

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA.]

## THE NITRATION OF HALOGENATED PHENOLS.

BY L. CHAS. RAIFORD.

Received August 8, 1921.

Armstrong and Harrow<sup>1</sup> found that when 2,4,6-tribromophenol was gradually added to conc. nitric acid (relative amounts employed are not specified) 2 of the halogen atoms were replaced by nitro groups and that the product was 2,4-dinitro-6-bromophenol. In a second experiment, when the trihalogenated phenol was dissolved in glacial acetic acid, one molecular proportion of nitric acid added, and the whole heated for some time on the water-bath, the *para* bromine atom only was displaced, and 2,6-dibromo-4-nitrophenol was obtained. The use of more nitric acid gave the dinitro compound mentioned above.

Claus and Hirsch<sup>2</sup> who studied the action of conc. nitric acid on 2,4,6-tribromo-*m*-cresol in glacial acetic acid solution in the cold, isolated a mononitro-dibromo derivative melting with decomposition at 143°, to which they assigned the structure, 2,6-dibromo-4-nitro-*m*-cresol.

Foster<sup>3</sup> working under the direction of Zincke, found that treatment of a glacial acetic acid solution of 2,4,6-tribromo-*m*-cresol with sodium nitrite gave a yield of 83% of a mononitro-dibromo derivative melting at 128° (Foster says nothing about decomposition upon melting) to which he gave the structure 2,6-dibromo-4-nitro-*m*-cresol, evidently identical with the product obtained by Claus and Hirsch. Zincke<sup>4</sup> has summarized this and similar work done by himself and students on the bromine derivatives of *ortho*, *meta* and *para* cresols, and has reached the conclusion that in the *meta* series this method of nitration gives products in which the halogen atom *para* to hydroxyl is replaced by the nitro group, while in the *ortho* and *para* series the atom *ortho* to hydroxyl is replaced. In no case has he reported the formation of isomeric compounds as the result of a single nitration.

It has long been known that phenol and the cresols, except the *para* compound, usually give when nitrated a mixture of *ortho* and *para* isomerides; but, so far as the author is aware, no one previous to 1910<sup>5</sup> has recorded the formation of isomeric nitro compounds as a result of the nitration of a halogenated phenol. In 1911 Raiford<sup>6</sup> had occasion to prepare

<sup>1</sup> Armstrong and Harrow, *J. Chem. Soc.*, 29, 477 (1876).

<sup>2</sup> Claus and Hirsch, *J. prakt. Chem.*, [2] 39, 61 (1889).

<sup>3</sup> Foster, *Dissertation*, Marburg, 1898.

<sup>4</sup> Zincke, *J. prakt. Chem.*, [2] 61, 561 (1900).

<sup>5</sup> Raiford and Heyl, *Am. Chem. J.*, 43, 393 (1910), and 44, 209 (1910).

<sup>6</sup> Raiford, *Am. Chem. J.*, 46, 417 (1911).

as starting material in another study<sup>7</sup> a considerable quantity of 2,6-dibromo-4-nitro-*m*-cresol ( $\text{OH} = 1$ ), and found a modification of Zincke's method of nitration of 2,4,6-tribromo-*m*-cresol the most convenient way of securing the desired product. Following the general directions given by Foster,<sup>3</sup> with the exception that these experiments were carried out at a temperature of 12–15°, and the reaction mixture was poured into water as soon as all nitrite had dissolved,<sup>8</sup> I found that the reaction gave isomeric mononitro-dibromo compounds that were proved very decisively to be 2,4-dibromo-6-nitro- and 2,6-dibromo-4-nitro-*m*-cresols, m. p. 87° and 134° (with decomp.),<sup>9</sup> respectively.

To test the possibilities of this reaction still further, Raiford and Heyl<sup>5</sup> subjected 2,4,6-tribromophenol and the corresponding tri-iodo compound to the action of nitrous acid under the conditions specified above, and found that in each case there were formed isomers in which the *ortho* and the *para* halogen atoms, respectively, were replaced by the nitro group.

In the course of a research now in progress in this laboratory, it was found necessary to prepare considerable quantities of several *ortho*-aminophenols containing acid-forming substituents, and it was thought that this might be done most easily through Zincke's method, starting with the various halogenated phenols which are readily obtained in good yield and which, according to his experience, are not difficult to purify.

The first product selected for this work was the dibromo-*o*-cresol, first prepared by Werner,<sup>10</sup> and to which Claus and Jackson<sup>11</sup> assigned the structure, 2,4-dibromo-*o*-cresol.

Upson<sup>12</sup> nitrated this compound according to Zincke's method, modified to the extent of allowing the reaction mixture to stand overnight before it was poured into water; the nitro compound was isolated by distillation with steam. His study of the product showed that, in the nitration, the bromine atom *ortho* to hydroxyl had been replaced by the nitro group. In 1906, Zincke and Hedenström<sup>13</sup> nitrated the same dibromo-*o*-cresol, and obtained a product that agreed in melting point and other properties with Upson's compound. Without reference to the work of the latter, and without recording any facts to support their views, Zincke and Heden-

<sup>7</sup> Though this work was not published until 1911, the experimental part of it was done in 1908.

<sup>8</sup> Foster specified no temperature limitations, and allowed his reaction mixture to stand until crystals were deposited.

<sup>9</sup> Though the melting points of these products did not agree with the figures given by previous observers for the same compounds (Claus and Hirsch<sup>2</sup> found 93° for the *ortho* compound and 143° for the *para* isomer, while Foster<sup>3</sup> recorded 128° for the latter one) there is no doubt about the structure and purity of my products.

<sup>10</sup> Werner, *Bull. soc. chim.*, **46**, 278 (1886).

<sup>11</sup> Claus and Jackson, *J. prakt. Chem.*, [2] **38**, 326 (1888).

<sup>12</sup> Upson, *Am. Chem. J.*, **32**, 33 (1904).

<sup>13</sup> Zincke and Hedenström, *Ann.*, **350**, 269 (1906).

ström assumed that their product was an *ortho* derivative. Each of the previous workers, however, appears to have overlooked the fact that this nitration gives rise to both *ortho* and *para* isomerides. In the work described below it will be shown that it is possible to isolate from the reaction mixture two mononitro-monobromo-*o*-cresols having the structures 2-nitro-4-bromo-*o*-cresol (m. p. 90–91°) and 2-bromo-4-nitro-*o*-cresol, (m. p. 120° with decomp.).

### Experimental.

The starting material employed in this work was *o*-cresol, obtained by fractionating the purest commercial product obtainable. The fraction boiling steadily at 190° was brominated according to Zincke's<sup>14</sup> method modified to the extent that the product was filtered once just before evaporation of the solvent, and again when the solvent ceased to come over on the water-bath; this removes foreign material which would otherwise contaminate the crystals to be separated eventually. The final liquid, which was thick and viscous, was poured into an evaporating dish and allowed to crystallize by evaporation of the remaining solvent. The product thus obtained melted at 57°, the temperature recorded by Zincke, and was nearly free from color. Repeated crystallization from 50% alcohol gave long silky needles that were free from color, and melted at 58°.

Twenty-six and six-tenths g. of this dibromo derivative was dissolved in about 10 times its weight of glacial acetic acid, and the resulting solution was cooled to about 18°; then 10% more than the calculated weight of sodium nitrite was added in small portions during a period of half an hour. When all of the nitrite had dissolved, the liquid was slowly poured into 6 volumes of cold water, while the mixture was stirred. It was allowed to stand for several hours, after which the yellow solid was removed by filtration, washed with water and dried on clay plate. A yield of 90% was obtained. This material melted at 72–79°, which suggested the possibility of a mixture.<sup>15</sup>

### Separation of the Isomers.

In the first attempt to purify this material, it was subjected to steam distillation as recommended by Upson.<sup>12</sup> The volatile product came over very slowly, and was not pure. Repeated crystallization of the distillate from alcohol gave a product having the melting point and other properties reported by Upson and by Zincke (88°); but further purification in the form of the potassium salt, decomposition of this salt by hydrochloric acid, and final crystallization from alcohol or ligroin, gave yellow needles that melted at 90–91°. In the present work examination of the non-

<sup>14</sup> Ref. 13, p. 275.

<sup>15</sup> A mixture of these isomers, purified as indicated in this paper, melts at 81–115°, with final indication of decomposition.

volatile material yielded an isomeride which was proved (see below) to have the *para* structure.

A method of separating these isomers which is much more satisfactory than that indicated above, was to treat the warm chloroform solution of the crude nitration product with about 4 volumes of ligroin (b. p. 60–70°), and allow the resulting mixture to stand for about 24 hours.<sup>16</sup> During this time, most of the *para* compound crystallized out. After decanting the clear supernatant liquid, which contained the *ortho* compound, the *para* isomer was collected and dried. An average yield of 10 to 12% from several nitrations was obtained. In this condition the material was dark colored, and melted at 110–112° with apparent decomposition. Repeated crystallization from benzene gave lemon-yellow colored blocks, apparently rhombic in shape, and nearly transparent when first removed from the mother liquor. When allowed to stand for some time in the air these crystals lost their transparency, while the blocks appeared to split into a mass of opaque, yellow irregularly-shaped crystals. The compound is soluble in other organic solvents; a portion was crystallized from glacial acetic acid. All samples of the pure product melted at 120° with apparent decomposition.

This product is probably identical with that obtained by Auwers<sup>17</sup> by the bromination of *p*-nitro-*o*-cresol, though he reports that his product separated in "white needles from acetic acid." Apparently by the nitration of *o*-bromo-*o*-cresol, the same compound was obtained by Robertson<sup>18</sup> who got "white crystals before the nitration was complete," and secured the purified product in the form of "white crystals from alcohol." So far as the records go, the identity of the products obtained by these chemists rests solely upon the accepted structures of the starting materials and analyses of the final product for bromine. Neither proved further the structure of his product, and Robertson studied only its potassium salt. In view of these facts and because my product was not "white" and had been obtained from a different starting material and by a method different from that used by either of the previous workers, it was analyzed for bromine, and its identity and structure definitely established by the preparation and study of several of its derivatives.

Subs., 0.1916: AgBr, 0.1596. Calc. for  $C_7H_5O_3NBr$ : Br, 34.46. Found: 34.54.

The Hydrochloride of 2-Hydroxy-3-bromo-5-aminotoluene,  $C_6H_3CH_3(OH)Br(NH_2HCl)$ .—Ten g. of the nitro compound described above was dissolved in 30 cc. of alcohol, and reduced with a hydrochloric acid solution of stannous chloride in the usual

<sup>16</sup> Attention is here called to the fact that this method of separation of the isomers that resulted from the nitration of 2-4-6-tribromo-*m*-cresol (*Am. Chem. J.*, **46**, 427 (1911)) caused an immediate precipitation of the *para* isomeride in a nearly pure condition.

<sup>17</sup> Auwers, *Ber.*, **39**, 3174 (1906).

<sup>18</sup> Robertson, *J. Chem. Soc.*, **93**, 788 (1908).

way.<sup>19</sup> The product obtained, which was faintly yellow, was finally secured as perfectly colorless crystals, free from tin salt, after two further crystallizations. The compound is readily soluble in water (difference from the *ortho* compound, see below) and in alcohol. Analysis for halogen agrees with the formula assigned.

*Analysis.* Subs., 0.2056: Ag Hal., 0.2868. Calc. for  $C_7H_5ONClBr$ : Hal., 48.40. Found: 48.60.

**2-Hydroxy-3-bromo-5-aminotoluene**,  $C_6H_2CH_3OHBrNH_2$ .—This free base was obtained by treatment of an aqueous solution of the hydrochloride above described with slightly more than the theoretically required amount of ammonium carbonate solution. The aminophenol, which was promptly precipitated, was quickly collected on a filter, washed with several small portions of cold water, and then dried on clay plate. It melted at  $142^\circ$  with apparent decomposition. From ligroin (b. p.  $100$ – $110^\circ$ ) it separated as crystalline plates that had a slight pink color, and that melted at  $144^\circ$ , and turned black.

*Analyses.*<sup>20</sup> Subs. 0.2039, 0.2169: AgBr, 0.1901, 0.2014. Calc. for  $C_7H_5ONBr$ : Br, 39.57. Found: 39.67, 39.51.

**2-Bromo-4-acetyl-amino-6-methylphenyl Acetate**,  $C_6H_2(OCOCH_3)Br(NHCOCH_3)-CH_3$ .—This compound was prepared by warming a mixture of 3.3 g. of the hydrochloride mentioned above and an equal weight of anhydrous sodium acetate with a slight excess of acetic anhydride for about 10 minutes. The cold reaction mixture was freed from sodium salts by extraction with water, after which the acetyl derivative was collected on a filter and dried; 3.63 g. was obtained, a yield of 93%. In this condition the product melted at  $165$ – $167^\circ$ , and was nearly pure. Repeated crystallization from ethyl acetate gave short, colorless prisms that were clear and glass-like when seen under the microscope, and which, in masses, viewed with the naked eye, gave a very faint, bluish reflection. The melting point was  $169$ – $170^\circ$ . A sample purified by treatment of a chloroform solution of the compound with two volumes of ligroin ( $60$ – $70^\circ$ ) gave small colorless flakes that melted at  $169^\circ$ . The substance does not dissolve readily in caustic alkali solution, and was regarded as a di-acetyl derivative. Analysis for bromine was in accord with this view.

*Analysis.* Subs., 0.3391: AgBr, 0.2246. Calc. for  $C_{11}H_{12}O_3NBr$ : Br, 27.95. Found: 28.18.

**2-Hydroxy-3-bromo-5-acetyl-amino-toluene**,  $C_6H_2CH_3(OH)Br(NH.COCH_3)$ .—This product was obtained by removal of the O-acetyl from the di-acetyl derivative described above, by saponification. 0.87 g. of the latter was mixed with 30 cc. of cold water containing 0.25 g. of sodium hydroxide (two equivalents), and the mixture frequently shaken during a period of several hours, after which it was allowed to stand overnight. Nearly all of the solid passed into solution, giving a pink colored liquid. The mixture was next filtered, the residue washed with water and dried. Its melting point ( $169$ – $170^\circ$ ) and other properties showed that it was unchanged di-acetyl derivative. When the combined filtrate and washings was acidified with hydrochloric acid, a gray solid was precipitated at once. This was collected on a filter, washed with several portions of water and dried on clay plate. The product in this form melted at  $154$ – $155^\circ$ . It was readily soluble in a solution of sodium hydroxide, and from this it was precipitated in the unchanged form by acids; this behavior indicated the presence of a free hydroxyl group. It was further purified by crystallization from benzene, from which it separated in the form of nearly colorless needles. Analysis for halogen is in accord with a formula requiring one acetyl radical.<sup>21</sup>

<sup>19</sup> Ref. 6, p. 419.

<sup>20</sup> I am indebted to Miss E. Mackintosh for these analyses.

<sup>21</sup> I am indebted to Messrs. H. A. Iddles and P. Glavincheff for these analyses.

*Analyses.* Subs., 0.1270, 0.1365: AgBr, 0.0987, 0.1049. Calc. for  $C_9H_{10}O_2NBr$ : Br, 32.76. Found: 33.06, 32.75.

#### Proof of the Structure of the Nitro Compound, Melting at 120°.

The derivatives prepared and analyzed up to this point show that the nitro compound melting at 120° has the composition assigned to it by Auwers and Robertson. To determine the relative positions of the hydroxide and nitro radicals, a portion of the corresponding amino compound (see above) was prepared and its oxidation product studied. One and two-tenths g. of the amino hydrochloride described above was dissolved in 30 cc. of water containing 3.25 g. of ferric chloride, and the mixture allowed to stand overnight. The solid present at the end of the period was filtered off, washed with water and dried on a clay plate. It weighed 0.75 g. which is a yield of 73%. In this form it melted at 93°, which is the temperature reported by Claus and Jackson<sup>11</sup> for 6-bromo-2-methyl-1,4-benzoquinone. Crystallization from ligroin (b. p. 60-70°) gave orange colored prisms that melted at 95°.

Further identification of the product was obtained by reduction to the corresponding hydroquinone. For this purpose 0.5 g. was ground to a paste with 10 cc. of water, the mixture saturated with sulfur dioxide, warmed until solution took place, cooled to the room temperature, again saturated with the gas, and allowed to stand overnight. The nearly colorless liquid was extracted with ether, the ether distilled, and the remaining viscous, nearly colorless liquid poured on a watch crystal. After a time it set to a mass of slightly bluish irregularly shaped crystals that melted at 115°. Claus and Jackson<sup>11</sup> report 112° as the melting point of this compound. The product was further purified by treatment of a hot saturated benzene solution of the material with two volumes of ligroin, when nearly colorless leaflets were deposited upon cooling. These melted at 117°.

The identity of the latter product was still further established by conversion of a portion of it into a di-acetyl derivative; 0.48 g. was mixed with an equal weight of anhydrous sodium acetate and heated with acetic anhydride. After the product cooled, the sodium salt and unchanged anhydride were removed by water, and the solid was collected on a filter, washed and dried; 0.58 g. was obtained, a yield of 92%. The crude product melted between 75° and 80°. Crystallization from ligroin (100-110°) gave colorless, flat rhombohedrons that melted to a clear colorless liquid at 79°. Claus and Jackson<sup>11</sup> acetylated this hydroquinone and obtained a product that melted at 57° which they did not analyze or study further. My product did not dissolve in a solution of caustic alkali and the analysis for bromine is in accordance with the formula for a di-acetyl derivative.

Subs., 0.2341: Ag Br, 0.1551. Calc. for  $C_{11}H_{11}O_4Br$ : Br, 27.85. Found: 28.19.  
The mononitro-monobromo-*o*-cresol melting at 90-91°, which was iso-

lated from the same reaction mixture as that one the derivatives of which have just been described, had previously been prepared by both Upson<sup>12</sup> and Zincke<sup>4</sup> and was identified by the former as an *ortho* compound. The work herewith reported shows that it is isomeric with the product melting at 120° (see above) and which has just been proved to have the *para* structure. My interest in these products lay in the probability that the corresponding amino-cresols, only one of which had hitherto been isolated, and this without the study of any of its derivatives or the proof of its structure, would provide suitable compounds with which to test further the migration of acyl from nitrogen to oxygen previously reported from this laboratory.<sup>22</sup> Accordingly, the reduction products and a few derivatives were prepared.

**The Hydrochloride of 2-amino-4-bromo-6-methylphenol**,  $C_6H_2OH(NH_2HCl) \cdot BrCH_3$ .—This product was obtained by reducing the corresponding nitro compound with stannous chloride in the usual way. It is much less soluble in water than the *para* isomer (see above), which made it necessary to use 50% alcohol in the crystallizations required to free the compound from tin salt. Analysis for halogen showed that the substance was pure.

*Analysis.* Subs., 0.2396: Ag Hal., 0.3349. Calc. for  $C_7H_9ONClBr$ : Hal., 48.40. Found: 48.70.

**2-Amino-4-bromo-6-methylphenol**,  $C_6H_2OHNH_2BrCH_3$ .—A base having this composition and probably this structure was isolated by Claus and Jackson<sup>11</sup> who did not study it further. In my work the product was obtained from the corresponding hydrochloride by triturating a thin paste of this salt and water with the theoretical amount of ammonium carbonate solution until effervescence ceased, and quickly filtering the mixture. After it was dried on clay plate, this material melted at 113°, and recrystallization by treatment of its warm alcoholic solution with water did not change this. Analysis for halogen gave figures that are in accord with the formula assigned.

*Analysis.* Subs., 0.1793: AgBr, 0.1675. Calc. for  $C_7H_8ONBr$ : Br, 39.56. Found: 39.75.

**2-Acetylamino-4-bromo-6-methylphenyl Acetate**,  $C_6H_2(OCOCH_3)(NHCOCH_3) \cdot BrCH_3$ .—The base described above was still further characterized by the preparation of its acetyl derivative. 4.77 g. of the hydrochloride was intimately mixed with an equal weight of anhydrous sodium acetate and the mixture warmed for 15 minutes with excess of acetic anhydride. The mass was cooled, powdered and extracted with water to remove sodium salts. The remaining solid was freed from excess of water by suction, and dried; 5.6 g. was obtained, a yield of 84%. In this condition the product melted at 190–193°. Repeated crystallization from alcohol gave colorless, long silky needles that melted at 199–200°. It is readily soluble in other organic solvents but crystallized best from alcohol. It did not dissolve at once in cold solution of caustic alkali, but disappeared slowly, due to saponification at the O-position. This behavior characterizes it as a di-acetyl derivative, which is in agreement with the analysis for bromine.

*Analyses.* Subs., 0.1474, 0.2160: AgBr, 0.0979, 0.1434. Calc. for  $C_{11}H_{12}O_4NBr$ : Br, 27.95. Found: 28.26, 28.25.

### Summary.

1. When the dibromo-*o*-cresol, melting at 58°, is nitrated by treatment

<sup>22</sup> THIS JOURNAL, 41, 2068 (1919).

of its glacial acetic acid solution with nitrous acid, it gives 2 isomeric mononitro-monobromo-*o*-cresols, melting at 90–91° and 120°, respectively. The latter has been proved to have the *para* structure.

2. The amino-cresols corresponding to these nitro compounds will be used in the further study of the migration of acyl from nitrogen to oxygen.

IOWA CITY, IOWA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, No. 378.]

## THE QUANTITATIVE DETERMINATION OF THE ANTISCORBUTIC VITAMIN (VITAMIN C).

By H. C. SHERMAN, V. K. LAMER AND H. L. CAMPBELL.

Received September 2, 1921.

Each vitamin is known by the physiological effects which result from its absence or from the intake of an insufficient quantity. These effects are failure of growth, or development of a deficiency disease, or both. The relative amounts of any one of the vitamins in different foods or in the same food before and after treatment can in general best be measured by feeding a suitable experimental animal, of standard initial age and size, with a basal diet adequate in all other respects but devoid of the vitamin in question, and finding how much of the food under investigation must be fed in order to supply enough of the vitamin to meet the needs of the standard test animal. This is sometimes determined in terms of the proportion in which the food under test when serving as the sole source of the vitamin in question must enter into the food mixture in order to render the food supply adequate in this respect. Or the food to be tested may be fed separately from the basal ration and the minimum quantity of the food which will thus suffice to protect the standard animal from vitamin deficiency may be determined in terms of the actual weight of food thus required as source of vitamin. This latter method is the one chiefly used in studies of the antiscorbutic vitamin and is sometimes referred to as determination of the minimum protective dose. See discussion by Chick and Hume.<sup>1</sup>

Holst and Frölich as early as 1912<sup>2</sup> made comparisons of the antiscorbutic properties of foods by finding whether or not certain arbitrarily chosen quantities which they fed would suffice to prevent the appearance of scurvy; but the basal diet which they employed, consisting usually of oats and water only, was deficient in other respects as well as in antiscorbutic vitamin.

Cohen and Mendel<sup>3</sup> devised a new basal ration planned to provide all necessary nutrients except the antiscorbutic, and showed that experimental scurvy can be induced in the guinea pig at will, and formulated more fully the criteria for the recognition

<sup>1</sup> Chick and Hume, *J. Biol. Chem.*, **39**, 203 (1919).

<sup>2</sup> Holst and Frölich, *Z. Hyg. Infektionsk.*, **72**, 1 (1912).

<sup>3</sup> Cohen and Mendel, *J. Biol. Chem.*, **35**, 425 (1918).