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To the Graduate Council:

I am submitting herewith a dissertation written by Ching Chen Tung entitled "The Synthesis and Pharmacologic Activity of Some Bis-(2-aminoethyl)-benzenes." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

J. H. Wood, Major Professor

We have read this dissertation and recommend its acceptance:

H. Johnson, William T. Smith, George P. Mueller, H. K. Garber

Accepted for the Council:

Carolyn R. Hodges

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

December 6, 1951

To the Graduate Council:

I am submitting to you a dissertation written by Ching Chen Tung entitled "The Synthesis and Pharmacologic Activity of Some Bis-(2-aminoethyl)-benzenes." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

W. H. Hood

Major Professor

We have read this dissertation and recommend its acceptance:

H. Johnson

Wm. J. Smith, Jr.

George P. Mueller

H. J. Garber

Accepted for the Council:

C. R. Watters

Dean of the Graduate School

THE SYNTHESIS AND PHARMACOLOGIC ACTIVITY OF SOME BIS-(2-AMINOETHYL)-BENZENES

A DISSERTATION

Submitted to
The Graduate Council
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the degree of
Doctor of Philosophy

---

by

Ching Chen Tung

December 1951

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation to Dr. J. H. Wood for his capable supervision of this research.

He would also like to express his gratitude to Mr. F. K. Chang, manager of China Synthetic Chemical Works, for encouragement and financial support to undertake advanced study in the United States of America.

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295809

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CHAPTER I

INTRODUCTION

The isolation of epinephrine from the medulla of the suprarenal gland and the discovery of its amazing therapeutic effects have stimulated intensive research on the synthesis of compounds possessing the basic skeleton of 2-aminoethylbenzene. The investigations in the past forty years have culminated in the preparation of a large number of this type of amine which are pharmacologically classified as "sympathomimetic" or "pressor" agents because they generally act on the sympathetic nervous system and cause an increase of blood pressure. However, the 2-aminoethylbenzene derivatives most thoroughly studied have been those whose molecules possessed only one aminoethyl side chain per benzene nucleus.

It was von Braun[1] who first reported the synthesis of 1,2-bis-(2-aminoethyl)-benzene in 1916 and further noted that this substance did not show the usual sympathomimetic activity of 2-aminoethylbenzenes. No other investigation on the derivatives of bis-aminoethylbenzenes has been reported until quite recently when Wood and Gibson[2] prepared a series of

---

(1) von Braun, J., Kruber, U., and Danziger, E., Ber., 49, 2642 (1916).

(2) Wood, J. H., and Gibson, R. E., J. Am. Chem. Soc., 71, 393 (1949).

p-(2-aminoethyl)-hydroquinones. Pharmacologic assay by the Lilly Research Laboratories of Eli Lilly and Company showed that these compounds possessed little activity. Since the compounds in this series were symmetrically constituted, it seemed desirable to prepare several bis-(2-aminoethyl)-benzenes in which the two 2-aminoethyl groups were unsymmetrically placed with respect to each other and with respect to other substituents of the molecule. Accordingly, M. A. Perry[3] instituted a program in this laboratory that covered the synthesis of o- and m-bis-(2-aminoethyl)-benzenes. At approximately the same time, this investigation was started with the purpose of developing procedures that would lead to o-, m-, and p-bis-(2-aminoethyl)-benzenes whose molecules possessed substituents, preferably the hydroxy or methyl or both, on the 1- and 2-carbons of the ethylamino side chain. In addition to this objective, this investigation was started with the purpose of developing suitable methods for obtaining the intermediates which were necessary in the synthesis of bis-(2-aminoethyl)-benzenes. From this point of view, chloromethylation reactions and the Sommelet reaction were to be studied. Finally, the new amines which resulted from these

---

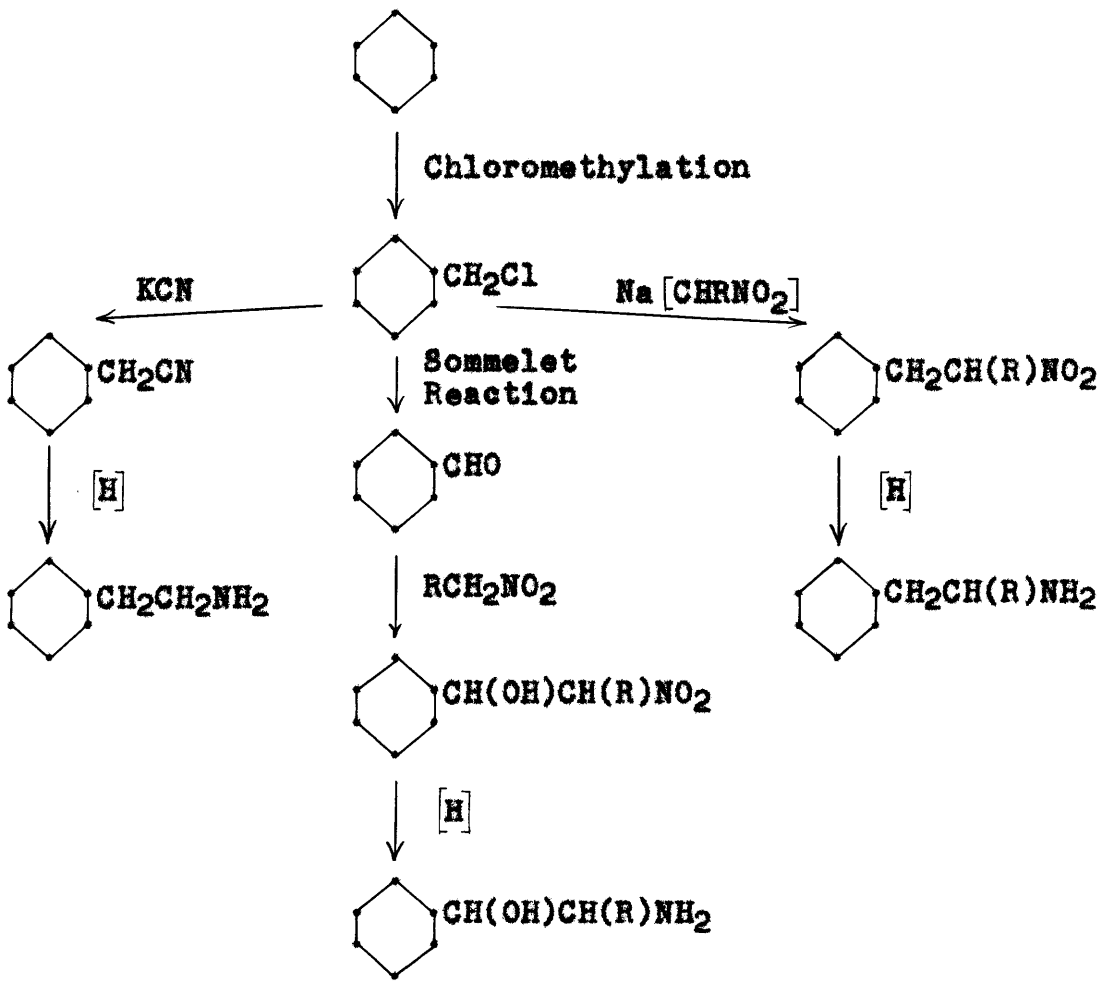
(3) Perry, M. A., "The Synthesis and Sympathomimetic Activity of Some o- and m-Bis-(2-aminoethyl)-benzenes," Doctoral Dissertation, The University of Tennessee, Knoxville, Tennessee, 1950.

investigations were to be prepared in quantity for submission to the Lilly Research Laboratories for pharmacologic testing.

CHAPTER II

HISTORICAL AND DISCUSSION OF RESULTS

The most commonly used routes to 2-aminoethylbenzenes may be illustrated graphically as follows:



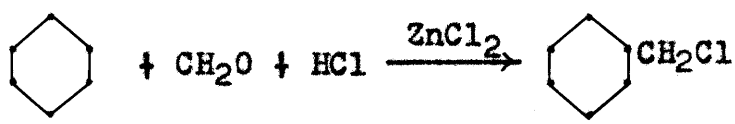
Since in this work all of the above methods were used, it became necessary to study in considerable detail chloromethylation reactions, the Sommelet reaction, and the

condensation of nitroalkanes with aldehydes and with chloromethyl compounds. Each of these then is described as somewhat of a separate piece of work.

A. Chloromethylation

1. Historical

As early as 1898, Grassi and Maselli[1] effected the replacement of a hydrogen atom in the benzene nucleus with a chloromethyl group by the action of hydrogen chloride and paraformaldehyde in the presence of zinc chloride:



The ease of the conversion of the chloromethyl group into other groups such as $-CHO$,[2] $-CH_2OH$, $-CH_2CN$, and $-CH_3$[3,4] established the importance of this reaction and thus led to extensive studies in this direction. As a consequence of these many independent investigations, the preparations of the more common chloromethyl derivatives have been adequately

---

(1) Grassi, G., and Maselli, C., Gazz. chim. ital., 28, II, 477 (1898).

(2) Sommelet, M., Compt. rend., 157, 852 (1913).

(3) Anderson, A. R., and Short, W. F., J. Chem. Soc., 485 (1933).

(4) Grummit, O., and Buck, A. C., J. Am. Chem. Soc., 65, 295 (1943).

described in the chemical literature. However, the present work required compounds containing two chloromethyl groups per molecule, and a survey of the literature revealed that very few such compounds had been prepared. For the few that had been previously prepared, the method of preparation in general was unsatisfactory for the present purpose since the bis-chloromethyl compound was generally a by-product of a reaction planned for another purpose.

2. Important Factors Which Influence Chloromethylation

a. Reagents, catalysts, and conditions.[5] Besides paraformaldehyde, as first employed by the Italian workers, Grassi and Maselli, formalin, diethyl formal, or dimethyl formal have been used with hydrochloric acid. Chloromethyl ether or dichloromethyl ether have also been found to be effective chloromethylating agents. There is no general rule for the choice of reagents, but due to the ready availability of formalin and hydrochloric acid these reagents are most commonly used. For reactive compounds such as pyrrol, chloromethyl ether or dichloromethyl ether are preferred since the use of these reagents makes it unnecessary to use strong acids, and the reaction can be carried out at low temperatures.[6]

---

(5) Fuson, R. C., and McKeever, C. H., "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 63.

(6) Wood, J. H., Perry, M. A., and Tung, C. C., J. Am. Chem. Soc., 72, 2989 (1950).

Catalysts are frequently necessary. Acetic acid,[7-11] sulfuric acid,[12,13] and zinc chloride[14-22] are among the commonest catalysts employed. A large variety of catalysts has been studied; in some cases, they are effective in increasing

---

(7) Darzens, G., and Levy, A., Compt. rend., 202, 73 (1936).

(8) Martin, I. R. H., Bull. soc. chim. Belges, 58, 87 (1949).

(9) Grummitt, O., and Buck, A. C., J. Am. Chem. Soc., 65, 295 (1943).

(10) Randall, D. I., and Buc, S. R., U. S. Patent 2,531,464, November 28, 1950.

(11) Vavon, G., Bolle, J., and Calin, J., Bull. soc. chim. (5), 6, 1025 (1939).

(12) Angyal, S. J., Tetaz, J. R., and Wilson, J. F., Org. Synthesis, 30, 67-69 (1950).

(13) Matsukawa, T., and Shirakawa, K., J. Pharm. Soc. Japan, 70, 535-537 (1950).

(14) Quelet, R., Compt. rend., 198, 102 (1934).

(15) Quelet, R., and Anglade, M., Bull. soc. chim. (5), 3, 2200 (1936).

(16) Quelet, R., and Allard, J., Bull. soc. chim. (5), 4, 620 (1937).

(17) Quelet, R., Bull. soc. chim. (4), 53, 510 (1933).

(18) Quelet, R., Compt. rend., 196, 1411 (1933).

(19) Quelet, R., Bull. soc. chim. (5), 1, 539 (1934).

(20) Quelet, R., Bull. soc. chim. (5), 1, 904 (1934).

(21) Quelet, R., and Allard, J., Compt. rend., 205, 238 (1937).

(22) Blanc, G., Bull. soc. chim. (4), 33, 313 (1923).

the yield of the bis-chloromethyl compound. This may be illustrated by the chloromethylation of benzene. If excess zinc chloride is used, the yields of the bis-chloromethyl derivative and diphenylmethane are relatively high; whereas, with a small amount of catalyst, almost no bis-chloromethyl compound is obtained. However, the yield of benzylchloride is also diminished.[23]

Temperature has also been found to be an important factor. Introduction of two chloromethyl groups is generally facilitated by using a temperature higher than 50° but is quite often accompanied by side reactions. The main side reaction that has been observed is the formation of the corresponding diarylmethane derivatives, a reaction which most frequently occurs with highly reactive compounds such as naphthalene,[24] anisole,[25] phenols,[26] etc.

b. Effects of substituents. The influence of various substituents on the chloromethylation of aromatic compounds may be classified as inhibiting and favoring effects. The inhibiting groups are mostly the electron-attracting groups

---

(23) Blanc, G., Bull. soc. chim. (4), 33, 313 (1923).

(24) Anderson, A. R., and Short, W. F., J. Chem. Soc., 485 (1933).

(25) Quelet, R., and Allard, J., Bull. soc. chim. (5), 3, 1796 (1936).

(26) Castiglioni, A., Gazz. chim. ital., 67, 324 (1937).

such as the nitro-,[27-29] aldehydo-,[30] halogeno-,[31,32] and carboxyl groups.[33] The presence of one of such groups in the benzene ring invariably renders the introduction of a chloromethyl group rather difficult or not possible at all. The electron-releasing groups such as alkyl[34] and hydroxyl groups, on the other hand, generally facilitate the entrance of a chloromethyl group. Phenolic compounds have been found to be so reactive that the reaction usually favors the formation of polymeric materials. A suitable device to overcome this difficulty is to chloromethylate the methylated phenols.[35-38]

---

(27) Stephen, H., Short, W. R., and Gladding, G., J. Chem. Soc., 117, 510 (1920).

(28) Vavon, G., Bolle, J., and Calin, J., Bull. soc. chim. (5), 6, 1025 (1939).

(29) Reichert, B., and Marquardt, H., Pharmazie, 5, 10-15 (1950).

(30) Ibid.

(31) Stephen, H., Short, W. F., and Gladding, G., loc. cit.

(32) Tschunkur, E., and Eichler, F., Ger. Pat. 509,149 C. A., 25, 711 (1931); Chem. Zentr., 102, I, 360 (1931).

(33) Matsukawa, T., and Shirakawa, K., J. Pharm. Soc. Japan, 70, 535-537 (1950).

(34) von Braun, J., and Nelles, J., Ber., 67, 1094 (1934).

(35) Sommelet, M., Bull. soc. chim. (4), 53, 853 (1933).

(36) Sommelet, M., and Marszak, I., Compt. rend., 198, 2256 (1934).

(37) Sommelet, M., Compt. rend., 197, 256 (1933).

(38) Wood, J. H., Perry, M. A., and Tung, C. C., J. Am. Chem. Soc., 72, 2989 (1950).

The introduction of a second chloromethyl group into chloromethylbenzene gives mainly the para isomer[39] although some of the ortho isomer is also formed.[40] With a strongly directing ortho para group such as $-OCH_3$ or $-CH_3$ also present, the orientation of the second chloromethyl group is governed largely by these groups rather than the chloromethyl group.[41,42]

When both inhibiting and favoring groups are present, their effects counteract each other. Nitrobenzene, for instance, is chloromethylated very slowly, whereas, with nitrophenol the reaction proceeds much more readily.

3. The Preparation of Bis-(chloromethyl)-benzenes

a. 2,4-Bis-(chloromethyl)-anisole (II). When anisole was subjected to conditions favorable for bis-chloromethylation, it was observed that a considerable amount of p,p'-dimethoxydiphenylmethane was obtained in addition to the bis-chloromethyl compound. The presence of this by-product rendered the purification of the desired product quite impossible. The preparation of 2,4-bis-(chloromethyl)-anisole

---

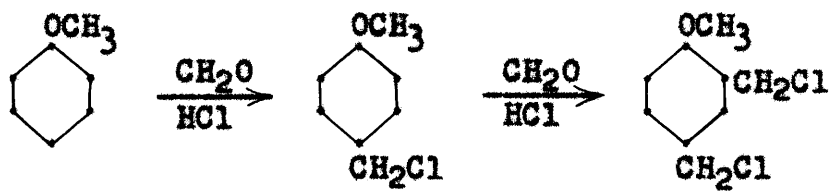
(39) Blanc, G., Bull. soc. chim. (4), 33, 313 (1923).

(40) Jacobs, W. A., and Heidelberger, M., J. Biol. Chem., 20, 659 (1915).

(41) Blanc, G., loc. cit.

(42) Quelet, R., and Anglade, M., Bull. soc. chim. (5), 3, 2200 (1936).

was found to be much more satisfactory when executed in a stepwise chloromethylation. To this end, p-chloromethylanisole (I) was first prepared by the method of Quelet and Allard[43] by treatment of anisole with formalin and hydrogen chloride at low temperature with zinc chloride as catalyst and petroleum ether as solvent. This monochloromethylated product was isolated, purified, and then subjected to further chloromethylation at high temperature without the use of catalyst and solvent. An over-all yield of 35 per cent of 2,4-bis-(chloromethyl)-anisole was thus obtained from anisole.



(I) (II)

Although (II) was prepared by Quelet and Anglade,[44] no evidence for the proposed structure was submitted. The structure was therefore established by conversion to the corresponding aldehyde through the Sommelet reaction[45] and the subsequent oxidation of the aldehyde to the known 4-methoxyisophthalic acid.

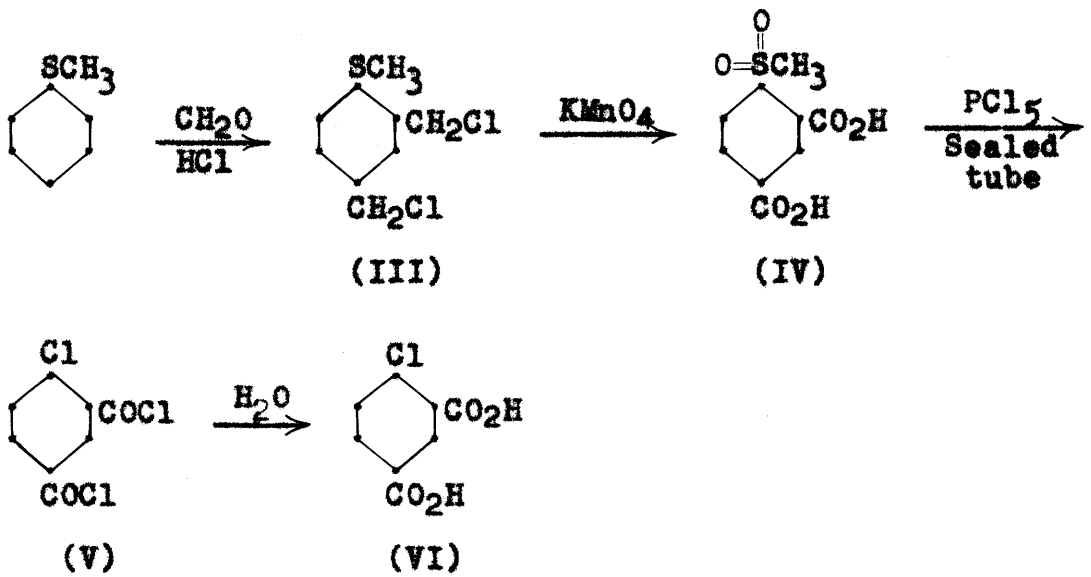
---

(43) Quelet, R., and Allard, J., Bull. soc. chim. (5), 3, 1796 (1936).

(44) Quelet, R., and Anglade, M., Bull. soc. chim. (5), 3, 2200 (1936).

(45) Sommelet, M., Compt. rend., 157, 852 (1913).

b. <u>2,4-Bis-(chloromethyl)-thiophenol methyl ether</u> (III). Brunner[46] has reported the preparation of this compound in a patent in 1933, but no details regarding the procedure of preparation and evidence of the structure were given. It was therefore desirable to give this compound further study. Phenyl methyl thioether was treated with formalin in hydrochloric acid and a stream of hydrogen chloride at room temperature. A product was isolated which agreed with Brunner's product in melting point. This product was assigned the structure 2,4-bis-(chloromethyl)-thiophenol methyl ether on the basis of the following sequence of reactions:



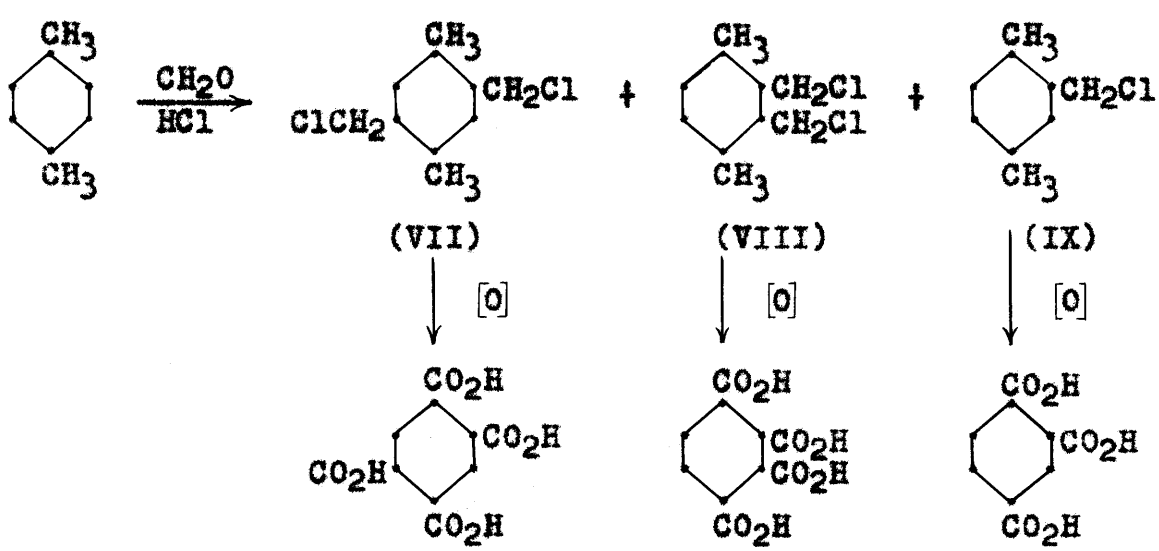
The analysis of (IV) agreed with that for the postulated structure of a sulfone dicarboxylic acid. Melting

---

(46) Brunner, A., U.S. Patent 1,887,396 (1933).

point and neutral equivalent of (VI) agreed with those for the known 4-chloroisophthalic acid.

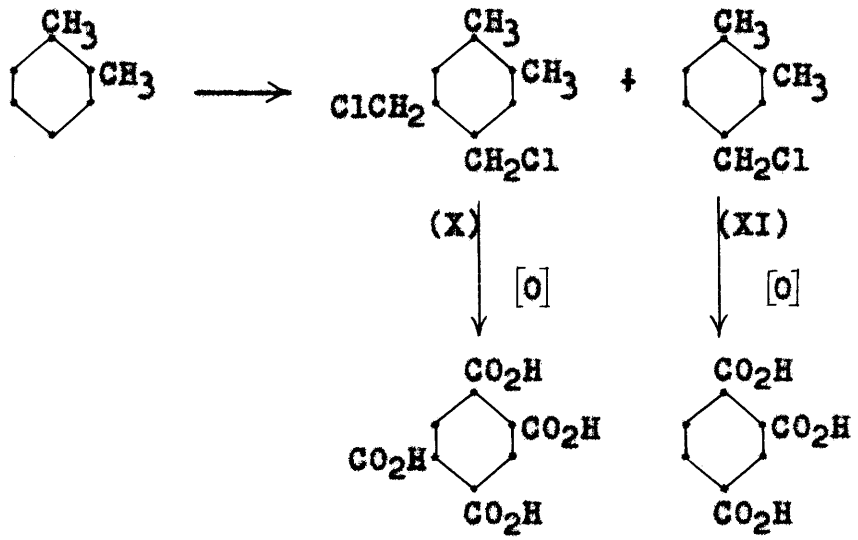
c. Chloromethylation of p-xylene. Bis-chloromethylation of p-xylene was first accomplished by von Braun and Nelles[47] with a 7 per cent yield of the 2,5-bis-(chloromethyl)-p-xylene (VII). After repeated trials with various modification of conditions, the yield has been improved to 55 per cent. The success of this reaction rests on the isolation of the product as soon as it was formed so as to avoid the possibility of polymerization under the experimental conditions (70°). From the mother liquor, some 2,3-bis-(chloromethyl)-p-xylene (VIII) was isolated. 2-Chloromethyl-p-xylene (IX) was also found to be present in the reaction product. The structures were ascertained by von Braun and Nelles through oxidation to the known acids.



(47) von Braun, J., and Nelles, J., Ber., 67, 1094 (1933).

4. Chloromethylation of o-Xylene

When o-xylene was chloromethylated by von Braun and Nelles,[48] they obtained 4,5-bis-(chloromethyl)-o-xylene (X) and monochloromethyl compound (XI). The structures were established by oxidation to the known acids.



In repeating the work, the same general results were obtained.

5. Chloromethylation of Resorcinol Dimethyl Ether

On account of the activating influence of the hydroxy group on the benzene ring, it was necessary to carry out the reaction with the dimethyl ether of resorcinol rather than resorcinol itself. Various conditions were tried to effect chloromethylation in such a way as to obtain the monochloromethyl or the bis-chloromethyl derivative, but the mildest conditions of temperatures and reagents that could be obtained

---

(48) von Braun, J., and Nelles, J., Ber., 67, 1094 (1933).

led to non-characterizable, high molecular weight polymers. That bis-chloromethylation was occurring was proved by letting the reaction run about three minutes under mild conditions and then adding an excess of hexamethylenetetramine. Thus, all chloromethyl compounds existing at the time of the addition were precipitated as the salts. From the hydrolysis products were isolated the dialdehyde corresponding to 4,6-bis-(chloromethyl)-resorcinol dimethyl ether and the monoaldehyde corresponding to 2,4-dimethoxybenzylchloride (see section on Sommelet reaction).

B. Sommelet Reaction

1. Introduction

The chloromethyl group in the aromatic nucleus is capable of forming a quarternary salt with hexamethylenetetramine which can be isolated in an anhydrous solvent, e.g., chloroform.[49] Delepine[50] developed an excellent method for the preparation of primary amines[51] by the hydrolysis of

---

(49) Delepine, M., Bull. soc. chim. (3), 13, 358 (1895).

(50) Ibid.

(51) Galat, A., and Elion, G., J. Am. Chem. Soc., 61, 3585 (1939).

these salts in strong hydrochloric acid solution. Ammonia and formaldehyde are also formed at the same time.

$$\left[ArCH_2C_6H_{12}N_4\right]^+x^- \xrightarrow[H_2O]{H^+} ArCH_2NH_2 + NH_3 + H_2O \qquad (1)$$

Sommelet[52] later showed that when the quarternary salt was hydrolyzed in water, it was broken down into an aromatic aldehyde accompanied by other products as indicated by the equation:

$$\left[ArCH_2C_6H_{12}N_4\right]^+x^- \xrightarrow{H_2O} ArCHO + CH_2O + ArCH_2NH_2 + CH_3NH_2 + NH_3 \qquad (2)$$

The decomposition may be hastened by using acetic acid as solvent.[53] This constitutes a general method for the preparation of aromatic aldehydes from the corresponding chloromethyl derivatives. Its suitability for the synthesis of aromatic dialdehydes, however, had not been studied until work in this laboratory established the general applicability of this reaction.

2. Synthesis of Aromatic Dialdehydes

The bis-chloromethyl compounds submitted to the conditions of the Sommelet reaction are indicated in Table I along with the yields of the aldehyde. This work indicates that the Sommelet reaction is an excellent method for the

---

(52) Sommelet, M., Compt. rend., 157, 852 (1913).

(53) Hewett, C. L., J. Chem. Soc., 297 (1940).

TABLE I

HEXAMETHYLENETETRAMINE SALTS OF CHLOROMETHYL COMPOUNDS AND THEIR HYDROLYSIS PRODUCTS

Chloromethyl Compound	Product	Yield* (%)
2,4-Bis-(chloromethyl)-anisole	4-Methoxyisophthalaldehyde	63
2,4-Bis-(chloromethyl)-thiophenol Methyl Ether	4-Thiomethylisophthalaldehyde	21
4,6-Bis-(chloromethyl)-resorcinol Dimethyl Ether	4,6-Dimethoxyisophthalaldehyde	**
2,4-Dimethoxybenzyl Chloride	2,4-Dimethoxybenzaldehyde	**
2,5-Bis-(chloromethyl)-p-xylene	2,5-Dimethylterephthalaldehyde	57
o-Xylylene Dibromide***	o-Xylylene Diamine Dihydrochloride	55
2-Chloromethyl-3-hydroxy-nitrobenzene	Bis-(2-hydroxy-6-nitrobenzyl)-amine	77
2,4-Bis-(chloromethyl)-mesitylene	Polymeric Nitrogen Compound	
Chloromethylmesitylene	N,N'-di-α^2-isodurylmethanediamine	100
Chloromethylmesitylene***	α^2-isodurylamine Hydrochloride	55

*Yield based upon the corresponding chloromethyl compound.

**The yield cannot be calculated since the amount of chloromethyl compound was unknown.

***Hydrolysis of the corresponding quarternary salt in acid medium.

preparation of aryl dialdehydes providing that the corresponding chloromethyl compounds are available and provided that certain steric conditions to be discussed later do not exist.

In all cases, one mole of the bis-chloromethyl compound reacted with two moles of hexamethylenetetramine to give a quantitative yield of the salt which could generally be isolated as white crystals. An aqueous solution of the salt was then hydrolyzed by heating under reflux for four hours. The yield of the dialdehyde generally was increased by the addition of formaldehyde in the hydrolysis solution. In the case of 2,5-bis-chloromethyl-p-xylene, the salt was a sticky, hygroscopic substance which made it difficult to work with. To overcome this, it was found that the hydrolysis to the desired dialdehyde could be carried out directly without isolation of the intermediary salt. Thus, when a mixture of 2,5-bis-chloromethyl-p-xylene and hexamethylenetetramine in 60 per cent ethanol was refluxed for eighteen hours, 2,5-dimethylterephthalaldehyde was obtained in 38 per cent yield. Attempts to isolate the chloromethyl compound from the reaction of resorcinol dimethyl ether with chloromethyl ether were unsuccessful, but when the reaction mixture was directly treated with hexamethylenetetramine, a mixture of quarternary salts of the chloromethyl compounds was obtained. This mixture of salts was hydrolyzed to yield 4,6-dimethoxyisophthalaldehyde and 2,4-dimethoxybenzaldehyde. The structures of

the aldehydes were determined by conversion to the known carboxylic acids.

The influence of other substituents in the ring on the formation of aldehydes by hydrolysis of the salt will be discussed under the section on "Abnormal Sommelet Reaction."

3. Mechanism of the Sommelet Reaction

In recent years there has been a revival of interest concerning the mechanism of the Sommelet reaction. The major contributions came from two different groups, Angyal and Rassack[54] in Australia, and Graymore and Davies[55] in England. They reviewed the tentative proposal given by Sommelet[56] in 1913 and which involved the following steps:

(1) Hydrolysis of the quarternary salt to methylenebenzylamine,

$$\left[ArCH_2C_6H_{12}N_4\right]^+x^- \longrightarrow ArCH_2N{=}CH_2 \qquad (3)$$

(2) Shifting of the double bond to give benzylidenemethylamine,

$$ArCH_2N{=}CH_2 \longrightarrow ArCH{=}NCH_3 \qquad (4)$$

(3) Hydrolysis of benzylidenemethylamine to benzaldehyde and methylamine,

$$ArCH{=}NCH_3 \longrightarrow ArCHO + CH_3NH_2 \qquad (5)$$

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(54) Angyal, S. J., and Rassack, R. C., J. Chem. Soc., 2700 (1949).

(55) Graymore, J., and Davies, D. R., J. Chem. Soc., 293 (1945).

(56) Sommelet, M., Compt. rend., 157, 852 (1913).

Notwithstanding the fact that Sommelet himself had not furnished any evidence for the mechanism he proposed, and moreover, had later expressed a change of view in two later publications,[57,58] Graymore and Davies, after a lapse of thirty years, provided experimental results in support of the first step of Sommelet's first suggestion. If methylene-benzylamine is an intermediate in the course of the formation of the aldehyde, it should itself give benzaldehyde under the conditions of the Sommelet reaction. Indeed, benzaldehyde was obtained by Graymore and Davies[59] in good yield when a mixture of benzylamine and formaldehyde was treated with hexamethylenetetramine. Furthermore, these workers showed that benzylamine or methylene benzylamine could not be converted to benzaldehyde in the absence of hexamethylene-tetramine.

(6)

The greatest objection to Sommelet's mechanism lies in the second step. The possibility of a prototropic

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(57) Sommelet, M., Bull. soc. chim. (iv), 17, 82 (1915).

(58) Sommelet, M., Bull. soc. chim. (iv), 23, 96 (1917).

(59) Graymore, J., and Davies, D. R., J. Chem. Soc., 293 (1945).

rearrangement in the Schiff's base, as remarked by Angyal and Rassack,[60] is highly improbable since it was pointed out by Ingold and Shoppee[61] that such a prototropic rearrangement only occurred to some extent in a solution of sodium ethoxide at 300°. This view was subsequently supported by von Auwers and Wunderlich[62] and by Shoppee.[63]

The role of hexamethylenetetramine has been shown by Graymore and Davies[64] and by Angyal and Rassack[65] to be more than merely that of salt formation. Nevertheless, both groups of investigators failed to offer a satisfactory explanation. On the basis that ammonia was evolved copiously during the hydrolysis of the quarternary salt, Graymore and Davies attempted to attribute the function of hexamethylenetetramine to its hydrolyzed product, aminomethyl alcohol, which according to them, took part in the third step of Sommelet's proposed mechanism in the following manner:

$$ArCH{=}NCH_3 + NH_2CH_2OH + H_2O \longrightarrow ArCHO + CH_3NHCH_2OH + NH_3 \quad (7)$$

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(60) Angyal, S. J., and Rassack, R. C., J. Chem. Soc., 2700 (1949).

(61) Ingold, C. K., and Shoppee, C. W., J. Chem. Soc., 1199 (1929).

(62) Auwers, K. V., and Wunderlich, H., Ber., 65, 70 (1932).

(63) Shoppee, C. W., Nature, 162, 619 (1948).

(64) Graymore, J., and Davies, D. R., J. Chem. Soc., 293 (1945).

(65) Angyal, S. J., and Rassack, R. C., loc. cit.

It is quite apparent that such a view cannot be entertained since benzylidenemethylamine is known to be hydrolyzed very smoothly at the pH of the reaction mixture without the need of any other reagent.

Angyal and Rassack's[66] explanation as to the role of hexamethylenetetramine was somewhat ingenious, albeit, not entirely convincing. They pointed out the existence of the following equilibrium at the pH of the reaction (pH 3 to 6):

$$ArCH_2N{=}CH_2 + H_2O \rightleftharpoons ArCH_2NH_2 + CH_2O \qquad (8)$$

The benzylamine present in the equilibrium mixture, according to them, underwent dehydrogenation resulting in an imine which was subsequently hydrolyzed to the aldehyde. That hexamethylenetetramine was indispensable in the acquirement of high yield of the aldehyde was due to the action of one of its hydrolysis products, methyleneimine, which functioned as a hydrogen acceptor. Thus they proposed the following steps for the mechanism of the Sommelet reaction:

$$\left[ArCH_2C_6H_{12}N_4\right]^+x^- \longrightarrow ArCH_2N{=}CH_2 \qquad (9)$$

$$ArCH_2N{=}CH_2 + H_2O \rightleftharpoons ArCH_2NH_2 + CH_2O \qquad (10)$$

$$C_6H_{12}N_4 + H_2O \rightleftharpoons CH_2{=}NH \qquad (11)$$

$$ArCH_2NH_2 + CH_2{=}NH \longrightarrow ArCH{=}NH + CH_3NH_2 \qquad (12)$$

$$ArCH{=}NH + H_2O \longrightarrow ArCHO + NH_3 \qquad (13)$$

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(66) Angyal, S. J., and Rassack, R. C., J. Chem. Soc., 2700 (1949).

In support of the foregoing viewpoint, the simple system of benzylamine hydrochloride and formaldehyde in water was studied by these workers. Attempts to increase the yield of aldehyde by varying the conditions were unsuccessful, but they found that the low yield was due to the formation of benzylmethylamine which was produced in as much as 50 - 65 per cent yield. This formation was accounted for by the occurrence of the following reactions:

$$ArCH_2NH_2 + CH_2O \rightleftharpoons ArCH_2N{=}CH_2 + H_2O \qquad (14)$$

$$ArCH_2N{=}CH_2 + CH_2O + H_2O \longrightarrow ArCH_2NHCH_3 + HCO_2H \qquad (15)$$

$$ArCH_2N{=}CH_2 + HCO_2H \longrightarrow ArCH_2NHCH_3 + CO_2 \qquad (16)$$

$$ArCH_2NH_2 + ArCH_2N{=}CH_2 + H_2O \longrightarrow ArCHO + NH_3 + ArCH_2NHCH_3 \qquad (17)$$

Hence, they further explained that there was a dual role played by hexamethylenetetramine, one as a hydrogen acceptor, as mentioned above, and the other as a substitute for methylenebenzylamine, thus diminishing the formation of benzylmethylamine, which, according to these workers, was the cause of the low yield of aldehyde in the absence of hexamethylenetetramine.

$$CH_2{=}NH + CH_2O + H_2O \longrightarrow CH_3NH_2 + HCO_2H \qquad (18)$$

$$ArCH_2NH_2 + CH_2{=}NH \longrightarrow CH_3NH_2 + ArCH{=}NH \qquad (19)$$

$$ArCH{=}NH + H_2O \longrightarrow ArCHO + NH_3 \qquad (20)$$

Our observation that hexamethylenetetraminebenzyl chloride on hydrolysis in basic solution affords benzylamine[67] enables us to state here that the equilibrium (8) tends to shift to the right in pH > 7. That the same is also true for pH < 3 is suggested by the fact that in Delepine's reaction both primary amine and formaldehyde are obtained. It is understandable, therefore, why Graymore and Davies[68] failed to obtain benzaldehyde from either benzylamine or methylenebenzylamine in the presence of an excess of hydrochloric acid.

According to the role ascribed by Angyal and Rassack to hexamine, it implies that the yield of benzaldehyde would be favored by (a) an excess of hexamethylenetetramine, and/or (b) a minimum amount of formaldehyde. The former was justified by the experimental results of these workers; the latter, however, is in direct conflict with our work. In order to attain higher yields of the aldehyde, we have found that it was necessary to add an excess of formaldehyde during the hydrolysis of the quarternary salt. This unexplainable disagreement between our observation and that of Angyal and Rassack cannot restrain us from casting some doubt upon the mechanism for the Sommelet reaction as proposed by the

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(67) Graymore, J., J. Chem. Soc., 1116 (1947).

(68) Graymore, J., and Davies, D. R., J. Chem. Soc., 293 (1945).

Australian workers. Nevertheless, we are only allowed to say that the role of hexamethylenetetramine in this reaction still remains quite mysterious.

4. Abnormal Sommelet Reaction

Fuson and Denton[69] first observed that chloromethylmesitylene, instead of undergoing the Sommelet reaction to yield the corresponding aldehyde, gave a basic nitrogen compound upon hydrolysis of its quarternary salt. They referred to this result as an abnormal case of the Sommelet reaction, and proposed a tentative structure, N,N'-di-α^2-isodurylamine, for the basic nitrogen product.

Angyal, Morris, Rassack, and Waterer[70] reported a more extensive study of the Sommelet reaction on a number of o- substituted chloromethyl compounds, and concluded that when two substituents, electron-attracting and electron-releasing groups alike, were present in positions ortho to the chloromethyl group, the Sommelet reaction was hindered. One ortho-substituent, on the other hand, did not prevent the reaction but was not entirely without hindrance effect. This was shown by diminished yield of the o-bromobenzaldehyde (50%)

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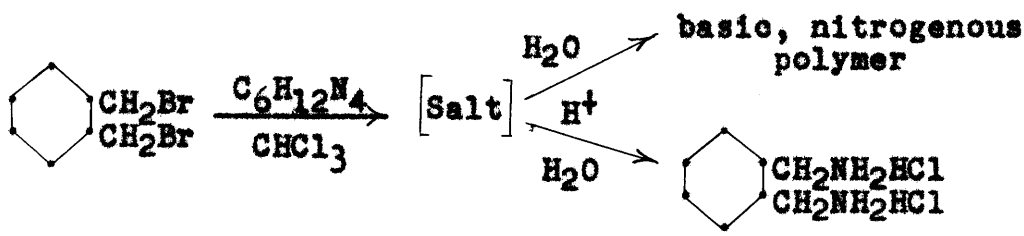
(69) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

(70) Angyal, S. J., Morris, P. J., Rassack, R. C., and Waterer, J. A., J. Chem. Soc., 2704 (1949).

as compared to the yield of the m- isomer (60%) and the p- isomer (62%).

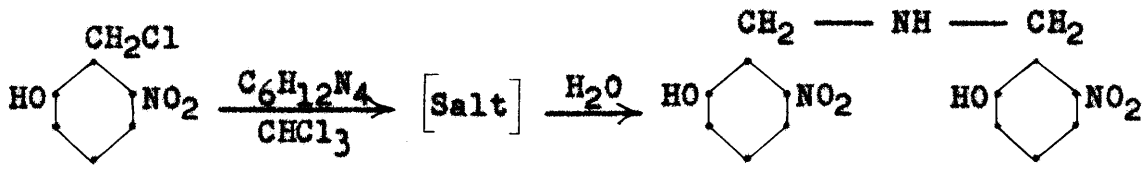
Similar conclusions are also indicated by the results of this work. Several chloromethyl compounds with ortho substituents were submitted to the reaction, and in all cases no aldehyde formation could be detected. These are described below.

An attempt to prepare phthalaldehyde from o-xylylene dibromide was made, but hydrolysis of the quarternary salt in acidic medium furnished o-xylylene diamine dihydrochloride (XII), while hydrolysis in water gave a highly polymerized product. In both instances no aldehyde was obtained. This is a case where one ortho-substituent does bring forth hindrance in the reaction.



(XII)

Although 2-hydroxy-6-nitrobenzyl chloride formed a white crystalline salt with hexamethylenetetramine, hydrolysis of this salt failed to produce the corresponding aldehyde but did produce a basic nitrogen compound to which the structure of bis-(2-hydroxy-6-nitrobenzyl)-amine (XIII) has been tentatively assigned.



(XIII)

Similarly, attempts to convert 2,4-bis-chloromethylmesitylene to the corresponding dialdehyde were in vain. Hydrolysis of its salt in water afforded a nitrogen containing polymer which probably resulted from the condensation of the amine formed with formaldehyde.

In the case of chloromethylmesitylene, the same basic nitrogen compound obtained by Fuson and Denton[71] resulted from hydrolysis of the salt in water, and α^2-isodurylamine hydrochloride was isolated when the hydrolysis was performed in acid. However, it was most striking that the transformation of the chloromethyl group to the aldehyde was achieved when 2-chloromethylmesitylene was treated with excess formaldehyde under refluxing temperature for twelve hours and then with hexamethylenetetramine for another twelve hours. Mesitylene aldehyde (XVI) was isolated in 47 per cent yield. It is believed that the course of the reaction is as follows:

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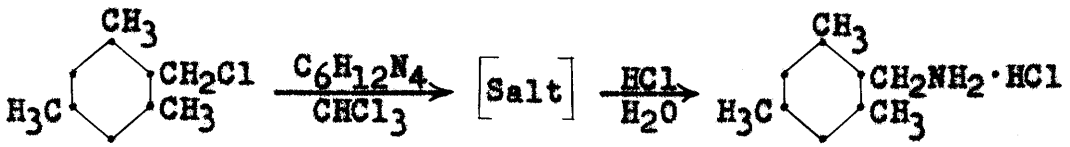
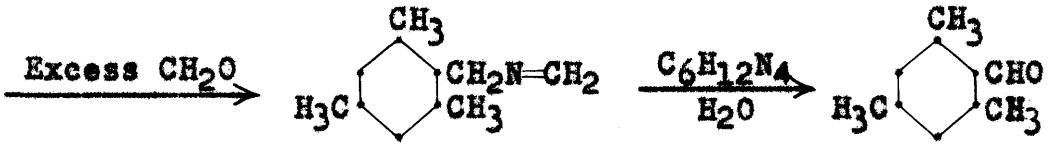
(71) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

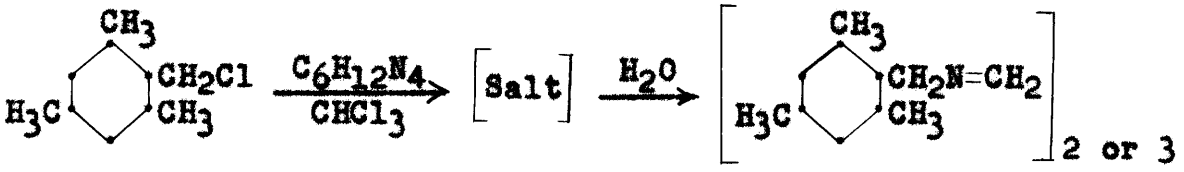


(XIV)



(XV) (XVI)

Angyal and Rassack[72] have reported the failure of transforming 2-isodurylamine hydrochloride (XIV) into mesitylene aldehyde under various conditions. Instead, they obtained the same compound that Fuson and Denton[73] obtained but disagreed with them as to its structure. They believed the compound to be a dimer or trimer of the methyleneamine as indicated below:



They postulated that steric hindrance inhibited the third step (equation 12) of their proposed mechanism for the Sommelet reaction. This view, however, is not in complete

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(72) Angyal, S. J., and Rassack, R. C., J. Chem. Soc., 2700 (1949).

(73) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

harmony with our accomplished conversion of α^2-isodurylamine into mesitylene aldehyde. Since all of the aforementioned investigators are in agreement that the Schiff's base formed upon hydrolysis of the hexamethylenetetramine salt is essential in the formation of the aldehyde,

$$ArCH_2N{=}CH \xrightarrow{C_6H_{12}N_4} ArCHO \ .$$

We are led to believe, therefore, that the formation of mesitylene aldehyde from the amine is proceeded by a Schiff's base type intermediate (XV). This view may further be supported by a consideration of the equilibrium

$$ArCH_2NH_2 + CH_2O \rightleftharpoons ArCH_2N{=}CH_2 + H_2O \ .$$

That the reaction to the right would be favored by the large excess of formaldehyde appears to be the main criterion for the success of this reaction. If this were true, the presence of o-substituents would be responsible for the inhibition of the formation of the Schiff's base intermediate in lieu of the third step (equation 12) as proposed by Angyal and Rassack. Clarification of this point awaits more detailed experimental evidence.

C. Condensation of Aromatic Dialdehyde with Nitroalkanes

It has been well established that aldehydes and nitroalkanes in the presence of a base undergo condensation to yield nitro alcohols or α,β-unsaturated nitro compounds. In

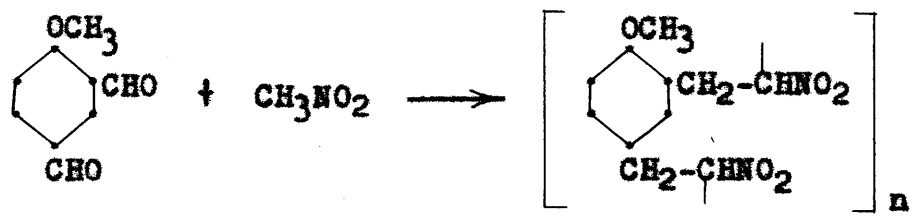
spite of the voluminous works reported in this field, there has been hitherto not a single case of the condensation of a nitroalkane with aromatic dialdehydes. With the purpose of preparing a number of bis-(2-aminoethyl)-benzenes containing various types of substituents, e.g., hydroxyl or methyl groups on the ethylamine side chain, a study of the condensation of nitromethane and nitroethane with two aromatic dialdehydes, 4-methoxyisophthalaldehyde and 2,5-dimethoxyterephthalaldehyde was carried out. A large number of different catalysts, including both inorganic and organic bases, under various conditions have been tried. The results are shown in Tables II, III, IV, and V.

From the experimental results it is not difficult for us to conclude that nitromethane is more reactive than nitroethane, and that m- dialdehydes undergo condensation more actively than p- dialdehydes. Thus 4-methoxyisophthalaldehyde in the presence of amylamine did yield invariably a brown polymer with nitromethane but a yellowish, crystalline product with nitroethane. In addition, 2,5-dimethylterephthalaldehyde with nitromethane gave a red, crystalline substance.

All the polymeric products were insoluble in ordinary organic solvents such as ethanol, methanol, benzene, and chloroform, but were soluble in acetone and cellusolve. Nevertheless, attempts to recrystallize the polymers from these two solvents were futile. Analytical data suggested

TABLE II

CONDENSATION OF 4-METHOXYISOPHTHALALDEHYDE WITH NITROMETHANE



(XVII)

Catalysts	Temperature	Products
25% Sodium hydroxide solution	-5°	No reaction
25% Sodium hydroxide solution	0°	No reaction
25% Sodium hydroxide solution	Room temperature	Brown polymer (XVII)
Sodium methoxide (with hydroquinone)	Room temperature	Yellow crystals m.p. 109-110°. Not reducible by catalytic hydrogenation or chemical reduction.
Sodium bicarbonate	Room temperature	No reaction
Pyridine	Room temperature	No reaction

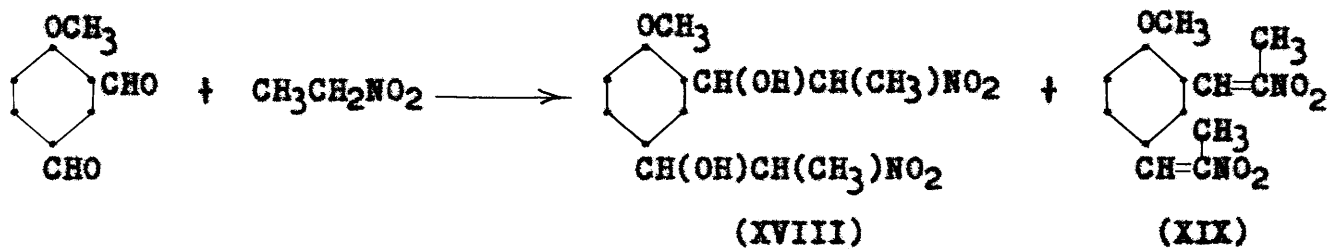
TABLE II

CONDENSATION OF 4-METHOXYISOPHTHALALDEHYDE WITH NITROMETHANE (continued)

Catalysts	Temperature	Products
Pyridine	Reflux in alcoholic solution	Brown polymer (XVII)
Methylamine	Room temperature	Brown polymer (XVII)
n-Butylamine	Room temperature	Brown polymer (XVII)
n-Amylamine	Room temperature	Brown polymer (XVII)
n-Amylamine	Dark, -5°	Brown polymer (XVII)
Trimethylamine	Room temperature	Brown polymer (XVII)

TABLE III

CONDENSATION OF 4-METHOXYISOPHTHALALDEHYDE WITH NITROETHANE



Catalysts	Temperature	Products
25% Sodium hydroxide solution	Reflux in alcoholic solution	No reaction
Sodium methoxide (with hydroquinone)	Room temperature	2,4-Bis-(1-hydroxy-2-nitropropyl)-anisole (XVIII)
Sodium bicarbonate	Room temperature	No reaction
Pyridine	Room temperature	No reaction
Pyridine	Reflux in alcoholic solution	Yellow crystals m.p. 102-103°. Not reducible by catalytic hydrogenation or chemical reduction.

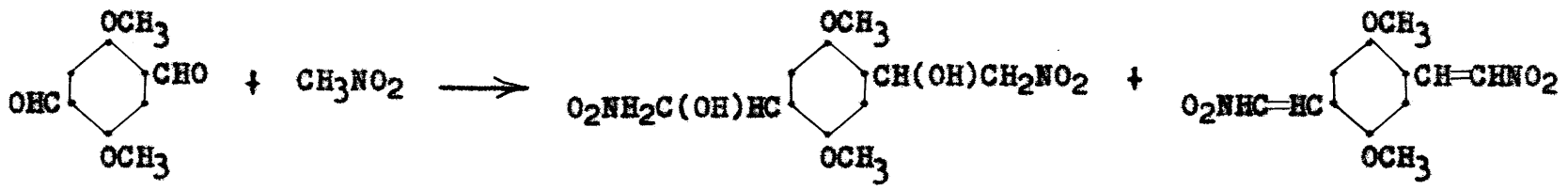
TABLE III

CONDENSATION OF 4-METHOXYISOPHTHALALDEHYDE WITH NITROETHANE (continued)

Catalysts	Temperature	Products
Trimethylamine	Reflux in alcoholic solution	Yellow crystals m.p. 102-103°. Not reducible by catalytic hydrogenation or chemical reduction.
Methylamine	Room temperature	Brown polymer
n-Butylamine	Room temperature	2,4-Bis-(2-nitropropenyl-1)-anisole (XIX)
n-Amylamine	Room temperature	2,4-Bis-(2-nitropropenyl-1)-anisole (XIX)
n-Butylamine	Reflux in alcoholic solution	2,4-Bis-(2-nitropropenyl-1)-anisole (XIX) with polymer

TABLE IV

CONDENSATION OF 2,5-DIMETHOXYTEREPHTHALALDEHYDE WITH NITROMETHANE



(XX) (XXI)

Catalysts	Temperature	Products
25% Sodium hydroxide solution	-5°	No reaction
25% Sodium hydroxide solution	0°	No reaction
25% Sodium hydroxide solution	Room temperature	2,5-Bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether (XX)
Sodium methoxide (with hydroquinone)	Room temperature	2,5-Bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether (XX)
Sodium bicarbonate	Room temperature	No reaction
Methylamine	Room temperature	Brown polymer

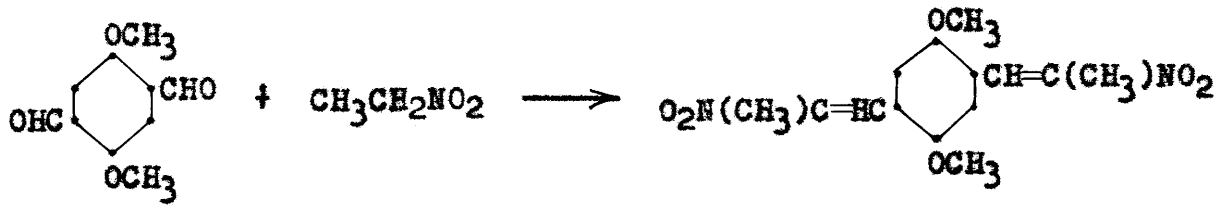
TABLE IV

CONDENSATION OF 2,5-DIMETHOXYTEREPHTHALALDEHYDE WITH NITROMETHANE (continued)

Catalysts	Temperature	Products
n-Butylamine	Room temperature	2,5-Bis-(2-nitroethylene)-hydroquinone dimethyl ether (XXI)
n-Amylamine	Room temperature	2,5-Bis-(2-nitroethylene)-hydroquinone dimethyl ether (XXI)

TABLE V

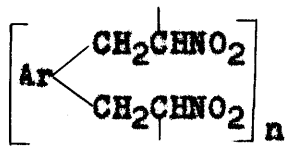
CONDENSATION OF 2,5-DIMETHOXYTEREPHTHALALDEHYDE WITH NITROETHANE



(XXII)

Catalysts	Temperature	Products
Pyridine (with piperidine)	Reflux in alcoholic solution	2,5-Bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether (XXII)
Methylamine	Room temperature	2,5-Bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether (XXII) with polymer
n-Butylamine	Room temperature	2,5-Bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether (XXII)
n-Amylamine	Room temperature	2,5-Bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether (XXII)

a possible general structure (XXIII) for these polymeric substances.



(XXIII)

It is interesting to note that polymers were neither reducible by catalytic hydrogenation nor by chemical reagents under the same conditions that simple nitro compounds are reducible.

In order to isolate the nitro alcohol, a trace of hydroquinone was added as a stabilizing agent. Otherwise, the products were converted to the corresponding nitro olefins through the loss of a molecule of water.

A rather remarkable property of the two nitro alcohols was observed during the course of purification. When the nitro alcohol was treated with saturated sodium bisulfite solution, it went into solution completely; then, when excess acid was added, the corresponding dialdehyde was regenerated. Moreover, when an alcoholic solution of the nitro alcohol was treated with 2,4-dinitrophenylhydrazine, only the hydrazone of the corresponding dialdehyde was isolated. In both cases, no detectable quantity of the original nitro alcohol was obtained after the treatment. It appears, therefore, that in aqueous or alcoholic solution the nitro alcohol is present in equilibrium with the corresponding dialdehyde:

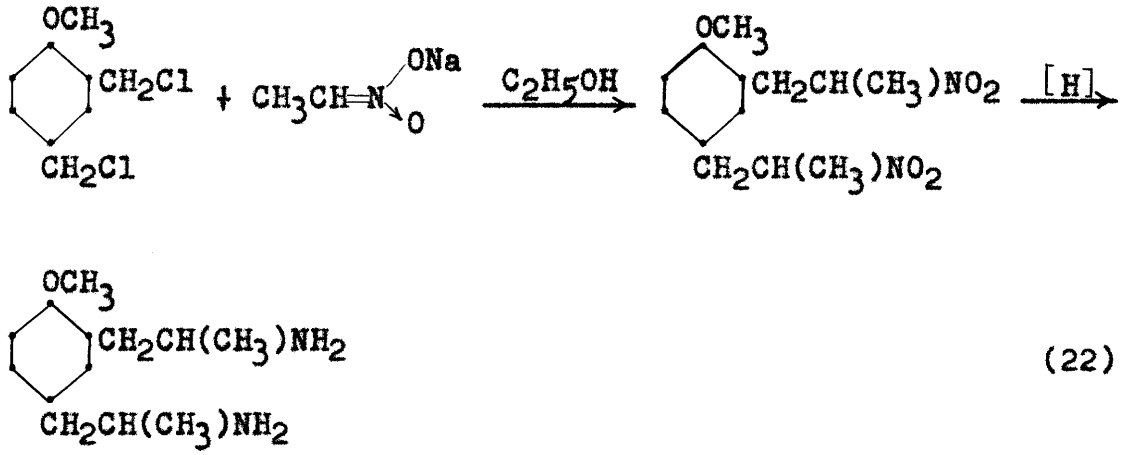
$$Ar\left[CH(OH)CH(R)NO_2\right]_2 \rightleftharpoons Ar(CHO)_2 + 2RCH_2NO_2 \quad (21)$$

$$R = H \text{ or } CH_3$$

This interesting equilibrium could be confirmed, in the opinion of the writer, by a comparison of the ultraviolet absorption spectrum of the nitro alcohol in aqueous or alcoholic solution with that of the dialdehyde. If the equilibrium does exist, the characteristic absorption curve of the aldehyde would be observed in the spectrum of the nitro alcohol.

D. The Condensation of Chloromethyl Compounds with Nitroalkanes

This involved direct condensation of the bis-chloromethyl compound with a nitroalkane in alcoholic solution with the aim of obtaining a saturated nitro-compound which might subsequently be reduced to the amine. Only one attempt was made by this method, namely the condensation of 2,4-bis-(chloromethyl)-anisole with the sodium salt of nitroethane. The anticipated results are summarized by the following equations:



(22)

When the condensation was carried out, a black viscous oil was obtained. Attempts were made to purify this product by a vacuum distillation under nitrogen atmosphere, but only a small amount of slightly yellow liquid was obtained which solidified upon standing. Repeated recrystallization of the yellow liquid from ethanol furnished a crystalline substance which did not contain nitrogen and which was not the starting bis-chloromethyl compound. It appears that this compound was formed by the decomposition during distillation of the condensation product, although it could have resulted from the unreacted 2,4-bis-(chloromethyl)-anisole since such molecules are known to undergo condensation with each other by the elimination of hydrogen chloride to form diphenylmethane types. No effort was made to characterize it, and neither was any effort made to characterize the tarry residue.

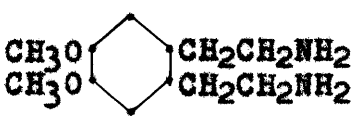
It was thought that this complication might be avoided by using dioxane or nitroethane as the solvent. However, in both cases the starting material was recovered. This is probably due to the insolubility of the sodium salt of nitroethane in these solvents.

E. Reduction of Nitriles and Nitro Compounds to 2-Aminoethylbenzenes

1. Reduction of Nitrile

In the reduction of 4,5-bis-(cyanomethyl)-veratrole (XXIV), Perry[74] was able to obtain a 25 per cent yield of the 4,5-bis-(2-aminoethyl)-veratrole (XXV) along with a 38 per cent yield of a lower boiling amine whose analysis corresponded to that of two isomeric substances, a benzazepine (XXVI) and an aminohydrindene (XXVII). The Hinsberg and nitrous acid tests which Perry made indicated

(XXIV)



(XXV)

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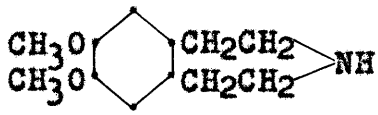
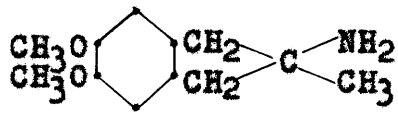
(74) Perry, M. A., "The Synthesis and Sympathomimetic Activity of Some o- and m-Bis-(2-aminoethyl)-benzenes," Doctoral Dissertation, The University of Tennessee, Knoxville, Tennessee, 1950, p. 83.

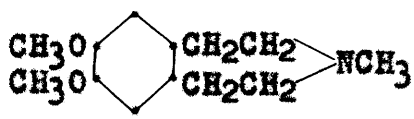


(XXVI)



(XXVII)

that the amine in question was a secondary one and consequently supported the azepine structure postulated by him. In order to obtain additional support, the preparation of bis-nitrile (XXIV) and its subsequent reduction were repeated and results similar to Perry's were obtained. The total methylation of the lower boiling amine was achieved by the method of Icke, et al.,[75] and the analysis for nitrogen was in good agreement with the calculated value for N-methyl benzazepine (XXVIII). Thus the analysis indicates that one



(XXVIII)

methyl group was introduced, a fact which supports the azepine (a secondary amine) rather than the hydrindene (a primary amine).

2. Reduction of Nitro Compounds to Amines

a. Reduction of 2,4-Bis-(2-nitropropenyl-1)-anisole. Two methods for the preparation of 2,4-bis-(2-aminopropyl)-anisole (XXX) from 2,4-bis-(2-nitropropenyl-1)-anisole (XXIX)

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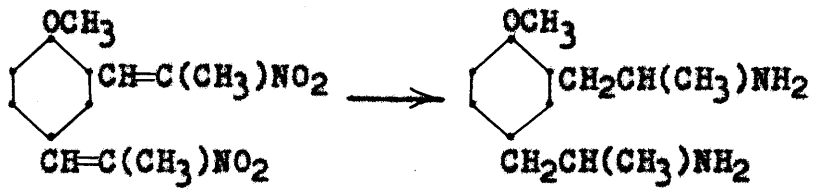
(75) Icke, R. N., Wisegarver, B. B., and Alles, G. A., Org. Synthesis, 25, 89 (1945).

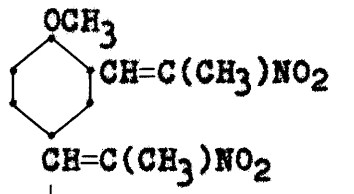
were attempted: (a) hydrogenation in the presence of Raney nickel, and (b) reduction by means of lithium aluminum hydride.



(XXIX) (XXX)

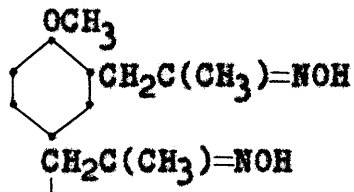
The hydrogenation method gave a product which melted at 133°, contained basic nitrogen, did not form an acetyl or benzoyl derivative, and was insoluble in ether. No further characterization was made since it was most likely not the desired product. In the lithium aluminum hydride reduction, a suitable solvent for the reduction could not be found. Ether, dioxane, and tetrahydrofuran were tried, but the nitro olefin was so insoluble in these solvents that no reduction was accomplished, and in every case 97 to 99 per cent of the starting material was recovered.

Finally a method of reduction was developed which gave an over-all yield of 52 per cent of the amine. This method is illustrated by the following equations:

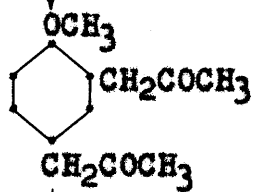


2,4-Bis-(2-nitropropenyl-1)-anisole

Fe + HCl

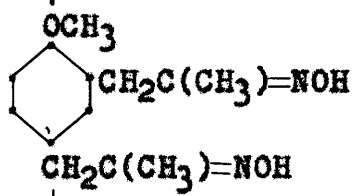


2,4-Diacetonyl Anisole Oxime which was hydrolyzed under the reaction condition



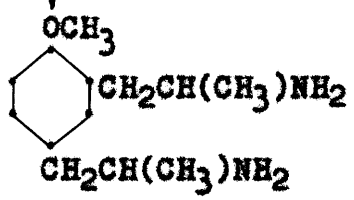
2,4-Diacetonyl Anisole

$NH_2OH \cdot HCl$
NaOH



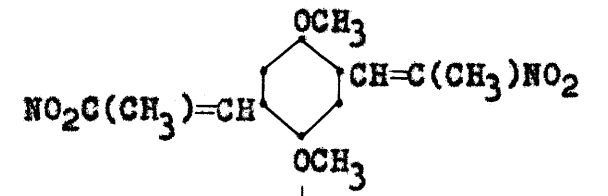
2,4-Diacetonyl Anisole Oxime

H_2 Ni



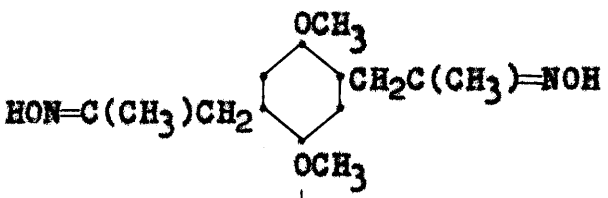
2,4-Bis-(2-aminopropyl)-anisole

b. <u>Reduction of 2,5-bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether</u>. The reduction was accomplished with 29 per cent over-all yield by the following sequence of reactions:

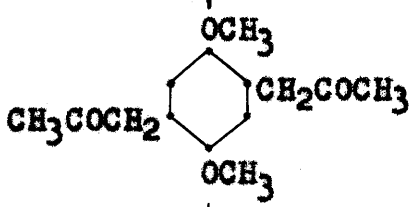


2,5-Bis-(2-nitro-propenyl-1)-hydroquinone Dimethyl Ether

Fe + HCl

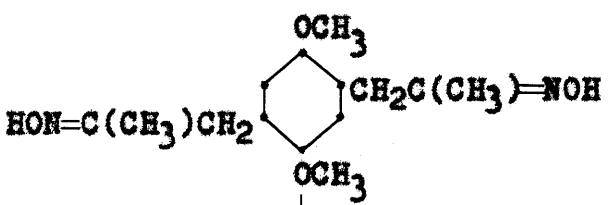


2,5-Diacetonyl Hydroquinone Dimethyl Ether Oxime which was hydrolyzed under the reaction condition

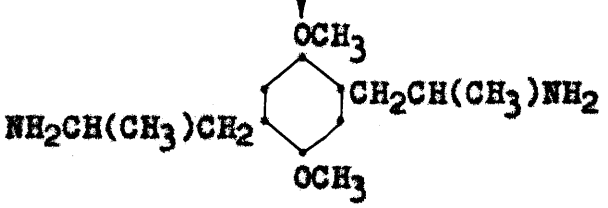


2,5-Diacetonyl Hydroquinone Dimethyl Ether

$NH_2OH \cdot HCl$
NaOH



2,5-Diacetonyl Hydroquinone Dimethyl Ether Oxime



2,5-Bis-(2-aminopropyl)-hydroquinone Dimethyl Ether

c. <u>Reduction of 2,5-bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether.</u> 2,5-Bis-(1-hydroxy-2-aminoethyl)-hydroquinone dimethyl ether has already been reported by Wood

and Gibson[76] by the catalytic hydrogenation of 2,5-bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether under a pressure of 3 to 4 atmospheres of hydrogen with a yield of 17 per cent based on the corresponding aldehyde. We have succeeded in improving the over-all yield to 29 per cent by high pressure hydrogenation in the presence of Raney nickel. The optimum conditions were found to be hydrogenation at room temperature with a hydrogen pressure of 1500 lbs. per sq. in. along with a carbon dioxide pressure of 300 lbs. per sq. in., giving a total pressure of 1800 lbs. per sq. in. According to Hoover and Hass,[77] the presence of carbon dioxide inhibited the formation of N-alkyl derivatives.

d. Attempted reductions. Attempts by catalytic hydrogenation and by the use of chemical reducing agents were made to reduce the compounds which were thought to be polymeric 2,4-bis-(2-nitroethylene)-anisole (XVII), 2,5-bis-(2-nitroethylene)-hydroquinone dimethyl ether (XXI), and 2,4-bis-(1-hydroxy-2-nitropropyl)-anisole (XVIII). In all cases, no evidence could be obtained that amines or oximes had formed. Of course, the structures of these assumed nitro-compounds have not been fully established. The method of preparation and the nitrogen analyses indicate that the structures

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(76) Wood, J. H., and Gibson, R. E., J. Am. Chem. Soc., 71, 393 (1949).

(77) Hoover, F. W., and Hass, H. B., J. Org. Chem., 12, 506 (1947).

proposed are probably correct. On the other hand, failure to undergo reduction casts doubt on these conclusions, and further work is needed to clarify this situation.

F. Physiological Activity of the New Amines

Two of the 2-aminopropylbenzenes, namely 2,4-bis-(2-aminopropyl)-anisole and 2,5-bis-(2-aminopropyl)-hydroquinone dimethyl ether, were submitted to Eli Lilly and Company for pharmacological tests. They were tested in the form of their hydrochloride salts. The results may be summarized as follows:

1. Activity of 2,4-Bis-(2-aminopropyl)-anisole Dihydrochloride

The following is quoted from the Lilly report:[78]

> Isolated guinea pig's tracheal chain--1 mg. = 5 of epinephrine. In anesthetized cat, 5 mg. by vein had no blood pressure action. Antispasmodic activity on isolated guinea pig ileum = 0.1% of that of atropine sulfate.

2. Activity of 2,5-Bis-(2-aminopropyl)-hydroquinone Dimethyl Ether Dihydrochloride

The following is quoted from the Lilly report:[78] "In anesthetized cat, 5 mg. by vein had no blood pressure action."

The pharmacological testing received by Eli Lilly and Company is not yet complete. Other possible pharmacological tests are being made.

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(78) Private communications to Dr. J. H. Wood.

The cause of the loss of sympathomimetic activity by the introduction of a second 2-aminoethyl group into the benzene nucleus is not understandable. This author suggests that further research may be directed along similar compounds of five and six membered heterocyclic rings, such as, thiophene, pyrrol, thiazole, pyrimidine, and pyridine.

CHAPTER III

EXPERIMENTAL

A. Synthesis of the Chloromethyl Compounds

1. 2,4-Bis-(chloromethyl)-anisole

While the 2,4-bis-(chloromethyl)-anisole was formed when a mixture of anisole in petroleum ether with an excess of formalin was saturated with hydrogen chloride gas, a considerable amount of p,p'-dimethoxydiphenylmethane made the purification of the desired product very difficult. It was therefore much more advantageous to synthesize the bis-chloromethyl anisole by the stepwise introduction of the two chloromethyl groups with the isolation and purification of the intermediate monochloromethyl derivative.

a. p-Chloromethyl anisole.[1] A mixture of 150 g. (1.39 moles) of anisole, 150 g. (1.75 moles) of 35 per cent formalin, 150 ml. of petroleum ether and 15 g. of zinc chloride was placed into an externally cooled, 1-l., three-necked flask provided with stirrer. A rapid stream of hydrogen chloride gas was introduced with vigorous stirring at a temperature of between 10 and 15°. The reaction was stopped after one hour and fifteen minutes. After separating the

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(1) Quelet, R., and Allard, J., Bull. soc. chim. (5), 3, 1796 (1936).

petroleum ether layer and washing it repeatedly with ice water, it was washed once with cold 10 per cent sodium carbonate solution and then twice more with ice water. The treatment with sodium carbonate solution was absolutely indispensable in order to remove the last trace of hydrogen chloride which would have eventually caused decomposition of the product upon distillation. Furthermore, the distillation of monochloromethyl anisole was possible only when the product was washed as described and then dried rapidly over anhydrous sodium sulfate. It was observed that the product, after standing for twenty four hours over anhydrous sodium sulfate, changed into a non-distillable substance. On carrying out the precautions indicated above, the product thus obtained was subjected to a fractional vacuum distillation. The portions obtained were as follows:

30 g. of unchanged anisole, b. p. 55-60°C/18 mm.

127 g. of p-chloromethyl anisole (54%),
b. p., 115-120°C/16 mm.

30 g. of p,p'-dimethoxydiphenylmethane, b. p.,
195-197°C/16 mm.

It was not possible to preserve the anhydrous p-chloromethyl anisole at ordinary temperature. At the end of twenty four hours hydrogen chloride fumes were noticeable, and in the course of several days the product had changed to an

uncrystallizable, pasty mass. The addition of a few drops of dilute hydrochloric acid prevented the decomposition.

The third fraction, which had solidified on standing, was recrystallized from petroleum ether. Brilliant leaflets which melted at 51° resulted. This agrees with the melting point of p,p'-dimethoxydiphenylmethane reported by Quelet and Allard.[2]

b. 2,4-Bis-(chloromethyl)-anisole. Into a mixture of 78 g. (0.5 mole) of the p-chloromethyl anisole, 78 g. (0.9 mole) of 35 per cent formalin and 78 g. of concentrated hydrochloric acid a rapid stream of hydrogen chloride gas was introduced with vigorous stirring. The reaction mixture was kept at 50° for five and one-half hours. The mixture was then cooled, whereupon a white, crystalline material separated. After filtering, washing with ice water until the wash water was neutral and then drying in air gave a product which weighed 93.6 g. (91.4 per cent) and melted at 64°. One recrystallization from ether gave 65.6 g. (64 per cent) of 2,4-bis-(chloromethyl)-anisole, m. p. 66°. The reported melting point[3] is 66°.

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(2) Quelet, R., and Allard, J., Bull. soc. chim. (5), 3, 1796 (1936).

(3) Quelet, R., and Anglade, M., Bull. soc. chim. (5), 3, 2200 (1936).

2. 2,4-Bis-(chloromethyl)-thiophenol Methyl Ether

Although this compound has been reported by Brunner,[4] specific details for its preparation and structural proof were not included. The following is an adaptation of Brunner's method.

A mixture of 10 g. (0.08 mole) of phenyl methyl thioether, 40 g. (0.47 mole) of 35 per cent formalin and 30 g. of concentrated hydrochloric acid was placed in a 100-ml., three-necked flask equipped with a mechanical stirrer. The flask was connected to a water trap in order to dispose of excess hydrogen chloride. A rapid stream of hydrogen chloride was introduced into the stirred mixture for thirty two hours at room temperature. After cooling, the white solid which had separated was removed by suction filtration, washed with ice water and dried. By this method there was obtained 11 g. (62.5%) of the crude bis-chloromethyl derivative, m. p. 44-45°. One recrystallization from cyclohexane gave white crystals, m. p. 46°. Further recrystallization failed to change the melting point. The reported melting point[5] of this compound is 46°.

a. Oxidation of 2,4-bis-(chloromethyl)-thiophenol methyl ether. To a suspension of 1 g. (0.005 mole) of the

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(4) Brunner, A., U.S. Pat. 1,887,396 (1933).

(5) Brunner, A., loc. cit.

2,4-bis-(chloromethyl)-thiophenol methyl ether in 15 ml. of 25 per cent sodium hydroxide was added saturated potassium permanganate solution until the pink color of the permanganate ion persisted. During this operation the temperature was maintained at about 80°. The manganese dioxide was removed by filtration, and solid sodium bisulfite was added to the acidified filtrate to remove unreacted permanganate. After cooling, a white solid formed. Purification by recrystallization from water gave 0.7 g. (63%) of 4-methylsulfonylisophthalic acid, m. p. 192-193°.

Anal. Calculated for $C_9H_8O_6S$: S, 13.12
Found: S, 13.67

b. Cleavage of 4-methylsulfonylisophthalic acid to the known 4-chloroisophthalic acid. A mixture of 1 g. (0.004 mole) of the 4-methoxysulfonylisophthalic acid and 7 g. (0.034 mole) of anhydrous phosphorous pentachloride was placed in a sealed pyrex glass tube of 17 cm. in diameter and 25 cm. in length. A rather large tube was necessary so as to allow ample space for the liberation of considerable amount of gases during the reaction. Such precaution is advisable since explosions have been experienced in a number of cases. The sealed glass tube was then placed inside a steel bomb and heated to 210-220° for five hours. The sealed tube was opened carefully after cooling to room temperature, and the content was poured into ice water. The product was an oil.

After separating and washing repeatedly with ice water, the oil was hydrolyzed by boiling water or dilute alkali to an acid which was purified by recrystallization from water. There resulted a 17 per cent yield of an acid which melted at 294°. This corresponded to the reported melting point of 294.5° for 4-chloroisophthalic acid.[6]

Neutral Equivalent. Calculated for $C_8H_5O_4Cl$, 100.2
Found, 101.0

3. 2,5-Bis-(chloromethyl)-p-xylene[7]

A stream of hydrogen chloride was introduced into a vigorously stirred mixture of 106 g. (1 mole) of p-xylene, 530 ml. of concentrated hydrochloric acid and 212 g. (2.6 moles) of 35 per cent formalin, all in a 2-l., three-necked flask at 70°, for a period of fifteen hours. The white, crystalline material which formed was removed by suction filtration (yield 50 g.). An additional 212 g. of formalin was added to the mother liquor and the whole was stirred with the continuous introduction of hydrogen chloride for another fifteen hours. The temperature was maintained at 70°. At the end of the second period the mixture was cooled and the white, solid material was removed by suction filtration. Forty one grams

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(6) Ullmann, F., and Uzbachian, J. B., Ber., 36, 1799 (1903).

(7) This compound was previously reported in 7 per cent yield by von Braun and Nelles, Ber., 67, 1094 (1933). The melting point reported was 133°.

of additional product was thus obtained. The same process was repeated for the third time to yield 24 g. of product. A fourth repetition of the process gave no appreciable amount of precipitate. The mother liquor was poured into a 2-l. separatory funnel and extracted three times with 200-ml. portions of petroleum ether. The combined extracts were washed thoroughly with water and dried over anhydrous magnesium sulfate. After filtering, the solvent was removed by evaporation to leave an oily substance. Vacuum distillation of the oil gave 35 g. of a material which came over between 103° and 145° at 14 mm. and consisted mostly of monochloromethyl-p-xylene which was identified by oxidizing with warm, dilute nitric acid to the known trimellitic acid, m. p. 225-235° (dec.). A second fraction of 10 g. came over between 150° and 160° at 14 mm. and solidified when cooled. This fraction was combined with the crude precipitate, and the whole was recrystallized twice from petroleum ether, yielding 111 g. (55%) of 2,5-bis-(chloromethyl)-p-xylene, white needles, m. p. 134° (cor.). Its structure was proved by oxidation in warm dilute nitric acid to the known pyromellitic acid, m. p. 276° (dec.).

From the mother liquor a white substance slowly separated. This was recrystallized from petroleum ether to yield 1.2 g. of a crystalline substance, m. p. 69-70°. This compound was proved to be 2,3-bis-(chloromethyl)-p-xylene, an

isomer of the main product, by oxidation with warm dilute nitric acid to the known prehnitic acid, m. p. 238° (dec.).

4. 4,6-Bis-(chloromethyl)-resorcinol Dimethyl Ether

In a number of trial runs, a stream of hydrogen chloride was passed into a mixture of formalin and resorcinol dimethyl ether in carbon disulfide, dioxane or petroleum ether as the solvents at temperatures of 5°, 0°, and -5°. The product obtained was invariably a pink colored lump. This material appeared to be a high molecular weight polymer, insoluble in ordinary organic solvents, sulfuric acid, nitric acid, and sodium hydroxide. The action of chloromethyl ether on resorcinol dimethyl ether at temperatures of 5°, 0°, and -5° in carbon disulfide and in the presence of stannic chloride gave a white powder which was also insoluble in ordinary solvents. No effort was made to characterize these products.

A somewhat unsatisfactory procedure to obtain the desired bis-chloromethyl derivative along with monochloromethyl derivative as the hexamethylenetetramine salt was worked out as follows:

To 5 g. (0.036 mole) of resorcinol dimethyl ether was added 10 g. (0.124 mole) of chloromethyl ether with vigorous stirring. After the reaction mixture had been stirred for three minutes at room temperature, 40 ml. of dry chloroform containing 17.4 g. (0.124 mole) of hexamethylenetetramine was

added slowly. A white powder began to appear after a few minutes. The stirring was continued for three hours. This solid material was removed from the solution by filtration and dried as much as possible by suction, and then dried in air. The product was believed to be a mixture of salts formed by all of the chloromethyl compounds existing when the hexamethylenetetramine was added. The initial presence of two chloromethyl compounds was verified by the isolation of 4,6-dimethoxyisophthalaldehyde and 2,4-dimethoxybenzaldehyde from the hydrolytic products of the salt.*

5. 2,4-Bis-(chloromethyl)-mesitylene

The following is a method developed by Nanta and Dienske.[8]

A mixture of 50 g. (0.417 mole) of mesitylene (b. p. 163-165°), 250 ml. of concentrated hydrochloric acid and 72 ml. (0.834 mole) of 35 per cent formalin was stirred rapidly at 65° in a 1-l., three-necked flask for six hours while a rapid stream of hydrogen chloride was introduced. Upon cooling, the upper layer became partially solid. The mixture was then transferred into a separatory funnel and

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*See Synthesis of 4,6-Dimethoxyisophthalaldehyde and 2,4-Dimethoxybenzaldehyde.

(8) Nanta, W. T. H., and Dienske, J. W., Rec. trav. chim., 55, 1000 (1936).

extracted three times with 300-ml. portions of ether. The ethereal solution was washed twice with water, then with 10 per cent sodium carbonate solution, and again with water. It was dried over calcium chloride. After evaporating the solvent completely, the residue was distilled under reduced pressure. The first fraction, which came over between 70-90° at 15 mm., weighed 3.0 g. and consisted mostly of unchanged mesitylene. The second fraction, b. p. 90-125° at 15 mm., consisted mostly of monochloromethyl mesitylene. A third fraction, b. p. 125-180° at 15 mm., consisted mostly of dichloromethyl mesitylene.

The second fraction was redistilled to give pure monochloromethyl mesitylene, b. p. 114-115°/10 mm., m. p. 37°, yield, 6 g. (8.5%). This compound was soluble in ordinary organic solvents.

Pure bis-chloromethyl mesitylene, m. p. 105°, yield 65 g. (72%), was obtained by repeated recrystallization of the third fraction from petroleum ether. This compound was soluble in ethanol, methanol and ether but slightly soluble in cold petroleum ether.

With half as much formalin as indicated above, i.e., one mole of mesitylene per mole of formaldehyde, and with the other conditions remaining unchanged, 50 g. of mesitylene gave 15 g. of unchanged mesitylene, 20.5 g. (29%) of the monochloromethyl derivative and 13 g. (14.4%) of the bis-chloromethyl derivative.

6. 4,5-Bis-(chloromethyl)-o-xylene

The method of von Braun and Nelles[9] was followed.

A mixture of 106 g. (1.0 mole) of o-xylene, 440 ml. of concentrated hydrochloric acid and 220 ml. (2.6 moles) of 35 per cent formalin was stirred rapidly at 60-70° in a 2-l., three-necked flask while a rapid stream of hydrogen chloride was introduced for seven hours. At the end of this period, the mixture was transferred to a separatory funnel and extracted with ether. The ethereal solution was washed twice with water, then with 10 per cent sodium carbonate, and again with water. The solution was then dried over anhydrous magnesium sulfate, and the ether solvent was removed by evaporation. An oil was obtained. This oil was subjected to a fractional vacuum distillation. The first fraction of 98 g. came over between 100-120° at 14 mm. (largely between 110-114°) and consisted mostly of monochloromethyl-o-xylene which was identified by oxidation with warm, dilute nitric acid to the known trimellitic acid, m. p. 225-235° (dec.). A second fraction of 95 g. came over between 145-180° at 14 mm. (largely at 160°) and mostly solidified on standing. The oil was removed from the solid phase as much as possible by absorbing it with filter paper. The solid material thus

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(9) von Braun, J., and Nelles, J., Ber., 67, 1094 (1933).

obtained melted at 98-101°. Recrystallization from petroleum ether gave 87 g. (43%) of a white crystalline solid, m. p. 105-106°. The reported melting point[10] of this compound is 106°.

7. 2,5-Bis-(chloromethyl)-hydroquinone Dimethyl Ether

This preparation was carried out according to Brunner's[11] method for the chloromethylation of aromatic compounds.

To a stirred solution of 103 g. (0.75 mole) of hydroquinone dimethyl ether, 600 ml. of dioxane and 100 ml. of concentrated hydrochloric acid was added 170 ml. (2 moles) of 35 per cent formalin. A vigorous stream of hydrogen chloride was passed through the solution for three hours. The solution was continuously stirred during this operation. After cooling, the solid material was removed by filtration and allowed to dry as much as possible. One recrystallization from acetone gave 137 g. of white, crystalline material, m. p. 163-165°. Further purification raised the melting point to 167.5° (reported m. p. 165°). The yield was 108 g. (62%). This compound on oxidation in alkaline permanganate solution gave the known 2,5-dimethoxyterephthalic acid.

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(10) von Braun, J., and Nelles, J., Ber., 67, 1094 (1933).

(11) Brunner, A., U.S. Pat. 1,887,396 (1933).

8. <u>o-Xylylene Dibromide</u>

The method of W. H. Perkin[12] was followed.

Fifty grams (0.47 mole) of pure o-xylene was placed in a 500-ml., two-necked flask. A dropping funnel was attached to one neck, and to the other was attached an 18-inch Vigreux column which terminated with a long reflux condenser. The temperature was carefully raised to 125-130° by means of an oil bath, and bromine, 160 g. (1 mole), was allowed to drop in very slowly through a dropping funnel. Hydrogen bromide was rapidly evolved, but the liquid remained almost colorless until the end of the operation, when it usually assumed a slightly brownish tint. It was necessary to add bromine very slowly, otherwise the reaction became too violent. It was also important to keep the temperature of the oil bath between 125 and 130°, and then the resulting product was almost colorless. As soon as the reaction was over, the resulting crude dibromide was poured into a small beaker, the beaker was covered with a watch-glass, and the whole was allowed to stand for twenty four hours. The product had solidified to a cake of crystals at the end of this period. These crystals were washed with chloroform and then recrystallized from this solvent, yield 36 g. (29%), m. p. 93°. The reported melting point[13] is 93°.

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(12) Perkin, W. H., <u>J. Chem. Soc.</u>, <u>53</u>, 5 (1888).

(13) Perkin, W. H., <u>loc. cit.</u>

B. Synthesis of Aromatic Dialdehydes by the Sommelet Reaction

1. 4-Methoxyisophthalaldehyde

A mixture of 25 g. (0.122 mole) of 2,4-bis-(chloromethyl)-anisole and 34 g. (0.244 mole) of hexamethylenetetramine in 250 ml. of dry chloroform was placed in a 1-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser. The mixture was simultaneously stirred and heated sufficiently to maintain boiling for a period of four hours. A white solid precipitated. The mixture was then allowed to cool to room temperature, and the solvent was removed from the solid as much as possible by suction filtration. The solid was transferred to an evaporating dish and dried by a current of air. The precipitate, in the form of finely divided, white powder, amounted to 59 g. (100%). The powder was dissolved in 500 ml. of water and placed in a 1-l., three-necked flask equipped with a condenser and a mechanical stirrer. After adding 20 ml. of 35 per cent formalin, the mixture was refluxed for four hours. A clear solution resulted after the first two hours but gradually changed to a light yellow color. The solution was filtered while hot to remove traces of a resinous substance formed during the reaction. Upon cooling, slightly yellowish crystals separated. These were removed by filtration and washed with

water. One crystallization from 60 per cent ethanol accompanied by treatment with Norite gave 12.6 g. (63%) of 4-methoxyisophthalaldehyde as white needles, m. p. 119-120°.

Anal. Calculated for $C_9H_8O_3$: C, 65.85, H, 4.88
Found: C, 65.85, 65.90
H, 4.83, 4.88

Alkaline oxidation of the 4-methoxyisophthalaldehyde by 5 per cent potassium permanganate solution gave 4-methoxyisophthalic acid, m. p. 275°. While the reported melting point[14] is 261°, there can be little doubt that the compound obtained was the 4-methoxyisophthalic acid. That is, the starting compound was known to be the corresponding 2,4-bis-(chloromethyl)-anisole, the analytical data on the aldehyde obtained checked the theoretical value, and the neutral equivalent on the oxidation product agreed with the calculated value. Whether the reported melting point was corrected or not, the writer has no means of knowing.

Neutral Equivalent. Calculated for $C_9H_8O_5$: 98
Found: 98, 97

The 4-methoxyisophthalaldehyde was also prepared without isolating the intermediate salt. The procedure follows.

A mixture of 25 g. (0.122 mole) of 2,4-bis-(chloromethyl)-anisole and 34 g. (0.244 mole) of hexamethylenetetramine

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(14) Jacobsen, O., Ber., 11, 898 (1879).

in 500 ml. of 60 per cent ethanol containing 20 ml. of 35 per cent formalin was placed in a 1-l., three-necked flask equipped with a mechanical stirrer and a reflux condenser. The mixture was heated to boiling and maintained at the boiling temperature for four hours. The solution was then filtered while hot to remove traces of resinous material. On cooling, yellowish crystals separated. These were collected on a filter and then heated with excess saturated sodium bisulfite solution on a steam cone. Thus the aldehyde formed an addition salt and dissolved while the non-aldehyde substances remained undissolved. The mixture was filtered while hot. The filtrate was then warmed on a steam plate in a hood, and sufficient concentrated hydrochloric acid was added with stirring to decompose the bisulfite salt. White needles separated immediately. The mixture was kept on the steam plate for an hour. The crystals were then removed by filtration, washed with water until the wash water was neutral, and then dried in a vacuum desiccator. Ninety-two grams (46%) of 4-methoxyisophthalaldehyde as white needles, m. p. 119-120°, was thus obtained.

2. <u>4-Thiomethylisophthalaldehyde</u>

Twenty-seven grams (0.122 mole) of 2,4-bis-(chloromethyl)-thiophenol methyl ether was dissolved in 250 ml. of dry chloroform in a 1-l., three-necked flask fitted with a condenser and a mechanical stirrer. The condenser outlet was

protected from moisture by attaching a calcium chloride drying tube. The mixture was heated with stirring to boiling. To the boiling solution was added 34 g. (0.244 mole) of hexamethylenetetramine in four portions at fifteen minute intervals. Thereafter, the mixture was maintained at the reflux temperature for four hours. At the end of this period, the mixture was cooled to room temperature, and the solid was removed by suction filtration. The solid was transferred to a vacuum desiccator and dried over anhydrous calcium chloride. The dried sample weighed 56 g. (92%). The addition salt was hygroscopic in nature and possessed a slightly yellowish color. Twenty-three grams of the dried addition salt was dissolved in 200 ml. of water and heated under reflux for four hours in a 500-ml., three-necked flask equipped with a condenser and a mechanical stirrer. At the end of four hours, the solution was filtered while hot to remove some black tar formed during the reaction. Upon cooling the filtrate in an ice-bath, yellow needles separated. The solid was removed by suction filtration and washed with cold water. The yield of the crude product was 2.1 g., m. p. 116°. One recrystallization from 60 per cent alcohol gave 1.8 g. (21%) of pure 4-thiomethylisophthalaldehyde, m. p. 118°.

<u>Anal.</u> Calculated for $C_9H_8O_2S$: S, 17.77

Found: S, 17.30

The 2,4-dinitrophenylhydrazone was prepared in the usual way, m. p. 295°.

Anal. Calculated for $C_{21}H_{16}O_8N_2$: N, 20.86

Found: N, 20.56

For additional evidence in support of the assigned structure for this aldehyde, see page 52 on the structure of 2,4-bis-(chloromethyl)-thiophenol methyl ether.

3. 4,6-Dimethoxyisophthalaldehyde and 2,4-Dimethoxybenzaldehyde

All attempts to isolate the necessary 4,6-bis-(chloromethyl)-resorcinol dimethyl ether by the chloromethylation of resorcinol dimethyl ether led to high molecular weight compounds which were insoluble in ordinary organic solvents, sulfuric acid, nitric acid, and concentrated alkali. The following represents a method of obtaining a small portion of the 4,6-bis-(chloromethylation)-resorcinol dimethyl ether with larger portion of p-chloromethyl resorcinol dimethyl ether as the hexamethylenetetramine salts. The salts were then convered to corresponding aldehydes.

To 5 g. (0.036 mole) of resorcinol dimethyl ether was added 10 g. (0.124 mole) of chloromethyl ether in a 250-ml., three-necked flask equipped with a mechanical stirrer and surrounded by a water bath. After the reaction mixture had been stirred for three minutes at room temperature, 40 ml. of dry chloroform containing 17.4 g. (0.124 mole) of hexamethylenetetramine was added with vigorous stirring. White, solid

material began to separate immediately, and thus all the chloromethyl compounds including the unchanged chloromethyl ether were precipitated as the addition salts. The mixture was stirred for three hours at room temperature, and the solid was then removed by suction filtration. The precipitate was transferred to an evaporating dish and dried with a current of air. The mixture of addition salt was then dissolved in 100 ml. of water and placed in a 250-ml., three-necked flask with a mechanical stirrer and a reflux condenser. The mixture was refluxed with stirring for four hours and then filtered while hot to remove a trace of resinous material. On cooling to room temperature, light yellowish needles separated. These were removed by filtration, the mother liquor was saved for the next operation, and the solid was crystallized from hot water. A yield of one-half gram of 4,6-dimethoxyisophthalaldehyde, m. p. 204°, was obtained.

<u>Anal.</u> Calculated for $C_{10}H_{10}O_4$: C, 61.84, H, 5.19
Found: C, 61.98, H, 5.28

Alkaline oxidation of the dialdehyde by 5 per cent potassium permanganate solution gave the known 4,6-dimethoxyisophthalic acid, m. p. 265°.

<u>Neutral Equivalent</u>. Calculated for $C_{10}H_{10}O_6$: 113
Found: 116

The mother liquor was evaporated to about 40 ml. on a hot plate. On cooling in an ice-bath, white needles separated.

These were removed and dried, m. p. 66°. One crystallization of the crude material from 60 per cent alcohol gave 2.5 g. (42%) of 2,4-dimethoxybenzaldehyde, m. p. 67-68°.

Anal. Calculated for $C_9H_{10}O_3$: C, 65.00, H, 6.03
Found: C, 65.00, H, 5.92

The 2,4-dinitrophenylhydrazone was prepared in the usual manner, m. p. 256-257°.

Anal. Calculated for $C_{15}H_{14}O_6N_4$: N, 16.18
Found: N, 16.48

4. 2,5-Dimethylterephthalaldehyde

The general method of first isolating the addition salt of the corresponding bis-chloromethyl compound and hexamethylenetetramine before hydrolysis to the aldehyde was not satisfactory in this case because of the hygroscopic nature of the salt. During its formation it absorbed considerable amount of moisture and yielded a gum-like material which made the stirring very difficult and which was otherwise difficult to handle. The following is a method for the formation of the salt and its simultaneous hydrolysis to the aldehyde.

To a solution containing 5 g. (0.025 mole) of 2,5-bis-(chloromethyl)-p-xylene in 100 ml. of 60 per cent ethanol in a 250-ml., three-necked flask equipped with a reflux condenser and a mechanical stirrer was added gradually 7 g. (0.05 mole) of hexamethylenetetramine. During the addition, the solution was heated sufficiently to maintain gentle refluxing while

being stirred. The refluxing and stirring were continued for eighteen hours. Upon cooling in an ice-bath, white needles separated. The solid was removed by filtration and dried in a vacuum desiccator. The weight of the dry material was 1.84 g. One crystallization of the crude product from 60 per cent alcohol gave 1.5 g. (38%) of 2,5-dimethylterephthalaldehyde, m. p. 102-103°, in the form of white needles.

Anal. Calculated for $C_{10}H_{10}O_2$: C, 74.07, H, 6.17
Found: C, 74.45, H, 6.15

The phenylhydrazone was prepared in the usual way, m. p. 232°.

Anal. Calculated for $C_{22}H_{22}N_4$: N, 16.37
Found: N, 16.29

C. Abnormal Sommelet Reactions

1. Attempted Preparation of 2-Hydroxy-6-nitrobenzaldehyde

To 4.7 g. (0.025 mole) of 2-chloromethyl-3-hydroxynitrobenzene, prepared by the method of Buehler, Deebel, and Evans,[15] in 50 ml. of dry chloroform was added 3.5 g. (0.025 mole) of hexamethylenetetramine. The mixture was refluxed with stirring for a period of four hours. A white solid began to appear after one hour and the amount gradually

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(15) Buehler, C. A., Deebel, G. F., and Evans, R., J. Org. Chem., 6, 216 (1941).

increased thereafter. The solid was removed by suction filtration and dried in air. The sample weighed 7.3 g. (89%). It was dissolved in 50 ml. of water to which 5 ml. of 35 per cent formalin was added, and the solution was then refluxed for four hours. The precipitate which formed was removed by filtration. One crystallization from 95 per cent ethanol resulted in 3.1 g. (77% based on the chloromethyl compound and 87% based on the hexamine salt) of a compound believed to be bis-(2-hydroxy-6-nitrobenzyl)-amine. The solid gave the Hinsberg secondary amine test.

Anal. Calculated for $C_{14}H_{13}O_6N_3$: N, 13.48
Found: N, 13.48, 13.50

No further attempt was made to support the proposed structure since it was clearly shown that no detectable quantity of the expected aldehyde had resulted.

2. Attempted Preparation of Phthalaldehyde

Twenty six grams (0.10 mole) of o-xylylene dibromide was dissolved in 200 ml. of dry chloroform in a 500-ml., three-necked flask equipped with a mechanical stirrer and a reflux condenser. To the solution at the boiling temperature was added 28 g. (0.20 mole) of hexamethylenetetramine. This mixture was refluxed with stirring for four hours. During this time the clear solution changed to a dark brown color, and a white precipitate formed. The mixture was then cooled

to room temperature, and the solid material was removed by suction filtration. The air-dried salt weighed 54 g. (100%).

a. Hydrolysis with water. Twenty grams of the dry salt was dissolved in 150 ml. of water to which 5 ml. of 35 per cent formalin was added. The solution was refluxed for four hours. After cooling, the mixture was acidified with hydrochloric acid and extracted with ether to remove the non-basic substance. The ether extract was dried over anhydrous magnesium sulfate. After filtering, the solvent was removed by evaporation to leave a brown, viscous oil. This decomposed when a vacuum distillation was attempted. No further attempt was made to identify the material. The aqueous layer was made alkaline and the precipitate which formed was removed by extracting with ether. The ether extract was dried over anhydrous magnesium sulfate. A current of dry hydrogen chloride gas was passed into the solution, resulting in the formation of a white solid. This was removed and dried in a vacuum desiccator. The solid (4 g.) was hygroscopic, melted at 252° (dec.), contained nitrogen, and was soluble in water. When boiled in absolute alcohol, white needles, melting point 155°, separated on cooling. Since the object of this work was to obtain the aldehyde, no effort was made to elucidate the structures of these nitrogenous compounds beyond noting that their properties indicated that they were amines.

b. Hydrolysis with acid. Twenty grams of dry salt was dissolved in 150 ml. of water which contained 60 ml. of concentrated hydrochloric acid. Although a white, solid material began to precipitate after two hours of refluxing, the solution was refluxed for ten hours with stirring. After cooling to room temperature, the solid was filtered and washed thoroughly with water. Two recrystallizations from boiling water gave 4.2 g. (55%) of white, crystalline o-xylylene diamine dihydrochloride, m. p. 275° (dec.).

Anal. Calculated for $C_8H_{14}Cl_2N_2$: N, 13.39

Found: N, 13.35, 13.40

The dihydrochloride when boiled in alcohol changed to a crystalline substance which melted at 175° (dec.). These substances were not further investigated for the reasons given above.

3. Attempted Preparation of 1,3,5-Trimethylisophthalaldehyde

Thirty four grams (0.244 mole) of hexamethylenetetramine was added to a solution of 26 g. (0.122 mole) of 2,4-bis-(chloromethyl)-mesitylene in 250 c.c. of dry chloroform. The mixture was refluxed for four hours with stirring in a 500-ml., three-necked flask equipped with a mechanical stirrer and reflux condenser.

A white powder appeared after one-half hour refluxing, and the amount increased gradually. After the mixture refluxed for four hours, it was cooled to room temperature, and

the salt was removed by filtration. The air-dried sample weighed 60 g. (100%).

a. Hydrolysis with water. A solution of 10 g. of the salt in 100 ml. of water containing 3 ml. of 35 per cent formalin was refluxed for four hours, during which time the white solid separated. The solid, collected on filter paper and dried, weighed 2.8 g. It was insoluble in chloroform, carbontetrachloride, ethanol, methanol, ethyl acetate, acetone, ether, benzene, and strong alkaline solution but was easily dissolved in acid solution. The elementary test for nitrogen was positive. The compound appeared to be a basic, nitrogenous substance of high molecular weight. Such a substance was possible through a poly condensation reaction between bis-(2-aminomethyl)-mesitylene and formaldehyde. No indication of the formation of an aldehyde was obtained.

b. Hydrolysis with acid. A solution of 30 g. of the salt in 150 ml. of water was placed in a 250-ml., three-necked flask to which 60 ml. of concentrated hydrochloric acid was added. The solution was refluxed for four hours. After cooling to room temperature, the solution was neutralized with 25 per cent sodium hydroxide solution. The oily substance which separated was removed and thoroughly washed with water. The oil was then subjected to a vacuum distillation, a process which brought about its decomposition. No further effort was made to purify the substance. The

Hinsberg test indicated that the oil was a primary amine. The dihydrochloride was made in the usual manner by passing hydrogen chloride into the ethereal solution. The salt was very hygroscopic, and the analysis did not agree with the calculated values for bis-(2-aminomethyl)-mesitylene dihydrochloride.

Anal. Calculated for $C_{11}H_{20}N_2Cl_2$: N, 11.11

Found: Special drying to constant weight at 80° vacuum.
Loss of weight: 3.51 Nitrogen 4.55
Loss of weight: 3.55 Nitrogen 4.75

4. Attempted Preparation of 2,4,6-Trimethylbenzaldehyde (Mesitylenealdehyde)

To a solution of 95 g. (0.565 mole) of monochloromethylmesitylene and 1 l. of dry chloroform in a 2-l., three-necked flask equipped with a reflux condenser and a mechanical stirrer was added 79 g. (0.565 mole) of hexamethylenetetramine. The mixture was refluxed for a period of four hours with stirring. The salt began to separate as a white powder after a half-hour of refluxing, and the amount steadily increased. The mixture was cooled to room temperature, and the solid material was removed by filtration. The air-dried sample weighed 167 g. (100%).

a. Hydrolysis with water. To 30 g. of the salt dissolved in 300 ml. of water was added 5 ml. of 35 per cent formalin. The mixture was refluxed for fifteen hours. On

cooling to room temperature, white crystals formed. This was removed by filtration. One crystallization from 95 per cent alcohol gave 30 g. (100%) of N,N'-di-α^2-isodurylmethanediamine, m. p. 152°. The reported melting point[16] was 152°.

b. Hydrolysis with acid. A solution of 31 g. of salt, 400 ml. of ethanol and 60 ml. of concentrated hydrochloric acid was placed in an evaporating dish and evaporated almost to dryness on a steam cone. During the beginning of heating on the steam cone, a white solid formed. This process of adding 500 ml. of ethanol and 60 ml. of concentrated hydrochloric acid and evaporating to dryness was repeated a second time. The solid was allowed to cool to room temperature and washed thoroughly with 400 ml. of cold water to remove the ammonium chloride formed during the reaction. The solid was then transferred into a beaker, and an excess of 25 per cent sodium hydroxide solution was added until the solution was strongly alkaline. The mixture was then extracted with 300 ml. of ether, and the ether extract was dried over anhydrous magnesium sulfate. After removing the spent magnesium sulfate by filtration, the solvent was removed by evaporation. A white solid resulted. One crystallization from absolute ethanol gave 8.2 g. (55%) of α^2-isodurylamine, m. p. 104-105°.

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(16) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

The hydrochloride was prepared by adding concentrated hydrochloric acid to an aqueous suspension of the free amine. One crystallization from hot water gave nice, white needles which melted at 315° with decomposition to a black tar. The reported melting point[17] is 315° with decomposition.

5. Attempted Preparation of 2,4,6-Trimethylbenzaldehyde (Mesitylenealdehyde) through Supposed N-Methylene-2,4,6-trimethylbenzylamine (N-Methylene-α^2-isodurylamine)

a. Hydrolysis with acid. Three grams (.02 mole) of purified α^2-isodurylamine was suspended in 30 ml. of water to which 2.2 ml. (0.02 mole) of 35 per cent formalin was added. The mixture was warmed on a steam bath for ten minutes, after which an excess of concentrated hydrochloric acid was added. After refluxing for ten minutes, 3 g. of hexamethylenetetramine dissolved in a small amount of warm water was added, and the mixture was refluxed for another hour. After cooling to room temperature, the solid which had formed was removed by filtration. This solid was digested with 200 ml. of boiling water for a few minutes, and the mixture was then filtered while hot. The filtrate, on cooling, gave 1.9 g. of α^2-isodurylamine hydrochloride. The solid which did not dissolve in the water was recrystallized from absolute alcohol. One gram of white needles, m. p. 151°,

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(17) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

was obtained. This compound was N,N'-di-α^2-isodurylmethanediamine.[18]

b. Hydrolysis with water. Three grams (0.02 mole) of purified α^2-isodurylamine was dissolved in 70 ml. of absolute ethanol, and 2.2 ml. (0.02 mole) of 35 per cent formalin was added. The solution was refluxed on a steam cone for a period of seven hours. On cooling, white crystals separated. These were removed and recrystallized three times from absolute alcohol to give a solid melting at 151°. This substance was N,N'-di-α^2-isodurylmethanediamine.[19]

c. Hydrolysis with base. One and one-half grams (0.01 mole) of purified α^2-isodurylamine was dissolved in 35 ml. of absolute ethanol, and 1 ml. of concentrated ammonium hydroxide and 1.1 ml. (0.01 mole) of 35 per cent formalin were added. The solution was refluxed for twelve hours. On cooling, white crystals formed. Three recrystallizations from absolute ethanol yielded a solid melting at 151°. This was N,N'-di-α^2-isodurylmethanediamine.

d. Hydrolysis in weakly acidic solution with an excess of formaldehyde. To 50 ml. of water was added 1.86 g. (0.01 mole) of α^2-isodurylamine hydrochloride. The mixture was heated until the solid dissolved. To the refluxing solution,

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(18) Fuson, R. C., and Denton, J. J., J. Am. Chem. Soc., 63, 654 (1941).

(19) Fuson, R. C., and Denton, J. J., loc. cit.

100 ml. of 35 per cent formalin was added, and refluxing was continued for twelve hours. Three grams of hexamethylenetetramine dissolved in a small amount of water was added, and the mixture was then refluxed for another twelve hours. The cooled solution was then extracted with ether, and the ether extract was dried over anhydrous magnesium sulfate. The ether was evaporated on a steam cone, leaving a yellowish oil as a residue. This oil was distilled at atmospheric pressure, and the fraction boiling between 235 to 240° was collected. This fraction proved to be the aldehyde, a colorless oil, and weighed 0.7 g. (47%). This structure was proved as follows:

An alcoholic solution containing the aldehyde was mixed with an aqueous solution of hydroxylamine hydrochloride. After adding a sufficient amount of 25 per cent sodium hydroxide solution to render the mixture just basic, it was refluxed for five minutes, and a sufficient amount of dilute hydrochloric acid was then added to make the solution just weakly acidic (the same results may be achieved by passing in carbon dioxide). Nice, white needles separated. After cooling in the ice-box, the oxime was removed by filtration and washed with cold water. Five recrystallizations from ether gave the pure oxime, m. p. 122-124°. The reported melting point[20] is 124°.

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(20) Hantzsch, A., and Lucas, A., Ber., 28, 746 (1895).

D. The Condensation of Nitroethane and Nitromethane with 4-Methoxyisophthalaldehyde and the Subsequent Reduction to Form Bis-(2-aminoethyl)-benzenes

1. 2,4-Bis-(2-nitropropenyl-1)-anisole

Six and one-half grams (0.04 mole) of 4-methoxyisophthalaldehyde, 6.00 g. (0.08 mole) of nitroethane, 2 ml. of n-butylamine* and 25 ml. of absolute ethanol were mixed with vigorous shaking for five minutes. During this time a clear solution resulted. A yellow precipitate started to appear after two days, and the amount had increased by the end of another day. The mixture was cooled in an ice-bath and filtered. The solid material was washed with saturated sodium bisulfite solution to remove the unchanged aldehyde and then washed thoroughly with a large amount of water and cold methanol. The dried sample weighed 7.5 g. and melted at 139°. Three recrystallizations from benzene gave 6.9 g. (62%) of bright yellow crystals, melting at 140-140.5°.

Anal. Calculated for $C_{13}H_{14}O_5N_2$: N, 10.07
Found: N, 9.88, 9.88

2. 2,4-Diacetonyl Anisole

To a stirred mixture of 13.5 g. (0.048 mole) of 2,4-bis-(2-nitropropenyl-1)-anisole, 40 g. of iron filings

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*n-Amylamine may be substituted for n-butylamine with essentially the same result.

(40-mesh), 100 ml. of water, 100 ml. of 95 per cent ethanol and 0.2 g. of ferric chloride, all in a 500-ml. three-necked flask, was added, at the reflux temperature and over an eight-hour period, 20 ml. of concentrated hydrochloric acid. At the end of this period, the mixture was filtered while hot, and most of the solvent was removed by evaporation on a steam cone. A wine-red oil separated. The oil was extracted with three 150-ml. portions of ether. The combined ether extracts were washed three times with 50-ml. portions of water and then dried over anhydrous magnesium sulfate. The ether was removed by evaporation, and the residual oil was subjected to fractional vacuum distillation. A slightly yellowish oil which came over at 160-163°/c mm. was collected. Yield, 8.0 g. (75.5%).

Anal. Calculated for $C_{13}H_{16}O_3$: C, 70.88, H, 7.32
Found: C, 70.80, H, 7.46

The 2,4-dinitrophenylhydrazone was prepared in the usual way, m. p. 65-77°.

3. 2,4-Diacetonyl Anisole Dioxime

Eight grams (0.036 mole) of 2,4-diacetonyl anisole was added to a solution containing 17 g. (0.25 mole) of hydroxylamine hydrochloride in 50 ml. of water. The mixture was made slightly alkaline with 10 per cent sodium hydroxide solution and then refluxed for fifteen minutes. After cooling to room

temperature, water was added to make the solution just turbid. When further cooled in an ice-bath, a viscous, milky oil separated. The supernatent liquid was decanted, and the oil was washed thoroughly with ice-water. This oil was dissolved in a small amount of hot, absolute alcohol. On cooling, a white crystalline precipitate* was obtained which weighed 7.0 g. (77%) and melted at 42-49°. The dioxime was probably a mixture of syn- and anti- isomers. No attempt was made to effect their separation.

Anal. Calculated for $C_{13}H_{18}O_3N_2$: N, 11.19
Found: N, 11.22

4. Reduction of 2,4-Diacetonyl Anisole Dioxime to 2,4-Bis-(2-aminopropyl)-anisole

Six grams (0.024 mole) of 2,4-diacetonyl anisole dioxime was placed in a 110-ml., stainless steel bomb. Fifty milliliters of absolute ethanol and 5 g. of freshly prepared Raney nickel catalyst were then added. Hydrogen was introduced to a pressure of 2000 lb. per sq. in. The bomb was shaken at room temperature. The pressure began to drop immediately and, after about one hour, it had dropped to 1900 lb. per sq. in. The pressure then ceased to drop. The bomb was opened, and the catalyst was removed by filtration. The filtrate was

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*After a few days in a vacuum desiccator the material liquefied.

placed back in the bomb along with 5 g. of freshly prepared Raney nickel catalyst, the bomb was again filled with hydrogen to a pressure of 2000 lb. per sq. in., and the shaking was continued at room temperature for seventeen hours. A pressure drop of 650 lb. per sq. in. occurred. This is approximately equal to that calculated for the reduction of two oxime groups to the amino groups.

The contents of the bomb were removed, and the Raney nickel catalyst was filtered off. The alcohol was then evaporated on a steam cone whereupon a colorless oil resulted. This product had a fish-like odor and weighed 4.8 g. (89%).

5. <u>2,4-Bis-(2-aminopropyl)-anisole Dihydrochloride</u>

Four and eight-tenths grams of 2,4-bis-(2-aminopropyl)-anisole were dissolved in 250 ml. of anhydrous ether, and the mixture was dried over an excess of anhydrous magnesium sulfate. During subsequent operations the mixture was not permitted to come in contact with moist air. The magnesium sulfate was removed, and hydrogen chloride was introduced at a rapid rate with vigorous shaking. A slightly yellow solid formed rapidly. The solid was separated from the mother liquor by suction under an atmosphere of dry air and then washed with 500 ml. of anhydrous ether. After drying in a vacuum desiccator, a white powder resulted which weighed 60 g. (94%). The dihydrochloride was so hygroscopic that an

analysis of chlorine was not made.* The acetyl derivative was a liquid. The benzoyl derivative was prepared by vigorously shaking a mixture of 2,4-bis-(2-aminopropyl)-anisole and benzoyl chloride in a small stoppered bottle. Sufficient 10 per cent sodium hydroxide solution was added from time to time until the odor of benzoyl chloride disappeared. On cooling, a crystalline product separated. Recrystallization from 95 per cent ethanol gave a product melting at 209-210°.

Anal. Calculated for $C_{27}H_{30}O_3N_2$: N, 6.51
Found: N, 6.54.

6. The Attempted Preparation of 2,4-Bis-(2-nitroethylene)-anisole

a. Three and three-tenths grams (0.02 mole) of 4-methoxyisophthalaldehyde, 2.50 g. (0.04 mole) of nitromethane, 0.8 ml. of n-amylamine and 15 ml. of absolute ethanol were mixed with stirring at room temperature. Some cooling in a water bath was necessary to maintain room temperature. After about thirty minutes, the suspended, white colored dialdehyde began to disappear while at the same time brown colored crystals slowly appeared. The mixture was permitted to stand at room temperature for a period of four days. The solid which had formed was removed by filtration and washed

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*A sample was submitted to a commercial laboratory for analysis. The laboratory reported that the compound could not be weighed because of its hygroscopic nature.

thoroughly with ethanol. It was insoluble in ethanol, methanol, benzene, chloroform, and soluble in acetone and cellosolve. However, a black, viscous substance was obtained when attempts were made to recrystallize the material from these two solvents. Purification was partially achieved by digesting five times with boiling ethanol. A yellowish solid which did not melt below 360° resulted.

Anal. Calculated for $C_{11}H_{10}O_5N_2$: N, 11.20

Found: N, 11.49, 11.44

Thus, the mode of preparation, color, and analysis indicate that the compound in question was the desired 2,4-bis-(2-nitroethylene)-anisole. It is the opinion of the writer, however, that a polymeric nitro-compound was obtained, because of the very high melting point and because attempts to reduce the substance to the corresponding bis-amine failed. The attempts at reduction will be described in a later portion of this thesis.

b. A solution of 1.5 ml. of 25 per cent sodium hydroxide in 20 ml. of 95 per cent ethanol was added to a 100-ml., round-bottomed flask containing 6.56 g. (0.04 mole) of 4-methoxyisophthalaldehyde and 4.88 g. (0.08 mole) of nitromethane. The flask was shaken vigorously for ten minutes. During this time, the solid aldehyde dissolved and a clear solution resulted. The mixture was then allowed to stand for two days at room temperature. At the end of this period, the

contents were neutralized with glacial acetic acid, and the solvent was then removed by distillation at reduced pressure. A viscous oil was obtained. The oil was washed with saturated sodium bisulfite solution to remove unreacted aldehyde, then with water, and then dissolved in dilute aqueous sodium hydroxide and reprecipitated by the addition of hydrochloric acid. A yellowish solid was thus obtained. This solid was insoluble in ethanol, methanol, and benzene but soluble in acetone and cellosolve. Attempt to recrystallize this solid from the latter two solvents yielded a black, viscous oil. Purification was achieved by five digestions with large quantities of boiling ethanol. A yellow solid, m. p. above 360°, was obtained.

Anal. Calculated for $C_{11}H_{10}O_5N_2$: N, 11.20
Found: N, 11.34, 11.28

Apparently the condensation of nitromethane with 4-methoxy-isophthalaldehyde by procedure (b) gave the same compound as was given by procedure (a).

7. Reduction of Supposed 2,4-Bis-(2-nitroethylene)-anisole Polymer

a. Reduction with iron and hydrochloric acid. Four and one-half grams (0.018 mole) of the nitrogen compound, 18 g. of iron filings (40-mesh), 30 ml. of 95 per cent alcohol, 30 ml. of water and 0.1 g. of ferric chloride were placed in a 250-ml., three-necked flask equipped with a reflux condenser

and mechanical stirrer. Nine milliliters of concentrated hydrochloric acid was added to the boiling mixture over a period of eight hours. Most of the solvent was then removed by heating on a steam cone. The solid which formed was removed by filtration, and the mother liquor was saved for the next operation. The residue was then extracted with two 150-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. After filtering, the ether was removed by evaporation on a steam cone. Nothing was left. The residue from the ether extraction was boiled with 30 ml. of acetone and filtered. The acetone was removed on a steam cone, and a black, viscous substance remained. The aqueous solution was then made alkaline by adding an excess of 25 per cent sodium hydroxide solution. The precipitate was filtered and extracted with three 150-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The solvent was removed by evaporating the ether on a steam cone. Nothing was left. It is obvious from these experiments that no bis-amine or oxime was formed.

The reduction with iron and hydrochloric acid was attempted twice more as described above except that in one case water was used as the medium for the reduction and in the other a cellosolve-water mixture was used. In both cases no evidence could be obtained that an amine had been formed.

b. Reduction with Raney nickel. Into a stainless steel bomb of 110-ml. capacity was placed 2.1 g. (.0084 mole) of the nitrogen compound, 50 ml. of absolute ethanol which had been previously saturated with ammonia gas, and 1 g. of Raney nickel. Hydrogen was introduced until the pressure was 1800 lbs. per sq. in. The bomb was then heated to 80° and maintained at that temperature with shaking for about two hours. After cooling to room temperature, the bomb was opened, the contents were poured on a filter paper to remove the catalyst, and the filtrate was evaporated until a small amount of a black oil remained. This was insoluble in acid, and consequently the desired amine had not been formed. No attempt was made to identify it.

8. 2,4-Bis-(1-hydroxy-2-nitropropyl)-anisole

To a stirred solution of 6.6 g. (0.04 mole) of 4-methoxy-isophthalaldehyde and 0.26 g. of hydroquinone in 26 ml. of methanol were added simultaneously 3.0 g. (0.08 mole) of nitroethane and 2 ml. of sodium ethoxide solution (0.02 g. sodium in 2 ml. methanol). The addition required five minutes, and a slightly yellow solution resulted. The mixture was then allowed to stand for twenty four hours, after which it was neutralized with glacial acetic acid. The solvent was then removed by distillation at reduced pressure, leaving an oil.

Crystallization from 50 per cent acetic acid and one recrystallization from 95 per cent ethanol gave yellowish crystals, m. p. 137-138°, which weighed 4.8 g. (50%).

Anal. Calculated for $C_{23}H_{18}O_7N_2$: N, 8.91

Found: N, 9.30

The compound was soluble in sodium hydroxide solution, and when hydrochloric acid was added to the solution, a bright yellow solid was formed, m. p. 140-140.5°. That this solid was 2,4-bis-(2-nitropropenyl-1)-anisole was proved by a mixed melting point with an authentic sample.

9. Attempted Reduction of 2,4-Bis-(1-hydroxy-2-nitropropyl)-anisole with Raney Nickel

Four and four-tenths grams (0.01 mole) of 2,4-bis-(1-hydroxy-2-nitropropyl)-anisole, 30 ml. of absolute ethanol and 1 g. of Raney nickel were placed in a steel hydrogenation bomb of 110-ml. capacity. Carbon dioxide was added to build up a pressure of 250 lbs. per sq. in., then hydrogen was introduced to bring the total pressure to 1800 lbs. per sq. in. The bomb was shaken at room temperature until the hydrogen pressure became constant, about two hours. The content was then removed, and the spent catalyst was separated by filtration. The filtrate was evaporated to a volume of about 10 ml., and then 50 ml. of water was added. The brown precipitate that resulted was decolorized by treating with Norite

in alcohol. Five recrystallizations from 95 per cent alcohol yielded 1.8 g. of a white, crystalline substance, m. p. 276° (dec.). This compound did not contain nitrogen and therefore was neither an amine nor an oxime.

10. A Possible Synthesis of 2,4-Bis-(1-hydroxy-2-nitroethyl)-anisole

To a stirred solution of 3.28 g. (0.02 mole) of 4-methoxyisophthalaldehyde and 0.13 g. of hydroquinone in 13 ml. of methanol were added simultaneously 2.44 g. (0.04 mole) of nitromethane and a quantity of sodium methoxide prepared by dissolving 0.02 g. of sodium in 2 ml. of methanol. The addition was completed in five minutes. After the mixture had been stirred for five minutes, the solution was neutralized with 5 per cent acetic acid. Evaporating the methanol at reduced pressure produced an oily residue. The oil was then dissolved in hot chloroform. On cooling, yellow crystals separated. Recrystallization from chloroform gave a well defined, yellow, crystalline material melting at 109-110°. Further recrystallization failed to raise the melting point.

Anal. Calculated for $C_{11}H_{14}N_2O_7$: N, 9.79
Found: N, 6.11, 6.08

The product was subjected to catalytic hydrogenation according to the procedure described on page 88. No evidence could be obtained that a bis-amine or an oxime had been formed. As

a matter of fact, no pressure drop occurred during the catalytic reduction and the writer is of the opinion that no reduction occurred.

E. The Condensation of Nitroethane and Nitromethane with 2,5-Dimethoxyterephthalaldehyde and the Subsequent Reduction to Form Bis-(2-aminoethyl)-benzenes

1. 2,5-Bis-(2-nitropropenyl-1)-hydroquinone Dimethyl Ether

To a mixture of 3.88 g. (0.02 mole) of 2,5-dimethoxyterephthalaldehyde and 3.00 g. (0.04 mole) of nitroethane in 13 ml. of absolute ethanol in a 250-ml. round-bottomed flask was added 1 ml. of n-butylamine.* The flask was shaken vigorously for five minutes with cooling. The solid aldehyde began to dissolve gradually in the reaction mixture, and the solution turned a light orange color. After allowing the mixture to stand for two hours at room temperature, a clear orange solution resulted. Orange colored crystals started forming after twenty four hours. The precipitation was complete after another twenty four hours. At the end of this period the solid material was removed from the mixture by filtration, placed in a separatory funnel and then shaken vigorously with saturated sodium bisulfite solution to remove

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*n-Amylamine may be substituted with no appreciable difference in the yield.

the unchanged aldehyde. After filtering, the solid was washed with water. Crystallization of the resulting solid from cellosolve gave 6.7 g. of crystalline, orange material, m. p. 229-230°. Recrystallization from cellosolve gave 5.1 g. (83%) of material, m. p. 237°. Further recrystallization failed to change the melting point.

Anal. Calculated for $C_{14}H_{16}O_6N_2$: N, 9.10
Found: N, 8.88

This compound was also prepared by using trimethylamine or piperidine as catalysts instead of n-butylamine. It was necessary, however, to carry the reactions out at the boiling point of the mixture rather than at room temperature. The yields were not nearly as good, being 18 and 26 per cent respectively.

2. 2,5-Diacetonyl Hydroquinone Dimethyl Ether

Eight and nine-tenths grams (0.029 mole) of recrystallized 2,5-bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether, 24 g. of iron filings (40-mesh), 60 ml. water, 30 ml. of 95 per cent ethanol and 0.1 g. ferric chloride were placed in a 500-ml., three-necked flask equipped with a mechanical stirrer. The mixture was maintained at the reflux temperature and stirred while 12 ml. of concentrated hydrochloric acid was added over an eight-hour period. At the end of this time the alcohol was removed over a steam cone, and the mixture was filtered after cooling. The solid residue in the funnel was

transferred to a separatory funnel and extracted with three 150-ml. portions of ether. The combined ether extracts were evaporated to dryness. Slightly pink-colored needles resulted. They were recrystallized from 95 per cent ethanol after treatment with Norite to give 2.7 g. of 2,5-diacetonyl hydroquinone dimethyl ether, m. p. 101-102°. The material was still slightly pink. A second recrystallization from 95 per cent ethanol accompanied with Norite treatment raised the melting point to 102-102.5°, but the color was not removed. Five additional recrystallizations yielded white needles but with no elevation of melting point, yield 2.1 g. (48 per cent based on the 2,5-bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether that reacted).

Anal. Calculated for $C_{14}H_{18}O_4$: C, 67.18, H, 7.25
Found: C, 67.30, H, 7.27

From the residue after extraction with ether, 3.5 g. of unchanged 2,5-bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether was recovered.

3. 2,5-Diacetonyl Hydroquinone Dimethyl Ether Dioxime

An alcoholic solution containing 2.1 g. (0.0084 mole) of 2,5-diacetonyl hydroquinone dimethyl ether was mixed with an aqueous solution made by dissolving 3.0 g. (0.044 mole) of hydroxylamine hydrochloride in 10 ml. water. After adding sufficient amount of 10 per cent sodium hydroxide solution to make the solution just basic, it was refluxed for five

minutes. The solution was then cooled to room temperature, and water was added until the solution showed a slight turbidity. After cooling in an ice-bath, light pink needles formed. The crystals were removed and washed with water. Crystallization from 95 per cent ethanol gave a solid material which melted at 170.5-175°. A second recrystallization from the same solvent accompanied by treatment with Norite gave 2.0 g. (85%) of 2,5-diacetonyl hydroquinone dimethyl ether dioxime in the form of colorless needles, m. p. 172-176°.

Anal. Calculated for $C_{14}H_{20}O_4N_2$: N, 10.00
Found: N, 10.18

4. Reduction of 2,5-Diacetonyl Hydroquinone Dimethyl Ether Dioxime to 2,5-Bis-(2-aminopropyl)-hydroquinone Dimethyl Ether

A mixture of 1.9 g. (0.0068 mole) of 2,5-diacetonyl hydroquinone dimethyl ether dioxime, 20 ml. of absolute alcohol and 3 g. of freshly prepared Raney nickel catalyst was placed into a stainless steel bomb of 110-ml. capacity. Hydrogen was introduced until the pressure was 2000 lb. per sq. in. The bomb was placed in a mechanical shaker. The shaking was started at room temperature and was continued for about two hours. At the end of this period the pressure had dropped by 116 lb. per sq. in. The bomb was opened, the contents were submitted to filtration to remove the spent catalyst, and the filtrate was evaporated on a steam cone. A white, crystalline

solid resulted. Three recrystallizations from an ether-alcohol solvent yielded 1.2 g. (70%) of 2,5-bis-(2-aminopropyl)-hydroquinone dimethyl ether, m. p. 120-129°.

5. <u>2,5-Bis-(2-aminopropyl)-hydroquinone Dimethyl Ether Dihydrochloride</u>

One and two-tenths grams of 2,5-bis-(2-aminopropyl)-hydroquinone dimethyl ether was dissolved in a mixture of 500 ml. of anhydrous ether and 200 ml. of absolute ethanol. The solution was dried over anhydrous magnesium sulfate. After filtering, dry hydrogen chloride gas was passed into the solution until saturation was reached. The solvent was then evaporated on a steam cone, and a white solid remained. Recrystallization from ether-alcohol mixture resulted in 1.50 g. (97%) of the dihydrochloride, m. p. 234-242° (dec.).

<u>Anal.</u> Calculated for $C_{14}H_{26}O_2N_2Cl_2$: Cl, 21.80
Found: Cl, 21.98

The benzoyl derivative was prepared by shaking an aqueous suspension of 2,5-bis-(2-aminopropyl)-hydroquinone dimethyl ether with benzoyl chloride, while adding sufficient 10 per cent sodium hydroxide solution to keep the mixture basic. A crystalline product separated after cooling. Recrystallization from 95 per cent ethanol gave a product melting at 281-282°.

<u>Anal.</u> Calculated for $C_{28}H_{31}O_4N_2$: N, 6.10
Found: N, 6.27

6. Attempted Preparation of 2,5-Bis-(2-nitroethylene)-hydroquinone Dimethyl Ether

A mixture of 3.88 g. (0.02 mole) of 2,5-dimethoxyterephthalaldehyde, 2.44 g. (0.04 mole) of nitromethane, 13 ml. of absolute ethanol and 1 ml. of n-amylamine was placed in a 250-ml., round-bottomed flask. The mixture was shaken vigorously for five minutes at room temperature. After ten minutes, the color changed from the original yellow to orange. On further standing, the color changed to deep red. After twenty four hours, the solid material which had formed was removed by filtration and washed with 100 ml. of cold ethanol. Two recrystallizations from cellosolve yielded 5.2 g. (83%) of red needles, m. p. 280-282°. This substance was first thought to be 2,5-bis-(2-nitroethylene)-hydroquinone dimethyl ether, and the analysis supported this view.

Anal. Calculated for $C_{12}H_{12}O_6N_2$: N, 10.00

Found: N, 10.18

However, it is the opinion of the writer now that the compound is a polymeric nitro-compound because attempts to reduce this substance to the corresponding oxime or the bis-amine failed. The reduction was carried out as follows.

7. Attempted Reduction of Supposedly 2,5-Bis-(2-nitroethylene)-hydroquinone Dimethyl Ether Polymer

Four and nine-tenths grams of the recrystallized nitrogen compound, 15 g. of iron filings (40-mesh), 20 ml. of

ethanol, 30 ml. of water and 0.1 g. of ferric chloride were placed in a 250-ml., three-necked flask equipped with a condenser and mechanical stirrer. The mixture was maintained at the boiling temperature, and 8 ml. of concentrated hydrochloric acid was added dropwise over a period of eight hours. At the end of this period, the alcohol was removed on a steam cone, and the solid was separated from the aqueous portion which was saved for the next operation. The solid was extracted with two 150-ml. portions of ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Upon evaporating the ether nothing remained. The residue was then extracted with cellosolve, and from the extract, 4 g. of the starting material was recovered. The aqueous solution was made alkaline by adding an excess of 25 per cent sodium hydroxide solution. The precipitate which formed was extracted with three 150-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, after which the ether was removed by evaporation. Nothing was left behind.

The reduction with iron and hydrochloric acid was attempted again as described above. In one case water was used as the medium and in the other case a cellosolve-water mixture was used. In both cases no evidence could be obtained that an oxime or an amine had been formed.

8. <u>2,5-Bis-(1-hydroxy-2-nitroethyl)-hydroquinone Dimethyl Ether</u>

To a stirred solution of 3.88 g. (0.02 mole) of 2,5-dimethoxyterephthalaldehyde and 0.13 g. of hydroquinone in 13 ml. of methanol were added separately and in an alternating dropwise fashion 2.44 g. (0.04 mole) of nitromethane and 2 ml. of sodium methoxide solution (0.02 g. sodium in 2 ml. methanol). The addition was completed in five minutes, and during this time the temperature was not permitted to rise above 20°. The mixture was stirred an additional ten minutes. By the end of this time the bright yellow color of the aldehyde had changed to a lighter cream color. The reaction mixture was neutralized with 5 per cent acetic acid solution and then filtered. The residue was washed thoroughly with 50 ml. of water and then with 50 ml. of cold methanol. Three grams of impure 2,5-bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether was obtained, m. p. 181-182°. One recrystallization from acetone gave 2.1 g. (33%) of light yellowish crystals, m. p. 189-190°. Further recrystallization failed to change the melting point.

<u>Anal.</u> Calculated for $C_{12}H_{16}O_8N_2$: N, 8.86
Found: N, 8.58, 8.50

When this compound was prepared by using catalysts such as 25 per cent sodium hydroxide solution, saturated bicarbonate solution, or triethylamine at room temperature, a much poorer

yield was obtained, and the crude material was difficult to purify by recrystallization.

9. 2,5-Bis-(1-hydroxy-2-aminoethyl)-hydroquinone Dimethyl Ether

A mixture of 2.0 g. (0.0063 mole) of 2,5-bis-(1-hydroxy-2-nitroethyl)-hydroquinone dimethyl ether, 20 ml. of absolute ethanol and 0.5 g. of Raney nickel was placed in a Parr hydrogenation bomb of 110-ml. capacity. Sufficient carbon dioxide was added to produce a pressure of 300 lbs. per sq. in., then hydrogen was introduced to bring the total pressure to 1800 lbs. per sq. in. Approximately two hours of shaking at room temperature was required for the hydrogen pressure to become constant. The bomb was opened and spent catalyst was removed by filtration. The filtrate was evaporated to a volume of about 5 ml., and then 30 ml. of water was added. The brown precipitate was first treated with Norite in alcohol and then recrystallized three times from absolute ethanol. White crystals were obtained, m. p. 238° (dec.), yield 1.42 g. (89%). The over-all yield from the aldehyde was 29 per cent. The reported melting point of this compound was 238° (dec.), while the reported over-all yield from the aldehyde was 17 per cent.[21]

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(21) Wood, J. H., and Gibson, R. E., J. Am. Chem. Soc., 71, 393 (1949).

F. The Structure Proof of 7,8-Dimethoxy-1,2,4,5-tetrahydrobenz[d]azepine

In the reduction of 4,5-bis-(cyanomethyl)-veratrole, Perry[22] was able to obtain a 25 per cent yield of the 4,5-bis-(2-aminoethyl)-veratrole along with a 38 per cent yield of a lower boiling amine for which he assigned the azepine structure. In order to obtain additional support, a total methylation was achieved by the method of Icke, *et al.*[23]

One hundred and forty milligrams (.000675 mole) of the amine in question was added with cooling to 180 mg. (.0034 mole) of 87 per cent formic acid. To this solution was then added 0.18 ml. (.0024 mole) of 35 per cent formalin. The mixture was warmed until the carbon dioxide started coming off and then refluxed on a steam cone for eleven hours. The mixture was allowed to cool, made acidic by adding 1 ml. of 4 N hydrochloric acid, and then evaporated to dryness under reduced pressure on a steam cone. A yellow solid resulted. Three recrystallizations of the yellow solid from 95 per cent alcohol gave white crystals, m. p. 359-361° (dec.). The above hydrochloride salt was taken up in 2 ml. of water, and the

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(22) Perry, M. A., "The Synthesis and Sympathomimetic Activity of Some *o*- and *m*-bis-(2-aminoethyl)-benzenes," Doctoral Dissertation, The University of Tennessee, Knoxville, Tennessee, 1950, p. 83.

(23) Icke, R. N., Wisegarver, B. B., and Alles, G. A., *Org. Synthesis*, *25*, 89 (1945).

amine was freed by adding an excess of concentrated sodium hydroxide solution. The basic mixture was extracted with ether, and the ether solution was dried over anhydrous magnesium sulfate. After filtering, the solvent was evaporated in a vacuum desiccator. White crystals were obtained, m. p. 40-41.5°.

Anal. Calculated for $C_{13}H_{19}O_2N$: N, 6.33

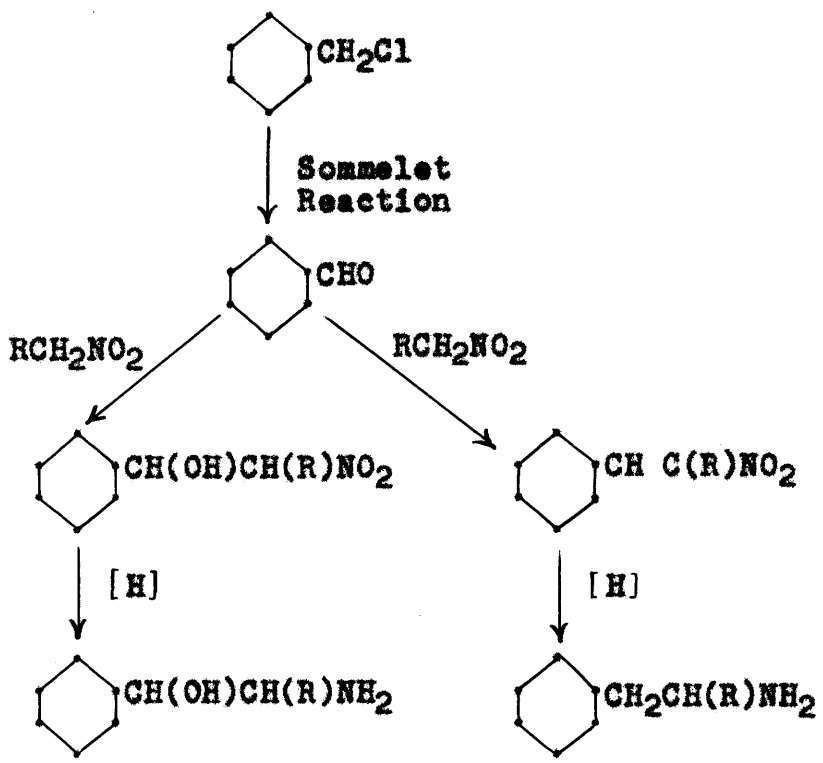
Found: N, 6.26

Thus the analysis indicates that one methyl group was introduced, a fact which supports the azepine (a secondary amine) rather than the hydrindene (a primary amine).

CHAPTER IV

SUMMARY

For the preparation of certain bis-(2-aminoethyl)-benzenes for pharmacological testing, the following routes were largely pursued:



The need of bis-chloromethylbenzenes as starting materials for the preparation of bis-(2-aminoethyl)-benzenes prompted the synthesis of various ortho-, meta- and para-bis-chloromethylbenzenes.

For the m- and p-bis-chloromethyl compounds, the corresponding m- and p-aryldialdehydes have been successfully synthesized by means of the Sommelet reaction. However, attempts

to prepare o-aryldialdehydes by a similar method were fruitless. This failure was ascribed to steric influences present in ortho-substituted chloromethylated compounds. A rather detailed study on the condition of the Sommelet reaction and the influence of substituents have cast some light on the mechanism of this reaction.

The condensation of aryldialdehydes with nitroalkanes has presented unpredicted difficulties, and in many cases, the condensation led to intractable polymeric substances. Nevertheless, 2,4-bis-(2-nitropropenyl-1)-anisole and 2,5-bis-(2-nitropropenyl-1)-hydroquinone dimethyl ether were obtained by condensation of nitroethane with 4-methoxyisophthalaldehyde and 2,5-dimethoxyterephthalaldehyde respectively.

The reduction of nitro olefins to the corresponding amines was not accomplished by catalytic hydrogenation nor by direct reduction with chemical reagents, but was achieved by the following sequence of reactions

$$Ar\left[CH{=}C(R)NO_2\right]_2 \xrightarrow{Fe+HCl} Ar\left[CH_2C(R){=}NOH\right]_2 \xrightarrow[Ni]{H_2} Ar\left[CH_2CH(R)NH_2\right]_2$$

The new amines were pharmacologically assayed by Eli Lilly and Company.

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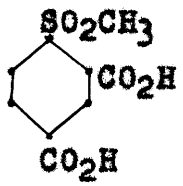
APPENDIX

APPENDIX

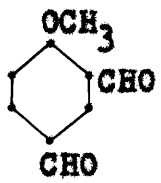
A LIST OF NEW COMPOUNDS, THEIR PROPERTIES AND DERIVATIVES



Soluble in alcohol and hot water

m. p. 192-193°

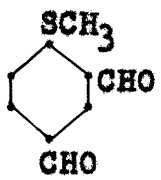
4-Methylsulfonylisophthalic Acid



Soluble in alcohol and hot water

m. p. 119-120°

4-Methoxyisophthalaldehyde



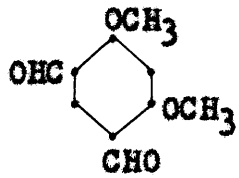
Soluble in alcohol and hot water

m. p. 118°

2,4-Dinitrophenylhydrazone

m. p. 295°

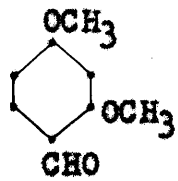
4-Thiomethylisophthalaldehyde



Soluble in alcohol and hot water

m. p. 204°

4,6-Dimethoxyisophthalaldehyde



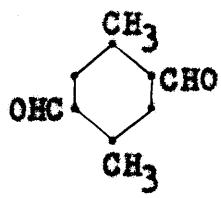
Soluble in alcohol and hot water

m. p. 67-68°

2,4-Dinitrophenylhydrazone

m. p. 256-257°

2,4-Dimethoxybenzaldehyde



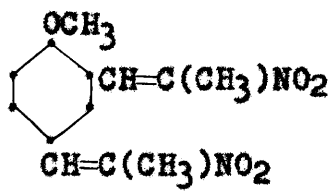
Soluble in alcohol and hot water

m. p. 102-103°

Phenylhydrazone

m. p. 232°

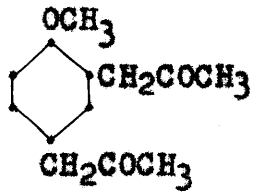
2,5-Dimethylterephthalaldehyde



Soluble in alcohol and benzene

m. p. 140-140.5°

2,4-Bis-(2-nitropropenyl-1)-anisole

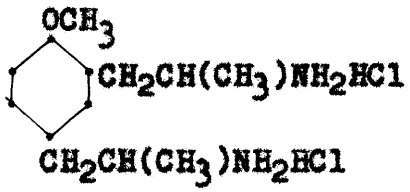


2,4-Diacetonyl Anisole

Soluble in alcohol and benzene

b. p. 160-163°/3 mm.

Dioxime, m. p. 42-49°

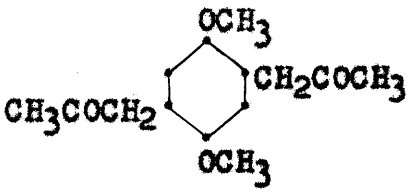


2,4-Bis-(2-aminopropyl)-anisole Dihydrochloride

Soluble in alcohol and water

Hygroscopic

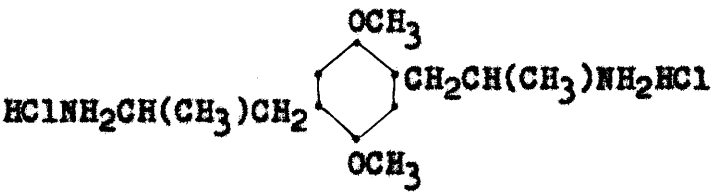
Benzoyl derivative of the free amine, m. p. 209-210°



2,5-Diacetonyl Hydroquinone Dimethyl Ether

Soluble in alcohol and benzene

m. p. 102-102.5°

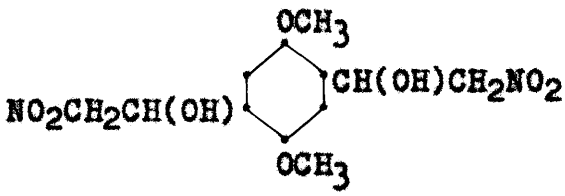


2,5-Bis-(2-aminopropyl)-hydroquinone Dimethyl Ether Dihydrochloride

Soluble in alcohol and water

m. p. 234-242° (dec.)

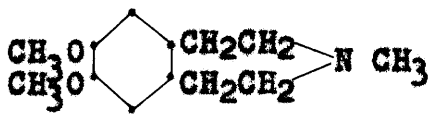
Benzoyl derivative of the free amine, m. p. 281-282°



Soluble in alcohol and acetone

m. p. 189-190°

2,5-Bis-(1-hydroxy-2-nitroethyl)-hydroquinone Dimethyl Ether*



Soluble in alcohol and hot water

m. p. 40-41.5°

N-Methyl-7,8-Dimethoxy-1,2,4,5-tetrahydrobenz[d]azepine

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*Although this compound has been previously reported, the discrepancy in the reported melting point (162°) and our observed melting point (189-190°) is sufficiently great to warrant inclusion here. See reference 21 in Chapter III.

VITA

Ching Chen Tung was born in Winchow, Chekiang Province, China, on April 21, 1921. He was educated in Shanghai Municipal Primary School from 1928 to 1934, and was graduated from Tai-tung High School, Shanghai, in the year of 1940. He received his B. S. degree from Chaio Tung University in June 1944. Between July 1944 and January 1948, he was employed by China Synthetic Chemical Works, Shanghai, as a research chemist. In February of 1948, he came to the United States of America for advanced study at Washington University in St. Louis. He transferred from there to the Chemistry Department of The University of Tennessee in June 1948.

The author is a member of Sigma Xi.