THE MERCURY COMPOUNDS DERIVED FROM 5-NITROGUAIACOL

By

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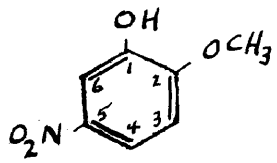
SECTION I

INTRODUCTION

The present work was undertaken as a part of a program of development of possible clinical usefulness of a group of organic mercury compounds of unusually low toxicity. Among this group, the most important is the compound or compounds obtained by direct mercuration of 5-nitroguaiacol. In addition to the present chemical study, a considerable amount of work on the pharmacological and clinical properties of mercurated 5-nitroguaiacol has been carried out. Some of this work is still in progress. It is expected that the more important results will be published soon in the appropriate current scientific journals.

The primary objective of this research was to determine the structure of the mercury compound or compounds obtained by the direct mercuration of 5-nitroguaiacol[1] with mercuric acetate. The structure of 5-nitroguaiacol is recorded below as an illustration of the numbering system used in this thesis for naming derivatives of guaiacol:



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[1]The numbering system indicated here is that commonly

SECTION II

REVIEW OF THE LITERATURE

A. The Mercury Compounds from Benzene Derivatives in which one or more of the Benzene Hydrogens have been replaced by Hydroxyl, Methoxyl, or Nitro groups.

The most obvious approach to a problem of structure determination of a mercury compound is a consideration of the methods previously employed in ascertaining the structure of mercury compounds as nearly similar to the compound in question as possible. It was found that the chemical literature contains a very great number of reports concerning the preparation, properties, and characterization of mercury compounds related to various benzene derivatives. Accordingly, the present review is limited to the literature concerning those benzene derivatives in which one or more of the hydrogens of benzene have been replaced by one or more of the groups present in 5-nitroguaiacol, i.e. nitro, hydroxyl, or methoxyl groups.

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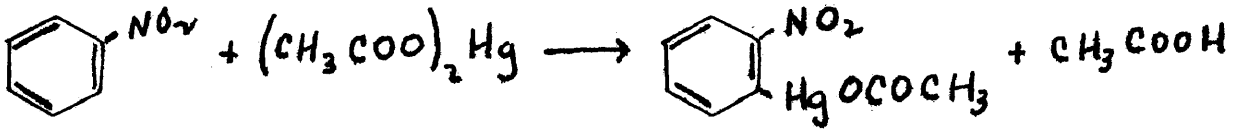
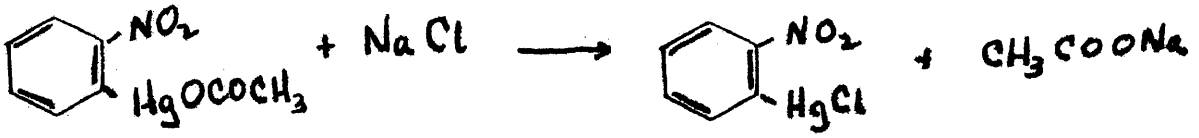
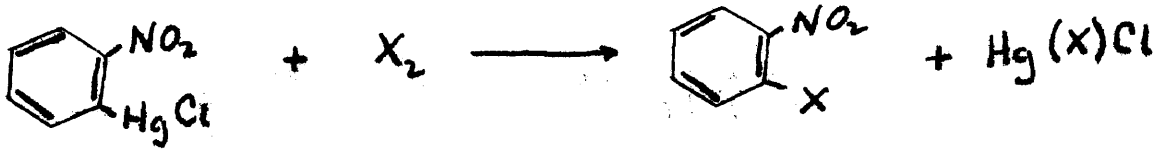
employed in chemical publications in the United States. Some confusion is created by the fact that it is the custom in certain other countries, notably Germany, to name these compounds on the basis of a different numbering system in which the methoxyl group is numbered "1" and the hydroxyl group "2". According to this system, the compound illustrated above would be named 4-nitroguaiacol. Similarly, the "5" and "6" positions would be reversed in the two systems of nomenclature.

It was established by the early work of Dimroth (59, page 129; 10-14) that the mercuration reaction is very nearly as general a reaction of benzene and its derivatives as nitration, sulfonation, or halogenation. Mercuric chloride, mercuric oxide, or, more generally, mercuric acetate have been used as mercurating agents. The general rules of orientation governing the position taken by groups introduced into the benzene nucleus by direct substitution reactions do not apply universally to the mercuration of aromatic compounds. Thus, when nitrobenzene is mercurated with mercuric acetate (13), the entering mercury is not directed to the meta position, as might be anticipated, but to the ortho position, resulting in the formation of o-acetoxymercurinitrobenzene, which, for convenience in isolating a pure compound, can be readily converted into the more insoluble o-chloromercurinitrobenzene (melting point: 182°) by treatment with an excess of sodium chloride solution. These reactions are illustrated by the following equations:





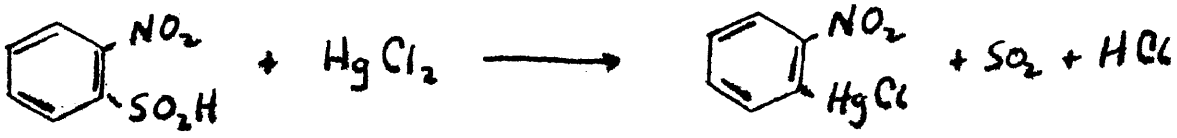
The position of the mercuri group in the latter product (o-chloromercurinitrobenzene) has been clearly established by two different methods which illustrate techniques that have been used in characterizing aromatic mercury compounds. The first of these is the analytical method devised by Dimroth (13). It is based upon a general reaction of compounds having a direct carbon-to-mercury linkage. The reaction is illustrated by the following equation:



The structure of the mercury compound is then obvious from identification of the resulting halogen derivative. Thus, in the above example, bromine was the halogen used by Dimroth; he identified the organic product as o-bromonitrobenzene. Therefore, direct mercuration of nitrobenzene introduces the mercuri group into the ortho position. Dimroth's method is the one that has been most widely used for characterization of aromatic mercury compounds. Its only limitations are the accessibility of the necessary halogen reference compounds by synthetic methods that clearly establish their structures, and the necessity that the mercury compound in question does not react with halogens in any other ways than by the cleavage of carbon-to-mercury

linkages.

A second method for determining the position of the mercuri group in aromatic compounds is based upon the synthesis of the mercury compound by the method of Peters (41) by the reaction of an aromatic sulfinic acid and mercuric chloride. Thus, the following reaction between o-nitrobenzenesulfinic acid and mercuric chloride takes place in aqueous alcohol:

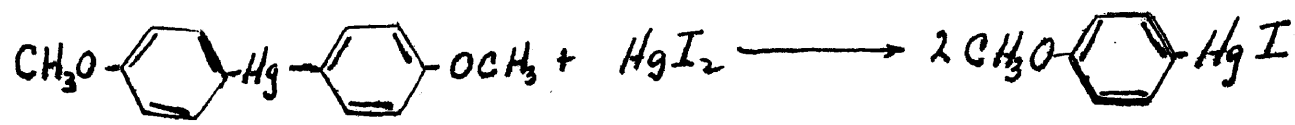


The mercury compound formed is identical in all respects with that obtained by direct mercuration of nitrobenzene (28). The sulfinic acid was prepared by the method of Gattermann from replacement of the corresponding diazonium group, which leaves no doubt as to its structure (17). The identity of the mercury compound synthesized in this way, therefore, with that obtained by direct mercuration is a proof of the structure of o-chloromercurinitrobenzene.

The meta and para isomers of chloromercurinitrobenzene have also been prepared in the same manner and their structures verified by conversion to meta and para bromonitrobenzene, respectively, by the method of Limroth (17).

Phenol is mercurated very much more readily than is nitrobenzene. A variety of mercurating agents have been used, including mercuric acetate (10,11,14,32,39,61), mercuric chloride (9,11,12,19), mercuric nitrate (11), and mercuric sulfate (11). With mercuric acetate in aqueous medium, the reaction proceeds rapidly, even at room temperature; a mixture of three products is formed. The mixture has been separated after conversion to the corresponding chlorides (14,32,61) into the ortho and para monomercurated compounds and the ortho-para dimercurated compound. Dimroth (10) characterized the monomercurated derivatives by the method outlined above. In this case, iodine was the halogen used, and the products were identified as o- and p-iodophenol, respectively. Dimroth (10) confirmed this evidence by converting the monomercurated phenols, by standard procedures, to o- and p-iodomercurianisole, respectively, and comparing the products with those that Michaelis and Rabinerson (35,36) had prepared earlier by another method for synthesising aromatic mercury compounds of known structure.

This method is based upon the reaction of mercuric salts with derivatives of diphenyl mercury, $C_6H_5-Hg-C_6H_5$, in which the mercury atom is linked to two different aromatic carbon atoms. The reaction is illustrated as follows:



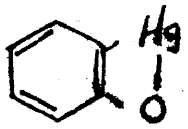
The necessary diphenyl mercury derivatives were obtained by the reaction of the appropriate bromobenzene derivative with sodium amalgam in the presence of catalytic quantities of ethyl acetate, as described by Otto and co-workers (15,16, 38).

The structure of the dimercurated compound from phenol has been determined by identification of the 2,4-diiodophenol formed by reaction with iodine. This reaction occurs so readily that it has been adapted to quantitative determination of the mercury content of such compounds (2).

The mercury compounds from phenol, in general, retain the chemical properties imparted by the phenolic hydroxyl group. They are soluble in aqueous alkali, forming alkali metal salts which may be precipitated with alcohol (14). In many cases, the sodium and potassium salts are crystalline. The hydroxyl group of the mercurated phenols has been alkylated (10), acetylated (61), and benzoylated (14). These mercury compounds have also been coupled with diazonium salts in the usual way with coupling taking place in free <u>para</u> and <u>ortho</u> positions (12,14,47). The p-nitroso derivative of <u>o</u>-chloromercuriphenol has been prepared by its reaction with nitrous acid (29).

Phenols having a mercuri group in the <u>ortho</u> position to the hydroxyl group, in general, possess the property of forming inner anhydrides. These compounds are precipitated from alkaline solutions of the <u>ortho</u>-mercurated phenols by

treatment with carbon dioxide and are extremely insoluble in nearly all solvents (14). For example, the inner anhydride formed from o-mercurated phenol itself may be represented as:



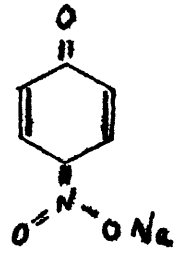
There is evidence that anhydride formation may occur by elimination of acetic acid from an o-acetoxymercuriphenol (58). The evidence presented by Kharasch (27) concerning the structure of the mercury compound obtained from direct mercuration of 2-nitro-4-hydroxymethylphenol indicates that failure to form an anhydride does not constitute proof that a phenolic mercury compound has not been mercurated in the ortho position, as was assumed by Hart and Hirschfelder (21).

Phenol ethers react much less readily with mercuric acetate than does phenol itself. A higher temperature is required and no dimercurated products have been reported. For example, when anisole is mercurated with mercuric acetate, the principal product is p-acetoxymercurianisole; only minute amounts of the ortho isomer are formed (14,61). Phenetole apparently is mercurated directly only in the para position (12,13,33).

When nitrophenols are mercurated with mercuric salts, the directive influence of the hydroxyl group is strongly predominant. Adequate proof of the structures of the compounds obtained by direct mercuration of several nitro-

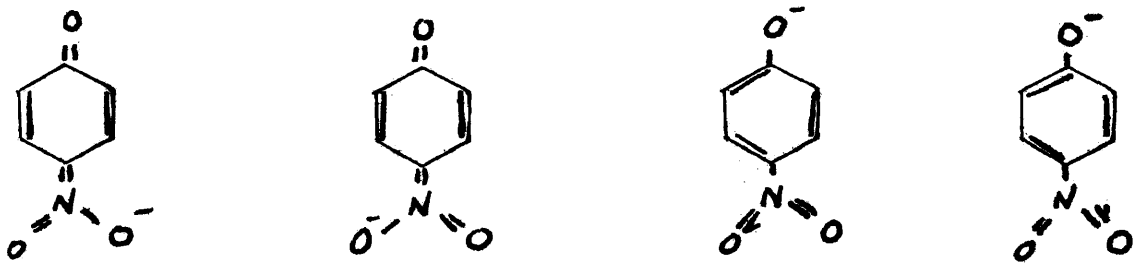
phenols is given by Hantsch and Auld (20), who studied the mercuration of picric acid, 2,4-dinitrophenol, o-nitrophenol, and p-nitrophenol, using the halogeration reaction of Dimroth to ascertain the position taken by the entering mercury atom. They established the fact that in each of these compounds, mercuration takes place readily in the free para or ortho position. Picric acid, in which the para and ortho positions are blocked, is mercurated only very slowly in the position meta to the hydroxyl group. Ortho-nitrophenol, in which both a para and an ortho position are free, is mercurated in the para position.

The primary products obtained by mercuration of nitrophenols appear to be anhydrides of an aci-nitro group and an hydroxymercuri group (20;59, page 270). The sodium salts obtained by precipitation with alcohol from alkaline solutions of these anhydrides are also very highly colored, and the structures assigned to them by Hantsch and Auld were those of salts of aci-nitroquinoid compounds, as illustrated below:



The more modern concept of resonance undoubtedly offers a more accurate structural interpretation for these compounds. For example, the following structures are probably the most important extremes in the "resonating" anion

of the above sodium salt:



No reference has been found to attempted mercurations of, or to mercury compounds from, m-nitrophenol. This would be of particular interest in connection with a study of the mercuration of 5-nitroguaiacol because the nitro and hydroxyl groups are in the same relative location in the two compounds. The widely used antiseptic, metaphen, is a di-mercurated derivative of 4-methyl-3-nitrophenol, and is assumed by Raizisa (44,45) to be mercurated in the positions ortho and para to the hydroxyl group, but no evidence has been recorded.

An evaluation of the relative effect of alkoxyl and nitro groups upon the introduction of mercury into compounds containing both groups is not possible, since no information has been found concerning the mercuration of nitro-substituted phenol ethers.

The mercuration of guaiacol has been reported in a private communication from Raizisa to Whitmore (59, pages 59 & 282). No data is given as to the structure of the product, which is assumed by Raizisa to be dimercurated in the ortho and para positions to the hydroxyl group.

Raizisa has also reported in a private communication to Whitmore (59, page 282) the preparation of a mercury com-

pound from p-nitroguaiacol (4-nitroguaiacol) by direct mercuration with aqueous mercuric acetate. He assumed that mercuration took place in the ortho position to the hydroxyl group, again without specific evidence of structure. No other reports of the mercuration of nitroguaiacols have been found.

From the results summarized above, it would be predicted that the mercuration of 5-nitroguaiacol would most probably take place in the para and ortho positions to the hydroxyl group, or in both these positions.

B. Bromo-, Nitro-, and Bromonitroguaiacols.

All of the available methods for establishing the positions which are affected by the mercuration of 5-nitroguaiacol would depend upon the availability of halonitroguaiacols of known structure in which the halogen atoms occupy the same positions as the mercury atoms of the mercuration product or products. Consequently, a search of the literature was made for bromine and iodine derivatives of 5-nitroguaiacol. Only two are recorded. Robertson (50) has reported the preparation of 6-bromo-5-nitroguaiacol (melting point: 150°) from bromination of 5-nitroguaiacol. No satisfactory proof of its structure is recorded. We have been unable to prepare this compound from Robertson's directions. We have attempted bromination of 5-nitroguaiacol in various solvents, including boiling acetic acid and have obtained virtually quantitative recovery of unchanged 5-nitroguaiacol. Robertson has given no information as to the source of the 5-nitroguaiacol he used for his experiments.

Raiford and Silker have prepared 4-bromo-5-nitroguaiacol (43). The evidence cited by them appears to constitute adequate proof of its structure and they have kindly furnished us with a sample of the product.

The bromoguaiacols were also considered as possible reference compounds since bromonitroguaiacols could be identified by elimination of the nitro group by reduction, diazotization, and replacement of the diazonium group with

hydrogen (31), or with bromine by means of the Sandmeyer Reaction, if the resulting bromoguaiacols were known. 4-Bromoguaiacol (melting point: 45-46°) has been reported in the patent literature (23) and also by Rosenmund and Kuhnhenn (51) and by Robertson (50). We have confirmed the structure of the bromoguaiacol of this melting point by its synthesis from a sample of 4-nitroguaiacol by reduction, diazotisation, and replacement of the diazonium group with bromine by a Sandmeyer reaction. 6-Bromoguaiacol (melting point: 63°) has also been reported by Robertson. We have also confirmed its structure by its synthesis from an authentic sample of the corresponding nitro compound by reactions analogous to those used for 4-bromoguaiacol.

Raiford and Silker (43) have described the synthesis of 4,5-dibromoguaiacol (melting point: 95°) and this appears to be the compound obtained earlier by Cousin (4) and also by Hoffmann (24). The tribromo derivative obtained by direct bromination of guaiacol has been reported by many workers (6-8; 22,43,53-55). It has been characterized by Zagirolami (65) as 4,5,6-tribromoguaiacol.

It was of fundamental importance, of course, that the samples of 5-nitroguaiacol used for this mercuration study should be authentic and pure. A search of the literature shows that syntheses of nitroguaiacols have been described by many workers (3,5,26,30,40,42,46,48,49,52,57). While all of the possible mononitro isomers have undoubtedly been

prepared, no fully satisfactory characterization of these compounds has appeared in the literature. However, in a private communication to the author, Jaeger has reported experimental details of their full characterization, as well as a synthesis of pure 5-nitroguaiacol. Details of the synthesis are recorded in Section III B of this thesis.

Jaeger's proof of the structures of the nitroguaiacols is a part of a broader study of the methoxynitrophenols, some of the results of which are summarized in Table I.[1] All of the compounds shown have been prepared. The various synthetic methods used in preparing them is not essential to the proof of their structures and hence are not quoted here.

Series I represents all of the possible methoxynitrophenols. The compounds listed in Series II were derived from those of Series I by reduction, diazotization, and replacement of diazonium groups by hydroxyl groups. The compounds in Series III were obtained by methylation of those of Series I. The compounds in Series IV were obtained from Series III by reduction, diazotization, and replacement of the diazonium groups by hydrogen. The compounds in Series V were prepared from Series II by methylation.

The proof of the structures of these compounds is based

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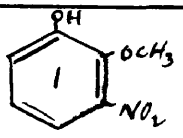
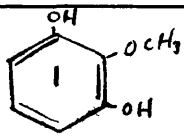
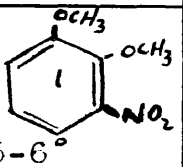
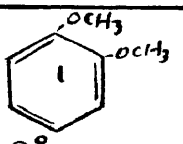
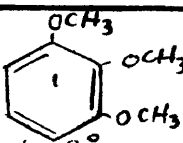
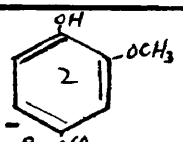
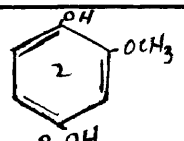
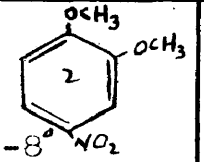
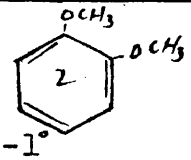
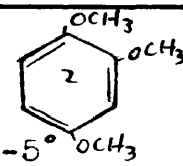
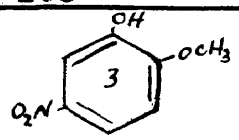
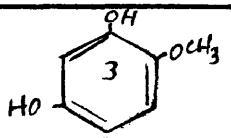
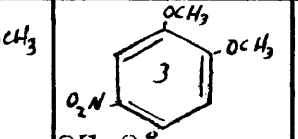
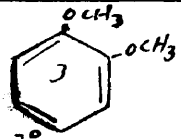
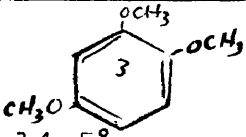
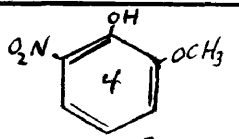
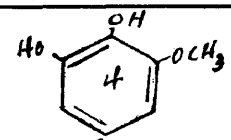
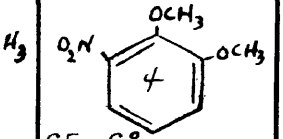
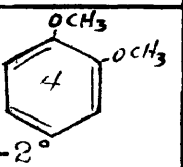
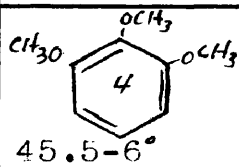
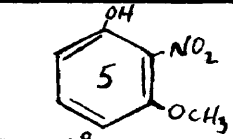
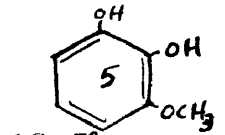
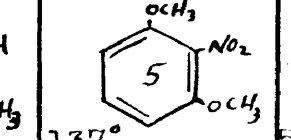
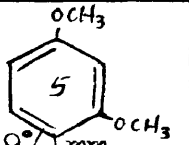
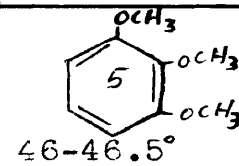
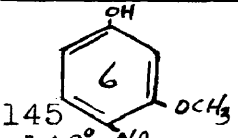
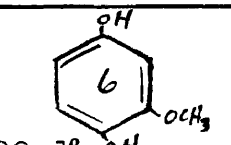
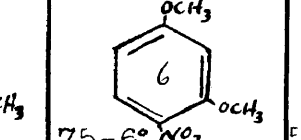
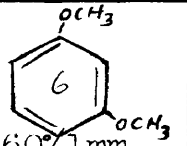
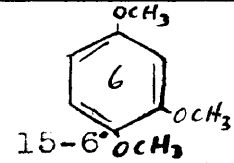
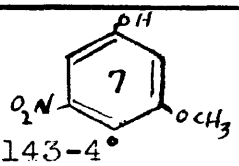
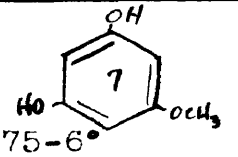
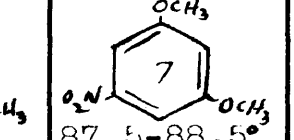
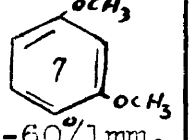
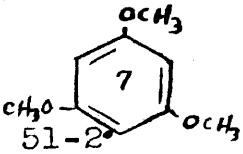
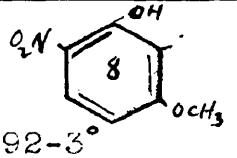
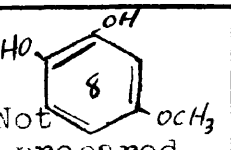
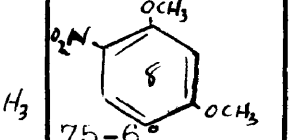
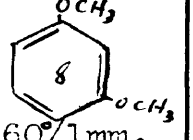
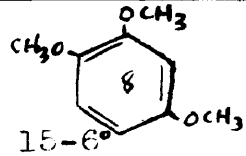
[1] In Table I, where boiling points are given for liquid compounds, the pressure is recorded. All the other physical constants given are melting points.

TABLE I

Derivatives of Methoxynitrophenols

Series I	Series II	Series III	Series IV	Series V
 69°	 84-5°	 65-6°	 21-2°	 45.5-6°
 102-103°	 90-1°	 97-8°	 20-1°	 14-5°
 104-5°	 71-2°	 97-8°	 20-1°	 14-5°
 63.5-64°	 42-3°	 65-6°	 21-2°	 45.5-6°
 53-4°	 42-3°	 137°	 57-9°/1mm.	 46-46.5°
 145-146°	 90-1°	 75-6°	 58-60°/1mm.	 15-6°
 143-4°	 75-6°	 87.5-88.5°	 58-60°/1mm.	 51-2°
 92-3°	 Not prepared	 75-6°	 58-60°/1mm.	 15-6°
80-1°	51.5-53°	72-3°	55.5-56°	17-8°
100.5-101°	70-1°	72-3°	55.5-56°	17-8°

upon two assumptions: first, that the groups introduced by replacement reactions took the same position as the group displaced, and second that no rearrangements of groups occurred during any of the reactions employed. Since drastic conditions were avoided and the theoretical number of isomers were obtained, these assumptions appear to be justified. Mixed melting point tests, analyses for carbon and hydrogen, and molecular weight determinations were used in comparing the compounds prepared and the results may be summarized as follows: In series III, compounds 1 and 4, 2 and 3, 6 and 8, and 9 and 10 were identical pairs, while 5 and 7 were not identical with each other nor with any other member of the series. Similarly in Series II, compounds 2 and 6, 3 and 10, and 4 and 5, were identical pairs, and compounds 8 and 9 may be so considered on the basis of the structures shown, while 1 and 7 were unique. The fact that compound 8 in this series was not prepared does not alter the proof of the structure of 5-nitroguaiacol. In Series IV, compounds 1, 2, 3, and 4 were identical as were 5,6,7, and 8; compounds 9 and 10 were prepared from identical compounds. In Series V, compound 7 was unique and must have the structure shown. The structure of compound 7 may also be deduced from the fact that it is unique in both Series II and III.

The structures of compound 1 in Series II and compound 5 in Series III were then clear as the only other compounds (besides 7) that were unique in these two series of compounds. The structure of compound 4 could then be deduced since com-

pounds 4 and 5 were identical in Series II. Also in Series II compound 10 was identical with compound 3, whereas in Series IV compound 10 was identical only with compound 9 and compound 3 was identical with 1,2, and 4. From these facts, the structures of compounds 10 and 3 could be deduced. It was thus proved that compound 3 of Series I had the structure shown and hence must be 5-nitroguaiacol.

Our samples of 5-nitroguaiacol, prepared according to the directions in Section III B of this thesis have been found to be identical with that characterized in this way. Hence, there can be no doubt as to the authenticity of the material used for mercuration.

SECTION III

EXPERIMENTAL PART

A. Discussion

The mercuration of 5-nitroguaiacol takes place smoothly at 90-100° with excess mercuric acetate in an aqueous solution containing 35% acetic acid and 1% sodium acetate. The product is an orange colored, amorphous solid. It is nearly insoluble in the reaction mixture at room temperature and is readily separated by filtration. Separation from excess inorganic mercury is accomplished readily since the mercuration product retains its phenolic properties and hence is soluble in dilute aqueous alkali. This would be expected as characteristic of mercurated nitrophenols from a consideration of the work of Hantsch and Auld (20). The alkaline solutions of mercurated 5-nitroguaiacol have a vivid deep red color. Alkali metal salts are precipitated from the alkaline solutions by addition of ethyl alcohol. The sodium salt has a dark blue color when dry. Deeply colored alkali salts were obtained from other mercurated nitrophenols by Hantsch and Auld (20).

Careful precipitation by acidification of an alkaline solution of the mercuration product with dilute acetic acid and complete drying yields a brick-red amorphous dust which readily dissolves in hot acetic acid and also redissolves in alkali. The acetic acid solutions are bright yellow in color. A number of other solvents were tried but none was

found that would dissolve significant amounts of this compound or compounds.

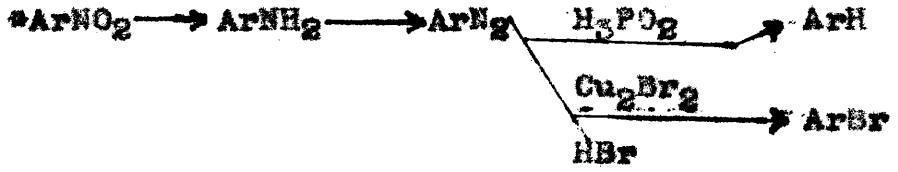
Assuming the mercuration product to be a mixture, attempts were made to separate pure components from it by differential solubility in acetic acid. Successive fractions, however, appeared to be identical and no separation was accomplished.

Chloromercuri (-HgCl), bromomercuri (-HgBr), and acetoxymercuri (-$HgOCOCH_3$) derivatives are readily available from the mercuration product and are easily interconvertible. These derivatives are obtained by precipitation from alkaline solutions with hydrochloric acid, hydrobromic acid, or excess acetic acid, respectively. Each is yellow in color and none has a clearly defined melting point. All are highly insoluble in all solvents tested except acetic acid and dilute aqueous alkali.

A consideration of the available methods of proof of structure leads to the conclusion that the method of Dimroth offers the most promise. The mercuri group or groups present in these compounds must be in one or more of the 3-, 4-, and 6-positions. The possible bromonitroguaiacols derived from the reaction of the mercuration products with bromine are 3-bromo-5-nitroguaiacol, 4-bromo-5-nitroguaiacol, 6-bromo-5-nitroguaiacol, 3,4-dibromo-5-nitroguaiacol, 3,6-dibromo-5-nitroguaiacol, and 4,6-dibromo-5-nitroguaiacol, assuming that the formation of a tri-mercurated derivative does not take place. This assumption appears to be

justified by the mercuration studies outlined in the literature review. Of these possible compounds, only one was available for direct comparison and that was the sample of 4-bromo-5-nitroguaiacol furnished by Raiford and Silker and prepared by them from nitration of 4,5-dibromoguaiacol.

The following equations and table illustrate the bromoguaiacols of interest for identification of the bromonitroguaiacols derived by the exchange of halogen for mercury by the method of Dimroth from all of the possible mono- and dimercurated 5-nitroguaiacols:



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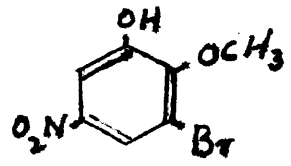
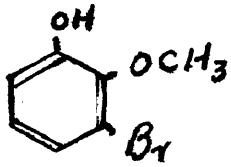
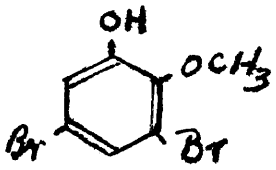
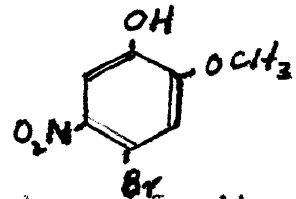
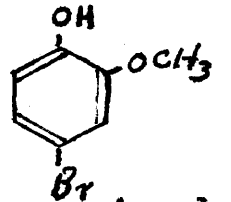
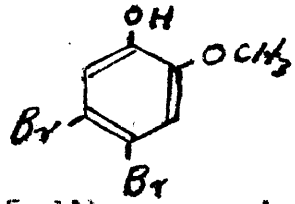
*Ar is used here as a general symbol to represent the formulae of the bromoguaiacols without the hydrogen of position 5. Thus $ArNO_2$ is a general formula for all bromo-5-nitroguaiacols, etc.

Bromonitroguaiacols from possible mercuration products. (ArNO2)	Bromoguaiacols from replacement of nitro group by hydrogen. (ArH)	Bromoguaiacols from replacement of nitro group by bromine. (ArBr)
		
3-bromo-5-nitroguaiacol	3-bromoguaiacol	3,5-dibromoguaiacol
		
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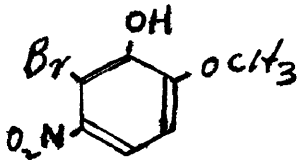
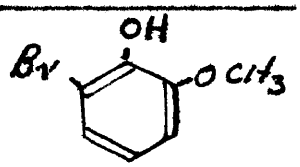
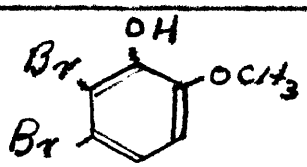
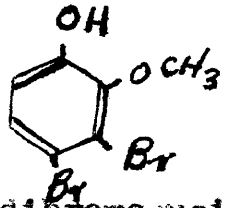
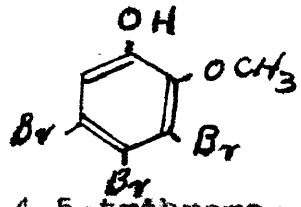
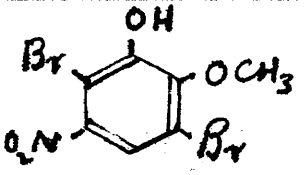
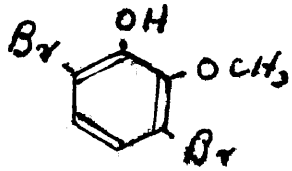
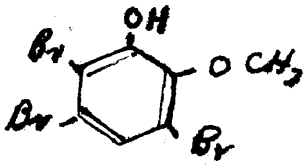
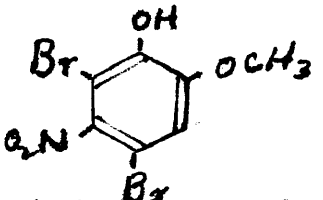
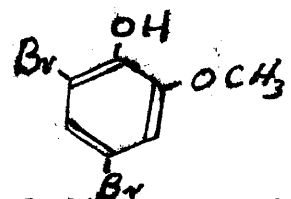
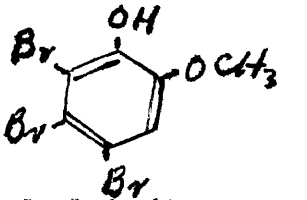
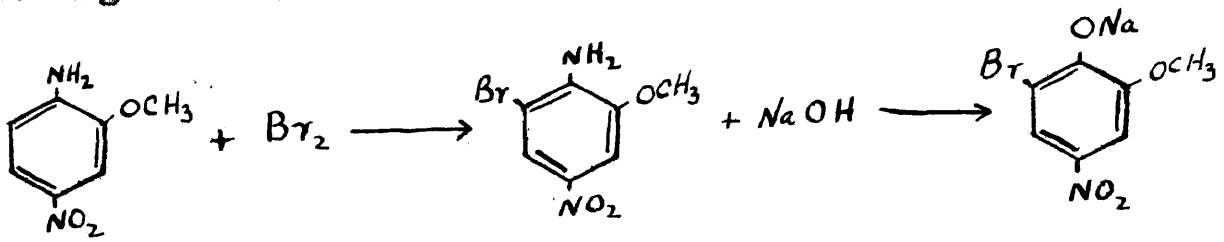
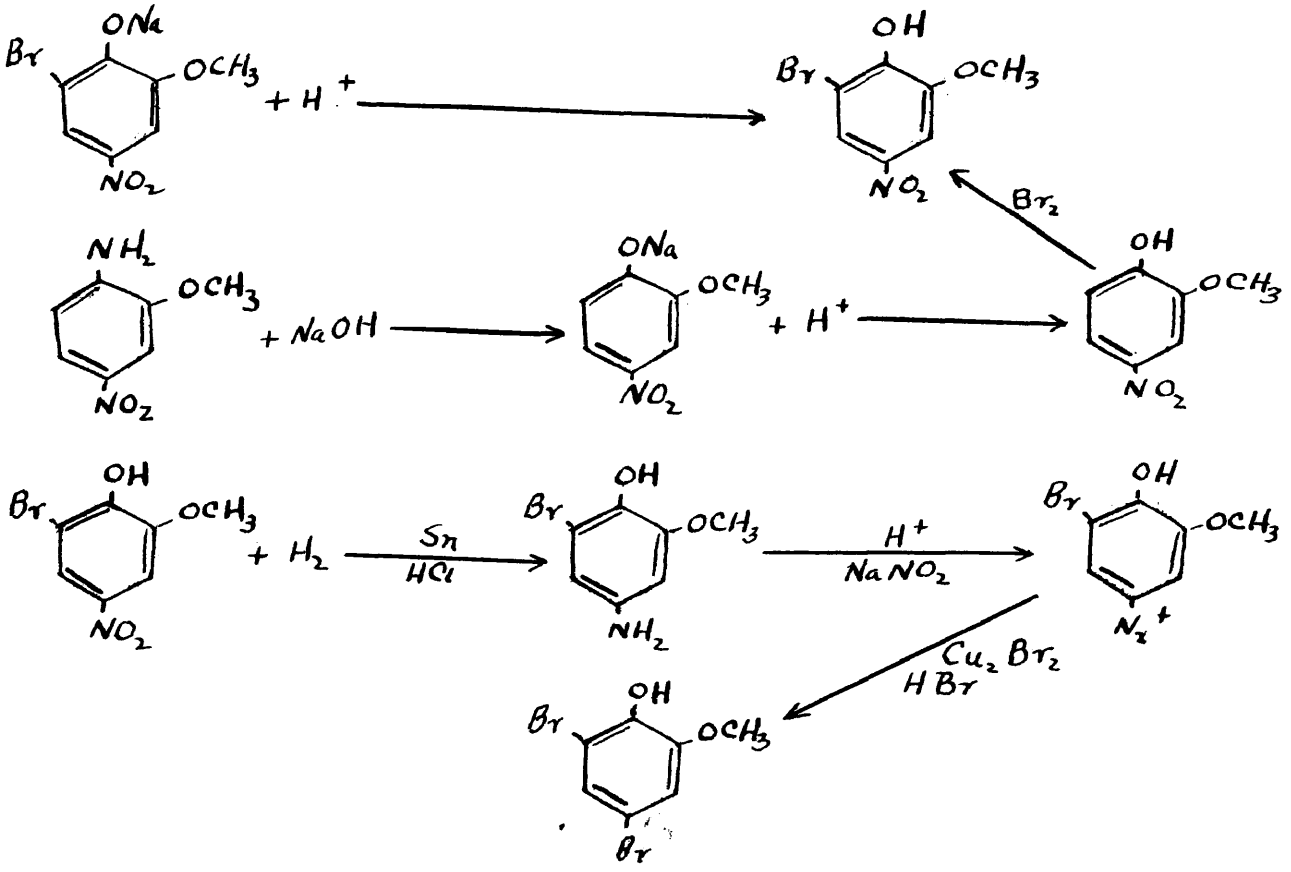
		
6-bromo-5-nitroguaiacol	6-bromoguaiacol	5,6-dibromoguaiacol
		
3,4-dibromo-5-nitroguaiacol	3,4-dibromoguaiacol	3,4,5-tribromoguaiacol
		
3,6-dibromo-5-nitroguaiacol	3,6-dibromoguaiacol	3,5,6-tribromoguaiacol
		
4,6-dibromo-5-nitroguaiacol	4,6-dibromoguaiacol	4,5,6-tribromoguaiacol

It was pointed out earlier that the most likely points of mercuration in 5-nitroguaiacol were the 4- and 6- positions ortho and para to the phenolic hydroxyl group. From the above table, the bromoguaiacols of most interest were 4-bromoguaiacol, 6-bromoguaiacol, 4,5-dibromoguaiacol, 4,6-dibromoguaiacol, 5,6-dibromoguaiacol, and 4,5,6-tribromoguaiacol. Of these, four were readily available. We had already obtained authentic samples of 4-bromoguaiacol and 6-bromoguaiacol from the corresponding nitro compounds, as indicated in Section II of this thesis. Two others, 4,5-dibromoguaiacol and 4,5,6-tribromoguaiacol were easily obtained from direct bromination of guaiacol, according to the directions of Halford and Silker (43).

A synthesis was developed for 4,6-dibromoguaiacol from 6-bromo-4-nitroguaiacol, which was obtained in two ways from 2-amino-5-nitroanisole. The latter substance was made by Meldola and Eyre (34), by Gribov, Ivanov, and Salomentine (18), and patented by the DuPont Company (56) as a dye intermediate. The samples used in the present work were obtained from the Eastman Kodak Company. The following equations illustrate the syntheses of 4,6-dibromoguaiacol:





The resulting compound, 4,6-dibromoguaiacol, was not found reported in the literature. It melts at 64-66 .

No literature information and no direct method were found for the synthesis of 5,6-dibromoguaiacol.

With these reference compounds available, the bromination of the mercury compound from 6-nitroguaiacol was undertaken. The bromination reaction was carried out by dissolving the mercury compound in acetic acid at the temperature of a steam bath. Bromine was added slowly until a very slight excess had been added, as indicated by a starch-iodide test for free bromine. The acetic acid was removed by distillation under reduced pressure and the product separated from the inorganic mercury by dissolving it in aqueous alkali and filtering or centrifuging. Acidification

of the alkaline solution caused the separation of a yellow, crystalline substance, together with a small amount of a gummy material, which was found to cause considerable difficulty in attempts at crystallization. This difficulty, apparently caused by minute amounts of undecomposed mercury compound, as indicated by qualitative tests for mercury, was eliminated by dissolving the dried material in anhydrous ether, treating the solution with a small quantity of bromine, filtering, extracting with dilute alkali, and again acidifying. The product so obtained was a bright yellow crystalline solid, melting point: 109--122°.

Great difficulty was encountered in attempts to isolate pure compounds from this mixture. Fractional crystallizations from dioxane, benzene, and petroleum ether were attempted, but no significant changes in melting point were effected. The mixture could not be distilled because of rapid decomposition at the boiling point even at a pressure of 1 millimeter of mercury.

Separation of pure components was finally effected by fractional crystallization from aqueous acetic acid. The process was long and tedious. Two components were isolated; the more insoluble melted at 151 - 152°, the second component isolated melted at 119 - 120°. Analysis shows that the first of these is a monobromoguaiacol, and that the second is a dibromoguaiacol.

The monobromoguaiacol was identified in the following manner: A mixed melting point test with the sample of 4-

bromo-6-nitroguaiacol furnished by Mulford and Hilker clearly eliminated the latter as a possibility. A large depression in melting point over a broad range of concentrations was obtained. The acetates of the two compounds have widely different melting points.

A sample of the unknown product was reduced with tin and hydrochloric acid and the tin was removed by treatment with hydrogen sulfide. The resulting amine was diazotized and the diazonium group removed by means of hypophosphorous acid (31). A white crystalline product obtained from the reaction mixture by steam distillation was found to be 6-bromoguaiacol. Analysis shows it to be a monobromoguaiacol. The mixed melting points of this product with an authentic sample of 6-bromoguaiacol show them to be identical.

The bromonitroguaiacol obtained from bromination of the mercury compound was, therefore, 6-bromo-5-nitroguaiacol, which proves that mercuration occurred in the 6- position, i.e. ortho to the hydroxyl group. Since no 4-bromo-5-nitroguaiacol was isolated, it appears that no significant amount of a mercurated product was formed having the mercuri group in the 4- position, i.e. para to the hydroxyl group.

The dibromoguaiacol was identified in similar fashion. Elimination of the nitro group by reduction, diazotization, and treatment with hypophosphorous acid yielded a crystalline product (melting point: 63-64°). Its analysis corresponds to that of a dibromoguaiacol. This product was found to be identical with the 4,6-dibromoguaiacol previ-

ously synthesized. The dibromonitroguaiacol is, therefore, 4,6-dibromo-5-nitroguaiacol.

This structure was further proved by a Sandmeyer reaction carried out with a portion of the above diazonium salt solution. The product was a white crystalline solid (melting point: 115-116°). Comparison with authentic samples shows this to be 4,5,6-tribromoguaiacol.

The mercuration of 5-nitroguaiacol, therefore, results in the 6-monomercurated derivative and the 4,6-dimercurated derivative. Quantitatively, the monomercurated product predominates. Analysis of the mixture of bromonitroguaiacols indicates <u>circa</u> 75% monobromoguaiacol and 25% dibromoguaiecol. This is in only fair agreement with the result calculated from the mercury analysis of the acetoxymercuri derivative of the mercuration product, which appears on page 28 of this thesis, and indicates 83% monomercurated product and 17% dimercurated product. Mercury analysis of the corresponding bromomercuri derivative indicates 84.3% mono- and 15.7% dimercurated product.

Determination of mercury was carried out by both the gravimetric and volumetric methods of Jamieson (25). Decomposition of the mercury compounds was effected by fuming nitric acid as in the work of Hart and Hershfelder (21).

B. Description of Experiments

1. Guaiacol Acetate. Redistilled guaiacol (boiling point: 204-5°) was acetylated practically quantitatively in the following manner: 124 grams (1 mole) of guaiacol was mixed with 204 grams (2 moles) of acetic anhydride and 1 ml. of concentrated sulfuric acid and the mixture was distilled at atmospheric pressure until the acetic acid formed in the reaction was completely removed as indicated by a stillhead temperature equivalent to the boiling point of pure acetic anhydride. The reaction mixture was then cooled, washed with cold water, dried over calcium chloride, and fractionated under reduced pressure. The yield was 164 grams of guaiacol acetate, which boiled at 123-4°/13mm.

2. 5-Nitroguaiacol. The 5-nitroguaiacol used in this research was prepared according to the following directions developed by Mr. Charles B. Jaeger, Jr., of Lynch and Company:

A mixture of 135 grams of guaiacol acetate dissolved in 120 ml. of glacial acetic acid was added all at once to a mixture of 115 ml. of fuming nitric acid (sp. gr. 1.5) dissolved in 180 ml. of glacial acetic acid in a beaker of at least three liters capacity. The temperature rose slowly at first and then more rapidly until an extremely vigorous nitration took place with much fuming and boiling and copious evolution of brown-red fumes. For safety this reaction was carried out under a closed hood. About 10 minutes after the boiling had subsided, the mixture was poured over several liters of crushed ice and water. Upon stirring, the oily

precipitate first formed crystallized at once. The crystalline product was washed by decantation several times with cold water, separated by filtration, further washed with cold water until free from acid, and dried in a vacuum desiccator over concentrated sulfuric acid.

The crude 5-nitroguaiacol acetate so obtained was hydrolyzed by suspending 100 grams of it in 1000 ml. of hot 10% sodium hydroxide and heating the mechanically stirred mixture to temperatures just below the boiling point until solution was complete. After addition of 100 grams of sodium chloride, the well-stirred mixture was cooled to 5° and the thick precipitate of the sodium salt of 5-nitroguaiacol filtered off, pressed as dry as possible on the filter, and washed with a small amount of cold, saturated sodium chloride solution. The product was dissolved in 2.5-3 liters of water and the solution filtered. The 5-nitroguaiacol was precipitated by the addition of hydrochloric acid, separated by filtration, washed with water, and dried in a vacuum desiccator over concentrated sulfuric acid. Purification was effected by vacuum distillation (boiling point: 110-112°/1 mm.) and by recrystallization from benzene. The melting point of the purified material was 104-104.5°. The yield, based on guaiacol acetate, was about 42%. It is possible that the vacuum distillation could be omitted since the product from hydrolysis is fairly pure. Experimental evidence for the structure of this material has been presented in Section II B of this thesis.

Guaiacol acetate can be nitrated by the usual methods but the products so obtained contain considerable amounts of 3-nitroguaiacol, which can be separated from 5-nitroguaiacol only with great difficulty.

3. Mercuration of 5-Nitroguaiacol. The following method for the mercuration of 5-nitroguaiacol was also developed by Mr. Charles B. Jaeger, Jr., of Lynch and Company:

One hundred grams of pure 5-nitroguaiacol and 400 grams of mercuric acetate were dissolved in 3500 ml. of a 35% aqueous solution of acetic acid containing 1% sodium acetate. The solution was stirred mechanically and heated on a steam bath for 6 hours, during which time an orange precipitate formed which gradually became very thick and deeper in color. After 6 hours, the mixture was cooled, filtered, washed well with water, and dissolved in dilute alkali; the product was then precipitated with the desired acid (i.e. acetic acid to convert the mercuri groups in the product to acetoxymercuri groups and hydrobromic acid to convert the mercuri groups to bromomercuri groups, etc.). The yield from such a run was about 325 grams. Analysis: Calculated for $C_9H_9O_6NHg$: Hg, 46.90%. Calculated for $C_{11}H_{11}O_8NHg_2$: Hg, 58.45%. Found: Hg, 48.90%.

The above analysis indicates a mixture composed of ca. 83% monomercurated product and 17% dimercurated product.

4. Bromomercuri Derivative. Fifty grams of the mercury compound was dissolved in hot 1 N potassium hydroxide and the solution was filtered through kieselguhr. Hydro-

bromic acid (48%) was added drop-wise, with stirring, to the cooled solution, until the yellow bromomercuri derivative was completely precipitated. The product was separated by filtration and pressed as dry as possible on the filter. It was removed from the funnel, triturated with water, refiltered and washed thoroughly with water.

It was dried in a vacuum desiccator over concentrated sulfuric acid. Yield: 51 grams. Analysis: Calculated for $C_7H_6O_4NBrHg$: Hg, 44.71%. Calculated for $C_7H_5O_4NBr_2Hg_2$: 56.18%. Found: 46.50%.

The above analysis indicates a mixture composed of ca. 84.3% mono- and 15.7% dimercurated product.

5. Elbert's Reaction (Mercurated 5-Nitroguaiacol and Bromine). Fifty grams of bromomercuri derivative was dissolved in 500 ml. of glacial acetic acid on a steam bath. Bromine was added slowly to the mechanically stirred mixture, with frequent starch-iodide tests for free bromine. When a positive test for free bromine persisted for a half an hour, addition of bromine was halted (ca. 15 grams were required) and the mixture was stirred an additional half an hour. The excess bromine was destroyed by a little sodium bisulfite and the acetic acid removed by distillation under reduced pressure. The residue was taken up in hot 1 N potassium hydroxide and the solution filtered through kieselguhr or centrifuged to remove inorganic mercury salts. Acidification with hydrochloric acid precipitated a yellow crystalline product that was contaminated with a small

amount of a gummy material that could not be made to crystallize.

The product was dried in an oven at 100°, taken up in anhydrous ether, treated with 1-2 drops of bromine, and filtered. The ether solution was extracted with 1 N potassium hydroxide, and the bright red aqueous layer freed from ether by boiling and then acidified with hydrochloric acid. The product was dried *in vacuo* over phosphoric anhydride in an Abderhalden pistol at the boiling point of ethyl alcohol. Yield: 23 grams, melting point: 109-122°. Analysis: Calculated for $C_7H_6BrNO_4$: Br, 32.22%. Calculated for $C_7H_5Br_2NO_4$: Br, 48.89%. Found: 37.10%.

This analysis corresponds to that of a mixture of *ca.* 75% monobromoguaiacol and 25% dibromoguaiacol.

After many unsuccessful attempts to separate this mixture by fractional distillation, by fractional crystallization from dioxane-water mixtures, alcohol-water mixtures, benzene, and benzene-petroleum ether mixtures, pure components were finally separated by a prolonged and tedious fractional crystallization from aqueous acetic acid (*ca.* 60% by volume). The general procedure suggested by Morton (37, p. 162) was used, and fractions of similar melting point were combined.

From 20 grams of mixture was obtained 10.7 grams of a product I (melting point: 151-152°) and 2.2 grams of a second product, II (melting point: 119-120°), and 5.1 grams of intermediate fractions. These products were finally re-

crystallized from methanol-water mixtures. Analysis: I: Calculated for $C_7H_6BrNO_4$: C, 33.87%; H, 2.44% Br, 32.22%. Found: C, 33.96%; H, 2.53%; Br, 32.33%. II: Calculated for $C_7H_5Br_2NO_4$: C, 25.71%; H, 1.54%; Br, 48.89%. Found: C, 25.59%; H, 1.70%; Br, 48.51%.

6. 6-Bromo-5-nitroguaiacol acetate. One gram of product I above (identified as 6-bromo-5-nitroguaiacol) was acetylated with 0.5 ml. of acetic anhydride with a trace of sulfuric acid as catalyst. The mixture was heated on a steam bath for half an hour, cooled and diluted with 5-10 ml. of cold water. The solid product was filtered off and recrystallized from a methanol-water mixture (ca. 4:1). The yield was 1 gram (85%). The material melts at 126-7°. Calculated for $C_9H_8BrNO_5$: C, 37.25%; H, 2.78%. Found: C, 37.40%; H, 2.90%.

7. 4,6-Dibromo-5-Nitroguaiacol acetate. One-half gram of product II above (identified as 4,6-dibromo-5-nitroguaiacol) was acetylated with 0.3 ml. of acetic anhydride with a trace of sulfuric acid as catalyst. The mixture was heated on a steam bath for a half an hour, cooled and diluted with 5-10 ml. of cold water. The solid product was separated by filtration and recrystallized from a methanol-water mixture (ca. 4:1). The yield was 0.52 grams (92%). The product melts at 135-36°. Analysis: Calculated for $C_9H_7Br_2NO_5$: C, 29.30%; H, 1.91%. Found: C, 29.50%; H, 2.13%.

8. 6-Bromoguaiacol from 6-bromo-5-nitroguaiacol. Two grams of 6-bromo-5-nitroguaiacol was reduced with tin and

hydrochloric acid. The solution was diluted with water, filtered, and freed from tin by treatment with hydrogen sulfide. Excess hydrogen sulfide was removed by boiling and the residual solution concentrated under reduced pressure to a volume of *circa* 15 ml. Two ml. of concentrated hydrochloric acid was added and the solution was cooled to 5°. The dissolved amine salt was diazotized by the slow addition of a cold solution of 0.6 grams of sodium nitrite in 5 ml. of water, using starch-iodide indicator. To the cold diazonium salt solution was added 16 grams of cold 50% hypophosphorous acid. The temperature was maintained at 0-5° for 1 hour and then the solution was stored in a refrigerator at 5-10° for 20 hours. Steam distillation of this solution yielded a white crystalline product which was recrystallized from an ethanol-water mixture (*ca.* 5:1), melting point: 62-63°. The yield was 0.46 grams (28%). The product showed no depression of melting point when mixed with varied quantities of 6-bromoguaiacol. Analysis: Calculated for $C_7H_7BrO_2$: Br, 39.38%. Found: 39.76%.

9. 2-Amino-3-bromo-5-nitroanisole. A 10.8 gram sample of 2-amino-5-nitroanisole (Eastman Kodak Company's product #P2389 recrystallized from ethanol, melting point 140-141°) dissolved in 250 ml. of glacial acetic acid was brominated with a 1 molar quantity of bromine added drop-wise with stirring. The mixture was warmed slightly with a flame to initiate the reaction. Stirring was continued 1 hour after all the bromine had been added. The acetic acid was removed

by distillation under reduced pressure and the product was washed with water and recrystallized from an ethanol-water mixture (5:1). The yield was 20 grams (81%). The substance melts at 139-140°.

10. 6-Bromo-4-nitroguaiacol from hydrolysis of 2-amino-3-bromo-5-nitroanisole. It was found that 2-amino-3-bromo-5-nitroanisole was slowly hydrolyzed to the corresponding phenol by prolonged boiling with 10% sodium hydroxide solution. After 48 hours boiling, nearly half the amine was recovered unchanged. For this reason, the reaction was attempted under pressure in a hydrogenation bomb. At 200° the product was largely decomposed; heating at 130° for 4½ hours, however, resulted in a conversion of 70% and yield of 93%.

Twenty grams of 2-amino-3-bromo-5-nitroanisole were placed in the bomb (capacity 270 ml.) and a solution of 4 grams of sodium hydroxide in 100 ml. of water added. The bomb was secured and heated electrically to 130° for 4½ hours. It was then cooled with running water, opened, and rinsed thoroughly with hot water. Six grams of starting material were recovered unchanged. The filtered alkaline solution was boiled to remove ammonia and then acidified. The yellow phenol was recrystallized from an ethanol-water mixture (5:1). The yield was 13 grams (93%). The product melts at 150° (with decomposition).

11. 6-Bromo-4-nitroguaiacol Acetate. One gram of 6-bromo-4-nitroguaiacol was acetylated with 0.5 ml. of acetic

anhydride and a trace of sulfuric acid as catalyst. The mixture was heated on a steam-bath for half an hour, cooled, and diluted with 5-10 ml. of cold water. The solid product was filtered and recrystallized from a methanol-water mixture (ca. 3.5:1). The yield was 1.1 gram (91%). The substance melted at 102-3°. Analysis: Calculated for $C_9H_8BrNO_5$: C, 37.27%; H, 2.78%. Found: C, 37.13%; H, 2.90%.

12. 4-Nitroguaiacol. The following directions were devised by Mr. Charles B. Jaeger, Jr., of Lynch and Company:

Fifty grams of 2-amino-5-nitroanisole was hydrolyzed with a solution of 50 grams of sodium hydroxide in 450 ml. of water by heating at the boiling point for 30 hours under reflux. When the reaction mixture was cooled, the sodium salt of 4-nitroguaiacol crystallized in bright red needles. The cold solution was filtered and the red crystals dissolved in 1⅛ liters of hot water, and the solution filtered, cooled, and acidified with hydrochloric acid. The 4-nitroguaiacol was filtered off, dried by azeotropic distillation with benzene and recrystallized from the benzene. The yield was 43.2 grams (86%). The product melts at 102-103°.

13. 6-Bromo-4-nitroguaiacol from bromination of 4-nitroguaiacol. A solution of 11.7 grams of 4-nitroguaiacol in 100 ml. of glacial acetic acid was brominated by the slow addition of 12.5 grams of bromine in 40 ml. of glacial acetic acid. After about 1-2 ml. of the bromine solution had been added, the mixture was warmed with a flame until the evolution of hydrobromic acid was evident and then the

addition was continued during 1 hour; stirring was continued an hour longer and the reaction mixture was then poured into 300 ml. of cold water. The yellow precipitate was filtered off and recrystallized from an ethanol-water mixture (5:1). The yield was 12.1 grams (70.3%); the substance melted at 150° (with decomposition). This compound was identical with that previously obtained by the alkaline hydrolysis of 2-amino-3-bromo-5-nitroanisole. Its acetate was also made and found to be identical with that previously prepared.

14. 4,6-Dibromoguaiacol from 6-bromo-4-nitroguaiacol.

Four grams of 6-bromo-4-nitroguaiacol was reduced with tin and hydrochloric acid. The solution was diluted, filtered, and freed from tin by precipitation with hydrogen sulfide. After boiling the solution to rid it of excess hydrogen sulfide, it was concentrated in vacuo to a volume of circa 30 ml. Three ml. of concentrated hydrochloric acid was added, and the solution cooled to 0° by immersion in an ice and salt mixture. The dissolved amine salt was diazotized by the addition of a cold solution of 1.2 grams of sodium nitrite in 20 ml. of water. Starch-iodide paper was used as indicator. A solution of cuprous bromide was prepared as follows: 5 grams of crystallized copper sulfate was dissolved in 16 ml. of boiling water and 2.4 grams of potassium bromide was dissolved in the hot solution. To this hot solution was added slowly a solution of 1.1 grams of sodium pyrosulfite ($Na_2S_2O_5$), and 0.75 grams of sodium hydroxide in 8 ml. of water. The precipitated cuprous bromide was then

washed twice with water by decantation and dissolved in 15 ml. of 48% hydrobromic acid. This solution was heated in an apparatus arranged for steam distillation. The cold diazonium solution above was added drop-wise and the mixture steam-distilled simultaneously. A white solid crystallized in the distillate. It was filtered and recrystallized from aqueous ethanol. The yield was 1.2 grams (25.6%). The substance melts at 64-65°. Analysis: Calculated for $C_7H_6Br_2O_2$: C, 28.02%; H, 2.14%; Br, 56.70%. Found: C, 28.13%; H, 2.23%; Br, 56.59%.

15. 4,6-Dibromoguaiacol from 4,6-dibromo-5-nitroguaiacol. One and one-half grams of 4,6-dibromo-5-nitroguaiacol was reduced with tin and hydrochloric acid. As before, the solution was diluted with water, filtered, and freed of tin by treatment with hydrogen sulfide. It was concentrated under reduced pressure to 15 ml. and 3 ml. of concentrated hydrochloric acid added. The solution was then cooled to 0° and the dissolved amine salt diazotized by addition of a cold solution of 0.35 grams of sodium nitrite dissolved in 15 ml. of water again using starch-iodide paper as an indicator. To the cold diazonium salt solution was added 10 grams of a cold 50% solution of hypophosphorous acid. The solution was maintained at 0-5° for 1 hour and then kept in a refrigerator at 5-10° for 24 hours. The solution was then steam distilled; a white solid crystallized in the distillate and was filtered and recrystallized from an ethanol-water mixture. The yield was 0.4 grams (31%), melting

point: 63-64°.

This product proved to be identical with that previously obtained from 6-bromo-4-nitroguaiacol. Mixed melting point tests resulted in no depression in melting point.

16. 4,5,6-Tribromoguaiacol from 4,6-dibromo-5-nitroguaiacol. One and one-half grams of 4,6-dibromo-5-nitroguaiacol were reduced with tin and hydrochloric acid, freed from tin, concentrated and diazotized as in the previous experiments. A solution of cuprous bromide in hydrobromic acid was prepared and the cold diazonium solution added drop-wise to it while steam was blown through the mixture. A white crystalline product was filtered from the distillate and recrystallized from an ethanol-water mixture. The yield was 0.31 grams (18.7%), melting point: 114-116°. This product shows no depression in melting point when mixed with varied quantities of authentic 4,5,6-tribromoguaiacol.

SECTION IV

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