3. β-Glucochloralose condenses with chloral to yield two dichloralglucoses identical with those previously reported in the literature.

4. It is pointed out that the present formulas for β-glucochloralose cannot explain the formation of the dichloralglucoses. The reaction reported by Hanriot and Kling by which both the aldehyde and glucose are identified would indicate an acetal rather than a carbon–carbon linkage.

AMES, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE COLLEGE OF WASHINGTON]

ORIENTATION IN THE BENZENE RING. THE BROMINATION OF 2-AMINORESORCINOL DIMETHYL ETHER[1]

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It has been shown in preceding papers[2] that the 2,6-dimethyl ether of pyrogallol gives on halogenation in an anhydrous medium a monohalogen substitution product in which the halogen atom has substituted meta to the hydroxyl group. The bromination of 2-aminoresorcinol dimethyl ether, which has an analogous structure, has been investigated in order to determine the mechanism of the reaction. Two courses are open for the entering halogen atom, it may substitute directly in the ring or else replace one of the amino hydrogens and subsequently migrate to the ortho-ortho-para positions as shown by Chattaway and Orton[3] in case of acetanilide. It may be assumed that in 2-aminoresorcinol the bromine atom enters the amino group and subsequently migrates to the para position, but such is not the case, apparently, since the product obtained has the bromine atom in the meta position to the amino group. It has not been possible to prepare the N-bromo derivative and actually determine whether the bromine atom migrates to the meta position. Every effort gave oxidation products.

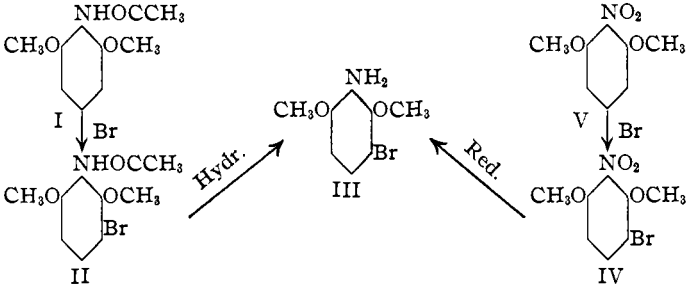
The acetanilide of 2-aminoresorcinol dimethyl ether was brominated with a calculated quantity of bromine in acetic acid as a solvent. Numerous attempts have been made to brominate the free base in an anhydrous medium. Satisfactory results have been obtained on bromination of the free base in glacial acetic acid containing a small quantity of acetic anhydride. The product obtained, however, was the corresponding monobromo-acetanilide. The formation of the acetanilide is rather unusual, taking place with the utmost ease at room temperature, while Kauffmann

[1] Abstracted from a thesis by Hooper Linford, presented to the Graduate Faculty of the State College of Washington in partial fulfilment of the requirements for the degree of Master of Science.

[2] (a) Levine, THIS JOURNAL, **48**, 2719 (1926); (b) **49**, 797 (1927).

[3] Chattaway and Orton, *Ber.*, **32**, 3573, 3635 (1899).

and Franck[4] found that 2-aminoresorcinol dimethyl ether acetylates with difficulty. It has also been found in this Laboratory that the monobromo derivative is not acetylated on prolonged boiling with acetic anhydride.



Determination of the Position of the Bromine Atom.—The bromoacetanilide (II) was hydrolyzed with alcoholic potassium hydroxide, giving the free base (III). This was compared and found identical with the compound (IV) obtained on bromination of 2-nitroresorcinol dimethyl ether (V) and subsequent reduction of this bromoderivative. It is assumed that the bromine atom enters into the ring in the meta position to the nitro group since the combined effect of the groups already present orient in that position. Efforts to oxidize the bromo derivative to the corresponding quinone have not yielded the desired product, complex oxidation products containing nitrogen being obtained. Likewise, attempts to diazotize and convert the brominated amine to the corresponding phenol, 3-bromo-2,6-dimethyl ether of pyrogallol, whose constitution has been established,[2b] have not been possible.

Experimental Part

Preparation of 2-Aminoresorcinol Dimethyl Ether.—This was prepared by the method of Kauffmann and Franck.[4] It was used without any further purification in the preparation of the acetanilide and in subsequent brominating experiments.

The acetanilide of 2-aminoresorcinol dimethyl ether was prepared by heating 5 g. of the free base with 50 cc. of freshly distilled acetic anhydride in a sealed tube for about four hours at a temperature of 150–160°. If the heating is continued for about ten hours, as recommended by Kauffmann and Franck, the chief product is not the acetanilide but a substance melting at 181°. This substance will be described in a subsequent paper.

Bromination of the Acetanilide of 2-Aminoresorcinol Dimethyl Ether.—Five grams of the acetanilide was dissolved in 50 cc. of glacial acetic acid and 4.5 g. of bromine dissolved in 15 cc. of acetic acid was added. The bromination occurred readily with evolution of hydrogen bromide. After standing for one-half hour the reaction mixture was poured into 300 cc. of water. A precipitate formed, which was filtered off and on crystallization from the glacial acetic acid two substances were obtained, a monobromo derivative melting at 161–162°, and a dibromo derivative melting at 212–213°.

[4] Kauffmann and Franck, *Ber.*, **40**, 4006 (1907).

Bromination of the Acetanilide with Four Equivalents of Bromine.—Five grams of the acetanilide dissolved in 50 cc. of acetic acid was treated with 9 g. of bromine dissolved in 15 cc. of acetic acid; on pouring the reaction mixture into water and crystallizing the product from acetic acid, a substance identical with the one above melting at 212–213° was obtained as the only product that could be isolated. If the bromination was carried out at the temperature of the steam-bath, either with four equivalents or an excess of bromine, a product melting at 187–188° was formed. This is a dibromo derivative isomeric with the one melting at 213–214°.

Bromination of the Free Base in Glacial Acetic Acid in the Presence of Acetic Anhydride.—To five grams of 2-aminoresorcinol dimethyl ether dissolved in 50 cc. of acetic anhydride was added 5.1 g. of bromine, in 10 cc. of glacial acetic acid. After one hour the resulting mixture was poured into 200 cc. of water. The precipitate was filtered off and recrystallized from alcohol. This product, melting at 161–162°, was identical with the bromo-acetanilide obtained above. If an excess of bromine was used and the reaction carried out at the temperature of the steam-bath, a product identical with the substance melting at 187–188° was obtained as the sole product.

The Acetanilide of 4-Bromo-2-aminoresorcinol Dimethyl Ether.—This was obtained on bromination of the acetanilide of 2-aminoresorcinol dimethyl ether or the free base. It was purified by repeated recrystallization from dilute acetic acid and subsequently from benzene until a constant melting point was obtained. From the former solvent it crystallized in hexagonal plates and from the latter in fine needles. It is soluble in alcohol, acetic acid, benzene and ether but insoluble in water and ligroin. It melts at 161–162°.

Anal. Subs., 0.2090, 0.2140: CO_2, 0.3320, 0.3424; H_2O, 0.0830, 0.0847. Subs., 0.2191, 0.2304: AgBr, 0.1528, 0.1610. Calcd. for $C_{10}H_{12}O_3NBr$: C, 43, 80; H, 4.41; Br, 29.70. Found: C, 43.34, 43.65; H, 4.44, 4.43; Br, 29.68, 29.74.

Hydrolysis of the Acetanilide.—Four grams of the above acetanilide was refluxed for two hours with 200 cc. of 2 *N* alcoholic solution of potassium hydroxide. The reaction mixture was acidified with hydrochloric acid and extracted with ether, yielding a small quantity of the original substance melting at 161–162°. The acid solution was made alkaline with sodium hydroxide and extracted with ether. The ethereal extract was dried with anhydrous sodium sulfate and on evaporation gave an oily product (3 g.) which solidified on cooling.

4-Bromo-2-aminoresorcinol dimethyl ether obtained as described above was crystallized from alcohol, forming small scale-like crystals melting at 67–68°. It is quite soluble in the usual organic solvents.

Anal. Subs., 0.0982, 0.1769: AgBr, 0.0785, 0.1426. Calcd. for $C_8H_{10}O_2NBr$: Br, 34.44. Found: 34.27, 34.41.

Reduction of 4-Bromo-2-nitroresorcinol Dimethyl Ether.—Ten grams of 4-bromo-2-nitroresorcinol dimethyl ether prepared by the method of Kauffmann and Franck[5] was refluxed with 15 g. of tin and 50 cc. of concentrated hydrochloric acid for one hour. On cooling enough water was added to keep the tin double salt in solution and enough potassium hydroxide added to make the solution strongly alkaline. The solution was extracted three times with ether and the ether extract was dried with anhydrous sodium sulfate. After evaporation of the ether an oily residue remained which solidified when cold. It was crystallized from alcohol and found to be identical with the bromo-2-aminoresorcinol dimethyl ether obtained on hydrolysis of the acetanilide described above.

Attempts have been made to prepare the acetanilide of 4-bromo-2-aminoresorcinol

[5] Ref. 4, p. 4002.

dimethyl ether by refluxing the free base obtained above with acetic anhydride; this has not been possible. The product obtained had lost a methoxy group. This will be discussed further in a subsequent paper.

The Acetanilide of Dibromo-2-aminoresorcinol Dimethyl Ether Melting at 213–214°.—This was obtained by bromination of the acetanilide or the free base in acetic acid and acetic anhydride as described above. It was repeatedly recrystallized from alcohol and subsequently from benzene, forming fine white needle-like crystals.

Anal. Subs., 0.1039: AgBr, 0.1087. Calcd. for $C_{10}H_{11}O_2NBr_2$: Br, 45.15. Found: Br, 45.52.

The isomeric dibromo derivative melting at 187–188° was obtained by brominating the acetanilide of 2-aminoresorcinol dimethyl ether at the temperature of the steam-bath. It was crystallized from benzene.

Anal. Subs., 0.1104: AgBr, 0.1175. Calcd. for $C_{10}H_{11}NBr_2$: Br, 45.15. Found: Br, 45.30.

Summary

It has been shown that the bromine atom enters the meta position to the amino group in 2-aminoresorcinol dimethyl ether.

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[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES]

DERIVATIVES OF MONO- AND DIAMINOHYDROXYPHENYLARSONIC ACIDS

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The practical significance of 3-amino-4-hydroxyphenylarsonic acid lies in its chemical relationship to such valuable medicinal products as arsphenamine and its derivatives, as well as stovarsol (acetarsone). The first is produced by reduction of 3-amino-4-hydroxyphenylarsonic acid, while the latter is the N-acetyl derivative of the same acid. Recent investigations indicate that 3-amino-4-hydroxyphenylarsonic acid itself is valuable in the treatment of protozoan infections.[1] The purpose of this paper is to describe several new derivatives of the above acid and also of the closely related diaminohydroxyphenylarsonic acid, all of which were synthesized by us in the course of chemotherapeutic research.

Of the halogenated 3-amino-4-hydroxyphenylarsonic acids, the 5-chloro[2] and 5-iodo[3] derivatives are known. We succeeded in preparing 5-bromo-3-amino-4-hydroxyphenylarsonic acid by first brominating the corresponding nitrohydroxyarsonic acid and then reducing the resulting product to the amino derivative. The direct bromination of 3-amino-4-

[1] Levaditi and Navarro-Martin, *Compt. rend. acad. sci.*, **174**, 893 (1922); Fourneau, Navarro-Martin and Mr. and Mrs. Trefouel, *Ann. inst. Pasteur*, **37**, 551 (1923); Petzetakis, *Presse Medicale*, March 7, 1925.

[2] Benda and Schmidt, U. S. Patent 1,595,498 (1926).

[3] Macallum, *J. Chem. Soc.*, 1645 (1926); Maschmann, *Ber.*, **59B**, 213 (1926).