# THE ELECTROLYTIC PREPARATION OF THE ISOINDOLINES

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The isoindolines have usually been prepared by laborious methods<sup>1,2,8,4,5</sup> which give rather poor yields.

The reduction of the phthalimide or the phthalimidine suggests itself as a likely possibility. However, attempts to carry out this reduction by the usual chemical methods have thus far been unsuccessful. Graebe<sup>6</sup> using tin and hydrochloric acid was able to reduce the imide only to the imidine, the second carbonyl group being unattacked.

Hope and Lankshear<sup>7</sup> in a preliminary report state that the preparation of isoindoline and methylisoindoline in high yields is possible by the electrolytic reduction of the corresponding phthalimidines, but nothing further has been published by them relating to this subject. Späth and Breusch<sup>8</sup> describe the successful preparation of isoindoline by the electrolytic reduction of phthalimide.

Sakurai<sup>9</sup> prepared a hydroxy compound and phthalimidine from phthalimide in an alcoholic sulfuric acid solution at lead and copper cathodes, but not the further reduction product, the isoindoline.

The work of these investigators indicated the desirability of carrying on a further investigation of the electrolytic preparation of the isoindolines, and it was with this object in view that the present work was undertaken.

#### Experimental

### PREPARATION OF METHYLISOINDOLINE

1. Reduction of Methylphthalimidine



The cathode materials used were mercury, lead, tin, and cadmium. A layer of freshly redistilled mercury of about 2 mm. thickness at the bottom of the vessel served as the mercury cathode. Connection was made with the

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<sup>&</sup>lt;sup>1</sup> Gabriel and Neumann: Ber. 26, 525 (1893).

<sup>&</sup>lt;sup>2</sup> Gabriel and Pinkus: Ber., 26, 2210 (1893).

<sup>&</sup>lt;sup>3</sup> Scholtz: Ber., 31, 414, 627, 1154, 1700 (1898).

<sup>&</sup>lt;sup>4</sup> Frankel: Ber., 33, 2808 (1900).

<sup>&</sup>lt;sup>5</sup> Braun and Kohler: Ber., 51, 100 (1918).

<sup>6</sup> Graebe: Ann., 247, 302 (1888).

<sup>&</sup>lt;sup>7</sup> Hope and Lankshear: Proc. Chem. Soc., 29, 224 (1913).

<sup>&</sup>lt;sup>8</sup> Späth and Breusch: Monatshefte, 50, 349 (1928).

<sup>&</sup>lt;sup>9</sup> Sakurai: Bull. Chem. Soc. Japan, 5, 184 (1930).

mercury cathode by means of a stout platinum wire sealed into a piece of glass tubing which was also filled with mercury. The rest of the cathodes were sheets of the pure metal  $4.5 \times 5$  cm. bent into a semi-circular shape of about 6 cm. diameter and 4.5 cm. height. The lead cathode was cut from commercial sheet lead and prepared according to the directions of Tafel.<sup>10</sup> A platinum spiral anode was inclosed in a small porous clay cup and placed at the center of the semi-circular cathode. In the case of the mercury cathode the anode was placed about 2 cm. directly above the center of the mercury layer. For the catholyte 5 grams of methylphthalimidine was dissolved in a solution of 6 cc. of concentrated sulfuric acid in 102 cc. of water. During electrolysis the catholyte was vigorously stirred by means of an air driven stirrer. The anolyte contained 2 cc. of concentrated sulfuric acid in 20 cc. of water. The accompanying table indicates the other experimental conditions such as temperature and duration of electrolysis, as they were varied in the different experiments.

At the end of the electrolysis the catholyte was made alkaline with caustic soda and steam distilled until no more oily drops came over or until about 100 cc. of the distillate had been collected. A crystalline hydrate of methyliso-indoline separated out in the distillate. This was filtered off and carefully dried in a dessicator. The hydrate melted at  $45-45.5^{\circ}$  which agrees well with the value  $45-46^{\circ}$  given by Braun.<sup>11</sup> The hydrate was readily dehydrated in a vacuum desiccator over sulfuric acid to give the free base which was a colorless oil having a strong basic odor. Upon standing in a closed vessel the base gradually assumed a darker color.

To further identify the compound the methiodide was prepared, which was identical with that prepared by Frankel<sup>12</sup> from isoindoline. The methiodide melted at 245-246°, turning to a dark color. This agrees with the value 244-245°, given by Frankel.

2. Reduction of Methyl Phtalimide



The procedure followed was similar to that for the imidine except that in this instance a suspension of the imide was used; the imide was quite insoluble, however, as the reduction progressed it gradually went into solution until at the end of about 7 ampere hours it had completely dissolved.

### PREPARATION OF ISOINDOLINE

1. Reduction of Phthalimidine



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Not all of the 5 grams of the imidine used in the catholyte was dissolved and a small portion was left in suspension. This readily passed into solution early in the electrolysis. At the end of the electrolysis the catholyte was made strongly alkaline with solid sodium hydroxide and was steam distilled, the distillate being run into hydrochloric acid solution. Upon evaporation of the distillate the hydrogen chloride salt of isoindoline remained. For identification the nitroso derivative was prepared which melted at  $96.5-97.5^{\circ}$  as compared to the recorded<sup>13</sup> value of  $96-97^{\circ}$ .

2. Reduction of Phthalimide



A suspension of 6 grams of phthalimide purified by sublimation was used in the catholyte. At the beginning of the electrolysis the catholyte was colored a greenish yellow, but at the completion was colorless.

## PREPARATION OF N-AMIDOISOINDOLINE

Reduction of Nitrosoisoindoline

$$\bigcirc CH_2 \\ CH_2 \\ N-NO + _4H \longrightarrow \bigcirc CH_2 \\ CH_2 \\ N-NH_2 + H_2O$$

About 5 grams of nitrosoisoindoline recrystallized from dilute alcohol was used in the catholyte. After the electrolysis an ether extraction was made on the catholyte to remove any possible nitrosoisoindoline that had escaped reduction. Then the catholyte was made strongly alkaline with solid sodium hydroxide and steam distilled into hydrochloric acid. This solution was evaporated almost to dryness when the hydrazine hydrochloride separated out. The hydrochloride was purified by recrystallizing from absolute alcohol. The yield of hydrazine was determined by oxidizing an aliquot portion of the catholyte with hot Fehling's solution and measuring the volume of nitrogen evolved. For identification the benzal hydrazone was prepared which gave a melting point of  $127-129^{\circ}$  which agrees with that given by Frankel.<sup>14</sup> With picric acid the hydrazine gives a picrate which melts at  $96-98^{\circ}$ .

#### **Discussion of Results**

It is remarkable that while no methylisoindoline was obtained from methylphthalimidine at a tin cathode, a small yield was obtained from methylphthalimide. This is apparently analogous to the reduction of cam-

<sup>&</sup>lt;sup>13</sup> Gabriel and Neumann: Loc. cit.

<sup>14</sup> Frankel: Ber., 33, 2812 (1900).

phoric-acid imide and camphidone reported by Tafel and Eckstein.<sup>15</sup> They obtained the  $\alpha$  and  $\beta$  camphidones and camphidine as reduction products of camphoric acid imide, but were unable to reduce camphidone itself to camphidine.

	Tabulation of Results						
Cathode	Time Hrs.	Temp.	Amp.	Volts	${ m Current}\ { m Density}\ { m amp/dm^2}$	Yield E Material	fficiency Current
		Reductior	ı of Me	thylphth	alimidine	%	%
$_{ m Hg}$	6	ıı°	I	6	2.97	38.0	23.0
$^{\mathrm{Pb}}$	3	I2°	3	5	4.66	57.I	23.I
$\mathbf{Pb}$	5	46 <b>-</b> 49°	3	5 · 5	4.45	68.6	16.7
$\operatorname{Sn}$	5.33	51°	3	5.2	4 · 45	00.0	00.0
$\mathbf{Cd}$	5.33	53°	3	5	4 · 45	4 · 4	2.0
		Reductio	on of N	Iethylph	thalimide		
$\operatorname{Sn}$	10.67	49-51°	3	5.6	4.45	$7 \cdot 7$	I.9
$_{\mathrm{Hg}}$	32.00	41°	I	5	2.97	31.1	7.8
$\operatorname{Cd}$	10.67	46°	3	5.4	4.45	57.I	I4·3
$\mathbf{Pb}$	10.67	50°	3	5	4 · 4 5	57.7	14.4
		Redu	ction of	f Phthali	midine		
$\operatorname{Cd}$	5.33	49°	3	4.5-5	4.45	71.6	.18.0
$\mathbf{Pb}$	5.67	45°	3	5-6.5	4.45	64.3	15.3
$\mathbf{Sn}$	8.67	52°	3	5 · 5	4.45	00.0	00.0
		Redu	action (	of Phthal	imide		
$\mathbf{Pb}$	10.67	50°	3	5.5-6	$4 \cdot 45$	73.2	16.7
		Reductio	on of N	-nitrosois	soindoline		
$^{\rm Pb}$	3.75	43°	3	5-5.2	4.45	72.0	21.1
Cd	3.75	44°	3	5-5.3	4 · 45	91.7	29.5

In accounting for their results they assume the camphidones to be extremely resistant towards further reduction and not to be intermediate products in the formation of camphidine. Furthermore they believe either that camphidine is formed only when both carbonyl groups of the acid imide are by accident simultaneously attacked by the reducing agent, or, that a carbinol-like intermediate product in which the second carbonyl group is electrolytically attackable, is already formed during the transformation of camphoric acid imide to camphidone.

The extension of this explanation to the analogous reductions of methylphthalimidine and methylphthalimide with tin cathodes leads one to conclude that no methylisoindoline was obtained from methylphthalimidine for the following reasons:

<sup>&</sup>lt;sup>15</sup> Tafel and Eckstein: Ber., 34, 3274 (1901).

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(1) Methylphthalimidine is incapable of undergoing further reduction;

(2) In view of this great resistance to reducing action it is unlikely that the imidine would be an intermediate product in the electrolytic reduction of the imide to the isoindoline. This is given some support by the fact that no imidine was isolated when a reduction of the imide was carried out for the theoretical length of time;

(3) Since the isoindoline is assumed to be formed only by the accidental simultaneous attack of two carbonyl groups by the reducing agent, it is obviously impossible for this to occur with the imidine which contains but one carbonyl group;

(4) Likewise the possibility of the formation of a carbinol-like intermediate product is excluded since this also is assumed to be formed from the imide.

The successful reduction of methylphthalimide with tin cathodes would therefore be explained on the basis of either the accidental simultaneous attack of both of its carbonyl groups or the formation of a readily reducible carbinol-like intermediate product.

However plausible this explanation may be it loses most of its force when considered in the light of the results obtained with mercury, lead and cadmium cathodes. Thus for example, good yields of the corresponding isoindolines were obtained from methylphthalimidine at mercury and lead cathodes, and from phthalimidine at cadmium and lead cathodes. Evidently the imidines are not "resistant enough to further reduction" to avoid being reduced when mercury, lead and cadmium cathodes are substituted for tin.

Reference to the data for the reduction of methylphthalimide shows that the yields of isoindoline were from four to seven times greater when lead, cadmium or mercury cathodes were substituted for the tin cathode. Therefore, according to the suggested explanation of Tafel and Eckstein it would appear either, that the chances for the simultaneous attack of the two carbonyl groups of the imide are very much less at tin than at lead, cadmium or mercury cathodes, or that the hypothetical carbinol-like intermediate product is less readily formed at a tin cathode than at the lead, cadmium or mercury cathodes. Since direct experimental evidence is lacking in support of either possibility and especially in view of the fact that the imidines were reduced a more satisfactory explanation is needed.

In the absence of catalytic effects, a stronger reducing action is obtained at a cathode having a high hydrogen overvoltage than at one having a low hydrogen over-voltage. The order of decreasing hydrogen over-voltages in  $N.H_2SO_4$  for the various cathodes used in this work is given by Caspari<sup>16</sup> as mercury, lead, tin and cadmium. From this one would expect a weaker reducing action with tin than with lead or mercury cathodes. The differences in reducing energies as expressed by the hydrogen over-voltages of the metals, would reasonably account, on the one hand, for the failure to reduce the imidine and for the low yields obtained from the imide, when tin cathodes

<sup>&</sup>lt;sup>16</sup> Caspari: Z. physik. Chem., 30, 89 (1899).

were used; and on the other, for the successful reduction of the imidine and the higher yields from the imide when mercury, lead and cadmium cathodes were used. In the case of methylphthalimide the fact that the yields obtained at mercury having the highest over-voltage are lower than those obtained at cadmium having the lowest over-voltage may be the result of the catalytic activity of the metals.

Similar variations in results predicted on the basis of over-voltages have been frequently observed. Löb and Moore<sup>17</sup> found that the reduction of nitrobenzene to aniline in a caustic soda solution proceeded better at a copper cathode than at metals of higher over-voltage.

Fichter and Stocker<sup>18</sup> studying the reduction of phenol to cyclohexanol were able to effect the reduction at platinum and unable to at a lead cathode.

Bancroft and George<sup>19</sup> have more recently investigated the electrolytic reduction of phenol and the catalytic hydrogenation of phenol vapor in the presence of platinum and nickel catalysts. They state: "The experiments of Fichter have been confirmed, that phenol is hydrogenated at a platinum cathode and practically not at all at a lead cathode, in spite of the high overvoltage of the latter. The effect of platinum in activating phenol is evidently more important than the reducing power of the hydrogen. . . . Platinum has a specific effect on the hydrogenation of phenol both when used as a cathode and as a catalyst."

In view of the influence of the over-voltage and catalytic activity of the metal cathodes in determining the course of a reaction, it seems that the results obtained in this work on the preparation of isoindolines can be more satisfactorily and reasonably accounted for on the basis of the hydrogen over-voltages and probable differences in the selective activation of the depolarizer by the various cathodes, than by the explanation offered by Tafel and Eckstein in connection with the reduction of camphoric acid imide.

If as suggested in the work of Bancroft and George<sup>20</sup> there is a probability that the oriented adsorption of the depolarizer is different at different metals, it is also probable that a relation may be found to exist between the lattice constants of the cathodes and the polar properties of the depolarizer. This point together with the factors such as, nature of surface, current density, duration of polarization, and previous treatment, which influence the overvoltage of the metals is being considered in connection with other electrolytic reductions now in progress in this laboratory.

#### Summary

1. Isoindolines have been prepared by the electrolytic reduction of methylphthalimidine, phthalimidine, methylphthalimide, and phthalimide.

<sup>&</sup>lt;sup>17</sup> Rideal and Taylor: "Catalysis in Theory and Practice," 2nd Ed., 428 (1926).

<sup>&</sup>lt;sup>18</sup> Fichter and Stocker: Ber., 47, 2015 (1914).

<sup>&</sup>lt;sup>19</sup> Bancroft and George: Trans. Am. Electrochem. Soc., 57, 399 (1930).

<sup>&</sup>lt;sup>20</sup> Loc. cit.

2. N-amidoisoindoline has been prepared by the electrolytic reduction of N-nitrosoisoindoline.

3. Variations in the yields obtained with different electrodes have been attributed to the hydrogen over-voltages and probable differences in selective activation of the depolarizer by the metals.

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