Electrolytic Reduction of Glutarimide and Its Derivatives.

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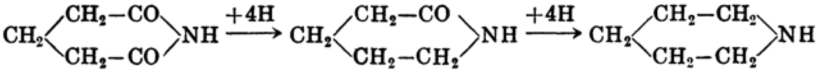
As a rule reduction of acid imides is very difficult; complete reduction of even one of two carbonyl groups is often found unattainable by purely chemical means, that of both carbonyls being almost impossible. Electrolytically, however, reduction takes place with much ease, and by controlling the conditions of reduction properly it is not difficult to prepare the reduction product in some desired stage.

The results of electrolytic reduction of succinic acid imide,⁽¹⁾ undertaken by the author were previously communicated. The work was now extended to next higher dibasic acid imide, i.e. glutarimide, and the result so far obtained is here reported.

So far as the author could find in chemical literature, no one seems to have yet succeeded in getting piperidone or piperidine and their derivatives by direct reduction of glutarimide and its derivatives. Wallach⁽²⁾ and L. Ruzicka⁽³⁾ tried to reduce *N*-ethyl-piperidone with metallic sodium in alcoholic solution, and obtained a condensation product consisting of two molecules of piperidone but not *N*-ethyl-piperidine.

When electrolytically reduced, glutarimide and its derivatives change into piperidines passing through the stage of piperidones:



$$\mathrm{CH_2}\left\langle\begin{matrix}\mathrm{CH_2-CO}\\ \mathrm{CH_2-CO}\end{matrix}\right\rangle\mathrm{NH}\xrightarrow{+4H}\mathrm{CH_2}\left\langle\begin{matrix}\mathrm{CH_2-CO}\\ \mathrm{CH_2-CH_2}\end{matrix}\right\rangle\mathrm{NH}\xrightarrow{+4H}\mathrm{CH_2}\left\langle\begin{matrix}\mathrm{CH_2-CH_2}\\ \mathrm{CH_2-CH_2}\end{matrix}\right\rangle\mathrm{NH}$$

The first reduction takes place smoothly when lead is used as cathode in sulphuric acid solution. For the second reduction lead cathode prepared with a special care according to Lukes and Smetachova⁽⁴⁾ should be used. The author found out that zinc amalgam is much more effective for the same purpose.

Of *N*-methyl-, *N*-ethyl-, and *N*-phenyl-glutarimides, the first two could be reduced easily and with comparatively little decomposition in an about 50% sulphuric acid solution, with lead cathode to *N*-methyl- and

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(1) B. Sakurai, this Bulletin, **10** (1935), 311; **11** (1936), 41; **13** (1938), 350.

(2) Wallach, *Ann.*, **324** (1902), 285.

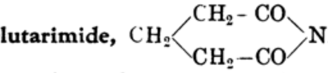
(3) L. Ruzicka, *Helv. Chim. Acta*, **4** (1921), 472.

(4) Lukes and Smetachova, *Collection Czechoslov. Chem. Commun.*, **5** (1933), 61.

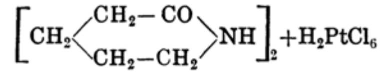
N-ethyl-piperidones, respectively, and with zinc amalgam cathode to *N*-methyl- and *N*-ethyl-piperidines.

Glutarimide and *N*-phenyl-glutarimide are much more liable to decompose in the same sulphuric acid catholyte. So that, if careful attention be not paid to the concentration of sulphuric acid, fruitless results are obtained. It is to be noted that the concentrations of sulphuric acid which cause decomposition of glutarimide and *N*-phenyl-glutarimide differ widely from each other. In the case of glutarimide the most suitable concentration of sulphuric acid is 20–30%. If more concentrated, glutarimide begins to be decomposed to glutaric acid and ammonia and finally in the solution containing H_2SO_4 more than 70% complete decomposition takes place giving no reduction product. In the case of *N*-phenyl-glutarimide the solution containing 80–90% H_2SO_4 is found the most favourable for reduction. If H_2SO_4 becomes less concentrated than 60%, phenyl-glutarimide completely decomposes into glutaric acid and aniline, yielding no reduction product. Reduction from piperidone to piperidine does not differ in both cases, smooth reduction taking place in an about 50% acid solution. The degree of decomposition also differs according to the kind of cathode, and as zinc amalgam causes less decomposition than lead, it is preferable to use a 50% sulphuric acid solution from the beginning in the case of glutarimide, and to increase the concentration of sulphuric acid in electrolytic solution by adding concentrated sulphuric acid to it after the first reduction has been completed. As it is impossible to employ 50% acid and zinc amalgam cathode for *N*-phenyl-glutarimide, a 90% acid solution is to be used with lead cathode for the first reduction, and then the electrolytic solution is diluted to make H_2SO_4 50% and at the same time lead cathode is replaced with zinc amalgam before electrolysis is continued for the second reduction.

Experimental.

I. **Glutarimide,**  $CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CO\end{matrix}\right\rangle NH$. Material was prepared after Bernheimer by fusing ammonium glutarate, and by recrystallizing the residue from alcohol. This forms colourless plates melting at 151°.

(1) *Reduction with lead cathode.* In order to obtain α-piperidone, electrolysis was undertaken under the following conditions. Cathode: lead, 100 sq. cm. Catholyte: 25% sulphuric acid with 3 g. of the imide dissolved in it. Current density: 5 amp. per 100 sq. cm. Current quantity: 7.2 F. per mol. Temperature: 20°.

The electrolytic bath was kept in a water tub full of cool water, and electrolyte was kept all the time stirred and cooled. After electrolysis colourless electrolyte was taken out, and treated with chloroform to extract unreduced material. Next it was shaken with ether to extract glutaric acid produced through the decomposition of the material. After that the liquid was made alkaline with a saturated solution of sodium carbonate, when smell peculiar to α-piperidone came out. It was extracted with ether, and after expelling ether by evaporation about 3 c.c. of a liquid solution were obtained. It was put in a desiccator and then cooled in an ice-box, whereupon 0.4 g. (15%) of α-piperidone crystallized out. On recrystallizing it from ether colourless crystals melting at 38° were obtained. The platinum double chloride was obtained in yellow plates soluble in water or alcohol and melting at 176° with decomposition. Found: Pt, 32.05. Calculated for  $\left[CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CH_2\end{matrix}\right\rangle NH\right]_2+H_2PtCl_6$: Pt, 32.07%.

From the above result, it is seen that, though the imide may be reduced to α piperidone, its greater part decomposes into glutaric acid and ammonia in the course of electrolysis.

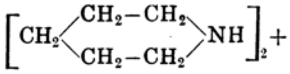
To see how the decomposition of glutarimide is related to concentration of sulphuric acid a series of experiments were carried out varying concentration of sulphuric acid. The results were summarised in Table 1.

Table 1.

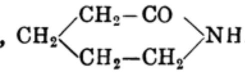
Conc. of sulphuric acid (%)	Unchanged material (%)	Glutaric acid (%)	α-Piperidone (%)
20	10	34	11
30	7.5	43	14
40	5.0	47	11
50	5.0	47	8.6
60	2.5	51	5.7
70	1.0	51	2.8
80	—	55	—
90	—	64	—

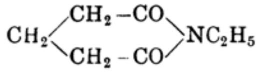
As is seen from the table, sulphuric acid of 20–30% seems to be most favourable for the production of α-piperidone.

(2) *Reduction with zinc amalgam cathode.* With the object of getting piperidine electrolysis was conducted using zinc amalgam as cathode under the following conditions. Cathode: zinc amalgam, 15.8 sq. cm. in area. Catholyte: 50% sulphuric acid 100 c.c. with 5 g. of imide dissolved in it. Anode: cylindrical plate of lead. Anolyte: 50% sulphuric acid. Current density: 88.6 amp. per 100 sq. cm. Current quantity: 70.8 F. per mol. Temperature: 25°.

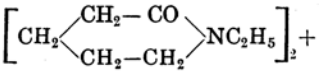
Into the catholyte a spiral lead tube was inserted, through which cold water was passed, while the electrolytic bath itself was put in a water tub full of cool water to prevent the temperature from rising. The catholyte was kept stirred all the time. After electrolysis no glutarimide was detected in the catholyte, but about 0.5 g. (8.5%) of glutaric acid was isolated from it. When it was made alkaline by adding a saturated solution of sodium carbonate, there came out a strong smell resembling that of ammonia. The alkaline solution was extracted with ether, and on the evaporation of ether about 3 c.c. of an aqueous liquid were obtained as the residue. This was made acidic by adding hydrochloric acid to it and evaporated to dryness on the water bath when 2.5 g. (47%) of piperidine hydrochloride was produced. Its platinum double chloride formed orange-red crystals easily soluble in water and alcohol, and melting at 198° with decomposition. Found: Pt, 33.60. Calculated for  $\left[CH_2\left\langle\begin{matrix}CH_2-CH_2\\CH_2-CH_2\end{matrix}\right\rangle NH\right]_2$ + H_2PtCl_6: Pt, 33.62%.

The particularly noteworthy fact observed is that the decomposition of the material is less with zinc amalgam cathode than with lead cathode, in the solution containing sulphuric acid of the same concentration.

II. **α-Piperidone,**  $CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CH_2\end{matrix}\right\rangle NH$. 1.5 g. of the piperidone obtained in the above experiment was subjected to 5 hours' electrolysis with zinc amalgam under the same conditions as above. As the result, 0.95 g. (52%) of piperidine hydrochloride was obtained, accompanied with a very little decomposition product. It is thus seen that piperidone is not so decomposable as glutarimide in sulphuric acid solution. The reason why the cathode of stronger reducing power, such as zinc amalgam, gives the better yield of reduction product is thus easily understood.

III. **N-Ethyl-glutarimide,**  $CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CO\end{matrix}\right\rangle NC_2H_5$. *N*-Ethyl-glutarimide employed in the experiment was prepared by neutralizing glutaric acid with ethylamine and then subjecting the product to distillation at 250–260°. It is a colourless liquid.

(1) *Reduction with lead cathode.* To get *N*-ethyl-piperidone first, electrolysis, was undertaken under the following conditions. Cathode: lead plate 100 sq. cm. in area. Catholyte: 100 c.c. of 50% sulphuric acid in which 5 g. of imide was dissolved. Anode: cylindrical lead plate. Anolyte: 50% sulphuric acid. Current density: 5 amp. per 100 sq. cm. Current quantity: 26.3 F. per mol. Temperature: 28°.

The material dissolved readily in electrolytic solution. The electrolytic bath was kept cooled in a water tub in which cool water was caused to circulate. After the completion of the electrolysis the electrolytic solution was shaken with ether to extract glutaric acid. About 0.25 g. (5%) of it was obtained. Next, after greater part of acid was neutralized with sodium bicarbonate, the catholyte was made slightly alkaline with a saturated solution of sodium carbonate and then extracted with ether when 3.25 g. of a colourless liquid was isolated. It boils at 105–106°, and is easily soluble in water forming a weakly alkaline solution. Its platinum double chloride melts at 164° with decomposition. Found: Pt, 29.39. Calculated for  $\left[CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CH_2\end{matrix}\right\rangle NC_2H_5\right]_2$ + H_2PtCl_6 : Pt, 29.40%. Yield of *N*-ethyl-piperidine in the above experiment is 72.1%.

In the reduction of *N*-ethyl-glutarimide, the concentration of sulphuric acid has close relation to the yield of reduction product; the greater the concentration, the smoother the reduction. If, however, the concentration becomes too great, it gives rise to the decomposition of the material, thereby lowering reduction rate.

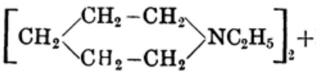
Results of the electrolysis showing the relation between the concentration of sulphuric acid and yield of the piperidone are shown in Table 2.

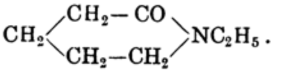
Table 2.

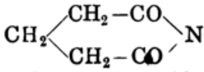
Conc. of H_2SO_4 (%)	Glutaric acid (%)	*N*-Ethyl-piperidone (%)
20	5.4	5.5
30	6.5	44.0
40	7.6	55.0
50	10.8	71.5
60	11.9	77.0
70	16.2	60.5
80	43.2	27.5
90	59.4	5.5

From the table it is seen that if the concentration of sulphuric acid exceeds 70%, decomposition increases rapidly, causing the lowering of reduction rate, and 40–70% sulphuric acid gives the most favourable results.

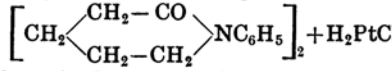
(2) *Reduction with zinc amalgam cathode.* Next electrolysis for complete reduction was conducted under the following conditions. Cathode: zinc amalgam 15.8 sq. cm. Catholyte: 100 c.c. of 50% sulphuric acid in which 5 g. of imide was dissolved. Anode: cylindrical lead plate. Anolyte: 50% sulphuric acid. Current density: 98 amp. per 100 sq. cm. Current quantity: 126 F. per mol. Temperature: 15°.

The electrolysis was carried out by inserting a spiral lead tube into a cylindrical biscuit vessel containing catholyte. Cold water was caused to flow through the lead tube to cool it from inside, while the electrolytic bath itself was put in a water tub, in which cold water constantly circulates to cool the bath from outside. After completion of electrolysis neither the glutarimide nor glutaric acid was detected to exist in the bath. The electrolyte was now diluted with water of three times volume and after neutralizing the acid with sodium bicarbonate it was made slightly alkaline with a saturated solution of sodium carbonate. It was then subjected to steam distillation, when a substance smelling like ammonia came out. The distillate reacting alkaline to litmus paper was neutralized with hydrochloric acid and evaporated to dryness on the water bath. About 4.0 g. of a sticky substance was left as the residue. The platinum double chloride prepared from the residue crystallized in orange-red prisms from a mixture of absolute alcohol and a small quantity of petroleum ether. It melted at 202° with decomposition. Found: Pt, 30.74. Calculated for  $\left[CH_2\left\langle\begin{array}{c}CH_2-CH_2\\CH_2-CH_2\end{array}\right\rangle NC_2H_5\right]_2+H_2PtCl_6$: Pt, 30.70%. The yield of *N*-ethyl-piperidine amounted to 75%.

IV. **N-Ethyl-piperidone,**  $CH_2\left\langle\begin{array}{c}CH_2-CO\\CH_2-CH_2\end{array}\right\rangle NC_2H_5$. Instead of directly reducing *N*-ethyl-glutarimide, 2 g. of *N*-ethyl-piperidone was subjected to 5 hours' electrolysis under exactly the same conditions as the above experiment. As the result *N*-ethyl-piperidine was obtained with the yield of 52%.

V. **N-Phenyl-glutarimide,** 
$CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CO\end{matrix}\right\rangle NC_6H_5$. *N*-Phenyl-glutarimide was prepared from glutaric acid and aniline and purified by recrystallizing the product from absolute alcohol. It formed colourless needles insoluble in water but easily soluble in hot alcohol, and melted at 145°.

(1) *Reduction with lead cathode.* With a view to obtaining *N*-phenyl-piperidone, hitherto unknown, reduction was carried out under the following conditions. Cathode: lead plate 100 sq. cm. Catholyte: 100 c.c. of 90% sulphuric acid in which 5 g. of imide was dissolved. Anode: cylindrical lead. Anolyte: 50% sulphuric acid. Current density: 5 amp. per 100 sq. cm. Current quantity: 56.4 F. per mol. (8 hours). Temperature: 18°.

Electrolysis was carried out by cooling the electrolytic bath with circulating water and keeping catholyte constantly vigorously stirred. The imide partly remained undissolved at first, but gradually disappeared as electrolysis proceeded. After electrolysis the catholyte was diluted with three times as much water and filtered. The clear solution thus obtained was found to contain nothing to be extracted with ether. It was then made slightly alkaline with sodium bicarbonate and sodium carbonate, and from this alkaline solution about 3.5 g. (75%) of *N*-phenyl-piperidone was extracted in the form of brownish crystals. When it was recrystallized from alcohol it formed colourless needles melting at 98°. Found: C, 75.10; H, 7.47; N (determined as ammonia), 8.04%; mol. wt. (ebullioscopy in benzene), 170. Calc. for $C_{11}H_{13}ON$: C, 75.43; H, 7.43; N, 8.00%; mol. wt., 175. The platinum double chloride of this substance formed red-brown scaly crystals melting at 176° with decomposition. Found: Pt, 25.65. Calculated for 
$\left[CH_2\left\langle\begin{matrix}CH_2-CO\\CH_2-CH_2\end{matrix}\right\rangle NC_6H_5\right]_2+H_2PtCl_6$: Pt, 25.69%.

As is obvious from the results of above experiment, the reduction of phenyl derivatives greatly differs from that of ethyl derivatives. For reduction of the former much more concentrated sulphuric acid solution is required. If more dilute sulphuric acid be used as in the reduction experiment for other imide derivatives, decomposition predominates over reduction, making reduction efficiency very bad. The relation existing between concentration of sulphuric acid and the yield of piperidone formed by reduction is shown in Table 3.

Table 3.

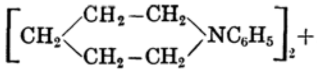
Conc. of sulphuric acid (%)	Unchanged material (%)	Glutaric acid (%)	*N*-Phenyl-piperidone (%)
90	—	—	76
80	10	—	54
70	—	48	36
60	20	58	—
50	25	64	—

Thus, high concentration of sulphuric acid favours the reduction. When concentration of sulphuric acid gets below 60% any reduction is effected no more. In order to reduce *N*-phenyl-glutarimide without any loss in material it is necessary to maintain the concentration of sulphuric acid at a value not smaller than 80%.

(2) *Reduction with zinc amalgam cathode.* In the experiment conducted with the object of obtaining the final reduction product, *N*-phenyl-piperidine, it is inconvenient to work with zinc amalgam cathode in a concentrated sulphuric acid bath. Because not only it checks the passage of electricity, but also it causes decomposition of sulphuric acid. So that, it is advisable to divide the experiment into two stages. In the first stage electrolysis is carried out, as with lead cathode, in 90% sulphuric acid solution to reduce the imide to the piperidone stage and then the electrolytic solution is diluted to make concentration of H_2SO_4 as low as 50% and further electrolysis is carried out with zinc amalgam.

The first stage of reduction carried out with 5 g. of imide was followed by the second stage of reduction, for which the following conditions were employed. Catholyte: 100 c.c. of 90% sulphuric acid which was diluted with 130 c.c. of water. Cathode: zinc amalgam, 15.8 sq. cm. in area. Anolyte: 50% sulphuric acid. Anode: cylindrical lead plate. Current density: 79 amp. per 100 sq. cm. Current quantity: 101.5 F. per mol. (6 hours). Temperature: 18°.

In the course of electrolysis, the electrolytic solution was cooled from both inside and outside. After electrolysis the catholyte contained some sulphur isolated by the decomposition of sulphuric acid. It was filtered and the filtrate was made alkaline with sodium bicarbonate and sodium carbonate solution, when oily *N*-phenyl-piperidine was isolated, which was extracted with ether. About 2.5 g. of the base (58% yield) was obtained. *N*-Phenyl-piperidine is a colourless oil, soluble in water, and easily produces a colourless soluble salt with hydrochloric acid. Its platinum double chloride is yellow crystals containing two molecules of water of crystallization, insoluble in water. It melts with decomposition. Found: Pt, 25.45. Calculated for



$$\left[CH_2\begin{matrix} CH_2-CH_2 \\ CH_2-CH_2 \end{matrix}NC_6H_5\right]_2+H_2PtCl_6\cdot 2H_2O:\ \text{Pt, } 25.42\%.$$

In this connection the author expresses his heartfelt thanks to Dr. Motooki Matsui, Professor emeritus of the Kyoto Imperial University, for his cordial suggestions.

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