

## Electroörganic Preparations

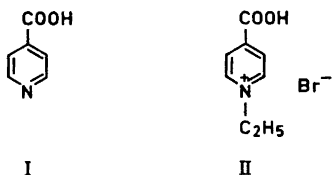
### XI. Reduction of Isonicotinic Acid in Acid Solution

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Isonicotinic acid and its N-alkyl derivative were reduced at constant cathode potential at a mercury electrode using different buffers. In acid solution the main product from isonicotinic acid is pyridine-4-aldehyde, and the N-alkyl derivative is reduced similarly. This seems to be the first example reported of a reduction of a free carboxyl group directly to an aldehyde group.

Isonicotinic acid<sup>1-3</sup> and its N-methyl derivative<sup>1</sup> have previously been investigated polarographically, but the products of the electrode reaction have not been identified. It has generally been assumed that the result of the observed two-electron reduction is a dihydroisonicotinic acid. The purpose of the present investigation was to establish the course of the electrode reaction. It has been studied by means of classical polarography and constant potential reductions at a macro mercury electrode.



#### POLAROGRAPHIC INVESTIGATION

The polarographic results of isonicotinic acid (I) agreed with those of previous workers<sup>2,3</sup>; the results from the investigation of 1-ethyl-4-carboxy-pyridinium bromide (II) are given in Table 1.

The half-wave potentials of II vary with pH in such a way that the curve can be approximated by three lines: one from pH 0.5 to 1.5 with a slope of 0.029 V/pH, a second one from pH 2 to 7 with a slope of 0.068 V/pH, and a third line from pH 8 to 13 with a slope of 0.007 V/pH. From this pH-dependence one would expect that, from pH 8 to 13, the reduced species contained the carboxyl group as a carboxylate ion and that, below 7, the reducible form possessed an undissociated carboxyl group. In part of the pH-interval, the carboxyl

Table 1. Limiting currents in  $\mu\text{A}$  and half-wave potentials vs S.C.E. of 1-ethyl-4-carboxy-pyridinium bromide. Concentration 40 mg/l. No maximum suppressor.

Buffer	pH	1. wave		2. wave	
		$i_l$	$-E_{\frac{1}{2}}$	$i_l$	$-E_{\frac{1}{2}}$
6 N HCl		11.3	0.74		
2.5 N HCl		9.9	0.73 <sub>s</sub>		
HCl—KCl	0.20	8.6	0.75		
HCl—KCl	0.60	7.9	0.76		
HCl—KCl	0.90	8.0	0.76 <sub>s</sub>		
HCl—KCl	1.45	7.8	0.78 <sub>s</sub>		
Glycine	2.10	7.6	0.82		
Citrate	2.60	7.3	0.83		
»	3.05	7.5	0.86		
Acetate	4.25	7.5	0.95 <sub>s</sub>		
»	4.75	7.7	1.00		
Succinate	5.05	8.5	1.02		
Phosphate	6.15	8.8	1.09	2.0	1.23
»	6.60	9.2	1.12 <sub>s</sub>	3.0	1.26
»	7.10	8.7	1.14 <sub>s</sub>	2.5	1.28
Borate	8.25	6.3	1.19 <sub>s</sub>		
»	9.10	6.3	1.20		
»	9.70	6.3	1.20		
Phosphate	11.2	4.5	1.21 <sub>s</sub>	1.8	1.38
»	11.8	4.3	1.22	2.2	1.38
0.1 N KOH		3.7	1.22	3.1	1.40

group may have been formed by a recombination reaction at the electrode surface. It is noteworthy that the change in slope of the pH-dependence occurs at about  $\text{p}K_1$  of the acid.

1-Ethyl-4-carboxy-pyridinium bromide behaves in acid solution very much like isonicotinic acid and is reduced at approximately the same potentials, but in alkaline solution differences exist. The most striking difference between II and I is that II shows no splitting of the wave around pH 8 in the form of a dissociation curve as does isonicotinic acid due to the difference in the reduction potential between its protonated and unprotonated form.

In order to explain this fact and the general polarographic behaviour of 1-ethyl-4-carboxy-pyridinium bromide it became of interest to know the  $\text{p}K$  of the compound. An attempt was made to determine  $\text{p}K$  for II by potentiometric titration, but  $\text{p}K$  was too low for that. The UV-spectra of the compound were, therefore, recorded at different pH-values. The changes in the extinction coefficient around  $270 \text{ m}\mu$  were very small from pH 0 to 12, whereas the position of the maximum changed with pH as shown in Fig. 1. The change to a shorter wave length with increasing pH was ascribed to the dissociation of the carboxyl group and, assuming this to be true, the  $\text{p}K$  of 1-ethyl-4-carboxy-pyridinium bromide is 1.75, as the "halfshift" is found at this pH, and the extinction coefficient in the maximum is approximately the same before and after the dissociation.

Isonicotinic acid has two acidic functions with  $\text{p}K_1 = 1.75$  and  $\text{p}K_2 = 4.9$ .<sup>4,5</sup> The  $\text{p}K_1$  has been ascribed<sup>4,5</sup> to the dissociation of the protonated ring-nitrogen and  $\text{p}K_2$  to the dissociation of the carboxyl group. However, in the UV-

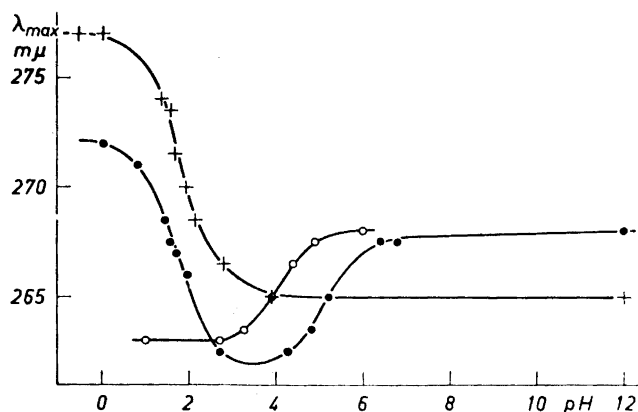


Fig. 1. Dependence of  $\lambda_{\max}$  around 270 mμ on pH in the UV-spectra of isonicotinic acid ●, 1-ethyl-4-carboxy-pyridinium bromide +, and isonicotinic amide O. The data of isonicotinic amide are taken from Fig. 2 in Ref.<sup>5</sup>

spectrum of isonicotinic acid in acid solution there is a maximum around 270 mμ. This maximum shifts to shorter wave lengths with increasing pH. The midpoint of the S-shaped curve (Fig. 1) is at pH = 1.75. A similar shift is found in the spectrum of 1-ethyl-4-carboxy-pyridinium bromide and here the shift is believed to be caused by the dissociation of the carboxyl group. This seems to indicate, that the assignment mentioned above should be reversed.

Also the maximum around 270 mμ in the spectra of isonicotinic amide<sup>5</sup> and isonicotinic ethyl ester changes with pH but in the opposite direction. The maximum of isonicotinic amide<sup>5</sup> shifts between pH 3 and pH 6 from 263 mμ to 268 mμ, and this shift is associated with the dissociation of the protonated pyridine ring-nitrogen. Isonicotinic acid shows a similar shift (Fig. 1) between pH 4 and 7 from 263 mμ to 268 mμ, and this shift can be explained in the same way.

The dependence of the UV-spectra of isonicotinic acid on pH can thus be accounted for by assuming that  $pK_1 = 1.75$  is associated with the dissociation of the carboxyl group and  $pK_2 = 4.9$  with the dissociation of the protonated ring-nitrogen. The isonicotinic acid would thus at the isoelectric point mainly exist as the zwitterion. This is in accordance with the findings of Green and Tong<sup>6</sup>.

The assumption made seems reasonable on the following grounds: (1) a protonated pyridine ring would exert a strong influence on the carboxyl group by raising the acid strength considerably; (2)  $pK_1 = 1.75$  for such a carboxyl group is acceptable in view of the fact that 1-ethyl-4-carboxy-pyridinium bromide has  $pK = 1.75$  and here the carboxyl group is activated similarly by a pyridine ring carrying a positive charge, and (3) the carboxylate ion would not be expected to influence the pyridine ring very much, and  $pK_2 = 4.9$  for the pyridine ring under these conditions is acceptable in view of  $pK = 5.1$  for pyridine itself.

If it is accepted that  $pK_1 = 1.75$  for isonicotinic acid is associated with the carboxyl group and  $pK_2 = 4.9$  with the pyridine ring, many features in the

If the assignment of the  $pK_1$  and  $pK_2$  is reversed in accordance with the arguments given above, Volke and Volkova's arguments based on the rate of the recombination reaction and Jellinek and Urwin's arguments based on the similarity in the recombination reaction of derivatives of isonicotinic acid can both be accepted without difficulty. This assignment would also explain the similarity in polarographic behaviour between isonicotinic acid and 1-ethyl-4-carboxy-pyridinium bromide in acid solution as both molecules in this pH-region would carry a similarly-situated positive charge. Furthermore, if the occurrence of two waves in alkaline solution of isonicotinic acid is connected with the loss of the positive charge on the ring-nitrogen, it can be understood that the wave of 1-ethyl-4-carboxy-pyridinium bromide does not split into two waves in alkaline solution in the way isonicotinic acid does.

In acid solution the main product from the reduction of isonicotinic acid was found to be pyridine-4-aldehyde. This compound was identified by means of polarography and by the m.p. and IR-spectrum of the phenylhydrazone. The yield of aldehyde was determined polarographically and also by the isolation of the phenylhydrazone. Besides pyridine-4-aldehyde, various amounts of some unidentified, coloured compounds were formed during the reduction. If the reduction was allowed to proceed to completion at the potential used, the aldehyde was reduced to the carbinol.

$$\begin{array}{l} \text{H}_5\text{C}_2-\text{N}+\text{C}_5\text{H}_4-\text{COOH} + 2\text{e}^- + 2\text{H}^+ \longrightarrow \left\{ \begin{array}{l} \text{H}_5\text{C}_2-\text{N}+\text{C}_5\text{H}_4-\text{CHO} + \text{H}_2\text{O} \\ \text{H}_5\text{C}_2-\text{N}+\text{C}_5\text{H}_4-\text{CH}(\text{OH})_2 \end{array} \right. \\ \text{H}_5\text{C}_2-\text{N}+\text{C}_5\text{H}_4-\text{CHO} + 2\text{e}^- + 2\text{H}^+ \longrightarrow \text{H}_5\text{C}_2-\text{N}+\text{C}_5\text{H}_4-\text{CH}_2\text{OH} \end{array}$$

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Table 2. Dependence of yield of pyridine-4-aldehyde on pH in the reduction of isonicotinic acid (see text).

pH	Yield (%) of aldehyde (found)	% non-reduced isonicotinic acid	Yield (%) of aldehyde (corrected)
0.1	29	6	31
1.2	41	14	48
2.6	60	7	65
2.85	66	5	69
3.25	65	6	69
4.85	28	21	35
6.15	10	18	12

fourth one the yield of pyridine-4-aldehyde based on the isonicotinic acid actually reduced. In Table 3 the corresponding results are given for 1-ethyl-4-carboxy-pyridinium bromide.

The yield of the aldehyde under polarographic conditions may be somewhat higher than that found by the macroscale electrolysis, where some of the aldehyde is reduced further. This reduction, probably, does not occur at the dropping mercury electrode where the concentration of the reduction product remains very low. It can be assumed that the amount of non-reduced isonicotinic acid corresponds to the amount of the further-reduced pyridine-4-aldehyde, but the validity of this assumption is uncertain as long as the nature of the coloured by-products is not known.

#### DISCUSSION

The direct reduction of a free carboxyl group to an aldehyde group with chemical reagents has not been reported, the general method being the reduction of the acid chloride, amide, or a lactone. The chemical reagents capable of attacking a free carboxyl group also reduce the aldehyde. The same holds true for catalytic reductions and the reported classical electrolytic reactions. Recently it has been reported <sup>7</sup> that during an indirect electrolytic reduction of 2,3-naphthol carboxylic acid in the presence of *p*-toluidine, a yield of 5–7 % of a reduction product from a Schiff's base, formed from an intermediate aldehyde, could be obtained.

The pyridine-4-aldehyde and 1-ethyl-4-formyl-pyridinium ion are reduced at potentials less negative than those of the corresponding acids. This is found

Table 3. Dependence of yield of 1-ethyl-4-formyl-pyridinium bromide on pH in the reduction of 1-ethyl-4-carboxy-pyridinium bromide (see text).

pH	Yield (%) of aldehyde (found)	% non-reduced acid	Yield (%) of aldehyde (corrected)
0.15	28	5	30
1.35	52	5.5	55
2.55	72	4	75
4.45	67	8	72
5.15	59	7	63
6.29	26	10	29
9.15	0	0	0

for all aldehydes and one might, therefore, expect that the aldehyde is reduced further as fast as it is formed. The explanation which is known from polarographic investigations is that pyridine-4-aldehyde<sup>8</sup> and 1-ethyl-4-formylpyridinium bromide<sup>9</sup> form a rather stable hydrate and that this hydrate is not reducible at the dropping mercury electrode. The wave height of pyridine-4-aldehyde is, in acid solution, much smaller than one would expect from a diffusion controlled wave. The height of the wave is dependent on the position of the hydratization equilibrium and the rate of the formation of the reducible free aldehyde from the hydrate at the surface of the electrode.

Isolation of an aldehyde as a reduction product from an electrolytic reduction of an acid can thus only be expected in cases where the aldehyde is protected against further reduction by the formation of a stable hydrate or acetal, or can be trapped as a non-reducible derivative in another way.

A proposed reduction route of isonicotinic acid and its N-alkyl derivative can only be of a speculative nature as long as the influence of the potential gradient in the electrical double layer at the cathode on the polarization of the molecule is not known. However, some facts which a reaction mechanism must be able to explain might be pointed out.

The pH-dependence of the yield of aldehyde together with the pH-dependence of the half-wave potentials gives some clues on the species reduced. The yield of aldehyde is dependent on two factors: the actual amount of aldehyde formed, which depends on the reduction route, and the effectiveness of the trapping of the aldehyde as the hydrate. If the latter factor could be estimated separately we could get the yield-pH-dependence needed for the evaluation of the reaction mechanism. As a first approximation one might assume that the amount of further-reduced aldehyde is equivalent to the acid which has not been reduced when two electrons per molecule have been consumed.

This amount can be found approximately by adding the percentage from columns 3 and 4 in Tables 2 and 3. It is seen that the assumption mentioned above does not alter the shape of the yield-pH-dependence curve, but brings the two curves closer together. The highest yield of aldehyde is found from pH 2 to 5. In this region the molecule is believed to exist in the bulk of the solution as the zwitterion. The polarographic results of 1-ethyl-4-carboxypyridinium bromide show, however, that the species reduced at the surface of the dropping mercury electrode contains an undissociated carboxyl group up to pH 7. The undissociated carboxyl group is, from pH about 2 to pH about 7, formed at the electrode surface by a recombination reaction between the zwitterion and a hydrogen ion. As the polarographic results thus suggest that the same species is reduced between pH 2 and 7 one might have expected the aldehyde to be formed in good yield up to pH 7. However, Tables 2 and 3 show that the yield decreases markedly in the pH-interval 5 to 7. Differences in the recombination reaction between the macro mercury electrode and the dropping mercury electrode might be responsible for this disagreement. Below pH 0 the yield of aldehyde diminishes and this decline can not be accounted for exclusively by less protection of the aldehyde as the hydrate found in this pH-region. In some step of the reaction the rate of proton uptake seems to determine whether aldehyde or other products are formed.

Pyridine-2-aldehyde forms a hydrate in a similar way as pyridine-4-aldehyde does. Like isonicotinic acid in acid solution, picolinic acid is reduced to the aldehyde in a yield which is comparable to that obtained by reduction of isonicotinic acid. The 1-ethyl-2-carboxy-pyridinium ion behaves in a similar way as the 4-carboxy derivative. Some aldehydes containing other pyridine-like heterocyclic nuclei, *e.g.* thiazole-2-carboxaldehyde and imidazole-2-carboxaldehyde, form hydrates, and the corresponding acids and derivatives thereof are being investigated.

The pyridine-4-aldehyde is a key-intermediate in the reduction of many derivatives of isonicotinic acid. Isonicotinic acid ethyl ester is reduced in a similar way as is the acid. The isonicotinic amide is reduced with less side reactions to the aldehyde than are the ester and the free acid. The same holds true for mono- and di-alkyl substituted isonicotinic amides. The second wave of isonicotinic hydrazide in acid solution has also been found to be caused by a reduction to pyridine-4-aldehyde. The aldehyde has not, however, been detected in the reduction of aryl-substituted isonicotinic amides or in isonicotinic thiamide. A detailed report of these results will be published later.

#### EXPERIMENTAL

The polarograph was a recording polarograph Radiometer PO 4d. The potentiostat was a Wadsworth Controlled Potential Electro-Depositor. The capillary delivered 2.45 mg of mercury per second at a corrected mercury column height of 48.5 cm. The drop time was 3.7 sec. ( $H_2O$ , open circuit).

1-Ethyl-4-carboxy-pyridinium bromide was prepared from isonicotinic acid and ethyl bromide in acetonitrile. M.p. 295°.

*Reduction of isonicotinic acid.* The following exemplifies the procedure used in all cases. 0.500 g of isonicotinic acid were dissolved in 170 ml of a deaerated, pre-electrolyzed solution containing 0.3 M citric acid buffer, pH 2.85, and 1 M potassium chloride. The solution was cooled to between 0° and 5° and the stirred solution reduced at a cathode potential of  $-1.0$  V vs S.C.E. The reduction was followed polarographically. When two electrons per molecule had been consumed, the reduction was stopped. The yield of pyridine-4-aldehyde was found by polarography of a sample in a deaerated phosphate buffer pH 7.1. 4 ml phenylhydrazine were added to the solution. After heating to boiling and cooling, the citric acid was partly neutralized by solid sodium carbonate. After standing over-night, 596 mg crude, crystalline phenylhydrazone m.p. 170°–175°, were collected. Recrystallization from aqueous alcohol raised the m.p. to 175°–177° (lit. 178°). The IR-spectrum of the compound was identical with the spectrum of authentic pyridine-4-aldehyde phenylhydrazone.

The reduction of 1-ethyl-4-carboxy-pyridinium bromide was made in the same way, but the yield of the aldehyde was determined polarographically at pH 13. The aldehyde was not isolated.

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