THE SYNTHESIS OF POLYHYDROXY ARYL SULPHONES AND THEIR TANNING ACTION ON COLLAGEN IN THE PRESENCE OF ALUMINIUM SALTS

by

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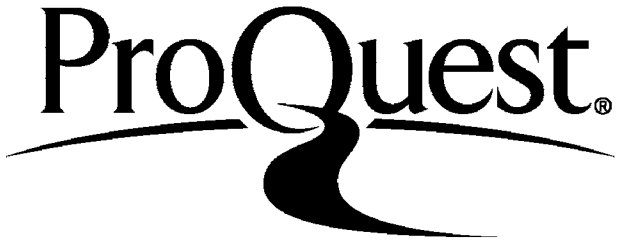

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ABSTRACT

The Synthesis of Polyhydroxy Aryl Sulphones and their Tanning Action on Collagen in the Presence of Aluminium Salts

by Stefan Tadeusz Orszulik

The action of a variety of polyphenolic compounds on collagen, when used in the presence of aluminium salts, has been investigated. This and further data obtained from deuterium exchange experiments on treated gelatine provide information on the mode of action of these tanning systems.

A variety of diaryl sulphones has been prepared by a) standard methods, b) the action of arylsulphinic acids on o-quinones, and c) the action of arylsulphinic acids on arylthalliums. ^{1}H and ^{13}C n.m.r. spectroscopy, and infrared spectroscopy were employed in the structural analysis of prepared compounds.

The proton-ligand stability constants of a number of polyphenolic compounds have been evaluated. The aluminium complexes of these polyphenolic compounds have been investigated by potentiometric and preparative methods. All constants were obtained after rigorous treatment of the experimental data by a) standard methods and b) computer techniques.

Investigations by ^{15}N n.m.r. and infrared spectroscopy indicate that glycine and β-alanine may act as bidentate ligands towards aluminium.

CONTENTS

I GENERAL INTRODUCTION

It has been a concern for many years in this country of the leather industry and its research association (B.L.M.R.A.) to improve the range and quality of coloured leathers for clothing manufacturers. The appearance of these garments depends in part upon the ability to dye satisfactorily an essentially white material in the first instance.

The raw material for the production of leather is animal skin, and the process by which putrescible animal skin is converted to the more stable product, leather, is called tanning. A fuller account of the chemistry of tanning processes is given in section IIA. One of the more important properties of leather is its resistance to denaturation by heat in the moist state. This hydrothermal denaturation is accompanied by a shrinkage of the material to less than one-third of its original size, and the temperature at which this occurs is therefore known as the shrinkage temperature (T_s). Most tanning processes involve the use of polyphenols or chromium salts, resulting in the production of fairly dark-coloured leathers. In order to obtain a white leather, various surface treatments and pigmentation processes are employed. It is important that white leather does not change colour appreciably during normal use. This colour-change is essentially a photochemical process, making fastness to light a very important property of any white leather. There is no established tanning process that results in a white, light-fast leather at the end of the tanning process and that also imparts the hydrothermal resistance to leather that is required for its fabrication and maintenance.

The search for alternative tanning agents has prompted the investigation of non-transition metal salts that have some tanning action and might be expected to give lighter-coloured leathers. Consequently

particular interest has been shown in salts of aluminium, since they are known to possess some tanning ability. However, the tanning action of aluminium salts is "reversible" since they may be readily leached out , thereby "de-tanning" the material.

Small molecular weight phenolic compounds such as catechol (1,2-dihydroxybenzene) and pyrogallol (1,2,3-trihydroxybenzene) have no tanning ability. Research carried out by the B.L.M.R.A. has shown that the tanning ability of aluminium salts is decreased by the presence of catechol, whereas the presence of pyrogallol results in a considerably improved tanning action as compared to tanning with aluminium salts alone. The methyl and ethyl esters of gallic acid (3,4,5-trihydroxy-benzoic acid) gave similar results to pyrogallol. However, the leathers produced by the use of these phenolic compounds in conjunction with aluminium salts were not white, but had initially pale colours which darkened rapidly on exposure to light.

4,4'-Dihydroxydiphenyl sulphone is used in the manufacture of certain synthetic tanning agents, the resulting leathers often being light-coloured and possessing good light-fastness properties. The presence of the sulphonyl group is thought to be responsible for imparting these colour qualities. By combining the colour properties conferred by the sulphonyl group with the tanning action exhibited by pyrogallol in the presence of aluminium salts, it was anticipated that a white, light-stable leather of good hydrothermal stability might result.

Therefore the aims of the project were two-fold, firstly, the synthesis of polyhydroxy diaryl sulphones to be used in conjunction with

aluminium salts as potential tanning agents to give white, light-fast leathers, and secondly the investigation of the behaviour of phenolic compounds in the presence of aluminium salts as tanning agents. A target shrinkage temperature was set at 110°. The synthesis of the organic compounds is discussed in section III. A study has been made of the interaction between o-phenols and aluminium ions, and this topic is discussed in section IV. ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy and infrared spectroscopy have played an important part in the characterisation of many of the synthesised compounds, and these aspects are considered in section V. During the course of the work, the possibility of using arylthalliums as intermediates in the synthesis of diaryl sulphones has been investigated. Though not directly related to the main theme of the project, such novel syntheses may be of notable importance where existing methods of synthesis are inadequate, and this subject is discussed in section VI.

II TANNING USING POLYHYDROXY COMPOUNDS IN THE PRESENCE OF ALUMINIUM SALTS

A. Introduction

Animal skins go through a number of processes prior to the tanning operation which converts them to leather. These are generally known as "pretanning" operations, and generally involve curing, soaking and unhairing. Since skins start to putrefy within about four hours of slaughtering, curing is required to preserve the skin for storage and transport. The cured skins are "soaked" in aqueous solution to restore the skins to their original condition. The unhairing operation loosens the hair, and is usually accomplished by treating the skin with an alkaline reducing medium. After the pretanning operations, the skin is known as "pelt".

Animal skin is composed mainly of water (ca. 65%) and proteinaceous materials (ca. 30%) together with some lipids, carbohydrates and mineral salts. After these pretanning operations, mainly the fibrous protein "collagen" remains. Apart from the skin, collagen also constitutes the major protein component of bone, tendon and all the other forms of connective tissue, and accounts for 25-30% by weight of all protein in mammalian body. Essentially the chemistry of the tanning processes is the chemistry of the reaction between a variety of tanning agents and the protein collagen. It is to be expected therefore that collagen has been extensively studied, and the substantial amount of information available has been compiled in several reviews.[1-4]

Chemically collagen is distinguished by an unusually high content of glycine and the imino acids proline and hydroxyproline, the presence of hydroxylysine, and notably only small amounts of aromatic

and sulphur-containing amino acids. Collagen consists of a fibrillar network of a highly ordered aggregation of stiff rod-like collagen monomers. The monomer consists of three polypeptide chains each containing approximately 1000 amino acid residues. Each chain exists as a left handed helix with a "pitch" of three amino acids. Three of these coils are twisted around one another forming a right handed triple helix, 2800 $\mathring{A}$ long and 14 $\mathring{A}$ in diameter, and possessing a molecular weight of about 300,000.

The most important consequence of the triple helical structure of the collagen molecule is that the polypeptide backbones are tightly packed so that every third position along the chains must be occupied by glycine, the smallest amino acid. This accounts for the glycine content of collagen being about one-third of the amino acid residues. The triple helix is held together by hydrogen-bonding between every third -NH- group on the backbone of one chain and every third C=O group of a neighbouring chain. The side chains of the other amino acids are directed towards the outside and are therefore available to partake in intermolecular interactions.

Initially the collagen monomers arrange themselves in a staggered array forming the fibrils in the direction of the length of the monomers. This staggering is caused by electrostatic forces. Basic and acidic groups are distributed along the collagen monomers in such a way as to result in a staggering of monomers by a quarter of their length, positive and negative charges of neighbouring monomers are aligned to stabilise the structure.

Collagen fibrils that are only stabilised by electrostatic forces are of weak tensile strength since the monomers can slip along one another, and may readily be solubilised. In living systems the fibrils "mature", the collagen molecules becoming cross-linked by covalent bonds. In contrast cross-linked collagen fibrils are insoluble and of high tensile strength. The process of cross-linking is enzymatically controlled, and results in a family of cross-links, many members of which have been isolated and identified.[5]

Observation under the electron microscope shows collagen to possess electron dense, thick regions alternating with thinner less electron dense regions. These regions are associated with polar and nonpolar amino acids respectively. Every third residue being glycine, the polar regions are associated with a distinct cluster of the polar amino acid residues lysine, arginine, glutamic acid, and aspartic acid, and it is this region that is capable of binding metal salts.[6] The presence of the more bulky polar amino acids results in an amorphous and less ordered structure, whereas the nonpolar sections, containing predominantly the compact imino acids proline and hydroxyproline, are more crystalline in character.[6] The stability of the triple helix greatly depends on these imino acids, for in general the denaturation temperature increases as the content of the imino acid residues increases.[7] The degree of hydroxylation of proline also has a significant effect, nonhydroxylated collagen having a denaturation temperature more than 15° lower than normally hydroxylated collagen.[8]

During the denaturation of collagen, the hydrogen-bonds are split and the triple helical structure becomes unstable and collapses. This results in a random structure which appears rubber-like since it is

still held together by covalent cross-links. In the case of soluble collagen, which is not appreciably cross-linked, the polypeptide chains are able to separate completely on boiling to give gelatine.

The collagen fibres of skin are already considerably stabilised by the presence of covalent cross-links. Tanning may be said to be a process by which this system of stabilisation is considerably improved upon by increasing the number of cross-links. This is achieved by reacting collagen with one or more of a variety of tanning agents. These tanning agents vary greatly in chemical composition, and can be organic or inorganic, natural of synthetic products. The basic salts of chromium, aluminium and zirconium, vegetable and synthetic tanning materials, and aldehydes are the main groups of tanning agents. Since the nonpolar, crystalline regions of collagen fibres are naturally very stable, tanning agents exert their action mainly in the polar and less stable regions. The tanning industry is a good example of technology long preceeding the application of scientific principles. However, much effort has been made in this century to try to gain an insight into the mechanism of the tanning process. This has given rise to an enormous amount of published material. Only a brief summary of the more salient points will be included here. For a more detailed introduction to the chemistry of the tanning process, the reader is referred to available published material[9,10] as well as the references given herein.

Aldehyde Tannages

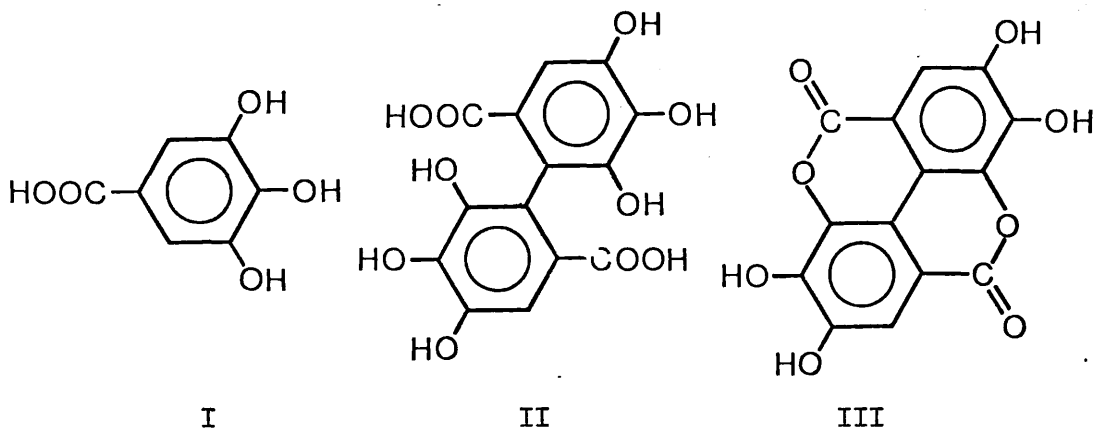
The use of formaldehyde as a tanning agent has been well established. Aldehydes play a major role in the formation of naturally occurring cross-links of collagen fibres,[5] and therefore this tanning method is unique in

that it can be said that it imitates the biosynthetic system. Formaldehyde is the most commonly used tanning agent of all the aldehydes since in general it possesses the greatest tanning ability, giving a shrinkage temperature of about 85-90°. Addition and condensation reactions of aldehydes are well known, and these types of reactions are thought to be responsible for the action of aldehyde tannages. Basic amino groups of collagen may react with formaldehyde to form methylol groups in the first place, cross-linking being achieved by further condensation reactions forming methylene and oxymethylene bridges. Imine, acid amide, guanidine, hydroxyl and peptide groups of collagen could also react with formaldehyde depending on pH, concentration, temperature and time.

Vegetable Tannages

The chemistry and tanning action of vegetable tannages have been adequately reviewed.[11-14] Vegetable tannages are a complex of polyphenolic compounds of plant origin. They occur in almost every part of the higher plants, including bark, wood, roots, leaves, fruit and pods. Vegetable tannins are not single component systems, and only polyphenolic compounds of molecular size 500-3000 have tanning ability. In aqueous solution the molecules aggregate to give an effective molecular weight of about 10,000. Vegetable tannins are generally classified under hydrolysable (pyrogallol type) and condensed (catechol type) tannins. The main distinction between these two groups arises from their action towards hydrolytic agents, particularly acids. The hydrolysable tannins have a polyester structure, and are readily hydrolysed by acids to give a sugar or related polyhydric alcohol and

a phenolic carboxylic acid. The latter is usually gallic acid (Fig. I-1,I) or hexahydroxydiphenic acid (Fig. I-1,II), and has given rise to a subdivision of the hydrolysable tannins into gallotannins and ellagitannins respectively. The hexahydroxydiphenic acid is usually isolated as its stable dilactone ellagic acid (Fig. I-1,III)



I II III

Fig. I-1

The condensed tannins, on the other hand, are more stable than the hydrolysable tannins with nuclei normally connected through -C-C- links. They are also known as flavotannins. In contrast to breaking down with acid, the condensed tannins undergo progressive polymerization yielding higher molecular weight tannins called phlobaphenes or tannin reds. Condensed tannins are composed of mixtures of products of varying degrees of polymerization of either catechin or catechin-like molecules. Polymerization of catechin, a tetrahydroxyflavanol (Fig. II-2) can also be caused by heat yielding substances of tanning potency.

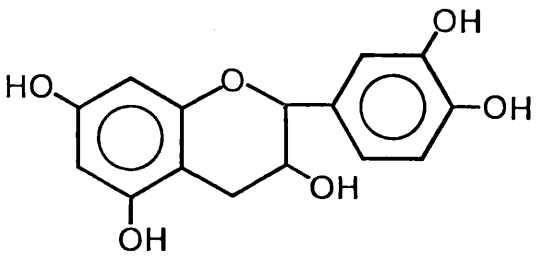


Fig. II-2

Vegetable tanned leather lacks resistance to water and heat, and in general is poor in light-fastness properties. Leather tanned with condensed tannins deteriorates on ageing, particularly in sulphur dioxide polluted atmospheres, and becomes dark, whereas leather tanned with hydrolysable tannins does have better light-fastness properties. This discolouration of tannins is caused by atmospheric and photo-oxidation inducing quinonoid formation and free radical polymerization.

Modern techniques of vegetable tanning have greatly reduced the time required for tanning. Early methods of tanning used leach liquors since extracts were not available, and the strength of these liquors was usually not greater than 5%. The tanning period using these dilute solutions was generally six months to a year. The use of tanning extracts making more concentrated liquors has reduced the tanning time to a month or two or even less.

Another very important factor in vegetable tannage is the hydrogen ion concentration. The degree of swelling of the collagen fibrils greatly depends on the pH. The polar regions, where the tanning

process is effected, are mainly responsible for the degree of swelling since at pH values other than the isoelectric point, the ionic interactions between the monomers in the polar regions are less effective. This tendency to swell makes the reactive groups of the protein more accessible to the tannins and thereby leads to an increase in fixation (uptake of tanning material). Vegetable tanning protects the molecular form of the collagen fibres by packing the morphous, polar regions of the fibrillar structure with tannins. Swelling can lead to a very rapid fixation of tannins with the exterior part of the hide which will retard or even prevent the further uptake of tannins.

Vegetable tannage involves the multipoint fixation of the hydroxyl groups present in the tannins with active groups of the collagen. Fixation of vegetable tannins is due mainly to hydrogen-bonding with nonionic sites mainly -CONH- groups of the protein backbone. E. Heidemann[15] examined the effect of vegetable tannins on collagen and gelatine by infrared spectroscopy involving deuterium exchange experiments. The data provided a measure of the degree of hydrogen-bonding involving the peptide linkages, and this was shown to be very well related to the hydrothermal stability of the protein. Polyphenolic compounds were shown to split some of the hydrogen-bonds of the protein, and then renew them. This was used to explain how large tanning molecules can penetrate into the fibril network of structured collagen. Smaller molecules form less stable hydrogen-bonds, and this indicates that hydrogen-bond stability between the peptide linkages and -OH phenolic groups increases with the size of the polyphenol and the number of hydroxyl groups per molecule.

Though it is generally agreed that vegetable tannins attach themselves to proteins mainly by hydrogen-bonding between the hydroxyl group of the tannin and the peptide linkage of the protein, the nature of this hydrogen bond is still a matter of some conjecture. K.H. Gustavson[16] has argued that the oxygen of the carbonylamino is involved with the hydroxyl groups of vegetable tannins. This view is perhaps difficult to reconcile with the findings of E. Heidemann,[15] since these involved the examination of the >NH group under deuterium exchange conditions, which according to K.H. Gustavson is not involved with the vegetable tannin.

Mineral Tannages

The most commonly used mineral tanning agents are the basic salts of chromium (chrome-tan), aluminium (alum-tan) and zirconium. Of these, chromium, usually used as the basic sulphate, holds an unrivalled position as a tanning agent since it imparts a high hydrothermal stability to leather in excess of 120°, in contrast to the other tannages (around 70-90°). There appear to be several properties of chromium that give it its high tanning ability. It is able to form stable basic salts that are soluble in water, and can coordinate in aqueous solution to form polynuclear complexes.[17] The most stable salts of chromium are the Cr^{III} octahedral complexes. Of the thousands of Cr^{III} complexes that are known, most exist in the hexacoordinate state. The simplest complex, the hexaquo ion $[Cr(H_2O)_6]^{3+}$, is a regular octahedral in aqueous solution. The formation of polynuclear complexes occurs via Cr-O-Cr links. The formation of polynuclear complexes is favoured by heat, increased concentration, increased basicity, and by time, and is

influenced by the anion present. The sulphate is generally used, since basic chromium sulphate forms polynuclear complexes most rapidly and extensively. In solution, however, these basic salts exist as species containing cationic, non-ionic and anionic complexes with charges varying from +3 to -3, and each in equilibrium with the others.

The cationic complexes appear to be responsible for the stabilization of collagen during the tanning process, reacting mainly with the free carboxylic acid groups of the protein. The main factors governing chromium fixation are temperature, concentration, pH, the nature of the anion, time and the condition of the pelt. The tanning action is brought about by the multipoint fixation of the polynuclear complexes involving complexation at the free carboxylic acid sites on the protein.

Apart from chromium salts, aluminium and zirconium salts are also used as tanning agents but to a lesser extent. The use of aluminium salts for tanning was practiced by the Romans and the Egyptians. The effectiveness of aluminium salts in tanning is reduced by their readiness to hydrolyse. This makes it difficult to form stable polynuclear basic complexes, hydrolysis resulting in the precipitation of aluminium hydroxide. In an attempt to overcome these difficulties, complexing agents such as citric acid have been used, thus enabling the formation of a basic complex. The use of various anions, such as formate, acetate, lactate, tartrate and citrate ions to prevent the precipitation of aluminium hydroxide has been studied by D. William-Wynn.[18] The fixation of aluminium depends on the pH, increasing greatly from pH 3.5 to 4.0,[19] and on the anion, decreasing in the series $SO_4^{2-} > Cl^- > NO_3^-$.[20] The addition of complexing agents

such as citrate also increases the fixation of aluminium by allowing the use of more basic tanning liquors.

The mechanism of the tanning process using aluminium salts is considered to be analogous to that involving chromium salts, in that the metal is fixed to the free carboxylic acid groups of collagen. It has been shown that when the carboxyl groups are blocked by methylation, the efficiency of alum-tanning is greatly reduced, whereas deamination has no adverse effect.[19] Since chromium salts are the stronger tanning agents, they readily remove aluminium from alum-tanned leather, whereas formaldehyde and vegetable tannins, whose fixation does not depend on the availability of carboxyl groups remove aluminium to a much lesser extent. The lower hydrothermal stability of alum-tanned leather as compared to chrome-tanned leather is attributed to the limitations in raising the pH due to precipitation difficulties, and to the weak nature of the links with the carboxyl groups of collagen. Aluminium resembles chromium in that it forms the octahedral hexaquo ion $[Al(H_2O)_6]^{3+}$ in aqueous solution, the hydroxide prepared from aqueous solution exists as an insoluble colloid, and it can form cationic, neutral and anionic complexes. Aluminium salts affect gelatine, increasing its viscosity, but differ from chromium salts in that no precipitation occurs. This suggests that chromium salts interact more strongly with gelatine than do salts of aluminium. Another difference which probably has great relevance to the difference in their tanning abilities is the stability of the carbonato complexes. In the case of chromium, the carbonato complexes that are formed on making solutions of chromium salts basic with carbonates hinder precipitation. Similarly with aluminium salts, precipitation is

hindered, but the complex is less stable since the solution soon becomes cloudy and bubbles of carbon dioxide appear. The chromium carbonato complexes are considerably more stable, being able to resist prolonged heating.

The readiness of aluminium salts to hydrolyse forming the insoluble hydroxide and thus making it difficult to form stable polynuclear basic complexes has been referred to. This important difference between aluminium and chromium salts lies in their respective hydrolysis constants. In the case of chromium, the first hydrolysis constant is much greater than the second and third, which are approximately equal, whereas the three hydrolysis constants of aluminium are about equal. Thus chromium salts form the monohydroxo-salt at a pH which is not conducive to the formation of further hydroxides, whereas the formations of the three hydroxides of aluminium occur approximately together.

Combination Tannages

Each tanning agent imparts to a leather definite characteristics and properties, some of which may be undesirable. By using two tannages in combination an improved leather can often be obtained, provided that the undesired qualities are eliminated whilst the desired qualities are retained. However, this need not always be the case, since some of the desired properties may be lost due to interaction between the tanning agents, or due to competition for specific sites on the protein. Nevertheless a compromise may often be found.
A further advantage of combination tanning is that the tanning process

is often speeded up. This tanning method can involve the use of any of the usual tanning agents, the retanning of chrome-tanned leather with vegetable tannins probably being the most extensively used. Fixation of vegetable tannins is increased by chrome-pretanning, whereas the binding of chromium is lowered by a vegetable pretannage of collagen.

Of the various established methods of combination tanning, the most relevant to the present work involves the use of alum and vegetable tannages. Since the interaction between the two tanning agents often results in precipitation, the tanning operation is usually carried out in two stages. The retanning of vegetable-tanned leather with alum is an ancient practice only recently re-discovered as it had become far less important with the introduction of chrome-tannages. Solutions of basic aluminium salts form both soluble and insoluble complexes with vegetable tannins, and the hydrolysable tannins tend to form complexes more readily and of greater solubility than the condensed tannins. The first step involves the use of vegetable tannins since less stripping of tanning material occurs as compared to the retannage of alum-tanned leather. The vegetable-aluminium combination tannage has been studied with respect to hydrothermal stability, pH, and uptake of tanning materials.[21-25] In general a higher pH results in a higher shrinkage temperature, which is often greater than can be accounted for by the tanning ability of two tanning agents acting separately. Furthermore, aluminium salts are often more effective than chromium salts in retanning a vegetable-tanned leather. The hydrolysable tannins generally have more tanning action than the condensed tannins in aluminium combination tanning, imparting a shrinkage temperature to leather of around 115-125° as

compared to 85-100°. These properties of vegetable-aluminium combination tannages are considered to be due to a considerable interaction between the metal ion and the polyphenol, and accordingly this interaction for the hydrolysable tannins is different to that for the condensed tannins. C.K. Rao and Y. Nayudamina[23] have suggested that the reaction between aluminium salts and the hydrolysable tannins involves the acidic sites like the carboxyl groups of these tannins, and that aluminium fixation by collagen occurs by reaction with nonionic sites, especially the carbonylamino groups, as well as with the carboxylic acid groups of the protein. Since condensed tannins lack acid groups such as carboxylic acids, this may serve to explain the greater tanning action when hydrolysable tannins are used. The vegetable-aluminium combination tannage has been of further interest due to the colour properties of the resultant leather. Though they do not approach white, the leathers are usually light in colour, and in this respect are considered to be more acceptable than chrome-retanned vegetable-tanned leather.

The importance of the molecular weight of vegetable tannins has already been discussed. Very little work has been done on small phenolic compounds such as gallic acid, since they have been shown to possess little or no tanning action.[26,27] However, gallic acid has been shown to have tanning ability when used in the presence of aluminium salts, imparting a shrinkage temperature of 90° as compared to 60° for hide tanned with aluminium salt alone.[23]

Synthetic Tannages

Many synthesised compounds have been shown to have some tanning potential and have thus been exploited by the tanning industry. They

are usually referred to as synthetic tannins or "syntans". Many organic polyacids possess an affinity for collagen, and these are often used to produce a synthetic tanning agent. Syntans are generally sulphonated condensation products of phenols or related compounds, and formaldehyde. They are made use of mainly in pretanning and in combination with other tanning agents, sometimes for bleaching purposes. The newer synthetic tanning agents are derived from a wide variety of types of compounds, and includes polyhydroxy phenols condensed with aldehydes, amino resins such as urea and melamin resins, acrylic syntans, polyepoxides and other polymeric materials.

4,4'-Dihydroxydiphenyl sulphone has been used in the preparation of many synthetic tanning agents which have been employed in the production of white, light-fast leathers.[28-30] These colour properties are thought to be conferred by the presence of the sulphonyl group.[31] Some of the problems encountered in the manufacture of leather that is white and light-stable have been discussed by G. Toth.[32] Since zirconium, chromium and aluminium salts are light-fast tanning agents, syntans can be used in combination tannages with these minerals in the production of white leather. However the syntans can cause yellowing on exposure to light or heat, even those syntans that are free from phenolic hydroxyl groups.[32] Therefore it is often better to use the minimum quantity of the synthetic tanning agent. Practically every kind of white leather, however, is liable to discolouration to some extent and therefore the final product is inevitably a compromise of the various qualities that are required.

IIB. Results and Discussion

The increased tanning ability of polyphenolic compounds when used in the presence of basic aluminium salts has already been discussed. Before designing compounds to imitate this tanning method to produce white, light-fast leathers it is first necessary to establish which types of compounds have the greatest promise. The aim of incorporating the sulphonyl group of a polyhydroxydiaryl sulphone is to impart the required whiteness and light-fast properties to the leather on the basis of results obtained using 4,4'-dihydroxydiphenyl sulphone.[28-30] To assess the optimum disposition of the hydroxyl groups in benzene rings several polyhydroxy compounds were tested. The shrinkage temperature (T_s) was chosen as a simple yet indicative parameter of the tanning effect of the compounds. Normally, vegetable-aluminium combination tanning is carried out in two stages; the initially vegetable-tanned leather is retanned with aluminium salts. This process is only feasible if "fixation" by the first tanning agent is such that upon retanning its loss is not substantial. Polyphenolic compounds of molecular weights less than about 500 possess little or no tanning ability,[13] suggesting that they cannot form stable cross-linkages with collagen. Since all the phenolic compounds used have molecular weights below 500, the very real possibility of loss of tanning material upon attempted retanning was avoided by carrying out the tanning procedure in one step. It has already been established[19,21-25] that the tanning potential of aluminium salts increases when the pH of the tanning liquor is increased. Therefore as basic conditions as possible were used whilst avoiding

precipitation of tanning material. In these tanning experiments the aluminium salt used was "Lutan B", a commercial product recommended by B.L.M.R.A. since higher shrinkage temperatures are often obtained than when the sulphate is used.[31] It is described as a 65% basic aluminium chloride, i.e. its formula is approximately $AlCl(OH)_2$, and it is made soluble in water due to the presence of complexing agents. The tanning procedure was carried out as described in VIII A,1, "Small Scale Tanning Experiments" and light-fastness was determined by the procedure described in VIII A,4, "Light-fastness". A scale of 1-6 for light-fastness is used, 6 being the most light stable. A reading of 4 is considered acceptable[31] and therefore represents the minimum target figure. The results and conditions are shown in Table II,1.

Table II,1 The Tanning Properties of some Polyhydroxy Compounds in the Presence of Basic Aluminium Chloride (Lutan B)

	pH	T_s °C	Colour	Light-fastness
Untanned Pelt	-	59	White	6
Basic Aluminium Chloride only	3.8	75	White	6
1,2-Dihydroxybenzene (catechol)	4.5	71	Green	3
1,2,3-Trihydroxybenzene (pyrogallol)	4.8	98	Brown	5
1,3,5-Trihydroxybenzene	3.9	72	Beige	3
Ethyl 2,3-dihydroxybenzoate	3.9	75	Beige	4
Ethyl 3,4-dihydroxybenzoate	4.0	62	Beige	3
Ethyl 2,3,4-trihydroxybenzoate	4.0	71	Grey	3
Ethyl 2,4,6-trihydroxybenzoate	3.8	72	Beige	4
Ethyl 3,4,5-trihydroxybenzoate	4.2	100	Grey	2

These results cannot be fully correlated since standard conditions with respect to pH were not used. On the basis that the highest shrinkage temperature is obtained when as basic as possible conditions are used without loss of tanning material due to precipitation, the results represent the optimum value of shrinkage temperature in each case. Furthermore, a full correlation of the light-fastness is not possible, since it is difficult to recognise the fading chracteristics of a sample that is already considerably darkened. Thus the light-fastness test cannot be considered to be exacting, and only when dealing with samples of the same shade of colour is it possible to make rigorous comparisons.

Certain general conclusions, however, can be drawn from the results shown in Table II,1. If the presence of a polyhydroxy compound does not impart any additional tanning effect and at the same time does not interfere with the tanning action of the aluminium salt, a shrinkage temperature of around 75° is expected.

The use of solutions of higher pH is limited by the formation of a precipitate. Nevertheless, Table II,1 indicates that the presence of the polyphenolic compound often hinders the formation of a precipitate and thus allows a solution of higher basicity to be used. This effect is similar to that already discussed in which complexing agents such as citrate and tartrate are used to inhibit the precipitation of aluminium hydroxide. Though the pH of tanning is recognised to be an important factor in tanning, the results shown in Table II,1 cannot be explained solely in terms of the increased basicity

of the tanning solutions. The presence of catechol allows a solution of higher pH to be used, but does not give a corresponding rise in the shrinkage temperature, rather the reverse.

It is observed that for the di- and trihydroxy compounds where the hydroxyl groups do not occupy adjacent positions, the presence of the organic compound does not result in a higher shrinkage temperature, rather the shrinkage temperature in most of these cases has been adversely effected. Furthermore, when the carbethoxy group is present, only the 3,4,5-disposition of hydroxyl groups results in a higher shrinkage temperature. Of the two compounds that have shown tanning ability in the presence of basic aluminium chloride, only pyrogallol has the required light-fastness properties with a value of 5. However, since the sample becomes considerably darkened during tanning, this figure may be misleading.

Since the organic compounds in Table II,1 do not possess any tanning action themselves, the tanning ability of pyrogallol and ethyl 3,4,5-trihydroxybenzoate, when used in the presence of basic aluminium chloride is probably due to an interaction between the organic compound and the aluminium salt rather than the two reagents acting independently. However the possibility that the action of one of the reagents is such that it enables the binding of the other reagent onto a site on the protein that was previously unavailable must remain.

Comparing pyrogallol to catechol, it is apparent that though both interact with the aluminium salt in that they inhibit the precipitation of aluminium hydroxide, the effects on shrinkage temperatures indicate that in the case of pyrogallol, this interaction enables the formation of cross-links within the protein fibrillar network in a way that is

not possible for catechol. The additional hydroxyl group of pyrogallol clearly has an important function in the tanning process and this may be due to its interaction with the aluminium salt or the collagen fibres, or perhaps both. Thus pyrogallol may interact with the aluminium salt in a way that is not possible for catechol, though it has already been noted that pyrogallol and catechol do interact with the aluminium salt in a similar manner in that they each inhibit the precipitation of aluminium hydroxide. Alternatively, there is the possibility that the additional hydroxyl group of pyrogallol participates in the formation of the cross-linkages by a direct interaction with collagen. It seems likely that such an interaction could be similar to that occurring between collagen and the hydroxyl groups of vegetable tannins.

With the trihydroxybenzoates, only the 3,4,5- and not the 2,3,4- disposition of hydroxyl groups results in a higher shrinkage temperature. The similarity in the values of the shrinkage temperatures for pyrogallol and ethyl-3,4,5-trihydroxybenzoate suggests that the hydroxyl group in position 2- of ethyl 2,3,4-trihydroxybenzoate may be inhibited from participating in the tanning process. It seems likely that this could be rationalised in terms of steric considerations.

On the basis of the information obtained from these results, and with a view that the colour properties required may be satisfied by the presence of a sulphonyl group, it is apparent that perhaps a diaryl sulphone with hydroxyl groups in positions 3,4 and 5 in each ring might combine the necessary structural features. However, since

3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone proved difficult to synthesise, the potential use of other polyhydroxydiphenyl sulphones was first tested using three more accessible diaryl sulphones, a tetra- and two hexahydroxy compounds. The conditions and results of the tanning experiments for these compounds are shown in Table II,2.

Table II,2 The Tanning Properties of some Polyhydroxydiaryl Sulphones in the Presence of Basic Aluminium Chloride (Lutan B)

	pH	T_s °C	Colour	Light fastness
3,3', 4,4'-tetrahydroxy-diphenyl sulphone	3.3	101	Pale pink	1
2,2', 3,3', 4,4'-hexa-hydroxydiphenyl sulphone	3.4	98	Pale pink	1
2,3,3',4, 4',5'-hexa-hydroxydiphenyl sulphone	3.4	104	Pale pink	1

The pH values given in Table II,2 show that here the presence of a polyhydroxydiphenyl sulphone does not hinder the precipitation of aluminium hydroxide, and moreover that precipitation occurs at an even lower pH value compared to the case in which only the aluminium salt is used. Therefore the interaction between these organic compounds and the aluminium salt causes insoluble matter to be formed more readily upon addition of base.

Despite the increased limitations of the pH for tanning, these compounds are shown to have tanning ability when used in the presence of aluminium salt, giving shrinkage temperatures around 100°. Catechol and ethyl-3,4-dihydroxybenzoate shown in Table II,1 can be considered analogues of 3,3', 4,4'-tetrahydroxydiphenyl sulphone, but they have no tanning action in the presence of the aluminium salt. However, when considering compounds that have an additional hydroxyl group they can possess tanning ability, as exemplified by pyrogallol and ethyl 3,4,5-trihydroxybenzoate respectively. It seems therefore, that when considering a 3,4-dihydroxyaryl system, the function of an additional hydroxyl group, specifically in position 5-, in increasing its tanning ability in the presence of the aluminium salt may also be satisfied by incorporation of another aromatic ring containing hydroxyl groups. The relative performances of the tetrahydroxy compound and 2,2', 3,3', 4,4'-hexahydroxyldiphenyl sulphone indicate that the hydroxyl groups on position 2 and 2' confer no beneficial influence on the tanning process, a similar finding to that obtained for the ethyl benzoates. Since 2,3,3',4,4',5'-hexahydroxydiphenyl sulphone has present a 3,4,5-disposition of hydroxyl groups, it is expected to exert the best tanning performance with respect to shrinkage temperature of the compounds shown in Table II,2, and this is indeed the case. However, the difference in the shrinkage temperature as compared to those obtained for the other sulphones is only small, and thus it appears that the substantial advantage of a 3,4,5-disposition of hydroxyl groups exhibited by the ethyl benzoates is to a large degree annulled in these polyhydroxy diaryl systems. This is in agreement with the considerations outlined above regarding the performance of 3,3',4,4'-tetrahydroxydiphenyl sulphone.

The view that the required colour and light-fastness properties could be satisfied by using compounds containing the sulphone group has only been partly justified, as the results in Table II,2 show. In terms of the colour of the product at the end of tanning, a more acceptable result has been obtained, the leather in all cases being slightly pink. The light-fastness results are however considerably below the minimum required value of 4, the three compounds giving a value of only 1.

All results from tanning experiments presented so far have been obtained using a standard tanning procedure described in VII A,1, "Small Scale Tanning Experiments". A series of experiments was carried out to see if the standard tanning experiment gave the optimum results in respect of the shrinkage temperature, colour and light-fastness for the compounds. 3,3',4,4'-Tetrahydroxydiphenyl sulphone was selected for this study and the conditions and results of these experiments are shown in Tables II, 3, 4 and 5. Only conditions that differ from those of the standard tanning experiment are given, and since more exacting comparisons are to be made, the pH of the solutions was ascertained and no longer made dependent upon the onset of precipitation.

Table II,3 indicates that over the range of quantities studied, the shrinkage temperature is adversely effected by a lack of the tetrahydroxy compound. The advantage of using larger amounts reaches a maximum, the use of even larger quantities not resulting in corresponding rises in the shrinkage temperature. Also, Table II,3 shows that within the scope of the experiments the colour and light-

fastness properties observed are not perceptably dependent on the quantity of the organic compound used.

Table II,3 Tanning Experiments using varying quantities of 3,3', 4,4'-Tetrahydroxydiphenyl Sulphone in the Presence of Basic Aluminium Chloride (Lutan B)

3,3', 4,4'-Tetrahydroxy-diphenyl Sulphone. mmol.	pH	T_s °C	Colour	Light-fastness
0.709	3.1	82	Pale pink	1
1.21	3.1	94	Pale pink	1
1.77	3.1	98	Pale pink	1
2.66	3.1	98	Pale pink	1

Table II,4 The Tanning Properties of 3,3', 4,4'-Tetrahydroxydiphenyl Sulphone in the Presence of Basic Aluminium Chloride (Lutan B) at various values of pH

3,3', 4,4'-Tetrahydroxy-diphenyl Sulphone. mmol.	pH	T_s °C	Colour	Light-fastness
1.77	3.0	94	Pale pink	1
1.77	3.1	98	Pale pink	1
1.77	3.3	101	Pale pink	1
1.77	3.4*	102	Pale pink	1

* a precipitate was present at this pH.

Table II,5 The Tanning Properties of 3,3', 4,4'-Tetrahydroxydiphenyl Sulphone in the Presence of Basic Aluminium Chloride (Lutan B) at various values of pH

3,3', 4,4'-Tetrahydroxy-diphenyl Sulphone. mmol.	pH	T_s °C	Colour	Light-fastness
2.66	3.1	98	Pale pink	1
2.66	3.3	99	Pale pink	1
2.66	3.4*	99	Pale pink	1

* a precipitate was present at this pH.

Tables II,4 and 5 show the effect of pH, in each case a different concentration of the tetrahydroxy compound being used. It can be seen that an increase in pH results in a higher shrinkage temperature, and that this increase in shrinkage temperature is limited, or nearly so, by the point at which precipitation begins to occur. It should be noted, however, that the results with respect to shrinkage temperature are higher in Table II,4 than the corresponding values in Table II,5, indicating that an increase in the quantity of the organic compound can have a detrimental effect, an observation that is not revealed in Table II,3. The colour and light-fastness properties contained in Tables II,4 and 5 have remained unaffected over the range of pH employed. Therefore it can be generally concluded from Tables II,3,4 and 5 that the standard tanning procedure gives the optimum conditions, or nearly so, with respect to shrinkage temperature, and that deviations from those conditions, such as those indicated in Tables II,3, 4 and 5, are not expected to result in a perceptible change in the colour or light-fastness of the product.

Consequently, the tanning potential of 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone was tested using the standard tanning procedure, the conditions and results being contained in Table II,6.

Table II,6 The Tanning Properties of 3,3', 4,4', 5,5'-Hexahydroxydiphenyl Sulphone on the Presence of Aluminium Salts

	pH	T_s °C	Colour	Light fastness
Basic aluminium chloride (Lutan B)	3.3	108	Pale pink	1
Aluminium Sulphate	3.4	105	White	1

It was found that the use of aluminium sulphate, though resulting in a slight decrease in shrinkage temperature as compared to using the basic chloride, gave a white product. However, the use of the sulphate did not improve the light-fastness property, and it is the poor light-fastness property obtained in this case that is regarded as its greatest failing. Nevertheless 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone was considered to be the most promising compound to achieve the required result for the reasons that have been fully discussed. These considerations have been justified in several respects. The use of polyhydroxydiphenyl sulphones has resulted in a light-coloured leather as exemplified by the compounds and results included in Tables II,2 and 6. Furthermore, Table II,6 shows that a white colour is possible. As expected, 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone gave the best result with respect to shrinkage temperature of the polyhydroxydiphenyl sulphones tested, though the target value of 110° was not

quite achieved. The presence of the sulphonyl group did not however impart to the resultant leather a reasonable degree of light-fastness, and this property was not perceptively susceptible to various changes in tanning conditions as shown in Tables II, 3, 4 and 5.

Since pyrogallol has tanning potency in the presence of an aluminium salt, whereas catechol does not, it has already been suggested that this may be due in part at least to the additional hydroxyl group of pyrogallol acting in a similar manner to the hydroxyls of the vegetable tannins, viz. hydrogen-bonding with -NH-CO- groups of the polypeptide chains. E. Heidemann and S.R. Srinivasan[16] investigated deuterium exchange properties by means of infrared spectroscopy in order to study hydrogen-bonding of phenolic compounds with soluble collagen and also with gelatine. They showed that stability of hydrogen-bonding between the peptide and hydroxyl groups increases with the size of the polyphenol and with the number of hydroxyl groups per molecule, and this was paralleled by a corresponding increase in shrinkage temperature. Thus the increased tanning ability of pyrogallol and the polyhydroxydiphenyl sulphones in the presence of aluminium salt, as compared to catechol, ought perhaps to be explained by similar considerations. Therefore the method used by E. Heidemann and S.R. Srinivasan was employed to investigate the action of catechol, pyrogallol and 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone on gelatine in the absence and presence of aluminium sulphate. This method involves placing a gelatine film in an atmosphere of deuterium oxide and observing the appearance of the amide -ND- deformation mode at about 1450 cm^{-1} relative to the amide -CO- stretching mode at about 1650 cm^{-1}, which remains approximately

constant throughout the experiment. The relationship after a period of time (T) gives a value of the exchange ratio (E.R.) defined by the expression

$$E.R. = \left(\frac{A_{II}}{A_I}\right)_{t=T} - \left(\frac{A_{II}}{A_I}\right)_{t=0} \qquad (II,1)$$

where A_I and A_{II} are the absorbances at 1650 cm^{-1} and 1450 cm^{-1} respectively. The readings obtained from a sample exposed to a water vapour atmosphere do not alter with time, and therefore are used to obtain the value at $t=0$, which refers to the ratio of the absorbances before any exchange has occurred. Since the exchange ratio is the relative absorbance of two different groups, it is not a value of the ratio of amide hydrogens exchanged, but is proportional to it. Fig. II-3 shows the infrared spectra of a film of gelatin before and after deuteration, and reveals that the absorption band at 1560 due to -NH- deformation decreases and the band at 1450 cm^{-1} increased upon deuteration.

The effect of hydrogen-bonding is detected by the extent and rate of exchange of deuterium for hydrogen. In general, the rate of exchange is rapid at first resulting in a fast increase in the value of E.R., and after about 1 hr rises only slowly. Thus the value of E.R. after 2 hr gives a relative indication of the proportion of amide hydrogens readily available for exchange and thus not involved to any appreciable extent in hydrogen-bonding. The initial rate of exchange is also dependent on the proportion of amide hydrogens available for exchange,

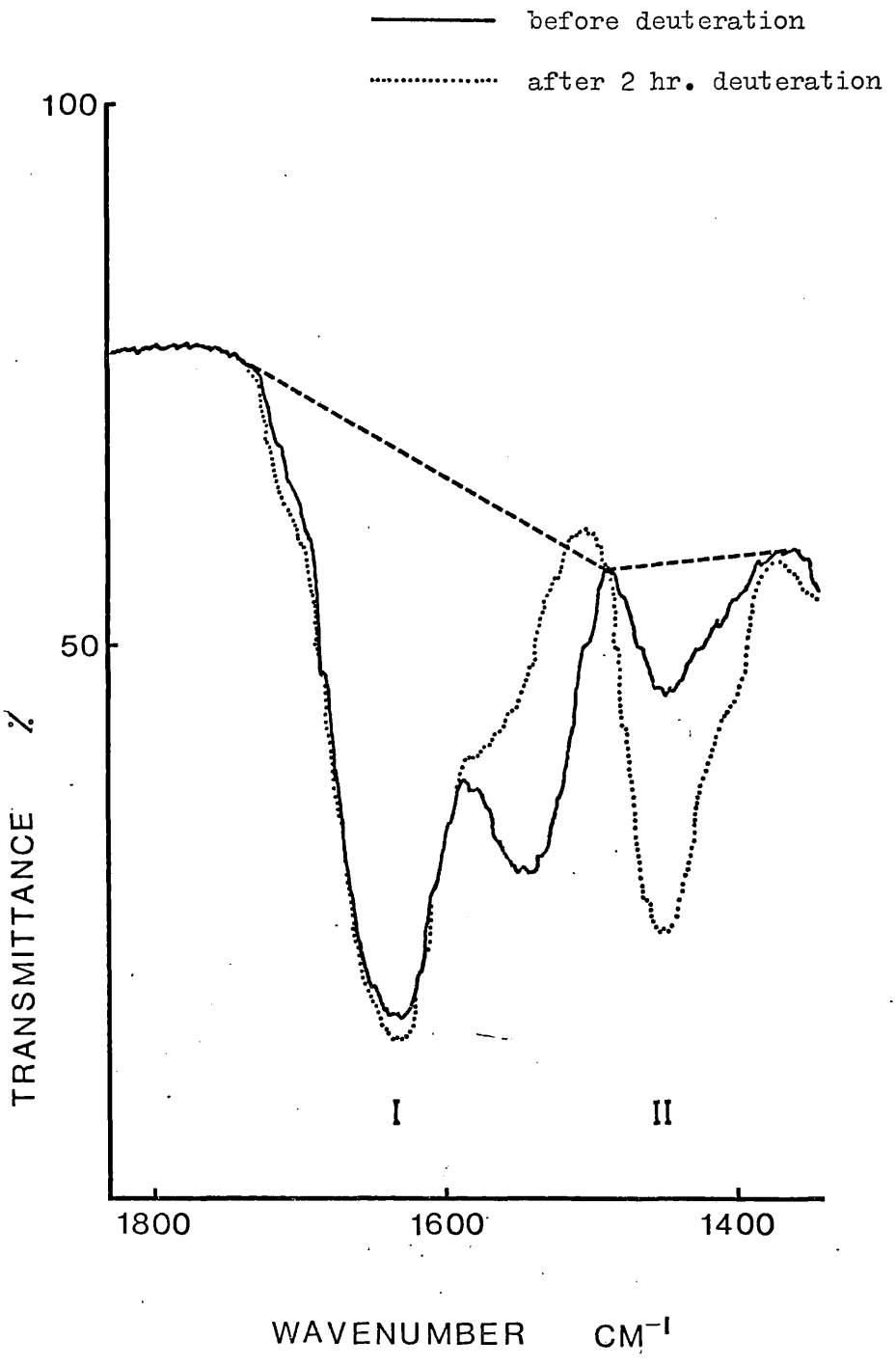


Fig. II-3. Infrared spectrum of gelatine before and after deuteration

but can be influenced by the presence of unstable hydrogen-bonding. Thus the involvement of the amide group in unstable hydrogen-bonding, though it will have only a small effect on the E.R. value after 2 hr, will result in a slower initial rate of exchange since the hydrogens are less readily exchangeable.

The deuterium exchange experiments are meaningful to the extent that the imitation of the tanning process is involved, but it should be noted that there are several important differences. The main difference is that gelatin is used, though it can be regarded as a good model of collagen, since it is essentially a less ordered form of collagen. The pH is known to be important in the tanning process, yet in these experiments it is not possible to control the pH. This is because the technique involves the formation of a gelatine film by evaporation, and the pH cannot be controlled during the drying process.

The results of these deuterium exchange experiments involving the use of catechol, pyrogallol, and 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone can be seen in Figs. II-4,5, and 6 respectively. Gelatine has an E.R. value of about 0.42 after 2 hr and when aluminium sulphate is present a similar figure is obtained, through the initial rate of exchange is slightly increased. This suggests that the extent of hydrogen-bonding is lowered, and may be due in part at least to hydrolysis of the aluminium salt giving a more acidic solution, rather than a direct interaction of the amide groups with the aluminium salt. Certainly the tanning action of the aluminium salt cannot be explained by this type

of interaction, since with respect to hydrogen-bonding involving the amide groups, a less ordered structure appears to have resulted.

Catechol and pyrogallol in the absence of the aluminium salt act differently towards gelatin, catechol resulting in a generally lower E.R. values whereas pyrogallol increases the E.R. values as compared to gelatine alone. Therefore it seems that catechol binds to the protein by forming hydrogen-bond linkages with the amide groups, whereas pyrogallol, though it may or may not similarly form linkages with the protein, overall more hydrogen-bonds are broken than are reformed. In both these cases, however, the changes in the E.R. values have been small, and therefore the interactions must be correspondingly small. E. Heidemann and S.R. Srinivasan found that hydrogen-bond stability between peptide and hydroxyl groups of phenolic compound increased with the size of the phenol and the number of hydroxyl group on each molecule, as judged by their E.R. values. Therefore the behaviours of pyrogallol and catechol are in opposition to those general findings. It is apparent, however, that since catechol has no tanning ability, its interaction with the protein does not result in the formation of any significant cross-linkages. The use of 3,3', 4,4', 5,5'-hexahydroxydiphenyl sulphone in the absence of the aluminium salts results in lower values of E.R., and the change in E.R. values relative to gelatin alone is appreciably greater than that found in the case of pyrogallol and of catechol. This shows that the diaryl sulphone forms more stable hydrogen-bonds with the amide groups of the protein than for pyrogallol or catechol, and this is to be expected from the findings of E. Heidemann and S.R. Srinivasan.

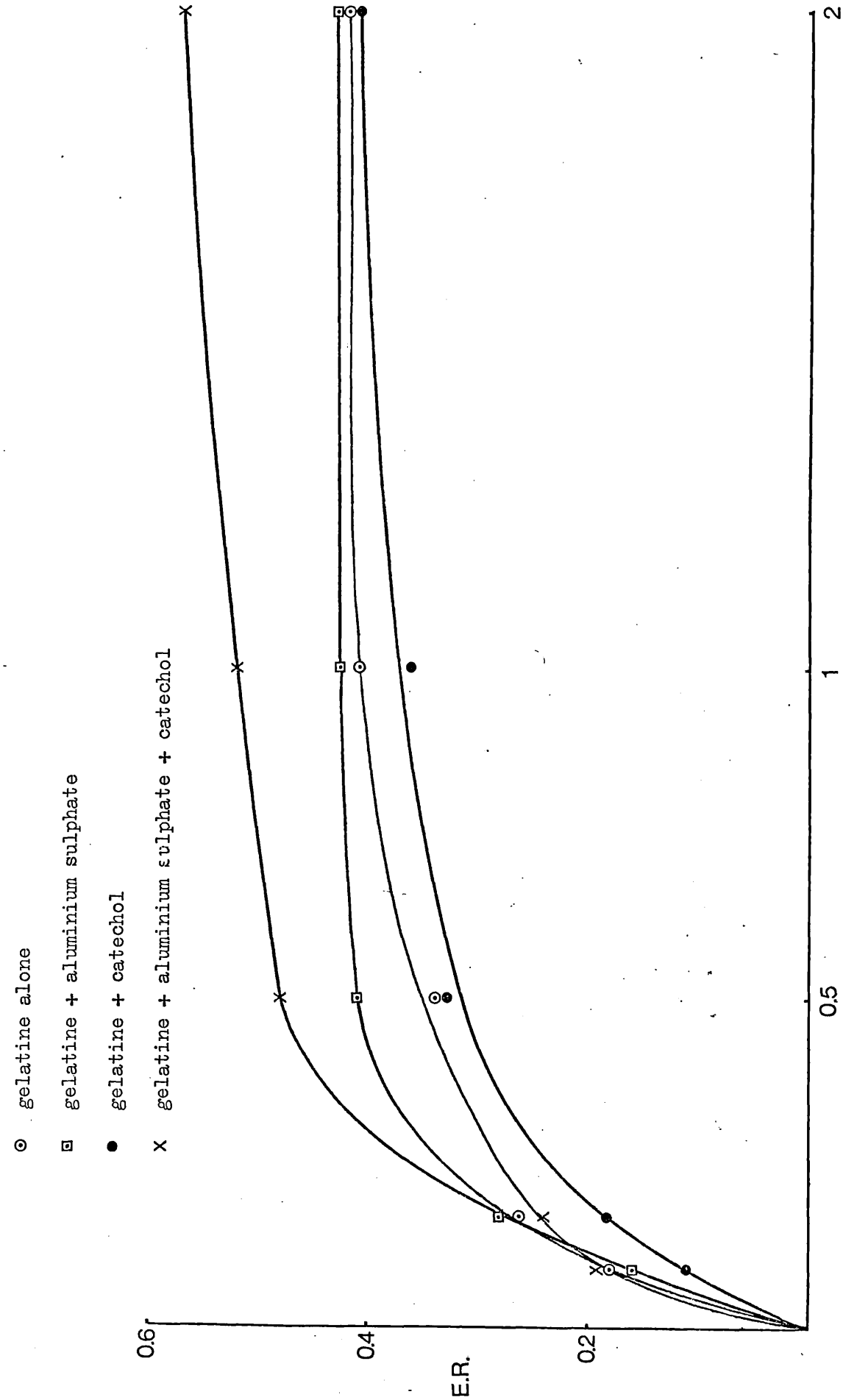


Fig. II-4. Deuterium exchange of gelatine in the absence and presence of aluminium sulphate and catechol.

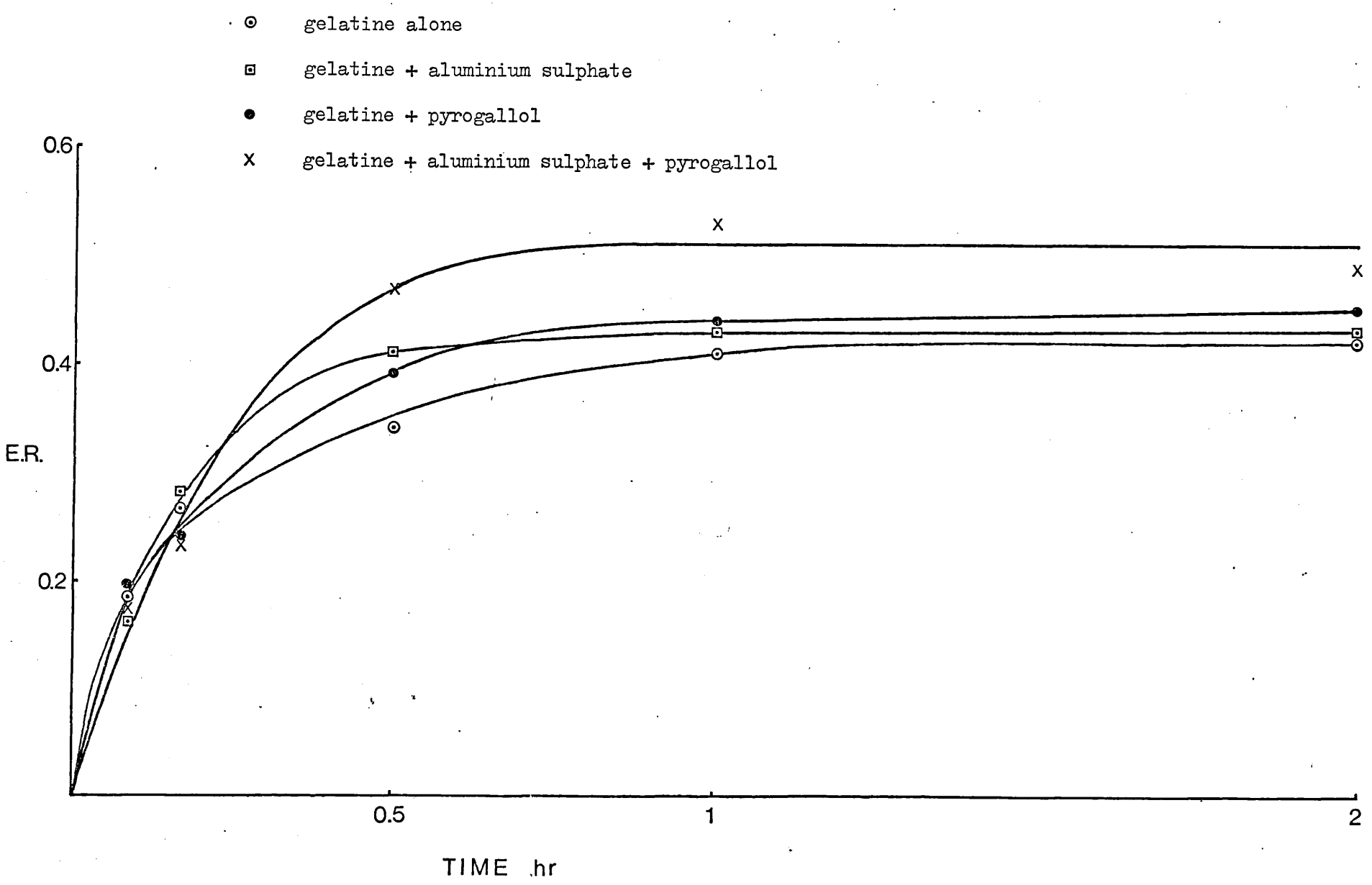


Fig. II-5. Deuterium exchange of gelatine in the absence and presence of aluminium sulphate and pyrogallol.

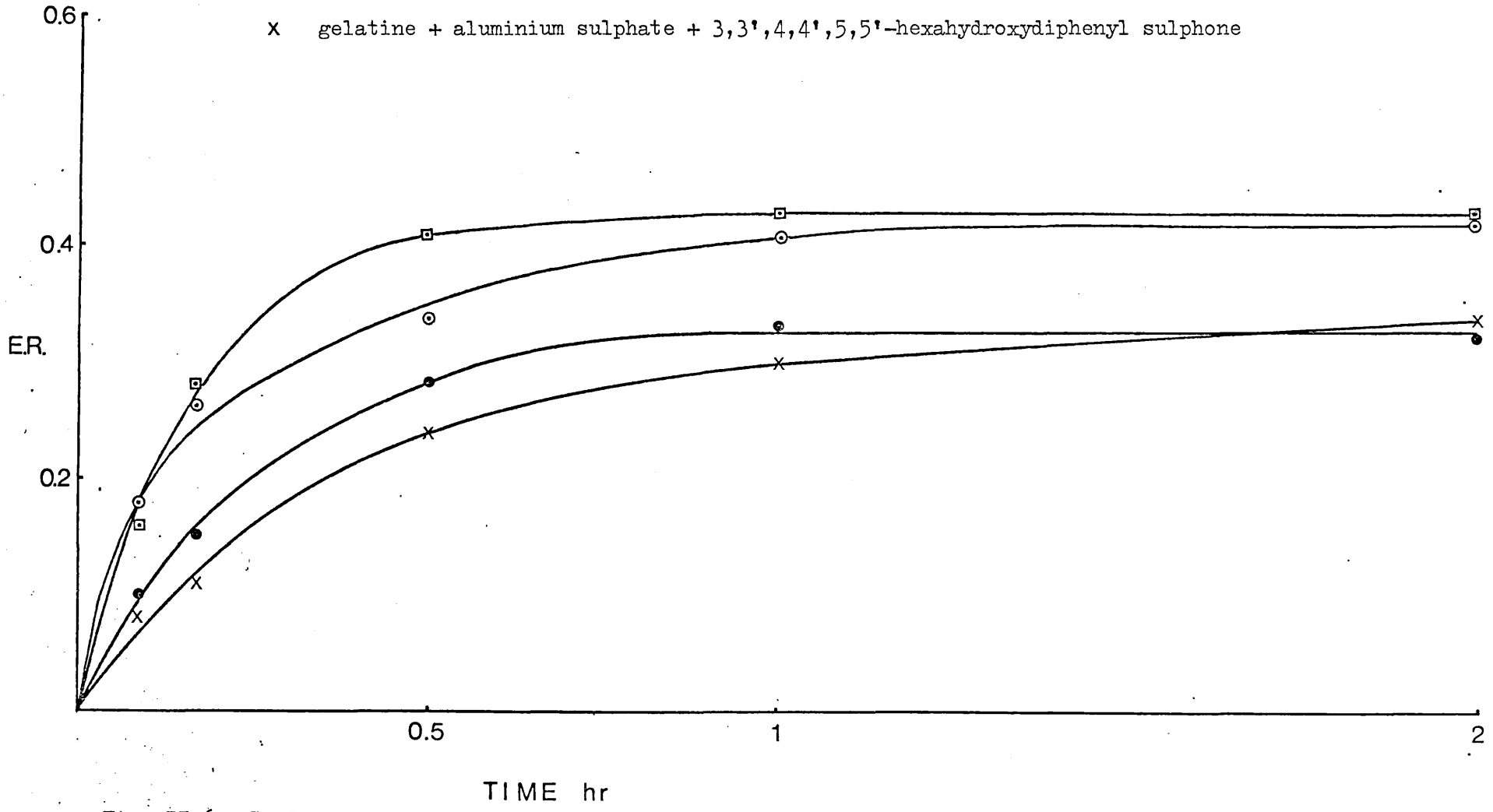


Fig. II-6. Deuterium exchange of gelatine in the absence and presence of aluminium sulphate and 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone.

In the presence of aluminium sulphate, catechol and pyrogallol both result in higher E.R. values after 2 hr as compared to gelatine alone, indicating that hydrogen-bonds involving amide groups have been broken, and this is particularly so with catechol. However, in the case of pyrogallol, and perhaps also catechol to a smaller extent, the initial rate of exchange has decreased, whereas if more hydrogens are readily exchangeable, an increase would be expected. This can be accounted for by the presence of unstable hydrogen-bonds, and though a proportion of the amide groups have lost their stable hydrogen-bond interaction, a higher proportion are involved in these unstable interactions. 3,3', 4,4', 5,5'-Hexahydroxydiphenyl sulphone has acted similarly in the presence and absence of the aluminium salt, the E.R. values obtained in both cases being lower than those for gelatine alone. This indicates that the use of the diaryl sulphone, whether the aluminium salt is present or not, results in a greater involvement of the amide groups in hydrogen-bonding, but the slower initial rate when the aluminium salt is present indicates that in this case additional unstable hydrogen-bonds are involved.

Thus in general it can be concluded that catechol, though it appears to bind onto the amide sites of the protein by hydrogen-bonding to some extent, when aluminium sulphate is present this interaction is prohibited or at least greatly inhibited, and a less ordered structure results. Likewise a less ordered structure results when pyrogallol is used in the presence of aluminium sulphate, but hydrogen-bonding of tanning material onto the amide sites appears to take place to some extent, and though it cannot provide a full explanation, this may be connected in part to the tanning ability of pyrogallol under these conditions. This is particularly

so since in the case of catechol, which has no tanning ability in the presence of aluminium salt, this type of interaction does not appear to occur, or at most occurs to a lesser extent. However, the use of the diaryl sulphone, whether the aluminium salt is present or not, results in a greater involvement of the amide groups in hydrogen-bonding and in the presence of aluminium sulphate, additional, unstable hydrogen-bonds are involved. It appears therefore that in this case hydrogen-bonding of the tanning agent onto the amide sites on the protein can contribute to the higher shrinkage temperature.

The role of the free carboxylic acid groups of collagen as binding sites in alum-tanning was investigated by treating pelt with aluminium isopropoxide in isopropanol. The free carboxylic acid groups are expected to react readily with aluminium isopropoxide, generating aluminium-carboxylate bonds. Further repeated reaction with a dicarboxylic acid followed by treatment with aluminium isopropoxide may be expected to sequentially build up aluminium-carboxylate linkages between the free carboxylic acid groups of collagen. Fumaric and terephthalic acids were chosen since the geometry of these dibasic acids is conducive to the formation of cross-linkages. However, the low solubility of terephthalic acid, in the various suitable solvents tried, made its use impracticable. Maleic and phthalic acids, whose conformations render the formation of cross-linkages less likely, were also tested for comparison. The tanning procedure, described in VIII A,2, "Small Scale Tanning Experiments Using Aluminium Isopropoxide and Dibasic Acids", involves treating the pelt first with aluminium isopropoxide and then with the dibasic acid. In the case of fumaric acid, various degrees of retanning were undertaken by further

treating the sample alternately with aluminium isopropoxide and the dibasic acid. At the end of the tanning procedure, the samples were treated with water, thus allowing hydrolysis to occur. The results of these tanning experiments which are shown in Table II,7 clearly indicate that no further tanning action has been conferred by the use of the dibasic

Table II,7 Tanning with Aluminium Isopropoxide and Some Dibasic Acids

	T_s °C
a) Aluminium isopropoxide only	72
b) Sample (a) treated with phthalic acid	71
c) Sample (a) treated with maleic acid	69
d) Sample (a) treated with fumaric acid	69
e) Sample (d) treated with aluminium isopropoxide	70
f) Sample (e) treated with fumaric acid	69

acids. Though this might have been anticipated in the case of phthalic and maleic acid, the use of fumaric acid was expected to exert some additional tanning action to the extent of the stability of the aluminium-carboxylate bonds concerned. Tanning with basic aluminium salts in aqueous medium is thought to involve polynuclear complexes containing Al-O-Al bridge units. The tanning procedure using aluminium isopropoxide and fumaric acid initially prohibits the formation of these types of units, aluminium atoms being linked by salt formation via the dicarboxylic acid. Therefore the lack of any additional tanning action conferred by the use of fumaric acid may be considered to emphasise the weak nature of the aluminium-carboxylate bond, probably due to its susceptibility to hydrolysis.

III SYNTHESIS OF POLYHYDROXY DIARYL SULPHONES

A. Introduction

Sulphones are compounds containing $\geq SO_2$ group in which the sulphur atom is bonded to two carbon atoms. Thus diphenyl sulphone has the structure given in Fig. III-1.

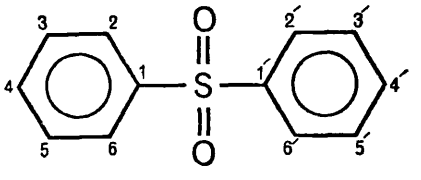


Fig. III-1

Sulphones may be readily prepared by the action of a variety of oxidizing agents on the corresponding sulphide (-S-) or sulphoxide ($\geq S{=}O$). The experimental results of various oxidative methods of synthesis have been compiled by C.M. Suter.[34] The reagents most commonly employed are potassium permanganate, chromic acid, and hydrogen peroxide. Potassium permanganate and chromic acid oxidations are usually effected in acetic acid-water mixtures. Hydrogen peroxide is used in acetic acid, and is the most recommended method since good yields are generally obtained, the final product is easily separated, and groups other than the sulphide or sulphoxide are rarely attacked. Thus hydrogen peroxide oxidations to generate sulphones may be carried out in the presence of hydroxyl groups.[35] Peroxide oxidations may be carried out in non-acidic media in the presence of catalytic amounts of molybdenum, tungsten, or vanadium salts.[36]

At low temperatures sulphoxides may be converted to sulphones in good yields with the use of N-chlorobenzotriazole.[37]

A widely used method for the preparation of aryl sulphones involves a Friedel-Crafts type reaction in which a sulphonyl halide reacts with an aromatic compound in the presence of a Lewis acid such as aluminium chloride, ferric chloride, or zinc chloride (III,1).[34,38]

$$ArH + RSO_2Cl \xrightarrow{AlCl_3} ArSO_2R + HCl \qquad (III,1)$$

Sulphonyl chlorides are most frequently used, although the bromides and fluorides also react.

The first step involves the formation of a complex between the catalyst and the sulphonyl halide (III,2).

$$RSO_2Cl + AlCl_3 \longrightarrow RSO_2Cl.AlCl_3 \qquad (III,2)$$

Subsequently the complex ionizes forming the sulphonylium ion and $AlCl_4^-$ (III,3), and the aromatic hydrocarbon is attacked by the electrophilic sulphonylium ion to give the sulphone (III,4)[39,40]

$$RSO_2Cl.AlCl_3 \rightleftharpoons RSO_2^+ + AlCl_4^- \qquad (III,3)$$

$$RSO_2^+ + AlCl_4^- + ArH \longrightarrow ArSO_2R.AlCl_3 + HCl \qquad (III,4)$$

A similar donor-acceptor complex exists between the sulphone product and aluminium chloride which is stronger than the initial complex formed with the sulphonyl chloride. For this reason at least a full equivalent of the Lewis acid is required, and in practice a slight excess is usually employed since this results in a higher rate of formation of the product.

The reactivity of a substituted aromatic sulphonyl chloride is influenced by the nature of the substituents. Electron-releasing groups para to the sulphonyl chloride group increase the rate of reaction, whereas electron-withdrawing substituents decrease the rate.

Substituents on the atomatic compound that is attacked by the sulphonylium ion exert the usual orientation effects. Thus the presence of electron-releasing groups results in predominantly para substitution. Electron-withdrawing groups deactivate the system towards electrophilic substitution, and strong deactivating groups such as nitro or nitrile prevent reaction altogether.

Sulphones are frequently produced as by-products in aromatic sulphonation reactions using sulphuric acid (III,5)[41]

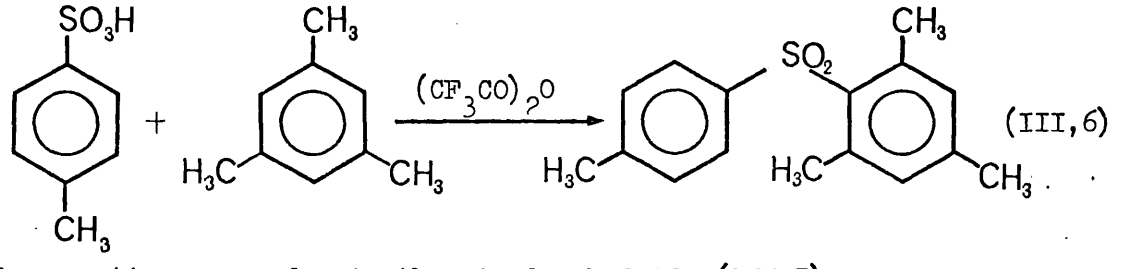
$$2ArH + H_2SO_4 \xrightarrow[(-2H_2O)]{} Ar_2SO_2 \qquad (III,5)$$

By removing the water produced in the reaction, the sulphone may be obtained as the major product. In the case of benzene, water can be removed as an azeotrope to give diphenyl sulphone.[42] When catechol is used, the water produced can be removed by distillation giving 3,3',4,4'-tetrahydroxydiphenyl sulphone in 28% yield.[43]

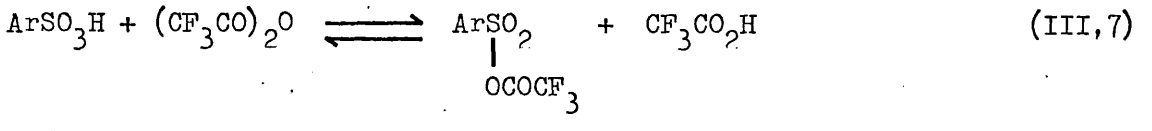
Similarly, unsymmetrical aryl sulphones may be prepared by the reaction of aryl sulphonic acid with an aromatic hydrocarbon. When the water produced in the reaction is removed by phosphorus pentoxide, this reaction is greatly enhanced.[44] B.M. Graybill[45] prepared aryl sulphones by reaction of sulphonic acids with aromatic hydrocarbons in the presence of polyphosphoric acid. The products of these reactions

conform to the same orientation rules as are observed using sulphonyl chlorides and aluminium chloride, and therefore it appears that the reaction proceeds *via* the $ArSO_2^+$ sulphonylium cation.

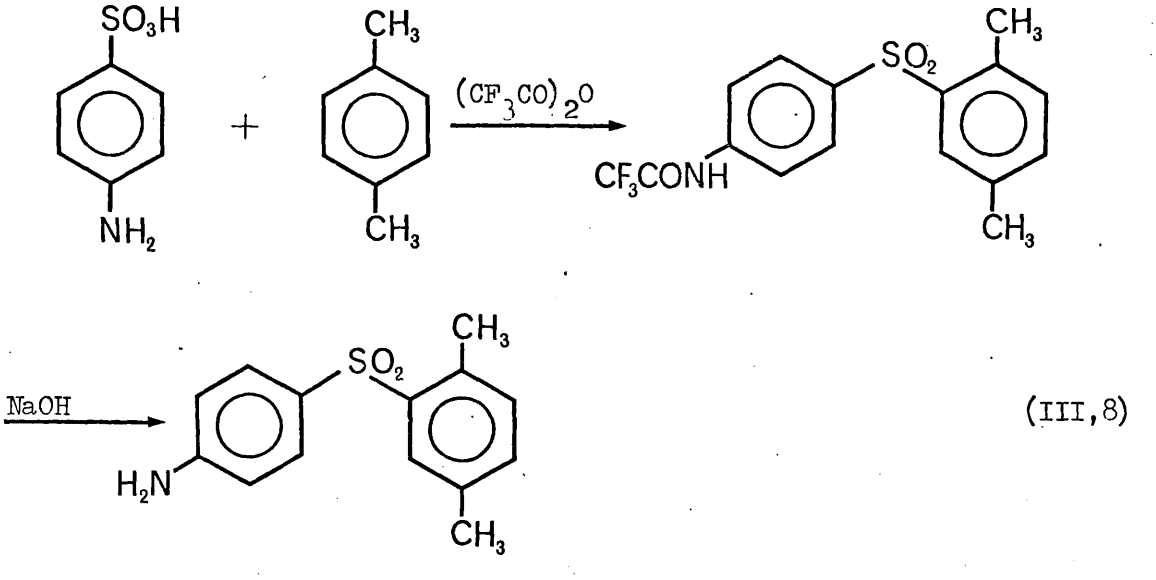
Trifluoroacetic anhydride has been shown to promote the formation of diaryl sulphones from *p*-toluenesulphonic acid with anisole or mesitylene[46] (III,6). It is proposed that



the reaction proceeds *via* the mixed anhydride (III,7).



The use of trifluoroacetic anhydride has been found to be useful in the preparation of aminoaryl sulphones[47] (III,8)



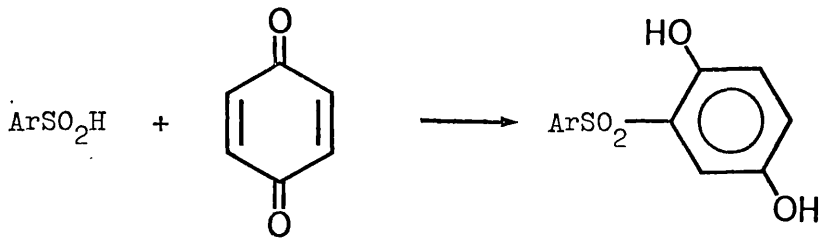
It is often more convenient to use sulphonic acids, rather than sulphonyl chlorides in the preparation of sulphones since sulphonic acids are generally more readily available. The preparation of aryl sulphonic acids and sulphonyl chlorides has been well documented.[34] The most convenient methods involve electrophilic attack on aromatic substrates, the products being subject to the orientation effects of the substituents. Where these effects are such that an electrophilic method is not applicable, other methods may be employed to generate the sulphonyl chloride or the sulphonic acid. Aromatic sulphur-compounds may be prepared from the corresponding primary amine *via* the aromatic diazo-compound.[48] A sulphonyl chloride may be obtained directly by reacting the diazonium salt with sulphur dioxide in glacial acetic acid in the presence of cuprous chloride[49] (III, 9)

$$ArN_2^+Cl^- + SO_2 \xrightarrow{CuCl} ArSO_2Cl + N_2 \qquad \text{(III, 9)}$$

Aromatic sulphonates may react with aryl halogen compound that are activated towards nucleophilic attack.[50-52] Aryl halides containing one or more nitro groups *ortho* or *para* to the halogen are sufficiently activated to give good yields of sulphones (III,10)

$$ArSO_2K + \text{(2-bromo-1-nitrobenzene)} \longrightarrow ArSO_2\text{(2-nitrophenyl)} \qquad \text{(III,10)}$$

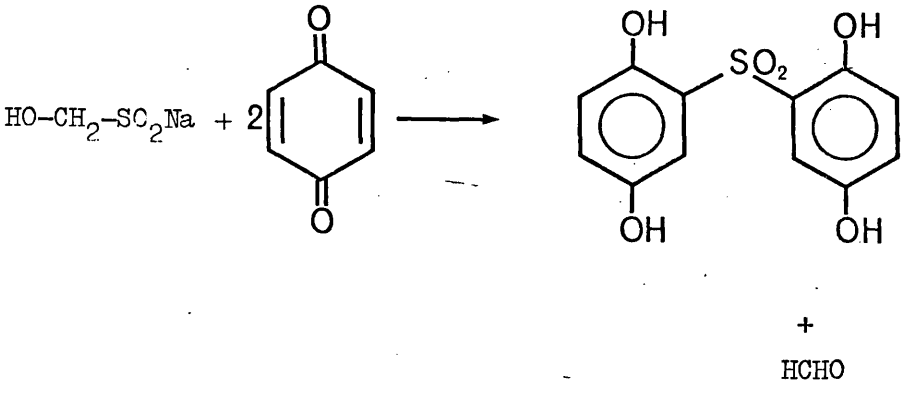
The reaction between aromatic sulphinic acids and benzoquinones may also yield sulphones, in this case dihydroxy-diaryl sulphones[53,54] (III,11). Y. Ogata[55] carried out a kinetic study of this reaction and



(III,11)

found that the rate of addition of substituted benzenesulphinic acids to p-benzoquinone can be well correlated with the Hammett σ-values. The reaction between benzenesulphinic acid and o-benzoquinone results in the formation of 3,4-dihydroxydiphenyl sulphone.[56,57] Synthetic and thermal reactions of o-benzoquinones have been reviewed by W.M. Horspool.[57]

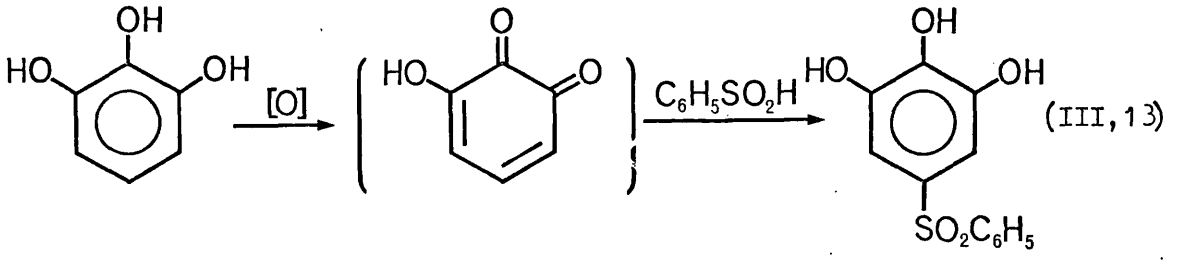
A closely related reaction is that between p-benzoquinone and sodium formaldehyde sulphoxylate. The product from this reaction is the tetrahydroxydiphenyl sulphone[58] (III,12). When o-benzoquinone is



(III,12)

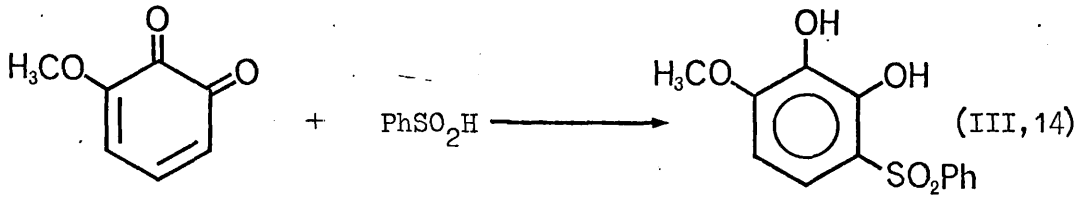
used, generated in situ by oxidation of catechol with potassium ferricyanide under alkaline conditions, the product of the reaction is 3,3',4,4'-tetrahydroxydiphenyl sulphone.[58]

Chromic acid oxidation of pyrogallol in the presence of benzenesulphinic acid results in the formation of a trihydroxydiphenyl sulphone.[56] L. Horner[59] showed that the hydroxyl groups are in the 3,4,5-disposition (III,13). However, when 3-methoxy o-benzoquinone



(III,13)

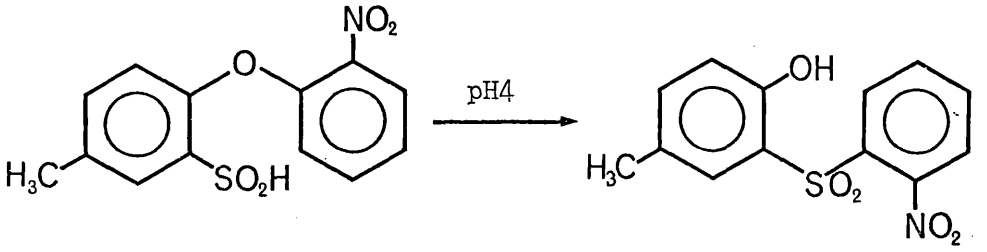
reacts with benzenesulphinic acid substitution occurs in the 6-position to give 1,2-dihydroxy-3-methoxydiphenyl sulphone[59] (III,14). The difference



(III,14)

in the behaviours of 3-hydroxy o-benzoquinone and 3-methoxy o-benzoquinone towards benzenesulphinic acid is not understood.[59]

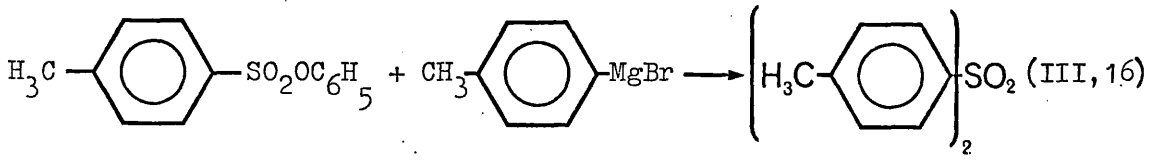
Diaryl ethers which have a sulphinate group in the ortho position of one ring and an electron-withdrawing substituent in the other ring may rearrange to give a diaryl sulphone [60] (III,15). This intramolecular



(III,15)

nucleophilic aromatic substitution involves the replacement of an electronegative bridge attached to an aromatic carbon by the conjugate base of an acidic center situated beyond the bridge on the molecule. This may be regarded as the reverse of a Smiles rearrangement, in which reaction III,15 proceeds in the opposite direction under basic conditions.[61] For the formation of the sulphone in III,15, a buffered solution is required such that the sulphinic acid is ionized but not the phenolic product.

Sulphones may be prepared by reactions of sulphonic acid derivatives with organometallic reagents. Sulphonate esters react with Grignard reagents to produce sulphones[62] (III,16).



(III,16)

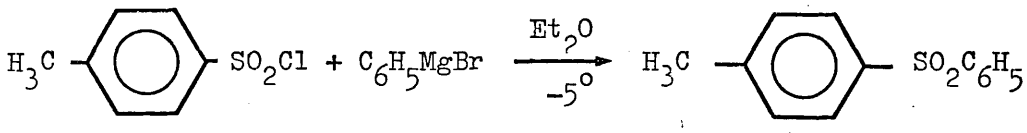
This method may be employed for the preparation of both alkyl and aryl sulphones where other substituents are unreactive towards Grignard reagents. However, since aryl Grignards give in general considerably better yields than the aliphatic reagents, this method is used mainly to produce diaryl and aryl alkyl sulphones.[62]

Sulphonyl halides also interact with Grignard reagents. H. Gilman and R.E. Fothergill[63] found that reactions III,17 and III,18 occur

$$ArSO_2Cl + PhMgBr \longrightarrow ArSO_2Ph \text{ and } MgBrCl \qquad (III,17)$$

$$ArSO_2Cl + PhMgBr \longrightarrow ArSO_2MgBr + PhCl \qquad (III,18)$$

at low temperatures. These findings were confirmed and further investigated by H. Burton and W.A. Davy,[64] who showed that besides the formation of other sulphur compounds such as sulphides and sulphoxides, a mixture of aryl sulphones may be obtained (III,19)



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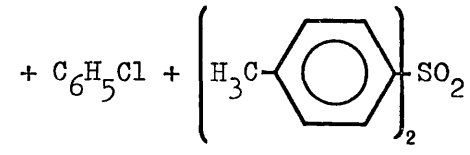
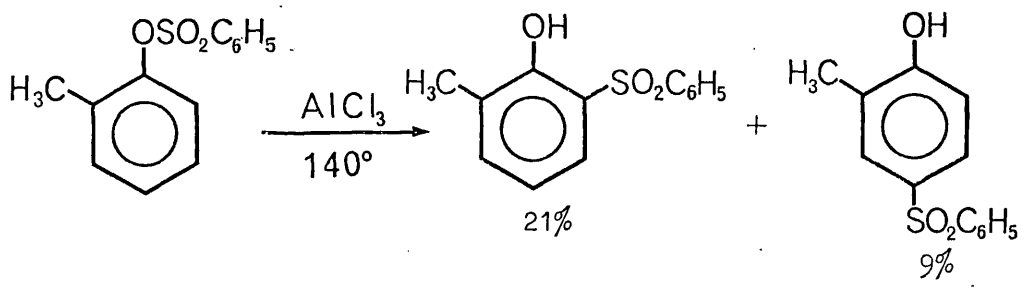


11% 11% (III,19)

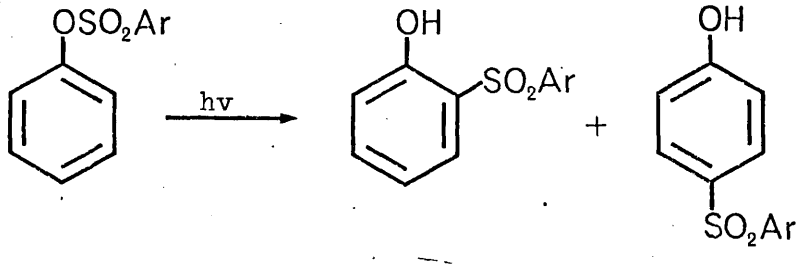
Sulphonyl halides have been shown to yield sulphones on reacting with organocadmium,[65] organomercury,[66] or organolithium compounds.[67,68] The sulphonyl fluorides give higher yields of sulphones than the chlorides when treated with either an organolithium or Grignard reagent.[67]

In the presence of a Lewis acid, aryl sulphonates rearrange to hydroxyaryl sulphones (III,20).[69] This reaction is a modified Fries



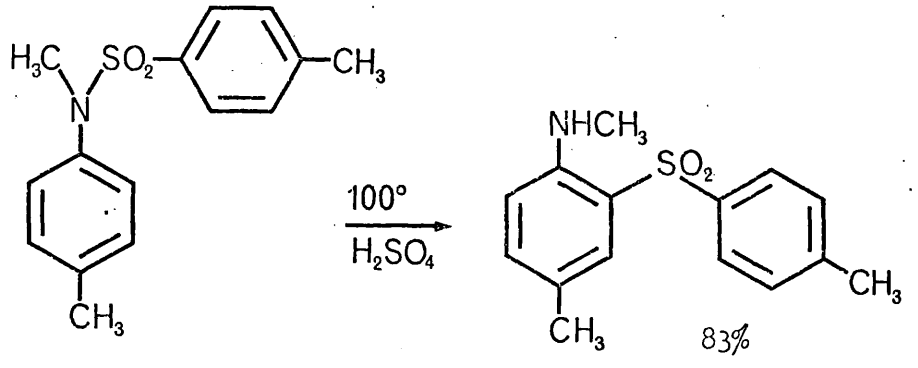
(III,20)

rearrangement, which has been more extensively investigated as the rearrangement of aryloxy carboxylates.[70] The Lewis acid catalyst chosen is most often aluminium chloride, although zinc chloride and hydrofluoric acid have also been used. The migration of the sulphonyl group occurs predominantly to the ortho position, but some para isomer is also formed. The rearrangement can also occur in the absence of a catalyst but under photolytic conditions (III,21).



(III,21)

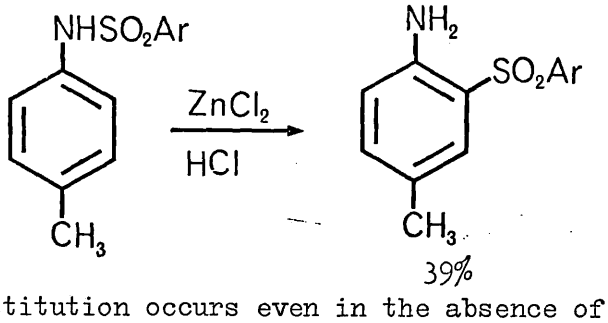
N,N-Diaryl and N-aryl-N-alkyl arylsulphonamides can rearrange when treated with hot sulphuric acid to give o-aminodiaryl sulphones (III,22).[71]



(III,22)

This reaction is analogous to the Fries rearrangement. Methanesulphonamides and primary anilides in general are hydrolysed under these conditions. Sulphonamides of N-alkylanilines undergo rearrangement more readily than those of diarylamines. The presence of electron-donating substituents on the N-aryl group facilitates the rearrangement, electron withdrawing substituents having the opposite effect. The nature of the substituents on the phenylsulphonyl moiety have little effect on sulphone formation.

Primary anilides may undergo rearrangement when heated in the presence of zinc chloride and hydrochloric acid to give predominantly the <u>para</u> isomer. If the <u>para</u> position is blocked, <u>ortho</u> substitution occurs (III,23). However, when an additional N-alkyl group is present

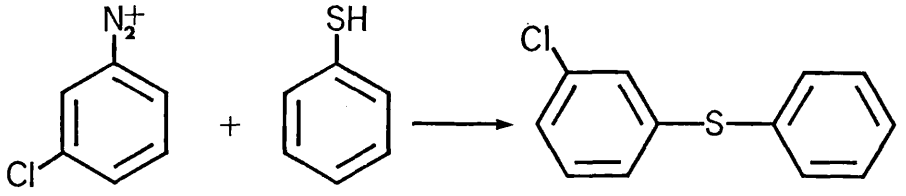


(III,23)

<u>ortho</u> substitution occurs even in the absence of the <u>para</u> blocking group.[72] The reason for this change in substitution orientation is not known.

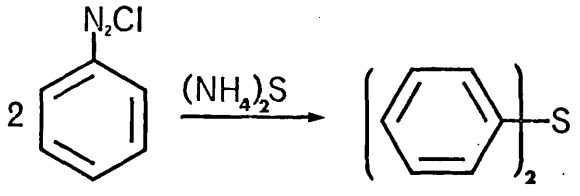
The oxidation of sulphides and sulphoxides as a convenient method for the preparation of the corresponding sulphone has already been discussed. Therefore the methods of synthesis of sulphides and sulphoxides are of interest in this context.

Diaryl sulphides may be produced by the action of a thiol on an aromatic diazonium salt (III,24).[73] This method is of particular



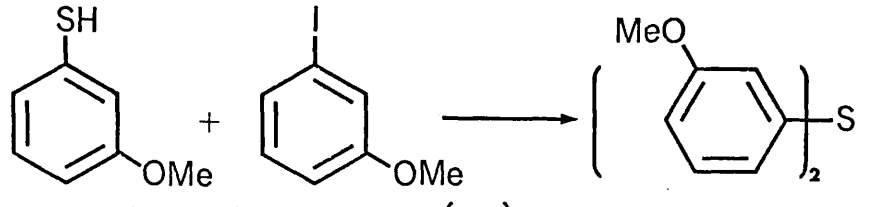
(III,24)

significance when orientation rules restrict the synthesis of the sulphur-compound by electrophilic methods. The ortho and para chlorodiphenyl sulphides can be prepared in a similar manner.[73] The reaction between phenyldiazonium chloride and ammonium sulphide has been shown to yield diphenyl sulphide [48] (III,25).



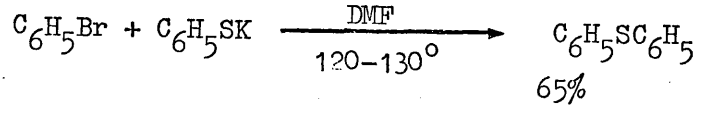
(III,25)

Unlike aliphatic halides, aromatic halides are generally unreactive towards thiols. However, diphenyl sulphides can be prepared by this method, particularly when the iodo compound is employed (III,26).[74]



(III,26)

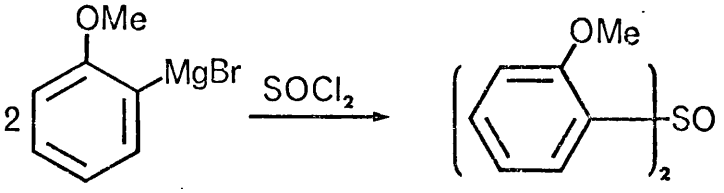
The use of dimethylformamide (DMF) as a solvent and an elevated temperature has resulted in the formation of a sulphide [75] (III,27).



(III,27)

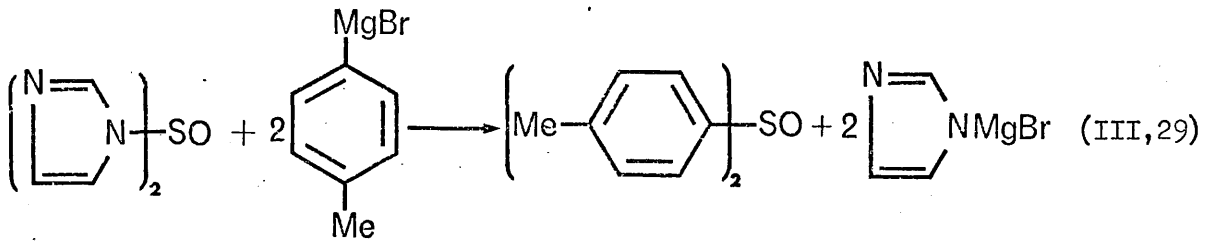
Diaryl sulphides may be prepared by Friedel-Crafts type reactions of aromatic hydrocarbons with chlorides of sulphur or with elemental sulphur in the presence of a catalyst such as aluminium chloride.[76] However, these methods are generally not employed in the route of the synthesis of sulphones since other Friedel-Crafts type reactions already discussed yield the sulphone directly, no oxidation stage being required.

Grignard reagents have been shown to yield symmetrical sulphoxides. o-Anisolemagnesium bromide reacts with thionyl chloride to give the corresponding diaryl sulphoxide[77] (III,28).



(III,28)

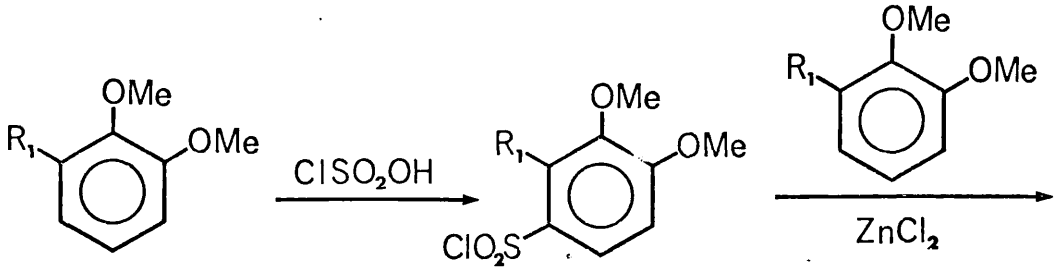
However, sulphides are usually also formed during the reaction between a Grignard reagent and thionyl chloride, due to the further reaction of sulphoxides with thionyl chloride.[77] For this reason the method of synthesis of symmetrical diaryl sulphoxides developed by S. Bast and K.K. Andersen[78] is considered to be superior. This method involves the reaction of an aryl Grignard reagent with N,N'-thionyldiimidazole, prepared from thionyl chloride and imidazole in tetrahydrofuran (III,29).

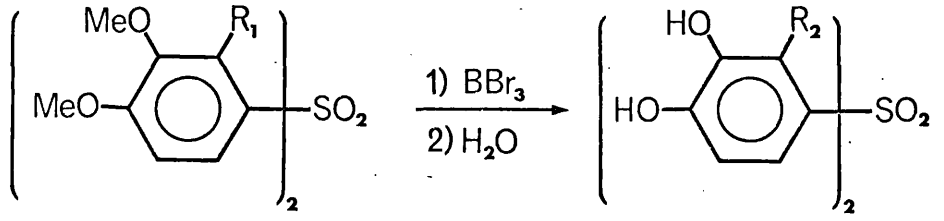


(III,29)

IIIB Results and Discussion

Two procedures were employed in the synthesis of 3,3',4,4'-tetrahydroxydiphenyl sulphone. In the first procedure (III, 30; $R_1 = R_2 = H$) the tetramethoxy sulphone was generated in two steps from the starting material, 1,2-dimethoxybenzene, using standard electrophilic methods. The first step involved the reaction between



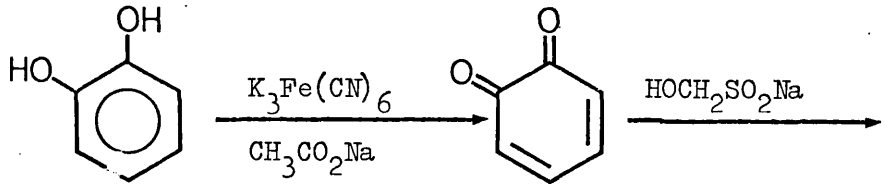


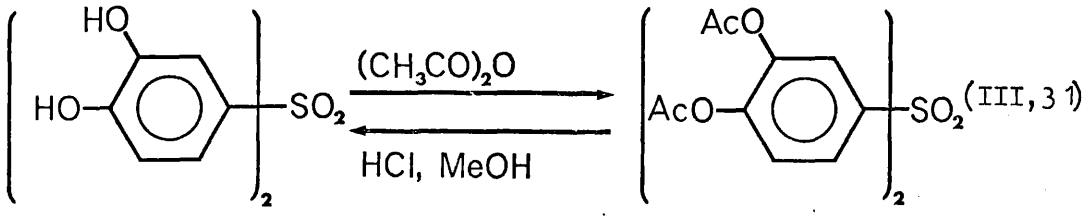
(III,30)

1,2-dimethoxybenzene and chlorosulphonic acid in chloroform (experiment 2), forming 3,4-dimethoxybenzenesulphonyl chloride. In the second step, the sulphonyl chloride was condensed with another molecule of 1,2-dimethoxybenzene in a Friedel-Crafts type reaction using zinc chloride as the catalyst (experiment 3). The reaction temperature (170-180°) was such as to maintain a steady evolution of hydrogen chloride. Since steam-distillation affords a convenient method of separating

1,2-dimethoxybenzene, which is steam-volatile, from the product, an excess of dimethoxybenzene was used. The product of this condensation reaction, 3,3',4,4'-tetramethoxydiphenyl sulphone, was demethylated with boron tribromide in toluene to give the tetrahydroxy compound (experiment 4A). At each step in the procedure (III,30) the infrared and n.m.r. spectra accorded with the required structure, and the melting points were in agreement with literature values.

The second procedure for the preparation of 3,3',4,4'-tetrahydroxydiphenyl sulphone (III,31) is similar to that described by R. Kerber and W. Gestrich.[58] o-Benzoquinone, which was generated *in situ* by oxidation of catechol with potassium ferricyanide, was treated with sodium formaldehyde sulphoxylate in aqueous medium to give the product. However, whereas R. Kerber and W. Gestrich obtained the



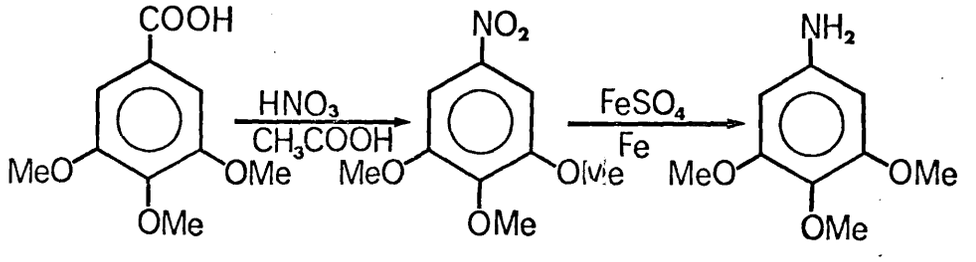


product from the reaction mixture by continuous extraction with ether, it was found more convenient to extract the product with butanone, in which it is very soluble, thus making a continuous extraction procedure unnecessary. Despite repeated recrystallisations from water, the product remained pale-brown in colour. However the nature of the tanning experiments requires a colourless product. The use of charcoal was found to result in a high loss of material without any substantial improvement in the colour of the compound. Chromatography on silica gel, eluting with water-saturated butanone, also failed to give a white product. Accordingly 3,3',4,4'-tetrahydroxydiphenyl sulphone was purified *via* the tetraacetoxy derivative, giving the required colourless product (experiment 4B).

2,2',3,3',4,4'-Hexahydroxydiphenyl sulphone was prepared in a similar manner to the preparation of 3,3',4,4'-tetrahydroxydiphenyl sulphone using the first procedure (III, 30, R_1 = OMe, R_2 = OH). Thus 1,2,3-trimethoxybenzene was treated with chlorsulphonic acid to yield 2,3,4-trimethoxybenzenesulphonyl chloride (experiment 5), which was then condensed with 1,2,3-trimethoxybenzene in the presence of zinc chloride to give 2,2',3,3',4,4'-hexamethoxydiphenyl sulphone (experiment 6). Subsequent demethylation with boron tribromide gave the hexahydroxy compound (experiment 7).

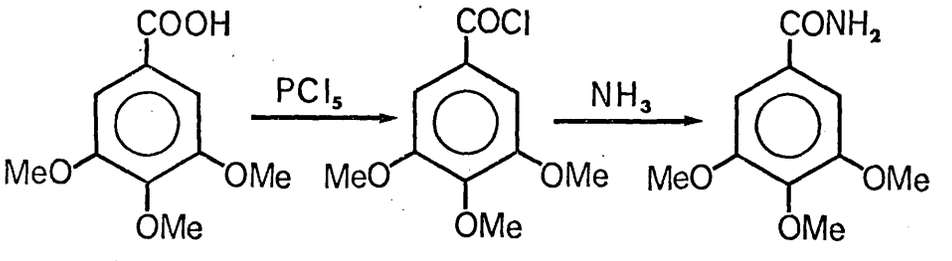
2,3,3',4,4',5'-Hexahydroxydiphenyl sulphone was prepared *via* the hexamethoxy compound, which was obtained by condensing 3,4,5-trimethoxybenzenesulphonyl chloride with 1,2,3-trimethoxybenzene in the presence of zinc chloride. The sulphonyl chloride was prepared from 3,4,5-trimethoxyaniline, which in turn was obtained from 3,4,5-trimethoxybenzoic

acid. G.K. Hughes *et al.*[80] showed that the aniline can be prepared by treating 3,4,5-trimethoxybenzoic acid with concentrated nitric acid in glacial acetic acid to give the decarboxylated nitro compound, which on subsequent reduction with iron powder and ferrous sulphate gives the aniline (III,32). However, R.C. Moreau *et al.*[81] have stated



(III,32)

that this method of preparation of the aniline gives only poor yields and the product is difficult to purify. They recommended that the aniline be prepared by a Hofmann rearrangement reaction on the corresponding benzamide. 3,4,5-Trimethoxybenzamide can be readily prepared from 3,4,5-trimethoxybenzoic acid *via* the benzoyl chloride (III,33). Thionyl chloride is a very convenient reagent for converting

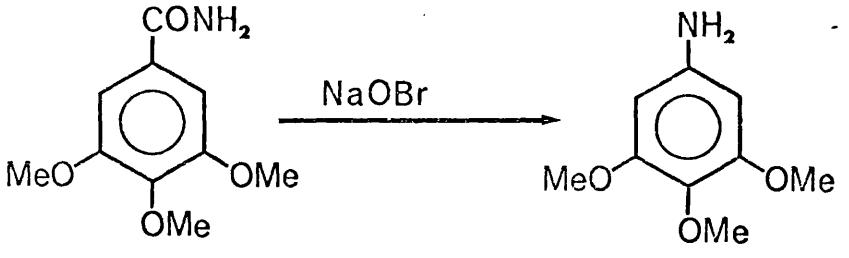


(III,33)

carboxylic acids to the acid chlorides since the by-products are gaseous. However, despite repeated attempts, 3,4,5-trimethoxybenzoic acid did not react with thionyl chloride (experiment 8A). Therefore, phosphorus

pentachloride, which has been employed by other workers[82,83] for this conversion, was used to yield the acid chloride (experiment 8B). The addition of concentrated ammonia solution to the benzoyl chloride gave 3,4,5- trimethoxybenzamide (experiment 9).

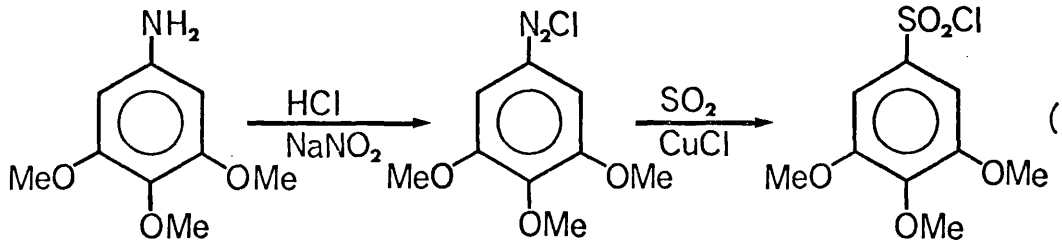
Both sodium hypobromite[83] and sodium hypochlorite[82,84] have been shown to perform the Hofmann rearrangement reaction on the amide to yield 3,4,5-trimethoxyaniline (III,34).



(III,34)

However, A. Critchlow *et al.*[84] have reported that the use of the hypobromite does not give the desired compound, but yields a brominated product. Since the preparation of the hypohalites involve the use of elemental halogens, it is more convenient to use the hypobromite. Consequently, 3,4,5-trimethoxybenzamide was treated with sodium hypobromite, and was found to yield the desired aniline as the product (III,34; experiment 9).

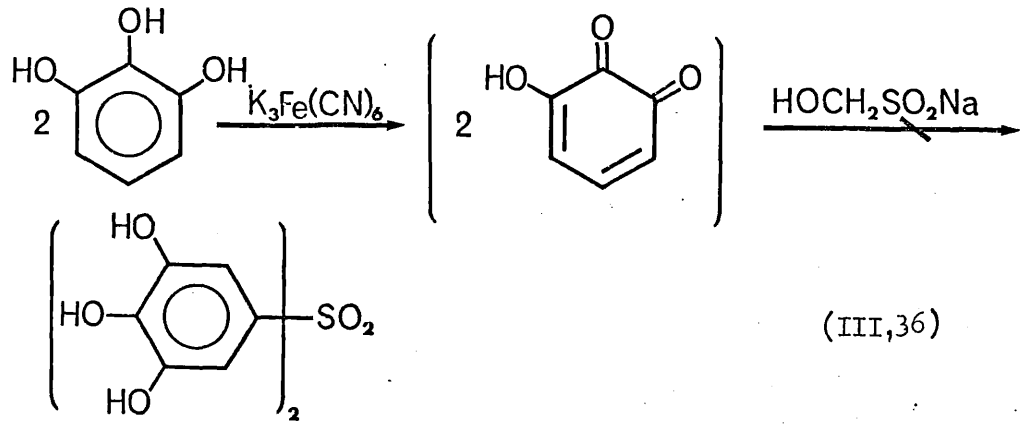
3,4,5-Trimethoxybenzenesulphonyl chloride was prepared from the aniline *via* the diazonium salt in a similar manner to that described by R.C. Moreau *et al.*[81] The procedure involves the treatment of the diazonium salt with sulphur dioxide dissolved in glacial acetic acid in the presence of cuprous chloride in a Sandmeyer-type reaction (III,35; experiment 10). Condensation of the sulphonyl chloride with 1,2,3-trimethoxybenzene gave the hexamethoxy compound (experiment 11)



(III,35)

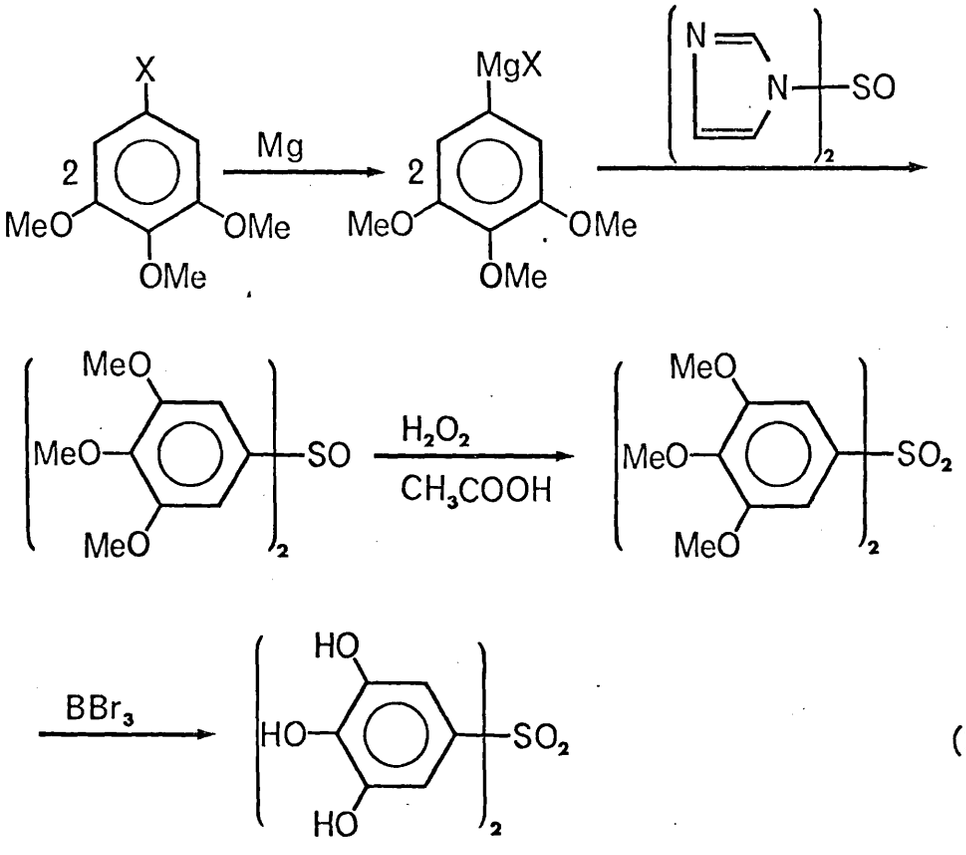
which was then demethylated with boron tribromide to yield 2,3,3',4,4',5'-hexahydroxydiphenyl sulphone (experiment 12).

Since the 4- and 6-positions of 1,2,3-trimethoxybenzene are those activated towards electrophilic substitution, a Friedel-Crafts reaction cannot be used to place a substituent at the 5-position. Therefore for the synthesis of 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone, alternative methods need to be employed. Now since o-benzoquinone reacts with sodium formaldehyde sulphoxylate to give the tetrahydroxydiphenyl sulphone,[58] and the reaction between benzenesulphinic acid and 3-hydroxy-o-benzoquinone yield 3,4,5-trihydroxydiphenyl sulphone[59] (III, 13), it might be expected that 3-hydroxy-o-benzoquinone would react with sodium formaldehyde sulphoxylate to give 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone. 3-Hydroxy-o-benzoquinone was generated *in situ* by oxidation of pyrogallol. However, infrared investigation indicated that there was no sulphone produced on interaction with sodium formaldehyde sulphoxylate (experiment 13; III,36).



(III,36)

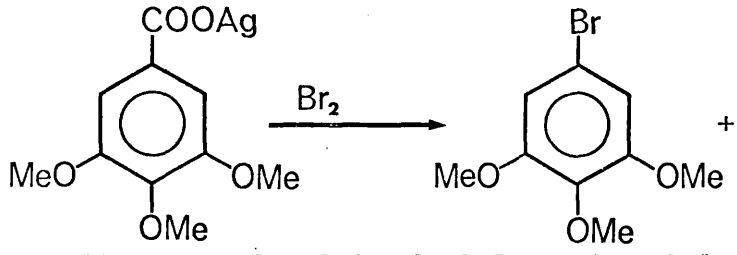
S. Bast and K.K. Andersen[79] have shown that aryl Grignard reagents may be converted to the corresponding symmetrical diaryl sulphoxides by reaction with N,N'-thionyldiimidazole (III,29). This method may be employed in the synthetic route to symmetrical diaryl sulphones by oxidation of the sulphoxide. Therefore in this case, 1-halo-3,4,5-trimethoxybenzene is required for the formation of the Grignard reagent; the subsequent reaction to give the sulphoxide, followed by oxidation to the sulphone and demethylation would yield the required product (III,37).



(III,37)

The starting material was 3,4,5-trimethoxybenzoic acid, and therefore a decarboxylation step was required. P.C. Dandiya et al.[85] have reported that 1-bromo-3,4,5-trimethoxybenzene can be prepared from

3,4,5-trimethoxybenzoic acid by the action of bromine on the silver salt of the acid (III,38). This type of reaction in which a carboxylic



$$+ AgBr + CO_2 \qquad (III,38)$$

acid salt is decarboxylated by halogen to a halide is known as the Hunsdiecker reaction.[86] However, the melting point of the product prepared by P.C. Dandiya (112°) is quite different from other literature values of the bromo compound prepared by other methods (78.5 - 80°[87], 78°[88]). Attempted preparation of 1-bromo-3,4,5-trimethoxybenzene by the method employed by P.C. Dandiya et al.[85] did not yield the desired product (experiment 14). This confirms the findings of G. Hardy et al.[89] who have reported that 3,4,5-trimethoxybenzoic acid does not yield the bromo compound under Hunsdiecker conditions.

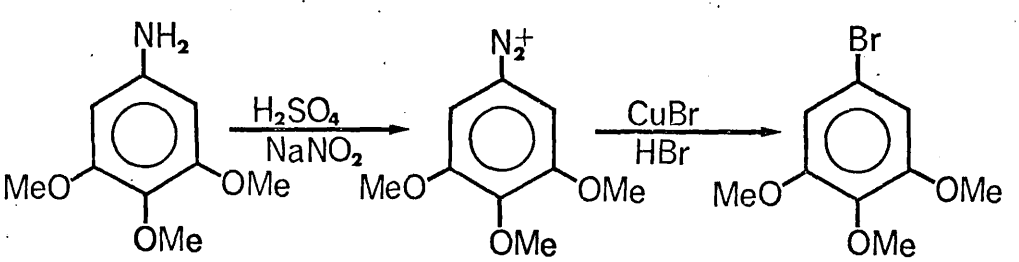
S.T. Cristol and W.C. Firth[90] have reported that free carboxylic acids may be treated with bromine in the presence of red mercuric oxide to yield the decarboxylated, bromo compound. This reaction is carried out in refluxing carbon tetrachloride (III,39). J.A. Davis et al.[91]

$$2RCOOH + HgO + 2Br_2 \xrightarrow{CCl_4} 2RBr + HgBr_2 + H_2O + 2CO_2 \qquad (III,39)$$

found that the Cristol-Firth reaction gives generally better yields of the bromo compound when 1,1,2,2-tetrachlorethane is used as the solvent in place of carbon tetrachloride. Benzoic acid, for instance, gives a 48% yield of bromobenzene in carbon tetrachloride, whereas in

1,1,2,2-tetrachloroethane a yield of 83% is obtained. Therefore the improved Cristol-Firth reaction as reported by J.A. Davis *et al.* was employed in an attempt to convert 3,4,5-trimethoxybenzoic acid to the bromo compound, but again the desired product was not obtained (experiment 15 A). A Hunsdiecker type reaction using the mercuric salt of 3,4,5-trimethoxybenzoic acid in 1,1,2,2-tetrachloroethane was attempted, but no 1-bromo-3,4,5-trimethoxybenzene was obtained (experiment 15 B).

The preparation of 1-bromo-3,4,5-trimethoxybenzene from the aniline *via* the diazonium salt has been reported[87] using a Sandmeyer reaction. This method, which involves treating the diazonium salt with hydrobromic acid in the presence of cuprous bromide was successfully employed to obtain the required bromo compound (III,40; experiment 16).



(III, 40)

It was envisaged that the next step would be the formation of the Grignard reagent, with subsequent formation of the sulphur-bridged diaryl compound by reaction with N,N'-thionyldiimidazole to give the sulphoxide (III,37). However, despite repeated attempts, 1-bromo-3,4,5-trimethoxybenzene did not react with magnesium in diethyl ether (experiment 17A). H. Normant[92] has shown that tetrahydrofuran is a

particularly useful solvent for the preparation of Grignard reagents, in that many organic halogen compounds which do not easily react with magnesium if at all, readily do so in tetrahydrofuran. Therefore the preparation of 3,4,5-trimethoxyphenylmagnesium bromide was attempted in tetrahydrofuran, but again no reaction occurred (experiment 17B).

Organic iodides are more reactive towards magnesium than bromides, which are themselves more reactive than the corresponding chlorides.[93] The iodides are not usually used to form Grignard reagents, since their relative higher reactivity is usually accompanied by relatively higher reactivity in side-reactions.[93] Nevertheless attempts were made to form the Grignard reagent from 1-iodo-3,4,5-trimethoxybenzene, prepared from 3,4,5-trimethoxyaniline by forming the diazonium salt and subsequent decomposition with potassium iodide (experiment 18). However, despite repeated attempts in both diethyl ether and in tetrahydrofuran as solvents, the iodo compound could not be induced to yield the Grignard reagent (experiment 19).

Benzenediazonium sulphate has been shown to react with ammonium sulphide to yield diphenyl sulphide.[48] This suggested the possibility of using a diazonium salt in a similar manner to generate 3,3',4,4',5,5'-hexamethoxydiphenyl sulphide. Subsequent oxidation to the sulphone, followed by demethylation would yield the required hexahydroxy compound. p-Anisidine was first employed in a trial experiment, the desired compound in this case being 4,4'-dimethoxydiphenyl sulphide. However, no crystalline material was obtained (experiment 20), and therefore this procedure was not investigated further.

Organolithium compounds exhibit many of the reactions of Grignard reagent, but are generally more reactive.[94] Since 1-bromo- and 1-iodo-3,4,5-trimethoxybenzene failed to form the Grignard reagents, it was proposed to use the corresponding organolithium compound instead to give the required product. Indeed the use of 1-lithium-3,4,5-trimethoxybenzene has been recorded,[89] in this case in the synthesis of 3,4,5-trimethoxybenzoic [^{14}C] acid by treating with solid carbon dioxide, a reaction that is similar to that performed by Grignard reagents.

1-Bromo-3,4,5-trimethoxybenzene was converted to the organolithium compound by a halogen-metal interconversion reaction, in a similar manner to that described by G. Hardy *et al.*[89] in which the bromo compound is treated with *n*-butyllithium. The organolithium compound was then used in place of the Grignard reagnet in eq. III,36 (experiment 21A). However the interaction of 1-lithium-3,4,5-trimethoxybenzene with N,N'-thionyldiimidazole did not yield the desired sulphur compound, and only 3,3',4,4',5,5'-hexamethoxybiphenyl was identified in the reaction mixture.

Both Grignard reagents and organolithium compounds have been reported to cleave S-Cl bonds yielding sulphur-containing compounds. In particular Grignards reagents react with sulphenyl chlorides,[95] thionyl chloride[77,78] and sulphonyl chlorides[64] to give the corresponding sulphides, sulphoxides and sulphones respectively. Phenyllithium reacts with benzylsulphonyl chloride to yield a variety of sulphones.[67] Therefore the possibility of preparing diaryl sulphur-bridged compounds

by the action of aryllithiums on sulphur halide compounds was investigated. p-Tolyllithium was used in these trial experiments, prepared by reacting p-bromotoluene with elemental lithium. This organolithium compound was treated with thionyl chloride (experiment 21B), sulphuryl chloride (experiment 21C), and with 3,4-dimethoxybenzene-sulphonyl chloride (experiment 21D).

In each case the desired compound was not obtained, and therefore this approach of reacting organometallic compounds with electrophiles was not investigated further.

Hence it was decided to re-examine the possibility of synthesizing the hexahydroxy compound using 3-hydroxy-o-benzoquinone, which has already been shown to react with benzenesulphinic acid to give 3,4,5-trihydroxydiphenyl sulphone, although in low yield.[56,59] The o-benzoquinone compound in that case was obtained by the oxidation of pyrogallol with aqueous potassium dichromate solution. The possible extension of this reaction using substituted arylsulphinic acids is further limited by the generally low solubility of sulphinic acids in aqueous media. Therefore, in order that this reaction may be of more general applicability, the reaction conditions were altered by using potassium ferricyanide as the oxidising agent in a mildly alkaline solution. The basic conditions permit the use of the more soluble sodium salt of the sulphinic acid. The reaction between pyrogallol and sodium benzenesulphinate under these conditions gave 3,4,5-trihydroxy-diphenyl sulphone in good yield (ca. 61%). However, the product was pale-brown despite repeated recrystallisation from ethanol-water. As in a previous case the use of charcoal resulted in a substantial loss of material. Therefore, the product was purified via the triacetoxy

derivative, which yielded the trihydroxy compound as colourless crystals (experiment 22). Under similar conditions, catechol and sodium benzenesulphinate reacted to give 3,4-dihydroxydiphenyl sulphone. After several recrystallisations, a colourless compound was obtained from the initially pale-yellow product in 89% yield (experiment 23).

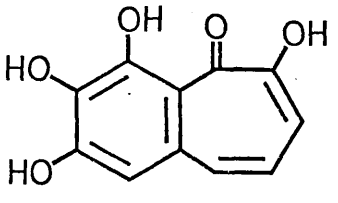
The procedure used in the preparation of the di- and trihydroxydiphenyl sulphones is particularly convenient since the starting materials are readily soluble whereas the product in each case is only slightly soluble in water, thus facilitating the separation of the crude product from the reaction mixture.

It seemed likely that the use of substituted sodium arylsulphinate in these types of reactions might yield the corresponding di- and trihydroxydiaryl sulphones. Hence the reaction between sodium 3,4,5-trimethoxybenzenesulphinate and 3-hydroxy-o-benzoquinone, generated *in situ* by the oxidation of pyrogallol, might yield 3,4,5-trihydroxy-3',4',5'-trimethoxydiphenyl sulphone. Subsequent demethylation would give the desired hexahydroxy compound. However, since sodium 3,4,5-trimethoxybenzenesulphinate is not readily accessible, the method was first tested using sodium 3,4-dimethoxybenzenesulphinate. This sodium sulphinate was prepared from 3,4-dimethoxybenzenesulphonyl chloride by reduction with sodium sulphite under mildly basic conditions. At the end of the reduction, the solution was acidified, precipitating the sparingly soluble sulphinic acid, which was collected and then reconverted to the sodium salt (experiment 24).

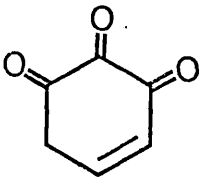
The reaction between sodium 3,4-dimethoxybenzenesulphinate and 3-hydroxy-o-benzoquinone was carried out in the usual manner, to give 3,4-dimethoxy-3',4',5'-trihydroxydiphenyl sulphone in approximately 56% yield. The product was purified *via* the triacetoxy derivative (experiment 25), and subsequent demethylation with boron tribromide gave 3,3',4,4',5-pentahydroxydiphenyl sulphone (experiment 26).

Similarly sodium 3,4,5-trimethoxybenzenesulphinate was prepared by the reduction of the sulphonyl chloride using sodium sulphite (experiment 27). The reaction between sodium 3,4,5-trimethoxybenzenesulphinate and 3-hydroxy-o-benzoquinone gave 3,4,5-trihydroxy-3',4',5'-trimethoxydiphenyl sulphone in approximately 55% yield. The trihydroxy compound was purified *via* the triacetoxy derivative (experiment 28), and subsequent demethylation yielded 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone (experiment 29).

Pyrogallol is readily converted into purpurogallin (Fig. III-2,I) by a variety of oxidising agents in neutral and weakly acidic solutions. It has been suggested that in this reaction pyrogallol is oxidised to 3-hydroxy-1,2-benzoquinone which may react in its tautomeric triketo-form[87] (Fig. III-2,II). The reaction of the sodium benzenesulphinates



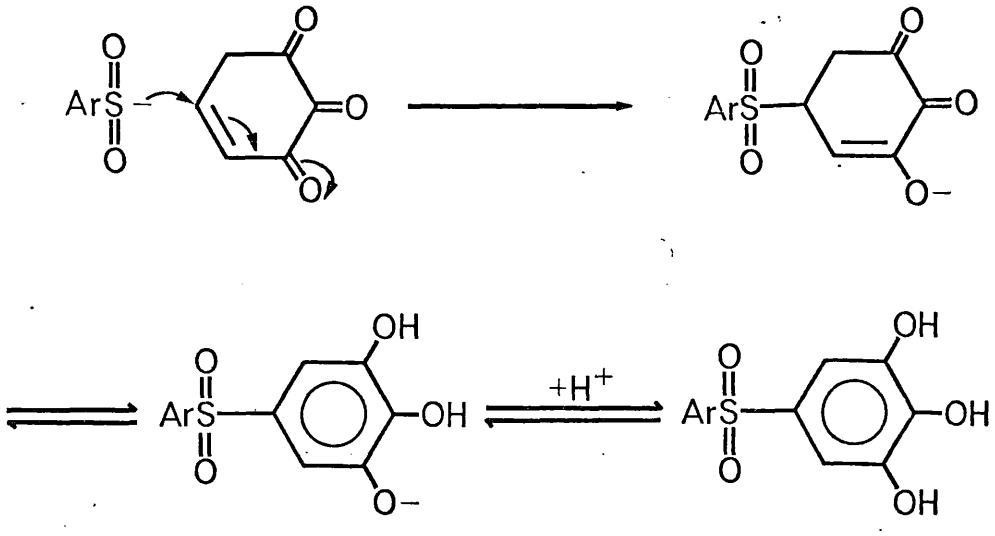
I



II

Fig. III-2

with 3-hydroxy-1,2-benzoquinone to give the 5-substituted sulphonyl derivative of pyrogallol may be rationalised by considering the reaction to proceed through the triketone. When nucleophilic attack occurs at the 5-position the anionic intermediate can be stabilized by delocalisation of the negative charge to the 1-keto oxygen in a Michael addition type reaction (III,41). This reaction was further investigated

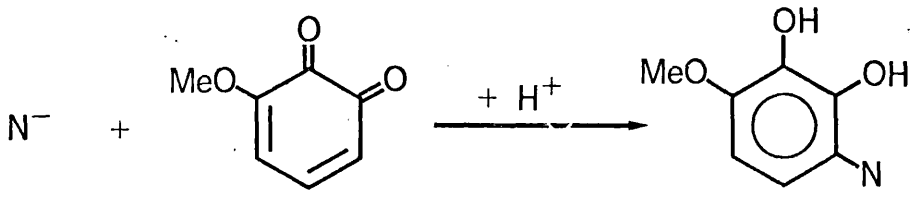


(III,41)

by employing nucleophiles other than sulphinate. Similar conditions were used, 3-hydroxy-1,2-benzoquinone again being generated <u>in situ</u> by ferricyanide oxidation of pyrogallol. However, the use of potassium iodide (experiment 30A) and of potassium thiocyanate (experiment 30B) did not yield the expected Michael addition products. Similarly the use of <u>o</u>-benzoquinone with potassium iodide and with potassium thiocyanate did not result in the expected products (experiment 30C). There is as

yet no rationalisation for the different behaviours of iodide and thiocyanate to that of the sulphinate anion in these reactions.

L. Horner and S. Göwecke have reported[59] that 3-methoxy, 1,2-benzoquinone reacts with benzenesulphinic acid and with thiophenol to give the 6-sulphonyl and the 6-thio derivative respectively (III,42). However,



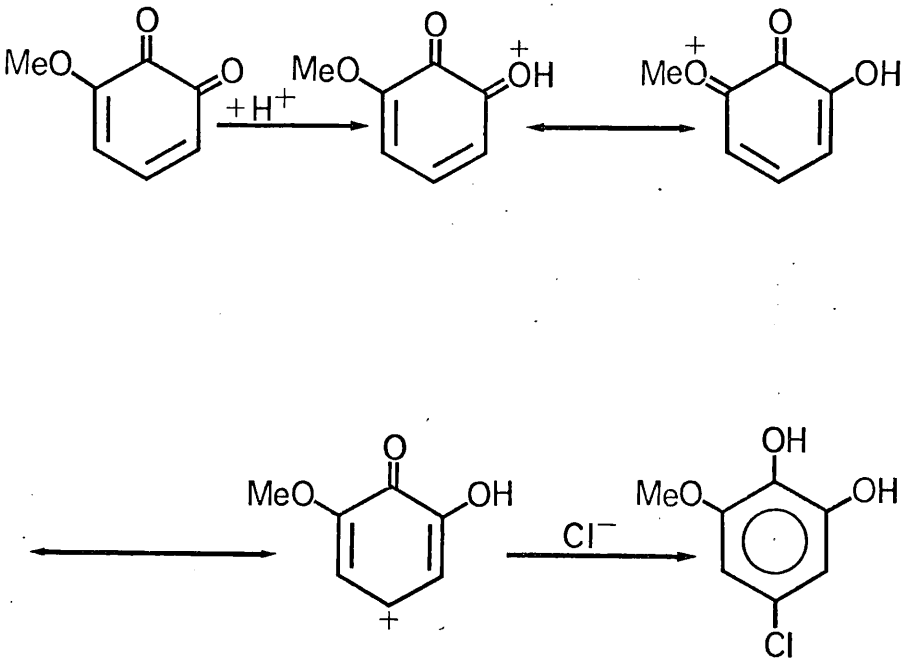
(III,42)

$N^- = PhSO_2^-$

or $N^- = PhS^-$

when concentrated hydrochloric acid is used, substitution occurs in the 5-position, giving 1-chloro-3,4-dihydroxy-5-methoxybenzene.

The difference in behaviours of 3-hydroxy-1,2-benzoquinone and its methyl ether may be due to the inability of 3-methoxy-1,2-benzoquinone to form the triketone. The anomolous behaviour of 3-methoxy-1,2-benzoquinone towards hydrogen chloride may be a result of the particularly acidic conditions used in this reaction. Protonation of the keto-oxygen on the 1-position, which could be resonance stabilized, may be responsible for activating the 5-position towards nucleophilic attack by the chloride anion (III,43). The use of benzenesulphinic acid and of thiophenol however result in media that are considerably less acidic, and therefore the conditions are less conducive to the protonation of the keto-oxygen.



(III,43)

IV THE STUDY OF ALUMINIUM CHELATES OF o-DIHYDROXYBENZENES

A Introduction

The hexaminecobalt(III) ion, shown in Fig. IV-1, is a typical example of a metal complex. The central metal atom, in this case cobalt, is the acceptor atom, the six ammonias act as the donating

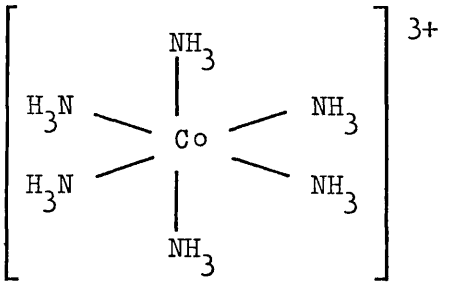
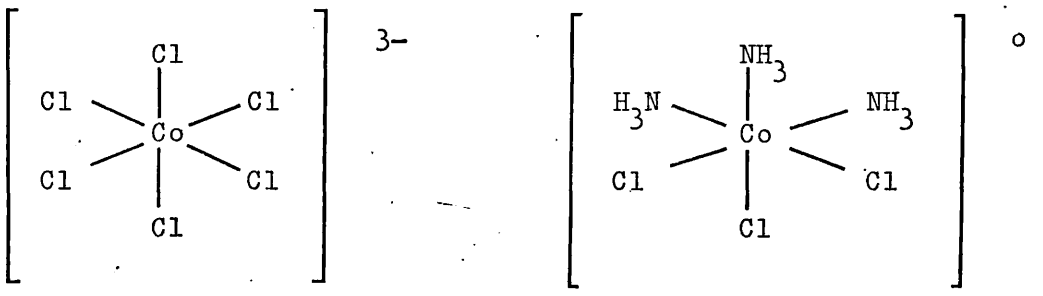


Fig. IV-1

groups. Similarly, chloride ions may complex with cobalt, as is exemplified by the hexachlorocobaltate ion shown in Fig. IV-2,I. The donating groups may be a mixture of both neutral and charged species,



I II

Fig. IV-2

as in the case of trichlorotriammino cobalt shown in Fig. IV-2,II. Thus, clearly complex formation can generate cationic, anionic or neutral species of greatly differing character. The negative ion or polar molecule attached to the metal atom (M) is generally called the ligand (L), and the bond between them the metal-ligand (M-L) bond.

Some ligands attach themselves to the metal by two or more donor groups, thereby forming cyclic complexes. The terms unidentate, bidentate, tridentate etc. are used to describe a ligand according to the number of donor groups it possesses. The glycinate ion is a typical bidentate complexing agent, and its behaviour is exemplified in copper glycinate shown in Fig. IV-3. The presence of the bidentate ligands

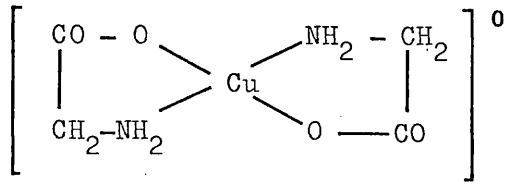


Fig. IV-3

has resulted in the formation of two five-membered rings. This type of ring is known as a chelate ring, and a metal complex in which a chelate ring is present is known as a metal chelate. The chemistry of metal chelate compounds has been comprehensively reviewed, and therefore for a more detailed account of this subject the reader is referred to available published material.[96,97]

Chelates are noted for their enhanced stability as compared to the stability of analogous systems involving similar but monodentate ligands, and this enhanced stability, which is only significant in the case of five- and six-membered rings, is known as the chelate effect. The equilibrium between a metal and a bidentate ligand is given by eq. IV,1, for which the thermodynamic equilibrium constant, ${}^{T}K_{b}$ is defined by eq. IV,2. The stoichiometric constant, K_{b}, is expressed in terms of a concentration quotient. Strict interpretations should only be made using ${}^{T}K_{b}$, which is related to K_{b} in terms of a quotient of activity

coefficients. γ is used to denote the activity coefficient of each species.

$$M + L \rightleftharpoons ML \qquad (IV,1)$$

$${}^{T}K_b = [ML]\,\gamma_{ML}/[M]\,\gamma_M\,[L]\gamma_L = K_b\,\gamma_{ML}/\gamma_M\gamma_L \qquad (IV,2)$$

For the analogous monodentate system (IV,3) the equilibrium constant is given in eq. IV,4. The increased stability of the metal chelate manifests itself in a higher equilibrium constant (${}^{T}K_b$) as compared

$$M + 2L \rightleftharpoons ML_2 \qquad (IV,3)$$

$${}^{T}K_m = [ML]\,\gamma_{ML}/[M]\,\gamma_M\,[L]^2\gamma_L^{\,2} = K_m\,\gamma_{ML}/\gamma_M\gamma_L^{\,2} \qquad (IV,4)$$

with that for the monodentate system (${}^{T}K_m$). These equilibrium constants may be considered in terms of the usual thermodynamic criteria (IV,5).

$$-RT\ \ln K = \Delta G = \Delta H - T\Delta S \qquad (IV,5)$$

Since R is a constant, and as comparisons are made at the same temperature, T, the chelate effect may originate in the enthalpy term, ΔH, or the entropy term, ΔS, or both.

When two monodentate anionic ligands are brought together to occupy adjacent sites on a metal, the electrostatic repulsion that needs to be overcome reflects itself in the ΔH term. In the case of a bidentate ligand, the very nature of the ligand inherently restricts the effect of repulsion, and this results in a comparatively lower ΔH term. Therefore in terms of enthalpy these considerations are expected to favour the stability of the chelated species. Similar arguments can be applied to uncharged ligands, since these are always dipolar.

An increase in randomness is associated with a corresponding increase in entropy, and therefore the effect on the ΔS value can be readily understood. A complex species has a lower entropy than that of its separated components. Therefore the ΔS term for the formation of

bidentate complex (IV,1) would be expected to be higher (less negative) than that for the analogous monodentate system (IV,3). Consequently, in terms of entropy the chelate is expected to be more stable. In general the chelate effect is considered to be more a consequence of change in entropy, with enthalpy effects playing a less significant role.

Since stoichiometric constants are more commonly used, the following discussion is expressed in terms of concentrations. The equilibrium constant for the formation of a metal-ligand complex is given in eq. IV,2, which is valid whether the ligand is mono- or multidentate. This constant is referred to as either a formation constant or a stability constant. However, more than one ligand may be complexed onto a metal, as in the case of copper glycinate (Fig. IV-3) and the hexachlorocobaltate ion (Fig. IV-2,1). Hence the equilibrium constant for the formation of the complex ML is known as the first stability constant, K_1. The second stability constant, K_2, for the formation of the ML_2 complex (IV,6) is given in eq. IV,7. Clearly a

$$ML + L \rightleftharpoons ML_2 \qquad (IV,6)$$

$$K_2 = [ML_2]/[ML][L] \qquad (IV,7)$$

stability constant, K_n is defined by

$$K_n = [ML_n]/[ML_{n-1}][L] \qquad (IV,8)$$

The constants K_1, $K_2 \ldots K_n$ are known as stepwise stability constants. The overall formation of a complex, ML_n (IV,9) is described by the constant β_n (IV,10), known as the n^{th} overall stability constant.

$$M + nL \rightleftharpoons ML_n \qquad (IV,9)$$

$$\beta_n = [ML_n]/[M][L]^n \qquad (IV,10)$$

There are the same number of stepwise stability constants as there are overall stability constants, and they are related to each other by the relationship given in eq. IV,11.

$$\beta_n = K_1 . K_2 . \ldots\ldots K_n = \prod_{i=1}^{n} K_i \qquad (IV,11)$$

As is shown by eq. IV,8, the evaluation of a stability constant, K_n requires the estimation of the concentrations of ML_n, ML_{n-1} and L. However, it is not usually possible to obtain directly the values of these concentrations, but it is generally more practicable to obtain a value for the average number of ligands bound to each metal atom. This value, $(\bar{n})$ is defined by eq. IV,12.

$$\bar{n} = \frac{[ML_1] + 2[ML_2] + \ldots . N[ML_N]}{[M] + [ML_1] + [ML_2] + \ldots . [ML_N]} = \frac{\sum_{n=1}^{N} n\,[ML_n]}{\sum_{n=0}^{N} [ML_n]} \qquad (IV,12)$$

where N is the maximum number of ligands, L, attached to M.

However, if eq. IV,13 (derived from eq. IV,10) and eq. IV,14 are taken

$$[ML_n] = \beta_n [M][L]^n \qquad (IV,13)$$

$$\sum_{n=0}^{N} [ML_n] = [M] + \sum_{n=1}^{N} [ML_n] \qquad (IV,14)$$

into consideration, the expression for $\bar{n}$ given above in eq. IV,12 now becomes

$$\bar{n} = \frac{\sum_{n=1}^{N} n\beta_n [M][L]^n}{[M] + \sum_{n=1}^{N} \beta_n [M][L]^n} = \frac{\sum_{n=1}^{N} n\beta_n [L]^n}{1 + \sum_{n=1}^{N} \beta_n [L]^n} \qquad (IV,15)$$

The stepwise stability constant (K_n) can be derived from eq. IV,15, to give an expression (IV,16) which can be used as an approximation formula.[98]

$$K_n = \frac{1}{[L]} \frac{\sum_{t=0}^{t=n-1} \frac{\bar{n} - n + 1 + t}{[L]^t K_{n-1} K_{n-2} \cdots K_{n-t}}}{\sum_{t=0}^{t=N-n} (n-\bar{n}+t)[L]^t K_{n+1} K_{n+2} \cdots K_{n+t}} \qquad (IV,16)$$

Therefore for various corresponding $\bar{n}$ and $[L]$ values, K_1, K_2 ... K_N must be chosen so that the equality in eq. IV,16 holds. Individual $\log_{10}K_n$ values may be determined from plots of $\bar{n}$ against pL ($-\log_{10}[L]$) by various numerical and graphical methods.[98] A plot of $\bar{n}$ against pL is known as a formation curve.

In the case of an uncharged ligand in which all the ligand present is either uncomplexed in the form L, or is bound to the metal as ML_n, $[L]$ can be readily evaluated from the expression

$$[L] = T_L - \bar{n}T_M \qquad (IV,17)$$

in which T_L is the total concentration of the ligand added, complexed and uncomplexed, and similarly T_M is the total concentration of metal. However, when the ligand is charged, as exemplified by Figs. IV-2,I and IV-3, L is the conjugate base of the acid HL. Therefore in the case of a weak acid, $[L]$ can only be estimated if the amount of ligand bound up in the form HL, as well as that complexed is known. A knowledge of the acid dissociation constant is thus required.

Acid-base equilibria can be treated in a similar manner to that already described for metal-ligand complexes. Hence the proton-ligand stability

$$LH_{n-1} + H \rightleftharpoons LH_n \qquad (IV,18)$$

constant K_n for the equilibrium IV,18, also known as the protonation constant, is defined by the expression

$$K_n = [LH_n]/[LH_{n-1}][H] \qquad (IV,19)$$

The relationship between the proton-ligand stability constant and the commonly used acidity constant (Ka_n) is given in eq. IV,20

$$K_{y-n+1} = 1/Ka_n \qquad (IV,20)$$

where y is the number of dissociable protons. The proton-ligand formation curve is a plot of the average number of protons attached to the ligand, $\bar{n}_A$, against pH, and the approximation formula shown in eq. IV,16 is valid, [H] being used in place of [L] throughout.

M.T. Beck[98] has discussed the various numerical and graphical methods available for calculation of complex stability constants. If the ratio of successive stability constants is great enough ($>10^4$), the steps of complex formation are distinct and do not appreciably overlap and the reciprocal value of the free ligand concentration is about equal to K_n at $\bar{n} = n - \frac{1}{2}$. At this point the species ML_{n-1} and ML exist in about equal concentrations. In cases where the ratio of successive constants is less than 10^4, this method of "interpolation at half $\bar{n}$ values" can only be considered to generate approximate stability constants. Other methods need to be employed for more accurate values.

In the case of a system N = 2, it follows from eq. IV,15 that the formation curve is symmetrical about its mid-point at $\bar{n} = 1$ (e.g. Fig. IV-10, theoretical formation curve) and therefore evaluation of the correct constants is less complicated. Thus K_1 and K_2 can be obtained using eq. IV,21 and IV,22 respectively,

$$\log K_1 = pL_{\bar{n}=1-d} + y \qquad (IV,21)$$

$$\log K_2 = pL_{\bar{n}=1+d} - y \qquad (IV,22)$$

where values of d are chosen such that $0.9 > d > 0.1$.

The term y, usually known as the correction term, is defined by

$$y = \log \frac{1-d}{d} + \log \left(1 - \frac{(1+d)[L]_{1-d}}{(1-d)[L]_{1+d}} \right) \qquad (IV,23)$$

In cases where there are three or more overlapping equilibria taking place, that is the ratios of successive constants is less than 10^4, then the evaluation of each constant becomes a more complex operation. This is so since a number of equilibria may contribute to a significant extent to the value of $\bar{n}$ at any particular concentration of L. Hence an exacting procedure requires that the constants be evaluated simultaneously, so that the overlap of equilibria can be taken into account. This point is clearly demonstrated in eq. IV,16, which shows that the calculation of a stability constant, K_n, requires a knowledge not only of $\bar{n}$ and $[L]$, but also of the influence of the other constants, namely K_1 to K_{n-1} and K_{n+1} to K_N. In principle therefore N sets of simultaneous equations which may be derived from eq. IV,16, need to be solved requiring N values of stability constants K.

R.P. Block and G.H. McIntyre[99] have described a numerical method whereby stability constants can be obtained by direct calculation of basic equations. Essentially the method is based on solutions of eq. IV,16 by algebraic methods. However the equations cannot be universally applied since some stability constants prove to be incalculable by this technique. Also this method is very susceptible to small experimental errors which may even result in negative values of K_n.

The determination of stability constants requires in the first place the estimation of the concentration of one or more of the species involved in the equilibria. There are many methods by which this can be accomplished, including potentiometry, polarography, infrared and n.m.r. spectroscopy,

solubility and liquid-liquid partition. For a full review of the applications of these methods, the reader is referred to available published material.[99-101]

In the event that the ligand, L, is the conjugate base of a weak acid HL, the formation of a complex results in the liberation of protons, thereby altering the pH of the solution (IV,24). Therefore

$$HL + ML_{n-1} \rightleftharpoons ML_n + H \qquad (IV,24)$$

potentiometric determination of the hydrogen ion concentration affords a very convenient method whereby such systems can be studied.

A stability constant may be expressed in terms of its activity quotient, in which case it is referred to as a "thermodynamic" stability constant. Such constants involve the activities of the species concerned, and therefore refer to the equilibrium at infinite dilution. It is generally difficult to determine accurately the values of these "thermodynamic" stability constants, especially for systems in which several complexes coexist. It is more usual therefore to express the equilibria in terms of concentration quotients, the constants being referred to as stoichiometric stability constants. These concentration quotients are determined in the presence of a large excess of salt thereby producing a background ionic medium. Under such conditions it is assumed that activity coefficients are independent of the concentrations of the species involved in the equilibria, and that they are dependent only on the nature and concentration of the salt.

H. Irving and H.S. Rossotti[102] have shown that when L is the conjugate base of a weak acid, the proton-ligand and the metal-ligand formation curves may be readily obtained from pH titration curves.

The procedure involves the determination of three titration curves (Fig. IV–9) in each case a high ionic strength being maintained by the presence of a salt. Curve 1 shows the titration curve for mineral acid, curves 2 and 3 that for a mixture of mineral acid and ligand in the absence and presence of the metal. The use of the mineral acid is to ensure that the ligand exists essentially in its protonated form at the beginning of the titration. The difference in the volume of alkali added to reach the same pH in curves 1 and 2 ($v''-v'$) is a measure of the concentration of protons removed from the ligand. Similarly, the difference in volume of alkali added in curves 2 and 3 at the same pH ($v'''-v''$) is a measure of the concentration of protons removed from the ligand upon complexation at that pH. The formation curves are evaluated from the titration curves using eq. IV,25,26, and 27.

$$\bar{n}_A = y - \frac{(v''-v')(N + E^o)}{(V^o + v')T^o_L} \qquad \text{(IV,25)}$$

$$\bar{n} = \frac{(v'''-v'')(N + E^o)}{(V^o + v'')\,\bar{n}_A\,T^o_M} \qquad \text{(IV,26)}$$

$$pL = \log_{10}\left[\frac{\sum_{i=0}^{y}\beta_i[H]^i}{T^o_L - \bar{n}\,T^o_M}\quad\frac{V^o + v'''}{V^o}\right] \quad \text{where } \beta_o = 1 \qquad \text{(IV,27)}$$

V^o is the initial volume, N the molarity of the alkali, and E^o the initial concentration of the mineral acid. y is the total number of dissociable protons attached to the ligand in the form H_yL, T^o_L and T^o_M are the total initial concentrations of ligand and metal respectively. β_i is the overall proton-ligand stability constant.

The aluminium(III) ion is capable of forming 4–, 5–, and 6–coordinate complexes which may be cationic, neutral or anionic. In aqueous solution

the ion forms the octahedral aquo complex $[AL(H_2O)_6]^{3+}$ cation. Neutral species may be exemplified by $AlCl_3(NMe_3)_2$, which is 5-coordinate, and by the tris(8-hydroxyquinolinate) complex (Fig. IV-4). The latter

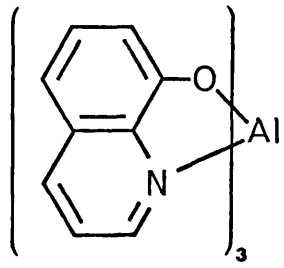
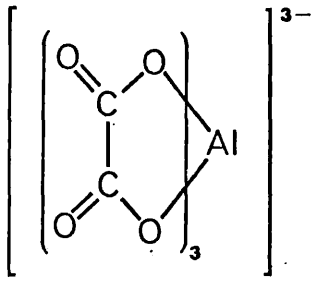
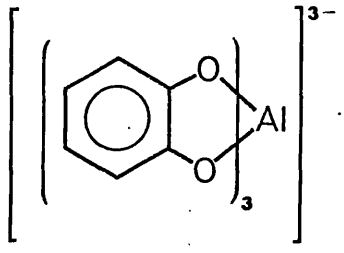


Fig. IV-4

complex, which is a 6-coordinate aluminium chelate, is important as a means of estimating aluminium (see VIII, A, 9 "Estimation of Aluminium"). Aluminium forms anionic complexes such as AlF_6^{3-} and chelates of oxalic acid (Fig. IV-5,I) and catechol (Fig. IV-5,II).



I



II

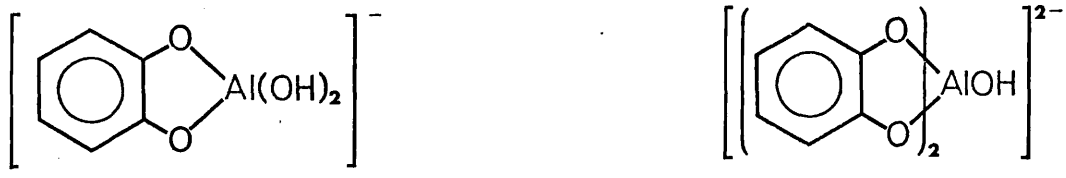
Fig. IV-5

The 1:1, 1:2, and 1:3 aluminium chelates of catechol have been investigated by potentiometric[103-105] and preparative[103] methods. The three species have been isolated as their potassium salts in the forms $K[Al(C_6H_4O_2)(OH)_2]\ 3.5H_2O$, $K[Al(C_6H_4O_2)_2].3H_2O$ and $K_3[Al(C_6H_4O_2)_3]3H_2O$.[103]

Attempts to try to resolve the aluminium-tris(catecholato) anion into its optical isomers have been unsuccessful due to rapid ligand exchange.[107]

S.N. Dubey and R.C. Mehrotra evaluated the stability constants of the aluminium - catechol system, giving values that are quite different from other literature values.[104-106] It has been pointed out[104] that there is an error in their evaluation of the formation curve from the potentiometric data, in that the $\bar{n}_A$ values in the calculation of $\bar{n}$ (eq. IV,26) have apparently been taken to equal unity. The value of $\bar{n}_A$ is dependent on pH, and over the range of pH studied $\bar{n}_A \sim 2$. Therefore the values of $\bar{n}$ should be approximately half those used.

Potentiometric studies carried out by S.N. Dubey and R.C. Mehrotra suggest the formation in solution of hydroxide forms of aluminium-catecholato complexes shown in Fig. IV-6, I and II.



I II

Fig. IV-6

The existence of the species shown in Fig. IV-6,I was confirmed by its isolation as the potassium salt. Other metal chelates of catechol have been extensively studied by potentiometric and other techniques, and include copper (II),[108] cobalt (II),[109] beryllium (II),[110] zinc (II),[109] iron (II),[111] manganese (II),[109] tin (IV),[112] nickel (II),[109] and tungsten (VI).[112] The stabilities of the first-row transition metal

complexes of catechol increase in the order Mn < Co < Ni < Zn < Cu, though rigorous comparisons cannot be made since the ionic media and temperatures used in some cases differ. This is in agreement with the Irving-Williams order,[113] which is given as Mn < Co < Ni < Cu > Zn. However, the order Ni < Zn is in contradiction to that found by D.P. Mellor and L. Maley,[114] although it should be noted that this reversal in the stabilities of nickel and zinc complexes has been observed in other studies with "oxygen-type" ligands.[115,116]

In general the stability of non-transition metal complexes decreases in the order of ionic potential which is defined as the formal charge/ ionic radius. Therefore the order $Al^{3+} > Sc^{3+} > Y^{3+} > La^{3+}$ is expected, provided that the ligand is the same throughout.

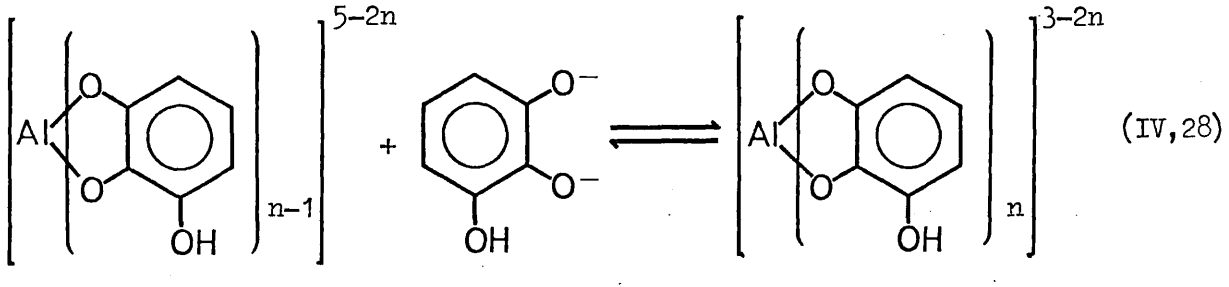
The concept of complex formation is analogous to the Lewis definition of acids and bases acting as electron acceptors and donors respectively. Thus 'hard' metal ions are those which parallel the proton in their attachment to ligands, are often small and of high charge, whereas 'soft' metal ions are large and usually of low charge. Similarly the ligands may be classified as either 'soft' bases, which are polarizable, or 'hard' bases, which are non-polarizable. On the whole it is observed that the most stable complexes are those of soft acids with soft bases and of hard acids with hard bases.

The metal-ligand stability constants of a series of o-diphenols have been correlated with their overall proton-ligand constants. N.P. Slabbert[104] observed a linear relationship for the o-diphenol complexes of Fe(III), Ge(IV) and Al(III), but in all cases the points for tiron (4,5-dihydroxy-benzene-1,3-disulphonic acid) were found to deviate appreciably from the lines. The slopes of the lines for the first metal-ligand stability constants (K_1) were greater than those for the second constants (K_2).

This shows that the dependence upon ligand acidity of successive metal-ligand stability constants progressively decreases, and further, this is so to such an extent that K_3 is virtually independent of ligand acidity. This is rationalised in terms of the progressive increase in the negative charge of successive complexes. Thus the effect of ligand acidity is greatest in the formation of AlL^{+}, diminishing progressively in the stabilities of species AlL_2^{-} and AlL_3^{3-}.

The 1:1, 1:2, and 1:3 aluminium chelates of pyrogallol have been investigated by potentiometric[104,106,117] and preparative[117] methods. S.N. Dubey and R.C. Mehrotra[117] prepared the three pyrogallolato complexes as their potassium salts, in the forms $K[Al(C_6H_4O_3)(OH)_2].4H_2O$, $K[Al(C_6H_4O_3)_2].5H_2O$, and $K_3[Al(C_6H_4O_3)_3].4H_2O$.

The stability constants of the pyrogallolato complexes of aluminium are analogous to those of the catecholato complexes, the chelating ligand being the ortho dianionic species as shown in IV,28. The proton-ligand



(IV,28)

stability constants of those positions involved in complexation, namely the 1- and 2-positions, are required for the evaluation of pL in eq. IV,27. If the first two dissociations constants, Ka_1 (K_3) and Ka_2 (K_2), may be ascribed to these positions, then they may be used in the calculation of pL, thus enabling the subsequent evaluation of the metal-ligand stability constants. However, due to the similarity in pKa_2 of resorcinol (11.06)

to that of pyrogallol (11.19). M. Bartušek and J. Zelinka[110] have reasoned that the hydroxyl groups meta to each other are those that are ionized in the di-dissociated species of pyrogallol (Fig. IV-7). As has been pointed out by N.P. Slabbert,[104] if this is the case then the

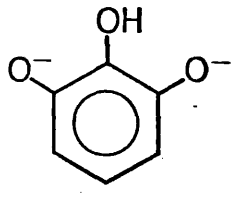


Fig. IV-7

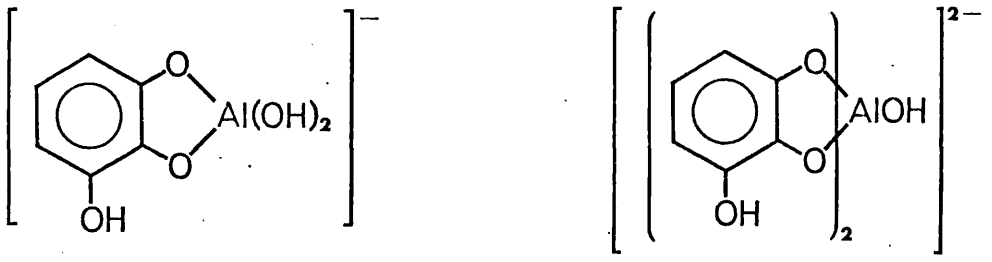
value of the third dissociation, Ka_3 (K_1), could not be used, as might have been expected, in determining the metal-ligand stability constants. This is because chelate formation occurs across the 1- and 2-positions, the third hydroxyl group remaining undissociated (IV,28), whereas Ka_3 is the constant for the formation of the fully dissociated species.

S.N. Dubey and R.C. Mehrotra[117] used values of Ka_1 and Ka_2 obtained by S.E. Sheppard[118] in the calculation of the aluminium-pyrogallolato stability constants. No justification is presented for considering Ka_1 and Ka_2 to refer to dissociations of hydroxyl groups ortho to each other, and N.P. Slabbert[104] has himself made no comment on this work. It should be further noted that S.E. Sheppard[118] has commented that his value of Ka_2 and Ka_3 'must be regarded to some extent hypothetical,' due to the overlapping of successive dissociations.

C.R. Jejurkar et al.[106] have reported values of the first two stability constants, log K_1 and log K_2, for the aluminium-pyrogallolato complexes. However, no details have been presented other than that the Irving-Rossotti titration technique was employed.

N.P. Slabbert[104] overcame the difficulty of requiring the pKa values of hydroxyl groups ortho to each other by using the value pKa_2 of 3-methoxycatechol. This was justified on the basis that the Hammett σ_o values for the hydroxyl and methoxy groups have been found to be the same.[119] Hence the value of the first dissociation constant (Ka_1) of pyrogallol was used in conjunction with the estimated value of the second constant (Ka_2), thereby enabling the evaluation of the aluminium-pyrogallolato stability constants. However in this case only the value of the first stability constant, log K_1, has been reported.

S.N. Dubey and R.C. Mehrotra[117] have presented evidence, based on potentiometric studies of aluminium nitrate in the presence of pyrogallol, that indicates the formation of complexed aluminium hydroxides in solution (Fig. IV-8,I and II).



I II

Fig. IV-8

The interaction between phenolic compounds and complexing agents may also be investigated by paper chromatography and paper electrophoresis.[120] Electrophoresis is the movement of charged particles in a conducting solution under the influence of an electrical field. The mobilities of phenolic compounds in a non-complexing electrolyte solution depend mainly on the

degree of ionization of the hydroxyl groups. However, when a complexing electrolyte solution is used, the formation of a complex is accompanied by a change in the ionic character of the molecule that results in a corresponding change in mobility. Therefore differences between the mobilities obtained using a complexing medium and those using a non-complexing solution indicate that complexation has occurred, and may also yield information about the nature of the complex or complexes involved.

IVB Results and Discussion

Paper chromatographic and paper electrophoretic techniques were employed in a qualitative investigation of the interaction between a number of phenolic compounds and aluminium III. In each case the results obtained in the presence and absence of the complexing agent are compared.

Paper chromatograms were obtained in the manner described in VIII,A,12 "Paper Chromatography". Three types of paper were used a) untreated paper, b) paper impregnated with sodium aluminate, c) paper impregnated with aluminium sulphate. The R_F values obtained from the paper chromatograms are shown in Table IV,1.

The R_F values shown in Table IV,1 are generally lower when the complexing agent is present, and this is particularly so in the case of sodium aluminate. This may be expected since sodium aluminate is associated with alkaline conditions, and the formation of a complex is accompanied by the release of hydrogen ions. It should be noted, however, that the lower R_F values associated with sodium aluminate may be due in part at least to the formation of the sodium salts of the phenols rather than the formation of aluminium complexes. The diaryl sulphones, compounds 4. - 8., which have all given high R_F values with the untreated paper and have not moved when sodium aluminate is present, have behaved differently to compound 3. 3,4-dihydroxydiphenyl sulphone, which has given in all cases high R_F values. The compounds 4. - 8. all possess hydroxyl groups ortho to each other in both rings, and therefore may complex on both sites forming polynuclear material. This is not so with 3. 3,4-dihydroxydiphenyl sulphone, and

Table IV,1 Paper chromatography of phenolic compounds in the presence and absence of aluminium III.

	a) untreated R_F	b) sodium aluminate, R_F	c) aluminium sulphate, R_F
1.	0.97	0.35	0.95
2.	0.90	0.08	0.90
3.	0.96	0.93	0.96
4.	0.95	0.00	0.93
5.	0.90	0.00	0.92
6.	0.88	0.00	0.88
7.	0.89	0.00	0.89
8.	0.94	0.00	0.84
9.	0.94	0.28	0.93
10.	0.97	0.06	0.95
11.	0.98	0.14	0.96
12.	0.98	0.58	0.95

1. catechol, 2. pyrogallol, 3. 3,4-dihydroxydiphenyl sulphone, 4. 3,3',4,4'-tetrahydroxydiphenyl sulphone, 5. 3,3',4,4',5-pentahydroxydiphenyl sulphone, 6. 2,3,3',4,4',5'-hexahydroxydiphenyl sulphone, 7. 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone, 8. 2,2',3,3',4,4'-hexahydroxydiphenyl sulphone, 9. ethyl-3,4,5-trihydroxybenzoate, 10. ethyl-2,3,4-trihydroxybenzoate, 11. ethyl-2,3-dihydroxybenzoate, 12. ethyl-3,4-dihydroxybenzoate.

therefore this may serve to account for its different behaviour.

Paper electrophoretograms were obtained as described in VIII,A,11 "Paper Electrophoresis" the results of which are shown in Table IV,2. Mobilities obtained using a) sodium aluminate solution (pH 13) are compared to those obtained using b) sodium hydroxide solution (pH 13). Similarly, comparisons are made between the mobilities obtained using c) aluminium sulphate solution (pH 3.39) and d) dilute sulphuric acid (pH 3.39). An increase in mobility torwards the cathode or a decrease in mobility towards the anode in the presence of the complexing agent suggests the formationof an AlL^{+} type complex between the metal ion, Al^{3+} and the phenol, H_2L. The reverse may arise due to the formation of AlL_2^{-} and AlL_3^{3-} complexes. The AlL^{+} complex may be of greater significance in acidic conditions, since alkaline conditions may favour the formation of anionic complexes AlL_2^{-} and AlL_3^{3-}.

Table IV,2 shows that the use of sodium aluminate has resulted in a lower mobilities towards the anode, which suggests the formation of AlL^{+} type complexes.

The use of aluminium sulphate has resulted in higher mobilities towards the cathode, which again indicates the formation of cationic complexes of the type AlL^{+}. In general the absolute changes in mobilities imparted by the use of aluminium sulphate is proportionately greater than by the use of sodium aluminate. Though in both cases the changes in mobilities may be rationalised in terms of the formation of AlL^{+} complexes, in the latter case the relatively lower changes may be due to the concurrent formation of anionic species of the types AlL_2^{-} and AlL_3^{3-}.

Table IV,2 Paper electrophoresis of phenolic compounds in the presence and absence of aluminium III

Phenolic compound*	Mobilities $cm^2\ V^{-1}\ sec^{-1}$			
	a) sodium aluminate	b) sodium hydroxide	c) aluminium sulphate	d) dil. sulphuric acid
	pH 13, towards anode, 10^{-5}		pH 3.39, towards cathode, 10^{-6}	
1.	15.2	21.0	16.9	16.3
2.	16.6	21.4	17.0	14.9
3.	14.7	21.8	41.3	5.4
4.	18.4	21.6	48.6	11.6
5.	20.7	21.6	35.4	9.6
6.	18.1	23.1	31.4	7.1
7.	18.8	22.9	33.9	6.6
8.	20.0	22.6	38.0	10.1

* compounds correspond to those in Table IV,

A more rigorous investigation, employing the potentiometric method described by H.M. Irving and H.S. Rossotti,[102] was undertaken on the aluminium chelates of four phenolic compounds, catechol, pyrogallol, 3,3',4,4'-tetrahydroxydiphenyl sulphone and 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone. Potentiometric titrations were carried out as described in VIII, A,7 "Potentiometry". The study of each phenolic compound requires three titration curves, as exemplified by those obtained for catechol shown in Fig. IV-9. The ionic strength was maintained at a constant value by the presence of a high concentration of salt (0.88$\underline{\underline{M}}$).

The proton-ligand formation curve (Fig. IV-10) of catechol was calculated from the titration curves using eq. IV,25. Approximate values of the successive constants were obtained by interpolation of half $\bar{n}$ values, the correction term method, using eq. IV,21,22 and 23, being employed to evaluate the correct constants. The values of each stability constant obtained from the correction term method at various values of d, chosen such that $0.9 > d > 0.1$, were averaged to give the final correct value. The proton-ligand stability constants of catechol are shown in Table IV,3.

The formation curve of the catecholato complexes of aluminium shown in Fig. IV-11 was calculated using eq. IV,26 and 27. The approximate values of the successive metal-ligand stability constants may be obtained from the formation curve by interpolation of half $\bar{n}$ values, and these are shown in Table IV,4.

In all the $\underline{o}$-diphenol complexes of aluminium studied by N.P. Slabbert,[104] K_2/K_3 was found to be greater than $10^{2.5}$. This therefore met the

requirement given by H.M. Irving and H.S. Rossotti,[121] by which stability constants can be obtained by interpolation of half $\bar{n}$ values without introducing considerable error. Therefore N.P. Slabbert obtained K_3 by taking the half $\bar{n}$ value, and calculated K_1 and K_2 for the system N=2. Such a method must always have the disadvantage of obtaining the value of K_3 from only one point on the formation curve. M.T. Beck[98] considers that the half-value method is sufficiently accurate when $K_1/K_2 > 10^4$, in which case the successive steps of complex formation are distinct. It is a question of degree as to whether a limit of $K_1/K_2 > 10^{2.5}$ or 10^4 should be applied to the use of the half-value method to obtain reasonably accurate stability constants, though of course the latter limitation must be regarded as the more exacting.

S.N. Dubey and R.C. Mehrotra used methods for N=2 systems in their calculation of correct stability constants for the aluminium complexes of catechol,[103] pyrogallol,[117] and tiron (1,2-dihydroxybenzene-3,5-disulphonic acid).[122] The correction term method was used in the usual manner to evaluate the first two stability constants, K_1 and K_2 from the points on the formation curve $\bar{n} = 1 + d$ and $1 - d$. The stability constants K_2 and K_3 were calculated in a similar manner at the points 2+d and 2-d. The values obtained for each stability constant were averaged to give the final value. However, the correction term method relies on some point of symmetry. With a system N=2, there is theoretically a point of symmetry at the mid-point of the formation curve at the point $\bar{n}=1$. S.N. Dubey and R.C. Mehrotra have therefore assumed theoretical points of symmetry for the portion of the formation curve $0 < \bar{n} < 2$ at the point $\bar{n}=1$, and similarly for the portion $1 < \bar{n} < 3$ at the point $\bar{n}=2$. However, when there are three overlapping equilibria concerned, there is no theoretical point of symmetry on the formation curve. The metal-ligand

formation curves in the case of catechol and tiron have furthermore been shown to be erroneous due to a mistake in the calculations.[104]

In a system in which there are overlapping equilibria, the calculation of a stability constant requires the evaluation of the contribution to $\bar{n}$ of the complexes involved in the other stability constants. This point is shown in eq. IV,16, in which corresponding values of $\bar{n}$ and [L] are clearly dependent not only on K_n, but also on the values of the other stability constants $K_1 \cdots K_{n-1}$ and $K_{n+1} \cdots K_N$.

Correct stability constants for the aluminium-catecholato complexes were obtained from the metal-ligand formation curve, shown in Fig. IV-11, by an iterative process using expressions obtained from eq. IV,16. In the aluminium-catecholato case the system is of the type N=3, for which eq. IV,29,30, and 31, one for each stability constant, may be derived.

$$\log_{10}K_1 = -\log_{10}[L] + \log_{10}\left(\frac{\bar{n}}{(1-\bar{n})+(2-\bar{n})[L]K_2+(3-\bar{n})[L]^2K_1K_2}\right) \qquad (IV,29)$$

$$\log_{10}K_2 = -\log_{10}[L] + \log_{10}\left(\frac{(\bar{n}-1)[L]\,K_1 + \bar{n}}{(2-\bar{n})[L]K_1 + (3-\bar{n})[L]^2K_1K_3}\right) \qquad (IV,30)$$

$$\log_{10}K_3 = -\log_{10}[L] + \log_{10}\left(\frac{(\bar{n}-2)[L]^2K_1K_2+(\bar{n}-1)[L]K_1 + \bar{n}}{(3-\bar{n})[L]^2K_1K_2}\right) \qquad (IV,31)$$

Three points were chosen on the formation curve, one for the computation of each stability constant, K_n, such that $n > \bar{n} > n-1$. The approximate values of K_2 and K_3, obtained by the half-value method, together with the relevant value of $\bar{n}$ and [L], were used in eq. IV,29 to compute a new value of $\log_{10} K_1$. This new value of K_1 was used in eq. IV,30 to calculate a

new value of $\log_{10} K_2$. Similarly a new value of $\log_{10} K_3$ was computed using the new values of K_1 and K_2 in eq. IV,31. This method was computerised and used iteratively until the sum of the absolute differences between successive approximations of the three stability constants was less than 10^{-6}. Other sets of values of $\bar{n}$ were chosen on the formation curve, and this whole process was repeated several times. The values obtained for each stability constant were then averaged to give the final value shown in Table IV,4. Points on the theoretical formation curves, calculated from eq. IV,15 using the final values of the stability constants, are included in Fig. IV-10 and 11 for comparison. In the case of the proton-ligand formation curve, [H] is used in place of [L] in eq. IV,15.

3,3',4,4'-Tetrahydroxydiphenyl sulphone was treated in a similar manner, on the basis that its structure is equivalent to two units of catechol. Thus two proton-ligand and three metal ligand constants were evaluated. It is assumed that due to the presence of the sulphonyl group, any change on one ring will have only negligible effect on the equivalent change on the other ring. Thus any differences between the corresponding constants of each ring are expected to be within the limits of accuracy of the experiment. The proton-ligand and metal-ligand formation curves are shown in Fig. IV-12 and 13, and the stability constants are given in Tables IV,3 and 4 respectively.

The proton-ligand formation curves of pyrogallol (Fig. IV-14) 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone (Fig. IV-16) were calculated in a similar manner to catechol and the tetrahydroxydiphenyl sulphone respectively. The correct proton-ligand stability constants shown in

Table IV,3, were evaluated by the iterative method using eq. IV,29,30 and 31, in which [H] and $\bar{n}_A$ were used in place of [L] and $\bar{n}$.

In the case of the metal-ligand formation curves of the trihydroxyphenyl systems, L refers to the species in which hydroxyl groups ortho to each other are ionised. In the case of pyrogallol N.P. Slabbert[104] evaluated pL by using Ka_1 of pyrogallol and Ka_2 of 3-methoxycatechol. This is rationalised on the basis that the diphenolate species of pyrogallol is 1,3-di-dissociated and therefore Ka_1 refers to the 1-position. However, this is not necessarily so, since the mono-dissociated species may be ionized on the 2-position, and thus may be stabilized due to hydrogen-bonding to the hydroxyl groups in the 1- and 3-positions. Subsequent further ionization gives the 1,3-di-dissociated species, which is expected to be the more stable dianion due to charge separation. This would require ligand exchange of a proton onto the 2-position. Such various mono- and di-dissociated species may exist in equilibrium; it is a question of which species predominate.

S.N. Dubey and R.C. Mehrotra[117] used the values of Ka_1 and Ka_2 of pyrogallol in their evaluations of pL, without justifying the assumption that the first two dissociations are those of ortho hydroxyl groups. Furthermore, in their calculations of the $\bar{n}$ values, S.N. Dubey and R.C. Mehrotra[117] have made the same error that N.P. Slabbert[104] noted in their work on catechol[103] and tiron[112]. N.P. Slabbert did not evaluate the value of Ka_3 of pyrogallol, but calculated the correct values for the first two dissociation constants on the basis of N=2 type system. Therefore it was not possible to take into account the influence of Ka_3 in the event of overlapping dissociations, and therefore this may be a source of some error.

In the case of the metal-ligand equilibria of the trihydroxyphenyl systems, the calculations of the formation curves were carried out with respect to the non-dissociated species (LH_2) as for the equilibrium shown in IV,32. Hence the value of $p([H]^2/[LH_2])$ was used in place of

$$AlL_{n-1} + LH_2 \rightleftharpoons AlL_n + 2H \qquad (IV,32)$$

pL in the metal-ligand formation curves of pyrogallol and 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone, shown in Fig. IV-15 and 17 respectively. The constant Ke_n for the equilibrium shown in IV,32 is given by the expression

$$Ke_n = [AlL_n][H]^2/[AlL_{n-1}][LH_2] \qquad (IV,33)$$

The relationship between Ke_n and the stability constant, K_n (eq. IV,8) is clearly

$$K_n[L] = Ke_n\,[LH_2]/[H]^2 \qquad (IV,34)$$

The first proton-ligand stability constant, K_1, has negligible effect over the range of pH at which the metal-ligand was studied, and therefore for these cases eq. IV,27 can be converted to give the expression

$$p\left(\frac{[H]^2}{[LH_2]}\right) = p\left[\left(\frac{[H]^2 + ([H]/K_3) + (1/K_2K_3)}{T_L^o - \bar{n}\,T_M^o}\right)\frac{V^o + v'''}{V^o}\right] \qquad (IV,35)$$

Eq. IV,35 was used in the calculation of the formation curve of pyrogallol (Fig. IV-15) and 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone (Fig. IV-17) the latter again being treated on the basis that its structure is equivalent to two units of pyrogallol.

In eq. IV,26 which is generally used to calculate $\bar{n}$ values, $\bar{n}_A$ refers to the number of protons released on the formation of a complex. In the

trihydroxyphenyl systems, where $\bar{n}_A$ has a maximum number of 3, the maximum number of protons removed on complexation is 2. One of the hydroxyl groups is not involved and to take this into account eq. IV,26 was altered in the calculation of $\bar{n}$ values for these systems to that shown in eq. IV,36. However, this treatment may not necessarily be

$$\bar{n} = \frac{(v'''-v'')(N+E^o)}{(V^o+v'')(\bar{n}_A-1)T_M^o} \qquad (IV,36)$$

valid when the conditions are such that the di-dissociated species is present in significant concentrations. Correct use of eq. IV,36 requires that no protons are released upon complexation of the dianionic species. If this species is ionized on the 1- and 3-positions, which as stated previously is more likely, then eq. IV,36 is only valid if complexation in this case is accompanied by proton transfer from the 2- to the 3-position. In the event that hydroxyl groups ortho to each other are those dissociated in the diphenolate species, no protons are removed upon complexation and therefore eq. IV,36 remains valid. However the calculation of $\bar{n}$ values for the trihydroxyphenyl systems involves a value of $\bar{n}_A$ such that $3 > \bar{n}_A > 2$. Under these conditions only the first dissociation is of significance, and the position to which this dissociation refers must be involved in complexation. Therefore the problem of whether the use of $(\bar{n}_A-1)$ in eq. IV,27 is the correct approach when used in cases where $\bar{n}_A < 2$ does not arise.

Approximate values for the equilibrium constants, pKe_n of the aluminium chelates of pyrogallol and 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone were obtained by interpolation of half $\bar{n}$ values. The iterative method was used

to compute the correct equilibrium constant, the value of $[LH_2]/[H]^2$ being used in place of [L] in eq. IV,29,30 and 31 and the results are shown in Table IV,5. Similarly, eq. IV,15 was altered to calculate the theoretical metal-ligand formation curves for the trihydroxyphenyl systems. N.P. Slabbert[104] estimated the dissociations of pyrogallol to the ortho dianion, p(KaKb), to be 22.65, and gave values of 16.60 and 5.95 for the first metal-ligand stability constant ($\log_{10} K_1$) and the first equilibrium constant (pKe_1) respectively. Where the relevant dissociation constants Ka and Kb are known, the relation between stability constants K_n and equilibrium constants Ke_n in eq. IV,34 gives the expression

$$K_n = Ke_n/KaKb \qquad (IV,37)$$

Therefore evidently N.P. Slabbert[104] has made an error in his calculations, and it is not possible to judge whether or not the mistake lies in the values given for the stability constants. The formation of hydroxide forms of aluminium chelates, such as those shown in Fig. IV-6 and 8, may possibly interfere in the titration curves of both the di- and trihydroxyphenyl systems. However, the titration curves reported by S.N. Dubey and R.C. Mehrotra of the 1:1, 1:2, and 1:3 molar ratios of aluminium to catechol[103] and to pyrogallol,[117] show that the inflections for the formation of these hydroxides occurs at a higher pH than the formation of the next successive complex. Since in all cases the procedure involved the use of considerable excess of the phenolic compound over aluminium nitrate, the formation of such hydroxides is not considered to have any significant effect.

The results given in Table IV,3 show the increased acidity of the hydroxyl groups due to the electron withdrawal effect of the sulphonyl group. This is particularly so in the case of the first dissociation, Ka_1 (K_3), the effect being less marked on subsequent dissociations, and this is to be expected on the grounds that the influence of previous ionizations would increasingly dominate the inductive effect of the sulphonyl group. The metal-ligand stability constants of the dihydroxyphenyl systems have been converted to equilibrium constants for comparison with the trihydroxyphenyl systems (Table IV,5). In general the dihydroxyphenyl compounds have higher values than the corresponding trihydroxyphenyl compounds. An anomaly however occurs at $\log_{10}K_3$ of catechol and pyrogallol.

N.P. Slabbert[104] found a linear correlation between metal-ligand and proton-ligand stability constants for aluminium complexes. It is to be expected therefore that the equilibrium constants shown in Table IV,5 would be in line with the value of the proton-ligand constants. Comparing corresponding systems, it can be seen that this is indeed generally so. The anomalous behaviour of tiron reported by N.P. Slabbert[104] may be due to the formation of a six-membered chelate ring involving the sulphonic acid.

S.N. Dubey and R.C. Mehrotra[117] prepared the 1:1, 2:1, and 3:1 pyrogallol complexes of aluminium as their potassium salts. A repeat of this work resulted in a black product, despite the added precaution of carrying out the reaction under nitrogen. However it has been found that the complexes may be prepared as their ammonium salts to give white products (experiment 32). The complexes were analysed as described in VIII,A,9 "Estimation of Aluminium" and 10 "Estimation of Pyrogallol", and were found to be as shown in Fig. IV-18.

Table IV,3 Proton-ligand Stability Constants

	Catechol	3,3',4,4'-tetrahydroxy-diphenyl sulphone	Pyrogallol	3,3',4,4',5,5'-hexa-hydroxydiphenyl sulphone
Interpolation at half $\bar{n}_A$ values				
$\log_{10}K_1$	12.50	12.10	12.73	12.59
$\log_{10}K_2$	9.46	7.80	11.62	10.38
$\log_{10}K_3$	-	-	9.20	7.46
Final values				
$\log_{10}K_1$	12.52	12.09	12.67	12.66
$\log_{10}K_2$	9.46	7.83	11.72	10.39
$\log_{10}K_3$	-	-	9.21	7.46
Literature values				
$\log_{10}K_1$	11.59,[107] 13.65[104]		14[109]	
$\log_{10}K_2$	9.13,[107] 9.36[104]		11.19,[109] 11.23[104]	
$\log_{10}K_3$			9.05,[109] 9.05[104]	

Table IV,4 Metal-ligand Stability Constants

	Catechol	3,3',4,4'-tetrahydroxy-diphenyl sulphone	Pyrogallol	3,3'4,4'5,5'-hexa-hydroxydiphenyl sulphone
Interpolation at half $\bar{n}$ values				
$\log_{10}K_1$	15.37	14.96		
$\log_{10}K_2$	12.37	12.74		
$\log_{10}K_3$	7.68	9.27		
Final values				
$\log_{10}K_1$	15.31	14.93		
$\log_{10}K_2$	12.36	12.65		
$\log_{10}K_3$	7.74	9.24		
Literature values				
$\log_{10}K_1$	16.75,[104] 16.9[105]		16.60,[104] 15.30[106] 14.3[117]	
$\log_{10}K_2$	13.60,[104] 13.6[105]		11.63,[106] 13.5[117]	
$\log_{10}K_3$	9.0,[104] 8.9[105]		11.9[117]	

Table IV,5 Metal-ligand Equilibrium Constants

	Catechol	3,3',4,4'-tetrahydroxy-diphenyl sulphone	Pyrogallol	3,3',4,4',5,5'-hexa-hydroxydiphenyl sulphone
Interpolation at half n values				
pK_1	6.61	4.96	6.02	4.68
pK_2	9.61	7.18	8.55	6.63
pK_3	14.30	10.65	14.47	9.57
Final values				
pK_1	6.67	4.99	6.00	4.73
pK_2	9.62	7.27	8.62	6.60
pK_3	14.24	10.68	14.67	9.57
Literature values				
pK_1	6.25[104]		5.95[104]	
pK_2	9.40[104]			
pK_3	14.0[104]			

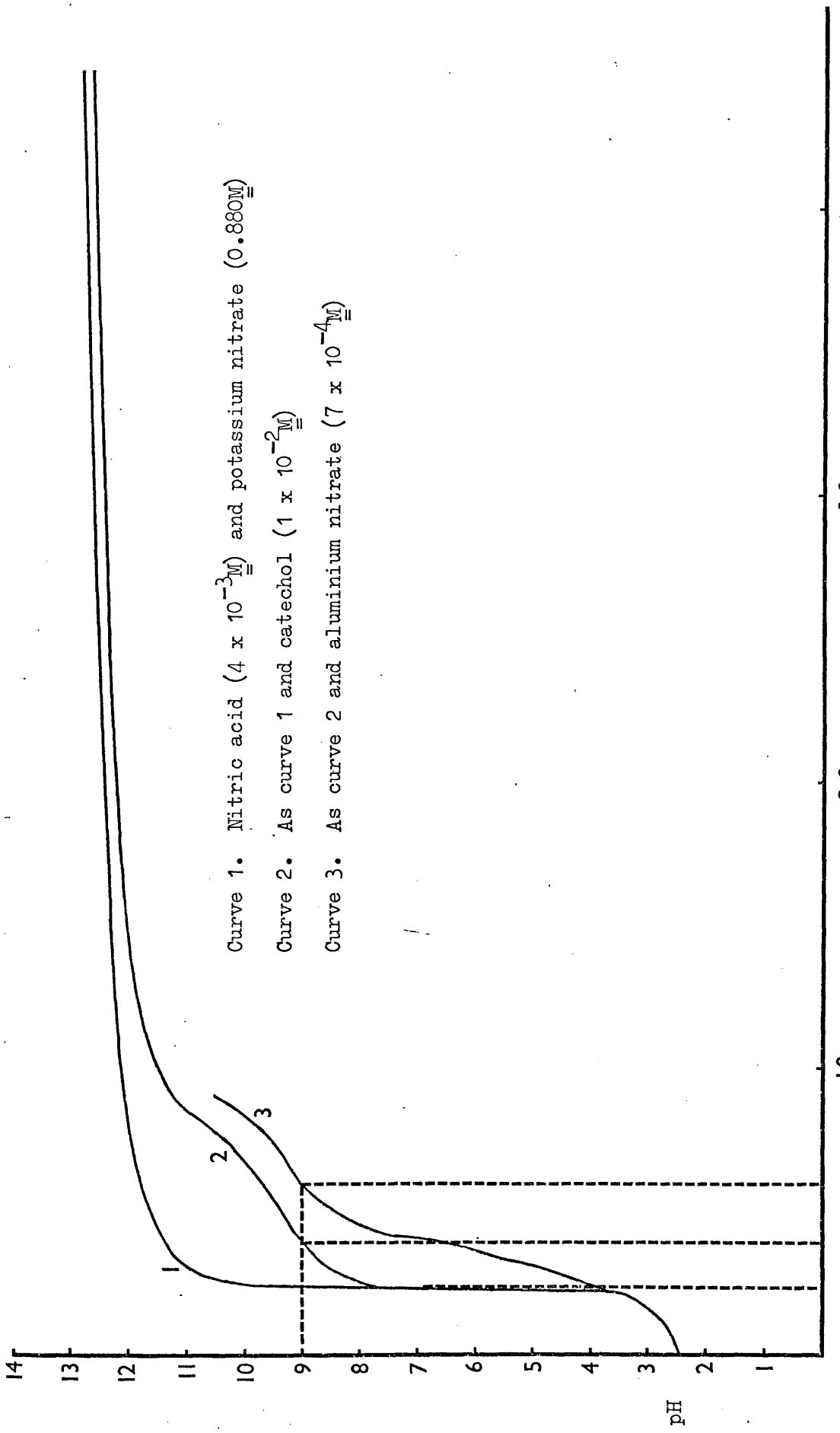


Fig. IV-9 Potentiometric titration of catechol in the absence and presence of aluminium

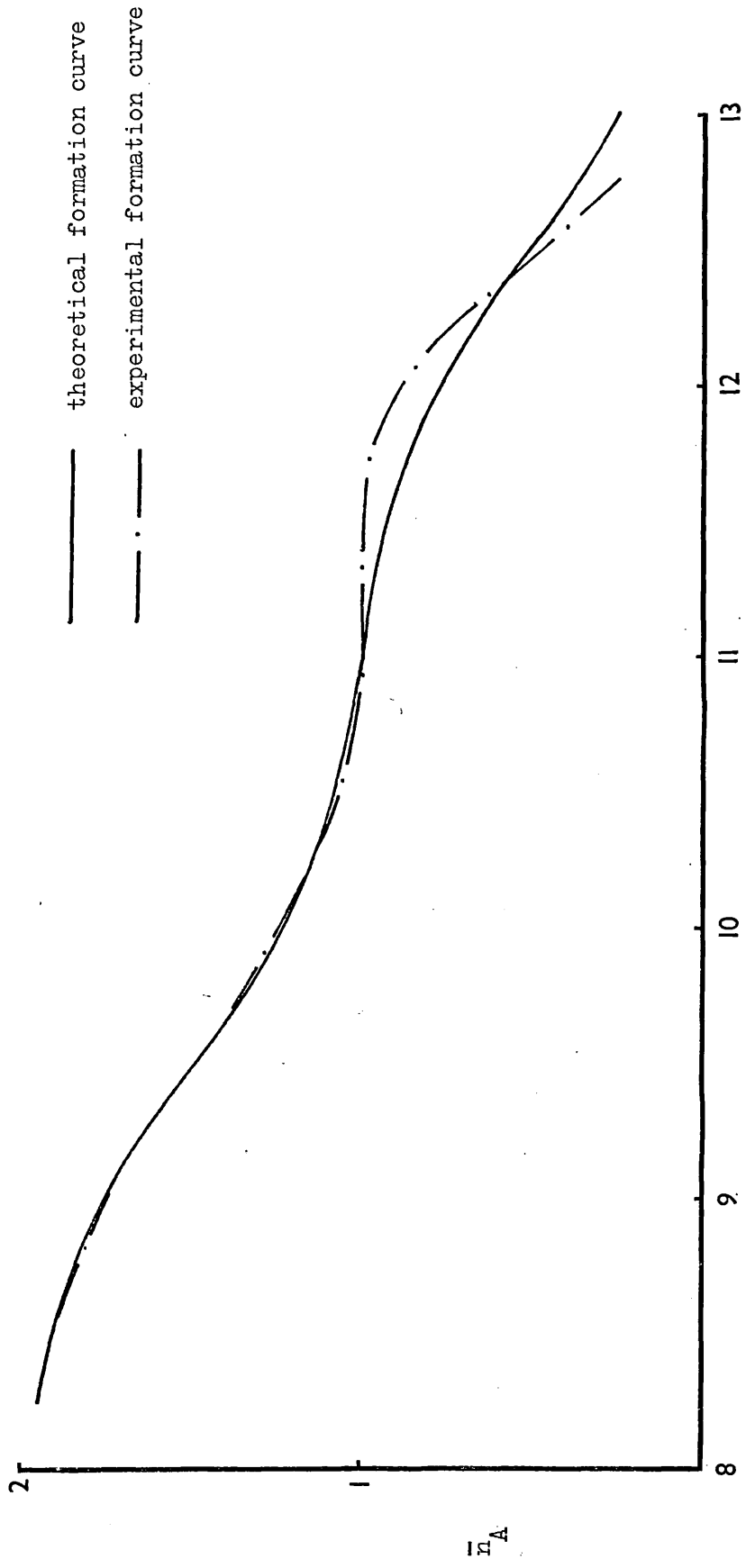


Fig. IV-10 Proton-ligand formation curve of catechol

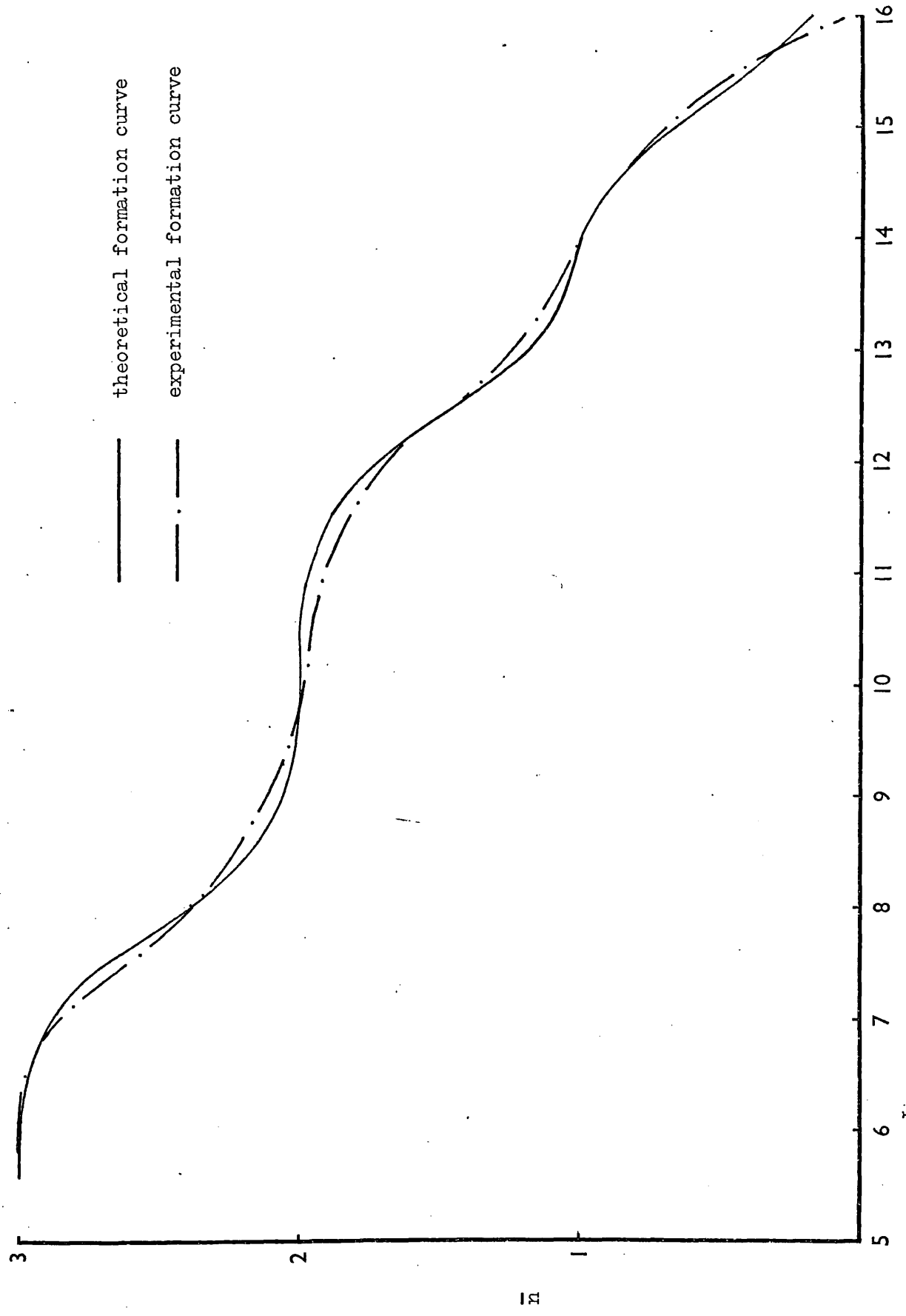


Fig. IV-11 Metal-ligand formation curve of the aluminium-catecholato complexes

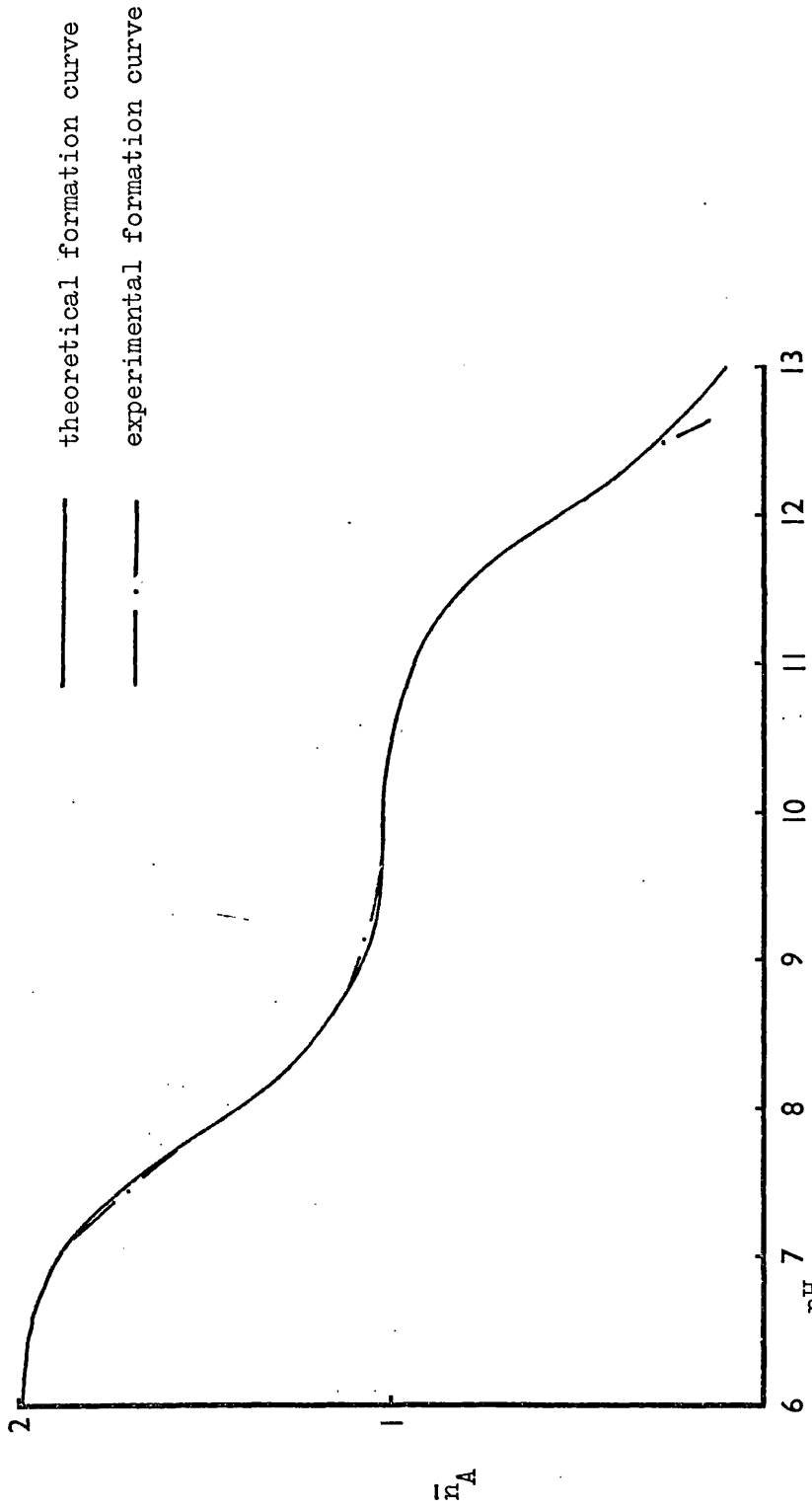


Fig. IV-12 Proton-ligand formation curve of 3,3',4,4'-tetrahydroxydiphenyl sulphone

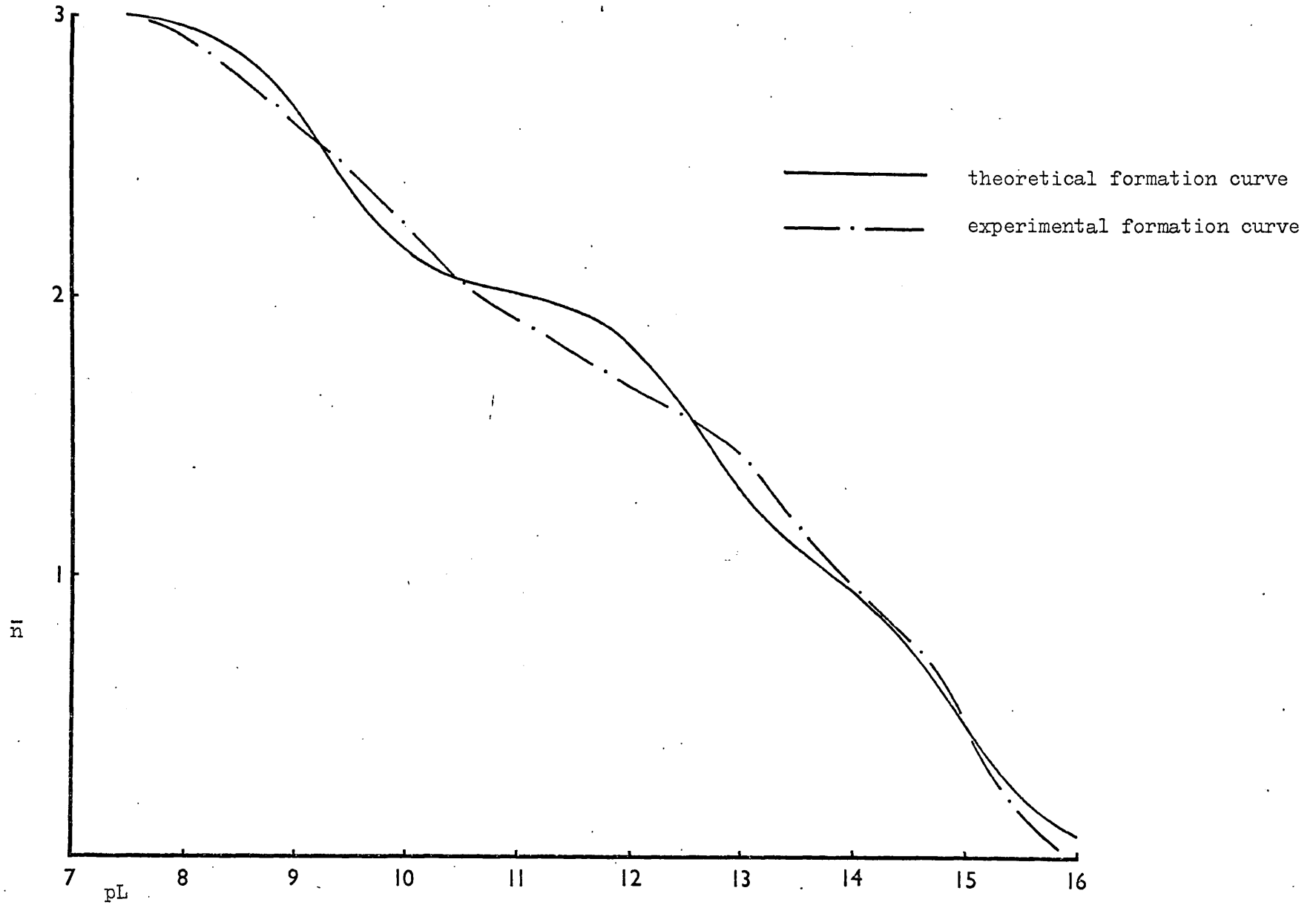


Fig. IV-13 Metal-ligand formation curve of the aluminium-3,3',4,4'-tetrahydroxydiphenyl sulphone complexes

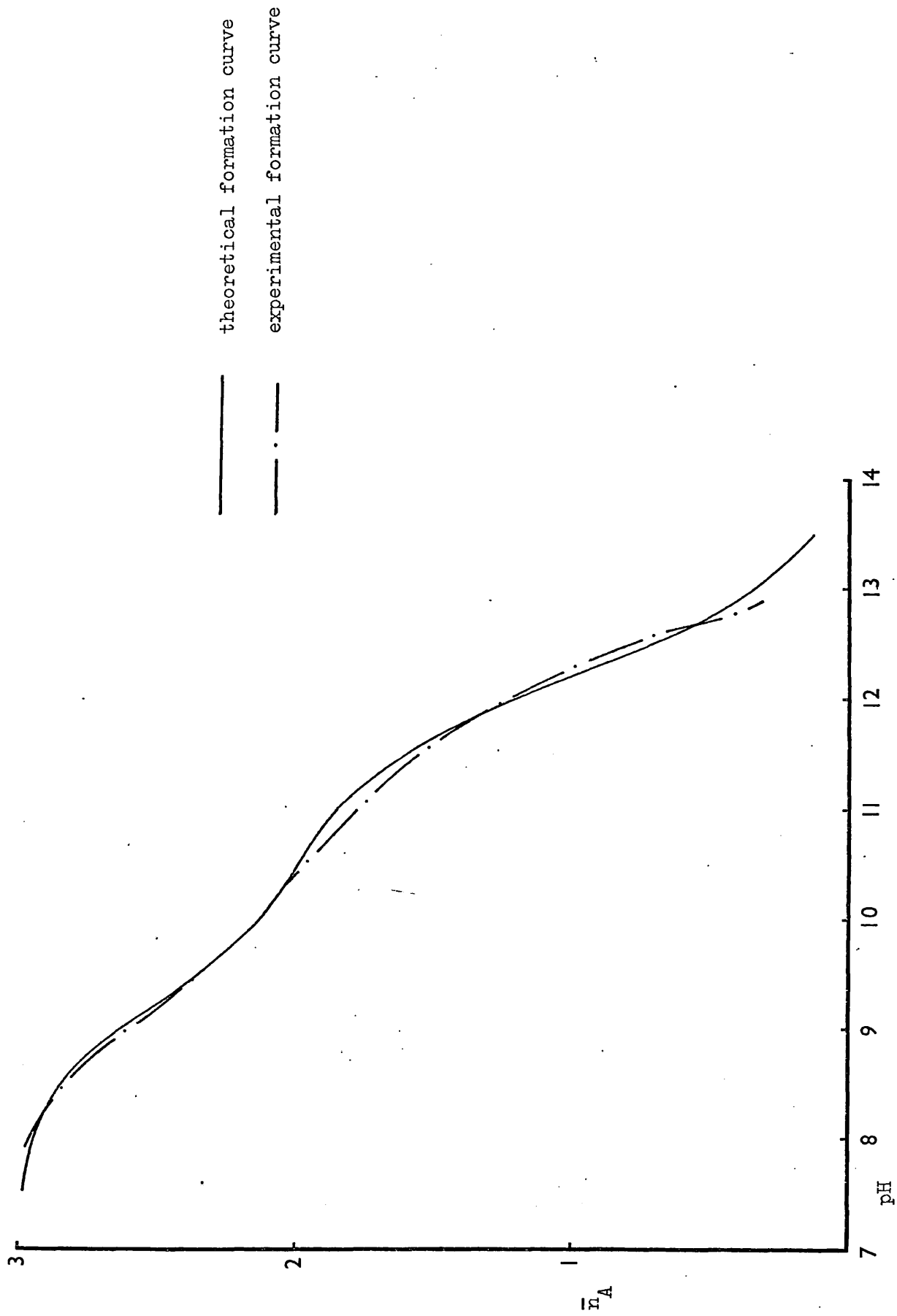


Fig. IV-14 Proton-ligand formation curve of pyrogallol

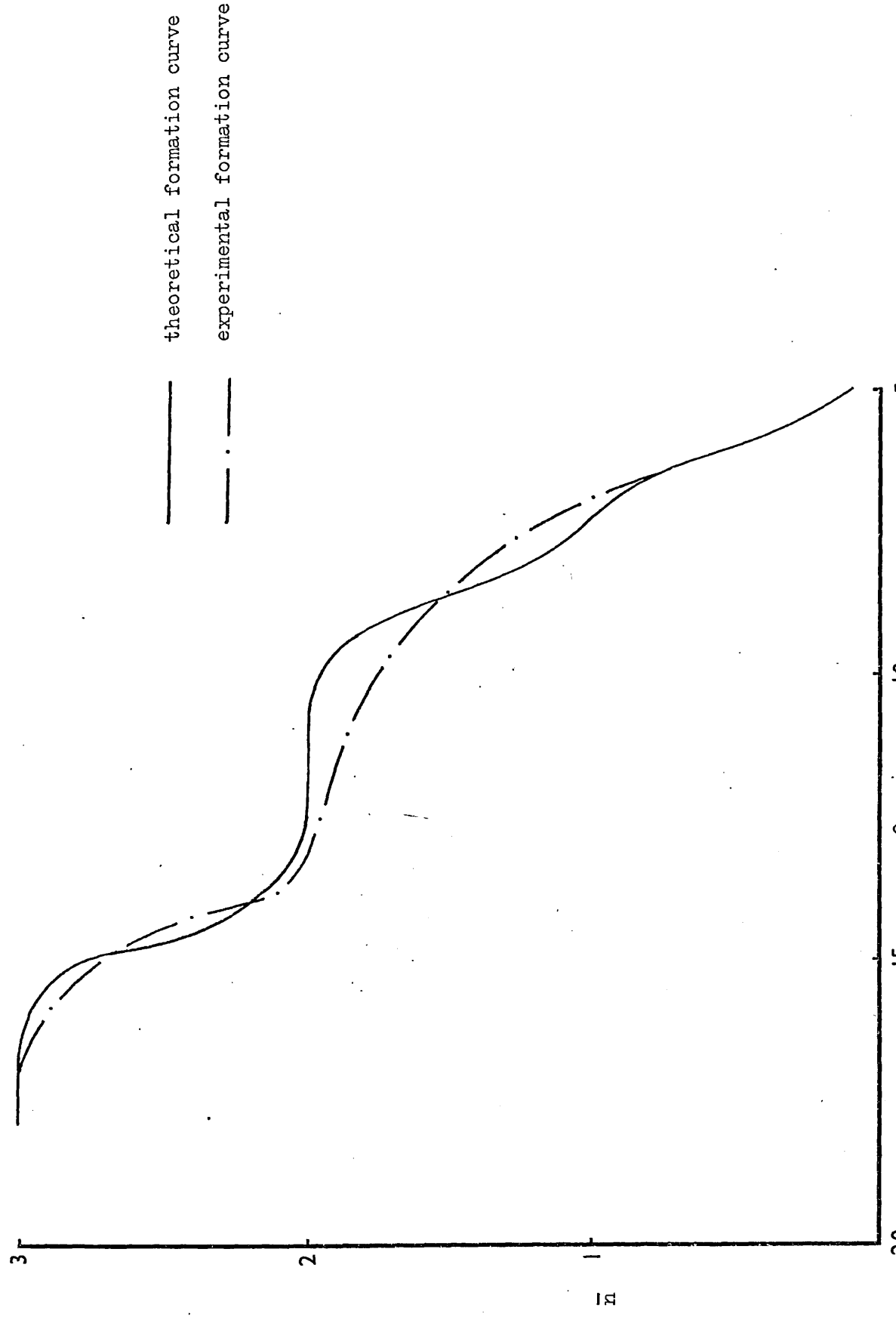


Fig. IV-15 Metal-ligand formation curve of the aluminium-pyrogallolato complexes

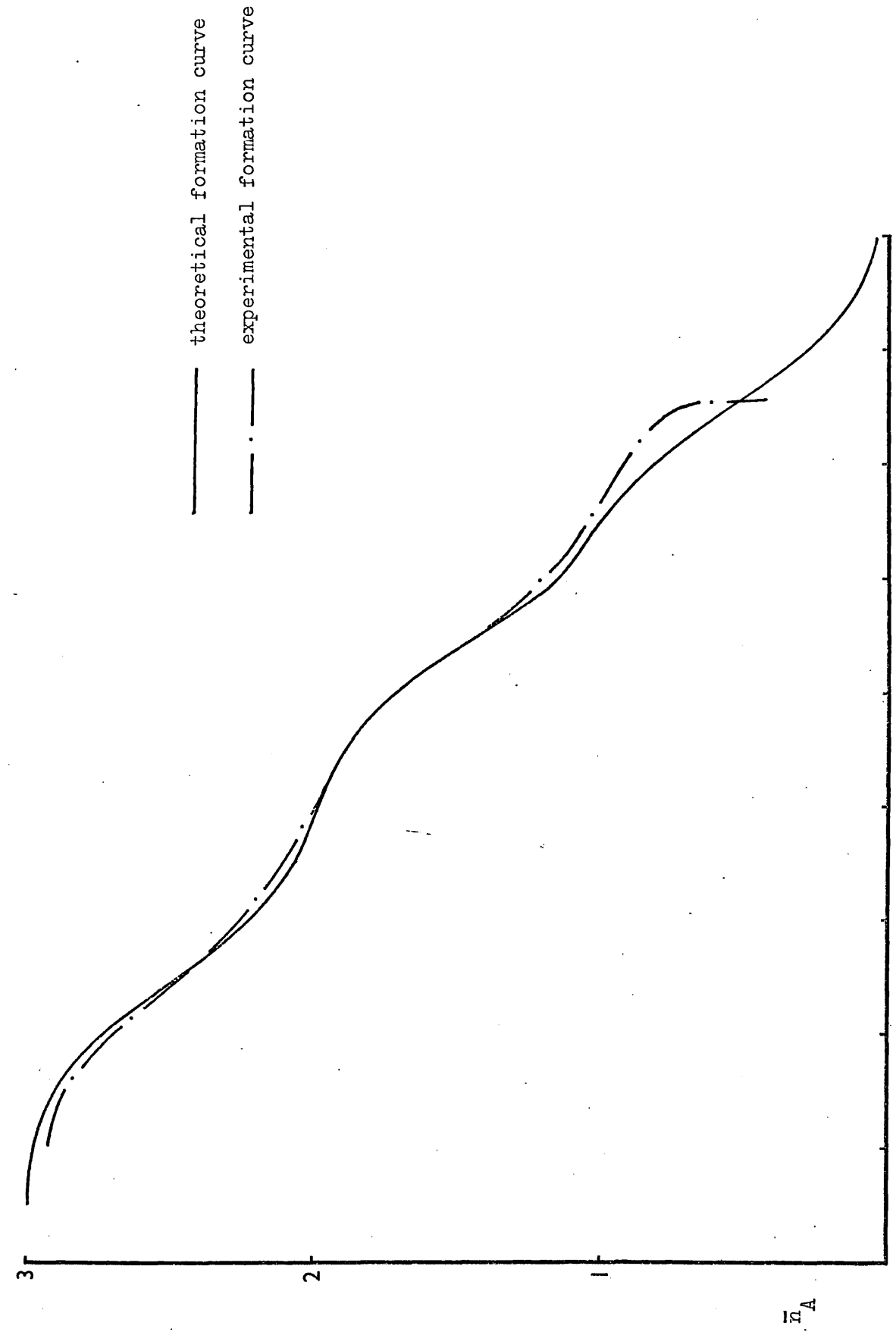


Fig. IV-16 Proton-ligand formation curve of 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone

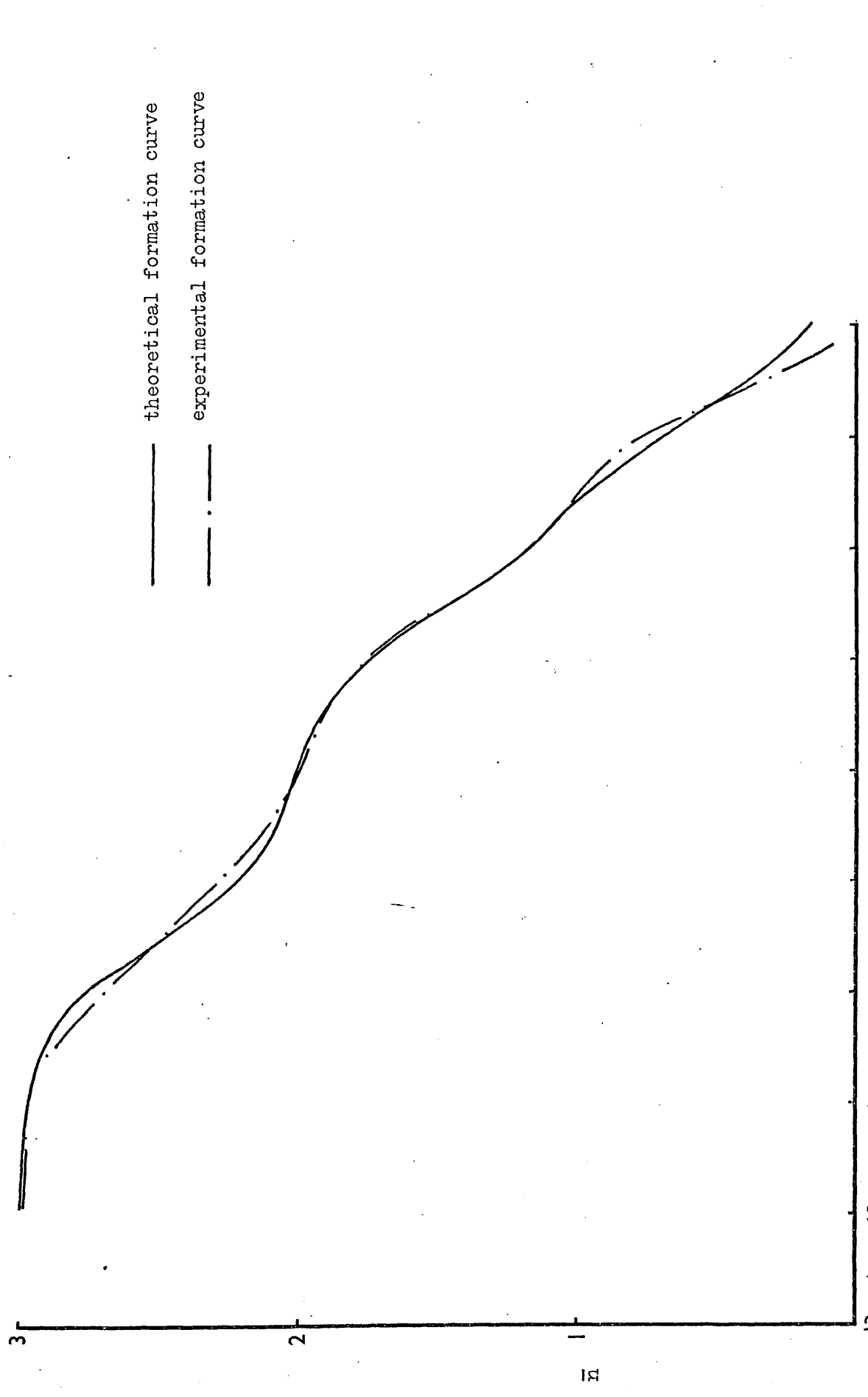


Fig. IV-17 Metal-ligand formation curve of the aluminium-3,3',4,4',5,5'-hexahydroxydiphenyl sulphone complexes

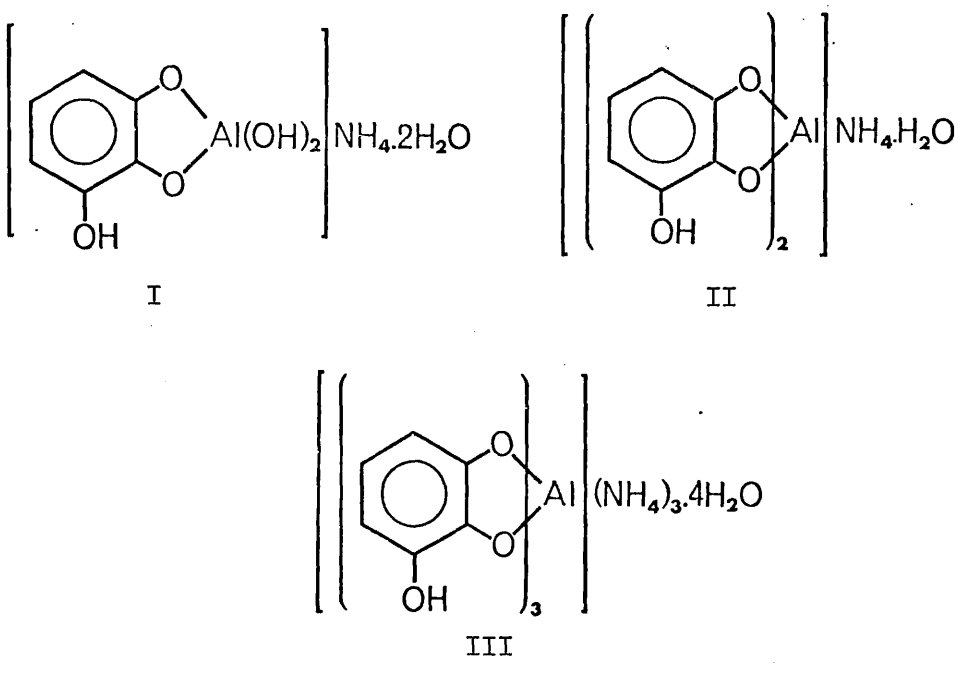


Fig. IV-18

As outlined earlier glycine acts as a bidentate chelating agent, utilizing the carboxylic and amino groups for bonding, as is exemplified by copper glycinate (Fig. IV-3). Further, "nitrogen-type" ligands have been shown to coordinate with aluminium, as in the case of aluminium tris(8-hydroxyquinolinate) shown in Fig. IV-4. Both ^{27}Al and ^{13}C n.m.r. spectroscopy have been used to investigate the coordination complex between aluminium and ethylenediamine.[123] As a possible model of parts of the protein chains in collagen an investigation has been undertaken into the nature of the aluminium salts of glycine, β-alanine, and 4-aminobutyric acid. In the event of these amino acids acting as bidentate ligands, glycine and β-alanine would form 5- and 6-membered rings respectively, of which the former would be expected to be slightly more stable by virtue of its greater chelate effect, whereas with 4-aminobutyric acid the chelate effect would be expected to be considerably less.[96-98]

The preparation of the amino acid salts of aluminium monocatecholato is described in experiment 33. These complexes were not purified by recrystallisation since no suitable solvent could be found. The glycine complex was sufficiently soluble in D.M.S.O. to enable ^{15}N n.m.r. to be used in the investigation of its structure. The chemical shift was compared with that of the nitrogen in the ethyl ester of glycine. The aluminium glycinate complex gave a $\delta_{\underline{\underline{N}}}$ value of 353 ppm whereas the ethyl ester of glycine gave a shift of 268 ppm ($\delta_{\underline{\underline{N}}}$ values upfield from nitromethane). Compounds such as amines, ammonia, and ammonium ions show the greatest shieldings due to their symmetric structures which results in a low paramagnetic contribution, and this is considered to be the dominant term in ^{15}N shifts.[124] This is particularly so when the atom has a closed-shell or inert gas configuration. Hence the greatly differing shift of the aluminium glycinate complex, where the nitrogen appears to be more shielded, as compared to that of the ethyl ester of glycine may be rationalised in terms of glycine acting as a bidentate ligand in the former case, as shown in Fig. IV-19. If this is so, then

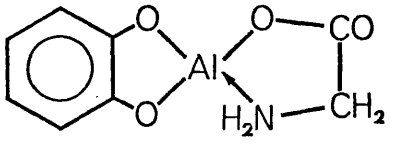


Fig. IV-19

the value of $\Delta\delta_{\underline{\underline{N}}}$ would be expected to be similar in the case of β-alanine to that found for glycine, but considerably smaller for 4-aminobutyric

acid. However, no values could be obtained for the β-alanine and 4-aminobutyric acid salts of the aluminium complex since no solvent could be found that would render these compounds soluble.

Therefore as an alternative to n.m.r. spectroscopy further investigations were undertaken using infrared spectroscopy, which has been employed widely in the study of metal chelate compounds.[125] The ethyl esters of the three amino acids each give an absorption at 1740 cm^{-1} due to the C=O stretching mode. The infrared spectra of the three amino acid salts of the aluminium catecholato complexes in the C=O stretching region are shown in Fig. IV-20. The proximity of the C=O stretching mode to the N-H bending mode in the glycine and β-alanine cases hinders the assignment of a definite frequency for these vibrations. However, Fig. IV-20 clearly indicates that the C=O stretching mode lies at lower frequency in the glycine and β-alanine cases compared to 4-aminobutyric acid (1670 cm^{-1}). The lower frequency indicates a lower C=O bond order, which may result from the formation of a donor-acceptor complex between the nitrogen and aluminium. These considerations together with the evidence obtained by ^{15}N n.m.r. spectroscopy indicate that glycine and β-alanine are each acting as bidentate chelating agents towards aluminium, as shown in Fig. IV-19 for the glycinate complex.

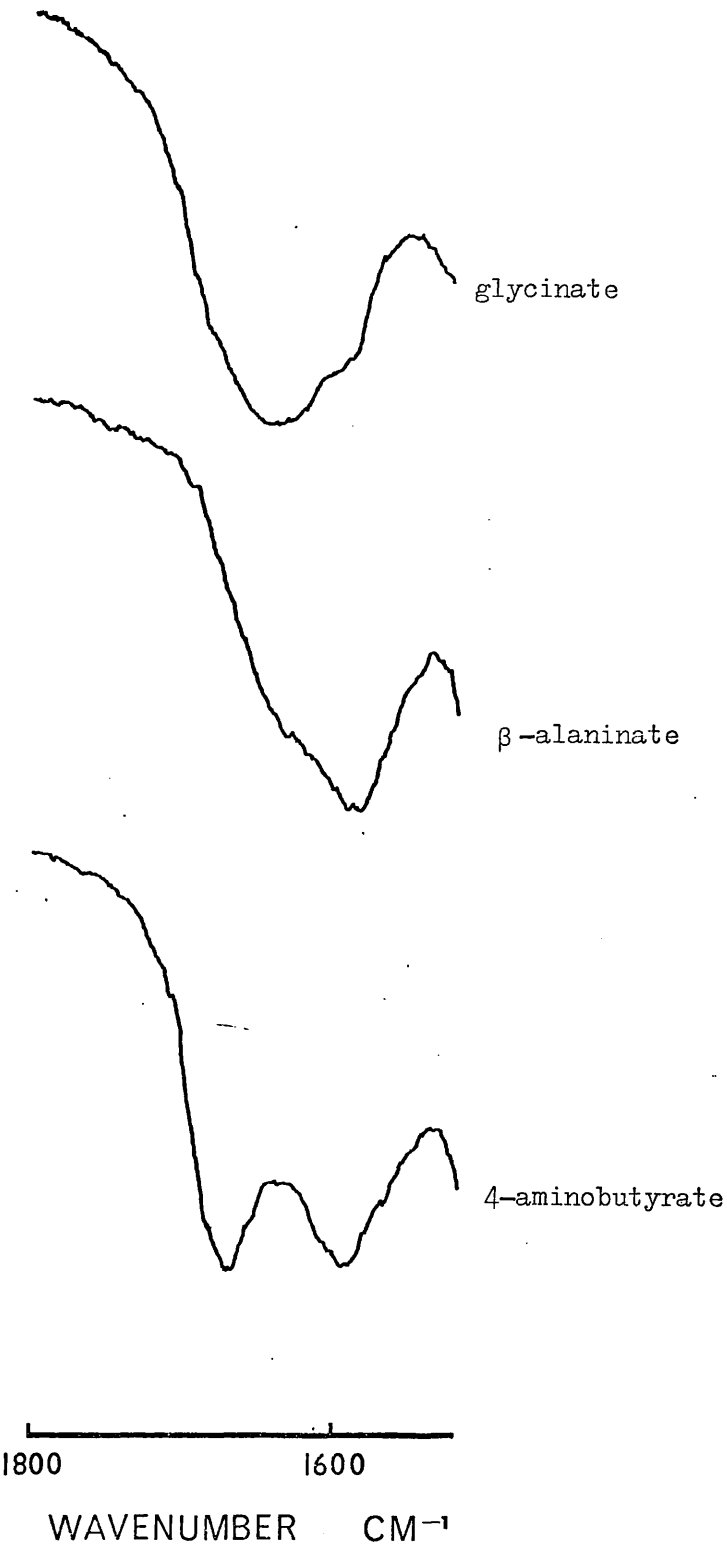
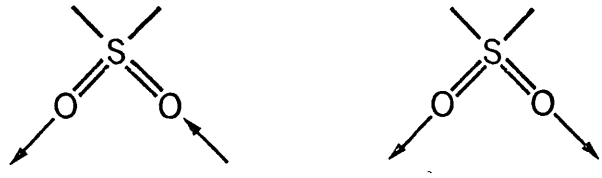


Fig. IV-20 Part of the infrared spectra of amino acid salts of the aluminium monocatecholato complex

V SPECTROSCOPIC STUDIES OF DIARYL SULPHONES AND RELATED COMPOUNDS

A Introduction

The infrared spectra of sulphonyl compounds have been extensively studied by several workers, and this subject has been reviewed by E.A. Robinson[126] and by L.J. Bellamy.[127,128] The SO_2 group, which in sulphonyl compounds is approximately tetrahedral about the sulphur atom, characteristically gives two strong absorption bands corresponding to the anti-symmetric and symmetric S=O stretching modes, shown in Fig. V-1,I and II respectively. E.A. Robinson[126] has suggested the



I II

Fig. V-1

ranges 1358 - 1336 and 1169 - 1159 cm^{-1} for the antisymmetric (ν_{as}) and the symmetric (ν_s) frequencies respectively of diaryl sulphones, though T. Momose *et al.*[129] have reported values as low as 1282 cm^{-1} for the *as* vibration and 1143 cm^{-1} for the *s* vibration.

There appears to be very little coupling between the symmetric and anti-symmetric S=O stretching modes, and other vibrations of the molecule. This is due to the comparatively large mass of sulphur, which results in the S=O vibrational extension being achieved mainly by the movement of the oxygen atoms. Therefore there is little alteration in the S=O frequencies caused by a change in the force constant of adjacent bonds. This leads directly to a simple, linear relationship between ν_s

and ν_{as} which was first described by L.J. Bellamy and R.L. Williams.[130] This linear relationship, which holds for a wide range of different compounds including sulphonyl halides, thiosulphonates, sulphonates, sulphones, sulphonic acids, and sulphates,[126,130] provides a useful check on the identification of a $\geq SO_2$ group.

The dominant influence on the shifts in the S=O stretching frequencies are the inductive effects of the substituents.

The sulphur-oxygen bond may be considered to be, in general, intermediate between the structures shown in Fig. V-2,I and II. In Fig. V-2,I, both electron pairs in the double bond are equally shared

I II

Fig. V-2

in what is essentially completely covalent bonding. Such a situation is favoured by electronegative groups attached to the sulphur. Decreasing the electronegativity of the substituents results in the double bond becoming increasingly polar, and thus approaching the situation shown in Fig. V-2,II. An increase in the double-bond character of the sulphur-oxygen bond, due to an increase in the -I effect of the substituents attached to the sulphur, will increase the force constant of the bond and hence the ν_{as} and ν_{s} vibrations will occur at higher frequencies. Conversely, an increase in the electron density of the sulphur atom will shift the absorption bands to lower frequencies.

T. Momose *et al.*[131] studied the S=O stretching frequencies of a number of benzenesulphonamide derivatives and found an approximately

linear relationship between the mean wave number, $(\nu_{as} + \nu_s)/2$, and the Hammett σ values of the substituents. A similar correlation was found between the mean wave number and the chemical shift parameters of the substituents.

Since bond length is related to bond order, in the absence of any coupling there would be expected to be a correlation between bond length and vibrational frequency for the S=O bond. This was first demonstrated by D. Bernard et al.,[132] who showed that there is in general an increase in frequency with a decrease in bond length. This work has been extended by R.T. Gillespie and E.A. Robinson,[133] who have also shown that there is some relationship between the mean of the stretching frequencies and the O=S=O bond angles, and they have also included a discussion of bond orders and force constants.

The stretching frequencies of arylsulphonyl chlorides occur at higher frequencies compared to the corresponding sulphones, which is to be expected on the grounds of dominant inductive effects. Indeed these bandsusually lie close to the mean values obtained for the sulphone and sulphuryl chloride. E.A. Robinson[126] has suggested the range 1390 - 1364 and 1185 - 1169 cm^{-1} for the ν_{as} and ν_s of the SO_2 group of both aryl and aliphatic sulphonyl chlorides.

^1H and ^{13}C n.m.r. spectroscopy are regarded as standard techniques of structural analysis in organic chemistry, and therefore a full discussion of these topics is not presented here. The reader is referred to standard monographs[134-137] where comprehensive accounts of these subjects are presented.

V B Results and Discussion

Infrared spectroscopy was employed in the structural analysis of all compounds containing the sulphonyl group. In each case the anti-symmetric and symmetric SO_2 band assignments are given in section VIII in the experiment in which the preparation of the compound is presented. The as and s frequencies given are consistent with the linear relationship of these vibrations described by L.J. Bellamy and R.L. Williams as is shown in Fig. V-3. R.J. Gillespie and E.A. Robinson[133] have shown that such results can be used directly to estimate the sulphur-oxygen bond order and also the O=S=O bond angle. However it should be noted that in their graph correlating bond angles with SO stretching frequencies, the value of the bond angles used were the calculated and not the observed angles. These calculated values were obtained from eq.V,1. Clearly, a correlation between the bond angle, 2α, and the mean frequency is

$$\nu_s/\nu_{as} = [(1 + \cos^2\alpha)/(1 + \sin^2\alpha)]^{\frac{1}{2}} \qquad (V,1)$$

expected since there exists a linear relationship between ν_{as} and ν_s. However, on the basis of eq. V,1 such a correlation between bond angles and stretching frequencies is not expected to be linear as shown by R.J. Gillespie and E.A. Robinson. The scatter of the points about the expected curve merely reflects the deviation of the observed ν_{as} and ν_s vibrations from their linear relationship described by L.J. Bellamy and R.L. Williams.

^1H and ^{13}C n.m.r. spectroscopy were employed in the structural investigation of synthesised compounds. Data on chemical shifts and coupling constants obtained from the ^1H n.m.r. spectra are presented

in section VIII. In the case of the 2,3,4-trimethoxy and -trihydroxy systems, as in, for example, 2,2',3,3',4,4'-hexamethoxydiphenyl sulphone, the shifts of the aromatic protons have been assigned on the basis that a proton ortho to the sulphonyl group is the more deshielded. This is rationalised by considering in each case the equivalent 3,4-dimethoxy or -dihydroxy system respectively, the shift of the proton on the 6-position lies downfield of that on the 5-position. Furthermore the substituent effect[138] of the additional methoxy or hydroxyl group in the trisubstituted phenylsulphonyl systems is such that difference in shifts of the protons on the 5- and 6-positions is expected to increase. Typical examples of ^{1}H n.m.r. spectra are exemplified by 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone, shown in Fig. V-4 and 5, and by 3,3',4,4',5-pentahydroxydiphenyl sulphone which is presented in Fig. V-6 and 7.

Data on shifts and coupling constants provided by ^{13}C n.m.r. spectroscopy are given in Table V,1. The values given complement well with those given by F. von Massow and M.A.R. Smith[138] for asymmetrically trisubstituted benzenes. Examples of ^{13}C n.m.r. spectra are shown in Fig. V-8 and 9, which give the spectra of 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone, and in Fig. V-10 and 11, in which the spectra of 3,4,5-trihydroxy-3',4',5'-trimethoxydiphenyl sulphone are presented.

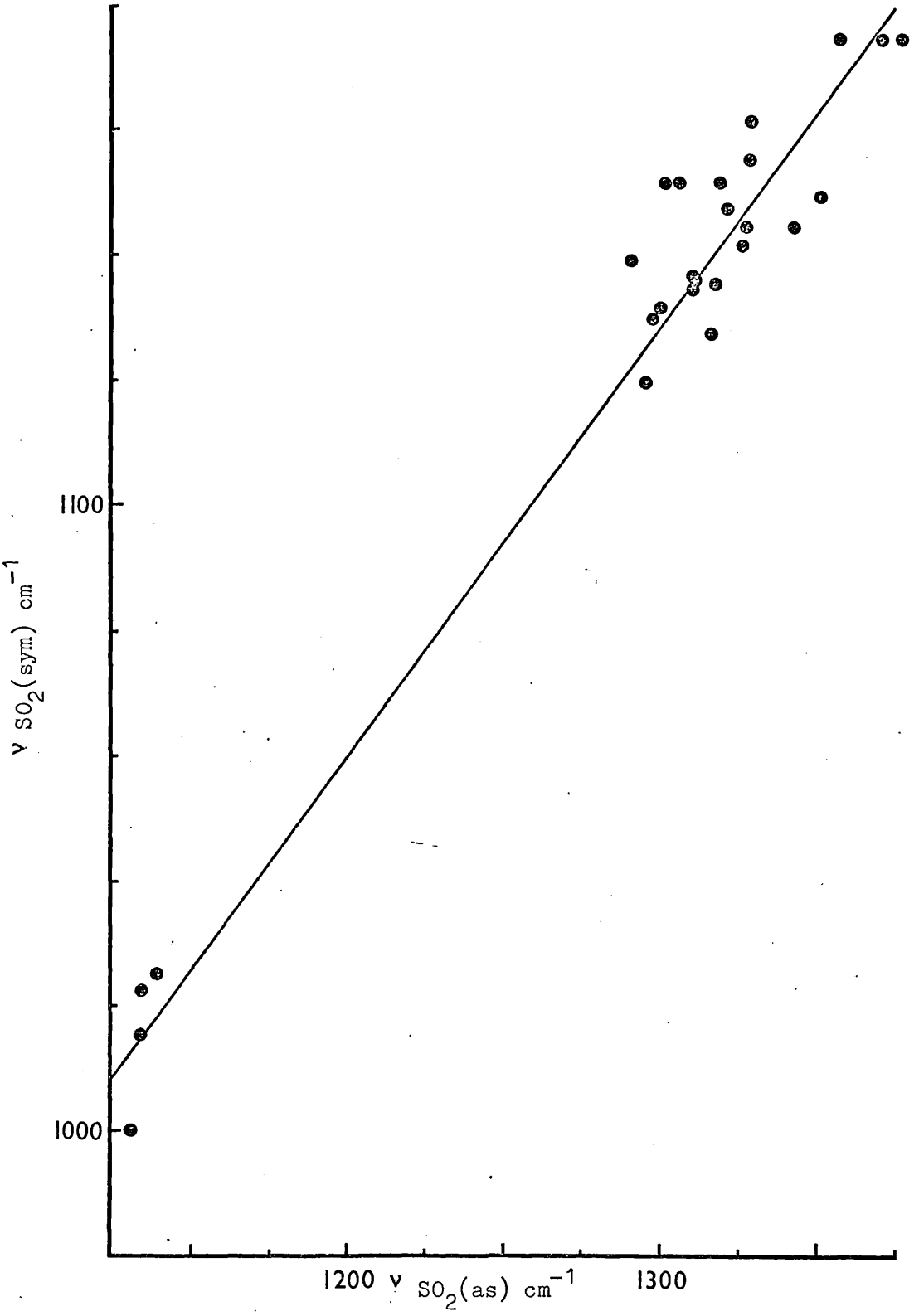


Fig. V-3: Correlation of symmetric and anti-symmetric SO_2 stretching frequencies.

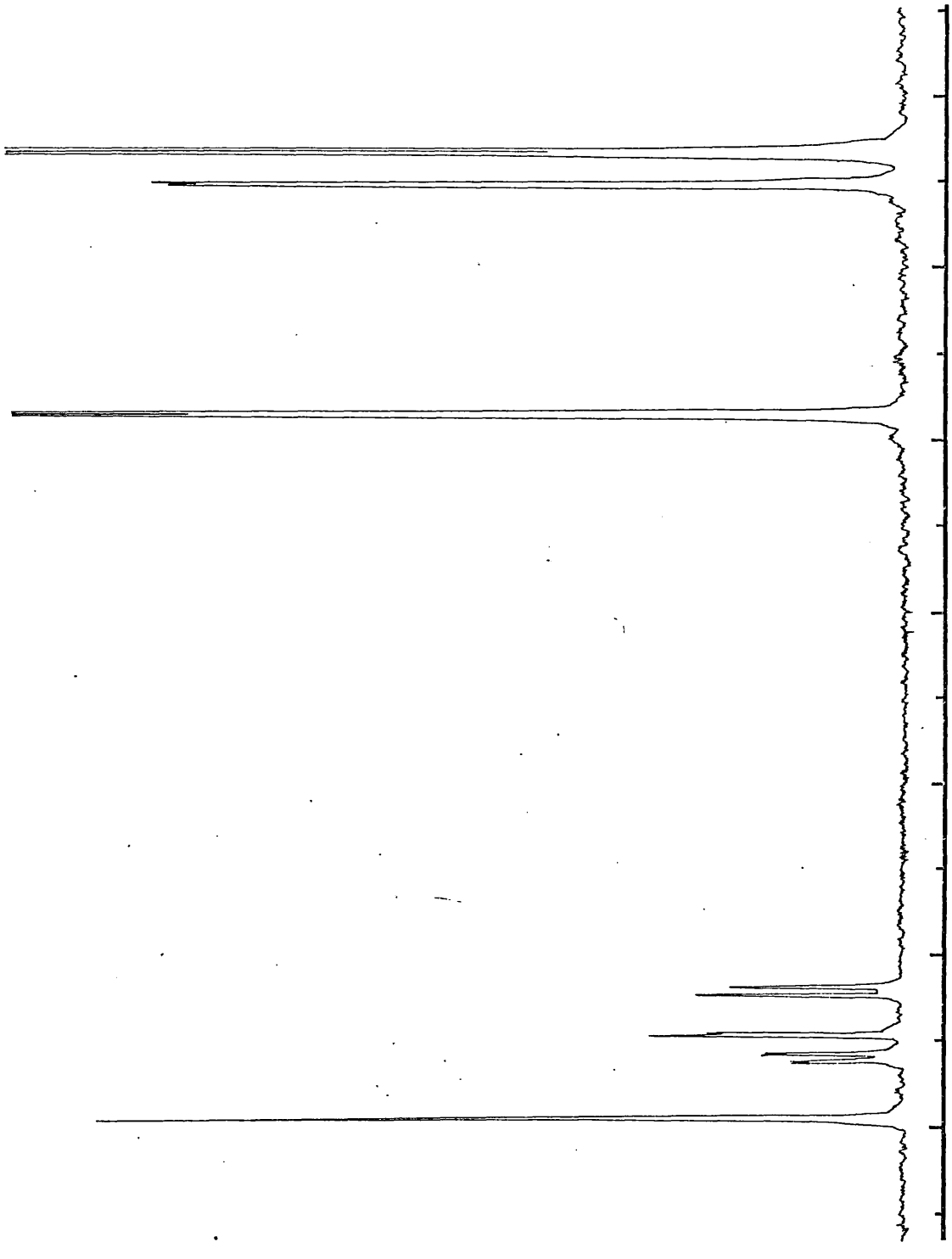


Fig. V-4: 220 MHz ^{1}H n.m.r. spectrum of 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone

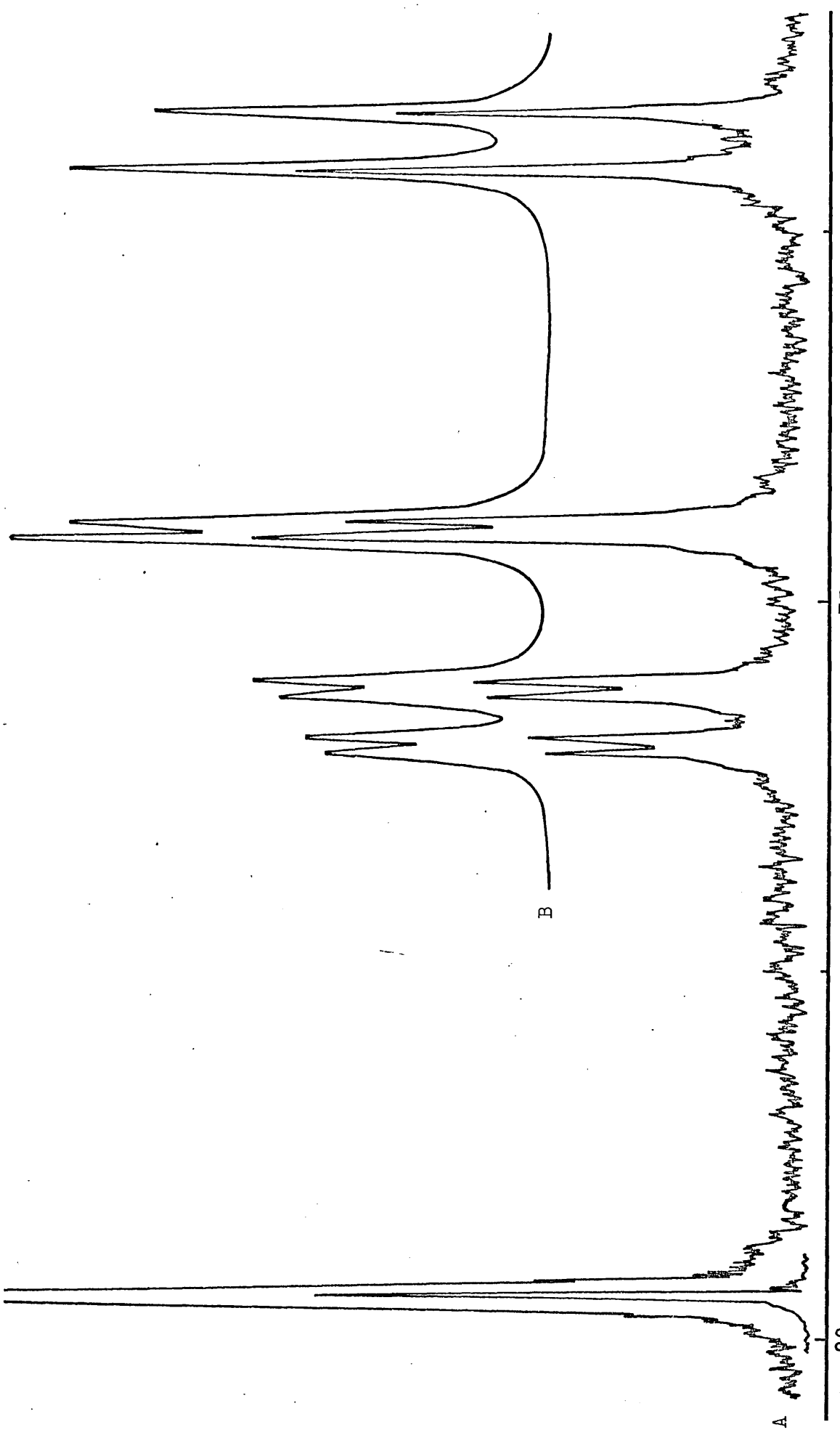


Fig. V-5 A: 220 MHz ^{1}H n.m.r. spectrum of 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone
B: Computer simulation of A.

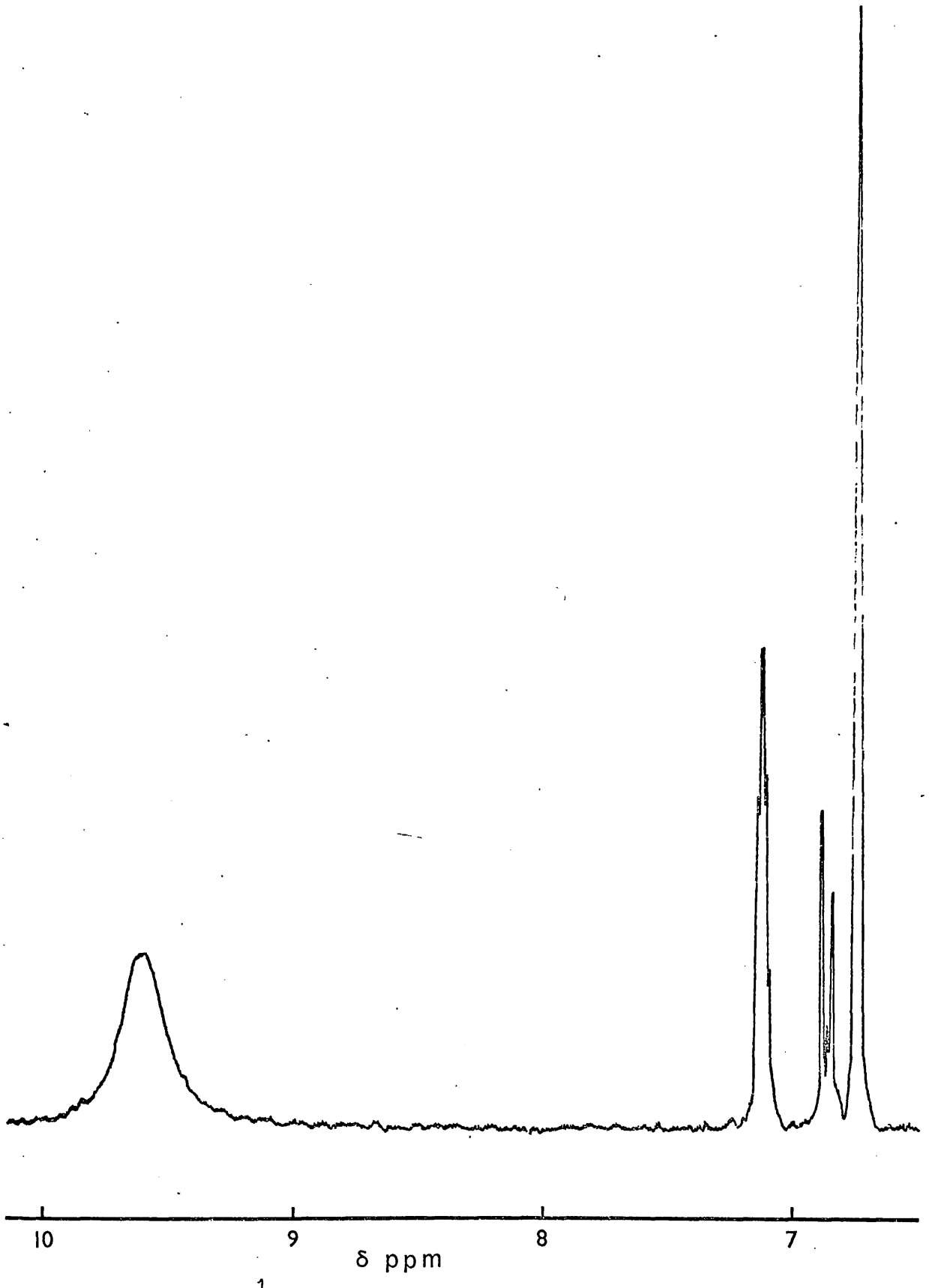


Fig. V-6: 220 MHz ^{1}H n.m.r. spectrum of 3,3',4,4',5-pentahydroxydiphenyl sulphone.

Fig. V-7: A: 220 MHz ^{1}H n.m.r. spectrum of 3,3',4,4',5-pentahydroxydiphenyl sulphone.
B: Computer simulation of A.

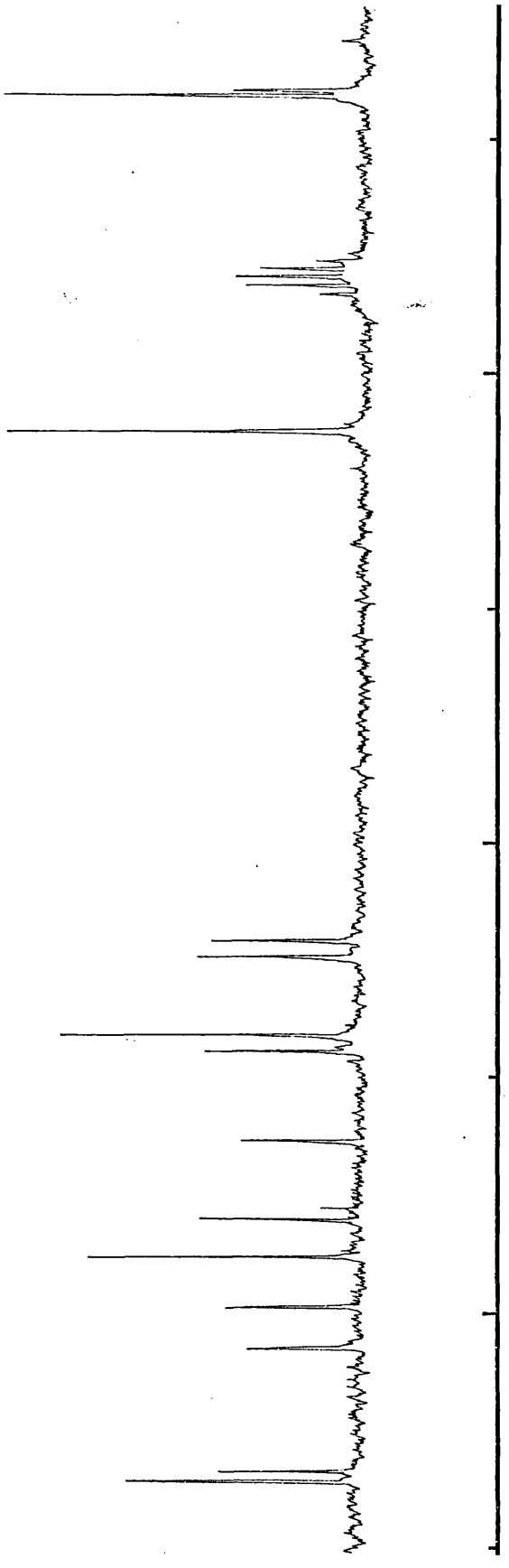


Fig. V-8: Decoupled ^{13}C n.m.r. spectrum of 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone.

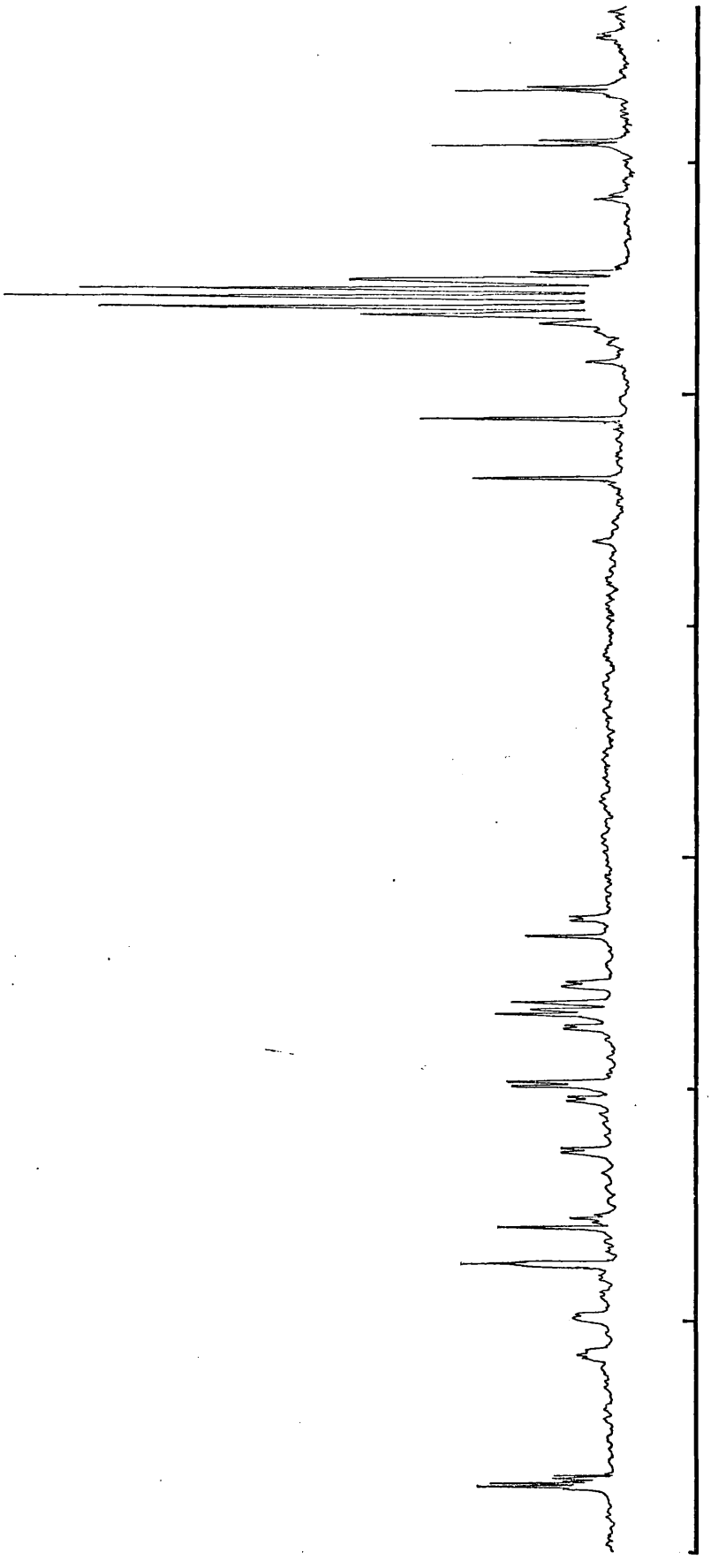


Fig. V-9: Undecoupled ^{13}C n.m.r. spectrum of 3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone.

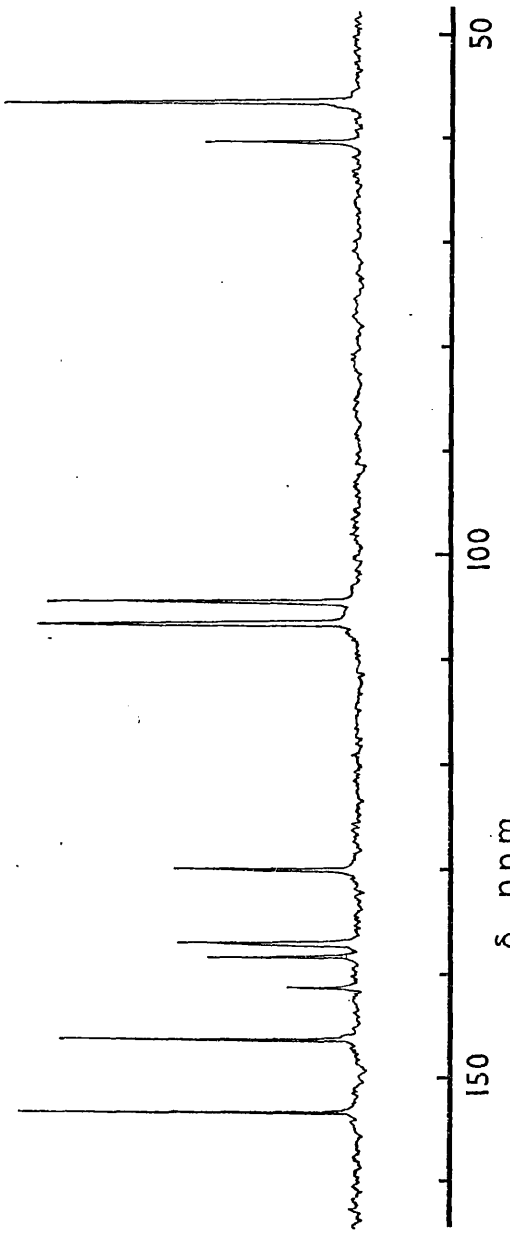


Fig. V-10: Decoupled ^{13}C n.m.r. spectrum of 3,4,5-trihydroxy-3',4',5'-trimethoxydiphenyl sulphone.

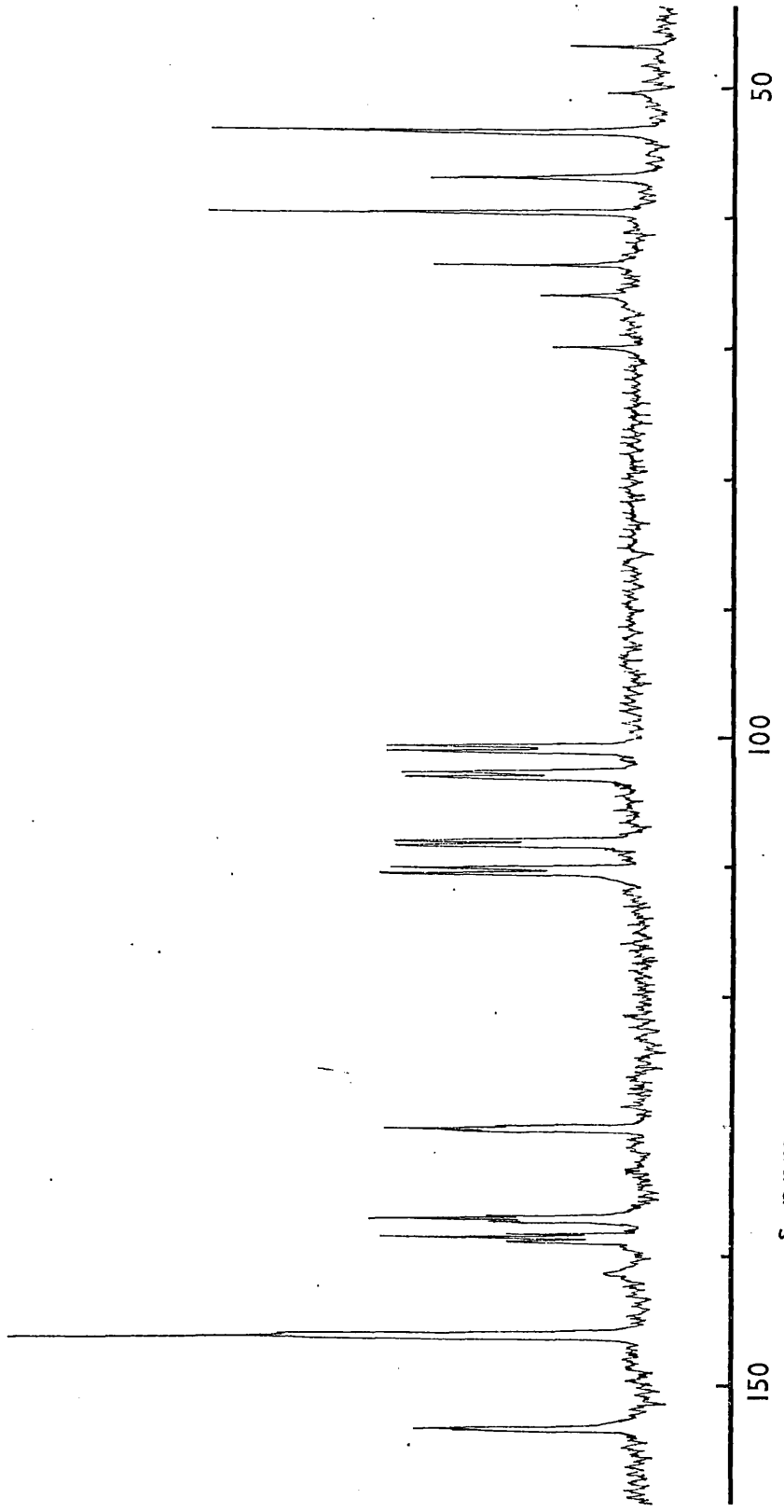


Fig. V-11: Undecoupled ^{13}C n.m.r. spectrum of 3,4,5-trihydroxy 3',4',5'-trimethoxydiphenyl sulphone.

Table V,1 ^{13}C n.m.r. of Aryl Sulphonyl Compounds

	shift (ppm)	coupling (Hz)
3,4,5-trimethoxybenzene-sulphonyl chloride		
	C-1 = 138.7	
	C-2 = C-6 = 103.3	C-2, H-2 = C-6, H-6 = 164 C-2, H-6 = C-6, H-2 = 6
	C-3 = C-5 = 152.4	
	C-4 = 142.1	C-4, H-2 = C-4, H-6 = 3
	$(C\text{-}3)O^{13}CH_3$ =	
	$(C\text{-}5)O^{13}CH_3$ = 56.1	145
	$(C\text{-}4)O^{13}CH_3$ = 60.1	145
3,3',4,4',5,5'-hexahydroxy-diphenyl sulphone		
	C-1 = C-1' = 131.1	
	C-2 = C-6 =	C-2, H-2 =
	C-2' = C-6' = 106.1	C-6, H-6 = C-2', H-2' = C-6', H-6' = 164 C-2, H-6 = C-6, H-2 = C-2', H-6' = C-6', H-2' = 6
	C-3 = C-5 =	
	C-3' = C-5' = 145.9	
	C-4 = C-4' = 137.7	C-4, H-2 = C-4, H-6 = C-4', H-2' = C-4', H-6' = 6
3,4,5-trihydroxy-3',4',5'-trimethoxydiphenyl sulphone		
	C-1 = 130.1	
	C-2 = C-6 = 106.5	C-2, H-2 = C-6, H-6 = 164 C-2, H-6 = C-6, H-2 = 6
	C-3 = C-5 = 146.2	
	C-4 = 138.4	C-4, H-2 = C-4, H-6 = 7

Table V,1 (continued)

	C-1' = 141.3	
	C-2' = C-6' = 104.4	C-2', H-2' = C-6', H-6' = 166 C-2', H-6' = C-6', H-2' = 6
	C-3' = C-5' = 153.2	
	C-4' = 137.1	C-4', H-2' = C-4', H-6' = 3
	$(C\text{-}3')O^{13}CH_3$ =	
	$(C\text{-}5')O^{13}CH_3$ = 56.3	145
	$(C\text{-}4')O^{13}CH_3$ = 60.2	145
3,4,5-triacetoxy-3',4',5'-trimethoxydiphenyl sulphone		
	C-1 = 138.9	
	C-2 = C-6 = 120.6	C-2, H-2 = C-6, H-6 = 172 C-2, H-6 = C-6, H-2 = 6
	C-3 = C-5 = 143.8	
	C-4 = 139.1	C-4, H-2 = C-4, H-6 = 6
	C-1' = 142.2	
	C-2' = C-6' = 105.3	C-2', H-2' = C-6', H-6' = 167 C-2', H-6' = C-6', H-2' = 7
	C-3' = C-5' = 153.4	
	C-4' = 134.8	C-4', H-2' = C-4', H-6' = 4
	$(C\text{-}3)O^{13}COCH_3$ =	
	$(C\text{-}5)O^{13}COCH_3$ = 167.8	7
	$(C\text{-}4)O^{13}COCH_3$ = 166.8	7
	$(C\text{-}3)OCO^{13}CH_3$ =	
	$(C\text{-}5)OCO^{13}CH_3$ = 20.3	131
	$(C\text{-}4)OCO^{13}CH_3$ = 19.8	130
	$(C\text{-}3')O^{13}CH_3$ =	
	$(C\text{-}5')O^{13}CH_3$ = 56.5	146
	$(C\text{-}4')O^{13}CH_3$ = 60.2	145

Table V,1 (continued)

3,4-dimethoxy-3',4',5'-triacetoxydiphenyl sulphone	C-1 = 131.4	C-1, H-5 = 10
	C-2 = 122.0 or	C-2, H-2 = 168
		C-2, H-6 = 6
	110.1	C-2, H-2 = 164
		C-2, H-6 = 6
	C-3 = 149.3	C-3, H-5 = 4
	C-4 = 153.5	C-4, H-2 = 7
		C-4, H-6 = 7
	C-5 = 112.0	C-5, H-5 = 165
	C-6 = 122.0 or	C-6, H-6 = 168
		C-6, H-2 = 6
	110.1	C-6, H-6 = 164
		C-6, H-2 = 6
	C-1' = 139.9	
	C-2' = C-6' = 120.3	C-2', H-2' =
		C-6', H-6' = 172
		C-2', H-6' =
		C-6', H-2' = 6
	C-3' = C-5' = 143.8	
	C-4' = 138.7	C-4', H-2' =
		C-4', H-6' = 8
	$(C\text{-}3)O^{13}CH_3$ = 56.0	145
	$(C\text{-}4)O^{13}CH_3$ = 56.0	145
	$(C\text{-}3')O^{13}COCH_3$ =	
	$(C\text{-}5')O^{13}COCH_3$ = 167.8	7
	$(C\text{-}4')O^{13}COCH_3$ = 166.8	7
	$(C\text{-}3')OCO^{13}CH_3$ =	
	$(C\text{-}5')OCO^{13}CH_3$ = 20.3	131
	$(C\text{-}4')OCO^{13}CH_3$ = 19.8	131
3,4-dimethoxy-3',4',5'-trihydroxydiphenyl sulphone	C-1 = 133.8	C-1, H-5 = 7
	C-2 = 121.0 or	C-2, H-2 = 168
		C-2, H-6 = 6
	109.5	C-2, H-2 = 164
		C-2, H-6 = 7

Table V,1 (continued)

	C-3 = 148.9	C-3, H-5 = 8
	C-4 = 152.5	C-4, H-2 = 7
		C-4, H-6 = 7
	C-5 = 111.7	C-5, H-5 = 163
	C-6 = 121.0 or	C-6, H-6 = 168
		C-6, H-2 = 6
	109.5	C-6, H-6 = 164
		C-6, H-2 = 7
	C-1' = 130.8	
	C-2' = C-6' = 106.4	C-2', H-2' =
		C-6', H-6' = 164
		C-2', H-6' =
		C-6', H-2' = 7
	C-3' = C-5' = 146.2	
	C-4' = 138.2	C-4', H-2' =
		C-4', H-6' = 7
	$(C\text{-}3)O^{13}CH_3$ = 56.9	145
	$(C\text{-}4)O^{13}CH_3$ = 56.9	145
3,3'4,4',5-pentahydroxy-diphenyl sulphone		
	C-1 = 131.2	
	C-2 = C-6 = 106.1	C-2, H-2 =
		C-6, H-6 = 164
		C-2, H-6 =
		C-6, H-2 = 6
	C-3 = C-5 = 146.0	
	C-4 = 137.8	C-4, H-2 =
		C-4, H-6 = 7
	C-1' = 132.2	C-1', H-5' = 9
	C-2' = 119.3 or	C-2', H-2' = 166
		C-2', H-6' = 6
	113.9	C-2', H-2' = 162
		C-2', H-6' = 6
	C-3' = 145.5	C-3', H-5' = 4
	C-4' = 150.0	C-4', H-2' = 7
		C-4', H-6' = 7

Table V,1 (continued)

	C-5' = 115.7	
	C-6' = 119.3 or	C-6, H-6 = 166
		C-6, H-2 = 6
	113.9	C-6, H-6 = 162
		C-6, H-2 = 6
3,4,5-triacetoxy-diphenyl sulphone		
	C-1 = 138.9	
	C-2 = C-6 = 120.5	C-2, H-2 =
		C-6, H-6 = 173
		C-2, H-6 =
		C-6, H-2 = 7
	C-3 = C-5 = 143.9	
	C-4 = 138.9	C-4, H-2 =
		C-4, H-6 = 3
	C-1' = 140.2	C-1', H-3' =
		C-1', H-5' = 6
	C-2' = C-6' = 127.6	C-2', H-2' =
		C-6', H-6' = 167
		C-2', H-4' =
		C-2', H-6' =
		C-6', H-2' =
		C-6', H-4' = 7
	C-3' = C-5' = 129.9	C-3', H-3' =
		C-5', H-5' = 165
		C-3', H-5' =
		C-5', H-3' = 6
	C-4' = 134.2	C-4', H-4' = 164
		C-4', H-2' =
		C-4', H-6' = 7
	$(C\text{-}3)O^{13}COCH_3$ =	
	$(C\text{-}5)O^{13}COCH_3$ = 167.7	7
	$(C\text{-}4)O^{13}COCH_3$ = 166.7	7
	$(C\text{-}3)OCO^{13}CH_3$ =	
	$(C\text{-}5)OCO^{13}CH_3$ = 20.3	131
	$(C\text{-}4)OCO^{13}CH_3$ = 19.8	131

VI THE APPLICATIONS OF ARYLTHALLIUMS IN THE SYNTHESIS OF DIARYL SULPHONES

A Introduction

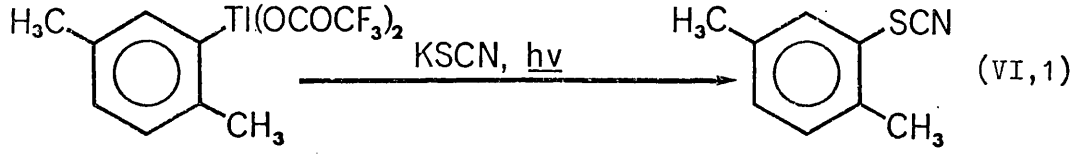
Electrophilic substitution reactions of aromatic compounds have probably been more extensively studied than any other field in organic chemistry. Trifluoroacetic acid (TFA) has been reported[139] to be an excellent medium for electrophilic substitution reactions, in that its use both decreases the extent of side reactions and increases the rates of reactions of nitration, bromination and mercuration.

A great deal of work has been carried out into investigating electrophilic mercuration of aromatic compounds. It is perhaps surprising that until recently very little work had been done on the preparation and synthetic applications of aromatic thallation reactions. Thallium is one of the Group IIIB elements, and as expected compounds of the type TlX_3 are good Lewis acids. The electrophilicity of TlX_3 can be varied substantially by variation of the nature of X. Thallium(III) nitrate (TTN) in TFA has been shown to be effective in nitration of aromatic compounds. In this case the function of TTN is as a Lewis acid in accelerating the rate of nitration, and the reaction is not considered to proceed *via* an arylthallium intermediate.[140]

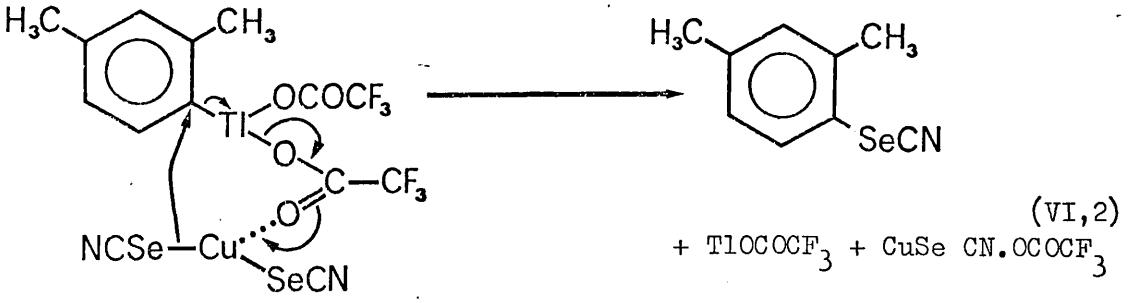
The thallation of an aromatic compound was first described by H. Gilman and R.K. Abbott Jr.[141] who prepared di-(4-dibenzofuryl)thallium chloride in 9% yield by reacting dibenzofuran with thallium(III)chloride. However, since A. McKillop *et al.*[142,143] reported that arylthallium compounds can be readily prepared in high yield using thallium (III) trifluoroacetate (TTFA) there has been a great deal of work carried out into the synthetic applications of arylthalliums. The substituent

effects normally encountered in electrophilic substitution are observed in aromatic thallation except when the steric effect predominates owing to the size of thallium. Also substituents that are capable of complexing with the incoming TTFA electrophile may influence the orientation of thallation. For example, thallation of benzoic acid occurs exclusively in the ortho position due to the formation of an intermediate substrate-electrophile complex.

The great synthetic applications of these arylthallium bis(trifluoracetates) lies in the ease with which the thallium group can be displaced by other substituents, which then occupy the originally thallated positions. These reactions usually proceed with a change in the valency of thallium from +3 to +1. Thus arylthalliums can be readily converted to phenols,[144] nitriles,[144,145] biphenyls,[146] iodides,[142-3,147-8] fluorides,[149] thiocyanates (VI,1),[150] and selenocyanates (VI,2).[151] Many of these and other reactions in which thallium compounds have been employed in organic synthesis have been reviewed by A. McKillop and E.C. Taylor.[152]



(VI,1)



(VI,2)

+ $TlOCOCF_3$ + CuSe CN.$OCOCF_3$

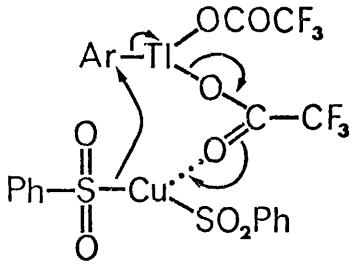
The use of organothallium intermediates is noted generally for the high yield obtained under usually mild conditions, the uniqueness of many of the transformations, and the ease with which the reactions are carried out in practice. This field represents a rapidly expanding area of organometallic chemistry, and many of the reactions involved are fast becoming standard techniques in synthetic organic chemistry.

VI B Results and Discussion

Since arylthallium bis(trifluoroacetate) has been shown to yield aryl thiocyanates[150] and aryl selenocyanates[151] when reacted with potassium thiocyanate and copper selenocyanate respectively, consideration was given to the possibility of generating diaryl sulphones *via* arylthallium intermediates. Initial experiments, in which the preparation of arylphenyl sulphones was attempted by treating arylthallium with sodium benzenesulphinate, proved unsuccessful.

The use of copper salts of cyanate[145] and of selenocyanate[151] have been shown to yield the required cyanide and selenocyanide respectively upon reaction with arylthalliums. Consequently the copper salt of benzenesulphinic acid was employed in the reaction with arylthallium bis(trifluoroacetate), and this procedure was found to yield the required arylphenyl sulphone (experiment 31). In this manner 2,4,6-trimethyl diphenyl sulphone, 2,4-dimethyldiphenyl sulphone, and 4-chlorodiphenyl sulphone were prepared, the thallium derivatives being first obtained by reacting mesitylene, *m*-xylene, and chlorobenzene respectively with thallium (III) trifluoroacetate. The displacement reaction is thought to proceed as a synchronous nucleophilic substitution after first coordination of copper by a trifluoroacetate ligand (VI,3) as has been postulated by S. Uemura *et al.*[151] in the case of copper selenocyanide (VI,2).

The yields obtained for the thallation reaction, and also the overall



$$\longrightarrow \quad Ar - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}} - Ph + TlOCOCF_3 + CuSO_2Ph.OCOCF_3 \qquad (VI,3)$$

yields of the sulphones are shown in Table VI,1. In the reaction of

Table VI 1 Thallation and Subsequent Sulphinatodethallation of Aryl Compounds

ArH	% yield of arylthallium compound*	% overall yield of aryl-phenyl sulphone
mesitylene	94	41
m-xylene	100	63
chlorobenzene	80**	47

* values taken from ref. 143

** isomer distribution,[143] o (23%), p (77%)

sodium benzenesulphinate with aryl thalliums, no attempt was made to maximise the yields. There was a considerable amount of suspended material in the reaction mixture throughout the procedure, and therefore the use of alternative solvent systems may prove to result in higher yields.

This method of preparation of diaryl sulphones has the advantage over the more usual electrophilic methods in that the conditions of reaction are comparatively mild, and therefore such a technique may prove in some instances to be of more general applicability.

VII GENERAL CONCLUSIONS

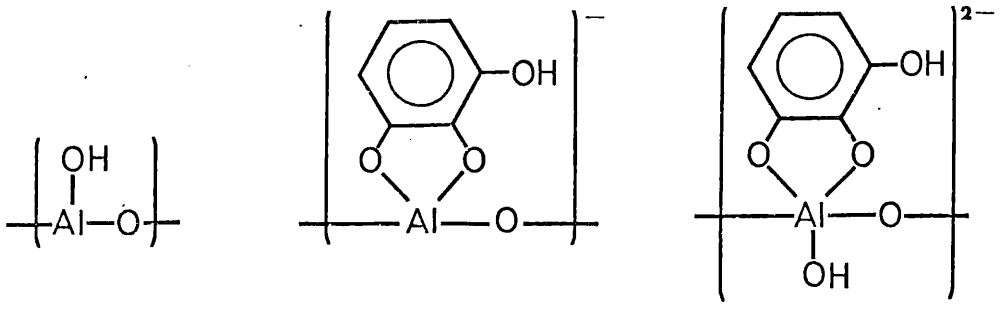
The aim of the project was in part the synthesis of compounds that when used in conjunction with aluminium salts should show promise in converting pelt into white, light-stable leather. Trial tanning experiments using a variety of compounds suggested strongly that 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone would be most likely to possess the required properties to achieve this aim.

Several synthetic routes by which this hexahydroxy compound might be prepared were investigated. A method was finally developed in which sulphinic acids (sodium salts) are reacted with o-benzoquinones to give the corresponding dihydroxyphenyl sulphones. This method, which appears to be of quite general applicability, was utilised in the preparation of the hexahydroxysulphone and other related compounds for which standard synthetic techniques proved to be inadequate.

The view that 3,3',4,4',5,5'-hexahydroxydiphenyl sulphone was expected to show promise in exhibiting the required tanning properties, when used in the presence of aluminium salts, was justified with respect to the hydrothermal stability and initial colour of the resultant leather. However, the light-fastness properties must be regarded as very poor. Therefore serious consideration should be given to the possibility that the use of polyphenolic compound is inherently incompatible with the

requirements of leather manufacturers in obtaining a white leather that is sufficiently light-stable.

The important function in tanning of the additional hydroxyl groups of compounds such as pyrogallol and ethyl gallate as compared to catechol has been noted. The formation of each aluminium-phenolic chelate ring involves two hydroxyl groups ortho to each other, and therefore it is thought that the additional hydroxyl groups function by interaction with the protein. However, the deuterium exchange characteristics of treated and untreated gelatine show that in the case of pyrogallol, such interactions cannot fully account for the observed tanning action. Taking pyrogallol as an example, it is proposed that polynuclear complexes containing units of the types shown in Fig. VII—1, I,II and III may be



I II III

Fig. VII—1

responsible for the observed tanning action. The tetra- and hexahydroxy-diphenyl sulphones, since they possess two complexing sites, would tend to form more extensive polynuclear complexes.

The complexes may be bonded to the protein by the interaction of Al-OH groups, either at the end of or along the polynuclear complexes, with carboxylic acid side groups forming aluminium-carboxylate bonds. However, the tanning experiments using aluminium isopropoxide would have fully utilised these types of bonds. This did not result in a corresponding rise in shrinkage temperature, indicating the limitation of the role aluminium -carboxylate bonds play in tanning. Other interactions, apart from those involving the phenolic-OH groups already discussed, may also play a part. Aluminium complexes may be charged and therefore it is possible that charge attractions may be involved to some extent. Evidence has been presented that suggests that in the case of aluminium catecholatoglycinate there exists a donor-acceptor interaction between nitrogen and aluminium. It is difficult to judge the extent to which such interactions may also contribute to tanning action.

Whatever species are responsible for tanning action, they must essentially form stable cross-linkages within the protein, and these species need not necessarily be those that are present in the greatest concentrations in the tanning solution. The irreversible nature of the tanning process leads to what is essentially the capture of tanning material from solution. Therefore, though it is possible to establish the optimum conditions of tanning, it need not necessarily follow that it is thereby possible to deduce the active species.

VIII EXPERIMENTAL

A General Techniques and Materials

1. Small Scale Tanning Experiments

The following is the general procedure used to investigate the potential tanning ability of compounds in the presence of aluminium salts, and was mainly carried out in conjunction with B.L.M.R.A. Any alteration to this procedure is specified in the text.

Acetone dehydrated pelt (0.5 g.) was thoroughly soaked in water and drained. A solution of Lutan B* (0.43 g., ca. 0.00185 g. atom. Al) or aluminium sulphate (0.58 g., 0.00184 g. atom. Al), and the phenolic compound (3.70 mmol.; in the case of the diaryl sulphones, 1.85 mmol.) in water (10 $cm.^3$) was prepared. In some cases, gentle heating followed by cooling, or the addition of a little acetone was required to dissolve all the solid. The pH was adjusted by dropwise addition of aq. sodium hydroxide (1M) solution to the point at which precipitation began to occur. This solution was added to the soaked pelt and shaken overnight. The "leather" was removed, washed several times with water, and then allowed to dry in the atmosphere.

2. Small Scale Tanning Experiments Using Aluminium Isopropoxide and Dibasic Acids

Acetone dehydrated pelt (0.5 g.) was thoroughly soaked in dry isopropyl alcohol and then added to a solution of aluminium isopropoxide (0.38 g., 1.86 mmol.) in isopropanol (20 cm^3) and shaken for 3 days. The pelt was then removed, blotted, and added to a solution of the dibasic acid (3.73 mmol.) in isopropanol (20 cm^3) followed by shaking for 3 days. Various degrees of retannage were accomplished by repeating the above process. The pelt was dried, soaked in water overnight and finally dried in the atmosphere.

* Trade mark of Bush Beach and Segner Bayley Ltd., England.

3. Thermal Analysis

Thermal analysis was carried out in conjunction with B.L.M.R.A. using a Dupont 900 Thermal Analyser. The "leather" was wetted either by soaking overnight in water or by leaving the immersed sample under reduced pressure for 5 min. and then at atmospheric pressure for a further 10 min. Small samples of this wetted "leather" were sealed in air-tight aluminium pans for analysis.

4. Light-fastness

Light-fastness was carried out by B.L.M.R.A. using a standard procedure in accordance with British Standards B.S.1006. This involves exposing the leather and standard samples of blue wool to light from a Xenotest lamp. The point at which the sample of leather begins to fade is noted against the fading of the standard wool samples, giving a value on the blue wool scale six (B.W.S. 6).

5. Nuclear Magnetic Resonance (n.m.r.) Spectroscopy

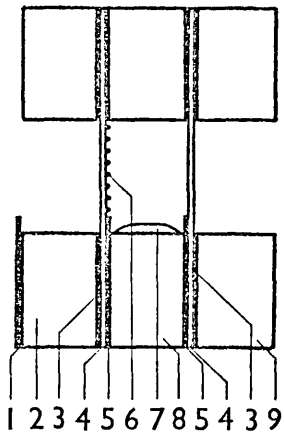
The 60 MHz ^{1}H n.m.r. spectra were recorded on a Varian EM 360 spectrometer. The 220 MHz ^{1}H spectra were recorded at the Physico-Chemical Measurements Unit (P.C.M.U.) Harwell on a Varian HR 220 spectrometer. The ^{13}C spectra were recorded on a Bruker HX 90E machine at P.C.M.U. operating at 22.63 MHz, and the ^{15}N spectra were also recorded at P.C.M.U. on a Bruker WH 180 spectrometer operating at 18.24 MHz. All spectra were run at ambient temperature. The internal references for ^{1}H and ^{13}C spectra were 3-(trimethylsilyl)-propanesulphonic acid sodium salt (T.S.P.) in the case of D_2O solutions, and tetramethylsilane (T.M.S.) for other solutions. For ^{13}N spectra, nitromethane was used as the external reference. Chemical shifts (δ) are expressed in parts per

million (ppm) relative to the resonance of the reference sample ($\delta = 0$). Coupling constants (J) are expressed in Hz. Spectrum simulation was carried out using program UEA NMR BAS filed at the University of London Computer Centre, together with a plotting routine, LIBRARY RHC PLOT, developed at Royal Holloway College Central Computer Services.

6. Infrared (i.r.) Spectroscopy

Infrared spectra were obtained using either a Perkin-Elmer 257 grating spectrophotometer, or a Perkin-Elmer 337 grating spectrophotometer. Compounds examined as their potassium bromide discs were of approximately 1% w/w composition.

In the case of the gelatine-deuterium exchange experiments, the spectra were obtained using a Perkin-Elmer 177 grating infrared spectrophotometer. These experiments were carried out in a manner similar to that described by Heidemann.[15] Gelatine (0.1 g.), and as required aluminium sulphate (0.025 g., 0.040 mmol.) and the phenolic compound (0.079 mmol., in the case of the diaryl sulphone 0.040 mmol.) were dissolved in water (5 cm^3). Gentle heating was required to dissolve all the solid, and the solution was then allowed to stand at room temperature for 2 hr. A thin layer of this solution was spread over a silver chloride plate, and dried under vacuum (P_2O_5) for 30 min. The cell was assembled in the usual manner using a 1 cm. spacer with the gelatine film facing inside as shown in Fig. VIII-1. The gelatine film was protected from liquid water by using a polythene seal between the plate and the spacer with a slightly smaller window than that of the spacer. Aluminium foil was used to blank-off any exposed polythene.



1. aluminium foil
2. front plate
3. polythene seal
4. silver chloride plate
5. polythene seal with smaller window
6. gelatine film
7. H_2O or D_2O saturated with NaCl
8. 1 cm. spacer
9. back plate

Fig. VIII-1

A few drops of H_2O saturated with sodium chloride were placed in the cell, and the i.r. readings were recorded. The cell was dismantled, the gelatine film was dried and the process was repeated using D_2O saturated with sodium chloride in place of H_2O. Each experiment was carried out in duplicate.

7. Potentiometry

Potentiometric measurements were performed using a Pye Unicam Model 290 pH Meter fitted with a E07 401 HA combined electrode. The meter was standardised using commercially available buffer solution tablets for pH 4.00 and 9.20, and a buffer at pH 13.00 made[153] using

potassium chloride solution (25 cm^3; 0.2$\underline{M}$) and sodium hydroxide solution (66 cm^3; 0.1$\underline{M}$) diluted to 100 cm^3. Potassium hydroxide solution was standardised against standard nitric acid solution and titrated at an initial rate of 0.02 cm^3 using a micro-burette into a solution of potassium nitrate (0.2 $\underline{M}$), nitric acid ($4 \times 10^{-3}\underline{M}$) and as required, the phenolic compound ($6 \times 10^{-3}\underline{M}$), and aluminium nitrate ($6 \times 10^{-4}\underline{M}$), of initial volume 50 cm^3. Nitrogen gas was bubbled through the solution in order to maintain an inert atmosphere and this also ensured adequate mixing. A loose-fitting perspex cover with holes for the electrode, burette and the nitrogen source was used. The potentiometric titrations were carried out at a temperature range of 22-25°. At the completion of each run the stability of the pH meter was checked using the standard buffer solutions.

8. Elemental Analysis

Microelemental analysis, except for analysis of aluminium, was carried out by The Butterworth Microanalytical Consultancy Ltd., Teddington.

9. Estimation of Aluminium

Aluminium was estimated gravimetrically as the oxinate as described by Vogel.[154] The amount of material containing 25-50 mg aluminium was dissolved in water (180 cm^3) containing concentrated hydrochloric acid (2.0 cm^3). Excess of 8-hydroxyquinoline (10% solution in 20% acetic acid) and urea (5 g. for each 25 mg. aluminium) were added. The solution was heated to boiling, and then at 95° for 2-3 hr. The initial greenish-yellow turned to an orange-yellow colour, indicating that precipitation was complete. The precipitate was collected from the cooled solution in a sintered glass crucible, washed with a little cold water and dried to constant weight at 130°. Aluminium was estimated as $Al(C_9H_6ON)_3$.

10. Estimation of Pyrogallol

Pyrogallol was estimated by oxidation with alkaline potassium permanganate by the method described by Böttger.[155] An accurately weighted amount of material to be analysed, equivalent to 0.01 - 0.02 g. pyrogallol was dissolved in water (10 cm^3). To this was added potassium permanganate solution (20 cm^3; 0.1$\underline{\underline{M}}$) and sodium hydroxide solution (10 cm^3; 7.50 $\underline{\underline{M}}$). The mixture was allowed to stand for 10 min., and then sulphuric acid (10 cm^3; 50% H_2SO_4) and oxalic acid (20 cm^3; 0.2776 $\underline{\underline{M}}$) was added. The solution was swirled until the colour was discharged, and then heated rapidly to 50°. The residual oxalic acid was titrated with potassium permanganate solution (0.02 $\underline{\underline{M}}$). This method was standardised against known weights of pyrogallol.

11. Paper Electrophoresis

Paper electrophoresis was performed on a Shandon High Voltage Electrophoresis instrument using Whatman No. 3MM, 11 cm. wide chromatography paper. 5-Hydroxymethylfurfuraldehyde was used as a non-migrating marker to correct for electroendosmosis. The solutions used as electrolytes were prepared as follows:

Solution 1. Aluminium sulphate $16H_2O$.(25 g.) was dissolved in water (250 cm^3) and a solution of sodium hydroxide (15 g.) in water (25 cm^3) was added with stirring. Barium hydroxide (8 g.) in water (60 cm^3) was added, and the precipitated barium sulphate was removed by filtration. The solution was made up to 1 l. and adjusted to pH 13 by addition of concentrated sodium hydroxide solution.

Solution 2. Sodium hydroxide solution (ca. 0.1M) at pH 13.

Solution 3. Aluminium sulphate solution (0.0397M) giving a solution of pH 3.39.

Solution 4. Sulphuric acid solution at pH 3.39.

The components were detected by fluorescence under U.V. light and by using diazotised p-nitroaniline - sodium hydroxide reagent. The latter was performed by spraying the paper with a solution of p-nitroaniline (5 cm^3, 0.5 g. in 100 cm^3 2M-hydrochloric acid) and aq. sodium nitrite (0.5 cm^3, 5%). The paper was allowed to dry, and then sprayed with ethanolic sodium hydroxide solution, made by dissolving sodium hydroxide (8 g.) in water (20 cm^3) and diluting to 200 cm^3 with ethanol.

12. Paper Chromatography

Descending paper chromatography was carried out using Whatman No. 1 chromatography paper. Papers impregnated with sodium aluminate and with aluminium sulphate were prepared by dipping in solutions 1 and 3 respectively (described above), blotting and then drying. The papers were developed using butanone saturated with water, and the components were detected in the manner described above.

13. Thin Layer Chromatography

Commercially available thin layer chromatography plates (Camlab. Cambridge), 5 x 20 cm. were used. The stationary phase was silica gel (Polygram Sil G) with a layer of 0.25 mm. The solvent systems used were:

Solvent A: Toluene-methanol 9:1 v/v

Solvent B: Butanone saturated with water.

Compounds on the thin layer chromatography plates were visualised by spraying with 95:5 v/v ethanol-conc. sulphuric acid, and then heating at 120°.

VIII B Experiments

Experiment 1 Preparation of the Ethyl Esters of Polyhydroxybenzoic Acids

Dry hydrochloric acid gas was passed through a solution of the polyhydroxybenzoic acid in ethanol for 1 hr. The mixture was refluxed for 30 min. and the solvent then evaporated off under reduced pressure. The residue was dissolved in ether, and this organic solution was washed with sodium bicarbonate solution, water, and then dried ($MgSO_4$). Ether was removed under reduced pressure to give the solid product, which was purified by recrystallisation from ethanol-water. The following ethyl esters were prepared: 2,3-dihydroxybenzoate, m.p. 65-66° (lit.[156] 69°); 3,4-dihydroxybenzoate, m.p. 133-134° (lit.[157] 133-134°); 2,3,4-trihydroxybenzoate, m.p. 101-102° (lit.[158] 102°); 2,4,6-trihydroxybenzoate, m.p. 92-93° (lit.[157] 94-95°).

Experiment 2 Preparation of 3,4-Dimethoxybenzenesulphonyl Chloride

Chlorsulphonic acid (175 g., 1.5 mol.) was added dropwise to a stirred solution of 1,2-dimethoxybenzene (41.4 g., 300 mmol.) in chloroform (75 cm^3) which was cooled to -10° in a dry ice-acetone bath. The mixture was allowed to warm to 5°, cooled again and then poured slowly with stirring into an ice-water mixture. The organic layer was separated off, washed with water (4 x 25 cm^3), and then dried ($CaCl_2$). The solvent was removed by rotary evaporation to give the product, which was then purified by recrystallisation from petroleum ether (b.p. 60-80°) - ethyl acetate. Yield 52.27 g. (74%) m.p. 72-73° (lit.[159] 76°), $\delta(CDCl_3)$ 4.10(6H,s,CH_3), 7.08 (1H_5, d, $J_{5,6}$ 9 Hz),

7.58 ($1H_2$, d, $J_{2,6}$ 2 Hz), 8.26 ($1H_6$, dd); $\nu_{max.}$ (KBr disc) 1375s (SO_2 as.), 1175m cm^{-1} (SO_2 s.).

Experiment 3 Preparation of 3,3',4,4'-Tetramethoxydiphenyl Sulphone

1,2-Dimethoxybenzenesulphonyl chloride (2.0 g., 8.46 mmol.) was mixed with 1,2-dimethoxybenzene (12.0 g., 87.0 mmol.) and anhydrous zinc chloride (2.5 g.), and the reaction mixture was heated at 170-180° for 30 min. A little water was added to the cooled mixture, and the excess dimethoxybenzene was removed by steam-distillation. The residue was extracted with warm ethanol and evaporation of this solution under reduced pressure gave the product which was then purified by recrystallisation from ethanol. Yield 1.72 g. (60%) m.p. 153-154° (lit.[160] 153-154°), δ(DMSO-d_6) 3.90 (12H, s, CH_3), 7.11 ($2H_{5,5'}$, d, $J_{5,6}$ 8.5 Hz), 7.42 ($2H_{2,2'}$, d, $J_{2,6}$ $J_{2',6'}$ 2 Hz), 7.53 ($2H_{6,6'}$, dd); $\nu_{max.}$ (KBr disc) 1310m (SO_2 as.), 1135s cm^{-1} (SO_2 s).

Experiment 4 Preparation of 3,3', 4,4'-Tetrahydroxydiphenyl Sulphone

A. Boron tribromide (7.28 g., 29.1 mmol.) was added dropwise with stirring to 3,3'4,4'-tetramethoxydiphenyl sulphone (1.29 g., 3.82 mmol.) in toluene (100 cm^3). The reaction mixture was refluxed for 1.5 hr., and then water was added dropwise to the cooled mixture. Evaporation of the solvents under reduced pressure gave a solid residue. Boric acid was removed as volatile methyl borate by repeated addition of methanol followed by evaporation. The product was purified by recrystallisation from water. Yield 1.02 g. (95%) m.p. 237-238.5°

(lit.[43] 237-240°), δ(DMSO-d_6) 7.05 ($2H_{5,5'}$, d, $J_{5,6}$ $J_{5',6'}$ 10 Hz), 7.38 ($2H_{2,2'}$,d,$J_{2,6}J_{2',6'}$ 2Hz), 7.38 ($2H_{6,6'}$, dd); $\nu_{max.}$ (KBr disc) 1342m (SO_2 as.), 1145s cm^{-1}(SO_2 s.).

B. The method used is similar to that described by Kerber[58] to give the crude product. A solution of catechol (22.0 g., 200 mmol.) and sodium formaldehyde sulphoxylate dihydrate (17.5 g., 114 mmol.) in water (125 cm^3) at 20° was slowly poured into a stirred solution of potassium ferricyanide (132.0 g., 401 mmol.) and sodium acetate trihydrate (120 g., 882 mmol.) in water (500 cm^3) also at 20°. The temperature was not allowed to rise above 35°. The mixture was stirred for a further 10 min., and then extracted with butanone (3 x 200 cm^3). The combined extracts were dried ($CaCl_2$), and the solvent was removed by rotary evaporation. The residue was recrystallised from water to give a pale-brown product. Yield 20.6 g. (ca. 73%) m.p. 236-237°.

The product was purified by first preparing the tetraacetoxy derivative; 3,3'4,4'-tetrahydroxydiphenyl sulphone (20.0 g., 70.9 mmol.) was added to a mixture of acetic anhydride (145 g., 1.42 mol.) and pyridine (20 cm^3) and the reaction mixture was stirred at room temperature for 30 min. and then at 100° for 1 hr. The cooled solution was poured into a stirred ice-water mixture (250 cm^3) and the crude product was filtered off and purified by recrystallisation from ethyl acetate (charcoal) giving 3,3',4,4'-tetraacetoxydiphenyl sulphone. Yield 13.64 g. (ca. 43%) m.p. 147-148° (lit.[58] 148°), δ(DMSO-d_6) 2.34 (12H, s, CH_3), 7.76 ($2H_{5,5'}$, d, $J_{5,6}$ $J_{5',6'}$ 10 Hz),

8.16 ($2H_{6,6'}$, dd, $J_{2,6}$ $J_{2',6'}$ 2 Hz, $J_{5,6}$ $J_{5',6'}$ 10 Hz) 8.20 ($2H_{2,2'}$,d); $\nu_{max.}$ (KBr disc) 1773s (C=O), 1330m (SO_2 as.), 1150m cm^{-1} (SO_2 s.).

3,3',4,4'-Tetraacetoxydiphenyl sulphone (13.21 g., 29.4 mmol.) was dispersed in methanol (200 cm^3) and deacetylated under a nitrogen atmosphere by passing dry hydrochloric acid gas through the mixture until all the solid went into solution (ca. 1½ hr.). The mixture was refluxed for 1 hr., and the solvent was evaporated off to give the product which was then purified by recrystallisation from water. Yield 7.41 g. (89%).

Experiment 5 Preparation of 2,3,4-Trimethoxybenzenesulphonyl Chloride

2,3,4-Trimethoxybenzenesulphonyl chloride was prepared by the procedure described in experiment 2, using chlorsulphonic acid (35.0 g., 300 mmol.), and 1,2,3-trimethoxybenzene (10.0 g., 59.46 mmol.) in chloroform (15 cm^3). Yield 8.45 g. (53%), m.p. 39-40° (lit.[161] 38-39°), $\delta(CDCl_3)$ 3.97 (3H, s, CH_3), 4.03 (3H, s, CH_3) 4.20 (3H, s, CH_3), 6.86 ($1H_5$, d, $J_{5,6}$ 9 Hz), 7.83 ($1H_6$, d); $\nu_{max.}$ (KBr disc) 1356s (SO_2 as.), 1175m cm^{-1} (SO_2 s.) [lit.[161] 1350 (SO_2 as.), 1170 (SO_2 s.)].

Experiment 6 Preparation of 2,2',3,3',4,4'-Hexamethoxydiphenyl Sulphone

The procedure is similar to that described in experiment 3. 2,3,4-Trimethoxybenzenesulphonyl chloride (2.98 g, 11.18 mmol.) and 1,2,3-trimethoxybenzene (6.0 g, 35.7 mmol.) were condensed together in the presence of anhydrous zinc chloride (2.5 g.) at 120° for 20 min. The excess 1,2,3-trimethoxybenzene was removed by steam distillation and

the product was purified by recrystallisation from ethanol. Yield 2.46 g. (55%) m.p. 151-152° (lit.[162] 152-153°), δ(DMSO-d_6) 3.57 (6H, s, CH_3), 3.77 (6H, s, CH_3), 3.97 (6H, s, CH_3), 7.18 ($2H_{5,5'}$, d, $J_{5,6}$ $J_{5',6'}$ 9.5 Hz), 7.87 ($2H_{6,6'}$, d); $\nu_{max.}$ (KBr disc) 1299s (SO_2 as.), 1132m cm^{-1} (SO_2 s.).

Experiment 7 Preparation of 2,2',3,3',4,4'-Hexahydroxydiphenyl Sulphone

2,2',3,3',4,4'-Hexamethoxydiphenyl sulphone (2.20 g., 5.53 mmol.) was demethylated by the procedure described in experiment 4A using boron tribromide (16.0 g., 63.9 mmol.) in toluene (250 cm^3). The product was purified by recrystallisation from water. Yield 1.62 g. (93%) m.p. 232-233°, δ(DMSO-d_6) 6.51 ($2H_{5,5'}$, d, $J_{5,6}$ $J_{5',6'}$ 9 Hz), 7.24 ($2H_{6,6'}$,d); $\nu_{max.}$ (KBr disc) 1321s (SO_2 as.), 1148s cm^{-1} (SO_2 s.) (Found: C, 45.80; H,3.23; S,10.13. $C_{12}H_{10}O_8S$ requires: C,45.87; H,3.21; S,10.20%).

Experiment 8 Preparation of 3,4,5-Trimethoxybenzoyl Chloride

A. 3,4,5-Trimethoxybenzoic acid (35 g., 170 mmol.) and thionyl chloride (29.75 g., 250 mmol.) was heated at reflux temperature for 4 hr. No evolution of gaseous by-products was observed during this time. Thionyl chloride was distilled off; attempted distillation under vacuum yielded no product.

B. 3,4,5-Trimethoxybenzoic acid (60.0 g., 0.283 mmol.) and phosphorus pentachloride (59.0 g., 0.283 mmol.) were thoroughly mixed, allowed to stand at room temperature for 1 hr. and then heated at 100° for 2 hr. Phosphoryl chloride was distilled off and the product distilled under reduced pressure. Yield 45.32 g. (69%), m.p. 78-79° (lit.[85] 77-78°).

Experiment 9 Preparation of 3,4,5-Trimethoxyaniline

3,4,5-Trimethoxybenzamide was prepared by dropwise addition of excess ammonia solution (S.G. 0.88) to 3,4,5-trimethoxybenzoyl chloride with stirring in an ice bath and purified by recrystallisation from water.

The amide was converted to the amine by the method similar to that described by Moreau[81]; 3,4,5-trimethoxybenzamide (36.0 g., 170 mmol.) was added with vigorous stirring to a solution of sodium hydroxide (25.0 g., 625 mmol.) and bromine (20.57 g., 257 mmol.) in water (75 cm^3) cooled by an ice-salt bath. Stirring was continued for a further 15 min. whereupon the solution became clear. The stirred solution was then heated at 70° for 1 hr., cooled and the crude amine filtered off, washed with a little cold water and recrystallised from ethanol (charcoal). Yield 17.86 g. (57%), m.p. 107-8° (lit.[81] 111°).

Experiment 10 Preparation of 3,4,5-Trimethoxy-benzenesulphonyl Chloride

The method used is similar to that described by Moreau.[81] 3,4,5-Trimethoxyaniline (15.0 g., 81.9 mmol.) was dissolved with stirring in a warm mixture of conc. hydrochloric acid (45 cm^3) and water (20 cm^3). The mixture was cooled to -10°, and then the aniline was diazotised using a solution of sodium nitrite (6.0 g., 87 mmol.) in water (15 cm^3) without allowing the temperature to rise above -5°. The end-point of the addition was monitored using starch-iodide paper. This mixture was added to a stirred solution of sulphur dioxide (at least 30%) in glacial acetic acid (85 cm^3), to which had been added cuprous chloride (5.0 g.) dispersed in water (5 cm^3). The reaction mixture was stirred at 30 - 35° until evolution of nitrogen ceased. The product was

filtered off, washed with a little cold water and dried *in vacuo* (P_2O_5), and then purified by recrystallisation from hexane (charcoal). Yield 11.44 g. (52%) m.p. 87-88° (lit.[81] 88-89°, $\delta(CDCl_3)$ 4.05 (9H, s, CH_3), 7.08 (2H, s, ArH); $\nu_{max.}$ (KBr disc) 1370s (SO_2 as.), 1175s cm^{-1} (SO_2 s.) [lit.[8] 1370 (SO_2 as.), 1175 cm^{-1} (SO_2 s.)].

Experiment 11 Preparation of 2,3,3',4,4',5'-Hexamethoxydiphenyl Sulphone

3,4,5-Trimethoxybenzenesulphonyl chloride (5.50 g., 20.6 mmol.) was mixed with 1,2,3-trimethoxybenzene (10 g., 59.5 mmol.) and zinc chloride (4.8 g.) and the reaction mixture was heated in an oil-bath at 150° for 30 min. A little water was added to the cooled mixture, and the excess trimethoxybenzene was removed by steam-distillation. The residue was extracted with warm ethanol, and evaporation of this solution under reduced pressure gave the product which was then recrystallised from ethanol-water (charcoal). Yield 2.84 g., (35%), m.p. 131-132°, $\delta(DMSO\text{-}d_6)$ 3.82 (9H, s, CH_3), 3.90 (6H, s, CH_3), 3.97 (3H, s, CH_3), 7.17 ($1H_5$, d, $J_{5,6}$ 9.5 Hz), 7.30 ($2H_{2',6'}$, s), 7.90 ($1H_6$, d); $\nu_{max.}$ (KBr disc) 1317s (SO_2 as.), 1136s cm^{-1} (SO_2 s.).

(Found: C,54.18; H, 5.75; S, 8.30. $C_{18}H_{22}O_8S$ requires: C, 54.26; H, 5.57; S, 8.05%).

Experiment 12 Preparation of 2,3,3',4,4',5'-Hexahydroxydiphenyl Sulphone

2,3,3',4,4',5'-Hexamethoxydiphenyl sulphone (1.61 g., 4.05 mmol.) was demethylated in toluene (50 cm^3) using boron tribromide (11.79 g., 47.1 mmol.) by the method described in experiment 4A. 2,3,3',4,4',5'-

Hexahydroxydiphenyl sulphone was recrystallised from water. Yield 0.98 g. (77%). The compound clears without melting when heated to 350°, δ(DMSO-d_6) 6.59 ($1H_5$, d, $J_{5,6}$ 9 Hz), 6.95 ($2H_{2',6'}$, s), 7.34 ($1H_6$, d); $\nu_{max.}$ (KBr disc) 1295s (SO_2 as.), 1120s cm^{-1} (SO_2 s.).

(Found: C, 45.83; H, 3.42; S, 10.21. $C_{12}H_{10}O_8S$ requires: C, 45.87; H, 3.21; S, 10.20%).

Experiment 13 Attempted Preparation of 3,3',4,4',5,5'-Hexahydroxydiphenyl Sulphone by the Method due to Kerber.[58]

The procedure used is the same as that described in experiment 4B to obtain the crude product, except that pyrogallol (25.22 g., 200 mmol.) was used in place of catechol. The extracts were each dried ($CaCl_2$) and the solvent was removed under reduced pressure. The i.r. spectrum of each extract indicated that there was no sulphone present.

Experiment 14 Attempted Hansdiecker Reaction on 3,4,5-Trimethoxybenzoic Acid (Silver Salt)

The procedure is similar to that described by Dandiya[85]

3,4,5-Trimethoxybenzoic acid (2.0 g., 9.4 mmol.) was dissolved in dilute ammonia solution, excess ammonia was boiled off and silver nitrate (1M) added to the cooled solution until precipitation was complete. The white solid was filtered off, washed with cold water and dried in vacuo (P_2O_5), m.p. 180-81(decomp.).

Bromine (3.0 g., 18.8 mmol.) was refluxed for 1 hr. with the silver salt of 3,4,5-trimethoxybenzoic acid. The cooled reaction mixture was extracted with ethanol (3 x 50 cm^3) and the solvent removed from the combined extracts, leaving a solid residue. This residue was dissolved

in carbon tetrachloride (75 cm^3), the resulting solution washed with aqueous sodium hydroxide (0.1M; 2 x 50 cm^3), then water (2 x 50 cm^3) and finally dried ($MgSO_4$). On removing the solvent only a very small amount of oily residue remained.

Experiment 15 Improved Cristol-Firth Type Reaction due to Davis[91] on 3,4,5-Trimethoxybenzoic Acid

A. 3,4,5-Trimethoxybenzoic acid (17 g., 80 mmol.) was mixed with red mercuric oxide (17.4 g., 80 mmol.) in dry 1,1,2,2-tetrachloroethane (100 cm^3). Bromine (12.8 g., 80 mmol.) in dry 1,1,2,2-tetrachloroethane (30 cm^3) was slowly added with stirring to the refluxing mixture, and heating continued for 90 min. The filtered organic solution was washed with sodium hydroxide solution (0.1M; 3 x 30 cm^3), water (3 x 30 cm^3) and then dried ($CaCl_2$). On removing the solvent, only a very small amount of oily residue remained.

B. Modification of the above

The mercuric salt of 3,4,5-trimethoxybenzoic acid (13.26 g., 21 mmol.), prepared via the ammonium salt, was dispersed in dry 1,1,2,2-tetrachloroethane (50 cm^3). Bromine (2.2 cm^3., 43 mmol.) in 1,1,2,2-tetrachloroethane (15 cm^3) was added and the reaction mixture refluxed for 75 min. After cooling, the organic solution was filtered, washed with sodium hydroxide solution (0.1M; 5 x 30 cm^3) water (3 x 50 cm^3) and then dried ($CaCl_2$). The solvent was removed by rotary evaporation, leaving no product.

Experiment 16 Preparation of 1-Bromo-3,4,5-trimethoxybenzene

The procedure followed was similar to that described by Vogel.[163] Copper sulphate (6.75 g., 27 mmol.) and sodium bromide (2.88 g., 28 mmol.) were dissolved in water (25 cm^3). Sodium sulphite (1.71 g., 14 mmol.) in water (20 cm^3) was added to the hot solution over 5 min. with stirring. The mixture was cooled in an ice-bath and the supernatant liquid decanted off. The precipitated cuprous bromide was washed twice by decantation with water containing a little sulphurous acid. The solid was dissolved in constant boiling point hydrobromic acid (15 cm^3; 48%) and cooled in an ice-salt mixture.

3,4,5-Trimethoxyaniline (5.35 g. 30 mmol.) was dispersed in water (25 cm^3), and conc. sulphuric acid (5.88 g.) was added dropwise with stirring. The mixture was warmed until all the solid dissolved, then cooled in an acetone-dry ice bath to -10°. Sodium nitrite (2.10 g., 30 mmol.) in water (4.5 cm^3) was added dropwise with stirring, and the temperature was not allowed to rise above -5°. The end-point of the addition was monitored using starch-iodide paper. This mixture was added to the cuprous bromide solution and allowed to stand at room temperature for 1 hr. with occasional stirring. The product was extracted with ether (3 x 50 cm^3). The combined extracts were washed with sodium bicarbonate solution (1$\underline{M}$; 50 cm^3), dilute hydrochloric acid (0.1$\underline{M}$; 50 cm^3) and then water (2 x 50 cm^3), and dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the product recrystallised from ligroin. Yield 5.26 g. (71%), m.p. 78-79° (lit.[87] 78.5 - 80°).

Experiment 17 Attempted Preparation of 3,4,5-Trimethoxyphenyl-magnesium Bromide

A. 1-Bromo-3,4,5-trimethoxybenzene (5.0 g., 20 mmol.) was dissolved in sodium dried diethyl ether (10 cm^3) and magnesium turnings (0.52 g.) were added. A dry nitrogen atmosphere was maintained throughout the experiment. A crystal of iodine was added and the mixture left for 1 hr., during which time no reaction occurred. The mixture was refluxed with gentle stirring for 2 hr, but again no reaction was observed. (The original weight of magnesium was recovered).

B. The above procedure was repeated using tetrahydrofuran (10 cm^3) in place of diethyl ether. However, no reaction occurred.

Experiment 18 Preparation of 1-Iodo-3,4,5-trimethoxybenzene

Diazotisation was carried out as in experiment 16 using 3,4,5-trimethoxyaniline (20 g., 109 mmol.), conc. sulphuric acid (10.8 cm^3) in water (45 cm^3), and sodium nitrite (7.90 g., 114 mmol.) in water (40 cm^3). A cold solution of potassium iodide (18.2 g., 109 mmol.) in water (20 cm^3) was added slowly with stirring. The reaction mixture was left at room temperature for 1 hr. and then heated in a boiling water bath for 5 min. The iodide was extracted with carbon tetrachloride (4 x 50 cm^3) and the combined extracts were washed with dil. sodium hydroxide solution (0.1M; 2 x 50 cm3), water (3 x 50 cm^3) and then dried ($MgSO_4$). The solvent was removed by rotary evaporation, and the iodide recrystallised from ligroin. Yield 22.5 g. (70%), m.p. 84.5 - 85.5° (lit.[87] 86-87°).

Experiment 19 Attempted Preparation of 3,4,5-Trimethoxyphenyl-magnesium Iodide

The procedure described in experiment 14 was carried out, using 1-iodo 3,4,5-trimethoxybenzene (5.88 g., 20 mmol.) instead of the bromo compound. Using the solvents in both A and B, the iodo compound failed to form the magnesium iodide.

Experiment 20 Attempted Preparation of 4,4'-Dimethoxydiphenyl Sulphide from p-Anisidine via the Diazonium Salt

Diazotisation was carried out as in experiment 16 using p-anisidine (11.07 g., 89.9 mmol.) conc. sulphuric acid (9 cm^3) in water (40 cm^3) and sodium nitrite (6.3 g., 91 mmol.) in water (20 cm^3). Ammonium sulphide (34% w/v; 9 ml., 45 mmol.) in water (20 cm^3) was added dropwise with stirring, and the temperature of the reaction mixture was not allowed to rise above 10^o. The mixture was stirred at room temperature for 1 hr. and then extracted with ether (3.5 cm^3). The combined extracts were washed with sodium bicarbonate solution (1M; 2 x 50 cm^3), water (2 x 50 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure, leaving an oil. Despite repeated attempts, no crystalline material could be obtained from this oil.

Experiment 21 Attempted Preparation of Diaryl Sulphur Compounds via Aryllithium Compounds

A. N,N'-Thionyldiimidazole was prepared by the method described by Bast.[79] Thionyl chloride (1.55 g., 13 mmol.) was added dropwise with stirring and cooling in an ice bath to a solution of imidazole

(1.77 g., 26 mmol.) in anhydrous tetrahydrofuran (25 cm^3). After cooling for several minutes the reaction mixture was filtered with suction in a nitrogen atmosphere.

1-Lithium 3,4,5-trimethoxybenzene was prepared under dry nitrogen by the dropwise addition of n-butyllithium in hexane (22%; 8.45 g.; 29 mmol.) to a stirred solution of 1-iodo-3,4,5-trimethoxybenzene (8.23 g., 28 mmol.) in ether (100 cm^3) cooled in an ice bath. After a few minutes, the solution of N,N'-thionyldiimidazole was added dropwise, and the reaction mixture stirred for a further 30 minutes at room temperature. The solution was then poured onto an ice-diluted hydrochloric acid mixture, the organic layer separated off and the aqueous layer extracted with ether (3 x 25 cm^3) the combined organic solutions were washed with aqueous sodium bicarbonate solution (1M; 2 x 25 cm^3), water (2 x 25 cm^3) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the product recrystallised from pet. ether (b.p. 80 - 100°). Upon investigation, this compound was found to be 3,3',4,4',5,5'-hexamethoxybiphenyl. Yield 0.64 g., m.p. 127-128° (lit.[83] 126°), $\delta(CDCl_3)$ 3.95 (3H, s, CH_3), 4.00 (6H, s, CH_3) 6.85 (2H, s, ArH).

(Found: C, 64.92; H, 6.86; S,0.00. Calc. for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63%).

B. p-Tolyllithium was prepared in the manner described by Vogel.[164] p-Bromotoluene (21.5 g., 126 mmol.) in ether (35 cm^3) was added dropwise to lithium wire (1.9 g.) in ether (35 cm^3) at such a rate that the solvent refluxed continuously. When the addition was complete the solution was refluxed by gentle heating for a further 1 hr. The mixture was filtered rapidly through glass wool. The procedure

outlined in A was followed, except that thionyl chloride (7.14 g., 60 mmol.) in ether (35 cm^3) was used instead of N,N'-thionyldiimidazole. Evaporation of the solvent resulted in a small amount of liquid which proved to be unreacted p-bromotoluene (i.r.).

C. The procedure outlined in B was followed, except that sulphuryl chloride (8.10 g., 60 mmol.) was used in place of thionyl chloride. Again only a small amount of unreacted p-bromotoluene was recovered.

D. The above was repeated using 3,4-dimethoxybenzenesulphonyl chloride (29.80 g., 126 mmol.) in place of sulphuryl chloride, with similar results.

Experiment 22 Preparation of 3,4,5-Trihydroxydiphenyl Sulphone

A solution of sodium benzenesulphinate (19.44 g., 119 mmol.) and pyrogallol (14.94 g., 119 mmol.) in water (100 cm^3) was added over a 1 min. period to a stirred solution of potassium ferricyanide (78.30 g., 238 mmol.) and sodium acetate trihydrate (16.32 g., 120 mmol.) in water (200 cm^3). After stirring for a further 10 min. the product was filtered off and recrystallised from ethanol-water giving pale-brown coloured crystals. Yield 19.15 g. (ca. 61%) m.p. 185 - 188°.

The product was purified via the triacetoxy derivative prepared by the procedure described in experiment 4B using 3,4,5-trihydroxyphenyl sulphone (18.51 g., ca. 70 mmol.) acetic anhydride (120 g., 1.18 mol.) and pyridine (20 cm^3). The triacetoxy derivative was recrystallised from ethanol-water (charcoal). Yield 18.66 g. (ca. 68%) m.p. 183 - 184°, (R_F = 0.36 in solvent A), δ (DMSO-d_6) 2.30 (6H, s, CH_3),

2.34 (3H, s, CH_3), 7.60 - 8.06 (7H, m, ArH), 7.96 ($2H_{2,6}$, s); $\nu_{max.}$ (KBr disc) 1783s (C=O), 1328m (SO_2 as.), 1156s cm^{-1} (SO_2, s.) (Found: C, 55.13; H, 4.13; S, 8.29. $C_{18}H_{16}O_8S$ requires: C, 55.10; H, 4.11; S, 8.17%).

3,4,5-Triacetoxydiphenyl sulphone (18.56 g., 47 mmol.) was deacetylated by the procedure described in experiment 4B. The solvent was removed by rotary evaporation leaving a white product which was then recrystallised from ethanol - water. Yield 11.75 g. (94%) m.p. 188 - 189° (lit.[56] 188°), δ(DMSO-d_6) 7.07 ($2H_{2,6}$, s, ArH), 7.60 - 8.20 (5H, m, ArH), 8.5 - 10.5 (*ca.* 3H, D_2O exchangeable, OH); $\nu_{max.}$ (KBr disc) 1325s (SO_2 as.) 1142s cm^{-1} (SO_2 s.).

Experiment 23 Preparation of 3,4-Dihydroxy-diphenyl Sulphone

The procedure described in experiment 19 was followed using catechol (13.10 g., 119 mmol.) in place of pyrogallol. The pale-yellow product was not purified *via* the diacetoxy derivative, and was recrystallised from ethanol-water. Yield 26.34 g. (89%), m.p. 165 - 166° (lit.[56] 164°), $\nu_{max.}$ (KBr disc) 1305s (SO_2 as.), 1152s cm^{-1} (SO_2 s.).

Experiment 24 Preparation of 3,4-Dimethoxybenzene Sulphinic acid (Sodium Salt).

3,4-Dimethoxybenzenesulphonyl chloride (34.65 g., 147 mmol.) was dispersed in a stirred solution of sodium sulphite (74.0 g. 294 mmol.) in water (100 cm^3). The pH, was carefully maintained at about pH 8 by dropwise addition of aq. sodium hydroxide solution (4M).

When most of the solid had gone into solution (ca. 5 hr.) the mixture was heated to 60° for 15 min. The cooled solution was filtered and then acidified by the dropwise addition of conc. hydrochloric acid until precipitation of the sulphinic acid was complete. The solid was washed with a little cold water and recrystallised from water. Yield 28.08 g. (95%) δ(DMSO-d_6) 3.83 (3H, s, CH_3), 3.84 (3H, s, CH_3), 7.12 ($1H_5$, d, $J_{5,6}$ 8.5 Hz), 7.23 ($1H_2$, d, $J_{2,6}$ 2Hz), 7.25 ($1H_6$, cld) $\nu_{max.}$ (KBr disc) 2350m (SH), 1135s (SO_2 as.), 1015s cm^{-1} (SO_2 s.).
(Found: C, 47.35; H, 4.91; S, 15.97. $C_8H_{10}O_4S$ requires: C, 47.51; H, 4.98; S, 15.86%).

3,4-Dimethoxybenzenesulphinic acid (27.23 g., 135 mmol.) was dissolved in a warm aqueous sodium hydroxide solution (1M; 137 cm^3). Water was evaporated off under reduced pressure, leaving the sodium sulphinate as a solid which was purified by recrystallisation from acetone-water. Yield 27.25 g. (90%), $\delta(D_2O)$ 3.82 (3H, s, CH_3), 3.89 (3H, s, CH_3), 7.00 ($1H_5$, d, $J_{5,6}$ 8Hz), 7.08 ($1H_2$, d, $J_{2,6}$ 2Hz), 7.19 ($1H_6$, dd); $\nu_{max.}$ (KBr disc) 1140m (SO_2 as.), 1025s cm^{-1} (SO_2 s.).

Experiment 25 Preparation of 3,4-Dimethoxy-3',4',5'-trihydroxyphenyl Sulphone

The procedure described in experiment 19 was followed using sodium 3,4-dimethoxybenzenesulphinate (15.00 g., 67 mmol.) and pyrogallol (8.44 g., 67 mmol.) in water (100 cm^3), and potassium ferricyanide (44.06 g., 134 mmol.) and sodium acetate (9.11 g., 67 mmol.) in water (150 cm^3). The product was pale-brown in colour.

Yield 12.17 g. (ca. 56%) m.p. 189-190°. The product was purified via the triacetoxy derivative, prepared by the method described in experiment 4B using crude 3,4-dimethoxy 3',4',5'-trihydroxydiphenyl sulphone (11.85 g., ca. 36 mmol.), acetic anhydride (60 g., 588 mmol.) and pyridine (10 cm^3). 3,4-Dimethoxy 3',4',5'-triacetoxydiphenyl sulphone was recrystallised from ethyl acetate (charcoal). Yield 9.96 g. (ca. 61%) m.p. 129-130° (R_F = 0.36 in solvent A; R_F = 0.78 in solvent B), δ(DMSO-d_6) 2.30 (6H, s, $COCH_3$), 2.32 (3H, s, $COCH_3$), 3.82 (3H, s, CH_3) 3.84 (3H, s, CH_3), 7.19 ($1H_5$, d, $J_{5,6}$ 8.5 Hz), 7.45 ($1H_2$, d, $J_{2,6}$ 2Hz), 7.58 ($1H_6$, dd), 7.94 ($2H_{2',6'}$, s); $\nu_{max.}$ (KBr disc) 1780s (C=O), 1326m (SO_2 as.), 1145s cm^{-1} (SO_2 s.). (Found: C, 53.03; H, 4.68; S, 6.93. $C_{20}H_{20}S$ requires: C, 53.10; H, 4.46; S, 7.09%).

3,4-Dimethoxy 3',4',5'-triacetoxydiphenyl sulphone (9.48 g. 21 mmol.) was deacetylated by the method described in experiment 4B. The solvent was evaporated under reduced pressure, leaving 3,4-dimethoxy 3',4',5'-trihydroxydiphenyl sulphone as a white solid which was then purified by recrystallisation from ethanol-water. Yield 6.33 g. (92%) m.p. 190-191°, δ(DMSO-d_6) 3.77 (6H, s, CH_3), 6.81 ($2H_{2',6'}$, s), 7.10 ($1H_5$, d, $J_{5,6}$ 8.5 Hz), 7.23 ($1H_2$, d, $J_{2,6}$ 2Hz), 7.37 ($1H_6$, dd); $\nu_{max.}$ (KBr disc) 1311m (SO_2 as.), 1137s cm^{-1}(SO_2 s.).

(Found: C, 51.39; H, 4.59; S, 9.73. $C_{14}H_{14}O_7S$ requires: C, 51.53; H, 4.32; S, 9.83%).

Experiment 26 Preparation of 3,3',4,4',5-Pentahydroxydiphenyl Sulphone

3,4-Dimethoxy-3',4',5'-trihydroxydiphenyl sulphone (5.39g. 16.5 mmol.) was demethylated in toluene (200 cm^3) using boron tribromide (21.0 g., 83.8 mmol.) by the method described in experiment 4A. 3,3'4,4'5-Pentahydroxydiphenyl sulphone was purified by recrystallisation from water. Yield 4.72 g. (96%) m.p. 269 - 270° (decom.), δ(DMSO-d_6) 6.78 ($2H_{2',6'}$, s), 6.89 ($1H_{5'}$, d, $J_{5',6'}$ 9Hz), 7.16 ($1H_{2'}$, d, $J_{2',6'}$ 2 Hz), 7.16 ($1H_{6'}$, dd); $\nu_{max.}$ (KBr disc) 1290s (SO_2 as.), 1140s cm^{-1} (SO_2 s.).

(Found: C, 48.28; H, 3.57; S, 10.59. $C_{12}H_{10}O_7S$ requires: C, 48.32; H, 3.38; S, 10.75%).

Experiment 27 Preparation of 3,4,5-Trimethoxybenzenesulphinic Acid (Sodium Salt)

3,4,5-Trimethoxybenzenesulphinic acid was prepared by the method described in experiment 24 using 3,4,5-trimethoxybenzenesulphonyl chloride (21.92 g., 82.3 mmol.) and sodium sulphite (41.48 g., 165 mmol.) in water (100 cm^3). The product was purified by recrystallisation from water. Yield 18.82 g. (99%) m.p. 104 - 105° (decom.), δ(DMSO-d_6) 3.80 (3H, s, CH_3), 3.93 (6H, s, CH_3), 7.13 (2H, s, $ArH_{2,6}$); $\nu_{max.}$ (KBr disc) 2450m (S-H), 1135s (SO_2 as.), 1022m cm^{-1} (SO_2 s.).

The sodium salt was prepared by the method described in experiment 21, and purified by recrystallisation from acetone-water. δ (D_2O) 3.78 (3H, s, CH_3), 3.92 (6H, s, CH_3), 6.98 (2H, s, $ArH_{2,6}$); $\nu_{max.}$ (KBr disc) 1132s (SO_2 as.), 1000s cm^{-1} (SO_2 s.).

Experiment 28 Preparation of 3,4,5-Trihydroxy-3',4',5'-trimethoxydiphenyl Sulphone

The procedure described in experiment 22 was followed using sodium 3,4,5-trimethoxybenzenesulphinate (14.62 g., 57.8 mmol.) and pyrogallol (7.28 g., 58 mmol.) in water (200 cm^3), and potassium ferricyanide (38.04 g., 116 mmol.) and sodium acetate (7.86 g. 57.8 mmol.) in water (200 cm^3). The product was recrystallised from ethanol-water, giving pale brown crystals. Yield 11.29 g (ca. 55%) m.p. 222-223°.

The product was purified via the triacetoxy derivative prepared by the method described in experiment 4B using the crude 3,4,5-trihydroxy-3,4,5-trimethoxydiphenyl sulphone (10.16 g. ca. 28.5 mmol.), acetic anhydride (50 g., 490 mmol.) and pyridine (10 cm^3). Recrystallisation of the product from ethyl acetate (charcoal) gave 3,4,5-triacetoxy-3',4',5'-trimethoxydiphenyl sulphone. Yield 8.36 g. (ca. 61%) m.p. 164 - 165°, δ(DMSO-d_6) 2.37 (9H, s, $COCH_3$), 3.83 (3H, s, CH_3), 3.97 (6H, s, CH_3), 7.45 ($2H_{2'}$, s); $\nu_{max.}$ (KBr disc) 1780s (C=O) 1316s (SO_2 as.), 1128s cm^{-1} (SO_2 s).

(Found: C,52.26; H, 4.68; S, 6.78. $C_{21}H_{22}O_{11}S$ requires: C, 52.28; H, 4.60; S, 6.65%).

3,4,5-Triacetoxy-3',4',5'-trimethoxydiphenyl sulphone (8.11 g., 16.8 mmol.) was deacetylated by the procedure described in experiment 4B. The solvent was removed under reduced pressure leaving a colourless product which was then purified by recrystallisation from ethanol-water. Yield 5.52g. (92%), m.p. 223-224°, δ(DMSO-d_6) 3.80 (3H, s, CH_3); 3.92 (6H, s, CH_3), 7.02 ($2H_{5,6'}$ s), 7.23 ($2H_{2',6'}$, s); $\nu_{max.}$ (KBr disc) 1297s (SO_2 as.), 1130s cm^{-1} (SO_2 s.).

(Found: C, 50.63; H, 4.60; S, 9.25. $C_{15}H_{16}O_8S$ requires: C, 50.56; H, 4.53; S, 9.00%).

Experiment 29 Preparation of 3,3',4,4',5,5'-Hexahydroxydiphenyl Sulphone

3,4,5-Trihydroxy-3',4',5'-trimethoxydiphenyl sulphone (5.36 g., 15.2 mmol.) was demethylated in toluene (200 cm^3) using boron tribromide (23.0 g., 91.8 mmol.) by the method described in experiment 4A. 3,3',4,4',5,5'-Hexahydroxydiphenyl sulphone was purified by recrystallisation from water. Yield 4.18 g. (88%). The compound clears without melting when heated to 350°, δ(DMSO-d_6) 6.92 (s, ArH); $\nu_{max.}$ (KBr disc) 1311s (SO_2 as.), 1136s cm^{-1} (SO_2 s.).

(Found: C, 45.73; H, 3.24; S, 10.21. $C_{12}H_{10}O_8S$ requires: C, 45.87; H, 3.21; S, 10.20%).

Experiment 30 Attempted Reactions with o-Quinones

A. A solution of pyrogallol (5.0 g., 39.7 mmol.) and potassium iodide (7.0 g., 42.2 mmol.) in water (50 cm^3) was slowly poured into a stirred solution of potassium ferricyanide (26.14 g., 79.4 mmol.) and sodium acetate (5.40 g., 39.7 mmol.) in water (150 cm^3). After about 10 min. the solution was extracted with ethyl acetate (3 x 50 cm^3), and the combined extracts were dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a residue which was acetylated in the usual manner. The acetylated product was purified by recrystallisation from ethanol (charcoal) to give only a small amount of 1,2,3-triacetoxybenzene. m.p. 162 - 163° (lit.[165] 165°).

B. The procedure described in A was followed, using potassium thiocyanate (5.0 g., 51.5 mmol.) in place of potassium iodide, giving a similar result.

C. The procedures described in A and B were followed, using catechol (4.37 g., 39.7 mmol.) in place of pyrogallol. In both cases, only a small amount of 1,2-diacetoxybenzene was isolated.

Experiment 31 The Action of Benzenesulphinic Acid (Cupric salt) on Arylthallium Compounds

Thallium(III) trifluoroacetate and arylthallium compounds were prepared by the method due to McKillop.[143] Thallic oxide (50 g., 109 mmol.), trifluoroacetic acid (200 cm^3) and water (25 cm^3) were protected from light, and the stirred mixture was refluxed for 12 hr. The cooled mixture was filtered to give a solution of thallium (III) trifluoroacetate (approximately 0.88M). (TTFA solution).

The arylthallium compounds were prepared in the following manner: mesitylene (0.96 g., 7.99 mmol.) was added to the TTFA solution (10 cm^3) and stirred for 1 hr. at room temperature: m-xylene (0.85 g., 8.02 mmol.) was added to the TTFA solution (10 cm^3) and stirred at room temperature for 50 min.: chlorobenzene (0.90 g., 7.99 mmol.) was added to the TTFA solution (10 cm^3) and the stirred mixture was refluxed for 30 min. Evaporation of the solvent, followed by co-evaporation with 1,1,2,2-tetrachloroethane under reduced pressure left the solid arylthallium bis(trifluoroacetate). Cupric sulphate (4.09 g., 16.4 mmol.) and sodium benzenesulphinate (10.76 g., 65.6 mmol.) in water (40 cm^3) were added to the arylthallium compound in 1,4-dioxan (40 cm^3). In each case the stirred mixture was protected from light and refluxed for 24 hr. The product was extracted with butanone (3 x 50 cm^3) and the combined extracts were washed with dil. hydrochloric acid (0.1M; 2 x 25 cm^3), aq. sodium bicarbonate solution (10%; 2 x 25 cm^3), water (2 x 25 cm^3) and then dried

(Na_2SO_4). Evaporation of the solvent under reduced pressure gave the product, which was then purified by recrystallisation.

2,4,6-Trimethyldiphenyl sulphone (from ligroin). Yield 0.85 g. (41%), m.p. 75-75° (lit.[45] 73°), δ (DMSO-d_6) 2.30 (3H, s, CH_3), 2.56 (6H, s, CH_3), 7.18 ($2H_{3,5}$, s), 7.52 - 8.10 (5H, ArH); $\nu_{max.}$ (KBr disc) 1301s (SO_2 as.), 1152s cm^{-1} (SO_2 s.).

2,4-Dimethyldiphenyl sulphone (from ligroin). Yield 1.24 g. (63%), m.p. 85-86° (lit.[45] 85°), δ (DMSO-d_6) 2.36 (6H, s, CH_3), 7.20 - 8.30 (8H, ArH); $\nu_{max.}$ (KBr disc) 1318s (SO_2 as.), 1152s cm^{-1} (SO_2s.).

4-Chlorodiphenyl sulphone (from ethanol-hexane). Yield 0.94 g. (47%), m.p. 89-90° (lit.[166] 91 - 91.5°), $\nu_{max.}$ (KBr disc) 1328s (SO_2 as.), 1162s cm^{-1} (SO_2 s.).

Experiment 32 Preparation of Aluminium-pyrogallolato Complexes (Ammonium Salts)

A. A solution of pyrogallol (6.31 g., 50.1 mmol.) and aluminium nitrate (18.75 g., 50.0 mmol.) in water (50 cm^3) was heated with stirring at 90° for 5 min. under a nitrogen atmosphere. A solution of ammonia (S.G. 0.88; 20 cm^3) in water (50 cm^3) was added dropwise, and the product was filtered off from the cooled reaction mixture and washed with acetone. The product was crystallised from aqueous solution by the addition of acetone. Yield 10.62 g. (89%).

(Found: pyrogallolato, 51.65; Al, 11.48. $C_6H_4O_3.Al(OH)_2.NH_4.2H_2O$ requires: pyrogallolato, 51.89; Al, 11.28%).

B. The method outlined in A was followed, using twice the amount of pyrogallol (12.61 g., 100 mmol.). At the end of addition of aq. ammonia solution, ethanol (50 cm^3) was added to the cooled

reaction mixture. The product crystallised from solution overnight, and was purified by crystallisation from water by addition of acetone. Yield 3.69 g. (24%).

(Found: pyrogallolato 79.41; Al, 8.96. $C_{12}H_8O_6$. $AlNH_4.H_2O$ requires: pyrogallolato, 79.75; Al, 8.67%).

C. The procedure described in B was followed, using pyrogallol (18.9 g., 150 mmol.) and aluminium nitrate (18.75 g., 50 mmol.). Yield 13.43 g. (51%).

(Found: pyrogallolato, 71.11; Al, 5.30. $C_{18}H_{12}O_9$. $Al(NH_4)_3.4H_2O$ requires: pyrogallolato, 70.85; Al, 5.13%).

Experiment 33 Preparation of Amino Acid Salts of Aluminium Monocatecholato Complex

The glycine, β-alanine and 4-aminobutyric acid salts of aluminium monocatecholato were prepared in the following manner. A mixture of the amino acid (45.4 mmol.) and aluminium isopropoxide (9.27 g., 4.54 mmol.) in dry isopropanol (70 cm^3) was refluxed with stirring for 3 hr. A solution of catechol (5.0 g., 45.4 mmol.) in isopropanol (20 cm^3) was added. After heating for a further 1 hr., the mixture was stirred overnight at room temperature, and the product was then filtered off.

Experiment 34 Preparation of the Ethyl Esters of Amino Acids

The ethyl esters of glycine, β-alanine and 4-aminobutyric acid were prepared from the corresponding amino acids. The procedure described in experiment 1 gave in each case the ethyl ester hydrochloride, which was purified by recrystallisation from water. The free amino

ethyl ester was liberated by passing gaseous ammonia through a solution or dispersion of the hydrochloride in chloroform for 5 min. Filtration followed by evaporation of the solvent and then vacuum distillation of the residue gave the pure amino ethyl ester.

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