LXXI.—*Contributions to the Chemistry of Phenol Derivatives.**

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Bromination and Nitration of Phenol.

THERE is some discrepancy between the statements of different authors respecting the action of bromine on phenol. Hübner and Brenken (*Ber.*, 1873, **6**, 170), by brominating phenol in acetic acid solution, obtained a solid (para) bromophenol, and stated that a "liquid isomeride" remained in the mother liquor after freezing out the solid modification. More recently, Gordon (*Proc.*, 1891, p. 64), repeating the experiment of Hübner and Brenken, came to the conclusion that the product was "practically pure parabromophenol." In a paper published by one of us with Messrs. Woolcott and Wray in 1896 (*Trans.*, p. 1326), it was stated that the bromination of phenol in glacial acetic acid gave a mixture of the para- and ortho-derivatives. The latter statement was based on indirect evidence derived from the study of the nitration of the crude product of the action of bromine on phenol, under the conditions specified. Among the bromonitrophenols thus formed there was always obtained a quantity of 2-bromo-4:6-dinitrophenol which seemed too great to be accounted for by isomeric change (*Armstrong, J. Chem. Soc.*, 1875, 520) under the conditions of nitration employed by us.

As the details of bromination and nitration were not given in the paper published in 1896, and as we have now obtained direct evidence of the presence of orthobromophenol in the product of bromination, it may be of interest to supply these details, as we are not sure whether our conditions of working were the same as either those of Hubner and Brenken or of Gordon. The phenol is dissolved in about its own weight of glacial acetic acid, and the calculated quantity of bromine

* For the first instalment, see *Trans.*, 1896, **69**, 1321.

dissolved in the same solvent (1 c.c. containing about 1.5 grams of bromine), allowed to fall, drop by drop, into the phenol solution, kept cold by immersion in water. The temperature during this operation does not exceed 21°. After all the bromine has been added, the solution is diluted with water, the oil which separates is washed repeatedly with water, and without further purification dissolved in about an equal volume of glacial acetic acid. The nitration is carried out in precisely the same way as the bromination, the calculated quantity of fuming nitric acid (sp. gr. 1.5), diluted with about three times its volume of acetic acid, being mixed gradually with the cooled solution of the bromophenols. The process of mixing takes about 2 hours, and the temperature does not exceed 22°. When about one-half the required quantity of nitric acid has been added, the solution begins to deposit crystals, and soon becomes semi-solid. The best method of treating the product was only discovered after a numerous series of operations with different lots of 50 or 100 grams of phenol, and the process now described may be considered as a summary of our experience.

After the completion of the nitration, the whole product is mixed with water, collected, washed until free from acid, and transferred to a flask with water. At this stage, three chief products are always present: (a) 4-bromo-2-nitrophenol predominating, (b) 2-bromo-4:6-dinitrophenol, (c) 2-bromo-4-nitrophenol. With respect to the origin of these products, we refer to the following portion of the paper. In order to separate them, the contents of the flask are steam distilled as long as anything comes over, the 4-bromo-2-nitrophenol being thus removed.* The residue in the flask is treated with ammonia in excess, so as to convert the bromonitro-compounds into ammonium salts, and when quite cold filtered, so as to remove the 2-bromo-4:6-dinitrophenol ammonium salt, which is but slightly soluble in cold water; the filtrate now contains the whole of the 2-bromo-4-nitrophenol and a certain quantity of the bromodinitrophenol. On acidifying with hydrochloric acid, the latter separates after stirring for a short time, and can be removed by filtration, whilst the filtrate containing the more soluble bromonitrophenol is reduced by evaporation and allowed to stand, when the latter compound separates in flat, white needles melting at 112°. This bromonitrophenol is identical with that obtained by Brunck (*Zeit. f. Ch.*, 1867, 204) and by Körner (*ibid.*, 1868, 323), but these authors, who obtained the compound by brominating paranitrophenol, assign to it a melting point of 102°; this discrepancy may be

* The bromodinitrophenol is very slightly volatile in steam, but to a quite inappreciable extent, and can be recognised at once by its remaining solid in the condenser when the temperature is allowed to rise by running off the cold water. When this stage is reached the distillation is stopped.

due to a misprint, or to a difference in the degree of purity of the product obtained by us, or, again, to the use of water as a solvent. We have satisfied ourselves that the products are identical, by a comparison and analysis of the barium salts. We may add that the relatively high degree of solubility of this bromonitrophenol in water was only discovered after we had familiarised ourselves with its properties by obtaining it pure from another source, namely, by the nitration of orthobromophenol, as will be explained subsequently.

The origin of the three products above referred to was determined by a series of experiments with pure para- and ortho-bromophenols. The mixture obtained by the direct bromination of phenol contains, not only ortho- and para-bromophenols, but always a certain quantity of unbrominated phenol and a certain quantity of 2:4-dibromophenol, the formation of which it is impossible to avoid, under the conditions of bromination described. We have not found it possible to separate these bromo-derivatives directly from the mixture, but if the whole product is methylated by heating with the necessary quantities of potassium hydroxide and methylic iodide in methyl alcohol solution, the bromanisoles thus obtained can be fractionally distilled. The monobromanisoles come over first, and the temperature then rises rapidly to 272°, the boiling point of 2:4-dibromanisol; the latter has a melting of 59°, as described by Körner. In the preparation of parabromophenol by the freezing out method of Hübner and Brenken, the other products are presumably contained in the mother liquor. The boiling points of ortho- (210°) and parabromanisol (223°) are too near to admit of satisfactory separation by fractional distillation without a large supply of material.

Nitration of Parabromophenol.

Pure parabromophenol was prepared by two methods, independently of the direct bromination of phenol. Parabromosalicylic acid, prepared by the bromination of salicylic acid, and subsequent purification of the product, was distilled with dry barium carbonate according to Cahours' method (*Annalen*, 52, 338); another preparation was made from pure parabromaniline by the diazo-method. These preparations were nitrated in acetic acid solution, as before, only in the latter case the nitration was carried on in a freezing mixture. Both preparations gave the same products, namely, 4-bromo-2-nitrophenol and a small quantity of 2-bromo-4:6-dinitrophenol; in these cases, therefore, the latter compound is undoubtedly produced by intramolecular change, since no orthobromophenol was present, and this accounts for the production of a portion of this bromodinitrophenol during the nitration of the mixture obtained by the direct bromination of phenol. It

is remarkable that this change should occur at the low temperature at which the nitration was effected, since no excess of nitric acid was used, and previous observers (Armstrong and Gordon) have always brought about the transformation by heating 4-bromo-2:6-dinitrophenol with bromine water or nitric acid. It has recently been shown by Reverdin (*Ber.*, 1896, **29**, 997, 2595 ; 1897, **30**, 2999) that a somewhat similar transference of iodine from the para- to the ortho-position takes place on nitrating periodoanisole, &c., but this observation is not really parallel to the present case, as will be made evident from the experiments described subsequently.

A specimen of parabromophenol purchased from Schuchardt gave the same results as our own preparations ; from this specimen we also obtained a small quantity of 2-bromo-4-nitrophenol in addition to the other products, thus indicating the presence of orthobromophenol. The crystals of this specimen were, however, wet with the acetic acid mother liquor, from which they had been only imperfectly drained, so the remainder was steam distilled to bring over any orthobromophenol ; the residue, on nitration, then give only the 4-bromo-2-nitro- and the 2-bromo-4:6-dinitrophenol, and not a trace of the 2-bromo-4-nitrophenol. This experiment shows that the latter compound results from the nitration of orthobromophenol, and thus proves the presence of this modification in the product of the direct bromination of phenol ; at the same time, the fact that pure parabromophenol does not give 2-bromo-4-nitrophenol on nitration shows that there is no analogy between this compound and the iodine derivatives nitrated by Reverdin under the conditions of nitration employed by us. This author shows, in fact (*Ber.*, 1896, **29**, 2598), that parabromanisole can be nitrated without a shifting of the bromine atom.

Direct evidence of the existence of orthobromophenol in the product of the bromination of phenol in acetic acid was obtained by following Hübner and Brenken's method ; two distinct experiments were made, the bromine solution in each case being dropped slowly into the acetic acid solution of the phenol cooled in melting ice. The temperature during this operation keeps at 2—3°. In one case, the solution, after bromination, was warmed so as to drive off hydrogen bromide, but this does not appear to influence the product in any way beyond giving a slightly better yield of parabromophenol. In both experiments, after bromination, the parabromophenol was frozen out by immersing the beaker containing the solution in ice and salt and stirring the contents ; the crystalline pulp was then collected, drained, and allowed to dry in the air, and finally purified by crystallisation from chloroform. The acetic acid mother liquor was diluted with water and the oily layer separated. The two products, consisting of (1) pure parabromophenol, and (2) an oily mixture of para- and ortho-

bromophenols, were then nitrated separately in acetic acid under the same conditions as described above, equal weights being taken so as to make the results comparable. From the parabromophenol there was obtained only 4-bromo-2-nitrophenol, and some of the 2-bromo-4:6-dinitrophenol. From the oily mixture there was obtained in addition some 2-bromo-4-nitrophenol, which was identified by its melting point, and a nitrogen determination.

0.1826 gave 9.8 c.c. moist nitrogen at 17° and 759 mm. $N = 6.20$.
 $C_6H_3Br \cdot NO_2 \cdot OH$ requires $N = 6.42$ per cent.

Nitration of Orthobromophenol.

Orthobromophenol was prepared from orthonitrophenol by reducing the latter to amidophenol with ammonium sulphide and replacing the NH_2 -group by bromine by Sandmeyer's method; the bromophenol is very readily distillable in a current of steam, and comes over as a colourless oil, having a marked and peculiar odour, which can be recognised in the product obtained by the direct bromination of phenol. The nitration was carried out in acetic acid solution as before, with the calculated quantity (1 mol.) of nitric acid (1.5 sp. gr.), cooling being effected by simply immersing the beaker containing the solution in cold water. The product on mixing with water sinks as a dark coloured oil, which does not solidify on standing for many days; it was found to consist of two bromonitrophenols, the 2-bromo-4-nitro-modification of Brunck and Körner melting at 112°, and a new modification which comes over readily on steam distillation. The 2:4-modification was identified with Brunck and Körner's compound by analysing the barium salt, which consists of orange-yellow needles having the composition $(NO_2 \cdot C_6H_3Br \cdot O)_2Ba + 6H_2O$.

0.620, dried under desiccator, gave 0.0549 $BaSO_4$. $Ba = 19.99$.

0.3217, dried at 160—170° until constant, lost 0.0517. $H_2O = 16.07$. The formula requires $Ba = 20.17$ per cent. and $H_2O = 15.90$ per cent.*

The new modification which comes over on steam distillation crystallises from dilute alcohol in pale yellow needles having a melting point of 67—68°.

0.20 gave 11 c.c. moist nitrogen at 13.5° and 746 mm. $N = 6.34$.

$C_6H_3Br(NO_2) \cdot OH$ requires $N = 6.42$ per cent.

The barium salt forms flat, reddish-yellow needles sparingly soluble in hot water.

* We have found that, under certain conditions, this bromonitrophenol can also form a hydrate containing 7 H_2O .

0.9146, dried at 160—170° until constant, lost 0.1650. $H_2O = 18.04$. The formula requires $H_2O = 18.07$ per cent.

0.1560, dried under desiccator, gave 0.0596 BaSO₄. Ba = 22.46.
 0.2328, dried under desiccator and then heated at 170°, lost 0.0136 H₂O = 5.84.
 (NO₂·C₆H₃Br·O)₂Ba + 2H₂O requires Ba = 22.57 and H₂O = 5.93 per cent.

The potassium salt is readily soluble in hot water and crystallises from this solvent in ruby-coloured needles.

0.1544, dried under desiccator, gave 0.0492 K₂SO₄. K = 14.28.
 0.1612, dried under desiccator and subsequently at 100°, lost 0.011 H₂O = 6.82.
 NO₂·C₆H₃Br·OK + H₂O requires K = 14.23 and H₂O = 6.56 per cent.
 0.1438, dried at 100°, gave 0.0494 K₂SO₄. K = 15.39.
 NO₂·C₆H₃Br·OK requires K = 15.23 per cent.

The silver salt, which was prepared for the purpose of obtaining the methylic ether, crystallises in ochreous needles fairly soluble in boiling water, but only sparingly in cold water. On heating with methylic iodide in methyl alcohol in a flask with a reflux condenser for some hours, the silver salt is decomposed and the methylic ether formed. The latter, purified by crystallisation from dilute alcohol, forms white, silvery scales melting at 67°.

0.0940 gave 4.75 c.c. moist nitrogen at 15.4° and 766.5 mm. N = 5.94.
 NO₂·C₆H₃Br·OCH₃ requires N = 6.03 per cent.

The constitution of the new bromonitrophenol is shown by its giving 2-bromo-4:6-dinitrophenol on further nitration, 2-bromo-4-nitrophenol giving the same dinitro-compound on further nitration. The new modification is thus 2-bromo-6-nitrophenol.

2-Bromo-6-nitraniline.—This compound, obtained by heating the methylic ether, above described with alcoholic ammonia in a sealed tube at 120° for 7 hours, crystallised from dilute alcohol in silky, orange needles melting at 73–74°.

0.1269 gave 13.9 c.c. moist nitrogen at 12° and 767 mm. N = 13.10.
 NO₂·C₆H₃Br·NH₂ requires N = 12.90 per cent.

The compound is soluble in all the ordinary organic solvents; it is but very feebly basic and resists acetylation even when boiled with acetic anhydride.

From the foregoing results, it thus appears that the 2-bromo-4:6-dinitrophenol, obtained by the nitration of the crude product of the action of bromine on phenol in acetic acid solution, owes its

origin to both the para- and ortho-bromophenols present in the mixture. Its formation from parabromophenol under the conditions of nitration employed is certainly remarkable, and since at first sight it appeared probable that the dinitro-compound resulted from the further nitration of 4-bromo-2-nitrophenol (with isomeric change), a number of experiments were made with the object of studying the action of nitric acid on the latter compound under various conditions. The results are summarised below.

(a) 4-Bromo-2-nitrophenol may be dissolved in excess of cold fuming nitric acid without transformation into 2-bromo-4:6-dinitrophenol, provided the temperature is not allowed to rise above 20° , and the action of the nitric acid is not allowed to continue for more than about 5 minutes. The product is 4-bromo-2:6-dinitrophenol.

(b) 4-Bromo-2-nitrophenol is not converted into 2-bromo-4:6-dinitrophenol by a large excess (ten times the theoretical quantity) of fuming nitric acid in 2—3 hours if the nitric acid is diluted with an equal volume of glacial acetic acid, and the temperature not allowed to exceed 15° . The product in this case also is 4-bromo-2:6-dinitrophenol.

(c) 4-Bromo-2-nitrophenol is completely converted into 2-bromo-4:6-dinitrophenol at ordinary temperatures if dissolved in excess of fuming nitric acid and allowed to stand for 2 or 3 hours.

The formation of 2-bromo-4:6-dinitrophenol thus appears to be due to the direct action of nitric acid on parabromophenol (and ortho-bromophenol), the para-modification not passing through the intermediate stage of 4-bromo-2-nitrophenol.

4-Bromo-2:6-dinitrophenol and Derivatives.

The above compound can be reduced by heating with ammonium sulphide solution. An excess of the reducing agent must be avoided or the reduction goes too far, and a highly oxidisable compound is formed. The product of the moderated reduction is 4-bromo-2-nitro-6-amidophenol. When crystallised from dilute alcohol, the compound consists of brown scales of distinctly basic properties melting at $141-142^{\circ}$.

0.1862 gave 19.1 c.c. moist nitrogen at 9.5° and 753.4 mm. $N = 12.18$.

$\text{NO}_2 \cdot \text{C}_6\text{H}_2\text{Br}(\text{NH}_2) \cdot \text{OH}$ requires $N = 12.01$ per cent.

The acetyl derivative, $\text{NO}_2 \cdot \text{C}_6\text{H}_2\text{Br}(\text{NHAc}) \cdot \text{OH}$, prepared by acetylating the base with acetic anhydride in acetic acid solution, after crystallisation from alcohol, acetic acid, and benzene successively, consists of whitish needles melting at $161-162^{\circ}$.

0.0949 gave 8.3 c.c. moist nitrogen at 15.2° and 759.5 mm. $N = 10.3$.

The formula requires $N = 10.18$ per cent.

The hydrochloric acid solution of the base, when treated with one molecular proportion of sodium nitrite, gives a brownish-yellow crystalline deposit of a diazoxide which, when dry, crystallises from benzene in brown, stumpy needles with a greenish, metallic lustre. The pure compound when heated rapidly, explodes with extreme violence at about 144° . The composition was established by analysis.

0.2166 gave 31.5 c.c. moist nitrogen at 13° and 762 mm. $N = 17.1$.

The formula requires $N = 17.2$ per cent.

The constitution is

In order to characterise the bromodinitrophenol further, the methylic ether, which does not appear to have been described, was prepared by heating the silver salt with methylic iodide in methyl alcoholic solution. The methylation is very imperfect, and the product, after purification by washing with dilute alkali and crystallisation from dilute alcohol, consists of slender, straw-coloured needles melting at $81-82^{\circ}$.

0.0783 gave 6.8 c.c. moist nitrogen at 20° and 764 mm. $N = 9.97$.

$C_6H_2Br(NO_2)_2 \cdot OCH_3$ requires $N = 10.10$ per cent.

This methylic ether most readily exchanges its methoxyl group for the amido-group on boiling for a short time with alcoholic ammonia, the product being the 4-bromo-2:6-dinitraniline crystallising in orange needles melting at 160° (Austen, *Ber.*, 1886, 9, 919).

0.0770 gave 10.9 c.c. moist nitrogen at 19° and 763 mm. $N = 15.98$.

$C_6H_2Br(NO_2)_2 \cdot NH_2$ requires $N = 16$ per cent.

The protecting influence of the two orthonitro-groups is shown by the fact that the compound is not acetylated on boiling for some time with acetic anhydride and anhydrous sodium acetate. On boiling with benzoyl chloride, it forms a benzoyl derivative which crystallises from alcohol in white, silky needles melting at $197-198^{\circ}$.

0.0578 gave 5.7 c.c. moist nitrogen at 19.5° and 769.8 mm. $N = 11.44$.

$C_6H_2Br(NO_2)_2 \cdot NH \cdot C_7H_5O$ requires $N = 11.47$ per cent.

Derivatives of Guaiacol.

Bromonitroguaiacols.—The origin of this experiment was an attempt to isolate a definite monobromoguaiacol by brominating guaiacol in glacial acetic acid with one molecular proportion of bromine, and the

conversion of the whole product into the benzoyl derivative by treatment with benzoyl chloride in the presence of caustic soda solution. The mixture of bromoguaiacol benzoates obtained by this method is, however, not crystallisable, and nitration was therefore resorted to as a means of isolating a definite compound. The product, consisting of a viscid, fragrant resin, was dissolved in glacial acetic acid, and allowed to stand for some hours in admixture with an excess of fuming nitric acid at the ordinary temperature. The nitro-derivative was thrown out by pouring the solution into water, and, after numerous crystallisations from alcohol, a definite compound consisting of slender pale-yellow needles, melting at 103—104°, was obtained.

0.120 gave 4.15 c.c. moist nitrogen at 15.5° and 745.5 mm. $N = 3.95$.

$\text{NO}_2 \cdot \text{C}_6\text{H}_2\text{Br}(\text{OCH}_3) \cdot \text{OC}_7\text{H}_5\text{O}$ requires $N = 3.98$ per cent.

The benzoyl derivative was hydrolysed by boiling it for some time with sodium hydroxide solution; the sodium salt of the bromonitroguaiacol thus formed crystallises in bright red needles readily soluble in hot water, but only sparingly in cold water, especially in the presence of excess of sodium hydroxide. The free compound obtained by the action of acids on the sodium salt, crystallises from hot water in pale yellow plates or flat needles having a melting point of 120°.

0.1426 gave 6.9 c.c. moist nitrogen at 18°, and 763 mm. $N = 5.60$.

$\text{NO}_2 \cdot \text{C}_6\text{H}_2\text{Br}(\text{OCH}_3) \cdot \text{OH}$ requires $N = 5.64$ per cent.

The constitution of this bromonitroguaiacol has been arrived at indirectly. The bromination of guaiacol might be expected to give rise to a mixture of the two compounds

These, on nitration, would yield respectively

It was found that the paranitroguaiacol corresponding with formula I (Meldola, Proc., 1896, p. 127), on bromination in acetic acid, gave a bromonitroguaiacol differing from formula I, so that the bromonitroguaiacol melting at 120° isolated by us is the 4-bromo-6-nitroguaiacol (formula II). The deep red colour of the sodium salt is also in favour of this formula.

The 4-nitro-6-bromoguaiacol (formula I) obtained by brominating paranitroguaiacol, crystallises from hot water in pale, slender, yellow needles melting at 142° .

0.1320 gave 6.1 c.c. moist nitrogen at 141° and 769.5 mm. $N = 5.49$.

The formula requires $N = 5.64$ per cent.

The sodium salt, which is much more soluble in water than that of the isomeride, crystallises in reddish needles, which are not so highly coloured as the sodium salt of the 4-bromo-6-nitroguaiacol.

The benzoyl derivative crystallises from benzene in thin, pale yellow tablets melting at $117-118^{\circ}$.

The bromamidoguaiacol, corresponding with the two bromonitroguaiacols above described, appear to be very easily oxidisable, and we have not yet succeeded in isolating them.

Orthacetamidoguaiacol.—The orthonitroguaiacol benzoate melting at $88-89^{\circ}$ (Proc., 1896, p. 127), when reduced by boiling in alcohol solution with tin and hydrochloric acid, loses the benzoyl group and gives orthamidoguaiacol. The latter is very unstable, and could not be isolated as a free base; the hydrochloride,

crystallises in white needles. The acetyl derivative, obtained by heating the hydrochloride with sodium acetate and acetic anhydride, crystallises from boiling water in flat, whitish needles with serrated edges, and melts at $122-123^{\circ}$ with decomposition.

0.1396 (dried in air) gave 8.05 c.c. moist nitrogen at 12° and 767 mm. $N = 6.9$.

0.6927, dried at 100° until constant, lost 0.0678. $\text{H}_2\text{O} = 9.78$.

$\text{OH} \cdot \text{C}_6\text{H}_3(\text{OCH}_3) \cdot \text{NH} \cdot \text{C}_2\text{H}_3\text{O} + \text{H}_2\text{O}$ requires $N = 7.03$ and $\text{H}_2\text{O} = 9.04$ per cent.

The compound is phenolic, and forms a nitroso-derivative when dissolved in glacial acetic acid and treated with sodium nitrite. This nitroso-derivative crystallises in reddish-brown crystals having a melting point of about 155° , but the quantity of substance at our disposal was extremely small, and we do not consider that it has yet been obtained in a pure condition.

We have pleasure in acknowledging the assistance which Mr. Percy P. Phillips has given in connection with some of these investigations.

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