i) antipyresis (reduction of fever), (ii) analgesia (relief of pain), (iii) relief of inflammation, (iv) antihemostasis, and (v) damage to epithelia, particularly the gastric mucosa. Obviously, not all of these actions are desirable, and the use of aspirin is not without hazard. It is, at least in part, these hazards which motivate research directed at development of new therapeutic agents related to aspirin; this dissertation describes one novel approach to this problem.

The following paragraphs present a brief treatment of the pharmacology of aspirin, in man and in experimental animals. This is followed by speculation on its mode of action, in particular, on the increasingly-attractive hypothe-

sis that all of the aforementioned effects may arise through a common mechanism--the inhibition of prostaglandin synthesis.¹²² Finally, the antibacterial activity of salicylic acid is briefly discussed.

Aspirin lowers human body temperature which has been elevated pathologically,¹²³ but it does not appreciably lower normal body temperature. The same effect has been observed in laboratory animals; in mouse, rat and guinea pig, aspirin was less effective in lowering normal body temperature than in lessening fever induced with yeast.¹²⁴ In comparison with sodium salicylate, aspirin is more effective both in experimental animals¹²¹ and in clinical fever.¹²⁵ Doses of 22-200 mg/kg have been shown to be sufficient to reduce fever induced by microbial toxins in every animal species tested.

Aspirin's analgetic properties account for much of its use, but it was not until 1953 that proof of its analgesia in man was obtained.¹²⁶ Since that time, effectiveness against muscle pain induced by pressure or by depletion of blood has been shown in several laboratories.¹²⁷⁻¹³⁰ Interestingly, aspirin is not effective against all kinds of pain, nor is it equally effective at all body sites in reducing the response to pain induced in a certain way. For example, aspirin is not effective against pain induced by pinching the tail or toes of mouse, rat or guinea pig,¹³¹⁻¹³⁴ although it does reduce the response to mechanical stimula-

tion of an inflamed site.¹³⁴ Concerning the site of irritation, aspirin suppressed the guinea pig's response to pain induced by the application of bradykinin in the circulatory system, but not in the skin.^{135,136} This selectivity in analgetic action distinguishes aspirin from agents such as morphine, which act on the central nervous system. Morphine has been effective in all tests of its analgetic activity in mammals.¹³³ Aspirin is significantly superior to sodium salicylate in analgetic potency.¹²¹

Aspirin has useful anti-inflammatory properties, which account for the widespread use of the drug in treatment of rheumatoid arthritis.¹³⁷ Inflammation is a process involving an influx of blood, exudation of fluid through the walls of blood vessels and infiltration and proliferation of cells at the affected site.¹²¹ Aspirin inhibits this process and is effective in reducing the size of joints inflamed by arthritis. The potencies of aspirin and sodium salicylate as anti-inflammatory agents do not appear to be substantially different.¹²¹

The antihemostatic properties of aspirin have been noted clinically and in experimental animals. Prolongation of prothrombin time,¹³⁸ prolongation of bleeding time in volunteers,¹³⁹ and inhibition of platelet aggregation¹⁴⁰⁻¹⁴² have all been observed. These properties have been put to use in the treatment of patients with synthetic heart valves in which the lifetime of platelets is reduced by contact

with the foreign surface. On the other hand, these same properties probably exacerbate the problem of gastric bleeding which sometimes accompanies administration of salicylates.

Damage to epithelia accompanying the administration of salicylates is usually manifest in the form of loss of blood in the feces. Continued treatment with aspirin results in the loss of more than 2 ml of blood daily in a majority of subjects, and loss of more than 15 ml in about 5% of subjects.^{121,143,144}

Because of the character of many of the pharmacological actions of aspirin, Collier¹²¹ suggested that it should be called an "anti-defensive" drug, i.e., that it inhibits the "defensive reactions" of the body. This is consistent with many of the actions of the drug, for example, its ability to lower pathologically-elevated body temperature without affecting normal temperature. Evidence that prostaglandins mediate many defensive reactions then led to the suggestion that aspirin acts by depressing the biosynthesis of prostaglandins, or by antagonizing prostaglandins already formed. This hypothesis was strengthened by the discovery that aspirin (and sodium salicylate) can inhibit the biosynthesis of prostaglandins in vitro in concentrations which are therapeutically significant.¹⁴⁵⁻¹⁴⁷ Finally, in a very recent paper, Roth and Siok have presented evidence that aspirin effects inhibition of prostaglandin synthesis

through acetylation of the amino-terminal seryl residue of prostaglandin synthetase.¹⁴⁸ Whether or not this mechanism can account for all of the actions of aspirin, it is becoming increasingly clear that the interaction of aspirin with prostaglandins is of tremendous importance in understanding the pharmacology of the world's most heavily-used drug.

Antibacterial Activity of Salicylic Acid. Although an authoritative source¹⁴⁹ has stated that "salicylic acid is unimportant as an antibacterial agent," it has been suggested that the very broad spectrum of its antimicrobial activity makes salicylic acid more useful in the treatment of skin infections than substances which are more potent against a narrower range of organisms.¹⁵⁰ Topical use allows application of high concentrations of antibacterial agents, offsetting the low potency of salicylic acid. Salicylic acid is active against a wide range of pathogenic bacteria, fungi and yeasts, and thus may be used in a large number of topical infections. This is significant with respect to the present work, since it is almost certainly in topical applications that biologically-active polymers will find their first major uses.

The mechanism of the antibacterial action of salicylic acid does not seem to have been firmly established, but it is likely to involve the chelation properties of the

compound.¹⁵¹ The stability constants of salicylic acid metal chelates are orders of magnitude greater than those of cellular chelators, and salicylic acid can thus compete successfully for physiologically-vital metals. This may results in killing of bacteria through the inactivation of bacterial enzymes. Should this be the case, the use of polymeric salicylic acids as antibacterial agents may be feasible, since the polymeric derivatives retain chelation properties.

F. Retardation of Radical Polymerization by Phenolic Compounds

An issue common to the polymerization of vinyl derivatives of salicylic acids and to that of 2,4-dihydroxy-4'-vinylbenzophenone is the possible interference of the phenol groups of these compounds in the radical chain growth reaction. Phenolic compounds, most commonly hydroquinone or its monomethyl ether, are frequently employed with much success as stabilizers in commercial vinyl monomers, and also as "shortstops" in processes such as emulsion copolymerization of styrene and butadiene. In view of these properties, it might be expected that severe branching, transfer or termination of the kinetic chain would preclude attainment of high molecular weight polymers from vinyl monomers bearing phenol groups. The following section examines the phenomena observed in radical polymerization in

the presence of phenolic compounds, in an attempt to clarify the question of their interference in polymer chain growth. Where appropriate, information gained in studies of inhibited oxidation reactions will be discussed as well. Oxidation of hydrocarbons is known to proceed through radical intermediates, and very thorough studies of this process have been made. Much of the available information concerning hydrogen abstraction reactions has been gathered in these experiments.

At the outset of this discussion, it is useful to mention briefly the distinction frequently made between inhibition and retardation of radical polymerization. This is a useful distinction when discussing observable phenomena, but does not speak directly to the question of mechanism. Ideal inhibitors are defined as substances which cause an induction period in the polymerization of vinyl monomers.¹⁵² During the induction period, the inhibitor consumes initiating radicals (and is itself consumed) at such a rate that polymerization does not occur. After the induction period, i.e., after complete consumption of the inhibitor, polymerization begins with the normal rate. Retarders, on the other hand, cause a reduction in rate during the entire polymerization without giving rise to an induction period. In fact, the division is not as clear-cut: inhibitors may form products during the induction period which later retard the polymerization, while retarders used in large quantity may

cause induction periods. Thus, while the phenomena may be distinguished in this way, it is far less useful to attempt to classify a compound, or a family of compounds, on this basis.

A study of the literature concerned with the effect of phenols on the radical polymerization of vinyl monomers reveals many apparent inconsistencies, but certain conclusions do appear to be justified. First, the effectiveness of phenols as polymerization inhibitors depends markedly on the presence of oxidizing agents, most typically oxygen, peroxides or quinones, in the reaction mixture. Breitenbach, Springer and Horeischy¹⁵³ made the original observation that hydroquinone in the absence of air has no effect on the rate of thermal polymerization of styrene, and this was supported by later work of Walling and Briggs¹⁵⁴ on methyl methacrylate, although the latter work indicated that quantities in excess of 0.1 weight percent led to a "slight drop in rate." Walling and Briggs found tert-butylcatechol and pyrogallol to be similarly ineffective at low concentration. On the other hand, hydroquinone and other phenols have been shown to be effective in inhibition or retardation of the polymerizations of styrene,^{155,156} methyl methacrylate,^{157,158} butadiene¹⁵⁹ and butadiene-styrene¹⁶⁰ in the presence of oxygen or benzoyl peroxide. Table 2 illustrates this situation for tert-butylcatechol in thermal polymerization of styrene:¹⁵⁵

TABLE 2

tert-Butylcatechol as Inhibitor of Styrene Polymerization^a

Conc (ppm)	Conversion	
	Air Present	In Vacuo
0	12%	13.3%
50	0	10.5
100	0	7.5

^a24 hr, 80°C

Only a slight reduction in rate is caused by the presence of 50 ppm of tert-butylcatechol in the absence of air, but in an open tube, the polymerization appears to be completely inhibited. These data are typical of the observations made with many phenolic compounds. A survey of these observations appears below.

Foord¹⁶¹ reported the first comprehensive study of inhibition and retardation of radical polymerization. Foord studied the bulk thermal polymerization of styrene at 60, 90, and 120°C, in the absence of oxygen. Approximately 130 compounds were evaluated, using a viscometric technique for rate determinations. Hydroquinone and catechol were found to produce some induction period, and catechol some retardation. Pyrogallol gave strong retardation with little induction period, and phenol and the cresols were relatively ineffective. Foord concluded that phenolic compounds should

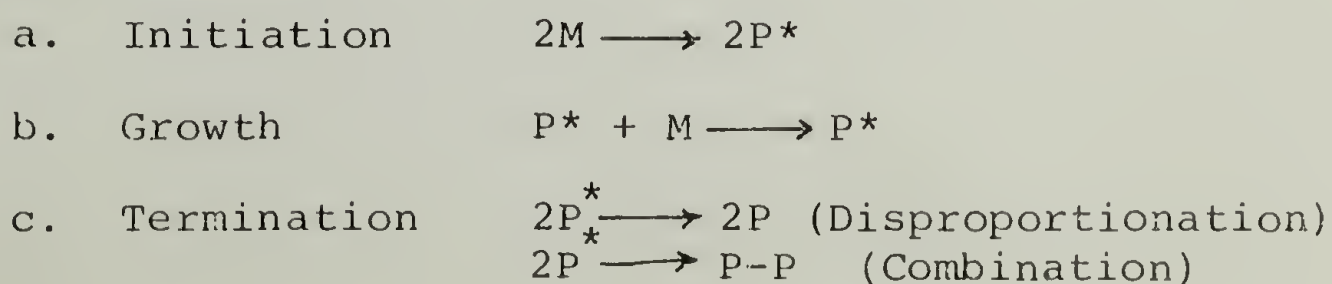
be classified as "retarding agents with a weak inhibiting action."

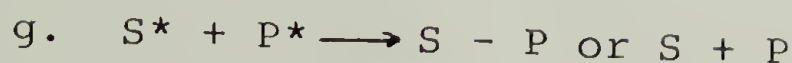
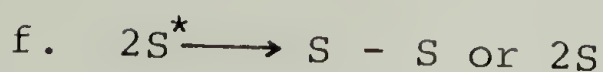
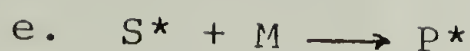
Frank and Adams¹⁶² then published a study of 12 inhibitors, or potential inhibitors--nitro compounds, quinones, amines, phenols and phosphites--under standard conditions in the thermal polymerizations of styrene, 3,4-dichlorostyrene and 5-ethyl-2-vinylpyridine. These reactions were run in sealed tubes, but it is not certain that oxygen was rigorously excluded. A viscometric technique was also used here, and the length of time required to obtain a measurable increase in viscosity was regarded as the induction period. Hydroquinone only slightly increased the induction period (from "less than 9 hours" to 9 hours) even at a concentration of approximately 10 percent by weight. *tert*-Butylcatechol produced an induction period of 34 hours; *p*-benzoquinone, 81 hours.

Walling¹⁶³ examined the polymerization of styrene in phenolic solvents (*m*-cresol and thymol) with the objective of clarifying an earlier report¹⁶⁴ that such polymerization was cationic in nature. Thermal and benzoyl peroxide-initiated systems were studied, in the absence of air, and the data were interpreted in terms of radical polymerization in which chain transfer to the solvent yielded rather unreactive solvent radicals. In the thermal reaction at 131°C, the rates in *m*-cresol and in thymol were substantially reduced with respect to that in toluene, and thymol was the more ef-

fective retarder. In the benzoyl peroxide-initiated reaction, inhibition was observed in *m*-cresol at 60 and 100°C, and was ascribed to rapid decomposition of the initiator. This decomposition was later shown to proceed, at least partially, through non-radical intermediates.¹⁶⁵ This interpretation differs from that given by Bartlett and Nozaki¹⁶⁶ in their study of induced decomposition of benzoyl peroxide in ethers, alcohols, phenols and amines. The latter authors assume a radical chain process, and attribute the observed lack of inhibition of the process by oxygen to the low reactivity of the phenoxy radical with oxygen. Walling and Hodgdon¹⁶⁵ however, showed that at 30°C, the presence of other radical traps (polymerizable monomers and iodine) has no effect on the rates or products of the reaction, and conclude that radical intermediates are not involved. Such a non-radical mechanism for the decomposition of initiator would account for the inhibition observed in Walling's experiments.

Walling also provided a basic kinetic scheme for inhibition and retardation--a scheme used by several later groups in interpretation of observations concerning phenolic compounds. This scheme is as follows (for thermal styrene polymerization):





where M is a styrene molecule, P is a polymer molecule, S is solvent (or phenol) and the asterisk represents an active center. This is an extension of the treatments of chain transfer given earlier by Flory¹⁶⁷ and by Mayo.¹⁶⁸ Reactions a) - c) represent the normal initiation, growth and termination steps common to radical chain processes. Reaction d) is responsible for transfer of the active center to solvent (or phenol), and the fate of such active centers may be described by any (or all) of reactions e) - g). Reaction e) represents normal chain transfer, and f) and g), termination (of one chain per solvent molecule in f), and of two chains per solvent molecule in g)). Analysis of the kinetics of thermal styrene polymerization at 131°C indicates reactions f) and g) are favored over e) when the reaction is run in m-cresol. In other words, radicals derived from m-cresol are ineffective in reinitiating chain growth.

Edwards, Harris and Seaman¹⁶⁹ also studied the thermal polymerization of styrene in the absence of oxygen, and determined rates and degrees of polymerization in the presence of pyrogallol, tert-butylcatechol, catechol and thymol. Retardation was observed in all four systems, with the retarding efficiency decreasing in the order given above.

Molecular weights were also found to be substantially reduced, and analysis of the kinetics according to Walling's scheme indicated regeneration of kinetic chains.

In a more extensive study, Godsay, Harpell and Russell¹⁷⁰ reported chain transfer constants for approximately 30 phenols in styrene polymerizations. These workers carried out the reaction in the absence of oxygen, and employed AIBN as a radical initiator. The observed phenomena were consistent with the work of Edwards, et al., but the interpretation differed with respect to the fate of the phenoxy radicals. Godsay, et al., observed that with many of the phenols the rate of polymerization was only slightly affected by the addition of the phenol. There was usually a small decrease in rate, but this could be simply ascribed to the decrease in monomer concentration. These compounds were treated using Walling's scheme, and appeared to behave as simple transfer agents. Significantly, a kinetic deuterium isotope effect of magnitude 6.4 was determined for 1-naphthol when the hydroxyl proton was replaced with deuterium, indicating that the primary transfer reaction involves abstraction of this hydrogen atom. The actual isotope effect may be significantly greater than this, since the degree of deuteration was less than 100%. Although no attempt was made to calculate a Hammett ρ -value for the transfer reaction, examination of the data indicates that electron donating substituents activate the phenol with

respect to abstraction.

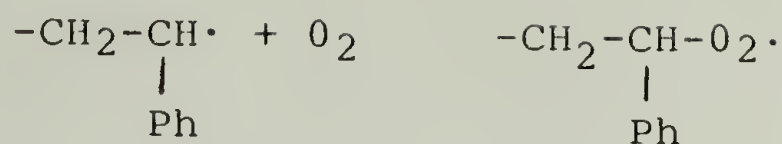
The above discussion is consistent with the suggestion that phenoxy radicals disappear by reinitiation of chain growth; however, Godsay, et al., observed that with a second group of phenols, retardation occurred.¹⁷⁰ Pyrogallol, tert-butylcatechol and catechol were in this group, and, consistent with earlier work, the retardation efficiency decreased in that order. Analysis of the kinetics, and calculation of the efficiency of reinitiation, however, indicated that only a very small fraction of the radicals produced successfully initiated the growth of new polymer molecules. Clearly, it is necessary to consider not only the generation of inhibitor radicals, but also their fate, when considering the question of inhibition efficiency.

Caldwell and Ihrig¹⁷¹ studied the effect of hydroquinone on the AIBN-initiated polymerization of methyl methacrylate, in the absence of oxygen. The kinetics were analyzed according to the usual scheme, and compared with results for benzoquinone and for 1,4-naphthalenediol. Benzoquinone was shown to be several hundred times more effective than hydroquinone in reducing the rate of polymerization. A significant difference in kinetics was also observed: with benzoquinone, the efficiency of reinitiation was essentially zero, while hydroquinone fit the equation calculated for high efficiency of reinitiation. This difference in kinetic behavior led these authors to suggest

that the inhibitor radicals formed in the two systems are different. Since the intermediate radical formed in benzoquinone-retarded polymerizations was thought to be a semiquinone, a substituted semiquinone or a semiquinone ether,¹⁷² the authors suggested that hydroquinone retardation does not involve hydrogen atom abstraction to give a semiquinone. Instead, a loose addition complex of the phenol with polymethyl methacrylate radicals was postulated. This is analogous to the complex suggested by Hammond, et al., in phenol-inhibited oxidation.¹⁷³ Hammond's suggestion was based largely on his failure to observe a deuterium isotope effect in the inhibition of tetralin oxidation by N-methylaniline or diphenylamine, but his work has been criticized by Ingold,¹⁷⁴ who has pointed out that rapid exchange of deuterium occurs with hydroperoxides formed in the oxidation. Thus, lack of an isotope effect does not require complex formation; however, the difference in behavior of radicals from benzoquinone vs those from hydroquinone is more difficult to reconcile with a straightforward hydrogen abstraction mechanism.

The above discussion was concerned with polymerizations carried out in the absence of oxygen. If reactions in the presence of oxygen are considered, the results are substantially different. There are two reasons why this is so: first, the addition of oxygen to a growing polymer radical is extremely rapid; in styrene polymerization, for

example, the reaction:



occurs approximately 2.5×10^5 times as rapidly as addition of styrene monomer.¹⁷⁵ This means that the polymer radical is no longer a substituted alkyl radical, but rather a peroxy radical. Secondly, many phenolic compounds may be oxidized to the corresponding quinones in the presence of oxygen. One then observes the retarding effect of the quinone, rather than the phenol. A similar situation arises in polymerizations initiated by peroxides: the first-formed radicals are alkoxy radicals, rather than alkyl radicals, and the phenolic inhibitor may be oxidized to the quinone or to related products.^{176,177} The following discussion concerns the inhibition of radical polymerization by phenolic compounds in the presence of oxygen or peroxides.

Cohen¹⁷⁸ studied the benzoyl peroxide-initiated polymerization of styrene in vacuum, although it does not appear that oxygen was rigorously excluded. Hydroquinone and its mono- and diethyl ethers were examined, along with 2,5-di-tert-butylhydroquinone and toluhydroquinone. The results appear in Table 3. As expected, hydroquinone diethyl ether had no effect on the polymerization. All of the phenolic compounds, however, reduced both the rate and the degree of polymerization. Cohen ascribed this to oxidation to benzoquinone by reaction with benzoyl peroxide

TABLE 3
Hydroquinones as Inhibitors of Styrene Polymerization^a

Additive ($4.5 \times 10^{-3}M.$)	Rate (%/hr)	η_{sp}/c (dl/g)
None	8.61	2.23
Hydroquinone Diethyl Ether	8.60	2.27
Hydroquinone Monoethyl Ether	6.06	1.91
2,5-Di-t-butylhydroquinone	5.20	1.71
Hydroquinone	4.04	1.56
Toluohydroquinone	0.51	---

^aStyrene 3.46 M.; Benzoyl Peroxide 2.5×10^{-2} M.

or its decomposition fragments.

In addition to use as stabilizers and antioxidants, phenolic compounds (particularly hydroquinone) are widely employed as "shortstops" in processes such as the production of GR-S rubber. In this process, the initial monomer feed contains 75% butadiene and 25% styrene, but the initially-formed copolymer contains only 17-18% styrene; thus, if the polymerization proceeds to very high conversion, the last-formed polymer is practically pure polystyrene.¹⁶⁰ It is therefore common practice to isolate the copolymer at a definite conversion. This is accomplished by addition of a compound which rapidly terminates polymerization, and which prevents further polymerization during processing--a "short-stop." Kluchesky and Wakefield¹⁶⁰ evaluated a large number of compounds in this application; an emulsion copolymerization of styrene and butadiene, initiated by a persulfate, was used as the model system. Hydroquinone, catechol, pyrogallol, p-phenylphenol, and 2-naphthol were very effective, essentially completely terminating the reaction at concentrations of 0.1-0.2%. These authors point out the importance of oxidation to the quinone; resorcinol, for example, is unsuitable as a stopping agent, in contrast to its more readily oxidized isomers. It should be mentioned, however, that this does not necessarily rule out hydrogen abstraction as an important step in terminating the polymerization. It has been shown¹⁷⁹⁻¹⁸¹ that the rates of hydrogen abstractions

from phenols are characterized by negative Hammett ρ -values, i.e., electron-donating substituents accelerate the reaction and electron-withdrawing substituents retard it. In both hydroquinone and resorcinol, the "substituent" is hydroxyl, but in the para-position it is electron-donating ($\sigma = -0.37^{182}$) while in the meta-position it is electron-withdrawing ($\sigma = 0.12^{182}$). On purely electronic grounds, then, one would expect hydroquinone to be the superior shortstop.

Kharasch, Kawahara and Nudenberg¹⁵⁹ also studied the shortstopping of butadiene polymerization with hydroquinone and related compounds. These workers used a tert-butylhydroperoxide/ferrous ammonium sulfate initiator, and carried out the reaction under nitrogen. It was found that, even when the hydroquinone/initiator ratio was 2/1, the initiator added to monomer before being trapped by hydroquinone. The primary reaction product was suggested to be that resulting from the coupling of a semiquinone with the 4-tert-butoxybutadienyl radical, although this was isolated in its oxidized (quinone) form. The same oxidized product was recovered from the reaction terminated with benzoquinone, and the most rapid shortstopping was observed when quinhydrone was used. Kharasch, et al., suggested that hydroquinone requires an oxidant for rapid reaction, while benzoquinone requires a reductant, and that the true inhibiting species is the semiquinone radical in each case.

The effectiveness of a hydroquinone/quinone mixture

was also indicated in the work of Georgieff,¹⁵⁸ who found substantial synergism in the 1/1 mixture. This mixture was found to be approximately 2.5 times as effective as would be expected on the basis of the activities of the individual compounds in inhibition of peroxide-initiated methyl methacrylate polymerization.

Caldwell and Ihrig¹⁵⁷ suggest that both factors mentioned earlier (a difference in the character of the chain-carrying radical, as well as oxidation of the phenol) may be important in interpreting the action of phenols in methyl methacrylate polymerization in air. These workers measured the induction periods and rates of polymerization in the presence of 20 phenols, and found that the addition of the phenol increased the induction period over that observed in the presence of air alone. It was suggested that the phenol prevented oxygen from becoming depleted too rapidly, thus maintaining an effective concentration for a longer time than would normally be the case. Also, the retardation efficiency of hydroquinone plus oxygen was found to be in good agreement with that of benzoquinone, suggesting that oxidation of the inhibitor is significant.

The foregoing discussion indicates that retardation and inhibition of radical polymerization by phenolic compounds may involve several elementary reactions: (i) abstraction of the phenolic hydrogen atom, (ii) oxidation to quinones by oxygen or peroxides, (iii) termination by coupling or dis-

proportionation, (iv) chain transfer by addition to monomer, and (v) reactions with initiator via radical or non-radical pathways. Reaction (i) is almost certainly of paramount importance when oxygen is rigorously excluded from the reaction mixture. As mentioned earlier, Hammond and coworkers¹⁷³ have criticized this mechanism on the basis of their failure to observe a deuterium isotope effect in the inhibition of tetralin oxidation by N-methylaniline or diphenylamine, and they were supported in this view by Caldwell and Ihrig¹⁷¹ who studied the inhibition of methyl methacrylate polymerization by hydroquinone. On the other hand, Ingold has raised very serious questions concerning Hammond's work,¹⁷⁴ and he¹⁸³ and Shelton¹⁸⁴ have successfully demonstrated isotope effects in similar systems. The observation of a large isotope effect on the chain transfer constant of 1-naphthol is perhaps the most direct evidence in support of the importance of hydrogen abstraction.¹⁷⁰

Absolute rate constants for hydrogen atom abstraction from phenols by several radical species have been measured, or at least estimated.¹⁸⁵ These figures show the methyl, t-butoxy and poly(peroxystyryl)peroxy radicals to be more efficient by a factor of 10^4 - 10^7 than the polystyryl radical in abstraction from phenol or 2,4,6-tri-tert-butylphenol. However, the value for polystyryl was estimated from chain transfer constants, and thus may not be fully

reliable. Perhaps the use of the phenylethyl radical produced via the decomposition of 1,1'-azobis(1-phenylethane)¹⁸⁶ would give a reliable figure for hydrogen atom abstraction by benzylic radicals. Analogous radical generators can be envisioned which would provide model radical species for analysis of other polymerization systems.

If the polymerization is carried out in the absence of oxidizing agents, formation of quinones becomes less important, and competition between reactions (iii) and (iv) determines the fate of the phenoxy radicals generated in the abstraction. If (iii) dominates severe retardation or inhibition results, while if (iv) dominates, little or no reduction in rate is observed. Termination rate constants for phenoxy radicals have been determined¹⁸⁷⁻¹⁹⁰ but little is known concerning their efficiency of initiation. Perhaps the use of an initiator such as diphenyl peroxalate could give a direct measure of this efficiency, since methods have been developed for accurate determination of initiator efficiency in radical polymerization.¹⁹¹

In the final analysis, the extent to which phenolic compounds interfere in radical polymerization depends primarily on the relative rates of hydrogen atom abstraction versus olefin addition for the radicals involved in chain initiation and growth. Interference is further modified by the possibility of radical or non-radical reactions of the

phenolic compound with the initiator molecule, especially in peroxide-initiated systems, and by possible oxidation of the inhibitor in the presence of oxidizing agents.

C H A P T E R I I
E X P E R I M E N T A L S E C T I O N

A. Materials

The following chemicals were obtained from the indicated sources.

Acetic Acid (F)	Fluorosulfonic Acid (A)
Acetic Anhydride (E)	Methacrylic Acid (E)
Azobisisobutyronitrile (A)	Picric Acid (E)
N-Bromosuccinimide (MCB)	Potassium tert-Butoxide (V)
tert-Butanol (E)	Potassium Carbonate (B)
Carbon Dioxide (Airco)	Potassium Hydroxide (F)
Carbon Tetrachloride (M)	Quinoline (E)
Collidine (A)	Sodium Hydroxide (F)
Cupric Acetate (F)	Sodium Methoxide (F)
N,N-Dimethylacetamide (A)	Tributylamine (E)
Dimethylsulfoxide (E)	Trifluoromethanesulfonic Acid (A)
3-Ethylphenol (A)	

Sources: A = Aldrich Chemical Co.; Airco = Airco, Incorporated; B = J. T. Baker Chemical Co.; E = Eastman Organic Chemicals; F = Fisher Scientific Co.; M = Mallinkrodt Chemical Works; MCB = Matheson, Coleman and Bell; V = Ventron Corporation

B. Purification of Solvents and Reagents

Distillations were done with a 30-cm Vigreux column. Reduced pressure distillations were carried out with magnetic stirring, and pressure was stabilized with a Cartesian diver-type manostat.

Acetic acid was distilled (b.p. 116.5-7.5°C) immediately before use.

Acetic anhydride was refluxed over anhydrous sodium acetate and distilled (b.p. 136°C) immediately before use.

Azobisisobutyronitrile (AIBN) was recrystallized three times from dry methanol and dried 24 hr at 0.01 mm at room temperature.

N-Bromosuccinimide (NBS) was dried overnight at 0.01 mm at room temperature over phosphorus pentoxide.

tert-Butanol was distilled from sodium under nitrogen. The first 10% of the distillate was discarded and material b.p. 82°C was used.

Carbon dioxide, Airco Grade 2.8, was used as received.

Carbon tetrachloride was spectral grade and was used as received.

N,N-Dimethylacetamide (DMAc) was stirred overnight with phosphorus pentoxide and distilled (b.p. 67°C/17 mm) immediately before use. A forerun of ca. 10% was discarded.

Dimethylsulfoxide (DMSO) was stirred with calcium

hydride and distilled (b.p. 93°C/25 mm), and then stored over 3A molecular sieves.

3-Ethylphenol was distilled (b.p. 114°C/18 mm) immediately before use.

Isopropanol was distilled and fraction b.p. 82.5-3.5°C collected and redistilled (b.p. 83.5°C) immediately before use.

Methacrylic acid was distilled (b.p. 68°C/15 mm) immediately before use.

Methanol was stirred overnight with calcium hydride and distilled immediately before use.

Potassium tert-butoxide was used as received, but handled only in a nitrogen-filled glove bag.

Potassium carbonate was dried 5 hr at 400°C and cooled in a dessicator over calcium chloride.

Tributylamine was distilled (b.p. 101°C/17 mm). A forerun of ca. 25% (b.p. 97-101°C/17 mm) was discarded.

Collidine, cupric acetate, fluorosulfonic acid, picric acid, potassium hydroxide, quinoline, silver nitrate, sodium hydroxide, sodium methoxide and trifluoromethane-sulfonic acid were used as received.

C. Preparation and Polymerization of 5-Vinylsalicylic Acid and 5-Vinylacetylsalicylic Acid

1. Methyl 5-Acetylsalicylate. Prepared according to Bailey,¹ (thesis, p. 68).

2. Methyl 5-Acetylacetylsalicylate. Prepared according to Bailey,¹ (thesis, p. 72).

3. Methyl 5-(1-hydroxyethyl)acetylsalicylate. Prepared according to Bailey,¹ (thesis, p. 73).

4. Dehydration of Methyl 5-(1-hydroxyethyl)acetylsalicylate. Performed according to Bailey,¹ (thesis, p. 76).

5. 5-Vinylsalicylic Acid. A 1-liter round-bottomed flask was charged with an approximately equimolar mixture of methyl 5-vinylacetylsalicylate and methyl 5-vinylsalicylate (21.7 g, 109 mmole, 164 mmole ester) and 530 ml of a 5% aqueous solution of sodium hydroxide (26.7 g, 669 mmole, 4-fold with respect to ester). The turbid mixture was heated to reflux, and became homogeneous as reflux was achieved. Reflux was continued for 15 min, and the solution was cooled to room temperature. The product was precipitated by adding the reaction mixture to 650 ml of 2N hydrochloric acid, filtered, washed with cold water, and dissolved in 250 ml 5% aqueous sodium bicarbonate. The solution was washed twice with chloroform, and the product precipitated from the aqueous phase with 150 ml 2N hydrochloric acid. Drying at approximately 20 mm Hg over phosphorus pentoxide yielded 16.0 g (95%) of a mixture of 5-vinylsalicylic acid and oligomers.

ANAL. Calcd for $(C_9H_8O_3)_n$: C, 65.85%; H, 4.91%.

Found: C, 65.58%; H, 5.11%.

The monomer was isolated in 56% yield as white needles (mp 136-138°C) by sublimation at 78-80°C at 0.01 mm pressure. The infrared spectrum (KBr) showed absorptions at 2800-3300 cm^{-1} (OH stretching) and 1680 cm^{-1} (C=O stretching). See p.193. The ^1H NMR spectrum (d-DMSO) showed δ 5.0-7.8 (vinyl and aromatic protons, 6; multiplicities and coupling constants as expected); 11.3 (Ar OH/COOH , 2). See p.172.

ANAL. Calcd for $\text{C}_9\text{H}_8\text{O}_3$: C, 65.85%; H, 4.91%.
Found: C, 65.75%; H, 4.76%.

6. 5-Vinylacetylsalicylic Acid. A 50-ml Erlenmeyer flask was charged with 5-vinylsalicylic acid (2.5 g, 15 mmole) and 18.8 ml acetic anhydride (20.3 g, 199 mmole). Concentrated sulfuric acid (5 drops) was added, and the 5-vinylsalicylic acid dissolved rapidly. The tightly stoppered flask was allowed to stand at room temperature for 5 hr, and the contents of the flask were poured into cold water in a vessel immersed in an ice-water bath. A colorless oil which precipitated was dissolved in 40 ml ether, and the aqueous phase was washed with 40 ml ether. The combined organic phases were washed three times with equal volumes of water and dried over magnesium sulfate. The ether was driven off by a stream of dry nitrogen to yield 2.5 g (78%) of a white solid from which 5-vinylacetylsalicylic acid (mp 144°C, dec.) could be separated in 58% yield from

oligomers by sublimation (78°C/0.01 mm). The infrared spectrum (KBr) showed absorptions at 2800-3300 cm^{-1} (OH stretching) and at 1760 cm^{-1} and 1685 cm^{-1} (C=O stretching). See p. 193. The ^1H NMR spectrum (CDCl_3) showed δ 2.32 (COCH_3 , 3); 5.2-8.2 (vinyl and aromatic protons, 6; multiplicities and coupling constants as expected); 11.5 (COOH , 1). See p. 172.

ANAL. Calcd for $\text{C}_{11}\text{H}_{10}\text{O}_4$: C, 64.07%; H, 4.89%.

Found: C, 64.23%; H, 4.89%.

7. Polymerization of 5-Vinylsalicylic Acid. A polymerization tube was charged with 5-vinylsalicylic acid (0.82 g, 5.0 mmole), AIBN (3.7 mg, 0.02 mmole, 0.4 mole-%), and isopropanol (2 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 24 hr at 60°C, the viscous polymer solution was diluted with 40 ml of an equal volume mixture of isopropanol and water, and the polymer was precipitated by adding the mixture to 100 ml of 2N HCl. The polymer was redissolved in a saturated sodium bicarbonate solution and again precipitated with 2N HCl. The polymer was washed with distilled water and dried overnight over calcium chloride at 0.01 mm; the procedure gave 0.63 g of polymer (77% yield). The polymer was further purified by two precipitations from dimethyl sulfoxide into chloroform, and finally by precipitation from 5% sodium hydroxide into 2N HCl followed by extraction with water for 18 hr and drying overnight over calcium chloride at 0.01 mm. The inherent viscosity

of the polymer (0.5% in DMSO, 30°C) was 0.58 dl/g. DSC revealed no decomposition below 340°C. The infrared spectrum (KBr) showed an absorption at 1670 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.194. The ^1H NMR spectrum (d-DMSO) showed δ 0.5-3.0 (CHCH_2 , DMSO); 6.1-9.6 (aromatic, OH/COOH). See p.173. The analytical sample was dried for 3 hr at 100°C/0.001 mm.

ANAL. Calcd for $(\text{C}_9\text{H}_8\text{O}_3)_n$: C, 65.85%; H, 4.91%.

Found: C, 66.08%; H, 4.68%.

8. Polymerization of 5-Vinylacetylsalicylic Acid. A polymerization tube was charged with 5-vinylacetylsalicylic acid (0.17 g, 0.84 mmole), AIBN (0.9 mg, 0.006 mmole, 0.6 mole-%), and acetic acid (2 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 24 hr at 60°C, the polymer was isolated by adding the tube contents dropwise to benzene, the suspension was filtered, the polymer was dried for 48 hr at room temperature and 0.01 mm; yield 0.12 g (71%). The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 0.46 dl/g, and DSC showed a decomposition endotherm at 315°C. The infrared spectrum (KBr) showed a broad absorption centered at 1720 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.194. The ^1H NMR spectrum (d-DMSO) showed δ 0.6-3.4 (CHCH_2 , COCH_3 , DMSO; 6.1-8.4 (aromatic); 11.9-13.4 (COOH). See p.174. The analytical sample was dried for 3 hr at 100°C/0.001 mm.

ANAL. Calcd for $(\text{C}_{11}\text{H}_{10}\text{O}_4)_n$: C, 64.07%; H, 4.89%.

Found: C, 64.68%; H, 4.98%.

9. Copolymerization of 5-Vinylsalicylic Acid with

Methacrylic Acid. A polymerization tube was charged with 5-vinylsalicylic acid (0.51 g, 3.1 mmole, 11.6 mole-%), methacrylic acid (2.04 g, 23.7 mmole, 88.1 mole-%), AIBN (12.0 mg, 0.07 mmole, 0.3 mole-%), and isopropanol (1 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 24 hr at 60°C, the contents of the tube had become a clear, glassy plug. The polymer was dissolved in 50 ml of 5% aqueous sodium hydroxide, precipitated by pouring the polymer solution into 65 ml of 2N hydrochloric acid. The polymer suspension was filtered, suspended in 100 ml of distilled water, stirred for several hours, filtered, dried at 0.01 mm over CaCl_2 ; the procedure gave 1.36 g (53% yield) of a fluffy white polymer. The polymer was purified by an additional precipitation from 5% aqueous NaOH into 2N HCl which was followed by extraction with water for 20 hr in a Soxhlet extractor. The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 2.74 dl/g. The infrared spectrum (KBr) showed a broad absorption centered at 1700 cm^{-1} ($\text{C}=\text{O}$ stretching). See p. 195. Copolymer composition was determined by recording the ^1H NMR spectrum in D_2O containing approximately 1% NaOD. The ratio of the integrated signal intensity of the aromatic protons (7) to the integrated signal intensity of the aliphatic protons (67) indicated that the copolymer consisted of approx-

imately 16 mole-% 5-vinylsalicylic acid and 84 mole-% methacrylic acid. See p.173.

ANAL. Calcd for $(C_9H_8O_3)_{16\%}(C_4H_6O_2)_{84\%}$: C, 58.48%; H, 6.46%. Found: C, 58.22%; H, 6.30%.

10. Copolymerization of 5-Vinylacetylsalicylic Acid with Methacrylic Acid. A polymerization tube was charged with 5-vinylacetylsalicylic acid (0.11 g, 0.54 mmole, 6.7 mole-%), methacrylic acid (0.65 g, 7.6 mmole, 93 mole-%), AIBN (4.5 mg, 0.03 mmole, 0.3 mole-%), and acetic acid (1 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 24 hr at 60°C, the polymer had precipitated to form a white, opaque plug which had absorbed all of the acetic acid. The polymer was dissolved in 10 ml of DMSO and precipitated by adding the solution slowly to chloroform (50 ml). Drying for 5 days at 60°C/0.01 mm gave 0.74 g (97%) of a glassy copolymer. The polymer was purified by precipitation from DMSO into an equal-volume mixture of acetic acid and water, followed by extraction with water for 6 hr. The copolymer was soluble in methanol and DMSO, but insoluble in acetone, trifluoroacetic acid, and CH_2Cl_2 . The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 3.18 dl/g. The infrared spectrum (KBr) showed a broad absorption centered at 1700 cm^{-1} ($C=O$ stretching). See p.195. The 1H NMR spectrum was recorded in D_2O containing 1% NaOD for the measurement of copolymer composition. The ratio of the inte-

grated intensity of the aromatic signal (3) to the integrated intensity of the aliphatic signals (70) indicated that the copolymer consisted of 7 mole-% 5-vinylacetylsalicylic acid and 93 mole-% methacrylic acid. See p. 175.

ANAL. Calcd for $(C_{10}H_{11}O_4)_7(C_4H_6O_2)_{93}$:
C, 57.06%; H, 6.69%. Found: C, 55.78%; H, 6.30%.

D. Preparation and Polymerization of Methyl 4-Vinylsalicylate, 4-Vinylsalicylic Acid and 4-Vinylacetylsalicylic Acid

1. 4-Ethylsalicylic Acid. A glass-lined, stainless steel autoclave was charged with 3-ethylphenol (43 g, 0.35 mole) and anhydrous potassium carbonate (175 g, 1.27 mole), and sealed. Carbon dioxide was introduced from a commercial cylinder, and the reactor was pressurized to 750 psi at room temperature. Over a period of one hour, the reactor temperature was raised to 175°C, resulting in a final pressure of 1000 psi. After 6½ hr at 175°C, the reactor was allowed to cool to room temperature. The solid yellow product was dissolved in 600 ml of warm (60°C) water, and the aqueous solution filtered to remove a small amount of dark, oily material. The filtrate was extracted with two 200 ml portions of ether to remove unreacted 3-ethylphenol, heated with charcoal, and filtered again. Acidification with 600 ml 6N HCl produced a voluminous tan precipitate. The product was collected by filtration and washed with water. Recrystallization from a large volume of water gave 45 g (77%) of

4-ethylsalicylic acid as white needles (m.p. 129-130.5°C, lit. m.p.¹⁹² 124°C). The infrared spectrum (KBr) showed absorptions at 3400-2000 cm^{-1} (OH stretching) and 1660 cm^{-1} (C=O stretching). See p.196. The ^1H NMR spectrum (CDCl_3) showed δ 1.2 (CH_2CH_3 , 3H, triplet), 2.6 (CH_2CH_3 , 2H, quartet), 6.6-7.9 (aromatic protons, 3H), and 10.1-11.1 (COOH/OH , 2H). See p.175.

The procedure was repeated on a larger scale, and gave, after 8 hr at 175°C, an 80% yield of crude 4-ethylsalicylic acid.

2. Methyl 4-Ethylsalicylate. A 2-l, 3-necked round-bottomed flask fitted with a mechanical stirrer and a reflux condenser topped with a calcium sulfate drying tube was charged with crude 4-ethylsalicylic acid (260 g, 1.56 mole) and methanol (650 ml, 16 mole). Sulfuric acid (65 ml) was added, causing vigorous bubbling. The dark reaction mixture was heated, held at reflux for 8 hr, and cooled to room temperature. Addition of the mixture to 2 liters of water caused separation of an oil. The oil was dissolved in 500 ml chloroform, and the aqueous phase washed with an additional 500 ml chloroform. The combined organic solutions were filtered through a pad of Celite, washed with 600 ml portions of 5% aqueous sodium bicarbonate and water, dried with magnesium sulfate, and filtered. Removal of the solvent on the rotary evaporator gave 265 g (94%) of crude product. Dis-

tillation (b.p. 143°C/18 mm) afforded 203 g (72%) of clear, colorless methyl 4-ethylsalicylate. The infrared spectrum (neat) showed absorptions at 3180 cm^{-1} (OH stretching) and 1625 cm^{-1} (C=O stretching). See p.196. The ^1H NMR spectrum (CDCl_3) showed δ 1.2 (CH_2CH_3 , 3H, triplet), 2.6 (CH_2CH_3 , 2H, quartet), 3.9 (CO_2CH_3 , singlet), 6.6-7.8 (aromatic protons, 3H) and 10.7 (OH, 1H, singlet). See p. 176.

ANAL. calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_3$: C, 66.65%; H, 6.71%.
Found: C, 66.36%; H, 6.86%.

3. Methyl 4-Ethylacetylsalicylate. A 125-ml Erlenmeyer flask was charged with methyl 4-ethylsalicylate (25 g, 0.14 mole) acetic anhydride (30 ml, 0.32 mole) and sulfuric acid (6 drops). The flask was tightly stoppered and allowed to stand at room temperature for 2½ hr. The contents of the flask were then added to a cold mixture of 12 g sodium bicarbonate and 400 ml water, causing formation of a colorless oil. The oil was extracted with two 150 ml portions of chloroform, and the combined organic phases were washed with 300 ml water, dried with magnesium sulfate, and filtered. Removal of the solvent on the rotary evaporator gave 36 g of colorless oil. The oil was further washed with 50 ml portions of water, cold 2% aqueous sodium hydroxide and water again, and then dried with magnesium sulfate and filtered to leave 30 g (97%) of colorless, odorless

methyl 4-ethylacetylsalicylate. An analytically-pure sample was prepared in 72% yield by distillation (b.p. $140^{\circ}\text{C}/0.4\text{ mm}$). The infrared spectrum (neat) showed absorptions at 1775 cm^{-1} and 1730 cm^{-1} ($\text{C}=\text{O}$ stretching). See p. 197. The ^1H NMR spectrum showed δ : 1.2 (CH_2CH_3 , 3H, triplet), 2.2 (OCOCH_3 , 3H, singlet), 2.6 (CH_2CH_3 , 3H, quartet), 3.8 (CO_2CH_3 , 3H, singlet) and 6.8-7.9 (aromatic protons, 3H). See p.176.

ANAL. calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85%; H, 6.35%.
Found: C, 64.80%; H, 6.34%.

4. Reaction of Methyl 4-Ethylacetylsalicylate with N-bromosuccinimide and AIBN. A 300 ml round-bottomed flask containing a magnetic stirring bar, was charged with methyl 4-ethylacetylsalicylate (20.0 g, 90 mmole), carbon tetrachloride (100 ml), N-bromosuccinimide (24.0 g, 135 mmole) and AIBN (0.1 g, 0.6 mmole). The flask was then fitted with a reflux condenser, flushed with nitrogen, and immersed in an oil bath at 90°C . Formation of succinimide was noted after 15 min, and the reaction became quite vigorous. After 50 min, the yellow color of the N-bromosuccinimide appeared to change rapidly to the white, fluffy succinimide, and after 1 hr, the reaction mixture was cooled to room temperature. The succinimide was removed by filtration and washed with carbon tetrachloride. Removal of the solvent at room temperature at 0.05 mm Hg left 27.1 g of off-

white solid. Recrystallization of the product from methanol gave a first crop of 9.2 g of white needles. The ^1H NMR spectrum (CCl_4) showed δ : 2.3 (OCOCH_3 , 3H, singlet), 2.9 (CBr_2CH_3 , 3H, singlet), 3.8 (CO_2CH_3 , 3H, singlet), 7.2-8.0 (aromatic protons, 3H). See p. 177.

5. Bromination of Methyl 4-Ethylacetylsalicylate. A 3-l, 3-necked, round-bottomed flask was charged with methyl 4-ethylacetylsalicylate (217.5 g, 0.98 mole), carbon tetrachloride (1200 ml) and N-bromosuccinimide (178 g, 1.00 mole). The flask was flushed with nitrogen, fitted with a mechanical stirrer, thermometer and reflux condenser, and heated to reflux under a flow of nitrogen. After 2 hr, heating and stirring were interrupted, and formation of succinimide (perhaps 50% conversion) was noted. After $4\frac{1}{2}$ hr, only a trace of yellow N-bromosuccinimide remained, and the reaction mixture was cooled to room temperature. The slightly yellow solution was filtered to remove succinimide and the solvent was removed at reduced pressure to leave 295 g (100%) of slightly yellow methyl 4-(1-bromoethyl)acetylsalicylate. The infrared spectrum (CCl_4) showed absorptions at 1775 cm^{-1} and 1730 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.197. The ^1H NMR spectrum showed δ : 1.9 (CHBrCH_3 , 3H, doublet), 2.2 (OCOCH_3 , 3H, singlet), 3.8 (CO_2CH_3 , 3H, singlet), 5.1 (CHBrCH_3 , 1H quartet) and 7.1-8.0 (aromatic protons, 3H). See p.177.

6. Reaction of Methyl 4-(1-bromoethyl)acetylsalicylate with Sodium Hydroxide. A 25 ml round-bottomed flask was charged with methyl 4-(1-bromoethyl)acetylsalicylate (1.0 g, 3.3 mmole) and a solution of sodium hydroxide (0.7 g, 17 mmole) in water (10 ml). The flask was fitted with a reflux condenser and heated to reflux, with stirring. After 2 hr, the flask was removed and cooled, and the contents were acidified with 10 ml of 4N HCl. After standing in ice for several minutes, a pink solid formed. The solid was collected by filtration and air-dried. The ^1H NMR spectrum (d-DMSO) showed removal of the esters, but no vinyl protons. See p.178.

7. Reaction of Methyl 4-(1-bromoethyl)acetylsalicylate with Ethanolic Potassium Hydroxide. A 25 ml round-bottomed flask was charged with methyl 4-(1-bromoethyl)acetylsalicylate (1.0 g, 3.3 mmole) and a solution of potassium hydroxide (0.56 g, 10 mmole) in 95% ethanol (10 ml). The flask was topped with a reflux condenser and placed in an oil bath at 90°C. After 30 min, the contents of the flask were cooled and added to 50 ml of distilled water. The aqueous solution was acidified with 10 ml of 4N HCl, causing formation of an oil. After the supernatant was decanted, the oil was dissolved in d-DMSO, and the ^1H NMR spectrum was recorded. The spectrum showed no signals which could be assigned to vinyl protons. See p.178.

8. Methyl 4-Vinylacetylsalicylate. A 2-l, 3-necked round-bottomed flask was charged with crude methyl 4-(1-bromoethyl)acetylsalicylate (152 g, 0.50 mole), DMAc (500 ml), tri-n-butylamine (450 ml, 1.89 mole), and a trace of picric acid as polymerization inhibitor. The flask was fitted with a mechanical stirrer, reflux condenser and thermometer, flushed with nitrogen, and immersed in an oil bath at 150°C. After 90 min, the flask was removed from the bath and cooled to room temperature, and the contents added carefully to 1 liter of 3N HCl, causing formation of a red oil and a dark, semisolid precipitate. The oil was extracted with three 400 ml portions of ether, and the combined organic phases were washed with 400 ml portions of 1N HCl, 5% aqueous sodium bicarbonate, and water, dried with magnesium sulfate, and filtered. The precipitate was extracted with two 300 ml portions of ether, and the ethereal solution was washed with four 250 ml portions of 1N HCl, one 250 ml portion of 5% aqueous sodium bicarbonate, and two 250 ml portions of water, then dried with magnesium sulfate and filtered. Removal of the ether from the combined solutions left 69 g (62%) of crude methyl 4-vinylacetylsalicylate. An analytical sample was prepared by dry-column chromatography on acidic alumina (elution with CHCl_3) followed by short-path distillation (b.p. 85°C/0.01 mm). The infrared spectrum (neat) showed absorptions at 1775 cm^{-1} and 1725 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.198. The ^1H NMR spectrum (CDCl_3)

showed δ 2.3 (OCOCH_3 , 3H, singlet), 3.8 (CO_2CH_3 , 3H, singlet), 5.3-6.9 (vinyl protons, 3H) and 7.0-8.1 (aromatic protons, 3H). See p.179.

ANAL. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_4$: C, 65.45%; H, 5.49%.
Found: C, 65.56%; H, 5.76%.

The procedure was repeated on a smaller scale, and again provided a 62% yield of crude methyl 4-vinylacetylsalicylate.

9. Methyl 4-Vinylsalicylate. A 125 ml Erlenmeyer flask was charged with crude methyl 4-vinylacetylsalicylate (10 g, 45 mmole), methanol (50 ml) and sodium methoxide (5.05 g, 94 mmole), and tightly stoppered. After 1 hr at room temperature, the reaction mixture was added cautiously to 150 ml of cold 1N HCl. The oily precipitate was extracted with 50 ml of chloroform, and the aqueous layer was washed with an additional 25 ml of chloroform. The combined organic layers were then washed with 50 ml portions of 1N HCl (twice), 5% aqueous sodium bicarbonate and water, dried with magnesium sulfate, and filtered. Removal of the solvent on the rotary evaporator left 6.6 g (81%) of crude methyl 4-vinylsalicylate. An analytical sample was prepared by distillation (b.p. 59-64°C/0.01 mm) followed by chromatography on silica gel (2/1 hexane/benzene as eluent). The infrared spectrum (neat) showed absorptions of 3180 cm^{-1} (broad, OH stretching) and 1680 cm^{-1}

(C=O stretching). See p.198. The ^1H NMR spectrum (CDCl_3) showed δ : 3.8 (CO_2CH_3 , 3H, singlet), 5.2-6.8 (vinyl protons, 3H), 6.8-7.8 (aromatic protons, 3H) and 10.7 (OH , 1H, singlet). See p. 179.

ANAL. calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$: C, 67.41%; H, 5.66%.
Found: C, 67.17%; H, 5.55%.

10. 4-Vinylsalicylic Acid. A 500 ml round-bottomed flask was charged with crude methyl 4-vinylacetylsalicylate (17 g, 77 mmole) and 200 ml of an aqueous solution containing 30.6 g (770 mmole) of sodium hydroxide. The flask was fitted with a reflux condenser and immersed in an oil bath at 120°C . After 15 minutes, the flask was cooled in an ice bath, and the cold reaction mixture was transferred to a separatory funnel and washed with two 200 ml volumes of chloroform. Acidification of the aqueous layer with 320 ml of 3N HCl caused formation of a brown precipitate, which was collected by filtration, washed with water, and dried overnight at room temperature over P_2O_5 . The yield of crude 4-vinylsalicylic acid was 10.1 g (80%). Sublimation at $80^\circ\text{C}/0.01\text{ mm}$ gave in 60% yield pure 4-vinylsalicylic acid as white needles (m.p. 130°C , dec.). The infrared spectrum (KBr) showed absorptions at $3400\text{--}2000\text{ cm}^{-1}$ (OH stretching) and 1650 cm^{-1} (C=O stretching). See p.199. The ^1H NMR spectrum (DMSO-d_6) showed δ : 5.3-7.0 (vinyl protons, 3H), 7.0-7.9 (aromatic protons, 3H) and 11.5-13.0 (COOH/OH , 2H).

See p.180.

ANAL. Calcd. for $C_9H_8O_3$: C, 65.85%; H, 4.91%.

Found: C, 65.89%; H, 5.20%.

11. Reaction of Methyl 4-Vinylacetylsalicylate with Acetic Acid. A 50 ml round-bottomed flask was charged with methyl 4-vinylacetylsalicylate (2.0 g), glacial acetic acid (30 ml) and 2 drops of concentrated sulfuric acid. The flask was fitted with an air condenser and placed in an oil bath at 80°C. After 2.5 hr, the reaction mixture was cooled to room temperature and added to 100 ml of 1N hydrochloric acid. The oil which precipitated was extracted with 50 ml of chloroform, and the solvent was removed at reduced pressure. The 1H NMR spectrum of the product (red oil) is shown on p.181.

12. 4-Vinylacetylsalicylic Acid. A 125 ml Erlenmeyer flask was charged with 4-vinylsalicylic acid (4.25 g, 26 mmole), acetic anhydride (25 ml, 260 mmole) and 5 drops of concentrated sulfuric acid. The flask was tightly stoppered and allowed to stand at room temperature, with occasional swirling, for 5 hr. The reaction mixture was then poured into 250 ml of cold water in a separatory funnel, and the oil which separated was extracted with three 100 ml portions of ether. The combined ether layers were then extracted with 100 ml of water, dried with magnesium sulfate, and filtered. The ether was removed at reduced pressure to leave 12.5 g

of slightly yellow oil. The oil was dissolved in 30 ml of warm ethanol, and the mixture added to 40 ml of warm water. The oil which precipitated was redissolved on heating to 65°C (odor of ethyl acetate), and the flask was scratched and cooled. A first crop (2.45 g) of 4-vinylacetylsalicylic acid (white needles, m.p. 124°C, dec) was collected. Two more crops were obtained from the mother liquor after reduction in volume, giving a yield of 4.12 g (77%) of 4-vinylacetylsalicylic acid. The infrared spectrum (KBr) showed absorptions at 3500-2000 cm^{-1} (OH stretching) and at 1760 cm^{-1} and 1690 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.199. The ^1H NMR spectrum (CDCl_3) showed δ : 2.3 (COCH_3 , 3H, singlet), 5.2-6.9 (vinyl protons, 3H), 7.0-8.1 (aromatic protons, 3H) and 11.6 (COOH , 1H, singlet). See p.182.

ANAL. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_4$: C, 64.07%; H, 4.89%. Found: C, 64.17%; H, 4.99%.

13. Polymerization of Methyl 4-Vinylsalicylate. A polymerization tube was charged with methyl 4-vinylsalicylate (1.00 g, 5.61 mmole) and AIBN (4.6 mg, 2.8×10^{-2} mmole, 0.5 mole percent) and flushed with nitrogen. The tube was then degassed by three freeze-thaw cycles at 0.01 mm, sealed at 0.01 mm, and placed in a constant temperature bath at 60°C. The tube contents were nearly rigid after 90 min, but the polymerization was allowed to continue for 24 hr.

The tube was then opened, and the contents dissolved in 30 ml of chloroform. The chloroform solution was filtered, and the polymer was precipitated by addition of the solution to 250 ml of hexane. The white, fibrous polymer was collected by filtration, washed with hexane, and dried for 10 days at room temperature and 20 mm to give 0.72 g (72%) of poly-(methyl 4-vinylsalicylate). The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 2.61 dl/g. The infrared spectrum (KBr) showed absorptions at 3500-2800 cm^{-1} (OH stretching) and at 1675 cm^{-1} (C=O stretching). See p.200. The ^1H NMR spectrum (CDCl_3) showed δ : 0.9-2.3 (CHCH_2 , 3H), 3.9 (CO_2CH_3 , 3H) 5.7-7.7 (aromatic protons, 3H) and 10.5 (OH , 1H). See p.182.

ANAL. Calcd. for $(\text{C}_{10}\text{H}_{10}\text{O}_3)_n$: C, 67.40%; H, 5.66%. Found: C, 67.34%; H, 5.63%.

14. Polymerization of 4-Vinylsalicylic Acid. A stock solution was prepared by weighing 3.92 g (23.8 mmole) of 4-vinylsalicylic acid into a 10 ml volumetric flask and filling to the mark with freshly-distilled N,N-dimethylformamide. Each of five polymerization tubes was charged with the desired amount of AIBN and stock solution (See Table 4), degassed by three freeze-thaw cycles at 0.01 mm, and sealed at 0.01 mm. After 15 hr in a constant temperature bath at 60°C, each tube was removed from the bath, and the contents were dissolved in 20 ml of absolute ethanol. Precipitation into 250 ml of a

TABLE 4
Polymerization of 4-Vinylsalicylic Acid

Experiment	Stock ^a Solution (ml)	Monomer in g. (in mmole)	AIBN in mg. (in mmole)	AIBN mole- %	η_{inh} dl/g
1	2.5	0.98 (6.0)	1.1 (6.7×10^{-3})	0.1	2.24
2	1.0	0.39 (2.4)	4.5 (2.7×10^{-2})	1.1	0.86
3	2.5	0.98 (6.0)	20 (1.2×10^{-1})	2.0	0.65
4	1.0	0.39 (2.4)	20 (1.2×10^{-1})	4.8	0.52
5	2.5	0.98 (6.0)	100 (6.1×10^{-1})	9.2	0.46
6 ^b				0.5	1.59

^aStock solution contained 3.92 g of 4-vinylsalicylic acid in 10 ml; DMF as solvent

^bIndependent experiment

10/1 mixture of dichloromethane and pentane afforded poly (4-vinylsalicylic acid) as an off-white powder. The yield was determined after drying overnight at room temperature at 20 mm over phosphorus pentoxide. After a similar re-precipitation and drying for 48 hr at 56°C/0.01 mm, the polymers were found, by elemental analysis, to contain 0.5% nitrogen. Each polymer was then treated with a large excess of sodium hydroxide (10% aqueous solution) for one hour at reflux, cooled, and acidified with concentrated hydrochloric acid. The polymer was collected by filtration, washed with three portions of deionized water and dissolved, while still wet, in approximately 25 ml of tert-butanol. Removal of the solvents by freeze-drying afforded poly(4-vinylsalicylic acid) as a white, fluffy powder. The inherent viscosities of the polymers are listed in Table 4. The infrared spectrum (KBr) showed absorptions at 3700-2200 cm^{-1} (OH stretching) and at 1670 cm^{-1} ($\text{C}=\text{O}$ stretching). See p.200. The ^1H NMR spectrum (d-DMSO) showed δ : 0.4-2.5 (CHCH_2 , 3H), 5.6-7.7 (aromatic protons, 3H) and 10.2-11.8 (COOH/OH , 2H). See p.183.

ANAL. Calcd. for $(\text{C}_9\text{H}_8\text{O}_3)_n$: C, 65.85%; H, 4.91%. Found: C, 65.56%; H, 5.00%.

15. Polymerization of 4-Vinylacetylsalicylic Acid. A polymerization tube was charged with 4-vinylacetylsalicylic acid (1.00 g, 4.85 mmole) AIBN (4.0 mg, 2.4×10^{-2} mmole,

0.5 mole-%) and DMSO (1.0 ml), degassed by three freeze-thaw cycles at 0.01 mm, and sealed at 0.01 mm. After 20 hr at 60°C, the rubbery tube contents were placed in 25 ml of absolute ethanol. After standing overnight, the polymer was highly swollen, but had not dissolved. The solvent was replaced by 50 ml of DMSO, and the mixture was warmed to 70°C for 4 days. The polymer was again highly swollen. A homogeneous solution was obtained by warming the polymer with 100 ml of 5% aqueous sodium hydroxide.

The polymerization was repeated using 4-vinylacetylsalicylic acid (0.50 g, 2.42 mmole), AIBN (2.0 mg, 1.2×10^{-2} mmole, 0.5 mole-%), and tert-butanol (2.0 ml). After 18 hr, a clear, rubbery polymer similar to that described above was obtained.

16. Copolymerization of 4-Vinylsalicylic Acid with Methacrylic Acid. A polymerization tube was charged with freshly-sublimed 4-vinylsalicylic acid (0.50 g, 3.05 mmole), freshly-distilled methacrylic acid (0.26 ml, 3.05 mmole) AIBN (5.0 mg, 3.0×10^{-2} mmole, 0.5 mole-%) and DMSO (1.0 ml), degassed by three freeze-thaw cycles at 0.01 mm, and sealed at 0.01 mm. After 20 hr at 60°C, the rubbery tube contents were dissolved in 25 ml of absolute ethanol, and the polymer recovered by dropwise addition of the solution to 150 ml of rapidly-stirred 1% (v/v) aqueous HCl. The white, fibrous product was transferred to a Soxhlet extractor, and extracted with water for 24 hr. After drying

overnight at room temperature and 20 mm over phosphorus pentoxide, and overnight again at 56°C/20 mm over phosphorus pentoxide, the yield of white polymer was 0.65 g (86%). The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 1.73 dl/g. The infrared spectrum (KBr) showed broad absorptions at 3700-2200 cm^{-1} (OH stretching) and at 1680 cm^{-1} (C=O stretching). See p.201. The ^1H NMR spectrum ($\text{D}_2\text{O}/\text{NaOD}$) showed δ : 0-3.1 (aliphatic protons, 13) and 6.0-8.1 (aromatic protons, 54). This corresponds to a copolymer consisting of 35 mole-% 4-vinylsalicylic acid and 65% methacrylic acid. See p.183.

ANAL. calcd. for $(\text{C}_9\text{H}_8\text{O}_3)_{33\%} (\text{C}_4\text{H}_6\text{O}_2)_{67\%}$: C, 60.67%; H, 6.00%. Found: C, 60.22%; H, 5.46%.

17. Copolymerization of 4-Vinylacetylsalicylic Acid with Methacrylic Acid. A polymerization tube was charged with 4-vinylacetylsalicylic acid (0.50 g, 2.42 mmole), freshly-distilled methacrylic acid (0.20 ml, 2.42 mmole), AIBN (4.0 mg, 2.4×10^{-2} mmole, 0.5 mole-%) and DMSO (1.0 ml), degassed by three freeze-thaw cycles at 0.01 mm, and sealed at 0.01 mm. After 20 hr at 60°C, the rubbery tube contents were placed in 25 ml of absolute ethanol. After standing overnight, the polymer was highly swollen, but had not dissolved. The polymer did not dissolve in DMSO or acetone, but did dissolve when warmed with 50 ml of 10% aqueous sodium hydroxide.

The polymerization was repeated, using the procedure described above, except that the DMSO was replaced by 2.0 ml of tert-butanol. A clear, rubbery polymer similar to that described above was obtained.

18. Poly(4-Vinylsalicylic Acid) Copper Complex. A solution of 50 mg (0.3 mmole) of poly(4-vinylsalicylic acid) in 2 ml of acetone was added dropwise to 10 ml of an aqueous solution containing a large excess of cupric acetate monohydrate. The light green precipitate was collected by filtration and washed with four 15 ml portions of deionized water. The apparent pH of the combined washes was 4.5 (pHydrion paper). During drying for 3 days at room temperature and 20 mm over phosphorus pentoxide, the polymer darkened considerably. The infrared spectrum (KBr) showed absorptions at $3700\text{--}2200\text{ cm}^{-1}$ (OH stretching) and 1585 cm^{-1} ($\text{C}=\text{O}$ stretching). See p. 201.

ANAL. Calcd. for $\text{C}_9\text{H}_6\text{O}_3\text{Cu}$: C, 47.90%; H, 2.68%; Cu, 28.15%. Found: C, 46.60%; H, 3.55%; Cu, 24.7%.

E. Preparation and Polymerization of
2,4-Dihydroxy-4'-Vinylbenzophenone

1. Reaction of 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone with Collidine. A 50 ml 3-necked, round-bottomed flask was charged with 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone (1.0 g, 2.5 mmole) and collidine (5 ml, 37 mmole), and fitted with a mechanical stirrer, thermometer, and reflux condenser. The system was flushed with nitrogen and immersed

in an oil bath at 200°C. Reflux began almost immediately (internal temperature 165°C) and was maintained for 2 hr. The flask was cooled to room temperature, and the tarry contents were dissolved in 20 ml of acetone, with the exception of 0.23 g of pink precipitate, presumably collidine hydrobromide. The excess collidine was removed by addition of 20 ml of 1N HCl, followed by filtration to remove collidine hydrochloride. Removal of the acetone at reduced pressure left a dark tar. The ^1H NMR spectrum (CDCl_3) showed removal of the CHBr signal, but no signals which could be assigned to vinyl protons. A rather broad signal at δ 2.1 indicated possible polymerization. See p.184.

This procedure was repeated at lower temperatures; at 50°C, the CHBr signal was unchanged after 5 days, and at 100°C, dark tarry products were obtained.

2. Reaction of 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone with Quinoline. An NMR tube was charged with a portion of a solution containing 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone (0.8 g, 2.0 mmole), quinoline (2.0 ml, 17 mmole), and a trace of picric acid, and placed in an oil bath at 155°C. After 10 min, the ^1H NMR spectrum of the solution showed complete removal of the CHBrCH_3 signal, and small vinyl signals in the region of δ 5.0-6.5. See p.184.

The reaction at 100°C was investigated in a similar fashion, and showed complete removal of the CHBr signal in 1 hr, but no vinyl protons. Instead a broad signal at

δ 2.0-2.5 increased in size with increasing reaction time, indicating possible polymerization. See p.185.

3. Reaction of 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone with Sodium Hydroxide in Aqueous DMSO. A 50 ml 3-necked, round-bottomed flask was charged with sodium hydroxide (1.60 g, 40 mmole), DMSO (8.5 ml), water (2.0 ml) and a trace of picric acid, and fitted with a mechanical stirrer and reflux condenser. The flask was flushed with nitrogen and immersed in an oil bath at 80°C, and 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone (1.00 g, 2.5 mmole) was rapidly added. After 15 min, the reaction mixture was cooled, added to 25 ml of water and acidified with 50 ml of 1N HCl. The flocculant precipitate was collected and dried at reduced pressure over CaCl₂. The ¹H NMR spectrum (d-DMSO) showed no vinyl signals, but rather prominent aliphatic signals at δ 1-2, indicating possible polymerization. See p. 185.

4. Reaction of 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone with Potassium tert-Butoxide. A 100 ml volumetric flask was charged, in a nitrogen-filled glove bag, with potassium tert-butoxide (3.55 g, 31.6 mmole) and 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone (0.50 g, 1.25 mmole), and then filled to the mark with a 9/1 mixture of tert-butanol and DMSO. The flask was then tightly closed and placed in a water bath at 50°C for 1 hr. The reaction mixture was fil-

tered, and acidified with 100 ml 1N HCl to give a red-brown homogeneous solution. The solution was extracted with 50 ml of ether, and the ether layer was washed with 5 50 ml portions of water, dried with magnesium sulfate, and filtered. Removal of ether at reduced pressure left a brown semi-solid. The ^1H NMR spectrum (d-DMSO) of the product is shown on p. 186.

5. Reaction of 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone with Silver Nitrate. A 25 ml round-bottomed flask was charged with 10 ml of absolute ethanol and 0.6 ml of water. 2,4-Diacetoxy-4'-(1-bromoethyl)benzophenone (0.25 g, 0.62 mmole) was then added. Addition of 2 ml of ethanol still did not afford a homogeneous solution, but this was accomplished by adding 3 ml of acetone. Silver nitrate (0.11 g, 0.65 mmole) was then added, and the flask shaken vigorously. A gray precipitate formed immediately. The flask was tightly closed, and was allowed to stand overnight in the dark. The reaction solution was filtered to remove the gray precipitate, and the solvents were removed at reduced pressure to leave 0.23 g of off-white, very viscous oil. The ^1H NMR spectrum (CDCl_3) of the product is shown on p. 186.

6. 2,4-Dihydroxy-4'-vinylbenzophenone. A 250 ml 3-necked, round-bottomed flask was charged with 10.0 g (24.6 mmole) of 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone, 50 ml of DMAc, 60 ml (46.8 g, 0.252 mmole) of tributylamine, and 0.50 g

(2.1 mmole) of picric acid as polymerization inhibitor. The flask was quickly fitted with a reflux condenser and thermometer, flushed with dry nitrogen, and then placed in an oil bath at 140°C while maintaining nitrogen flow. The mixture consisted of two phases below 65°C, but became homogeneous above that temperature. The reaction mixture darkened slightly during the reaction, becoming red-orange in color. After 80 min at 140°C, the flask was removed from the bath and cooled to room temperature. The contents were poured into 500 ml of water, forming two liquid phases plus a red-brown solid. The liquid phases were extracted with two 100 ml portions of ether, and the combined extracts were washed with 100 ml portions of water, 3N hydrochloric acid, water, 1N hydrochloric acid, water, 5% NaHCO₃, and finally water again. The ether layer was dried over magnesium sulfate and filtered, and the ether was removed at 20 mm at room temperature. After drying for 1 hr at 10⁻³ mm at room temperature, the crude product was obtained as an orange oil (6.5 g, 81% yield). This crude product gave both a positive silver nitrate test and a positive Beilstein test, indicating contamination with unreacted starting material.

A 500 ml, 3-necked, round-bottomed flask was charged with crude 2,4-diacetoxy-4'-vinylbenzophenone (7.6 g, approx. 23 mmole), methanol (150 ml) and water (25 ml). The flask was fitted with a thermometer and reflux condenser

and flushed with nitrogen. Sodium bicarbonate (7.6 g, 90 mmole) was added quickly, and the flask was immersed in an oil bath at 90°C. The system was held at reflux for 1 hr, and then removed from the bath and cooled to room temperature. The contents of the flask were poured into 600 ml of distilled water, causing formation of an oily precipitate. The precipitate was extracted with 100 ml of ether, and the aqueous phase was washed with 100 ml portions of ether, chloroform (twice), and ether again. The combined organic phases were washed with water, dried with magnesium sulfate, and filtered, and the solvents were removed at 20 mm at room temperature to leave 4.2 g (75% yield) of crude 2,4-dihydroxy-4'-vinylbenzophenone as a sticky, orange solid. The yield of crude product based on 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone was 61%. The ^1H NMR spectrum indicated that the crude product contained approximately 70% olefin, the remainder being primarily unreacted bromoethyl compound.

The sticky orange solid was chromatographed on silica gel, using the dry-column technique with 5:1 pentane:acetone as eluent, and gave 2.3 g (33%, based on 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone) of pure 2,4-dihydroxy-4'-vinylbenzophenone, m.p. 96°C (dec, by DSC). The infrared spectrum (KBr) showed absorptions at 2800-3600 cm^{-1} (OH stretching), 1625 cm^{-1} (C=O stretching), plus 900 cm^{-1} and 985 cm^{-1} (vinyl C-H bending). See p. 202. The ^1H NMR spectrum (d-DMSO) showed δ : 5.5-7.9 (vinyl and aromatic protons and

ArOH , 11) and 12.1 (broad, ArOH , 1). See p. 187. The UV spectrum (methanol) showed maxima at 329 and 291 nm, with molar extinction coefficients of 12.8×10^3 and $15.5 \times 10^3 \text{ l mole}^{-1} \text{ cm}^{-1}$, respectively.

ANAL. calcd. for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.98%; H, 5.03%.
Found: C, 74.84%; H, 4.77%.

7. Polymerization of 2,4-Dihydroxy-4'-Vinylbenzophenone.

A polymerization tube was charged with 2,4-dihydroxy-4'-vinylbenzophenone (0.250 g, 1.04 mmole), AIBN (1.0 mg, 6×10^{-3} mmole, 0.6 mole-%), and freshly distilled DMF (1.5 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 30 hr at 60°C, the tube was opened, and the viscous contents diluted with twice their volume of acetone. The acetone solution was added dropwise to 80 ml of rapidly stirred distilled water, and the polymer precipitated as an off-white fluffy solid. The polymer was dried overnight at 30 mm at room temperature, and then stirred with CHCl_3 to remove unreacted monomer; the yield of polymer was 0.149 g (60%). The polymer was purified by precipitation from methanol into an equal-volume mixture of hexane and anhydrous ether; the suspension was filtered after standing overnight, and the polymer was dried for 3 days at 56°C/0.01 mm. The inherent viscosity of the polymer (0.5% in DMSO, 30°C) was 0.57 dl/g. The infrared spectrum (KBr) showed an absorption at 1625 cm^{-1} ($\text{C}=\text{O}$ stretching)

plus a very broad O-H stretching band centered at 3360 cm^{-1} . See p. 202. The ^1H NMR spectrum (d-DMSO) showed δ : 0.7-3.9 ($\text{CH}-\text{CH}_2$, DMSO); 5.3-8.3 (aromatic protons and ArOH); and 12.3 (ArOH). See p. 187. The UV spectrum (methanol) showed maxima at 324, 292 and 248 nm, with molar extinction coefficients of 9.10×10^3 and 7.00×10^3 $\ell \text{ mole}^{-1} \text{ cm}^{-1}$, respectively.

ANAL. calcd. for $(\text{C}_{15}\text{H}_{12}\text{O}_3)_n$: C, 74.98%; H, 5.03%. Found: C, 75.01%; H, 5.11%.

8. Copolymerization of 2,4-Dihydroxy-4'-Vinylbenzophenone with Methacrylic Acid. A polymerization tube was charged with 2,4-dihydroxy-4'-vinylbenzophenone (0.240 g, 1.00 mmole, 7.5 mole-% of monomer feed), freshly distilled methacrylic acid (1.06 g, 12.3 mmole, 92.5 mole-% of monomer feed), AIBN (10.9 mg, 0.066 mmole, 0.5 mole-%) and DMF (1.0 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 6 hrs at 60°C, the tube contents had solidified to form an opaque plug. The plug was dissolved in 30 ml of methanol, and the solution was added dropwise to 250 ml of CHCl_3 . The polymer was collected by filtration, dried overnight at 30 mm at room temperature, ground finely and then dried overnight at 0.01 mm at room temperature. The weight of recovered material was 1.26 g, indicating nearly quantitative yield of polymer. The copolymer was purified by precipitation from methanol solution into anhy-

drous ether, and dried for 3 days at 56°C/0.01 mm. The inherent viscosity of the copolymer (0.5% in DMSO, 30°C) was 1.74 dl/g. The infrared spectrum (KBr) showed carbonyl absorptions at 1705 cm^{-1} and 1625 cm^{-1} . See p. 202. The ^1H NMR spectrum ($\text{D}_2\text{O}/\text{NaOD}$) showed δ : 0.0-2.2 [CHCH_2 , $\text{CH}_2\text{C}(\text{CH}_3)$, 70]; 6.8-7.3 (aromatic protons, 3). See p. 188. Independent ^1H NMR experiments established the positions of signals, as well as the fact that both phenol protons appear under the solvent peak. According to the ^1H NMR spectrum, the copolymer consisted of 3 mole-% 2,4-dihydroxy-4'-vinylbenzophenone and 97 mole-% methacrylic acid. The ultraviolet spectrum (methanol) showed absorptions at 325 nm ($5.51 \text{ l g}^{-1} \text{ cm}^{-1}$), 291 nm ($6.83 \text{ l g}^{-1} \text{ cm}^{-1}$) and 246 nm ($3.59 \text{ l g}^{-1} \text{ cm}^{-1}$).

ANAL. calcd. for $(\text{C}_4\text{H}_6\text{O}_2)_{97\%}(\text{C}_{12}\text{H}_{15}\text{O}_3)_3\%$: C, 57.33%; H, 6.87%. Found: C, 57.43%; H, 7.09%.

A polymerization was carried out under similar conditions with 15 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone in the monomer feed. A 79% yield of copolymer with an inherent viscosity of 0.68 dl/g was obtained. The ^1H NMR spectrum indicated the presence of 6 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone in the copolymer. See p. 188.

ANAL. calcd. for $(\text{C}_4\text{H}_6\text{O}_2)_{92\%}(\text{C}_{12}\text{H}_{15}\text{O}_3)_8\%$: C, 59.55%; H, 6.64%. Found: C, 59.60%; H, 6.80%.

9. Copolymerization of 2,4-Dihydroxy-4'-Vinylbenzophenone with Styrene. Polymerizations were performed in duplicate. The same solutions of styrene and initiator in DMF were used for the homopolymerization of styrene and for the preparation of copolymerization mixtures. Homopolymerizations and copolymerizations were performed simultaneously, and under identical conditions. The copolymerization of 2,4-dihydroxy-4'-vinylbenzophenone with styrene, with AIBN as initiator, illustrates the procedure.

A polymerization tube was charged with 2,4-dihydroxy-4'-vinylbenzophenone (0.042 g, 0.174 mmole, 2 mole-%), freshly-distilled styrene (0.01 g, 8.74 mmole, 98 mole-%), AIBN (7.2 mg, 0.043 mmole, 0.4 mole-%), and DMF (0.5 ml). The tube was degassed by the freeze-thaw technique and sealed at 0.01 mm. After 18 hrs at 60°C, the viscous tube contents were diluted to 15 ml with benzene, and the polymer was precipitated via dropwise addition of the solution to 100 ml of rapidly-stirred methanol. After two additional reprecipitations, the yield of fluffy, white polymer was 0.30 g (31%). The inherent viscosity of the polymer (0.5% in THF, 25°C) was 0.356 dl/g, and the average molecular weights obtained from gel permeation chromatography were $\bar{M}_n = 48,200$; $\bar{M}_w = 83,000$. The infrared spectrum (KBr) showed a weak carbonyl absorption at 1625 cm^{-1} , as well as bands at 1275 cm^{-1} and 1115 cm^{-1} which are prominent in the spectrum of poly(2,4-dihydroxy-4'-vinylbenzophenone). See

p. 203. The ultraviolet spectrum (THF) showed an absorption at 326 nm ($1.76 \text{ l g}^{-1} \text{ cm}^{-1}$). The ^1H NMR spectrum (CCl_4) showed δ : 0.8-2.8 (CHCH_2 , 30) and 5.8-8.0 (aromatic protons, 50). See p. 189.

ANAL. calcd. for $(\text{C}_8\text{H}_8)_{97\%}(\text{C}_{12}\text{H}_{15}\text{O}_3)_3$: C, 91.13%; H, 7.53%. Found: C, 91.06%, 90.63%; H, 7.35%, 7.30%.

Experiments with benzoyl peroxide were performed under similar conditions, except that the initiator was 0.5 mole percent of the comonomer mixture, and the reaction time was 27 hr. Infrared and ^1H NMR spectra were as described above. See pp. 203 and 189. Elemental analysis of the copolymers indicated that 3 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone was incorporated into the copolymer.

ANAL. calcd. for $(\text{C}_8\text{H}_8)_{97\%}(\text{C}_{12}\text{H}_{15}\text{O}_3)_3$: C, 91.13%; H, 7.53%. Found: C, 91.01%; 91.36%; H, 7.35%, 7.62%.

10. Polymerization of Styrene in Presence of 2,4-Dihydroxy-4'-Ethylbenzophenone. A solution of freshly distilled styrene (10 ml, 9.1 g, 87.4 mmole) benzoyl peroxide (0.106 g, 0.44 mmole, 0.5 mole-%), and DMF (5 ml) was prepared in a flask capped with a serum stopper, under a flow of dry nitrogen. When the solution was homogeneous, 1.5 ml of solution were transferred to each of eight polymerization tubes, each of which contained the desired quantity (see Table 7, p.145) of 2,4-dihydroxy-4'-ethylbenzophenone. The tubes were de-

gassed by 3 freeze-thaw cycles at 10^{-3} mm, and then sealed at 10^{-3} mm and placed in a constant temperature bath at 60°C . After 27 hr at 60°C , the tubes were removed from the bath and cooled to room temperature. Each tube was opened, the contents diluted with 10 ml. of benzene, and the resulting solution was added dropwise to 100 ml of rapidly-stirred methanol to precipitate the polymer. The precipitated polymer was stirred for 1-2 hr in methanol, collected by filtration, and dried overnight at room temperature at 10^{-3} mm. Yields ranged from 54% to 60%. The peak molecular weights of the polymers were determined by gel permeation chromatography, and inherent viscosities were measured at 25°C in THF.

F. Attempted Preparation of Methyl
3-Acetylsalicylate and 3-Acetylsalicylic Acid

1. Reaction of Methyl Salicylate with Acetic Anhydride
and Fluorosulfonic Acid or Trifluoromethanesulfonic Acid.

A 25 ml round-bottomed flask was charged with methyl salicylate (5 g, 33 mmole), fluorosulfonic acid (0.2 ml, 3.4 mmole), and acetic anhydride (3.1 ml, 33 mmole), and fitted with a reflux condenser topped with a calcium chloride drying tube. The flask was then heated, with stirring, to 100°C for 30 min and then 130°C for 2 hr. The reaction mixture turned yellow in color. After cooling to room temperature, the reaction mixture was diluted with 20 ml

of chloroform, and the resulting solution was washed with 5% aqueous sodium bicarbonate, dried with sodium sulfate, and filtered. After removal of the chloroform at reduced pressure, the infrared spectrum (neat) of the product was recorded. See p. 204.

The procedure was repeated, using 0.4 ml (4.5 mmole) of trifluoromethanesulfonic acid in place of fluorosulfonic acid. The infrared spectrum (neat) of the reaction product is shown on p. 204.

2. Methyl Acetylsalicylate. Prepared according to Bailey.¹

3. Reaction of Methyl Acetylsalicylate with Fluorosulfonic Acid. A 25 ml round-bottomed flask was charged with acetic acid (5 ml), fluorosulfonic acid (0.5 ml, 8.6 mmole) and methyl acetylsalicylate (6.40 g, 33 mmole), and then fitted with a reflux condenser topped with a calcium chloride drying tube. The flask was immersed in an oil bath at 130°C, and the solid methyl acetylsalicylate dissolved rapidly. After 2 hr, the flask was removed from the bath and cooled to room temperature. The reaction mixture was diluted to 25 ml with chloroform, and the solution was washed with 50 ml of 5% aqueous sodium bicarbonate, dried with magnesium sulfate, and filtered. The infrared spectrum (neat) of the product was recorded after removal of the chloroform at reduced pressure. See p. 204. The product was then redissolved in chloroform, and the resulting solution

was washed with two 50 ml portions of 5% aqueous sodium hydroxide. The aqueous washes were combined and acidified with 40 ml of 6N hydrochloric acid, causing formation of an oil. The oil was dissolved in two 100 ml portions of chloroform, the solution dried with magnesium sulfate and filtered, and the chloroform removed to leave a yellow solid. The ^1H NMR spectrum (CDCl_3) is shown on p. 190.

4. Reaction of Salicylic Acid with Acetic Anhydride and Fluorosulfonic Acid or Trifluoromethanesulfonic Acid. A

25 ml round-bottomed flask was charged with salicylic acid (5.0 g, 36 mmole), acetic anhydride (3.1 ml, 33 mmole), and fluorosulfonic acid (0.2 ml, 3.4 mmole). The flask was then fitted with a reflux condenser topped with a calcium chloride drying tube, and immersed in an oil bath at 105°C . After 20 min, the temperature was raised to 130°C , and after 2.5 hr, the flask was removed from the bath and cooled. The contents of the flask were dissolved in 400 ml of 5% aqueous sodium bicarbonate, and the solution was filtered to remove a small amount of tar and then acidified with 100 ml of 3 N hydrochloric acid. The oil which precipitated was extracted with two 100 ml portions of chloroform, and the combined extracts were dried with magnesium sulfate and filtered. Removal of the solvent at room temperature left a yellow solid. The ^1H NMR spectrum of the product is shown on p. 190. The product was then dissolved in 50 ml of 5% aqueous sodium hydroxide, heated to reflux

for 15 min, and cooled. Acidification with 50 ml of 2N HCl produced an off-white, crystalline precipitate. The precipitate was collected by filtration, washed with water, and dried. The ^1H NMR spectrum is shown on p. 191.

The procedure was repeated, using 0.3 ml (3.3 mmole) of trifluoromethanesulfonic acid in place of fluorosulfonic acid. The ^1H NMR spectrum of the product (after hydrolysis) is shown on p. 191.

G. Measurements

Infrared spectra were recorded on Perkin-Elmer Model 727 or Model 283 spectrophotometers. Solid samples were measured as KBr pellets and liquid samples were measured between sodium chloride plates. The peak assignments were made to the nearest 5 cm^{-1} .

The ^1H NMR spectra of low molecular weight compounds were measured on a 60 MHz R-24 Hitachi Perkin-Elmer spectrometer. Most polymer spectra were recorded on a 90 MHz R-32 Perkin-Elmer spectrometer.

Ultraviolet spectra were recorded on a Beckman MVI spectrometer in a double-beam servo mode. The maximum absorbances and corresponding wavelengths were determined by dialing in the wavelength and recording the absorbance value presented on the digital display.

The glass transition temperatures of polymers were determined on a Perkin-Elmer DSC-1B differential scanning

calorimeter at a scanning rate of 20°C/min. The instrument was calibrated against an indium standard. Regular melting points were measured on a MEL-TEMP capillary melting point apparatus and are uncorrected. Thermal decomposition data were obtained using a Perkin-Elmer TGS-1 thermobalance at a heating rate of 20°C/min under a flow of nitrogen gas.

Gel permeation chromatography was performed on a Waters Associates Model 201 liquid chromatograph, using a set of five MicroStyragel columns (500, 10^3 , 10^4 , 10^5 , and 10^6 A). Tetrahydrofuran was employed as solvent, at a flow rate of 1.5 mL/min. The columns were calibrated using a set of nine narrow-distribution polystyrenes obtained from Waters Associates.

Microanalyses were done by the Microanalytical Laboratory, Office of Research Services, University of Massachusetts, Amherst, Massachusetts.

CHAPTER III

RESULTS AND DISCUSSION

A. Objectives

The objectives of this work were the synthesis and polymerization of several vinylsalicylic acid derivatives and 2,4-dihydroxy-4'-vinylbenzophenone. The polymers obtained are of potential interest as biologically-active agents and as ultraviolet stabilizers.

5-Vinylsalicylic acid and 5-vinylacetylsalicylic acid were prepared in overall yields of 26% and 12%, respectively, starting with methyl salicylate. Each monomer was successfully homopolymerized, and copolymerized with methacrylic acid, using AIBN as the radical initiator.

Methyl 4-vinylsalicylate, 4-vinylsalicylic acid and 4-vinylacetylsalicylic acid were prepared in overall yields of 28%, 21%, and 16%, respectively, starting with 3-ethylphenol. Radical polymerization behavior of all three monomers was investigated. Methyl 4-vinylacetylsalicylate was also prepared, in 35% yield, but no polymerization experiments were performed with this monomer.

2,4-Dihydroxy-4'-vinylbenzophenone was prepared in 33% yield from 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone,

an intermediate supplied by D. Bailey. This completed a five-step synthesis from p-ethylbenzoic acid, in an overall yield of 14%. Homopolymerization and copolymerizations with methacrylic acid and with styrene were accomplished. The influence of the model compound, 2,4-dihydroxy-4'-ethylbenzophenone, on styrene homopolymerization was also investigated.

Fluorosulfonic acid and trifluoromethanesulfonic acid were investigated as potential catalysts for Fries rearrangement of methyl acetylsalicylate and acetylsalicylic acid. The objective was preparation of the corresponding 3-acetyl derivatives, which would then be used for syntheses of 3-vinylsalicylic acid and its esters. However, no rearranged products were isolated.

Thirteen monomeric and polymeric derivatives of 5-vinylsalicylic acid were subjected to preliminary studies of antibacterial activity through the courtesy of L.G. Donaruma of the New Mexico Institute of Mining and Technology. Activities vs. *Escherichia Coli* vs. *Bacillus Subtilis* were determined by applying the sample compound to cultured bacteria and measuring the resultant zone of growth inhibition. These results are reported in Appendix A.

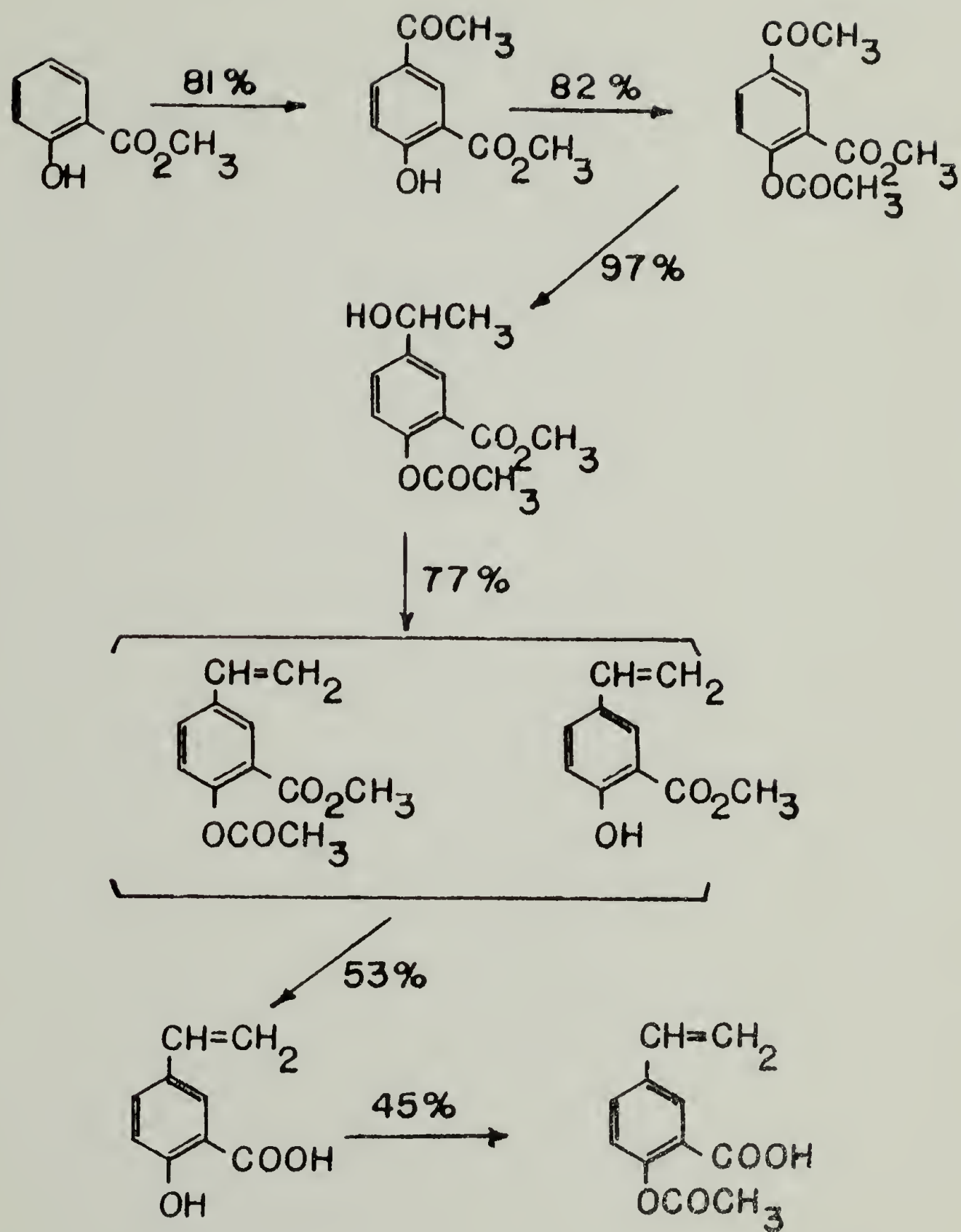
B. Preparation and Polymerization of 5-Vinylsalicylic Acid and 5-Vinylacetylsalicylic Acid

1. Introduction. 5-Vinylsalicylic acid and 5-vinylacetylsalicylic acid were prepared in overall yields of 26% and 12%, respectively, starting with methyl salicylate. Each monomer was successfully homopolymerized, and copolymerized with methacrylic acid, using AIBN as the radical initiator.

2. Preparation of 5-Vinylsalicylic Acid and 5-Vinylacetylsalicylic Acid. The first four steps of the synthesis were those employed by Bailey¹ in the preparation of methyl 5-vinylacetylsalicylate (Figure 4). Methyl salicylate was acetylated in the 5-position via a Friedel-Crafts reaction with acetyl chloride. Acetylation of the phenol, followed by reduction and dehydration then afforded, in 50% overall yield, an approximately equimolar mixture of methyl 5-vinylsalicylate and methyl 5-vinylacetylsalicylate. These steps were performed according to the procedures in reference 1, and no attempt was made to improve on the yields reported therein. The yields reported up to this point in the synthesis are those given in reference 1.

For the preparation of 5-vinylsalicylic acid, the mixture of methyl 5-vinylsalicylate and methyl 5-vinylacetylsalicylate obtained from the dehydration of methyl 5-(1-hydroxyethyl)acetylsalicylate was hydrolyzed with 5% aqueous NaOH (4-fold excess of NaOH with respect to ester). The

Figure 4. Synthesis of 5-vinylsalicylic acid and 5-vinylacetylsalicylic acid.



reaction was carried out at reflux for a period of 15 min and produced a 95% yield of a mixture of 5-vinylsalicylic acid and its oligomers. Sublimation at 78-80°C/0.01 mm separated pure monomer as white needles, mp 136-138°C, in an overall yield of 53%. Melting occurred with no visible decomposition, and upon cooling to below the melting point, rapid recrystallization occurred. This is in contrast to the behavior of the acetylated monomer (see below).

Although it was realized that hydrolysis of the vinyl monomer mixture could cause substantial oligomerization, this route was chosen for two reasons. First, a sample of a low molecular weight analog of poly(5-vinylsalicylic acid) was desired for future characterization and testing. Such a sample was indeed obtained, as the oligomer was obtained with an inherent viscosity of 0.09 dl/g after exhaustive removal of monomer at 100°C/ 10^{-3} mm (6 hr). Secondly, it was anticipated that 5-vinylsalicylic acid would be a solid compound, and that the hydrolysis of methyl 5-(1-hydroxyethyl)salicylate followed by dehydration would therefore be experimentally inconvenient.

Acetylation of 5-vinylsalicylic acid with acetic anhydride/ H_2SO_4 produced a 78% yield of monomeric and oligomeric 5-vinylacetylsalicylic acid. Sublimation at 78°C/0.01 mm again provided a convenient means of separating the monomer in pure form. The monomer was obtained in an overall yield of 45% as a white solid which decomposed slowly at 144°C. In contrast to the behavior of 5-vinylsalicylic

acid, exhaustive removal of monomer ($100^{\circ}\text{C}/10^{-3}$ mm, 6 hr) produced not a linear oligomer, but a crosslinked material containing only a small acetone-soluble fraction. It is likely that crosslinking occurred through the p-acetoxy group, since gentle warming of the material (55°C , 1.5 hr) in 5% aqueous sodium hydroxide dissolved the material completely. Such branching through the acetate group is well established in the polymerization of vinyl acetate;¹⁹³ however, it involves a more reactive growing radical. It is also possible that the crosslinking reaction is an intermolecular polyesterification reaction of the acid and phenol functions of the salicylic acid portion of the molecule. Polyesterification between the acetate of a phenol group and an acid function is more readily accomplished than that between a free phenol and an acid function. This reaction has been used for the production of aromatic polyesters from diacetates of bisphenols.¹⁹⁴ Spectral evidence discussed below indicates that it is the latter suggestion which is the more likely.

The difference in melting behavior of 5-vinylsalicylic acid and 5-vinylacetylsalicylic acid monomers and in the thermal behavior of the corresponding oligomers suggests the possibility that the free phenol confers some degree of thermal (or thermal oxidative) stability upon the phenol compounds relative to the acetylated analogs.

3. Preparation of Polymers of 5-Vinylsalicylic Acid and 5-Vinylacetylsalicylic Acid. The polymerization of 5-vinylsalicylic acid was carried out in isopropanol solution in a sealed tube at 60°C with AIBN as the initiator and gave in 24 hr a 77% yield of polymer with an inherent viscosity of 0.58 dl/g. Isopropanol was a convenient solvent, selected on the basis of its moderate chain-transfer constant in radical polymerization of styrene. No substantial interference of the phenol group in the polymerization was observed; for a full discussion of this point, see Section D. Poly(5-vinylsalicylic acid) is soluble in acetone, DMSO, and aqueous sodium hydroxide, and insoluble in chloroform, benzene, and aqueous hydrochloric acid. DSC showed no transition below 340°C.

The infrared spectrum was consistent with the expected structure of poly(5-vinylsalicylic acid), with a strong carbonyl absorption at 1670 cm^{-1} , as well as a lack of the strong vinyl C-H stretching bands (910 and 1000 cm^{-1}) present in the spectrum of the monomer. The ^1H NMR spectrum also was consistent with the proposed structure with broad methine and methylene proton resonance in the 0.5 to 2.5 ppm range and overlapping broad signals centered at 6.6 and 8.1 ppm due to the aromatic protons and the carboxylic acid-phenol proton exchange, respectively. The precise position of the signal due to the proton exchange was dependent upon the concentration of the polymer in the

NMR sample solution.

The copolymerization of methacrylic acid with 12 mole-% 5-vinylsalicylic acid was successfully carried out in isopropanol solution in a sealed tube at 60°C for 24 hr. The copolymer was obtained in 53% yield as a brittle glass, uniformly swollen by the solvent. The inherent viscosity of the copolymer was 2.74 dl/g, and the infrared spectrum was consistent with the expected structure of the copolymer, showing a broad carbonyl absorption at 1700 cm^{-1} .

The composition of the copolymer was determined from its ^1H NMR spectrum and from elemental analysis for carbon and hydrogen. The ^1H NMR spectrum was recorded in D_2O containing approximately 1% NaOD, in order to avoid overlap of the signals of the polymer backbone protons with the signal of the residual protons in deuterated DMSO, the solvent used to record the homopolymer spectrum. Peak positions were determined relative to DMSO (assigned a value of 2.5 ppm), a trace of which was added to the sample after careful integration of the spectrum. The signals of interest (the aliphatic region at 0-2.5 ppm and the aromatic region at 6.1-7.2 ppm) were clearly distinguishable by this method. The ratio of the integrated signal intensity of the aromatic protons (7) to the integrated signal intensity of the aliphatic protons (67) corresponded to a copolymer containing 16 mole-% 5-vinylsalicylic acid. The same composition was obtained by elemental analysis.

The aromatic region of the ^1H NMR spectrum was more complex for the copolymer than for the homopolymer; two overlapping signals centered at 6.4 and 7.1 ppm appeared in the spectrum of the copolymer. The ratio of integrated intensities of the signals is approximately 1:2, which indicated that the higher field signal was that of the proton in the 3-position (ortho to the phenol), while the 7.1 ppm signal was due to the protons in the 4- and 6- positions absorbed at 7.5-7.9 ppm. The assignment is tentative, however, because the peaks were poorly separated and the integration is not fully reliable.

The polymerization of 5-vinylacetylsalicylic acid in acetic acid solution with 0.6 mole-% AIBN as initiator produced a 71% yield of poly(5-vinylacetylsalicylic acid) of inherent viscosity 0.46 dl/g. The polymerization was carried out in a sealed tube at 60°C over a period of 24 hr. The polymer was soluble in acetone and DMSO, and insoluble in isopropanol, benzene, and chloroform. The polymer began to decompose at 315°C by DSC; this is at least 25°C below the decomposition temperature of poly(5-vinylsalicylic acid) under the same conditions and is another indication of the enhanced stability of the free phenol compounds.

The infrared spectrum showed a broad carbonyl absorption centered at 1720 cm^{-1} , corresponding to the $\text{C}=\text{O}$ stretching vibrations of the acid and ester groups. This coalescence of the carbonyl bands was not observed in the

spectrum of the 5-vinylacetylsalicylic acid monomer, in which the acid (1685 cm^{-1}) and ester (1760 cm^{-1}) absorptions were clearly resolved. The general features of the infrared spectrum of the polymer are consistent with the proposed structure of poly(5-vinylacetylsalicylic acid).

The ^1H NMR spectrum of the polymer consisted of a broad signal centered at 1.7 ppm due to the methylene and methine protons, a relatively sharp singlet at 2.2 ppm due to the acetate protons, a broad aromatic signal at 6.1-8.4 ppm, and a broad COOH signal at 11.0-13.4. The ^1H NMR spectrum on page 174 is that of a polymerization of 5-vinylacetylsalicylic acid in deuterated DMSO, and clarifies the question of crosslinking during the sublimation of the monomer. A mixture of 5-vinylacetylsalicylic acid, d-DMSO, and AIBN was prepared in a polymerization tube, deoxygenated in a stream of nitrogen, and the tube was sealed. After 48 hr at 60°C , the spectrum showed the development of a very sharp singlet at 1.9 ppm; this was assigned to acetic acid after addition of a drop of acetic acid caused a sharp increase in the size of the signal. Apparently, transesterification of acetylsalicylic acid residues with release of acetic acid becomes important even at 60°C , and it is perhaps fortuitous that polymerization experiments with this monomer were performed in acetic acid solution. This is consistent with the observation, discussed in the following section, that polymerization of 4-vinylacetylsalicylic acid

in either DMSO or t-butanol gives cross-linked products.

The copolymerization of 5-vinylacetylsalicylic acid and methacrylic acid was carried out in solution in acetic acid; 5-vinylacetylsalicylic acid constituted 7 mole-% of the monomer feed. Polymerization for 24 hr at 60°C in a sealed tube containing 0.3 mole-% AIBN produced in 97% yield a copolymer of inherent viscosity 3.17 dl/g. Infrared and ^1H NMR spectra were consistent with the proposed structure of the copolymer. The ^1H NMR spectrum was recorded in $\text{D}_2\text{O}/\text{NaOD}$ in the same manner as for the 5-vinylsalicylic acid/methacrylic acid copolymer. The spectrum consisted of a broad signal at 0-2.6 ppm due to the aliphatic backbone protons, a relatively sharp singlet (COCH_3) at 2.7 ppm, and a broad aromatic signal at 6.4-7.6 ppm. Integration of the spectrum indicated incorporation of 5-vinylacetylsalicylic acid to the extent of 7 mole-%. The aromatic signal was again split into two overlapping signals; the tentative explanation for such splitting is the same as that for the 5-vinylsalicylic acid/methacrylic acid copolymer.

C. Preparation and Polymerization of Methyl 4-Vinylsalicylate, 4-Vinylsalicylic Acid and 4-Vinylacetylsalicylic Acid

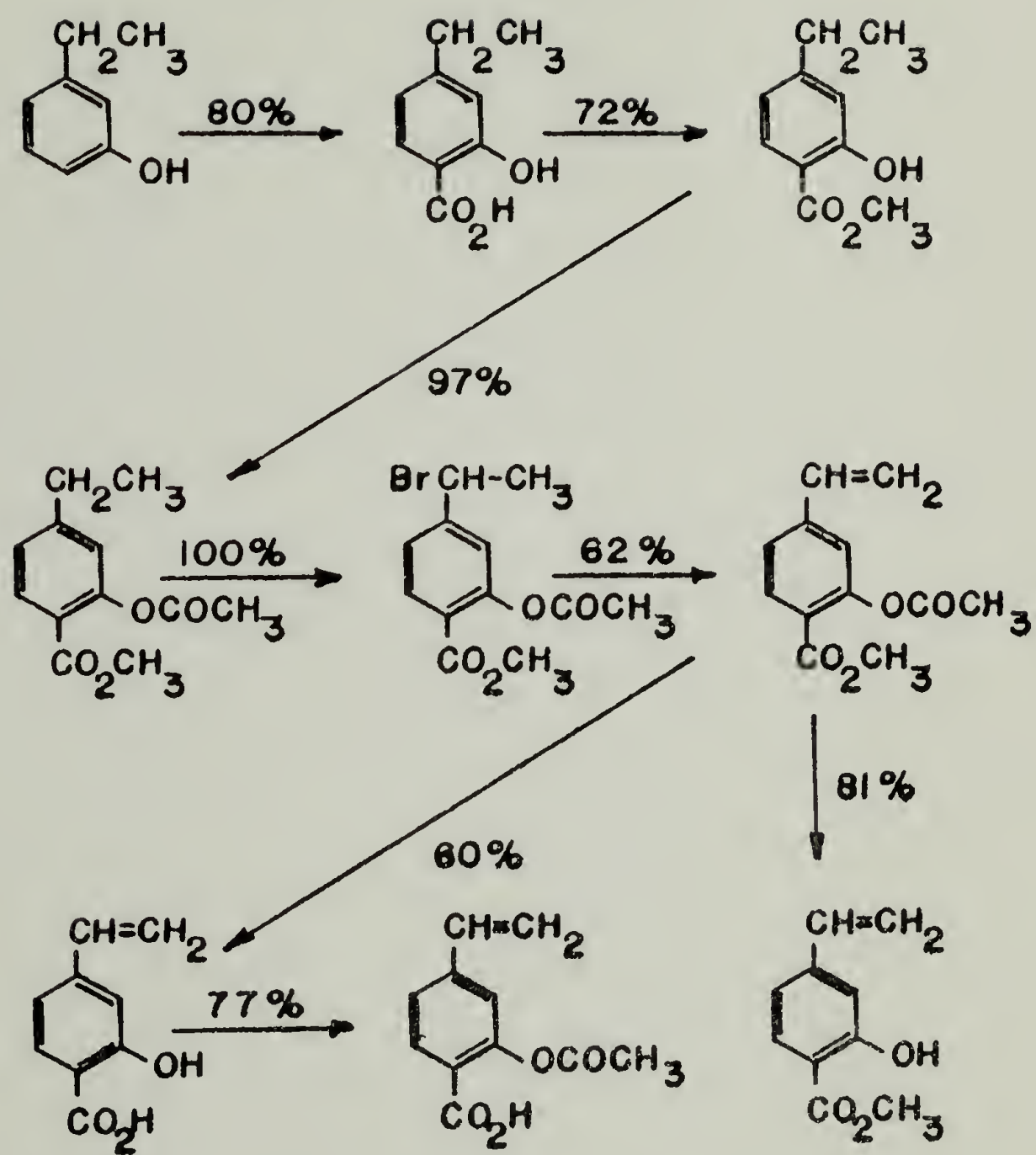
1. Introduction. Methyl 4-vinylsalicylate, 4-vinylsalicylic acid and 4-vinylacetylsalicylic acid were prepared

in overall yields of 28%, 21%, and 16%, respectively, starting with 3-ethylphenol. Radical polymerization behavior of all three monomers was investigated. Methyl 4-vinylacetylsalicylate was also prepared, in 35% yield, but no polymerization experiments were performed with this monomer.

The syntheses of these 4-vinylsalicylic acid derivatives are shown in Figure 5. 3-Ethylphenol was carbonated in the position ortho to the phenol group by the Marasse modification of the Kolbe-Schmitt reaction, to give an 80% yield of 4-ethylsalicylic acid. Esterification with methanol and sulfuric acid provided methyl 4-ethylsalicylate in 72% yield, and acetylation of the product with acetic anhydride and sulfuric acid proceeded in 97% yield. Treatment of methyl 4-ethylacetylsalicylate with N-bromosuccinimide then gave quantitative benzylic bromination. Dehydrobromination of methyl 4-(1-bromoethyl)acetylsalicylate with tributylamine in DMAc gave, in 62% yield, methyl 4-vinylacetylsalicylate, which was then converted to each of the three desired vinyl monomers. Removal of the acetyl group with sodium methoxide in methanol gave methyl 4-vinylsalicylate in 81% yield, and saponification with sodium hydroxide produced a 60% yield of 4-vinylsalicylic acid. Acetylation of the latter compound afforded 4-vinylacetylsalicylic acid in 77% yield.

Methyl 4-vinylsalicylate was polymerized in bulk

Figure 5. Synthesis of 4-vinylsalicylic acid derivatives.



with AIBN as initiator, and gave a 72% yield of poly(methyl 4-vinylsalicylate) of inherent viscosity 2.61 dl/g. A series of homopolymerizations of 4-vinylsalicylic acid produced polymers with inherent viscosities ranging from 0.46 dl/g to 2.24 dl/g, and copolymerization with methacrylic acid gave a copolymer containing 34 mole-% 4-vinylsalicylic acid, with an inherent viscosity of 1.73 dl/g. Homopolymerization of 4-vinylacetylsalicylic acid, and copolymerization of this monomer with methacrylic acid, gave gelled polymerization mixtures in DMSO and in tert-butanol; dissolution of these polymers in warm aqueous sodium hydroxide indicated cross-linking through the acetoxy group, consistent with observations made in polymerization of 5-vinylacetylsalicylic acid in DMSO.

A poly(4-vinylsalicylic acid)--copper complex containing 88% of the stoichiometric quantity of copper was prepared. This complex was insoluble in water.

2. Preparation of Methyl 4-Vinylsalicylate, 4-Vinylsalicylic Acid, and 4-Vinylacetylsalicylic Acid. Carbonation of 3-ethylphenol via the Marasse modification of the Kolbe-Schmitt reaction gave 4-ethylsalicylic acid in 80% yield (77% after recrystallization from water). This reaction was performed in a glass-lined stainless steel autoclave at 1000 psi and 175°C, according to the procedure of Baine, et al.¹⁹⁵ The product was identified as 4-ethylsalicylic acid by its melt-

ing point (129-30.5°C, lit. m.p.¹⁹² 124°C) and its ¹H NMR and UV spectra. The aromatic region of the ¹H NMR spectrum was essentially identical to that of 4-methylsalicylic acid,¹⁹⁶ and the ultraviolet spectrum showed absorption maxima at 243 nm and 303 nm, characteristic of salicylic acids.¹⁹⁷ The other possible product of the carbonation, 2-ethyl-4-hydroxybenzoic acid, would be expected to show a single absorption maximum near 253 nm, as observed in the spectrum of p-hydroxybenzoic acid.¹⁹⁸ 2-Ethyl-4-hydroxybenzoic acid has apparently not been reported in the literature, so direct spectral comparison was not possible.

Crude 4-ethylsalicylic acid was esterified with methanol and sulfuric acid, and gave a 72% yield of methyl 4-ethylsalicylate. Acetylation of the product with acetic anhydride and sulfuric acid then provided methyl 4-ethylacetylsalicylate in 97% yield. The phenol group was acetylated in order to avoid complications similar to those encountered by Bailey in the bromination of 2,4-dihydroxy-4'-ethylbenzophenone, in which it was found that bromination occurred on the aromatic ring unless the phenols were blocked by acetylation. Since benzylic bromination was desired in the present work also, methyl 4-ethylsalicylate was acetylated to methyl 4-ethylacetylsalicylate before treatment with N-bromosuccinimide.

Benzylic bromination of methyl 4-ethylacetylsalicylate proceeded smoothly, and gave the desired benzylic

bromide in quantitative yield when a stoichiometric quantity (or a very slight excess) of NBS was employed. This was in contrast to the results obtained when the reaction was performed according to the usual procedure,¹⁹⁹ i.e. with a large excess of NBS in the presence of a free radical activator such as AIBN: in this case, only a small amount of the desired benzylic bromide was obtained, and a substantial yield of methyl 4-(1,1-dibromoethyl)acetylsalicylate was isolated. The ^1H NMR spectrum of this product is shown on p. 177. Apparently, in the presence of AIBN, both benzylic hydrogen atoms may be replaced by bromine.

Dehydrobromination of methyl 4-(1-bromoethyl)acetylsalicylate was accomplished in 62% yield by treatment with tributylamine in DMAc at 150°C. An analytically-pure sample of the product, methyl 4-vinylacetylsalicylate, was obtained by chromatography on acidic alumina followed by short-path distillation (b.p. 85°C/0.01 mm), but no polymerization experiments were performed with this monomer.

Two other dehydrobrominating agents were investigated without success. Treatment of methyl 4-(1-bromoethyl)acetylsalicylate with refluxing aqueous sodium hydroxide gave saponification, but no dehydrobromination. Similarly, reaction with ethanolic potassium hydroxide afforded a product of which the ^1H NMR spectrum (p.178) showed no vinyl protons.

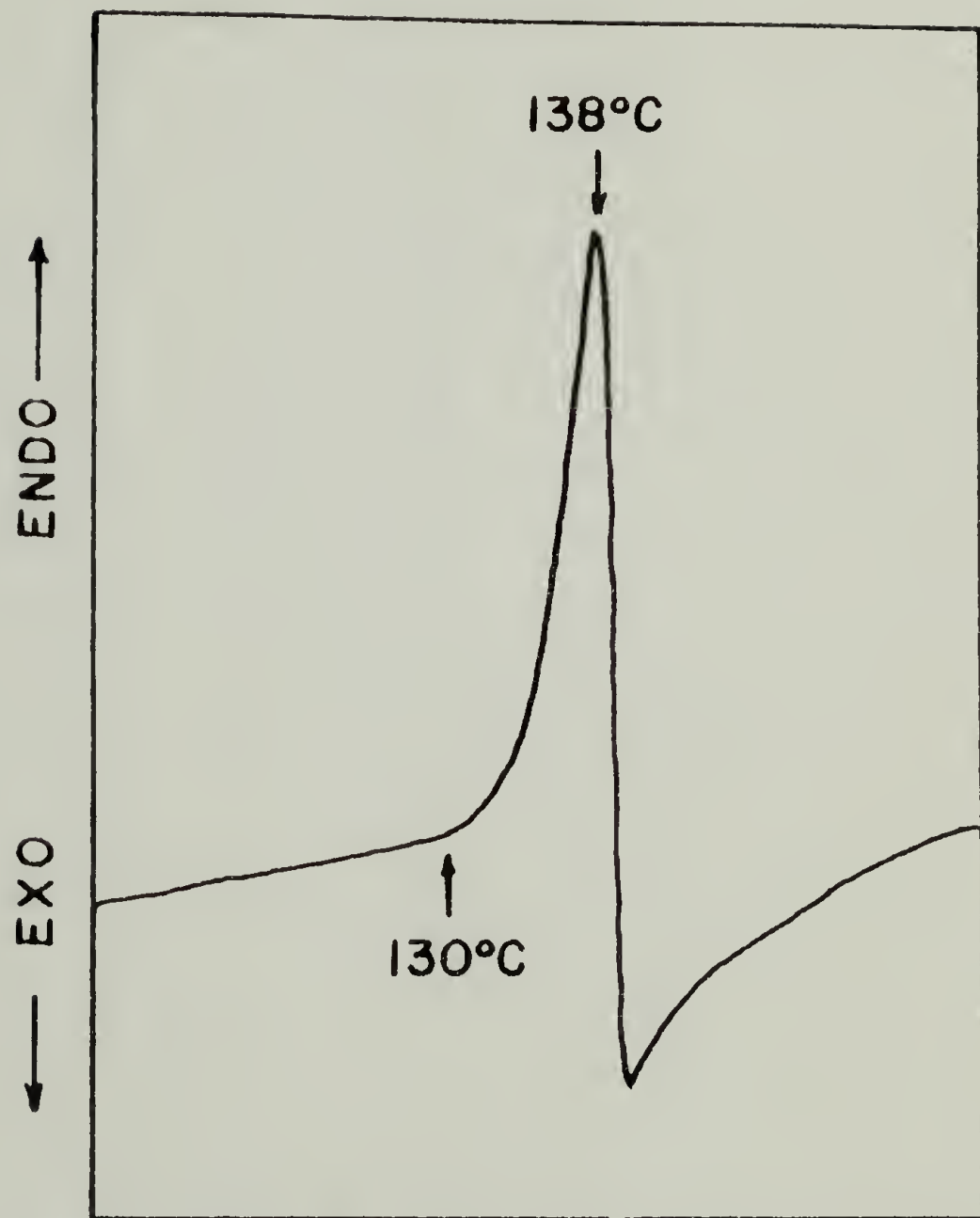
Methyl 4-vinylacetylsalicylate was converted to

methyl 4-vinylsalicylate in 81% yield by treatment with sodium methoxide in methanol. An analytically-pure sample was obtained by distillation (b.p. 59-64°C/0.01 mm) followed by chromatography on silica gel, and was used in homopolymerization experiments.

4-Vinylsalicylic acid was prepared from methyl 4-vinylacetylsalicylate by saponification with aqueous sodium hydroxide. The yield of 4-vinylsalicylic acid after sublimation (80°C/0.01 mm) was 60% (white needles, m.p. 130°C, dec). Visual determination of the melting point of this compound (and that of 4-vinylacetylsalicylic acid) is unreliable, since melting is apparently accompanied by polymerization. In fact, if the melting experiment is carried out in the differential scanning calorimeter, one observes a melting endotherm followed immediately by an exotherm due to polymerization of the compound (Figure 6).

4-Vinylacetylsalicylic acid was prepared in 77% yield from 4-vinylsalicylic acid by acetylation with acetic anhydride and sulfuric acid. The product was obtained as white needles, melting at 124°C with decomposition. An attempt was made to prepare this compound by transesterification of methyl 4-vinylacetylsalicylate with acetic acid, but this was unsuccessful; after 2½ hr at 80°C, the ¹H NMR spectrum showed no evidence of removal of the methyl ester (p. 181).

Figure 6. Differential scanning calorimetry of 4-vinylsalicylic acid.



3. Preparation of Polymers of Methyl 4-Vinylsalicylate, 4-Vinylsalicylic Acid and 4-Vinylacetylsalicylic Acid. Bulk

polymerization of methyl 4-vinylsalicylate at 60°C with AIBN as initiator afforded a 72% yield of poly(methyl 4-vinylsalicylate) of inherent viscosity 2.61 dl/g. This is consistent with Bailey's observations in the polymerization of methyl 5-vinylsalicylate; in Bailey's work, a 70% yield of poly(methyl 5-vinylsalicylate) of inherent viscosity 2.46 dl/g was obtained under similar conditions. The similarity in polymerization behavior of the two monomers suggests that intramolecular deactivation of the growing chain (through quinonemethide formation) is not an important side reaction. If it were, the 4-vinyl derivative would be expected to give polymers of substantially higher molecular weight, since the active center cannot be delocalized to the phenol group by resonance. This suggestion is consistent with the work of Kato,²⁰⁰ who studied the radical polymerization behavior of hydroxystyrenes with AIBN, and found essentially normal kinetics and mechanism in the polymerizations of the meta- and para-hydroxy compounds. In the case of ortho-hydroxystyrene, an intramolecular deactivation of the growing chain was postulated to account for significantly reduced molecular weight and anomalous kinetic behavior.

A series of poly(4-vinylsalicylic acids) was pre-

pared by solution polymerization of the monomer in DMF in the presence of varying concentrations of AIBN. The inherent viscosities of the polymers ranged from 0.46 dl/g to 2.24 dl/g (0.5% in DMSO), as shown in Table 4. The systematic decrease in the molecular weights of the polymers with increasing initiator concentration was expected in this radical polymerization, but no effort was made to fit these data to quantitative predictions of the dependence of kinetic chain length on initiator concentration. Conversions in these experiments were in the range of 40-100%, and quantitative treatments are thus invalid.

An unexpected difficulty in these polymerizations was the contamination of the resulting polymers by nitrogen-containing impurities, presumably by transamidation with the solvent (DMF). The polymers could be purified, however, by treatment with aqueous sodium hydroxide, and were then isolated as fluffy white powders by acidification, washing with water, and freeze-drying of the moist polymer from tert-butanol. Hydrolysis did not cause degradation of the polymer, since the inherent viscosity in DMSO remained essentially unchanged after this treatment.

A copper (II) complex of poly(4-vinylsalicylic acid) was prepared by treatment of an acetone solution of the polymer with an aqueous solution of cupric acetate. The light green polymer complex precipitated as the solutions were mixed, and elemental analysis for copper indicated up-

take of 88% of the stoichiometric quantity of the metal. Kennedy and coworkers have shown that suspensions of poly(5-acrylamidosalicylic acid) can complex essentially 100% of the theoretical amount of copper at pH 4.5-6.0, but that the uptake is somewhat time-dependent.⁴⁰ Perhaps longer equilibration times would allow additional complexation of copper by poly(4-vinylsalicylic acid).

The avidity of the polymer for metal ions was also evidenced in other ways: a stainless steel spatula in contact with the moist polymer quickly showed signs of attack, the polymer repeatedly failed to elute from a GPC apparatus equipped with copper tubing, and a THF solution of the polymer containing a clean copper wire developed a bright green coloration on standing overnight. The reversibility of this complexation has not been determined.

Copolymerization of 4-vinylsalicylic acid with methacrylic acid in a feed molar ratio of 1:1 produced a copolymer containing approximately 34 mole-% of 4-vinylsalicylic acid, with an inherent viscosity of 1.73 dl/g. The copolymer was obtained in 86% yield after 20 hr at 60°C in DMSO. Copolymer composition was determined from the ¹H NMR spectrum, recorded in D₂O containing a small amount of NaOD, and from elemental analysis for carbon and hydrogen. The two methods were in good agreement: integration of the ¹H NMR spectrum indicated 35 mole-% of 4-vinylsalicylic acid, and a value of 33 mole-% gave the best fit

to the elemental analysis.

Polymerization of 4-vinylacetylsalicylic acid, and copolymerization of this monomer with methacrylic acid in a feed molar ratio of 1:1 produced gelled polymerization mixtures in DMSO and in tert-butanol. These polymerizations were carried out using the same experimental procedure as in previous runs--AIBN as initiator, 60°C in a sealed tube for 24 hr. The resulting polymers were insoluble in DMSO, ethanol and acetone, although all were highly swollen in DMSO. Warming of the polymers with aqueous sodium hydroxide caused complete dissolution, indicating that cross-linking had occurred through the acetoxy group. This cross-linking is almost certainly a result of intermolecular transesterification, as observed in the polymerization of 5-vinylacetylsalicylic acid (p. 106).

4. A Note on the Polymerizability of Vinylsalicylic Acids.

Because they contain phenolic hydroxyl groups, derivatives of 4- and 5-vinylsalicylic acids might have been expected to show anomalous radical polymerization behavior. It has been shown in this work, however, that polymerizations of these monomers proceed quite normally when AIBN is used as the radical initiator, and when the polymerizations are run with careful exclusion of oxygen. Although the retardation of radical polymerization by phenolic compounds is discussed in more detail in Section F of Chapter I and in

the next section of this chapter, an additional note is appropriate here.

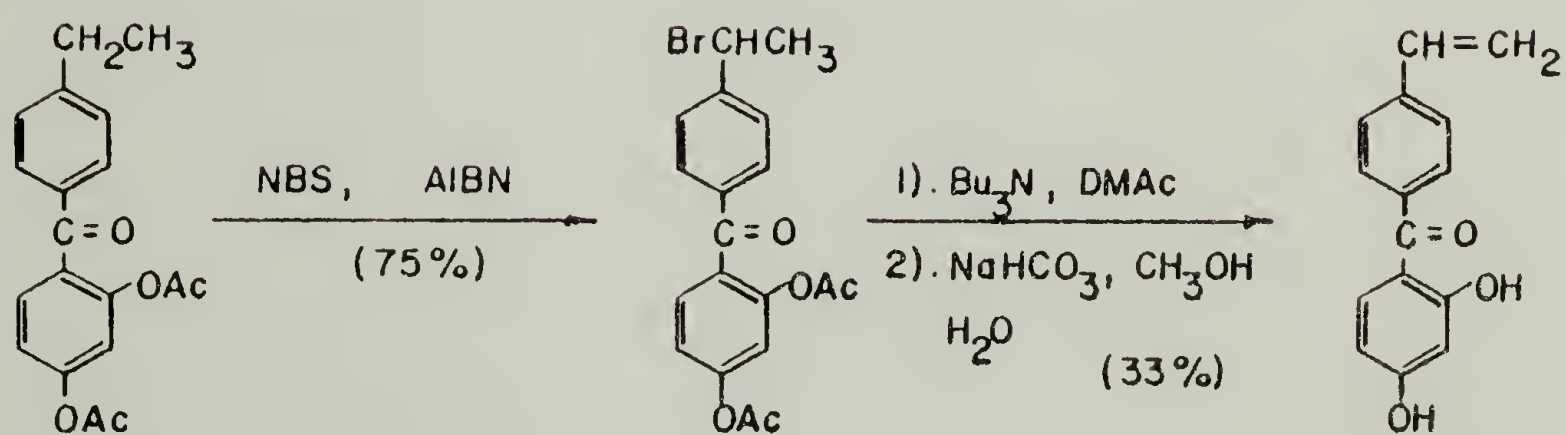
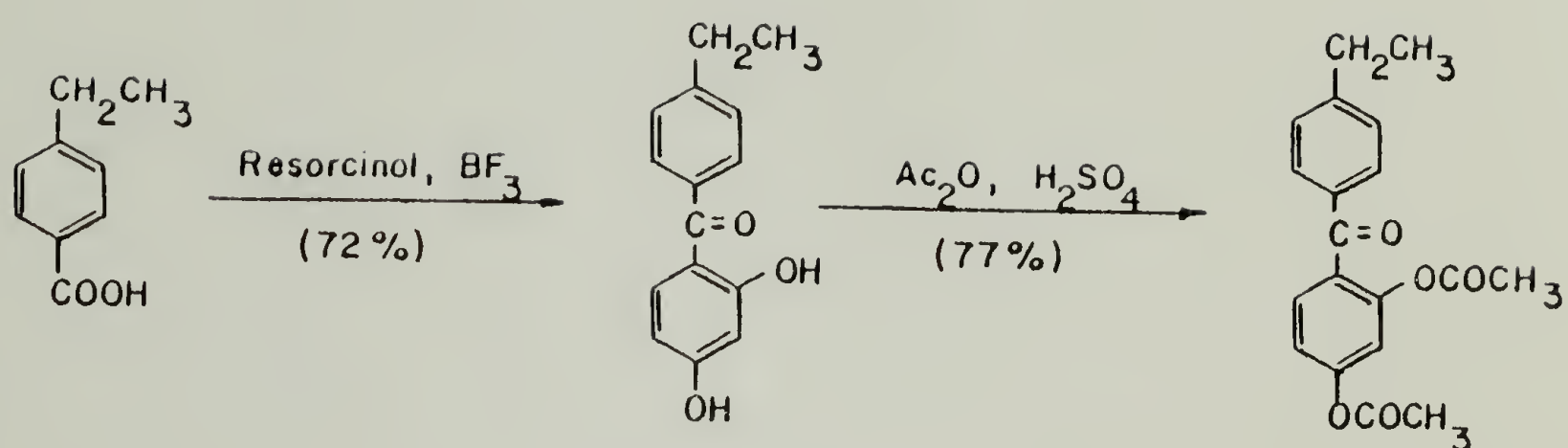
Kennedy and coworkers have stated that 4- and 5-acrylamidosalicylic acids do not polymerize via free radical initiation except at high pH (above 9) or in the presence of complexed borate.⁹ These authors claim inhibition of the polymerization by these compounds. Since this is inconsistent with the repeated successful polymerization of 4- and 5-vinylsalicylic acid derivatives accomplished in this work, it is of interest to examine the differences between the two systems. It is possible that the electron-donating effect of the p-N-acylamino group activates the phenol group of 5-acrylamidosalicylic acid with respect to hydrogen atom abstraction, but this would not hold for the 4- isomer. An explanation that appears to be more likely, but cannot be fully substantiated, is that Kennedy and coworkers may not have excluded oxygen from their polymerization systems. Although the details are not given, there is no mention of degassing or even of the use of nitrogen in reference 9. In view of the discussion in Chapter I, it is clear that the presence of oxygen may have a great effect on the polymerizability of vinylsalicylic acids and other phenol-containing vinyl monomers, and that oxygen should be rigorously excluded from polymerizations involving these compounds.

D. Preparation and Polymerization of
2,4-Dihydroxy-4'-Vinylbenzophenone

1. Introduction. The synthesis of 2,4-dihydroxy-4'-vinylbenzophenone is shown in Figure 7. 2,4-Dihydroxy-4'-vinylbenzophenone was prepared in 33% yield in two steps from 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone an intermediate supplied by D. Bailey. Bailey prepared this intermediate in 42% yield from p-ethylbenzoic acid, so the present work completes the synthesis of the title compound in an overall yield of 14%.

The preparation of 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone is described in detail by Bailey.¹ Briefly, 2,4-dihydroxy-4'-ethylbenzophenone was prepared by acylation of resorcinol with p-ethylbenzoic acid. The phenol groups were blocked by acetylation, and the side chain was brominated in the benzylic position through treatment with N-bromosuccinimide. In the present work, 2,4-diacetoxy-4'-(1-bromoethylbenzophenone) was dehydrobrominated with tributylamine, and the phenols were deprotected by treatment of the crude elimination product with sodium bicarbonate in aqueous methanol. After purification by column chromatography and recrystallization, homopolymerization and copolymerization of 2,4-dihydroxy-4'-vinylbenzophenone were investigated. In addition, the effect of the model compound, 2,4-dihydroxy-4'-ethylbenzophenone, on the polymerization of styrene was determined.

Figure 7. Synthesis of 2,4-dihydroxy-4'-vinylbenzophenone.



2. Preparation of 2,4-Dihydroxy-4'-Vinylbenzophenone. Dehydrobromination of 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone was accomplished by treatment with tri-n-butylamine in DMAc at 140°C; an 81% yield of crude (2,4-diacetoxy-4'-vinylbenzophenone) was obtained. The product was not purified, but was treated with sodium bicarbonate in aqueous methanol to unblock the phenol groups. After purification by dry-column chromatography and recrystallization, a 33% yield of pure 2,4-dihydroxy-4'-vinylbenzophenone was obtained.

Several other dehydrohalogenation agents were investigated for the elimination of hydrogen bromide from 2,4-diacetoxy-4'-(1-bromoethyl)benzophenone. Strong bases such as NaOH, KOH, and sodium and potassium tert-butoxides were investigated, in protic solvents and in aprotic solvents, with little success. In general, tarry products were obtained, with the NMR spectra indicating very low yields of olefin. Weak bases, such as lithium chloride and tetraethylammonium chloride (in DMAc or DMF), afforded only low conversion to the olefin, even after 36 hr at 100°C.¹ Silver nitrate in aqueous alcohol, although reacting rapidly with the benzylic bromide to produce a solid precipitate, produced little olefin in 17 hours in the dark at room temperature. Several tertiary amines were then investigated, with mixed results. Collidine produced no reaction even in

45 hr at 100°C, while the use of quinoline at the same temperature cause complete disappearance of starting material within one hour (with formation of little or no olefin). Pyridine and triethylamine were similarly ineffective.¹

The purification of 2,4-dihydroxy-4'-vinylbenzophenone was found to be surprisingly difficult. Although the elimination reaction was run at high temperature, the crude product of the reaction contained substantial starting material, as evidenced by spectral data and by qualitative analyses for bromine (see Experimental). The high molecular weight of 2,4-dihydroxy-4'-vinylbenzophenone precluded distillation at a temperature at which the double bond is stable with respect to polymerization, and contamination with the bromide thwarted numerous attempts at crystallization. Similarly, dry-column chromatography was complicated by the presence of the bromide, since the chromatographic behavior of these compounds is dominated by the 2,4-dihydroxybenzophenone structure, with the side-chain contributing very little to the adsorption process. After many unsuccessful attempts, however chromatography on silica gel with a 5/1 pentane/acetone solvent system produced a material capable of crystallization. Recrystallization from 2/1 pentane/chloroform then afforded pure 2,4-dihydroxy-4'-vinylbenzophenone as needles or platelets, depending on the rate of cooling. The compound polymerized at (or below) its melting point; differential scanning calorimetry at 20°C/

min. showed no melting endotherm, but rather a substantial exotherm beginning at 96°C and with a maximum at ca. 120°C (Figure 8).

3. Preparation and Characterization of Polymers of 2,4-Dihydroxy-4'-Vinylbenzophenone. 2,4-Dihydroxy-4'-vinylbenzophenone was successfully polymerized in solution in DMF with AIBN as initiator to give poly(2,4-dihydroxy-4'-vinylbenzophenone) with an inherent viscosity of 0.57 dl/g. The polymer was obtained in 60% yield after 30 hr at 60°C in a sealed tube. The UV spectrum showed the three absorption maxima characteristic of the 2,4-dihydroxybenzophenones (at 324, 292 and 248 nm), indicating that the polymer structure is a substantially linear vinyl polymer structure. The extinction coefficient of the polymer is, however, significantly lower than those of model compounds throughout the ultraviolet spectral region (Figure 9, Table 5). This hypochromic effect is not surprising in view of earlier work on the ultraviolet spectra of vinyl polymers; for example, Gallo and Russo²⁰¹ and Stutzel, Miyamoto and Cantow²⁰² have described hypochromic effects in styrene-methyl methacrylate copolymers, and Gibson²⁰³ has reported a similar phenomenon in polymers containing carbazole chromophores.

Poly(2,4-dihydroxy-4'-vinylbenzophenone) exhibited no detectable glass transition in the differential scanning

TABLE 5

Molar Extinction Coefficients of 2,4-Dihydroxybenzophenones

Compound	Wavelength (λ_{max} , nm)	Extinction Coefficient ($\ell/\text{mole-cm}$)
2,4-Dihydroxybenzo- phenone	242	10800
	289	14300
	322	10400
2,4-Dihydroxy-4'- Ethylbenzophenone	246	9400
	289	14600
	326	11400
2,4-Dihydroxy-4'- Vinylbenzophenone	290	16300
	335	14800
Poly (2,4-dihydroxy-4'- vinylbenzophenone)	248	7400
	292	11600
	324	9600

Figure 8. Differential scanning calorimetry of 2,4-dihydroxy-4'-vinylbenzophenone.

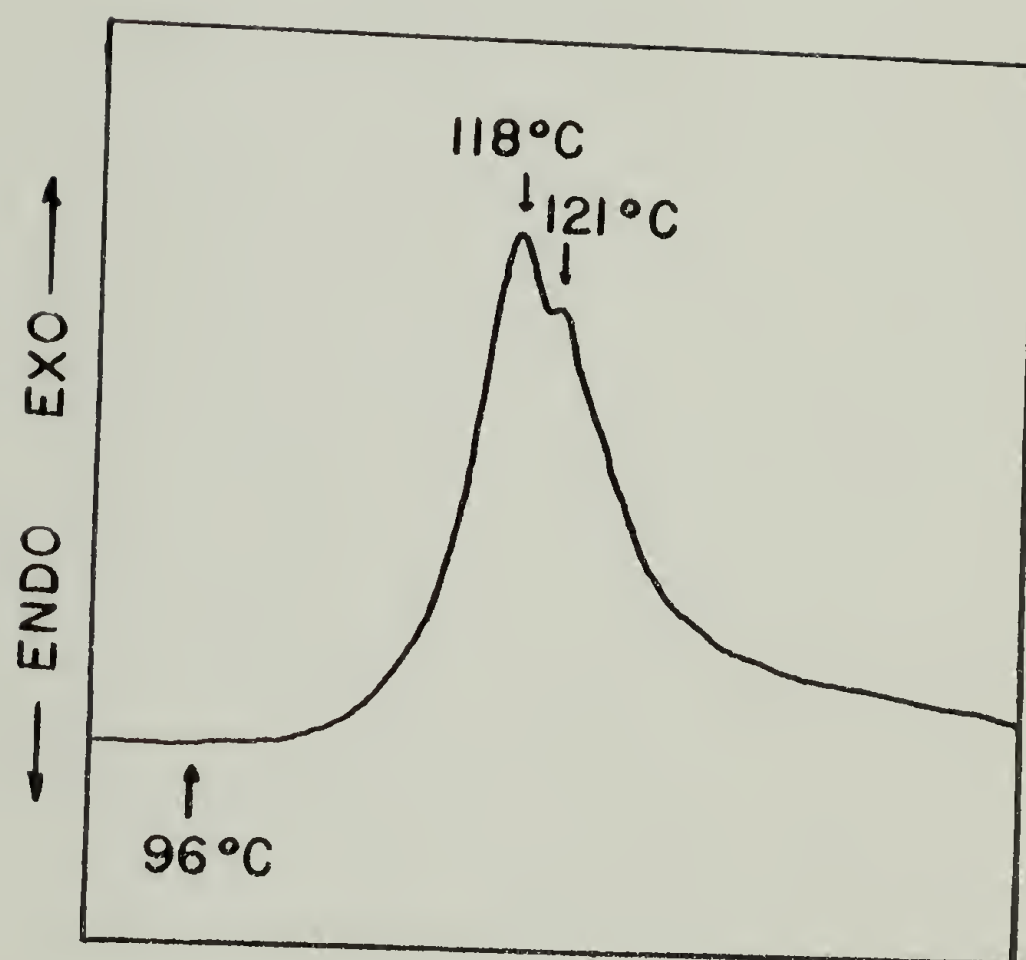
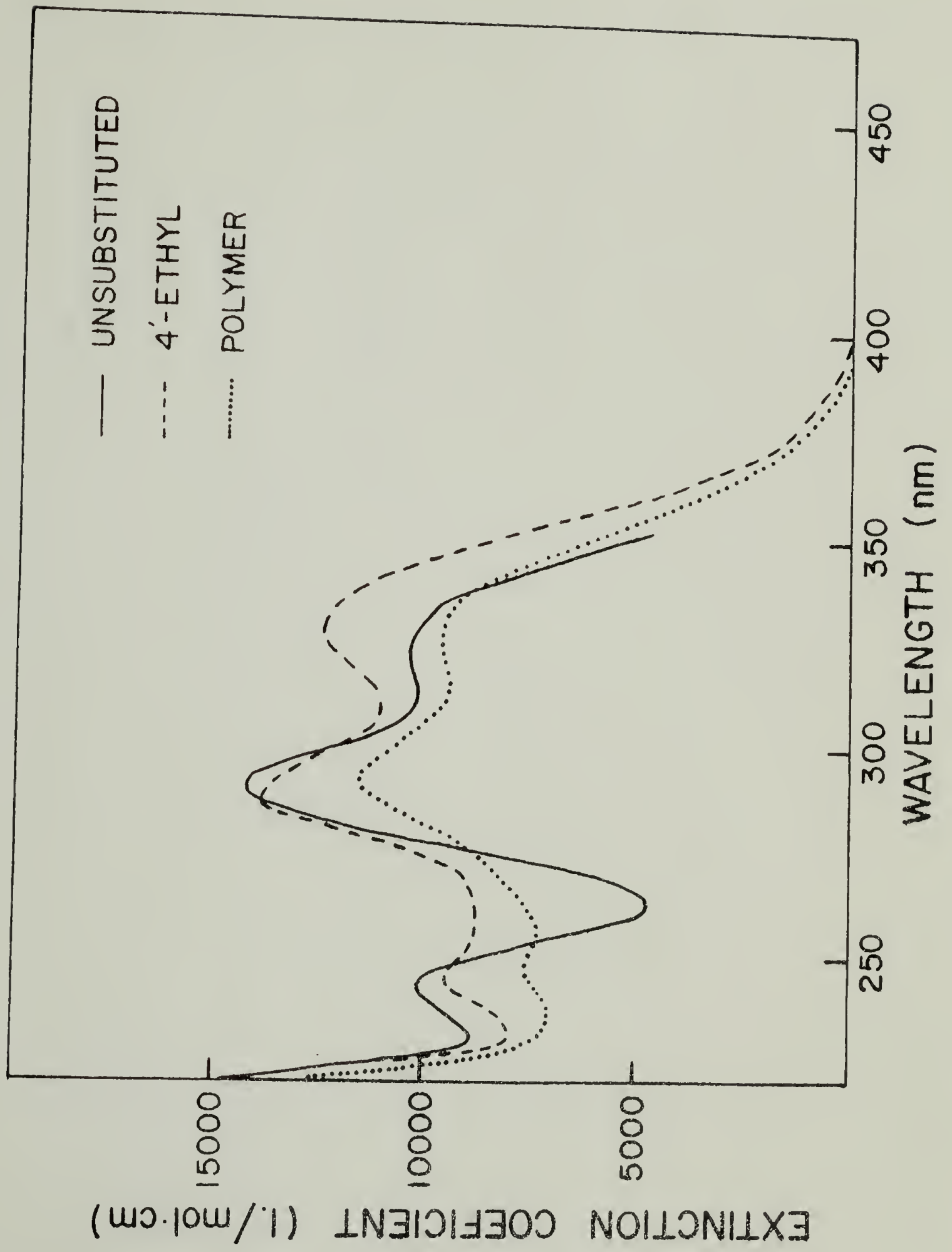


Figure 9. Ultraviolet spectra of 2,4-dihydroxybenzophenone derivatives.



calorimeter between room temperature and 400°C, at a heating rate of 20°C/min. Differential thermogravimetric analysis indicated a maximum degradation rate at 385-400°C, at a heating rate of 20°C/min, under nitrogen. The thermogravimetric spectrum was extremely broad, and a residue of 57% of the sample weight remained even after heating to 510°C. This is in accord with the recently published work of Still and Whitehead²⁰⁴ on the degradation of poly(p-hydroxystyrene). These authors found a residue of approximately 30% of sample weight on heating to 480°C, in contrast to poly(p-methoxystyrene) and conventional polystyrene, each of which produced 100% volatile products at temperatures below 450°C. A carbonization reaction in poly(p-hydroxystyrene) was demonstrated, both in thermogravimetric analysis and in vacuum pyrolysis experiments, and was believed to account for the increased residue formation. A similar reaction may explain the substantial residue formed in degradation of poly(2,4-dihydroxy-4'-vinylbenzophenone); we have made no attempt to investigate this phenomenon.

4. Copolymerization of 2,4-Dihydroxy-4'-Vinylbenzophenone with Styrene. Although the infrared, ¹H NMR and ultraviolet spectra of poly(2,4-dihydroxy-4'-vinylbenzophenone) gave no indication of substantial branching in the polymer, the presence of two phenol groups in the structure of the mono-

mer caused concern about the potential of branching and/or chain transfer in the free-radical polymerization of this monomer. In order to investigate these possibilities, the copolymerization of 2,4-dihydroxy-4'-vinylbenzophenone with styrene was examined. The analysis of styrene-rich copolymers by gel permeation chromatography was used to detect possible interference of the phenol groups in the polymerization, since significant branching and chain transfer would produce measurable changes in the molecular weight and molecular weight distribution of the polymer. Polymerization experiments were performed in sealed tubes in DMF, with either AIBN or benzoyl peroxide (BPO) as initiator. Styrene homopolymers were prepared simultaneously, under identical conditions, and all experiments were performed in duplicate. 2,4-Dihydroxy-4'-vinylbenzophenone constituted 2 mole percent of the monomer feed, and the initiator concentration was 0.4-0.5 mole percent. Figures 10 and 11 show GPC traces for copolymers prepared at 60°C; the molecular weight data are shown in Table 6. In each case, elemental analysis of the copolymers indicated incorporation of 3 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone units.

It is apparent that the presence of 2,4-dihydroxy-4'-vinylbenzophenone affected the polymer molecular weight and molecular weight distribution very little when AIBN was used as the initiator (Figure 10); in fact, the number-average

TABLE 6
Copolymerization of 2,4-Dihydroxy-4'-
Vinylbenzophenone with Styrene

Initiator	[2,4-DHVB] (mole %)	η_{inh} (a) (dl/g)	M_w	M_n	M_w/M_n
AIBN	1.9	0.36	83,000	48,000	1.73
AIBN	0	0.33	77,000	44,000	1.75
BPO	1.9	0.40	104,000	48,000	1.79
BPO	0	0.33	69,000	39,000	1.77

(a) 25°C, 0.5 wgt % in THF.

Figure 10. Gel permeation chromatography of polystyrene and copolymer of styrene with 3 mole-% 2,4-dihydroxy-4'-vinylbenzophenone; AIBN as initiator.

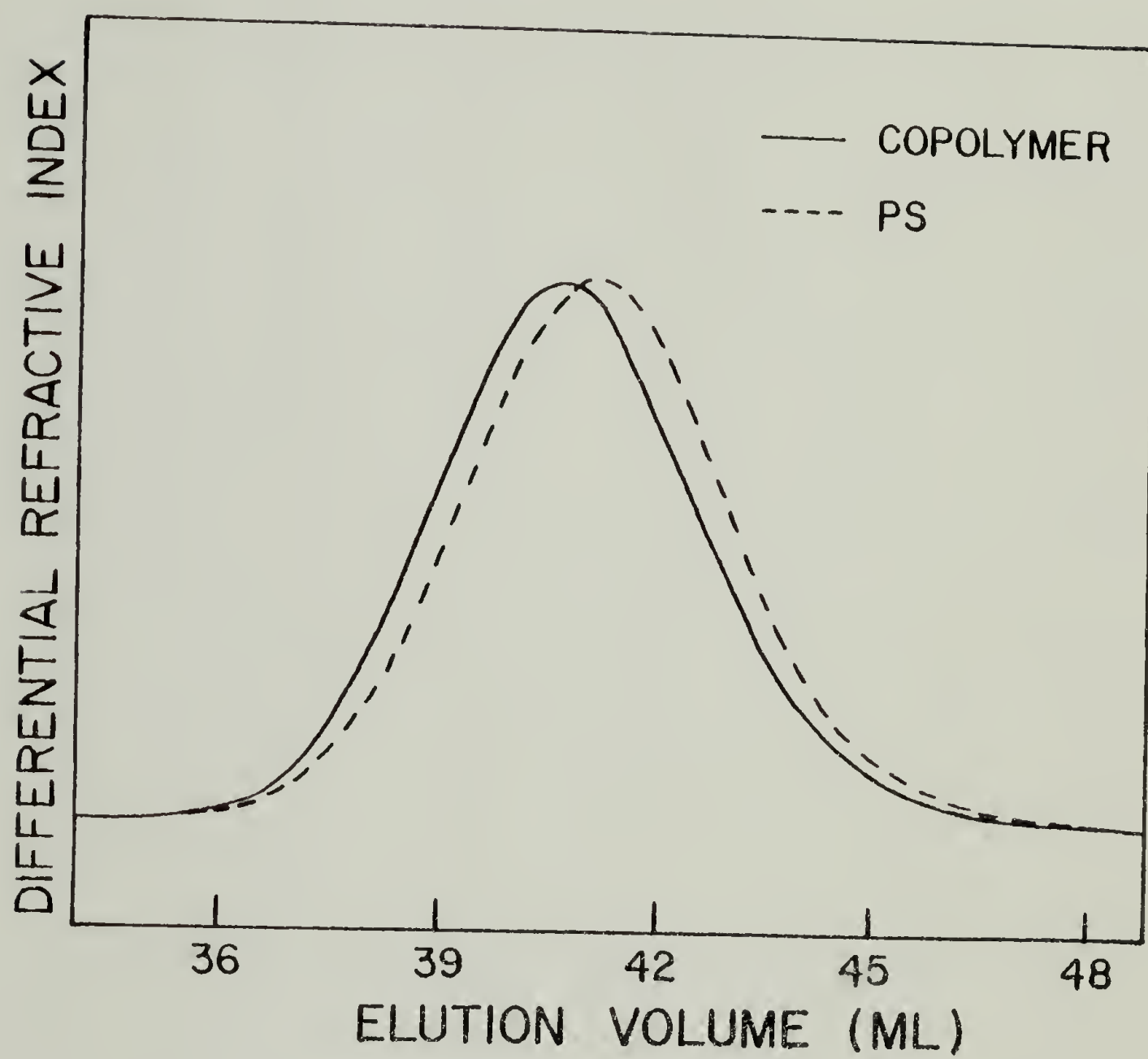
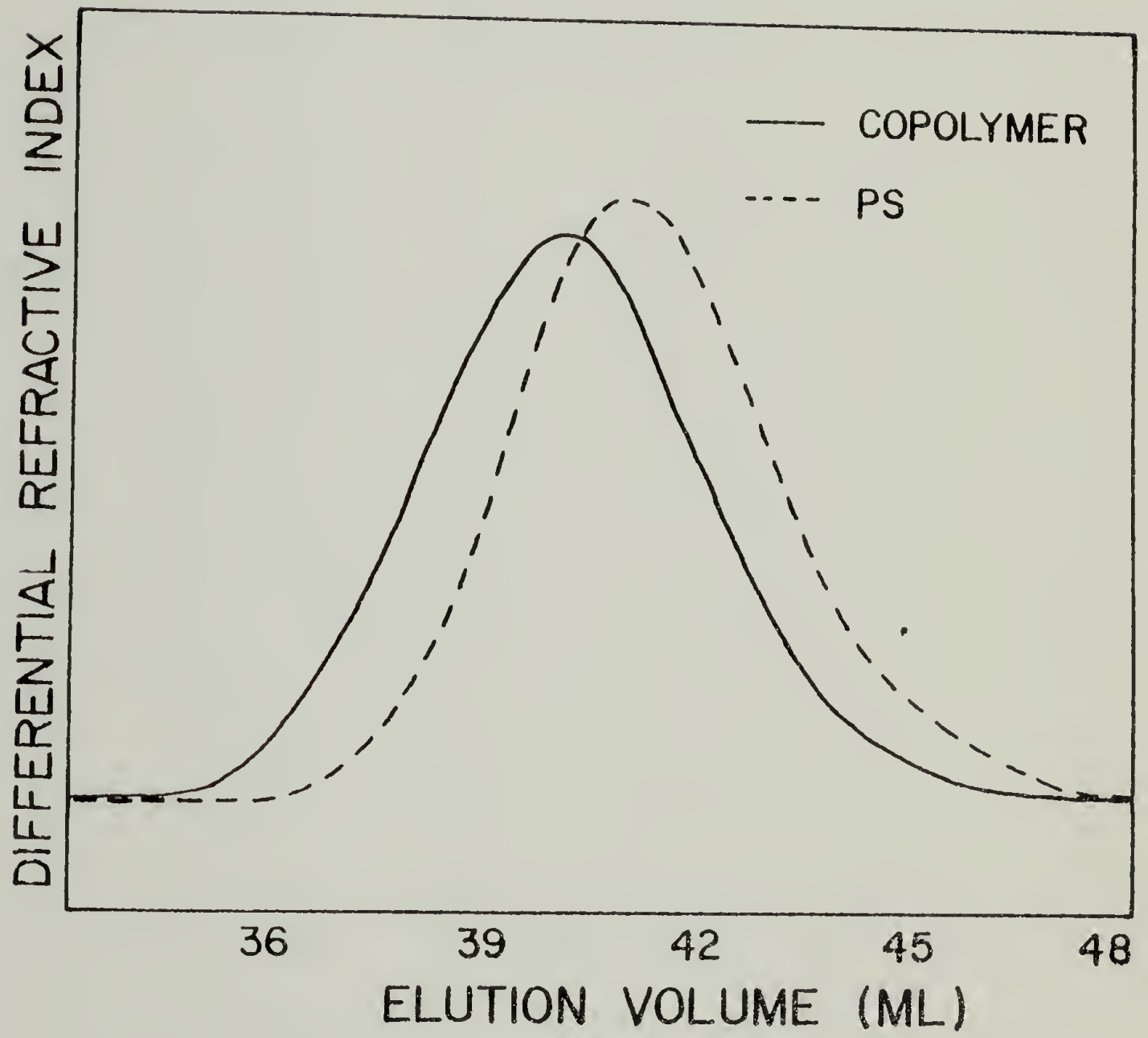


Figure 11. Gel permeation chromatography of polystyrene and copolymer of styrene with 3 mole-% 2,4-dihydroxy-4'-vinylbenzophenone; benzoyl peroxide as initiator.



and weight-average molecular weights of the copolymer and styrene homopolymer may be regarded as identical within the precision of the experiment. In contrast, addition of the compound to the peroxide-initiated system results in a significant increase in molecular weight, again without substantial broadening of the distribution (Figure 11). The weight-average molecular weight of the copolymer is 104,000 vs 69,000 for the styrene homopolymer, with a polydispersity index of 1.8 in each case. (Actually, a polydispersity index closer to 2.0 might be expected in these polymerizations. The figures given here are based on calibration by nine narrow-distribution polystyrenes obtained from Waters Associates, but are otherwise uncorrected. Conclusions drawn from these comparative studies are not dependent upon the absolute value of the polydispersity index.)

The increased molecular weight of the copolymer suggests two possibilities: first, the copolymer may have aggregated in the GPC analysis (in THF), for example, through hydrogen-bonding of the phenol groups. The apparent molecular weight increase would then have been an artifact, merely a result of an increase in the effective size of the polymer molecule in solution. The second possibility is that the effect was genuine, i.e., that the presence of 2,4-dihydroxy-4'-vinylbenzophenone did indeed result in an increased molecular weight of the copolymer

with styrene, at least when benzoyl peroxide was used as the initiator. The difference in behavior between the AIBN system and the benzoyl peroxide system suggests that this effect resulted from a reaction involving the initiator or initiator fragments, rather than with the end of the growing chain. Should this be the case, it is not surprising that the behavior of benzoyl peroxide as initiator for the polymerization differed from that of AIBN.

Benzoyl peroxide initially decomposes by homolytic scission of the peroxide bond, and may then further decompose to yield the phenyl radical and carbon dioxide. The result is that the polymerization is initiated by a mixture of benzoyloxy radicals, in which the unpaired spin is borne by the oxygen atom, and phenyl radicals, which are carbon radicals. This scheme is well-known, and Bevington and Ito²⁰⁵ have done quantitative radiotracer studies of labeled benzoyl peroxide as initiator for styrene polymerization in DMF at 60°C, proving that there are indeed both benzoyloxy and phenyl endgroups in polystyrene prepared under these conditions. The difference in the behavior of the initiators in our experiments may thus result from a difference in the character of the initiator fragments--the benzoyloxy radical from benzoyl peroxide, vs. the resonance-stabilized carbon radical from AIBN.

Recent work by Kato²⁰⁶ and by Pacifici and Browning²⁰⁷

has shown that these two types of radicals do indeed behave differently, in a very important manner. In a study of the vinyl polymerization of hindered phenol compounds, Kato²⁰⁶ found that these compounds polymerized normally with AIBN as initiator, but not with benzoyl peroxide, cumene hydroperoxide or tetraethylthiuram disulfide. It was suggested that the resonance-stabilized carbon radical derived from AIBN preferentially underwent addition to the double bond, while the other species abstracted the phenolic hydrogen atom, resulting in inhibition of polymerization. Pacifici and Browning²⁰⁷ found that this preference for addition vs. abstraction was great enough to allow the use of α -(3,5-di-tert-butyl-4-hydroxyphenyl)-N-tert-butyl nitron for the differentiation of oxy radicals and carbon radicals. Oxy radicals abstracted the phenolic hydrogen atom of this compound, giving a stable phenoxyl radical, whereas carbon radicals preferentially added to the α -carbon of the nitron to yield a stable nitroxide. The esr spectra of these stable species were easily differentiated. Experiments using AIBN and benzoyl peroxide were found to be consistent with the discussion given above, i.e., AIBN gave only the nitroxide signal, and benzoyl peroxide gave both nitroxide and phenoxyl signals. The implications of this behavior in our experiments are clear: one would expect AIBN to undergo addition to the vinyl double bond, even in the presence of the phenol groups of 2,4-dihydroxy-4'-vinylbenzo-

phenone,, and the molecular weight should be affected very little. Benzoyl peroxide, on the other hand, produces benzoyloxy radicals which are prone to abstraction of the phenolic hydrogen atom; this may result in a decrease in initiator efficiency (f) and an increase in molecular weight, since the kinetic chain length is, ideally, proportional to $f^{-\frac{1}{2}}$.²⁰⁸ Chain transfer, and a resultant decrease in molecular weight, would not be expected in either system, since the active center of the polymerization is itself a resonance-stabilized carbon radical, with little tendency to undergo the abstraction reaction.

An alternative mechanism which would account for the observed increase in molecular weight also requires a decrease in initiator efficiency. It was pointed out in Chapter I that phenolic compounds cause rapid decomposition of benzoyl peroxide, through radical or non-radical pathways, resulting in reduced efficiency. The above discussion is not intended to rule out this mechanism in explaining the observed molecular weight changes, but is meant to emphasize what may well be a critical difference in the reactivities of carbon and oxygen radicals.

5. 2,4-Dihydroxy-4'-Ethylbenzophenone in Styrene Polymerization. The results of the copolymerization experiments are thus understandable in terms of the reactivities of the radical species involved in the chain growth. In order to

rule out the possibility of artifacts in the GPC analysis, and to study the phenomenon more systematically, a second experiment was conducted. Homopolymerization of styrene in the presence of the model compound, 2,4-dihydroxy-4'-ethylbenzophenone, was performed, with the concentration of model compound varying from 0 to 10 mole %. The reactivity of the ethyl-substituted compound was expected to be similar to that of the vinyl compound, but the polymers obtained were pure polystyrenes, making the chromatographic analysis unambiguous.

The polymerizations were run at 60°C in DMF, in sealed tubes, with benzoyl peroxide as 0.5 mole % of the monomer/initiator mixture. The appropriate amount of 2,4-dihydroxy-4'-ethylbenzophenone was added to each polymerization tube, followed by the monomer/initiator mixture in DMF; the same solution was used for all tubes, in order to be certain that the monomer/initiator ratio was constant. After completion of the polymerization, the polymers were analyzed by GPC and by inherent viscosity measurements; these results are summarized in Table 7, and in Figure 12. Addition of 2,4-dihydroxy-4'-ethylbenzophenone did not significantly affect the yield of polymer; yields varied only from 54% to 60%.

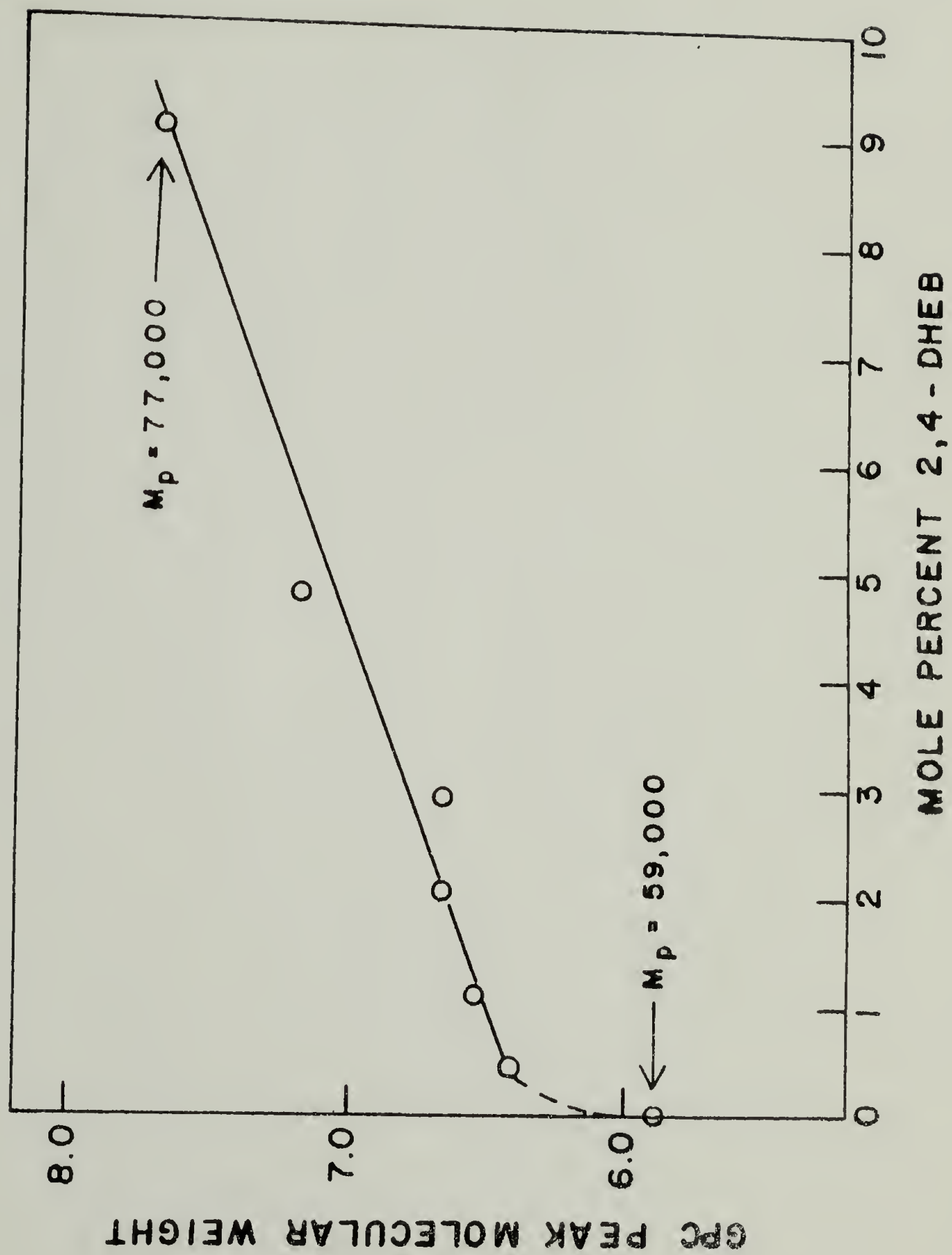
Although the effect is not large, the GPC data clearly indicate an increase in the molecular weight of the polymer with increasing concentration of 2,4-dihydroxy-4'-

TABLE 7
Polymerization of Styrene with Added 2,4-
Dihydroxy-4'-Ethylbenzophenone

[2,4-DHEB] (mole percent)	η_{inh} (a) (dl/g)	Peak MW in GPC
0	0.362	59,000
0.43	0.376	64,000
1.08	0.379	66,000
2.01	0.376	67,000
2.88	0.374	67,000
4.72	0.397	72,000
9.01	0.408	77,000

(a) 25°C, 0.5 wgt. % in THF

Figure 12. Effect of added 2,4-hydroxy-4'-ethylbenzophenone on styrene polymerization; benzoyl peroxide as initiator.



ethylbenzophenone. This is supported by inherent viscosity measurements, with the polymer prepared in the presence of 9 mole % of the additive exhibiting an inherent viscosity of 0.408 dl/g, vs. 0.362 dl/g for the control polymer. The ethyl compound is apparently not as active as the vinyl derivative in influencing the molecular weight, but nevertheless, the effect is measurable, and is consistent with the behavior of 2,4-dihydroxy-4'-vinylbenzophenone in copolymerization with styrene. The results obtained in the copolymerization studies clearly cannot be solely ascribed to artifacts in the chromatographic analysis.

6. Thermal Analysis of Copolymers. The thermal behavior of styrene/2,4-dihydroxy-4'-vinylbenzophenone copolymers was examined, via differential scanning calorimetry and thermogravimetric analysis. The copolymers were prepared with 2 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone in the monomer feed, and were shown by elemental analysis to contain 3 mole percent of these units. The glass transition temperature of the copolymers (measured at a heating rate of 20°C/min) was found to be slightly higher than that of styrene homopolymer; a value of 104-5°C was found for copolymers prepared with either AIBN or BPO as initiator, vs. 101-2°C for styrene homopolymer. A slight loss in chain flexibility may occur as a result of association of the dihydroxybenzophenone units in the polystyrene

matrix.

Thermogravimetric analysis showed little difference between the copolymers and styrene homopolymer; the only effect of the comonomer appeared to be formation of a small amount (1-2 wgt %) of char, which was to be expected in view of the previously discussed degradation behavior of the 2,4-dihydroxy-4'-vinylbenzophenone homopolymer.

7. Copolymerization of 2,4-Dihydroxy-4'-Vinylbenzophenone with Methacrylic Acid. 2,4-Dihydroxy-4'-vinylbenzophenone was also copolymerized with methacrylic acid, using AIBN as the initiator. The copolymers were found to be enriched in methacrylic acid with respect to the monomer feed, indicating that the 2,4-dihydroxybenzoyl group probably behaved as an electron-withdrawing substituent, reducing the electron density at the double bond. With 15 mole percent of 2,4-dihydroxy-4'-vinylbenzophenone in the feed, a reaction time of 6 hrs. at 60°C afforded a copolymer containing 7 mole percent of these units, with an inherent viscosity of 0.68 dl/g (30°C, 0.5 wgt % in DMSO). Under similar conditions with 7.5 mole percent in the feed, a copolymer containing 3 mole percent 2,4-dihydroxy-4'-vinylbenzophenone units, with an inherent viscosity of 1.74 dl/g, was obtained.

E. Attempted Preparation of Methyl 3-Acetylsalicylate and 3-Acetylsalicylic Acid

Attempts to prepare methyl 3-acetylsalicylate and 3-acetylsalicylic acid were based on a literature report²⁰⁹ of the preparation of the latter compound in 73% yield via a perchloric acid-catalyzed Fries rearrangement of O-acetylsalicylic acid. Unfortunately, this preparation requires the use of perchloric acid/acetic anhydride mixtures at elevated temperature, so an attempt was made to find a less hazardous catalyst for the Fries rearrangement. It was felt that perhaps the high acidity of the catalyst (perchloric acid is the strongest of the mineral acids) promoted rearrangement to the 3-position rather than the 5-position, so two strong acids, fluorosulfonic acid and trifluoromethanesulfonic acid, were investigated. All attempts were, however, unsuccessful, and no rearranged products were isolated.

The infrared spectra of the products of the reaction of methyl salicylate with acetic anhydride in the presence of either fluorosulfonic acid or trifluoromethanesulfonic acid showed a strong $\text{C}=\text{O}$ stretching band at 1760 cm^{-1} , due to the acetoxy group of methyl acetylsalicylate, indicating that acetylation, but little rearrangement, had occurred. The band at 1680 cm^{-1} probably indicates unacetylated starting material.

Treatment of methyl acetylsalicylate with fluorosul-

fonic acid was also unsuccessful. The infrared spectrum of the product showed a new absorption at 1680 cm^{-1} which could have represented rearranged product, but the NMR spectrum of the product after saponification showed no acetyl proton signal. Evidently, the 1680 cm^{-1} band was due to methyl salicylate.

Salicylic acid was also investigated as a possible starting material, with the objective of preparing 3-acetylsalicylic acid. The NMR spectra of the products of the reactions of salicylic acid with acetic anhydride in the presence of either fluorosulfonic acid or trifluoromethanesulfonic acid showed that acetylation, but no rearrangement, had occurred.

F. Conclusions and Further Work

This dissertation describes the synthesis and polymerization of several vinylsalicylic acid derivatives and 2,4-dihydroxy-4'-vinylbenzophenone. The polymers obtained are of potential interest as biologically-active agents and as ultraviolet stabilizers.

The preparation of polymeric salicylic acid derivatives was undertaken with both of these applications in mind. Polymers of methyl 4-vinylsalicylate and methyl 5-vinylsalicylate are of potential value in protection of synthetic polymers and in protection of the skin from light-induced damage, and the polymers of 4- and 5-vinylsalicylic

acids and of 4- and 5-vinylacetylsalicylic acids may show at least some of the pharmacological activities of the parent compounds. In fact, the real significance of this work can be evaluated only after further biological testing of these polymers. This point is discussed below.

The synthesis and polymerization of 2,4-dihydroxy-4'-vinylbenzophenone were undertaken with the objective of preparing novel polymeric ultraviolet absorbers. The synthetic objectives were achieved, and in addition, new insight into the behavior of phenolic compounds in radical polymerization was provided. Further work in this area will be performed in collaboration with the laboratory of R. S. Porter; the polymeric ultraviolet absorbers based on 2,4-dihydroxy-4'-vinylbenzophenone will be blended with polymers such as polystyrene, and their distribution and effectiveness will be determined (principally through the use of attenuated total reflectance infrared spectroscopy).

Further work in the area of salicylic acid polymers may take one (or both) of two directions: further synthesis, or biological testing. Additional synthetic objectives might include preparation and polymerization of 3- and 6-vinylsalicylic acid derivatives or comparable investigations of 3-allylsalicylic acid. However, it is the opinion of the author that the real value of this research will be derived not from additional synthesis, but from careful, meaningful testing of the polymers hitherto prepared. First of all,

polymer samples which are free of contamination by low molecular weight substances must be prepared by dialysis or ultrafiltration. It will probably be necessary to perform isotope-dilution experiments using radioactively-labelled salicylic acids in order to ascertain freedom from contamination. Once pure samples are available, additional biological testing should be undertaken. This should begin with antibacterial testing, with special attention to the metal content in the growth medium. Antibacterial testing should be followed by tests of these polymers as inhibitors of prostaglandin synthesis, and possibly of the ability of the acetylsalicylic acid polymers to acetylate prostaglandin synthetase.

The field of biologically-active polymers is just waiting for a breakthrough: a new polymeric drug with a well-defined application which avoids all of the problems associated with systemic administration. The development of salicylic acid polymers for use in skin infections could provide such a breakthrough, but it must await a much more careful, thorough understanding of the behavior of these new polymers.

REFERENCES

1. D. Bailey, Ph.D. Thesis, University of Massachusetts, 1975.
2. L. G. Donaruma and O. Vogl, Eds., Polymeric Drugs, Academic Press, New York, 1978.
3. L. G. Donaruma, in Progress in Polymer Science, Vol. 4, A. D. Jenkins, Ed., Pergamon Press, New York, 1974, p. 1.
4. H. G. Batz, Adv. Polym. Sci., 23, 25 (1977).
5. H. Ringsdorf, J. Polym. Sci., Symp., 51, 135 (1975).
6. C. L. Shapiro (Acryvin Corp. of America) U.S. 2,529,108 (1950); Chem. Abstr. 45: 1815 e.
7. M. Greiger (CIBA, Ltd.) Swiss 318,201 (1957); Chem. Abstr. 53: 7663 f.
8. S. A. Barker, J. F. Kennedy and J. Epton (Aspro-Nicholas Ltd.) Ger. Offen. 2,242,703 (1973); Chem. Abstr. 79: 5880 c.
9. J. F. Kennedy, S. A. Barker, J. Epton and G. R. Kennedy, J. Chem. Soc. Perkin Trans. I., 1973, 488.
10. N. N. Kuznetsova, K. P. Papukova, N. M. Myagkova-Romanova, and G. V. Samsonov, U.S.S.R. 384,841 (1973); Chem. Abstr. 80: 37760 a.
11. T. Abdukhodzhaev, et al., U.S.S.R. 405,909 (1973); Chem. Abstr. 81: 106309 v.
12. K. Kojima, et al., Chiba Daigaku Kogakuba Kenkyu Hokoku 25(48), 65 (1974); Chem. Abstr. 82: 17554 z.
13. A. A. Selezneva, et al., Ionity Ionnyi Obmen, 1975, 216; Chem. Abstr. 85: 42679 p.
14. A. E. Perelman, et al., Khim. Farm. Zh. 10(7), 51 (1976); Chem. Abstr. 86: 100993 j.

15. W. Reppe, et al., Ann. 601, 81 (1956).
16. H. Hopff and H. Lussi, Makromol. Chem 18/19, 227 (1956).
17. G. Hardy, V. Spiegel and K. Nyitrai, Vysokomol. Soedin. 3, 144 (1961).
18. S. Banerjee and M. S. Muthana, J. Polym. Sci., 37, 469 (1959).
19. G. Pizzirani, P. Pagagnini and P. Giusti, J. Polym. Sci., A-2, 9(6), 1133 (1971).
20. F. Hrabek, Collection Czech. Chem. Commun. 29, 1966 (1964); Chem. Abstr. 61: 10794 g.
21. A. I. Goldberg, J. Fertig and M. Skoultchi (National Starch and Chemical Co.) U.S. 3,290,270 (1966); Chem. Abstr. 66: 29376 a.
22. D. Braun and H. Boudevska, Eur. Polym. J. 12(8), 525 (1976).
23. S. I. Kotenko, Y. I. Linsunkin, V. Y. Pochinok, Farm. Zh. (Kiev) 27(1), 12 (1972); Chem. Abstr. 77: 164 w.
24. S. N. Ushakov, L. B. Trukmanova, E. V. Drozdova, and T. M. Markelova, Dokl. Acad. Nauk. U.S.S.R. 141, 1117 (1961); Chem. Abstr. 56: 12795 d.
25. I. S. Varga and Z. Wolkober, Acta Chim. Acad. Sci. Hung. 41(4), 431 (1964); Chem. Abstr. 62: 9252 g.
26. L. B. Trukmanova, S. N. Ushakov and T. M. Markelova, Vysokomol. Soedin. 6(7), 1346 (1964); Chem. Abstr. 61: 12107 d.
27. M. Covello, G. Ciampa and A. Vittoria, Ric. Sci. 37(1), 66 (1967); Chem. Abstr. 67: 11771 m.
28. S. Tocker (E.I. du Pont de Nemours and Co.) U.S. 2,983,696 (1961); Chem. Abstr. 55: 18198 c.
29. V. G. Sinyavs'kii, A. I. Turbina and M. Y. Romankevich, Dopovidi Akad. Nauk. Ukr. R.S.R., 1963(5), 613; Chem. Abstr. 59: 8935 a.
30. V. M. Tolmachov, B. M. Kolesnikova and E. B. Bobok Vysokomol. Soedin. 7(11), 1941 (1965); Chem. Abstr. 64: 6830 d.

31. V. M. Tolmachov, B. M. Kolesnikova and D. M. Hong, Zh. Obshch. Khim, 38(1), 18 (1968); Chem. Abstr. 68: 7265 v.
32. E. I. du Pont de Nemours and Co., Brit. 867,899 (1961); Chem. Abstr. 55: 21934 d.
33. J. Campbell, J. Pharm. Sci. 52, 76 (1962).
34. T. K. Abdukhodzhaev, V. A. Kropachev, L. B. Trukhmanova, and L. M. Vil'ner, Nauchn. Tr. Tashk. Gos. Univ., 502, 170 (1976); Chem. Abstr. 87: 177781 c.
35. V. L. Lapenko and A. I. Slivkin, Tr. Voronezh. Univ. 95(2), 31 (1972); Chem. Abstr. 78: 98051 a.
36. J. F. Kennedy and J. Epton, Carbohydrate Res. 27(1), 11 (1973).
37. S. A. Barker, J. F. Kennedy and J. Epton, Ger. Offen. 2,242,710 (1973); Chem. Abstr. 78: 151364 w.
38. Aspro-Nicholas, Ltd., Fr. Demande 2,150,959 (1973), Chem. Abstr. 79: 123102 y.
39. J. F. Kennedy, J. Epton and G. R. Kennedy, Antimicrob. Agents Chemother. 3(1), 29 (1973); Chem. Abstr. 79: 670 z.
40. J. F. Kennedy, S. A. Barker, A. W. Nicol and A. Hawkins, J. Chem. Soc. Dalton Trans. 1973 (11), 1129.
41. E. I. du Pont de Nemours and Co., Brit. 848,354 (1960); Chem. Abstr. 56: 14479 b.
42. E. T. Cline and D. Tanner (to E. I. du Pont de Nemours and Co.) U.S. 3,068,122 (1962); Chem. Abstr. 58: 5827 c.
43. S. Tocker, Makromol. Chem., 101, 23 (1967).
44. S. Tocker, Belgium Patent 629,480 (1963); Chem. Abstr., 61, 8484 f (1964).
45. S. Tocker, Belgium Patent 629,109 (1963); Chem. Abstr., 60, 13453 g (1964).
46. S. Tocker, British Patent 885,986 (1962); U.S. Patent 3,107,199 (1963).

47. British Patent 898,065 (1962); Chem. Abstr., 57, 11402 i (1962).
48. Z. Osawa, K. Matsui and Y. Ogiwara, J. Macromol. Sci.-Chem., A1, 581 (1967).
49. Z. Osawa, M. Suzuki and Y. Ogiwara, J. Macromol. Sci.-Chem., A1, 275 (1971).
50. J. Fertig, A.I. Goldberg and M. Skoultchi, U.S. Patent 3,341,493 (1967); Chem. Abstr., 67, 117582 r (1967).
51. A. I. Goldberg, M. Skoultchi and J. Fertig, U.S. Patent 3,162,676 (1964); Chem. Abstr., 62, 7693 c (1965).
52. A. I. Goldberg, M. Skoultchi and J. Fertig, U.S. Patent 3,202,716 (1965); Chem. Abstr., 64, 3425 e (1966).
53. J. Fertig, M. Skoultchi and A. I. Goldberg, U.S. Patent 3,340,231 (1967); Chem. Abstr., 67, 100657 (1967).
54. J. Fertig, M. Skoultchi and A. I. Goldberg, U.S. Patent 3,173,893 (1965); Chem. Abstr., 63, 1951 g (1965).
55. J. Fertig, A. I. Goldberg and M. Skoultchi, J. Appl. Polym. Sci., 10, 663 (1966).
56. R. L. Horton and H. G. Brooks, U.S. Patent 3,313,866 (1967); Chem. Abstr., 67, 121434 (1967).
57. W. B. Hardy, W. S. Forster and R. A. Coleman, U.S. Patent 2,962,533 (1960); Chem. Abstr., 55, 10396 (1961).
58. J. P. Millionis and F. J. Arthen, U.S. Patent 3,049,503 (1962); Chem. Abstr., 58, 478 g (1963).
59. J. Luston, J. Gunis and Z. Manasek, J. Macromol. Sci.-Chem., A7, 587 (1973).
60. J. Luston, N. Schubertova and Z. Manasek, J. Polym. Sci., Polym. Symp., 40, 33 (1972).
61. S. Tocker, Makromol. Chem., 101, 23 (1967).

62. W. O. Kenyon, G. P. Waugh and C. C. Unruh (Eastman Kodak Co.) U.S. 2,713,570 (1955); Chem. Abstr. 51: 125466.
63. W. J. Gensler, E. M. Healy, I. Onshuus and A. L. Bluhm, J. Am. Chem. Soc., 78, 1713 (1956).
64. A. A. Reid, et al., J. Chem. Soc., Perkin Trans. 1., 1973, 2543.
65. D. Braun and I. Loefflund, Makromol. Chem., 53, 219 (1962).
66. G. M. Pogosyan, G. A. Zhamkochyan and S. G. Matsoyan, Arm. Khim. Zh., 22(10), 908 (1969); Chem. Abstr. 72: 89972 a.
67. G. M. Pogosyan, G. A. Zhamkochyan and S. G. Matsoyan, Arm. Khim. Zh., 22(4), 364 (1969); Chem. Abstr. 71: 50600 g.
68. G. M. Pogosyan, G. A. Zhamkochyan and S. G. Matsoyan, Arm. Khim. Zh., 23(9), 814 (1970).
69. D. Braun, W. Neumann and J. Faust, Makromol. Chem., 85, 143 (1965).
70. C. P. Pinazzi and A. Fernandez, Makromol. Chem., 167, 147 (1973).
71. C. P. Pinazzi and A. Fernandex, Madromol. Chem., 168, 19 (1973).
72. J. F. Yanus and J. M. Pearson, Macromolecules, 7(6), 716 (1974).
73. S. H. Merrill, C. C. Unruh and E. M. Robertson (Eastman Kodak Co.) U.S. 2,831,768 (1958); Chem. Abstr. 52: 14400 g.
74. E. V. Kuznetsov, I. P. Prokhorova and D. A. Faizullina, Vsokomol. Soedin., 3, 1544 (1961); Chem. Abstr. 56: 10382 a.
75. D. Braun, Makromol. Chem., 44-46, 269 (1961); Chem. Abstr. 55: 22214 g.
76. S. Tocker (E. I. du Pont de Nemours and Co.) U.S. 3,418,397 (1968); Chem. Abstr. 70: 48276 s.

77. C. Pinazzi and A. Fernandez, Makromol. Chem., 177, 3089 (1976).
78. R. Searle, et al., Makromol. Chem., 107, 246 (1967).
79. R. Roser and H. Cassidy, J. Polym. Sci., Lett., 2, 545 (1964).
80. H. A. Hammond, J. C. Doty, T. M. Laakso and J. L. R. Williams, Macromolecules, 3(6), 711 (1970).
81. C. David, W. Demarteau and G. Geuskens, Polymer, 10(1), 21(1969).
82. C. David, W. Demarteau and G. Geuskens, Eur. Polym. J., 6(3), 537 (1970).
83. C. David, V. Naegelen, W. Piret and G. Geuskens, Eur. Polym. J., 11(8), 569 (1975).
84. C. David, D. Baeyens-Volant and G. Geuskens, Eur. Polym. J., 12(2), 71 (1976).
85. G. Geuskens, F.A.T.I.P.E.C. Congress, 9, 20 (1968); Chem. Abstr. 69: 67949 j.
86. P. Hrdlovic, I. Lukac, J. Polym. Sci., Symp. 47, 319 (1974).
87. J. Danecek, P. Hrdlovic and I. Lukac, Eur. Polym. J., 12(8), 513 (1976).
88. G. Greber and G. Egle, Makromol. Chem., 53, 206 (1962).
89. G. Greber and G. Egle, Makromol. Chem., 54, 136 (1962).
90. E. Huseman, Ger. 1,241,990 (1967); Chem. Abstr. 67: 64969.
91. H. Takida and T. Moriyama, Kobunshi Kagaku, 24, 57 (1967); Chem. Abstr. 67: 33041 a.
92. H. Sumitomo, K. Nobutoki and K. Susaki, J. Polym. Sci., A-1, 9(3), 809 (1971).
93. D. Braun, W. Neumann and G. Arcache, Makromol. Chem., 112, 97 (1968).
94. D. Braun, M H. Tio and W. Neumann, Makromol. Chem., 123, 29 (1969).

95. D. Braun and G. Traser, *Makromol. Chem.*, 175(8), 2275 (1974).
96. G. A. Reynolds and D. G. Borden, *Def. Publ., U.S. Pat. Off.* 903,024 (1972).
97. M. Kato and M. Yamazi, *Japan Kakai* 74 62,581 (1974).
98. H. Hayatsu and H. G. Khorana, *J. Am. Chem. Soc.*, 89(15), 3880 (1967).
99. F. Cramer, et al., *Angew. Chem.*, 78, 640 (1966).
100. M. Baer (Montsanto) U.S. 3,370,040 (1968); *Chem. Abstr.* 68: 69742 q.
101. C. P. Pinazzi, A. Fernandex and M. Rupin, *Fr. Demande* 2,183,633 (1974).
102. D. Bailey and O. Vogl, *J. Macromol. Sci (Rev.)* C14(2), 267 (1976).
103. *Chemical Week*, July 5, 1978, p. 19.
104. S. I. Kreps and R. L. Goldenberg, in "Cosmetics Science and Technology," Vol. 1, M. S. Balsam and K. Sagarin, Eds., Wiley(Interscience), New York, 1972.
105. G. W. van Ham and W. P. Herzog, in "Drug Design," Vol. IV E. J. Ariens, Ed., Academic Press, New York, 1973.
106. J. Beurey et al., *Ann. Med. Nancy* 5, 969-74 (1966); *C. A.* 66: 11449 k.
107. M. Gross and L. A. Greenberg, "The Salicylates: A Critical Bibliographic Review" Hillhouse Press, New Haven, 1948.
108. A. S. Black and W. H. Feinsteone, U.S. 3,821,363 (1974); *Chem. Abstr.* 31: 140874 k.
109. G. Karg (Avon Products, Inc.) U.S. 3,895,104 (1975); *Chem. Abstr.* 83: 168334 z.
110. N. Noruse, R. Yasumoto, and S. Inoue (Toray Industries, Inc.), *Japan* 73 25,423 (1973); *Chem. Abstr.* 80: 121859 x.

111. M. Skoultchi and E. A. Meier (National Starch and Chemical Corp.), U.S. 3,795,733 (1974); Chem. Abstr. 81: 68554 m.
112. M. Skoultchi and E. A. Meier (National Starch and Chemical Corp.), U.S. 3,836,571 (1974); Chem. Abstr. 82: 17829 t.
113. J. P. Ciaudelli (Avon Products, Inc.), U.S. 3,864,473 (1975); Chem. Abstr. 83: 15499 g.
114. B. Jacquet, C. Papantoniou, P. Dufaure, and C. Mahieux (S. A. Oreal), Brit. 1,407,670 (1975); Chem. Abstr. 84: 79602 p.
115. B. Jacquet, C. Papantoniou, P. Dufaure, and C. Mahieux (S. A. Oreal), Ger. Offen. 2,333,305 (1975); Chem. Abstr. 83: 84713 j.
116. S. A. Oreal, Neth. Appl. 73, 09,147 (1974); Chem. Abstr. 83: 48095 a.
117. B. Jacquet, C. Papantoniou, P. Dufaure, and C. Mahieux (S. A. Oreal), Fr. Demande 2,237,912 (1975); Chem. Abstr. 83: 152205 x.
118. B. Jacquet, C. Papantoniou, P. Dufaure, and C. Mahieux (S. A. Oreal), Ger. Offen. 2,333,306 (1974); Chem. Abstr. 80: 134227 q.
119. R. Johnston (Gillette) Brit. 1,460,649 (1977); Chem. Abstr. 87: 11467 c.
120. J. F. Gerecht and M. B. Epstein (Colgate-Palmolive Co.) U.S. 4,004,074 (1977); Chem. Abstr. 86: 145804 a.
121. H. O. J. Collier, Adv. Pharmacol. Chemother., 7, 333 (1969).
122. H. O. J. Collier, Nature, 232, 17 (1971).
123. H. G. Barbour, Arch. Internal Med., 24, 624 (1919). Chem. Abstr. 14: 427.
124. C. Bianchi, B. Lumachi and L. Pegrassi, Arzneimittel-Forsch., 17, 246 (1967); Chem. Abstr. 66: 103801 d.
125. J. C. Seed, Clin. Pharmacol. Therap., 6, 354 (1965).

126. H. K. Beecher, A. S. Keats, F. Mosteller and L. Lasagna, *J. Pharmacol. Exptl. Therap.*, 109, 393 (1953); *Chem. Abstr.* 48: 2241 c.
127. G. H. Deneau, R. A. Wand and C. W. Gowdey, *Can. J. Med. Sci.*, 31, 387 (1953). *Chem. Abstr.* 48: 10230 c.
128. F. B. Benjamin, *Science*, 128, 303 (1958).
129. M. W. Williams, *Toxicol. Appl. Pharmacol.*, 1, 590 (1959).
130. M. W. Williams, C. S. Williams, M. J. Karchner, *Toxicol. Appl. Pharmacol.*, 7, 45 (1965). *Chem. Abstr.* 68: 13746 e.
131. H. O. J. Collier and G. B. Chesher, *Brit. J. Pharmacol.*, 11, 20 (1956); *Chem. Abstr.* 50: 9616 a.
132. H. O. J. Collier, B. T. Warner, and R. J. Skerry, *Brit. J. Pharmacol.*, 17, 28 (1961).
133. H. O. J. Collier, in D. R. Laurence and A. L. Bacharach, eds., *Evaluation of Drug Activities: Pharmacometrics*, Vol. I., Academic Press, New York, 1964, p. 183.
134. C. A. Winter and L. Flataker, *J. Pharmacol. Exptl. Therap.*, 148, 373 (1965); *Chem. Abstr.* 63: 7527 f.
135. V. Gjuris, B. Heicke and E. Westermann, *Arch. Exptl. Pathol. Pharmacol.*, 248, 540 (1964); *Chem. Abstr.* 62: 783 e.
136. H. O. J. Collier and I. R. Lee, *Brit. J. Pharmacol.*, 21, 155 (1963); *Chem. Abstr.* 59: 7808 d.
137. W. Modell, ed., *Drugs of Choice, 1978-1979*, C. V. Mosby Company, 1978, p. 563.
138. A. J. Quick and L. Clescari, *J. Pharmacol. Exptl. Therap.*, 128, 95 (1960); *Chem. Abstr.* 54: 4887.
139. H. J. Weiss, L. M. Aledorf and S. Kochwa, *J. Clin. Invest.*, 47, 2169 (1968); *Chem. Abstr.* 69: 95018 y.
140. J. L. Beaumont, A. Willie and J. Lenegre, *Bull. Soc. Med. Hop. Paris*, 71, 1077 (1955).
141. C. D. W. Morris, *Lancet*, 1967(1), 279.

142. M. B. Zucker and J. Peterson, Proc. Soc. Exptl. Biol. Med., 127, 547 (1968); Chem. Abstr. 68: 103161 m.
143. R. N. Pierson, P. R. Holt, R. M. Watson and R. P. Keating, Am. J. Med., 31, 259 (1961).
144. L. Stubbe, Ned. Tijdschr. Geneesk., 105, 1673 (1961). Chem. Abstr. 56: 4062 g.
145. J. R. Vane, Nature New Biology, 231, 232 (1971).
146. S. H. Ferreira, S. Moncada and J. R. Vane, Nature New Biology, 231, 237 (1971).
147. J. B. Smith and A. L. Willis, Nature New Biology, 231, 235 (1971).
148. G. J. Roth and C. J. Siok, J. Biol. Chem. 253(11), 3782 (1978).
149. J. W. Baker, I. Schumacher and D. P. Roman, in A. Burger, ed., Medicinal Chemistry, 3rd Edition, Wiley, New York, 1970, p. 634.
150. F. Knuesel and E. G. Weirich, Dermatologica, 145(4), 233 (1972), Chem. Abstr. 78: 53308 y.
151. A. Korolkovas, Essentials of Molecular Pharmacology, Wiley, New York, 1970, p. 309.
152. F. A. Bovey and I. M. Kolthoff, Chem. Revs, 42, 491 (1947).
153. J. W. Breitenbach, A. Springer and K. Horeischy, Chem. Ber., 71, 1438 (1938).
154. C. Walling and E. R. Briggs, J. Am. Chem. Soc., 68, 1141 (1946).
155. E. T. Borrows, R. N. Howard, R. Porges and J. Street, J. Appl. Chem., 5, 379 (1955).
156. S. G. Cohen, J. Am. Chem. Soc., 69, 1057 (1947).
157. R. G. Caldwell and J. L. Ihrig, J. Am. Chem. Soc., 84, 2878 (1962).
158. K. K. Georgieff, J. Appl. Polym. Sci., 9, 2009 (1965).

159. M. S. Kharasch, F. Kawahara and W. Nudenberg, J. Org. Chem., 19, 1777 (1954).
160. E. F. Kluchesky and L. B. Wakefield, Ind. Eng. Chem., 41(8), 1768 (1949).
161. S. G. Foord, J. Chem. Soc., 48, 1940.
162. R. L. Frank and C. E. Adams, J. Am. Chem. Soc., 68, 908 (1946).
163. C. Walling, J. Am. Chem. Soc., 66, 1602 (1944).
164. J. K. Moore, R. E. Burk and H. P. Lankelma, J. Am. Chem. Soc., 63, 2954 (1941).
165. C. Walling and R. B. Hodgdon, J. Am. Chem. Soc., 80, 228 (1958).
166. P. D. Bartlett and K. Nozaki, J. Am. Chem. Soc., 69, 2299 (1947).
167. P. J. Flory, J. Am. Chem. Soc., 59, 241 (1937).
168. F. R. Mayo, J. Am. Chem. Soc., 65, 2324 (1943).
169. E. G. Edwards, G. F. P. Harris and C. E. Seaman, Chem. Ind., 1955, 625.
170. M. P. Godsay, G. A. Harpell and K. E. Russell, J. Polym. Sci., 57, 641 (1962).
171. R. G. Caldwell and J. L. Ihrig, J. Polym. Sci, 46, 507 (1960).
172. C. Walling, Free Radicals in Solution, Wiley, New York, 1957, p. 166.
173. G. S. Hammond, C. E. Boozer, C. E. Hamilton and J. N. Sen, J. Am. Chem. Soc., 77, 3238 (1955).
174. K. U. Ingold, J. Phys. Chem., 64, 1636 (1960).
175. Reference 172, p. 170.
176. S. L. Cosgrove and W. A. Waters, J. Chem. Soc., 3189 (1949).
177. S. L. Cosgrove and W. A. Waters, J. Chem. Soc., 388 (1951).

178. S. G. Cohen, J. Am. Chem. Soc., 69, 1057 (1947).
179. J. A. Howard and K. U. Ingold, Can. J. Chem., 41, 1744 (1963).
180. K. U. Ingold, Can. J. Chem., 41, 2816 (1963).
181. M. P. Godsay, D. H. Lohmann, and K. E. Russell, Chem. Ind., 1603 (1959).
182. D. H. McDaniel and H. C. Brown, J. Org. Chem., 23, 420 (1958).
183. J. A. Howard and K. U. Ingold, Can. J. Chem., 40, 1851 (1962).
184. J. R. Shelton and D. N. Vincent, J. Am. Chem. Soc., 85, 2433 (1963).
185. K. U. Ingold, in J. K. Kochi, ed., Free Radicals, Vol. I., Wiley, New York, 1973, p. 80.
186. S. G. Cohen, J. Am. Chem. Soc., 72, 3947 (1950).
187. G. Dobson and L. I. Grossweiner, Trans. Faraday Soc., 61, 708 (1965).
188. S. A. Weiner, J. Am. Chem. Soc., 94, 581 (1972).
189. S. A. Weiner and L. R. Mahoney, J. Am. Chem. Soc., 94, 585 (1972).
190. S. A. Weiner and L. R. Mahoney, J. Am. Chem. Soc., 94, 1412 (1972).
191. G. Odian, Principles of Polymerization, McGraw-Hill, New York, 1970, p. 196.
192. H. Richtzenhain, Chem. Ber., 82, 405.
193. G. M. Burnett, M. H. George and H. W. Melville, J. Polym. Sci., 16, 31 (1955).
194. E. R. Walsgrove and F. Reeder, Brit. Pat. 636,429 (1950).
195. O. Baine, et al., J. Org. Chem., 19, 510 (1954).
196. Sadtler Standard Spectra, Sadtler Research Laboratories, NMR Spectrum 23153 M.

197. Reference 196, UV Spectrum 3804.
198. Reference 196, UV Spectrum 3277.
199. L. Horner and E. H. Winkelmann, in *Newer Methods of Preparative Organic Chemistry*, Vol. 3, W. Foerst, Ed., Academic Press, New York, 1964, p. 176.
200. M. Kato, *J. Polym. Sci A-1*, 7, 2175 (1969).
201. B. M. Gallo and S. Russo, *J. Macromol. Sci.-Chem.*, A8, 521 (1974).
202. B. Stutzel, T. Miyamoto and H. J. Cantow, *Polym. J.*, 8, 247 (1976).
203. H. W. Gibson and F. C. Bailey, *Macromolecules*, 9, 688 (1976).
204. R. H. Still and A. Whitehead, *J. Appl. Polym. Sci.*, 21, 1199 (1977).
205. J. C. Bevington and T. Ito, *Trans. Faraday Soc.*, 64, 1329 (1968).
206. M. Kato, Y. Takemoto, Y. Nakano and M. Yamazaki, *J. Polym. Sci., Polym. Chem. Ed.*, 13, 1901 (1975).
207. J. G. Pacifici and H. L. Browning, *J. Am. Chem. Soc.*, 92, 5231 (1970).
208. P. J. Flory, Principles of Polymer Chemistry, Cornell Univ. Press, Ithaca, New York, 1953.
209. M. Leonte, M. Beschia, E. Pascaru and M. Stoica, *Studia Univ. Babes-Bolyai, Ser. Chem.*, 8, 291 (1963); *Chem. Abstr.* 61: 11922 g (1964).

APPENDIX A

PRELIMINARY RESULTS OF TESTS OF
ANTIBACTERIAL ACTIVITY IN
5-VINYLSALICYLIC ACID DERIVATIVES

Appendix A. Preliminary Results of Tests of Antibacterial Activity in 5-Vinylsalicylic Acid Derivatives

Thirteen monomeric and polymeric derivatives of 5-vinylsalicylic acid were subjected to preliminary studies of antibacterial activity through the courtesy of L. G. Donaruma of the New Mexico Institute of Mining and Technology. Activities vs. *Escherichia Coli* and vs. *Bacillus Subtilis* were determined by the agar-plate test on Difco-Mueller-Hinton medium. In this test, the sample compound is applied to cultured bacteria, and the resulting zone of growth inhibition is measured. Results of these tests are summarized in Table 8, in which the diameter of the zone of growth inhibition is listed for each test substance against each bacterial strain.

The inactive compounds were methyl 5-acetylsalicylate, homopolymers of methyl 5-vinylsalicylate and of methyl 5-vinylacetylsalicylate, copolymers of these compounds with methacrylic acid, and a high molecular weight copolymer ($\eta_{inh} = 2.74$ dl/g) containing 16 mole-% 5-vinylsalicylic acid and 84 mole-% methacrylic acid.

It should be emphasized that these are preliminary results, and that further testing is required. For example, it has not been determined whether or not the polymers tested contain traces of the vinylsalicylic acid monomers, which are quite potent antibacterials (Table 8). Also, the agar-plate test can only serve as a first step in the evalua-

TABLE 8
Preliminary Antibacterial Test Results for
5-Vinylsalicylic Acid Derivatives

Compound	Activity vs. <i>E. coli</i>	Activity vs. <i>B. subtilis</i>
5-Vinylsalicylic acid	3 cm ^C	1 cm
5-Vinylacetylsalicylic acid	1 cm	0.5 cm
Poly(5-vinylsalicylic acid) ^a	0.5 cm	0.5 cm
Poly(5-vinylacetylsalicylic acid) ^b	0.5 cm	Inactive
Methyl 5-acetylacetylsalicylate	0.2 cm	Inactive
Inactive in these tests:		
DT - 221 - 126		
DT - 222 - 003		
DB - 53 - 127 - 13		
DB - 53 - 143 - 22		
DB - 53 - 135 - 11		
DB - 53 - 243 - 16		
DB - 53 - 131 - 17		

^a $\eta_{inh} = 0.09$ dl/g; polymer with $\eta_{inh} = 0.57$ dl/g was inactive in these tests

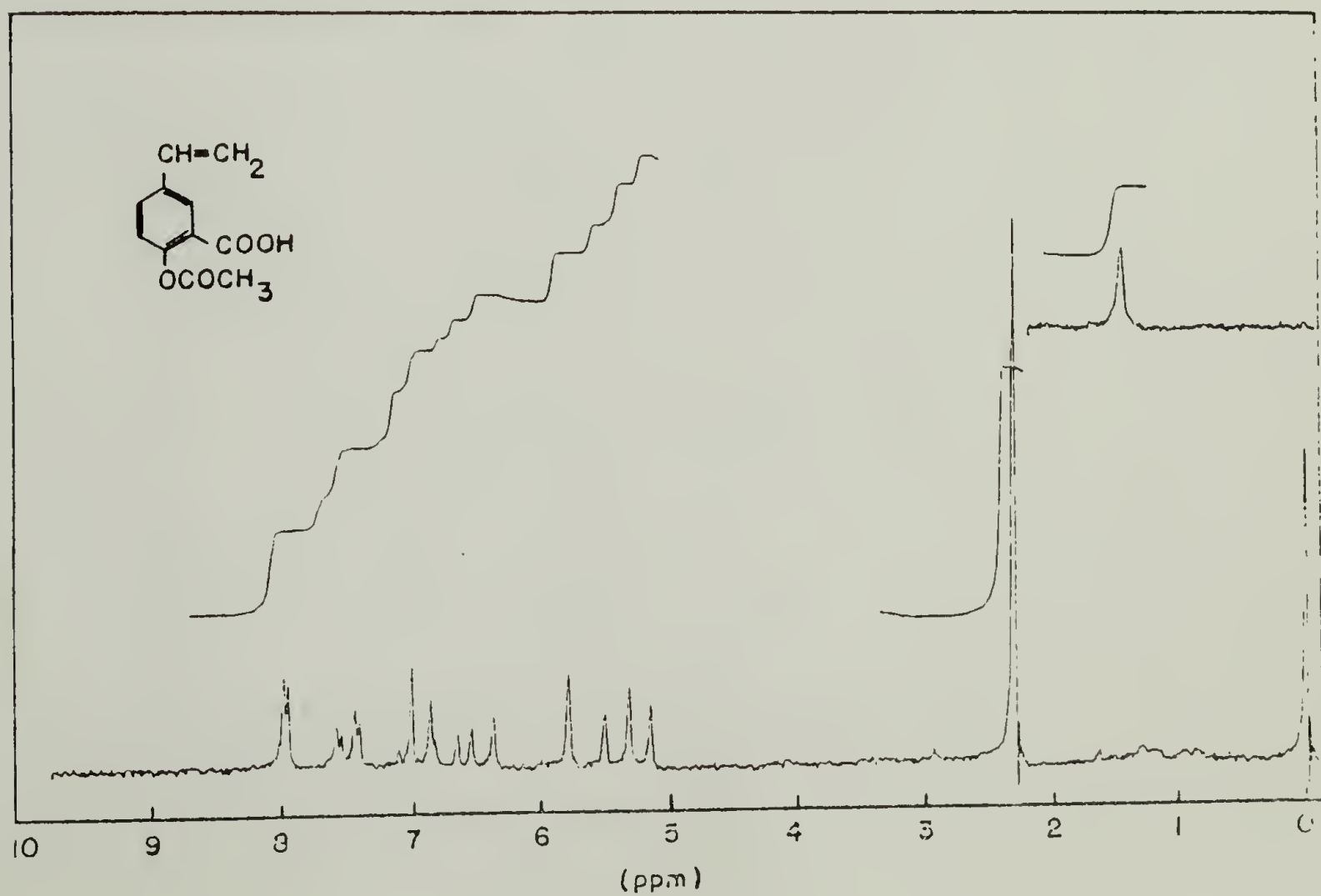
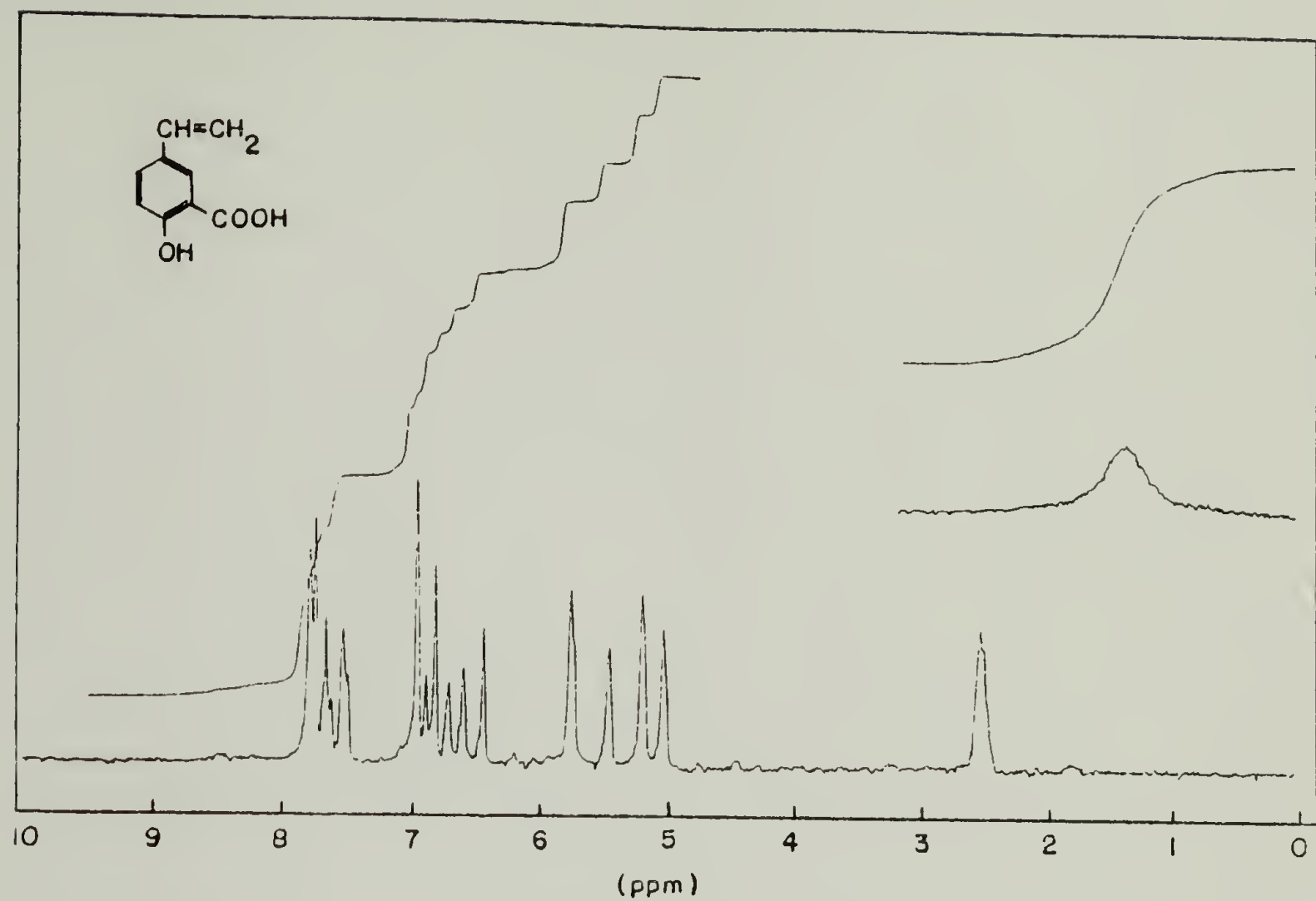
^b $\eta_{inh} = 0.46$ dl/g

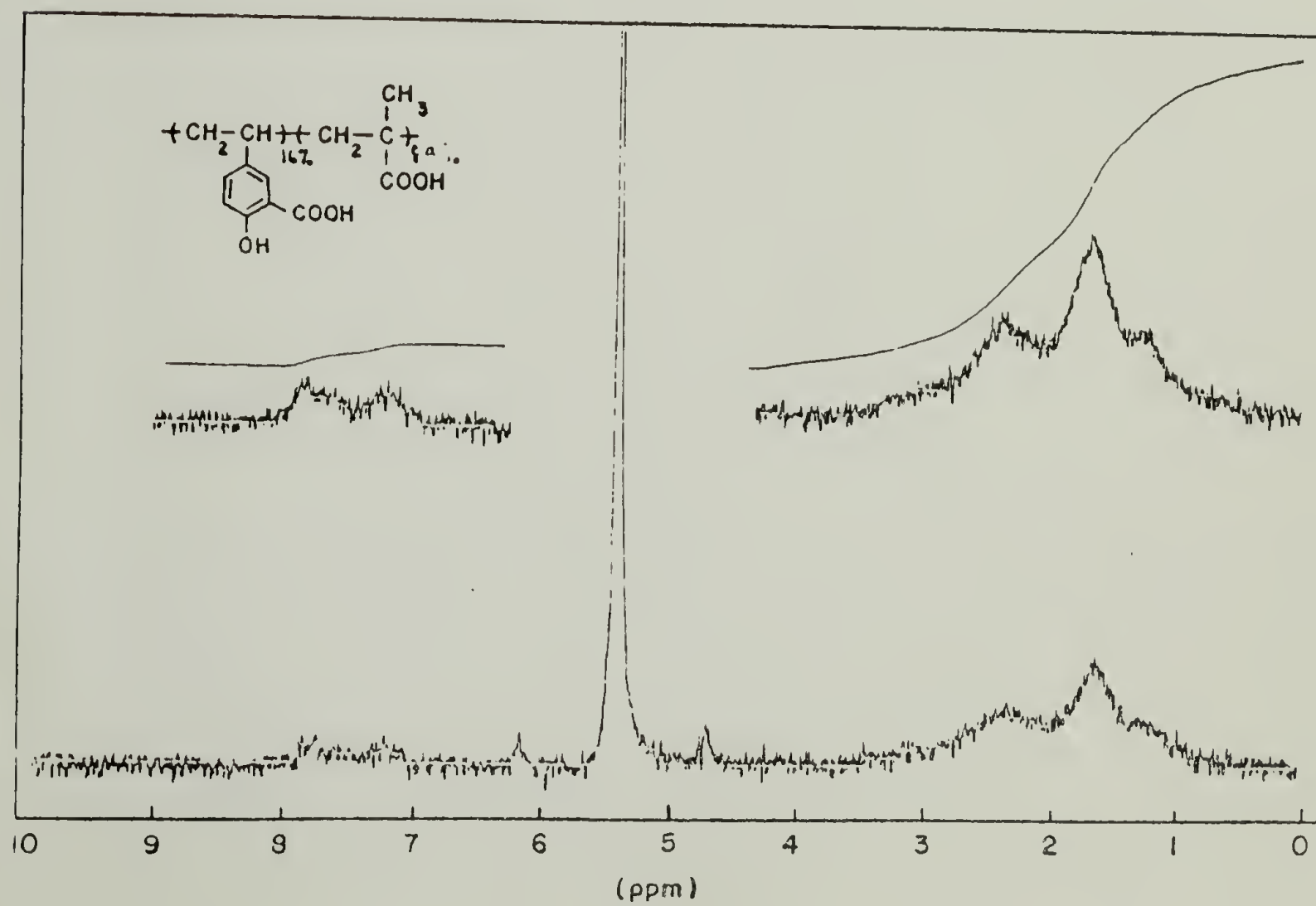
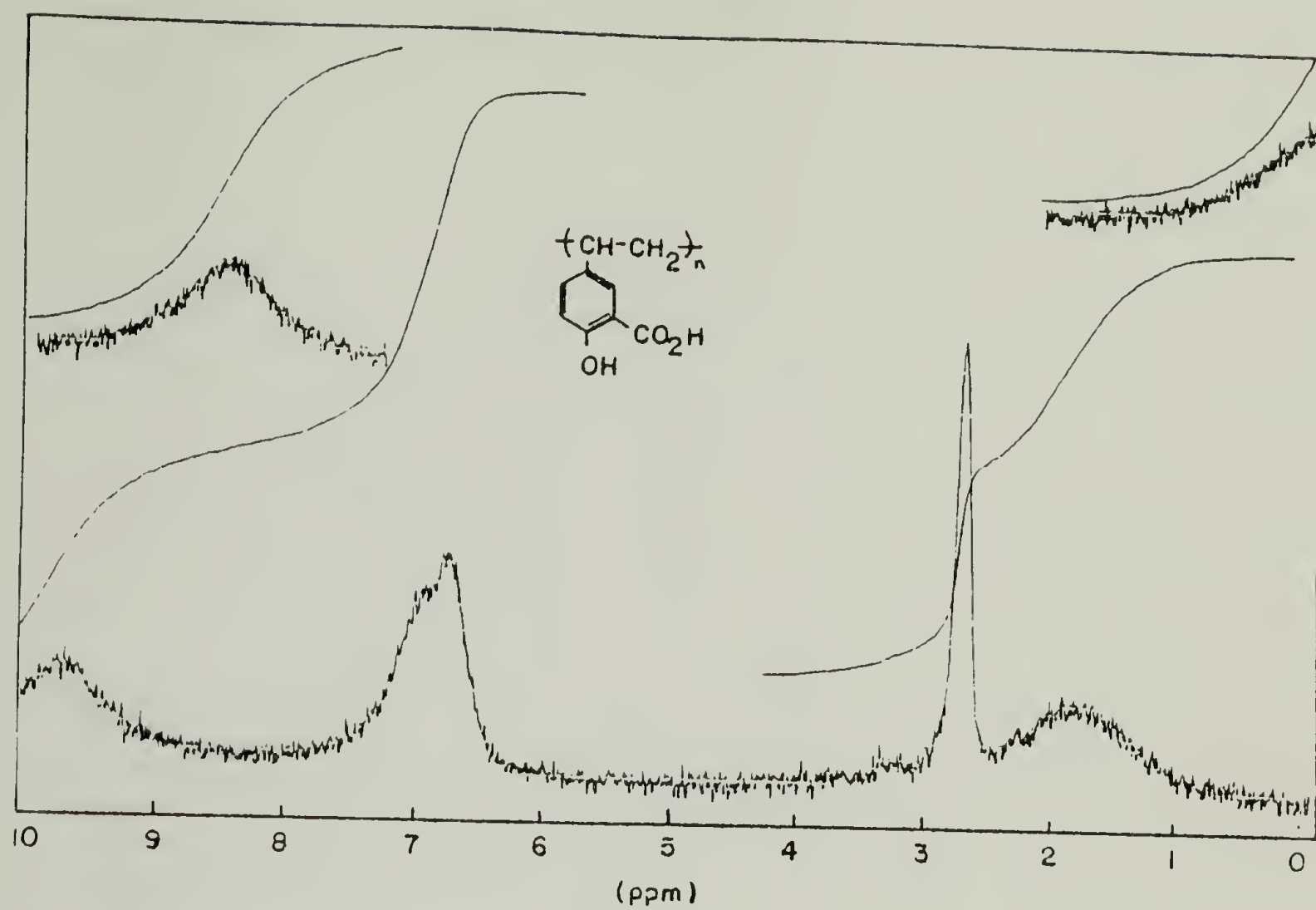
^cDiameter of zone of growth inhibition.

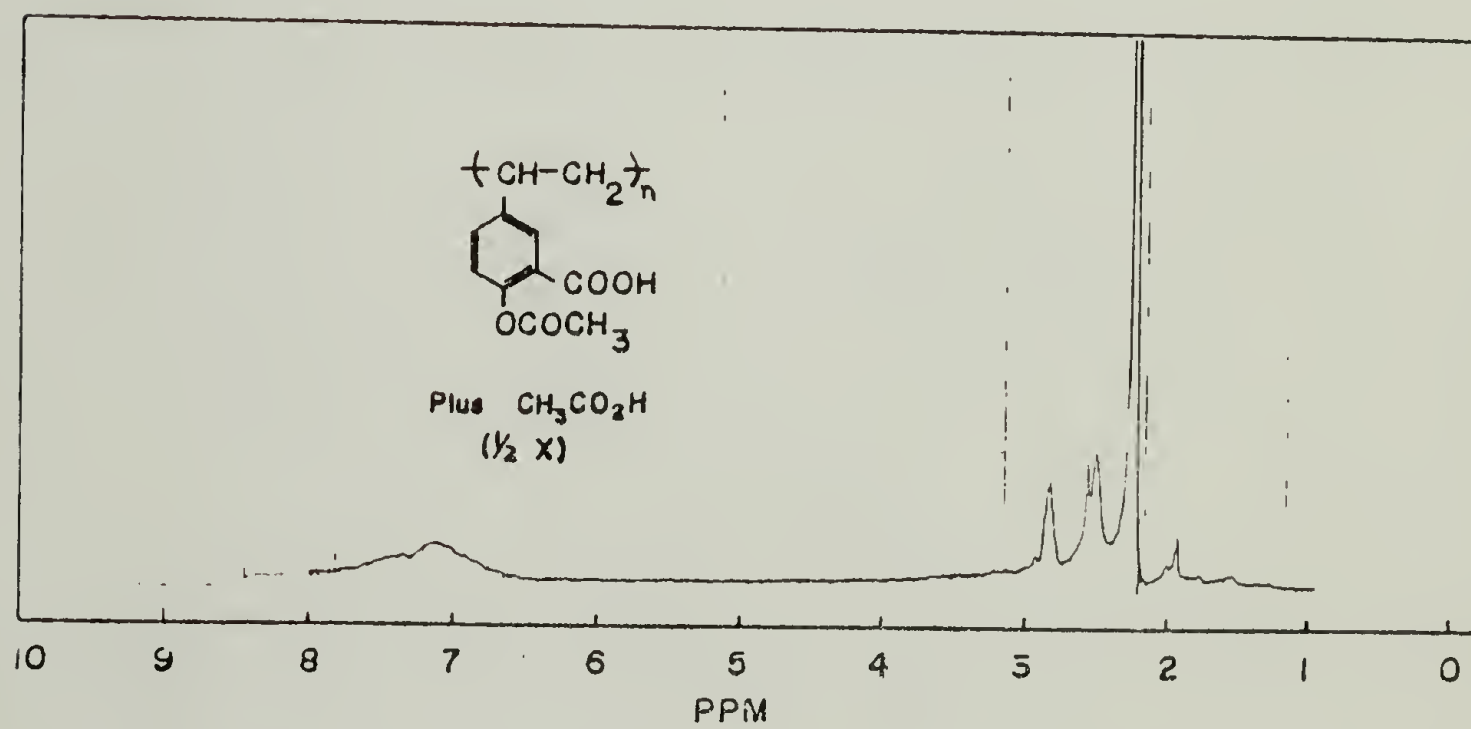
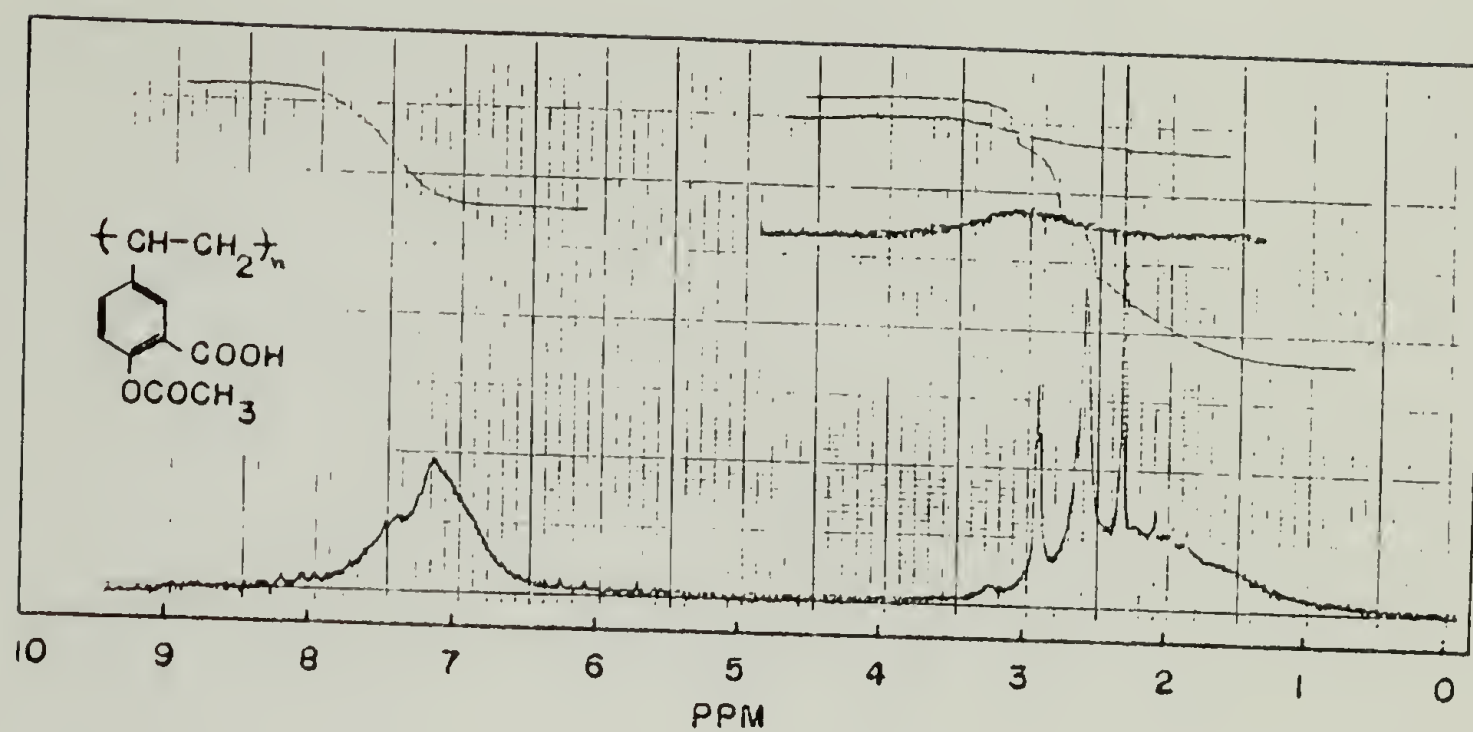
tion of polymeric antibacterial agents, since the size of the zone of growth inhibition probably reflects not only cytotoxicity, but also transport of the agent. Evaluation of these materials is continuing, with the objective of determining the effectiveness and the mechanism of action of polymeric salicylic acid derivatives as antibacterial agents.

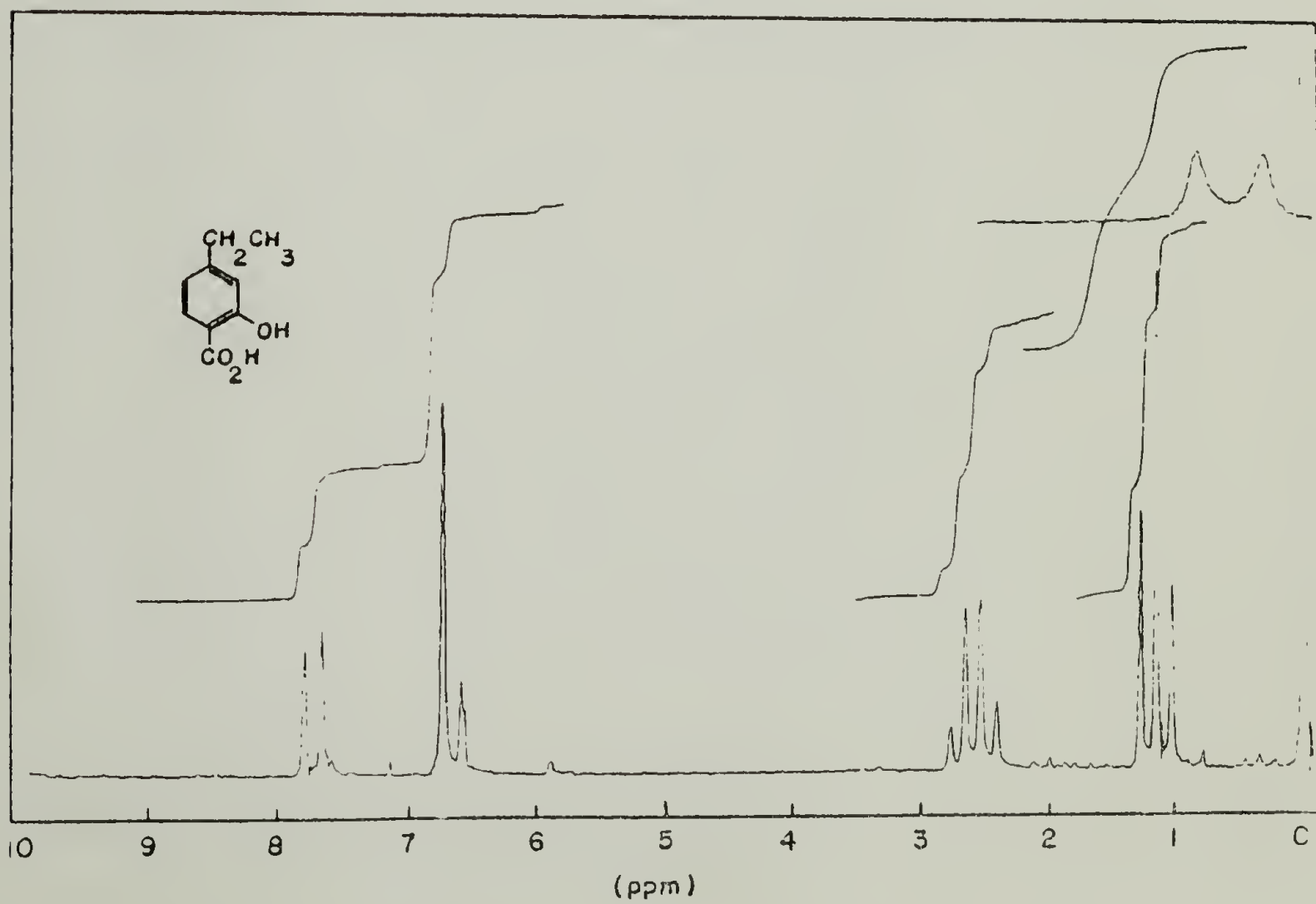
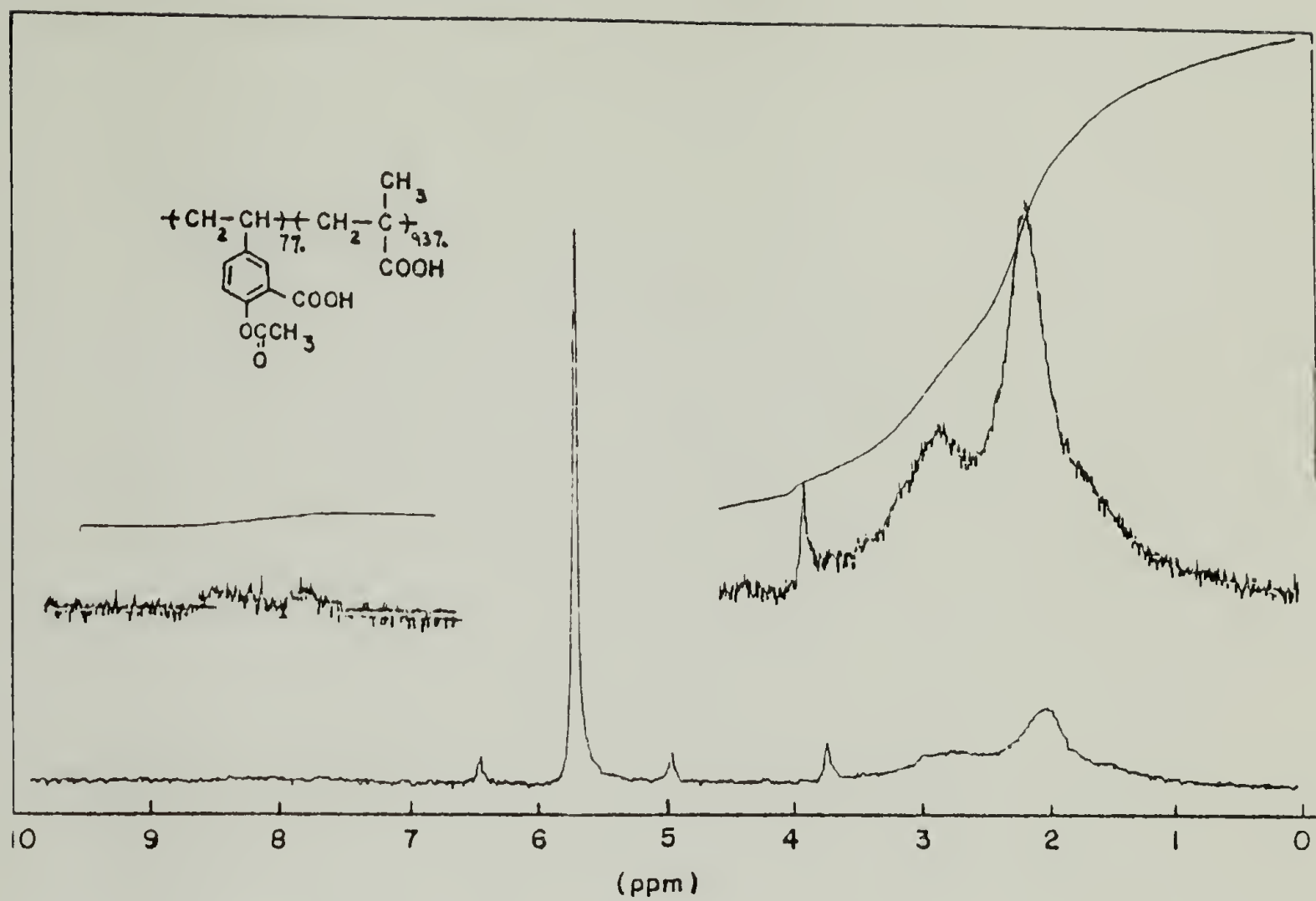
APPENDIX B

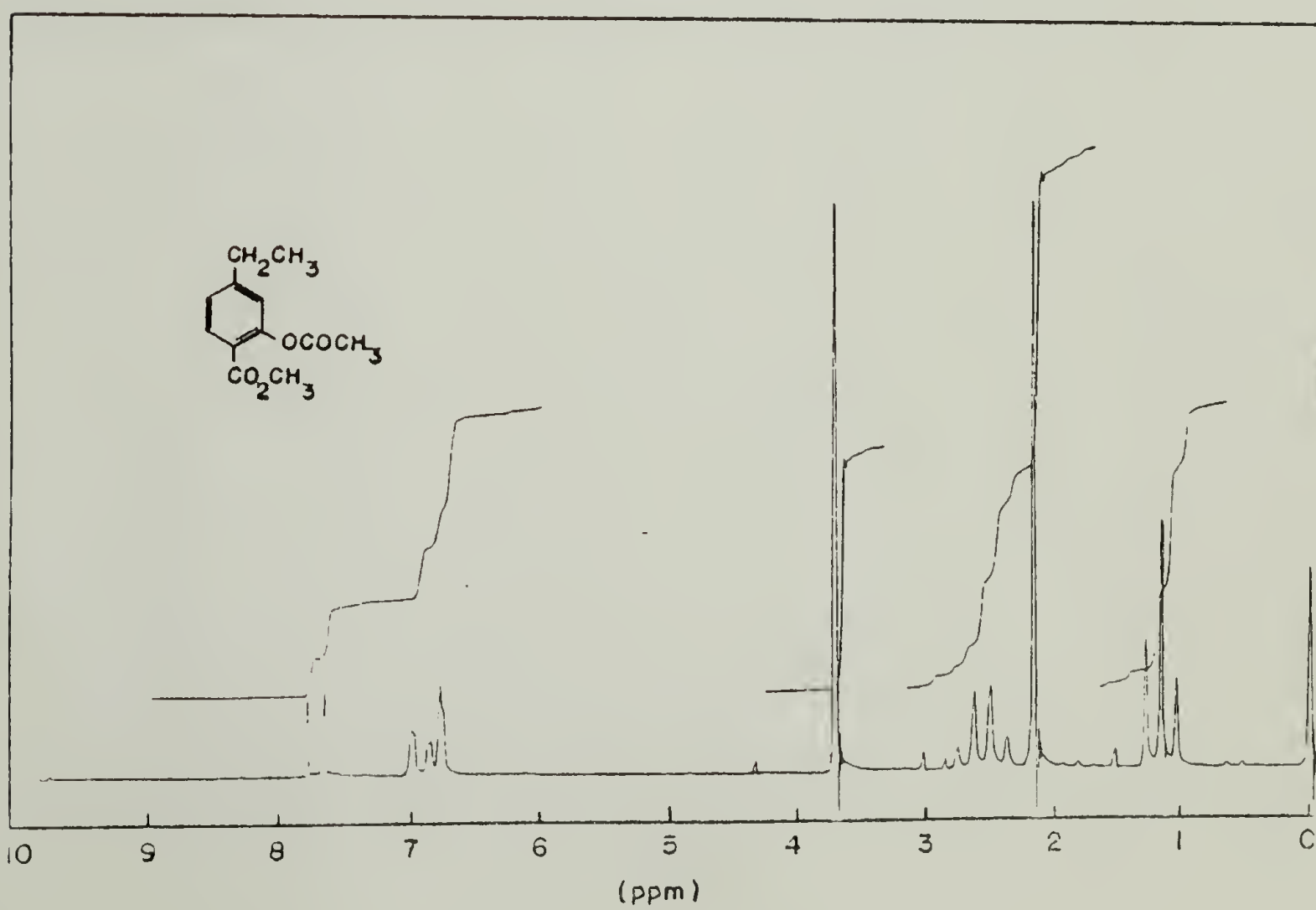
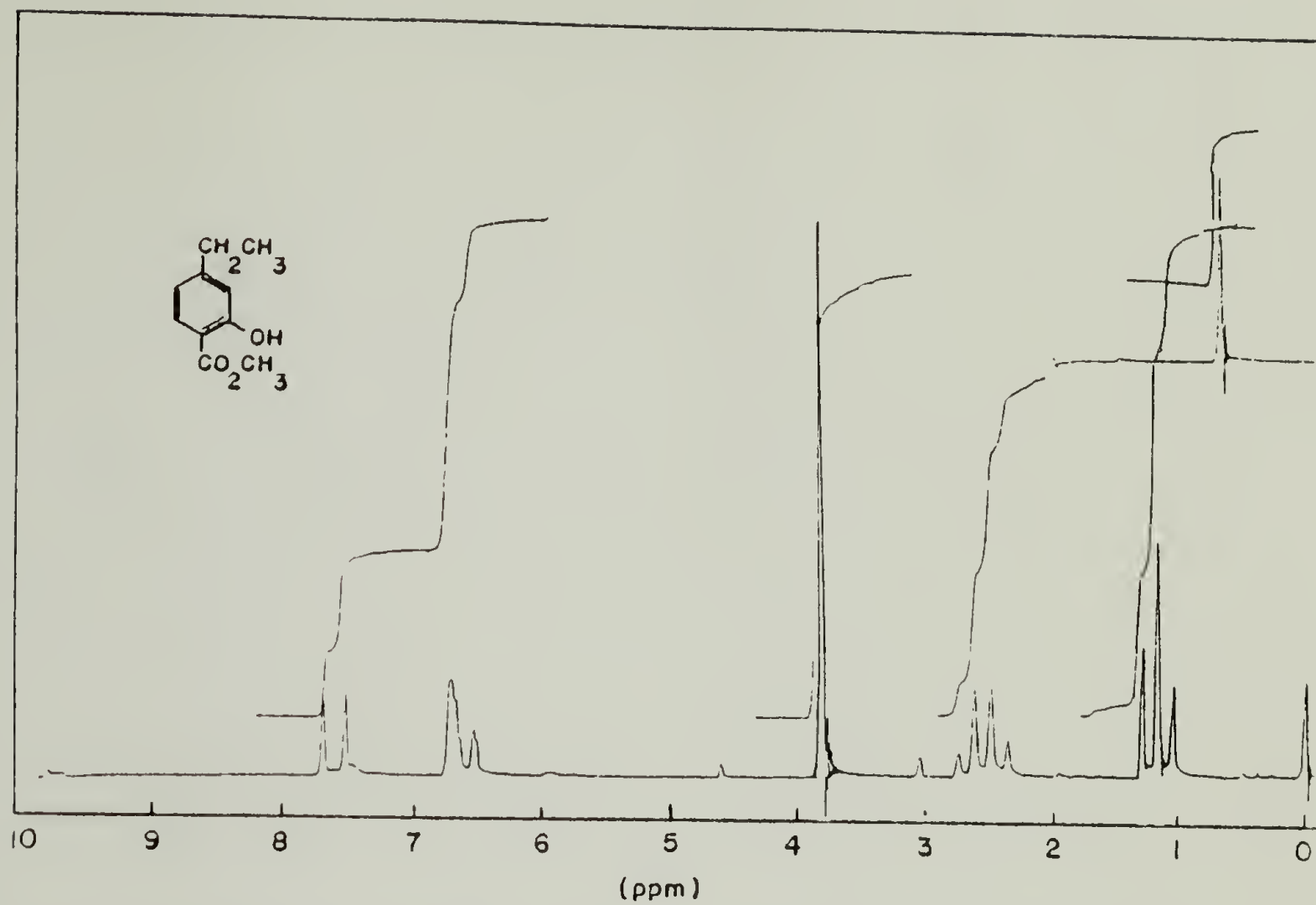
PROTON MAGNETIC RESONANCE SPECTRA

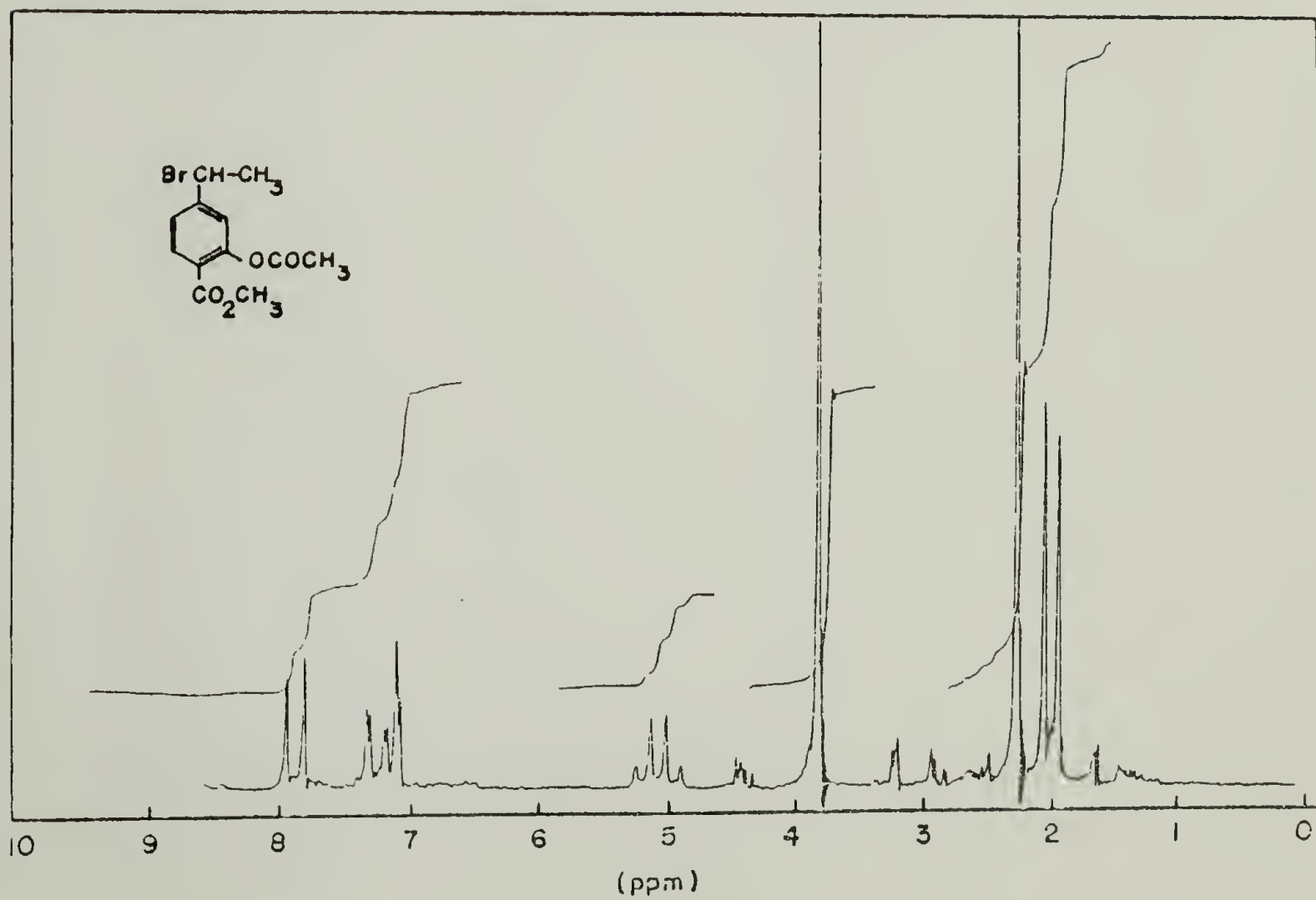
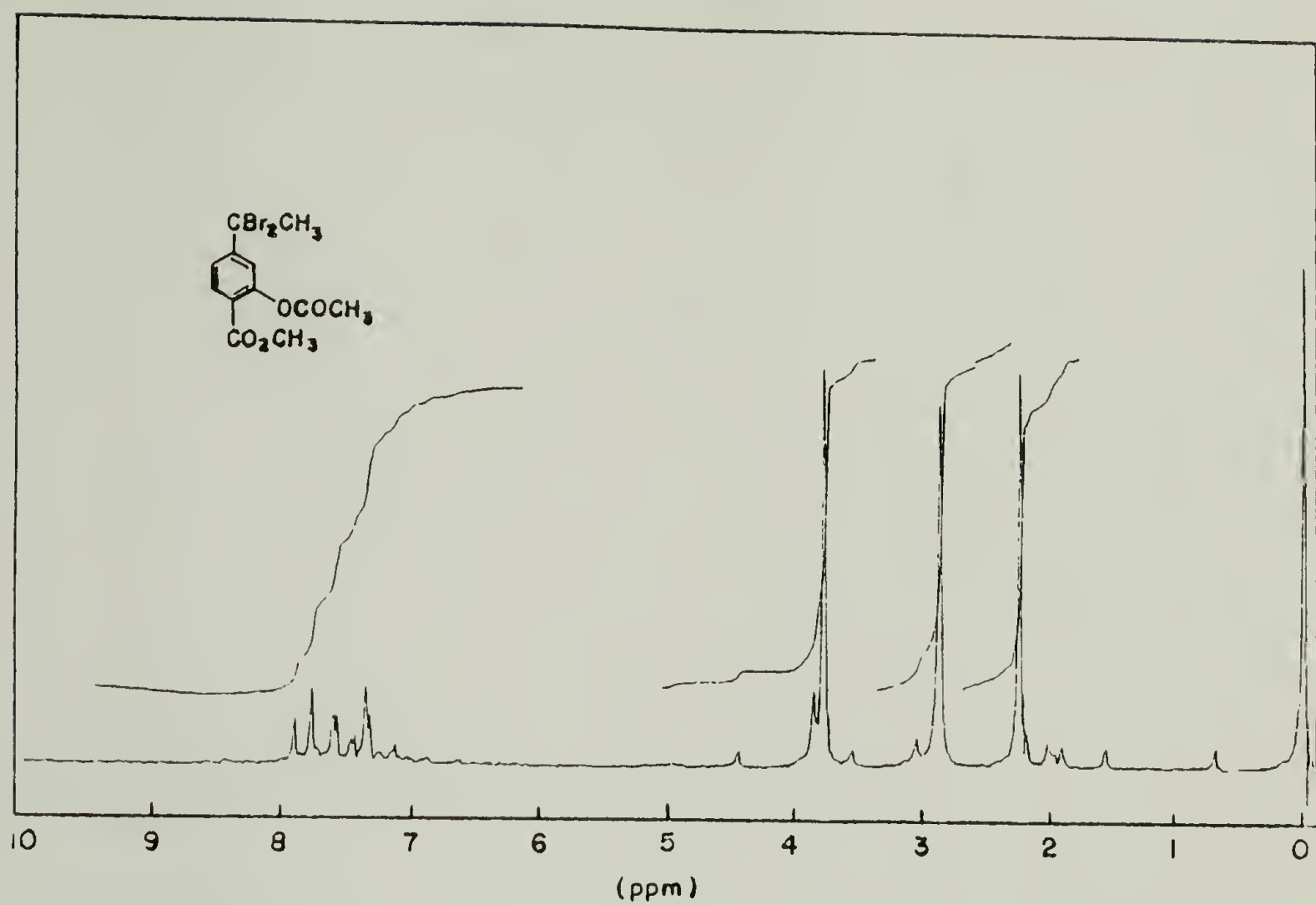


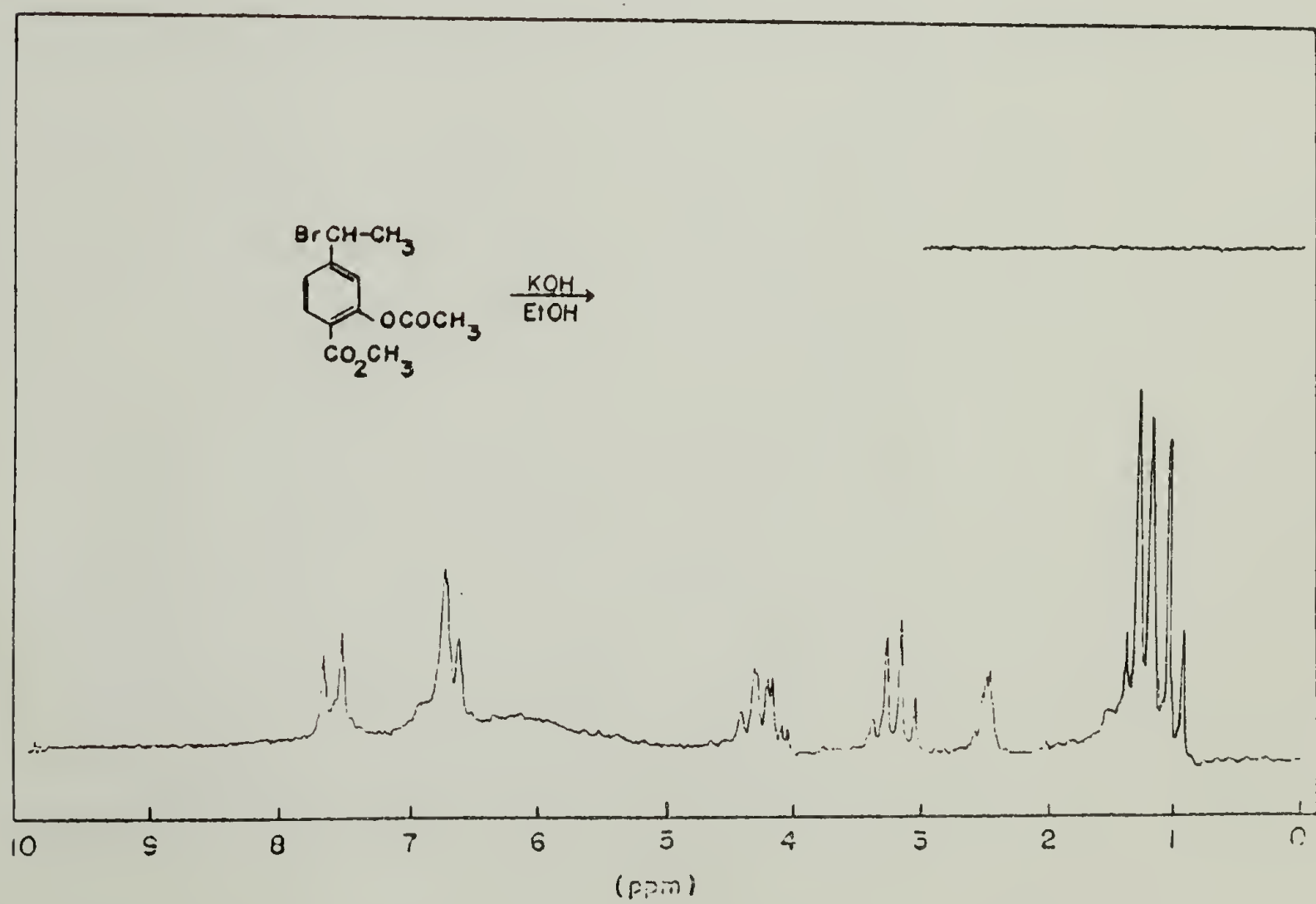
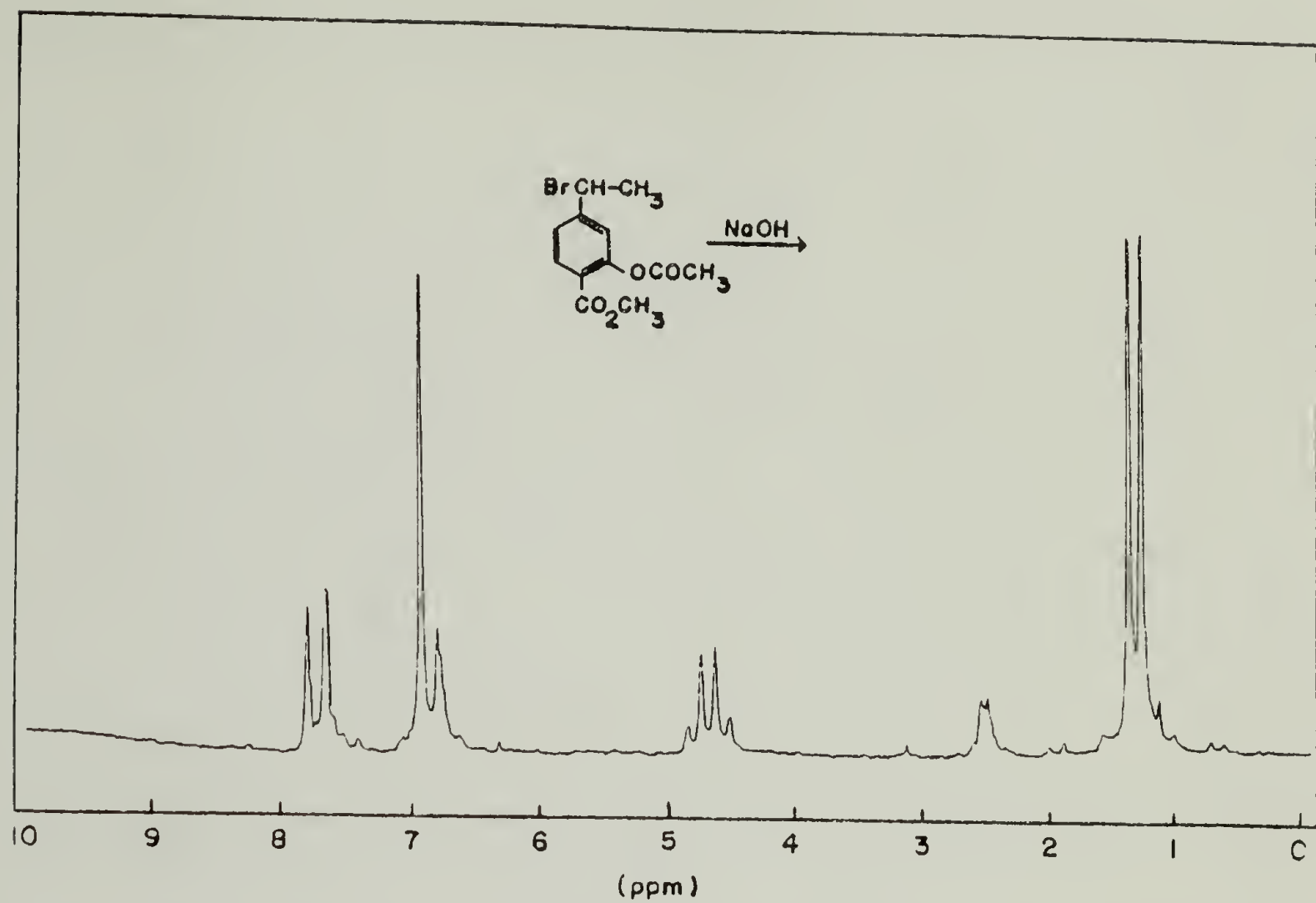


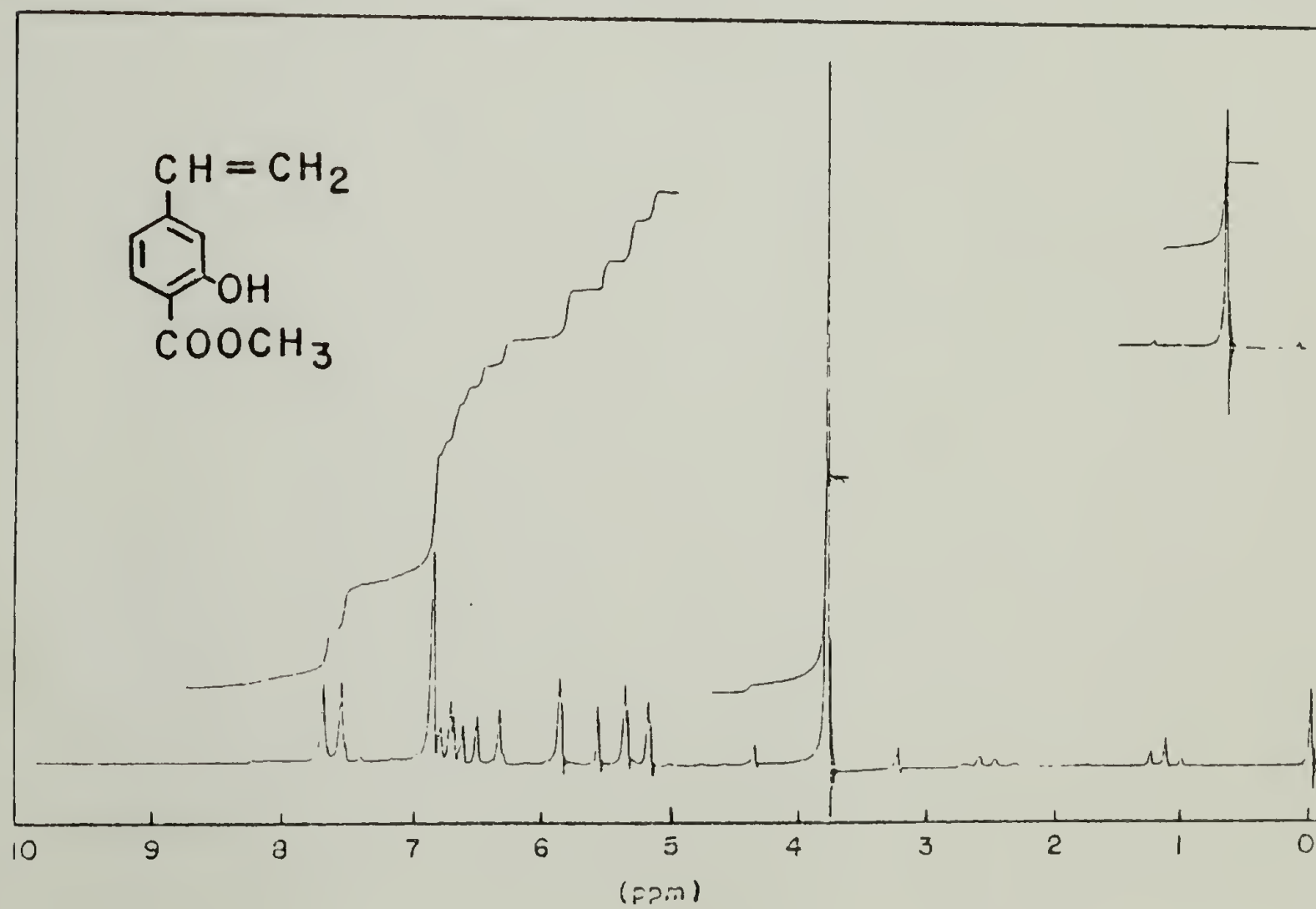
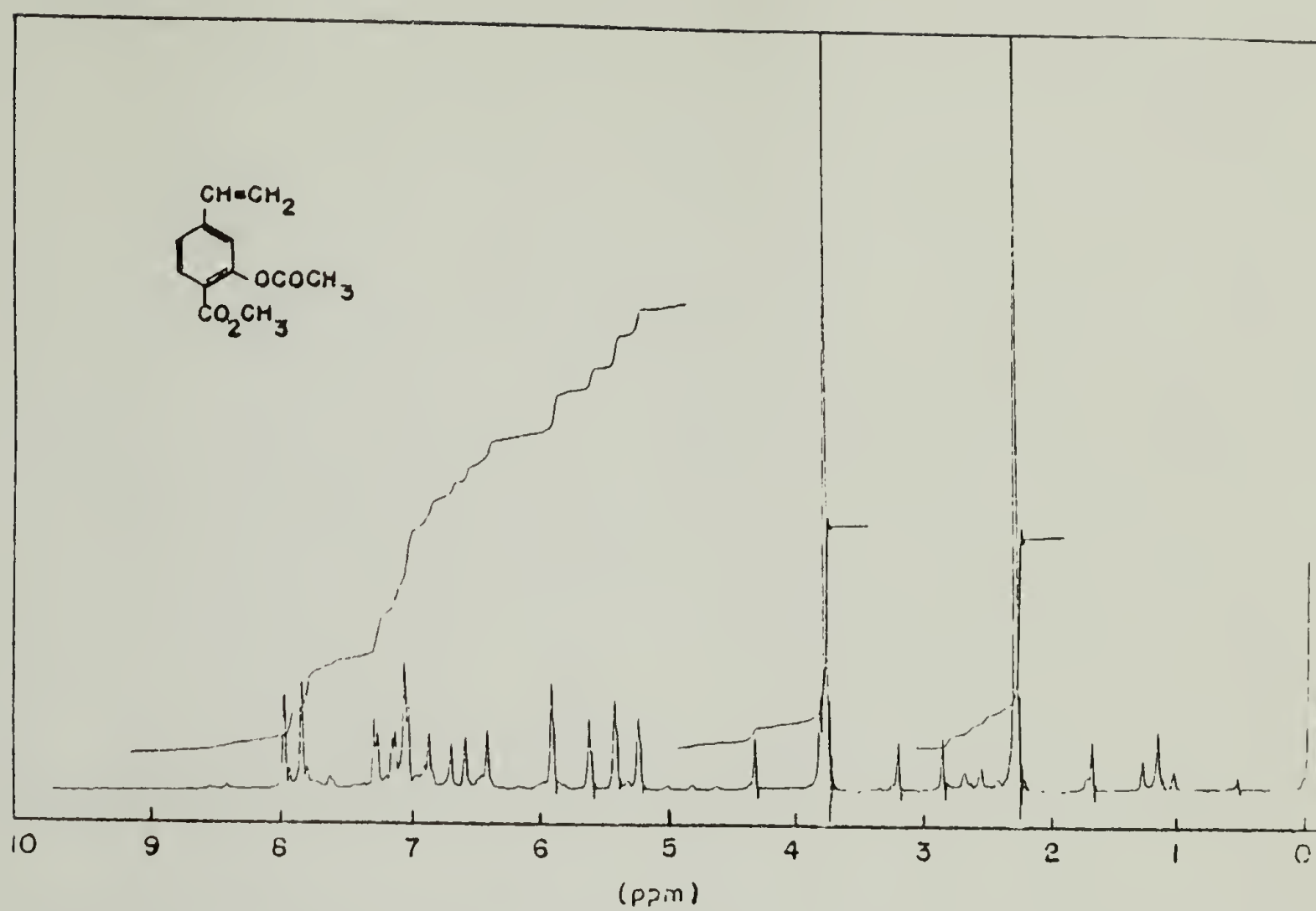


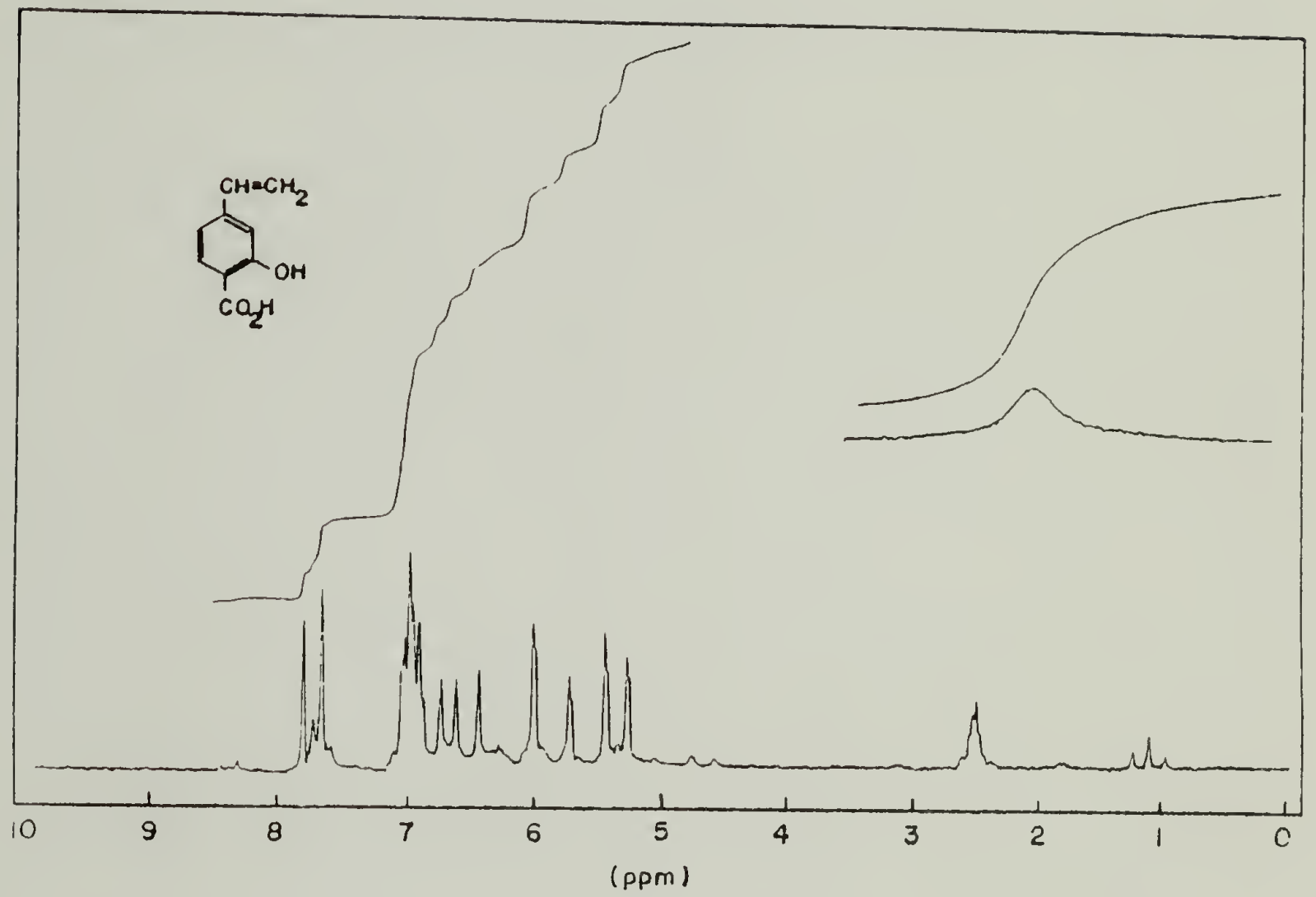


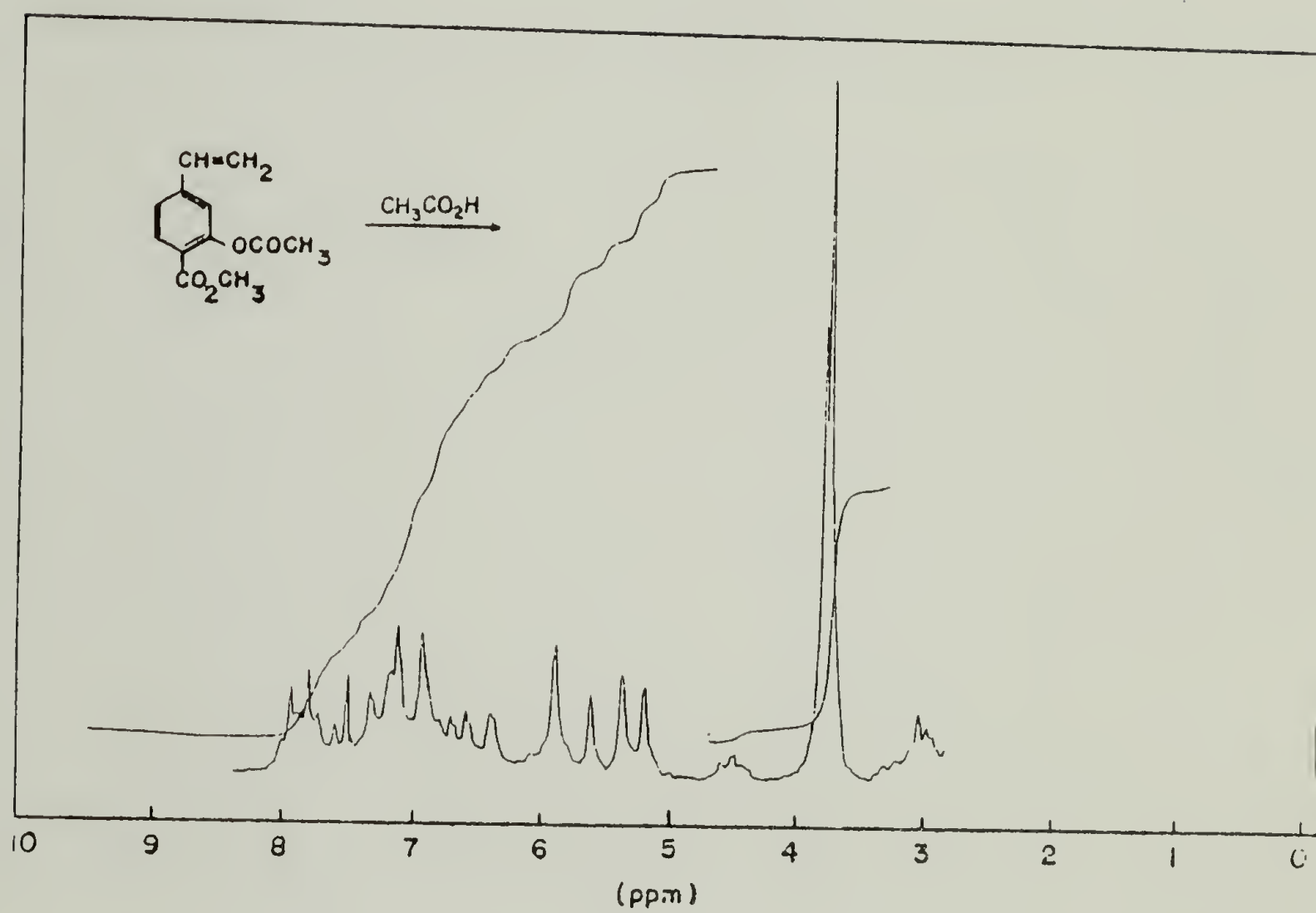


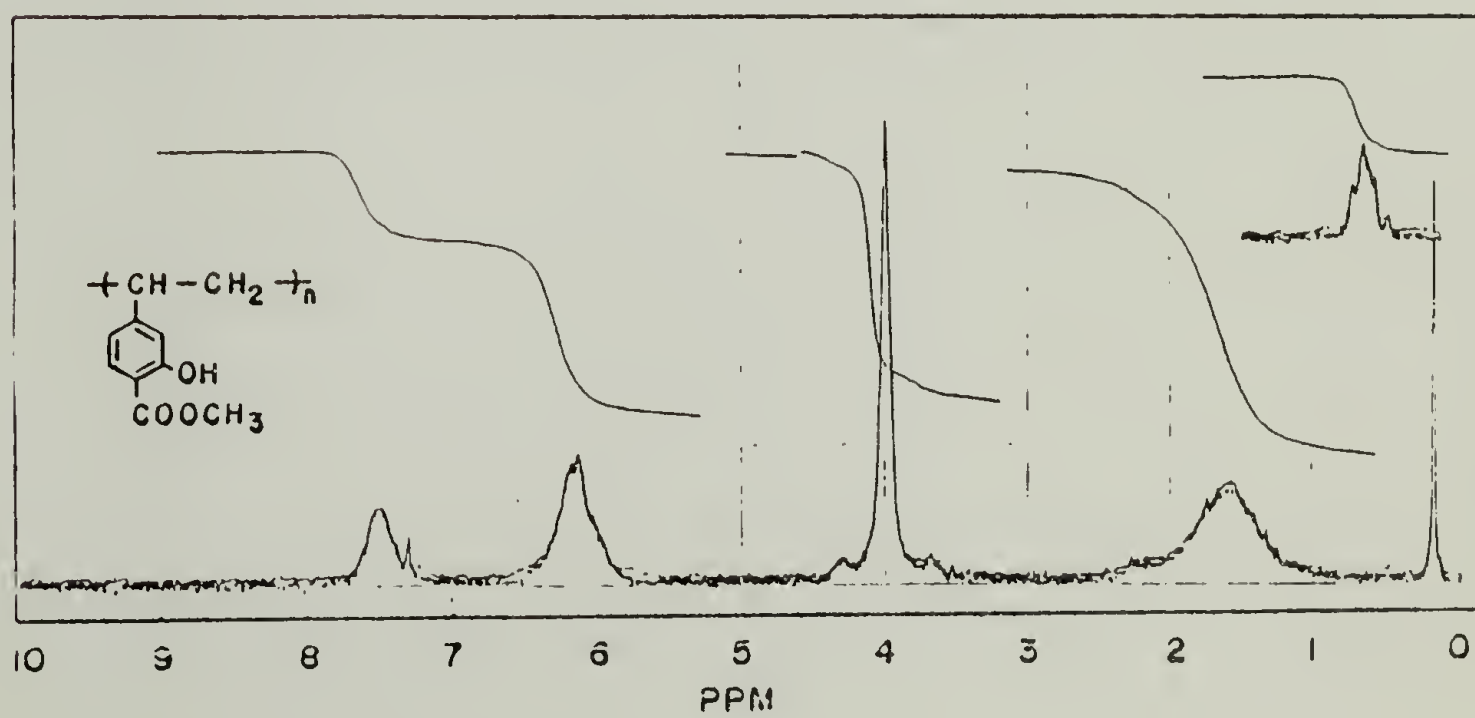
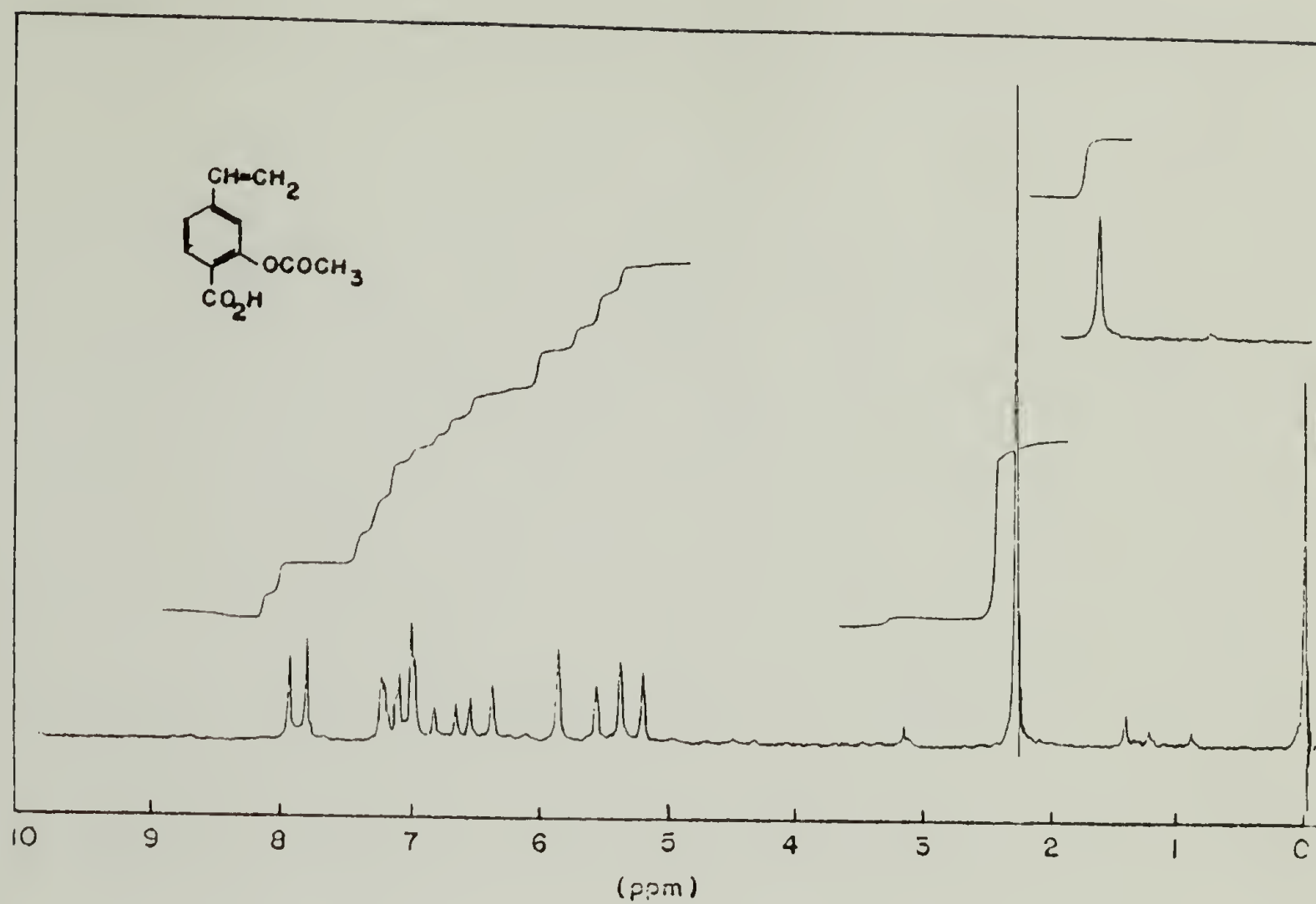


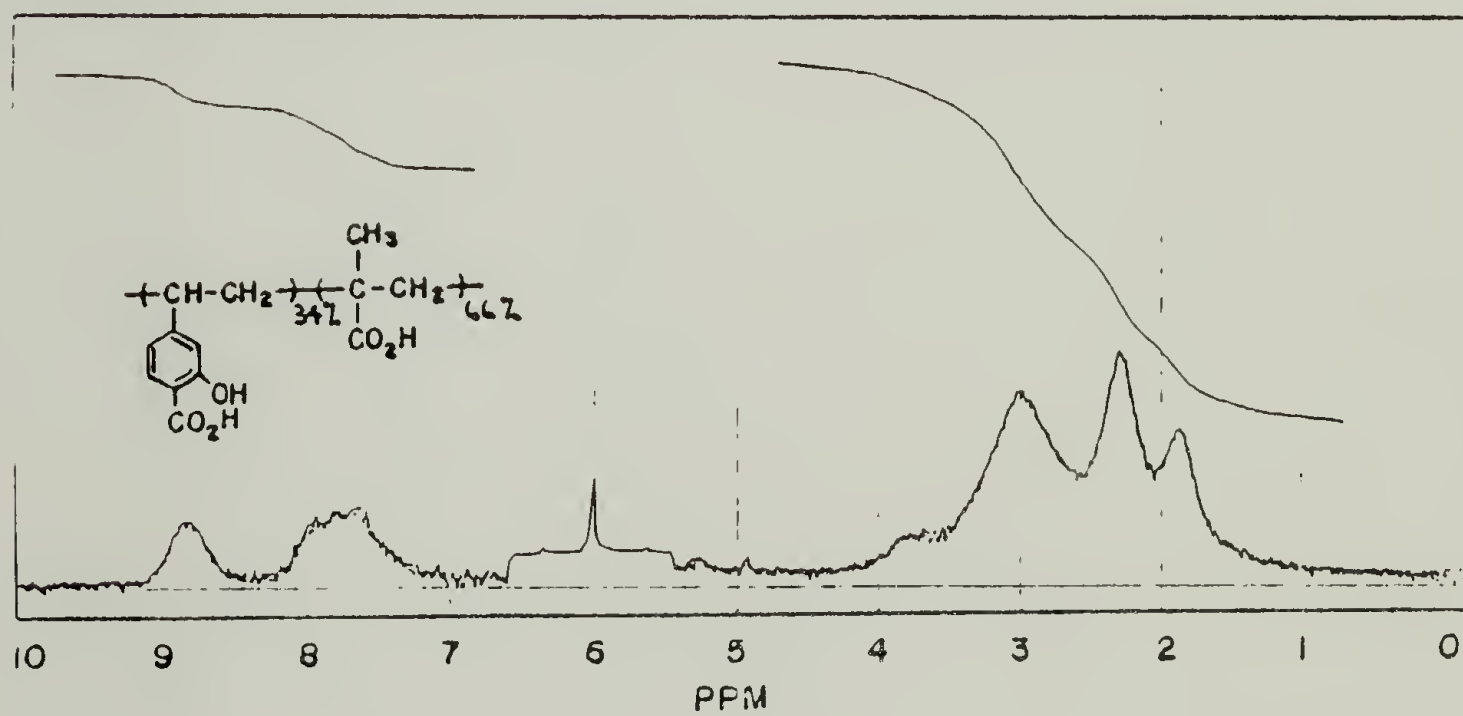
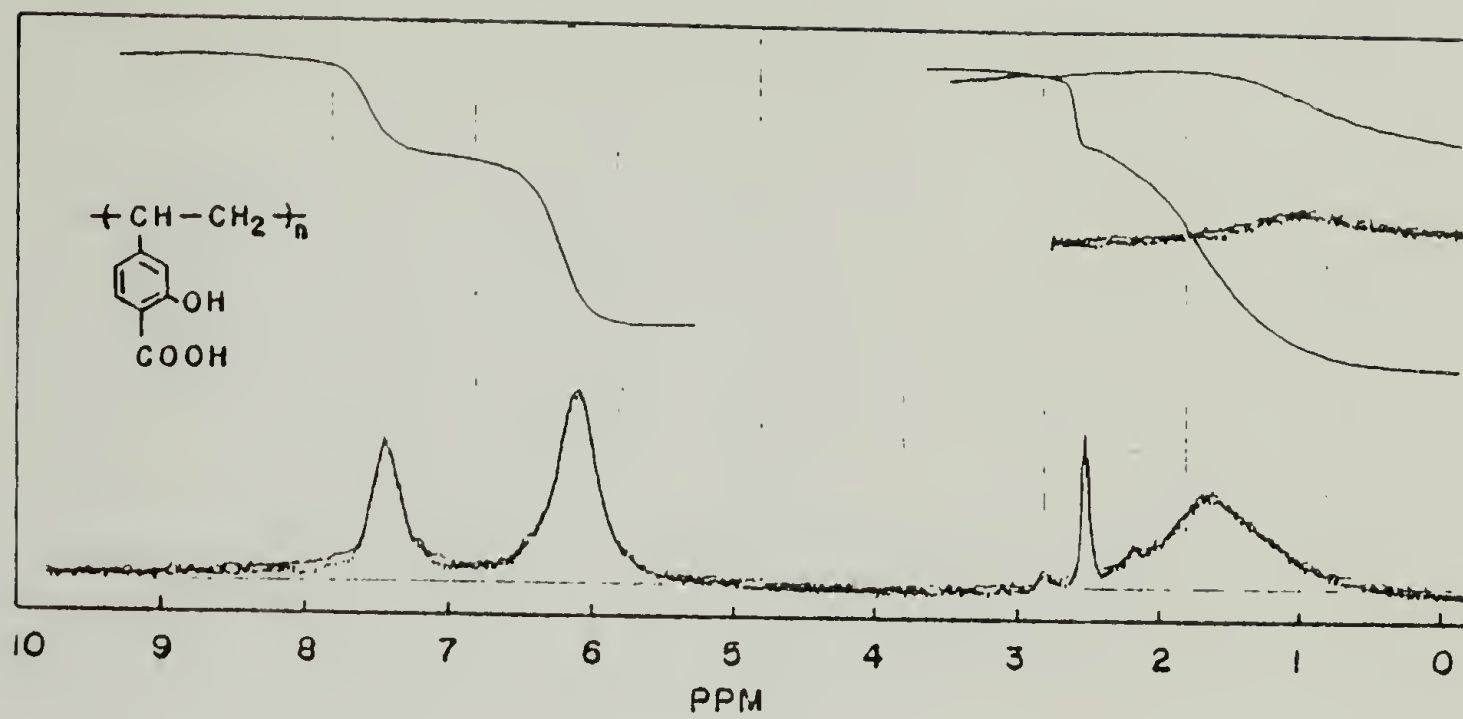


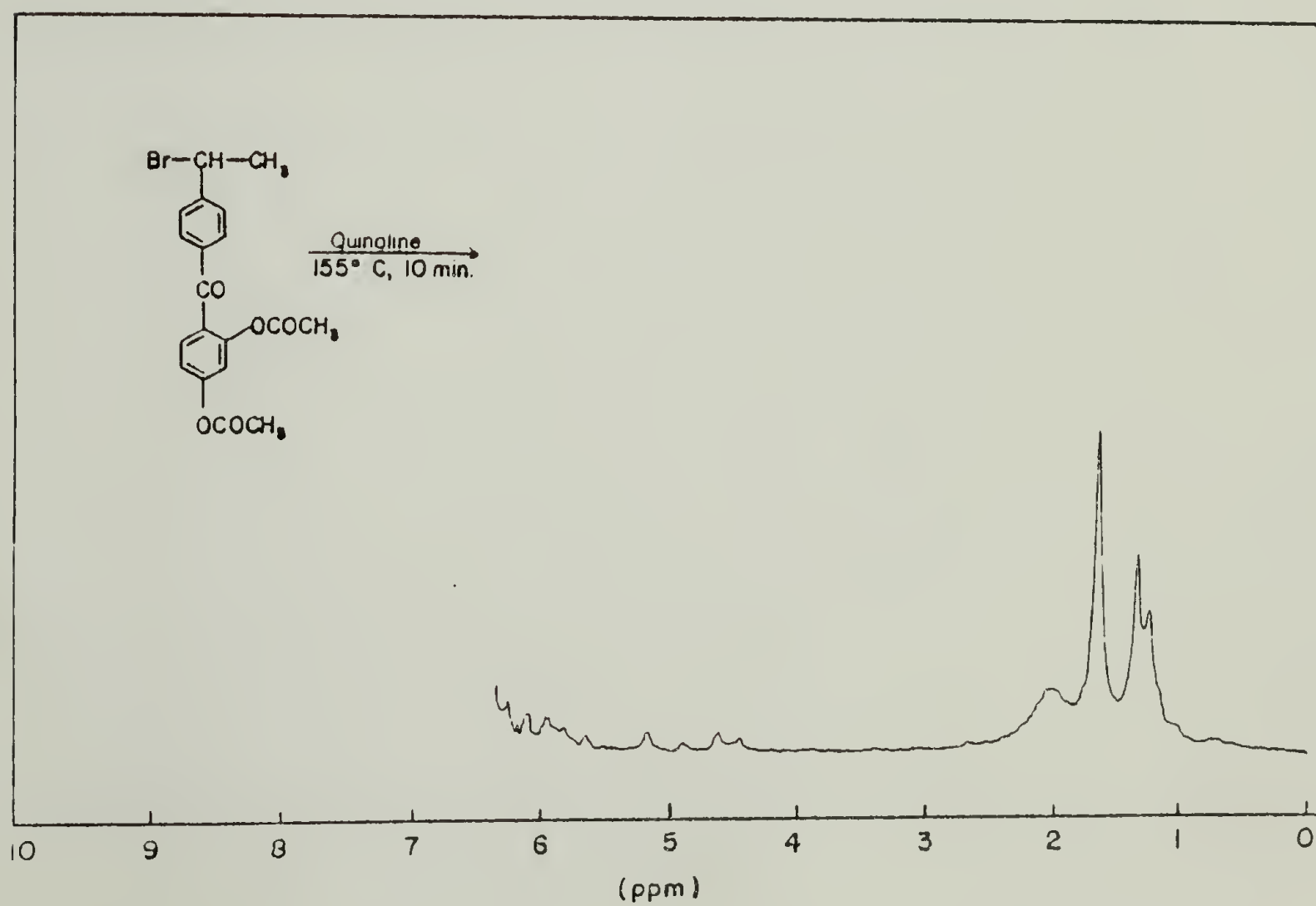
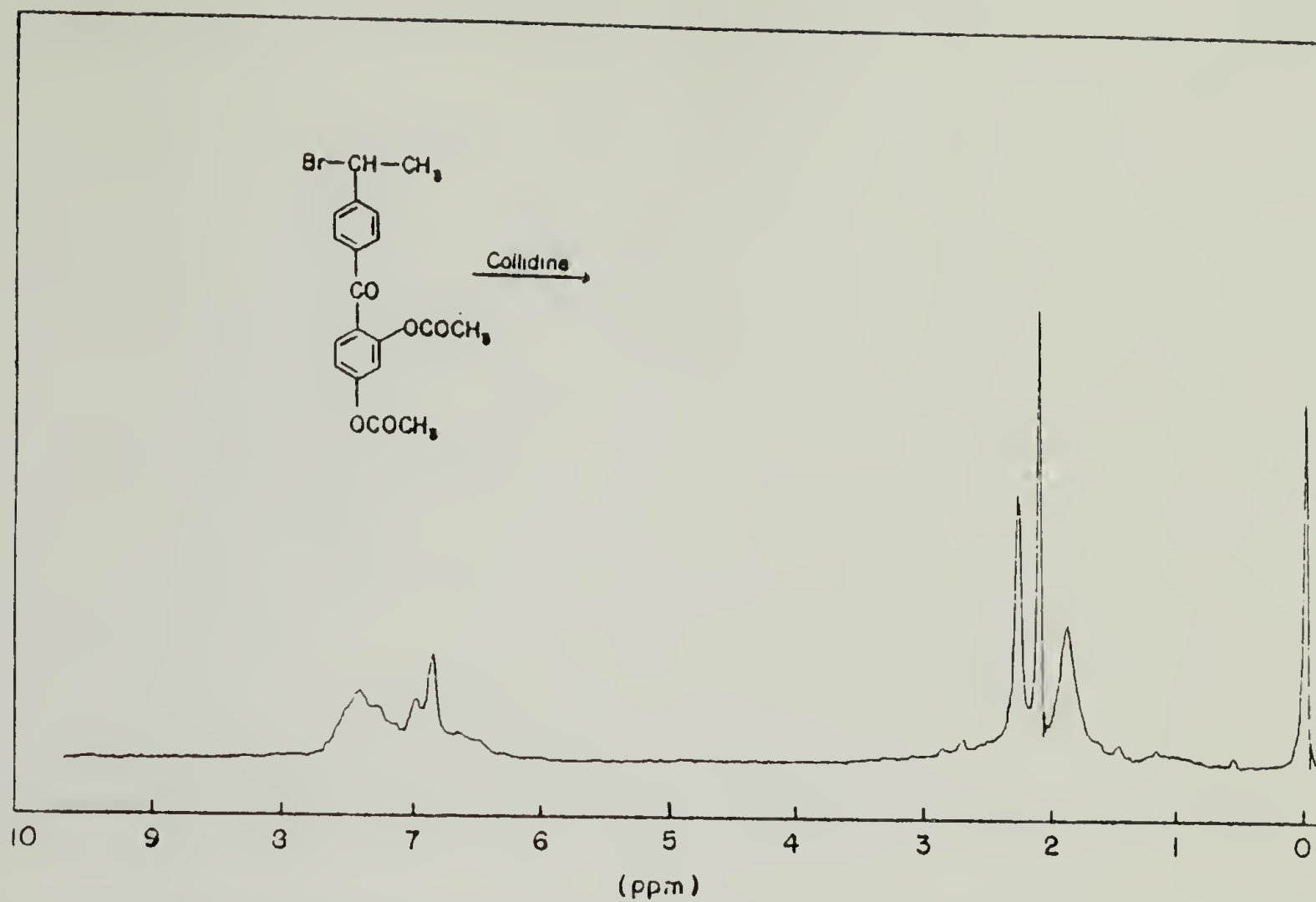


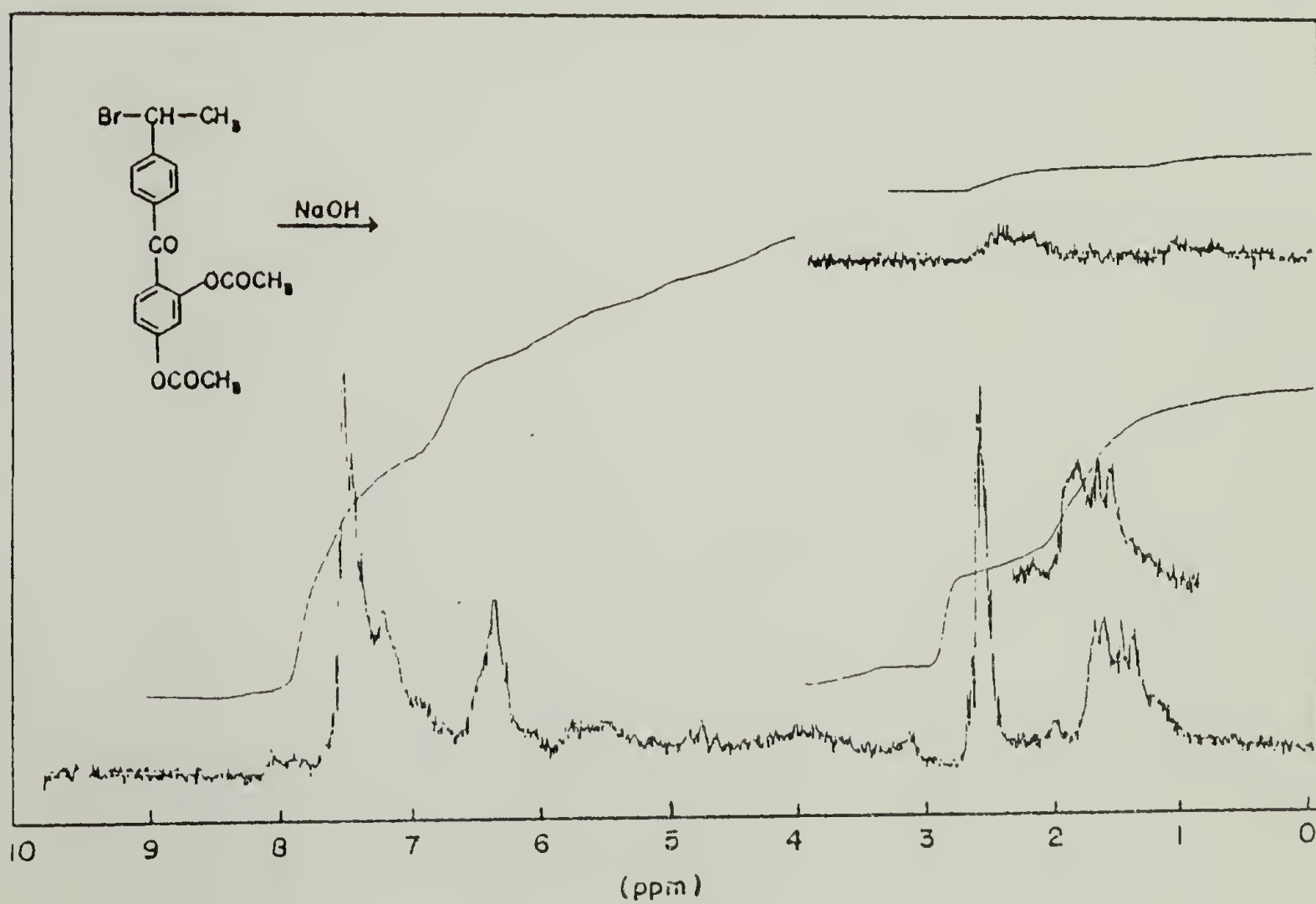
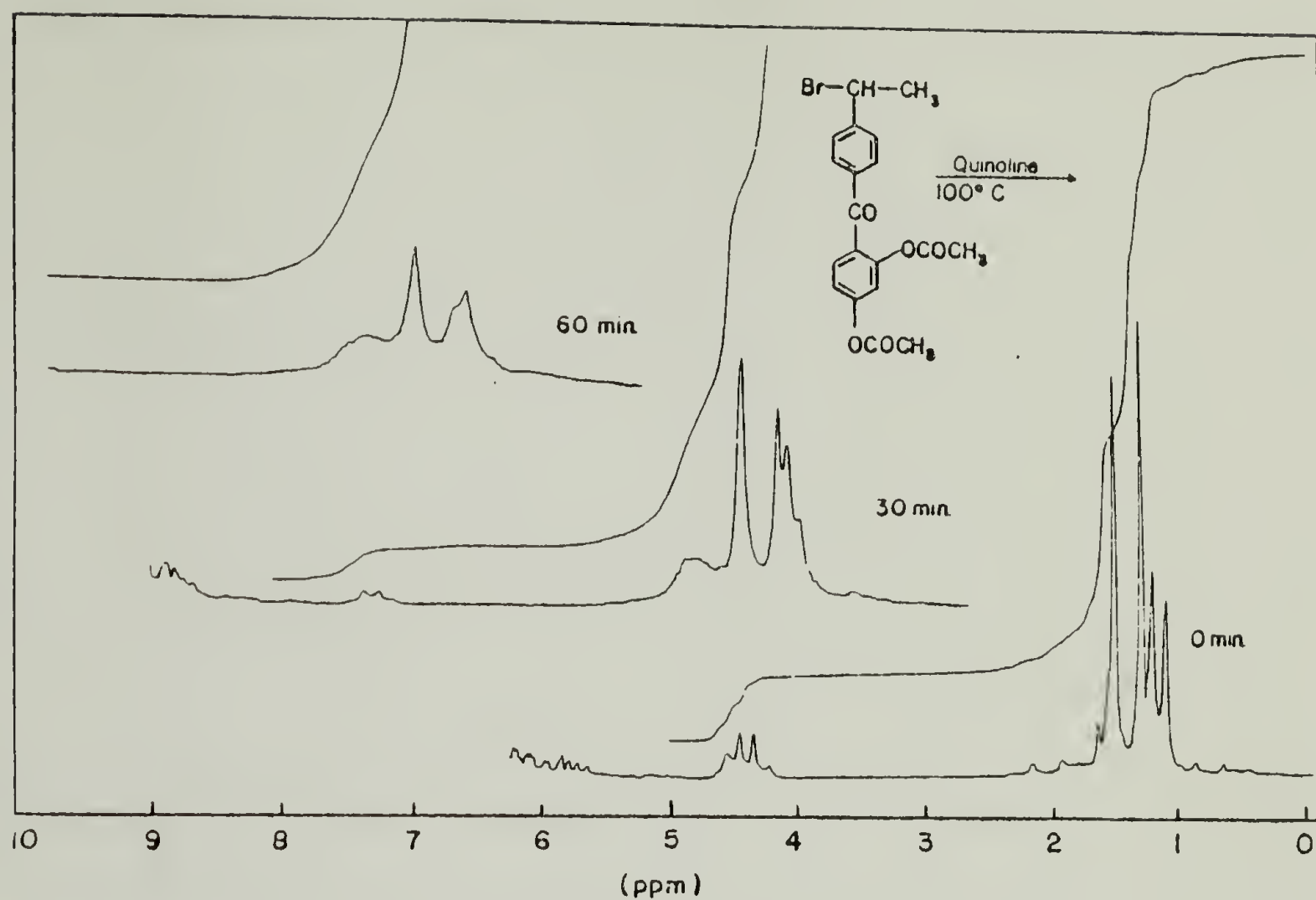


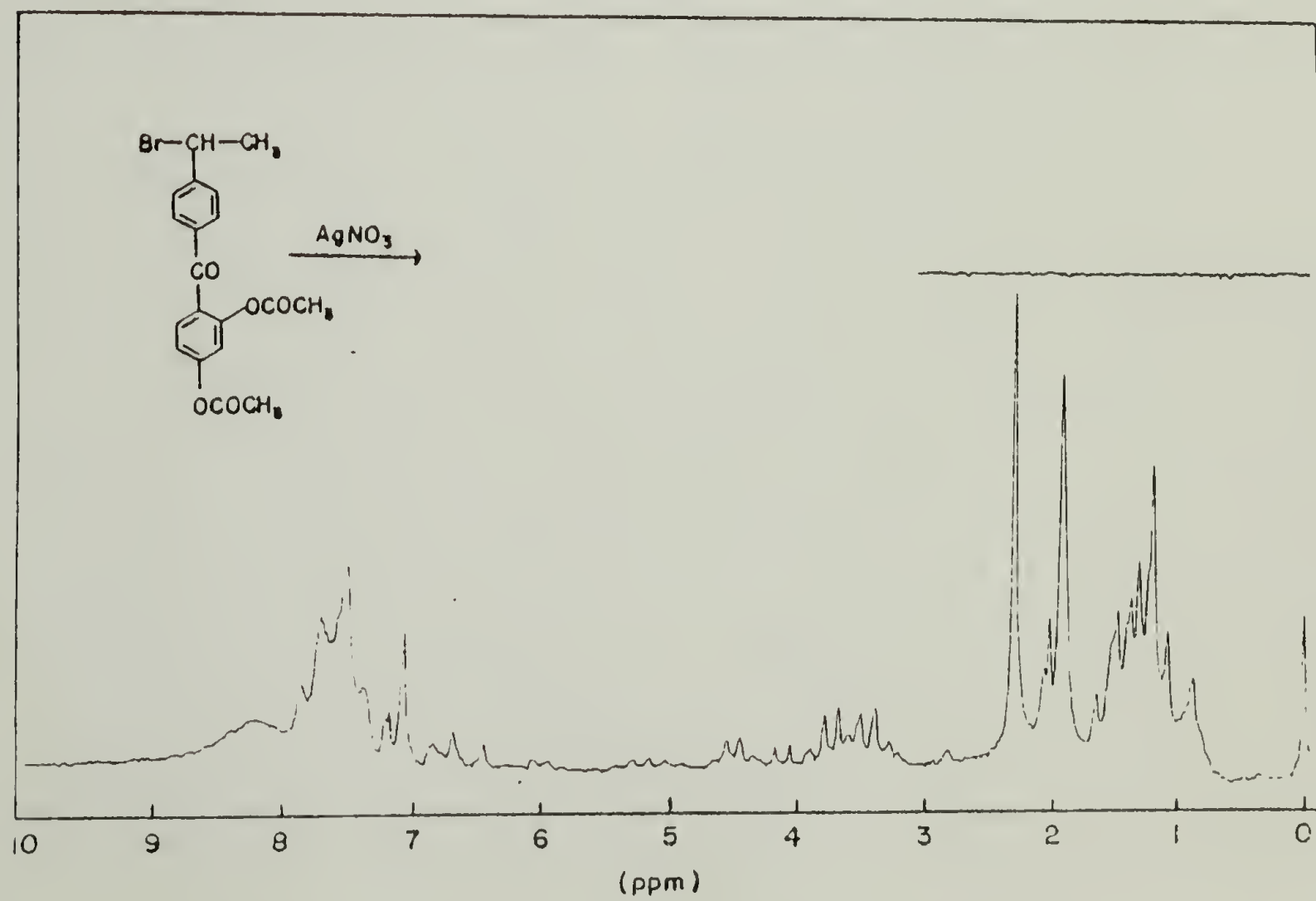
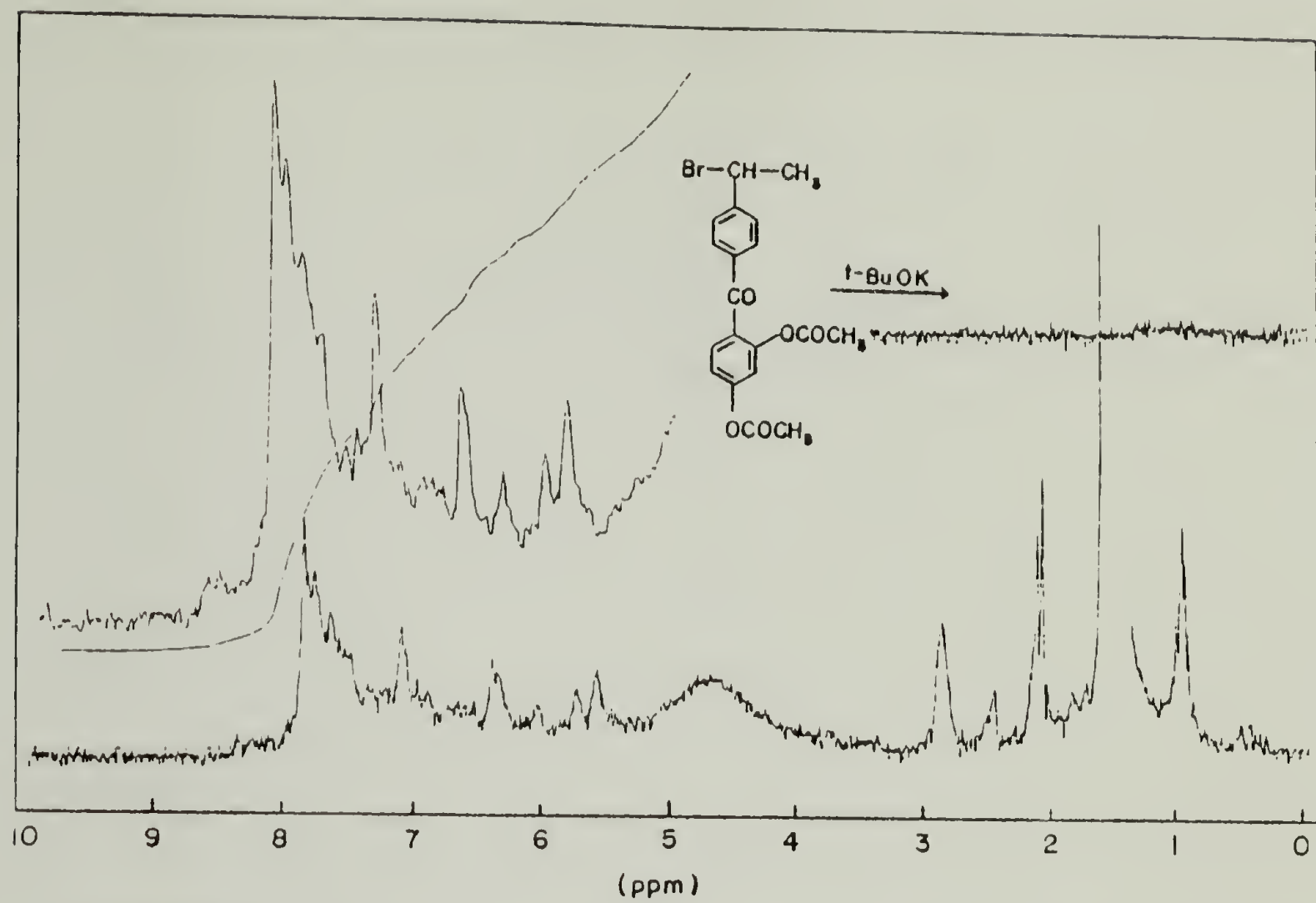


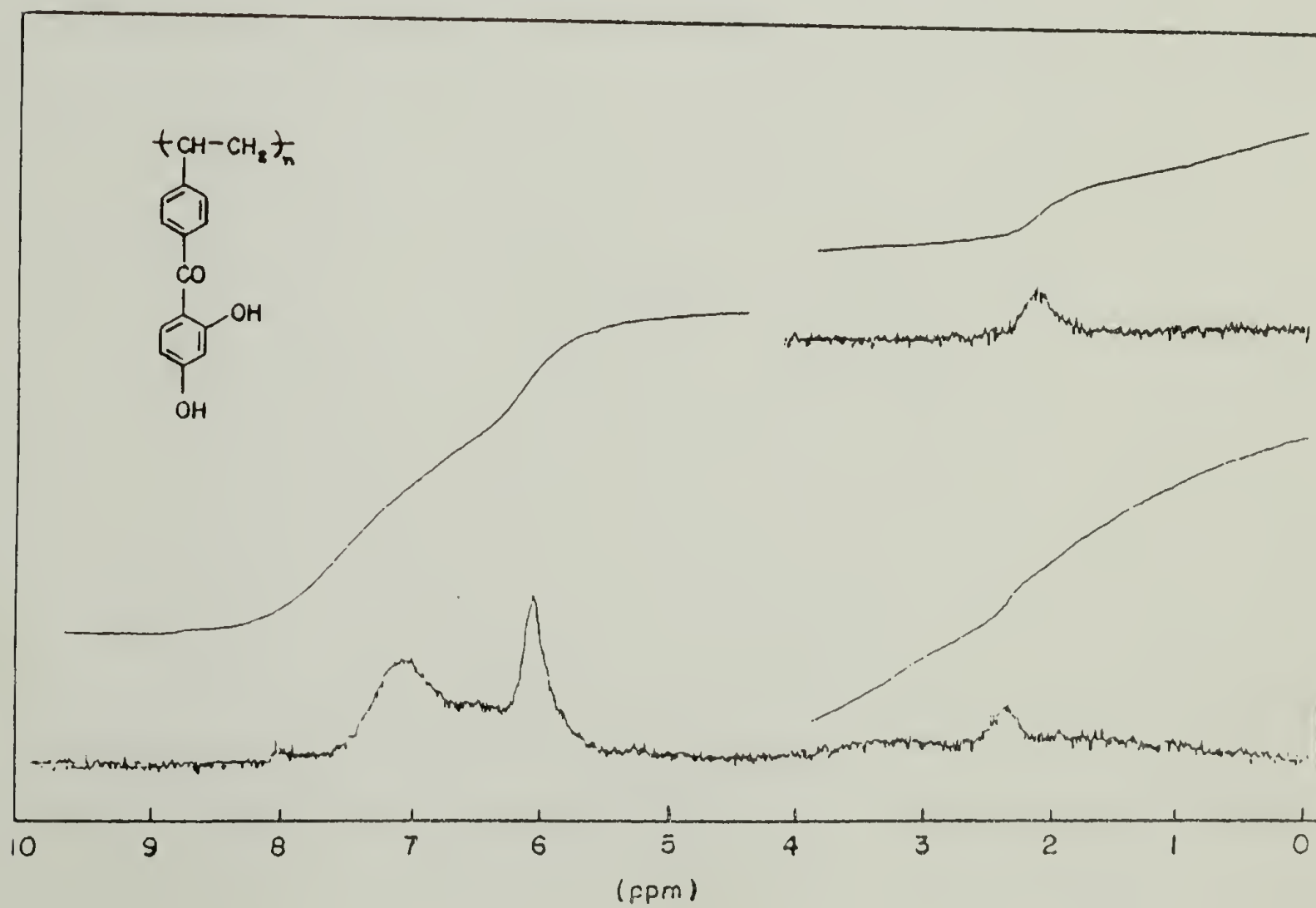
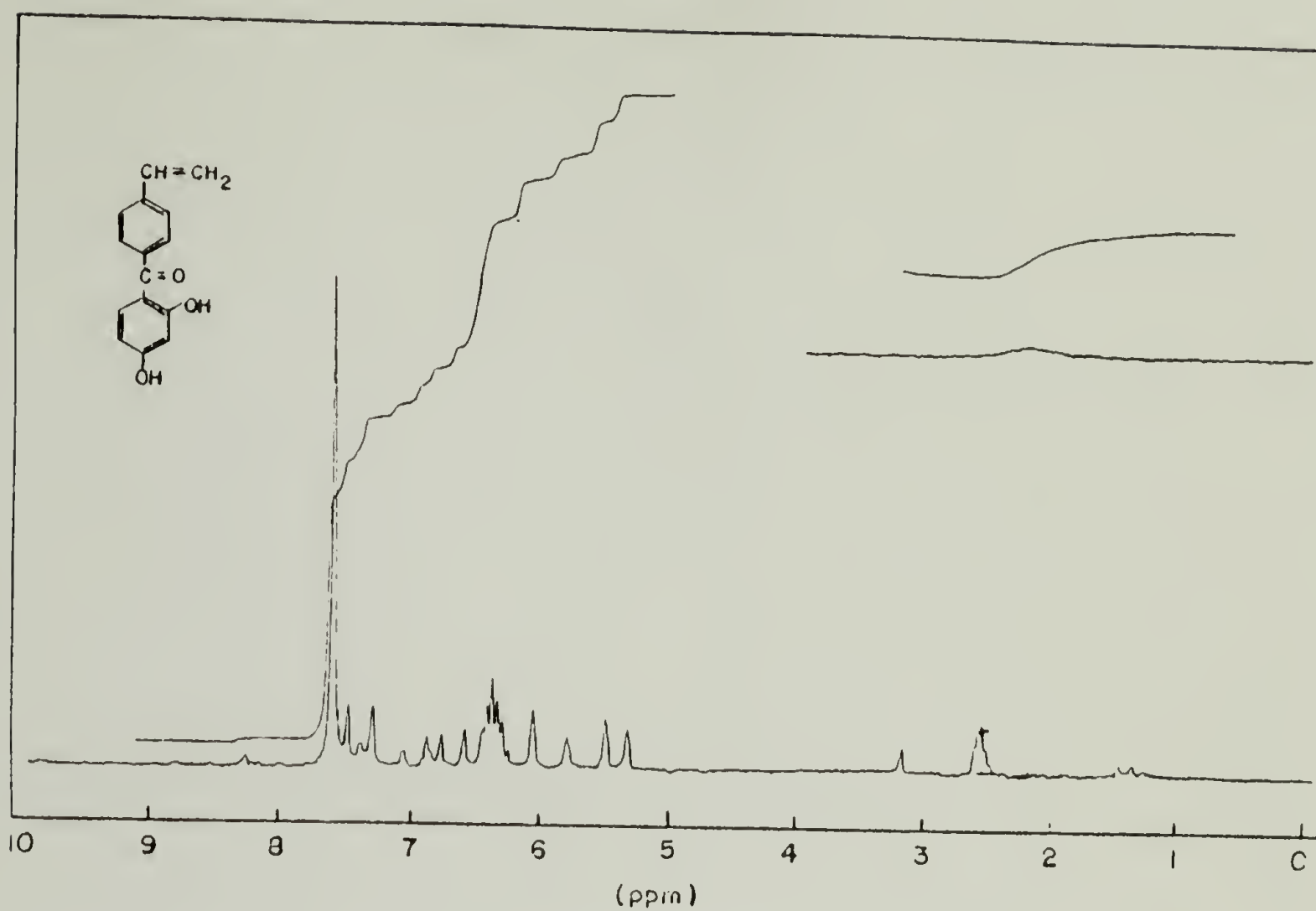


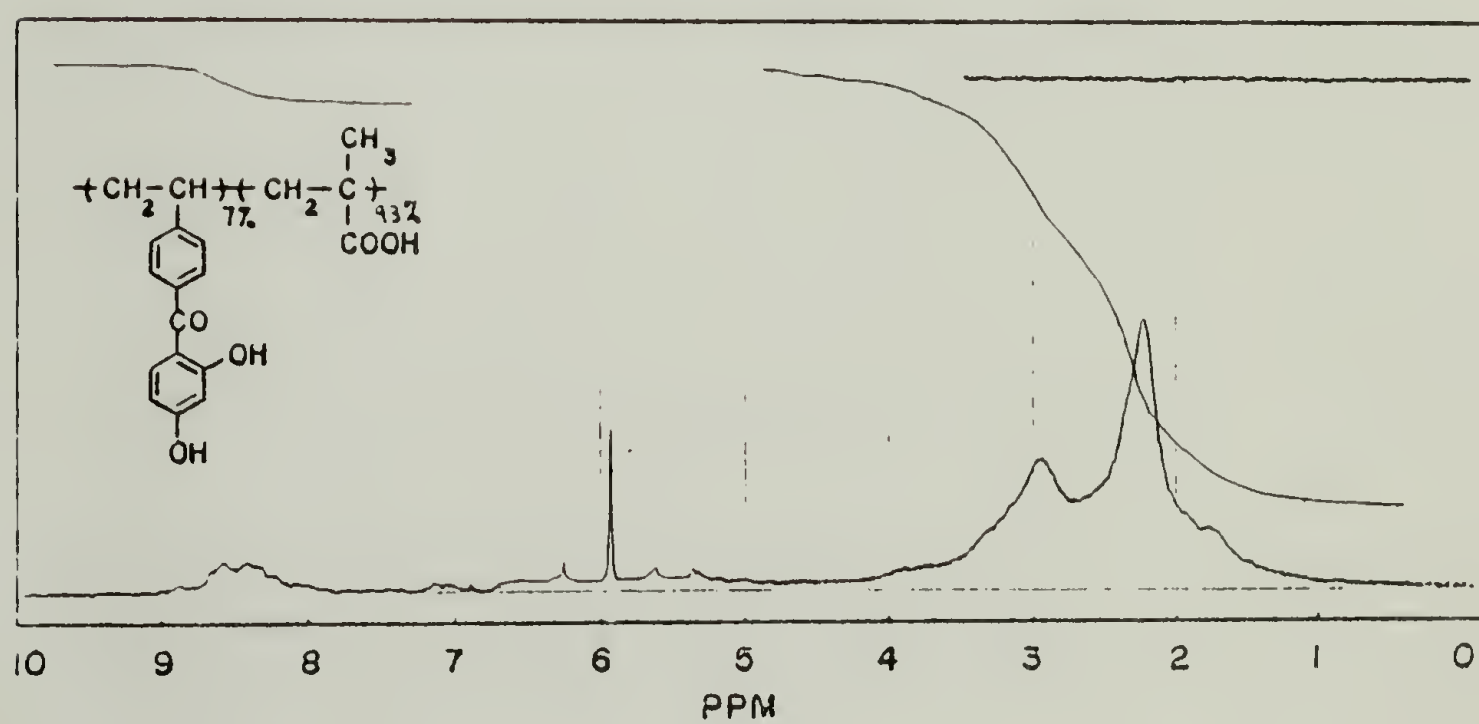
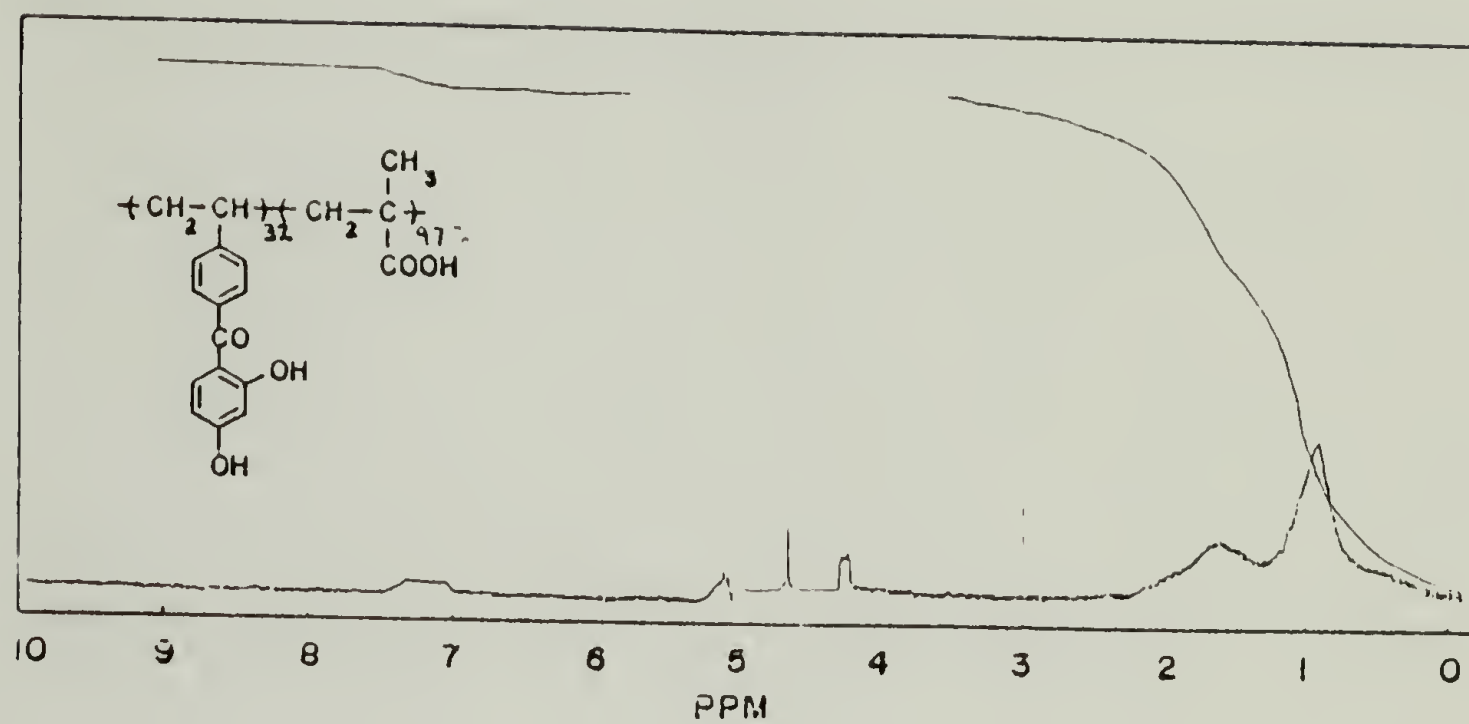


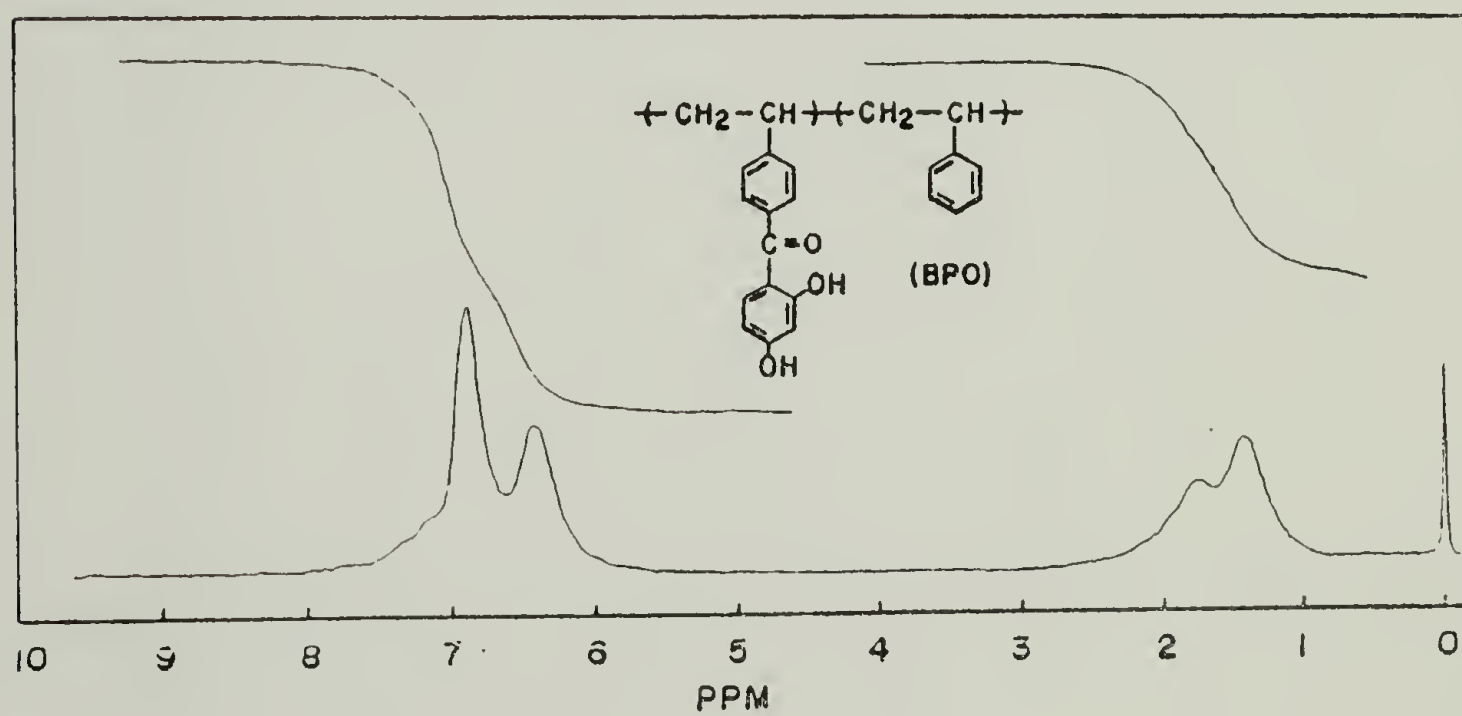
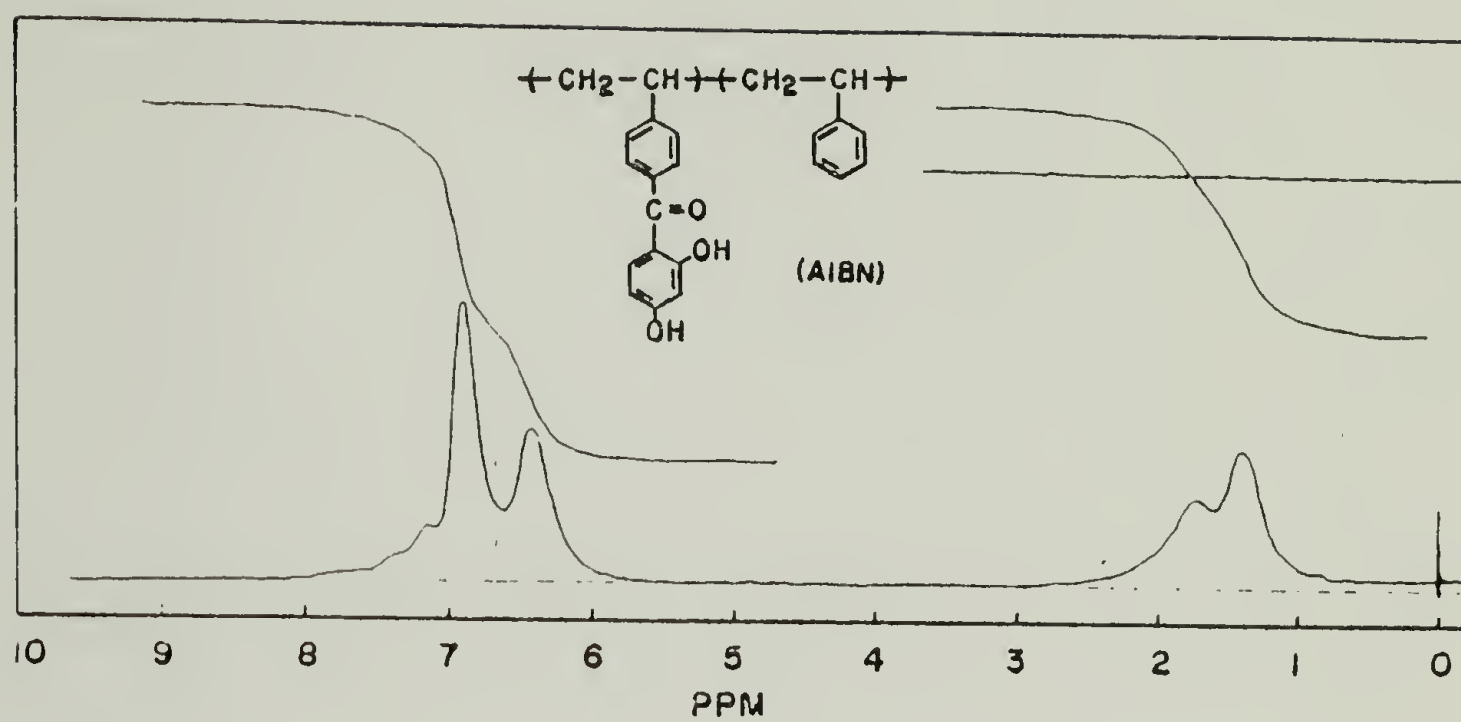


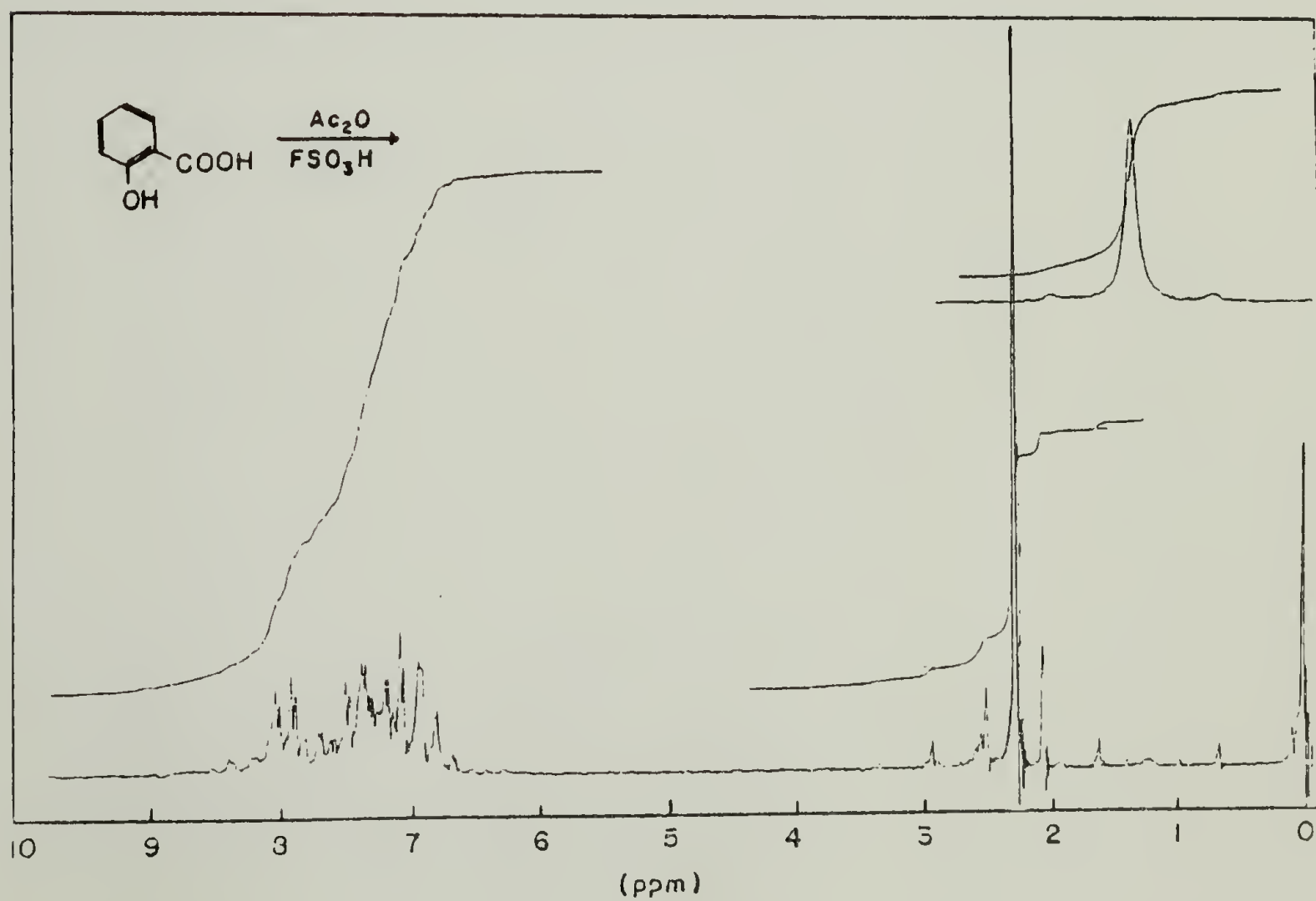
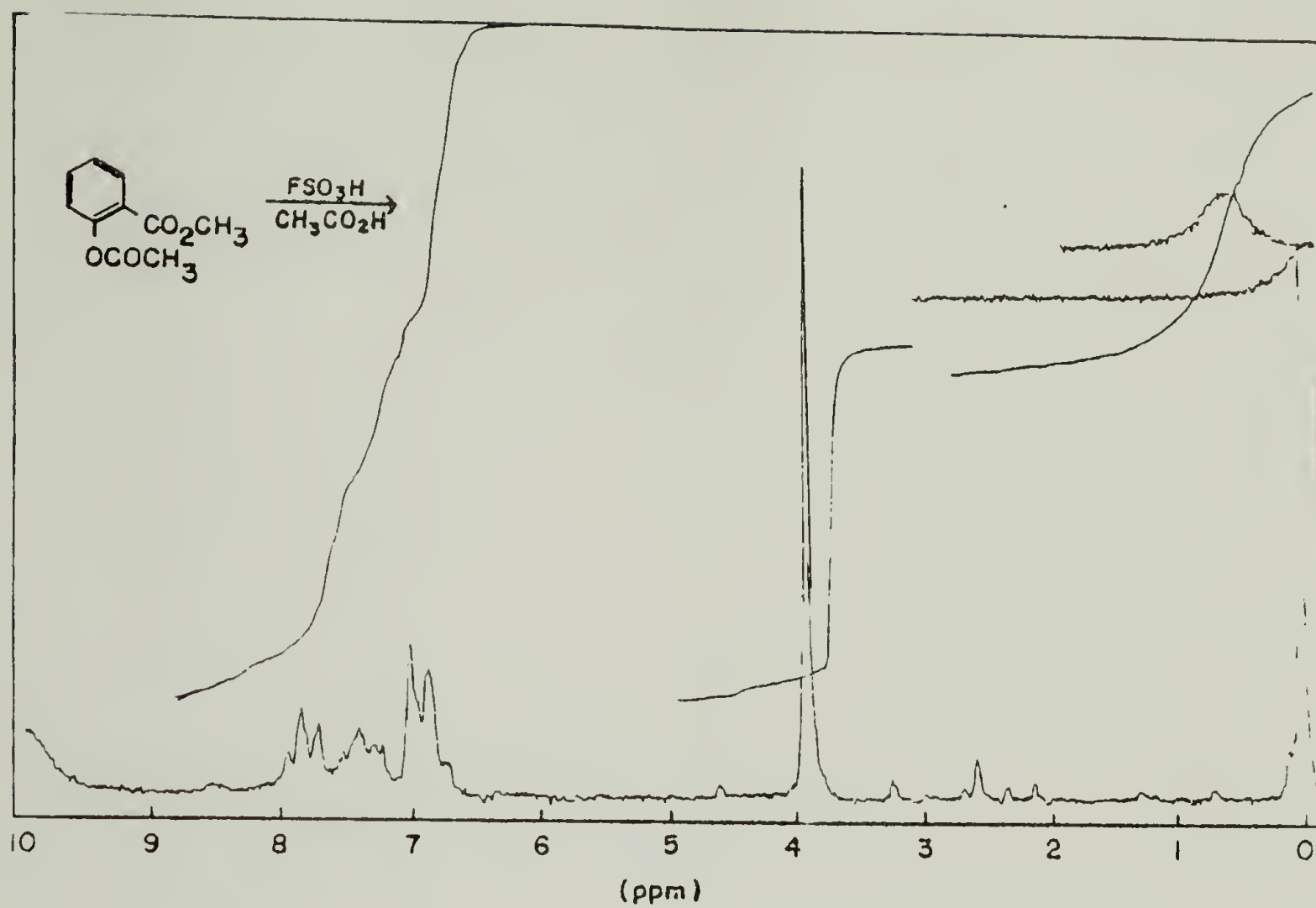


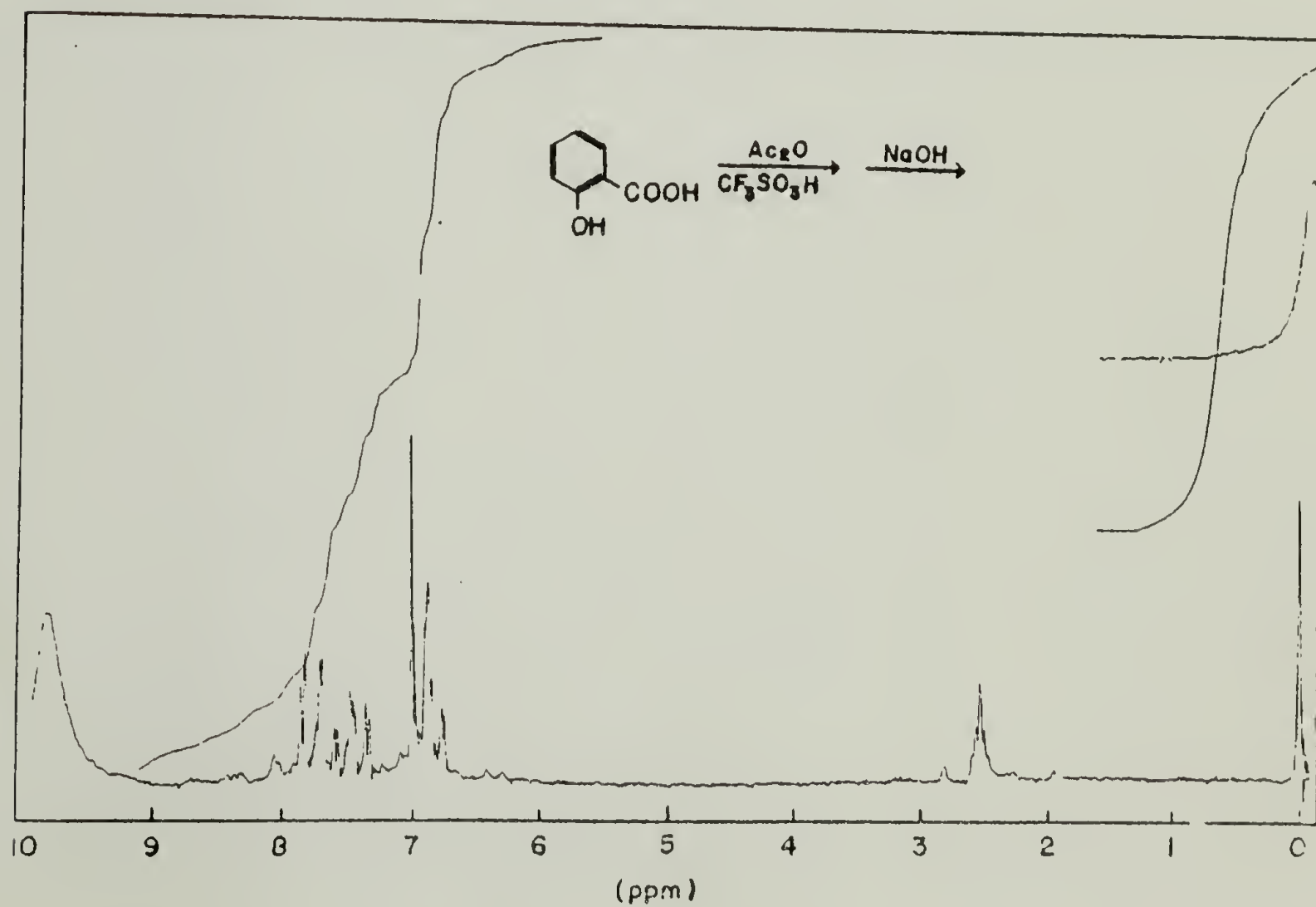
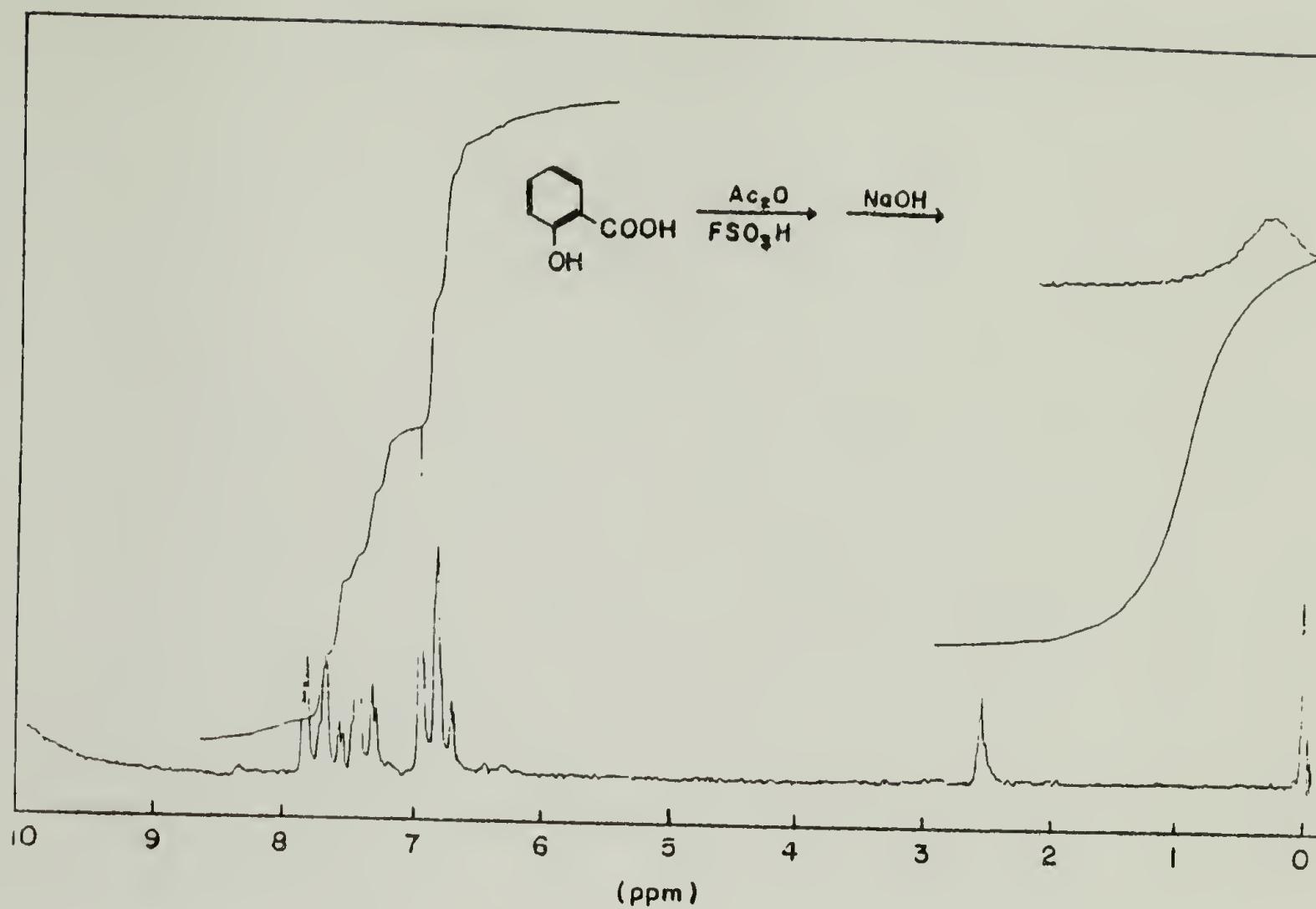












APPENDIX C

INFRARED SPECTRA

