Electrolytic Reduction of Isatin and Its Derivatives. I. Reduction of Isatin.

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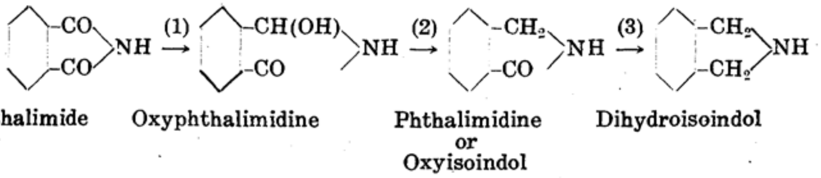
In the previous communication(1) it was reported that the electrolytic reduction of phthalimide and its derivatives was found to proceed in the manner represented in the following scheme:



When reduced in a sulphuric acid solution with copper cathode one of the two carbonyls is reduced so as to give oxyphthalimidine, while with lead cathode the reduction goes further on and gives phthalimidine. For the reduction of another carbonyl the cathode with much stronger reducing power, such as zinc amalgam must be used. By using zinc amalgam cathode, powerful reducing action of which has previously been affirmed by Prof. M. Matsui and his collaborators, and by carefully controlling current density and temperature even a complete reduction may, without much difficulty, be achieved. Dihydroisoindol, which could not be obtained by purely chemical reduction of phthalimide, may thus be prepared. In the present experiment the author tried to make investigation on isatin, isomer of phthalimide.

Now, the author deemed it to be very interesting to see how isatin, an isomer of phthalimide, behaves toward the similar reduction process. In phthalimide both carbonyls are situated just in symmetrical position, each combining with carbon and nitrogen in similar manner. But in isatin, though one carbonyl is in combination with carbon and nitrogen as in phthalimide, another carbonyl has rather ketonic structure, combining only with carbon. The main object of this experiment was to ascertain how this difference of structure between phthalimide and isatin influences on their behaviours toward electrolytic reduction.

In purely chemical reduction, hitherto conducted by various authors, isatin was reduced to dioxyindol and further to oxyindol. But in no case the reduction of oxyindol to dihydroindol seems to have as yet succeeded. Spaeth and Breusch(2) reported that they obtained dihydroindol by reducing isatin with lead electrode in 50% sulphuric acid. But even in this case the yield of dihydroindol was not more than 4%.

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(1) *This Bulletin*, **5** (1930), 184; **7** (1932), 155.

(2) *Monatsch.*, **50** (1928), 349.

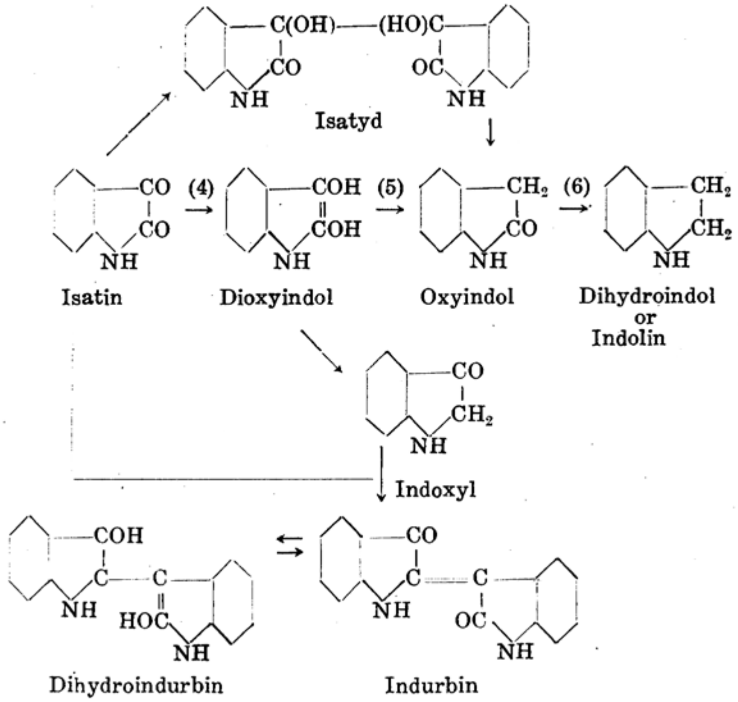
Now taking into consideration what causes had hitherto made the reduction of oxyindol to dihydroindol impossible or at least very unsatisfactory, the author tried to find favourable conditions by which both carbonyls in isatin could be reduced smoothly to $>CH_2$ group.

According to the author's experiment, weak alkaline solution is more suitable than acid solution for reducing isatin to dioxyindol, and especially the use of sodium bicarbonate seems to render very smooth and constant reduction. As such conditions may be deemed to act favourable in the case of electrolytic reduction too, the author tried to reduce isatin, suspended in the mixture of saturated sodium bicarbonate solution and alcohol, with lead cathode, constantly neutralizing the alkali, produced in the course of electrolysis with carbon dioxide. *p*H value of the electrolyte remained almost constant at 8.8–9.0. The yield of dioxyindol was satisfactory.

Next, dioxyindol was found to be easily reduced to oxyindol with sodium amalgam. In this case the *p*H value of solution gives considerable influence on the progress of reduction; if the solution is acidic, no reduction takes place and even if it is alkaline, *p*H value must be maintained between 7.2 and 7.4. In order to keep electrolyte in this condition, the use of sodium sulphate is most preferable and the alkali produced in the course of electrolysis should be neutralized with sulphuric acid, testing the *p*H value from time to time by means of test paper. In the electrolysis thus carried out with mercury cathode, oxyindol was produced with a pretty good yield. As it is rather impracticable to keep *p*H at a constant value by neutralizing alkali from time to time through a long course of electrolysis, an automatic neutralization method was sought, and the use of solid carbon dioxide was at last found to give the best results. It also serves at the same time as a cooling agent. When dioxyindol was reduced under the same condition as with isatin, a great deal of isatyd is produced together with oxyindol, and gradually changes into oxindol through electrolysis. Isatyd may thus be considered as an intermediate product which is produced when isatin is reduced to oxyindol. As dihydroindol is a substance of greater negativity, an acid solution may be regarded as suitable electrolyte for its production. From this consideration 50% sulphuric solution was used and under nearly the same conditions as in (2) electrolysis was conducted with greater current density. The results were satisfactory, producing the complete reduction product with 20% yield. As is apparent from what mentioned above, each intermediate substance, which is produced in the electrolysis of isatin, differently behaves towards electrolytic reduction and especially differs in the *p*H value, suitable for its reduction. This clearly explains the reason for the failure of the predecessors who attempted to obtain the final reduction product of isatin by using only one and same electrolyte.

When isatin or dioxyindol is reduced under the condition of (5), at the temperature above 20°, the electrolyte assumes red colour on the surface. This coloured substance may be extracted with ether, but its quantity is comparatively small, and is mixed with oxyindol so as to make its isolation difficult. It is, however, doubtlessly indurbin. Indoxyl, being extremely unsuitable, changes into indurbin in the moment it is produced by combining with isatin.

It was found out that indoxyl, though small in quantity, is produced in company with oxyindol, both of which are the immediate reduction products of dioxyindol. The synopsis of the process of the reduction is formulated as follows:



Experimental.

(1) **Reduction of Isatin to Dioxyindol.** For this purpose electrolysis was carried out under such conditions as follows:

Cathode: lead plate 100 sq. cm.; Cathodic solution: 60 c.c. of a saturated solution of sodium bicarbonate and 40 c.c. of alcohol, in which 5 g. of isatin were suspended; Anode: lead plate; Anodic solution: a saturated solution of sodium bicarbonate; Current density: 2.5 amp. per 100 sq. cm.; Time of electrolysis: 2.5 hours; Current quantity: 6.8 Faraday per mol.; Temperature: 16°–20°.

Here the *p*H value of the catholyte was kept constantly between 9–10 by passing CO_2 gas into the catholyte for neutralization. As the electrolysis advanced, isatin turned brown by degree, and in an hour and a half its colour disappeared almost completely. After 2.5 hours' electrolysis the deposit was filtered, and re-crystalized from acetone, whereupon yellow-brown needle-like crystals, melting at 168°, were obtained. This was dioxyindol. The yield (4.6 g.) was calculated to be 85%. When the filtrate was made acidic and extracted with ether, a bit of red needle-like crystals of isatin were isolated from the ether extract.

When copper, silver, or nickel is substituted for lead as cathode, electrolysis takes much longer time and the yield lowers slightly, but dioxyindol can be obtained easily. For instance, when copper or silver was used as cathode with the other conditions unchanged, electrolysis took 2.5 hours until the red colour of isatin had completely disappeared and the yield of dioxyindol was 75% and 41.5% respectively. Higher temperature of the electrolyte, lowers the yield. Perhaps it brings forth evolution of carbon dioxide and makes it difficult to keep the *p*H of the catholyte at favourable value.

(2) **Reduction of Isatin to Oxyindol.** In the reduction of isatin to oxyindol the use of electrode, which has a strong reducing power or of high current density, is by no means helpful, if reduction is conducted with sodium bicarbonate solution. When sulphuric acid solution is employed as electrolyte, the results are still worse, giving no appreciable progress of reduction. Accordingly electrolysis was performed with neutral Na_2SO_4 solution using mercury as cathode and carefully neutralizing the alkali, thereby produced. The electrolysis was conducted as follows:

Cathode: mercury 1 cm. dip and 16 sq. cm. of surface area; Cathodic solution: mixture of 90 c.c. of 10% sodium sulphate solution and 10 c.c. of alcohol, in which 5 g. of isatin were suspended; Anode: lead plate; Anodic solution: 10% solution of sodium sulphate; Current density: 15.6 amp. per 100 sq. cm.; Time of electrolysis: 6 hours; Current quantity: 16.3 Faraday per mol.; Temperature: 17°–20°.

The electrolysis was carried out by cooling the electrolytic bath from outside with ice and stirring it vigorously. In order to neutralize alkali in the course of electrolysis, about 10% dilute sulphuric acid was added drop by drop from the capillary tube prepared at one end of a separating funnel and the *p*H value was kept between 7.2 and 7.4 testing it constantly by means of brom-thymol-blue paper. In two hours the catholyte turned from orange-yellow gradually to yellow-brown. The amount of the sulphuric acid, required for neutralization, was small at first in spite of the constant current density, but gradually increased till at last it became almost constant.

The electrolyte, taken out after electrolysis, contained yellow-brown deposit, which was filtered (1.0 g.) and re-crystalized from acetone. This melted at 170° and was confirmed to be dioxyindol, the yield of which amounts to 19.7%. The ether extract of the filtrate coloured reddish. From this extract 0.4 g. of red crystals, melting at 120°, was obtained. This was examined on the microscope and found to be a mixture of colourless and red crystals. This was put in a crystal dish covered with the bottom of a flask filled with water and was slowly heated on a sand-bath, when colourless plate first, and then a small amount of red needle crystals were obtained. The former was oxyindol, melting at 126°, and the latter was doubtlessly indurbin, inferring from the fact that it was hard to melt but readily soluble in alcohol or ether, and when reduced with sodium amalgam, it became colourless. When shaken with ether, it gradually dissolves in the ether, thereby resuming red colour. Now the filtrate was slightly acidic with sulphuric acid, extracted with ether, when 1.0 g. of oxyindol was procured. The amount of total oxyindol was calculated to correspond to 31%.

Next, the remaining slightly acidic electrolyte was evaporated to dryness on the water-bath, and the residue was extracted with acetone, when 1.0 g. of yellow crystals was obtained after the evaporation of the solvent. This substance, melting at 243°, was evidently isatyd obtained through the reduction of isatin by ammonia sulphate. This was reduced to oxindol electrolytically under the same condition as in the case of isatin.

As the composition of electrolyte greatly influences the manner of reduction, a series of experiments were carried out by varying the composition of electrolyte, the results of which are summarized as follows:

Composition of Cathodic Solution (c.c.)		Reduction Product (%)		
10% soln. of Na_2SO_4	alcohol	dioxyindol	oxyindol	isatyd
90	10	19.7	31.0	20.1
80	20	59.9	11.1	15.3
70	30	64.9	4.4	10.0
60	40	67.5	3.0	5.8
50	50	69.1	2.6	4.5

As this experiment is rather time-wasting, another convenient method was adopted, in which solidified carbon dioxide (ordinary dry ice) was thrown into the catholyte, thereby performing neutralization and cooling at the same time. This brought in almost as good results as the former.

(3) **Reduction of dioxyindol to oxyindol.** 5 g. of dioxyindol was electrolyzed under the same condition as in the reduction of isatin to oxyindol. 1.7 g. (38%) of oxyindol were obtained after 1.5 hours' electrolysis.

(4) **Reduction of oxyindol to dihydroindol.** In order to reduce oxyindol further to dihydroindol, zinc amalgam was used as cathode and sulphuric acid was employed as electrolyte. Electrolysis was carried out under the following conditions:

Cathode: zinc amalgam 1.58 sq. cm.; Cathodic solution: mixture of 50 c.c. of 50% sulphuric acid and 50 c.c. of alcohol, in which 2 g. of oxyindol were dissolved; Anode: lead plate; Anodic solution: 50% sulphuric acid; Current density: 68.8 amp. per 100 sq. cm.; Temperature: 23°; Time of electrolysis: 6.0 hours; Current quantity; 327 F. per mol.

Electrolysis was conducted by cooling the electrolyte chamber from outside by putting it in a water-bath full of ice water, and from inside by passing cold water through a spiral lead tube inserted to the catholyte, thereby preventing the rise of temperature. The catholyte was always kept vigorously stirring. In three hours oxyindol had completely dissolved. The electrolyte was taken out after electrolysis, and when it was made alkaline with caustic soda, ammonia-like smell came out; thereupon it was subjected to steam distillation, collecting the distillate in dilute hydrochloric acid solution as long as it continued to react alkaline. The hydrochloric acid solution was then evaporated to dryness, when 0.52 g. of white substance, melting at 218°, was left as residue. On the other hand, a part of the electrolyte was made alkaline with a caustic soda solution and its ether extract was treated with picric acid, when needle-like colourless crystals, melting at 169°, were obtained. These two products are evidently the chloride, and the picric, of dihydroindol respectively, and the yield was found to be 20%.

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