

LXXXIX.—*The Active Substance in the Iodination of Phenols.*

By VICTOR COFMAN.

NUMEROUS methods are known for the preparation of iodophenols, and the entrance of iodine in the molecule has been accounted for in various ways. The object of this communication is to prove that hypiodous acid is solely responsible for the iodination in a number of processes investigated, and to show that the presence of the above-mentioned substance as an intermediate compound satisfactorily explains the formation of iodophenols by the various known methods.

That hypiodous acid has the property of reacting with phenols, producing iodo-substituted compounds, is no new discovery. Selivanov (*Ber.*, 1894, **27**, 1012) pointed out that the iodination of phenol by means of nitrogen iodide is due to the hydrolysis of the latter compound and the consequent production of hypiodous acid; various other authors (Bray, *Zeitsch. physikal. Chem.*, 1906, **54**, 563; Cohn and Schultz, *Ber.*, 1905, **38**, 3294; Gardner and Hodgson, *T.*, 1909, **96**, 1822) have suggested that the same compound may be responsible for the formation of iodophenols by the "iodine and alkali" methods, but no definite proofs have been adduced in support of this view, nor has it yet been attempted to ascribe the production of iodophenols in all the known instances to the presence of one and the same substance in the various reacting mixtures.

The earliest mention of any iodophenol is that made by Piria (*Compt. rend.*, 1843, **18**, 187), but the merit of a first investigation of this class of compounds rests with Lautemann (*Annalen*, 1861, **120**, 299), who prepared several iodophenols and iodo-salicylic acids. From his method of preparation, Lautemann inferred that, on heating iodine with salicylic acid, a direct substitution takes place, although he could not explain what happened to the displaced hydrogen.

Later, Kekulé (*Annalen*, 1864, **131**, 221) showed that the compounds obtained by Lautemann's process were formed only when the mixture of iodine and salicylic acid was dissolved in alkalis. He prepared the same compounds by the action of iodine and iodic acid on salicylic acid, and explained their formation thus:

- (i)  $C_7H_6O_3 + I_2 + KOH = C_7H_5O_3I + KI + H_2O.$
- (ii)  $5C_7H_6O_3 + 2I_2 + HIO_3 = 5C_7H_5O_3I + 3H_2O.$

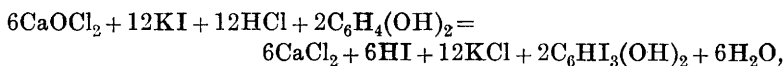
Kekulé's opinion was that iodine has the property of displacing the hydrogen atoms of certain organic compounds in the presence of a third substance capable of oxidising, or removing in some other fashion, the hydriodic acid formed during the reaction. This explanation has since been put forward to account for the formation of iodophenols by other methods, namely, (i) the "iodine and mercuric oxide" method (*Ber.*, 1872, **5**, 380); (ii) the "iodine and sodium phosphate" method (*J. Pharm. Chim.*, 1902, [vi], **15**, 217); (iii) the iodine monochloride method (*ibid.*).

According to this view, in every one of the above cases, the first part of the reaction is  $\text{HR} + \text{I}_2 = \text{IR} + \text{HI}$  (where R = phenolic radicle), and the second part consists in the removal of the hydriodic acid thus formed by the third substance present.

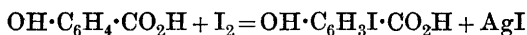
The production of iodo-substituted compounds by means of iodine monochloride was originally given a similarly simple interpretation (Brown, *Phil. Mag.*, 1854, [iv], **8**, 201):



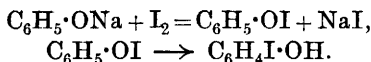
A more complicated equation was put forward by Dagener (*J. pr. Chem.*, 1879, [ii], **20**, 324) as representing the course of the reaction in his hypochlorite method of obtaining tri-iodoresorcinol:



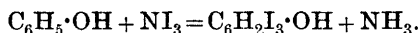
whilst in the "dry" reactions of Birnbaum (*Ber.*, 1882, **15**, 459) and Schall (*Ber.*, 1883, **16**, 1897), the authors assume that the hydrogen atom displaced by the iodine wanders in one case to the carboxyl, and in the other to the hydroxyl group, thus:



and



Finally, Willgerodt (*J. pr. Chem.*, 1888, [ii], **37**, 446) supplied for his method the equation



#### EXPERIMENTAL.

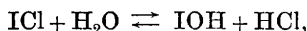
The opinion that the formation of iodophenols must be due to the presence of hypiodous acid suggested itself to the present author during the preparation of di-iodosalicylic acid by the action of iodine monochloride on salicylic acid. It was observed, on the one hand, that the reaction did not take place in the absence of

water, whilst, on the other hand, an aqueous solution of iodine monochloride soon lost its power of combining with salicylic acid. The gradual disappearance of the "active iodine" (that is, iodine capable of attacking the phenolic molecule) from such a solution is strikingly shown in the table given below. The method employed was to add 10 c.c. of a solution of iodine monochloride in glacial acetic acid (Wijs' solution) to 100 c.c. of water; the mixture was allowed to remain at the ordinary temperature (12°) for the specified time, after which excess of sodium salicylate (5 c.c. of a 10 per cent. solution) was added to combine with the "active iodine"; this was followed after one minute by the addition of an excess of potassium iodide and titration with *N*/10-thiosulphate solution.

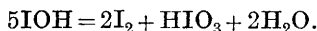
*Table showing the Rapid Decrease in the Amount of "Active Iodine" Present in Aqueous Iodine Monochloride Solution.*

Time solution was allowed to remain.	No. of c.c. of <i>N</i> /10-thiosulphate required.	"Active iodine."
0	0	27.8
10 sec.	4.1	23.7
20 "	5.8	22.0
30 "	7.3	20.5
1 min.	10.5	17.3
2 "	13.3	14.5
3 "	16.8	11.0
5 "	17.1	10.7
10 "	18.1	9.7
30 "	20.2	7.6
1 hr.	21.9	5.9
2 hrs.	23.3	4.5
16 "	25.1	2.7
24 "	26.2	1.6

How is this rapid decrease in the activity of iodine monochloride solutions explained? As is well known, iodine monochloride is partly hydrolysed in aqueous solution,



the hypiodous acid formed quickly decomposing into iodic acid and free iodine, the reaction being usually represented thus:



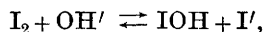
Now, it is highly probable that the decrease in the activity of the solution is due to this decomposition of the hypiodous acid, but, owing to our imperfect knowledge of the constitution of iodine monochloride solutions, this cannot be definitely proved. Other products of decomposition, such as the compound  $\text{ICl}_2\text{HCl}$  and

iodine trichloride, are present, and these may have a bearing on the matter.

Nevertheless, it is quite clear that the present view, which ascribes the iodination of phenols in iodine monochloride solution to the action of the iodic acid formed, is untenable, since the amount of iodophenol produced actually diminishes as the concentration of iodic acid and free iodine increases.

The next step was to investigate the formation of iodophenols in alkaline iodine solutions. In this case, thanks to the fact that the kinetics of the system iodine-potassium iodide-sodium hydroxide has been fully investigated by Schwickler (*Zeitsch. physikal. Chem.*, 1895, **16**, 303), Forster (*J. Physical Chem.*, 1903, **56**, 324), Bray (*Zeitsch. physikal. Chem.*, 1906, **54**, 563), and Skrabal (*Monatsh.*, 1907, **28**, 217; 1909, **32**, 167, 815), it is possible to show that, in such solutions, *the mass of "active iodine" is at any instant equal to the amount of hypiodous acid present*, thus proving them conclusively to be one and the same substance.

Without going too deeply into the kinetics of hypiodite solutions, it may be stated that the first reaction which takes place when iodine is dissolved in alkalis, namely,



attains rapidly a state of equilibrium and, in strongly alkaline solutions, the concentration of free iodine is negligible. The decomposition of the resulting hypiodous acid, on the contrary, is relatively slow, proceeding with measurable velocity. It has thus been found possible to prove that the reaction is one of the second order, the rate of change being expressed by the empirical formula

$$-\frac{d[\text{IOH}]}{dt} = \frac{[\text{I}'] + e(E)}{[\text{OH}']} \cdot ka[\text{IOH}]^2,$$

where  $E$  = total concentration of electrolytes and  $e$  = a variable factor depending on the concentration of  $\text{I}'$  and  $\text{OH}'$ .

Under special experimental conditions (when  $\text{OH}'/\text{I}' < 10$ ), the member  $e(E)$  of the equation becomes negligibly small, and the simpler formula

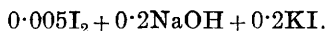
$$-\frac{d[\text{IOH}]}{dt} = \frac{[\text{I}']}{[\text{OH}']} \cdot [\text{IOH}]^2,$$

expresses the rate of change.

In the experiments which follow, the initial concentration of iodine ions and hydroxyl ions was twenty times greater than that of the hypiodous acid, so that, despite the fact that hydroxyl ions

are used up and iodine ions formed during the reaction, the ratio  $[I]/[OH']$  remained practically constant.

The method of procedure was as follows: Two hundred c.c. of a  $N/50$ -iodine solution (in potassium iodide) were rapidly mixed with an equal volume of  $0.4N$ -sodium hydroxide solution, so that the concentration of the mixture was (in mols. per litre)



Successive quantities of this solution (20 c.c. each) were removed after the specified time; excess of phenol (3 c.c. of a 5 per cent. solution) was added to combine with the "active iodine," the mixture acidified with acetic acid, and the iodine thus liberated (from the iodate and iodide) was titrated with  $N/10$ -thiosulphate.

Two explanatory remarks are here needed:

(i) The reaction between phenol and "active iodine" in the presence of excess of the former is very rapid. This may be seen by simply adding phenol to a freshly prepared solution of iodine in alkali; the yellowish-green colour of the latter immediately disappears. The speed of the reaction was also proved by allowing phenol to act for various lengths of time (from 0.5 to 20 minutes) on solutions of equal "active iodine" content; the amount of iodine used up was the same, irrespective of the time allowed before acidifying.

(ii) It is essential that acetic acid or some other weak acid is employed for acidifying the mixture. If a strong mineral acid is used, then iodine is liberated from the iodate and iodide present before the whole of the hydroxyl ions have been neutralised; hypoiodous acid is consequently formed and acts on the phenol, causing an apparent increase in the amount of "active iodine." This phenomenon was first described by Kekulé, and its effect on the estimation of hypoiodous acid was later eliminated by saturating the solution with carbon dioxide before acidifying (Batey, *Analyst*, 1911, **38**, 132). If acetic acid is used, the treatment with carbon dioxide becomes unnecessary; this was proved by means of blank experiments on a mixture of sodium iodate and iodide in the presence of phenol.

In the table below, the third column gives the amount of "active iodine" in terms of c.c. of  $N/100$ -iodine solution;  $k_1$ ,  $k_2$ , and  $k_3$  are constants corresponding with reactions of the first, second, and third order respectively, that is,

$$k_1 = \frac{1}{t_2 - t_1} \cdot \log \frac{c_1}{c_2}; \quad k_2 = \frac{c_1 - c_2}{(t_2 - t_1)c_1c_2}; \quad k_3 = \frac{1}{2(t_2 - t_1)} \cdot \frac{1}{c_2^2} - \frac{1}{c_1^2}$$

Table showing the Velocity of Decomposition of the "Active Iodine Compound" in Alkaline Solution.

Time.	C.c. of N/100-thiosulphate required.	c="active iodine."	$10^3k_1$	$10^3k_2$	$10^4k_3$
0	0	19.5	—	—	—
1 min.	2.0	17.5	4.20	5.8	3.15
2 "	3.7	15.8	4.43	6.14	3.65
3 "	5.0	14.5	3.73	5.67	3.8
5 "	7.4	12.1	4.43	6.84	5.35
8 "	10.1	9.4	3.66	7.90	7.5
10 "	11.3	8.2	2.96	7.78	8.9
14 "	13.0	6.5	2.52	7.96	11.0
18 "	14.1	5.4	2.01	7.83	13.4
25 "	15.2	4.3	1.41	6.80	14.1
30 "	15.8	3.7	1.30	7.53	19.0
40 "	16.5	3.0	0.91	6.31	19.1
60 "	17.3	2.2	0.67	6.01	23.8
90 "	18.7	1.5	0.53	7.07	39.7
			Mean $10^3k_2=$	6.90	

The temperature of the solution remained approximately constant ( $10.3-10.7^\circ$ ) throughout the experiment.

It will be seen from the foregoing table that whilst  $k_1$  and  $k_3$  vary considerably,  $k_2$  remains satisfactorily constant over a wide range of concentration, thus proving the decomposition of the "active substance" to be a bimolecular reaction, just as is the case with hypoiodous acid; the occurrence of a maximum in the value of the constant is also suggestive of the decomposition of hypoiodous acid, and, finally,  $k_2$  as above determined can be shown, after applying the necessary corrections, to have the same value as the constant obtained by other authors for the rate of decomposition of hypoiodous acid.

Thus, Skrabal (*Monatsh.*, 1911, **32**, 171), working at  $20.2^\circ$  with alkaline iodine-potassium iodide solutions of the same concentration as employed above, obtained for the constant of the rate of decomposition of hypoiodous acid ( $k'_2$ ) the mean value  $2.63 \times 10^3$ . Two corrections are needed to make the constant found for the "active substance" comparable with that obtained by Skrabal, namely, (i) a correction for the difference in the amount of solution analysed, and (ii) a correction for the difference in the temperature.

(i) From the equation

$$k_2 = \frac{c_1 - c_2}{(t_2 - t_1)c_1c_2}$$

it is easily seen that  $k_2$  is inversely proportional to the quantity of solution analysed at a time. As this was 89.49 c.c. in Skrabal's

Q Q\*

case, whilst the present author used only 19.5 c.c., the first correcting factor for the constant will be  $\frac{19.5}{89.49}$ .

(ii) The temperature-coefficient of the constant was found by Skrabal to be 2.1 (per 10°). Now,  $k_2$  was determined at 10.5° and  $k'_2$  at 20.2°, a difference of 9.7°, hence the second correcting factor for the constant is  $\frac{2.1 \times 9.7}{10}$ .

Applying these two corrections, we obtain

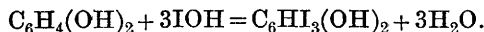
$$\begin{aligned} k_{2(\text{corrected})} &= 6.90 \times \frac{19.50}{89.49} \times 2.1 \times \frac{9.7}{10} \times 10^3 \\ &= 3.06 \times 10^3. \end{aligned}$$

The agreement between the two constants is good, bearing in mind that the "mean value" (that is, the arithmetical mean) of the constants made use of in the above calculations is only a rough approximation to their true value.

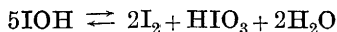
Having thus proved that the iodine which combines with the phenol in alkaline solutions is present as hypoiodous acid, and having shown that there is strong evidence for assuming that the same compound is the active substance in iodine monochloride solutions, other methods used in the preparation of iodophenols may be examined. A close scrutiny will show that in most, if not all, the processes by which these compounds are obtained, hypoiodous acid is an intermediate product.

(1) "*Iodine and Mercuric Oxide*" *Method*.—The formation of hypoiodous acid from these two substances in the presence of water is a matter of common knowledge (Köne, *Ann. Phys. Chem.*, 1845, [ii], **66**, 300; Taylor, *Chem. News*, 1897, **76**, 22).

(2) "*Hypochlorous Acid and Potassium Iodide*" *Method*.—The interaction between hypochlorous acid and potassium iodide, resulting in the formation of hypoiodous acid, has been studied by Klimenko (*Zeitsch. physikal. Chem.*, 1897, **23**, 552, 558) and confirmed by Bray (*ibid.*, 1906, **54**, 563). We may therefore substitute for Dagener's complicated formula the following:



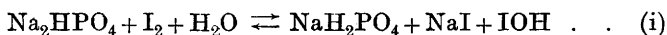
(3) "*Iodine and Iodic Acid*" *Method*.—The reaction



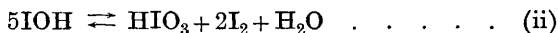
is a reversible one, and the continuous removal of hypoiodous acid by the phenol causes it to proceed towards the left.

(4) "*Iodine and Sodium Phosphate*" *Method*.—Iodine dissolves

in a solution of disodium hydrogen phosphate, the simplest way of formulating the reaction being



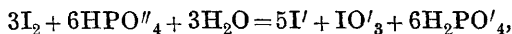
The hypoiodous acid thus formed decomposes further,



so that, finally, hypoiodous acid is in equilibrium on the one hand with iodine and sodium phosphate, and on the other with iodine and iodic acid. The following experiment confirms this view.

A solution of iodine and disodium hydrogen phosphate in water was prepared and allowed to remain for a fortnight, so that equilibrium was attained; the solution was still of a red colour, showing that free iodine (or, more correctly,  $\text{I}'_3$ ) was present. To one portion of this solution phenol was added, which combined with the "active iodine" and decolorised the solution; the mixture was then immediately acidified, and the iodine liberated from the iodide and iodate present was titrated with  $N/100$ -thiosulphate. Another portion of the same solution, after adding phenol, was allowed to remain for twenty-four hours before acidifying and titrating as above. The amount of iodine used by the phenol was in both cases the same. This is exactly what is to be expected from the equations put forward above; the addition of phenol removes the hypoiodous acid present, thus disturbing both equilibria, but, since reaction (i) has a far greater velocity than reaction (ii), practically the whole of the free iodine combines with the sodium phosphate, leaving the iodate ion unaffected.

The reaction between iodine and disodium hydrogen phosphate is formulated in a rather different way by Skrabal and Gruber (*Monatsh.*, 1916, **37**, 543), who give the equation

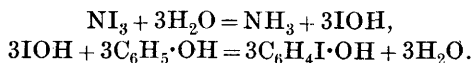


but it is obvious from the result of the above experiment that this equation does not represent the actual state of affairs; for, if it did, since the reaction is a balanced one, the removal of the free iodine by the phenol (supposing this to be possible without the intermediate formation of hypoiodous acid) would cause the reaction to proceed towards the left until no more iodate ion remained in solution. This, however, is not the case, for, as we have seen, the iodate remains unaffected by the removal of the "active iodine."

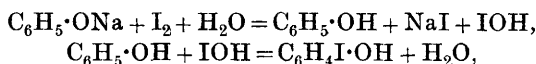
(5) *Nitrogen Iodide Method*.—Selivanov (*loc. cit.*) proved that this compound yielded hypoiodous acid on hydrolysis, and sug-



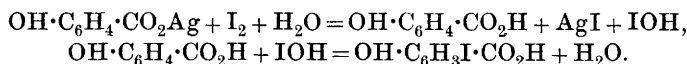
gested that the iodination is due to the last-mentioned substance. He gave the following equations:



(6) Passing on to the "dry" reactions of Birnbaum and Schall, we see that even here the formation of hypiodous acid is not excluded. A very small quantity of moisture would be sufficient, since the water used up in the first part of the reaction is regenerated at the end. Thus in Schall's method



and in Birnbaum's



This new way of formulating the reactions obviates the necessity of assuming any intramolecular change. It should be further noted that Kekulé's criticism of Lautemann's method applies also to the last-mentioned reaction; in all probability, the formation of iodo-salicylic acid does not take place on heating iodine with silver salicylate, but during the subsequent treatment. In any case, the preliminary heating is quite superfluous; if to a suspension of silver salicylate in alcohol is added a solution of iodine (in alcohol), the colour of the latter disappears quickly at first, the reaction becoming slower as the ratio between silver salicylate and iodine added approaches unity. After removing excess of iodine by shaking with mercury and filtering, there is obtained, on evaporating the alcohol, a mixture of iodosalicylic acids.

The theory that the formation of iodophenols is due to the action of hypiodous acid is thus seen to explain the preparation of those compounds by many different methods. The real test for a useful theory, however, is its capability of predicting new phenomena and suggesting fresh lines of research. It will be seen that the above theory stands this test.

(i) For instance, it is evident that on the above theory any method of obtaining hypiodous acid could also be used for the preparation of iodophenols; thus, it can be predicted that iodophenols will be formed by the action of silver carbonate or sulphate and iodine on phenols.

(ii) The converse proposition, that any method of preparing iodophenols may be made to yield hypiodous acid, is probably

also true. This has been shown to be the case in the iodine and sodium phosphate method of Richard.

(iii) A further successful line of research suggested by the present theory, namely, the estimation of hypoiodous acid, will be dealt with in a later paper.

So far, the hypoiodous theory of iodination has been applied to phenolic compounds only, but many of the methods for the preparation of iodophenols, such as Kekulé's (iodine and iodic acid) and Weselsky's (iodine and mercuric oxide), have been successfully used in introducing iodine atoms into other organic compounds. Again, the formation of iodoform from alcohol and from acetone has been proved to be due to hypoiodous acid (Daventer and van't Hoff, *Rec. trav. chim.*, 1888, **1**, 35; Pieroni, *Gazzetta*, 1912, **42**, i, 534). It will be seen from this that hypoiodous acid as an iodinating agent has a much wider range than that outlined above. Its formation might possibly explain the action of concentrated sulphuric and nitric acids, ferric chloride, etc., as iodine carriers (Neumann, *Annalen*, 1887, **241**, 84; Meyer and Schwalb, *ibid.*, 1885, **231**, 195; Datta and Chatterjee, *J. Amer. Chem. Soc.*, 1917, **39**, 441).

Throughout this paper, the term "hypoiodous acid" has been employed to denote the compound IOH, although, so far as its properties are concerned, "iodine hydroxide" would be a more suitable term. The latter name has been avoided, as it suggests the existence of positive iodine ions, which many chemists regard with suspicion. The work of Walden (*Zeitsch. physikal. Chem.*, 1903, **43**, 385) on the conductivity of iodine in inorganic solvents, as well as other considerations (Abegg and Auerbach, "Handbuch d. anorg. Chem.," IV, (ii), 455), lend, nevertheless, considerable support to the view that iodine cations do exist. If this be really the case, then the previous statement may be modified to: the formation of iodophenols, and that of hypoiodous acid, is brought about by the presence of positive iodine ions.

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