THE ORTHO ALKYLATION OF PHENOLS WITH AROMATIC ALCOHOLS IN THE PRESENCE OF p-TOLUENESULFONIC ACID

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The author wishes to express his deep appreciation for the help and guidance of Professor Ralph L. Guile during the course of this investigation.

Dedication

To my wife and children for
encouragement and understanding
beyond the call of duty.

ABSTRACT

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by Herbert Bowers Rickert

A new method for the ortho alkylation of phenols by aromatic alcohols has been discovered. The aromatic alcohol and phenol were refluxed in cyclohexane with a p-toluenesulfonic acid catalyst to yield water of reaction and ortho-alkylated products. Smaller amounts of the para isomers were formed. When benzyl alcohol and phenol were the reactants, as much as 4.4 parts of o-benzylphenol for each one part of p-benzylphenol were obtained.

Benzyl alcohol may also be used to alkylate substituted phenols. In particular the benzylation of the three isomeric cresols and the six isomeric xylenols was studied. Good yields of ortho-benzylated products were obtained with all the cresols. In the benzylation of the six xylenols, good yields of the ortho isomers were obtained except with 2,6-xylenol. In the latter case ortho alkylation is not possible and both the 3- and 4-benzyl products were formed.

Substituted benzyl alcohols may also be used for the acid-catalyzed ortho alkylation of phenols. Phenol was successfully alkylated with p-methyl-, p-isopropyl-,

p-chloro-, p-bromo-, o-chloro-, and 2,4-dichlorobenzyl alcohols. The ortho/para ratios are highest (4.5-5.3/1) for alcohols containing electron-releasing substituents. Ortho/para ratios for alcohols containing halogen (electron-withdrawing) substituents are in the order of 2.5-3.0/1.

The rate of the reaction may be determined by measuring the amount of water removed per unit time. Benzyl alcohols containing electron-releasing substituents react faster than benzyl alcohol itself; alcohols containing electron-withdrawing groups react slower.

A mechanism is proposed whereby ortho alkylation proceeds via a cyclic intermediate complex. Para alkylation is assumed to take place via free carbonium ions.

Acid-catalyzed ortho alkylation may also be carried out at 140-150°C. without a solvent in the presence of p-toluenesulfonic acid. The yields by this method are as good as with the solvent method.

Other catalysts such as Dowex 50 and benzenesulfonic acid may also be used, but somewhat lower ortho/para ratios are obtained.

The benzylated products may be analyzed by means of their infrared spectra. The O-H stretching bands at 2.7-3.0μ, the O-H deformation bands at 8.2-8.5μ and the out-of-plane C-H deformation bands at 10-15μ

are the most useful for qualitative analysis. The latter bands are most valuable for the quantitative estimation of isomers.

There is no other good method known for the preparation of ortho-alkylated phenols from aromatic alcohols. The only other general method described for the ortho benzylation of phenols is that of Claisen. In this latter method benzyl halides and not the alcohols are the alkylating agents.

Many substituted aromatic alcohols are now available from the reduction of readily available aromatic acids or aldehydes by means of complex metal hydrides. Most of the substituted benzyl alcohols used in this research were prepared by the sodium borohydride reduction of the corresponding benzaldehydes. Thus the acid-catalyzed alkylation of phenols with aromatic alcohols should prove a valuable synthetic tool for the organic chemist.

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I. INTRODUCTION

In 1920 Huston (1) published a brief report on the alkylation of phenol with benzyl alcohol in the presence of aluminum chloride. Since that time Huston, Guile, and co-workers at Michigan State University have carried out considerable work on the benzylation of phenols.

They have studied the aluminum-chloride-catalyzed condensations of benzyl alcohol with phenol (1)(2)(3), o-cresol (4), m-cresol (5) and p-cresol (6), benzyl chloride and o-cresol (7), 2-chlorobenzyl chloride and phenol (8), 4-chlorobenzyl chloride and phenol (8), and 4-bromobenzyl chloride and phenol (9). They have also studied the condensation of 4-bromobenzyl alcohol and phenol (10) as well as the alkylation of o-cresol with ortho-, meta-, and para-bromobenzyl chlorides (7).

In addition to studies of aluminum chloride alkylation, Huston, Guile, and co-workers also studied the Claisen condensation of benzyl chloride with o-cresol (4)(7), m-cresol (5) and p-cresol (6)(7), and the condensation of phenol with 2-chlorobenzyl chloride (8), 4-chlorobenzyl chloride (8) and 4-bromobenzyl chloride (9). Huston and Gyorgy (7) studied the Claisen condensation of o-cresol with ortho-, meta-, and para-bromobenzyl chlorides, as well as the condensation of p-cresol with these same benzyl chlorides.

In 1956 interest in the condensation of benzyl alcohols with phenols was revived by a combination of three factors:

1) The substituted benzyl alcohols were now readily available by the Brown (11) sodium borohydride reduction of substituted benzaldehydes.

2) A large number of pure substituted phenols was now available as starting materials. In particular, all six of the isomeric xylenols were now readily available and alkylation of these seemed a logical extension of the work with the cresols.

3) An infrared spectrophotometer was now available at Michigan State University and could be used to study the spectra of benzylated phenols. Infrared analysis promised to be a powerful tool in the determination of isomers, since both the O-H stretching band at 2.75μ and the benzene substitution bands in the 10-15μ region could be used for correct assignment of structure.

Initial work, which began on the aluminum chloride condensation of benzyl alcohols with phenols, was shifted to the use of p-toluenesulfonic acid as a catalyst when it was demonstrated that the condensation of benzyl alcohol in the presence of this catalyst yielded large amounts of o-benzylphenol. A similar method was originally reported by Pratt, Preston and Draper (12), who claimed that phenol could be alkylated with benzyl alcohol in the presence of p-toluenesulfonic acid to yield p-benzylphenol.

Two other features make a sulfonic acid catalyst more desirable for the study of alkylation reactions than the use of aluminum chloride, namely the homogeneous reaction in solution and the ease of determining rates of reaction by measuring the amount of water as it is removed by azeotropic distillation.

Pratt, Preston and Draper (12) found that alkylation of the benzene solvent took place during the reaction. This undesirable side reaction occurring in the Pratt method was eliminated by the use of cyclohexane as a solvent inert to benzylation.

With a new method of benzylation it was decided that the benzylation of phenol and the cresols would be repeated by the p-toluenesulfonic acid method and compared with the earlier aluminum chloride and Claisen methods. Following this, the p-toluenesulfonic acid method could then be extended to other substituted phenols and benzyl alcohols.

As the problem developed, it was found expedient to divide it into the following separate parts:

1) Alkylation of phenol by benzyl alcohol with a p-toluenesulfonic acid catalyst and comparison of the results with other methods.

2) Alkylation of the three isomeric cresols with benzyl alcohol and determination of the products.

3) Alkylation of the six isomeric xylenols with benzyl alcohol and determination of the products.

4) Alkylation of phenol with a number of substituted benzyl alcohols and determination of the products.

5) Investigation of the relative rates of benzylation of phenol in relation to structure of the substituted benzyl alcohols.

6) Investigation of the scope of ortho alkylation using p-toluenesulfonic acid as a condensing agent.

II. HISTORICAL

A. Benzyl Phenols

In 1872 Paterno (13) heated a mixture of benzyl chloride and phenol in the presence of a zinc catalyst. The crude reaction mixture was separated from the zinc and distilled. The main fraction, collected at 180-190°C. (6 mm.), solidified to a mass of needles contaminated with an oil which was pressed out and discarded. Recrystallization of the needles gave p-benzylphenol melting at 84°C. Paterno also prepared p-benzylphenol by treating p-benzylanisole with hydriodic acid for eight hours at 170°C.

In 1875 Paterno and Fileti (14) prepared p-benzyl phenol by condensing benzyl alcohol and phenol in the presence of sulfuric and acetic acids. Again an unidentified oil was obtained in addition to the crystalline p-benzylphenol.

Rennie (15) in 1882 also alkylated phenol with benzyl chloride in the presence of zinc to obtain p-benzylphenol. Zinc chloride was used as a condensing agent by Leibmann (16) in the same year for the alkylation of phenol with benzyl alcohol to produce p-benzyl phenol.

Later, in 1886 Rennie (17) made a study of the oil which occurs along with the crystals of p-benzylphenol. He concluded that this oil was the isomeric o-benzyl phenol.

Backunin (18) in 1903 also studied the condensation of benzyl chloride and phenol in the presence of zinc. The same method was used by Zincke and Walter (19) in 1904 to prepare p-benzylphenol.

In 1920 Gomberg and Buchler (20) showed that benzylphenols (isomers not isolated) may be prepared by heating phenol and benzyl chloride to 150-180°C. without a catalyst. In the presence of copper the reaction proceeds at 115-120°C.

The same year Huston (1) published a brief report on the condensation of benzyl alcohol and phenol in the presence of aluminum chloride to produce p-benzylphenol. Three years later Claisen (21) discovered that if benzyl chloride is reacted with sodium phenate in toluene mainly o-benzylphenol is obtained. A small quantity of the para isomer was also isolated. If a polar solvent such as ethyl alcohol is used in the above reaction the product is almost entirely benzyl phenyl ether.

In 1924 Huston (2) published a more complete report on the reaction of benzyl alcohol and phenol in the presence of aluminum chloride. He noted that the main product was p-benzylphenol along with a smaller amount of an oil. Five years later Maxfield (3), one of

Huston's students, showed the oily impurity to be o-benzylphenol and studied the effect of reactant proportions on the amount of o-benzylphenol formed. He showed that as the molar excess of phenol was increased, the amount of o-benzylphenol also increased.

Von Braun and Reich (22) in 1925 heated benzyl phenyl ether and 38% hydrochloric acid in a sealed tube at 100°C. to give a mixture of ortho and para benzyl phenols. Similar results were obtained with a mixture of benzyl chloride and phenol.

In 1926 Kropp and co-workers (23) patented a process for the preparation of o-benzylphenol. Phenol and a benzyl halide were treated with a solution of barium hydroxide and heated. The cooled liquid was filtered to remove the insoluble barium salt of p-benzylphenol. The o-benzylphenol was recovered from the filtrate by acidulation.

Von Alphen (24) in 1927 heated benzyl phenyl ether with zinc chloride at 160°C. to obtain p-benzylphenol and higher molecular weight materials. Short (25) in 1928 reported that benzyl phenyl ether would rearrange when heated to 225°C. with zinc chloride or heated to 180°C. in a stream of hydrogen chloride. He obtained a mixture of phenol, o-benzylphenol, p-benzylphenol, and higher boiling products. A year later (26) he reported that 2,4-dibenzylphenol is one of the main products of the rearrangement. Behagel and Freiensehuer

(27) in 1934 found that if benzyl phenyl ether is heated to 250°C. without a catalyst it will rearrange to give the same products isolated by Short.

Foldi (28) in 1928 studied the alkylation of phenol with benzyl benzenesulfonate at 150°C. He found the reaction yielded 25% p-benzylphenol, 30% o-benzylphenol, and a small amount of benzyl phenyl ether.

In 1929 Meyer and Bernhauer (29) found that if phenol is alkylated with benzyl alcohol at 40°C. with a sulfuric acid catalyst, p-benzylphenol is formed along with a small amount of the ortho isomer.

Akimoff (30) found in 1935 that the ortho and para isomers of benzylphenol could be separated by extracting the dry sodium salts with xylene to effect selective solution of o-benzylphenol. In the same year Sharma and Dutt (31) alkylated phenol with benzyl chloride in the presence of titanium to obtain p-benzylphenol. Also in 1935 Lal (32) used an uranium catalyst for the condensation of benzyl chloride with phenol. He obtained mostly p-benzylphenol along with small amounts of o-benzylphenol and benzyl phenyl ether.

A year later McMaster and Bruner (33) studied the reaction of benzyl chloride and phenol at 125-75°C. without an added catalyst. At 125°C. with a 10:1 mole excess of phenol they obtained 50% o-benzylphenol and 40% p-benzylphenol, whereas with a 2:1 mole excess of phenol they obtained 32% o-benzylphenol and 18% p-benzyl phenol. The same year Andrianov (34) found that refluxing benzyl chloride with phenol in toluene in the presence of phosphorus pentoxide at 130°C. gave both ortho and para benzylphenols.

In 1941 Monacelli and Hennion (35) treated phenol with benzyl n-propyl ether in the presence of boron trifluoride to obtain p-benzylphenol. The benzyl n-propyl ether was added during cooling and the reaction mixture then heated on the steam bath for two hours.

Four years later Teterin (36) studied the dehydration of benzyl alcohol in the presence of acid catalysts. Dehydration at 120°C. in the presence of activated clay, with the separation of one mole of water per two moles of benzyl alcohol, yielded a benzylphenyl phenyl ether and benzyl alcohol. Dehydration of dibenzyl ether under the same conditions also yielded a benzylphenyl phenyl ether. On the other hand, dehydration of benzyl alcohol in the presence of p-aminobenzenesulfonic acid at 140-80°C. yielded only dibenzyl ether.

The reaction of benzyl alcohol with aluminum chloride was investigated in 1948 by Illari (37) to determine if benzyl chloride was formed. He concluded that benzyl chloride was probably not an intermediate in the reaction of benzyl alcohol with benzene. Huston (2) had previously shown that benzyl chloride was not an intermediate in the reaction of phenol and benzyl alcohol in the presence of aluminum chloride.

In 1949 Cheney and co-workers (38) prepared o-benzylphenol by the Claisen method. No para isomer was isolated, but appreciable quantities of 2,6-dibenzyl phenol were formed. They also obtained o-benzylphenol from the commercially available "Santophen 7", which is a mixture of ortho and para benzylphenols supplied by Monsanto Chemical Co. This mixture is evidently produced by the condensation of benzyl chloride with an excess of phenol as described by McMaster and Bruner (33). Cheney separated the isomers in the mixture by utilizing the marked difference in the water solubility of their barium salts.

The same year Hart and Simons (39) studied the reaction of benzyl chloride with phenol at 45°C. without an added catalyst. They found that the reaction proceeded very slowly with a half life estimated at 1600 minutes. The reaction was not carried to completion and no products were isolated.

Pratt, Preston and Draper (12) studied the alkylation of phenol with benzyl alcohol in the presence of p-toluenesulfonic acid. Benzene was used as an azeotroping solvent to remove the theoretical amount of water in nine hours. They reported a 28% yield of p-benzylphenol and a 50% yield of diphenylmethane.

The same year Zalkind and Kurlina (40) studied the high temperature (120-40°C.) condensation of benzyl alcohol with phenol in the presence of three catalysts:

anhydrous p-aminobenzene sulfonic acid, activated clay, and concentrated sulfuric acid. The products of condensation of two moles of benzyl alcohol with itself and of benzyl alcohol with phenol were found, but the latter predominated. The monobenzylphenol fraction contained mainly the para isomer along with a smaller amount of o-benzylphenol.

A year later Setkina and Kursanov (41) heated phenol with 1-benzylpyridinium chloride for six hours at 180-200°C. They found the products of this reaction to be 18% benzyl phenyl ether, 29% p-benzylphenol, 17% mixed dibenzylphenols, and 18% mixed isomeric benzyl ethers of benzylphenols.

Tarbell and Petropoulos (42) in 1952 found that benzyl phenyl ether was converted very rapidly by aluminum bromide in chlorobenzene solution to a mixture of phenol, o-benzylphenol and dichlorodiphenylmethane. The ratio of the phenolic products was the same at -40°C. as at 25°C. and was unaffected by the use of benzene or nitrobenzene solvents. This same year Kharasch, Stampa and Nudenber (43) found that benzyl phenyl ether when irradiated with ultraviolet light in an isopropanol solution yielded p-benzylphenol plus a small amount of phenol.

In 1955 Kindler (44) reported that benzyl chloride may be added to phenol at 100°C. in the presence of a small amount of ferric oxide to yield benzylphenols.

He did not specify the amounts of ortho and para isomers in his product.

Elkobaisi and Hickinbottom (45) in 1958 studied the Claisen alkylation of phenol with benzyl chloride in refluxing toluene. In their procedure phenol was dissolved in dry toluene and this solution added to finely powdered sodium hydride, also suspended in toluene. The whole mixture was refluxed and treated with benzyl chloride to obtain the desired o-benzylphenol.

In 1959 Elkobaisi and Hickinbottom (46) studied the thermal rearrangement of benzyl phenyl ether. They found that heating benzyl phenyl ether at reflux for twenty hours gave 4% p-benzylphenol. They also recovered 53% of unchanged starting material. If heating were carried out for seven days at 250°C. in a sealed tube, they were able to isolate 3% o-benzylphenol, 7% p-benzylphenol, and less than 1% 2,4-dibenzylphenol.

The same year Kornblum and Lurie (47) alkylated sodium and potassium phenoxides in a variety of solvents with benzyl bromide. Sodium phenoxide and benzyl bromide, when reacted in ethylene glycol dimethyl ether at 35°C., gave a 72% yield of benzyl phenyl ether, a 15% yield of o-benzylphenol, and a 5% yield of 2-benzyloxydiphenylmethane. Furthermore the same reactants in toluene at 60°C. gave 63% carbon- and 30% oxygen-benzylation. Potassium phenoxide and benzyl bromide reacted at 50°C. in petroleum ether yielded

33% carbon- and 55% oxygen-benzylation.

The same year Coutinho (48) reacted benzyl chloride with phenol at 100-10°C. to yield among other compounds o- and p-benzylphenols. He found the yield of monobenzylphenols to increase when the phenol/benzyl chloride ratio was increased.

In 1960 Elkobaisi and Hickinbottom (49) continued their study of the thermal rearrangement of benzyl phenyl ether. They heated this compound in four solvents: α-naphthol, β-naphthol, quinoline, and isoquinoline. Both o- and p-benzylphenols were isolated in all four cases along with products resulting from benzylation of the solvent. They concluded that this rearrangement depends primarily on homolysis into benzyl- and phenoxy-radicals.

B. Benzyl Cresols

Paterno and Mazzara (50) in 1878 prepared 2-benzyl-4-methylphenol by treating a mixture of benzyl chloride and p-cresol with zinc.

In 1901 Venturi (51) prepared 3-methyl-4-benzylphenol from m-cresol and benzyl alcohol in the presence of a zinc chloride catalyst.

Claisen and co-workers (52) in 1925 prepared 2-benzyl-4-methylphenol by the action of benzyl chloride on the sodium salt of p-cresol suspended in toluene. The same year Schorigin (53) used the Claisen method to prepare 2-methyl-6-benzylphenol from sodium o-cresolate and benzyl chloride.

In 1929 Meyer and Bernhauer (29) reacted o-cresol and benzyl alcohol in the presence of 70% sulfuric acid to obtain 4-benzyl-2-methylphenol. A year later Huston, Swartout, and Wardwell (4) used an aluminum chloride catalyst for the alkylation of o-cresol with benzyl alcohol to obtain 4-benzyl-2-methylphenol along with a small amount of the isomeric 2-benzyl-6-methylphenol. They also prepared this latter compound by Claisen's method and showed the two products to be identical.

A year later Huston and Lewis (6) prepared 2-benzyl-4-methylphenol from p-cresol and benzyl alcohol in the presence of an aluminum chloride catalyst. The same compound was also prepared by Claisen's method and the two shown to be identical.

Huston and Houk (5) in 1932 completed the series of studies on the benzylation of the three isomeric cresols with their work on the benzylation of m-cresol. They found that m-cresol treated with benzyl alcohol and aluminum chloride gave 4-benzyl-3-methylphenol and 2-benzyl-5-methylphenol. They also treated m-cresol with sodium and benzyl chloride to obtain 2-benzyl-5-methylphenol and 2-benzyl-3-methylphenol.

In 1934 Chichibabin (54) reacted o-cresol with benzyl alcohol in the presence of phosphoric acid to yield a benzylated phenol. He assigned the structure of 6-benzyl-2-methylphenol to this product. Two years later Andrianov (34) studied the action of benzyl chloride on monohydric phenols in refluxing toluene in the presence of phosphorus pentoxide. From o-cresol he obtained supposedly 2-benzyl-6-methylphenol, from m-cresol he obtained a benzyl-m-cresol, and from p-cresol he obtained a benzyl-p-cresol.

Hart and Haglund (55) in 1950 showed that the product obtained by Chichibabin (54) by the reaction of o-cresol and tert-butyl alcohol was indeed 4-tert-butyl-o-cresol and not 6-tert-butyl-o-cresol as claimed by Chichibabin. Thus it is probable that Chichibabin had actually prepared 4-benzyl-2-methylphenol and not 6-benzyl-2-methylphenol as he had claimed. Apparently, Andrianov was influenced by Chichibabin's work and also called his product 6-benzyl-2-methylphenol.

The same year Huston and Gyorgy (7) prepared 4-benzyl-2-methylphenol by the aluminum chloride catalyzed condensation of o-cresol and benzyl chloride. They also reacted benzyl chloride and sodium o-cresolate by the Claisen method to obtain 2-benzyl-6-methylphenol as well as benzyl o-cresyl ether. In the Claisen alkylation of p-cresol with benzyl chloride they obtained benzyl p-cresyl ether as well as 2-benzyl-4-methylphenol. The 2-benzyl-4-methylphenol was concurrently prepared by Wheatley and co-workers (56) as an intermediate in the preparation of substituted imidazolines.

In 1955 Kindler (44) claimed the preparation of a benzyl-o-cresol, a benzyl-m-cresol, and 2-benzyl-4-methylphenol.

Elkobaisi and Hickinbottom in 1958 (45) describe the preparation of 2-benzyl-6-methylphenol and 2-benzyl-4-methylphenol by their modification of the Claisen method.

The same workers (46) heated benzyl o-tolyl ether for ten days at 250°C. to give, in addition to other products, 2-benzyl-6-methylphenol and 4-benzyl-2-methylphenol. They also determined that 4-benzyl-2-methylphenol was formed in 6% yield if benzyl p-tolyl ether was refluxed for forty hours.

Bailey-Wood and Cullinane (57) reported in the same year that heating benzyl p-tolyl ether in boiling benzene with a small amount of sulfuric acid gives 85% 2-benzyl-4-methylphenol plus some p-cresol and 2,6-dibenzyl-4-methylphenol.

C. Benzyl Xylenols

Schorigin (53) in 1925 heated (2,4-dimethyl) phenyl benzyl ether with sodium in a tube at 100°C. for a prolonged period to obtain a compound said to be 6-hydroxy-3-methyldibenzyl. The editors of Beilstein (58) have a note in their reference to the reaction which states that this compound may be 2-benzyl-4,6-dimethylphenol.

Five years later Auwers and Janssen (59) rearranged 2,6-dimethylphenyl benzoate in the presence of aluminum chloride to obtain 4-benzoyl-2,6-dimethylphenol. Reduction of the benzoyl phenol by Clemmensen's method yielded 4-benzyl-2,6-dimethylphenol. Hey and Waters (60) in 1955 also prepared 4-benzyl-2,6-dimethylphenol by the same method.

In 1956 Buu-Hoi, Sy, and Lejeune (61) prepared 4-benzyl-3,5-dimethylanisole by refluxing benzyl chloride and 3,5-dimethylanisole in chloroform solution in the presence of zinc chloride. The benzyl anisole was demethylated to yield 4-benzyl-3,5-dimethylphenol.

In 1959 Elkobaisi and Hickinbottom (46) found that heating benzyl-2,4-dimethylphenyl ether for a prolonged period at 250°C. gave a variety of products including 2-benzyl-4,6-dimethylphenol. Similarly treated, benzyl-2,6-dimethylphenyl ether gave 4-benzyl-2,6-dimethylphenol.

D. Alkylation of Phenol with Substituted Benzyl Alcohols and Halides

Klarmann, Gates, and Shtenov (62) in 1932 condensed p-chlorobenzyl chloride with phenol in the presence of zinc chloride to obtain 4-(p-chlorobenzyl) phenol. They also alkylated phenol with p-chlorobenzyl chloride by the Claisen method to obtain the isomeric 2-(p-chlorobenzyl) phenol.

A year later Huston and co-workers (9) condensed phenol with 4-bromobenzyl chloride by the Claisen and by the aluminum chloride methods. In the first case they obtained 2-(p-bromobenzyl) phenol, whereas in the second case they obtained the corresponding para isomer.

In the same year Huston and co-workers (8) studied the condensation of phenol with chlorobenzyl chlorides. By the Claisen method phenol and 2-chlorobenzyl chloride gave 2-(o-chlorobenzyl) phenol, whereas with the aluminum chloride method the corresponding para isomer was formed. They also found that 4-chlorobenzyl chloride and phenol, when reacted by the Claisen method, produced 2-(p-chlorobenzyl) phenol, while reaction by the aluminum chloride method gave 4-(p-chlorobenzyl) phenol.

Wheatley, Cheney, and Binkley (63) in 1949 prepared 2-(p-isopropylbenzyl) phenol by first forming sodium phenate from phenol and sodium hydride and then refluxing with 4-isopropylbenzyl chloride in toluene. Wheatley and co-workers (64, 56) also prepared 2-(p-chlorobenzyl) phenol by the same method.

A year later Wu, Guile, and Huston (10) studied the condensation of p-bromobenzyl alcohol and phenol in the presence of aluminum chloride. They obtained 4-(p-bromobenzyl) phenol and proved its structure by showing it to be identical with the product of the reduction of 4-bromo-4'-hydroxybenzophenone.

In 1955 Kindler (44) reported the preparation of (p-methylbenzyl) phenol by the treatment of phenol with p-methylbenzyl chloride in the presence of Fe_2O_3.

E. Biological Activity of Ortho Benzyl Phenols

Ortho benzyl phenols are of biological interest themselves or are useful as intermediates in the preparation of biologically active substances.

Schulemann (65) reported that o-benzylphenol is an active anthelmintic agent. Weichert (66) stated that the o-benzylphenyl esters of substituted carbamic acids also show anthelmintic activity.

Shumard (67) showed that 2-benzyl-4-chlorophenol is effective as a fungicide against *Aspergillus niger* and other fungi. The bactericidal action of this phenol in aqueous soap solutions was studied by Berry (68). Monsanto Chemical Co. sells 2-benzyl-4-chlorophenol as a commercial germicide and disinfectant under the trade name of "Santophen 1".

Huston and co-workers (7) reported that 2-(p-bromobenzyl) phenol, 2-(o-chlorobenzyl) phenol, and 2-(p-chlorobenzyl) phenol show specific antibacterial activity.

Klarmann, Gates, and Shtenov (62) reported that 2-benzyl-4-chlorophenol and 2-benzyl-6-chlorophenol are potent bactericides which show high activity against *Staphylococcus aureus* and *Streptococcus haemol*.

Cheney, Smith, and Binkley (38) utilized 2-benzylphenol for the preparation of 2-benzylphenyl-β-dimethyl aminoethyl ether. They found the hydrochloride of this compound to be relatively non-toxic and to possess greater antihistaminic activity in animals than Benadryl.

Wheatley and co-workers (64) prepared a series of β-(o-benzylphenoxy)-ethyl-β-chloroethylamines using o-benzylphenols as starting materials. They found that certain of these amines possessed marked sympatholytic and antihistaminic properties.

Wheatley and co-workers (69) also prepared a series of quaternary ammonium halides derived from substituted N,N-dimethyl-o-benzylphenoxyethylamines. They found these compounds possessed a high degree of vasopressor activity.

The reaction of 2-benzylphenol with formaldehyde and dimethylamine was found by Wheatley and Cheney (70) to yield mainly 2-benzyl-6-dimethylaminomethylphenol. A similar Mannich reaction with 2-benzyl-4-chlorophenol yielded 2-benzyl-4-chloro-6-dimethylaminomethylphenol. From these and other phenolic Mannich bases, Wheatley and co-workers (71) prepared a series of N,N-dialkyl carbamates which were converted to the quaternary ammonium salts. One of these salts, [3-benzyl-2-dimethyl carbamyloxy)-benzyl] trimethylammonium iodide, was quite effective in producing curare-like paralysis at low doses.

III. EXPERIMENTAL

A. Infrared Analysis

1. General Method

A Perkin-Elmer Model 137 (Infracord) spectrophotometer was used to record spectra of the various samples.

The Model 137 is a double beam instrument with direct linear transmittance vs. linear wavelength recording. It has a range of 2.5-15μ on 8½"x11" size paper.

Sodium chloride cells with a 0.5 ml. sample thickness were used with the Model 137. The reference cell was filled with pure solvent and the sample cell was filled with a 1-4% solution of the compound to be analyzed. Carbon disulfide (reagent grade) was the solvent used in most cases. With a double beam instrument carbon disulfide will give good spectra from 2.5 to 4.2μ, 4.9 to 6.0μ and 7.3 to 15μ. These regions are the most important in the study of alkylated phenols and their derivatives. In the 4.2-4.9μ and 6.0-7.3μ regions poor spectra are obtained as the pen goes "dead", since carbon disulfide has intense absorption in these regions.

2. Analysis of Benzyl Alcohols

Infrared analysis of liquid alcohols such as p-tolyl alcohol could be carried out at the standard concentration of 4% in carbon disulfide. However the solid halogenated alcohols such as o-chlorobenzyl alcohol were less soluble in carbon disulfide and were prepared in 2-3% solutions.

The main bands of interest to be found in the benzyl alcohols were the following:

1) Free O-H stretching frequencies to be found at 2.75μ. Sharp and of medium intensity.

2) Hydrogen bonded O-H stretching frequencies at 2.9-3.1μ. Broad and of strong intensity.

3) Carbon-hydrogen stretching frequencies at 3.25μ. Sharp and of medium to strong intensity.

4) Oxygen-hydrogen deformation bands at 9.6-9.8μ. Broad and of strong intensity.

5) Aromatic substitution bands at 8.7-10μ. Sharp and of weak intensity.

6) Aromatic substitution bands at 10-15μ. These are usually of strong intensity.

The identification of the benzyl alcohols prepared for use in these experiments presents no problem. Since the benzyl alcohols are prepared from the corresponding aldehydes the appearance of an O-H stretching band is proof that reduction has proceeded. As the C=O stretch is a very strong band any traces of aldehyde can easily be detected in the product.

The aromatic substitution bands in the 10-15μ region are fairly simple as the alcohols contain only one aromatic ring.

3. Analysis of Benzyl Phenols

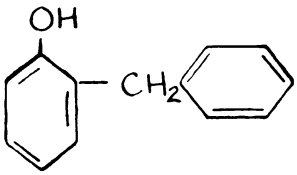
The benzylphenols are all soluble in carbon disulfide to the extent of at least 4%. The infrared spectra were prepared at this concentration.

The same main bands are present as are present in benzyl alcohols. However, the oxygen-hydrogen deformation bands occur at 8.3-8.5μ in phenols.

The infrared spectra of these benzylphenols are valuable tools in the identification of various isomers formed in the alkylation reaction.

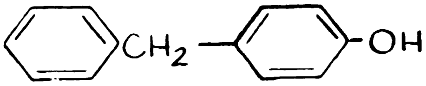
The shape of the C-H stretching band can be used as a sensitive method to detect the presence of ortho-substituted products. The presence of alkyl groups in the positions ortho to the hydroxyl group will decrease hydrogen bonding and produce a more narrow band. From the shape of this band in the infrared spectra of the products of an alkylation reaction a decision can be made as to whether ortho or para alkylation took place.

The aromatic substitution bands in the 10-15μ region can be used to determine the aromatic substitution pattern of the products. Thus o-benzylphenol



has two types of aromatic substitution. The monosubstitution of the benzyl ring gives two strong bands at 13.75μ and 14.35μ. The 1,2-substitution of the phenolic ring is shown in the infrared spectra by a strong band at 13.30μ.

Now with p-benzylphenol



we find that the monosubstitution of the benzyl ring also gives two strong bands at 13.75μ and 14.35μ. Since 1,2-substitution is not present there is no 13.30μ band as in o-benzylphenol. Instead there are two strong bands at 12.45μ and 12.75μ which show the presence of 1,4-substitution in the phenolic ring.

4. Analysis of Phenyl Urethanes

These materials are rather difficult to dissolve in carbon disulfide. Infrared determinations were carried out at a concentration of 2%.

Aromatic substitution bands are present in the phenyl urethanes as well as in the benzyl alcohols and the benzyl phenols. However the O-H stretching and deformation bands are no longer present. Instead there are two important new bands present in the urethanes.

1) The nitrogen-hydrogen stretching band at 2.9μ is sharp and of medium intensity.

2) The C=O stretching vibration at 5.7μ is sharp and of strong intensity.

These two bands are not present in the parent phenols and can be used to show that preparation of the urethane has been carried out.

The aromatic substitution in the 10-15μ region is rather complex since there are are at least three aromatic rings present in the urethane of a benzylated phenol. The 13-15μ region is especially crowded; however in certain cases bands in the 11-13μ can be used to substantiate assignments made by a study of the aromatic substitution patterns in the benzylated phenols.

B. Reagents and Materials

1. Commercial Chemicals Used without Purification

The following materials were obtained from the indicated sources and used without further purification.

Compound	Company	Grade
Aluminum chloride	J. T. Baker	C.P., anhydrous granular
o-Aminophenol	Eastman Kodak	Practical
tert-Amyl alcohol	" "	"
Benzene	Matheson, Coleman & Bell	Reagent
Benzenesulfonic acid	Eastman Kodak	Practical
Benzhydrol	" "	White label
Benzyl alcohol	" "	" "
Benzyl bromide	" "	" "
Benzyl chloride	" "	" "
o-Chlorobenzaldehyde	" "	" "
p-Chlorobenzaldehyde	" "	" "
Cinnamyl alcohol	Matheson, Coleman & Bell	Pure
m-Cresol	" "	"
Dibenzyl ether	Eastman Kodak	White label
2,4-Dichlorobenzaldehyde	" "	" "
Dimethyl ether of diethylene glycol	Ansul Chemical	Technical
2,3-Dimethylphenol	Aldrich Chemical	Pure
2,4-Dimethylphenol	Eastman Kodak	White label
2,5-Dimethylphenol	" "	" "

Compound	Company	Grade
2,6-Dimethylphenol	Eastman Kodak	White label
3,4-Dimethylphenol	" "	" "
3,5-Dimethylphenol	" "	" "
Dowex 50 W X2 cross-linked, 200-400 mesh	J. T. Baker	Reagent
N-Methyl aniline	" " "	"
n-Octane	" " "	Practical
Phenol	Matheson, Coleman & Bell	Reagent
β-Phenylethyl alcohol	Eastman Kodak	White label
Phenyl isocyanate	Matheson, Coleman & Bell	Pure
dl-Phenylmethyl carbinol	" "	"
p-Isopropylbenzaldehyde	Eastman Kodak	White label
Sodium borohydride	Metal Hydrides	Technical
p-Tolualdehyde	Eastman Kodak	White label
p-Toluenesulfonic acid (monohydrate)	" "	" "

2. Commercial Chemicals Further Purified

n-Butyl Ether

The original chemical was Matheson, Coleman & Bell "pure" grade. About 900 ml. of the n-butyl ether was treated with ferrous ammonium sulfate hexahydrate to reduce any peroxides. Distillation with a two foot Vigreux column at 100 mm. yielded a first fraction of 150 ml. containing some water. When no more water distilled, a second fraction of 660 ml. boiling at 79-80°C. was collected and used as an alkylation solvent.

o-Cresol

Eastman Kodak practical grade o-cresol (500 ml.) was distilled with a two foot Vigreux column at 15 mm. The first fraction of 60 ml. was collected up to 92°C. At 92-92.5°C. a second fraction of about 400 ml. was collected. This second fraction was used in the alkylation experiments.

p-Cresol

p-Cresol (Hercules Powder Co.) was distilled at 16 mm. with a 30" Vigreux column. The first fraction was collected at 93.5-95.5°C. A second fraction was collected at 95.5-96.0°C. and used in the alkylation experiments.

Cyclohexane

Cyclohexane (Eastman Kodak practical grade) was purified as follows: It was first washed several times with concentrated sulfuric acid to remove any aromatic or olefinic compounds and then washed several times with water to remove residual acid. The water-washed material was agitated with Drierite, decanted and distilled. About 5% of the material was collected as a first fraction and discarded. A product fraction boiling at 83-4°C. (760 mm.) was collected (about 90% of the material) and used as an alkylation solvent.

o-Ethylphenol

This material, obtained from Koppers Chemical Co., was distilled at 50 mm. employing a two foot Vigreux column. The first fraction was collected at 120.0-125.5°C. and discarded. The second fraction, collected at 125.5-127.0°C., was used in this research.

p-Ethylphenol

Eastman Kodak practical grade p-ethylphenol was distilled with an 18" Vigreux column at 25 mm. The first fraction was collected at 133-140°C. and discarded. The second fraction was collected at 140.0-141.5°C. and used in the alkylation experiments.

n-Heptane

This chemical was Eastman Kodak practical grade material which was washed with sulfuric acid and water in the same manner as cyclohexane. The washed material was distilled and the fraction boiling at 98-99°C. at 760 mm. was collected and used as an alkylation solvent.

3. Preparation of the Substituted Benzyl Alcohols

The method of preparation of the substituted benzyl alcohols was based on the work of Chaikin and W. G. Brown (72) and the work of H. C. Brown and co-workers (11).

The aldehyde or ketone to be reduced was placed in a one liter flask and dissolved in methanol or isopropanol. Sodium borohydride dissolved in water or dilute sodium hydroxide was added to the solution of the carbonyl compound. During addition the flask was cooled with a water bath if necessary to keep the reaction mixture from refluxing too vigorously. The reaction mixture was stirred for 15-30 minutes after the addition of the sodium borohydride. Sodium hydroxide solution (10-15%) was added and the contents refluxed for 30 minutes. The reaction mixture was allowed to cool and diluted with water; at this point the solid benzyl alcohols precipitated out of solution. The solid alcohols were recrystallized from ethanol-water mixtures to give the pure benzyl alcohols. If the alcohols separated as liquids they were taken up in cyclohexane, washed with water, and purified by distillation.

In most cases a substituted benzyl alcohol was prepared a number of times to secure the desired amount of product. However in each case only one experiment is described, as the method of preparation was essentially the same for any one alcohol.

o-Chlorobenzyl Alcohol

One mole of o-chlorobenzaldehyde reduced by 0.3 mole of sodium borohydride yielded 113.5 g. (80%) of o-chlorobenzyl alcohol, m.p. 71.0-1.5°C., lit. (73) m.p. 72°C.

The infrared spectrum of o-chlorobenzyl alcohol shows the expected C-H stretching band at 2.75-3.15μ. There is no trace of a C=O stretching band in the carbonyl region, so little if any residual aldehyde is present. The strong band at 13.3μ is characteristic of ortho substitution.

p-Chlorobenzyl Alcohol

Sodium borohydride (0.3 mole) and one mole of p-chlorobenzaldehyde yielded 104.7 g. (73%) of p-chlorobenzyl alcohol, m.p. 71-2°C., lit. (73) m.p. 73°C.

The infrared spectrum of p-chlorobenzyl alcohol shows an C-H stretching band at 2.75-3.15μ. There is no band in the 5.8μ (aldehyde) region of the spectrum.

There is a strong band at 12.45μ which is characteristic of para substitution.

2,4-Dichlorobenzyl Alcohol

Sodium borohydride (0.43 mole) in 150 g. of 4% sodium hydroxide and 1.43 moles 2,4-dichlorobenzaldehyde

in 1000 ml. isopropanol yielded 189.6 g. (71%) of 2,4-dichlorobenzyl alcohol after recrystallization from an ethanol-water mixture. A second recrystallization from cyclohexane gave white crystals of 2,4-dichlorobenzyl alcohol, m.p. 58.5-6.0°C.

Analysis

Calculated for $C_7H_6Cl_2O$: C,47.50; H,3.42; Cl,40.06

Found : C,47.58; H,3.55; Cl,40.18

There is an O-H stretching band at 2.75-3.15μ in the spectrum of 2,4-dichlorobenzyl alcohol. There is also a possible trace of aldehyde in the alcohol since a very weak band is present at 5.8μ in the aldehyde (C=O stretch) region.

The bands at 11.5μ and 12.2μ are characteristic of 1,2,4-benzene substitution. The band at 11.5μ would be due to the single hydrogen between the 2 and 4 substituents, whereas the band at 12.2μ would be due to the two adjacent aromatic hydrogens.

p-Methylbenzyl Alcohol

p-Tolualdehyde (2.08 moles) was reduced by 0.63 mole of sodium borohydride to yield 173.3 g. (67%) of p-methylbenzyl alcohol as a colorless liquid, b.p. 137.5-8.0°C. at 12 mm., $n_D^{25°} = 1.5300$. Cannizzaro (74) gives a b.p. of 217°C. at 760 mm. for this compound.

The O-H stretching band is present at 2.75-3.15μ in the spectrum of p-methylbenzyl alcohol. In addition there is a weak band at 5.85μ which may be due to the

presence of a small amount of unreduced p-tolualdehyde. This is a C=O band and will show when only traces of carbonyl are present since it is a very strong band.

The band in the aromatic region at 12.75μ is characteristic of para substitution.

p-Isopropylbenzyl Alcohol

p-Isopropylbenzaldehyde (1.69 moles) was reduced by 0.51 mole of sodium borohydride to yield a crude product. An identical run was made and the two crude products were combined and distilled to yield 370.7 g. (73%) of p-isopropylbenzyl alcohol as a colorless liquid, b.p. 156.5-8.5°C. at 13 mm., $n_D^{25^\circ} = 1.5169$. An authentic sample of p-isopropylbenzyl alcohol (Aldrich Chemical Co.) gave a $n_D^{25^\circ} = 1.5166$.

The O-H band in the spectrum of p-isopropylbenzyl alcohol is similar to the bands found in the rest of the benzyl alcohols. There is no band in the carbonyl region, therefore unreacted aldehyde is absent.

The strong band at 12.25μ is due to para substitution in the benzene ring.

p-Bromobenzyl Alcohol

This material was a student preparation obtained from Dr. R. L. Guile. It was recrystallized from ethanol-water to give white crystals, m.p. 78°C. Wu (10) reports a m.p. of 76-7°C. for this compound.

The infrared spectrum of this compound shows an

O-H band at 2.75-3.00 μ and a para substitution band at 12.55 μ.

C. Alkylations

1. Benzylation of Phenol

Most of the phenol benzylations were carried out with benzyl alcohol as the alkylating agent and p-toluenesulfonic acid as the catalyst. Variations in the ratio of reactants as well as type of solvent and reaction temperature were investigated to determine the conditions affecting the yield of o-benzylphenol.

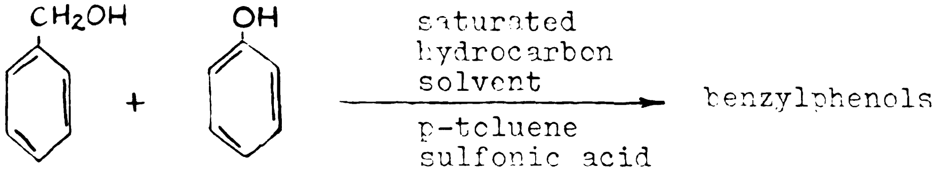
Some further alkylations were carried out in which the use of other alkylating agents and/or catalysts was explored.

a. Benzylation with a p-toluenesulfonic acid catalyst.

Results from twenty benzylations of phenol using a p-toluenesulfonic acid catalyst are included in this thesis. In seventeen experiments benzyl alcohol was used as the alkylating agent. In two experiments benzyl ether and in one experiment benzyl chloride were the alkylating agents.

Benzylations with benzyl alcohol: Low temperature method with saturated hydrocarbon solvents.

In nine experiments a saturated hydrocarbon solvent was used for the alkylation of phenol with benzyl alcohol in the presence of p-toluenesulfonic acid.



The general procedure used in these nine experiments was as follows:

A three-neck flask (24/40 joints) of appropriate size was used for the reaction. The flask was equipped with a motor-driven glass stirrer and a Dean-Stark water trap fitted with a reflux condenser.

The saturated hydrocarbon solvent, p-toluenesulfonic acid, and phenol were placed in the reaction flask. In some cases the benzyl alcohol was first mixed with the other reactants, and in others it was added during the course of the reaction. The reaction mixture was refluxed until the theoretical amount of water had been collected in the water trap. Cyclohexane was used as the solvent in most of the experiments. In these cases the reflux temperature varied from 80-84°C. When n-heptane was used as a solvent the temperature varied from 98-102°C.

When the reaction mixture had cooled to room temperature it was washed with 5% sodium bicarbonate solution and then washed with water. The hydrocarbon solvent was removed by distillation under diminished pressure (water aspirator) employing a Claisen-type distillation head. A twelve inch Vigreux column was used to remove the unreacted phenol by vacuum distillation. The residue from this distillation was fractioned with a three foot Vigreux column.

Four separate fractions were collected during the product distillation. The first fraction contained any residual phenol. The second fraction was o-benzyl phenol and the third fraction was a mixture of the ortho and para isomers. The fourth fraction was p-benzylphenol. Benzyl phenyl ether boils about thirty degrees below o-benzylphenol and would have been collected in a separate fraction if present. However, in none of these experiments was a fraction collected which boiled in the range of benzyl phenyl ether.

Experimental conditions and results are given in Table I.

The hydrocarbon solvents used in this series of experiments were cyclohexane, n-heptane, and n-octane. As the boiling point of the solvent increased, the reaction temperature was also increased, with a corresponding increase in the rate at which water was collected. In experiment 7 where n-octane was the solvent, water was collected as quickly as benzyl alcohol was added.

Table I. Solvent Method of Phenol Alkylation with Benzyl Alcohol in Saturated Hydrocarbon Solvents

Exp.	Phenol (moles)	Benzyl alcohol (moles)	Tosyl acid (moles)	Solvent (ml.)	Add'n time (hrs.)	%Yield mono-benzyl phenols	Ortho/para ratio o/p
1	3.0	1.5	0.11	500 n-heptane	-	47	3.5/1
2	2.0	1.0	0.10	2000 n-heptane	-	54	3.4/1
3(a)	2.0	1.0	0.10	500 cyclohexane	1.5	56	2.5/1
4(a)	2.0	1.0	0.10	1000 cyclohexane	1.8	51	3.0/1
5	1.5	0.75	0.10	500 cyclohexane	4.4	62	4.4/1
6	1.5	0.75	0.10	500 n-octane	0.9	47	2.0/1
7(b)	4.0	2.0	0.25	1300 cyclohexane	2.1	52	3.7/1
8	3.0	1.0	0.05	1000 cyclohexane	15.8	59	3.9/1
9(c)	3.0	1.5	0.07	500 cyclohexane	0.3	60	1.4/1

(a) The cyclohexane used in these experiments was Eastman Kodak practical grade material.

(b) A small amount of crude product was lost during purification.

(c) This reaction was stopped when only 71% of the theoretical amount of water had been collected in order to see if benzyl phenyl ether or dibenzyl ether was an intermediate in the reaction.

However, it is not possible to correlate directly the rate of the reaction with reaction temperature since the rate of distillation is also dependent on reflux temperature.

Good yields of o-benzylphenol were obtained from benzyl alcohol and phenol in the presence of p-toluenesulfonic acid with either purified cyclohexane or purified n-heptane as solvent when the reaction was carried to completion. When practical grade n-octane was used as a solvent the ortho/para ratio (2.0/1) was somewhat less (experiment 6).

The use of practical grade cyclohexane which had not been purified (experiments 3 and 4) gave somewhat smaller ortho/para ratios than the use of purified cyclohexane (experiments 5, 7, and 8).

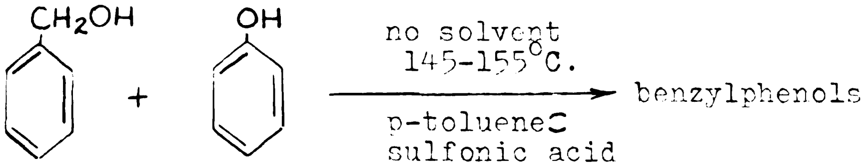
When the amount of excess phenol was increased, the yield of monobenzyl phenol was also increased as would be expected, but the ortho/para ratio appeared to remain about the same during an increase of the phenol/benzyl alcohol ratio from two to three.

The length of time during which the benzyl alcohol was added appears to have little influence upon the ortho/para ratio.

High temperature method

Four of the experiments in which phenol was alkylated with benzyl alcohol in the presence of p-toluenesulfonic acid were carried out at temperatures from

145-155°C.



This method was similar to the solvent method except that little or no hydrocarbon solvent was used. When no hydrocarbon solvent was used, a small amount of phenol vapor co-distilled with the water. A small amount of solvent was usually added, sufficient to fill the Dean-Stark trap, plus enough additional solvent to aid in removing the water. In the purification of the product, cyclohexane was added to the cooled reaction mixture in order to facilitate handling of the solution during washing.

Experimental conditions and results of these experiments are given in Table II.

Table II. High Temperature Method Alkylation of Phenol with Benzyl Alcohol without Added Solvent

Exp.	Phenol (moles)	Benzyl alcohol (moles)	Tosyl acid (moles)	Temp. (°C.)	Add'n time (hours)	%Yield mono-benzyl phenol	Ortho/para ratio o/p
1	2.0	1.0	0.02	138-73	-	54	3.5/1
2	2.0	1.0	0.02	148-55	1.1	57	4.0/1
3	3.0	1.0	0.01	143-52	4.5	66	3.6/1
4	3.0	1.0	0.01	136-60	-	67	3.6/1

No benzyl phenyl ether was obtained in any of these experiments.

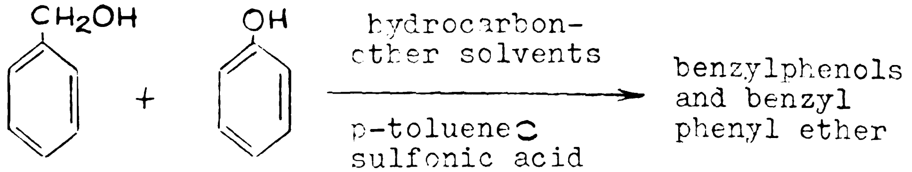
In two of the experiments all the benzyl alcohol was present at the start of the reaction. In these cases, when the temperature reached 136-8°C., water started to distill very rapidly, so that within ten minutes almost the calculated amount of water had been collected. A small amount of phenol vapor co-distilled with the water and was collected in the Dean-Stark trap.

Good yields of o-benzylphenol were obtained by this method in which excess phenol was actually the solvent.

An increase in the phenol/benzyl alcohol ratio increased the yield of monobenzylphenols but did not change the ortho/para ratio.

Low temperature method with mixed solvents

In three further experiments a mixed hydrocarbon-ether solvent was used to determine the effect of solvent polarity upon the products.



Cyclohexane and the dimethyl ether of diethylene glycol were used as the solvent system in the first reaction. In the last two reactions varying amounts of cyclohexane and n-butyl ether were used as the solvent

system.

Results of these experiments are summarized in Table III.

Table III. Mixed Solvent Method Alkylation of Phenol with Benzyl Alcohol

Exp.	Phenol (moles)	Benzyl alcohol (moles)	Tosyl acid (moles)	Solvent (ml.)	Add'n time (hours)	Products
1	1.5	0.75	0.1	150, cyclohexane; 250, dimethyl ether of diethylene glycol	-	4% yield p-benzyl phenol
2	1.5	0.75	0.1	300, cyclohexane; 200, n-butyl ether	1.1	13% benzyl phenyl ether 28% o-benzyl phenol 10% p-benzyl phenol Total = 51%
3	1.5	0.75	0.1	120, cyclohexane; 460, n-butyl ether	3.7	10% benzyl phenyl ether 12% o-benzyl phenol 18% p-benzyl phenol Total = 40%

In experiment 1 the distillation of product was stopped when the distilling head temperature reached 159°C. at 3 mm., since at this point all the monobenzyl phenols would have distilled. The residue from the distillation was a dark purple viscous oil which weighed 43.7 g. Apparently this residue contains materials of

a higher molecular weight than monobenzylated phenols.

In experiment 2 n-butyl ether was substituted for some of the cyclohexane used in the first series of experiments. There was a decrease in the ortho/para ratio. In addition some benzyl phenyl ether was formed, and there was a decrease in the total yield of ether and phenols.

In experiment 3 an increase in the percentage of n-butyl ether caused a further reduction in the ortho/para ratio as well as a reduction in the total yield.

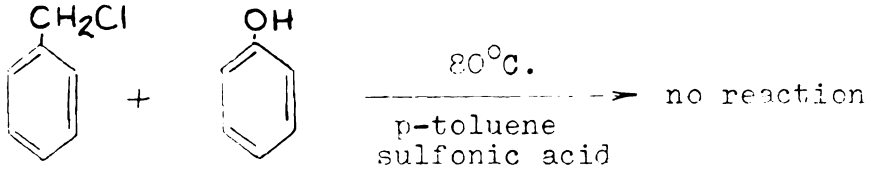
Attempted alkylation with benzyl chloride

The same general procedure was used as in the alkylation of phenol with benzyl alcohol in hydrocarbon solvents. The following quantities of reagents were used in this experiment:

phenol = 1 mole
benzyl chloride = 1 mole
cyclohexane = 400 ml.
p-toluenesulfonic acid = 0.05 mole

All the reactants, except for the benzyl chloride, were mixed together and heated to reflux temperature. The benzyl chloride was added over a period of seventy minutes, after which heating was continued for thirty minutes. At the end of this time, the reaction mixture was treated in the manner described earlier for the first series of solvent alkylations (see page 35). Most of the reaction mixture distilled below 124°C. at 50 mm.

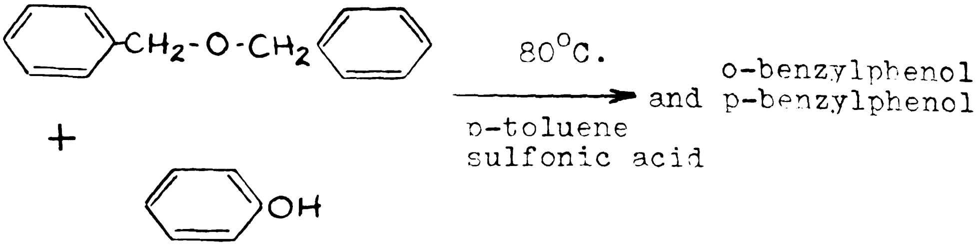
in the range of phenol and benzyl chloride. The distillation was stopped at this point as only 6.9 g. of a dark brown residue was left.



Alkylation with benzyl ether

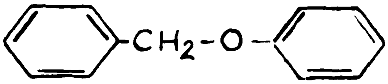
To one mole of phenol and 0.5 mole dibenzyl ether was added 400 ml. cyclohexane and 0.05 mole p-toluenesulfonic acid. The reaction mixture was heated to reflux temperature, and heating was continued for seventy-four minutes during which time 8.4 ml. of water was collected. As 0.9 ml. of the water was from the catalyst, a net amount of 7.5 ml. water was formed (83% of the calculated amount).

The reaction mixture was treated as before to yield 41.2 g. of o-benzylphenol and 15.2 g. of p-benzylphenol. Based on the actual amount of water formed, this is equivalent to a 37% yield of monobenzylphenol and an ortho/para ratio of 2.7/1.



Rearrangement of benzyl phenyl ether

Benzyl phenyl ether was prepared from sodium phenate and benzyl chloride by the method of Short and Stewart (75). The crude product was distilled at 3 mm. to yield a fraction of benzyl phenyl ether boiling at 132-3°C. This fraction solidified to give white crystals with a m.p. of 38.5-9.0°C. Short and Stewart (75) give a m.p. of 39°C. for this compound.



Examination of the infrared spectrum of benzyl phenyl ether shows the absence of an O-H stretching band at 2.75μ. The strong band at 8.15μ is characteristic of aromatic ethers.

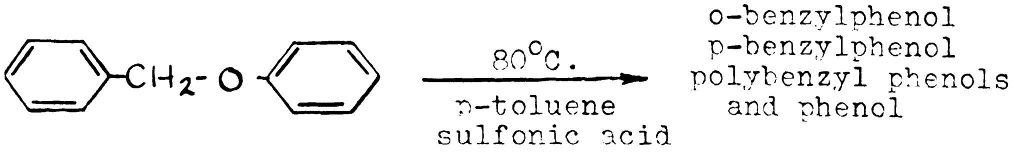
Benzyl phenyl ether (0.89 mole) was mixed with 400 ml. cyclohexane and 0.07 mole of p-toluenesulfonic acid. The reaction mixture was refluxed for 5 hours and 25 minutes during which time 0.8 ml. of water was removed from the catalyst. The mixture was cooled and washed in the usual manner with sodium bicarbonate solution followed by water.

The cyclohexane was removed under aspirator vacuum. Toward the end of the distillation some water backed up into the still pot and the distillation blew out at the still head. Some material was lost, but 140.5 g. of

a viscous oil was left in the flask. Since 164.2 g. of benzyl phenyl ether had been used in the reaction, up to 23.7 g. of oil may have been lost. Thus, at least 85% of the crude product was saved.

The viscous oil was distilled with a two foot Vigreux column to give 5.0 g. of a white solid, b.p. 105-113°C. at 50 mm., identified as phenol.

The residue was distilled with a three foot Vigreux column to give 24.2 g. of o-benzylphenol and 20.2 g. of p-benzylphenol. This corresponds to an ortho/para ratio of 1.2/1. The rest of the material (105.8 g.) did not distill below 163°C. at 2 mm.



Since phenol is much lower boiling than the benzylated phenols, it is possible that most of the 23.7 g. which was lost was phenol. In effect the phenol could have been rapidly steam-distilled out of the flask when the explosion occurred. If the 23.7 g. lost was phenol, then a total of 28.7 g. of 0.31 mole of phenol was produced during the rearrangement. If all the residue (105.8 g.) was dibenzylated product, it would be equivalent to 0.39 mole, and if tribenzylated product, equivalent to 0.29 mole. Thus the residue likely contains a mixture of di- and tribenzylated products. Of course

some polymers of the benzyl fragment could also be present.

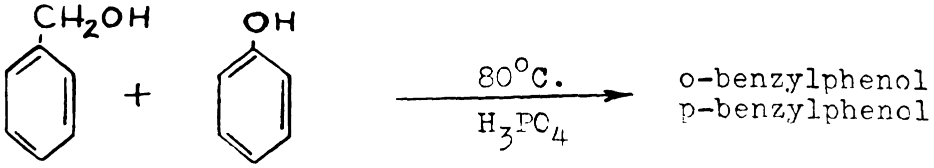
b. Benzylation with mineral acid catalysts

Two experiments were carried out in which a strong mineral acid was used as a catalyst for the alkylation of phenol with benzyl alcohol in a cyclohexane solvent.

Phosphoric acid catalyst

To 500 ml. cyclohexane and 1.5 moles phenol was added 0.1 mole 85% phosphoric acid. This mixture was heated to reflux temperature and 0.75 mole benzyl alcohol added over a period of eighty minutes. During the reaction the phosphoric acid appeared to be present as a separate phase. Heating was continued for three hours and forty five minutes during which time 14.7 ml. of water was collected.

The reaction mixture was treated as before and the crude product distilled to yield 11.9 g. of o-benzylphenol and 54.9 g. of p-benzylphenol.

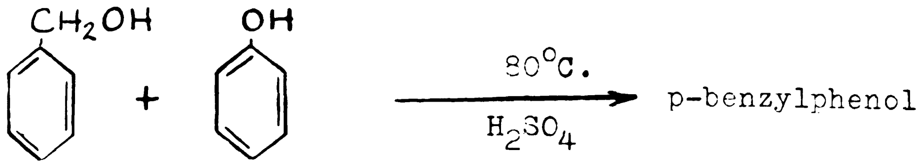


Sulfuric acid catalyst

To 250 ml. cyclohexane and one mole phenol was added 250 ml. of 67% sulfuric acid. A two phase system resulted. This mixture was heated to reflux temperature.

Benzyl alcohol (one mole) was added over a period of eighty-six minutes during vigorous agitation. Heating was continued for an additional hour and the reaction mixture allowed to cool. The upper (cyclohexane) layer was separated and treated as before.

Fractionation of the crude product gave 67.0 g. of o-benzylphenol (36% yield). Less than 5 g. of material distilled below 151°C. at 3 mm. in the boiling range of o-benzylphenol.



c. Benzylation with a Dowex 50 catalyst

Solvent method

Phenol (3 moles), 1.5 moles of benzyl alcohol, 30 g. of Dowex 50, and 500 ml. of n-heptane were mixed and refluxed for forty-five minutes until all the water from the Dowex 50 had been collected. Refluxing was continued for eighty-eight minutes, but very little water was collected. As the reaction rate under these conditions was very slow, the experiment was discontinued.

High temperature method

Phenol (2 moles) and 40 g. Dowex 50 were heated for one hour at 117-150°C. at the end of which time all the water present in the catalyst had been removed. Heating

at 149-151°C. was continued while one mole of benzyl alcohol was added over a period of one hour. As soon as the last of the benzyl alcohol had been added, the water stopped distilling.

The reaction mixture was allowed to cool to 90°C., and the Dowex 50 was removed by filtration. Unreacted phenol was removed from the filtrate by vacuum distillation. The residue was fractionated, using a three foot Vigreux column, to give 77.3 g. of o-benzylphenol and 33.9 g. of p-benzylphenol. This is a 60% yield of monobenzylphenols and an ortho/para ratio of 2.3/1.

A similar run was carried out with three moles of phenol, one mole of benzyl alcohol (added over two hours and 28 minutes), and 10 g. of Dowex 50. Fractionation of the product yielded 95.2 g. of o-benzylphenol and 39.9 g. of p-benzylphenol. This is a 73% yield of monobenzylphenols with an ortho/para ratio of 2.4/1.

d. Benzenesulfonic acid catalyst

Phenol (1.5 moles), benzenesulfonic acid (0.1 mole) and 500 ml. cyclohexane were mixed and heated to reflux temperature. Benzyl alcohol (0.75 mole) was added over a period of two hours and 27 minutes, after which refluxing was continued for 29 minutes.

The reaction mixture was washed as usual, and solvent and unreacted phenol were removed by vacuum distillation. Fractionation of the residue yielded 48.6 g. of o-benzylphenol and 20.2 g. of o-benzylphenol.

This is a 50% yield of monobenzylphenols and an ortho/para ratio of 2.4/1.

e. Attempted alkylation without a catalyst

Phenol (2 moles) was added to one mole of benzyl alcohol and the mixture heated at 168-173°C. for 41 minutes. No water was formed during this time; therefore it was assumed no alkylation took place.

f. Identification of products

A sample of p-benzylphenol, prepared by the p-toluenesulfonic acid method, was recrystallized four times from ligroin (60-90°C.) to give white crystals, m.p. 84.5°C. This corresponds to the m.p. of 84°C. found by Paterno (13).

The sample of p-benzylphenol obtained in this work was mixed with an authentic sample of p-benzylphenol and a melting point was taken. There was no depression of the melting point.

The infrared spectrum of the prepared sample of p-benzylphenol was compared with the infrared spectrum of an authentic sample of p-benzylphenol. The spectra were identical.

The infrared spectrum of p-benzylphenol is consistent with its structure. The O-H stretching band at 2.7μ has a hydrogen-bonded shoulder at 2.85μ which is typical of phenols with no ortho substituents. The aromatic substitution band at 12.45μ is typical of

compounds which have 1,4-aromatic substitution.

The recrystallized sample of p-benzylphenol was reacted with phenyl isocyanate to give a phenylurethane which on recrystallization from ligroin (60-90°C.) melted at 133.5-4.0°C. This urethane is not recorded in the literature.

Analysis

Calculated for $C_{20}H_{17}NO_2$: N, 4.65

Found : N, 4.68

A sample of o-benzylphenol, prepared by the p-toluenesulfonic acid method, was distilled three times with a three foot Vigreux column to yield a fraction boiling at 142-3°C. at 3 mm. This fraction solidified to yield a white solid with a m.p. of 53-4°C. Claisen and co-workers (52) give 52°C. as the melting point of o-benzylphenol.

The infrared spectrum of o-benzylphenol shows the expected differences from that of p-benzylphenol. The O-H stretching band at 2.75μ contains no hydrogen bonded shoulder as does the O-H band of p-benzylphenol. The ortho alkyl group decreases the intermolecular hydrogen bonding and thus causes the change in the spectrum. The 12.45μ band present in the spectrum of p-benzylphenol is absent. Instead there is a band at 13.3μ which is typical of compounds with 1,2-aromatic substitution.

The purified sample of o-benzylphenol was reacted

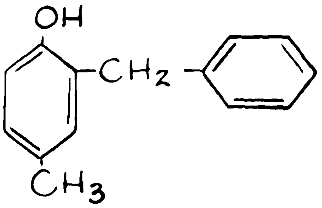
with phenyl isocyanate to give a phenylurethane, which on recrystallization from ligroin (60-90°C.), melted at 120°C. Claisen and co-workers (52) give the melting point of this phenylurethane as 117.5-8.0°C.

Purified o-benzylphenol (0.25 g.) was mixed with purified p-benzylphenol (0.25 g.) and ground together in a mortar with a pestle. The melting point of the mixture was 38-42°C.

2. Benzylation of Cresols

a. Benzyl alcohol and p-cresol

Two moles of p-cresol, 0.002 mole p-toluenesulfonic acid, and 40 ml. cyclohexane were heated for four hours at 127-42°C. while adding 0.7 mole benzyl alcohol. During the reaction period 13.2 ml. of water were collected by distillation. Purification and distillation of the reaction mixture yielded 87.1 g. crude 2-benzyl-4-methylphenol in 63% yield. The crude product was redistilled (126-8°C. at 0.1 mm.) to yield white crystals of 2-benzyl-4-methylphenol, m.p. 35-6°C. Hickinbottom (45) records a melting point of 36°C. for this compound.



The infrared spectrum of 2-benzyl-4-methylphenol is consistent with its assigned structure. The O-H stretching band at 2.7μ is of medium width with just a trace of a hydrogen-bonded shoulder. It is the same size and shape as that of 2-benzyl-3,5-dimethylphenol, which also has one ortho benzyl group. The strong band at 12.4μ is characteristic of 1,2,4-aromatic substitution.

Phenyl isocyanate was reacted with 2-benzyl-4-methylphenol to yield the phenylurethane as white crystals (from hexane), m.p. 147°C. Hickinbottom (45) records a m.p. of 146°C. for this urethane.

b. Benzyl alcohol and o-cresol

Three experiments were carried out in which benzyl alcohol was used for the ortho alkylation of o-cresol. One experiment was of the low temperature type, whereas the other two were high temperature alkylations.

Low temperature alkylation

One and one-half moles of o-cresol, 0.75 mole benzyl alcohol, 0.1 mole p-toluenesulfonic acid and 500 ml. cyclohexane were placed in a one-liter flask. This mixture was heated to reflux temperature and heating was continued for two hours and 33 minutes, at the end of which time 14.7 ml. of water had been collected. Purification and fractionation yielded 59.2 g. of 2-benzyl-6-methylphenol and 26.3 g. of 4-benzyl-2-methylphenol.

High temperature alkylation

Two moles of o-cresol and 0.02 mole p-toluenesulfonic acid were heated to 150°C., and one mole of benzyl alcohol added over a period of one hour and ten minutes at a temperature of 141-53°C. Heating was continued for nine minutes at 150-2°C. During the reaction period 15 ml. of water was collected.

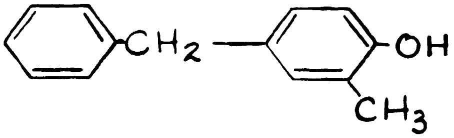
Purification and fractionation yielded 85.3 g. of 2-benzyl-6-methylphenol and 30.1 g. of 4-benzyl-2-methylphenol.

In a second experiment two moles of o-cresol, 0.002 mole p-toluenesulfonic acid, and 45 ml. of cyclohexane were heated to 150°C., and 0.75 mole of benzyl alcohol added over a period of four hours and 27 minutes at a temperature of 140-151°C. Heating was continued for ten minutes at 151-2°C. During this period 13.4 ml. of water was collected by azeotropic distillation.

Purification and fractionation yielded 68.8 g. of 2-benzyl-6-methylphenol and 21.4 g. of 4-benzyl-2-methylphenol.

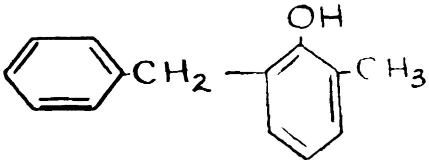
Identification of Products

4-Benzyl-2-methylphenol. Distilled 4-benzyl-2-methylphenol was redistilled to yield a fraction boiling at 162-3°C. at 1 mm. This fraction was recrystallized twice from ligroin (60-90°C.) to obtain white crystals with a m.p. of 51.0-1.5°C. Huston (4) gives a m.p. of 49.5-50.5°C. for this compound.



Examination of the infrared spectrum of 4-benzyl-2-methylphenol shows a medium width O-H stretching band at 2.70-3.05μ with a shoulder on the right due to some hydrogen bonding. This type of band is characteristic of phenols which have one ortho methyl substituent. The shape of this band is similar to the OH band of 4-benzyl-2,3-dimethylphenol. The strong band at 12.4μ is characteristic of the 1,2,4-substitution of the phenolic ring. Such a band is also present in 2-benzyl-4-methylphenol.

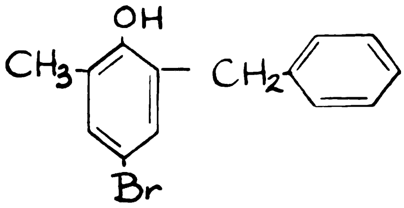
<u>2-Benzyl-6-methylphenol</u>. Distilled 2-benzyl-6-methylphenol was redistilled to yield a fraction boiling at 147.5°C. at 1.8 mm. This white solid had a m.p. of 49-50°C. as compared to the value of 49.5-50.5°C. recorded by Huston and co-workers (4).



The narrow O-H band at 2.75μ is characteristic of phenols containing two ortho alkyl groups. In the aromatic region the band at 13.3μ is characteristic of phenols with 1,2,3-aromatic substitution.

One-tenth mole of 2-benzyl-6-methylphenol was dissolved in 100 ml. of chloroform and cooled to 2°C. One-tenth mole of bromine in 50 ml. chloroform was added over a period of 47 minutes, maintaining the temperature at 2°C. The reaction mixture was aerated to remove hydrogen bromide and washed with dilute sodium bicarbonate. The chloroform was removed from the solvent layer by distillation.

The crude 2-benzyl-4-bromo-6-methylphenol was distilled to yield a fraction boiling at 167-8°C. at 0.5 mm. This fraction yielded white crystals with a m.p. of 63.5-4.0°C. Huston and co-workers (4) give a m.p. of 63-4°C. for this compound.



Summary of results

The results of three alkylations of o-cresol with benzyl alcohol and a p-toluenesulfonic acid catalyst are summarized in the following table.

Table IV. Benzylation of o-Cresol

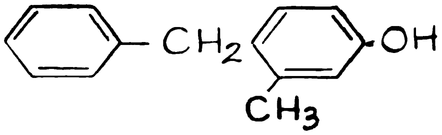
Exp.	Moles o-cresol	Moles benzyl alcohol	Moles catalyst	Ml. cyclohexane	Temp. °C.	% Monobenzyl cresols	Ortho/para ratio o/p
1	1.50	0.75	0.1	500	85	57	2.3/1
2	2.00	1.00	0.2	None	141-153	58	2.8/1
3	2.00	0.75	0.002	45	140-151	61	3.2/1

c. Benzyl alcohol and m-cresol

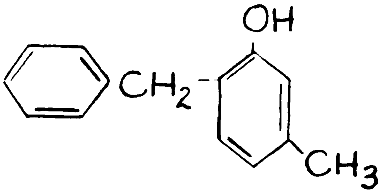
Two moles of m-cresol, 0.13 mole p-toluenesulfonic acid and 650 ml. of cyclohexane were heated to reflux temperature (81°C.) and one mole of benzyl alcohol added over a period of one hour. During the reaction period 18 ml. of water were collected by distillation.

Purification and fractionation of the crude product yielded 101.2 g. of a fraction containing the two o-benzylated m-cresols and 18.3 g. of 4-benzyl-3-methylphenol. This is a monobenzyl yield of 59% and an ortho/para ratio of 5.5/1.

The crude 4-benzyl-3-methylphenol was recrystallized from hexane and found to have a m.p. of 95°C. Huston and Houk (5) give a melting point of 93°C. for 4-benzyl-3-methylphenol.

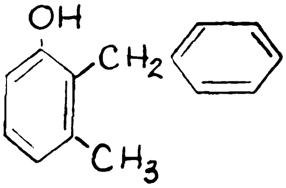


There are two ortho isomers which were isolated by Huston and Houk (5) in the benzylation of m-cresol.



2-benzyl-5-methylphenol

m.p. = 46-7°C.



2-benzyl-3-methylphenol

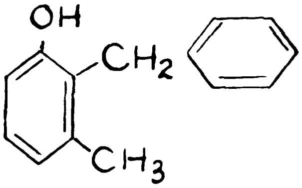
m.p. = 71-2°C.

Since these melting points are considerably lower than 93°C., the assignment of 4-benzyl-3-methylphenol would seem to be correct for the 93°C. material. In addition this latter compound is the higher boiling fraction, and such a physical property would agree with its assignment. Both of the o-benzyl isomers are lower boiling since the presence of the o-benzyl groups lowers the boiling point by decreasing intermolecular hydrogen bonding.

That this assignment of the para isomer is correct may be seen by a study of its infrared spectrum. The large hydrogen bonded shoulder in the OH band (2.7-3.1μ)

is typical of phenols which do not contain an ortho substituent. An O-H band of similar shape is found in the spectrum of p-benzylphenol.

The crude o-benzylated m-cresol containing two possible isomers was distilled at 1 mm. to give a colorless liquid boiling at 148.0-0.5°C. When this material was placed in the refrigerator a white solid formed. The solid was removed by filtration, dried and recrystallized to give crystals which melted at 68-70°C. Further recrystallization from hexane gave white crystals, m.p. 74.5°C. These crystals must be 2-benzyl-3-methylphenol, which melts at 71-2°C. according to Huston and Houk (5).



They could not be 2-benzyl-5-methylphenol, as this isomer melts at 46-7°C. according to Huston and Houk (5).

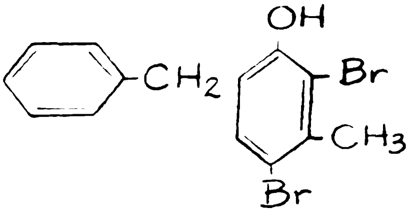
Examination of the infrared spectrum of 2-benzyl-3-methylphenol shows this assignment to be correct. There is a strong band present at 13.4μ which is completely absent in 4-benzyl-3-methylphenol. The strong band at 12.95μ is characteristic of 1,2,3-benzene substitution; for example, it is found at 13.0μ in 2-benzyl-6-methylphenol. Furthermore, the 1,2,4-substitution band found at 12.5μ in 4-benzyl-2-methylphenol, and at

12.4μ in 2-benzyl-4-methylphenol, is completely absent from the spectrum of 2-benzyl-3-methylphenol.

The mixed melting point of 2-benzyl-3-methylphenol and 4-benzyl-3-methylphenol was found to be 60-65°C. This value shows that these two materials are different compounds.

If the infrared spectrum of the crude ortho benzyl material is examined, it is easily seen that another material in addition to either 2-benzyl-3-methylphenol or 4-benzyl-3-methylphenol is present. There is a band at 9.15μ which is not present in either 4-benzyl-3-methylphenol or 2-benzyl-3-methylphenol. Furthermore in 2-benzyl-3-methylphenol there are no bands in the 11.5-12.7μ region. Since there are considerable differences in this region between the crude ortho-benzylated m-cresol and 4-benzyl-3-methylphenol, the differences must be due to a third constituent.

The 2-benzyl-3-methylphenol was isolated as a crystalline material which separated from the crude ortho benzyl material on standing. A portion of the mother liquor, after separation of the 2-benzyl isomer, was treated with bromine dissolved in carbon tetrachloride. After evolution of HBr had ceased, the carbon tetrachloride was removed by distillation and the residue recrystallized from hexane to give white crystals, m.p. 102.5-3.5°C. This is apparently 2-benzyl-4,6-dibromo-5-methylphenol, which is reported by Huston and Houk (5) to have a melting point of 102-103°C.



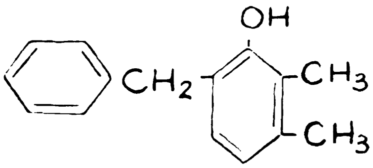
The strong band at 13.4μ of 2-benzyl-3-methylphenol can be used to measure the percent of this isomer in the crude ortho-benzylated m-cresol fraction. This band is present in the crude fraction as a shoulder on the strong 13.75μ band. The pure 2-benzyl-3-methylphenol gives an absorbance of 36% when measured from the base line, whereas this band in the mixture has an absorbance of 9% when measured from its base line. Thus the mixture contains about 25% 2-benzyl-3-methylphenol and 75% 2-benzyl-5-methylphenol.

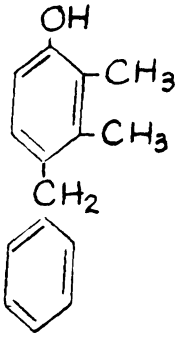
3. Benzylation of Xylenols

The alkylation of the xylenols was carried out by the same general method used for the benzylation of phenol and described on p. 35.

a. Benzylation of 2,3-xylenol

A solution of 122.2 g. (one mole) 2,3-xylenol and 3.8 g. (0.02 mole) p-toluenesulfonic acid in 300 ml. cyclohexane was heated to reflux temperature and the water was removed from the acid catalyst. To this solution was added 54.1 g. (0.5 mole) benzyl alcohol over a period of six hours and 30 minutes. The mixture was then refluxed for an additional one hour and 48 minutes. During this time 8.3 ml. of water were collected. After washing the reaction mixture as usual, distillation yielded 70.2 g. of 6-benzyl-2,3-dimethylphenol and 10.4 g. of 4-benzyl-2,3-dimethylphenol. This corresponds to a monobenzyl yield of 76% and an ortho/para ratio of 6.7/1.





The crude 6-benzyl-2,3-dimethylphenol was redistilled to yield a white solid boiling at 160-1°C. at 2 mm. and melting at 58-60°C. This redistilled material was recrystallized from ethanol-water to give white crystals with a melting point of 64.5°C.

Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60
Found : C, 84.88; H, 7.66

Examination of the infrared spectrum of this compound shows a narrow C-H stretching band at 2.75μ which is characteristic of phenols substituted in both positions ortho to the OH group. The band at 12.55μ is characteristic of 1,2,3,4-substituted benzenes.

The phenylurethane of 6-benzyl-2,3-dimethylphenol was prepared by reaction of the phenol with phenyl isocyanate. It was recrystallized from hexane to give white crystals, m.p. 136.5-137.0°C.

Analysis:

Calculated for $C_{22}H_{20}NO_2$: N, 4.24
Found : N, 4.46

The crude 4-benzyl-2,3-dimethylphenol was a white solid with a m.p. of 84-8°C. It was recrystallized once from ethanol-water and again from hexane to give white crystals, m.p. 104.0°C.

Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60
Found : C, 85.38; H, 7.53

Examination of the infrared spectrum of this compound shows an O-H stretching band of medium width at 2.75μ. Such a band is characteristic of phenols substituted in one of the positions ortho to the hydroxyl group. The band at 12.55μ is characteristic of a 1,2,3,4-substituted benzene.

b. Benzylation of 2,4-xylenol

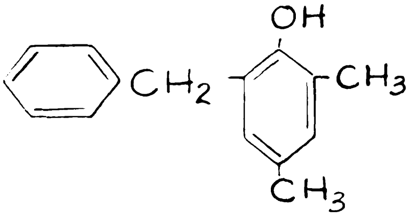
A solution of 100 g. (0.818 mole) 2,4-xylenol, 59.1 g. (0.547 mole) benzyl alcohol, 9.5 g. (0.05 mole) p-toluenesulfonic acid, and 350 ml. cyclohexane was refluxed for one hour and 47 minutes. During this time 9.8 ml. of water were collected. The reaction mixture was washed as usual and the solvent and unreacted xylenol removed by distillation.

The residue was distilled at 3 mm. to yield 48.5 g. of 2-benzyl-4,6-dimethylphenol, a white solid. This is a 42% yield. The solid was recrystallized repeatedly from petroleum ether (60-90°C.), benzene, and cyclohexane, but the crystals would always "felt out" as described by Houston and Houk (5). Most of the material was lost during recrystallization, so another experiment was carried out in which the product was purified by distillation.

A solution of 98.7 g. (0.8 mole) 2,4-xylenol and 3.8 g. (0.02 mole) p-toluenesulfonic acid in 300 ml. cyclohexane was heated to reflux temperature and the water from the catalyst removed. To this solution was added 54.1 g. (0.5 mole) benzyl alcohol over a period of four hours and 35 minutes. The mixture was refluxed for an additional six hours. During this time 8.7 ml. of water were collected.

The mixture was washed as usual and the solvent and unreacted 2,4-xylenol removed by distillation. The crude product solidified on cooling.

The crude product was distilled to yield 64.7 g. of a white solid boiling at 159-168°C. at 2 mm. This corresponds to a yield of 61% of 2-benzyl-4,6-dimethylphenol.



The product was redistilled at 2 mm. to give 39.7 g. of a white solid boiling at 159.5-161.5°C. and melting at 65.0-65.5°C. This material was again redistilled at 2 mm. to give 26.1 g. of a white solid boiling at 160.5-1.0°C. and melting at 66°C. Elkobaisi and Hickinbottom (46) record a melting point of 67°C. for 2-benzyl-4,6-dimethylphenol.

The infrared spectrum of 2-benzyl-4,6-dimethylphenol was consistent with the assigned structure. It showed a narrow O-H stretching band at 2.70μ which is characteristic of phenols with two alkyl groups in the ortho positions. The strong band at 12.65μ is characteristic of 2,4,6-trialkylphenols (1,2,3,5-benzene substitution).

A phenylurethane of 2-benzyl-4,6-dimethylphenol was prepared by reaction of the phenol with phenyl isocyanate. The crude phenylurethane was recrystallized from ligroin (60-90°C.) to yield white crystals, m.p. 143.5-4.0°C. Elkobaisi and Hickinbottom (46) record a melting point of 136°C. for the phenylurethane.

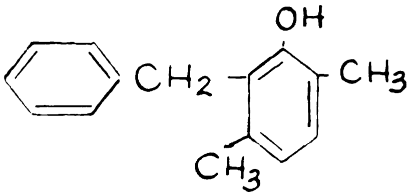
c. Benzylation of 2,5-xylenol

Experiment No.1. A solution of 100 g. (0.818 mole) 2,5-xylenol, 9.5 g. (0.05 mole) p-toluenesulfonic acid, and 350 ml. cyclohexane were heated to reflux temperature. During a period of two hours and 29 minutes, 59.1 g. (0.547 mole) benzyl alcohol were added while refluxing was continued. A total of 10.1 ml. of water was collected. The reaction mixture was washed as usual, and the cyclohexane was removed under reduced pressure.

When the residue was distilled to remove unreacted 2,5-xylenol, the vacuum take-off became plugged with crystals of the xylenol. To prevent this, 100 ml. of 1,2,4-trichlorobenzene was added. Since 1,2,4-trichlorobenzene has about the same boiling point as the xylenol, the mixture co-distilled without further difficulty.

The crude product was distilled at 3 mm. to yield 45.1 g. of 2-benzyl-3,6-dimethylphenol and 13.6 g. of 4-benzyl-2,5-dimethylphenol. This corresponds to a monobenzyl yield of 51% and an ortho/para ratio of 3.3/1.

The crude 2-benzyl-3,6-dimethylphenol was recrystallized once from cyclohexane-ligroin (90-120°C.) and twice from ligroin (60-90°C.) to yield white crystals which melted at 75.0-75.5°C.



Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60

Found : C, 84.84; H, 7.51

Examination of the infrared spectrum of this compound showed a narrow O-H stretching band at 2.70μ which is characteristic of phenols substituted in both positions ortho to the OH group. The strong band at 12.45μ is characteristic of compounds which have 1,2,3,4-benzene substitution.

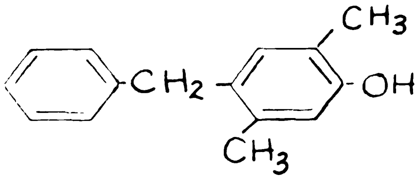
A phenylurethane was prepared by reaction of 2-benzyl-3,6-dimethylphenol with phenyl isocyanate. The crude phenylurethane was recrystallized from ligroin (60-90°C.) to yield white crystals, m.p. 150.0-150.5°C.

Analysis:

Calculated for $C_{22}H_{20}NO_2$: N, 4.24

Found : N, 4.38

The crude 4-benzyl-2,5-dimethylphenol was recrystallized once from benzene-cyclohexane and twice from ligroin (60-90°C.) to yield white crystals which melted at 58-9°C.



Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60

Found : C, 85.08; H, 7.59

Examination of the infrared spectrum of this compound showed an O-H band of medium width which is typical of phenols substituted by an alkyl group in one of the ortho positions. The two bands at 11.30μ and 11.85μ are characteristic of 1,2,4,5-benzene substitution.

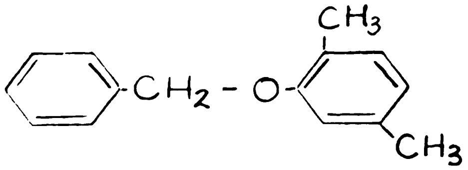
A sample of 2-benzyl-3,6-dimethylphenol was mixed with a sample of 4-benzyl-3,6-dimethylphenol. The mixture melting point of 55-60°C. shows that these are different compounds.

Experiment No.2. Benzyl alcohol, 108.2 g. (one mole), 2,5-xylenol, 122.2 g. (one mole), 300 ml. cyclohexane, and 300 ml. 67% sulfuric acid were refluxed for two hours. The reaction mixture was washed as usual, and solvent and unreacted 2,5-xylenol were removed by vacuum distillation.

Distillation of the residue yielded 12.1 g. of

2-benzyl-3,6-dimethylphenol and 19.3 g. of 4-benzyl-2,5-dimethylphenol. This is a monobenzyl phenol yield of 15% and an ortho/para ratio of 0.62/1. In addition, a fraction of 4.1 g. (2%) was obtained which boiled at 134-144°C. at 1 mm., about ten degrees below the fraction containing 2-benzyl-3,6-dimethylphenol.

Examination of the spectrum of this low-boiling fraction shows that it is probably impure benzyl-2,5-dimethylphenyl ether.

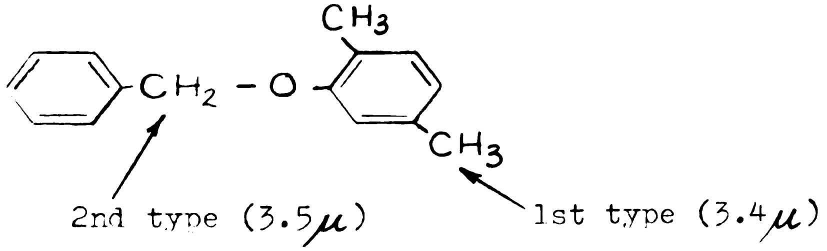


There is a weak O-H stretching band at 2.7μ which would be due to the presence of 2-benzyl-3,6-dimethylphenol as an impurity. This band has about 20% of the absorbance that it does in pure 2-benzyl-3,6-dimethylphenol, therefore the ether fraction may contain about 20% of this phenol.

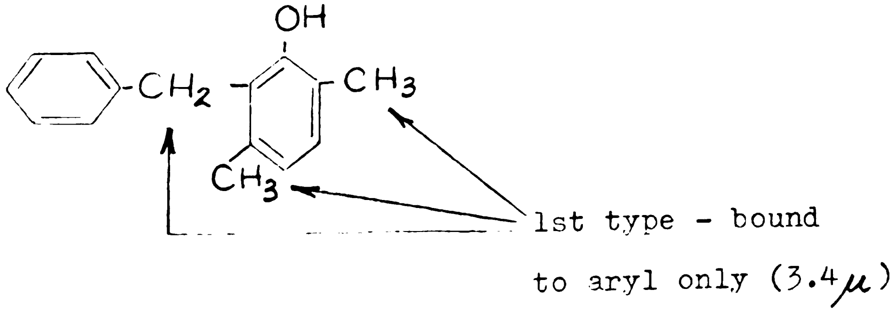
Four other bands present in the spectrum of 2-benzyl-3,6-dimethylphenol are also present as weak bands in the ether fraction. These are bands present at 8.1, 8.3, 9.5, and 10.3μ.

There is a band at 8.85μ in the ether fraction which is not present in the spectrum of 2-benzyl-3,6-dimethylphenol. This is a strong band which may be due to the CH_2-O vibration. In addition, the aliphatic

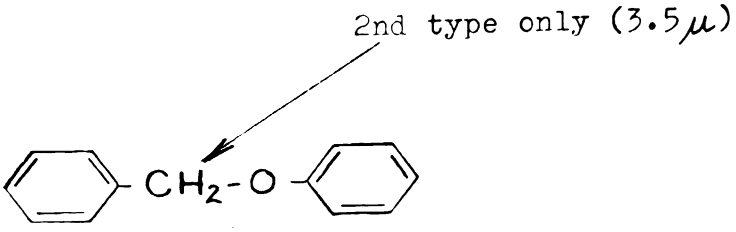
C-H stretching band in the 3.4-3.5μ region is present as a doublet in the spectrum of the ether fraction. This doublet would be consistent with the fact that in benzyl 2,5-dimethylphenyl ether there are two kinds of aliphatic C-H bonds: the type bound only to aryl, and the type bound to aryl and oxygen.



In 2-benzyl-3,5-dimethylphenol there is only the first type of C-H bond, bound to aryl alone.

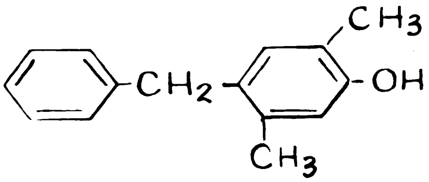


Only the second type of aliphatic C-H bond would be present in benzyl phenyl ether.



If the spectrum of the above compound is examined there is a C-H band at 3.5μ, but not at 3.4μ.

The crude 4-benzyl-2,5-dimethylphenol was recrystallized from hexane to yield white crystals, m.p. 59.5-60.0°C.



Comparison of the spectrum of this sample of 4-benzyl-2,5-dimethylphenol with a spectrum of a sample prepared by the p-toluenesulfonic acid method showed that they were the same compound.

A phenylurethane was prepared by reaction of 4-benzyl-2,5-dimethylphenol with phenyl isocyanate. Recrystallization from hexane yielded white crystals, m.p. 159.0-159.5°C.

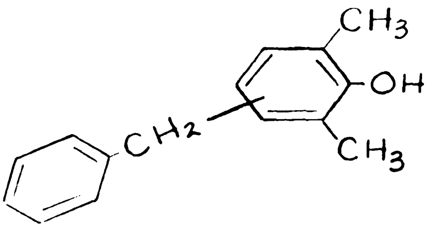
Analysis:

Calculated for $C_{22}H_{20}NO_2$: N, 4.24
Found : N, 4.35

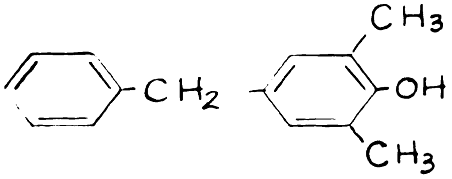
d. Benzylation of 2,6-xylenol

Experiment No.1. To 450 ml. of cyclohexane was added 100 g. (0.818 mole) 2,6-xylenol and 19.0 g. (0.1 mole) p-toluenesulfonic acid. This mixture was heated to reflux temperature, and 75.7 g. (0.7 mole) benzyl alcohol was added over a period of five hours and 30 minutes. Refluxing was continued for an additional hour. During the reaction period 13.7 ml. of water were removed.

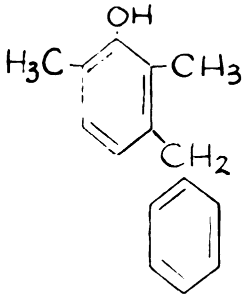
The reaction mixture was washed as usual and the solvent and unreacted xylenol removed by vacuum distillation. The residue was distilled at 153-61°C. at 3 mm. and crystallized to give 45.4 g. of a soft white solid. This corresponds to a 31% yield of monobenzyl-2,6-dimethylphenol.

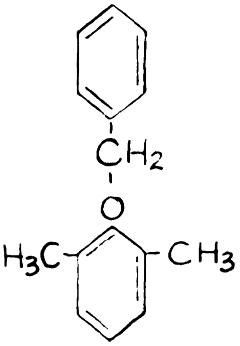


The crude monobenzyl-2,6-dimethylphenol had a melting point of 41-4°C. An examination of its infrared spectrum showed bands at 12.1, 12.55, and 12.80μ. Not all these bands should be present in a 2,4,6-substituted phenol such as the expected 4-benzyl-2,6-dimethylphenol.



Apparently the monobenzyl fraction was a mixture of isomers. The other possible monobenzyl isomers would be 3-benzyl-2,6-dimethylphenol or benzyl 2,6-dimethylphenyl ether.





The crude monobenzyl fraction was recrystallized from hexane to give white crystals, m.p. 51-2°C. The mother liquor was set aside for further examination. The crystals melted at 51-2°C., and had an infrared spectrum which showed a much stronger band at 12.80μ and much weaker bands at 12.1μ and 12.55μ. This material was further recrystallized from ethanol-water to yield a compound with a m.p. of 68.0-68.5°C. Elkobaisi and Hickinbottom (46) report a m.p. of 66°C. for 4-benzyl-2,6-dimethylphenol.

The infrared spectrum of the pure material showed a still stronger band at 12.80μ whereas the bands at

12.1μ and 12.55μ had disappeared.

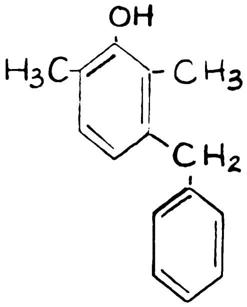
A phenylurethane was prepared by reaction of 4-benzyl-2,6-dimethylphenol with phenyl isocyanate. The urethane was recrystallized from hexane to give white crystals, m.p. 154°C. Elkobaisi and Hickinbottom (46) report a melting point of 153°C. for the phenyl urethane of 4-benzyl-2,6-dimethylphenol.

The mother liquor from the first recrystallization was evaporated until most of the remaining xylenol had separated as a solid. The solid was isolated by filtration and the small amount of mother liquor evaporated to yield a yellow oil. The infrared spectrum of this oil showed stronger 12.1μ and 12.55μ bands and a weaker 12.8μ band.

The yellow oil was dissolved in hexane and cooled in the refrigerator. A white solid separated and was shown by its infrared spectrum and mixture melting point to be more 4-benzyl-2,6-dimethylphenol. Solvent was removed from the mother liquor to yield a yellow oil.

On standing additional crystals formed in the yellow oil. The crystals were separated and shown to be more 4-benzyl-2,6-dimethylphenol. The remaining yellow oil was dissolved in carbon disulfide and an infrared spectrum prepared. The infrared spectrum of the yellow oil showed that the bands at 12.1μ and 12.55μ were larger and the band at 12.8μ weaker. There was now a shoulder on the 12.8μ band at 12.9μ.

The yellow oil should contain 3-benzyl-2,6-xylenol, since the other isomer was shown to be 4-benzyl-2,6-xylenol. Furthermore the band at 12.55μ (the strongest band in this region) is characteristic of 2,3,6-substituted phenols.



Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60
Found : C, 82.55; H, 7.35

The low carbon and hydrogen values show this isomer is not pure. As only a few drops of yellow oil were obtained, further purification was not attempted.

Experiment No.2. To 450 ml. of cyclohexane was added 100 g. (0.818 mole) 2,6-xylenol, 108.1 g. (one mole) benzyl alcohol, and 19.0 g. (0.1 mole) p-toluenesulfonic acid. This mixture was refluxed for eight hours, during which time 17.6 ml. of water were removed.

The reaction mixture was washed as usual, and the solvent and unreacted xylenol were removed by vacuum distillation. The residue was distilled at 3 mm. to give 59.6 g. of monobenzyl-2,6-dimethylphenol, a yield of 34%.

A considerable amount of residue remained from the distillation of the monobenzyl-2,6-dimethylphenol. This residue was distilled at 2 mm. to give 40.7 g. of a yellow liquid boiling at 213-8°C. which crystallized to give a light yellow solid.

The solid was recrystallized from benzene-ligroin and further recrystallized from hexane to yield white crystals, m.p. 117.5-118.0°C.

Analysis:

Calculated for $C_{22}H_{22}O$: C, 87.37; H, 7.34

Found : C, 87.31; H, 7.46

From the boiling point and elemental analysis of the unknown substance it is apparent that two moles of benzyl alcohol have been condensed with one mole of 2,6-xylenol.

The infrared spectrum of this compound was examined and the following facts noted:

1) There was a strong O-H stretching band at 2.70μ. Therefore the compound is a dibenzyl dimethylphenol and not an ether. The narrow width of this band is characteristic of phenols with alkyl groups in both ortho positions.

2) The band at 3.30μ (aromatic C-H) was about the same depth as the band at 3.40μ (aliphatic C-H). In a monobenzyl dimethylphenol the 3.30μ band is not as deep as the 3.40μ band. In a dibenzyl dimethylphenol there would be ten aliphatic hydrogens and eleven aromatic hydrogens whereas with a monobenzyl dimethylphenol

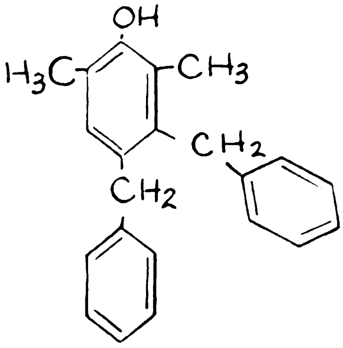
there are eight aliphatic hydrogens and seven aromatic hydrogens.

3) There was no band between 12 and 13μ, thus it is unlikely that there is either para or 1,2,3,5-substitution present.

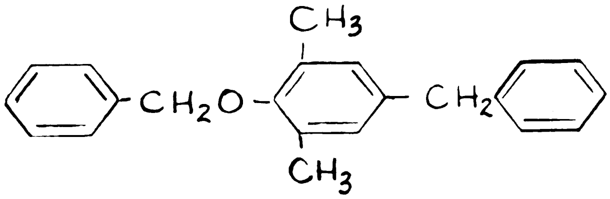
4) The monosubstitution band at 13.70μ was much larger than the monosubstitution band of a benzyl dimethylphenol. This indicates that two monosubstituted rings are present.

5) There was a band at 10.95μ which is not present in 4-benzyl-2,6-dimethylphenol. This band is characteristic of pentasubstituted benzenes.

It was shown that 4-benzyl-2,6-dimethylphenol and probably 3-benzyl-2,6-dimethylphenol were present in the monobenzyl fraction. In view of all these facts it seems likely that this dibenzyl dimethylphenol is 3,4-dibenzyl-2,6-dimethylphenol.



Elkobaisi and Hickinbottom (46) report a high boiling compound melting at 118°C. which they isolated from the reaction of benzyl alcohol and 2,6-xylenol in petroleum ether (60-90°C.) with an aluminum chloride catalyst. They claim the structure of their compound to be benzyl (4-benzyl-2,6-dimethylphenyl) ether.



However it seems possible that their so-called ether was 3,4-dibenzyl-2,6-dimethylphenol.

A urethane of 3,4-dibenzyl-2,6-dimethylphenol was prepared by reaction with phenyl isocyanate. Recrystallization of this compound from hexane gave white crystals, m.p. 184-5°C.

Analysis:

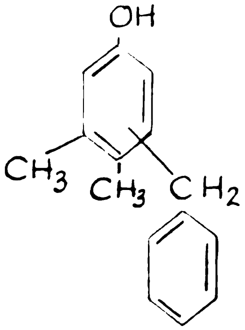
Calculated for $C_{29}H_{28}NO_2$: N, 3.34

Found : N, 3.75

e. Benzylation of 3,4-xylenol

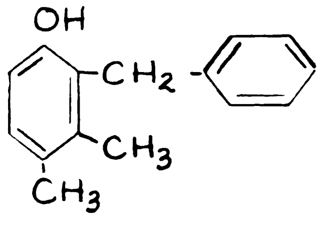
To 500 ml. of cyclohexane were added 183.2 g. (1.5 moles) 3,4-xylenol and 19.0 g. (0.1 mole) p-toluenesulfonic acid, and the mixture was heated to reflux temperature. To this was added 108.1 g. (one mole) benzyl alcohol over a period of three hours and 37 minutes. After addition was complete, refluxing was continued for one hour.

The reaction mixture was washed as usual, and the solvent and unreacted xylenol removed by vacuum distillation. The residue was distilled at 3 mm. to yield 119 g. of a monobenzyl 3,4-dimethylphenol (56% yield).

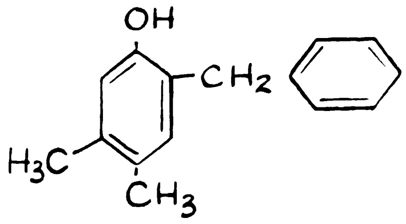


Examination of the infrared spectrum of the monobenzyl 3,4-dimethylphenol shows an O-H stretching band of medium width at 2.7μ, characteristic of phenols substituted in one ortho position. The shape of the O-H stretching band at 2.7μ cannot be used to distinguish between the two possible ortho isomers; its shape would be about the same for each isomer, since each isomer would have one ortho substituent.

However, an examination of the 10-15μ region indicates that a mixture of two isomers is present. A band at 12.55μ is characteristic of 1,2,3,4-benzene substitution and indicates the presence of 2-benzyl-3,4-dimethylphenol.



The bands at 11.35μ and 11.85μ are characteristic of 1,2,4,5-substitution and indicate the presence of 2-benzyl-4,5-dimethylphenol.



The crude product was redistilled to yield 60.9 g. of a colorless liquid boiling at 173.5°C. at 2.5 mm. Upon standing, a solid separated from the liquid. The solid was recrystallized from hexane to give white crystals, m.p. 46.5-47.0°C.

<u>Analysis</u>:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60

Found : C, 84.15; H, 7.69

Examination of the infrared spectrum shows an ortho substituted phenol with bands at 11.35μ and 11.85μ, characteristic of 1,2,4,5-benzene substitution. The band at 12.55μ (characteristic of 1,2,3,4-substitution) is absent. Apparently this solid is 2-benzyl-4,5-dimethylphenol.

Phenyl isocyanate was reacted with 2-benzyl-4,5-dimethylphenol to yield a phenylurethane. Recrystallization from hexane yielded white crystals, m.p. 159.0-159.5°C.

<u>Analysis</u>:

Calculated for $C_{22}H_{20}NO_2$: N, 4.24

Found : N, 4.37

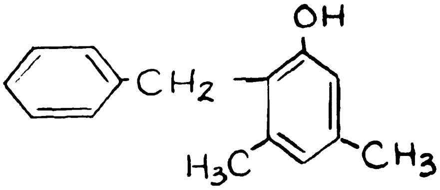
The spectrum of the original crude product, containing a mixture of the two ortho isomers, was re-examined. The band at 11.85μ, which is present in 2-benzyl-4,5-dimethylphenol, can be used to measure the amount of this isomer present in the crude product. Comparison of the absorption of the bands in the spectra of the two isomers showed the crude product to contain about 70% of 2-benzyl-4,5-dimethylphenol. The other 30% of the mixture should be 2-benzyl-3,4-dimethylphenol.

f. Benzylation of 3,5-xylenol

To 400 ml. cyclohexane were added 183.2 g. (1.5 moles) of 3,5-xylenol and 3.8 g. (0.02 mole) p-toluenesulfonic acid, and the mixture was heated to reflux temperature. A solution of 81.1 g. (0.75 mole) benzyl alcohol in 100 ml. cyclohexane was added over a period of five hours and 40 minutes. The mixture was refluxed for an additional hour and 44 minutes. A total of 13.6 ml. of water were removed.

The reaction mixture was washed as usual, the layers were separated, and 1,2,4-trichlorobenzene added to the organic layer. Cyclohexane was removed by distillation and then the unreacted xylenol co-distilled with the trichlorobenzene. The residue was distilled at 0.8 mm. to give 84.4 g. of 2-benzyl-3,5-dimethylphenol and 14.4 g. of 4-benzyl-3,5-dimethylphenol. This is a monobenzyl yield of 64% and an ortho/para ratio of 5.9/1.

A sample of 2-benzyl-3,5-dimethylphenol was recrystallized once from benzene-ligroin (90-120°C.), once from cyclohexane-ligroin, and once from hexane to give white crystals, m.p. 77.5-78.5°C.



Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60

Found : C, 84.85; H, 7.61

The infrared spectrum of this compound showed an O-H band of medium width at 2.75μ. Such a band is characteristic of a phenol with an alkyl group in one of the ortho positions. There were two bands at 11.85μ and 12.0μ, characteristic of 1,2,3,5-benzene substitution.

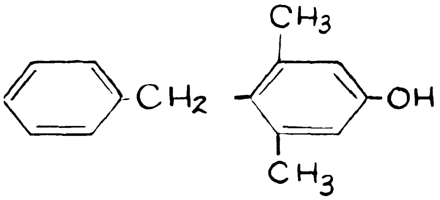
A phenylurethane of 2-benzyl-3,5-dimethylphenol was prepared by reaction with phenyl isocyanate. The urethane was recrystallized from hexane to give white crystals, m.p. 127.5-128.0°C.

Analysis:

Calculated for $C_{22}H_{20}NO_2$: N, 4.24

Found : N, 4.25

A sample of 4-benzyl-3,5-dimethylphenol was recrystallized from cyclohexane to yield white crystals, m.p. 105.0-105.5°C.



Buu-Hoi, Sy, and Lejeune (61) record a melting point of 112°C. for this compound.

The infrared spectrum of this compound shows a wide O-H band characteristic of a phenol which has no ortho substituents. The bands at 11.65μ and 11.95μ are characteristic of compounds which have 1,2,3,5-benzene substitution.

Since the melting point of 4-benzyl-3,5-dimethylphenol was somewhat lower than recorded by Buu-Hoi, Sy, and Lejeune (61), the compound was prepared by another method.

To 150 ml. of cyclohexane were added 150 ml. of 67% sulfuric acid and 61.3 g. 3,5-xylenol (0.5 mole). The reaction mixture was heated to reflux and 54.1 g. (0.5 mole) benzyl alcohol were added over a period of three hours. Heating was continued for an additional 50 minutes.

The organic layer was separated and washed twice with water, whereupon crystals formed. Recrystallization from cyclohexane yielded white crystals, m.p. 106°C. The infrared spectrum of this sample showed it to be the same compound as the 4-benzyl-3,5-dimethylphenol prepared with a p-toluenesulfonic acid catalyst. A mixture melting point of the two samples of 4-benzyl-3,5-dimethylphenol showed no depression. However, when a sample of 4-benzyl-3,5-dimethylphenol was mixed with a sample of 2-benzyl-3,5-dimethylphenol, the depressed melting point (63.0-72.0°C.) showed that these were two different compounds.

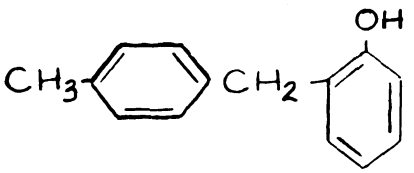
4. Alkylation of Phenol with Substituted Benzyl Alcohols

a. Alkylation of phenol with p-methylbenzyl alcohol

To 500 ml. cyclohexane were added 61.1 g. (0.5 mole) p-tolyl alcohol, 141.1 g. (1.5 moles) phenol, and 19.0 g. (0.1 mole) p-toluenesulfonic acid. The mixture was refluxed for one hour and 27 minutes. During this time 9.6 ml. of water were collected.

The reaction mixture was washed as usual, and solvent and unreacted phenol removed by distillation. The residue was distilled at 2 mm. to yield 60.4 g. of 2-(p-methylbenzyl) phenol and 11.5 g. of 4-(p-methylbenzyl) phenol. This is a monobenzyl yield of 68% and an ortho/para ratio of 5.3/1.

The crude 2-(p-methylbenzyl) phenol was redistilled at 1 mm. to yield a colorless liquid boiling at 146.5-148.0°C. This material was again distilled at 2 mm. to yield a colorless liquid, b.p. 156.0-6.5°C., $n_D^{25^\circ} =$ 1.5883.



Analysis:

Calculated for $C_{14}H_{14}O$: C, 84.77; H, 7.07

Found : C, 84.78; H, 7.10

An infrared spectrum of this compound showed an O-H band of medium width at 2.75μ. Such a band is characteristic of phenols substituted by an alkyl group in one of the ortho positions. The very strong band at 13.3μ is also characteristic of 1,2-benzene substitution.

Phenyl isocyanate was reacted with 2-(p-methylbenzyl) phenol to form a phenylurethane. Recrystallization from hexane yielded white crystals, m.p. 101.5-2.0°C.

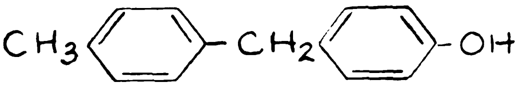
Analysis:

Calculated for $C_{21}H_{19}NO_2$: N, 4.41

Found : N, 4.58

An infrared spectrum of the phenylurethane showed an N-H stretching band at 2.9μ and a C=O stretching band at 5.7μ. The strong band at 13.3μ is characteristic of 1,2-benzene substitution.

Distilled 4-(p-methylbenzyl) phenol had a boiling point of 171-80°C. at 2 mm. and $n_D^{25°}$ = 1.5872.



Analysis:

Calculated for $C_{14}H_{14}O$: C, 84.77; H, 7.07

Found : C, 83.20; H, 7.14

An infrared spectrum of this compound shows an O-H band which has considerable hydrogen bonded character. Such a band would be present in a phenol such as

4-(p-methylbenzyl) phenol, which does not contain a group in the ortho position. There are bands at 12.4μ and 12.65μ, in the region where absorption due to 1,4-benzene substitution occurs.

Phenyl isocyanate was reacted with 4-(p-methylbenzyl) phenol to form a phenylurethane. Recrystallization from hexane yielded white crystals, m.p. 98.0-8.5°C.

<u>Analysis</u>:

Calculated for $C_{21}H_{19}NO_2$: N, 4.41
Found : N, 4.50

Examination of the infrared spectrum of the phenylurethane shows the expected N-H band at 2.95μ and the C=O band at 5.75μ.

A small sample of the phenylurethane of 2-(p-methylbenzyl) phenol was mixed with a small sample of the phenylurethane of 4-(p-methylbenzyl) phenol. The melting point of the mixture was 89.0-93.0°C.

Examination of the infrared spectra of the two phenylurethanes also shows they are not the same compounds. The most noticeable differences are a strong band at 9.7μ, which is present in the para isomer but not in the ortho, and a band at 9.2μ which is very much stronger in the ortho than in the para spectrum.

The carbon analysis for 4-(p-methylbenzyl) phenol, prepared by the p-toluenesulfonic acid method, was lower than the calculated value. This compound was therefore prepared by an alternate method.

To 50.5 g. (0.54 mole) phenol was added 65.6 g. (0.54 mole) p-tolyl alcohol, 150 ml. cyclohexane, and 150 ml. 67% sulfuric acid. The resulting two phase system was refluxed for one hour and 30 minutes.

The reaction mixture was cooled, the organic layer separated, and washed as usual with 5% sodium bicarbonate and water. Solvent and unreacted phenol were removed by vacuum distillation.

The residue was distilled at 1 mm. to yield 17.7 g. of 2-(p-methylbenzyl) phenol and 23.6 g. of 4-(p-methyl benzyl) phenol. This is a monobenzyl yield of 39% and an ortho/para ratio of 0.75/1. The spectra of the two isomers were the same as those of the two isomers prepared by the p-toluenesulfonic acid method.

The fraction containing 4-(p-methylbenzyl) phenol had the following analysis:

Analysis:

Calculated for $C_{14}H_{14}O$: C, 84.77; H, 7.07

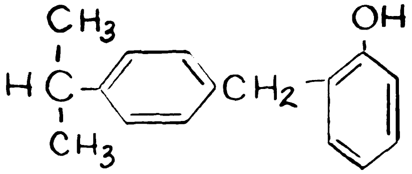
Found : C, 84.21; H, 6.91

b. Alkylation of phenol with p-isopropylbenzyl alcohol.

Experiment No.1. To 500 ml. cyclohexane were added 75.1 g. (0.5 mole) of p-isopropylbenzyl alcohol, 141.1 g. (1.5 moles) of phenol, and 19.0 g. (0.1 mole) of p-toluenesulfonic acid. The mixture was heated to boiling and refluxed for one hour and 11 minutes, during which time 10.9 ml. of water were collected.

The cooled reaction mixture was washed as usual, and the solvent and unreacted phenol removed by distillation. The crude product was fractionated to yield 66.5 g. of 2-(p-isopropylbenzyl) phenol and 14.0 g. of 4-(p-isopropylbenzyl) phenol. This is a monobenzyl yield of 71% and an ortho/para ratio of 4.8/1.

The crude 2-(p-isopropylbenzyl) phenol was redistilled at 0.5 mm. to yield a colorless liquid boiling at 145.5-7.0°C. This material was again distilled at 0.9 mm. to yield a colorless liquid boiling at 155.5-156.5°C., $n_D^{25°} = 1.5720$. Wheatley, Cheney, and Binkley (63) give an $n_D^{25°} = 1.5722$ for this compound.



The infrared spectrum of this compound showed an O-H band of medium width at 2.75μ. Such a band is characteristic of phenols which have an alkyl group in one of the ortho positions. The very strong band at 13.3μ is characteristic of 1,2-substituted benzenes. The band at 12.25μ should be due to the para substitution on the benzyl ring.

The 2-(p-isopropylbenzyl) phenol was reacted with phenyl isocyanate to form a phenylurethane. Recrystallization of the urethane from hexane yielded white crystals, m.p. 101.5-2.5°C.

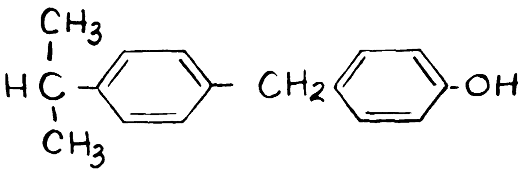
Analysis:

Calculated for $C_{23}H_{23}NO_2$: N, 4.06

Found : N, 4.15

The infrared spectrum of the phenylurethane shows an N-H band at 2.9μ and a C=O band at 5.7μ. There is also a strong band at 13.3μ characteristic of 1,2-benzene substitution.

Crude 4-(p-isopropylbenzyl) phenol as distilled from the reaction mixture melted at 57-61°C. It was recrystallized from methanol-water to yield white crystals, m.p. 71-2°C.



Analysis:

Calculated for $C_{16}H_{18}O$: C, 84.93; H, 8.03

Found : C, 84.85; H, 8.12

The infrared spectrum of 4-(p-isopropylbenzyl) phenol had an O-H band at 2.7μ which showed considerable hydrogen bonded character. Such a band is characteristic of phenols which have no ortho substituents. There was also a very strong band at 12.2μ with a shoulder at 12.35μ. Such a band would be present in phenols which have two types of para substitution present.

Experiment No.2. To 45.7 g. phenol (0.49 mole) were added 73.0 g. p-isopropylbenzyl alcohol (0.49 mole), 150 ml. cyclohexane, and 150 ml. 67% sulfuric acid. This mixture was refluxed for one hour and 15 minutes.

The reaction mixture was allowed to cool, an organic layer separated and was washed as usual. Solvent and unreacted phenol were removed by vacuum distillation. The residue was distilled at 1 mm. to yield 28.1 g. of 2-(p-isopropylbenzyl) phenol and 21.0 g. of 4-(p-isopropylbenzyl) phenol. This is a monobenzyl yield of 44% and an ortho/para ratio of 1.3/1.

The 4-(p-isopropylbenzyl) phenol fraction froze when seeded with a crystal from the previous experiment to give a soft white solid. Recrystallization from hexane yielded white crystals, m.p. 73.5-74.0°C.

Comparison of the spectrum of this material with a spectrum of 4-(p-isopropylbenzyl)phenol prepared by the p-toluenesulfonic acid method showed these two materials to be the same compound.

The 4-(p-isopropylbenzyl) phenol prepared by the sulfuric acid method was reacted with phenyl isocyanate to form a phenylurethane. Recrystallization of the urethane from hexane yielded white crystals, m.p. 126.5-127.0°C.

Analysis:

Calculated for $C_{23}H_{23}NO_2$: N, 4.06

Found : N, 4.11

A small sample of this phenylurethane was mixed with a small sample of the phenylurethane of 2-(p-isopropylbenzyl) phenol. The mixture melting point of 92.0-95.0°C. showed the two compounds were different.

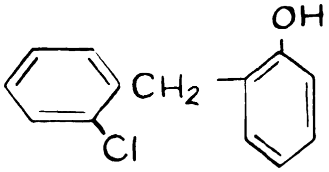
c. o-Chlorobenzyl alcohol and phenol.

To 500 ml. of cyclohexane were added 71.3 g. (0.5 mole) o-chlorobenzyl alcohol, 141.1 g. (1.5 moles) phenol, and 19.0 g. (0.1 mole) p-toluenesulfonic acid. The mixture was refluxed for four hours and 27 minutes, during which time 10.9 ml. of water were collected.

The reaction mixture was washed as usual, and the cyclohexane and unreacted phenol removed by distillation. Fractionation of the residue yielded 53.2 g. of 2-(o-chlorobenzyl) phenol and 21.0 g. of 4-(o-chlorobenzyl) phenol. This is a monobenzyl phenol yield of

68% and an ortho/para ratio of 2.5/1.

The 2-(o-chlorobenzyl) phenol was redistilled to yield a colorless liquid, b.p. 157-8°C. at 1 mm., $n_D^{25^\circ} = 1.6010$.



Huston and co-workers (8) give a boiling point of 146-51°C. at 3 mm. for this compound.

Examination of the infrared spectrum of this compound showed an O-H band of medium width at 2.75μ. This type of O-H band is characteristic of phenols which have an alkyl substituent in one of the ortho positions. There was also a very strong band at 13.3μ which indicates there are two 1,2-benzene substitutions present in the molecule.

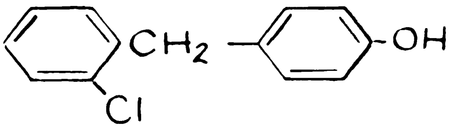
Reaction of 2-(o-chlorobenzyl) phenol with phenyl isocyanate yielded a phenylurethane. Recrystallization of the urethane from hexane yielded white crystals, m.p. 127.5-8.0°C.

Analysis:

Calculated for $C_{20}H_{16}ClNC_2$: N, 4.31

Found : N, 4.27

The crude 4-(o-chlorobenzyl) phenol was recrystallized several times from hexane to yield white crystals, m.p. 71.0-71.5°C.



Huston and co-workers (8) report a melting point of 68-9°C. for this compound.

The infrared spectrum of this compound showed a wide O-H band at 2.75μ characteristic of phenols which contain no groups ortho to the hydroxyl group. In addition to the ortho substitution band at 13.3μ from the ortho substituted Cl in the benzyl group, there is also a band at 12.4μ which indicates the benzyl group is para to the hydroxyl group on the phenolic ring.

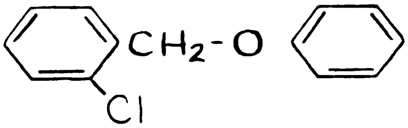
Reaction of 4-(o-chlorobenzyl) phenol with phenyl isocyanate yielded a phenylurethane which on recrystallization from hexane gave white crystals, m.p. 88-9°C.

Analysis:

Calculated for $C_{20}H_{16}ClNO_2$: N, 4.31

Found : N, 4.31

A low boiling fraction had distilled at 150-157°C. at 1 mm. Examination of this fraction showed that, in addition to about 60% 2-(o-chlorobenzyl) phenol, there was probably present about 40% of o-chlorobenzyl phenyl ether.



This deduction is based on the following spectral evidence:

1) The O-H stretching band has about 60% of the absorbance present in 2-(o-chlorobenzyl) phenol. Thus the impurity does not contain an O-H group.

2) There are new bands present at 7.3μ, 8.1μ, and 11.35μ. All these bands are also present in the spectrum of benzyl phenyl ether. The 8.1μ band in particular is characteristic of all aryl ethers being due to a C-O stretching vibration.

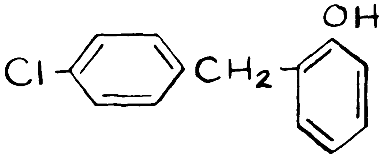
If this impurity is o-chlorobenzyl phenyl ether, then it was formed in a yield of 5%.

d. p-Chlorobenzyl alcohol and phenol

To 500 ml. cyclohexane were added 99.8 g. (0.7 mole) p-chlorobenzyl alcohol, 211.4 g. (2.1 moles) phenol, and 9.5 g. (0.05 mole) p-toluenesulfonic acid. The mixture was refluxed for five hours and 23 minutes, during which time 14.0 ml. of water were collected.

The reaction mixture was washed as usual, and solvent and unreacted phenol removed by distillation. The residue was distilled at 0.5 mm. to yield 83.7 g. of 2-(p-chlorobenzyl) phenol and 27.8 g. of 4-(p-chloro-benzyl) phenol. This is a monobenzyl yield of 73% and and ortho/para ratio of 3.0/1.

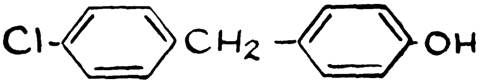
The 2-(p-chlorobenzyl) phenol was recrystallized from hexane to yield white crystals, m.p. 61-2°C. Huston and co-workers (8) give a melting point of 60-1°C. for this compound.



The infrared spectrum of 2-(p-chlorobenzyl) phenol has a fairly narrow O-H band at 2.7μ. Such a band is characteristic of phenols with one ortho substituent. The band at 8.3μ is also characteristic of ortho substituted phenols. The very strong band at 13.3μ is due to the 1,2-substitution of the phenolic ring, whereas the band at 12.4μ is due to the para substitution of the other benzene ring.

The 4-(p-chlorobenzyl) phenol was recrystallized from hexane to yield white crystals, m.p. 88.0-88.5°C. Huston and co-workers (8) give a melting point of 87.0-87.5°C. for this compound.

Examination of the infrared spectrum of 4-(p-chloro benzyl) phenol showed the expected differences from the ortho isomer. There is a strong hydrogen bonded shoulder at 2.85μ on the C-H stretching band. This shoulder is characteristic of phenols which do not contain an ortho substituent. The 8.3μ band, present in the ortho isomer, is absent in this spectrum as is the band at 13.3μ. Since both of these bands are due to 1,2-substitution, we would expect them to be absent. In addition the band at 12.25-12.35μ is very much stronger since in this compound there are two types of 1,4-substitution present.



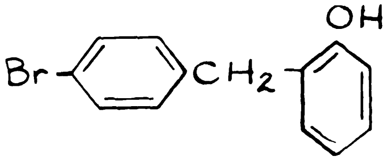
e. p-Bromobenzyl alcohol and phenol

To 500 ml. of cyclohexane were added 93.5 g. (0.5 mole) p-bromobenzyl alcohol, 141.1 g. (1.5 moles) phenol, and 19.0 g. (0.1 mole) p-toluenesulfonic acid. The reaction mixture was refluxed for two hours and 11 minutes, during which time 10.5 ml. of water were collected.

The reaction mixture was washed as usual and the solvent and unreacted phenol removed by distillation.

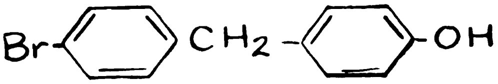
Distillation of the residue yielded 63.4 g. of 2-(p-bromobenzyl) phenol and 26.2 g. of 4-(p-bromobenzyl) phenol. This corresponds to a 68% yield of monobenzyl product and an ortho/para ratio of 2.4/1.

Crude 2-(p-bromobenzyl) phenol was distilled at 0.5 mm. to yield a white solid boiling at 163-5°C. This material was recrystallized from hexane to give white crystals, m.p. 72-3°C. Huston and co-workers (60) give a melting point of 72-3°C. for this compound.



The infrared spectrum of 2-(p-bromobenzyl) phenol has a fairly narrow O-H stretching band at 2.7μ. Such a band is characteristic of phenols which contain an ortho substituent. There is also a strong band at 8.3μ characteristic of ortho substituted phenols. The band at 12.5μ is characteristic of 1,4-benzene substitution and would be due to the para substitution on the other benzene ring. Also the band at 13.0μ would be due to the 1,2-substitution of the phenolic ring.

The crude 4-(p-bromobenzyl) phenol was recrystallized from hexane to give white crystals, m.p. 84-5°C. Wu, Guile, and Huston (6) give a melting point of 85.0-85.5°C. for this compound.



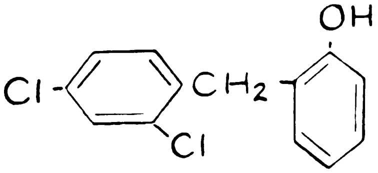
Examination of the infrared spectrum of this compound showed the expected bands. There is a strong hydrogen bonded shoulder at 2.85μ on the O-H stretching band, since there are no substituents ortho to the hydroxyl group. The band at 8.3μ, which was present in the ortho isomer, is absent as is the band at 13.0μ. There is a new band at 11.95μ which may be due to the type of para substitution present in the phenolic ring. The band at 12.4μ is present, as in the ortho isomer, and would be due to the 1,4-substitution pattern of the other benzene ring.

f. 2,4-Dichlorobenzyl alcohol and phenol

There were added 88.5 g. (0.5 mole) 2,4-dichloro-benzyl alcohol, 141.1 g. (1.5 moles) phenol and 19.0 g. (0.1 mole) p-toluenesulfonic acid to 500 ml. of cyclo hexane. This mixture was heated to reflux temperature and 10.9 ml. of water were collected over a period of ten hours.

The reaction mixture was allowed to cool, washed as usual, and the organic layer distilled to remove solvent and unreacted phenol. The residue from this distillation was fractionated at 3 mm. to yield 66.2 g. of 2-(2,4-dichlorobenzyl) phenol and 26.3 g. of 4-(2,4-dichlorobenzyl) phenol. This is a monobenzyl yield of 73% and an ortho/para ratio of 2.5/1.

The crude 2-(2,4-dichlorobenzyl) phenol was redistilled to yield a colorless liquid, b.p. 158.5-160.5°C., which solidified on standing. The solid was recrystallized from hexane to yield white crystals, m.p. 66-67°C.



Analysis:

Calculated for $C_{13}H_{10}Cl_2O$: C, 62.07;H,3.98;Cl,28.02

Found : C, 61.76;H,4.15;Cl,28.24

Examination of the infrared spectrum of this compound showed a fairly narrow O-H stretching band at 2.7μ characteristic of phenols containing a bulky group in one ortho position. The strong band at 13.3μ is due to the presence of 1,2-benzene substitution on the phenolic ring. There was also a strong band at 8.3μ characteristic of ortho-substituted phenols. It is most probably an O-H deformation band whose frequency is sensitive to the amount of hydrogen bonding.

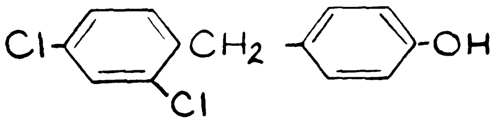
A phenylurethane of 2-(2,4-dichlorobenzyl) phenol was prepared by reaction with phenyl isocyanate. Recrystallization from hexane yielded white crystals, m.p. 123.0-123.5°C.

Analysis:

Calculated for $C_{20}H_{15}Cl_2NO_2$: N, 3.77

Found : N, 4.08

Crude 4-(2,4-dichlorobenzyl) phenol was recrystallized from hexane to yield white crystals, m.p. 72.0-72.5°C.



Analysis:

Calculated for $C_{13}H_{10}Cl_2O$: C, 62.07;H,3.98;Cl,28.02

Found : C, 61.94;H,3.93;Cl,28.30

Examination of the infrared spectrum showed an O-H stretching band at 2.7μ with a large hydrogen bonded shoulder. Such a band is characteristic of phenols which do not contain an ortho substituent. The strongest band in the spectrum is a very strong and broad band at 12.1-12.4μ. Since both 1,2,4- and 1,4-substituted benzenes absorb in this region, and since both types of substitution are present in the molecule, the size of the band is reasonable. The band at 8.3μ, which was present in the spectrum of the ortho isomer, is absent in this spectrum.

A small sample of 2-(2,4-dichlorobenzyl) phenol was mixed with a small sample of 4-(2,4-dichlorobenzyl) phenol. The mixture melting point of 48.5-54.5°C. showed these compounds were different.

A phenylurethane of 4-(2,4-dichlorobenzyl) phenol was prepared by reaction with phenyl isocyanate. Recrystallization from hexane yielded white crystals, m.p. 142.5°C.

<u>Analysis</u>:

Calculated for $C_{20}H_{15}Cl_2NO_2$: N, 3.77

Found : N, 3.87

5. Relative Rate of Phenol Benzylation by Substituted Benzyl Alcohols

The relative rate of phenol benzylation by substituted benzyl alcohols was determined in the following manner:

The substituted benzyl alcohol (0.5 mole), phenol (1.5 moles), p-toluenesulfonic acid (0.1 mole), and 500 ml. cyclohexane were heated rapidly to boiling and the reaction mixture was refluxed until the calculated amount of water had been collected. The reaction rate was followed by recording the amount of distillate collected in the Dean-Stark trap and the time of the reading. Amount of water was plotted on graph paper as a function of time, and the time at which half of the calculated water had been collected was determined. As 1.9 ml. of water was distilled from the catalyst at the start of the reaction, the reaction half time was the time at which 1.9 ml. + 4.5 ml. (0.25 mole) or 6.4 ml. of water had been collected.

An experiment of this type was carried out for benzyl alcohol and five substituted benzyl alcohols. The data (ml. of water collected and time) for these six experiments are to be found in the first section of the appendix. The six graphs from the plotting of these data are also in the appendix.

The reaction half times were calculated from the graphs and recorded in the following table.

Table V. Rate of Phenol Alkylation with Benzyl Alcohols

Exp.	Benzyl alcohols	Half time of reaction in minutes
1	p-isopropyl	26
2	p-methyl	32
3	unsubstituted	36
4	p-chloro	47
5	o-chloro	130
6	2,4-dichloro	254

The structure of products formed in these reactions was established in the preceding Experimental section. For purposes of comparison, it is assumed that the products formed are similar in all cases. However this is not strictly true, as has been shown by the variation of the ortho/para ratios.

The quality of the reagents used in these six experiments was the same as the quality of the reagents used in the preceding Experimental section. No attempt was made to prepare reagents of special purity, as the purpose of these experiments was not to carry out a detailed kinetic study of this alkylation, but rather to see if the half times of reaction fell in an order that was consistent with the sigma or substituent constant of the substituent on the benzyl alcohol.

6. Scope of the Acid-Catalyzed Ortho Alkylation

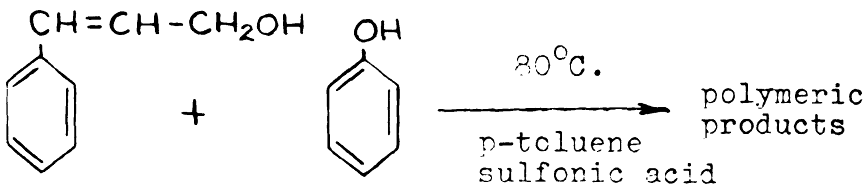
In order to determine the scope of the acid-catalyzed ortho alkylation of phenols, a number of experiments were carried out in which a series of available substituted aromatic and aliphatic alcohols were heated to reflux temperature with benzyl alcohol. In all cases a cyclohexane solvent was used.

The formation of water and its distillation during reflux indicated some type of alkylation was taking place. In some cases, where nearly the calculated amount of water for the alkylation reaction distilled, the reaction mixture was washed with sodium bicarbonate solution and distilled.

a. Phenol and various alkylating agents

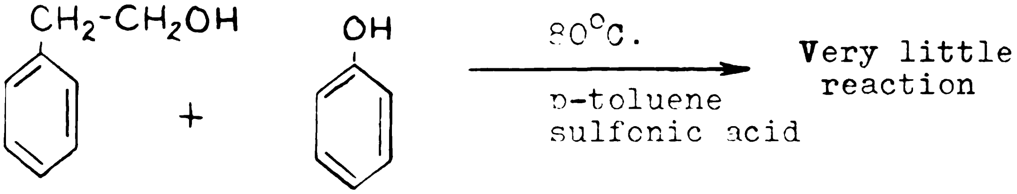
Cinnamyl alcohol and phenol

Cinnamyl alcohol (0.75 mole), one mole of phenol, and 0.05 mole p-toluenesulfonic acid were reacted at reflux temperature in cyclohexane, and the calculated amount of water removed by distillation. The product was a dark viscous polymer.



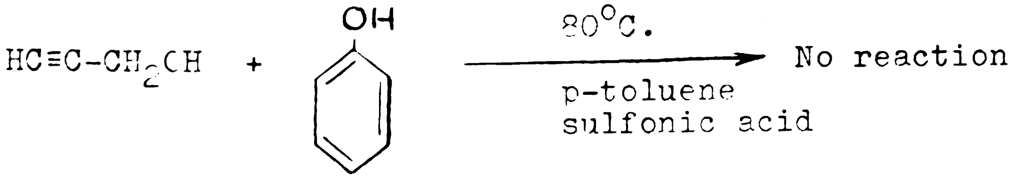
2-Phenylethyl alcohol and phenol

Refluxing 0.72 mole 2-phenylethyl alcohol, 1.5 moles phenol, and 0.2 mole p-toluenesulfonic acid in cyclohexane gave 0.07 mole water after four hours.



Propargyl alcohol and phenol

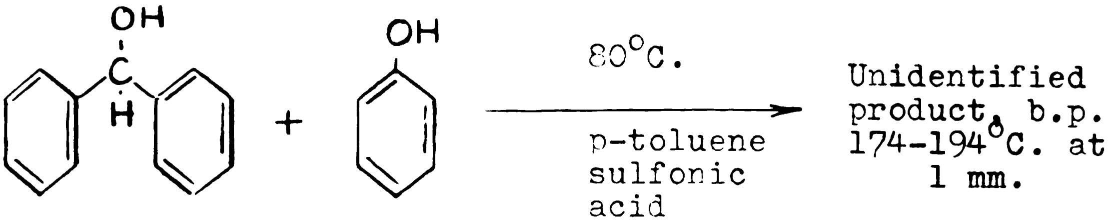
No reaction was observed on refluxing one mole phenol, one mole propargyl alcohol, and 0.05 mole p-toluenesulfonic acid in cyclohexane for 6.9 hours.



Benzhydrol and phenol

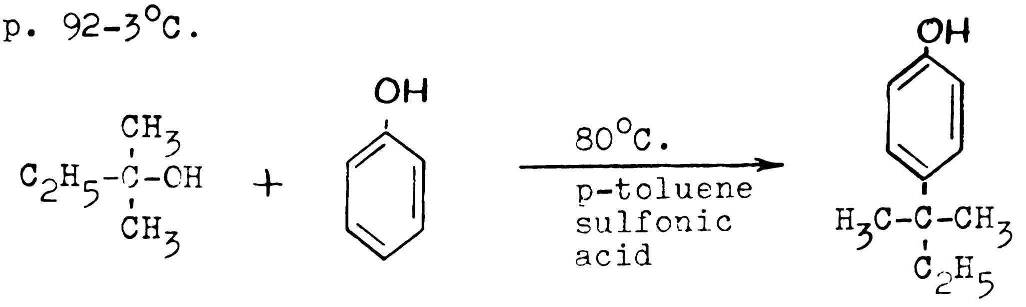
Water was eliminated on refluxing 0.4 mole benzhydrol, 0.8 mole phenol and 0.02 mole p-toluenesulfonic acid in cyclohexane. The reaction product was washed, and solvent and unreacted materials removed by distillation. The residue was distilled to give 69.1 g. of an unidentified yellow solid, b.p. 174-194°C. at 1 mm.

This boiling point would be reasonable for a condensation product of one mole benzhydrol with one mole of phenol.



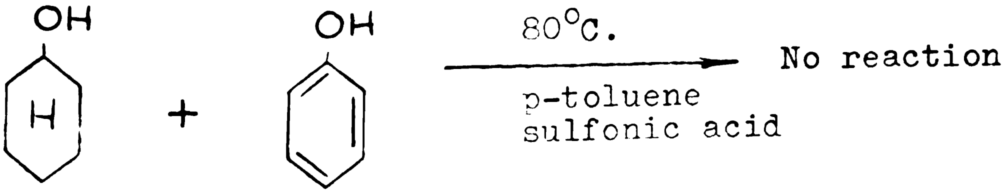
tert-Amyl alcohol and phenol

Refluxing 0.75 mole tert-amyl alcohol, 1.5 moles phenol, and 0.1 mole p-toluenesulfonic acid in cyclohexane for four hours and 35 minutes yielded 14.3 ml. of water. Washing the reaction mixture as usual, removing solvent and unreacted phenol by distillation, and distillation of the residue yielded 37.5 g. of p-tert-amylphenol, m.p. 92-3°C.; literature (76) m.p. 92-3°C.



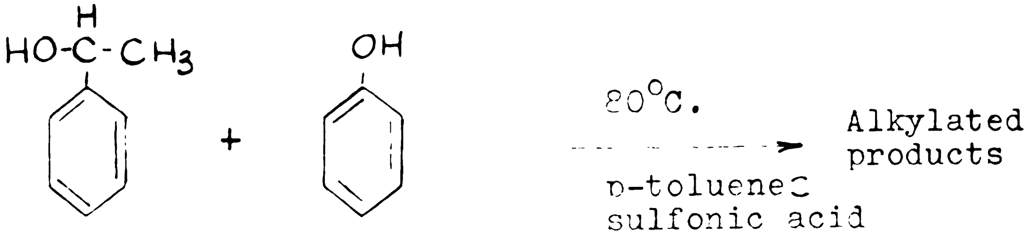
Cyclohexanol and phenol

Heating one mole cyclohexanol, one mole phenol, and 0.1 mole p-toluenesulfonic acid in cyclohexane yielded no water after 37 minutes.



α-Phenylethyl alcohol and phenol

To 1.5 moles phenol in 500 ml. cyclohexane was added 0.02 mole p-toluenesulfonic acid and the mixture heated to reflux temperature. α-Phenylethyl alcohol (0.75 mole) was added over a period of two hours and 42 minutes and refluxing continued for another 42 minutes. At the end of this time 13.8 ml. of water had been collected.

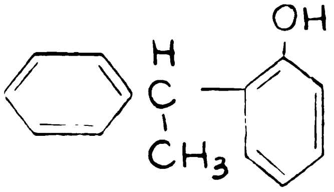


The reaction mixture was washed as usual, and solvent and unreacted phenol removed by distillation. The residue was distilled at 3 mm. to yield the following fractions:

Fraction	Boiling range	Weight	Description
1	81-154.5°C.	Very small amount	Colorless liquid
2	155-159°C.	42.6 g.	Colorless liquid
3	159-162.5°C.	16.2 g.	Colorless liquid
4	163.5-169.0°C.	15.9 g.	Colorless liquid

Fraction 2 was redistilled at 3 mm. to yield 24.4 g. of a colorless liquid with a boiling point of 150.0-151.5°C. The infrared spectrum of this fraction was compared with the spectrum of an authentic sample of

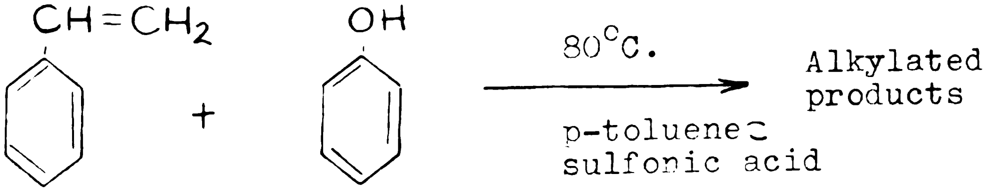
2-(α-phenylethyl) phenol obtained from Prof. H. Hart.



Except for a slight shoulder on the 11.9μ band of the authentic sample, the spectra of the two samples were identical. Fraction 2 is therefore assumed to be 2-(α-phenylethyl) phenol.

Styrene and phenol

Phenol (1.4 moles), 0.1 mole p-toluenesulfonic acid, and 500 ml. cyclohexane were heated to reflux temperature. Styrene (0.7 mole) was added over a period of one hour and refluxing continued for an additional hour.



The reaction mixture was washed as usual, and the solvent and unreacted phenol removed by distillation. The residue was distilled at 3 mm. to yield the following fractions:

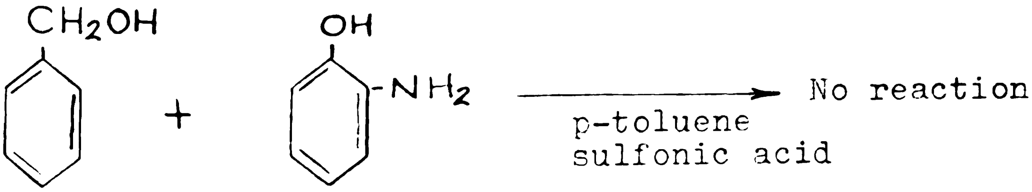
Fraction	Boiling point	Weight	Description
1	82-151°C.	0.9 g.	Colorless liquid
2	151.5-157.0°C.	44.3 g.	Colorless liquid
3	157.0-160.5°C.	9.4 g.	Colorless liquid
4	161.5-168.0°C.	20.0 g.	Colorless liquid

The amount of product (from 0.7 mole alkylating agent) distilling in the 151.5-168.0°C. range was 73.7 g. compared to 74.7 g. of material in the 155-169°C. range obtained in the previous experiment from 0.75 mole of alkylating agent.

b. Benzyl alcohol and various substrates

Benzyl alcohol and o-aminophenol

No reaction was observed on refluxing 0.75 mole benzyl alcohol, one mole o-aminophenol, and 0.05 mole p-toluenesulfonic acid in cyclohexane for two hours.

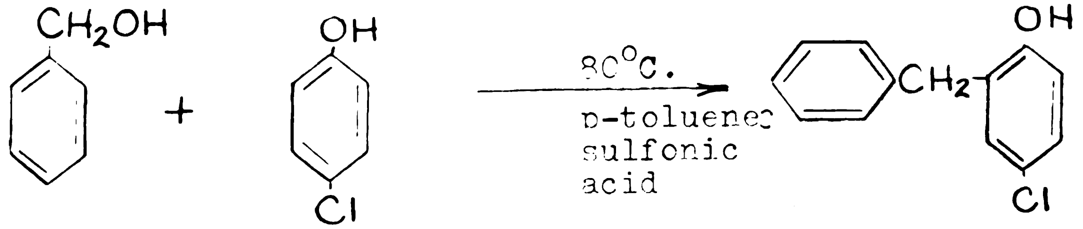


Benzyl alcohol and p-chlorophenol

To 400 ml. cyclohexane was added 1.2 moles p-chlorophenol and 0.05 mole p-toluenesulfonic acid. This mixture was heated to reflux temperature and 0.5 mole benzyl alcohol added over a period of three hours and

45 minutes. Refluxing was continued for an additional one hour and 43 minutes. During this time 13.7 ml. of water were removed.

The reaction mixture was washed as usual, and solvent and unreacted p-chlorophenol removed by distillation. The residue was distilled at 1 mm. to yield 63.4 g. of a colorless liquid, b.p. 154-160°C. The colorless liquid solidified on standing, to give white crystals of 2-benzyl-4-chlorophenol, m.p. 48.5-9.0°C. Klarmann, Gates, and Shtenov (62) report a m.p. of 48.5°C. for this compound.

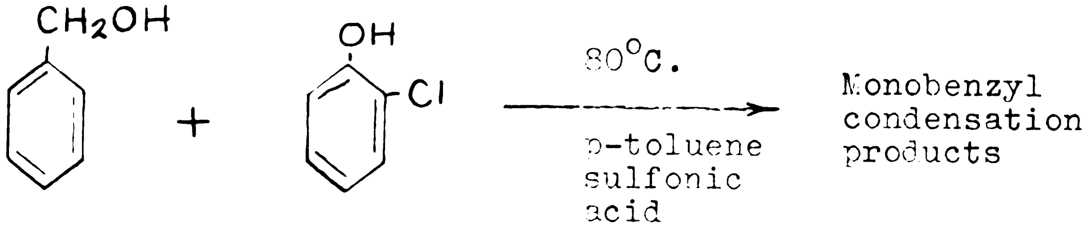


Examination of the infrared spectrum shows the expected features. The O-H stretching band at 2.75μ is of fairly narrow width since there is one ortho substituent. There is a 1,2,4-substitution doublet at 12.15μ and 12.40μ very similar to that found in 2-benzyl-4-methylphenol. In addition, there is the expected band at 8.3μ characteristic of ortho substituted phenols.

Benzyl alcohol and o-chlorophenol

Water was eliminated (14.1 ml.) on refluxing 0.7 mole benzyl alcohol, 1.2 moles o-chlorophenol and 0.1

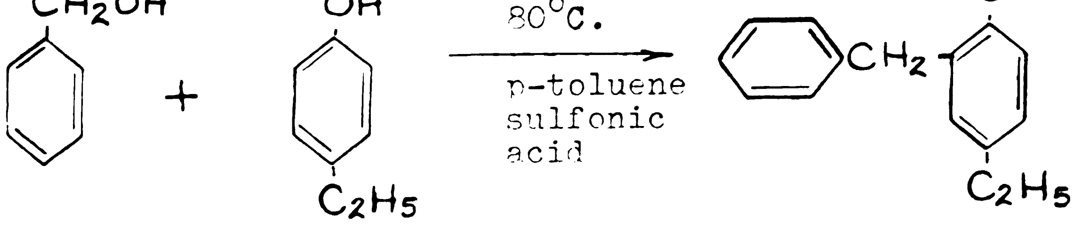
mole p-toluenesulfonic acid in cyclohexane. Washing and distillation yielded 70.7 g. of an unidentified liquid, b.p. 150-165°C. at 3 mm.



Benzyl alcohol and p-ethylphenol

Experiment No.1. To 450 ml. of cyclohexane were added one mole p-ethylphenol and 0.07 mole p-toluenesulfonic acid. The mixture was heated to reflux temperature and 0.6 mole benzyl alcohol was added over a period of one hour and 49 minutes. Heating was continued for an additional 50 minutes. During this time 12.6 ml. of water were removed.

The reaction mixture was washed as usual, and solvent and unreacted p-ethylphenol removed by distillation. Distillation of the residue at 3 mm. yielded 53.3 g. of 2-benzyl-4-ethylphenol, boiling at 164.5-169.5°C.



Redistillation of the crude product gave a colorless liquid, b.p. 164.0-164.5°C. at 3 mm., $n_D^{25°} = 1.5779$.

Analysis:

Calculated for $C_{15}H_{16}O$: C, 84.88; H, 7.60

Found : C, 85.04; H, 7.54

Wojahn (77) reports a boiling point of 197°C. at 17 mm. for this compound.

Examination of the infrared spectrum of this compound showed the expected bands. Except for position and intensity of the C-H bands, the spectrum is almost the same as that of 2-benzyl-4-methylphenol. The 1,2,4-substitution doublet at 12.1μ and 12.3μ is at a little lower wavelength than the doublet of 2-benzyl-4-methylphenol.

Phenyl isocyanate was reacted with 2-benzyl-4-ethylphenol to give a phenylurethane. Recrystallization from hexane yielded white crystals, m.p. 117.5-118.5°C.

Analysis:

Calculated for $C_{22}H_{21}NO_2$: N, 4.24

Found : N, 4.25

Experiment No.2. To one mole p-ethylphenol were added 2 g. of Dowex 50W-X2 (200-400 mesh) and 25 ml. of cyclohexane, and the mixture heated to 155°C. Benzyl alcohol (0.4 mole) was added dropwise and heating continued until 7.9 ml. of water had been removed. The reaction mixture was filtered while hot and the filtrate fractioned to yield 49.6 g. of 2-benzyl-4-ethylphenol

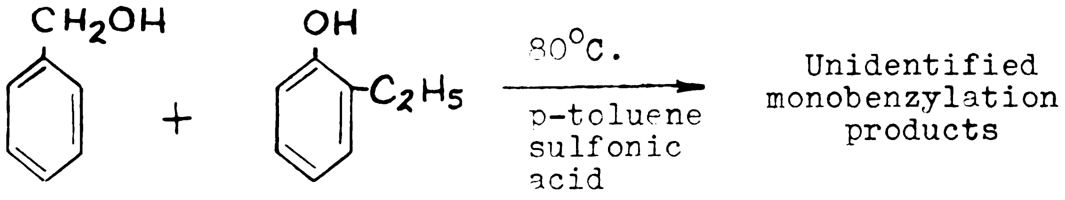
(58% yield), b.p. 171-4°C. at 2 mm.

The infrared spectrum of this material was compared with the spectrum of 2-benzyl-4-ethylphenol prepared in the first experiment and found to be identical.

Benzyl alcohol and o-ethylphenol

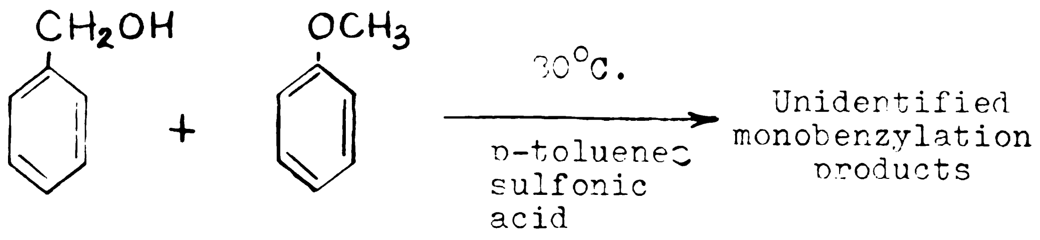
To 350 ml. cyclohexane were added 0.59 mole o-ethylphenol and 0.07 mole p-toluenesulfonic acid. The mixture was heated to reflux temperature and 0.5 mole benzyl alcohol added over a period of two hours and 39 minutes. Refluxing was continued for an additional 40 minutes and a total of 10 ml. of water were removed.

Washing and distillation yielded 45.8 g. of material boiling at 157-175°C. at 3 mm.



Benzyl alcohol and anisole

Water was eliminated on refluxing 0.7 mole benzyl alcohol, 1.4 moles anisole, and 0.1 mole p-toluenesulfonic acid in cyclohexane. Distillation of the crude reaction product yielded 65.6 g. of an unidentified liquid boiling at 137-146°C. at 3 mm.



Benzyl alcohol and catechol

Refluxing one mole catechol, one mole benzyl alcohol and 0.05 mole p-toluenesulfonic acid in cyclohexane gave a rapid evolution of water. Purification and distillation at 3 mm. yielded the following fractions:

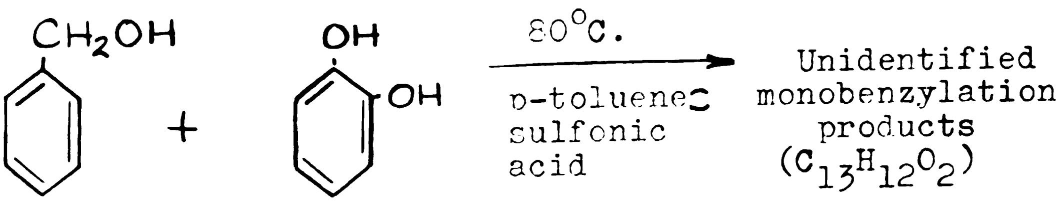
Fraction	Boiling point	Weight	Description
1	142-78°C.	6.7 g.	Soft white solid
2	180.0-6.5°C.	27.2 g.	Colorless liquid
3	187-90°C.	7.8 g.	Light yellow liquid
4	191-4°C.	13.0 g.	Colorless liquid

Fraction 2 was recrystallized four times from cyclohexane to give white crystals, m.p. 94.5-5.5°C.

Analysis:

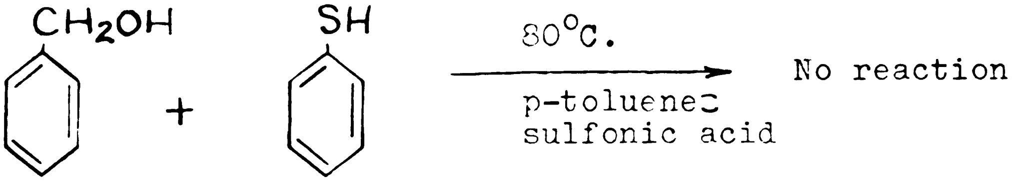
Calculated for $C_{13}H_{12}O_2$: C, 77.97; H, 6.04

Found : C, 78.43; H, 6.01



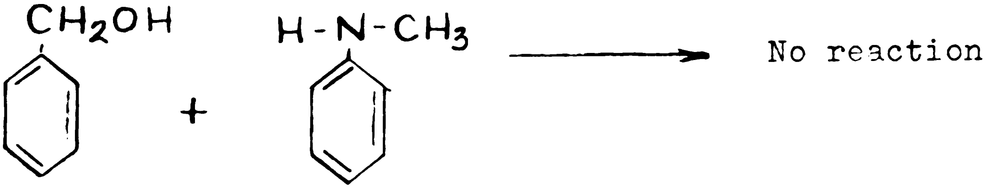
Benzyl alcohol and thiophenol

As evidenced by the absence of water formation, no reaction was observed after 85 minutes refluxing of 0.5 mole benzyl alcohol, 0.5 mole thiophenol, and 0.05 mole p-toluenesulfonic acid in cyclohexane.



Benzyl alcohol and N-methyl aniline

No water was obtained after 47 minutes refluxing of 0.5 mole benzyl alcohol, 0.5 mole N-methylaniline and 0.1 p-toluenesulfonic acid in cyclohexane.



IV. DISCUSSION

A. Infrared Analysis of Phenols

The infrared spectra of benzylated phenols has been shown to be a valuable tool for the characterization of the products obtained in this work. The three most valuable regions were the O-H stretching bands at 2.7-3.0μ, the O-H deformation bands at 8.2-8.6μ, and the aromatic substitution region from 10-15μ.

1. Oxygen-Hydrogen Stretching Bands

The O-H stretching band at 2.7-3.0μ consists of two parts in phenol itself, a non-hydrogen-bonded part at 2.7μ and a hydrogen-bonded shoulder at 2.8-3.0μ. If a phenol is substituted (with an alkyl group) in the para position, there should be no interference with the hydrogen bonding of the O-H group. A para or meta substituted phenol would have a large hydrogen-bonded shoulder. All phenolic products obtained in this research which do not have an ortho substituent have a spectrum with this type of O-H bond.

The introduction of an ortho alkyl group interferes with hydrogen bonding of the O-H group for steric reasons.

All benzylated phenols which contain one ortho substituent have an O-H band of medium width and little or no shoulder.

The introduction of two ortho groups greatly reduces the amount of hydrogen bonding of the O-H group. It was found that all benzylated phenols with two ortho substituents have narrow O-H stretching bands.

For benzylated phenols, the C-H stretching band offers positive evidence as to whether ortho or para alkylation has occurred for a particular sample. If two ortho isomers are possible, this region is of no value in deciding which ortho isomer is present.

2. Aromatic Substitution Region at 10-15μ

The strong bands in this region are caused by out-of-plane deformation vibrations of the hydrogen atoms remaining on the ring. The nature of the substituents does not have too much influence on the position of these bands.

These bands are well suited for quantitative work because of their high intensity. Many applications have been described for the estimation of relative proportions of isomers. One such application is described by Chumaevski (78), who examined structures of o-, m-, and p-cresol as 5% solutions in CS_2. He measured the optical density of bands at 12.35μ and 12.85μ which correspond to the absorption bands of p- and m-cresol. The o-cresol is considered as a solvent for the other two isomers, and is obtained by difference. This method can be extended to include xylenols.

Whiffen and Thompson (79) have used bands in this region to determine mixtures of cresols as well as mixtures of xylenols. The analysis of phenols, cresols, xylenols, and ethyl phenols has been described by Friedel, Peirce, and McGovern (80).

These bands were used a number of times to make estimations of the isomers present in products of this research. In some cases, such as the reaction of p-chlorobenzyl and p-bromobenzyl alcohols with phenol, both ortho and para isomers were isolated. The spectra of the pure isomers were used for the quantitative estimation of these isomers in each distillation fraction.

In some cases mixtures of isomers were obtained from which one isomer could be separated as a solid. However, the other isomer could not be obtained in a pure state. Such was the case with the following mixtures:

1) 2-benzyl-3-methylphenol and 2-benzyl-5-methylphenol
2) 2-benzyl-3,4-dimethylphenol and 2-benzyl-4,5-dimethylphenol
3) 3-benzyl-2,6-dimethylphenol and 4-benzyl-2,6-dimethylphenol

The structure of the isolated solid isomer was first determined. Comparison of the spectrum of the isolated isomer with that of the mixture showed the bands in the mixture belonging to the isomer which could not be isolated. These bands could be used to check the structure of this isomer. An estimation of the relative amounts of the two isomers could be made by measuring the strength of a band in the 10-15μ region of the mixture belonging to the isolated isomer.

The bands in the 10-15μ region are very useful for the qualitative identification of aromatic compounds. In monosubstituted benzenes the out-of-plane CH bending absorption gives rise to a very strong band in the 14.0-14.4μ region. In 1,2-substituted benzenes the four adjacent hydrogens give rise to a band in the 13.2-13.4μ region.

Three adjacent free hydrogen atoms yield a band with strong absorption in the 12.5-13.0μ region. Further reductions in the number of hydrogens keep shifting the band to higher frequencies (lower μ values) and reduce its strength.

Parc (81) has determined the spectra of 31 alkylated phenols in CS_2 and CCl_4 on a linear μ scale. Many of the compounds were alkylated xylenols for which he had made correlation charts in the 10-15μ region. These charts were found to be useful in determining where substitution bands should occur for similar products obtained in this research.

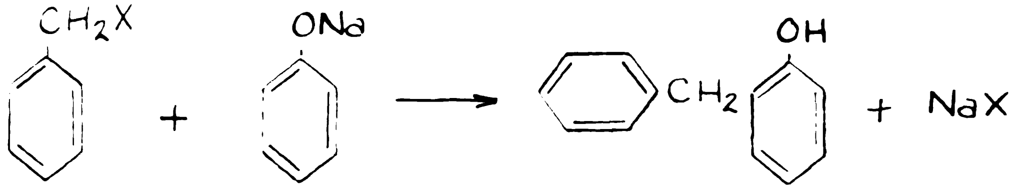
B. Benzylation of Phenol

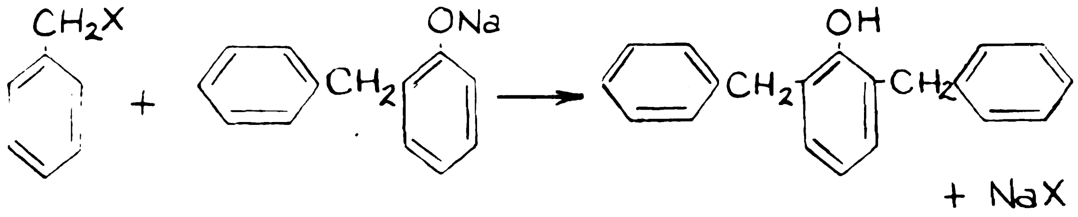
The discovery of the acid-catalyzed ortho benzylation of phenols makes possible the synthesis of o-benzylphenols from benzyl alcohols.

In the past, o-benzylphenols have usually been prepared from benzyl chlorides and phenolic salts by the Claisen (21) method. McMaster and Bruner (33) described the preparation of o-benzylphenol from benzyl chloride and free phenol at 125-75°C., however their yields of ortho-substituted product were poorer than found with the Claisen method.

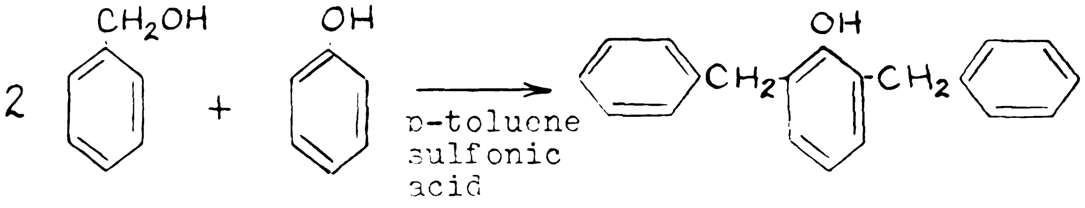
When the benzyl alcohols are more readily available than the corresponding halides, the p-toluenesulfonic acid method may be preferable to the Claisen method. In addition the Claisen method requires the use of phenolic salts and in cases where the alkaline phenol is subject to oxidation, the Claisen method may not be suitable.

The Claisen method is not suitable for the direct preparation of 2,6-dibenzylated phenols. Reaction of benzyl chloride with sodium phenate gives a mono benzylated product of the free phenol. The free benzyl phenol must be converted to the phenoxide and alkylated with another mole of benzyl halide.

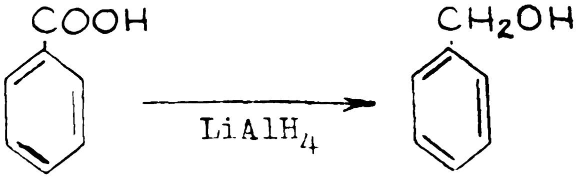




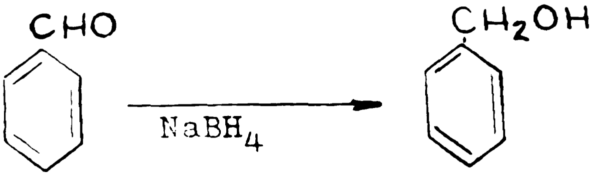
The p-toluenesulfonic acid method may give the dibenzylated product in one step.



Aromatic alcohols are readily accessible from aromatic acids and aldehydes. Aromatic acids are reduced to the corresponding alcohols by lithium aluminum hydride.



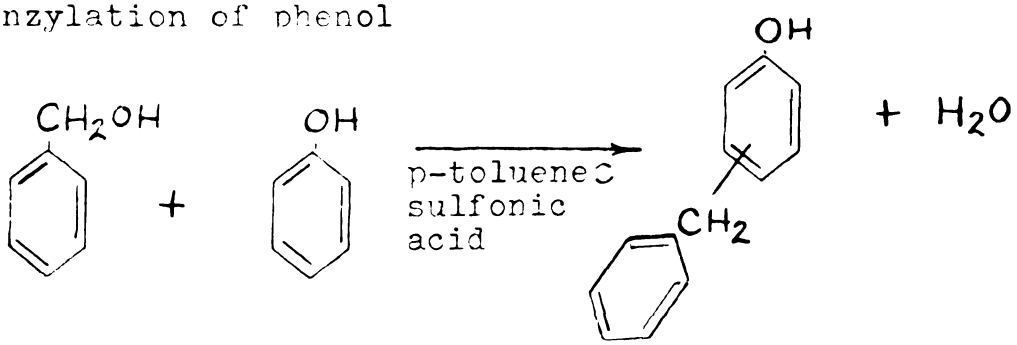
Aromatic aldehydes are reduced to the alcohols by sodium borohydride.



The ready availability of many aromatic alcohols makes the p-toluenesulfonic acid method a valuable preparative tool.

In the laboratory it is easier to handle benzyl alcohols than benzyl halides. The halides are lachrymators and severe skin irritants, whereas the alcohols are very innocuous materials.

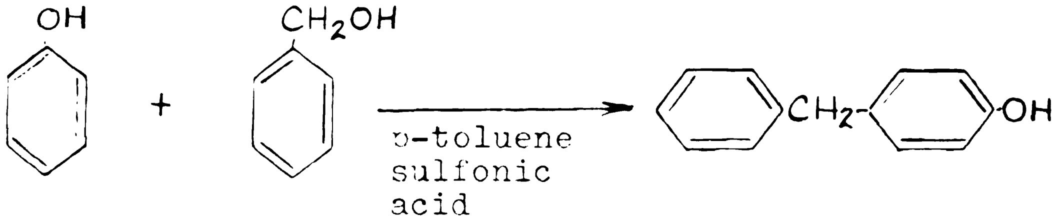
As water is a by-product in the acid-catalyzed benzylation of phenol



the rate of reaction may be determined by measuring the amount of water removed at various times during the reaction.

Pratt, Preston, and Draper (12) studied the alkylation of phenol with benzyl alcohol in the presence of p-toluenesulfonic acid with benzene as a solvent. They reported a 28% yield of p-benzylphenol and a 50% yield of diphenyl methane. Because of the interference of the benzene solvent, paraffin and cycloparaffin solvents were used in the work carried out in this laboratory. Quite unexpectedly the main product with saturated hydrocarbon solvents was ortho and not para-benzylphenol. Despite the dozens of workers who had studied the benzylation of phenols, this method had remained undiscovered up to now.

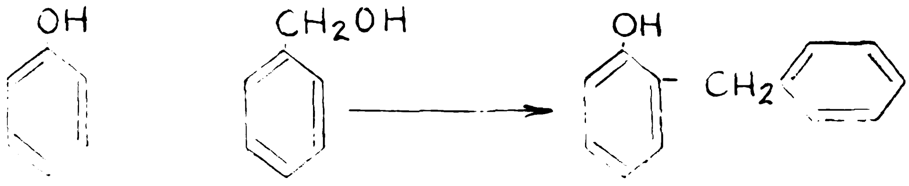
The system of phenol, benzyl alcohol and p-toluene sulfonic acid is a complex one and there are a number of possible products. One possible reaction would be alkylation of the phenol to produce p-benzylphenol.



Reaction of p-benzylphenol with another molecule of benzyl alcohol would form 2,4-dibenzylphenol. Unless a considerable excess of phenol is used, a large amount of dialkylated product is formed.

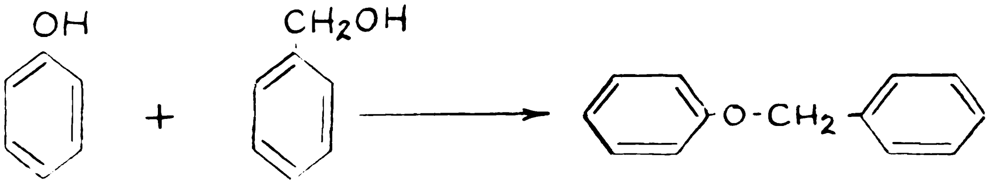
Benzyl groups have electron-releasing properties and increase the susceptibility of an aromatic ring to electrophilic attack. Ortho and para benzylphenols are more easily alkylated than phenol; therefore dibenzyl phenols are formed in large quantities when benzyl alcohol and phenol are reacted in molar quantities. Furthermore dibenzyl phenols would be more easily alkylated than either phenol or a monobenzylphenol. If desired, tribenzyl phenols could probably be isolated from the reaction of benzyl alcohol and phenol.

Reaction of phenol with one mole of benzyl alcohol might also yield o-benzylphenol.



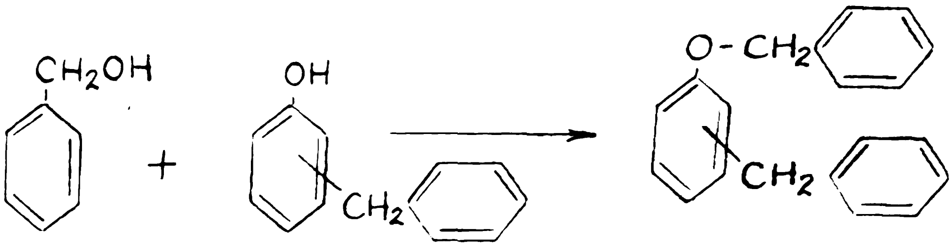
Subsequent reaction of o-benzylphenol with benzyl alcohol might give either the 2,4- or the 2,6-dibenzyl phenol.

Phenol and benzyl alcohol might also react to give benzyl phenyl ether.

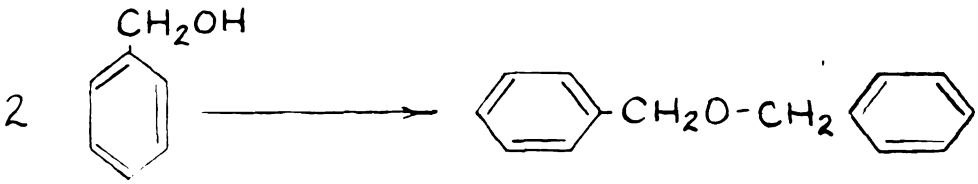


Benzyl phenyl ether might rearrange to give benzylated phenols.

Ether formation might also take place if a molecule of benzyl alcohol reacted with a molecule of a benzyl phenol.

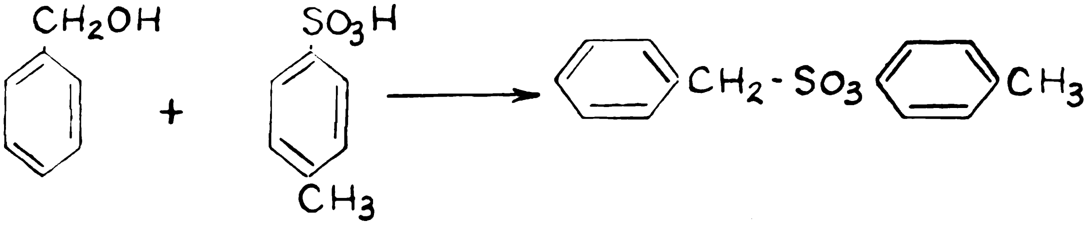


Reaction of a molecule of benzyl alcohol with another molecule of benzyl alcohol might also take place to give dibenzyl ether.

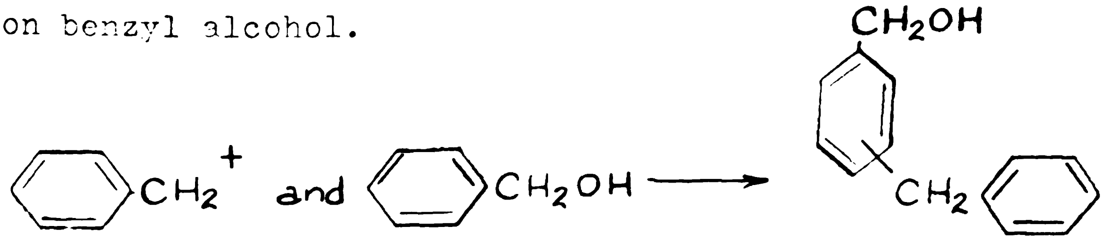


Dibenzyl ether could then act as an alkylating agent to give benzylated phenols.

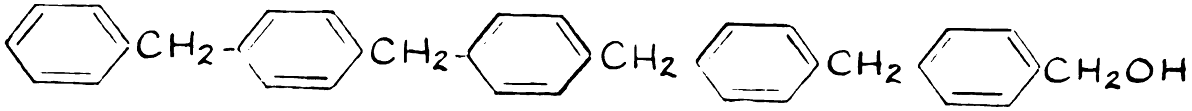
Benzyl alcohol might react with p-toluenesulfonic acid to give benzyl tosylate.



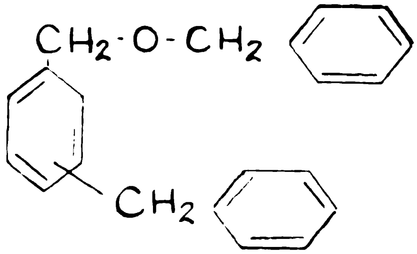
Benzyl tosylate might act as an alkylating agent to form benzylated phenols or ethers. Benzylated benzyl alcohols might be formed by the attack of benzyl cations on benzyl alcohol.



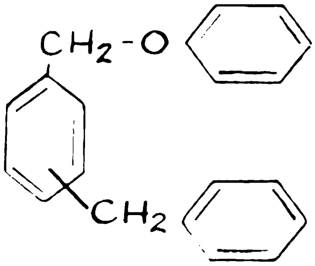
These benzylated benzyl alcohols could further react to give polymeric polybenzyl compounds



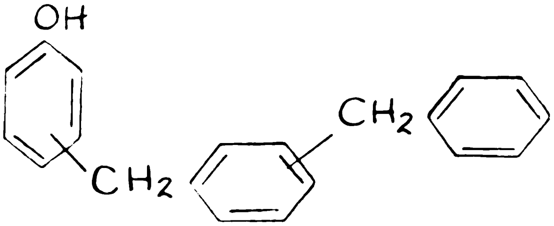
or might form dibenzyl ethers



or benzyl phenyl ethers

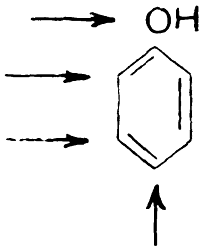


or react with a molecule of phenol to form alkylated phenols.



A perusal of the Historical section of this thesis will show that most of these products have been isolated by one or more of the many workers who studied the benzylation of phenol.

A study of the structure of phenol



shows that alkylation can occur on both oxygen and carbon. Alkylation on carbon might take place in all three (ortho, meta, para) positions. As alkylation of the ring is an electrophilic substitution the ortho and para positions are favored since they are rich in electrons.

According to Kornblum and Lurie (82), the formation of para substituted phenols is indicative of a carbonium ion process. The view that para alkylation is due to carbonium ion intermediates is supported by the fact that those halides which give carbonium ions readily are the ones which most easily give para alkylation. Thus tertiary alcohols or halides give almost exclusively para substituted phenols with most acid catalysts. Price (83) reports that secondary alcohols or halides often give substantial proportions of ortho isomers with the same acid catalysts.

Curtin, Crawford, and Wilhelm (84) found that benzyl halides and sodium phenoxide give carbon alkylation only at the ortho position. On the other hand they found that benzhydryl chloride, which readily gives carbonium ions, yielded para-substituted products with sodium phenoxide. Busch and Knoll (85) found that trityl chloride, which likewise readily gives carbonium ions, yields para-substituted products with sodium phenoxide.

Strong acids and high concentrations of acids will tend to give carbonium ions and subsequent para alkylation. Some para alkylation is observed with p-toluenesulfonic acid, a fairly strong acid. However, p-toluenesulfonic acid is soluble in many organic solvents and can be employed in varying concentration in solution as a catalyst. Most acid catalyzed alkylations of phenols are heterogeneous and present high acid concentrations at the catalyst interface.

Dowex 50 gives a higher percentage of para isomer than p-toluenesulfonic acid although it is not a stronger acid. The same ortho/para ratios are obtained in both experiments with Dowex 50, although in one case four times as much catalyst is used. Apparently the acid concentration at the resin bead surface is the determining factor in the amount of ortho and para isomers formed. The use of other sulfonated polystyrene derivatives as catalysts might yield different results.

Rodia and Freeman (86) have discussed the problem of why the para position of a phenol is usually the favored point of benzylation with acid catalysis, even though two ortho positions are available. They claim that a phenolic hydroxyl group will solvate protons to yield $ArOH_2^+$. Since the benzyl carbonium ion also carries a positive charge, mutual repulsion of these charges would hinder formation of the para isomer. Thus, the para isomer would be at a maximum at low pH. Finn and Musty (87) report that in the phenol-formaldehyde reaction the percent of ortho-linked diphenylmethane isomer increases with increasing pH.

Phenol-formaldehyde resins with a high percentage of ortho-linked diphenylmethane isomer have certain desirable physical properties. It may be that p-toluene sulfonic acid and similar catalysts would have considerable utility in the preparation of high ortho resins. Such utility should certainly be investigated.

In this research it was found that phosphoric acid gave a larger percentage of ortho isomer than sulfuric acid in the benzylation of phenol. Phosphoric acid is a weaker acid than sulfuric and should be less likely to yield carbonium ions. In addition it may be that some of the phosphoric acid was soluble in the cyclohexane phase of the reaction mixture. The acid in the cyclohexane phase may tend to give ortho rather than para alkylation.

The correlation of ease of carbonium ion formation with para alkylation is obscured by two factors. One factor is steric interaction in the ortho position which would be greater with the more highly branched alkylating agents that form carbonium ions more easily. The second factor would be isomerization of an initially formed ortho isomer to give the corresponding para isomer. Goldsmith, Schlatter, and Toland (88) reported that ortho alkylated phenols are readily isomerized by the usual alkylation catalysts to yield the more stable para derivatives. The more highly branched alkyl groups would also be the most subject to dealkylation. Isomerization would also increase with decreasing pH.

Although the details are obscure it seems clear that formation of para-substituted phenols takes place by carbonium-ion intermediates. Hart and Eleuterio (89) show that in nuclear alkylation of phenols with optically active α-phenylethyl chloride, the para isomer is optically active. A carbonium ion intermediate would of course be planar and cause racemization.

Uncatalyzed thermal alkylation with olefins to give ortho-sec-alkylphenols has been known for a long time. Skraup and co-workers (90) report that heating phenol and cyclohexane at 300°C. for 75 hours gives a 30% conversion to o-cyclohexylphenol, and that m-cresol may be thermally alkylated with propylene to yield a 50-60% conversion to thymol after 70 hours at 370°C.

Recently Goldsmith, Schlatter, and Toland (88) described the thermal alkylation of phenol at 320°C. with 1-butene to give o-tert-butylphenol and with cyclo hexene to give o-cyclohexylphenol.

Cyclohexanol has been condensed with phenol under mild acid catalysis to give the ortho isomer. Thus Gardner (91) reacted half mole quantities of phenol and cyclohexanol at 85°C. for 40 minutes in the presence of polyphosphoric acid to yield 17% p-cyclohexylphenol and 22% o-cyclohexylphenol.

Tertiary alkyl chlorides and tertiary olefins can also be used for the ortho alkylation of phenols. Plank and Socolofsky (92) alkylated phenol with tert-butyl chloride in the presence of boron trifluoride treated drying oils to give o-tert-butylphenol. It has also been reported (93) that 20-61% yields of o-tert-butylphenol are obtained when phenol is alkylated with isobutylene in the presence of 0.6% phosphorous oxychloride at 38-55°C.

Goldsmith, Schlatter, and Toland (88) have found that when phenol and isobutylene are heated to 320°C. for several hours excellent yields of o-tert-butylphenol are obtained with little or no para isomer.

In addition to the well known Claisen ortho alkylation of sodium phenoxides with allylic and benzylic halides, Kundiger and Pledger (94) have found that an allylic chloride will give ortho alkylation either thermally or with an acid catalyst. For example, refluxing (143-67°C.) phenol and 1,1,3-trichloro-2-methyl-1-propene for seven hours gives the ortho as well as the para isomer. Similarly phenol, 1,1,3-trichloro-2-methyl-1-propene and aluminum chloride at 55-60°C.

give both ortho and para isomers.

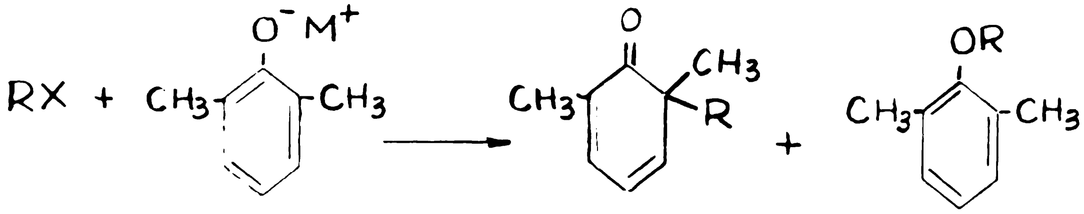
Hart and Eleuterio (89) report that α-phenylethyl chloride and phenol in the presence of potassium carbonate yield more ortho than para isomer.

Bader and Bean (95) have reacted isoprene with phenol in the presence of phosphoric acid to yield both ortho and para alkylated phenols.

Aluminum phenoxide catalyzed alkylation appears to be a general method for the ortho alkylation of phenols. Two independent groups of workers, Stroh et al.(96), and Kolka et al. (97) have reported extensive research on this reaction. Phenols and substituted phenols may be alkylated with ethylene, propylene, and isobutylene to yield mainly the mono or di-ortho substituted phenols.

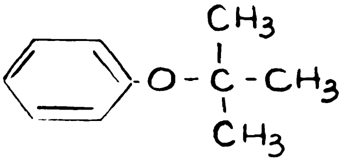
Thus in basic or neutral media ortho alkylation of phenols appears to be rather common, provided of course that other criteria are also met. For example, in the reaction of benzyl and allylic halides with sodium phenoxide, C-alkylation will take place in a non-polar solvent (benzene), whereas O-alkylation will take place in a polar (ethanol) solvent. In 1926 Ingold (98) suggested that the ortho alkylation of sodium phenoxides in non-polar solvents involved the reaction of the alkyl halide with associated sodium phenoxide, whereas the formation of alkyl phenyl ethers in polar solvents involved reaction of the dissociated phenoxide ion.

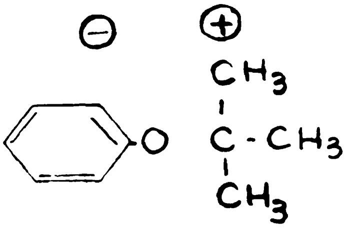
Curtin, Crawford, and Wilhelm (84) have studied the alkylation of alkali phenoxides with benzyl and allyl halides to give either alkyl aryl ethers or 2,4-cyclohexadienones

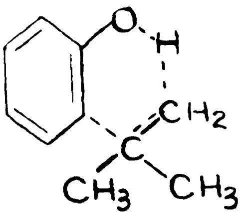


They found that dienone formation was favored by non-polar solvents and ether formation by polar solvents. Their explanation is essentially a modification of the picture presented by Ingold for preferential ortho alkylation in non-polar solvents.

Goldsmith, Schlatter, and Toland (88) discuss the reason for almost exclusive formation of o-tert-butylphenol in thermal alkylation. They feel there are three possible intermediates:







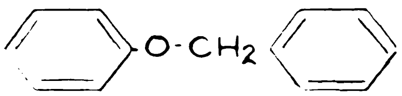
I II III

They reject the ether (I) as unlikely, since tert-butylphenol ether rearranges on heating to give para, not ortho-tert-butylphenol.

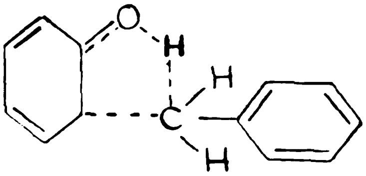
The second intermediate (II) represents an ion pair which, because of the low dielectric constant of the medium, would remain closely associated until reaction occurred. They reject this since the primary carbonium ion from ethylene would be much less stable than a tertiary carbonium ion so that ethylene should alkylate phenol more slowly than isobutylene. Instead the rates are of the same order of magnitude.

The concerted process involving a transition state of type III is considered best by Goldsmith et al. (88) to explain uncatalyzed ortho alkylation of phenols.

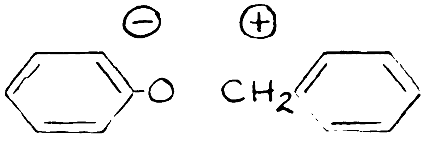
The same three types of intermediates might be considered for the ortho benzylation of phenol.



I



III



II

In this case I is a possible intermediate since it has been shown to rearrange under the conditions of the experiment to give ortho as well as para-benzyl phenol. However, since approximately equal proportions of the two isomers were shown to be formed in the rearrangement, it is probable that I is not the sole intermediate in the reaction.

Transition state II could help to explain why ortho-benzyl phenol is formed in good yields in a cyclo hexane solvent, but in poor yields in a more polar solvent. In a non-polar solvent the ion pair would be tightly held as the cyclohexane medium would not favor dissociation. Ortho alkylation would take place by collapse of the ion pair. Para alkylation would take place by dissociation of some of the ion pairs to give a free benzyl ion which would attack the para position of the phenol.

A concerted process involving a cyclic intermediate of type III is also possible in this reaction, although it would not be the sole path since some para alkylation takes place. It does not seem probable that the ortho benzylphenol will rearrange to yield the para isomer.

Goldsmith et al. (88) suggest that the strong inhibiting effect of pentane dilution on the formation of o-tert-butylphenol may indicate more than one molecule of phenol is present in the intermediate complex. Maxfield's (3) data suggest this also, since he showed that as the molar excess of phenol was increased, the amount of o-benzylphenol also increased.

In some of the experiments reported in this thesis no hydrocarbon solvent was used, although good yields of o-benzylphenol were still realized. Since all evidence in the literature points to a non-polar solvent as favoring ortho alkylation, it seems strange that this should be, since phenol is a fairly polar solvent. If we assume that more than one molecule of phenol is involved in the transition state, we can explain this fact.

Hart and Simons (39) showed that the uncatalyzed reaction of tert-butyl chloride with phenol was first order in alkyl halide, but second to sixth order in phenol, depending on the solvents used.

In addition to the intermediates shown it is possible for benzyl tosylate to be formed initially and act as an alkylating agent. Hickinbottom and Rogers (99) reported that cyclohexyl tosylate and phenol gave 55% monocyclohexylphenols with approximately equal amounts of ortho and para isomers. Anisole and cyclohexyl tosylate also yield 61% of cyclohexylanisoles with approximately equal amounts of ortho and para isomers. According to these data it is not necessary to have a hydrogen atom on the hydroxyl group for some ortho alkylation to take place. In these cases both ortho and para alkylation might take place via carbonium ions.

This new method of ortho benzylation of phenol in the presence of p-toluenesulfonic acid yields three to four times as much ortho as para benzylphenol with cyclohexane solvent. It is more convenient than the Claisen method to carry out since the sodium salt need not be previously formed. In addition, no ether formation takes place as with the Claisen method.

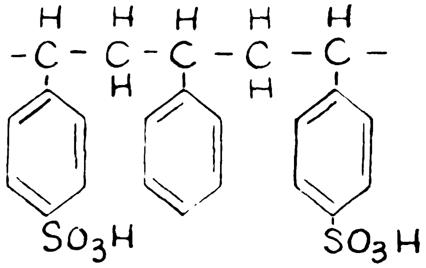
The p-toluenesulfonic acid gives ortho/para ratios superior to the McMaster-Bruner high temperature reaction of benzyl chloride and phenol. In addition, the total monobenzylphenol yield is higher with the p-toluenesulfonic acid method.

In addition to alkylation with a p-toluenesulfonic acid catalyst in a hydrocarbon solvent, the reaction may be carried out at higher temperatures without a hydrocarbon solvent. This high temperature method has several advantages over the solvent method. First, a smaller reaction vessel may be employed for equivalent quantities of primary reactants. If a large preparation of benzylated phenol is desired, this advantage becomes very important as there is a practical limit to the size flask which can be handled in the laboratory. Second, considerable time is saved in the purification of the product as it is unnecessary to remove the solvent by distillation. And third, purification and recovery of solvent are eliminated.

A disadvantage of the high temperature method is the constant attention required during the benzyl alcohol addition to maintain the correct temperature.

In the high temperature reaction considerably less p-toluenesulfonic acid is required as a catalyst.

The ortho benzylation of phenol may also be carried out with a sulfonated polystyrene resin catalyst. Such a resin is similar in structure to p-toluenesulfonic acid as it consists of a number of p-toluenesulfonic acid units connected by methylene and benzylidene bridges in the polystyrene chain.



If the resin is used as a catalyst with a n-heptane solvent, the formation of water does not take place at an appreciable rate. However, if excess phenol is used as a solvent so that a higher temperature (150°C.) of reaction can be realized, alkylation of phenol with benzyl alcohol will proceed readily. The yields of monobenzyl phenol are slightly better than those obtained with a p-toluenesulfonic acid catalyst, but the ortho/para ratio is significantly less. Thus ortho/para ratios of 2.3/1 and 2.4/1 are obtained with a resin catalyst, whereas high temperature alkylation with p-toluenesulfonic acid yields ortho/para ratios of 3.5/1 to 4.0/1. It may be that a steric effect in a cyclic intermediate decreases the yield of the ortho isomer when a resin catalyst is used. The cyclic intermediate would form less readily and if present, would dissociate more rapidly to form a carbonium ion.

Formation of a carbonium ion would result in para benzylation.

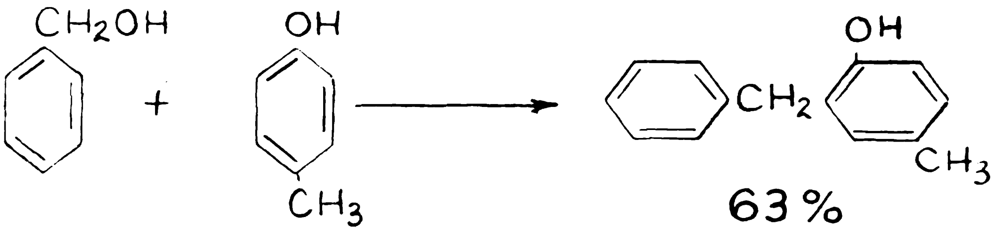
The resin catalyst method involves the simplest method of purification. The hot reaction mixture is filtered to remove the resin and the crude product fractionated at once. No washing or solvent distillation is necessary.

When the polarity of the solvent is increased by the addition of n-butyl ether to cyclohexane the ortho/para ratio decreases sharply. This would be expected as the more polar solvent will tend to stabilize a carbonium ion responsible for para alkylation.

C. Benzylation of Cresols

1. Benzylation of p-cresol

In the reaction of benzyl alcohol with p-cresol in the presence of p-toluenesulfonic acid para alkylation is not possible and 2-benzyl-4-methylphenol is formed in good yield.

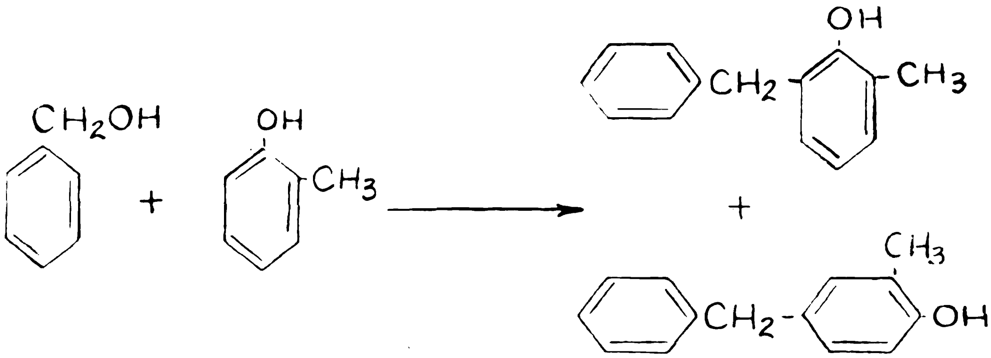


The physical properties of 2-benzyl-4-methylphenol and its phenylurethane agree with those recorded in the literature. In addition the infrared spectrum shows the bands expected in the assigned structure. As the meta isomer boils higher than the ortho isomer, if 5% or more was present, a separate fraction should have been collected. The directive influence of the methyl group would favor meta orientation although the directive influence of the hydroxyl group is much stronger.

The reaction of benzyl alcohol and p-cresol in the presence of p-toluenesulfonic acid was carried out by the high temperature method. This reaction should be a very suitable one to carry out with a Dowex 50 catalyst. Although with benzyl alcohol and phenol lower ortho/para ratios are achieved with Dowex 50 than with tosyl acid, here no para alkylation is possible. Thus p-cresol could be heated with a Dowex 50 catalyst to 140°C., benzyl alcohol added, the water of reaction collected, and the hot reaction mixture filtered to yield the crude product.

2. Benzylation of o-cresol

The benzylation of o-cresol in the presence of p-toluenesulfonic acid yields 2-benzyl-6-methylphenol and 2-benzyl-4-methylphenol.



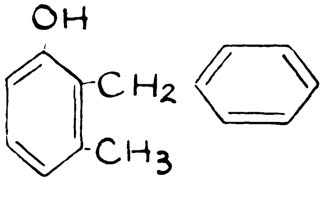
The range of ortho/para values (2.3/1 to 3.2/1) is lower than found in the benzylation of phenol. This is expected since now only one ortho position is open for alkylation instead of the two in phenol. Apparently the lower yield of ortho isomer in this case is a statistical matter.

The high temperature method (Exps. 2 and 3) yields better results than the low temperature (Exp. 1) method. Also the use of a large molar excess of o-cresol and a smaller amount of catalyst appears to yield the best results in Exp. 3. The low concentration of acid would be unfavorable to the formation of carbonium ions necessary for para alkylation. If more than one molecule of o-cresol is present in the transition state, a larger molar excess of o-cresol would favor ortho alkylation.

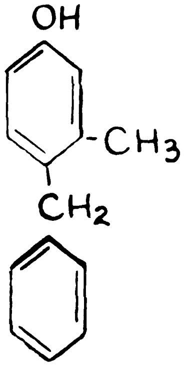
Huston, Swartout, and Wardwell (4) obtained only a small amount of the ortho isomer on benzylation of o-cresol by the aluminum chloride method. On the other hand, the benzylation of phenol by the aluminum chloride method (3) gives a somewhat larger amount of o-benzylphenol. In this work it was also found that benzylation in the presence of p-toluenesulfonic acid gives somewhat more ortho isomer with phenol than with o-cresol.

3. Benzylation of m-cresol

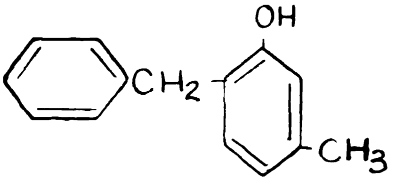
The benzylation of m-cresol is more complex since two ortho isomers as well as a para isomer are possible. They are shown below.



2-benzyl-3-methylphenol

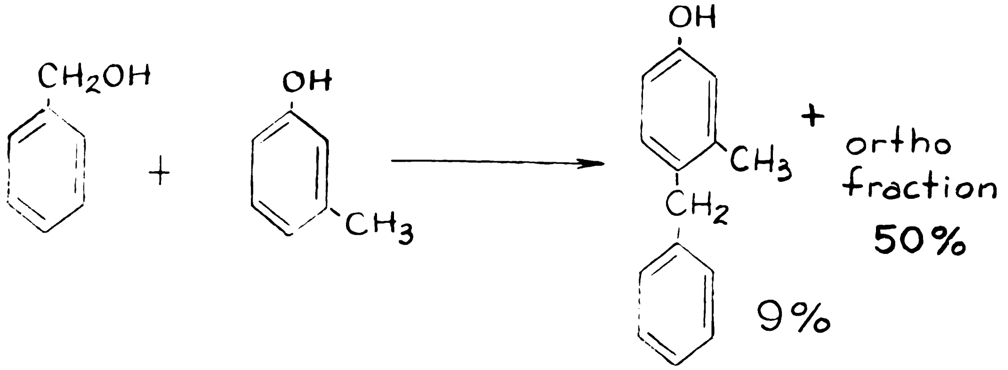


4-benzyl-3-methylphenol



2-benzyl-6-methylphenol

Benzylation of m-cresol in the presence of p-toluene sulfonic acid by the cyclohexane method yields a fraction containing both ortho isomers and a higher boiling mixture containing the para isomer.



There is a lower percentage of para isomer formed than in the benzylation of phenol. This may be due to steric hindrance of the meta methyl group which hinders formation of 4-benzyl-3-methylphenol but not formation of 2-benzyl-5-methylphenol. Huston and Houk (5) had found in the aluminum chloride catalyzed alkylation of m-cresol with benzyl alcohol that less para isomer was formed than in the benzylation of phenol.

Since the formation of 2-benzyl-3-methylphenol would also be sterically hindered by the methyl group, it would be expected that more of the 2-benzyl-5-methyl isomer would be formed. As expected, only 25% of the ortho fraction was shown to be the 2,3-isomer by the following method:

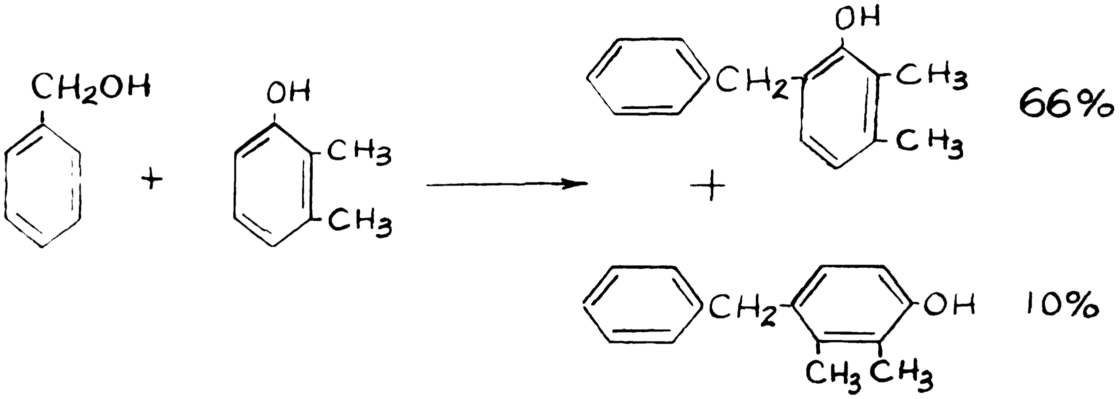
The liquid ortho fraction was cooled in the refrigerator to yield a white solid and a colorless oil. The white solid was recrystallized and shown to be 2-benzyl-

3-methylphenol. Infrared analysis then showed the crude ortho fraction to contain about 25% of the 2,3-isomer. An infrared spectrum of the oil separated from the solid 2,3-isomer showed bands corresponding to substitution patterns found in the 2,5-isomer. The presence of this latter isomer was also shown by bromination of the oil to yield 2-benzyl-4,5-dibromo-5-methylphenol, first prepared by Huston and Houk (5).

D. Benzylation of Xylenols

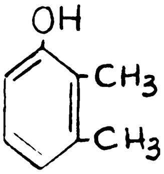
1. Benzylation of 2,3-xylenol

Reaction of benzyl alcohol with 2,3-xylenol in the presence of p-toluenesulfonic acid in cyclohexane yields ortho and para benzylated isomers.



Both 6-benzyl-2,3-dimethylphenol and 4-benzyl-2,3-dimethylphenol are new compounds. Boiling points, analysis, yields, and infrared spectra are in agreement with their proposed structures.

An examination of the structure of 2,3-xylenol



shows the directive influences of the methyl groups would cancel each other, therefore from an electronic viewpoint the isomer distribution should be similar to that of phenol. The presence of a 3-methyl group should decrease the amount of para isomer because of steric hindrance. On the other hand there is only one ortho position open, so from a statistical viewpoint less ortho isomer should be formed. The ortho/para ratio is actually a little higher than with m-cresol, so there may be a "buttressing" effect of the 3-methyl group by the 2-methyl group.

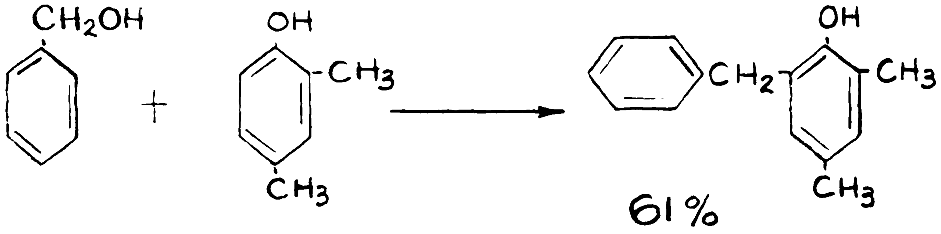
As in phenol we would expect very little of the meta substitution product to be formed. If formed, it should distill in the same fraction with 4-benzyl-2,3-dimethylphenol. No meta isomer was detected.

Benzyl-2,3-dimethylphenyl ether, if formed, would distill lower than 6-benzyl-2,3-dimethylphenol. None of the ether was detected.

There is also formed a high-boiling residue as in the benzylation of phenol and the cresols. This residue is probably the dibenzyl product, however no attempt was made to distill and identify the material.

2. Benzylation of 2,4-xylenol

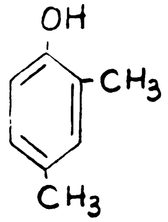
Reaction of benzyl alcohol with 2,4-xylenol in the presence of p-toluenesulfonic acid in cyclohexane yields 2-benzyl-4,6-dimethylphenol.



This compound was previously prepared by Elkobaisi and Hickinbottom (46) who recorded a melting point of 67°C., as compared to the 66°C. found in this work. The boiling point and infrared spectrum also agree with the assigned structure.

The melting point of the phenylurethane was 143.5-144.0°C. instead of 136°C. as recorded by Elkobaisi and Hickinbottom. The N-H and C=O bands in the infrared spectra of the phenylurethanes are similar to those found in the urethane spectra of 6-benzyl-2,3-dimethylC phenol, 2-benzyl-3,6-dimethylphenol and 2-benzyl-3,5-dimethylphenol. There seems to be no question that this is indeed a phenylurethane and it seems possible that it is purer than that prepared by Elkobaisi and Hickinbottom.

The structure of 2,4-xylenol

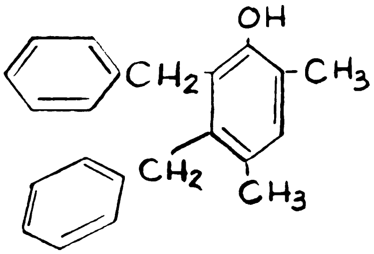


shows that only one ortho and no para alkylation products are possible. Two meta alkylation products are possible and of course, in opposition to the influence of the OH group, the two methyl groups favor meta instead of ortho alkylation. However meta alkylation would probably proceed by a carbonium ion mechanism as does para alkylation. Therefore ortho alkylation would be favored by the mechanism as well as by the directive influence. Moreover meta alkylation would be inhibited by steric hindrance of the methyl group(s).

If meta isomer were present in considerable quantity, it should have distilled as a slightly higher boiling fraction than the 2-benzyl isomer. No such fraction was collected.

No benzyl 2,4-dimethylphenyl ether was detected. If present, it would have been collected as a lower boiling fraction.

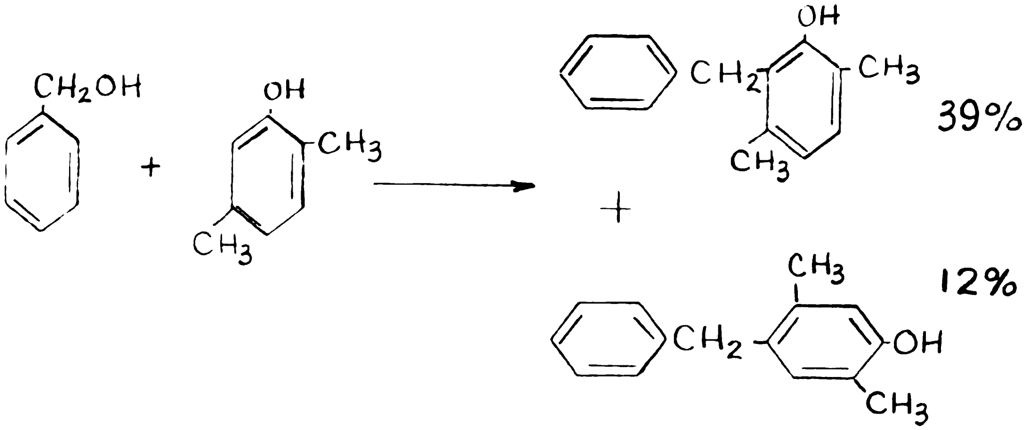
Again there was present a very high boiling material which was not distilled. This might contain a dibenzyl isomer such as



As shown in the benzylation of 2,6-xylenol such meta alkylation does take place when the ortho positions are blocked and the two methyl groups favor the alkylation.

3. Benzylation of 2,5-Xylenol

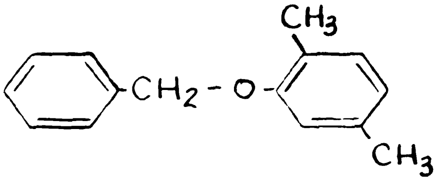
Benzylation of 2,5-xylenol in the presence of p-toluenesulfonic acid in cyclohexane yields the following products:



Both of these isomers are new compounds. The boiling point, spectrum, and analysis showed the assigned structure of 2-benzyl-3,6-dimethylphenol to be correct. A mixture melting point showed the 2- and 4-benzyl isomers to be different compounds. The boiling point and spectrum of 4-benzyl-2,5-dimethylphenol indicated the assigned structure to be correct.

An alternate method of benzylation consisted of refluxing a mixture of benzyl alcohol, 67% sulfuric acid, 2,5-xylenol, and cyclohexane. As expected, the majority of the monobenzyl product was 4-benzyl-2,5-dimethylphenol. Comparison of its spectrum with that of the previous sample showed that they are the same compound.

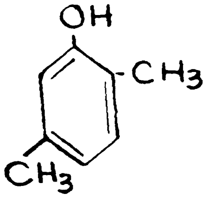
In the latter method of preparation a small fraction of a lower boiling material was collected which is believed to be benzyl 2,5-dimethylphenyl ether.



The spectrum of this fraction shows evidence for such a structure. In one other instance, the reaction of o-chlorobenzyl alcohol and phenol, the presence of an ether was detected in the alkylation products. In this latter experiment alkylation was carried out in cyclohexane with a p-toluenesulfonic acid catalyst.

The detection of such a small amount of ether in this experiment is good evidence that considerable amounts of ethers were not formed in the other alkylations described in this research.

Examination of the structure of 2,5-xylenol

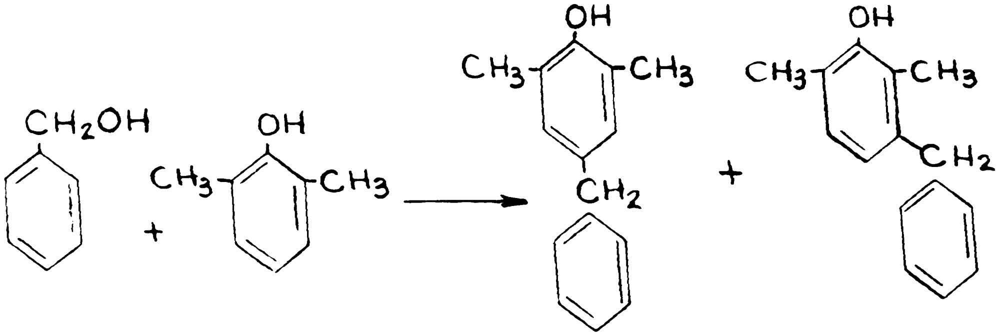


shows that one ortho and a para isomer would be expected. The ortho/para ratio found in the benzylation of 2,5-xylenol is about the same as found in the benzylation of phenol. Since in phenol two ortho positions are open to one para position, here with 2,5-xylenol para alkylation must be more susceptible to steric hindrance from the methyl group than the ortho alkylation.

There is also a meta position open for alkylation, although the directive influences of the methyl groups cancel each other. No meta isomer was detected.

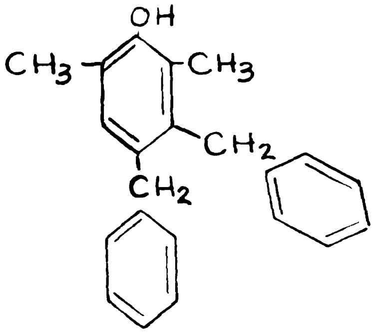
4. Benzylation of 2,6-Xylenol

In the benzylation of 2,6-xylenol both ortho positions are blocked so that no ortho alkylation is possible. Para alkylation is favored by the directive influence of the hydroxyl group whereas meta alkylation is favored by the directive influence of the two methyl groups. As the directive strength of the hydroxyl group is equal to that of 3 to 4 methyl groups we find that both para and meta alkylation take place.



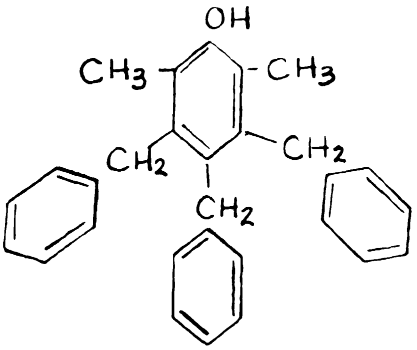
The separation **and** identification of these isomers provide an interesting example of the usefulness of infrared analysis. The existence of two isomers was first suspected on examination of the crude monobenzyl product spectrum. Bands corresponding to both 1,2,3,5 and 1,2,3,4 substitution patterns were present. As the isomers were separated by fractional crystallization, the growth of some bands and the disappearance of others were noticed as spectra of the various fractions were examined.

A considerable amount of dibenzyl product was also isolated. It is believed to be the following isomer:

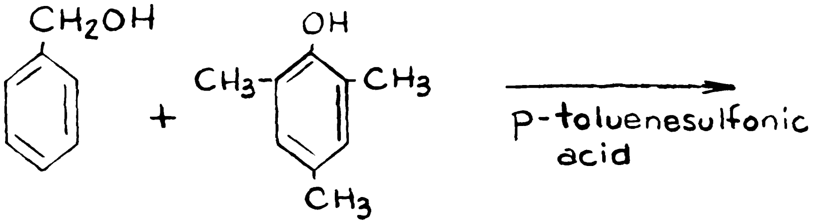


The evidence concerning its structure is given in detail in the Experimental portion of this thesis. Elkobaisi and Hickinbottom (46) also have obtained a dibenzylated 2,6-dimethylphenol with the same melting point. It is possible that these two compounds are identical. However since their compound was prepared by a different method this fact could not be proven unless their actual work was repeated.

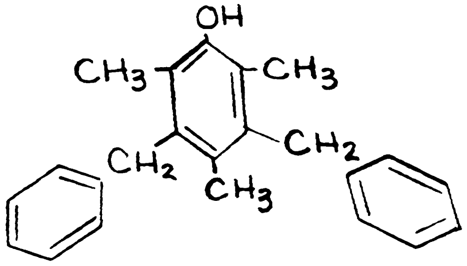
An interesting extension of this present work would be an attempt to prepare the trialkylated product.



Another interesting extension would be an investigation of the following reaction:

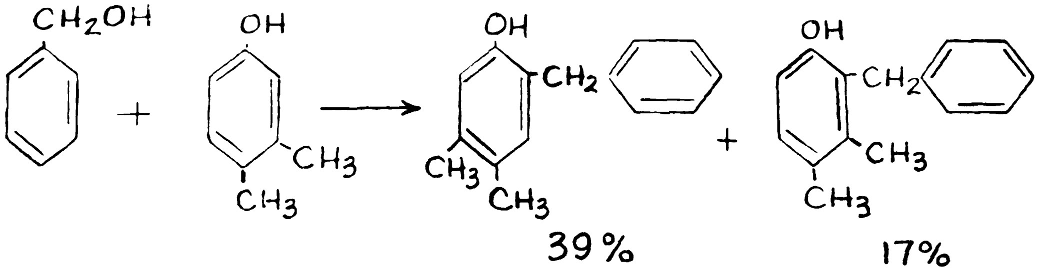


A monobenzyl product seems likely, however the formation of a dibenzyl product, containing six groups on the benzene ring, might require more vigorous reaction conditions.



5. Benzylation of 3,4-Xylenol

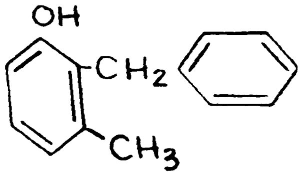
Reaction of benzyl alcohol and 3,4-xylenol in cyclohexane in the presence of p-toluenesulfonic acid yields a mixture of the two possible ortho isomers.



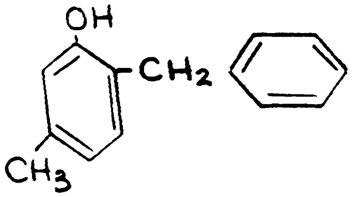
The yield of monobenzyl product is somewhat low as only a 50% excess of the xylenol was used.

In determining which ortho isomer would be formed the directive influence of the methyl groups would cancel each other. Therefore the relative amounts of the two ortho isomers should be determined by steric considerations. Apparently this is the case, since about 70% of the monobenzyl product is 2-benzyl-4,5-dimethylphenol and the other 30% is 2-benzyl-3,4-dimethylphenol.

The benzylation of m-cresol also yielded two ortho isomers:



25% of the ortho isomers

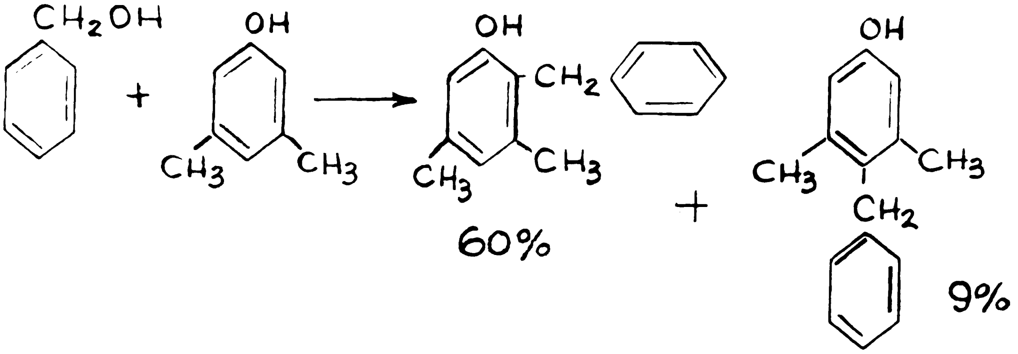


75% of the ortho isomers

As with 3,4-xylenol one position is sterically hindered. Thus in two similar cases the relative amounts of hindered and unhindered isomers are about the same.

6. Benzylation of 3,5-Xylenol

Benzylation of 3,5-xylenol in cyclohexane in the presence of p-toluenesulfonic acid yields the expected products.



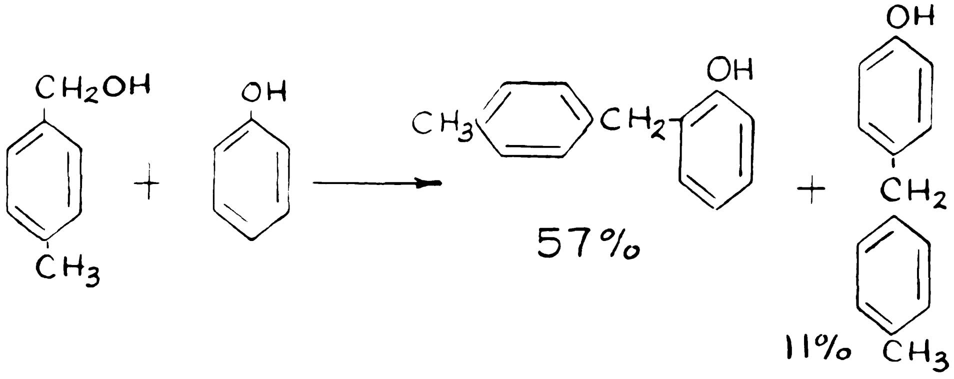
These are the only two possible monobenzyl isomers. The ortho/para ratio should be similar to that of phenol as there are two open ortho positions. However the actual ratio with 3,5-xylenol is 5.9/1. It may be that para alkylation compared with phenol is more hindered by two methyl groups than ortho alkylation is by one methyl and one hydroxy group. This seems logical since in the alkylation of phenol, ortho alkylation is subject to hindrance from one hydroxy and no methyls, whereas para alkylation is subject to no hindrance.

The melting point of the 4-benzyl-3,5-dimethylphenol was lower than that found by Buu-Hoi, Sy and Lejeune (61). More of this isomer was prepared by the cyclohexane-sulfuric acid method but after repeated recrystallizations of this latter sample, the melting point remained the same as that of the material prepared by the p-toluenesulfonic acid method. Spectra and mixed melting points showed the two samples of 4-benzyl-3,5-dimethylphenol to be identical. Spectra and mixed melting points also showed the samples of 4-benzyl-3,5-dimethylphenol to be a different compound than 2-benzyl-3,5-dimethylphenol. As there are no other possible monobenzyl isomers and the spectrum of 4-benzyl-3,5-dimethylphenol agrees with its assignment, the structure should be as indicated.

E. Alkylation of Phenol with Substituted Benzyl Alcohols

1. Alkylation of Phenol with p-Methylbenzyl Alcohol

When phenol in cyclohexane was alkylated with p-methylbenzyl alcohol in the presence of p-toluenesulfonic acid, the following products were formed:

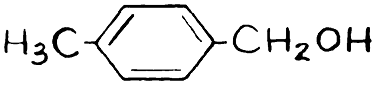


Possibly both of these isomers are new compounds, although Kindler (44) mentions the preparation of a (p-methylbenzyl) phenol in his patent. He does not specify which isomer, nor does he mention any physical data. As this material is one of a number of compounds claimed to have been prepared, it may be the paper invention of a patent attorney. The use of non-existent "typical examples" is well known in the patent art.

When the ortho and para benzyl isomers were solids, a mixed melting point was taken to prove that the two compounds were indeed different. In the reaction of p-methylbenzyl alcohol with phenol, both of the monobenzyl isomers were liquids. However, when phenyl urethanes of the two isomers were mixed, the depressed melting point clearly showed these two compounds to be different.

In the reaction of p-methylbenzyl alcohol with phenol the orientation possibilities are the same as with phenol. No possibility of meta substitution should exist as it does with the xylenols. However it is possible that substituents on the benzyl ring may affect the relative rates of ortho and para benzylation. That such an effect does occur is apparent in the high ortho/para ratio of 5.3/1. Alkylation of phenol with benzyl alcohol generally gives ortho/para ratios in the range of 3-4/1.

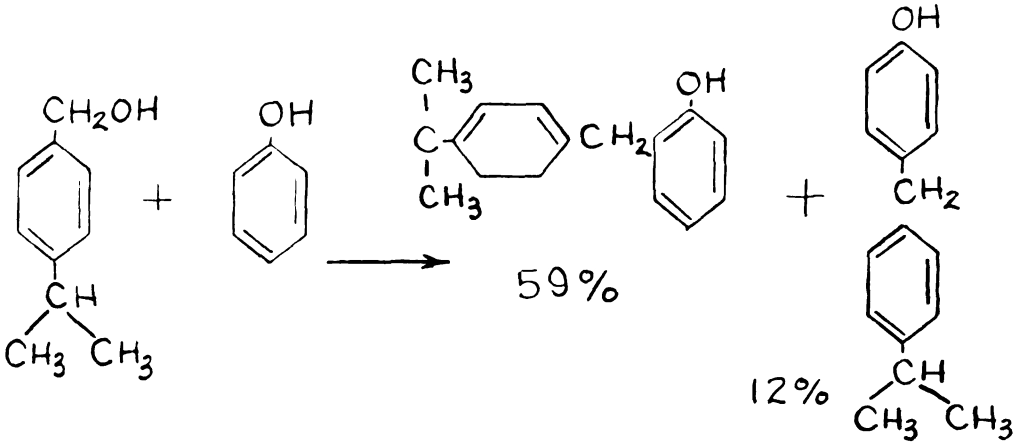
The methyl group on the benzyl ring of the alcohol



is an electron-releasing group. Kinetic studies on relative rates of benzylation in this work showed total alkylation was faster with p-methylbenzyl than with benzyl alcohol. Since total alkylation is faster, the rate of ortho alkylation must be increased, although the rate of para alkylation could be increased less than the ortho, remain the same as before, or be decreased.

2. Alkylation of Phenol with p-Isopropylbenzyl Alcohol

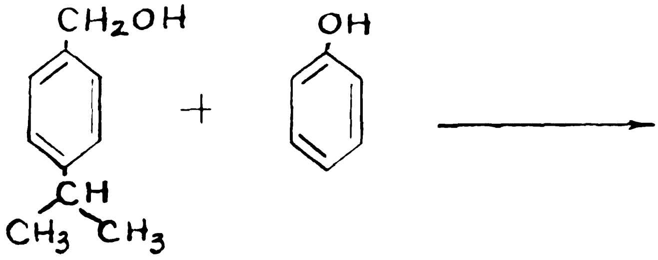
Alkylation of phenol with p-isopropylbenzyl alcohol in the presence of p-toluenesulfonic acid yields a high ratio of ortho to para isomer.



The ortho/para ratio is higher than in a similar reaction of benzyl alcohol and phenol. As the isopropyl group on the benzyl ring is electron-releasing, the rate of ortho benzylation may be accelerated by such an effect. The same high ortho/para ratio was also noticed in the reaction of p-methylbenzyl alcohol and phenol.

As there are no methyl groups present on the phenol ring, little if any meta isomer should be formed. None was detected. The remainder of the 29% yield is probably polybenzylated phenols.

Identification of the ortho and para isomers seems to offer no problems. However recrystallization of the 4-(p-isopropylbenzyl) phenol did not give sufficient pure material to be used in the preparation of a phenyl urethane derivative. Therefore an additional alkylation was carried out with a sulfuric acid catalyst.

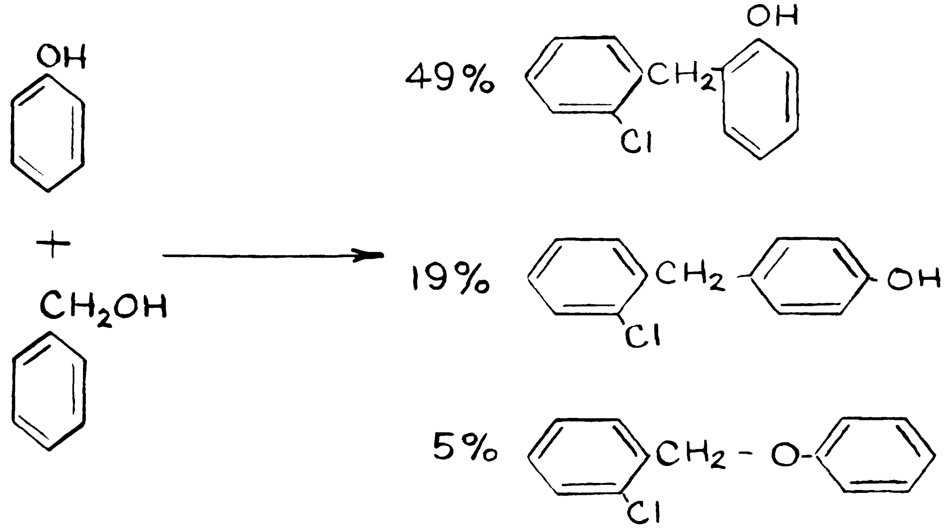


1.3/1 ratio of ortho/para isomers

Surprisingly enough, the tendency toward ortho alkylation is so strong with p-isopropylbenzyl alcohol that even with a sulfuric acid catalyst more ortho than para isomer is formed.

3. Alkylation of Phenol with o-Chlorobenzyl Alcohol

Alkylation of phenol with o-chlorobenzyl alcohol in the presence of p-toluenesulfonic acid yields the following products:



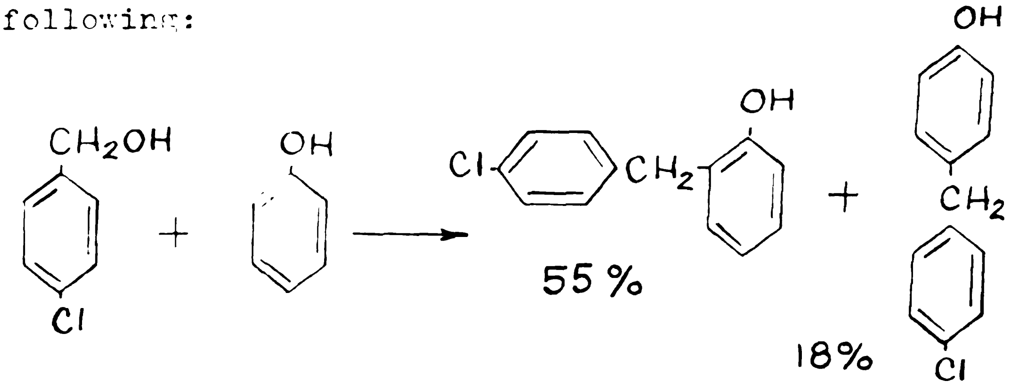
Total monobenzyl products amount to 73%, about the same percentage of monobenzyl product as found in the alkylation of phenol with o-methylbenzyl and p-iso propyl alcohols. However here the ratio of ortho to para isomers is much lower.

Chlorine on the benzyl ring has an electron-withdrawing effect and appears to hinder the rate of ortho alkylation. The ortho/para ratio is lower than found in the alkylation of phenol with benzyl alcohol. This same lower ortho/para ratio is found in the alkylation of phenol with p-chlorobenzyl, p-bromobenzyl, and 2,4-dichlorobenzyl phenols.

Huston and co-workers (8) found in the Claisen condensation of o-benzyl chloride with phenol that poorer yields of the ortho benzylated phenol were obtained than with benzyl chloride and phenol. They also found when 2-, 3-, and 4-chlorobenzyl chlorides were condensed with phenol in the presence of aluminum chloride ortho-benzylated product was formed only with the 2-benzyl chloride. Apparently in alkylation with a 2-chloro substituted agent, rate of both para and ortho alkylation is reduced. In the case of o-chlorobenzyl alcohol in the presence of p-toluenesulfonic acid, as reported here, the ortho and para alkylation rates must be retarded to the point where some (5%) of the ether is formed.

4. p-Chlorobenzyl Alcohol and Phenol

Alkylation of phenol with p-chlorobenzyl alcohol in the presence of p-toluenesulfonic acid yields the following:



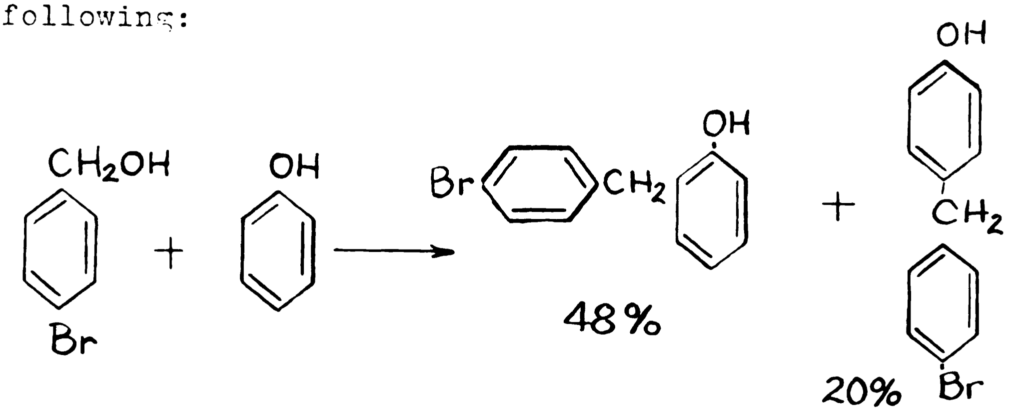
No ether was isolated in this reaction, although some had been found in the reaction of o-chlorobenzyl alcohol with phenol.

Under similar reaction conditions an ortho/para ratio of 3.5-4.0/1 would be realized with benzyl alcohol and phenol. Thus p-chlorobenzyl alcohol gives a lower 3.0/1 ratio, as do the rest of the halogen substituted benzyl alcohols.

Separation of ortho from para isomers by distillation works rather well for most of the alkylations carried out in this research. However 2-(p-chlorobenzyl) phenol is difficult to separate from 4-(p-chlorobenzyl) phenol by the type of distillation used. A similar difficulty was experienced with the separation of 2-(p-bromobenzyl) phenol and 4-(p-bromobenzyl) phenol. Calculation of isomer yields was carried out in both cases by isolation of the pure compounds and use of their spectra to analyze isomer content of the distillation fractions.

5. p-Bromobenzyl Alcohol and Phenol

Alkylation of phenol with p-bromobenzyl alcohol in the presence of p-toluenesulfonic acid yields the following:

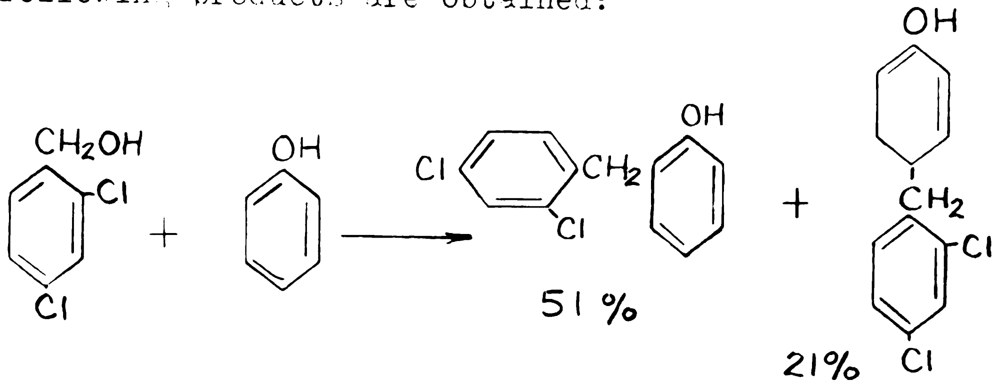


The ortho/para ratio of 2.4/1 is less than that found with p-chlorobenzyl alcohol (3.0/1). A p-Br substituent has only a slightly more positive sigma value (+0.232 compared to +0.226) than p-Cl, so that the difference in ratios is not all due to differences in electronic effects on the reaction rates.

The melting point of the 4-(p-bromobenzyl) phenol agrees with the value recorded by Wu, Guile, and Huston (60) for the high melting crystalline modification. The sample in this research was slowly recrystallized from more than the minimum amount of hexane necessary to dissolve the sample at reflux. Similar conditions are described by Wu, Guile, and Huston (60) for their preparation of the high melting modification. None of the low melting modification was obtained.

6. 2,4-Dichlorobenzyl Alcohol and Phenol

If phenol is alkylated with 2,4-dichlorobenzyl alcohol in the presence of p-toluenesulfonic acid the following products are obtained:



The ortho/para ratio of 2.5/1 is lower than found with benzyl alcohol and phenol and thus fits the general pattern found with halogen substituted benzyl alcohols.

As about 5% of an ether was believed to have been formed in the alkylation of phenol with o-chlorobenzyl alcohol, the distilled products in this experiment were carefully examined for the presence of an ether. There was no fraction in the ether range boiling below the 2-(2,4-dichlorobenzyl) phenol fraction. Therefore the infrared spectrum of this fraction was carefully examined for evidence of an ether impurity. There is a slight shoulder on the 8.0μ band at 8.15μ which might be due to a trace of ether. However as the 8.15μ ether band is an extremely strong one, there should not be more than a small amount present.

F. Relative Rate of Benzylation of Substituted Benzyl Alcohols

The relative rate of phenol benzylation was determined with six different benzyl alcohols. The rates with these alcohols fell in the following order:

p-iso-Pr $\rangle$ p-Me $\rangle$ H $\rangle$ p-Cl $\rangle$ o-Cl $\rangle$ 2,4-Cl

In general the greater the electron releasing ability of the substituent on the benzyl ring, the greater the rate of alkylation. The considerable decrease in rate of the ortho- over the para-chloro alkylation may be due to steric hindrance.

The following table shows the reaction rates as well as the ortho/para ratios for the six alcohols studied.

Table VI. Phenol Alkylation with Benzyl Alcohols

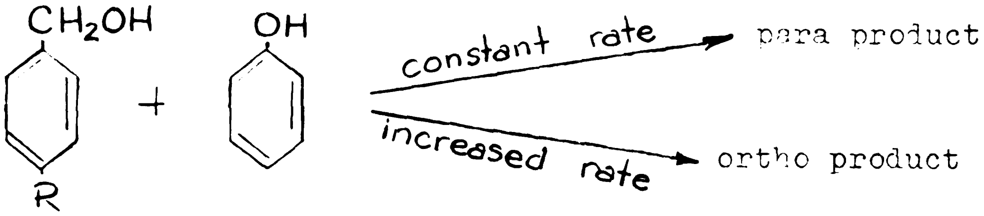
Benzyl alcohol	Reaction half-times min.	% Monobenzyl phenols	Ortho/para ratio	Hammett sigma function
p-isopropyl	26	71	4.8/1	-
p-methyl	32	68	5.3/1	-0.170
unsubstituted	36	(a)	(a)	0.000
p-chloro	47	73	3.0/1	+0.226
o-chloro	130	68	2.5/1	-
2,4-dichloro	254	73	2.5/1	-

(a) The monobenzyl yields and ortho/para ratios were not determined for this particular experiment. However, judging from similar experiments with benzyl alcohol the monobenzyl yield should be about 70% and the ortho/para ratio about 3.5-4.0/1.

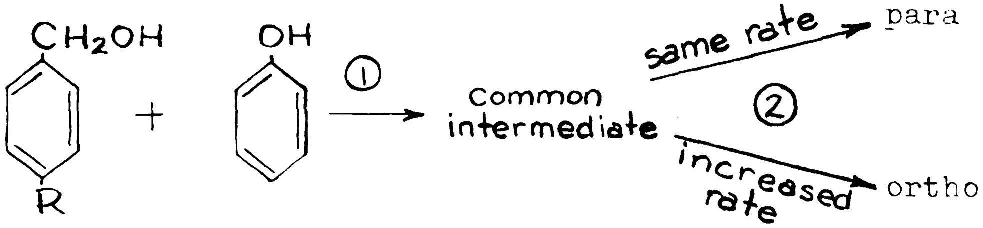
It is seen that the monobenzyl yields are all about equivalent, so the experiments can be compared on the basis of their reaction rates and ortho/para ratios.

The reaction half times vary from 26 minutes to 254 minutes, whereas the ortho/para ratios vary only from 2.5/1 to 5.3/1. Therefore the rate of either ortho or para alkylation does not appear to remain constant while the total rate changes. However, the reactions with o-chloro- and 2,4-dichlorobenzyl alcohols are possibly subject to steric hindrance. If this is true, there is a good correlation between the reaction rates of the other four benzyl alcohols and their ortho/para ratios. The faster the reaction rate, the larger the ortho/para ratio.

This correlation between reaction rate and ortho/para ratios could mean the rate of para alkylation is constant while the rate of ortho alkylation increases. The reaction may proceed as follows:



or the reaction could go through a common intermediate:



In this latter case step one could be subject to steric hindrance from ortho substituents and cause the large decrease in rate noted for o-chloro- and 2,4-dichlorobenzyl alcohols. It should also be noted for the latter two alcohols that their ortho/para ratios are substantially the same as that of p-chlorobenzyl alcohol, even though the rates are much slower. This means that it must be step one which is subject to steric hindrance.

Pratt, Preston, and Draper (12) found that in the alkylation of anisole by substituted benzyl alcohols, the reaction rates varied with the substituent on the alcohol. The rates decreased in the following order:

$$CH_3O > CH_3 > H > Cl$$

They also found that p-nitrobenzyl alcohol reacted very sluggishly. Their reaction rates decreased with decreasing ability of the substituent to release electrons. The same order was found to hold true in this research.

Pratt and Erickson (100) studied the etherification of triphenylcarbinol and benzhydrol with n-butyl alcohol in the presence of p-toluenesulfonic acid. They found an increase in the electron-releasing ability of the para substituent of a benzyl alcohol would increase the rate of etherification.

The N-alkylation of anilines by benzyl alcohols in the presence of activated nickel and sodium benzylate was studied by Pratt and Frazza (101). They found the reaction rate decreased with decreasing ability to release electrons. The reverse order was found to hold true with para-substituents on the anilines.

It has also been shown (102) that the rearrangement rates of alkyl p-X-phenyl ethers may be correlated by Hammett's equation using σp^+ constants. The rate decreases as sigma becomes more positive. Again this is the same order as found in the present research.

Thus the variation in reaction rates is about what may be expected from a study of related work in the literature.

G. Scope of the Acid-Catalyzed Ortho Alkylation

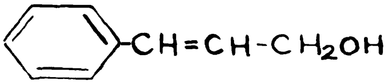
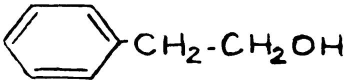
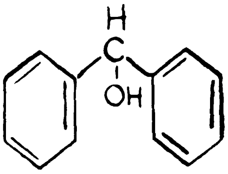
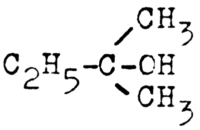
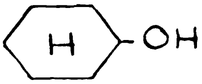
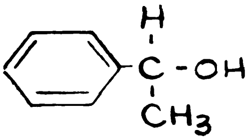
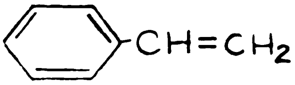
1. Phenol and Various Alkylating Agents

A number of alkylating agents were refluxed in cyclohexane in the presence of phenol and p-toluenesulfonic acid.

In general, the alkylating agent should be a benzyl type alcohol, vinylog of a benzyl alcohol, or an olefin derived from a benzyl alcohol, in order for alkylation to take place under these conditions.

The results are listed in the following table.

Table VII. Phenol and Various Alkylating Agents

Alkylating agent	Structure	Results
Cinnamyl alcohol		Polymeric products
2-Phenylethyl alcohol		No reaction
Propargyl alcohol	$HC\equiv C-CH_2OH$	No reaction
Benzhydrol		Monobenzyl products
tert-Amyl alcohol	 $C_2H_5-\overset{CH_3}{\underset{CH_3}{C}}-OH$	p-tert-amylphenol
Cyclohexanol		No reaction
1-Phenylethyl alcohol		Monobenzyl products including 2(1-phenylethyl) phenol
Styrene		Monobenzyl products

If cinnamyl alcohol were added very slowly and the acid concentration made very low, it might be possible to isolate alkylated phenolic products.

Benzhydrol has a very fast reaction rate and yields products boiling in the monobenzhydryl range. However, benzhydryl chloride has been found by Curtin, Crawford, and Wilhelm (84) to yield para-substituted products with sodium phenoxide. The reaction of benzhydrol with phenol should be investigated further.

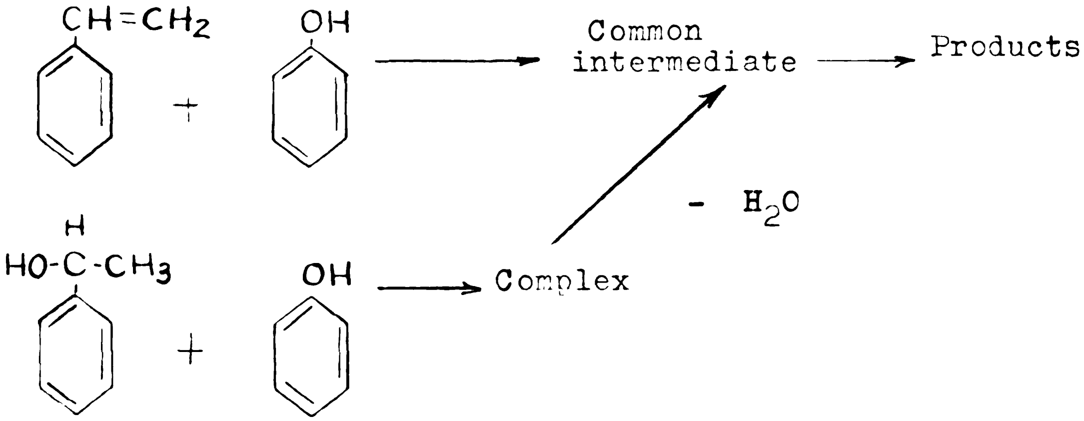
Tertiary alcohols or tertiary halides give almost exclusively para-substituted phenols with most acid catalysts since they very readily form carbonium ions. This tendency toward para alkylation is so strong that p-tert-amyl phenol was the main product when tert-amyl alcohol was used as an alkylating agent. Tert-amyl alcohol, rather than tert-butyl alcohol, was chosen for this experiment as it has a higher boiling point than tert-butyl alcohol and was less likely to be lost by distillation during reaction.

It would be expected that 1-phenylethyl alcohol would give good yields of ortho product because it is a homologue of benzyl alcohol. An ortho/para ratio of 2.1/1, lower than with benzyl alcohol, was found for the phenylethylated products. Apparently 1-phenylethyl alcohol more readily forms carbonium ions to yield para alkylated products than does benzyl alcohol.

Although the monostyrenated phenol fractions were not identified, it appears from their boiling ranges that fraction 2 would be 2-(1-phenylethyl) phenol and fraction 4 would be 4-(1-phenylethyl) phenol. If this is so, then the following comparison can be made:

Alkylating agent	g. ortho	g. para	Ortho/para ratio
1-Phenylethyl alcohol	50.7	24.0	2.1/1
Styrene	49.0	24.7	2.0/1

This close agreement of results suggests that both alkylations might proceed through the same intermediate:



2. Benzyl Alcohol and Various Substrates

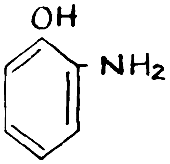
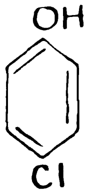
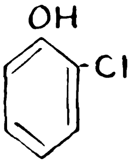
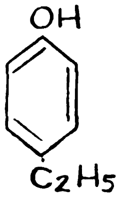
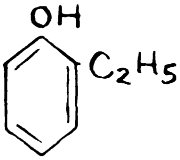
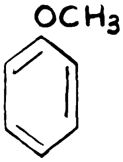
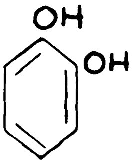
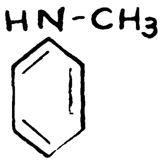
A number of nucleophilic substrates were refluxed in cyclohexane in the presence of benzyl alcohol and p-toluenesulfonic acid.

In general, phenols with alkyl, halo, and hydroxy groups will undergo alkylation by benzyl alcohol. Although not tested, it is felt that a nitro group would make the aromatic nucleus more difficult to alkylate. Phenolic ethers will also undergo benzylation as expected.

Aromatic amino groups do not themselves react and apparently inhibit the reactivity of adjacent hydroxy groups. Thiophenols are not alkylated under these conditions.

Results are listed in the following table.

Table VIII. Benzyl Alcohol and Various Substrates

Nucleophile	Structure	Results
o-Aminophenol		No reaction
p-Chlorophenol		2-benzyl-4-chloro phenol
o-Chlorophenol		Monobenzyl products
p-Ethylphenol		2-benzyl-4-ethyl phenol
o-Ethylphenol		Monobenzyl products
Anisole		Monobenzyl products
Catechol		Monobenzyl products
Thiophenol		No reaction
N-Methyl aniline		No reaction

The benzylation of anisole appears to give a mixture of isomers which boils closer together than do the benzylated phenols. This is expected since the lower boiling point of ortho-benzylphenol, as compared with para-benzylphenol, is due to the interference of the ortho-benzyl group with intermolecular hydrogen bonding of the OH groups.

Perhaps the isomeric mixture of benzylated anisoles could be determined by demethylation to yield mixed benzylphenols which could then be separated by distillation. Alternatively, the pure methyl ethers of ortho- and para-benzylphenols could be made by methylation of the phenols. The spectra of these pure ethers could be used as standards for the determination of relative amounts of ortho- and para-benzylanisoles.

In the benzylation of catechol, if fraction 2 is the 3-benzyl isomer and fraction 4 is the 4-benzyl, the ortho/para ratio would be 1.8/1. Such a result would suggest that catechol is more susceptible than phenol to para alkylation. However the presence of two adjacent hydroxyl groups might sterically interfere with the path of the ortho reaction.

Thiophenol is not alkylated under these conditions although this in no way precludes the fact that a reaction may take place if conditions were altered. Thiophenols have a greater tendency to form thio ethers than phenols do to form ethers. In fact, thiophenol is very difficult to C-alkylate but instead usually forms S-alkylation products. One of the few exceptions is recorded by Laufer (103) who reacted thiophenol with ethylene, propylene, 1-butene, 2-butene, 1-pentene, cyclopentene, cyclohexene, and cyclopropane. He obtained o-alkylthiophenols, 2,6-dialkylthiophenols, and alkyl aryl sulfides. No meta alkylation and little or no para alkylation took place. Aluminum chloride and certain other Lewis acids were used as catalysts at temperatures below 30°C. and in some cases as low as -70°C.

Neither N-methyl aniline nor o-aminophenol was benzylated in refluxing cyclohexane with a p-toluenesulfonic acid catalyst. However, it is felt that conditions might be found under which ortho alkylation would take place. The literature contains scattered reports of similar reactions with amines. Kolka, Ecke, and Closson (104) reported the ortho alkylation of aniline by olefins using an aluminum anilide catalyst. This reaction is analogous to the reaction of Kolka et al. (97) where phenols are ortho alkylated by olefins using an aluminum phenoxide catalyst. Hart and Kosak (105) reported the ortho alkylation of aniline with styrene in the presence of aniline hydrochloride.

H. Mechanism of Ortho Alkylation

Much additional work is needed on this reaction before a mechanism can be established. Reaction rates should be studied, kinetic orders established, the influence of substituents of both alcohol and phenol studied, and possible intermediates investigated. This present work was concerned largely with the discovery of a new synthetic tool, determination of favorable reaction conditions for it, and an investigation of the scope of the reaction.

The influence of substituents on the benzyl alcohol on reaction rate was studied, but such a study helps to predict for what type of aromatic alcohols this reaction will be suitable, rather than establishes a mechanism. It was shown that alcohols having electron-releasing substituents should give the best yields of ortho isomers.

In another instance a benzylation of phenol was stopped when 71% of the water had been removed and the product examined for dibenzyl ether or benzyl phenyl ether as intermediates in the reaction. Neither was found.

In a further experiment benzyl phenyl ether was rearranged in the presence of p-toluenesulfonic acid and the products determined. The ortho/para ratio of 1.2/1 is much lower than obtained in alkylation of phenol with benzyl alcohol. However, in this case a better reaction method may have been to add the benzyl ether slowly to

a cyclohexane solution containing p-toluenesulfonic acid and excess phenol.

Alkylation of one mole of phenol with 0.5 mole (equivalent to 1.0 mole benzyl alcohol) dibenzyl ether gave an ortho/para ratio of 2.7/1. This is somewhat lower than that obtained in most benzylations of phenol, however higher ratios may have been obtained if an excess of phenol were used.

Although very little work has been done to elucidate a mechanism, it is possible to write one for the reaction with the understanding that such a mechanism is tentative.

This mechanism should explain certain facts:

1. Why the ortho position is favored over the para position by more than a 2:1 statistical factor.

2. Why non-polar solvents favor the production of the ortho isomers, whereas polar solvents inhibit this reaction.

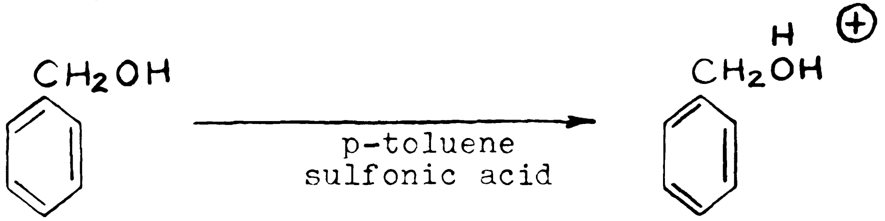
3. Why a high temperature method is possible with excess phenol as the solvent. Or, to phrase it another way, why the ortho-alkylation is dependent on the concentration of phenol.

4. Why the rate of total alkylation is subject to steric hindrance (as found with o-chloro- and 2,4-dichlorobenzyl alcohols).

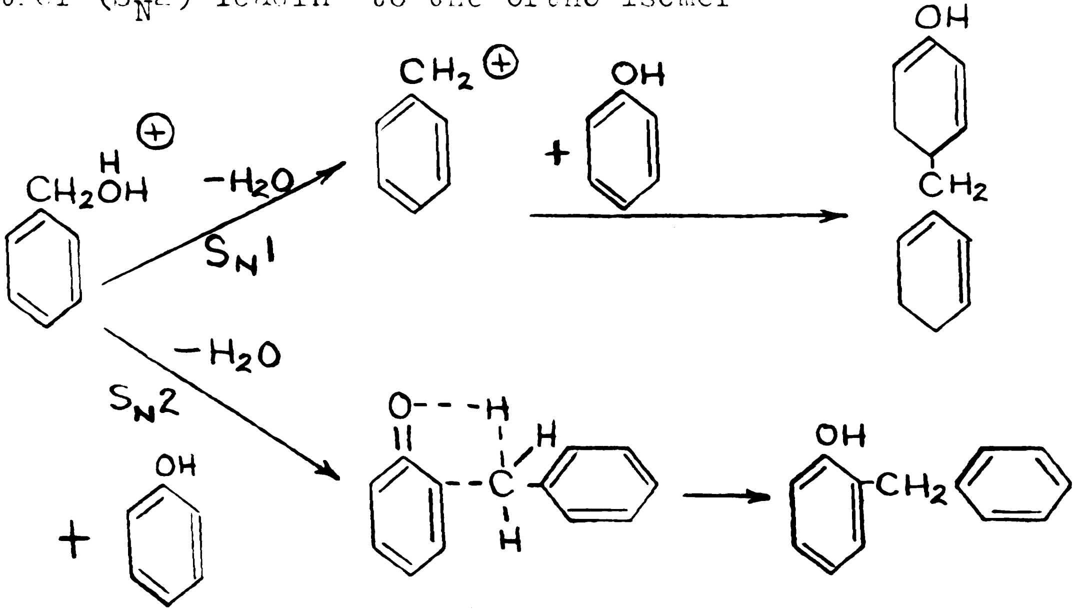
5. Why the rate of ortho-alkylation is enhanced over para-alkylation by electron-releasing substituents on the benzyl alcohol.

A plausible mechanism would be the following:

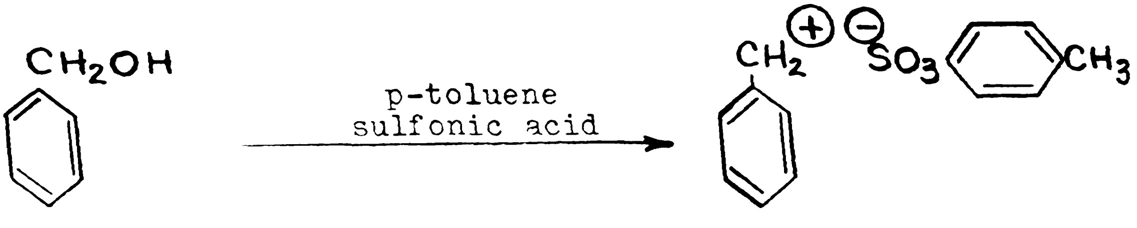
A molecule of benzyl alcohol is protonated by the acid catalyst



The protonated alcohol then reacts by two different paths, one (S_N1) path leading to the para isomer and the other (S_N2) leading to the ortho isomer



The mechanism could be written so that the primary intermediate is an ion pair containing the acid.



Despite the exact nature of the common intermediate it seems very reasonable to assume that it then reacts by two paths (S_N1) and (S_N2) as shown to give rise to both ortho and para isomers.

The mechanism of this reaction and the nature of the intermediates should be further investigated.

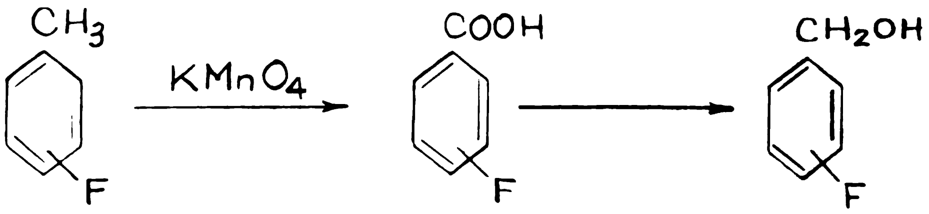
I. Extensions of Present Work

There are a number of areas in which this work could be extended:

1. Synthesis

a. Alkylating agents

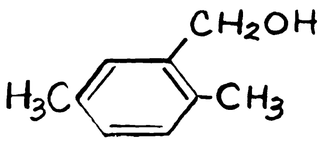
The alkylation of phenols with fluorobenzyl alcohols has never been studied. Such an area would be a logical extension of the work on the chloro- and bromobenzyl alcohols. The fluorobenzyl alcohols are readily accessible via the fluorotoluenes



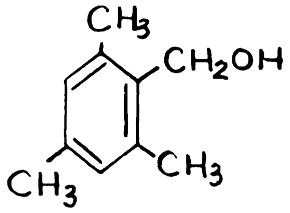
The present method of alkylation using mild acid conditions for catalysis should be investigated for very active aromatic alcohols, some of which undergo decomposition under acidic conditions. Alkylation with cinnamyl alcohol should be reinvestigated. In addition alkylation with the following alcohols should be studied: anisyl alcohol, furfuryl alcohol, and 1,1-dimethylbenzyl alcohol.

As electron-releasing groups are placed on the benzyl alcohol, both the reaction rates and the ortho/

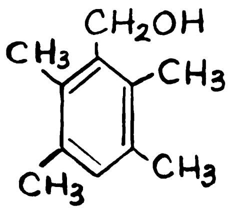
para ratios increase. The following types of alkylating agents should be of interest:



from p-xylene



from mesitylene



from durene

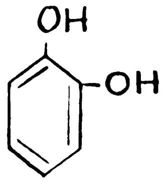
and also allyl type alcohols

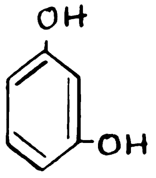
$$R-CH=CH-CH_2OH$$

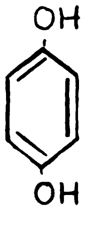
which are high boiling enough not to co-distill with the water during reaction in cyclohexane.

b. Phenols

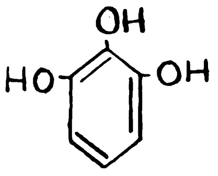
Of interest would be the alkylation of dihydroxy phenols





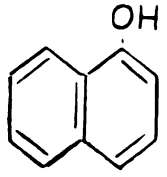


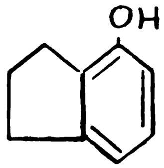
and trihydroxy compounds such as pyrogallol



which are sensitive to alkaline oxidation and therefore not too suitable for benzylation by the Claisen method.

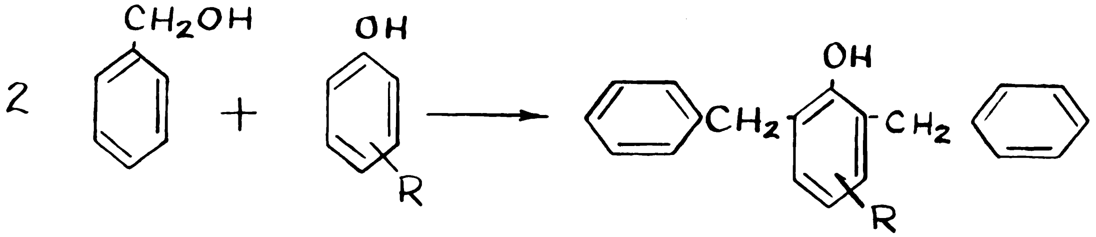
The alkylation of other aromatic phenols such as naphthols and indanols should also be studied.





c. Di-benzylated compounds

The preparation of 2,6-dibenzyl phenols should occur easily with a p-toluenesulfonic acid catalyst.



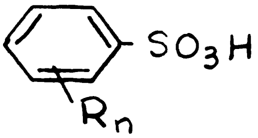
In this way products would be obtained which otherwise would take two separate alkylation steps by the Claisen method.

2. Catalyst

Additional acids of the sulfonic acid type should be investigated as catalysts. One type of interest would be aliphatic and alicyclic sulfonic acids

$$R\text{-}SO_3H$$

Another type would be additional aromatic sulfonic acids

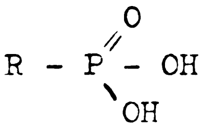


where the R's may be alkyl, halo or mixtures.

Other types would be benzene polysulfonic acids, naphthalene sulfonic acids, and phenanthrene and anthracene sulfonic acids.

Also of interest would be sulfonic acids with heterocyclic nuclei.

The phosphonic acids

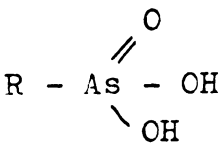


$$R - P(=O)(OH) - OH$$

where R is alkyl, cycloalkyl, aromatic or heterocyclic, should also be investigated as mild acid catalysts for the ortho alkylation of phenols.

Other phosphorus acids such as hypophosphorous acid and polyphosphoric acid may be applicable as they are more soluble in organics than is phosphoric acid.

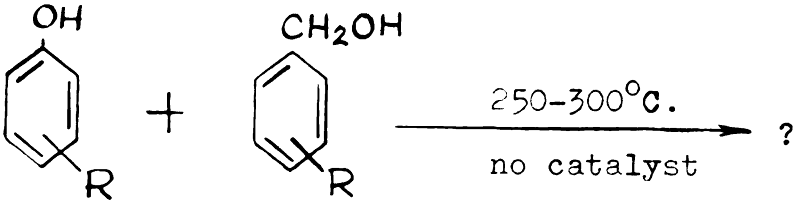
Arsonic acids should also be investigated



$$R - As(=O)(OH) - OH$$

3. Reaction Conditions

It has been shown that benzyl alcohol will not alkylate phenol at 168-173°C. without a catalyst. As this is very close to the boiling point of phenol the temperature of such a reaction mixture could not be raised much higher at atmospheric pressure. However, if a higher boiling phenol and a higher boiling alcohol were used, a reaction mixture could be heated to much higher temperatures:

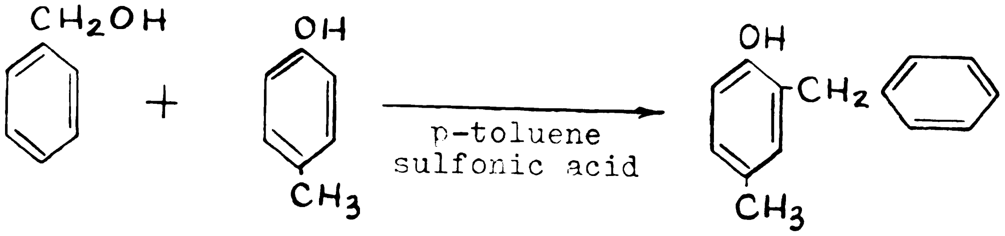


It would be interesting to see if thermal alkylation takes place under such conditions.

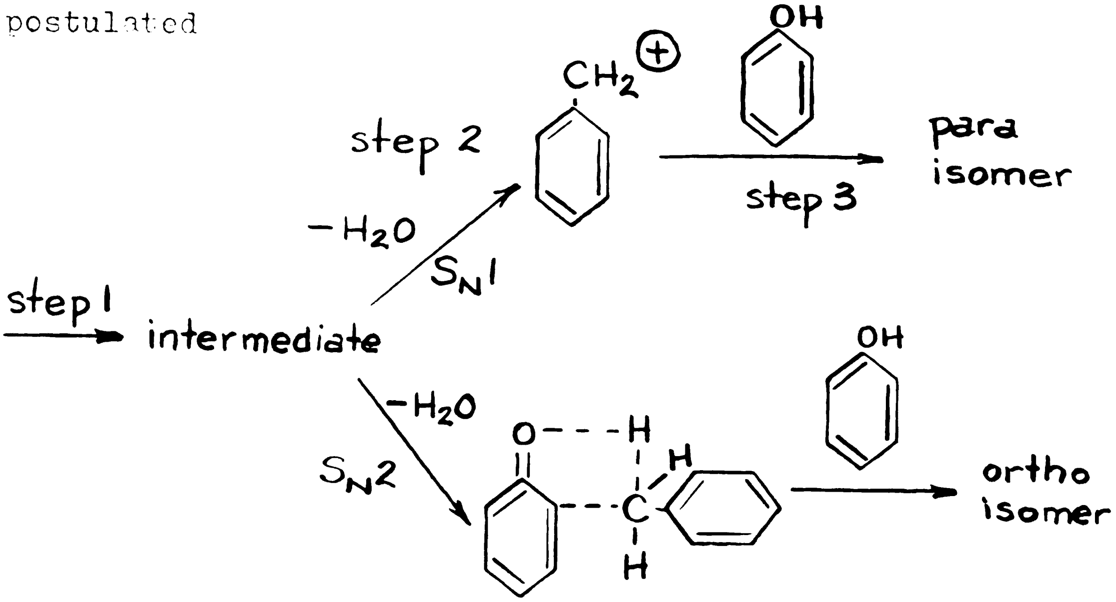
It would also be of interest to investigate very small amounts of catalyst (0.0001 mole) in the 200°C. range to see if very mild acid conditions would give very high ortho/para ratios.

4. Kinetics and Mechanism

In the benzylation of p-cresol only ortho alkylation can take place

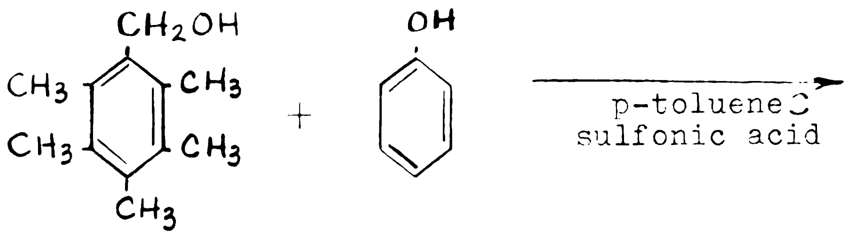


However if the mechanism of alkylation for phenol is as postulated



and water is removed in step 2, then in the alkylation of p-cresol some ortho alkylation could take place via the carbonium ion and the rate of formation of water would not give the S_N2 rate.

Since electron-releasing groups on the aromatic alcohol enhance the rate of ortho alkylation perhaps the following reaction would be of value:



This reaction may give almost all ortho isomer and thus the rate of water formation may be a close approximation of the rate of the S_N2 reaction. The presence of the five methyl groups on the benzyl alcohol would prevent self-alkylation. If the kinetics of the ortho alkylation were known, the order of reaction could be determined.

It would also be of interest to extend the series of para-substituted benzyl alcohols used in this research to include p-CH_3O, p-NO_2, and other substituents to determine their reaction rates. Also of interest would be the influence of phenol substituents on the rate of alkylation.

V. SUMMARY

1. Phenol was alkylated with benzyl alcohol in the presence of p-toluenesulfonic acid to yield 3.5-4.0 parts o-benzylphenol for each part of p-benzylphenol.
2. Good yields of the ortho-benzyl isomers were obtained in the acid-catalyzed alkylations of ortho-, meta-, and para-cresols with benzyl alcohol.
3. Benzyl alcohol was used for the acid-catalyzed ortho alkylation of five of the six isomeric xylenols. In the case of 2,6-xylenol, ortho alkylation was not possible and both the 3- and 4-benzyl products were formed.
4. Substituted benzyl alcohols were used for the acid-catalyzed ortho alkylation of phenol. The ortho/para ratios (4.8-5.3) were highest for alcohols containing electron-releasing groups such as p-methyl and p-isopropyl. Ortho/para ratios for alcohols containing halogen (electron-withdrawing) groups were in the order of 2.5-3.0/1.
5. The reaction rate of substituted benzyl alcohols

was determined by measuring the amount of water removed per unit time. Benzyl alcohols containing electron-releasing groups reacted faster than did benzyl alcohol. Alcohols containing electron-withdrawing groups reacted more slowly than did benzyl alcohol. Alcohols containing o-substituents reacted very slowly.

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APPENDIX I

DATA AND GRAPHS FOR KINETIC RUNS OF SUBSTITUTED BENZYL ALCOHOLS

Rate of Phenol Alkylation with p-iso-Propylbenzyl Alcohol

Time in minutes	Ml. of water distilled
2	0.9
7	2.0
13	3.2
15	3.8
19	4.9
24	6.1
28	6.9
33	7.9
38	8.5
46	9.5
55	10.3
63	10.6
71	10.9

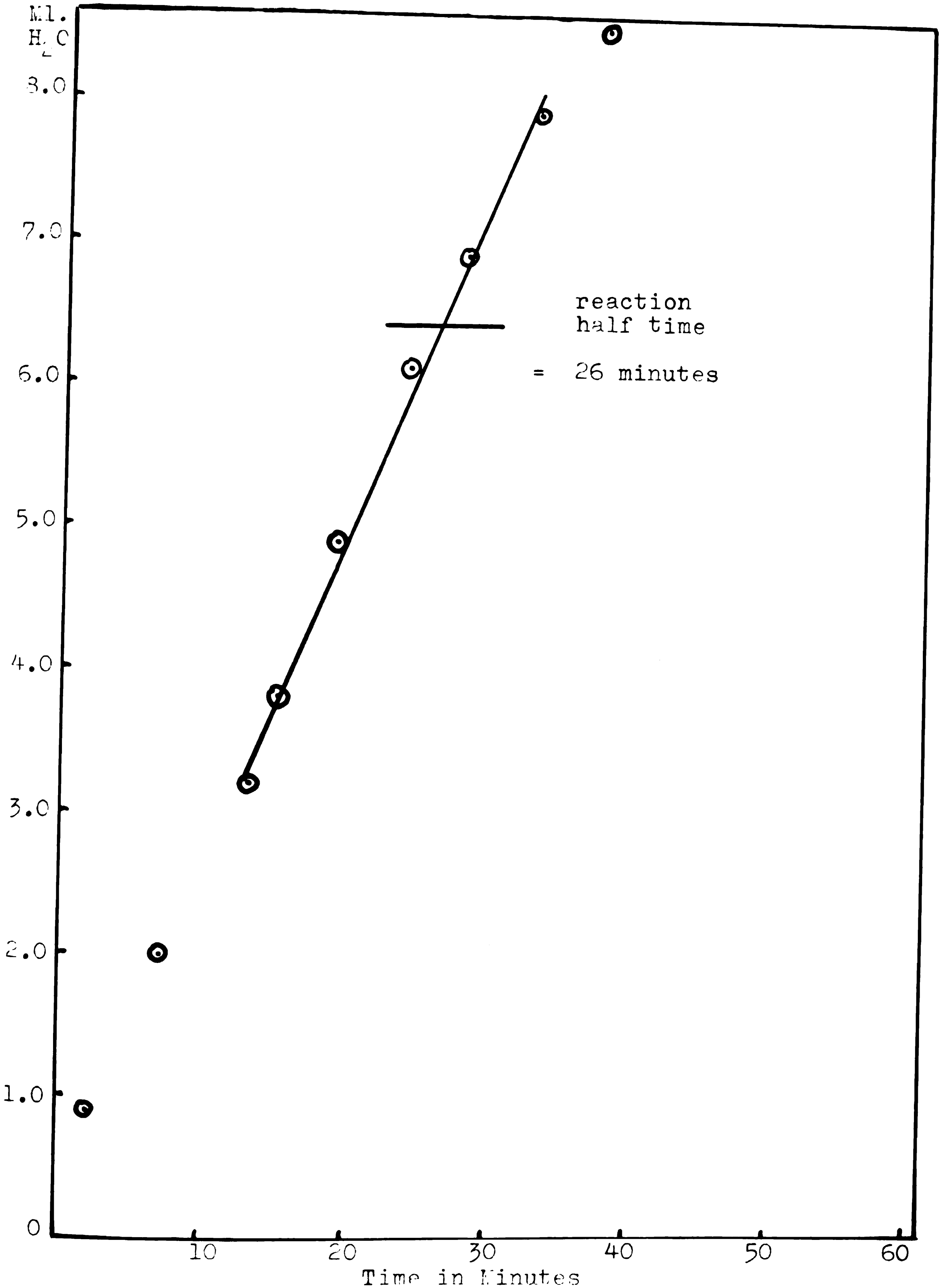


Fig.1. Alkylation of phenol by o-iso-propylbenzyl alcohol

Rate of Phenol Alkylation with p-Methylbenzyl Alcohol

Time in minutes	Ml. of water distilled
4	0.6
8	1.5
13	2.5
18	3.7
22	4.7
25	5.3
32	6.5
37	7.5
41	8.1
47	9.0
52	9.5
58	10.1
62	10.6
68	10.9

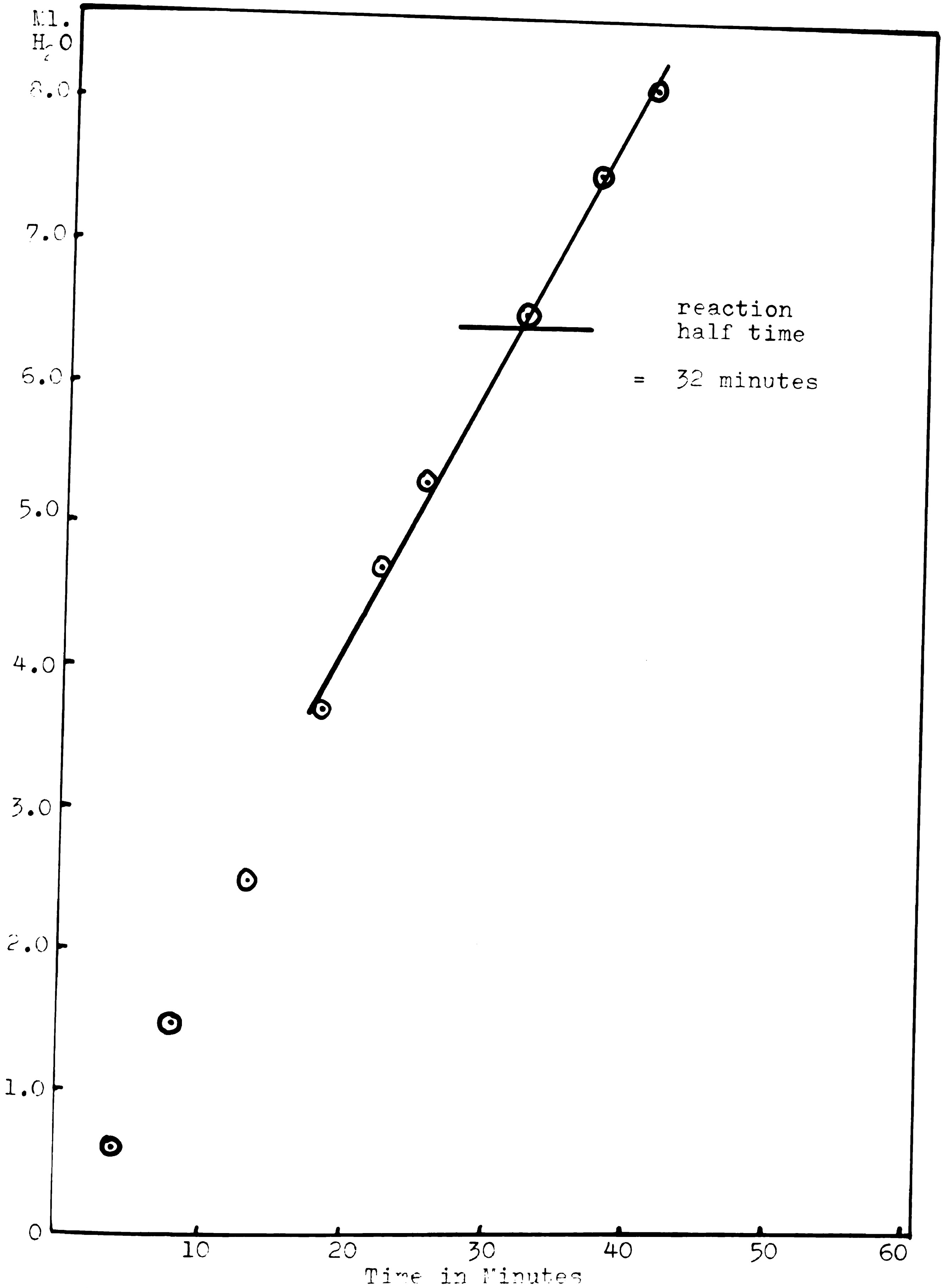
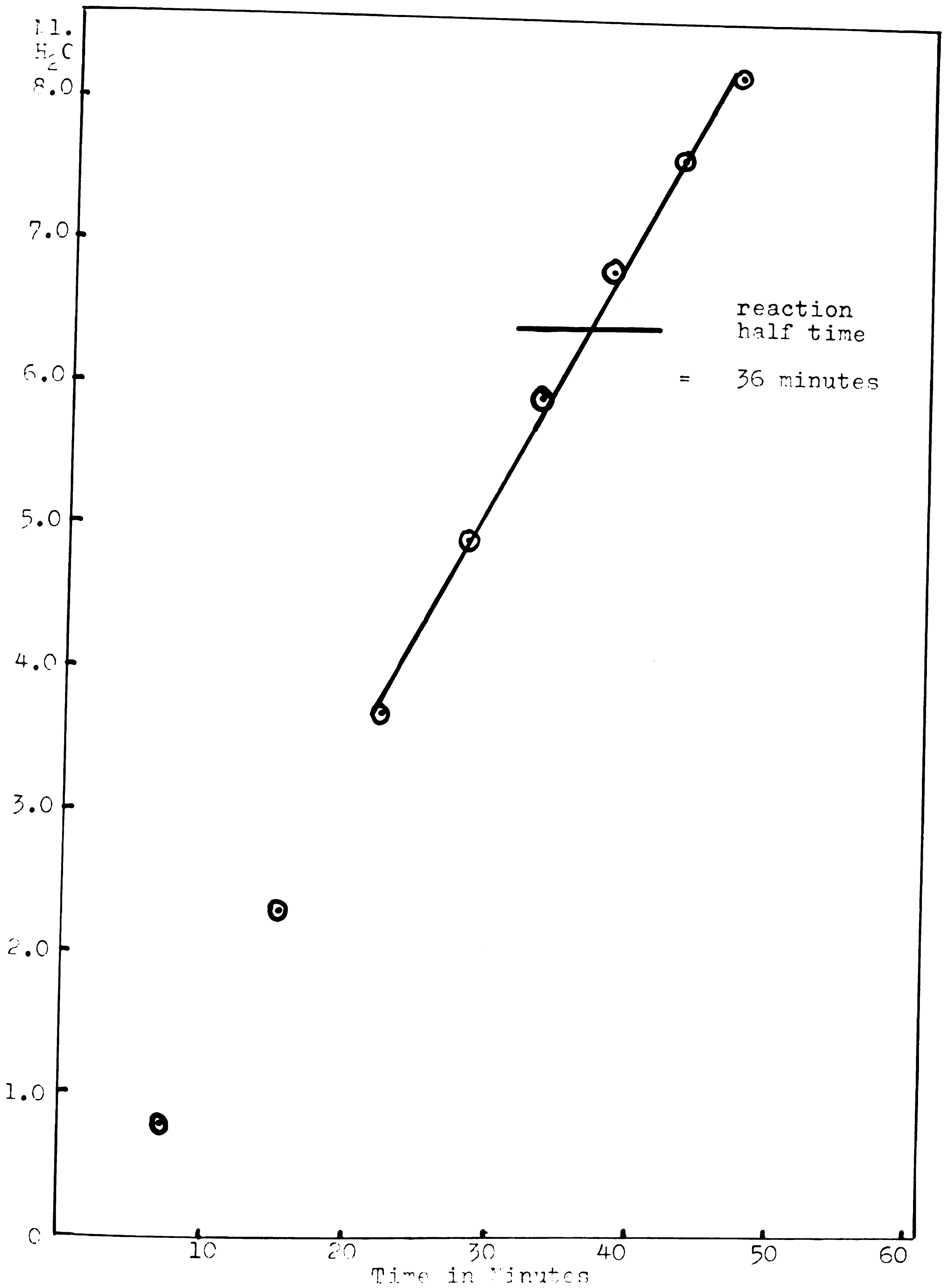


Fig.2. Alkylation of phenol by p-methylbenzyl alcohol

Rate of Phenol Alkylation with Benzyl Alcohol

Time in minutes	Ml. of water distilled
7	0.8
15	2.3
22	3.7
28	4.9
33	5.9
38	6.8
43	7.6
47	8.2
52	8.7
62	9.7
72	10.2
92	10.6
102	10.9



reaction
half time

= 36 minutes

Fig.7. Alkylation of phenol by benzyl alcohol

Rate of Phenol Alkylation with p-Chlorobenzyl Alcohol

Time in minutes	Ml. of water distilled
4	0.5
8	1.0
17	2.2
22	2.9
31	4.1
37	5.0
43	6.1
52	7.2
60	8.1
66	8.8
71	9.3
77	10.0
87	10.5
97	10.8

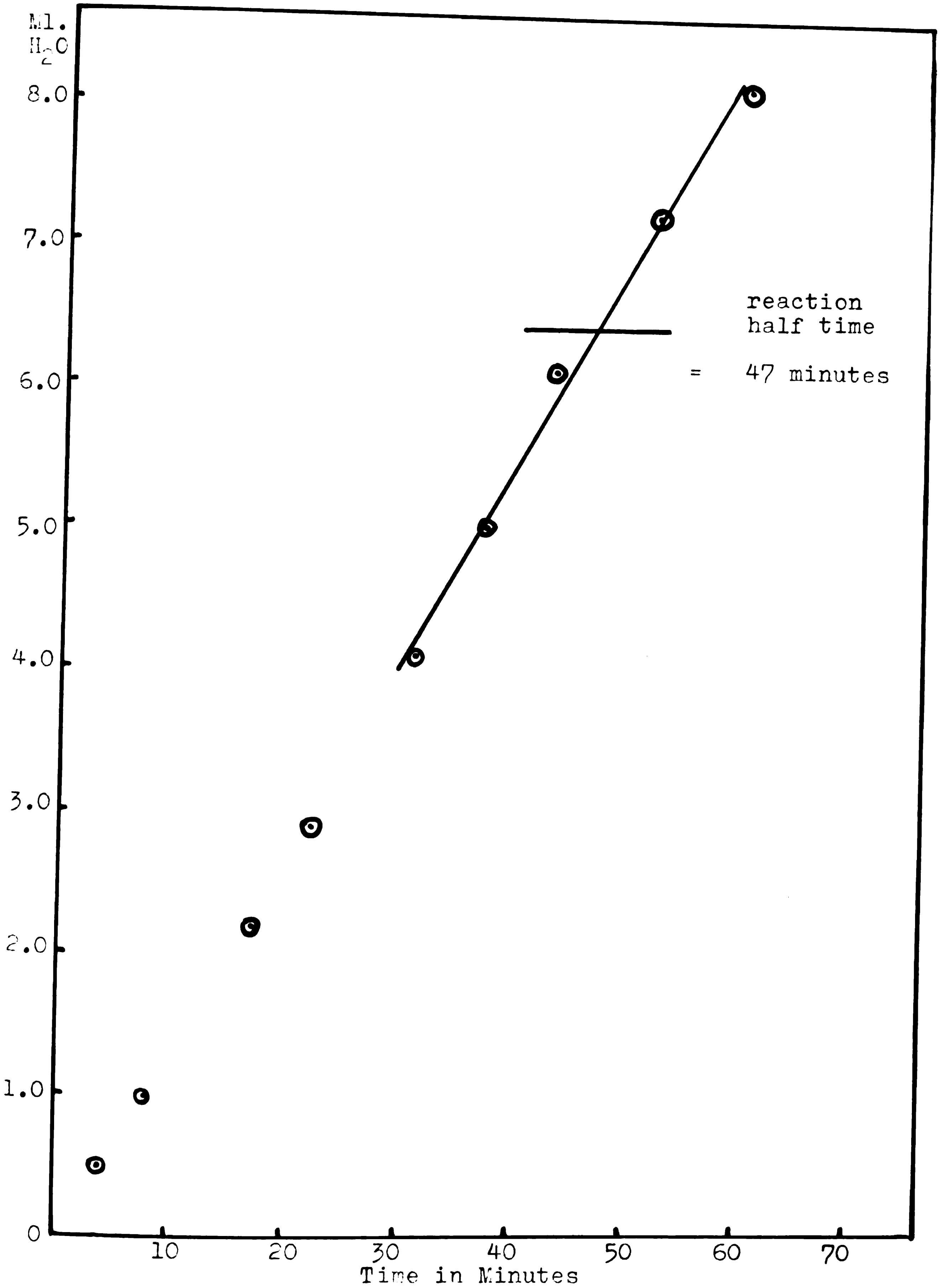


Fig.4. Alkylation of phenol by p-chlorobenzyl alcohol

Rate of Phenol Alkylation with o-Chlorobenzyl Alcohol

Time in minutes	Ml. of water distilled
4	0.4
10	1.2
18	1.8
26	2.4
43	3.1
64	3.9
87	4.8
115	5.5
134	6.6
146	7.0
158	7.3
267	10.9

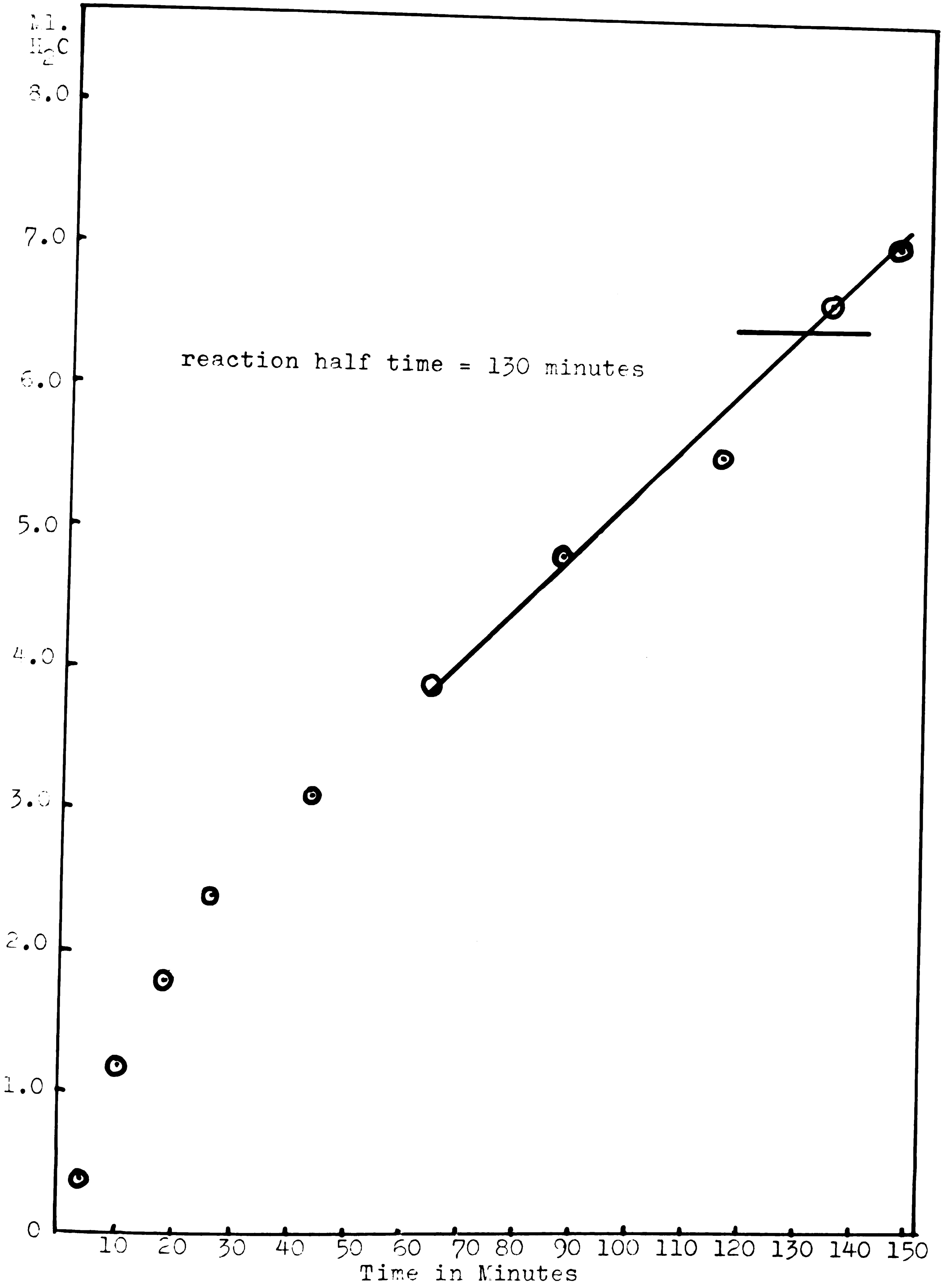


Fig.5. Alkylation of phenol by o-chlorobenzyl alcohol

Rate of Phenol Alkylation with 2,4-Dichlorobenzyl Alcohol

Time in minutes	Ml. of water distilled
8	0.6
17	1.1
34	1.8
59	2.5
77	2.9
107	3.5
133	4.0
152	4.4
182	5.1
220	5.8
327	8.0
355	8.4
380	8.8
434	9.5
517	10.3
607	10.9

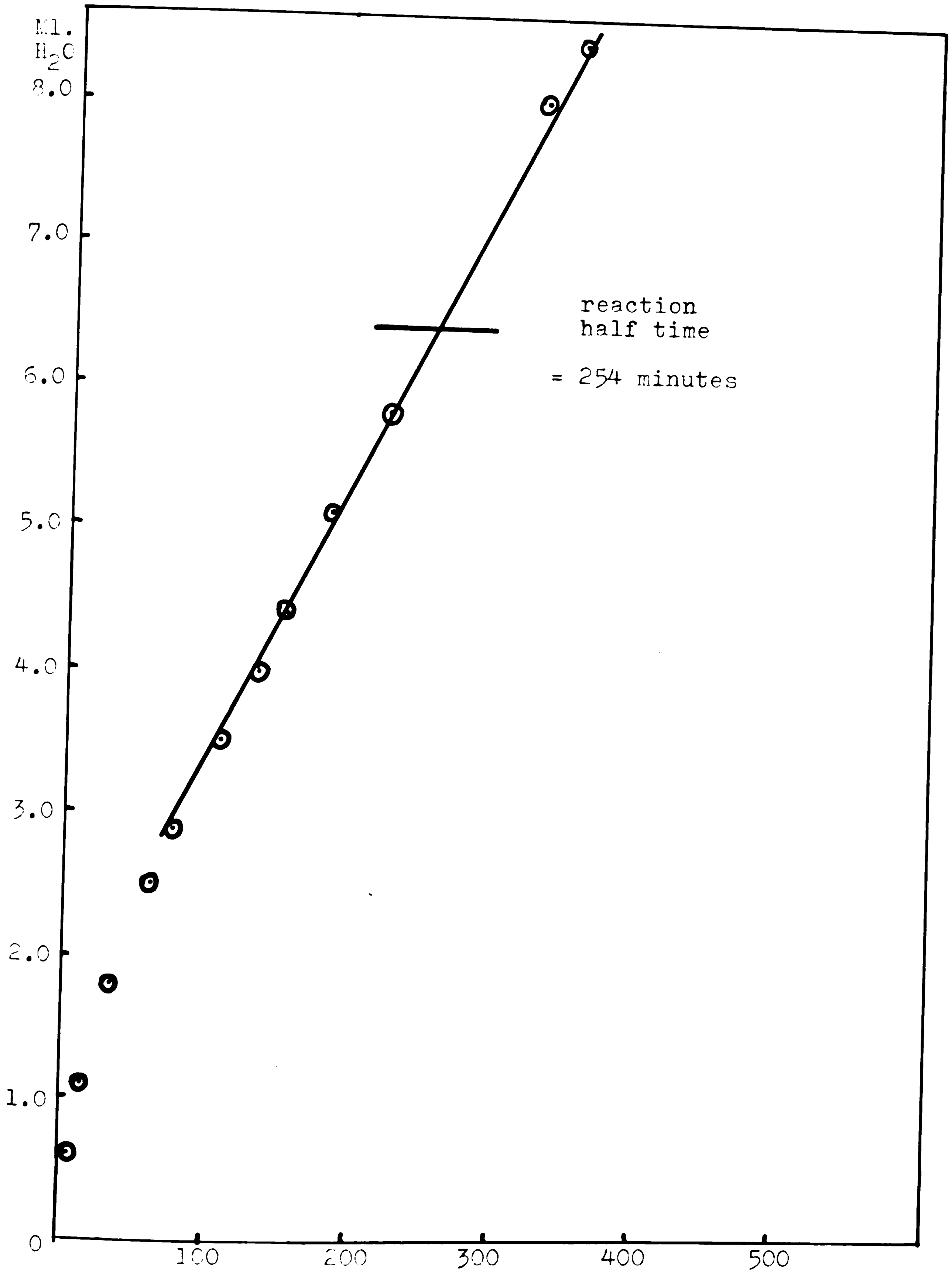
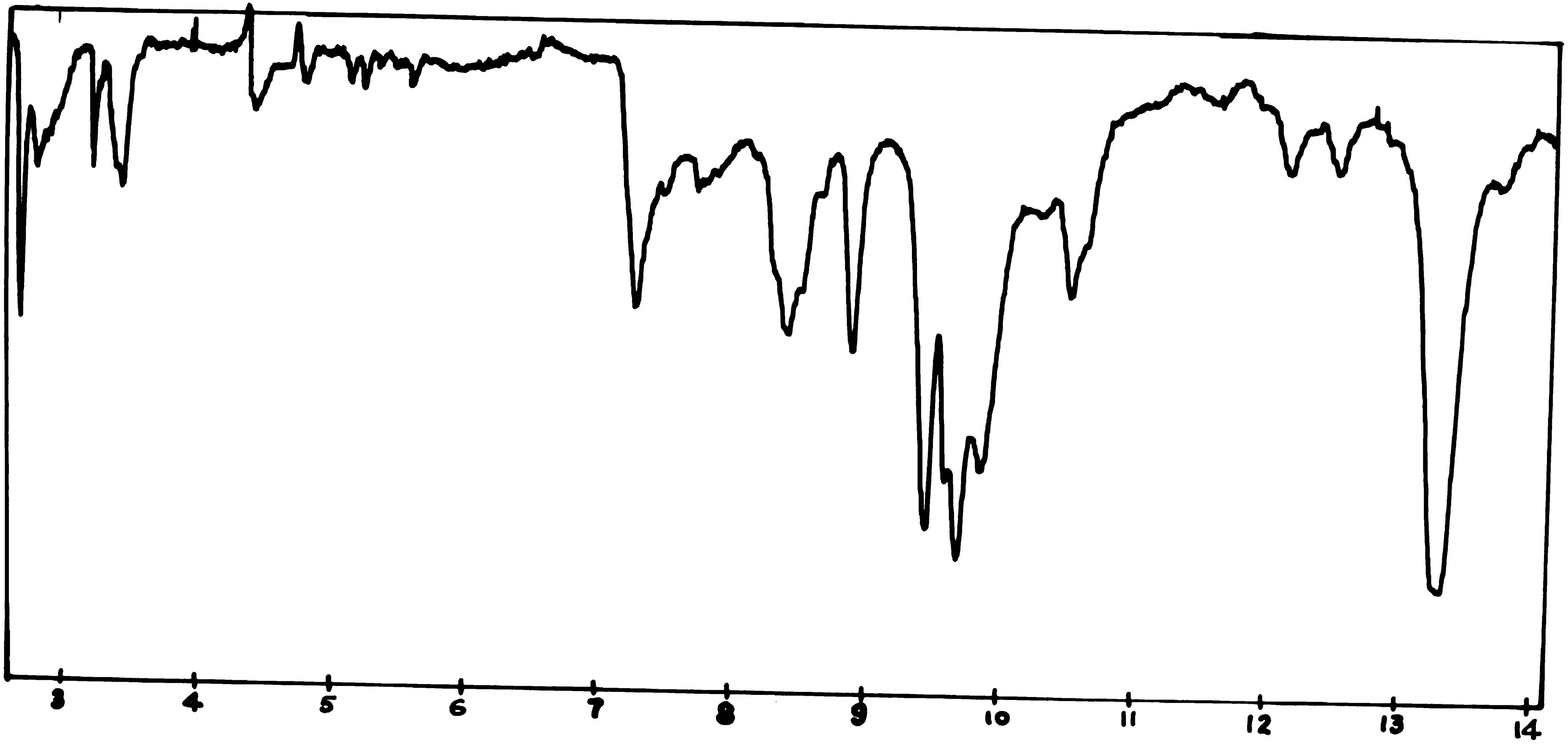


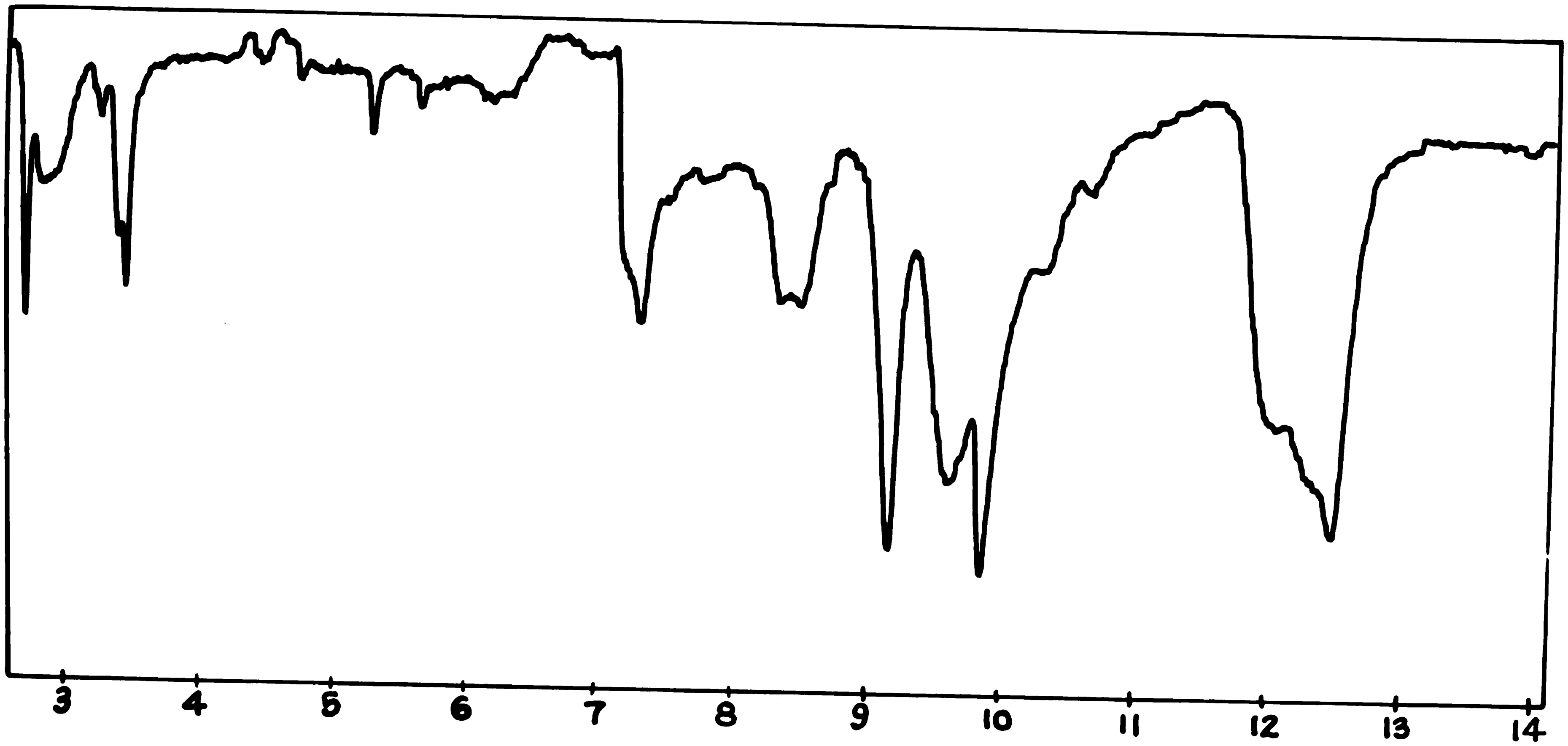
Fig.6. Alkylation of phenol by 2,4-dichlorobenzyl alcohol

APPENDIX II

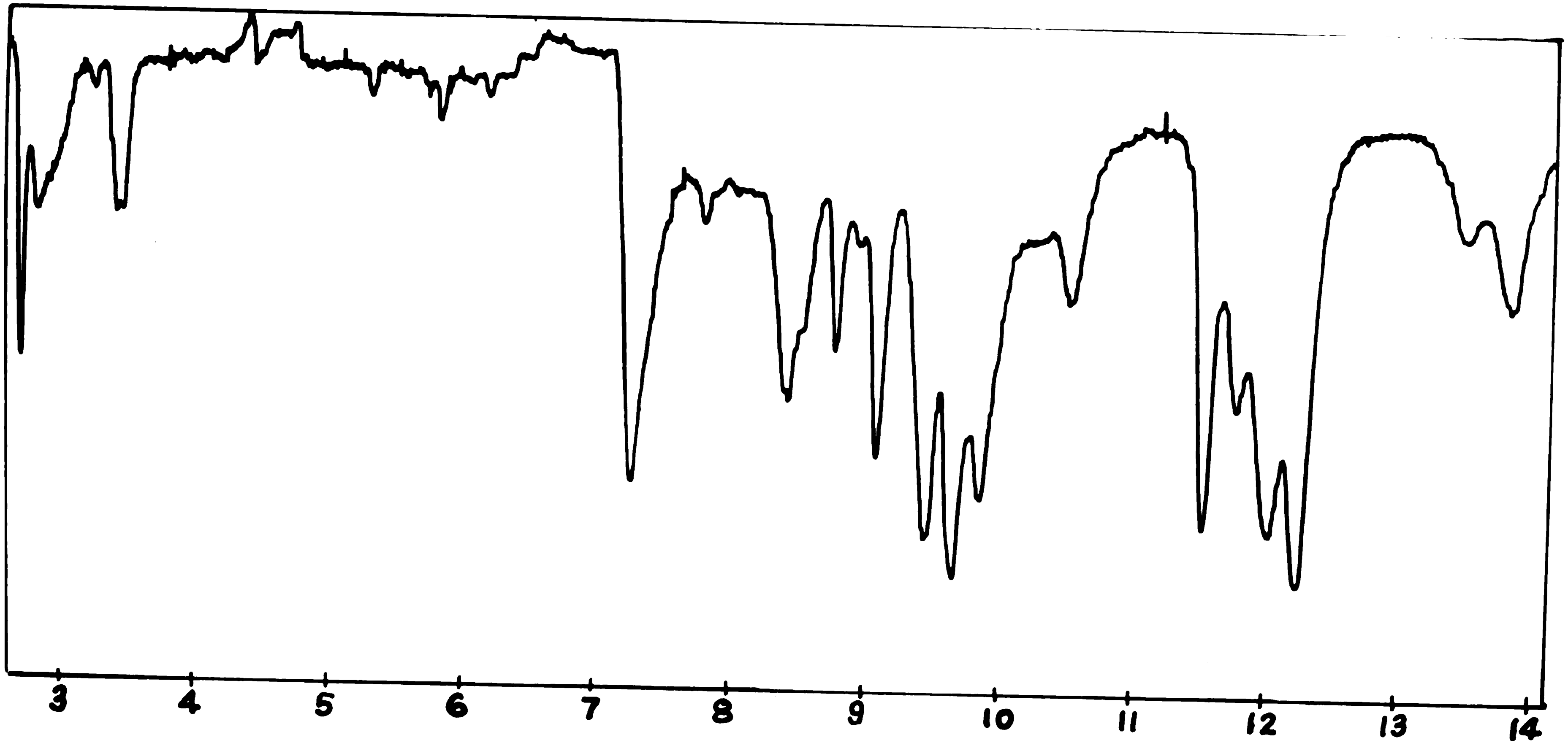
INFRARED SPECTRA



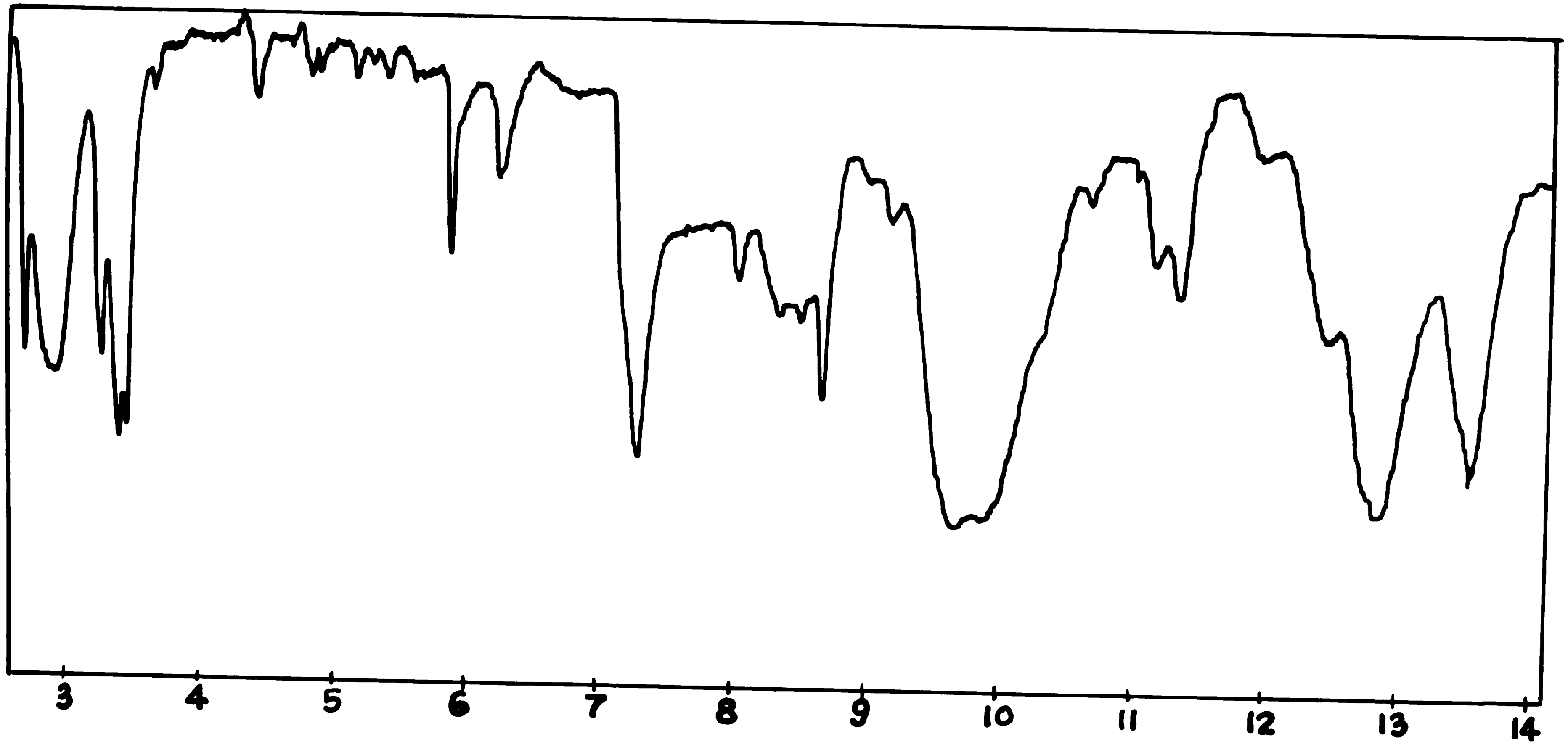
o-Chlorobenzyl Alcohol



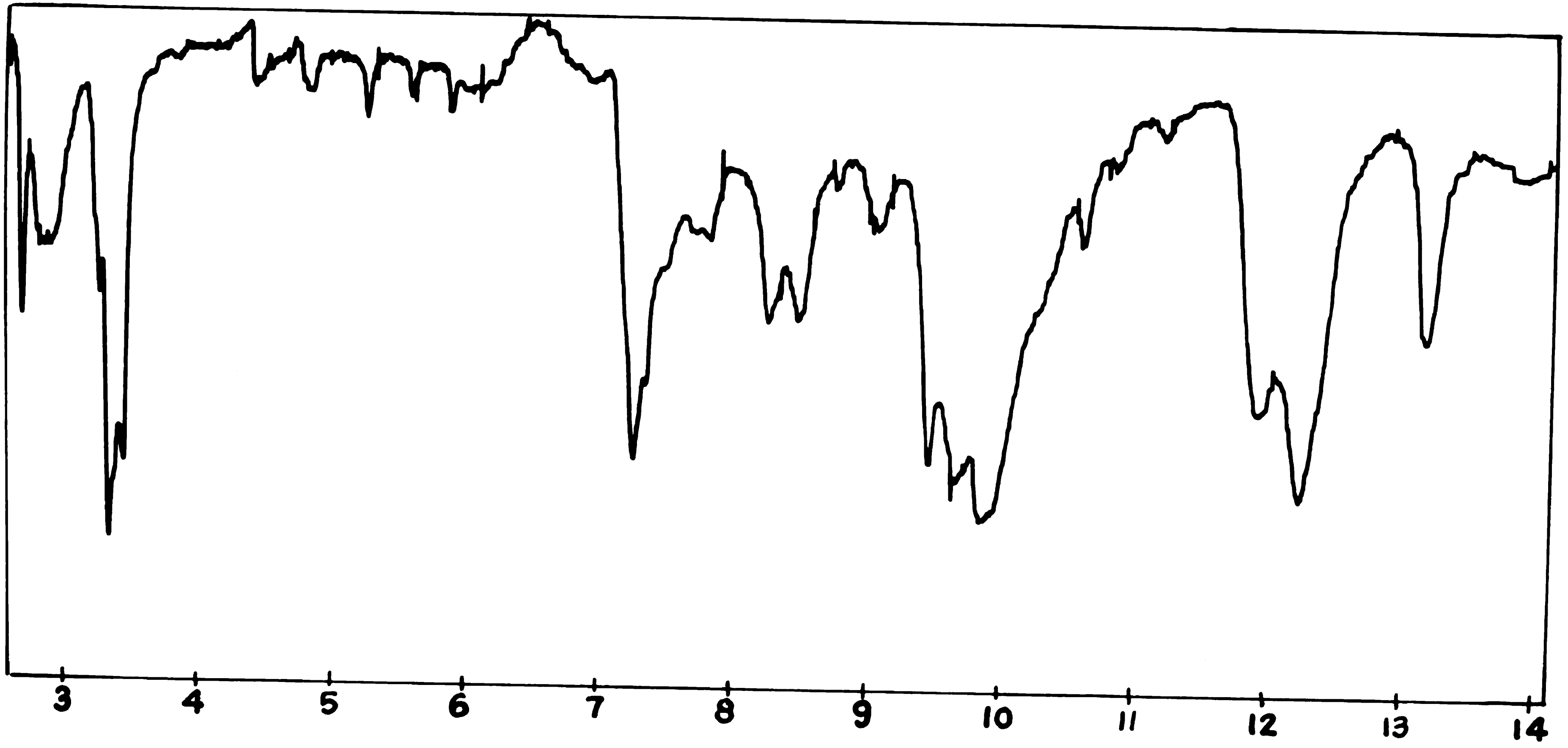
p-Chlorobenzyl Alcohol



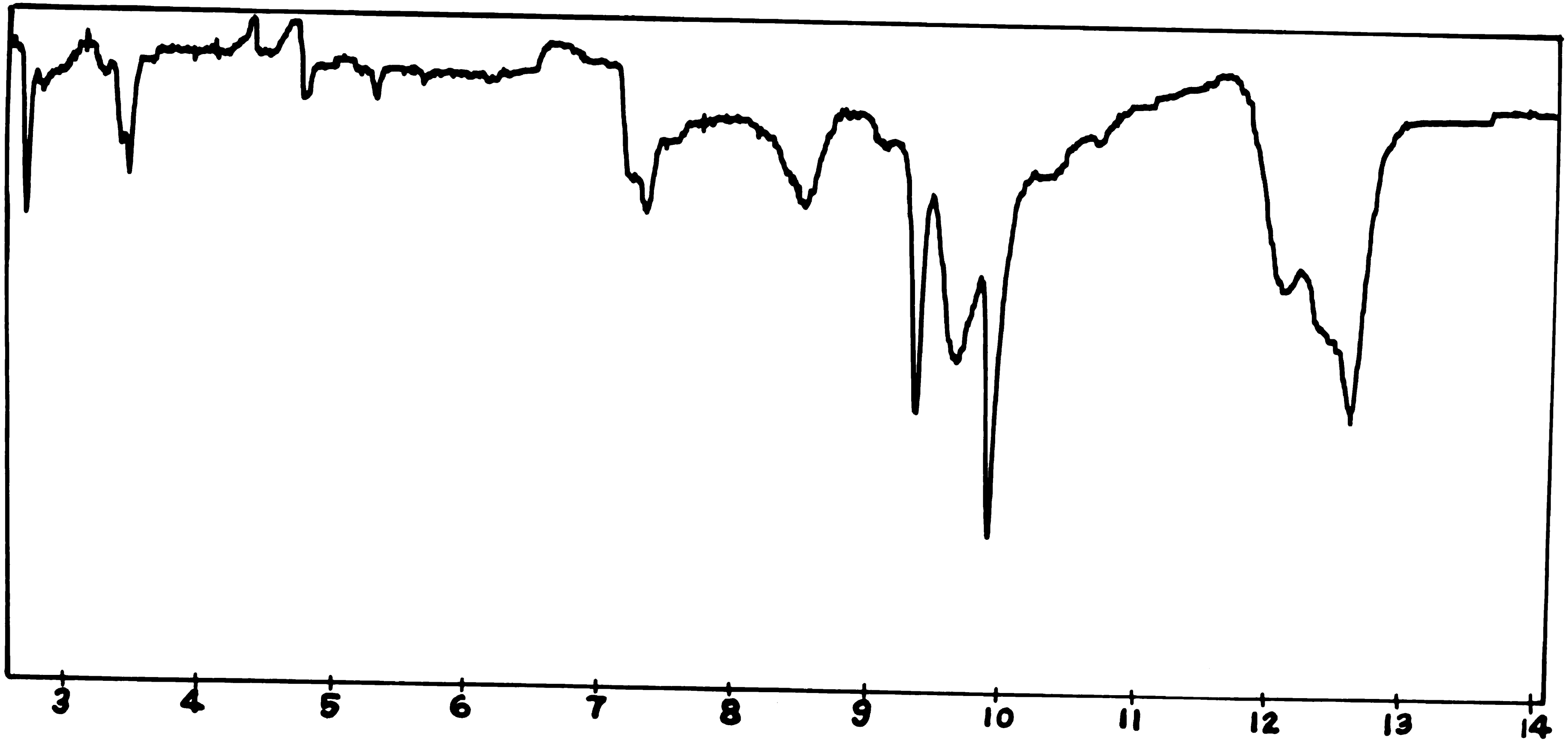
2,4-Dichlorobenzyl Alcohol



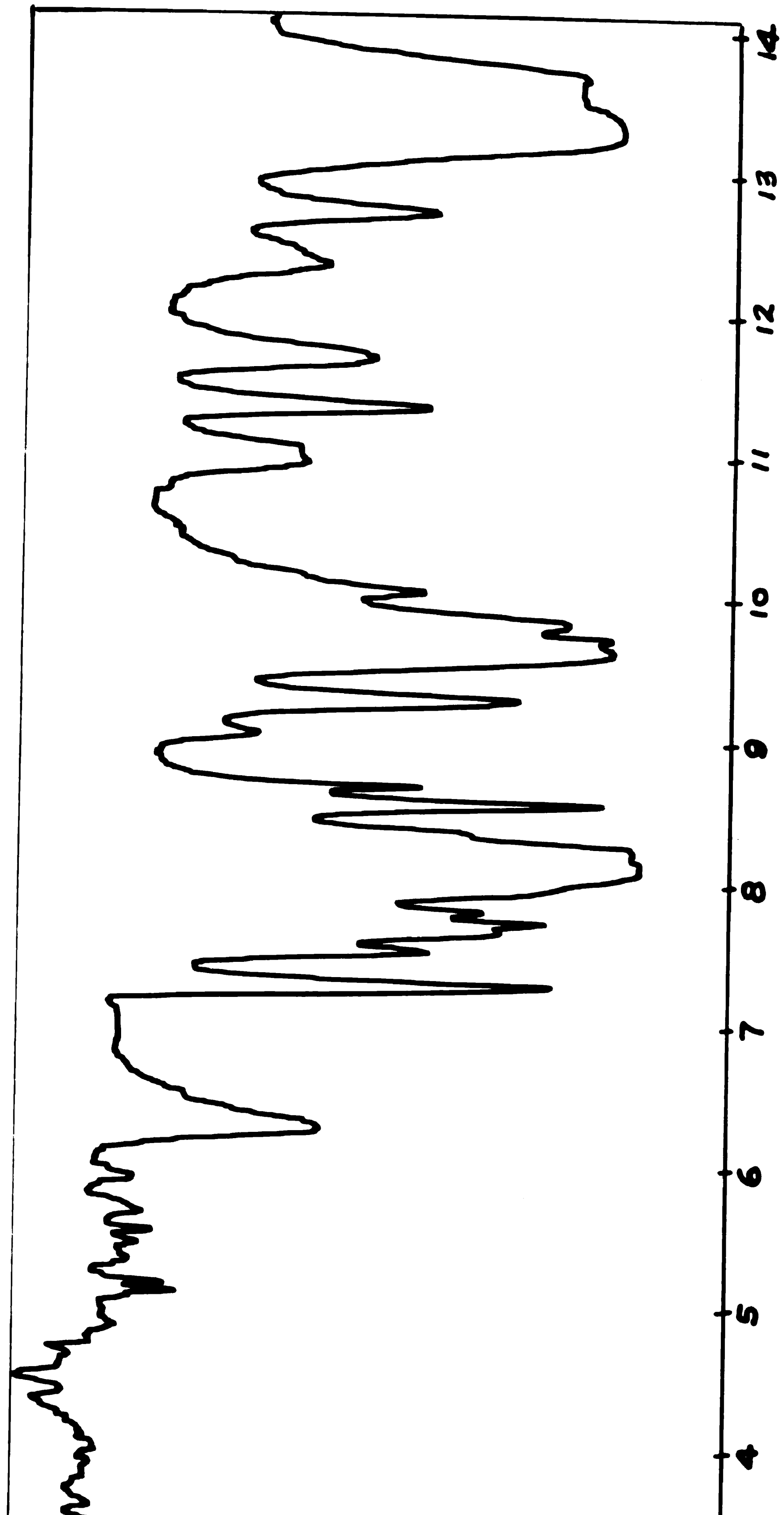
p-Methylbenzyl Alcohol



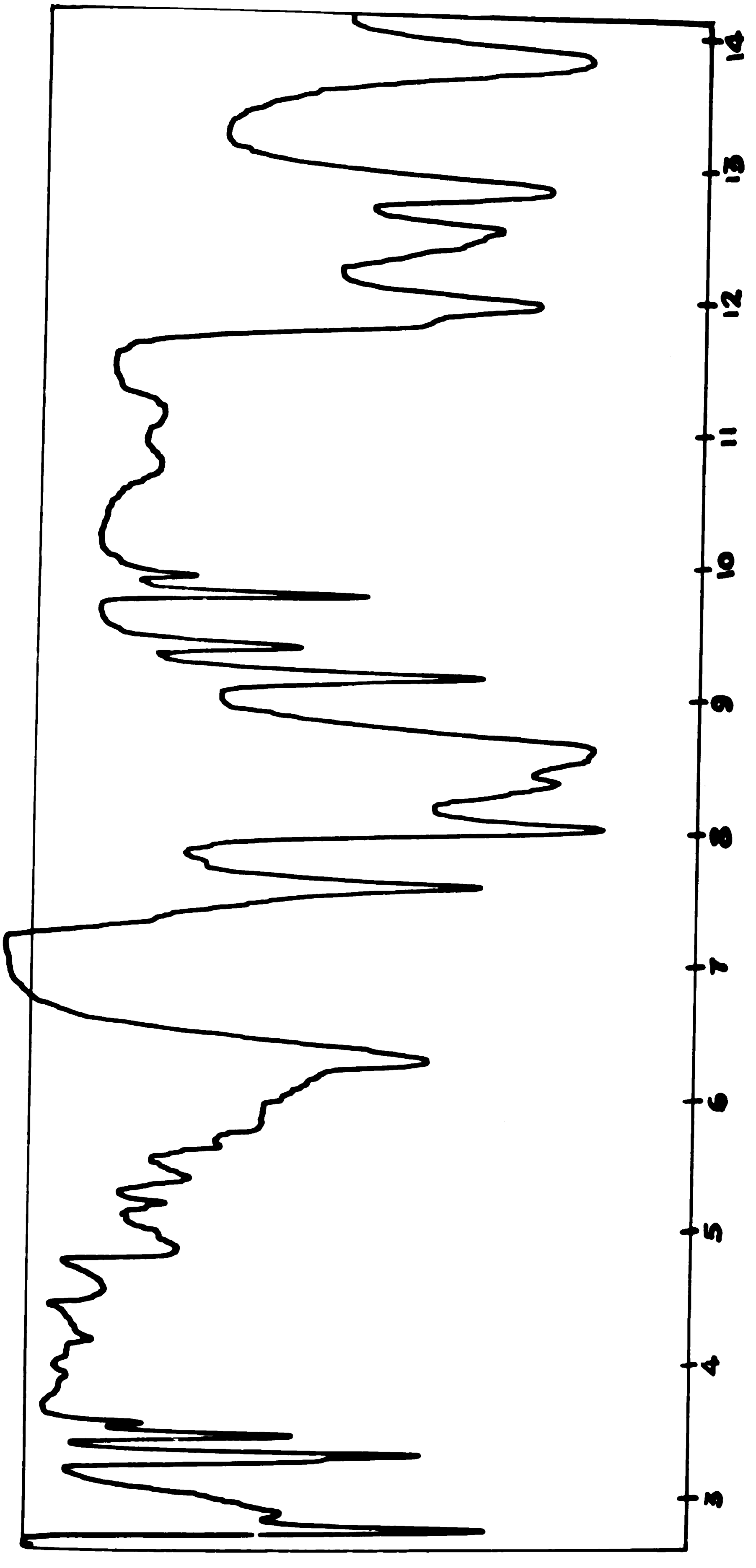
p-Isopropylbenzyl Alcohol



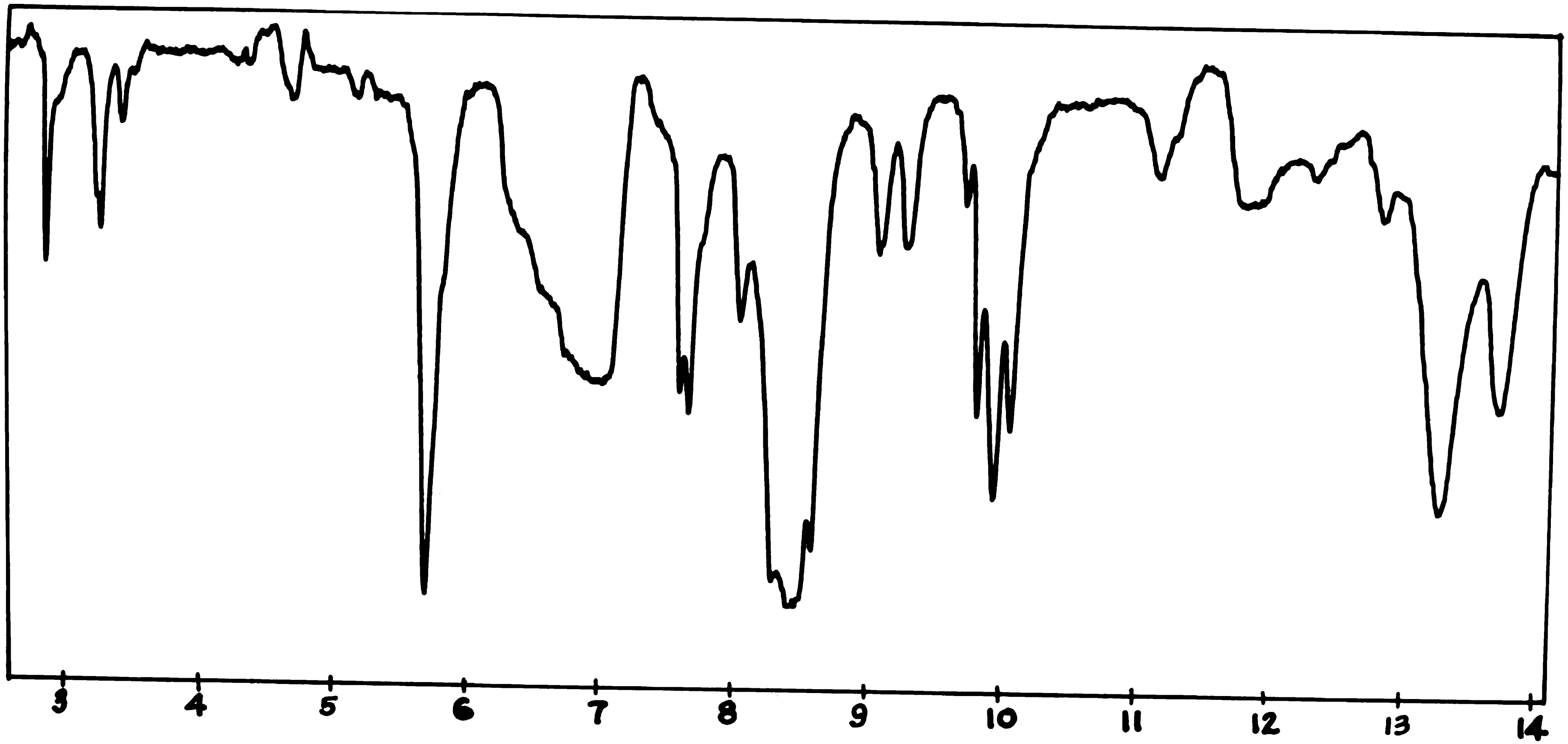
p- Bromobenzyl Alcohol



Benzyl Phenyl Ether



p- Benzylphenol



Phenyl Urethane
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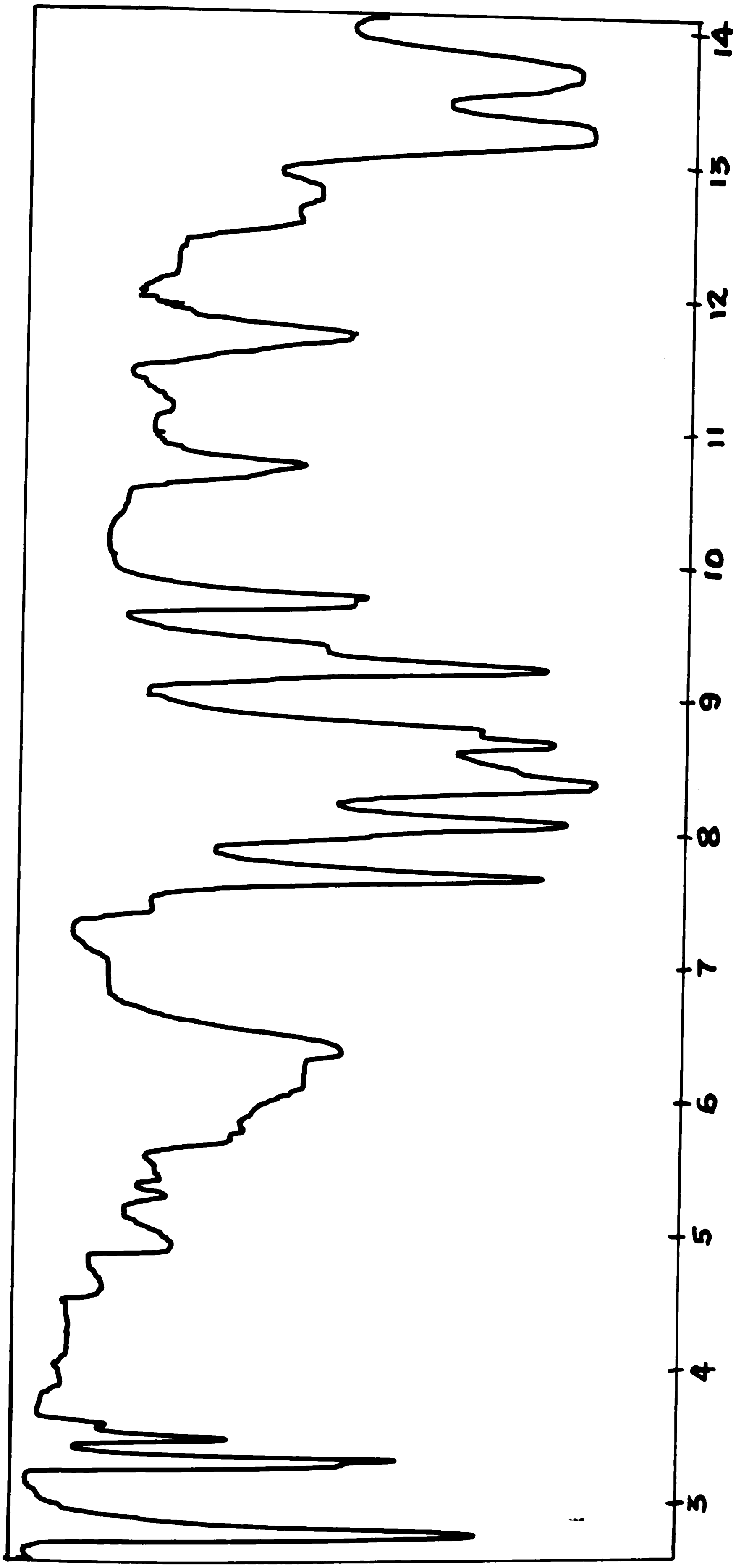
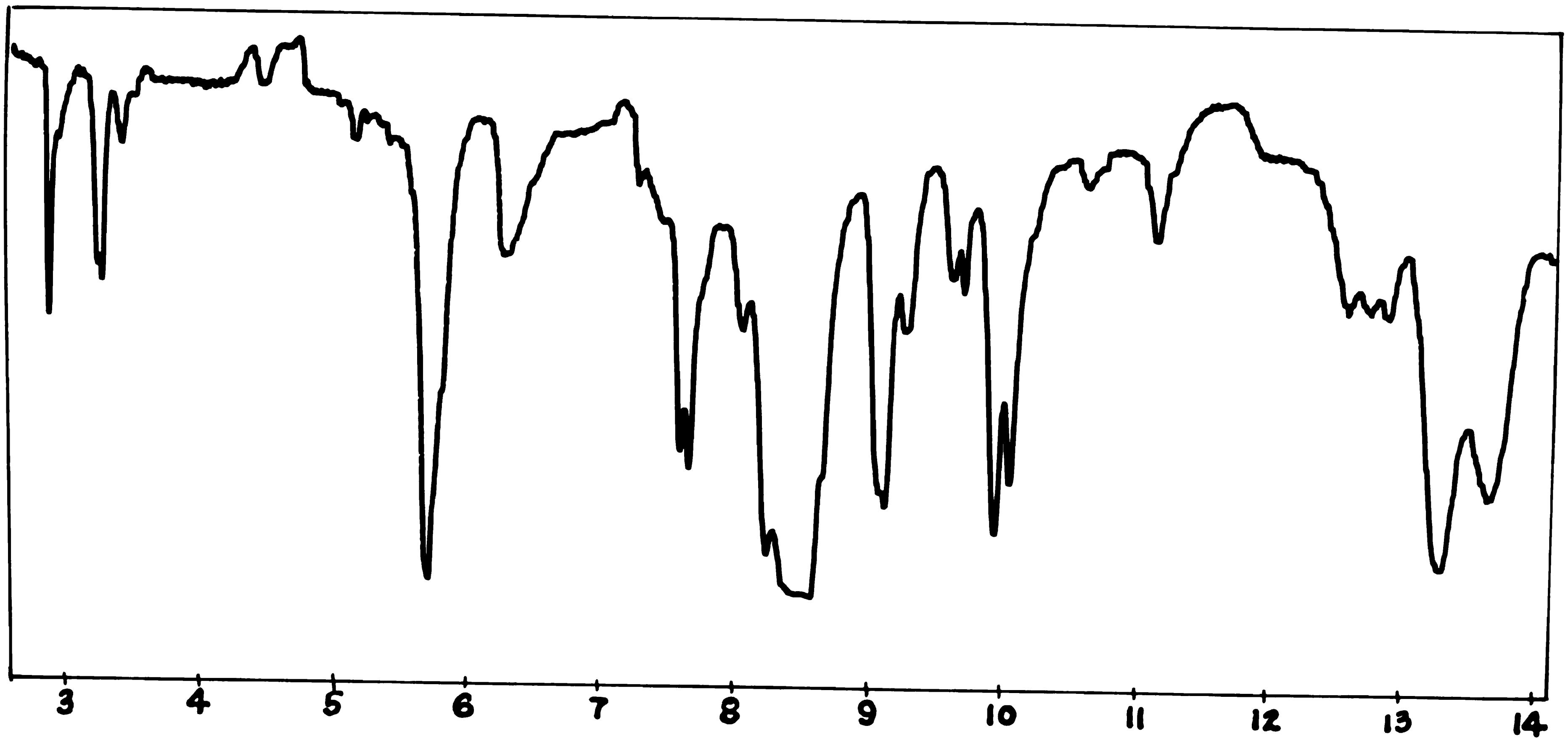


o-Benzylphenol



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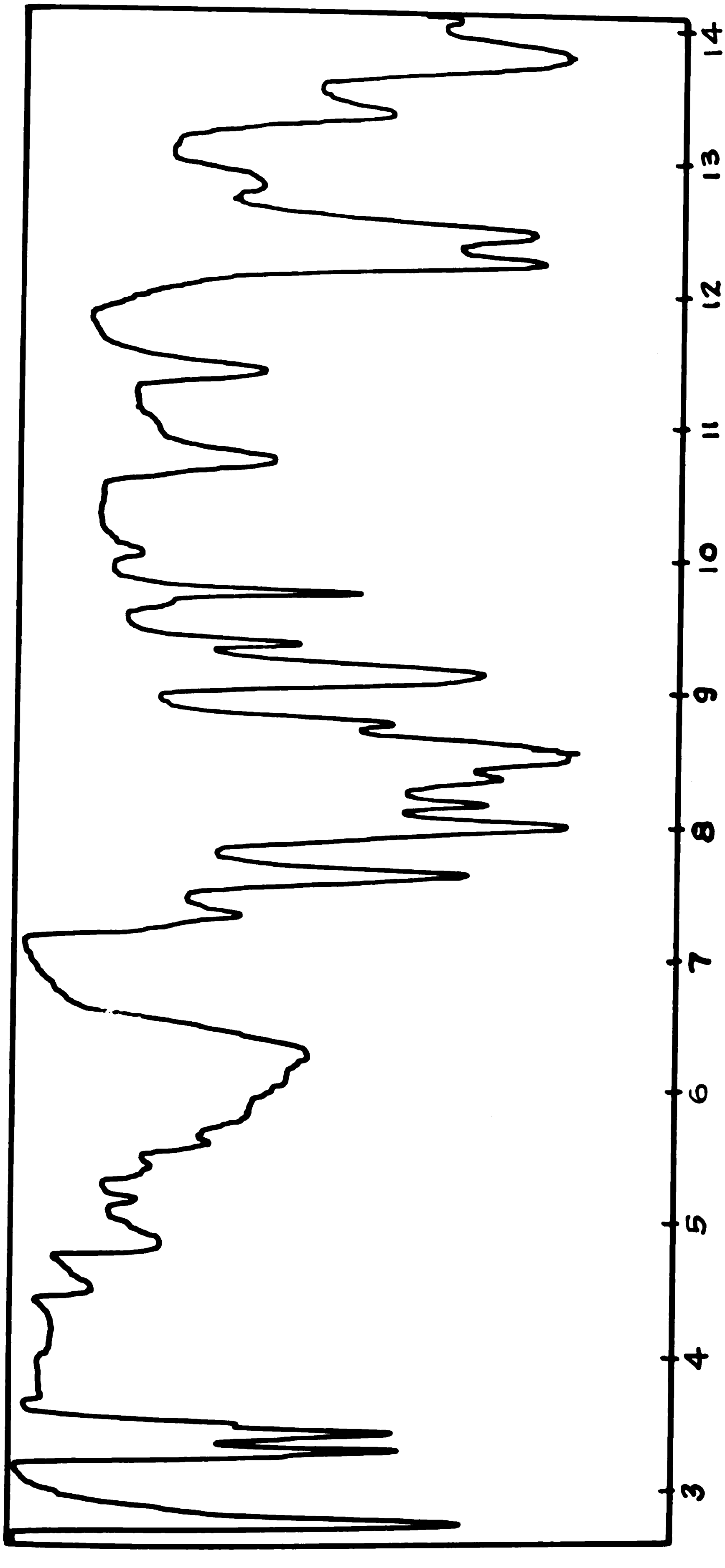
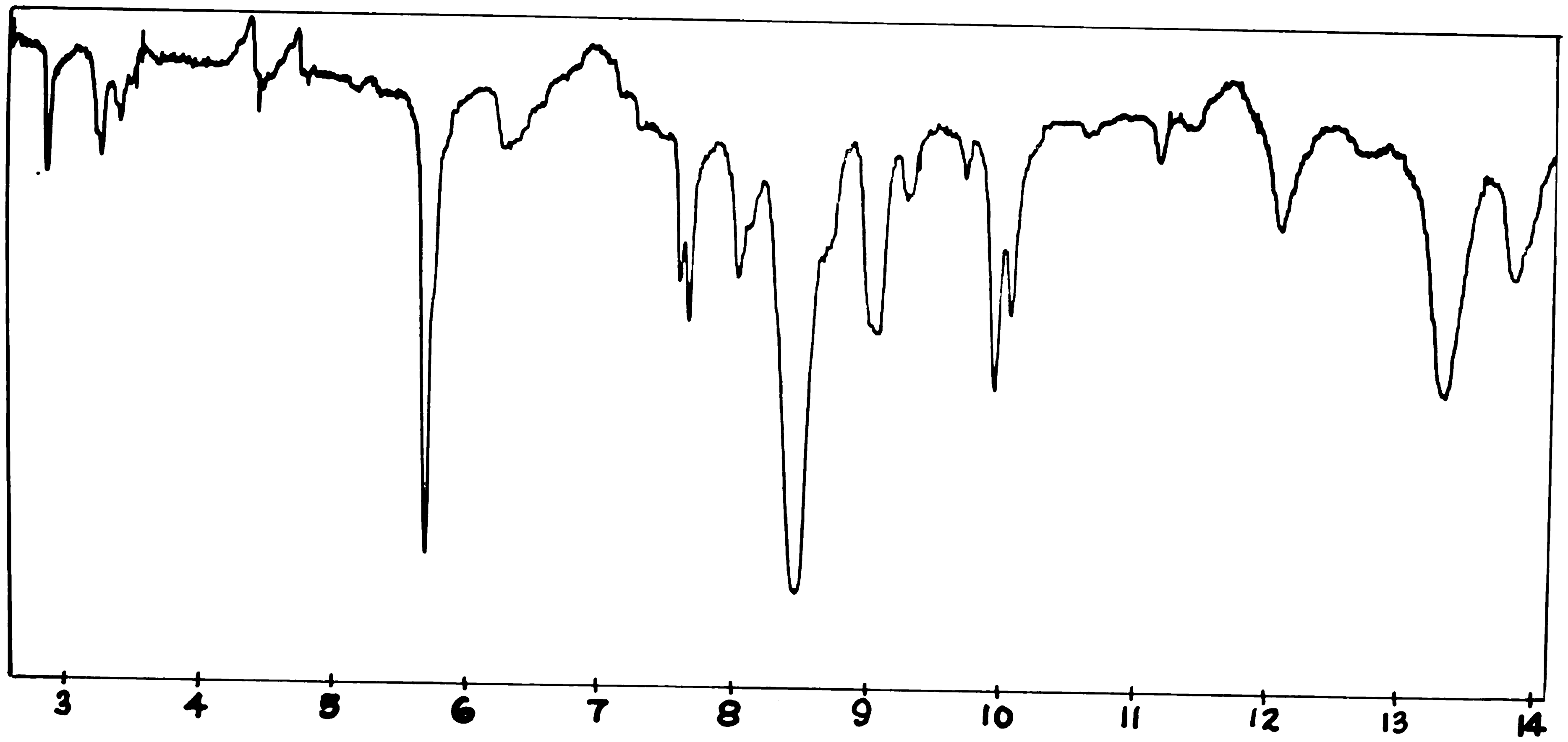


2-Benzyl-4-methylphenol



Phenyl Urethane
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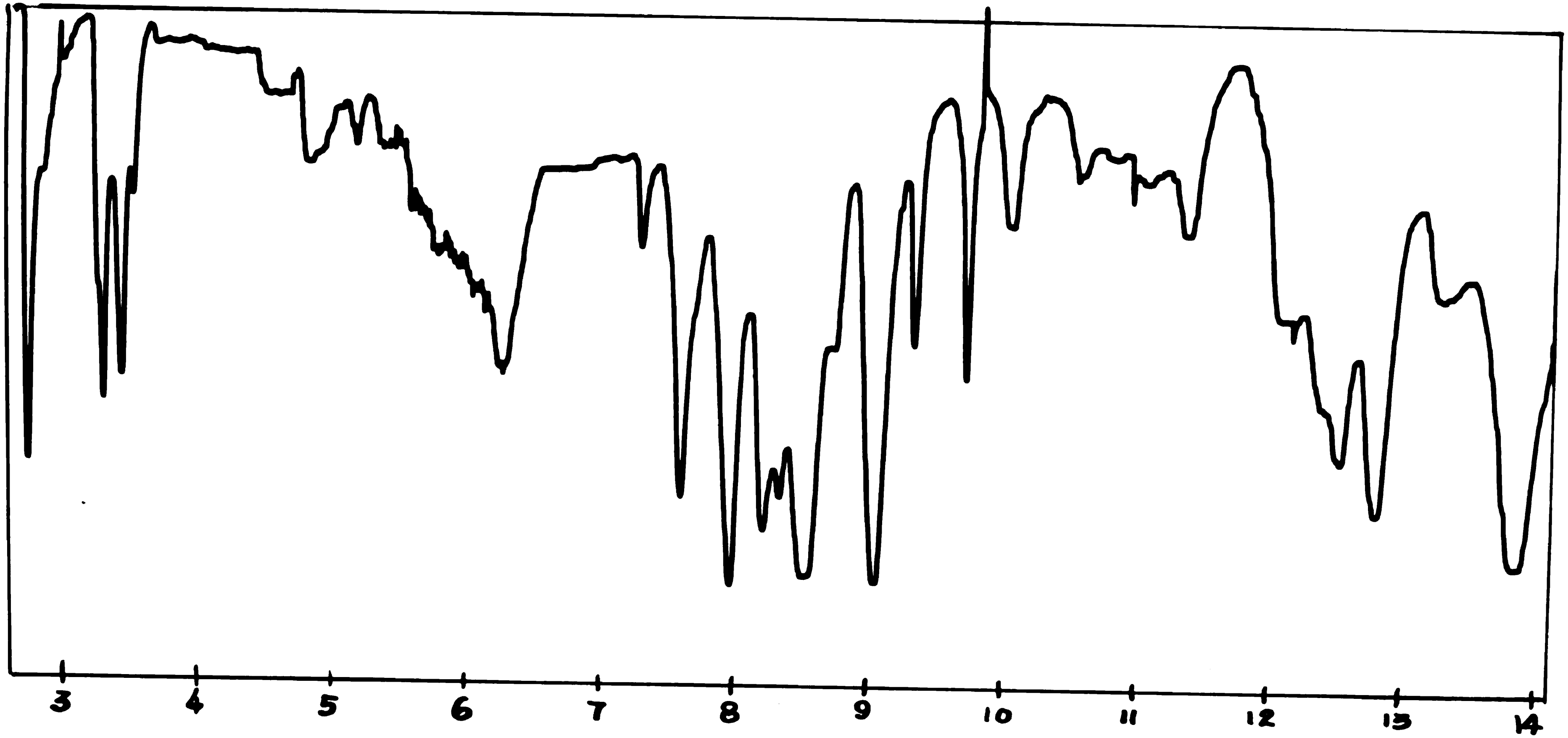
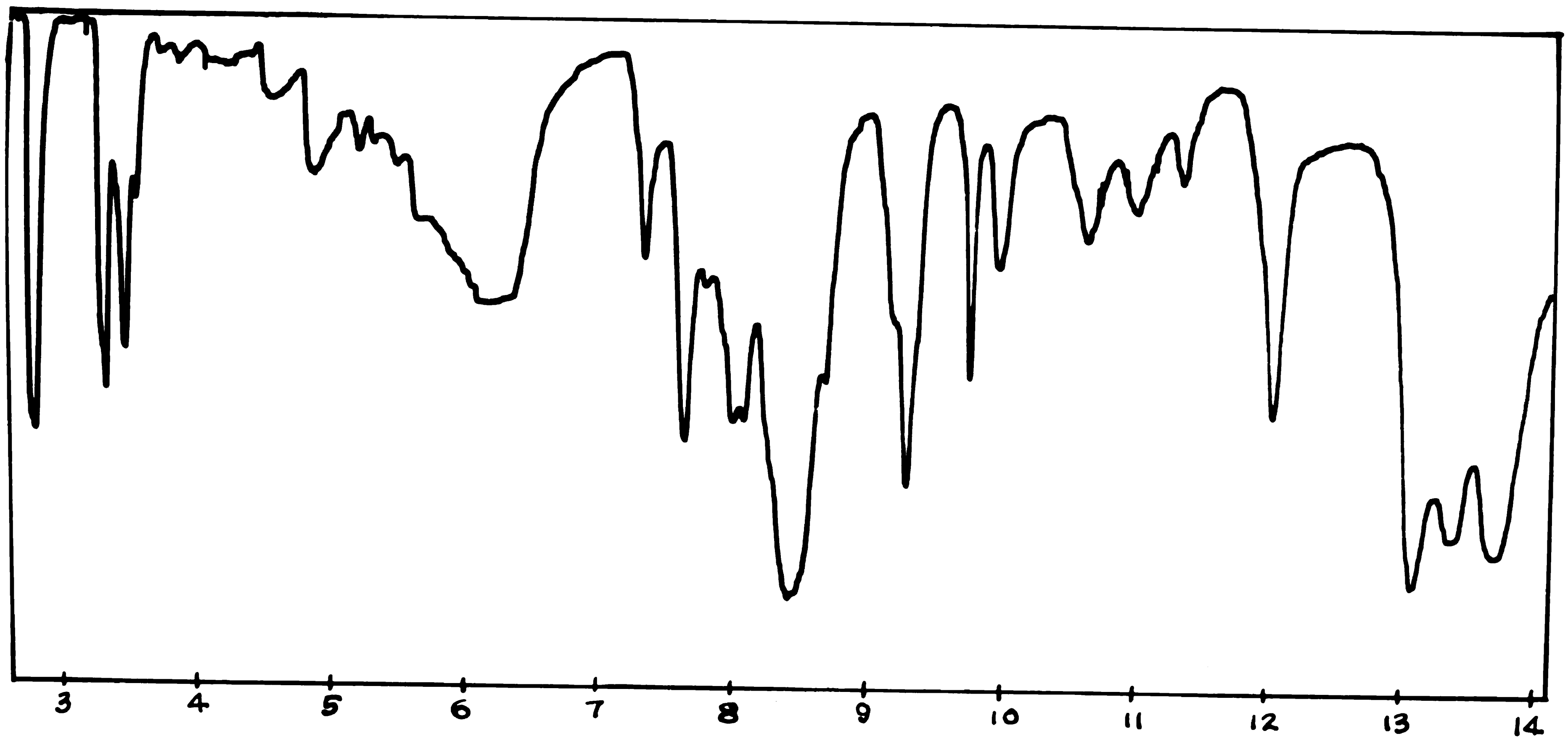
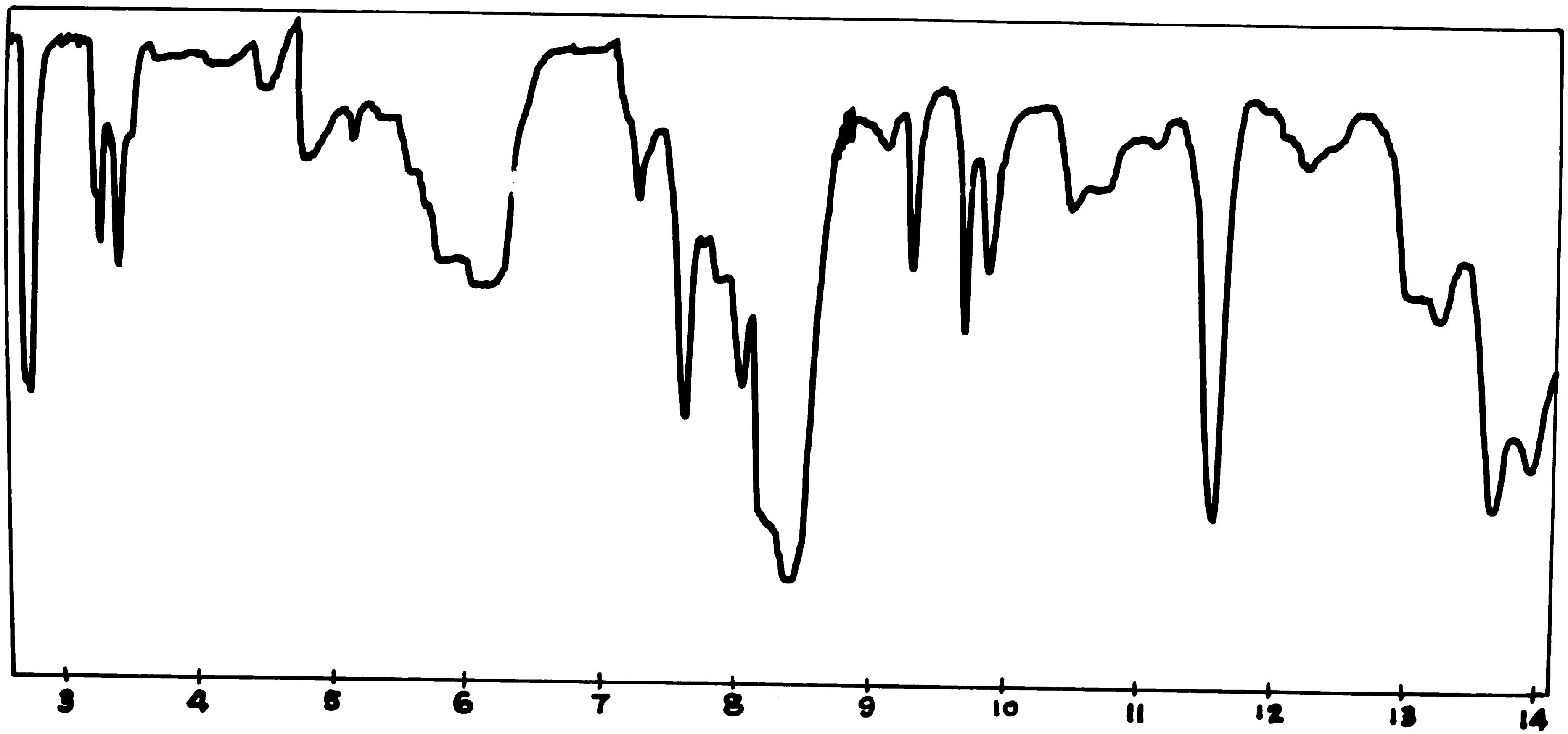


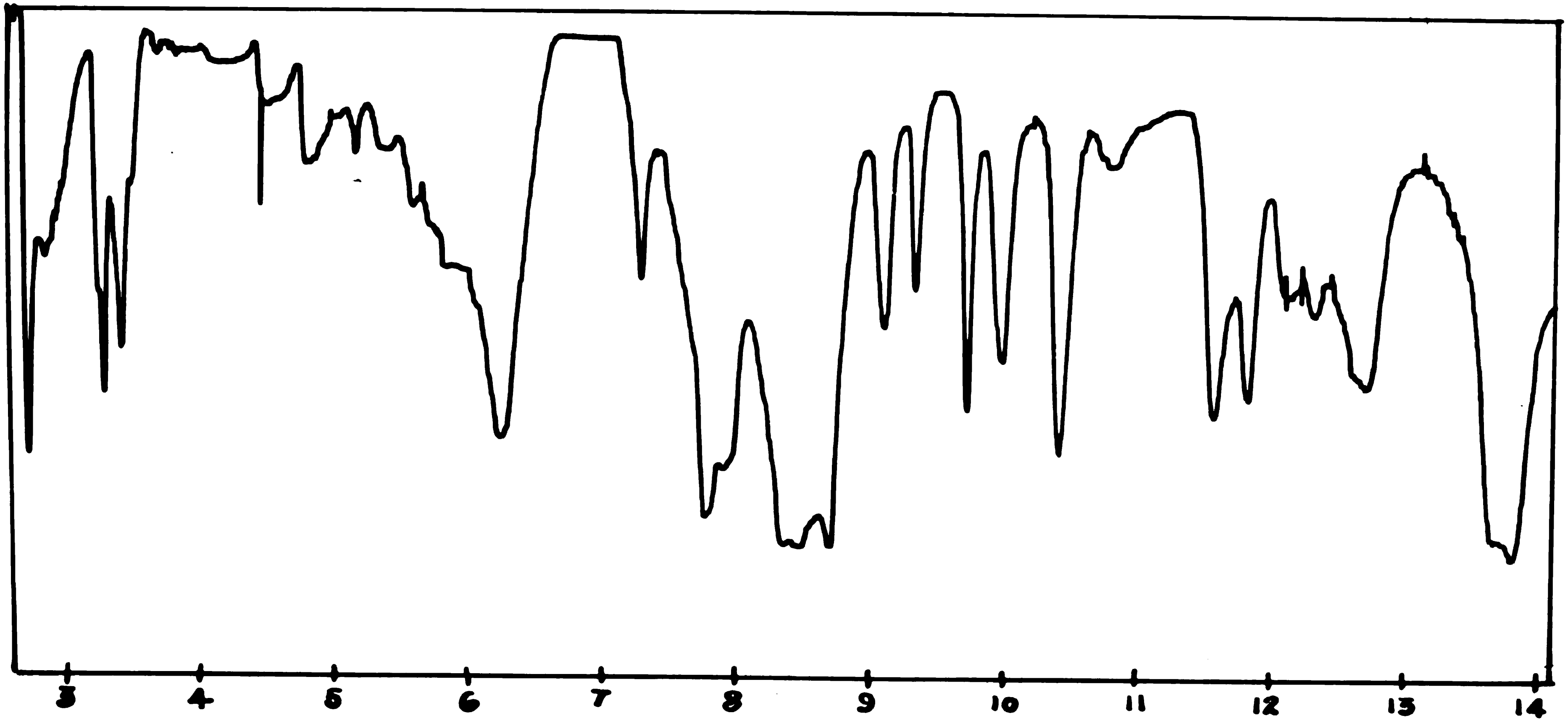
4-Benzyl-2-methylphenol



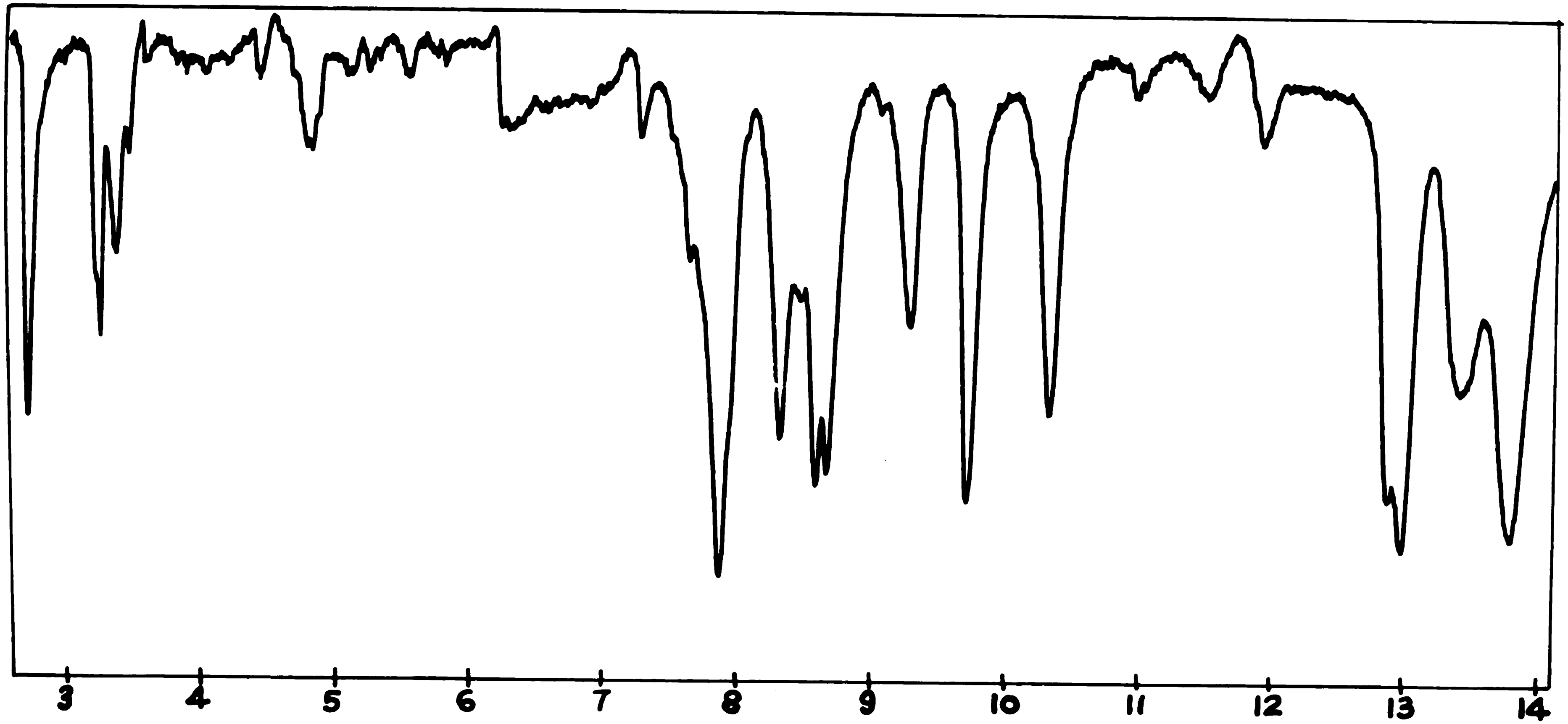
2 - Benzyl - 6 - methylphenol



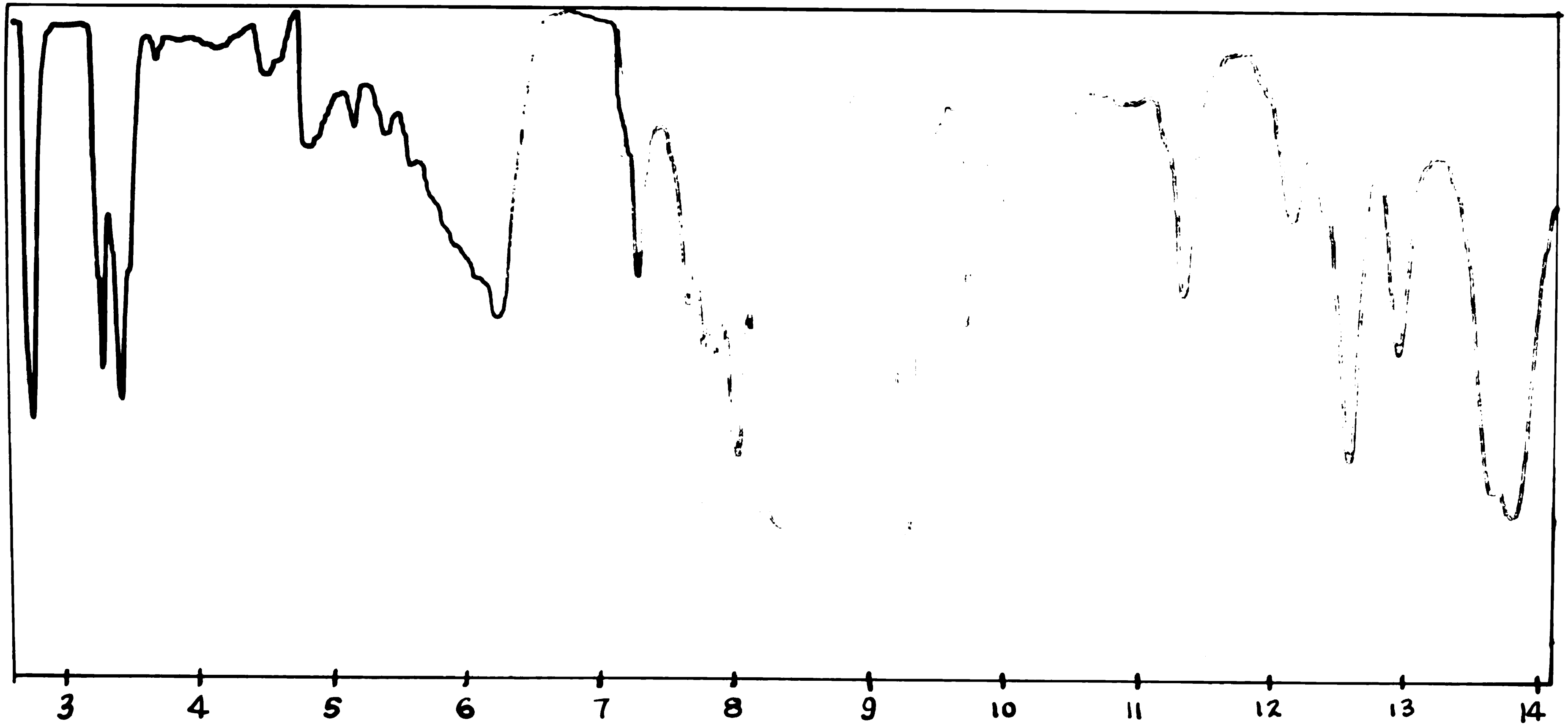
2-Benzyl-4-bromo-6-methylphenol



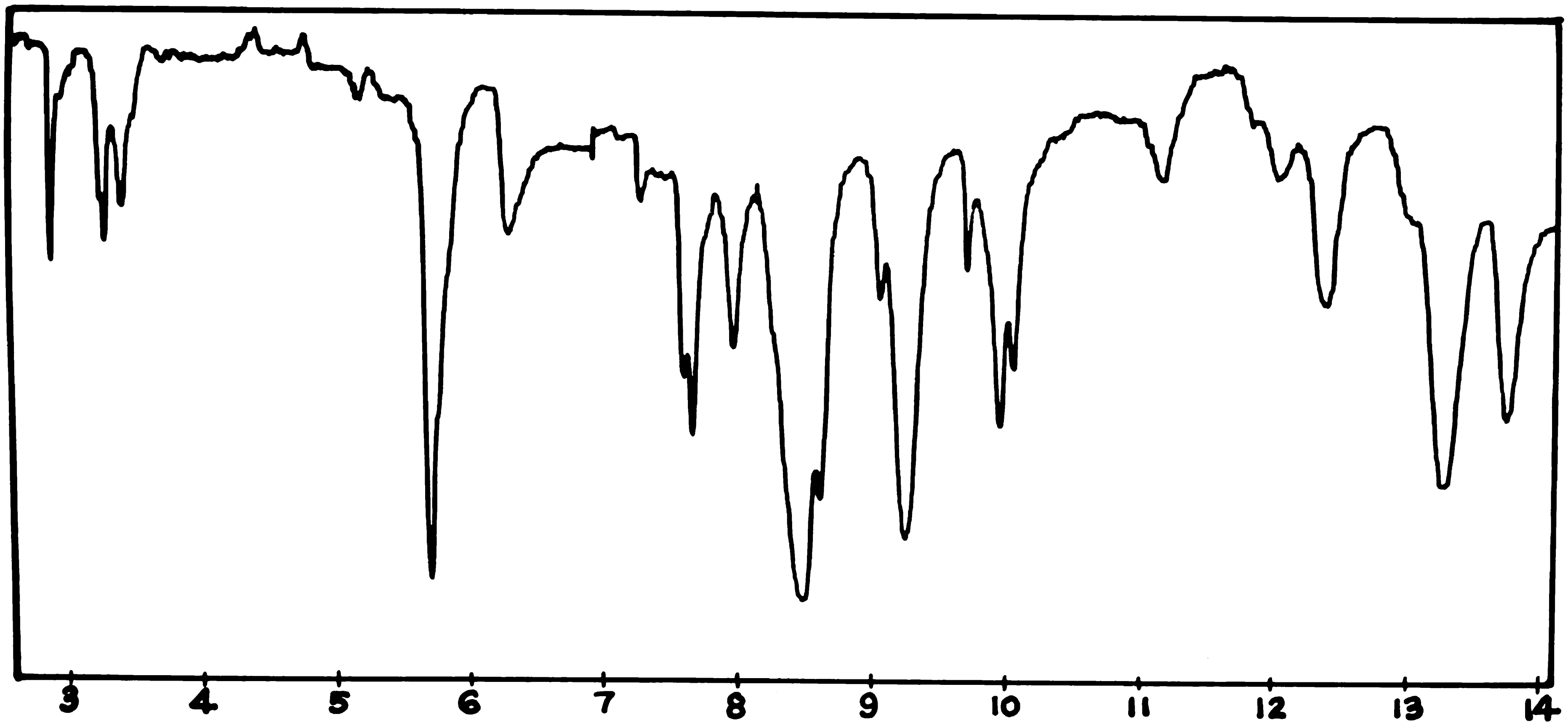
4 - Benzyl - 3 - methylphenol



2- Benzyl-3-methylphenol



6-Benzyl-2,3-dimethylphenol



Phenyl Urethane
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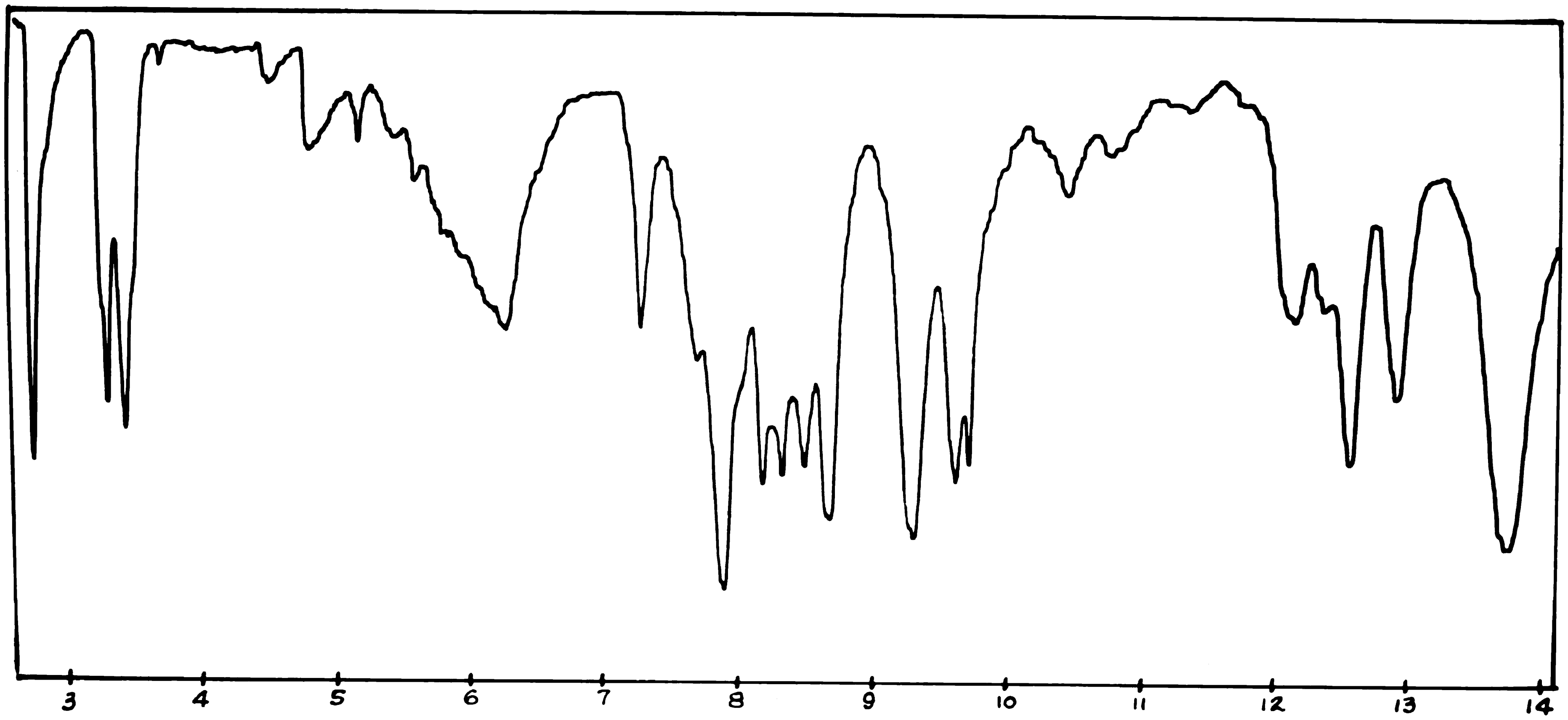
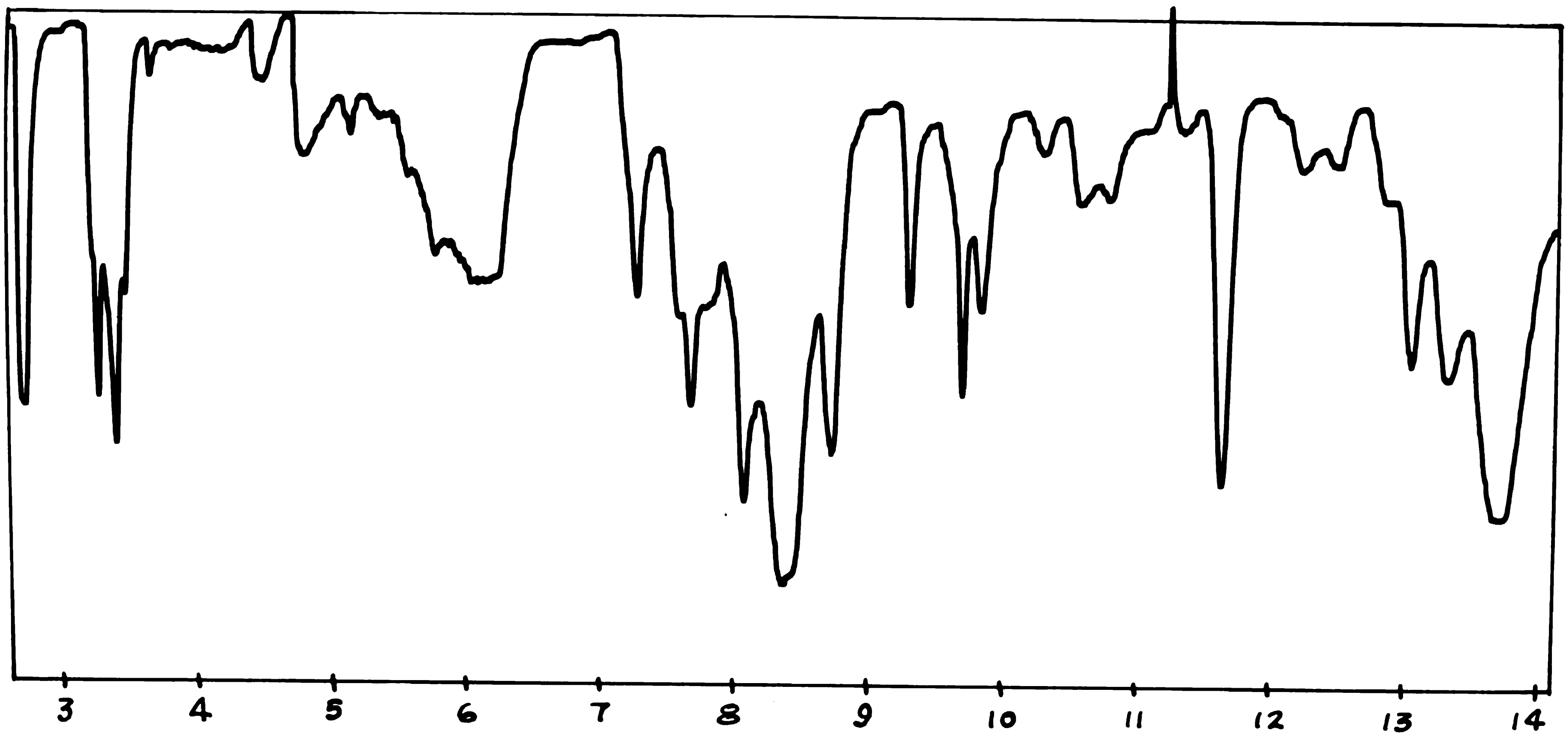
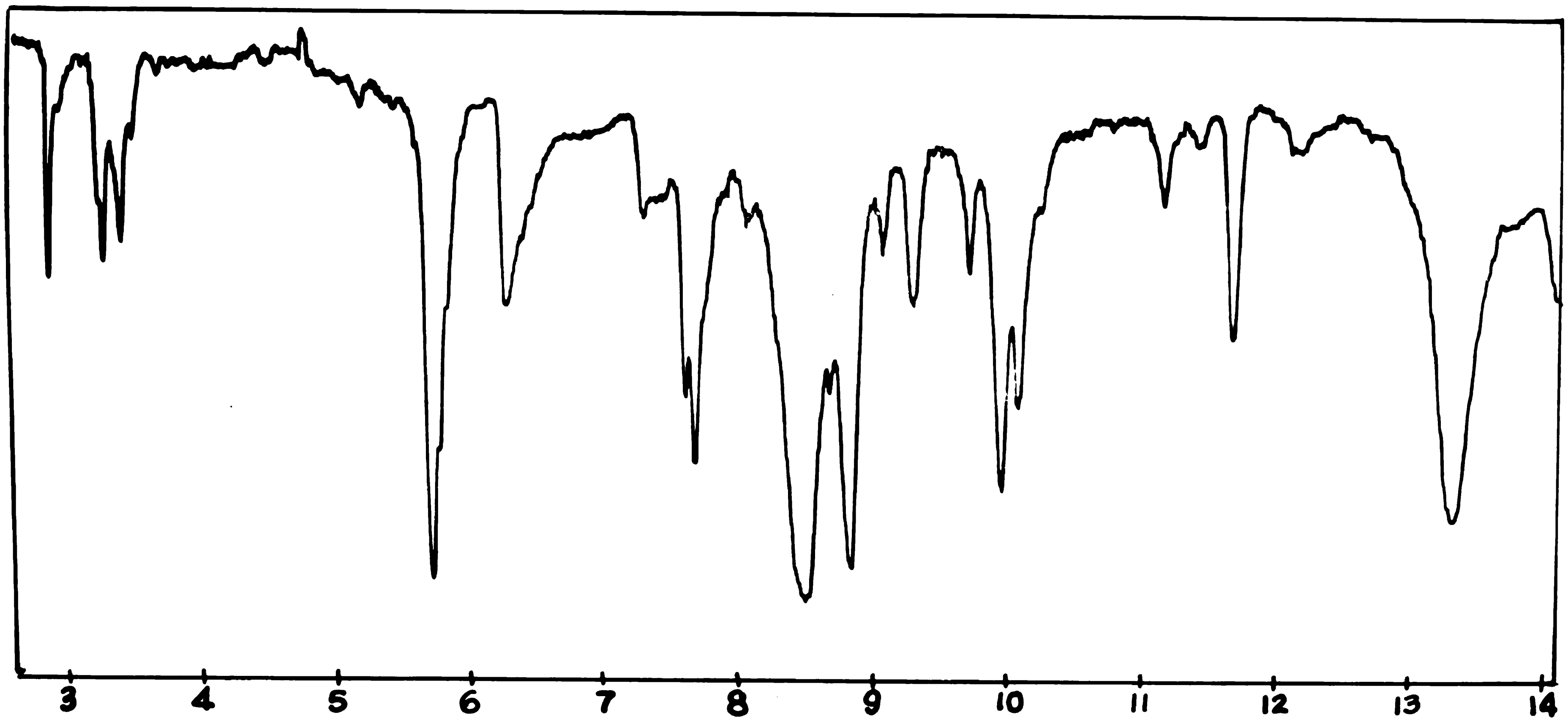


4-Benzyl-2,3-dimethylphenol



2-Benzyl-4,6-dimethylphenol



Phenyl Urethane
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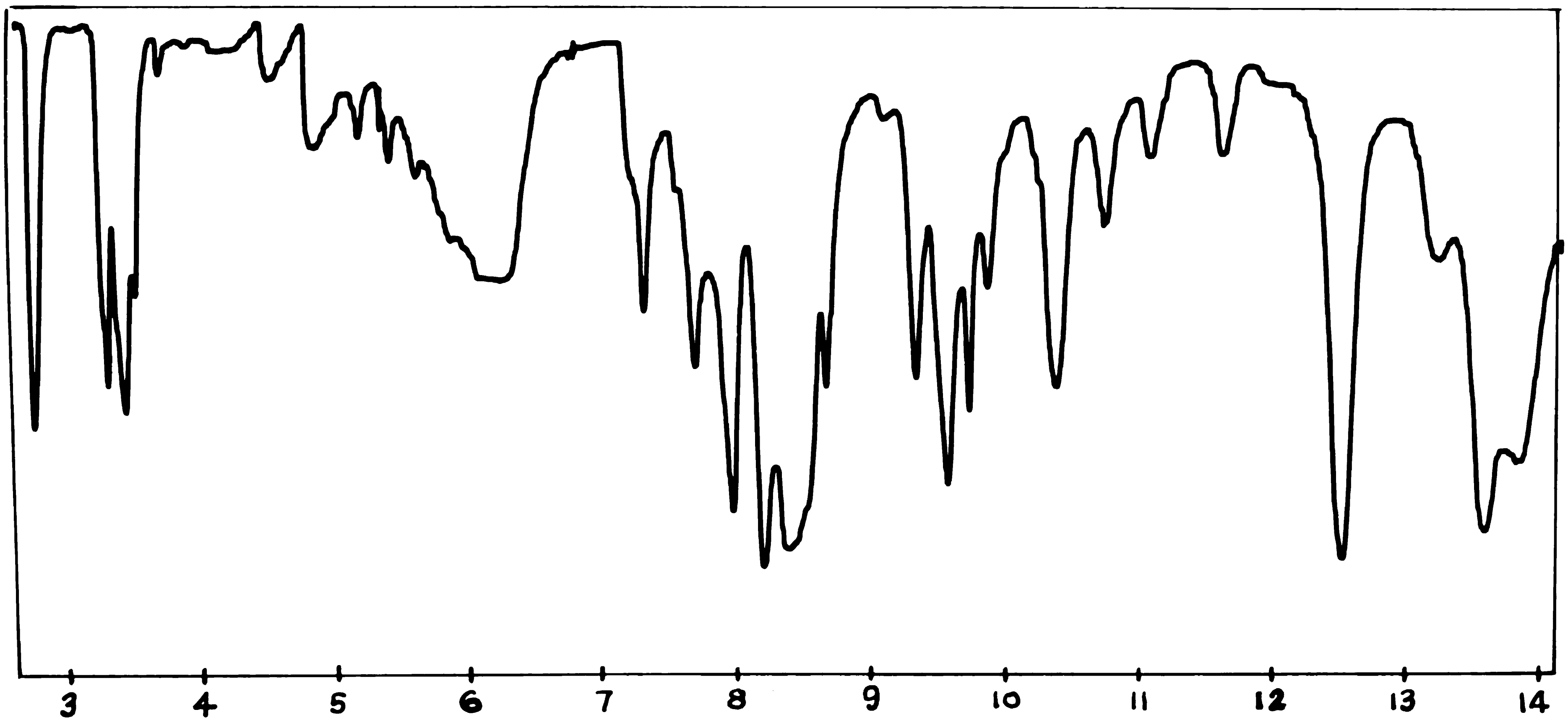
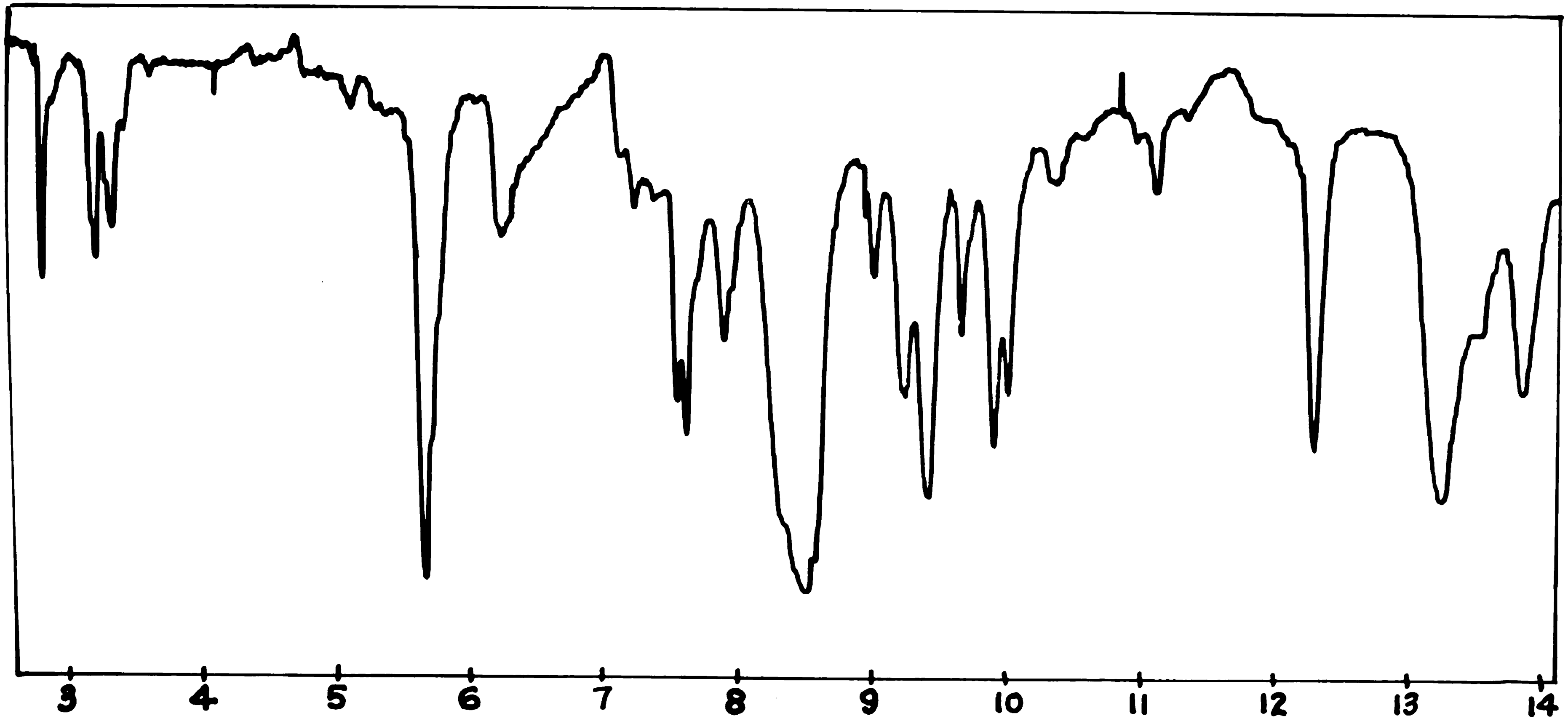


2-Benzyl-3,6-dimethylphenol



Phenyl Urethane
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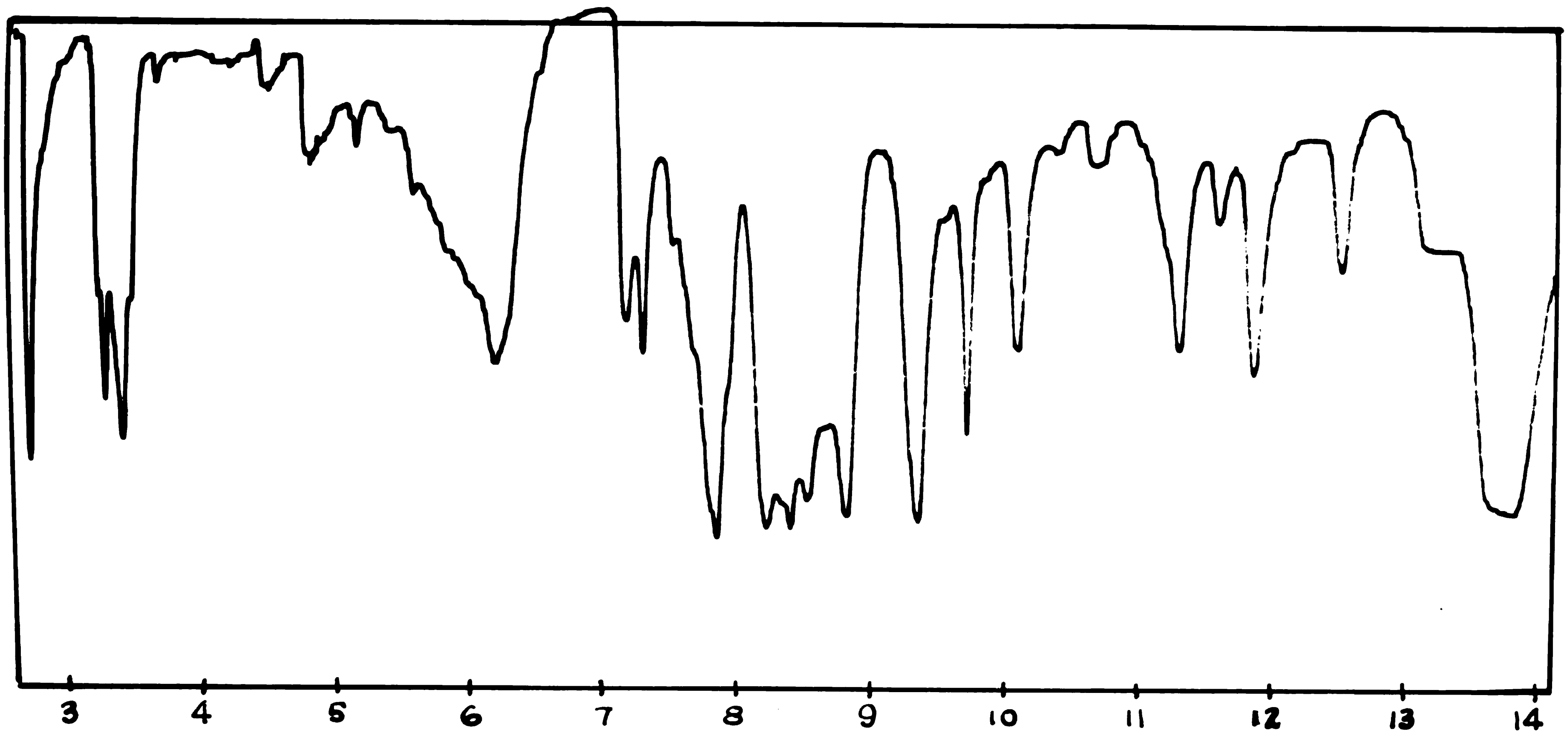
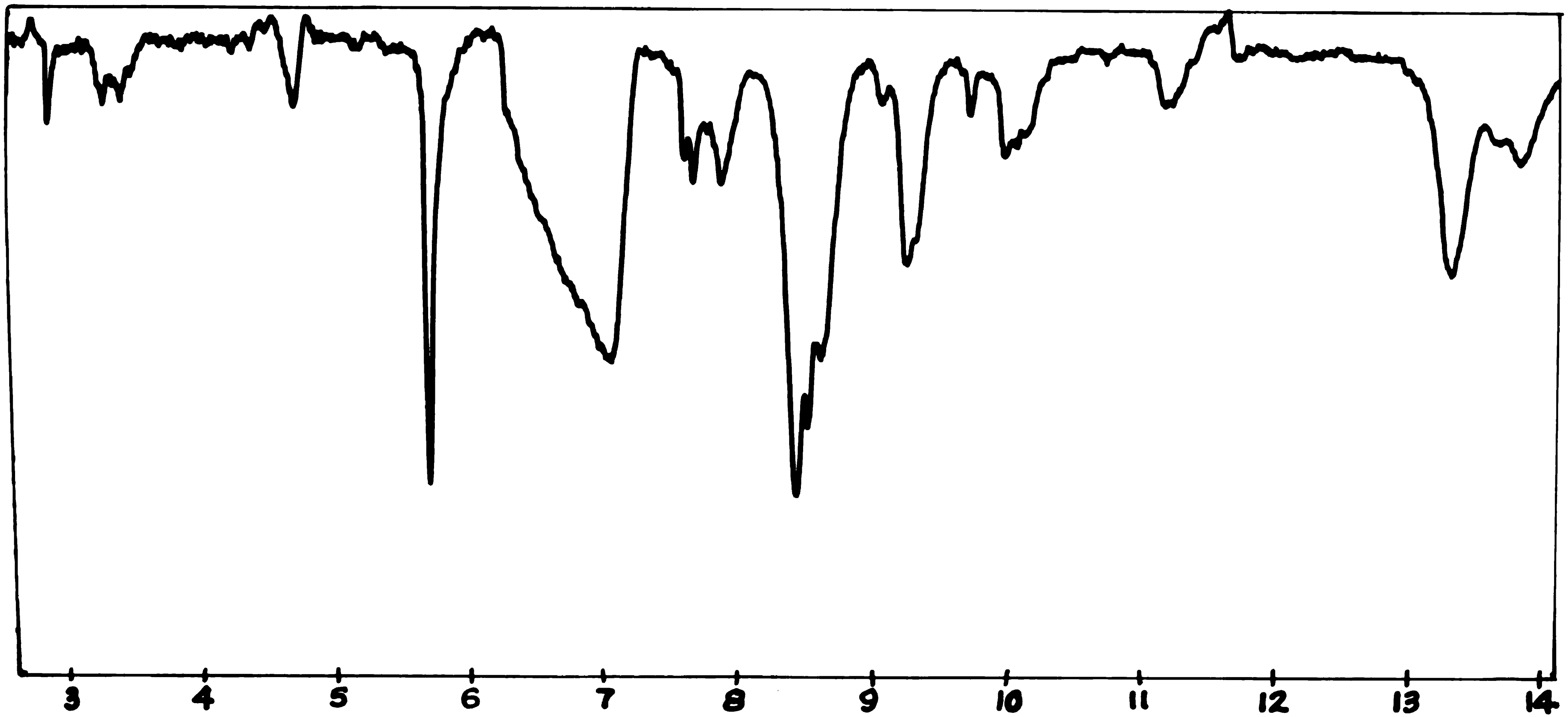


4 - Benzyl - 2,5 - dimethylphenol



Phenyl Urethane
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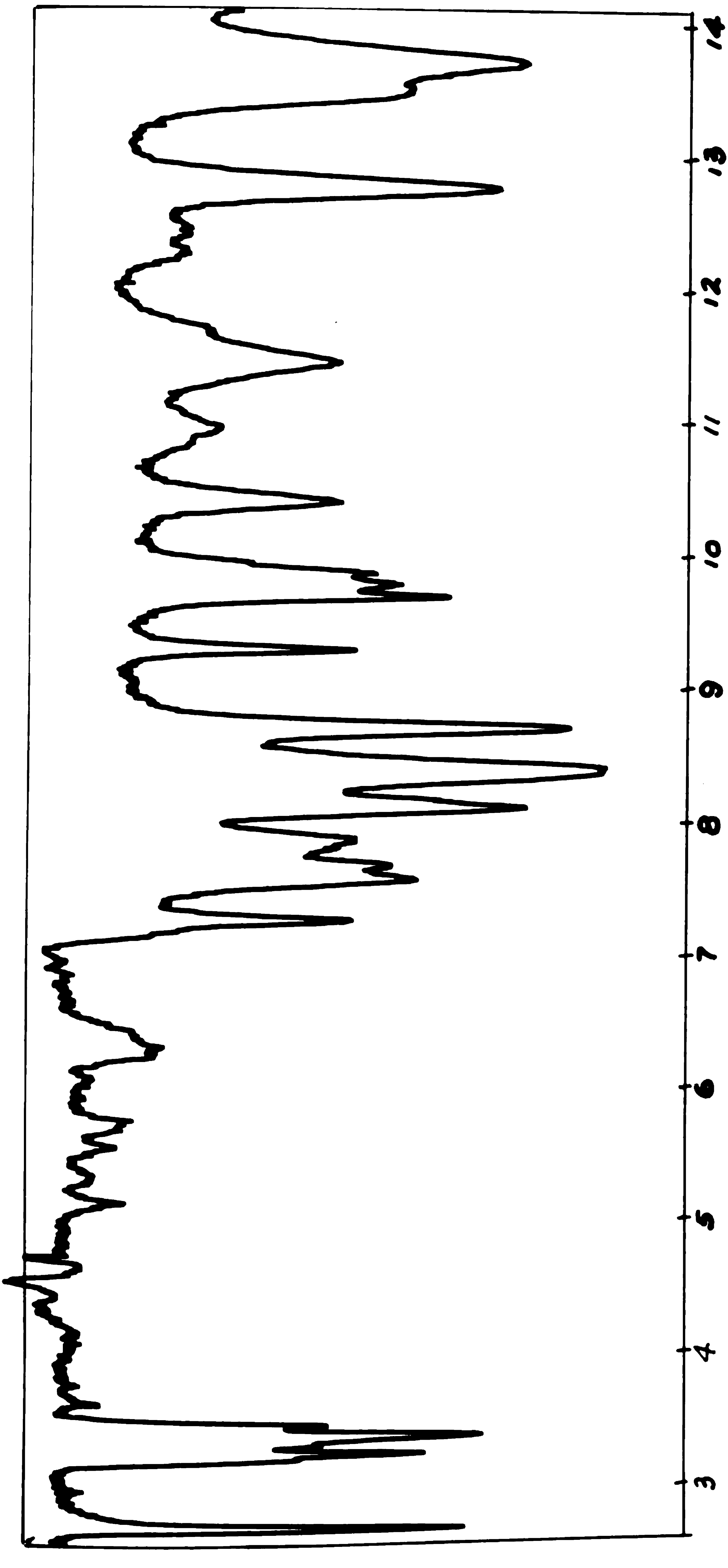
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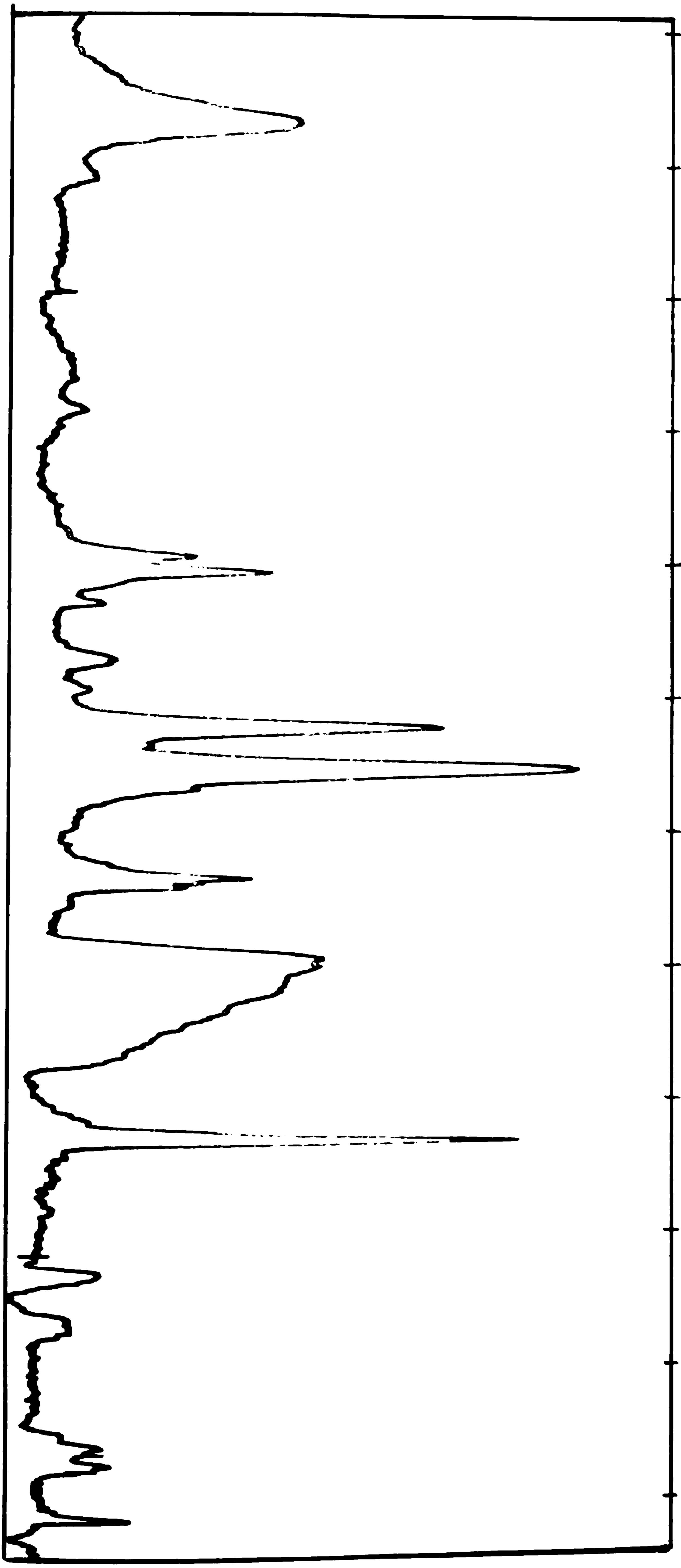

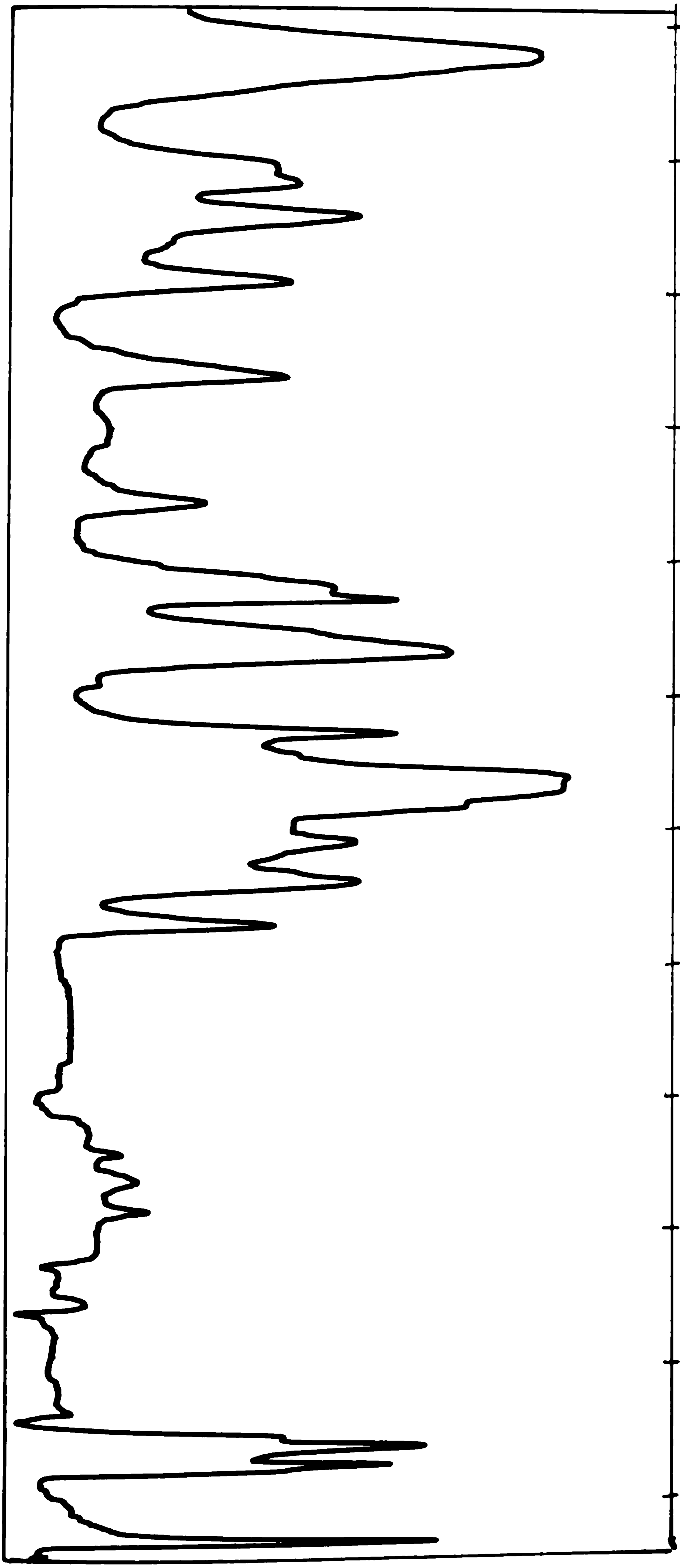

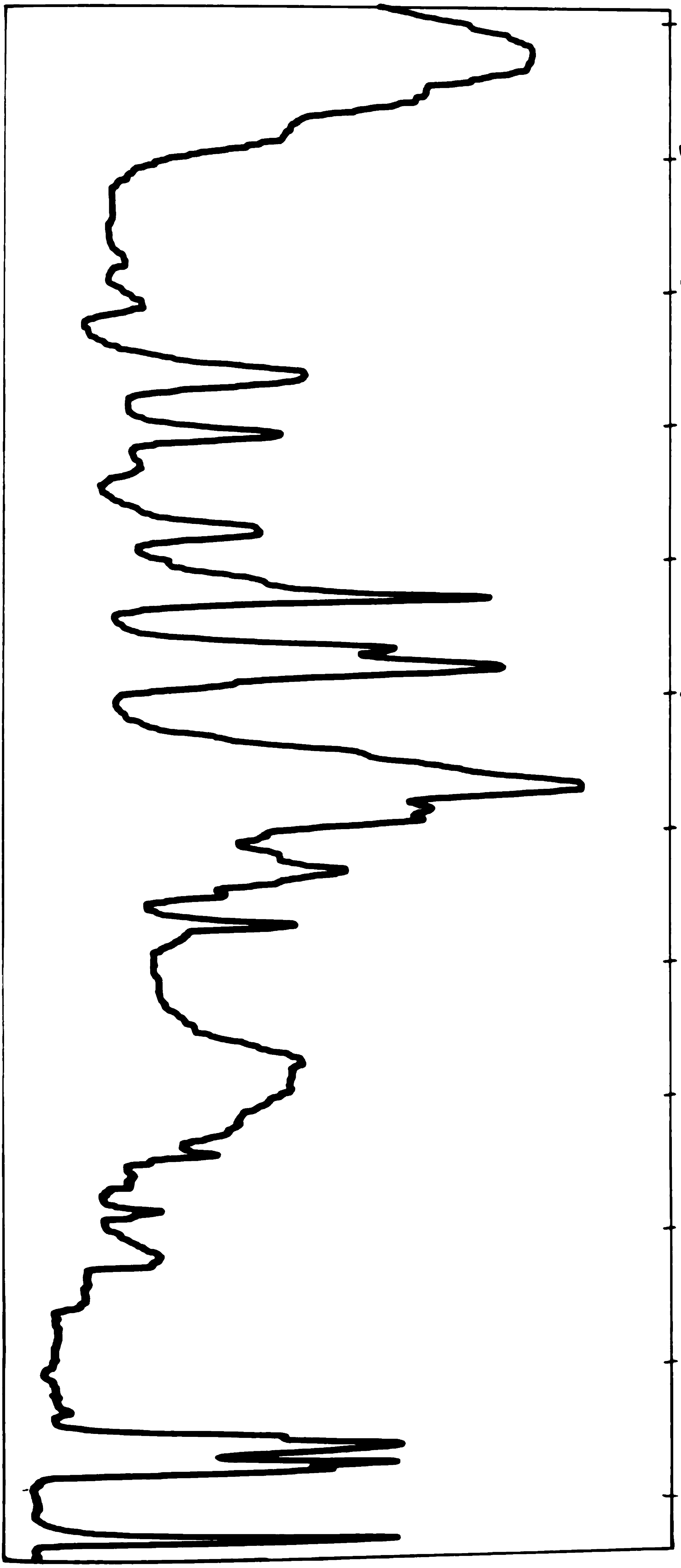

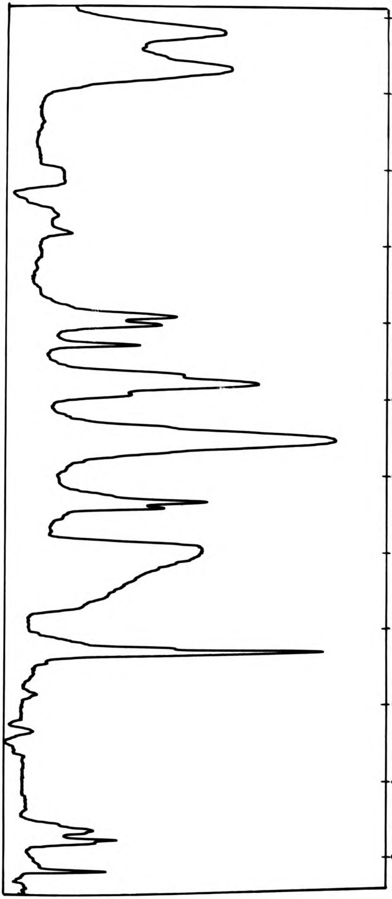

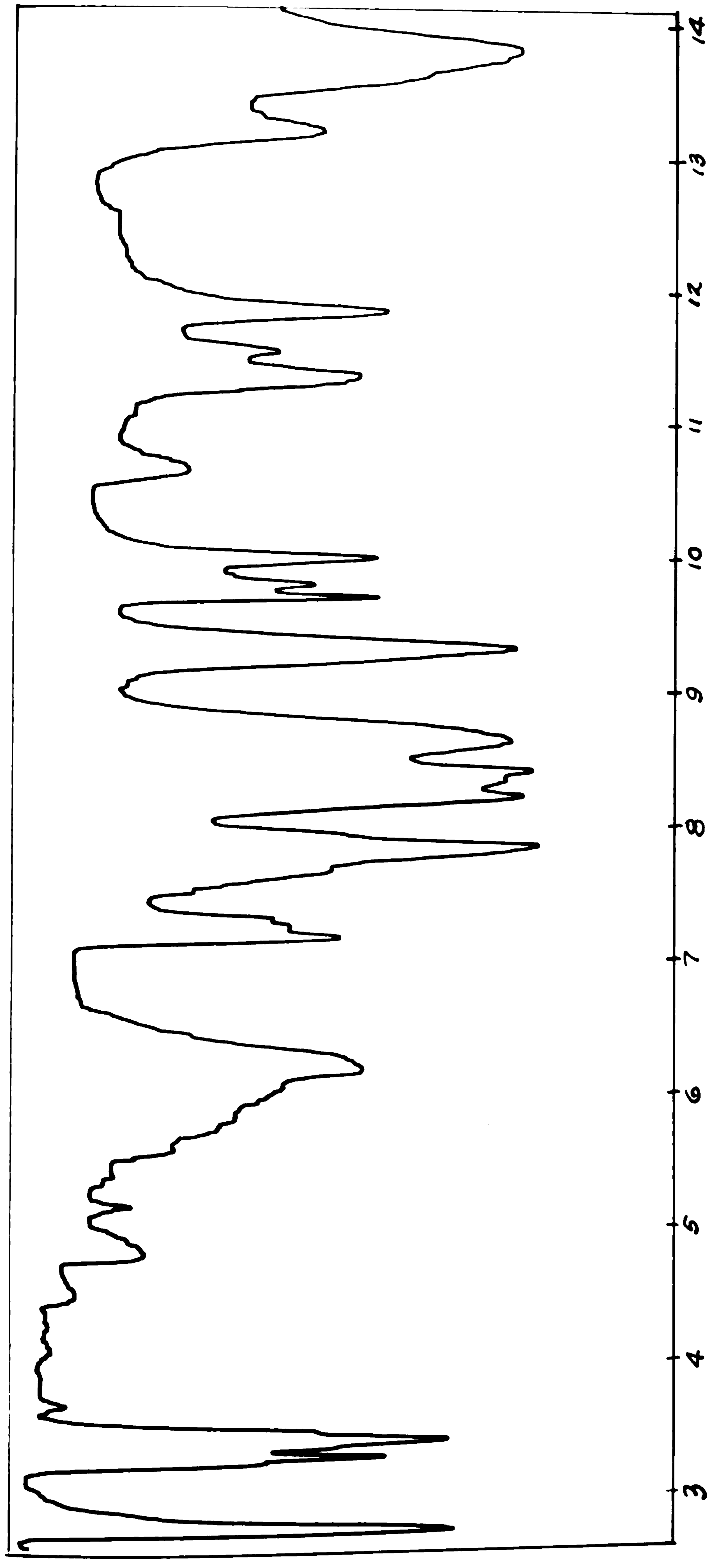
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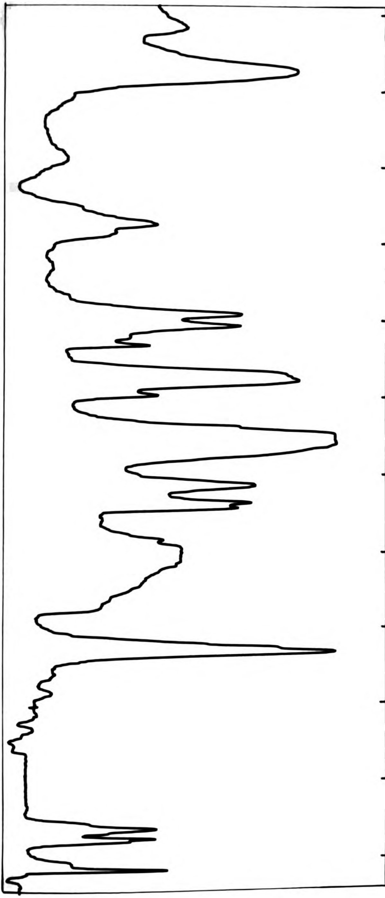

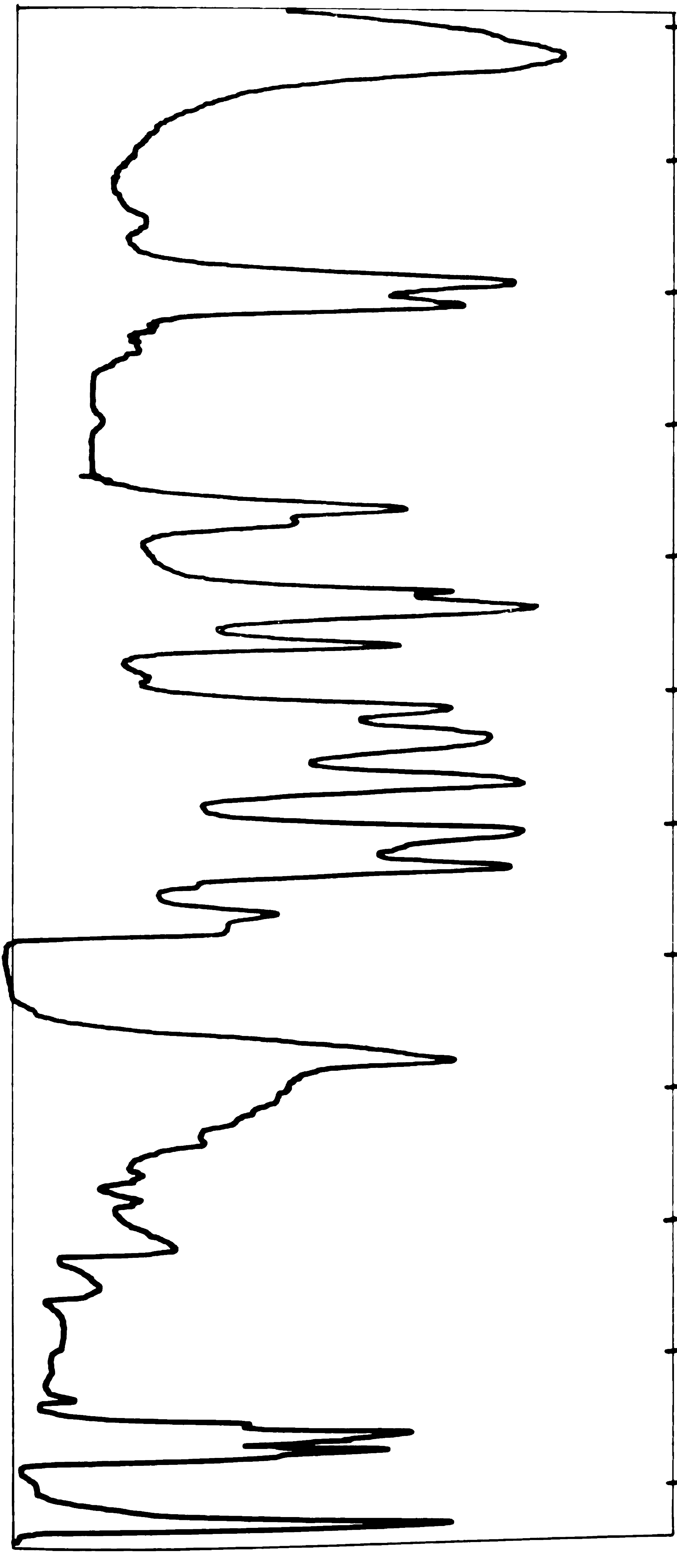

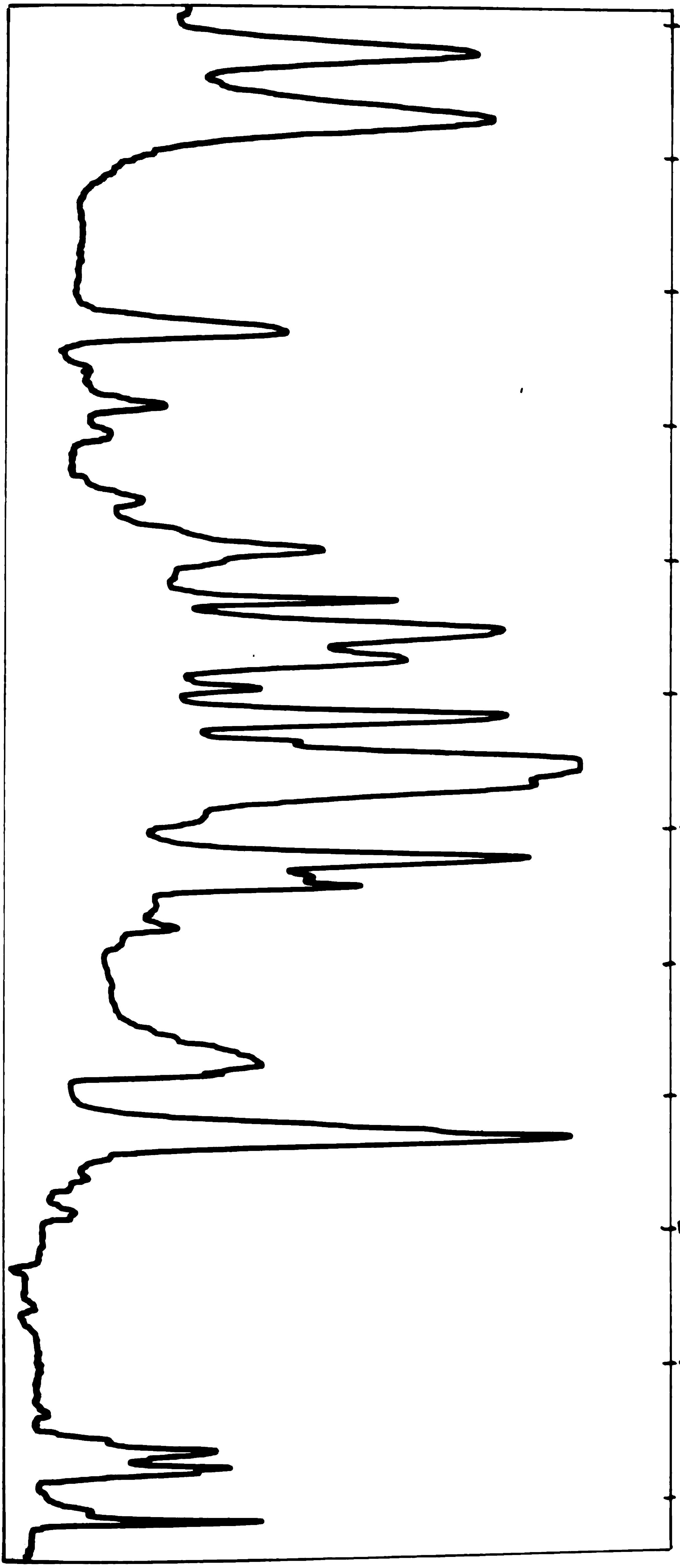

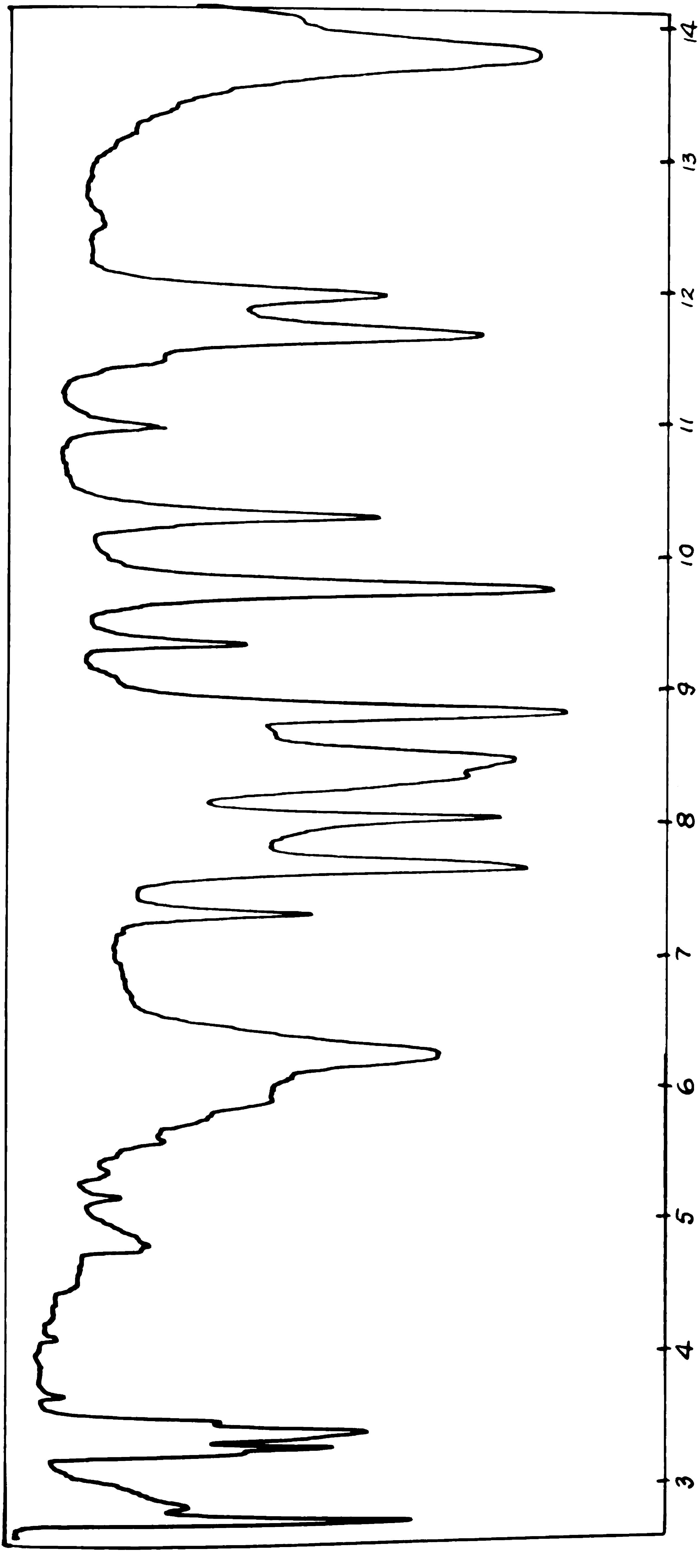
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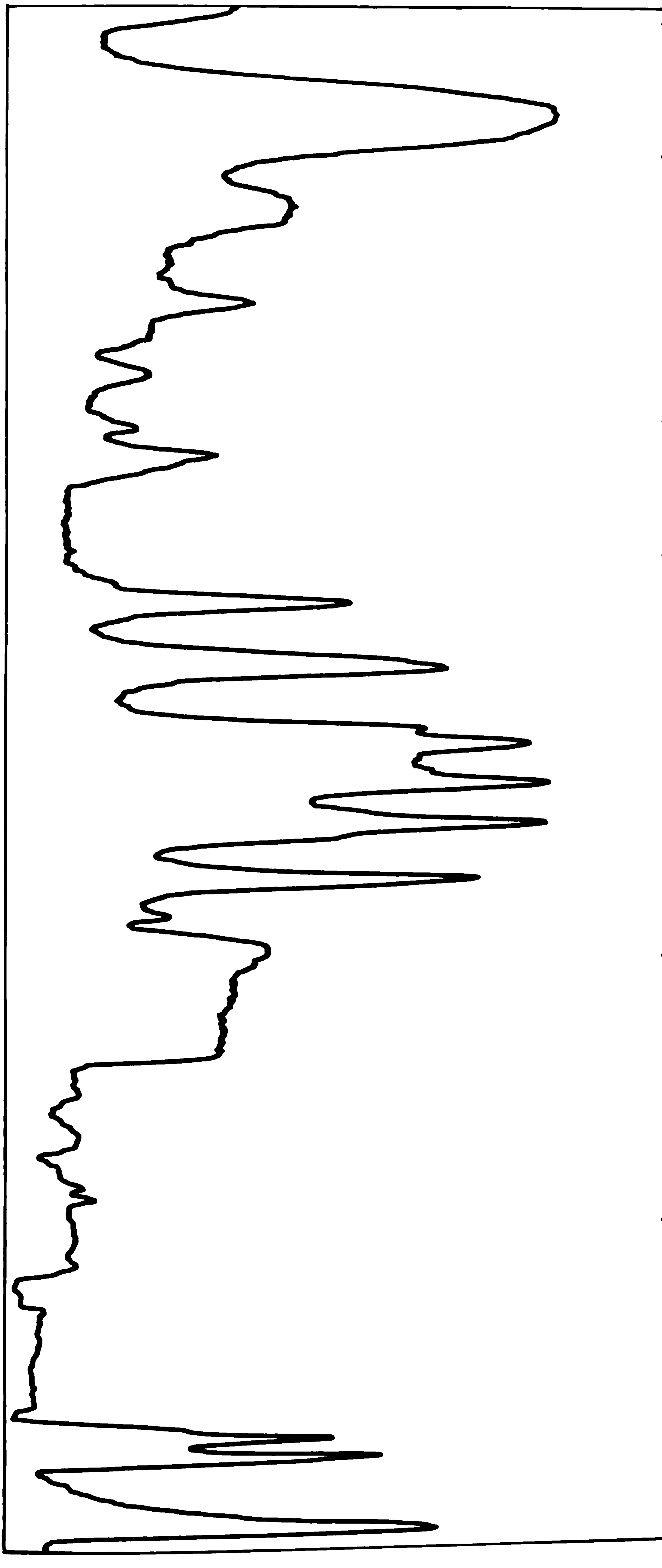

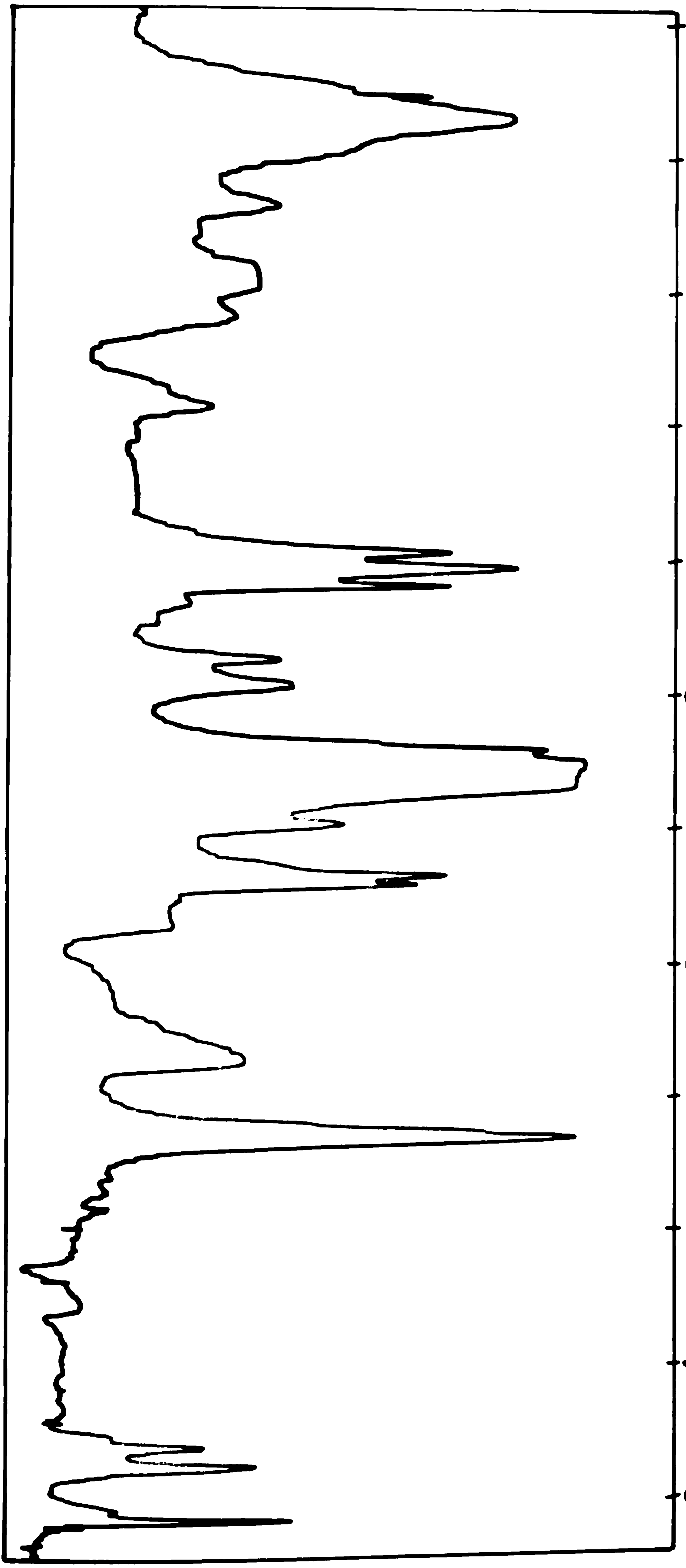

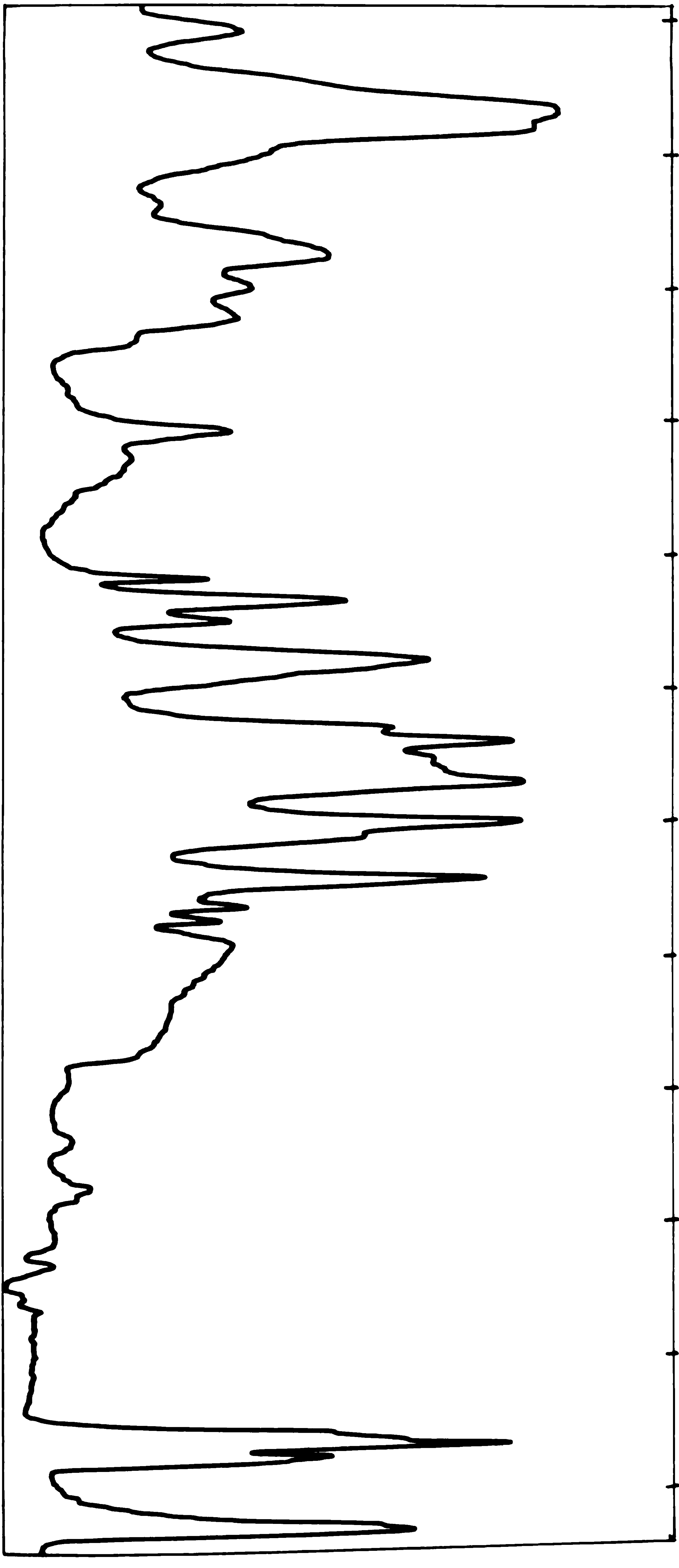

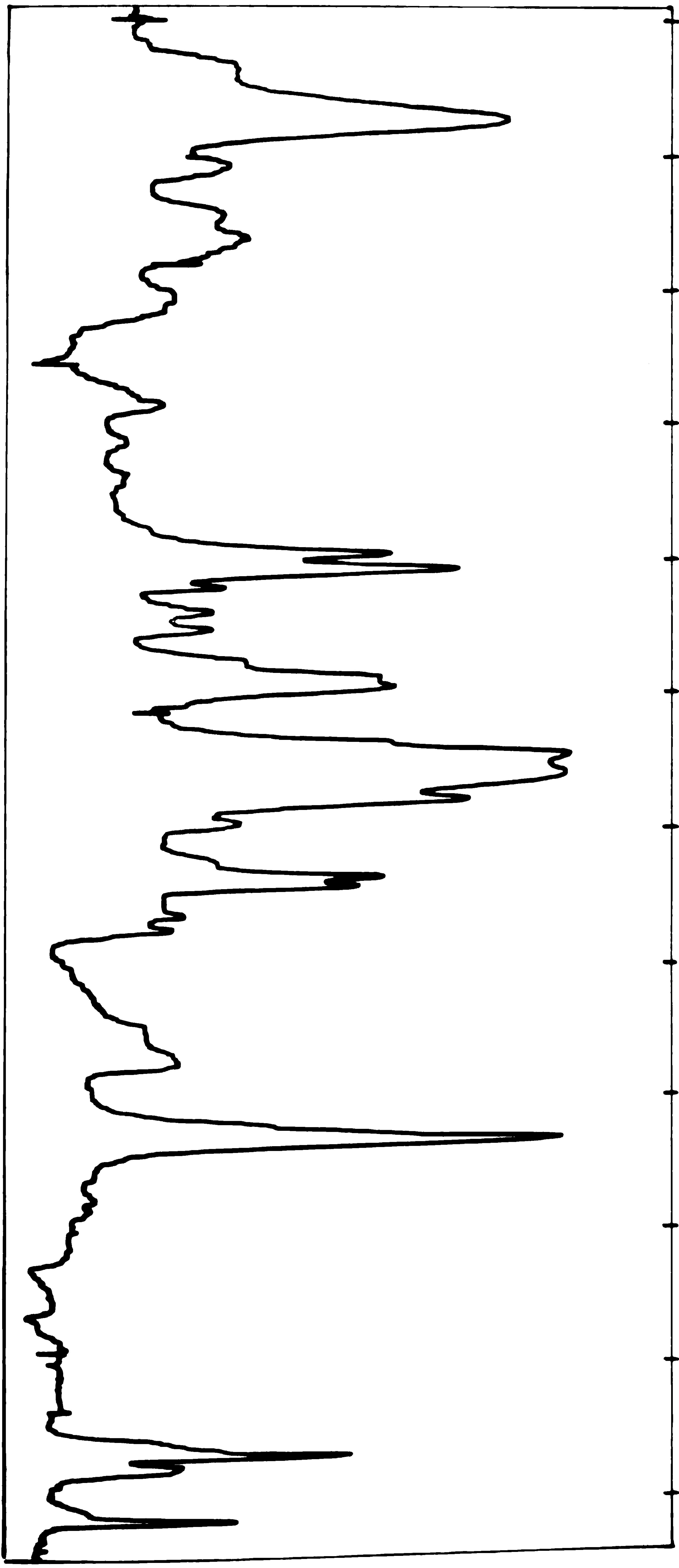

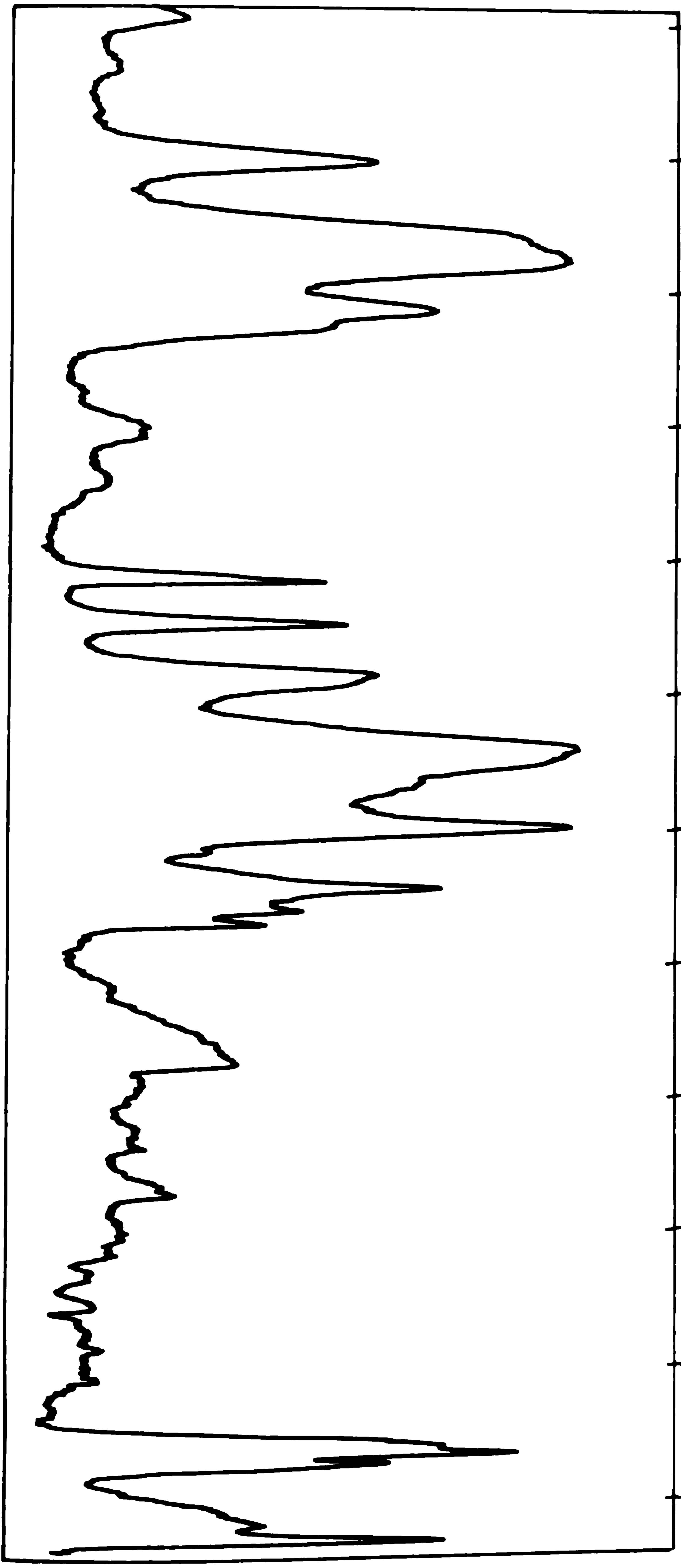

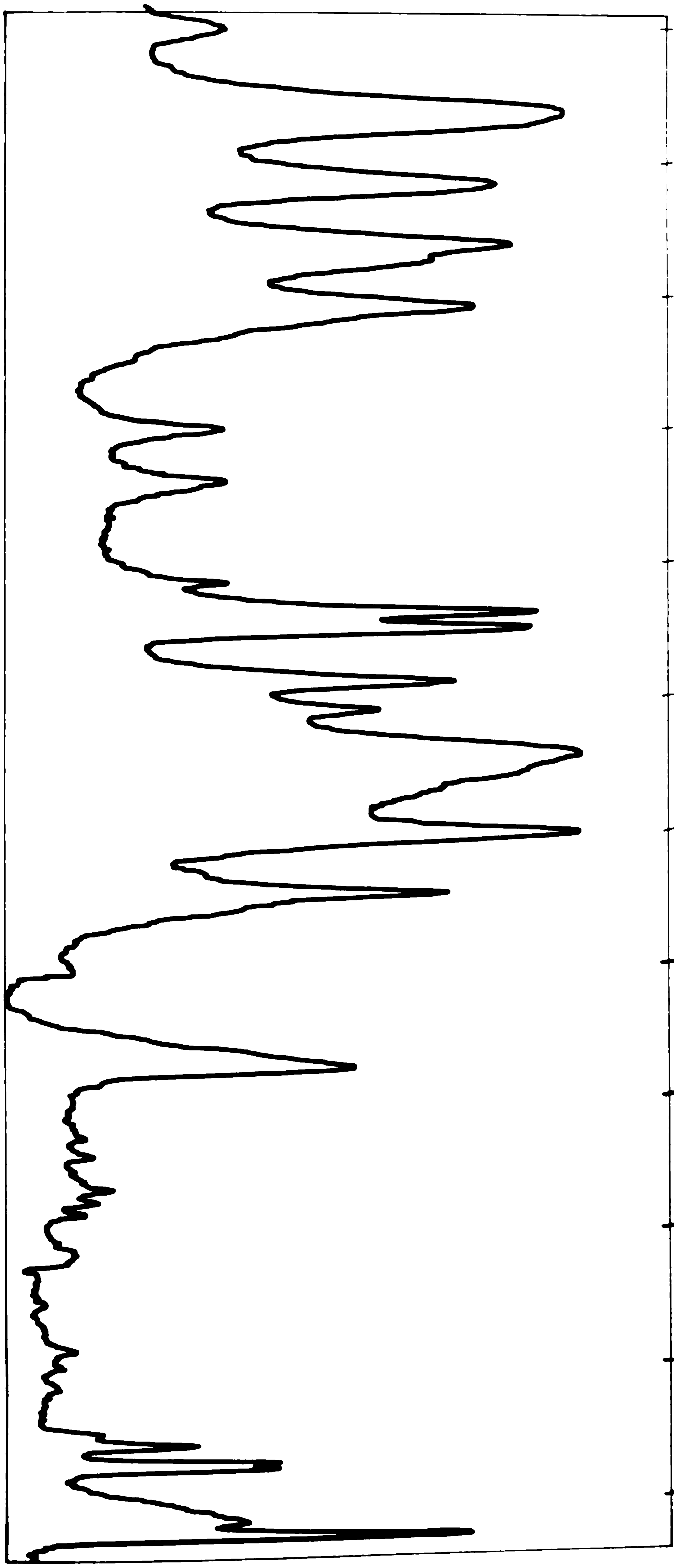

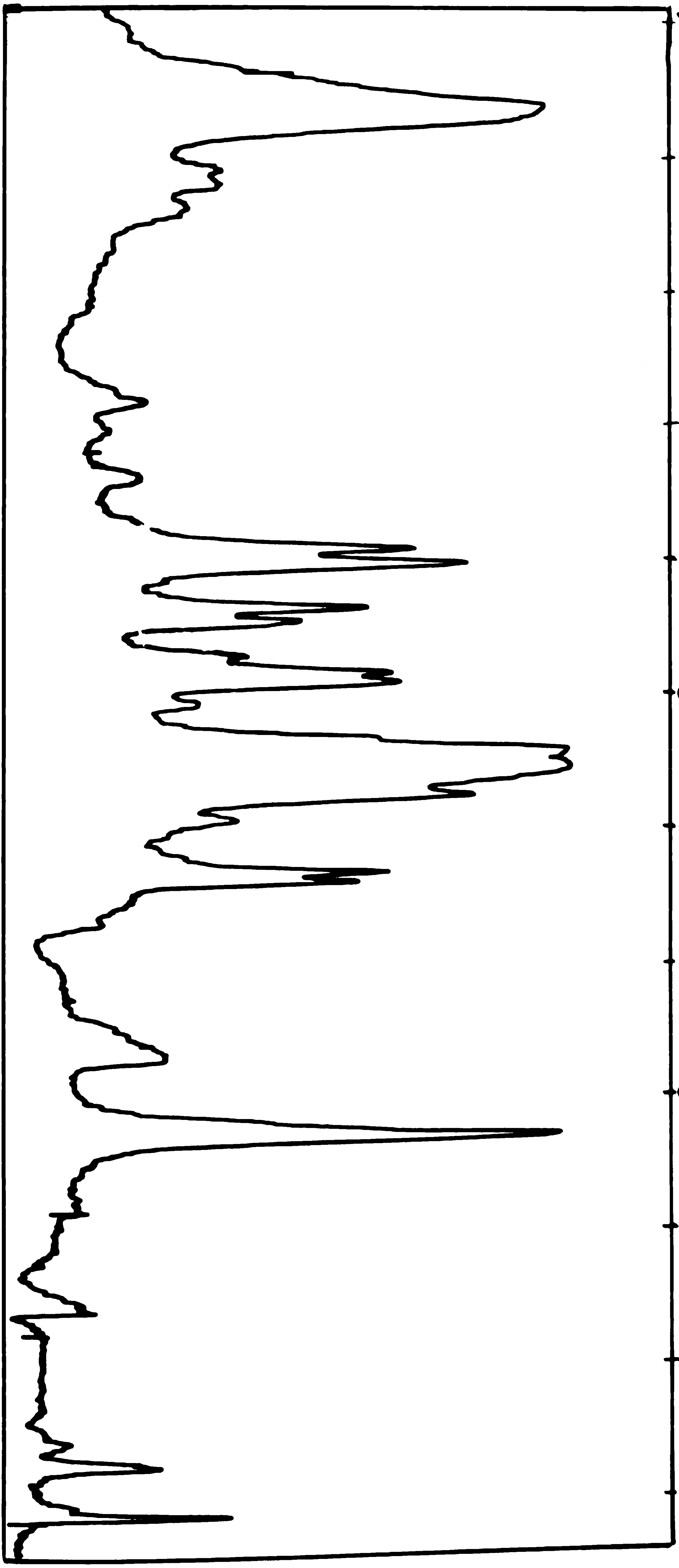

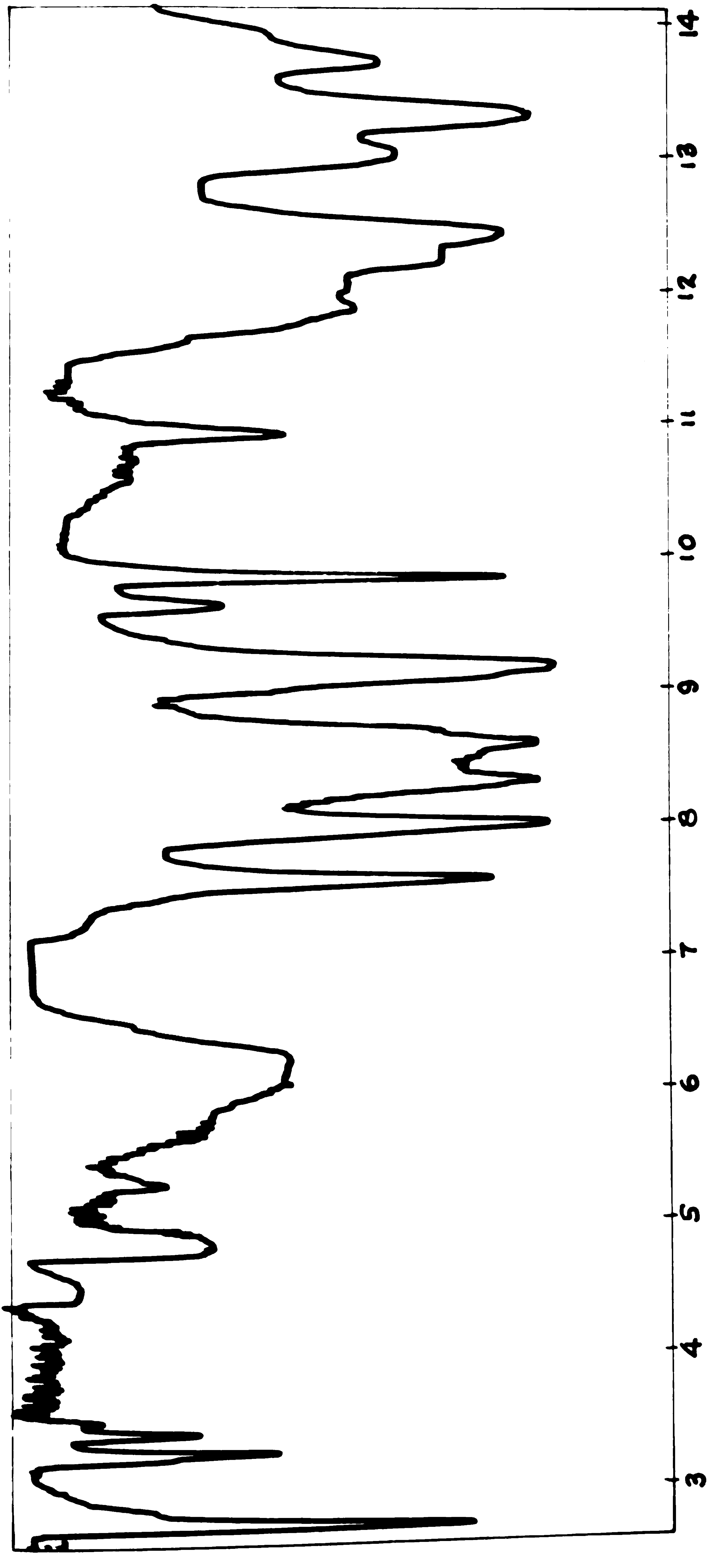
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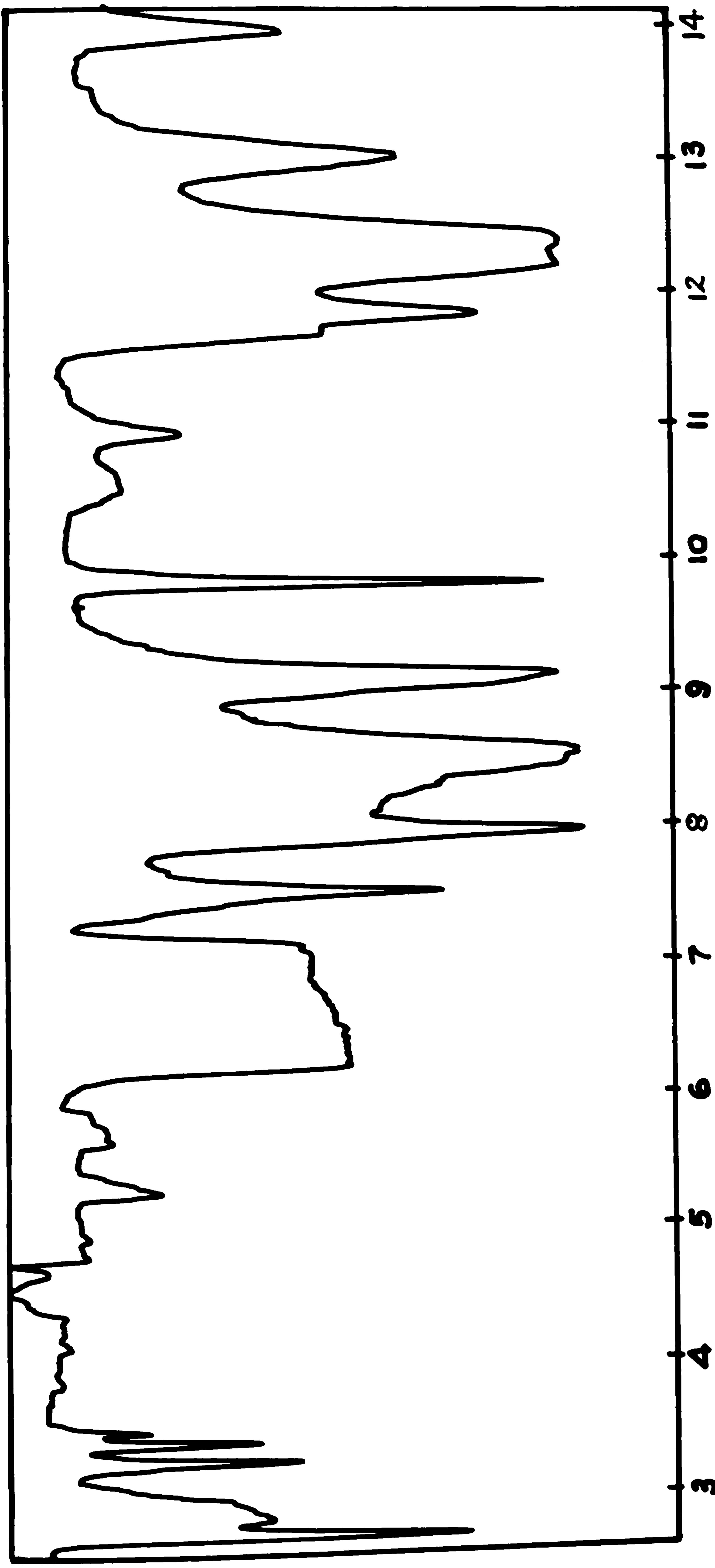
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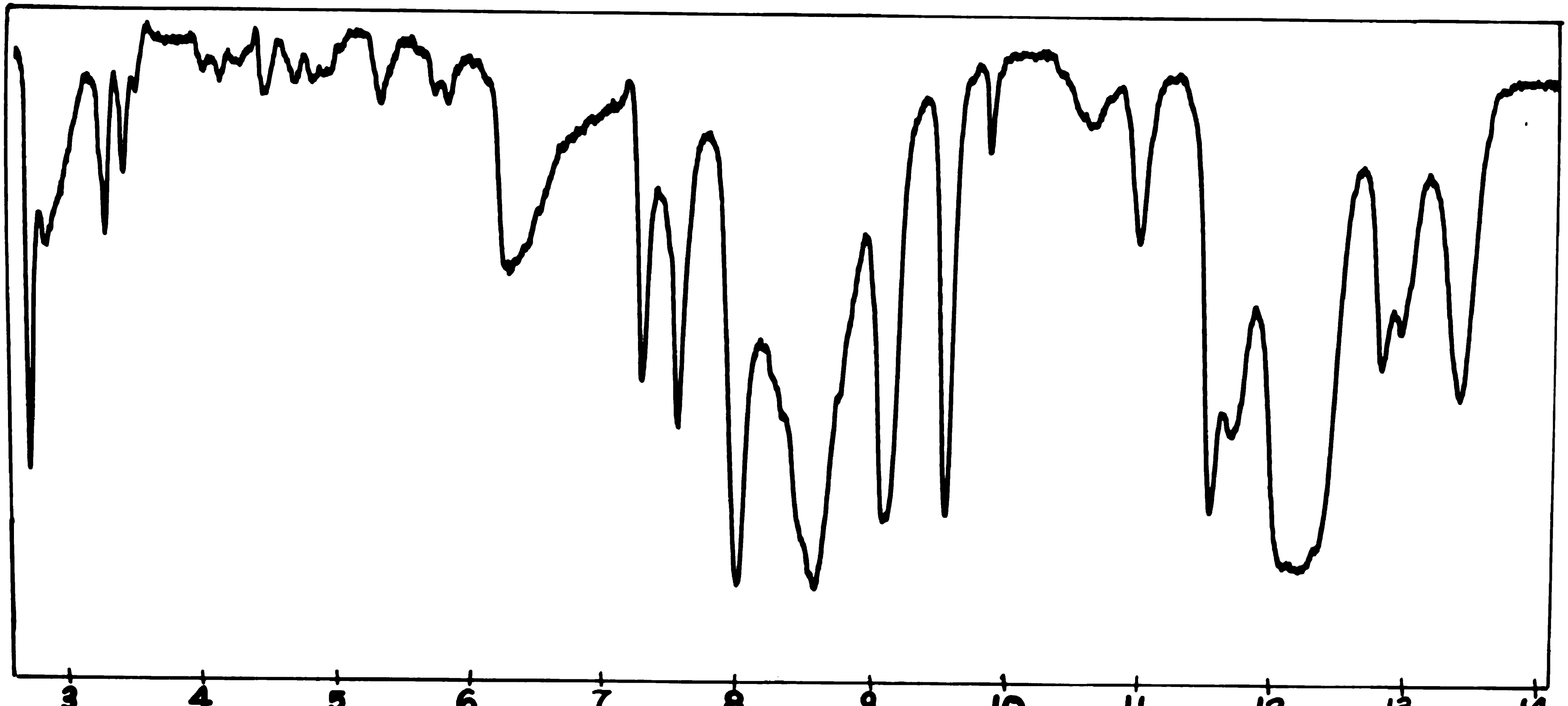
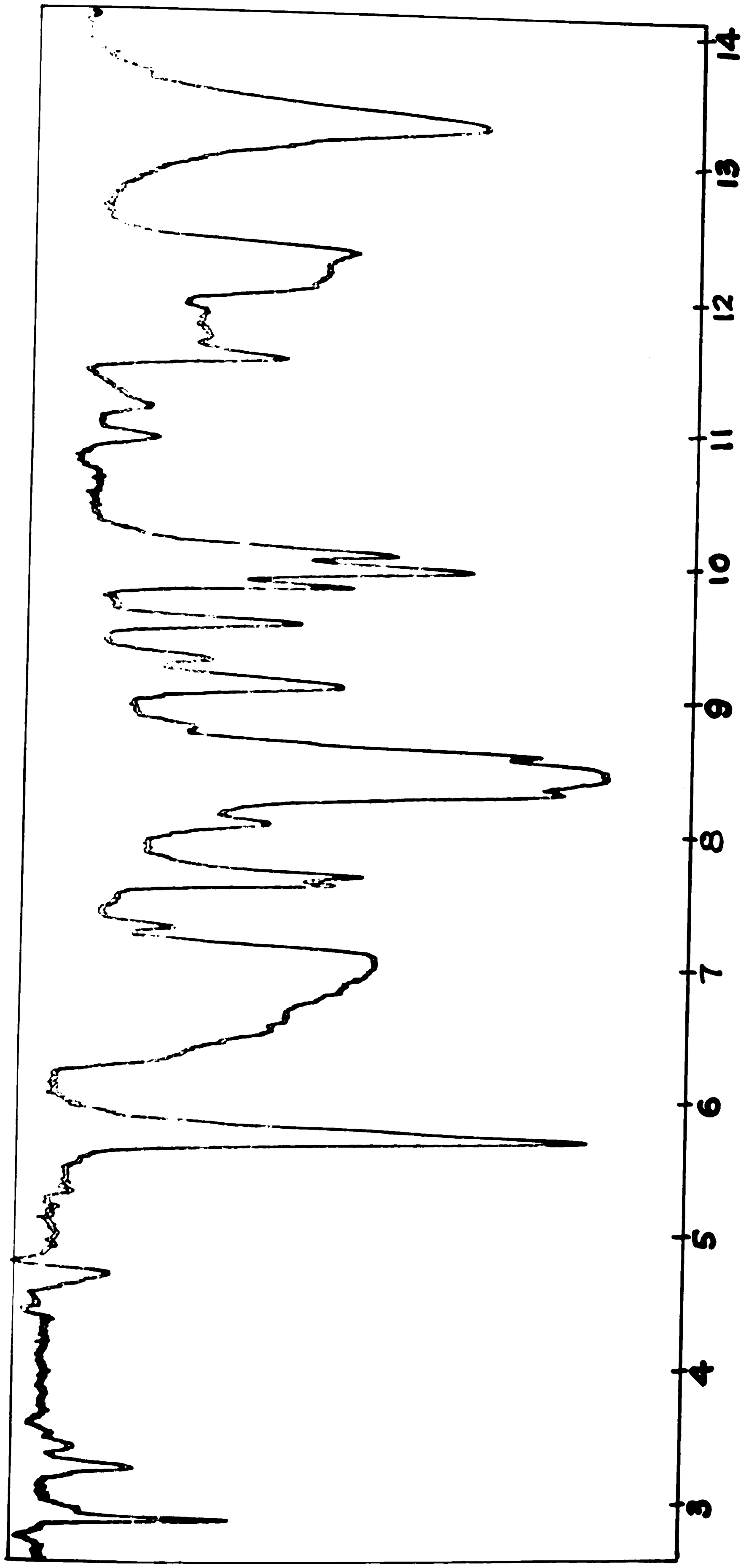
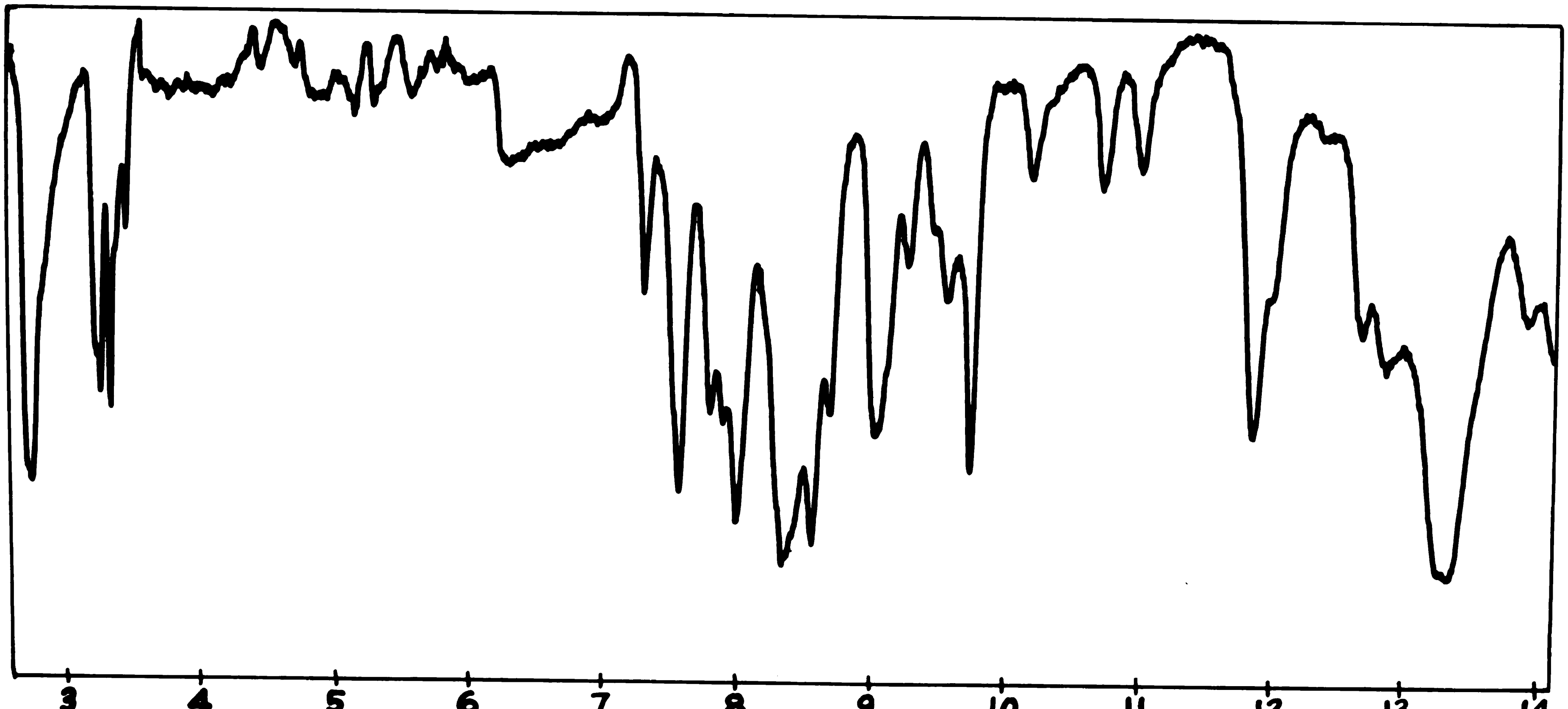


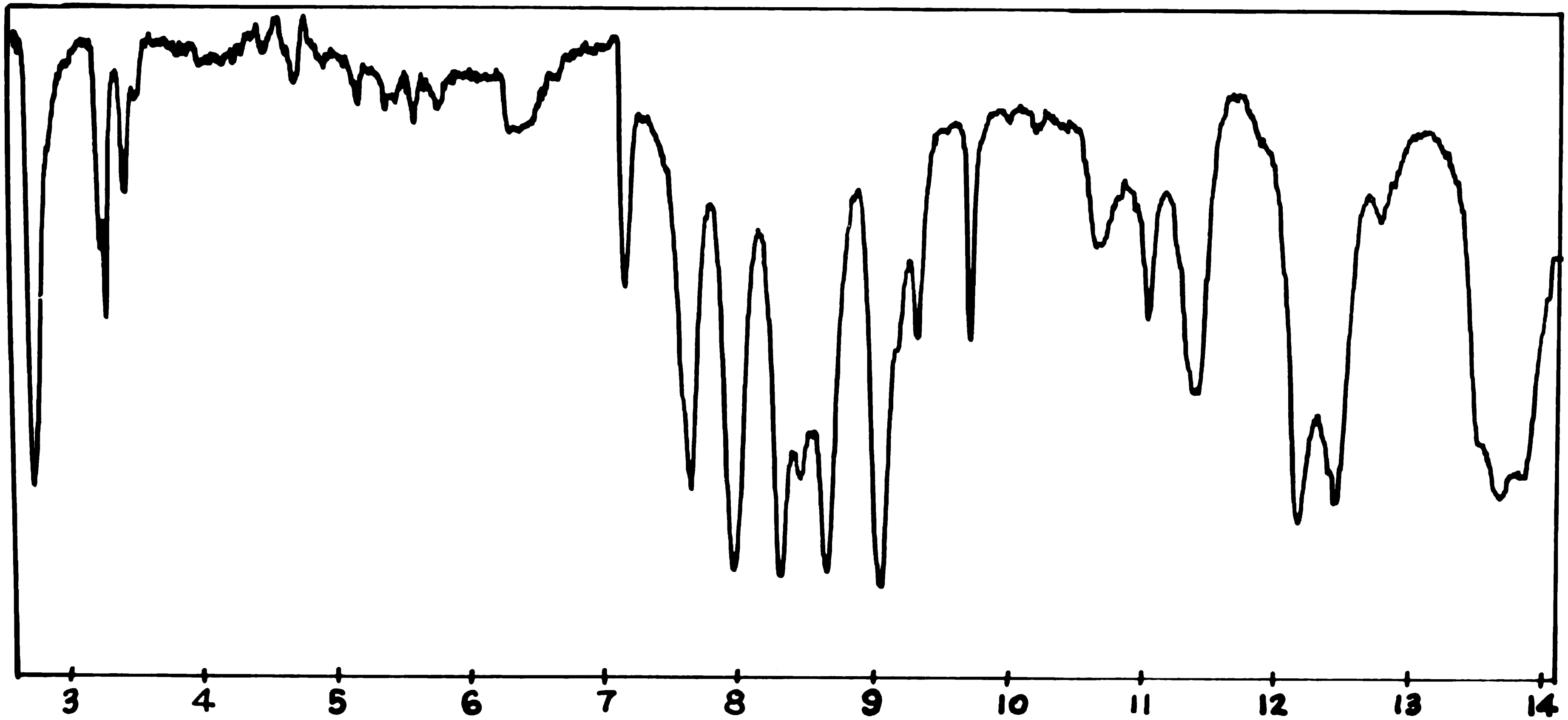
4-(2,4-Dichlorobenzyl) phenol



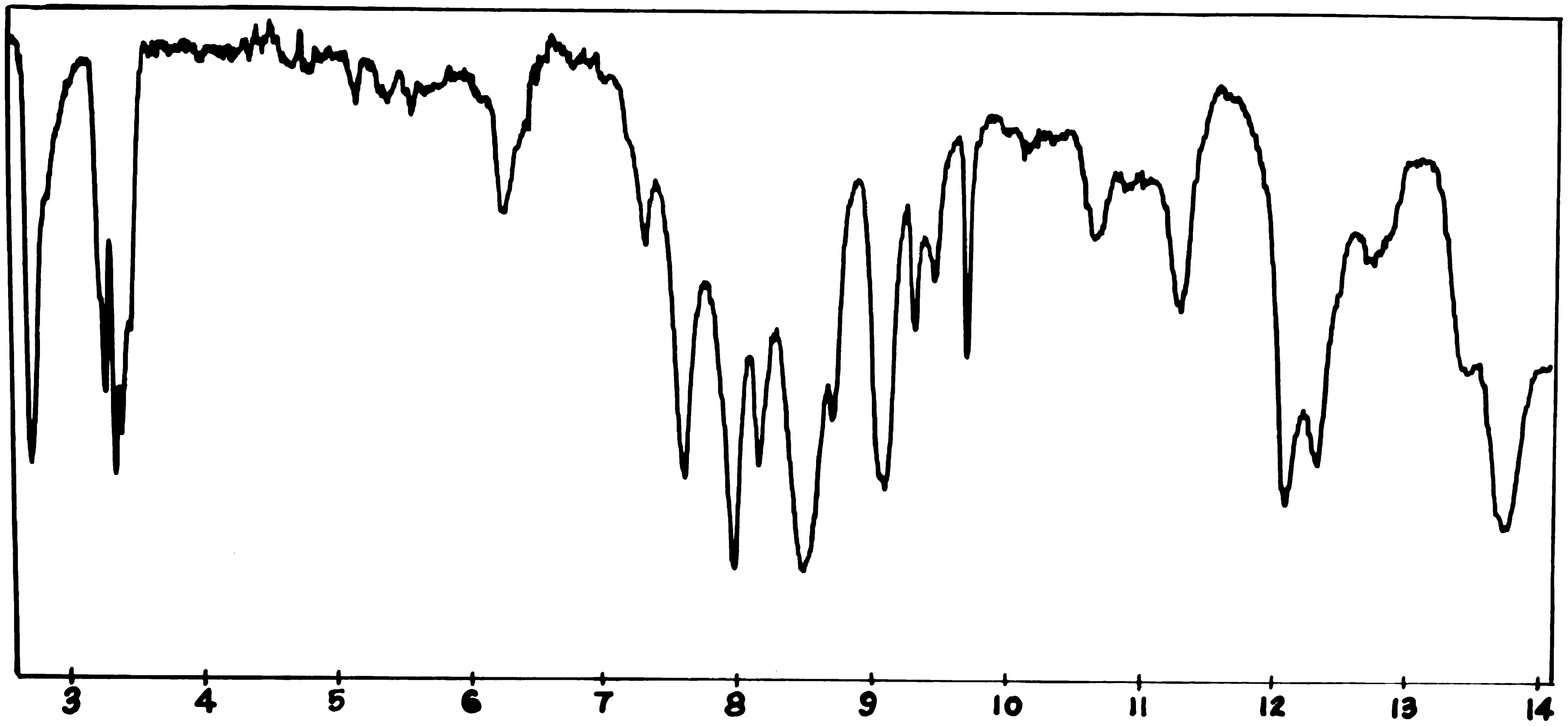
Phenyl Urethane
of 4-(2,4-Dichlorobenzyl) phenol



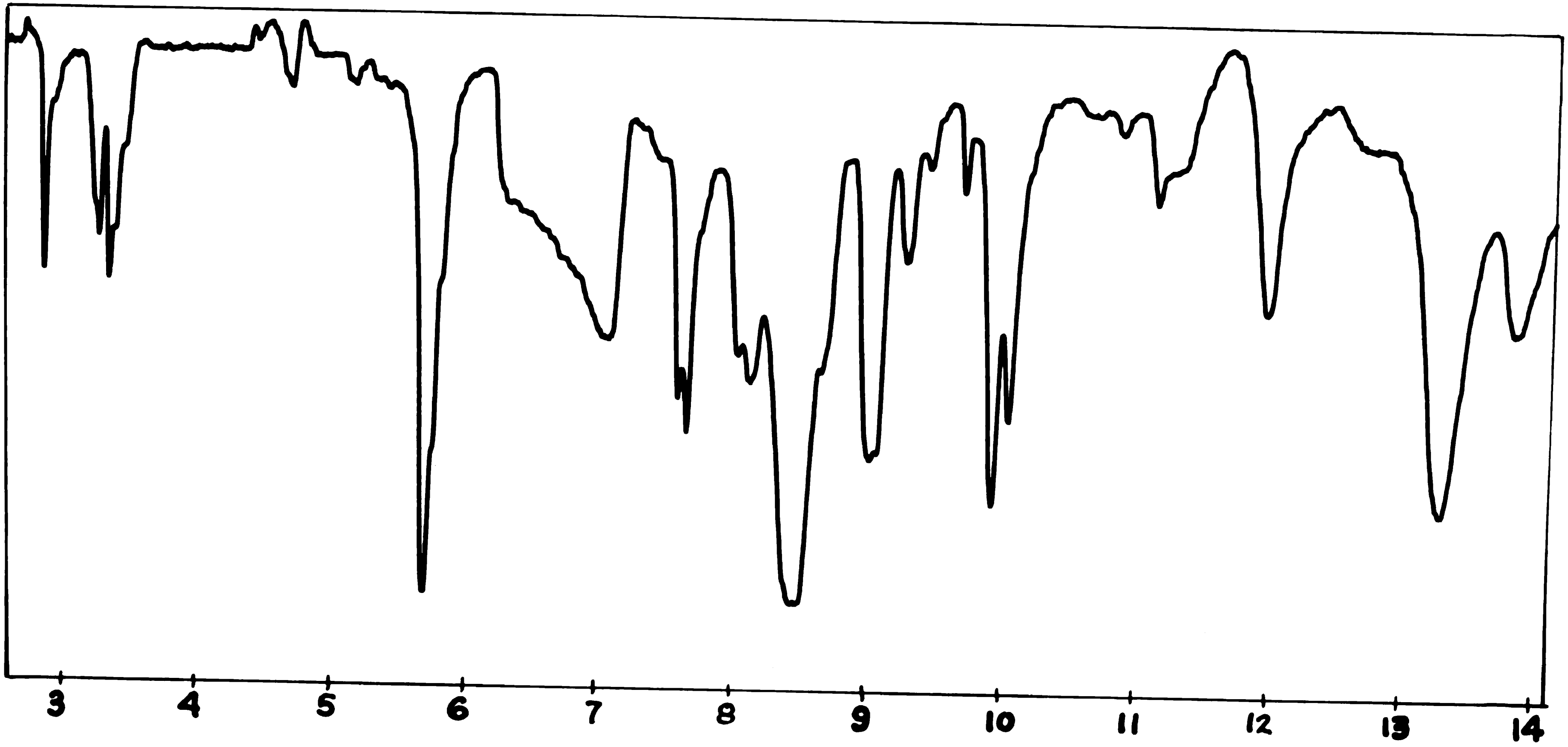
2-(1-Phenylethyl) phenol



2-Benzyl-4-chlorophenol



2-Benzyl-4-ethylphenol



Phenyl Urethane
of 2-Benzyl-4-ethylphenol